Cediranib in patients with relapsed platinum-sensitive ovarian cancer (ICON6): a randomised, double-blind, placebo-controlled phase 3 trial

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Lancet 2016; 387: 1066–74

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Summary

Background Angiogenesis is a validated clinical target in advanced epithelial ovarian cancer. Cediranib is an oral antiangiogenic vascular endothelial growth factor receptor 1–3 inhibitor that has shown antitumour activity in recurrent ovarian cancer. We assessed efficacy and safety of cediranib in combination with platinum-based chemotherapy and as continued maintenance treatment in patients with first relapse of platinum-sensitive ovarian cancer.

Methods In this randomised, three-arm, double-blind, placebo-controlled phase 3 trial, we randomly assigned patients aged 18 years or older with relapsed platinum-sensitive ovarian cancer at 63 centres in Australia, Canada, New Zealand, Spain, and the UK. Participants received up to six cycles of platinum-based chemotherapy (once every 3 weeks) then entered a maintenance phase. Participants were randomly allocated (2:3:3), with five stratification factors and in alternating blocks, to receive placebo alongside chemotherapy and then placebo only maintenance (arm A; reference), cediranib 20 mg once-daily alongside chemotherapy then placebo only maintenance (arm B; concurrent), or cediranib 20 mg once-daily alongside chemotherapy then cediranib 20 mg once-daily maintenance (arm C; maintenance). Patients continued treatment to progression or excessive toxic effects. The primary efficacy endpoint was progression-free survival between arms A and C. Efficacy analysis was by intention to treat. Safety was assessed in all patients who received the allocated study drug. This trial is registered with ClinicalTrials.gov, number NCT00532194; the ISRCTN registry, number ISRCTN68510403; and ANZ Clinical Trials Registry, number ACTRN12610000016003.

Findings We randomly assigned 456 women between Nov 13, 2007, and Dec 23, 2011; results presented are for 456 patients randomly assigned subsequent to the 30mg safety phase. During a median of 19·5 months (IQR 14–26) follow-up, 113 (96%) of 118 women assigned to arm A and 141 (86%) of 164 assigned to arm C had disease progression. Median progression-free survival was 11·0 months (95% CI 10·4–11·7) in arm C and 8·7 months (7·7–9·4) in arm A (hazard ratio 0·56, 0·44–0·72, p<0·0001). 156 (90%) of 174 patients in arm B had disease progression, and median progression-free survival was 9·9 months (95% CI 9·4–10·5). Diarrhoea, neutropenia, hypertension, and voice changes were significantly more common, during chemotherapy with cediranib, and diarrhoea, hypothyroidism and voice changes were more common during maintenance. Poor compliance with cediranib was noted during maintenance treatment with toxic effects being the most common cause for discontinuation.

Interpretation Cediranib, when given orally with chemotherapy and continued as maintenance, yielded a meaningful in progression-free survival in women with recurrent platinum-sensitive ovarian cancer, albeit with added toxic effects. The positive results in ICON6 could provide women with a new therapeutic option for recurrent ovarian cancer. Assessment of the secondary endpoint of overall survival will need longer follow-up.

Funding Medical Research Council, Cancer Research UK, Canadian Cancer Society Research Institute, Cancer Australia, National Gynecological Cancer Centre, and AstraZeneca.

Introduction

Ovarian cancer, the leading cause of death from gynaecological tumours in high-income countries, initially responds well to surgery and platinum-based chemotherapy. Most patients develop recurrent treatable disease, albeit with diminishing benefit from each subsequent regimen.[1] Although the cumulative effect of successive lines of chemotherapy might be to extend survival, the duration of response shortens with each line of therapy, and the potential to increase the interval between treatments by using maintenance treatment to delay the need for further chemotherapy is deemed a clinically valuable research objective and beneficial for patients. One way of achieving this goal is to inhibit angiogenesis, the process of new blood vessel formation, which is needed for tumour growth.[2] This approach has been validated through phase 3 trials with the monoclonal antibody to vascular endothelial growth factor (VEGF),

Research in context

Evidence before this study

In 2003, we published the results of the International Collaborative for Ovarian Neoplasia (ICON) 4 trial in *The Lancet*, showing the value of platinum-combination treatment for women relapsing more than 6 months after completing first-line treatment for ovarian cancer. This set a new standard of care with an improvement in overall survival, but the benefit was slight. In around 2006, unpublished data began to emerge showing that inhibitors of angiogenesis, blocking either the vascular endothelial growth factor (VEGF) ligand or its receptor could lead to shrinkage of ovarian tumours and delayed disease progression. We designed a three-arm, placebo-controlled, randomised trial (ICON6) in collaboration with the Gynaecological Cancer InterGroup adding the VEGF receptor tyrosine kinase inhibitor cediranib to chemotherapy and then continued as maintenance treatment. No previous trials of maintenance treatment with a molecularly targeted treatment in ovarian cancer had been done, although during this time, trials with the monoclonal antibody bevacizumab were in development for first-line treatment and for women with first relapse. ICON6 was an academic-led trial and complemented AstraZeneca-sponsored or supported studies with cediranib (as cediranib was only available through the company) in lung and colon cancer and in glioblastoma.

