## Title

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

## Acronym

rEECur

## Trial Design

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

## Objectives

The objective of rEECur is to identify the optimum systemic anticancer regimen for recurrent and refractory Ewing sarcoma based on the balance between efficacy and toxicity.

## Outcome Measures

**Primary outcome measures**

Phase II: For the initial four-way and three-way randomisation, imaging response by CT or MRI after 4 cycles of trial treatment was the primary outcome measure (see below for the definition).

From protocol version 6: EFS is the primary outcome measure and is defined as the time from randomisation until first event (progression, recurrence following response, second malignancy or death without progression or recurrence). For those patients who do not experience an event during the course of the trial, EFS times will be censored at the date of their last available trial assessment.

**Secondary outcome measures**

* Imaging response by CT or MRI after 2, 4 and 6 cycles (not for the IFOS arm) of trial treatment and at the end of trial treatment. Response is measured using the RECIST 1.1 criteria (see Appendix 1). Patients who are not assessable for response – e.g. because of early stopping of treatment or death – will be assumed to be non-responders. Patients without measurable disease will not contribute to this endpoint. CR or PR will constitute an OR. For comparisons involving the CE arm, EFS (as defined above) is the primary outcome measure.
* PFS is defined as the time from randomisation until first event (progression, recurrence following response or death without progression or recurrence). Second malignancy is not classified as an event for PFS. For those patients who do not experience an event during the course of the trial, PFS times will be censored at the date of their last available trial assessment.
* 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.
* Toxicity, defined by CTCAE v4.0.
* PET-CT response after cycle 4.
* QoL will be assessed at baseline and after 2 and 4 cycles using age-appropriate tools:
* ≥18 years: EORTC QLQ-C30 and PedQL™ Generic Core Scales and Cancer Specific Module
* <18 years: PedsQL™ Generic Core Scales and Cancer Specific Module
* Days spent in hospital while on trial chemotherapy treatment.

## Patient Population

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

## Main Eligibility Criteria

**Principal inclusion criteria**

* Histologically proven, Ewing or Ewing-like sarcoma of the bone or soft tissues
* Radiological evidence of disease progression during or after completion of first or any subsequent line of treatment.
* Medically fit to receive trial treatment
* Age ≥2years

**Principal exclusion criteria**

* Radiotherapy to target lesion within previous six weeks
* Cytotoxic chemotherapy or other investigational medicinal product within previous two weeks
* Myeloablative therapy within previous eight weeks
* Previous randomisation in the rEECur trial
* Glomerular filtration rate that would preclude use of ifosfamide or carboplatin

## Trial Duration

Anticipated time to complete accrual:

* Phase II – with 3 arms, estimated 1.6 years to accrue 50 patients per arm, 2.4 years to accrue 75 patients per arm
* Phase III –to accrue 200 patients per arm, estimated 6.25 years with 3 arms, 4.2 years with 2 arms

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

## Treatment Summary

Patients will be randomised to one of the available chemotherapy regimens:

* Topotecan and Cyclophosphamide (TC): 6 cycles, of 21 days, additional cycles at clinician’s discretion
* High dose Ifosfamide (IFOS), 4 cycles, of 21 days, additional cycles at clinician's discretion.
* Carboplatin and Etoposide (CE): 6 cycles of 21 days, additional cycles at clinician’s discretion

Local disease control measures are encouraged where possible. However, these should be delayed if possible until completion of protocol defined treatment (6 cycles of TC or CE, 4 cycles of IFOS).

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, (6 cycles of TC or CE, 4 cycles of IFOS) or as a minimum must be delayed until after the response assessment following cycle 4..

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

## Trial Schema

