# EWING 2008

Published: 12-09-2011
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Primary objectives:Standard Risk R1: in a randomised trial, to examine whether add-on treatment with fenretinide or zoledronic acid, or zoledronic acid plus fenretinide in addition to induction and maintenance chemotherapy improves event-free...

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| **Ethical review** | Approved WMO |
| **Status** | Recruitment stopped |
| **Health condition type** | Skeletal neoplasms malignant and unspecified |
| **Study type** | Observational non invasive |

## Summary

### ID

NL-OMON46854

**Source**
ToetsingOnline

**Brief title**
EWING 2008

### Condition

- Skeletal neoplasms malignant and unspecified

**Synonym**
bone tumour, Ewing sarcoma

**Research involving**
Human

### Sponsors and support

**Primary sponsor:** Stichting Kinderoncologie Nederland
**Source(s) of monetary or material Support:** Ministerie van OC&W

### Intervention

**Keyword:** bone tummour, chemotherapy, Ewing sarcoma, malignancy

## Outcome measures

### Primary outcome

Outcome:

To analyse outcome (EFS, OS) of the entire group of patients.

Quality of life: To describe the quality of life (QOL) longitudinally (i.e. during the course of treatment and thereafter) in patients and to determine the impact on QOL of the additional treatment (R1 and R3) after randomisation for consolidation treatment. Also when R2 patients have to remain consistent with EURO-E.W.I.N.G. 99, the assessment of QOL within the current trial does not violate any of the basic codes of practice defined within this treatment protocol.

Value of Positron Emission Tomography: To examine the value of positron emission tomography in the diagnosis and treatment response of Ewing sarcomas.

Time to Diagnosis: To investigate the impact of the time to diagnosis on the presentation and outcome of the patients.

Add-on studies:

Pharmacogenetic study:

SNP-analysis data correlated with response and outcome data

### Secondary outcome

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## Study description

### Background summary

EWING 2008 is a joint protocol of European and North American Ewing sarcoma study groups. The protocol is aimed at optimising treatment and treatment results of patients with Ewing sarcomas.The EWING 2008 protocol is open to all patients diagnosed with Ewing sarcomas, localised or metastatic, who are considered eligible for neoadjuvant chemotherapy. All patients registered will receive induction chemotherapy consisting of six cycles of vincristine, ifosfamide, doxorubicin and etoposide (VIDE). The decision regarding local therapy must be made following the fifth cycle of induction treatment, with a preference for surgical intervention with or without additional radiotherapy. Preoperative radiotherapy may be considered to improve the operability of otherwise inoperable lesions. In patients with localised disease or with pulmonary metastases, local treatment should be performed following the 6th cycle of VIDE chemotherapy, and should be a complete tumour resection, whenever feasible. Post-operative radiotherapy is determined by the completeness of surgery and the histological response to chemotherapy.

Standard Risk R1
Good responders (R1) (< 10% viable tumour cells) with localised disease are allocated to the standard risk arm and will receive a further eight cycles of chemotherapy composed of vincristine, actinomycin D, and cyclophosphamide (VAC) (females) or ifosfamide instead of cyclophosphamide (VAI) (males). They will be randomised to receive add-on treatment with either fenretinide, zoledronic acid, fenretinide plus zoledronic acid, or no add-on treatment. The fenritinide arm is still closed since the drug is not available and the formulation is still unknown. Therefore an amendment for this part of the study will be handed in later.

High Risk R2 (closed per december 2015)
Poor responders (R2) with localised disease will continue to be randomised as in EURO-E.W.I.N.G. 99 to receive either eight cycles of VAI chemotherapy or high dose treatment with busulfanmelphalan (R2loc). Patients with primary pulmonary metastases are also allocated to continue to be randomised as in EURO-E.W.I.N.G. 99 to receive either eight cycles of VAI chemotherapy or high dose treatment
with busulfan-melphalan (R2pulm).

