

# ICON8 Trials Programme

<b>Submission date</b> 27/05/2011	<b>Recruitment status</b> No longer recruiting	<input type="checkbox"/> Prospectively registered <input type="checkbox"/> Protocol
<b>Registration date</b> 27/05/2011	<b>Overall study status</b> Completed	<input type="checkbox"/> Statistical analysis plan <input checked="" type="checkbox"/> Results
<b>Last Edited</b> 20/01/2025	<b>Condition category</b> Cancer	<input type="checkbox"/> Individual participant data

## Plain English summary of protocol

<http://cancerhelp.cancerresearchuk.org/trials/a-trial-looking-at-weekly-chemotherapy-for-ovarian-cancer-icon8>

<https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-looking-at-chemotherapy-with-or-without-bevacizumab-for-advanced-ovarian-cancer-icon8b>

<http://www.icon8trial.org/patients/icon8-trial-summary/>

## Contact information

### Type(s)

Scientific

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## Additional identifiers

### Clinical Trials Information System (CTIS)

2010-022209-16

### Integrated Research Application System (IRAS)

64812

### ClinicalTrials.gov (NCT)

NCT01654146

**Protocol serial number**

9812

## **Study information**

**Scientific Title**

ICON8: An international phase III randomised trial of dose fractionated chemotherapy compared to standard three weekly chemotherapy, following immediate primary surgery or as part of delayed primary surgery, for women with newly diagnosed epithelial ovarian, fallopian tube or primary peritoneal cancer

and

ICON8B: A phase III randomised trial investigating the combination of dose-fractionated chemotherapy and bevacizumab compared to standard three weekly chemotherapy and bevacizumab for the first-line treatment of women with newly diagnosed high-risk stage III-IV epithelial ovarian, fallopian tube or primary peritoneal cancer

**Acronym**

ICON8 and ICON8B

**Study objectives**

Ovarian cancer is the most lethal gynaecological malignancy in the UK. Most patients respond well to firstline treatment, surgery and chemotherapy, but the majority go on to develop relapsed disease and the 5-year survival rate for patients with advanced disease is only 30%. There is a significant need to develop more effective first-line treatments.

**ICON8:**

Standard firstline chemotherapy is a combination of two drugs: carboplatin and paclitaxel, given once every 3 weeks for 6 cycles. However, giving these agents weekly may be more effective; this is called dose-fractionated chemotherapy. In ICON8 two dose-fractionated chemotherapy regimens are compared with standard carboplatin-paclitaxel.

The main outcome measures are whether dose-fractionated chemotherapy extends the time until ovarian cancer relapses (improved progression-free survival) and whether women who receive it live longer (improved overall survival). Secondary outcome measures are comparative toxicity, impact on quality of life and costeffectiveness. Two interim-analyses are planned: the first looking at feasibility and safety of the dose-fractionated regimens; and the second at their activity.

Women with newly diagnosed epithelial ovarian, fallopian tube or primary peritoneal cancers are eligible; including those with highrisk early stage (FIGO IC/IIA) or advanced (FIGO IIBIV) cancers. They can enter the trial either following primary surgery or with a plan to undergo delayed primary surgery between the 3rd and 4th cycles of chemotherapy. Women will be randomised to receive either: standard chemotherapy; or carboplatin given 3-weekly with weekly paclitaxel; or both carboplatin and paclitaxel weekly. Treatment duration in all three arms is 18 weeks.

**ICON8B (added 12/08/2015):**

As of 2014, the incorporation of bevacizumab and weekly dose dense paclitaxel respectively into the first-line management of ovarian cancer have shown improved survival in phase III clinical trials, hence both of these approaches can be considered new standards of care. They do

however have markedly different economic implications for healthcare providers, and also place distinct burdens on patients with respect to treatment-related toxicity and duration of therapy. Hence there is an urgent need to compare these treatment approaches in a randomised trial. In ICON8B standard 3-weekly carboplatin-paclitaxel and bevacizumab will be compared to dose fractionated chemotherapy with or without bevacizumab in a randomised controlled trial.

The main outcome measures are to determine whether dose-fractionated chemotherapy with bevacizumab extends the time until ovarian cancer relapses (improved progression-free survival) and whether women who receive it live longer (improved overall survival). Secondary outcome measures are comparative toxicity, impact on quality of life and cost effectiveness. One interim analysis is planned after 50 delayed primary surgery patients have been randomised to each trial arm to establish the safety of bevacizumab in the neo-adjuvant treatment of patients undergoing delayed primary ovarian cancer surgery.

### **Ethics approval required**

Old ethics approval format

### **Ethics approval(s)**

1. Approved 06/06/2011, London- Chelsea (Research Ethics Committee (REC) London Centre, 2 Redman Place, London, E20 1JQ, United Kingdom; +44 (0)207 104 8150; chelsea.rec@hra.nhs.uk), ref: 11/LO/0043
2. NRES Committee London - Chelsea, 08/04/2011, ref: 11/LO/0043

### **Study design**

Randomized; Interventional; Design type: Treatment

### **Primary study design**

Interventional

### **Study type(s)**

Treatment

### **Health condition(s) or problem(s) studied**

Ovarian/gynaecological cancer

### **Interventions**

Current interventions as of 01/10/2021:

ICON8:

1. Dose-fractionated carb-pacl (carboplatin and paclitaxel given by intravenous infusion once every week)
2. The treatment course is 6 cycles with each cycle lasting 3 weeks
3. Dose-fractionated paclitaxel, carboplatin given by intravenous infusion once every 3 weeks at standard dose
4. Dose-fractionated paclitaxel given by intravenous infusion once every week
5. The treatment course is 6 cycles with each cycle lasting 3 weeks.
6. Standard treatment, carboplatin and paclitaxel given by intravenous infusion once every 3 weeks for 6 cycles.
7. Study entry: single randomisation only

ICON8B:

1. Arm B1: (Control arm): Carboplatin (AUC5 by intravenous infusion over 30-60 minutes) and

paclitaxel (175mg/m<sup>2</sup> by intravenous infusion over 3 hours) plus bevacizumab (7.5mg/kg by intravenous infusion over 30-90 minutes) on day 1 of a 21-day cycle for 6 cycles followed by bevacizumab (7.5mg/kg by intravenous infusion over 30-90 minutes) as maintenance therapy to complete 18 cycles in total