Added value of this study

In ICON6 we have shown that the addition of cediranib to platinum-based chemotherapy prolongs the progression-free survival of women with ovarian cancer. The three-arm trial shows an effect of maintenance cediranib over and above the effect of adding it to chemotherapy. The magnitude of benefit was similar to a trial with bevacizumab in a similar group of patients. Survival data are immature, but ICON6 is the first trial to show the benefit of a VEGF receptor tyrosine kinase inhibitor in recurrent ovarian cancer. Toxic effects, particularly diarrhoea, fatigue, and hypertension, are problematic in some patients, and a proportion of the patients stopped the trial early because of side-effects. However, the results of cediranib and bevacizumab trials show that antiangiogenic treatment is a new treatment option for women with relapsed ovarian cancer, and cediranib is the first oral drug to be beneficial in this setting.

Implications of all the available evidence

Development of treatments to prolong disease control of ovarian cancer is a key therapeutic aim. Trials of cediranib in other tumour types showed no evidence of a benefit, but the positive results in ICON6 have led the manufacturer to re-start development of cediranib in ovarian cancer. Another trial in the USA has shown that the addition of cediranib to the PARP inhibitor olaparib improves progression-free survival in a similar group of patients, further extending the potential of cediranib in this disease. The results of ICON6 have been shared with AstraZeneca who have now applied to the European Medicines Agency for market authorisation. A successful application will provide women with a new therapeutic option for recurrent ovarian cancer.

bevacizumab, which increases the response rate to chemotherapy[3–5] and extends progression-free survival.[3–6]

Cediranib is an oral VEGF receptor (VEGFR 1–3) and c-Kit[7] inhibitor that has shown antitumour activity in recurrent ovarian, colorectal, advanced biliary tract, renal, and lung cancers, and glioblastoma and alveolar soft-part sarcoma.[8–14] On the basis of the phase 2 activity in ovarian cancer,[8] we investigated the efficacy and safety obtained by giving cediranib with chemotherapy and as maintenance treatment in patients with platinum-sensitive[15] ovarian cancer who had radiological evidence of recurrence more than 6 months after completion of first-line chemotherapy. The International Collaboration for Ovarian Neoplasia 6 (ICON6) trial was an investigator-initiated, academically led trial developed through the Gynecologic Cancer InterGroup, and led by the Medical Research Council Clinical Trials Unit at University College London in the UK.

Methods

Study design and participants

We did an international, three-arm, randomised, double-blind, placebo-controlled, phase 3 trial of cediranib in patients with relapsed platinum-sensitive ovarian cancer in 63 centres in Australia, Canada, New Zealand, Spain, and the UK. Participants were at least 18 years old and had CT or MRI evidence of recurrent ovarian, fallopian tube, or primary peritoneal cancer requiring further platinum-based chemotherapy at least 6 months after completing first-line chemotherapy. Patients had Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 but were ineligible if they had poorly controlled hypertension, arterial thrombotic events within 12 months, substantial haemorrhage, or major surgery in the preceding 2 weeks before the start of treatment. Following ethical approval all patients provided written informed consent. The study protocol is available online.

For more on the **study protocol** see http://www.icon6.org/protocol/

Randomisation and masking

Patients were randomly assigned (2:3:3) to three parallel treatment arms: in arm A (reference) patients received platinum-based chemotherapy plus once-daily oral placebo tablets during the chemotherapy phase, then received placebo alone during the maintenance phase; in arm B (concurrent), patients received platinum-based chemotherapy plus once-daily oral cediranib, then switched to placebo during the maintenance phase; in arm C (concurrent plus maintenance), patients received once-daily oral cediranib during both phases.

