

International clinical research programme to improve outcomes in newly diagnosed Ewing sarcoma – Trial 1

Submission date 20/12/2022	Recruitment status Recruiting	<input type="checkbox"/> Prospectively registered <input type="checkbox"/> Protocol
Registration date 07/09/2023	Overall study status Ongoing	<input type="checkbox"/> Statistical analysis plan <input type="checkbox"/> Results
Last Edited 07/09/2023	Condition category Cancer	<input type="checkbox"/> Individual participant data <input type="checkbox"/> Record updated in last year

Plain English Summary

Background and study aims

Ewing Sarcoma is a cancer of bone or soft tissue that occurs in children and adults. Treatment usually includes chemotherapy, surgery and/or radiotherapy. Many patients can be cured with this combination; however, survival rates are lower if the tumour has spread to other areas of the body and/or does not respond to initial treatment, or comes back. INTER-EWING-1 is an international clinical trial open to patients of all ages, which aims to answer the following key questions:

- Does giving an extra drug (in addition to standard treatment) improve survival for patients where their disease has spread?
- How long should chemotherapy be given – does giving a longer period of less intensive chemotherapy at the end of standard treatment improve survival?
- For patients whose tumour cannot be removed with surgery, do higher doses of radiotherapy reduce the risk of the tumour coming back?
- Where the tumour is known to be more likely to come back after an operation (for example, if the tumour is large, or does not respond to chemotherapy), can lower doses of radiotherapy reduce the side effects but not increase the risk of the tumour coming back?

In INTER-EWING-1, we want to find if having standard chemotherapy plus a type of drug designed to target tumour cells, called a multi-tyrosine kinase inhibitor (MTKI) is better for patients.

Who can participate?

Patients aged 2 years or older, with Ewing sarcoma.

What does the study involve?

The MTKI regorafenib will be given to patients who have tumours which have spread to other parts of the body. As this is the first time patients will have been given this combination, initial safety testing will be done in a separate study first.

In some other cancers, continuing low dose chemotherapy at the end of standard treatment has been shown to improve survival. In INTER-EWING-1 we want to find if having an additional 6 months of chemotherapy is better for patients or not.

Outcomes for patients after failure to control disease are very poor. INTER-EWING-1 aims to optimise the radiotherapy doses given to achieve best outcomes.

What are the possible benefits and risks of participating?

Benefits:

We cannot promise that patients will benefit from participating in the trial. It is possible that the treatment options on trial, such as adding maintenance chemotherapy or changing the dose of the radiotherapy given, may improve response and survival but we don't know this yet. However, all the information that we get from this study will help improve the treatment of children and adults with ES in the future.

Risks:

This trial involves the use of many established chemotherapy drugs, many of which are either currently licenced for use for this indication or which have been explored in other trials. The toxicities associated with the IMPs on this trial are well known. However, new combinations or prolonged therapy may give increased risk of toxicity.

As many of the chemotherapy agents are associated with different types of toxicity, all patients must be fit to receive treatment as per the eligibility, and specific stipulations are in place to ensure that patients have sufficiently recovered from haematological, hepatic and neurological toxicity. Haematology and Biochemistry will be performed at baseline and prior to each cycle of IMP and further monitoring as per institutional guidelines.

The IMPs in this trial are also toxic to the newborn/ foetus and therefore patients cannot be pregnant, become pregnant or breastfeed during study treatment and for a year afterwards. There are FDG-PET CT scans as part of this trial. Most of these scans are standard of care: however they are associated with a very small increased risk of secondary cancer.

The use of preoperative radiotherapy can increase the short term risk of wound complications and may reduce some long term toxicities. An increase in radiotherapy dose may cause additional toxicity but may result in better clinical results.

Radiotherapy carries the following risks of long term side effects however, as radiotherapy is part of the standard treatment pathway for patients with ES, the risks are similar to those if not treated as part of this trial:

- developing second cancers
- problems with puberty and fertility (pelvic radiotherapy)
- growth and development problems (cranial/head and neck radiotherapy)
- effects on kidney and liver function
- effects on heart and lung function
- effects on spinal cord function

Therefore, all individual per-patient radiotherapy plans will be reviewed by a radiation clinician and medical physics expert within the QUARTET programme prior to commencing radiotherapy, to ensure that the plans are in-line with the protocol and safe to deliver.

Radiotherapy is very carefully planned in advance so that the radiation doses which will be received by healthy parts of the body are kept as low as reasonably achievable and within recognised safe limits. For this reason, sometimes the intended tumour dose is limited.