2. Arm B2 (Control arm): Carboplatin (AUC55 by intravenous infusion over 30-60 minutes) on day 1 and dose-fractionated weekly paclitaxel (80mg/m<sup>2</sup> by intravenous infusion over 1 hour) on day 1, 8 and 15 of a 21-day cycle for 6 cycles (Closed 05/05/2017)

3. Arm B3 (Research arm): Carboplatin (AUC55 by intravenous infusion over 30-60 minutes) on day 1 and dose-fractionated weekly paclitaxel (80mg/m<sup>2</sup> by intravenous infusion over 1 hour) on day 1, 8 and 15 of a 21-day cycle plus bevacizumab (7.5mg/kg by intravenous infusion over 30-90 minutes) on day 1 of a 21-day cycle for 6 cycles followed by bevacizumab (7.5mg/kg by intravenous infusion over 30-90 minutes) as maintenance therapy to complete 18 cycles in total.

4. Study entry: Single randomisation only

Previous interventions:

ICON8:

1. Dose-fractionated carb-pacl (carboplatin and paclitaxel given by intravenous infusion once every week)

2. The treatment course is 6 cycles with each cycle lasting 3 weeks

3. Dose-fractionated paclitaxel, carboplatin given by intravenous infusion once every 3 weeks at standard dose

4. Dose-fractionated paclitaxel given by intravenous infusion once every week

5. The treatment course is 6 cycles with each cycle lasting 3 weeks.

6. Standard treatment, carboplatin and paclitaxel given by intravenous infusion once every 3 weeks for 6 cycles.

7. Study entry: single randomisation only

ICON8B (added 12/08/2015):

1. Arm B1: (Control arm): Carboplatin (AUC5 by intravenous infusion over 30-60 minutes) and paclitaxel (175mg/m<sup>2</sup> by intravenous infusion over 3 hours) plus bevacizumab (7.5mg/kg by intravenous infusion over 30-90 minutes) on day 1 of a 21-day cycle for 6 cycles followed by bevacizumab (7.5mg/kg by intravenous infusion over 30-90 minutes) as maintenance therapy to complete 18 cycles in total

2. Arm B2 (Control arm): Carboplatin (AUC55 by intravenous infusion over 30-60 minutes) on day 1 and dose-fractionated weekly paclitaxel (80mg/m<sup>2</sup> by intravenous infusion over 1 hour) on day 1, 8 and 15 of a 21-day cycle for 6 cycles

3. Arm B3 (Research arm): Carboplatin (AUC55 by intravenous infusion over 30-60 minutes) on day 1 and dose-fractionated weekly paclitaxel (80mg/m<sup>2</sup> by intravenous infusion over 1 hour) on day 1, 8 and 15 of a 21-day cycle plus bevacizumab (7.5mg/kg by intravenous infusion over 30-90 minutes) on day 1 of a 21-day cycle for 6 cycles followed by bevacizumab (7.5mg/kg by intravenous infusion over 30-90 minutes) as maintenance therapy to complete 18 cycles in total.

4. Study entry: Single randomisation only

## Intervention Type

Drug

## Phase

Phase III

## Drug/device/biological/vaccine name(s)

Carboplatin, paclitaxel, bevacizumab

### **Primary outcome(s)**

Current primary outcome measure as of 01/10/2021:

ICON8:

Progression-free survival and overall survival in dose-fractionated arms. Timepoint(s): analyses will take place when the required number of events have occurred

ICON8B:

Progression-free survival. Timepoint(s): analyses will take place when the required number of events have occurred

Previous primary outcome measure:

ICON8:

Progression-free survival and overall survival in dose-fractionated arms. Timepoint(s): analyses will take place when the required number of events have occurred

ICON8B (added 12/08/2015):

Progression-free survival and overall survival in the experimental arm. Timepoint(s): analyses will take place when the required number of events have occurred

### **Key secondary outcome(s)**

Current secondary outcome measures as of 01/10/2021:

ICON8:

1. Activity of dose-fractionated arms; timepoint(s): after first 186 (approx) pts enter the trial and 9 months after randomisation
2. Feasibility and safety of dose-fractionated arms
3. Timepoint(s): when first 50 pts randomised to each arm could have completed 6 cycles of chemotherapy
4. Feasibility and safety of DPS dose-fractionated patients  
Timepoint(s): when 1st 50 pts randomised each arm (with planned DPS) could have completed 6 cycles of chemotherapy

ICON8B:

1. Safety of neo-adjuvant bevacizumab in patients undergoing DPS. Timepoint(s): when first 50 DPS pts randomised to each arm could have completed 6 cycles of chemotherapy
2. Overall Survival. Timepoints(s): analyses will take place only if a positive PFS result is observed.

Previous secondary outcome measures:

ICON8:

1. Activity of dose-fractionated arms; timepoint(s): after first 186 (approx) pts enter the trial and 9 months after randomisation
2. Feasibility and safety of dose-fractionated arms
3. Timepoint(s): when first 50 pts randomised to each arm could have completed 6 cycles of chemotherapy
4. Feasibility and safety of DPS dose-fractionated patients  
Timepoint(s): when 1st 50 pts randomised each arm (with planned DPS) could have completed 6 cycles of chemotherapy

ICON8B (added 12/08/2015):

Safety of neo-adjuvant bevacizumab in patients undergoing DPS. Timepoint(s): when first 50 DPS pts randomised to each arm could have completed 6 cycles of chemotherapy

## Completion date

24/12/2024

# Eligibility

## Key inclusion criteria

Current ICON8 inclusion criteria as of 12/09/2018:

