

# Chemotherapy for the treatment of recurrent and primary refractory Ewing sarcoma

<b>Submission date</b> 09/01/2014	<b>Recruitment status</b> Recruiting	<input checked="" type="checkbox"/> Prospectively registered <input type="checkbox"/> Protocol
<b>Registration date</b> 14/02/2014	<b>Overall study status</b> Ongoing	<input type="checkbox"/> Statistical analysis plan <input type="checkbox"/> Results
<b>Last Edited</b> 10/01/2025	<b>Condition category</b> Cancer	<input type="checkbox"/> Individual participant data <input checked="" type="checkbox"/> Record updated in last year

## Plain English summary of protocol

<http://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-looking-at-chemotherapy-for-ewings-sarcoma-reecur>

## Study website

<https://www.birmingham.ac.uk/research/crctu/trials/reecur>

## Contact information

### Type(s)

Scientific

### Contact name

Prof Martin McCabe

### Contact details

rEECur Trial Office  
Cancer Research UK Clinical Trials Unit (CRCTU)  
Institute of Cancer and Genomic Sciences  
University of Birmingham  
Edgbaston  
Birmingham  
United Kingdom  
B15 2TT  
+44 (0) 121 415 9877  
[reecur@trials.bham.ac.uk](mailto:reecur@trials.bham.ac.uk)

## Additional identifiers

### EudraCT/CTIS number

2014-000259-99

**IRAS number**

149572

**ClinicalTrials.gov number****Secondary identifying numbers**

vn 8.0 vd 11-Apr-2024

## **Study information**

**Scientific Title**

rEECur: an international randomised controlled trial of chemotherapy for the treatment of recurrent and primary refractory Ewing sarcoma

**Acronym**

rEECur

**Study objectives**

Current study hypothesis as of 10/01/2025:

To identify the optimum systemic anticancer regimen for recurrent and refractory Ewing sarcoma based on the balance between efficacy and toxicity.

Previous study hypothesis:

To compare four chemotherapy regimens: topotecan and cyclophosphamide (TC); irinotecan and temozolomide (IT); gemcitabine and docetaxel (GD) and high-dose ifosfamide (IFOS) in relapsed Ewing sarcoma with respect to efficacy, toxicity and acceptability to patients.

**Ethics approval required**

Old ethics approval format

**Ethics approval(s)**

NRES Committee North West - Greater Manchester Central, 29/08/2014, 14/NW/1110.

**Study design**

Multi-Arm, Multi-Stage (MAMS), randomised phase II/III, open-label multicentre international trial

**Primary study design**

Interventional

**Secondary study design**

Randomised controlled trial

**Study setting(s)**

Hospital

**Study type(s)**

Treatment

**Participant information sheet**

Not available in web format, please use the contact details below to request a patient information sheet

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

Paediatrics, Recurrent/refractory Ewing sarcoma

## **Interventions**

Current intervention as of 10/01/2025:

At trial entry, patients will be randomised to one of the available chemotherapy regimens:

1. High dose Ifosfamide (IFOS): 4 cycles of 21 days, additional cycles at clinician's discretion.
2. High dose Ifosfamide and Lenvatinib (IFOS-L): 4 cycles of 21 days, additional IFOS cycles at clinician's discretion. Lenvatinib capsules are taken once daily continuously throughout and for up to 2 years in total.

Local disease control measures are encouraged where possible. However, these should be delayed if possible until the completion of protocol-defined treatment (4 cycles of IFOS) or completion of 4 IFOS cycles for patients on IFOS-L.

Stem cell harvesting may be carried out in patients for whom high-dose therapy is planned. However, if an alternative chemotherapy regimen is planned for stem cell mobilisation, it should be delayed if possible until completion of protocol-defined treatment, (i.e after completion of IFOS-L or, 6 cycles of CE or, 4 cycles of IFOS) or as a minimum must be delayed until after the response assessment following cycle 4. Patients who continue to receive Lenvatinib (see section 7.2.3.5) should not receive chemotherapy other than ifosfamide at the protocol-defined dose. If these are planned, lenvatinib must be permanently discontinued prior to treatment.

Myeloablative therapy may be given at the discretion of the treating physician after 6 cycles of CE or after 4 cycles of IFOS. High-dose therapy may not be given simultaneously with lenvatinib. If high-dose therapy is planned, lenvatinib must be permanently discontinued beforehand.

