ICON 9- An international phase III randomised study to evaluate the efficacy of maintenance therapy with olaparib and cediranib or olaparib alone in patients with relapsed platinum-sensitive ovarian cancer following a response to platinum-based chemotherapy.

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Abstract

Background: Two novel biological agents, cediranib, targeting angiogenesis, and olaparib targeting DNA repair processes, have individually led to an improvement in ovarian cancer control. The aim of ICON9 is to investigate the combination of cediranib and olaparib maintenance in recurrent ovarian cancer following platinum-based therapy.

Primary Objective: To assess the efficacy of maintenance treatment with olaparib in combination with cediranib compared to olaparib alone following a response to platinum-based chemotherapy in women with platinum-sensitive ovarian, fallopian tube or peritoneal cancer in first relapse.

Study Hypothesis: Maintenance therapy with cediranib and olaparib in combination will be associated with improved patient outcomes compared to olaparib alone.

Trial Design: International phase III randomised controlled trial. Following a response to platinum-based chemotherapy patients are randomised 1:1 to either oral olaparib and cediranib (intervention arm) or oral olaparib alone (control arm).

Major Inclusion Criteria: Known diagnosis of high grade serous or endometrioid carcinoma of the ovary, fallopian tube or peritoneum, progressing more than 6 months after first-line platinum-based chemotherapy, who have responded to second-line platinum-based chemotherapy.

Primary Endpoints: Progression-free and overall survival. Co-primary endpoints to be assessed using a fixed-sequence gatekeeping approach: i) Progression-free survival, all patients; ii) Progression-free survival, BRCA wild type; iii) Overall survival, all patients; iv) Overall survival, BRCA wild type.

Sample Size: 618 patients will be recruited.

Estimated Dates for Completing Accrual and Presenting Results: Accrual is expected to be completed at 2024 with presentation of results in 2025.

Trial Registration: ClinicalTrials.gov: NCT03278717

Manuscript

Introduction

Worldwide, there are an estimated 295,000 cases and 184,000 ovarian cancer related-deaths recorded annually[1]. Platinum-based chemotherapy remains the cornerstone of treatment but despite advances in treatment, about 80% of women with advanced cancer have a recurrence that is ultimately fatal. Retreatment with platinum-based therapy in patients relapsing more than 6 months after first-line treatment is considered a standard of care. It delays death but the median survival after first relapse is about 21 months [2].

Maintenance therapy that continues beyond chemotherapy is an important area of research to extend the chemotherapy-free interval and prolong disease control. Bevacizumab, a vascular endothelial growth factor-A inhibitor was the first molecularly targeted therapy to be approved for the treatment of epithelial ovarian cancer (EOC) given with platinum-based chemotherapy and as maintenance following therapy of first-line and recurrent disease[3]. Cediranib, is a potent oral broad-spectrum tyrosine kinase inhibitor, principally inhibiting vascular endothelial growth factor receptor (VEGFR TKI-1/2/3). It has demonstrated significant anti-tumour activity and delayed tumour progression when given as maintenance therapy in women with recurrent ovarian cancer[4]. Other VEGFR TKIs have shown similar positive effects[3], however none of them are licensed for treatment of EOC.

Over the last 15 years, research with oral inhibitors of poly (ADP-ribose) polymerase (PARP) have led to significant changes in the management of recurrent ovarian cancer. Initial trials of maintenance therapy with olaparib following a response to platinum-based chemotherapy demonstrated significant improvements in progression-free survival and a delay in the re-use of chemotherapy. The benefit was particularly marked in tumours with a BRCA mutation, but there was also a benefit in patients with BRCA wild-type tumours [5, 6]. The improvement in progression-free survival, irrespective of a BRCA mutation has been confirmed in trials with niraparib and rucaparib[7]. Some of these patients have

remained on olaparib for several years without needing further chemotherapy[8, 9]. However, progression of disease occurs in most patients and other strategies are needed to improve the effectiveness of maintenance therapy.

Defective repair of DNA damage by homologous recombination (HRD) is the hallmark for sensitivity to PARP inhibitors. Preclinical data suggest that anti-angiogenic drugs might increase the degree of HRD and thus increase the effectiveness of PARP inhibitors[10, 11]. This is supported by clinical studies using either cediranib or bevacizumab in combination with olaparib or niraparib respectively. In two randomised phase II studies, and a recent phase III trial, the addition of the anti-angiogenic drug to olaparib or niraparib led to a longer progression-free survival than with the PARP inhibitor alone[12-14]. It should be noted that none of these studies investigated this combination as maintenance following a response to platinum-based chemotherapy. In the ICON9 trial we hypothesise that maintenance therapy with a combination of olaparib and cediranib may be more effective than single agent olaparib in controlling cancer growth following a response to platinum-based chemotherapy.