1. Females aged  $\geq 18$  years
2. Signed informed consent and ability to comply with the protocol
3. Histologically confirmed, with core biopsy from a disease site as minimum requirement (cytology alone is insufficient for diagnosis):
  - 3.1. Epithelial ovarian carcinoma
  - 3.2. Primary peritoneal carcinoma of Müllerian histological type
  - 3.3. Fallopian tube carcinoma
  - 3.4. Ovarian carcinosarcoma (malignant mixed Müllerian tumour (MMMT) of the ovary).
4. FIGO (1988) stage IC or above, which may be based on clinical and radiological assessment in patients who have not undergone immediate primary surgery
5. Confirmed high-risk histological subtype for patients with FIGO (1988) stage IC/IIA disease, namely:
  - 5.1. High grade serous carcinoma
  - 5.2. Clear cell carcinoma
  - 5.3. Other histological subtype considered poorly differentiated/grade 3
6. ECOG Performance Status (PS) 0-2
7. Life expectancy  $> 12$  weeks
8. Adequate bone marrow function:
  - 8.1. Absolute Neutrophil Count (ANC)  $\geq 1.5 \times 10^9/l$
  - 8.2. Platelets (Plt)  $\geq 100 \times 10^9/l$
  - 8.3. Haemoglobin (Hb)  $\geq 9$  g/dl (can be post transfusion)
9. Adequate liver function:
  - 9.1. Serum bilirubin (BR)  $\leq 1.5 \times$  ULN
  - 9.2. Serum transaminases  $\leq 3 \times$  ULN in the absence of parenchymal liver metastases or  $\leq 5 \times$  ULN in the presence of parenchymal liver metastases
10. Adequate renal function as defined by:
  - 10.1. Directly measured GFR (Glomerular Filtration Rate)  $\geq 30$  ml/min, or
  - 10.2. Calculated creatinine clearance  $\geq 60$  ml/min
11. Able to start chemotherapy within 8 weeks after immediate primary surgery (where applicable)

Previous ICON8 inclusion criteria:

1. Females aged 18 years and above
2. Signed informed consent and ability to comply with the protocol
3. Histologically confirmed, with core biopsy from a disease site as minimum requirement (cytology alone is insufficient for diagnosis):
  - 3.1. Epithelial ovarian carcinoma
  - 3.2. Primary peritoneal carcinoma of Müllerian histological type
  - 3.3. Fallopian tube carcinoma
4. FIGO stage IC or above, which may be based on clinical and radiological assessment in patients who have not undergone immediate primary surgery
5. Confirmed high-risk histological subtype for patients with FIGO stage IC/IIA disease, namely:
  - 5.1. High grade serous carcinoma
  - 5.2. Clear cell carcinoma

- 5.3. Other histological subtype considered poorly differentiated/grade 3
6. ECOG Performance Status (PS) 02
7. Life expectancy >12 weeks
8. Adequate bone marrow function:
  - 8.1. Absolute Neutrophil Count >  $1.5 \times 10^9/l$
  - 8.2. Platelets (Plt) >  $100 \times 10^9/l$
  - 8.3. Haemoglobin (Hb) > 9g/dl (can be post transfusion)
9. Adequate liver function (within 28 days prior to randomisation)
  - 9.1. Serum bilirubin =  $1.5 \times \text{ULN}$
  - 9.2. Serum transaminases =  $3 \times \text{ULN}$  in the absence of parenchymal liver metastases or =  $5 \times \text{ULN}$  in the presence of parenchymal liver metastases
10. Adequate renal function as defined by GFR (Glomerular Filtration Rate) = 30ml/min
11. Target gender: female
12. Lower age limit 18 years

Current ICON8B inclusion criteria as of 12/09/2018:

1. Females aged  $\geq 18$  years
2. Signed informed consent and ability to comply with the protocol
3. Histologically confirmed, with core biopsy from a disease site as minimum requirement (cytology alone is insufficient for diagnosis):
  - 3.1. Epithelial ovarian carcinoma
  - 3.2. Primary peritoneal carcinoma of Müllerian histological type
  - 3.3. Fallopian tube carcinoma
  - 3.4. Ovarian carcinosarcoma (malignant mixed Müllerian tumour (MMMT) of the ovary)
4. High-risk disease defined as:
  - 4.1. FIGO (2013) Stage IIIA1(ii), IIIA2 with positive retroperitoneal lymph nodes >10mm in diameter, IIIB or IIIC disease
    - 4.1.1. With >1 cm residual disease following IPS or
    - 4.1.2. Planned to undergo primary chemotherapy with or without DPS
  - 4.2. FIGO Stage IV disease
    - 4.2.1. With any volume of residual disease following IPS or
    - 4.2.2. Planned to undergo primary chemotherapy with or without DPS
5. ECOG Performance Status (PS) 0-2
6. No clinical symptoms or radiological evidence of bowel obstruction (including sub-acute obstruction), abdominal fistulae or extensive recto-sigmoid involvement on imaging related to ovarian cancer
7. No recent history of proven active peptic ulcer disease, diverticulitis or inflammatory bowel disease (Crohn's Disease and ulcerative colitis) or any prior episode of gastrointestinal perforation.
8. Life expectancy >12 weeks
9. Adequate bone marrow function:
  - 9.1. Absolute Neutrophil Count (ANC)  $\geq 1.5 \times 10^9/l$
  - 9.2. Platelets (Plt)  $\geq 100 \times 10^9/l$
  - 9.3. Haemoglobin (Hb)  $\geq 9$  g/dl (can be post transfusion)
10. Adequate liver function:
  - 10.1. Serum bilirubin (BR)  $\leq 1.5 \times \text{ULN}$
  - 10.2. Serum transaminases  $\leq 3 \times \text{ULN}$  in the absence of parenchymal liver metastases or  $\leq 5 \times \text{ULN}$  in the presence of parenchymal liver metastases.
- 11 Adequate renal function as defined by:
  - 11.1. Directly measured GFR (Glomerular Filtration Rate)  $\geq 30$  ml/min, or
  - 11.2. Calculated creatinine clearance  $\geq 60$  ml/min.
12. Adequate coagulation profile:

- 12.1. International normalised ratio (INR)  $\leq 1.5$
- 12.2. Activated prothrombin time (APTT)  $\leq 1.5 \times \text{ULN}$
13. Able to start chemotherapy within 8 weeks after IPS (where applicable)

Previous ICON8B inclusion criteria (added 12/08/2015):

