Clinical trial results:
EWING 2008

Summary

EudraCT number	2008-003658-13
Trial protocol	DE AT BE NL SE HU FI LT PL
Global end of trial date	30 June 2019

Results information

Result version number	v1 (current)
This version publication date	12 January 2020
First version publication date	12 January 2020

Trial information

Trial identification

Sponsor protocol code	EWING2008

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	ClinicalTrials.gov: NCT00824083

Notes:

Sponsors

Sponsor organisation name	Universitätsklinikum Münster
Sponsor organisation address	Albert-Schweitzer-Campus 1, Gebäude D5, Münster, Germany, 48149
Public contact	EWING 2008 Trial Office, Universitätsklinikum Münster, 49 2017238082, ewing@uk-essen.de
Scientific contact	EWING 2008 Trial Office, Universitätsklinikum Münster, 49 2017238082, ewing@uk-essen.de

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	30 June 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 June 2019
Global end of trial reached?	Yes
Global end of trial date	30 June 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Randomised trial to test for superiority regarding event-free survival (EFS)
Standard Risk R1: in localised Ewing tumour (ET) with good histological response or initial tumour volume <200ml: fenretinide or bisphosphonates or bisphosphonates+fenretinide add-on to induction and maintenance chemotherapy versus no add-on treatment.
High Risk R2: in localised Ewing tumour with unfavourable histological response or tumour volume>200ml (R2loc): busulfan/melphalan high dose chemotherapy (HDT) and autologous stem cell reinfusion versus standard chemotherapy.
In pulmonary metastases: busulfan/melphalan HDT and autologous stem cell reinfusion (SCT) versus standard chemotherapy plus whole lung irradiation (R2pulm).
Very High Risk R3: in primary disseminated disease: treosulfan-melphalan HDT and autologous SCT add-on to 8 cycles of standard adjuvant chemotherapy versus 8 cycles of standard adjuvant chemotherapy alone.

Protection of trial subjects:

This study is conducted in accordance with applicable laws and regulations including, but not limited to, the ethical principles that have their origins in the Declaration of Helsinki and the International Conference on Harmonisation Guideline for Good Clinical Practice (GCP). Before any subjects are enrolled competent authorities and ethics committees concerned must grant authorisation and approval of this clinical trial. Before any procedures specified in this protocol are performed, the subject or subject’s parent(s)/legal guardian must sign and date the approved informed consent form according to requirements stated in national law.

Background therapy:

Sufficient hydration (~ 2-3 L/m²/d), with appropriate electrolyte supplementation, during chemotherapy.
Antiemetic therapy was administered according to institutional policy, e.g., ondansetron 5 mg/m² BSA (maximum single dose 8 mg) orally or IV every 12 hours for 5 days.
Radiation of Blood Products: Due to the risk of graft-versus-host reactions in patients under chemotherapy, especially in case of high-dose therapy, all blood products (except fresh frozen plasma) were irradiated with at least 20 Gy prior to transfusion, according to national policies. The use of leukocyte filters for leukocyte depletion (CMV negativity) was advised.
Red blood cells: Haemoglobin should be kept above 6 g/dl (haematocrit above 20 %).
Platelets: Platelet substitution was advised when platelets are <10,000/µL or with clinical evidence of bleeding.
Central Lines: The use of central lines was strongly recommended. In HDT patients, multi-lumen central lines should be used for PBPC sampling and supportive care.
Pneumocystis carinii prophylaxis according to the recommendations of the national groups was mandatory.
Treatment of Infections (especially neutropenic infection) according to accepted general principles of supportive care.

Evidence for comparator:

EWING 2008 is a phase 3, open label, multi-centre, randomised controlled trial of international study groups with the intention of optimising treatment and treatment results in patients with localised and advanced Ewing sarcomas. The primary objective was to assess whether either of the randomised treatments is superior regarding 3-year event-free survival. The treatment was stratified according to prognostic factors as determined by previous studies. All patients received VIDE chemotherapy as induction treatment. Disease assessment was performed prior to treatment and after the 2nd (latest 3rd) and 5th (latest 6th) cycle of VIDE chemotherapy. Depending on the presentation at the time of diagnosis and on the histological response to induction chemotherapy, patients were stratified into to

the risk groups.

Actual start date of recruitment	01 October 2009
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Safety
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 81
Country: Number of subjects enrolled	Poland: 8
Country: Number of subjects enrolled	Sweden: 19
Country: Number of subjects enrolled	Austria: 57
Country: Number of subjects enrolled	Belgium: 38
Country: Number of subjects enrolled	Czech Republic: 41
Country: Number of subjects enrolled	Finland: 7
Country: Number of subjects enrolled	Germany: 585
Country: Number of subjects enrolled	Hungary: 21
Country: Number of subjects enrolled	Lithuania: 1
Country: Number of subjects enrolled	Switzerland: 19
Country: Number of subjects enrolled	Australia: 30
Worldwide total number of subjects	907
EEA total number of subjects	858

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	251
Adolescents (12-17 years)	399
Adults (18-64 years)	257
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The patients were recruited from 120 trial sites in 12 countries. The recruitment period was from October 2009 to March 2018.

Pre-assignment

Screening details:

The study included patients with histologically confirmed Ewing sarcoma of bone or soft tissue, either sex and age > 48 months (for Germany) and < 50 years at the date of diagnostic biopsy.