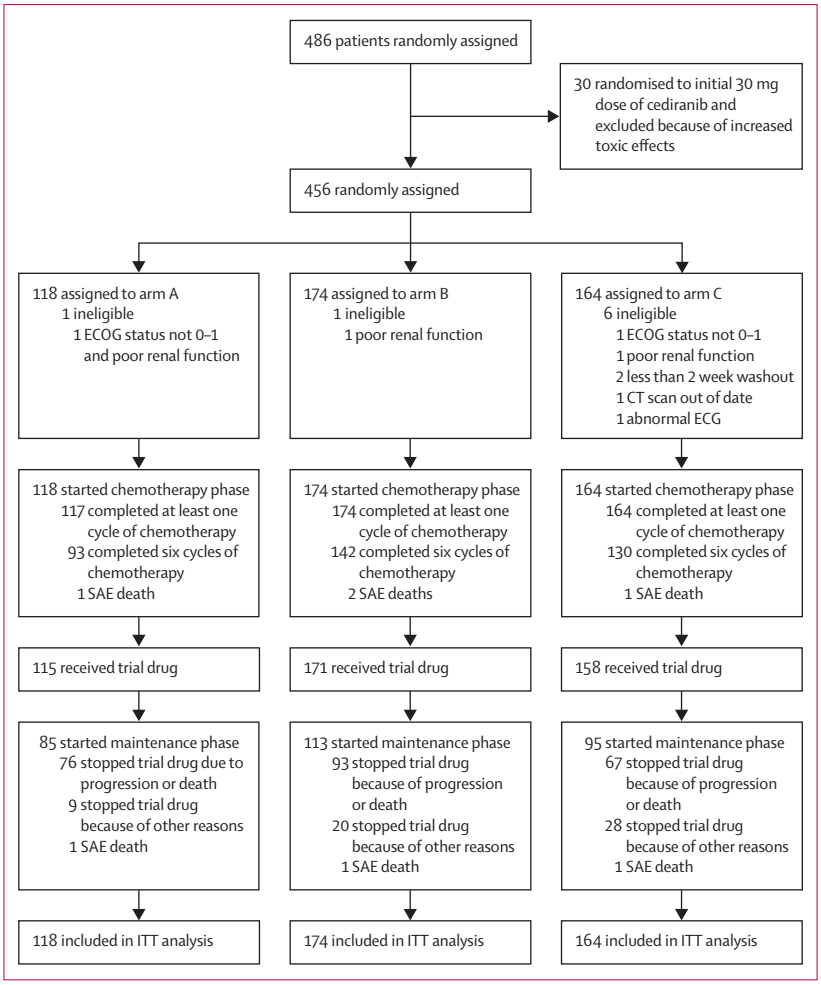

Figure 1: **Trial profile**
SAE=serious adverse events. ITT=intention to treat. ECOG=Eastern Cooperative Oncology Group.

Randomisation was done centrally by a third party via an interactive voice and web response system. Permuted blocks were used (alternating between eight and 16) stratified by Gynecologic Cancer InterGroup, first-line chemotherapy (paclitaxel or other), relapse-free interval (6–12 months *vs* >12 months), planned chemotherapy regimen, and previous bevacizumab treatment. Both patients and the treating clinician were masked to the assigned treatment. Before the start of the trial, the Clinical Trials Unit tested samples of cediranib and matched placebo for effectiveness of match with a panel of five testers. Samples were examined for colour, shape/consistency, smell, and taste. No significant differences were detected in any of the four features or overall between the cediranib and matched placebo

See Online for appendix

Procedures

Six cycles of chemotherapy (once every 3 weeks) were planned, but patients unable to complete six cycles and who were responding to treatment could begin maintenance treatment after at least four cycles were completed. Maintenance treatment for 18 months from initiation of all treatment for relapse was originally planned; however, a protocol modification in February, 2010, allowed patients to continue masked treatment beyond 18 months to progression if they were thought to be still deriving clinical benefit by the treating clinician. Recommended chemotherapy was carboplatin with either paclitaxel or gemcitabine. Carboplatin monotherapy was permitted, as was cisplatin, if carboplatin could not be given.[16,17] Protocol-defined dose reductions of chemotherapy were done if necessary.

The trial drug, cediranib or placebo, was started with chemotherapy and continued to progression or excessive toxic effects. An initial safety phase used a single daily dose of 30 mg. After review of the first 30 patients in November, 2008,[18] the Independent Data Monitoring Committee recommended reduction of the dose of cediranib to 20 mg, in line with ongoing combination phase 3 trials in lung cancer, colorectal cancer, and glioblastoma,[9,19,20] and continuation of the trial. Clinicians were provided with clinical management guidelines to help early management of the main toxic effects of cediranib, which are hypertension, diarrhoea, proteinuria, and fatigue. Interruption of trial drug for up to 2 weeks as a result of toxic effects was permitted to allow recovery to grade 1 or less. A dose reduction to 15 mg was permitted, and needed for toxic effects of grade 3 or more. Cediranib or placebo was discontinued permanently if gastrointestinal perforation, arterial thromboembolic events, grade 4 haemorrhage, hypertensive crisis, or reversible posterior leukoencephalopathy syndrome occurred.

Baseline measurable disease was not needed. Tumour assessments were done by CT or MRI before treatment, at chemotherapy completion (week 18), and thereafter at weeks 52, 78, and when clinically needed. Patients were reviewed before each chemotherapy cycle and every 6 weeks during maintenance treatment. Increasing CA-125 concentrations alone did not define progression, but could trigger unscheduled CT or MRI assessment to detect progression at any time (for full definition of investigator-declared progression see appendix). Patients were not unmasked on progression.

Outcomes

ICON6 was originally planned with three stages: safety, efficacy with a progression-free survival outcome using RECIST criteria,[21] and a third expanded phase with overall survival as the primary outcome. We had to redesign the trial towards the end of the second phase because continuation to the third phase was not possible when AstraZeneca discontinued cediranib development in October, 2011, after disappointing outcomes in pivotal trials of other cancer types.[9,12] The prospective analysis plan was modified (with no outcome analysis done) to account for shortage in future drug supply. The primary outcome changed to a progression-free survival

comparison between arms A and C, which was deemed most clinically relevant in view of emerging data for maintenance bevacizumab. Progression-free survival was defined as time from randomisation to disease progression or death from any cause (appendix).[3,4,6] Overall survival and comparison of progression-free survival in all three arms became secondary endpoints, along with assessment of toxicity and quality of life. The timeline for key milestones in the trial procedure, including the redesign, are outlined in the appendix. Toxicity was assessed locally by investigators and all adverse events were reported.