Methods

Trial Design

ICON9 is an international, phase III open-label randomised (1:1) trial of olaparib with or without the addition of cediranib in women with relapsed ovarian cancer progressing more than 6 months after first-line chemotherapy. The study was approved by the national and local Research Ethics Committee (REC) and written informed consent was obtained from all patients. Potential trial participants are registered following 3- 4 cycles of second line platinum-based chemotherapy to permit tumour BRCA testing of archival tumour specimens, a key stratification factor. Patients with a RECIST criteria or a GCIG CA125 (if non-measurable disease) response at the end of a minimum of 4 cycles of chemotherapy are randomised, and

94 treatment is continued unless there is unacceptable toxicity or progression of disease such that
95 the patient is no longer deriving clinical benefit. Trial schema is shown in Figure 1.

96 Currently there are 42 sites recruiting patients for the ICON9 trial in the UK, Australia and New
97 Zealand with further international sites due to open shortly.

98

99 ## Participants

100 Inclusion criteria for registration and randomisation are outlined in table 1. All patients must
101 have adequate bone marrow, renal and liver function as well as adequate blood pressure and
102 thyroid function control. CA125 criteria are described in table 1.

103

104 ## Endpoints

105 The co-primary endpoints are progression-free survival, measured from the date of
106 randomisation to date of objective progression (investigator assessed using RECIST v1.1) or
107 date of death from any cause, and overall survival measured from the date of randomisation to
108 the date of death from any cause. Patients without an event will be censored at the date they
109 were last seen in clinic or known to be alive. Progression-free survival and overall survival will
110 be assessed using a fixed-sequence gatekeeping approach for all patients and for $BRCA^{wt}$
111 patients.

112 Secondary endpoints include: toxicity; compliance; investigator assessed response (RECIST
113 v1.1 and/or CA-125) at 16 weeks of treatment; progression-free survival and overall survival
114 measured from the start of second-line chemotherapy; progression-free survival by CA-125
115 (GCIG criteria); time from randomisation to start of second subsequent treatment or death from
116 any cause (TSST); quality of life (EORTC QLQ-C30 and OV28); cost effectiveness using EQ-
117 5D-5L for health economic evaluation.

118

Sample Size

Progression-free survival, determined radiologically, and overall survival are co-primary endpoints. 344 patients are required to detect a progression-free survival hazard ratio (HR) of 0.70 with 90% power from a median of 8.4 months in the control arm, and 588 patients are required to detect an overall survival HR=0.75 with 80% power from a median of 29.8 months in the control arm. Assuming two-sided 5% significance levels, 36 months accrual and 36 months additional follow-up with up to 5% dropout, the total target sample size is 618.

These will be analysed using a fixed-sequence gatekeeping approach: i) progression-free survival, all patients; ii) progression-free survival, $BRCA^{wt}$; iii) overall survival, all patients; iv) overall survival, $BRCA^{wt}$. To detect a progression-free survival HR=0.70 with 90% power and overall survival HR=0.70 with 80% power within the $BRCA^{wt}$ subgroup, the number of $BRCA^{mut}$ patients may be capped at around 250 to allow ≥350 $BRCA^{wt}$ patients to be recruited. No formal interim analyses are planned as part of the design.

Randomisation

Following registration, and completion of chemotherapy, patients meeting eligibility criteria will be randomised in a 1:1 ratio to one of two arms:

Arm 1 - Oral olaparib 300mg tablets twice daily and cediranib 20mg tablets once daily;

Arm 2 - Oral olaparib 300mg tablets twice daily.

Minimisation will be used to allocate patients to either treatment arm, with the following stratification factors: 6-12 vs. >12 month platinum-free interval (defined by the time following completion of first line platinum based chemotherapy); surgery vs. no surgery at relapse prior to chemotherapy; prior vs. no prior bevacizumab therapy; $BRCA^{wt}$ vs. $BRCA^{mut}$ (germline and/or somatic); country.

There is no placebo as the toxicity profile of the two agents is so distinct. A blinded independent clinical review (BICR) of a proportion of CT/MRI scans will be undertaken for quality control purposes and to ensure that scans are reported consistently.

Statistical Methods

Survival analyses with Kaplan-Meier plots and Cox regression analyses to produce HRs will be performed using a stratified log-rank test on an intention-to-treat basis, using a fixed-sequence testing strategy (as detailed above). If non-proportional hazards are observed, an analysis of restricted mean survival times will be presented. Multivariable Cox regression will be used to adjust for the randomisation stratification factors, and to analyse treatment effects within these subgroups including tests for interaction.