Pre-assignment period milestones

Number of subjects started	907
Number of subjects completed	441

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Other: 85
Reason: Number of subjects	Medical contraindication/toxicity: 47
Reason: Number of subjects	Organisational reasons: 40
Reason: Number of subjects	Progress: 20
Reason: Number of subjects	Not available: 2
Reason: Number of subjects	Consent withdrawn by patient/parents: 172
Reason: Number of subjects	Physician decision: 100

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	R1 Add-on

Arm description:

Patients with localised disease and good histological response at surgery after induction chemotherapy and patients with initial surgery or in whom surgery was not feasible and who have small tumours < 200 mL at diagnosis were included in the risk group Standard Risk R1.
Patients who were randomized into the R1 Add-on arm received 6 courses of vincristine, ifosfamide, doxorubicin, and etoposide (VIDE) as intensive induction chemotherapy followed by 8 cycles of either VAI (vincristine, actinomycin-D, ifosfamide) or VAC (vincristine, actinomycin-D, cyclophosphamide). In addition to induction and maintenance chemotherapy, patients were treated with zoledronic acid (Add-on treatment).

Arm type	Experimental
Investigational medicinal product name	Vincristine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

VIDE chemotherapy (cycles 1-6 at 21-day intervals): Vincristine is given on day 1 in a dose of 1.5 mg/m²/d per cycle.

VAI chemotherapy (cycles 7-14 at 21-day intervals): Vincristine is given on day 1 in a dose of 1.5 mg/m²/d per cycle.
VAC chemotherapy (cycles 7-14 at 21-day intervals): Vincristine is given on day 1 in a dose of 1.5 mg/m²/d per cycle.

Investigational medicinal product name	Ifosfamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

VIDE chemotherapy (cycles 1-6 at 21-day intervals): Ifosfamide is given on day 1,2 and 3 in a dose of 3.0 g/m²/d per cycle.
VAI chemotherapy (cycles 7-14 at 21-day intervals): Ifosfamide is given on day 1 and 2 in a dose of 3.0 g/m²/d per cycle.

Investigational medicinal product name	Doxorubicin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

VIDE chemotherapy (cycles 1-6 at 21-day intervals): Doxorubicin is given on day 1, 2 an 3 in a dose of 20 mg/m²/d per cycle.

Investigational medicinal product name	Etoposide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

VIDE chemotherapy (cycles 1-6 at 21-day intervals): Etoposide is given on day 1, 2 an 3 in a dose of 150 mg/m²/d per cycle.

Investigational medicinal product name	Actinomycin D
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for injection
Routes of administration	Intravenous use

Dosage and administration details:

VAI chemotherapy (cycles 7-14 at 21-day intervals): Actinomycin D is given on day 1 and 2 in a dose of 1.5 mg/m²/d per cycle.
VAC chemotherapy (cycles 7-14 at 21-day intervals): Actinomycin D is given on day 1 and 2 in a dose of 1.5 mg/m²/d per cycle.

Investigational medicinal product name	Cyclophosphamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

VAC chemotherapy (cycles 7-14 at 21-day intervals):Cyclophosphamide is given on day 1 in a dose of 1500 mg/m²/d per cycle.

Investigational medicinal product name	Zoledronic acid
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for injection
Routes of administration	Intracavernous use

Dosage and administration details:

Patients randomised for zoledronic acid received zoledronic acid at 28-day intervals beginning with cycle 6 of VAC/VAI consolidation chemotherapy (cycle 12 from start of chemotherapy) for a maximum of nine

cycles. Patients < 18 years received 0.05 mg/kg BW by IV infusion 30 min-1 h. In patients >= 18 years zoledronic acid was dosed according to body weight: Patients > 40kg received 4 mg by IV infusion 30 min–1 h. Patients 20-40 kg received 2 mg by IV infusion 30 min–1 h.

Arm title	R1 No Add-on

Arm description:

Patients with localised disease and good histological response at surgery after induction chemotherapy and patients with initial surgery or in whom surgery was not feasible and who have small tumours < 200 mL at diagnosis were included in the risk group Standard Risk R1.
Patients who were randomized into the R1 No Add-on arm received only 6 courses of vincristine, ifosfamide, doxorubicin, and etoposide (VIDE) as intensive induction chemotherapy followed by 8 cycles of either VAI (vincristine, actinomycin-D, Ifosfamide) or VAC (vincristine, actinomycin-D, Cyclophosphamide). No additional treatment with zoledronic acid was administered to the patients (No Add-on treatment).

Arm type	Active comparator
Investigational medicinal product name	Vincristine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

VIDE chemotherapy (cycles 1-6 at 21-day intervals): Vincristine is given on day 1 in a dose of 1.5 mg/m²/d per cycle.
VAI chemotherapy (cycles 7-14 at 21-day intervals): Vincristine is given on day 1 in a dose of 1.5 mg/m²/d per cycle.
VAC chemotherapy (cycles 7-14 at 21-day intervals): Vincristine is given on day 1 in a dose of 1.5 mg/m²/d per cycle.

Investigational medicinal product name	Ifosfamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

VIDE chemotherapy (cycles 1-6 at 21-day intervals): Ifosfamide is given on day 1,2 and 3 in a dose of 3.0 g/m²/d per cycle.
VAI chemotherapy (cycles 7-14 at 21-day intervals): Ifosfamide is given on day 1 and 2 in a dose of 3.0 g/m²/d per cycle.

Investigational medicinal product name	Doxorubicin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

VIDE chemotherapy (cycles 1-6 at 21-day intervals): Doxorubicin is given on day 1, 2 an 3 in a dose of 20 mg/m²/d per cycle.

Investigational medicinal product name	Etoposide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

VIDE chemotherapy (cycles 1-6 at 21-day intervals): Etoposide is given on day 1, 2 an 3 in a dose of 150 mg/m²/d per cycle.

Investigational medicinal product name	Actinomycin D
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for injection
Routes of administration	Intravenous use

Dosage and administration details:

VAI chemotherapy (cycles 7-14 at 21-day intervals): Actinomycin D is given on day 1 and 2 in a dose of 1.5 mg/m²/d per cycle.
VAC chemotherapy (cycles 7-14 at 21-day intervals): Actinomycin D is given on day 1 and 2 in a dose of 1.5 mg/m²/d per cycle.

