Title

An international randomised controlled trial of chemotherapy for the treatment of recurrent and primary refractory Ewing sarcoma (ES).

Acronym

rEECur

Trial Design

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

Objectives

The objectives of the study are to compare four chemotherapy regimens in recurrent/refractory ES: cyclophosphamide & topotecan, irinotecan & temozolomide, gemcitabine & docetaxel, and high dose ifosfamide, in order to identify the best one for use as a backbone in future treatment with respect to efficacy (imaging response and survival), toxicity and acceptability to patients

Outcome Measures

Primary outcome measures

Phase II: Objective imaging response (OR) after 4 cycles of trial treatment, measured according to RECIST criteria

Phase III: Event Free Survival (EFS)

Secondary outcome measures

- EFS (phase II)
- OR (phase III)
- PFS
- Overall survival (OS)
- Toxicity, defined by National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v4.0
- Imaging response after cycles 2 and 6 (for TC, IT and GD arms) and at the end of trial treatment (as per primary outcome for Phase II)
- PET-CT response will be analysed as per primary outcome for Phase II
- Quality of life (QoL)
- Days spent in hospital

Patient Population

Patients with recurrent and primary refractory Ewing sarcoma of the bone or soft tissues

Sample Size

- A minimum of 275 patients for the phase II part
- A target of at least 400 patients for the phase III part

Patients who take part in the phase II evaluation will contribute to the phase III evaluation.

Main Eligibility Criteria

Principal inclusion criteria

- Histologically proven, recurrent or primary refractory Ewing sarcoma of the bone or soft tissues
- Disease progression (during or after completion of first line treatment) or any subsequent recurrence
- Measurable disease by cross-sectional imaging (RECIST). Patients with bone lesions without a soft tissue component or with bone marrow disease only will be eligible for entry onto the study but will not contribute to the phase II primary outcome measure.
- Medically fit for cytotoxic chemotherapy
- Age ≥4 years and <50 years

Principal exclusion criteria

- Radiotherapy within previous six weeks to target lesion
- Cytotoxic chemotherapy or other investigational medicinal product (IMP) within previous two weeks
- Myeloablative therapy within previous eight weeks
- No previous randomisation into the rEECur trial

Trial Duration

Anticipated time to complete accrual:

- Phase II – 2.2 years
- Phase III – 4 years

Follow-up will be for a minimum of 5 years, or until death if sooner.

Treatment Summary

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

- Topotecan and Cyclophosphamide (TC):
  6 cycles, of 21 days, additional cycles may be given at clinician's discretion..
- Irinotecan and Temozolomide (IT):
  6 cycles, of 21days, additional cycles may be given at clinician's discretion.
- Gemcitabine and Docetaxel (GD):
  6 cycles, of 21 days, additional cycles may be given at clinician's discretion
- High dose Ifosfamide (IFOS):
  4 cycles of 21 days.

Local disease control measures are encouraged where possible but must be delayed until after 4 cycles of chemotherapy.

Stem cell harvesting may be carried out in patients for whom high dose therapy is planned but the first 4 chemotherapy cycles must be given according to the randomised regimen.

Myeloablative therapy may be given at the discretion of the treating physician after 6 cycles of TC, IT or GD, or after 4 cycles of IFOS.

Trial Schema