Very High Risk R3
Patients with disseminated disease, i.e. dissemination to bone and/or other sites and possibly additional pulmonary dissemination (R3), receive six cycles of VIDE induction chemotherapy. Patients are then randomised to either continue with eight cycles of vincristine, actinomycin D and cyclophosphamide (VAC) chemotherapy or high dose treosulfan-melphalan (TreoMel)chemotherapy followed by autologous stem cell reinfusion followed thereafter by eight cycles of VAC chemotherapy. Local therapy in R3 patients is following VIDE induction, whenever feasible prior to high dose therapy (HDT). When long periods of immobilisation following surgery are anticipated, e.g pelvic reconstruction, surgery following HDT may be advisable. Depending on clinical response to induction chemotherapy radiotherapy prior to HDT and surgery may be an option to be considered in such patients. Any delay between VIDE and HDT for reasons of e.g. local treatment must be bridged with VAC cycles. The total number of VAC cycles is not to exceed eight cycles.

Add-on study:
Pharmacogenetics
Genetic polymorfisms of metabolic enzymes active in cytostatic drugs are related in part with outcome of anti-tumour treatment. This study aims to correlate such data for Ewing tumours. On the long run this study might enable taylored therapy for Ewing tumour patient increasing efficacy and reducing toxicity.

Amendment:

Randomisations are halted.. Studie is only a registry of patients receiving conventional therapy

## Study objective

Primary objectives:
Standard Risk R1: in a randomised trial, to examine whether add-on treatment with fenretinide or zoledronic acid, or zoledronic acid plus fenretinide in addition to induction and maintenance chemotherapy improves event-free survival in patients with localised Ewing sarcoma and good histological response or with initial tumour volume <200ml compared to no add on treatment. The fernretinide part of this study will be submitted for assessment at a later stage.
High Risk R2: in a randomised trial, to examine whether high dose chemotherapy using busulfan-melphalan with autologous stem cell reinfusion, compared with standard chemotherapy, improves event-free survival in patients with localised Ewing sarcoma and unfavourable histological response or tumour volume>200ml (R2loc). In patients with pulmonary metastases high dose busulfan-melphalan chemotherapy with autologous stem cell reinfusion is randomised versus standard chemotherapy plus whole lung irradiation (R2pulm).
Very High Risk R3: in a randomised trial, to examine whether the addition of high dose chemotherapy using treosulfanmelphalan followed by autologous stem

cell reinfusion to eight cycles of standard adjuvant chemotherapy, compared to eight cycles of standard adjuvant hemotherapy alone, improves eventfree survival in patients with primary disseminated disease.
Secondary objectives:
Overall survival
R1: To investigate whether add-on fenretinide, zoledronic acid or zoledronic acid plus fenretinide improves overall survival compared to no add on treatment.
R2: To investigate whether high dose chemotherapy with busulfan-melphalan improves overall survival.

Toxicity /Safety: To evaluate short term toxicity and long term toxicity in all risk groups.

Add-on study:
Pharmacogenetics
This study aims to correlate pharmaocogenetic data for Ewing tumours. On the long run this study might enable taylored therapy for Ewing tumour patient increasing efficacy and reducing toxicity.

Amendment:

Randomisations are halted.. Studie is only a registry of patients receiving conventional therapy

**Study design**

Registration: * 45 days after diagnostic biopsy.

Reference pathology: * 60 days after diagnostic biopsy.

Radiol. response evaluation: After VIDE 2 (earliest) or 3 (latest), After VIDE 5 (earliest) or 6 (latest), Prior to high dose chemotherapy, Prior to add-on in R1, i.e. after cycle 11 of chemotherapy, e.g. 6 VIDE + 5 VAI/VAC.
Stem cell harvest: After 3-4 cycles of VIDE.

Surgery for primary tumour: After 6 cycles of VIDE, In R3 patients prior to or after HDT.

Randomisation:
R1 and R2: After 6 cycles of VIDE when histology is available.
R1 and R2: Latest after 6 cycles of VIDE when surgery is not indicated.
R3: Latest after 6 cycles of VIDE.

Surgery for metastases: After 2 cycles of consolidation treatment or after high dose treatment.

Definitive radiotherapy: After 6 cycles of VIDE parallel to consolidation

chemotherapy, In R3 patients prior to or after HDT.
Pre-operative radiotherapy:
Prior to surgery. Post-operative radiotherapy: Concurrently with consolidation chemotherapy. In patients receiving HDT, 8-10 weeks after HDT.

Quality of Life assessment: After VIDE 1 (earliest) or 2(latest), After VIDE 6 (prior to local treatment), After completion of protocol treatment, After 2 years follow-up.