Previous intervention:

At trial entry patients will be randomised to one of four chemotherapy regimens:

1. Topotecan and cyclophosphamide (TC): 6 cycles. Additional cycles may be given at the discretion of the treating clinician.
2. Irinotecan and temozolomide (IT): 6 cycles. Additional cycles may be given at the discretion of the treating clinician.
3. Gemcitabine and docetaxel (GD): 6 cycles. Additional cycles may be given at the discretion of the treating clinician.
4. High-dose Ifosfamide (IFOS): 4 cycles.

Clinicians are encouraged to use local disease control measures where possible after four cycles of chemotherapy. Stem cell harvesting may be carried out in patients for whom high-dose therapy is planned but the first four chemotherapy cycles must be given according to the randomised regimen. Patients randomised to receive TC, IT or GD who have not progressed on treatment may continue to receive the randomised regimen for more than six cycles at the discretion of the treating physician. Myeloablative therapy may be given at the discretion of the treating physician after six cycles of TC, IT or GD, or after four cycles of IFOS.

## **Intervention Type**

Drug

**Phase**

Phase II/III

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

Ifosfamide, lenvatinib

**Primary outcome measure**

Current primary outcome measure as of 10/01/2025:

Event-free survival time (EFS)

Previous primary outcome measure:

Phase II: Objective Response Rate (ORR) will be measured by cross-sectional imaging according to RECIST criteria

Phase III: Progression-Free Survival (PFS) is defined as the time from randomisation until the first event (progression, recurrence following response or death without progression or recurrence). Second malignancy is not classified as an event for progression-free survival. For those patients who do not experience events during the trial, progression-free survival times will be censored at the date of their last available trial assessment.

**Secondary outcome measures**

Current secondary outcome measure as of 10/01/2025:

1. Objective imaging response (OR) according to RECIST 1.1 criteria after 2 and 4 cycles of IFOS and IFOS-L, and at the end of trial treatment for all arms
2. Progression-free survival time (PFS)
3. Overall survival time (OS)
4. Toxicity, defined by National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v4.0
5. PET-CT response after 4 cycles (this sub-study is now closed and being analysed)
6. Quality of life (QoL)
7. Days spent in hospital

Previous secondary outcome measure:

1. Overall Survival (OS) is defined as the time from randomisation to death, irrespective of the cause. Surviving patients will be censored at their last follow-up date. OS will only be analysed for the first randomisation for each patient (re-randomisations will not be considered). Analysis methods will be as per PFS.
2. Adverse events and toxicity: Safety data will be summarised by arm for all treated patients using appropriate tabulations and descriptive statistics. Exploratory standard statistical tests will be performed to compare the arms.
3. Quality of Life (QoL) will be assessed at the following time points: baseline, following chemotherapy cycle 2, following chemotherapy cycle 4 using  $\geq 18$  years: EORTC QLQ-C30,  $< 18$  years: PedsQL™ Generic Core Scales and Multidimensional Fatigue Score
4. Days spent in the hospital while on trial treatment or due to trial treatment. The number (range) and proportion (with confidence intervals) of days in hospital will be presented for each arm and overall. Exploratory standard statistical tests will be performed to compare the arms.

**Overall study start date**

31/03/2014

**Completion date**

30/09/2031

# Eligibility

## Key inclusion criteria

Current participant inclusion criteria (since 03-May-2023) as of 10/01/2025:

1. Histologically confirmed Ewing or Ewing-like sarcoma of the bone or soft tissues. Histological confirmation either at initial diagnosis or disease progression.
2. Radiological evidence of disease progression during or after completion of the first or any subsequent line of treatment.
3. Age  $\geq 2$  years\*.
4. Eligible for randomisation between at least two open study arms.
5. Adequate renal function is defined as GFR  $\geq 60$  ml/min/1.73m<sup>2</sup>. If GFR is calculated and is  $< 90$  ml/min/1.73m<sup>2</sup>, an isotopic GFR should be performed to confirm adequate renal function.
6. Patient assessed as medically fit to receive trial treatment
7. Date of planned randomisation within 4 weeks of baseline imaging.
8. Documented negative pregnancy test for female patients of childbearing potential.
9. Patient agrees to use effective contraception during therapy and for 12 months after the last trial treatment, where applicable.
10. Written informed consent from the patient and/or parent/legal guardian.

\* Trial sites in Austria will only recruit patients aged  $\geq 2$  years  $< 30$  years due to the conditional approval issued by their ethics committee.

Additional criteria for the CE arm (This treatment arm has been closed to recruitment since 15-Aug-2024. Therefore, this criterion no longer applies):

Carboplatin is contraindicated in patients with actively bleeding tumours. Therefore, patients with actively bleeding tumours are not eligible for CE randomisation.

