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Chemotherapy for the treatment of recurrent and primary refractory Ewing sarcoma

Submission date 09/01/2014	**Recruitment status** Recruiting	[X] Prospectively registered [_] Protocol [_] Statistical analysis plan [_] Results [_] Individual participant data [X] Record updated in last year
Registration date 14/02/2014	**Overall study status** Ongoing	
Last Edited 10/01/2025	**Condition category** Cancer	

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

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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 ≥18 years: EORTC QLQ-C30, <18 years: PedsQL™ Generic Core Scales and Multidimensional Fatigue Score
4. Days spent in hthe ospital 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 ≥ 2 years*.
4. Eligible for randomisation between at least two open study arms.
5. Adequate renal function is defined as GFR ≥60 ml/min/1.73m2. If GFR is calculated and is <90 ml/min/1.73m2, 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 ≥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 x ULN and ALT or AST < 5 x ULN
2. Left ventricular ejection fraction ≥50% at baseline as determined by echocardiography.
2. Adequately controlled blood pressure (BP) with or without antihypertensive medications, defined as: a. BP <95th percentile for sex, age, and height. Subjects >18 years of age should have BP ≤150/90 mm Hg at screening.
3. Urine dipstick <2+ for proteinuria. If ≥2+ proteinuria on dipstick, a spot urine protein: creatinine ratio test must be < 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 ≥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 x 109/L or platelets <75 x 109/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 109/L or platelets <75 x 109/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
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Study participating centre
Addenbrooke's Hospital
Hills Road
Cambridge
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CB2 0QQ

Study participating centre
Alder Hey Children's Hospital
Eaton Road
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United Kingdom
L12 2AP

Study participating centre
Beatson West of Scotland Cancer Centre
1053 Great Western Road
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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
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Study participating centre
Clatterbridge Cancer Centre
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Study participating centre
Freeman Hospital
Freeman Road,
High Heaton
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United Kingdom
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Study participating centre
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Oxford
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Study participating centre
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Study participating centre
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Study participating centre
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Study participating centre
Starship Children's Hospital
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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
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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?
HRA research summary			28/06/2023	No	No