Discussion

Despite the significant improvements seen using PARP inhibitor maintenance therapy in recurrent EOC, relapse eventually occurs in the majority of patients, posing a significant clinical challenge. This is particularly the case for patients without BRCA mutations where only 11% remain progression free at 6 years[5]. One approach to delay progression and improve survival is to combine two treatments that individually have been shown to improve the progression-free survival of women with recurrent ovarian cancer.

Anti-angiogenic therapy with bevacizumab, given with chemotherapy and as maintenance, has demonstrated an improvement in progression-free survival. Similarly, a benefit in progression-free survival was seen in ICON6, an international phase III trial in which cediranib, an oral anti-angiogenic tyrosine kinase inhibitor, was added to platinum-based chemotherapy and continued as maintenance

treatment[4]. There is a clear rationale for combining these anti-angiogenic drugs with PARP inhibitors; they have different modes of action and synergistic activity has been demonstrated in vitro [11]. In a randomised phase 2 study a 6 month improvement in progression-free survival was seen following treatment with a combination of olaparib and cediranib compared to olaparib alone in women with platinum sensitive recurrent ovarian cancer[15]. An unplanned exploratory analysis suggested that the benefit of the combination therapy appeared greatest in the $BRCA^{wt}$ population.

ICON9 has been designed to build on the hypothesis that cediranib may increase the activity of olaparib and that this might best be observed in a maintenance setting. Trials with olaparib in recurrent ovarian cancer have shown that in a treatment setting it is difficult to demonstrate superiority of a PARP inhibitor over chemotherapy[16], or indeed the combination of cediranib and olaparib[14]. The approach in ICON9 is to start combination therapy after platinum-based chemotherapy that has resulted in a reduction in tumour burden. As maintenance therapy with a PARP inhibitor is now a standard of care, all patients in ICON9 will receive olaparib and half will have cediranib in addition. Randomisation will be stratified on BRCA status, limiting the total number of patients with a BRCA mutation as we hypothesize that a larger effect will be seen in the $BRCA^{wt}$ patients. Similarly, there will be stratification of patients who had surgery at relapse, as they are likely to have minimal residual disease as they enter chemotherapy and the trial.

Quality of life assessments and patient reported outcomes are important secondary endpoints in ICON9 as the potential benefits of maintenance therapy must be balanced with their tolerability and acceptability to patients, who may remain on treatment for a number of years. Within the ICON6 trial the cediranib discontinuation rate was 30% during the initial combination with chemotherapy, but this fell significantly to 10% during the maintenance phase (cediranib alone). A lowering of the initial starting dose of cediranib from 30mg to 20mg also helped to reduce toxicity, and since preclinical data suggests similar efficacy, 20mg is the starting dose used in the ICON9 trial. From previous experience in ICON6, early intervention to manage diarrhoea will be used to reduce severe side effects and discontinuation of cediranib.

Collection of archival tissue for prospective BRCA testing and later translational studies is a key element of the ICON9 trial. These studies will, for example, assess HRD genes, signatures for angiogenesis and other molecular subtyping to gain further insight into the factors that influence the activity of olaparib and the combiantion of cediranib with olaparib.

A potential modification to the ICON9 trial design in order to extend the accrual period and bring the trial in-line with other recently published trials of PARP inhibitors, where progression-free survival has been the primary outcome, is currently under consideration by the investigators and funders.The primary results of ICON9 are expected in 2024/5.

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The co-ordination, management and oversight of the trial is provided by the sponsor UCL and the Cancer Research UK and UCL Cancer Trials Centre. IQVIA are conducting on-site monitoring on behalf of the sponsor. The co-ordination of the trial in Australia and New Zealand is provided by Australia New Zealand Gynaecological Oncology Group (ANZGOG).

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Figures and Legends

Table 1 – Inclusion criteria

Registration criteria	Randomisation criteria

• Age > 18
• Histology:
  ○ High grade serous cancer
  ○ Endometrioid cancer
• Progressing ≥ 6 months after day 1 of the last cycle of first-line platinum-based chemotherapy and requiring treatment with platinum-based chemotherapy
• Relapsed disease
  ○ CT/MRI proven
  ○ Have had secondary debulking surgery
• Available FFPE tumour sample
• ECOG performance status 0-1
• Informed consent
	• Completed 4-6 cycles of second-line platinum-based chemotherapy
	• Response criteria:
	  ○ Measurable disease
	  ▪ CR/PR RECIST v.1.1
	  ○ Non measurable disease
	  ▪ GCIG CA125 response
	  ○ After secondary debulking surgery
	  ▪ No evidence of disease progression on CT/MRI
	• CA-125 Criteria
	  ○ 1st screening CA125 value is below the ULN
	  ○ If the 1st screening CA125 value is greater than ULN*:2nd assessment required at least 7 days after the first to confirm eligibility.
	  ○ If the 2nd CA125 has risen by 15%- patient not eligible
	*ULN- upper limit of normal

Trial Schema