Statistical analysis

After protocol amendment to the primary endpoint, the revised sample size needed 440 patients randomly assigned to receive cediranib 20 mg, excluding those who received 30 mg (see appendix for analysis of these patients). 176 events in arms A and C would provide at least 80% power to detect a progression-free survival hazard ratio (HR) of 0·65 with a 5% two-sided significance level. In October, 2012, the target number of events was imminent, but the statistical analysis plan was revised (with no outcome analysis having been done) because a substantial proportion of patients in arms B and C who were receiving treatment had not yet reached 18 months of treatment. As the primary analysis was between no cediranib (arm A) and a planned 18 months of cediranib (arm C), we deemed it wise to delay the analysis by a few months until an estimated 5% or less of patients were on cediranib or placebo.

Analyses were done on an intention-to-treat basis. Patients were censored at date of last follow-up if they had not progressed or died by the time of analysis. For the overall survival analysis, which included death from any cause, the date of censoring was brought forward to the data cutoff date for any patients who were confirmed to have been alive at a later date (appendix). Preliminary results were presented in 2013;[22] the results presented here follow subsequent extensive data cleaning, although differences are slight and detailed in the appendix. Other sensitivity analyses are also described (appendix).

The log-rank test was used as the primary test of an overall difference between Kaplan-Meier curves for both progression-free survival and overall survival. A prespecified plan to address the proportionality of hazards was made because of the difficulty of interpreting the HR in the presence of time-dependent treatment effects. The presence of non-proportional hazards was assessed with the Grambsch-Therneau test.[23] With evidence of non-proportionality at the 5% level, survival data would be modelled by a flexible parametric model (3 degrees of freedom for the baseline hazard function, 1 degree of freedom for the time-dependent treatment effect) and differences in restricted mean survival time would be estimated.[24] Without evidence of non-proportional hazards, a standard Cox model would be used instead.

This trial is registered with ClinicalTrials.gov, number NCT00532194; the ISRCTN registry, number ISRCTN68510403; and ANZ Clinical Trials Registry, number ACTRN1261000016003.

	Arm A (reference group; n=118)	Arm B (concurrent group; n=174)	Arm C (maintenance group; n=164)	Overall (n=456)
Age (years)	62 (53–67; 37–77)	62 (54–69; 30–85)	62 (54–68; 32–86)	62 (54–68; 30–86)
ECOG status				
0	69 (58%)	109 (63%)	95 (58%)	273 (60%)
1	47 (40%)	64 (37%)	67 (41%)	178 (39%)
2	1 (1%)	0	0	1 (<1%)
3	0	0	1 (1%)	1 (<1%)
Not available	1	1	1	3
Primary tumour type				
Ovary	98 (83%)	139 (80%)	131 (80%)	368 (81%)
Fallopian	1 (1%)	6 (3%)	6 (4%)	13 (3%)
Peritoneal	19 (16%)	29 (17%)	27 (16%)	75 (16%)
Histology				
Serous	87 (74%)	129 (75%)	116 (71%)	332 (73%)
Endometrioid	3 (3%)	7 (4%)	9 (6%)	19 (4%)
Clear cell	3 (3%)	8 (5%)	5 (3%)	16 (4%)
Mucinous	0	3 (2%)	1 (1%)	4 (1%)
Mixed or other	21 (18%)	26 (15%)	30 (18%)	77 (17%)
Undifferentiated	3 (3%)	0	2 (1%)	5 (1%)
Not available	1	1	1	3
Tumour grade				
Well differentiated	1 (1%)	6 (4%)	5 (3%)	12 (3%)
Moderately differentiated	18 (16%)	20 (13%)	24 (16%)	62 (15%)
Poorly differentiated	97 (84%)	132 (84%)	117 (80%)	346 (82%)
Not assessable or missing	2	16	18	36
First-line chemotherapy included paclitaxel				
Yes	104 (89%)	151 (88%)	149 (91%)	404 (89%)
No	13 (11%)	20 (12%)	15 (9%)	48 (11%)
Not available	1	3	0	4
Previous bevacizumab				
Yes	6 (5%)	9 (5%)	9 (5%)	24 (5%)
No	112 (95%)	165 (95%)	155 (95%)	427 (95%)
Time since last chemotherapy				
6–12 months	43 (36%)	59 (34%)	50 (30%)	152 (33%)
>12 months	75 (64%)	115 (66%)	114 (70%)	304 (67%)
Time from first histological diagnosis to randomisation (weeks)	82·6 (60–117; 29–449)	82·9 (64–135; 37–676)	87·4 (65–117; 45–369)	84·6 (62–123; 29–676)
Planned chemotherapy				
Carboplatin alone	12 (10%)	19 (11%)	18 (11%)	49 (11%)
Carboplatin plus paclitaxel	89 (75%)	130 (75%)	121 (74%)	340 (75%)
Carboplatin plus gemcitabine	17 (14%)	25 (14%)	25 (15%)	67 (15%)

Data are median (IQR; range) or n (%). ECOG=Eastern Cooperative Oncology Group.