Investigational medicinal product name	Cyclophosphamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

VAC chemotherapy (cycles 7-14 at 21-day intervals):Cyclophosphamide is given on day 1 in a dose of 1500 mg/m²/d per cycle.

Arm title	R2loc VAI

Arm description:

Patients with localised disease and poor histological response at surgery after induction chemotherapy and patients with initial surgery or in whom surgery was not feasible and who have large tumours > 200 mL at diagnosis were included in the risk group High Risk localised disease R2loc.
Patients who were randomized into the R2loc VAI arm received 6 courses of vincristine, ifosfamide, doxorubicin, and etoposide (VIDE) as intensive induction chemotherapy followed by 8 cycles of standard chemotherapy VAI (vincristine, actinomycin-D, ifosfamide).

Arm type	Active comparator
Investigational medicinal product name	Vincristine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

VIDE chemotherapy (cycles 1-6 at 21-day intervals): Vincristine is given on day 1 in a dose of 1.5 mg/m²/d per cycle.
VAI chemotherapy (cycles 7-14 at 21-day intervals): Vincristine is given on day 1 in a dose of 1.5 mg/m²/d per cycle.

Investigational medicinal product name	Ifosfamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

VIDE chemotherapy (cycles 1-6 at 21-day intervals): Ifosfamide is given on day 1,2 and 3 in a dose of 3.0 g/m²/d per cycle.
VAI chemotherapy (cycles 7-14 at 21-day intervals): Ifosfamide is given on day 1 and 2 in a dose of 3.0 g/m²/d per cycle.

Investigational medicinal product name	Doxorubicin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

VIDE chemotherapy (cycles 1-6 at 21-day intervals): Doxorubicin is given on day 1, 2 an 3 in a dose of 20 mg/m²/d per cycle.

Investigational medicinal product name	Etoposide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

VIDE chemotherapy (cycles 1-6 at 21-day intervals): Etoposide is given on day 1, 2 an 3 in a dose of 150 mg/m²/d per cycle.

Investigational medicinal product name	Actinomycin D
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for injection
Routes of administration	Intravenous use

Dosage and administration details:

VAI chemotherapy (cycles 7-14 at 21-day intervals): Actinomycin D is given onday 1 and 2 in a dose of 1.5 mg/m²/d per cycle.

Arm title	R2loc Bu-Mel

Arm description:

Patients with localised disease and poor histological response at surgery after induction chemotherapy and patients with initial surgery or in whom surgery was not feasible and who have large tumours > 200 mL at diagnosis were included in the risk group High Risk localised disease R2loc.
Patients who were randomized into the R2loc Bu-Mel arm received 6 courses of vincristine, ifosfamide, doxorubicin, and etoposide (VIDE) as intensive induction chemotherapy followed by high-dose chemotherapy using busulfan-melphalan with autologous stem cell reinfusion.

Arm type	Experimental
Investigational medicinal product name	Vincristine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

VIDE chemotherapy (cycles 1-6 at 21-day intervals): Vincristine is given on day 1 in a dose of 1.5 mg/m²/d per cycle.

Investigational medicinal product name	Ifosfamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

VIDE chemotherapy (cycles 1-6 at 21-day intervals): Ifosfamide is given on day 1,2 and 3 in a dose of 3.0 g/m²/d per cycle.

Investigational medicinal product name	Doxorubicin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

VIDE chemotherapy (cycles 1-6 at 21-day intervals): Doxorubicin is given on day 1, 2 an 3 in a dose of 20 mg/m²/d per cycle.

Investigational medicinal product name	Etoposide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

VIDE chemotherapy (cycles 1-6 at 21-day intervals): Etoposide is given on day 1, 2 an 3 in a dose of 150 mg/m²/d per cycle.

Investigational medicinal product name	Busulfan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Busulfan–Melphalan High-Dose Chemotherapy with autologous stem cell reinfusion (cycle 8): Busulfan is given on day -6, -5, -4 and -3 before Stem cell reinfusion.
Adults: 0.8 mg/kg body weight (BW), children and adolescents: <9 kg = 1 mg/kg BW, 9-<16 kg = 1.2 mg/kg BW, 16-23 kg = 1.1 mg/kg BW, >23-34 kg = 0.95 mg/kg BW, >34 kg = 0.8 mg/kg BW.

Investigational medicinal product name	Melphalan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Busulfan–Melphalan High-Dose Chemotherapy with autologous stem cell reinfusion (cycle 8): Melphalan is given on day -2 before Stem cell reinfusion (140 mg/m² IV infusion, 30 min.).

Investigational medicinal product name	Adult haematopoietic stem cells
Investigational medicinal product code	
Other name	Autologous adult haematopoietic stem cells
Pharmaceutical forms	Suspension for injection
Routes of administration	Intravenous use

Dosage and administration details:

Busulfan–Melphalan High-Dose Chemotherapy with autologous stem cell reinfusion (cycle 8): Stem cell reinfusion (min. 3 x 1000000/kg CD 34+) after busulfan–melphalan Treatment (d 0).

Arm title	R2pulm VAI

Arm description:

Patients with a Ewing sarcoma metastatic to the lungs and/or pleura, but not to any other sites, at the time of diagnosis were included in the risk group High Risk primary lung metastases R2pulm.
Patients who were randomized into the R2pulm VAI arm received 6 courses of vincristine, ifosfamide, doxorubicin, and etoposide (VIDE) as intensive induction chemotherapy followed by 8 cycles of standard chemotherapy VAI (vincristine, actinomycin-D, ifosfamide) plus whole lung irradiation.

