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

Submission date
20/12/2022

Recruitment status
Recruiting

Registration date
07/09/2023

Overall study status
Ongoing

Last Edited
27/09/2024

Condition category
Cancer

[ ] Prospectively registered
[ ] Protocol
[ ] Statistical analysis plan
[ ] Results
[ ] Individual participant data
[ ] Record updated in last year

Plain English summary of protocol

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
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https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-looking-at-improving-treatment-for-children-and-adults-with-newly-diagnosed-ewings-sarcoma

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Scientific

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Additional identifiers

Clinical Trials Information System (CTIS)
2021-005061-41

Integrated Research Application System (IRAS)

1005108

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
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 objectives
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

Study type(s)
Treatment

Health condition(s) or problem(s) studied

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 cyclosphosphamide (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(s)
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.

Key secondary outcome(s))
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

Completion date
30/11/2032

Eligibility

Key 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 x ULN and ALT or AST < 5 x 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

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
2 years

Sex
All

Key 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

Date of first enrolment
30/04/2023

Date of final enrolment
30/11/2030

Locations

Countries of recruitment
England

Northern Ireland

Scotland

Wales

Australia

Denmark

France

Italy

Netherlands

New Zealand

Norway

Poland

Spain

Switzerland

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Royal Manchester Childrens Hospital
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Study participating centre
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Study participating centre
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Sponsor information

Organisation
University of Birmingham

ROR
https://ror.org/03angcq70

Funder(s)

Funder type
Charity

Funder Name
Cancer Research UK

Alternative Name(s)
CR_UK, Cancer Research UK - London, Cancer Research UK (CRUK), CRUK

Funding Body Type
Private sector organisation

Funding Body Subtype
Other non-profit organizations

Location
United Kingdom

Results and Publications

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