1. Females aged  $\geq 18$  years
2. Signed informed consent and ability to comply with the protocol
3. Histologically confirmed, with core biopsy from a disease site as minimum requirement (cytology alone is insufficient for diagnosis):
  - 3.1. Epithelial ovarian carcinoma
  - 3.2. Primary peritoneal carcinoma of Müllerian histological type
  - 3.3. Fallopian tube carcinoma
  - 3.4. Ovarian carcinosarcoma (malignant mixed Müllerian tumour (MMMT) of the ovary).
4. High-risk disease defined as
  - 4.1. FIGO (2013) Stage IIIA1(ii), IIIA2 with positive retroperitoneal lymph nodes  $> 10\text{mm}$  in diameter, IIIB or IIIC disease
    - 4.1.1. With  $> 1\text{cm}$  residual disease following IPS or
    - 4.1.2. Planned to undergo primary chemotherapy with or without DPS
  - 4.2. FIGO Stage IV disease
    - 4.2.1. With any volume of residual disease following IPS or
    - 4.2.2. Planned to undergo primary chemotherapy with or without DPS.
5. ECOG Performance Status (PS) 0-2
6. Life expectancy  $> 12$  weeks
7. Adequate bone marrow function:
  - 7.1. Absolute Neutrophil Count (ANC)  $\geq 1.5 \times 10^9/\text{l}$
  - 7.2. Platelets (Plt)  $\geq 100 \times 10^9/\text{l}$
  - 7.3. Haemoglobin (Hb)  $\geq 9\text{g/dl}$  (can be post transfusion).
8. Adequate liver function:
  - 8.1. Serum bilirubin (BR)  $\leq 1.5 \times \text{ULN}$
  - 8.2. Serum transaminases  $\leq 3 \times \text{ULN}$  in the absence of parenchymal liver metastases or  $\leq 5 \times \text{ULN}$  in the presence of parenchymal liver metastases.
9. Adequate renal function as defined by:
  - 9.1. Directly measured GFR (Glomerular Filtration Rate)  $\geq 30 \text{ ml/min}$ , or
  - 9.2. Calculated creatinine clearance  $\geq 60 \text{ ml/min}$ .
10. Adequate coagulation profile:
  - 10.1. International normalised ratio (INR)  $\leq 1.5$
  - 10.2. Activated prothrombin time (APTT)  $\leq 1.5 \times \text{ULN}$ .
11. Able to start chemotherapy within 8 weeks after IPS (where applicable).

### **Participant type(s)**

Patient

### **Healthy volunteers allowed**

No

### **Age group**

Adult

### **Lower age limit**

18 years

## Sex

Female

## Total final enrolment

2144

## Key exclusion criteria

Current ICON8 exclusion criteria as of 12/09/2018:

1. Non-epithelial ovarian cancer
2. Peritoneal cancer that is not of Müllerian origin, including mucinous histology
3. Borderline tumours (tumours of low malignant potential)
4. Prior systemic anti-cancer therapy for ovarian cancer (for example chemotherapy, monoclonal antibody therapy, tyrosine kinase inhibitor therapy or hormonal therapy)
5. Previous malignancies within 5 years prior to randomisation apart from:
  - 5.1. adequately treated carcinoma in-situ of the cervix, breast ductal carcinoma in-situ, non-melanomatous skin cancer; or
  - 5.2. previous/synchronous early-stage endometrial cancer defined as stage IA (FIGO 2009) grade 1 or 2 endometrioid cancers with no lymphovascular space invasion
6. Pre-existing sensory or motor neuropathy grade  $\geq 2$
7. Evidence of any other disease/metabolic dysfunction that in the opinion of the investigator would put the subject at high-risk of treatment-related complications or prevent compliance with the trial protocol
8. Planned intraperitoneal cytotoxic chemotherapy
9. Planned maintenance treatment with systemic anti-cancer therapy following completion of protocol treatment and prior to protocol defined progression
10. Any previous radiotherapy to the abdomen or pelvis
11. Sexually active women of childbearing potential not willing to use adequate contraception (eg. oral contraceptives, intrauterine device or barrier method of contraception in conjunction with spermicidal jelly or surgically sterile) for the study duration and at least six months afterwards
12. Pregnant or lactating women who are currently breastfeeding
13. Treatment with any other investigational agent prior to protocol defined progression
14. Known hypersensitivity to carboplatin, paclitaxel or their excipients (including cremophor)
15. History or clinical suspicion of brain metastases or spinal cord compression. CT/MRI of the brain is mandatory in the case of suspected brain metastases. Spinal MRI is mandatory in the case of suspected spinal cord compression. Patients with brain or meningeal metastases are not eligible.

Previous ICON8 exclusion criteria:

1. Non-epithelial ovarian cancer, including malignant mixed Müllerian tumours (carcinosarcomas)
2. Peritoneal cancer that is not of Müllerian origin, including mucinous histology
3. Borderline tumours (tumours of low malignant potential)
4. Prior systemic anticancer therapy for ovarian cancer (for example chemotherapy, monoclonal antibody therapy, tyrosine kinase inhibitor therapy or hormonal therapy)
5. Previous malignancies within 5 years prior to randomisation apart from: adequately treated carcinoma insitu of the cervix, breast ductal carcinoma insitu, nonmelanomatous skin cancer; or previous/synchronous early-stage endometrial cancer defined as stage IA (FIGO 2009) grade 1 or 2 endometrioid cancers with no lymphovascular space invasion
6. Preexisting sensory or motor neuropathy grade =2
7. Evidence of any other disease/metabolic dysfunction that in the opinion of the investigator would put the subject at highrisk of treatment-related complications or prevent compliance with

the trial protocol

8. Planned intraperitoneal cytotoxic chemotherapy
9. Any previous radiotherapy to the abdomen or pelvis
10. Sexually active women of childbearing potential not willing to use adequate contraception (eg. oral contraceptives, intrauterine device or barrier method of contraception in conjunction with spermicidal jelly or surgically sterile) for the study duration and at least six months afterwards
11. Pregnant or lactating women
12. Treatment with any other investigational agent prior to protocol defined progression
13. Known hypersensitivity to carboplatin, paclitaxel or their excipients (including cremophor)
14. History or clinical suspicion of brain metastases or spinal cord compression. CT/MRI of the brain is mandatory in the case of suspected brain metastases. Spinal MRI is mandatory in the case of suspected spinal cord compression. Patients with brain or meningeal metastases are not eligible

Current ICON8 exclusion criteria as of 12/09/2018:

1. Non-epithelial ovarian cancer
2. Peritoneal cancer that is not of Müllerian origin, including mucinous histology
3. Borderline tumours (i.e. tumours of low malignant potential)
4. Clinical symptoms or radiological evidence of bowel obstruction (including sub-acute obstruction) or extensive recto-sigmoid involvement on imaging related to ovarian cancer
5. Prior systemic anti-cancer therapy for ovarian cancer (for example chemotherapy, monoclonal antibody therapy, tyrosine kinase inhibitor therapy or hormonal therapy)
6. Previous malignancies within 5 years prior to randomisation apart from:
  - 6.1. adequately treated carcinoma in-situ of the cervix, breast ductal carcinoma in-situ, non-melanomatous skin cancer; or
  - 6.2. previous/synchronous early-stage endometrial cancer defined as stage IA (FIGO 2009) grade 1 or 2 endometrioid cancers with no lymphovascular space invasion
7. Pre-existing sensory or motor neuropathy CTCAE grade  $\geq 2$
8. Proteinuria at baseline:  $>1$  g protein/24 h by a 24-hour urine collection
9. Significant co-existing or previous medical conditions that are contra-indications to treatment with bevacizumab, including:
  - 9.1. Cerebrovascular disease, including transient ischaemic attacks (TIAs), cerebrovascular accident (CVA; i.e. stroke) and intracranial bleeds (i.e. intra-cerebral haemorrhage, sub-arachnoid haemorrhage or sub-dural haemorrhage) within 6 months before trial entry
  - 9.2. Cardiovascular disease as follows:
    - 9.2.1. Uncontrolled hypertension, defined as sustained BP  $>150/100$  mmHg while receiving anti-hypertensive medication  
NB. Patients with a BP  $>150/100$  mmHg prior to randomisation should be commenced on a calcium-channel blocker or other anti-hypertensive agent; or in the case of patients already on anti-hypertensives, medical therapy should be optimised. The BP should then be re-checked a few days later, if BP is controlled to  $\leq 150/100$  mmHg the patient may be entered into the trial
    - 9.2.2. Myocardial infarction or unstable angina within 6 months prior to randomization
    - 9.2.3. New York Heart Association (NYHA) grade  $\geq 2$  congestive heart failure
    - 9.2.4. Poorly controlled cardiac arrhythmia despite medication  
NB. Patients with rate-controlled atrial fibrillation are eligible
    - 9.2.5. Peripheral vascular disease grade  $\geq 3$ , i.e. symptomatic and interfering with activities of daily living requiring repair or revision
  - 9.3. History or evidence of bleeding diathesis or coagulopathy (in patients not on therapeutic anti-coagulant medication)
10. Chronic daily use of high-dose aspirin,  $>325$  mg/day, within 10 days prior to study entry
11. Surgery (including open biopsy) or significant traumatic injury within 28 days prior to

anticipated date of first dose of bevacizumab

12. Serious non-healing wound, worse than CTCAE Wound Complication or Wound Dehiscence grade 1
13. Active ulcer or bone fracture
14. Anticipated to require extensive dental work during protocol treatment
15. Evidence of any other disease/metabolic dysfunction that in the opinion of the investigator would put the subject at high-risk of treatment-related complications or prevent compliance with the trial protocol
16. Evidence of intra-abdominal free air not explained by paracentesis or recent surgical procedure
17. Symptomatic abdominal fistulae
18. History or clinical suspicion of brain metastases or spinal cord compression. CT/MRI of the brain is mandatory in the case of suspected brain metastases. Spinal MRI is mandatory in the case of suspected spinal cord compression. Patients with brain or meningeal metastases are not eligible
19. Sexually active women of childbearing potential not willing to use adequate contraception (e.g. oral contraceptives, intrauterine device or barrier method of contraception in conjunction with spermicidal jelly or surgically sterile) for the study duration and at least six months afterwards
20. Pregnant or lactating women who are currently breastfeeding
21. Known hypersensitivity to carboplatin, paclitaxel, bevacizumab or their excipients (including cremophor)
22. Planned intraperitoneal cytotoxic chemotherapy
23. Planned treatment with any other systemic anti-cancer therapy following completion of protocol treatment and prior to protocol defined progression
24. Any previous radiotherapy to the abdomen or pelvis
25. Treatment with any other investigational agent prior to protocol defined progression.

Previous ICON8B exclusion criteria (added 12/08/2015):

1. Non-epithelial ovarian cancer
2. Peritoneal cancer that is not of Müllerian origin, including mucinous histology
3. Borderline tumours (i.e. tumours of low malignant potential)
4. Prior systemic anti-cancer therapy for ovarian cancer (for example chemotherapy, monoclonal antibody therapy, tyrosine kinase inhibitor therapy or hormonal therapy)
5. Previous malignancies within 5 years prior to randomisation apart from:
  - 5.1. Adequately treated carcinoma in-situ of the cervix, breast ductal carcinoma in-situ, non-melanomatous skin cancer; or
  - 5.2. Previous/synchronous early-stage endometrial cancer defined as stage IA (FIGO 2009) grade 1 or 2 endometrioid cancers with no lymphovascular space invasion.
6. Pre-existing sensory or motor neuropathy CTCAE grade  $\geq 2$
7. Proteinuria at baseline:  $>1$  gm protein/24h by a 24-hour urine collection. NB. Proteinuria should be initially assessed by urine dipstick. If urine protein is  $\geq 2+$  on urine dipstick, a 24-hour urine protein collection must be performed.
8. Significant co-existing or previous medical conditions that are contra-indications to treatment with bevacizumab, including:
  - 8.1. Cerebrovascular disease, including transient ischaemic attacks (TIAs), cerebrovascular accident (CVA; i.e. stroke) and intracranial bleeds (i.e. intra-cerebral haemorrhage, sub-arachnoid haemorrhage or sub-dural haemorrhage) within 6 months before trial entry
  - 8.2. Cardiovascular disease as follows:
    - 8.2.1. Uncontrolled hypertension, defined as sustained BP  $>150/100$  mmHg while receiving anti-hypertensive medication. NB. Patients with a BP  $>150/100$  mmHg prior to randomisation should be commenced on a calcium-channel blocker or other anti-hypertensive agent; or in the case of

patients already on anti-hypertensives, medical therapy should be optimised. The BP should then be re-checked a few days later, if BP is controlled to  $\leq 150/100$ mmHg the patient may be entered into the trial