Table 1: **Baseline characteristics**

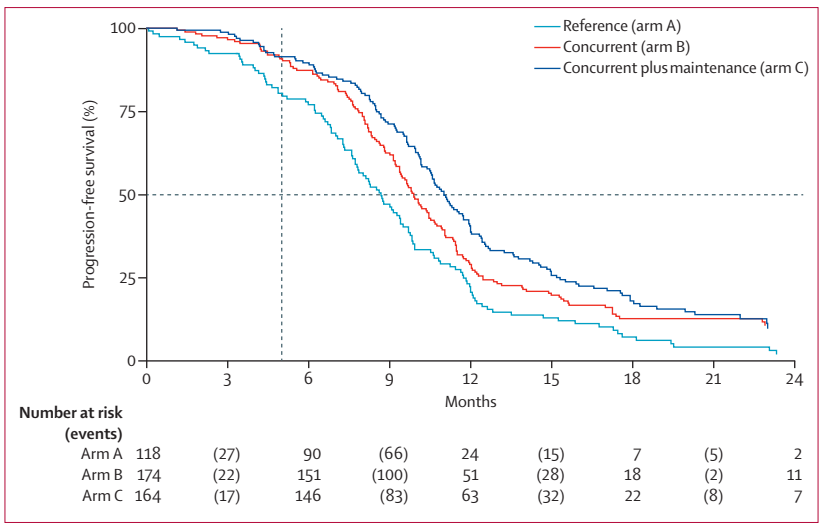

***Figure 2*: Kaplan-Meier plot of progression-free survival over 2 years**
Vertical reference line shows the median time to completion of the chemotherapy phase. Number at risk every 6 months shown with the number of failure events in parentheses, after the time in which the number at risk was calculated.

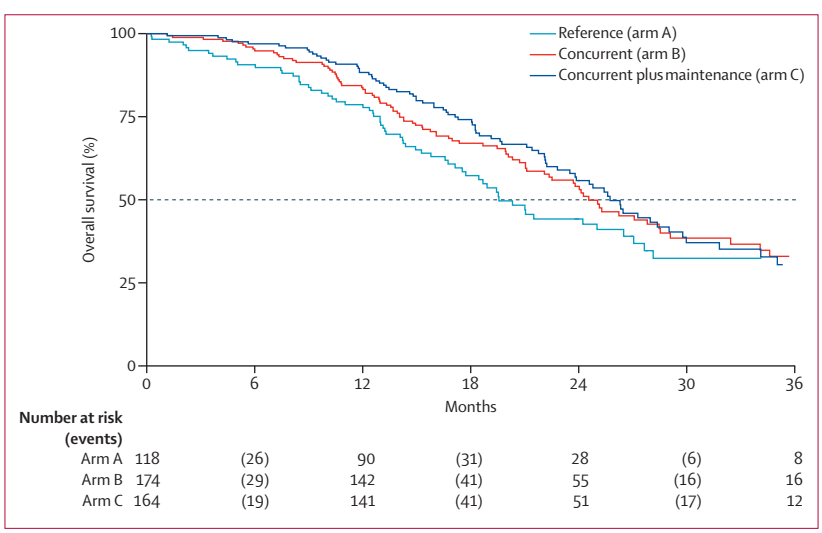

***Figure 3*: Kaplan-Meier plot of overall survival over 3 years**
Number at risk every 12 months shown with the number of failure events in parentheses, after the time in which the number at risk was calculated.

Role of the funding source

The funders of the study had no role in the study design, data collection (except for the collection of images for masked central imaging review), data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Recruitment of patients to ICON6 took place between Dec 10, 2007, and December, 2011, at 63 centres in the UK, Canada, Australia, New Zealand, and Spain. 486 patients were randomly assigned; however, the results presented here are for the 456 patients randomly assigned after the cediranib dose was reduced to 20 mg per day in November, 2008 (30 patients were randomly assigned to receive 30 mg cediranib, but then the trial was restarted at 20 mg because of toxicity and to bring it inline with other cediranib trials; figure 1). Baseline characteristics were well balanced between groups (table 1). 22 (5%) patients had a second debulking attempt that was done before randomisation. No patients were lost to follow-up and five withdrew consent for collection of further data (one patient in arm A, one in arm B, and three in arm C).

Median follow-up was 19·5 months (IQR 14–26), during which 410 (90%) of the 456 patients had disease progression, including 113 (96%) of 118 patients in arm A, 156 (90%) of 174 patients in arm B, and 141 (86%) of 164 patients in arm C. Median progression-free survival was 11·0 months (95% CI 10·4–11·7) in arm C and 8·7 months (7·7–9·4) in arm A (HR 0·56, 0·44–0·72, p<0·0001). 156 (90%) of 174 patients in arm B had disease progression, and median progression-free survival was 9·9 months (9·4–10·5). Some evidence of non-proportional hazards was noted (p=0·06) and the restricted mean survival time over 2 years was 12·5 months (11·7–13·4) in arm C and 9·4 months (8·6–10·2) in arm A.

The difference between groups in progression-free survival was statistically significant when arm B, concurrent cediranib, was included in the analysis (likelihood ratio p_{trend}<0·0001). For this secondary analysis, the median progression-free survival was 9·9 months (9·4–10·5) and restricted mean survival time over 2 years was 11·0 months (10·4–11·5). Kaplan-Meier plots (figure 2) seem to suggest similar survival in arms B and C during the chemotherapy phase when both groups were receiving cediranib, then worsening survival in arm B after the switch to placebo.