Arm type	Active comparator
Investigational medicinal product name	Vincristine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

VIDE chemotherapy (cycles 1-6 at 21-day intervals): Vincristine is given on day 1 in a dose of 1.5 mg/m²/d per cycle.
VAI chemotherapy (cycles 7-14 at 21-day intervals): Vincristine is given on day 1 in a dose of 1.5 mg/m²/d per cycle.

Investigational medicinal product name	Ifosfamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

VIDE chemotherapy (cycles 1-6 at 21-day intervals): Ifosfamide is given on day 1,2 and 3 in a dose of 3.0 g/m²/d per cycle.
VAI chemotherapy (cycles 7-14 at 21-day intervals): Ifosfamide is given on day 1 and 2 in a dose of 3.0

g/m²/d per cycle.

Investigational medicinal product name	Doxorubicin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

VIDE chemotherapy (cycles 1-6 at 21-day intervals): Doxorubicin is given on day 1, 2 an 3 in a dose of 20 mg/m²/d per cycle.

Investigational medicinal product name	Etoposide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

VIDE chemotherapy (cycles 1-6 at 21-day intervals): Etoposide is given on day 1, 2 an 3 in a dose of 150 mg/m²/d per cycle.

Investigational medicinal product name	Actinomycin D
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for injection
Routes of administration	Intravenous use

Dosage and administration details:

VAI chemotherapy (cycles 7-14 at 21-day intervals): Actinomycin D is given on day 1 and 2 in a dose of 1.5 mg/m²/d per cycle.

Arm title	R2pulm Bu-Mel

Arm description:

Patients with a Ewing sarcoma metastatic to the lungs and/or pleura, but not to any other sites, at the time of diagnosis were included in the risk group High Risk primary lung metastases R2pulm.
Patients who were randomized into the R2pulm Bu-Mel arm received 6 courses of vincristine, ifosfamide, doxorubicin, and etoposide (VIDE) as intensive induction chemotherapy followed by high dose busulfan-melphalan chemotherapy with autologous stem cell reinfusion.

Arm type	Experimental
Investigational medicinal product name	Vincristine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

VIDE chemotherapy (cycles 1-6 at 21-day intervals): Vincristine is given on day 1 in a dose of 1.5 mg/m²/d per cycle.

Investigational medicinal product name	Ifosfamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

VIDE chemotherapy (cycles 1-6 at 21-day intervals): Ifosfamide is given on day 1,2 and 3 in a dose of 3.0 g/m²/d per cycle.

Investigational medicinal product name	Doxorubicin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

VIDE chemotherapy (cycles 1-6 at 21-day intervals): Doxorubicin is given on day 1, 2 an 3 in a dose of 20 mg/m²/d per cycle.

Investigational medicinal product name	Etoposide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

VIDE chemotherapy (cycles 1-6 at 21-day intervals): Etoposide is given on day 1, 2 an 3 in a dose of 150 mg/m²/d per cycle.

Investigational medicinal product name	Busulfan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Busulfan–Melphalan High-Dose Chemotherapy with autologous stem cell reinfusion (cycle 8): Busulfan is given on day -6, -5, -4 and -3 before Stem cell reinfusion.
Adults: 0.8 mg/kg body weight (BW), children and adolescents: <9 kg = 1 mg/kg BW, 9-<16 kg = 1.2 mg/kg BW, 16-23 kg = 1.1 mg/kg BW, >23-34 kg = 0.95 mg/kg BW, >34 kg = 0.8 mg/kg BW.

Investigational medicinal product name	Melphalan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Busulfan–Melphalan High-Dose Chemotherapy with autologous stem cell reinfusion (cycle 8): Melphalan is given on day -2 before Stem cell reinfusion (140 mg/m² IV infusion, 30 min.).

Investigational medicinal product name	Adult haematopoietic stem cells
Investigational medicinal product code	
Other name	Autologous adult haematopoietic stem cells
Pharmaceutical forms	Suspension for injection
Routes of administration	Intravenous use

Dosage and administration details:

Busulfan–Melphalan High-Dose Chemotherapy with autologous stem cell reinfusion (cycle 8): Stem cell reinfusion (min. 3 x 1000000/kg CD 34+) after busulfan–melphalan Treatment (d 0).

Arm title	R3 VAC

Arm description:

Patients with metastatic disease not confined to the lungs and/or pleura, i.e. patients with bone metastases, bone marrow metastases or other metastases (e.g. lymph nodes, liver, CNS, etc) with and without additional pulmonary metastases at the time of diagnosis were included in the risk group Very High Risk R3.
Patients who were randomized into the R3 VAC arm received 6 courses of vincristine, ifosfamide, doxorubicin, and etoposide (VIDE) as intensive induction chemotherapy followed by 8 cycles of VAC (vincristine, actinomycin-D, cyclophosphamide).

Arm type	Active comparator
Investigational medicinal product name	Vincristine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

VIDE chemotherapy (cycles 1-6 at 21-day intervals): Vincristine is given on day 1 in a dose of 1.5 mg/m²/d per cycle.
VAC chemotherapy (cycles 7-14 at 21-day intervals): Vincristine is given on day 1 in a dose of 1.5

mg/m²/d per cycle.

Investigational medicinal product name	Ifosfamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

VIDE chemotherapy (cycles 1-6 at 21-day intervals): Ifosfamide is given on day 1,2 and 3 in a dose of 3.0 g/m²/d per cycle.

Investigational medicinal product name	Doxorubicin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

VIDE chemotherapy (cycles 1-6 at 21-day intervals): Doxorubicin is given on day 1, 2 an 3 in a dose of 20 mg/m²/d per cycle.

Investigational medicinal product name	Etoposide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

VIDE chemotherapy (cycles 1-6 at 21-day intervals): Etoposide is given on day 1, 2 an 3 in a dose of 150 mg/m²/d per cycle.