Some patients who are very young may require general anaesthetic to lie still when receiving radiotherapy. However, the use of play specialists often minimizes the need for general anaesthetic.

Current government guidelines and local safety procedures will be adhered to in relation to the ongoing pandemic in order to mitigate any risks of exposure to the virus.

Where is the study run from?

University of Birmingham (UK)

When is the study starting and how long is it expected to run for?
December 2021 to November 2032

Who is funding the study?
Cancer Research UK

Who is the main contact?
INTER-EWING1@trials.bham.ac.uk
Professor Bernadette Brennan, Bernadette.Brennan@mft.nhs.uk

Contact information

Type(s)
Scientific

Contact name
Ms Maria Khan

Contact details
CRCTU Institute of Cancer and Genomic Sciences
University of Birmingham
Birmingham
United Kingdom
B15 2TT
+44 121 415 9877
INTER-EWING1@trials.bham.ac.uk

Type(s)
Principal Investigator

Contact name
Prof Bernadette Brennan

Contact details
Oxford Road
Manchester
United Kingdom
M13 9WL
+44 161 7018419
INTER-EWING1@trials.bham.ac.uk

Additional identifiers

EudraCT/CTIS number
2021-005061-41

IRAS number
1005108

ClinicalTrials.gov number

Nil known

Secondary identifying numbers

RG_21-151, IRAS 1005108

Study information

Scientific Title

International clinical research programme to improve outcomes in newly diagnosed Ewing sarcoma – Trial 1 (INTER-EWING-1)

Acronym

INTER-EWING-1

Study hypothesis

The primary objectives for this trial are related to each of the trial questions.

For the chemotherapy questions, the objectives are to determine:

- whether outcome in newly diagnosed metastatic Ewing sarcoma patients can be improved with the addition of regorafenib to the standard backbone chemotherapy VDC/IE when compared with VDC/IE alone (Randomisation A)
- whether the addition of 6 cycles of maintenance chemotherapy of vinorelbine and cyclophosphamide improves the outcome for patients. (Randomisation C)

For the radiotherapy questions, the objectives are to determine:

- whether dose escalation of radiotherapy improves the outcome in patients with inoperable disease (Randomisation B1)
- which of the two post-operative radiotherapy doses following surgical resection of the primary tumour site will result in achieving optimal outcome (Randomisation B2)

Ethics approval required

Ethics approval required

Ethics approval(s)

Approved 19/07/2023, East of England - Cambridge South Research Ethics Committee (2 Redman Place, Stratford, London, E20 1JQ, United Kingdom; +44 2071048194; cambridgesouth.rec@hra.nhs.uk), ref: 23/EE/0023

Study design

Interventional randomized controlled trial

Primary study design

Interventional

Secondary study design

Randomised controlled trial

Study setting(s)

Hospital

Study type(s)

Treatment

Participant information sheet

Condition

Ewing Sarcoma

Interventions

Study entry

INTER-EWING-1 includes a study entry point where all patients with Ewing sarcoma (ES) may give consent for the analysis of their biological samples and/or undergo additional scans, alongside the collection of very basic patient characteristics, a treatment summary, and follow-up data for events.

Treatment questions

Patients may be entered into more than one treatment question following study entry. Separate consent is required for study entry and for each trial question. Newly diagnosed patients should, where possible, be entered into the INTER-EWING-1 study at the time of initial diagnosis prior to receiving any chemotherapy. However, patients may enter the study at any point of the treatment pathway as long as they are eligible.

Screening assessments

A histologically confirmed diagnosis of ES is required for Study Entry.

The majority of screening assessments for subsequent randomisations are standard of care, and will include blood tests, urine tests, physical exam, and scans (e.g. CT, MRI, PET-CT).

Induction chemotherapy for newly diagnosed patients (randomisation A):

This section will be updated after the recommended phase II dose has been established from the externally sponsored phase Ib study.

Radiotherapy for newly diagnosed disease:

This trial also contains radiotherapy randomisations for patients with newly diagnosed ES.

For patients with non-resectable disease (disease that cannot be removed by surgery) there is the B1 randomisation, in which the patient will be randomised to receive either a standard dose 54Gy or higher dose of radiotherapy 64.8Gy.

For patients with resectable disease there is the B2 randomisation in which patients will receive a radiotherapy dose of 54Gy or a lower dose of radiotherapy 45Gy.