Overall survival data are immature because only 236 (52%) of 456 of patients had died at data cutoff (figure 3). Median overall survival was 26·3 months (95% CI 23·8–30·0) in arm C and 21·0 months (17·7–27·6) in arm A (HR 0·77, 95% CI 0·55–1·07, p=0·11). We noted evidence of non-proportional hazards (p=0·001), and restricted mean survival time over 3 years was 25·7 months (24·3–27·2) in arm C and 22·8 months (20·7–24·8) in arm A (difference 3 months, 95% CI 0·3–5·7). The difference in overall survival was non-significant (likelihood ratio trend p=0·3) across the three randomised arms, again with evidence of non-proportional hazards (p=0·005). An updated survival analysis with more mature data will be reported at a later stage.

About 80% of patients completed six cycles of chemotherapy in all arms (figure 1). Treatment was not started in 12 patients (three in arm A, three in arm B, and six in arm C) who were thus excluded from the safety analysis.

	Arm A (reference group)	Arm B (concurrent group)	Arm C (maintenance group)	Overall
Chemotherapy delivery				
Overall	118 (100%)	174 (100%)	164 (100%)	456 (100%)
Six cycles completed	93 (79%)	142 (82%)	130 (79%)	365 (80%)
Four or five cycles	12 (10%)	14 (8%)	20 (12%)	46 (10%)
Fewer than four cycles	13 (11%)	18 (10%)	14 (9%)	45 (10%)
Trial drug discontinuation				
Overall				
n	115 (100%)	171 (100%)	158 (100%)	444 (100%)
Toxic effects	14 (12%)	47 (27%)	62 (39%)	123 (28%)
Progression or death	90 (78%)	93 (54%)	70 (44%)	254 (57%)
Other reasons	5 (4%)	17 (10%)	14 (9%)	36 (8%)
Chemotherapy phase				
n	115 (100%)	171 (100%)	158 (100%)	444 (100%)
Toxic effects	10 (7%)	39 (23%)	43 (27%)	92 (21%)
Progression or death	16 (14%)	5 (3%)	7 (4%)	28 (6%)
Other reasons	4 (3%)	14 (8%)	13 (8%)	31 (7%)
Maintenance phase				
n	85 (100%)	113 (100%)	95 (100%)	293 (100%)
Toxic effects	4 (5%)	8 (7%)	19 (20%)	31 (11%)
Progression or death	74 (87%)	88 (78%)	64 (67%)	226 (77%)
Other reasons	2 (2%)	6 (5%)	4 (4%)	12 (4%)

Chemotherapy delivery for all patients randomly assigned to the intention-to-treat analysis (n=456) and discontinuations of trial drug for patients included in the safety analysis (n=444). 2 patients in arm A, 7 in arm B, and 3 in arm C reported adverse events and disease progression as reasons for trial drug discontinuation, so for this table they were assigned as discontinuing because of toxic effects.

Table 2: **Chemotherapy delivery and trial drug discontinuation**

149 (33%) of 456 patients discontinued treatment with cediranib or placebo early, before progressive disease or death occurred. Discontinuation before progression was more common with cediranib than placebo, most frequently for adverse events (table 2). Overall, drug discontinuation was high in all three arms excluding stopping due to progression or death (19 [17%] of 115 patients in arm A, 64 [37%] of 171 in arm B, and 76 [48%] of 158 in arm C). These discontinuations were disproportionately higher in the two experimental arms despite provision of clinical guidelines for the management of cediranib toxic effects. Most discontinuations also occurred while patients were still receiving chemotherapy: 14 (74%) of the 19 discontinuations in arm A, 53 (83%) of the 64 in arm B, and 56 (74%) of the 76 in arm C. Median time receiving cediranib or placebo was 8·0 months (5·1–11·0) in arm A, 7·4 months (2·6–10·8) in arm B, and 7·5 months (2·5–11·9) in arm C, and at time of analysis, 5% of patients continued unblinded on trial treatment. No dose reductions of cediranib or placebo occurred in arm A, but 14 (8%) of 171 patients in arm B and 21 (13%) of 158 patients in arm A and C received a reduced drug dose.

Adverse events, reported with Common Terminology Criteria for Adverse Events, are described separately for the chemotherapy phase, and for the maintenance phase when patients received cediranib or placebo without other treatment (table 3).

In line with previous early-phase studies of cediranib,[8,9,13,19] we noted an increased incidence of diarrhoea, neutropenia, hypertension, and voice changes, but not fatigue, nausea, or anorexia during chemotherapy in arms B and C compared with arm A. During cediranib maintenance treatment, an increased incidence of diarrhoea, hypothyroidism, and voice changes occurred, but not of hypertension because this seemed to be controlled after prompt management in the early chemotherapy phase. Four (3%) of 115 patients in arm A and 38 (12%) of 329 patients in arms B and C had grade 3 or higher hypertension during chemotherapy, reducing to 8 (4%) of 198 patients in arms A and B and 5 (5%) of 95 patients in arm C during maintenance (table 3). During chemotherapy, the most common adverse event was fatigue at any grade (412 [93%] of 444 patients), and diarrhoea at any grade was also common (350 [79%] of 444 patients; table 3).