Investigational medicinal product name	Actinomycin D
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for injection
Routes of administration	Intravenous use

Dosage and administration details:

VAC chemotherapy (cycles 7-14 at 21-day intervals): Actinomycin D is given on day 1 and 2 in a dose of 1.5 mg/m²/d per cycle.

Investigational medicinal product name	Cyclophosphamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

VAC chemotherapy (cycles 7-14 at 21-day intervals):Cyclophosphamide is given on day 1 in a dose of 1500 mg/m²/d per cycle.

Arm title	R3 Treo-Mel

Arm description:

Patients with metastatic disease not confined to the lungs and/or pleura, i.e. patients with bone metastases, bone marrow metastases or other metastases (e.g. lymph nodes, liver, CNS, etc) with and without additional pulmonary metastases at the time of diagnosis were included in the risk group Very High Risk R3.
Patients who were randomized into the R3 Treo-Mel arm received 6 courses of vincristine, ifosfamide, doxorubicin, and etoposide (VIDE) as intensive induction chemotherapy followed by high dose chemotherapy using treosulfan-melphalan and autologous stem cell reinfusion.

Arm type	Experimental

Investigational medicinal product name	Vincristine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

VIDE chemotherapy (cycles 1-6 at 21-day intervals): Vincristine is given on day 1 in a dose of 1.5 mg/m²/d per cycle.

Investigational medicinal product name	Ifosfamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

VIDE chemotherapy (cycles 1-6 at 21-day intervals): Ifosfamide is given on day 1,2 and 3 in a dose of 3.0 g/m²/d per cycle.

Investigational medicinal product name	Doxorubicin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

VIDE chemotherapy (cycles 1-6 at 21-day intervals): Doxorubicin is given on day 1, 2 an 3 in a dose of 20 mg/m²/d per cycle.

Investigational medicinal product name	Etoposide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

VIDE chemotherapy (cycles 1-6 at 21-day intervals): Etoposide is given on day 1, 2 an 3 in a dose of 150 mg/m²/d per cycle.

Investigational medicinal product name	Treosulfan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Treosulfan–Melphalan High-Dose Chemotherapy with autologous stem cell reinfusion: Treosulfan (12 g/m²/dose IV infusion, 2 hours) is given on day -5, -4 and -3 before Stem cell reinfusion.

Investigational medicinal product name	Melphalan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Treosulfan–Melphalan High-Dose Chemotherapy with autologous stem cell reinfusion (cycle 8): Melphalan is given on day -2 before Stem cell reinfusion (140 mg/m² IV infusion, 30 min.).

Investigational medicinal product name	Adult haematopoietic stem cells
Investigational medicinal product code	
Other name	Autologous adult haematopoietic stem cells
Pharmaceutical forms	Suspension for injection
Routes of administration	Intravenous use

Dosage and administration details:

Treosulfan–Melphalan High-Dose Chemotherapy with autologous stem cell reinfusion (cycle 8): Stem cell reinfusion (min. 3 x 1000000/kg CD 34+) after treosulfan–melphalan Treatment (d 0).

Number of subjects in period 1[1]	R1 Add-on	R1 No Add-on	R2loc VAI
Started	142	142	12
Completed	101	135	11
Not completed	41	7	1
Protocol deviation	41	7	1

Number of subjects in period 1[1]	R2loc Bu-Mel	R2pulm VAI	R2pulm Bu-Mel
Started	14	11	11
Completed	7	10	8
Not completed	7	1	3
Protocol deviation	7	1	3

Number of subjects in period 1[1]	R3 VAC	R3 Treo-Mel
Started	54	55
Completed	46	41
Not completed	8	14
Protocol deviation	8	14

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 907 patients were eligible for the study and therefore study patients. Since 466 patients were not eligible for randomization or could not be randomized, only 441 started the randomized study. These patients are reported in the baseline period.

Reporting groups

Reporting group title	R1 Add-on

Reporting group description:

Patients with localised disease and good histological response at surgery after induction chemotherapy and patients with initial surgery or in whom surgery was not feasible and who have small tumours < 200 mL at diagnosis were included in the risk group Standard Risk R1.
Patients who were randomized into the R1 Add-on arm received 6 courses of vincristine, ifosfamide, doxorubicin, and etoposide (VIDE) as intensive induction chemotherapy followed by 8 cycles of either VAI (vincristine, actinomycin-D, ifosfamide) or VAC (vincristine, actinomycin-D, cyclophosphamide). In addition to induction and maintenance chemotherapy, patients were treated with zoledronic acid (Add-on treatment).

Reporting group title	R1 No Add-on

Reporting group description:

Patients with localised disease and good histological response at surgery after induction chemotherapy and patients with initial surgery or in whom surgery was not feasible and who have small tumours < 200 mL at diagnosis were included in the risk group Standard Risk R1.
Patients who were randomized into the R1 No Add-on arm received only 6 courses of vincristine, ifosfamide, doxorubicin, and etoposide (VIDE) as intensive induction chemotherapy followed by 8 cycles of either VAI (vincristine, actinomycin-D, Ifosfamide) or VAC (vincristine, actinomycin-D, Cyclophosphamide). No additional treatment with zoledronic acid was administered to the patients (No Add-on treatment).

Reporting group title	R2loc VAI

Reporting group description:

Patients with localised disease and poor histological response at surgery after induction chemotherapy and patients with initial surgery or in whom surgery was not feasible and who have large tumours > 200 mL at diagnosis were included in the risk group High Risk localised disease R2loc.
Patients who were randomized into the R2loc VAI arm received 6 courses of vincristine, ifosfamide, doxorubicin, and etoposide (VIDE) as intensive induction chemotherapy followed by 8 cycles of standard chemotherapy VAI (vincristine, actinomycin-D, ifosfamide).