All sites and patients participating in the radiotherapy questions will participate in the Radiotherapy Quality Assurance programme, facilitated via the SIOPE QUARTET (Quality and Excellence in Radiotherapy and Imaging for Children and Adolescents with Cancer across Europe in Clinical Trials) initiative. All sites will be required to be approved for radiotherapy delivery via QUARTET, and radiotherapy plans for each individual patient will be uploaded to the online system for approval. There will also be a retrospective Quality Control review of all scans and cross-sectional imaging received as part of the radiotherapy QA review process.

Maintenance Chemotherapy (randomisation C):

For the majority of patients the treatment of ES includes intensive chemotherapy and either surgery, radiotherapy or a combination of the two.

Currently, once this initial treatment phase finishes, no further treatment is given. However, several other childhood cancers may give patients additional chemotherapy – this is called maintenance chemotherapy. The aim of maintenance chemotherapy is to stop the cancer from returning or to get rid of any traces of cancer that are left over from previous treatment.

In this part of the INTER-EWING-1 trial, patients will either stop treatment or receive 6 cycles of maintenance chemotherapy. The chemotherapy for this randomisation is vinorelbine and cyclophosphamide (VnC) and the cycles are each 28 days. Vinorelbine can be given in either an intravenous or oral format.

Imaging sub-studies:

Patients who have a Diffusion Weighted MRI scan at diagnosis may be offered further scans after 3 and then 9 cycles of induction chemotherapy to see whether these additional scans can indicate how well treatment will work in the long term.

The study will also investigate whether whole body-MRI scans are better than FDG-PET scans at measuring how widespread disease is before treatment. Where these scans do not form part of standard care, patients will be asked for consent to have a whole body-MRI scan at diagnosis for research purposes.

This study will also encourage an FDG PET-CT or FDG PET-MRI scan after 3 and then 9 courses of induction chemotherapy to determine prospectively its prognostic value. Should this not be standard of care, the patient will be asked to consent to these optional sub-studies.

QoL sub-study:

Patients will also be asked to complete Quality of Life questionnaires at various timepoints.

Follow-up:

Following completion of treatment, the frequency of follow-up assessments should be as per local practice.

Intervention Type

Drug

Phase

Phase III

Drug/device/biological/vaccine name(s)

Vinorelbine, cyclophosphamide

Primary outcome measure

1. Event-free survival time (EFS), defined as the time from the date of each randomisation to the date of the first failure event, where failure events are defined as:
 - 1.1. Relapse or progression of existing disease, or recurrence of disease at new sites,
 - 1.2. Death from any cause without disease progression,
 - 1.3. Second malignant neoplasm.

Patients without an event at the time of analysis will be censored at the date when they were last known to be alive and event-free.

Secondary outcome measures

Randomisation A (Induction chemotherapy): OS, Toxicity, QoL, Histological response (if surgery is performed)

Randomisation B1 (Radiotherapy): LFFS, OS, Toxicity, Achievement of local control, Acute post radiotherapy toxicity, Late toxicity, QoL

Randomisation B2 (Radiotherapy): LFFS, OS, Toxicity, Achievement of local control, Acute post radiotherapy toxicity, Late toxicity, QoL

Randomisation C (Maintenance therapy): OS, toxicity, QoL

OS – Overall survival time measured using patient records

QoL – Cancer quality of life measures (PedsQL and EORTC QLQ-C30)

LFFS – Local failure-free survival time measured using patient records

Adverse events and toxicity will be categorised and graded using CTCAE v5.0.

Histological response is the percentage of viable tumour cells observed post-induction chemotherapy surgery of the primary tumour.

Achievement of local control is radiologically confirmed at the end of treatment.

Acute post radiotherapy toxicity is defined as a radiotherapy related adverse event grade 3 and above during and up to 120 days after completing radiotherapy

Late toxicity is defined as radiotherapy related adverse event grade 3 and above occurring from 120 days after completing radiotherapy

Overall study start date

01/12/2021

Overall study end date

30/11/2032

Eligibility

Participant inclusion criteria

Inclusion Criteria for study entry – Mandatory first point of study entry, for all patients

1. Any histologically and genetically confirmed Ewing sarcoma of bone or soft tissue, or round cell sarcomas which are 'Ewing's-like' but negative for EWSR1-Fli gene rearrangement
2. Age > 2 years
3. Written informed consent from the patient and/or the parent/legal guardian

inclusion criteria for randomisation A will be defined on completion of the externally sponsored phase 1b study. A substantial amendment will be submitted to the relevant competent authority and ethics committee(s) to include these details prior to the opening of Randomisation A.