Toxic effects were reduced in the maintenance phase, with fatigue, diarrhoea, and nausea occurring most commonly. We noted differences between arms A and B and arm C with diarrhoea, voice changes, and haemorrhage. Reports of toxic effects in placebo treatment (arms A and B) were not uncommon.

A full analysis of quality-of-life data will be described elsewhere. The primary outcome compared global

	Chemotherapy phase (n=444)		Maintenance phase (n=293)	
	Arm A: no cediranib (n=115)	Arms B plus C: cediranib (n=329)	Arms A plus B: no cediranib (n=198)	Arm C: cediranib (n=95)
Fatigue				
Grade 1 or 2	96 (83%)	253 (77%)	155 (78%)	75 (79%)
Grade ≥3	9 (8%)	54 (16%)	2 (1%)	6 (6%)
Nausea or vomiting				
Grade 1 or 2	81 (70%)	242 (74%)	87 (44%)	48 (51%)
Grade ≥3	7 (6%)	23 (7%)	8 (4%)	3 (3%)
Diarrhoea*				
Grade 1 or 2	63 (55%)	251 (76%)	107 (54%)	76 (80%)
Grade 3	2 (2%)	34 (10%)	2 (1%)	10 (11%)
Grade 4	0	0	0	1 (1%)
Hypertension†				
Grade 1 or 2	38 (33%)	148 (45%)	59 (30%)	33 (35%)
Grade 3	4 (3%)	38 (12%)	8 (4%)	5 (5%)
Grade 4 or 5	0	0	0	0
Hypothyroidism				
Grade 1 or 2	9 (8%)	36 (11%)	18 (9%)	24 (25%)
Grade ≥3	0	0	1 (<1%)	0
Febrile neutropenia				
Grade 1 or 2	1 (1%)	3 (1%)	1 (1%)	1 (1%)
Grade ≥3	4 (3%)	22 (7%)	0	1 (1%)
Neutropenia				
Grade 1 or 2	28 (24%)	141 (43%)	52 (26%)	22 (23%)
Grade ≥3	27 (23%)	85 (26%)	13 (7%)	6 (6%)
Thrombocytopenia				
Grade 1 or 2	36 (31%)	129 (39%)	35 (18%)	18 (19%)
Grade ≥3	3 (3%)	25 (8%)	4 (2%)	2 (2%)
Proteinuria				
Grade 1 or 2	11 (10%)	55 (17%)	21 (11%)	16 (17%)
Grade ≥3	0	2 (1%)	0	0
Voice changes				
Grade 1 or 2	7 (6%)	77 (23%)	14 (7%)	24 (25%)
Grade ≥3	0	1 (<1%)	0	0
Thrombosis or embolism				
Grade 1 or 2	0	6 (2%)	1 (<1%)	2 (2%)
Grade ≥3	1 (1%)	10 (3%)	1 (<1%)	3 (3%)
Haemorrhage or bleeding				
Grade 1 or 2	15 (13%)	79 (24%)	14 (7%)	15 (16%)
Grade ≥3	0	0	0	0
CNS cerebrovascular ischaemia				
Grade 1 or 2	0	1 (<1%)	0	0
Grade ≥3	0	5 (2%)	0	1 (1%)

Summary of adverse events as maximum grade reported by phase of trial in safety analysis patients (n=444). Groups are split into cediranib-containing and non-cediranib-containing arms according to the phase of the trial. Seven grade 5 serious adverse events occurred: pneumonia and somnolence in arm A; pneumonia, gastrointestinal perforation, and cardiac ischaemia in arm B; and pancreatitis and hypoxia in arm C. *Diarrhoea seems to be the only toxic effect that could have a carryover effect into the maintenance phase, with arm B having greater grade 1 and 2 levels than arm A. †No grade 4 or 5 hypertension (hypertensive crisis or death).

Table 3: **Adverse events**

quality of life at 12 months between arms A and C, measured by the Quality of Life Questionnaire-C30 and adjusted for baseline value. 235 patients were in follow-up at 12 months and had quality-of-life data at baseline and 12 months. Mean global quality of life was 4·5 points higher in arm C than in arm A, which is not a clinically or statistically significant difference (p=0·2, although the 95% CI of –2·0 to 11·0 includes a moderate difference of 10 points). We recorded no significant difference between groups in each of three secondary hypotheses (appendix). There was also no significant difference between groups in each of three secondary hypotheses.

Discussion

This phase 3 trial showed that the addition of cediranib to platinum-based chemotherapy followed by maintenance cediranib in patients with recurrent platinum-sensitive ovarian cancer was associated with prolonged progression-free survival compared with chemotherapy alone. Bevacizumab studies also suggest that the greatest benefit of an antiangiogenic drug is achieved by adding it to chemotherapy and continuing the drug as a maintenance treatment.[3,4,6] We were able to distinguish these two components in ICON6 to show that the greatest benefit was from concurrent plus maintenance treatment, whereas in the concurrent-only group, the early benefit of addition of cediranib to chemotherapy seemed to dissipate as patients switched to placebo maintenance.