Additional criteria for the IFOS-L arm:

1. Adequate liver function: bilirubin  $< 3 \times$  ULN and ALT or AST  $< 5 \times$  ULN
2. Left ventricular ejection fraction  $\geq 50\%$  at baseline as determined by echocardiography.
2. Adequately controlled blood pressure (BP) with or without antihypertensive medications, defined as: a. BP  $< 95$ th percentile for sex, age, and height. Subjects  $> 18$  years of age should have BP  $\leq 150/90$  mm Hg at screening.
3. Urine dipstick  $< 2+$  for proteinuria. If  $\geq 2+$  proteinuria on dipstick, a spot urine protein:creatinine ratio test must be  $< \text{CTCAE grade 2 Proteinuria}$ .

Previous participant inclusion criteria as of 14/12/2018:

1. Histologically confirmed ES.
2. Disease progression (during or after completion of first line treatment) or any subsequent recurrence OR Refractory disease, defined by progression during first line treatment or within 12 weeks of its completion. Disease progression will be based on RECIST criteria. The appearance of new bone lesions on bone scan will require confirmation with cross-sectional imaging.
3. Soft tissue disease component evaluable by cross-sectional imaging (RECIST). Patients with bone disease without a measurable soft tissue component or bone marrow disease only will be eligible for the study but will not contribute to the phase II primary outcome measure.
4. Age  $\geq 4$  years and  $< 50$  years.
5. Patient assessed as medically fit to receive cytotoxic chemotherapy.
6. Documented negative pregnancy test for female patients of childbearing potential.
7. Patient agrees to use effective contraception during therapy and for 12 months after last trial treatment, where applicable.
8. Written informed consent from the patient and/or parent/legal guardian.

Previous participant inclusion criteria:

1. Histologically confirmed Ewing sarcoma
2. Disease recurrence after completion of first-line treatment
3. Refractory disease, defined by progression during first-line treatment or within 12 weeks of its completion
4. Soft tissue disease component evaluable by cross-sectional imaging. Patients with bone disease without a measurable soft tissue component or bone marrow disease only will be eligible for the study but will not contribute to the phase II primary outcome measure.
5. Age 2-50 years
6. Patient assessed as medically fit to receive cytotoxic chemotherapy
7. Documented negative pregnancy test for female patients of childbearing potential
8. Patient agrees to use contraception during therapy and for 12 months after last trial treatment (females) or 5 months after last trial treatment (males), where applicable
9. Written informed consent from the patient and/or the parent/legal guardian

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

Patient

### **Age group**

Mixed

### **Lower age limit**

2 Years

### **Sex**

Both

### **Target number of participants**

275 for phase II; 400 for phase III

### **Key exclusion criteria**

Current participant exclusion criteria (since 03-May-2023) as of 10/01/2025:

1. Absolute Neutrophil Count (ANC)  $<1.0 \times 10^9/L$  or platelets  $<75 \times 10^9/L$ .
2. Cytotoxic chemotherapy or other investigational medicinal product (IMP) within the previous two weeks.
3. Myeloablative therapy within the previous eight weeks.
4. Radiotherapy to target lesion within the previous six weeks.
5. Pregnant or breastfeeding women.
6. Pre-existing medical condition that would necessitate a dose modification during cycle 1 as described in section 7.
7. Any central neurotoxicity with previous ifosfamide treatment
8. Clinical evidence of nephrotic syndrome
9. Follow-up is not possible due to social, geographic or psychological reasons.
10. Previous randomisation into the rEECur trial
11. Patients with a contraindication or hypersensitivity to any IMP may not be randomised to receive an arm that contains the contraindicated IMP.
12. Patients who have previously received one of the trial regimens off-trial may not be randomised to receive that regimen again. Patients who have had ifosfamide during first-line therapy may receive the IFOS or IFOS-L arm. There is no requirement for a minimum time between receiving first-line ifosfamide and entry to rEECur.

Additional exclusion criteria for the IFOS-L arm:

1. Clinically significant ECG abnormality, including a marked baseline prolonged QT or QTc interval (eg, a repeated demonstration of a QTc interval >480 msec).
2. History of aneurysm
3. Arterial Thromboembolism in previous 6 months
4. Gastrointestinal or non-gastrointestinal fistula.
5. Gastrointestinal bleeding or active haemoptysis within the previous 3 weeks
6. Major surgery within the previous 3 weeks
7. Previous treatment with tyrosine kinase inhibitors
8. Radiographic evidence of intratumoral cavitation, encasement, or invasion of a major blood vessel, or proximity to major blood vessels with the potential risk of severe haemorrhage associated with tumor shrinkage/necrosis after lenvatinib therapy.