Reporting group title	R2loc Bu-Mel

Reporting group description:

Patients with localised disease and poor histological response at surgery after induction chemotherapy and patients with initial surgery or in whom surgery was not feasible and who have large tumours > 200 mL at diagnosis were included in the risk group High Risk localised disease R2loc.
Patients who were randomized into the R2loc Bu-Mel arm received 6 courses of vincristine, ifosfamide, doxorubicin, and etoposide (VIDE) as intensive induction chemotherapy followed by high-dose chemotherapy using busulfan-melphalan with autologous stem cell reinfusion.

Reporting group title	R2pulm VAI

Reporting group description:

Patients with a Ewing sarcoma metastatic to the lungs and/or pleura, but not to any other sites, at the time of diagnosis were included in the risk group High Risk primary lung metastases R2pulm.
Patients who were randomized into the R2pulm VAI arm received 6 courses of vincristine, ifosfamide, doxorubicin, and etoposide (VIDE) as intensive induction chemotherapy followed by 8 cycles of standard chemotherapy VAI (vincristine, actinomycin-D, ifosfamide) plus whole lung irradiation.

Reporting group title	R2pulm Bu-Mel

Reporting group description:

Patients with a Ewing sarcoma metastatic to the lungs and/or pleura, but not to any other sites, at the time of diagnosis were included in the risk group High Risk primary lung metastases R2pulm.
Patients who were randomized into the R2pulm Bu-Mel arm received 6 courses of vincristine, ifosfamide, doxorubicin, and etoposide (VIDE) as intensive induction chemotherapy followed by high dose busulfan-melphalan chemotherapy with autologous stem cell reinfusion.

Reporting group title	R3 VAC

Reporting group description:

Patients with metastatic disease not confined to the lungs and/or pleura, i.e. patients with bone metastases, bone marrow metastases or other metastases (e.g. lymph nodes, liver, CNS, etc) with and without additional pulmonary metastases at the time of diagnosis were included in the risk group Very High Risk R3.
Patients who were randomized into the R3 VAC arm received 6 courses of vincristine, ifosfamide, doxorubicin, and etoposide (VIDE) as intensive induction chemotherapy followed by 8 cycles of VAC

(vincristine, actinomycin-D, cyclophosphamide).

Reporting group title	R3 Treo-Mel

Reporting group description:

Patients with metastatic disease not confined to the lungs and/or pleura, i.e. patients with bone metastases, bone marrow metastases or other metastases (e.g. lymph nodes, liver, CNS, etc) with and without additional pulmonary metastases at the time of diagnosis were included in the risk group Very High Risk R3.
Patients who were randomized into the R3 Treo-Mel arm received 6 courses of vincristine, ifosfamide, doxorubicin, and etoposide (VIDE) as intensive induction chemotherapy followed by high dose chemotherapy using treosulfan-melphalan and autologous stem cell reinfusion.

Reporting group values	R1 Add-on	R1 No Add-on	R2loc VAI
Number of subjects	142	142	12
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	59	48	1
Adolescents (12-17 years)	50	66	6
Adults (18-64 years)	33	28	5
From 65-84 years	0	0	0
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	60	66	5
Male	82	76	7

Reporting group values	R2loc Bu-Mel	R2pulm VAI	R2pulm Bu-Mel
Number of subjects	14	11	11
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	4	0	3
Adolescents (12-17 years)	3	5	5
Adults (18-64 years)	7	6	3
From 65-84 years	0	0	0
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	4	3	3
Male	10	8	8

Reporting group values	R3 VAC	R3 Treo-Mel	Total
Number of subjects	54	55	441

Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	12	13	140
Adolescents (12-17 years)	24	23	182
Adults (18-64 years)	18	19	119
From 65-84 years	0	0	0
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	31	24	196
Male	23	31	245

End points

End points reporting groups

Reporting group title	R1 Add-on

Reporting group description:

Patients with localised disease and good histological response at surgery after induction chemotherapy and patients with initial surgery or in whom surgery was not feasible and who have small tumours < 200 mL at diagnosis were included in the risk group Standard Risk R1.
Patients who were randomized into the R1 Add-on arm received 6 courses of vincristine, ifosfamide, doxorubicin, and etoposide (VIDE) as intensive induction chemotherapy followed by 8 cycles of either VAI (vincristine, actinomycin-D, ifosfamide) or VAC (vincristine, actinomycin-D, cyclophosphamide). In addition to induction and maintenance chemotherapy, patients were treated with zoledronic acid (Add-on treatment).

Reporting group title	R1 No Add-on

Reporting group description:

Patients with localised disease and good histological response at surgery after induction chemotherapy and patients with initial surgery or in whom surgery was not feasible and who have small tumours < 200 mL at diagnosis were included in the risk group Standard Risk R1.
Patients who were randomized into the R1 No Add-on arm received only 6 courses of vincristine, ifosfamide, doxorubicin, and etoposide (VIDE) as intensive induction chemotherapy followed by 8 cycles of either VAI (vincristine, actinomycin-D, Ifosfamide) or VAC (vincristine, actinomycin-D, Cyclophosphamide). No additional treatment with zoledronic acid was administered to the patients (No Add-on treatment).

Reporting group title	R2loc VAI

Reporting group description:

Patients with localised disease and poor histological response at surgery after induction chemotherapy and patients with initial surgery or in whom surgery was not feasible and who have large tumours > 200 mL at diagnosis were included in the risk group High Risk localised disease R2loc.
Patients who were randomized into the R2loc VAI arm received 6 courses of vincristine, ifosfamide, doxorubicin, and etoposide (VIDE) as intensive induction chemotherapy followed by 8 cycles of standard chemotherapy VAI (vincristine, actinomycin-D, ifosfamide).