The 8·7 month median progression-free survival in the reference group of ICON6 is consistent with other trials[4,17,25] and the improvement in progression-free survival to a median of 11·0 months with maintenance cediranib is similar to that reported with bevacizumab maintenance after chemotherapy in a similar population.[4,26]

By comparison with intravenous bevacizumab, oral antiangiogenic drugs are easier to give, but have a different toxic profile of hypertension, fatigue, diarrhoea, and nausea.[27] Prompt management of toxic effects to restrict the number of patients needing a dose reduction or discontinuing cediranib is important and was helped by the inclusion of clinical management guidelines in ICON6. Planned chemotherapy cycles were not compromised by cediranib (80% of patients completing six cycles, consistent across groups); however, during the chemotherapy phase, 32% of patients in the two cediranib arms discontinued cediranib because of toxic effects compared with 10% of those receiving placebo. In the maintenance phase, 10% of patients discontinued cediranib because of toxic effects compared with 2% of those on placebo. Whether planned brief dose interruptions were sufficiently used is hard to tell and should be investigated in further studies as a strategy for managing discontinuations. From experience, treatment interruptions and prompt dose reductions have proved to be successful in other widely used tyrosine kinase inhibitors.[28]

The revised sample size, due to the shortage of cediranib supply, reduced the power to show a significant difference in overall survival. A significant

survival difference has not been noted with any antiangiogenic drug trials in recurrent ovarian cancer. In ICON6, a 5·3 month difference in median overall survival was reported between reference and maintenance cediranib arms. With a 3-year restricted mean survival time analysis, the overall survival difference was 3 months. However, the ICON6 overall survival analysis was done when only 52% of expected deaths had occurred and it will be assessed again when more than 80% of deaths have occurred, although because of the small sample size, the power to detect a realistic difference will be restricted.

In absolute terms, survival in all groups was somewhat shorter than reported in other trials of combination therapy in recurrent ovarian cancer, with or without maintenance treatment.[4,25] This probably reflects differences between trial cohorts in timing of initiation of second-line treatment, because the median duration of survival as measured from the time of original diagnosis, 46 months with cediranib, compares favourably with other trials.

The improvement in time to progression seen with the combination of cediranib and chemotherapy, followed by maintenance cediranib, represents a clinically relevant prolongation in progression-free survival for patients with recurrent ovarian cancer and is in line with other VEGF maintenance trials.[4] Two other oral VEGFR inhibitors, pazopanib and nintedanib,[29,30] have shown slight improvements in progression-free survival in first-line treatment of ovarian cancer. However, toxic effects of cediranib and other VEFR inhibitors can be problematic[29] and need careful management. The three-arm ICON6 trial has shown that the benefit in progression-free survival with cediranib is derived from continuing cediranib as a maintenance treatment after chemotherapy. Cediranib is a new treatment option that should be considered for the treatment of patients with platinum-sensitive recurrent ovarian cancer.

Contributors

JAL, ACE, FR, AMS, RSK, and MKBP contributed to the study design. JAL, ACE, FR, TJP, GCJ, GJSR, SBK, HH, EE, MV, MF, AG-M, DS, EC, LF, AMS, AC, RSK, and MKBP collected and interpreted the data. ACE and AC compiled the data and did the statistical analysis. JAL, ACE, and FR prepared the manuscript with input from all authors. JAL, ACE, FR, TJP, GCJ, GJSR, SBK, HH, EE, MV, MF, AG-M, DS, EC, LF, AMS, AC, RSK, and MKBP were members of the Trial Management Group.

Declaration of interests

JAL has attended AstraZeneca,Merck, and Clovis Advisory Boards and spoken at symposia with remuneration by AstraZeneca to University College London. TJP reports grants, personal fees, and non-financial support from Roche; personal fees from Novartis; personal fees from AstraZeneca; and other fees paid to the Leeds Institute of Cancer Medicine and Pathology from several other pharmaceutical companies and research organisations in connection with the costs of running a broad research portfolio, outside the submitted work. GCJ attended Advisory Board meetings for AstraZeneca and has received research funding for investigator-led trials from AstraZeneca and Roche and a research grant from Roche. GJSR has attended Advisory Board meetings for AstraZeneca, Amgen, and Oxigene. SBK has attended Advisory Board meetings for AstraZeneca, Roche, and Merck. MF has attended Advisory Board meetings for AstraZeneca, Roche, and Clovis. RSK reports grants from Cancer Research UK and AstraZeneca, and drug supply from AstraZeneca. MKBP reports an educational grant from AstraZeneca. ACE, FR, HH, EE, MV, MF, AG-M, DS, EC, LF, AMS, and AC declare no competing interests.

Acknowledgments

The trial was funded by the Medical Research Council, Cancer Research UK (CRUK/07/025), Canadian Cancer Society Research Institute (015469 and 021039), Cancer Australia (APP1006602) and National Gynecological Cancer Centre, and AstraZeneca. The trial is registered with the ISRCTN registry, number ISRCTN68510403; ClinicalTrials.gov, number NCT00532194; and ANZ Clinical Trials Registry, number ACTRN1261000016003. ICON6 was managed by the Medical Research Council Clinical Trials Unit at University College London and employees were central to the completion of the trial and the development of this manuscript. I Tannock (Princess Margaret Cancer Centre, Toronto, ON, Canada) provided a critical review of the manuscript. See appendix for a full list of collaborators.

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