8.2.2. Myocardial infarction or unstable angina within 6 months prior to randomization

8.3.3. New York Heart Association (NYHA) grade  $\geq 2$  congestive heart failure

8.3.4. Poorly controlled cardiac arrhythmia despite medication. NB. Patients with rate-controlled atrial fibrillation are eligible

8.3.5. Peripheral vascular disease grade  $\geq 3$ , i.e. symptomatic and interfering with activities of daily living requiring repair or revision

8.3. History or evidence of bleeding diathesis or coagulopathy (in patients not on therapeutic anti-coagulant medication)

8.4. Recent history of proven active peptic ulcer disease, diverticulitis or inflammatory bowel disease (Crohn's Disease and ulcerative colitis)

8.5. Previous gastrointestinal perforation.

9. Chronic daily use of high-dose aspirin,  $>325$ mg/day, within 10 days prior to study entry

10. Surgery (including open biopsy) or significant traumatic injury within 28 days prior to anticipated date of first dose of bevacizumab. NB. If IPS was performed within 28 days of planned start of treatment, patients are eligible but bevacizumab must be omitted from cycle 1.

11. Serious non-healing wound, worse than CTCAE Wound Complication or Wound Dehiscence grade 1

12. Active ulcer or bone fracture

13. Anticipated to require extensive dental work during protocol treatment

14. Evidence of any other disease/metabolic dysfunction that in the opinion of the investigator would put the subject at high-risk of treatment-related complications or prevent compliance with the trial protocol

15. Clinical symptoms or radiological evidence of bowel obstruction (including sub-acute obstruction) or extensive recto-sigmoid involvement on imaging related to ovarian cancer

16. Evidence of intra-abdominal free air not explained by paracentesis or recent surgical procedure

17. Symptomatic abdominal fistulae

18. History or clinical suspicion of brain metastases or spinal cord compression. CT/MRI of the brain is mandatory in the case of suspected brain metastases. Spinal MRI is mandatory in the case of suspected spinal cord compression. Patients with brain or meningeal metastases are not eligible

19. Sexually active women of childbearing potential not willing to use adequate contraception (e.g. oral contraceptives, intrauterine device or barrier method of contraception in conjunction with spermicidal jelly or surgically sterile) for the study duration and at least six months afterwards

20. Pregnant or lactating women who are currently breastfeeding

21. Known hypersensitivity to carboplatin, paclitaxel, bevacizumab or their excipients (including cremophor)

22. Planned intraperitoneal cytotoxic chemotherapy

23. Planned treatment with any other systemic anti-cancer therapy following completion of protocol treatment and prior to protocol defined progression

24. Any previous radiotherapy to the abdomen or pelvis

25. Treatment with any other investigational agent prior to protocol defined progression

**Date of first enrolment**

29/04/2011

**Date of final enrolment**

08/04/2020

## **Locations**

### **Countries of recruitment**

United Kingdom

England

Northern Ireland

Scotland

Wales

Australia

Ireland

Korea, South

Mexico

New Zealand

Switzerland

### **Study participating centre**

**Aberdeen Royal Infirmary**  
Foresterhill Health Campus  
Foresterhill Road  
Aberdeen  
United Kingdom  
AB25 2ZN

### **Study participating centre**

**Addenbrooke's Hospital**  
Hills Road  
Cambridge  
United Kingdom  
CB2 0QQ

### **Study participating centre**

**Airedale General Hospital**  
Skipton Road

Steeton  
Keighley  
United Kingdom  
BD20 6TD

**Study participating centre**  
**Beatson West of Scotland Cancer Centre**  
1053 Great Western Road  
Glasgow  
United Kingdom  
G12 0YN

**Study participating centre**  
**Bedford Hospital**  
Kempston Road  
Bedford  
United Kingdom  
MK42 9DJ

**Study participating centre**  
**Belfast City Hospital**  
51 Lisburn Road  
Belfast  
United Kingdom  
BT9 7AB

**Study participating centre**  
**Birmingham Heartlands Hospital**  
Bordesley Green E  
Birmingham  
United Kingdom  
B9 5SS

**Study participating centre**  
**Blackpool Victoria Hospital**  
Whinney Heys Road  
Blackpool  
United Kingdom  
FY3 8NR

**Study participating centre**  
**Bradford Royal Infirmary**  
Duckworth Lane  
Bradford  
United Kingdom  
BD9 6RJ

**Study participating centre**  
**Bristol Haematology & Oncology Centre**  
Horfield Road  
Avon  
Bristol  
United Kingdom  
BS2 8ED

**Study participating centre**  
**Broomfield Hospital**  
Court Road  
Broomfield  
Chelmsford  
United Kingdom  
CM1 7ET

**Study participating centre**  
**Huddersfield Royal Infirmary**  
Acre Street  
Huddersfield  
United Kingdom  
HD3 3EA

**Study participating centre**  
**Castle Hill Hospital**  
Castle Road  
Cottingham  
United Kingdom  
HU16 5JQ

**Study participating centre**  
**Cheltenham General Hospital**  
Sandford Road

Cheltenham  
United Kingdom  
GL53 7AN

**Study participating centre**

**Christie Hospital**

Wilmslow Road  
Manchester  
United Kingdom  
M20 4BX

**Study participating centre**

**Churchill Hospital**

Old Road  
Oxford  
United Kingdom  
OX3 7LE

**Study participating centre**

**City Hospital**

Dudley Road  
Birmingham  
United Kingdom  
B18 7QH

**Study participating centre**

**The Clatterbridge Cancer Centre**

Clatterbridge Road  
Birkenhead  
United Kingdom  
CH63 4JY

**Study participating centre**

**County Hospital**

151 Weston Road  
Stafford  
United Kingdom  
ST16 3SA

**Study participating centre**  
**Cumberland Infirmary**  
Newtown Road  
Carlisle  
United Kingdom  
CA2 7HY

**Study participating centre**  
**Diana, Princess of Wales Hospital**  
Scartho Road  
Grimsby  
United Kingdom  
DN33 2BA