Reporting group title	R2loc Bu-Mel

Reporting group description:

Patients with localised disease and poor histological response at surgery after induction chemotherapy and patients with initial surgery or in whom surgery was not feasible and who have large tumours > 200 mL at diagnosis were included in the risk group High Risk localised disease R2loc.
Patients who were randomized into the R2loc Bu-Mel arm received 6 courses of vincristine, ifosfamide, doxorubicin, and etoposide (VIDE) as intensive induction chemotherapy followed by high-dose chemotherapy using busulfan-melphalan with autologous stem cell reinfusion.

Reporting group title	R2pulm VAI

Reporting group description:

Patients with a Ewing sarcoma metastatic to the lungs and/or pleura, but not to any other sites, at the time of diagnosis were included in the risk group High Risk primary lung metastases R2pulm.
Patients who were randomized into the R2pulm VAI arm received 6 courses of vincristine, ifosfamide, doxorubicin, and etoposide (VIDE) as intensive induction chemotherapy followed by 8 cycles of standard chemotherapy VAI (vincristine, actinomycin-D, ifosfamide) plus whole lung irradiation.

Reporting group title	R2pulm Bu-Mel

Reporting group description:

Patients with a Ewing sarcoma metastatic to the lungs and/or pleura, but not to any other sites, at the time of diagnosis were included in the risk group High Risk primary lung metastases R2pulm.
Patients who were randomized into the R2pulm Bu-Mel arm received 6 courses of vincristine, ifosfamide, doxorubicin, and etoposide (VIDE) as intensive induction chemotherapy followed by high dose busulfan-melphalan chemotherapy with autologous stem cell reinfusion.

Reporting group title	R3 VAC

Reporting group description:

Patients with metastatic disease not confined to the lungs and/or pleura, i.e. patients with bone metastases, bone marrow metastases or other metastases (e.g. lymph nodes, liver, CNS, etc) with and without additional pulmonary metastases at the time of diagnosis were included in the risk group Very High Risk R3.
Patients who were randomized into the R3 VAC arm received 6 courses of vincristine, ifosfamide, doxorubicin, and etoposide (VIDE) as intensive induction chemotherapy followed by 8 cycles of VAC

(vincristine, actinomycin-D, cyclophosphamide).

Reporting group title	R3 Treo-Mel

Reporting group description:

Patients with metastatic disease not confined to the lungs and/or pleura, i.e. patients with bone metastases, bone marrow metastases or other metastases (e.g. lymph nodes, liver, CNS, etc) with and without additional pulmonary metastases at the time of diagnosis were included in the risk group Very High Risk R3.
Patients who were randomized into the R3 Treo-Mel arm received 6 courses of vincristine, ifosfamide, doxorubicin, and etoposide (VIDE) as intensive induction chemotherapy followed by high dose chemotherapy using treosulfan-melphalan and autologous stem cell reinfusion.

Subject analysis set title	R1 Add-on (First interim analysis)
Subject analysis set type	Full analysis

Subject analysis set description:

The first interim analysis was performed after observing 17 events of 121 randomized patients in the Add-on group.

Subject analysis set title	R1 No Add-on (First interim analysis)
Subject analysis set type	Full analysis

Subject analysis set description:

The first interim analysis was performed after observing 16 events of 121 randomized patients in the no Add-on group.

Subject analysis set title	R3 VAC (First interim analysis)
Subject analysis set type	Full analysis

Subject analysis set description:

The first interim analysis was performed after observing 19 events of 32 randomized patients in the R3 VAC Group.

Subject analysis set title	R3 Treo-Mel (First interim analysis)
Subject analysis set type	Full analysis

Subject analysis set description:

The first interim analysis was performed after observing 9 events of 30 randomized patients in the R3 Treo-Mel Group.

Subject analysis set title	R1 Add-on (Per protocol)
Subject analysis set type	Per protocol

Subject analysis set description:

The per protocol collective is defined as all R1 Add-on patients completing the study without major protocol deviations.

Subject analysis set title	R1 No Add-on (Per protocol)
Subject analysis set type	Per protocol

Subject analysis set description:

The per protocol collective is defined as all R1 No Add-on patients completing the study without major protocol deviations.

Subject analysis set title	R3 VAC (Per Protocol)
Subject analysis set type	Per protocol

Subject analysis set description:

The per protocol collective is defined as all R3 VAC patients completing the study without major protocol deviations.

Subject analysis set title	R3 Treo-Mel (Per protocol)
Subject analysis set type	Per protocol

Subject analysis set description:

The per protocol collective is defined as all R3 Treo-Mel patients completing the study without major protocol deviations.

Primary: R1: Event-free survival (EFS)

End point title	R1: Event-free survival (EFS)[1]

End point description:

The primary endpoint of event-free survival (EFS) was estimated according to the method of Kaplan and Meier (1958). EFS time starts at the date of randomisation and ends at the date of first event

(progression of disease, relapse of disease, diagnosis of secondary malignancy, or death of the patient irrespective of its cause) or at the date of the patient's most recent consultation. Patients lost to follow-up without event were censored at the date of their last consultation. Progression of disease is defined as recurrent disease under active oncological therapy. Relapse of disease is defined as recurrent disease in patients with complete clinical remission after completion of active oncological therapy. The Primary Analysis was performed according to the Intention-to-treat (ITT) principle in the full analysis set.

End point type	Primary

End point timeframe:

From randomisation to first event or last follow-up in case of no event.

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The R2 randomization of the EURO-E.W.I.N.G. 99 trial was continued in the EWING2008 Trial. The EWING2008 R2 data were transferred to the EURO-E.W.I.N.G. 99 data center and was analyzed by the EURO-E.W.I.N.G. Group. The results were already published (see online references).

