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Euro Ewing 2012

Submission date 30/08/2013	**Recruitment status** No longer recruiting	[X] Prospectively registered [X] Protocol [_] Statistical analysis plan [X] Results [_] Individual participant data
Registration date 04/11/2013	**Overall study status** Completed	
Last Edited 16/04/2025	**Condition category** Cancer	

Plain English summary of protocol
https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-looking-treatment-ewings-sarcoma-family-of-tumours-euro-ewing-2012

Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number
2012-002107-17

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
N/A

Study information

Scientific Title
International randomised controlled trial for the treatment of newly diagnosed Ewing's sarcoma family of tumours (ESFT)

Acronym
EE2012

Study objectives
For randomisation 1 - To compare the Vincristine, Ifosfamide, Doxorubicin, Etoposide (VIDE) strategy [VIDE induction and VAI/VAC (Vincristine, Actinomycin D, Ifosfamide/ Vincristine, Actinomycin D, Cyclophosphamide) consolidation] with the Vincristine, Doxorubicin, Cyclophosphamide/Ifosfamide, Etoposide (VDC/IE) strategy (compressed to VDC/IE induction and IE/VC consolidation).

Ethics approval required
Old ethics approval format

Ethics approval(s)
NRES Committee North West - Greater Manchester Central, 01/02/2013

Study design
Multi-centre international Phase III open-label randomized controlled 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 to request a patient information sheet

Health condition(s) or problem(s) studied
Ewing's sarcoma

Interventions
Randomisation R1
At trial entry, patients will be randomised to one of the following treatment arms:
1. Arm A (VIDE strategy): VIDE induction; VAI/VAC consolidation
Induction chemotherapy: 6 cycles of VIDE
Consolidation chemotherapy: 1 cycle of VAI and 7 cycles of VAC or 8 cycles of VAI (unless randomised to Bu-Mel at R2)

2. Arm B (VDC/IE strategy): VDC/IE induction; IE/VC consolidation
Induction chemotherapy: 9 cycles of alternating VDC and IE
Consolidation chemotherapy: 5 cycles of alternating IE and VC (unless randomised to Bu-Mel at R2)

Randomisation R2zol
Following induction chemotherapy, patients who fulfil the eligibility criteria for R2zol and consent to take part in the randomisation will receive consolidation chemotherapy as allocated at trial entry and be randomised to receive either:
1. 9 cycles of zoledronic acid following the first cycle of consolidation chemotherapy (either VAI (Arm A) or IE (Arm B))
OR
2. No zoledronic acid

Randomisation R2loc
Following induction chemotherapy, patients who fulfil the eligibility criteria for R2loc and consent to take part in the randomisation will be randomised to receive either:
1. Consolidation chemotherapy as assigned at R1 either 8 cycles of VAI (Arm A) or 5 cycles of alternating IE and VC (Arm B)
OR
2. 1 cycle of VAI (Arm A) or 1 cycle of IE (Arm B), followed by high-dose treatment with busulfan and melphalan

Randomisation R2pulm
Following induction chemotherapy, patients who fulfil the eligibility criteria for R2pulm and consent to take part in the randomisation will be randomised to receive either:
1. Consolidation chemotherapy as assigned at R1 either 8 cycles of VAI (Arm A) or 5 cycles of alternating IE and VC (Arm B), plus lung irradiation
OR
2. 1 cycle of VAI (Arm A) or 1 cycle of IE (Arm B), followed by high-dose treatment with busulfan and melphalan

Drug names, frequency of administration and dose;

Arm A:
VIDE Vincristine (d1; 1.5mg/m2), Ifosfamide (d1, d2,d3; 3g/m2/d), Doxorubicin (d1,d2,d3; 20mg /m2/d), Etoposide (d1,d2,d3; 150mg/m2/d).
VAI Vincristine (d1; 1.5mg/m2), Actinomycin D (d1, d2; 0.75mg/m2/d), Ifosfamide (d1,d2; 3g/m2 /d)
VAC Vincristine(d1; 1.5mg/m2), Actinomycin D (d1, d2; 0.75mg/m2/d), Cyclophosphamide (d1; 1500mg/m2)
Arm B:
VDC Vincristine(d1; 1.5mg/m2), Doxorubicin (d1, d2; 37.5mg/m2/d), Cyclophosphamide (d1; 1200mg/m2)
IE Ifosfamide (d1,d2,d3,d4,d5; 1800mg/m2/d), Etoposide (d1,d2,d3,d4,d5; 100mg/m2/d)
VC- Vincristine(d1; 2mg/m2), Cyclophosphamide (d1; 1200mg/m2)

Following treatment, patients will be followed up for progression and death until all trial objectives have been met.

Intervention Type
Drug

Phase
Phase III

Drug/device/biological/vaccine name(s)
Vincristine, ifosfamide, doxorubicin, etoposide, actinomycin D, cyclophosphamide

Primary outcome measure
Event-free survival, defined as the time from randomisation to first event, where an event is progression without complete remission, recurrence (following complete remission), diagnosis of secondary malignancy or death. Patients who have not had an event will be censored at their last follow-up date. Patients lost to follow-up without an event will be censored at the date of their last consultation.