**Study participating centre**  
**Doncaster Royal Infirmary**  
Thorne Road  
Doncaster  
United Kingdom  
DN2 5LT

**Study participating centre**  
**Dorset County Hospital**  
Williams Avenue  
Dorchester  
United Kingdom  
DT1 2JY

**Study participating centre**  
**Essex County Hospital**  
Lexden Road  
Colchester  
United Kingdom  
CO3 3NB

**Study participating centre**  
**Freeman Hospital**  
Freeman Road  
High Heaton

Newcastle upon Tyne  
United Kingdom  
NE7 7DN

**Study participating centre**  
**George Eliot Hospital**  
College Street  
Nuneaton  
United Kingdom  
CV10 7DJ

**Study participating centre**  
**Glan Clwyd Hospital**  
Rhuddlan Road  
Bodelwyddan  
Rhyl  
United Kingdom  
LL18 5UJ

**Study participating centre**  
**Gloucestershire Royal Hospital**  
Great Western Road  
Gloucester  
United Kingdom  
GL1 3NN

**Study participating centre**  
**Great Western Hospital**  
Marlborough Road  
Swindon  
United Kingdom  
SN3 6BB

**Study participating centre**  
**Guy's & St. Thomas' Hospital**  
Great Maze Pond  
London  
United Kingdom  
SE1 9RT

**Study participating centre**  
**Hammersmith Hospital**  
150 Du Cane Road  
White City  
London  
United Kingdom  
W12 0HS

**Study participating centre**  
**Hereford County Hospital**  
Stonebow Road  
Hereford  
United Kingdom  
HR1 2BN

**Study participating centre**  
**Hinchingbrooke Hospital**  
Parkway  
Hinchingbrooke  
Huntingdon  
United Kingdom  
PE29 6NT

**Study participating centre**  
**Ipswich Hospital**  
Heath Road  
Ipswich  
United Kingdom  
IP4 5PD

**Study participating centre**  
**James Cook University Hospital**  
Marton Road  
Middlesbrough  
United Kingdom  
TS4 3BW

**Study participating centre**  
**James Paget Hospital**  
Lowestoft Road

Gorleston-on-Sea  
Great Yarmouth  
United Kingdom  
NR31 6LA

**Study participating centre**  
**Leicester Royal Infirmary**  
Infirmary Square  
Leicester  
United Kingdom  
LE1 5WW

**Study participating centre**  
**Lincoln County Hospital**  
Greetwell Road  
Lincoln  
United Kingdom  
LN2 5QY

**Study participating centre**  
**Lister Hospital**  
Stevenage  
United Kingdom  
SG1 4AB

**Study participating centre**  
**Liverpool Women's Hospital**  
Crown Street  
Liverpool  
United Kingdom  
L8 7SS

**Study participating centre**  
**Maidstone Hospital**  
Hermitage Lane  
Maidstone  
United Kingdom  
ME16 9QQ

**Study participating centre**  
**Walsall Manor Hospital**  
Moat Road  
Walsall  
United Kingdom  
WS2 9PS

**Study participating centre**  
**Mount Vernon Hospital**  
Rickmansworth Road  
Northwood  
United Kingdom  
HA6 2RN

**Study participating centre**  
**Musgrove Park Hospital**  
Parkfield Drive  
Taunton  
United Kingdom  
TA1 5DA

**Study participating centre**  
**New Cross Hospital**  
Wolverhampton Road  
Heath Town  
Wolverhampton  
United Kingdom  
WV10 0QP

**Study participating centre**  
**Ninewells Hospital**  
James Arrott Drive  
Dundee  
United Kingdom  
DD2 1SY

**Study participating centre**  
**Norfolk & Norwich University Hospital**  
Colney Lane

Norwich  
United Kingdom  
NR4 7UY

**Study participating centre**  
**North Devon District Hospital**  
Raleigh Park  
Barnstaple  
United Kingdom  
EX31 4JB

**Study participating centre**  
**Northampton General Hospital**  
Cliftonville  
Northampton  
United Kingdom  
NN1 5BD

**Study participating centre**  
**Nottingham City Hospital**  
Hucknall Road  
Nottingham  
United Kingdom  
NG5 1PB

**Study participating centre**  
**Peterborough City Hospital**  
Edith Cavell Campus  
Bretton Gate  
Peterborough  
United Kingdom  
PE3 9GZ

**Study participating centre**  
**Pilgrim Hospital**  
Sibsey Road  
Boston  
United Kingdom  
PE21 9QS

**Study participating centre**  
**Dorset Cancer Centre**  
Poole Hospital NHS Foundation Trust  
Longfleet Road  
Poole  
United Kingdom  
BH15 2JB

**Study participating centre**  
**Queen Alexandra Hospital**  
Portsmouth  
United Kingdom  
PO6 3LY

**Study participating centre**  
**Queen Elizabeth, The Queen Mother Hospital**  
St Peter's Road  
Margate  
United Kingdom  
CT9 4AN

**Study participating centre**  
**Queen Elizabeth Hospital, King's Lynn**  
Gayton Road  
King's Lynn  
United Kingdom  
PE30 4ET

**Study participating centre**  
**Queen Elizabeth Hospital, Birmingham**  
Mindelsohn Way  
Birmingham  
United Kingdom  
B15 2TH

**Study participating centre**  
**Queen's Hospital, Burton-on-Trent**  
Belvedere Road

Burton-on-Trent  
United Kingdom  
DE13 0RB

**Study participating centre**  
**Queen's Hospital, Romford**  
Rom Valley Way  
Romford  
United Kingdom  
RM7 0AG

**Study participating centre**  
**Royal Berkshire Hospital**  
21 Craven Road  
Reading  
United Kingdom  
RG1 5LE

**Study participating centre**  
**Royal Blackburn Hospital**  
Haslingden Road  
Blackburn  
United Kingdom  
BB2 3HH

**Study participating centre**  
**Royal Cornwall Hospital**  
Treliske  
Truro  
United Kingdom  
TR1 3LQ

**Study participating centre**  
**Royal Derby Hospital**  
Uttoxeter Road  
Derby  
United Kingdom  
DE22 3NE

**Study participating centre**  
**Royal Devon & Exeter Hospital**  
Barrack Road  
Exeter  
United Kingdom  
EX2 5DW

**Study participating centre**  
**Royal Lancaster Infirmary**  
Ashton Road  
Lancaster  
United Kingdom  
LA1 4RP

**Study participating centre**  
**Furness General Hospital**  
Dalton Lane  
Barrow-in-Furness  
United Kingdom  
LA14 4LF