Radiotherapy Randomisations – B1 and B2

Inclusion Criteria

1. Entered into the INTER-EWING-1 study
2. Received induction/consolidation chemotherapy with a VDC/IE/VC based regimen
3. Patient assessed as medically fit to receive the radiotherapy
4. Documented negative pregnancy test for female patients of childbearing potential
5. Patient agrees to use contraception during therapy and for 12 months after last trial treatment (females) or 6 months after last trial treatment (males), where patient is sexually active
6. Written informed consent from the patient and/or the parent/legal guardian

Randomisation B1 specific Inclusion criteria– Definitive radical radiotherapy dose finding randomisation

1. Patients requiring definitive radical radiotherapy to primary tumour site as sole local therapy following discussion by local multidisciplinary team.
2. Patients who have undergone an R2 resection of the primary tumour (macroscopic residual tumour), requiring definitive radical radiotherapy

Randomisation B2 specific Inclusion criteria– Post-operative radiotherapy dose finding randomisation

1. Patients requiring post-operative radiotherapy following discussion by local multidisciplinary team according to multidisciplinary team meeting.

Randomisation C – Maintenance chemotherapy randomisation

Inclusion Criteria

1. Entered into the INTER-EWING-1 study
2. Received induction/ consolidation chemotherapy with a VDC/IE/VC based regimen
3. Have responded to induction treatment and not progressed
4. Medically fit to receive treatment
5. Absence of severe vincristine neuropathy – i.e. requiring discontinuation of vincristine treatment
6. Adequate liver function: bilirubin $<3 \times$ ULN and ALT or AST $< 5 \times$ ULN
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 6 months after last trial treatment (males), where patient is sexually active
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

900

Participant exclusion criteria

Exclusion Criteria for study entry

1. Previous malignancy

Exclusion criteria for randomisation A will be defined on completion of the externally sponsored phase 1b study. A substantial amendment will be submitted to the relevant competent authority and ethics committee(s) to include these details prior to the opening of Randomisation A.

Exclusion Criteria Radiotherapy Randomisations – B1 and B2

1. Previous radiotherapy to the same site
2. Pregnant or breastfeeding women
3. BuMel high dose chemotherapy within previous 10 weeks

Randomisation B1 specific Exclusion criteria– Definitive radical radiotherapy dose finding randomisation

1. Patients who have had a R1 or R0 surgical resection of their tumour
2. Previous high dose chemotherapy including busulfan when specified dose constraints to critical organs cannot be met (please see INTER-EWING-1 Quartet RTQA guidelines for more details)

Randomisation B2 specific Exclusion criteria– Post-operative radiotherapy dose finding randomisation

1. R2 resection (macroscopic residual tumour)
2. Patients treated by surgery with wide resection (R0 and all tissues involved by the prechemotherapy tumour volume have been completely resected), good histological response (< 10% viable cells), small tumour volume (< 200 mls at diagnosis), of the limb.

Randomisation C – Maintenance chemotherapy randomisation

Exclusion Criteria

1. Urinary outflow obstruction that cannot be relieved prior to starting treatment
2. Uncontrolled significant inter-current illness or active infection
3. Active inflammation of the urinary bladder (cystitis)
4. Known contraindication or hypersensitivity to any of the treatments or excipients
5. Pregnant or breastfeeding women

Recruitment start date

30/04/2023

Recruitment end date

30/11/2030

Locations

Countries of recruitment

Australia

Denmark

England

France

Italy

Netherlands

New Zealand

Northern Ireland

Norway

Poland

Scotland

Spain

Switzerland

Wales

Study participating centre

Royal Manchester Childrens Hospital

Oxford Road

Manchester

United Kingdom

M13 9WL

Study participating centre

Manchester University NHS Foundation Trust

Cobbett House

Oxford Road

Manchester

United Kingdom

M13 9WL

Study participating centre

Cambridge University Hospitals NHS Foundation Trust

Addenbrooke's Hospital

Hills Road

Cambridge

United Kingdom

CB2 0QQ

Study participating centre

NHS Grampian

Summerfield House

2 Eday Road

Aberdeen

United Kingdom

AB15 6RE

Study participating centre

Belfast Health and Social Care Trust

Knockbracken Healthcare Park
Saintfield Road
Belfast
United Kingdom
BT8 8SG

Study participating centre

Alder Hey Children's NHS Foundation Trust

Alder Hey Hospital
Eaton Road
West Derby
Liverpool
United Kingdom
L12 2AP

Study participating centre

Birmingham Women's and Children's NHS Foundation Trust

Steelhouse Lane
Birmingham
United Kingdom
B4 6NH

Study participating centre

University Hospital Southampton NHS Foundation Trust

Southampton General Hospital
Tremona Road
Southampton
United Kingdom
SO16 6YD

Study participating centre

University Hospitals Bristol and Weston NHS Foundation Trust

Trust Headquarters
Marlborough Street
Bristol
United Kingdom
BS1 3NU

Study participating centre
Cardiff & Vale University LHB
Corporate Headquarters
Heath Park
Cardiff
United Kingdom
CF14 4XW