Secondary outcome measures
1. Overall survival defined as the time from randomisation to death, irrespective of cause. Surviving patients will be censored at their last follow-up date
2. Adverse events and toxicity - measured by CTCAE
3. Histological response of the primary tumour to induction chemotherapy if surgery is performed as local control - tumours will be graded using the Salzer-Kuntschik scale
4. Achievement of local control at the end of treatment, defined as complete surgical resection following induction chemotherapy, or no measurable disease assessed by end of treatment MRI scan, or no change in measurable residual tumour over a 6-month period from the end of treatment assessed by MRI scan at the end of treatment and 6 months after the end of treatment
5. Growth parameters and jaw osteonecrosis (R2zol only), defined as the change in Standard Deviation height score between baseline, end of treatment and throughout follow-up

Overall study start date
16/09/2013

Completion date
02/01/2025

Eligibility

Key inclusion criteria
R1 Inclusion criteria:
1. Histologically confirmed ESFT of bone or soft tissue
2. Localised or pulmonary and/or pleural metastatic disease
3. Age >2 years and <50 years (from second birthday to 49 years and 364 days) at the date of diagnostic biopsy
4. Randomisation ≤45 days after diagnostic biopsy/surgery
5. Patient assessed as medically fit to receive the treatment in either of the R1 treatment arms
6. No prior treatment for ESFT other than surgery
7. Documented negative pregnancy lactation 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 parent/legal guardian

R2zol Inclusion criteria:
1. No evidence of metastatic disease
2. Age >5 years (from fifth birthday) at date of randomization
3. Localised tumour of any tumour volume with surgery after chemotherapy alone, and good histological response to induction chemotherapy (<10% viability)
OR
4. Localised tumour with initial tumour volume <200ml with resection after chemotherapy and early radiotherapy, and good histological response to induction chemoradiotherapy (<10% viability)
OR
5. Localised tumour with initial tumour volume <200ml and surgery at diagnosis
OR
6. Localised tumour with initial tumour volume <200ml with resection after chemotherapy alone and extracorporeal irradiation of the primary tumour at surgery
OR
7. Localised unresected tumour with initial tumour volume <200ml and at least a partial radiological response to induction chemotherapy (≥50% regression of evaluable soft tissue component)
8. Consolidation chemotherapy as per protocol intended
9. Patient assessed medically fit to receive zoledronic acid if allocated
10. Written informed consent from the patient and/or parent/legal guardian

R2loc Inclusion criteria:
1. No evidence of metastatic disease
2. Localised tumour of any tumour volume with surgery after chemotherapy alone, and poor histological response to induction chemotherapy (≥10% viability)
OR
3. Localised tumour with initial tumour volume ≥200ml with surgery after chemotherapy and early radiotherapy, irrespective of histological response
OR
4. Localised tumour with initial tumour volume ≥200ml and surgery at diagnosis
OR
5. Localised tumour with initial tumour volume ≥200ml with extracorporeal irradiation of the primary tumour at surgery, and no progression under induction chemotherapy
OR
6. Localised unresected tumour with initial tumour volume <200ml treated by radiation therapy alone as local therapy and with poor radiological response to induction chemotherapy (<50% regression of evaluable soft tissue component) but no progression under induction chemotherapy
7. Consolidation chemotherapy as per protocol intended
8. Patient assessed medically fit to receive the treatment in either of the R2loc treatment arms
9. Written informed consent from the patient and/or parent/legal guardian

R2pulm Inclusion criteria:
1. Pulmonary and/or pleural metastatic disease only at diagnosis
2. Partial response of the lung metastatses and no progression of the primary tumour during induction chemotherapy
3. Consolidation chemotherapy as per protocol intended
4. Patient assessed medically fit to receive the treatment in either of the R2pulm treatment arms
5. Written informed consent from the patient and/or the parent/legal guardian

Participant type(s)

Patient

Age group
Mixed

Sex
Both

Target number of participants
600

Total final enrolment
640

Key exclusion criteria
R1 Exclusion criteria:
1. Extrapulmonary metastatic disease
2. Contra-indication to the treatment in either of the R1 treatment arms
3. Second malignancy
4. Pregnant or breastfeeding women
5. Follow-up not possible due to social, geographic or psychological reasons

R2zol Exclusion criteria:
1. History of dental surgery (extraction or jaw surgery) in the 6 months preceding the start of zoledronic acid treatment, or planned dental surgery within the treatment period or within 6 months after the end of treatment
2. Ewings tumour of the maxilla or of the mandible
3. Progression of the primary tumour or appearance of new lesions

R2loc Exclusion criteria:
1. Radiotherapy required encompassing spine, a significant volume of digestive tract or lungs (such patients should be discussed during a web conference before randomisation for technique, volume, and dose validation with the national radiotherapy committee)
2. Progression of the primary tumour or appearance of new lesions

R2pulm Exclusion criteria:
1. Radiotherapy required encompassing spine, a significant volume of digestive tract or lungs (such patients should be discussed during a web conference before randomisation for technique, volume, and dose validation with the national radiotherapy committee)
2. Progression of the primary tumour or appearance of new lesions

Date of first enrolment
20/12/2013

Date of final enrolment
30/04/2019

Locations

Countries of recruitment
England

France

United Kingdom

Study participating centre
Royal Manchester Children's Hospital
Manchester
United Kingdom
M13 9WL

Sponsor information

Organisation
University of Birmingham (UK)

Sponsor details
Edgbaston
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B15 2TT

Sponsor type
University/education

ROR
https://ror.org/03angcq70

Funder(s)

Funder type
Charity

Funder Name
Cancer Research UK (UK); C5952/A14745

Results and Publications

Publication and dissemination plan

Planned publication in a high-impact peer-reviewed journal.

Intention to publish date
01/08/2025

Individual participant data (IPD) sharing plan
The data sharing plans for the current study are unknown and will be made available at a later date

IPD sharing plan summary
Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article	protocol	17/01/2020	20/01/2020	Yes	No
Results article		29/10/2022	16/12/2022	Yes	No
Plain English results			17/03/2023	No	Yes
Other publications	Secondary analysis	20/12/2024	20/01/2025	Yes	No