**Study participating centre**  
**The Royal Marsden Hospital**  
203 Fulham Road  
Chelsea  
London  
United Kingdom  
SW3 6JJ

**Study participating centre**  
**The Royal Marsden Hospital (Sutton)**  
Downs Road  
Sutton  
United Kingdom  
SM2 5PT

**Study participating centre**  
**Royal Preston Hospital**  
Sharoe Green Lane North  
Fulwood  
Preston

United Kingdom  
PR2 9HT

**Study participating centre**  
**Royal Shrewsbury Hospital**  
Mytton Oak Road  
Shrewsbury  
United Kingdom  
SY3 8XQ

**Study participating centre**  
**Royal Stoke Hospital**  
Newcastle Road  
Stoke-on-Trent  
United Kingdom  
ST4 6QG

**Study participating centre**  
**Royal Surrey County Hospital**  
Egerton Road  
Guildford  
United Kingdom  
GU2 7XX

**Study participating centre**  
**Royal Sussex County Hospital**  
Barry Building  
Eastern Road  
Brighton  
United Kingdom  
BN2 5BE

**Study participating centre**  
**Royal United Hospital**  
Combe Park  
Avon  
Bath  
United Kingdom  
BA1 3NG

**Study participating centre**  
**Scunthorpe General Hospital**  
Cliff Gardens  
Scunthorpe  
United Kingdom  
DN15 7BH

**Study participating centre**  
**Singleton Hospital**  
Sketty Lane  
Sketty  
Swansea  
United Kingdom  
SA2 8QA

**Study participating centre**  
**Southampton General Hospital**  
Tremona Road  
Southampton  
United Kingdom  
SO16 6YD

**Study participating centre**  
**Southend Hospital**  
Prittlewell Chase  
Southend-on-Sea  
United Kingdom  
SS0 0RY

**Study participating centre**  
**St Bartholomew's Hospital**  
W Smithfield  
London  
United Kingdom  
EC1A 7BE

**Study participating centre**  
**St George's Hospital**  
Blackshaw Road  
London

United Kingdom  
SW17 0QT

**Study participating centre**

**Whiston Hospital**  
Warrington Road  
Rainhill  
Prescot  
United Kingdom  
L35 5DR

**Study participating centre**

**St James's University Hospital**  
Beckett Street  
Leeds  
United Kingdom  
LS9 7TF

**Study participating centre**

**Torbay Hospital**  
Newton Road  
Torquay  
United Kingdom  
TQ2 7AA

**Study participating centre**

**University Hospital Coventry**  
Clifford Bridge Road  
Coventry  
United Kingdom  
CV2 2DX

**Study participating centre**

**Velindre Cancer Centre**  
Velindre Road  
Cardiff  
United Kingdom  
CF14 2TL

**Study participating centre**  
**Warwick Hospital**  
Lakin Road  
Warwick  
United Kingdom  
CV34 5BW

**Study participating centre**  
**West Cumberland Hospital**  
Homewood Road  
Whitehaven  
United Kingdom  
CA28 8JG

**Study participating centre**  
**Weston General Hospital**  
Grange Road  
Weston-super-Mare  
United Kingdom  
BS23 4TG

**Study participating centre**  
**Weston Park Hospital**  
Whitham Road  
Sheffield  
United Kingdom  
S10 2SJ

**Study participating centre**  
**Wexham Park Hospital**  
Wexham Street  
Slough  
United Kingdom  
SL2 4HL

**Study participating centre**  
**Worthing Hospital**  
Lyndhurst Road  
Worthing  
United Kingdom  
BN11 2DH

**Study participating centre**  
**Wrexham Maelor Hospital**  
Croesnewydd Road  
Wrexham  
United Kingdom  
LL13 7TD

**Study participating centre**  
**Yeovil District Hospital**  
Higher Kingston  
Yeovil  
United Kingdom  
BA21 4AT

**Study participating centre**  
**York Hospital**  
Wigginton Road  
York  
United Kingdom  
YO31 8HE

**Study participating centre**  
**Ysbyty Gwynedd Hospital**  
Bangor  
United Kingdom  
LL57 2PW

**Study participating centre**  
**Good Hope Hospital**  
Rectory Road  
Sutton Coldfield  
United Kingdom  
B75 7RR

**Study participating centre**  
**Pinderfields General Hospital**  
Aberford Road  
Wakefield

United Kingdom  
WF1 4DG

**Study participating centre**  
**Kantonsspital Frauenfeld**  
Pfaffenholzstrasse 4  
Frauenfeld  
Switzerland  
CH-8501

## Sponsor information

**Organisation**  
MRC Clinical Trials Unit at UCL (UK)

**ROR**  
<https://ror.org/001mm6w73>

## Funder(s)

**Funder type**  
Charity

**Funder Name**  
Cancer Research UK Clinical Trials Advisory and Awards Committee (UK)

## Results and Publications

### Individual participant data (IPD) sharing plan

Data will be made available on request following the MRC CTU Data Sharing Policy. Data release applications will be reviewed by the Trial Management Group and Trial Steering Committee before final approval. Data-sharing contracts will be put in place between the applicant and UCL.

### IPD sharing plan summary

Available on request

### Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
	ICON8 results	07/12	04/12		

<a href="#">Results article</a>		/2019	/2019	Yes	No
<a href="#">Results article</a>	ICON8 quality-of-life results	01/07 /2020	05/07 /2020	Yes	No
<a href="#">Results article</a>	ICON8 overall survival and progression-free survival results	08/06 /2022	13/06 /2022	Yes	No
<a href="#">HRA research summary</a>	ICON8		28/06 /2023	No	No
<a href="#">Plain English results</a>	ICON8	11/01 /2018	25/01 /2022	No	Yes
<a href="#">Study website</a>	Study website	11/11 /2025	11/11 /2025	No	Yes