Add on study:
Pharmacogenetic study;
On 10 ml periferal blood SNP analysisi will be done and will be correlated with response and outcoma data.

Immunological study:
NK- and T-cells will be generated on 2 occasions (prior to start of chemotherapy and after finishing treatment). Activity against Ewing cells, will be studied using Ewing cells obtained at the diagnostic biopsy done to confirm the diagnosis of Ewing tumors.

Amendment:

Randomisations are halted.. Studie is only a registry of patients receiving conventional therapy

**Intervention**

R1 patients.
Standard chemotherapy will be given. After local therapy 10 infusion with zoledronic acid will be given.

R2 patients:
The standard seven courses of consolidation therapy are exchanged with high dose chemotherapy and autologous stemcell rescue.

R3 patients
Additional high dose chemotherapy with autologous stem cell rescue.

Add-on study:
no interventions

**Study burden and risks**

Patients will be treated according to normal standard currently used in Ewing sarcoma. In respect to this study the following changes should be mentioned

R1 patients.
Standard chemotherapy will be given. After local therapy 10 infusion with zoledronic acid will be given at standard moments of check-up at the physicians office / hospital. In total this will be add a 5 to 10 hours to the total standard treatment. The medication will be given over an already existing permanent intravenous device, so pain and discomfort will be minimal. Side effects will be low frequent and will be monitored. Benefit can be improvement of survival.
R2 patients: (closed per December 2015)
The standard seven courses of consolidation therapy are exchanged with high dose chemotherapy and autologous stemcell rescue. Total hospitalization in respect to numbers of days of admission will be equal. The side effects of the high dose therapy can be more prononced, however, this can outweigh the side effects during the prolonged period of the seven intensive chemotherapy courses that would have been administered. Benefit can be an improved survival.
R3 patients
Additional high dose chemotherapy with autologous stem cell rescue. Risks are related to the well known side effects of intensive chemotherapy. Benefit can be an improved survival in these patients with otherwise a very poor outcome.

Add-on
Pharmacogenetic study:
10 ml blood sampling at the moment of regular blood sampling

Amendment:

Randomisations are halted.. Studie is only a registry of patients receiving conventional therapy

## Contacts

**Public**
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**Scientific**
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# Trial sites

## Listed location countries

Netherlands

# Eligibility criteria

**Age**
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Children (2-11 years)
Elderly (65 years and older)

## Inclusion criteria

- Histologically confirmed Ewing tumour of bone or soft tissue. ;- Either sex, age >48 months (for GPOH patients) and <50 years at the date of diagnostic biopsy.;- Registration within 45 days after diagnostic biopsy/surgery.;- Start of chemotherapy within 45 days after diagnostic biopsy/surgery.;- Informed consent signed prior to study entry. ;- Lansky or Karnofsky score > 50%, may be modified for handicapped patients.;- Haemoglobin > 8 g/dl, Platelets > 80.000/µl, WBC > 2000/µl.;- LVSF > 40%, FS >28%.

## Exclusion criteria

- More than one cycle of chemotherapy prior to registration;- Second malignancy;- Pregnancy and lactation;- Any other medical, psychiatric, or social condition incompatible with the protocol treatment

# Study design

## Design

**Study type:** Observational non invasive

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| Masking: | Open (masking not used) |
| Control: | Uncontrolled |

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| Primary purpose: | Other |

### Recruitment

NL

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| Recruitment status: | Recruitment stopped |
| Start date (anticipated): | 18-10-2011 |
| Enrollment: | 87 |
| Type: | Actual |

## Ethics review

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| Approved WMO Date: | 12-09-2011 |
| Application type: | First submission |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 04-09-2012 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 09-04-2013 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 14-11-2013 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 17-06-2015 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 05-08-2015 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |
| Approved WMO | |

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|---|---|
| Date: | 10-06-2016 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 08-07-2016 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 04-09-2018 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 25-09-2018 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |

# Study registrations

## Followed up by the following (possibly more current) registration

No registrations found.

## Other (possibly less up-to-date) registrations in this register

No registrations found.

## In other registers

| Register | ID |
|---|---|
| EudraCT | EUCTR2008-003658-13-NL |
| CCMO | NL31313.018.11 |