Previous participant exclusion criteria as of 14/12/2018:

1. Bone marrow infiltration resulting in Absolute Neutrophil Count (ANC) <1.0 x 10<sup>9</sup>/L or platelets <75 x 10<sup>9</sup>/L.
2. Cytotoxic chemotherapy or other investigational medicinal product (IMP) within previous two weeks.
3. Myeloablative therapy within previous eight weeks.
4. Radiotherapy to target lesion within previous six weeks.
5. Pregnant or breastfeeding women.
6. Follow-up not possible due to social, geographic or psychological reasons.
7. Previous randomisation into the rEECur trial

Additional criteria for specific arms:

1. Patients with a contraindication to any IMP may be entered into the study but may not be randomised to receive an arm that contains a contraindicated IMP. They will be eligible for trial entry as long as they can be randomised between a minimum of two study arms.
2. Patients who are unable to receive one or more IMPs due to local or national funding arrangements will be eligible for trial entry as long as they can be randomised between a minimum of two study arms.
3. Patients and investigators may decline randomisation to one or more trial regimens but will be eligible for trial entry as long as they can be randomised between a minimum of two study arms.
4. Patients who have previously received one of the trial regimens off-trial may not be randomised to receive that chemotherapy regimen again. However, patients who have received cyclophosphamide during first line therapy may be randomised to receive the TC arm and patients who have had ifosfamide during first line therapy may receive the ifosfamide arm if they do not have pre-existing renal or other toxicity that would necessitate in rEECur a dose modification. There is no requirement for a minimum time between receiving first line ifosfamide and entry to rEECur.

Previous participant exclusion criteria:

1. Conventional dose cytotoxic chemotherapy or other investigational medicinal product (IMP) within previous four weeks
2. Myeloablative dose chemotherapy within previous 8 weeks
3. Radiotherapy to target lesions within previous 6 weeks
4. Pregnant or breastfeeding women
5. Follow-up not possible due to social, geographic or psychological reasons

Additional criteria for specific arms:

1. Patients who have previously received one of the randomised regimens may not be randomised to receive that chemotherapy regimen again
2. Patients with a contraindication to any IMP may be entered into the study but may not be randomised to receive an arm that contains a contraindicated IMP
3. Patients who have received cyclophosphamide during first-line therapy may be randomised to receive the TC arm
4. Patients who have had ifosfamide during first-line therapy may be randomised to receive the IFOS arm if they do not have pre-existing renal or other toxicity that would necessitate a dose modification. There is no requirement for a minimum time between receiving first-line ifosfamide and randomisation to IFOS as part of the rEECur trial.

**Date of first enrolment**

01/12/2014

**Date of final enrolment**

30/09/2025

## **Locations**

**Countries of recruitment**

Australia

Belgium

Czech Republic

Denmark

England

Finland

France

Germany

Hungary

Italy

Netherlands

New Zealand

Northern Ireland

Norway

Poland



Scotland

Spain

Sweden

Switzerland

United Kingdom

Wales

**Study participating centre**

**Christie Hospital**

Manchester

United Kingdom

M20 4BX

**Study participating centre**

**Addenbrooke's Hospital**

Hills Road

Cambridge

United Kingdom

CB2 0QQ

**Study participating centre**

**Alder Hey Children's Hospital**

Eaton Road

Liverpool

United Kingdom

L12 2AP

**Study participating centre**

**Beatson West of Scotland Cancer Centre**

1053 Great Western Road

Glasgow

United Kingdom

G12 0YN

**Study participating centre**

**Birmingham Children's Hospital**  
Steelhouse Lane  
Birmingham  
United Kingdom  
B4 6NH

**Study participating centre**  
**Bristol Royal Hospital for Children**  
Upper Maudlin Street  
Bristol  
United Kingdom  
BS2 8BJ

**Study participating centre**  
**Churchill Hospital**  
Old Road  
Oxford  
United Kingdom  
OX3 7LE

**Study participating centre**  
**Clatterbridge Cancer Centre**  
Clatterbridge Road  
Birkenhead  
United Kingdom  
CH63 4JY

**Study participating centre**  
**Freeman Hospital**  
Freeman Road,  
High Heaton  
Newcastle upon Tyne  
United Kingdom  
NE7 7DN

**Study participating centre**  
**John Radcliffe Hospital**  
Headley Way,  
Headington

Oxford  
United Kingdom  
OX3 9DU

**Study participating centre**  
**Leeds General Infirmary**  
Great George Street  
Leeds  
United Kingdom  
LS1 3EX

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

**Study participating centre**  
**Noah's Ark Children's Hospital for Wales**  
Heath Park Way  
Cardiff  
United Kingdom  
CF14 4XW