Study participating centre
Great Ormond Street Hospital for Children NHS Foundation Trust
Great Ormond Street
London
United Kingdom
WC1N 3JH

Study participating centre
Oxford University Hospitals NHS Foundation Trust
John Radcliffe Hospital
Headley Way
Headington
Oxford
United Kingdom
OX3 9DU

Study participating centre
Leeds Teaching Hospitals NHS Trust
St. James's University Hospital
Beckett Street
Leeds
United Kingdom
LS9 7TF

Study participating centre
University Hospitals of Leicester NHS Trust
Leicester Royal Infirmary
Infirmary Square
Leicester
United Kingdom
LE1 5WW

Study participating centre
Nottingham University Hospitals NHS Trust
Trust Headquarters
Queens Medical Centre
Derby Road
Nottingham
United Kingdom
NG7 2UH

Study participating centre
NHS Lothian
Waverley Gate
2-4 Waterloo Place
Edinburgh
United Kingdom
EH1 3EG

Study participating centre
NHS Greater Glasgow and Clyde
J B Russell House
Gartnavel Royal Hospital
1055 Great Western Road Glasgow
Glasgow
United Kingdom
G12 0XH

Study participating centre
The Royal Marsden NHS Foundation Trust
Fulham Road
London
United Kingdom
SW3 6JJ

Study participating centre
The Newcastle upon Tyne Hospitals NHS Foundation Trust
Freeman Hospital
Freeman Road
High Heaton
Newcastle upon Tyne
United Kingdom
NE7 7DN

Study participating centre
Sheffield Children's NHS Foundation Trust
Western Bank
Sheffield
United Kingdom
S10 2TH

Study participating centre
University College London Hospitals NHS Foundation Trust
250 Euston Road
London
United Kingdom
NW1 2PG

Study participating centre
Velindre NHS Trust
Unit 2
Charnwood Court
Heol Billingsley
Cardiff
United Kingdom
CF15 7QZ

Study participating centre
The Christie NHS Foundation Trust
550 Wilmslow Road
Withington
Manchester
United Kingdom
M20 4BX

Study participating centre
The Clatterbridge Cancer Centre NHS Foundation Trust
Clatterbridge Hospital
Clatterbridge Road
Bebington
Wirral
United Kingdom
CH63 4JY

Study participating centre
University Hospitals Birmingham NHS Foundation Trust
Queen Elizabeth Hospital
Mindelsohn Way
Edgbaston
Birmingham
United Kingdom
B15 2GW

Sponsor information

Organisation

University of Birmingham

Sponsor details

Research Strategy and Services Division
Research Park
University of Birmingham
Birmingham
United Kingdom
B15 2TT
+44 121 415 9877
researchgovernance@contacts.bham.ac.uk

Sponsor type

University/education

Website

<http://www.birmingham.ac.uk/index.aspx>

ROR

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

Funder(s)

Funder type

Funder Name

Cancer Research UK

Results and Publications

Publication and dissemination plan

Peer reviewed scientific journals
Internal report
Conference presentation
Publication on website
Other publication
Submission to regulatory authorities

Intention to publish date

30/11/2033

Individual participant data (IPD) sharing plan

The CRCTU is committed to responsible and controlled sharing of anonymised clinical trial data with the wider research community to maximise potential patient benefit while protecting the privacy and confidentiality of trial participants. Data anonymised in compliance with the Information Commissioners Office requirements, using a procedure based on guidelines from the Medical Research Council (MRC) Methodology Hubs and Information Commissioners Office, will be available for sharing with researchers outside of the trials team within 6 months of the primary publication.

More detailed information on the CRCTU's Data Sharing Policy and the mechanism for obtaining data can be found on the CRCTU website: <https://www.birmingham.ac.uk/research/activity/mds/trials/crctu/index.aspx>.

IPD sharing plan summary

Available on request