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

**Study participating centre**  
**Queen's Medical Centre**  
Derby Road  
Nottingham  
United Kingdom  
NG7 2UH

**Study participating centre**  
**Royal Aberdeen Children's Hospital**  
Westburn Road  
Aberdeen  
United Kingdom  
AB25 2ZG

**Study participating centre**  
**Royal Belfast Hospital for Sick Children**  
180 Falls Road  
Belfast  
United Kingdom  
BT12 6BE

**Study participating centre**  
**Royal Hospital for Children Glasgow**  
1345 Govan Road  
Glasgow  
United Kingdom  
G51 4TF

**Study participating centre**  
**Royal Hospital for Sick Children Edinburgh**  
9 Sciennes Road  
Edinburgh  
United Kingdom  
EH9 1LF

**Study participating centre**  
**Royal Manchester Childrens Hospital**  
Oxford Road  
Manchester  
United Kingdom  
M13 9WL

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

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

**Study participating centre**  
**Royal Victoria Infirmary**  
Queen Victoria Road  
Newcastle upon Tyne  
United Kingdom  
NE1 4LP

**Study participating centre**  
**Sheffield Children's Hospital**  
The Mount,  
Glossop Road  
Sheffield  
United Kingdom  
S10 3FL

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

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

**Study participating centre**

**The Queen Elizabeth Hospital**

Mindelsohn Way  
Birmingham  
United Kingdom  
B15 2TH

**Study participating centre**

**University College London Hospital**

235 Euston Road  
London  
United Kingdom  
NW1 2BU

**Study participating centre**

**Weston Park Hospital**

Whitham Road  
Sheffield  
United Kingdom  
S10 2SJ

**Study participating centre**

**Hospital Universitari Vall D'hebron**

119-129  
Barcelona  
Spain  
08035

**Study participating centre**

**Istituto Ortopedico Rizzoli**

Via Giulio Cesare Pupilli, 1  
Bologna  
Italy  
40136

**Study participating centre**

**Helsinki Children's Hospital**

Stenbäckinkatu 11  
Helsinki  
Finland  
00290

**Study participating centre**  
**Oslo University Hospital**  
Sognsvannsveien 20  
Oslo  
Norway  
0372

**Study participating centre**  
**University Hospital Rigshospitalet**  
Blegdamsvej 9  
København  
Denmark  
2100

**Study participating centre**  
**Institut Gustave Roussy**  
114 Rue Edouard Vaillant  
Villejuif  
France  
94800

**Study participating centre**  
**Semmelweis Universitat li**  
Üllői út 26  
Budapest  
Hungary  
1085

**Study participating centre**  
**U.Z Leuven- Campus Gasthuisberg**  
Herestraat 49  
Leuven  
Belgium  
3000

**Study participating centre**  
**Maria Skłodowska-curie Memorial Cancer Center and Institute of Oncology**  
Wawelska 15 B  
Warszawa

Poland  
00-001

**Study participating centre**  
**University Hospital Motol**  
V Úvalu 84  
Praha  
Czech Republic  
150 06

**Study participating centre**  
**Leiden University Medical Centre**  
Albinusdreef 2  
Leiden  
Netherlands  
2333 ZA

**Study participating centre**  
**Princess Margaret Hospital**  
Roberts Road,  
Subiaco  
Perth  
Australia  
6008

**Study participating centre**  
**Starship Children's Hospital**  
2 Park Road,  
Grafton  
Auckland  
New Zealand  
1023

**Study participating centre**  
**Universitäts Kinderspital beider Basel**  
Spitalstrasse 33  
Basel  
Switzerland  
4056



# Sponsor information

## Organisation

University of Birmingham (UK)

## Sponsor details

Edgbaston  
Birmingham  
England  
United Kingdom  
B15 2TT

## Sponsor type

University/education

## ROR

<https://ror.org/03angcq70>

# Funder(s)

## Funder type

Government

## Funder Name

Seventh Framework Programme

## Alternative Name(s)

EC Seventh Framework Programme, European Commission Seventh Framework Programme, EU Seventh Framework Programme, European Union Seventh Framework Programme, FP7

## Funding Body Type

Government organisation

## Funding Body Subtype

National government

## Location

# Results and Publications

## Publication and dissemination plan

Planned publication in a high-impact peer-reviewed journal with intention of publishing one year post planned interim analyses.

## Intention to publish date

28/02/2031

## Individual participant data (IPD) sharing plan

The datasets generated during and/or analysed during the current study are not expected to be made available as the majority of countries the study is open in do not permit this on a regulatory level.

## IPD sharing plan summary

Not expected to be made available

## Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
<a href="#">HRA research summary</a>			28/06/2023	No	No