End point values	R1 Add-on	R1 No Add-on	R1 Add-on (First interim analysis)	R1 No Add-on (First interim analysis)
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	142	142	121	121
Units: Events	22	30	17	16

End point values	R1 Add-on (Per protocol)	R1 No Add-on (Per protocol)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	101	135		
Units: Events	14	28		

Statistical analyses

Statistical analysis title	Final analysis (superiority)

Statistical analysis description:

Because the number of the initially planned number of events (n=146) could not be reached, an adaptive design change was performed based on the data from the 1st interim analysis, according to which only an additional analysis is planned. The conditional rejection error probability (CREP) (Müller & Schäfer 2001) was calculated for each direction of the null hypothesis (superiority of Add-on +=0.0086 and inferiority of Add-on -=0.0126). The CREPs were used as new local significance levels.

Comparison groups	R1 Add-on v R1 No Add-on
Number of subjects included in analysis	284
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	= 0.0242 [3]
Method	Increment of the logrank test statistic
Parameter estimate	Hazard ratio (HR)
Point estimate	0.735
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.424
upper limit	1.275

Notes:

[2] - In the final analysis the one-sided null hypotheses was tested by calculating the approximately normally distributed independent increment of the logrank test statistic. The independent increment of the logrank test statistic was -1.0987, leading to the one-sided single-stage p-values p_end+=0.0242> 0.0086=+ and p_end-=0.9758> 0.0126=-.

[3] - The independent increment of the logrank test statistic was -1.0987, leading to the one-sided single-stage p-values p_end+=0.0242> 0.0086=+ and p_end-=0.9758> 0.0126=-.

Statistical analysis title	First interim analysis

Statistical analysis description:

The primary endpoint is event-free survival (EFS) starts at the date of randomization and ends at the date of first compound event (progression of disease, relapse of disease, diagnosis of secondary malignancy, or death of the patient irrespective of its cause) or at the date of the patient's most recent consultation. The EFS was analyzed using the intention-to-treat principle in the full-analysis set. A multiple type 1 error rate (significance level) of α = 5% (two-sided) was controlled.

Comparison groups	R1 Add-on (First interim analysis) v R1 No Add-on (First interim analysis)
Number of subjects included in analysis	242
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	= 0.9058 [5]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.042
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.526
upper limit	2.064

Notes:

[4] - An adaptive two-sided group sequential design with four equally weighted stages using an inverse normal combination function and O'Brien & Fleming boundaries was applied (Wassmer 2006, O'Brien & Fleming 1979). The first interim analysis was performed based on data from 20 March 2017 after observing 33 events.

[5] - Stage I two-sided p-value is reported. Stage I p-value (one-sided) for superiority (H1: HR < 1) p=0.5471 and for inferiority (H1: HR > 1) p=0.4529.

Statistical analysis title	Final analysis (inferiority)

Statistical analysis description:

Because the number of the initially planned number of events (n=146) could not be reached, an adaptive design change was performed based on the data from the 1st interim analysis, according to which only an additional analysis is planned. The conditional rejection error probability (CREP) (Müller & Schäfer 2001) was calculated for each direction of the null hypothesis (superiority of Add-on +=0.0086 and inferiority of Add-on -=0.0126). The CREPs were used as new local significance levels.

Comparison groups	R1 Add-on v R1 No Add-on
Number of subjects included in analysis	284
Analysis specification	Pre-specified
Analysis type	other[6]
P-value	= 0.0126 [7]
Method	Increment of the logrank test statistic
Parameter estimate	Hazard ratio (HR)
Point estimate	0.735
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.424
upper limit	1.275

Notes:

[6] - In the final analysis the one-sided null hypotheses was tested by calculating the approximately normally distributed independent increment of the logrank test statistic. The independent increment of the logrank test statistic was -1.0987, leading to the one-sided single-stage p-values p_end+=0.0242> 0.0086=+ and p_end-=0.9758> 0.0126=-.

[7] - The independent increment of the logrank test statistic was -1.0987, leading to the one-sided single-stage p-values p_end+=0.0242> 0.0086=+ and p_end-=0.9758> 0.0126=-.

Statistical analysis title	Final analysis (Per protocol)
Comparison groups	R1 Add-on (Per protocol) v R1 No Add-on (Per protocol)
Number of subjects included in analysis	236
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1794
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.34
upper limit	1.23

Primary: R3 trial: Event-free survival (EFS)

End point title	R3 trial: Event-free survival (EFS)[8]

End point description:

The primary endpoint of event-free survival (EFS) was estimated according to the method of Kaplan and Meier (1958). EFS time starts at the date of randomisation and ends at the date of first event (progression of disease, relapse of disease, diagnosis of secondary malignancy, or death of the patient irrespective of its cause) or at the date of the patient's most recent consultation. Patients lost to follow-up without event were censored at the date of their last consultation. Progression of disease is defined as recurrent disease under active oncological therapy. Relapse of disease is defined as recurrent disease in patients with complete clinical remission after completion of active oncological therapy. The Primary Analysis was performed according to the Intention-to-treat (ITT) principle in the full analysis set.

End point type	Primary

End point timeframe:

From randomisation to first event or last follow-up in case of no event.

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The R2 randomization of the EURO-E.W.I.N.G. 99 trial was continued in the EWING2008 Trial. The EWING2008 R2 data were transferred to the EURO-E.W.I.N.G. 99 data center and was analyzed by the EURO-E.W.I.N.G. Group. The results were already published (see online references).

End point values	R3 VAC	R3 Treo-Mel	R3 VAC (First interim analysis)	R3 Treo-Mel (First interim analysis)
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	54	55	32	30
Units: Events	43	39	19	9

End point values	R3 VAC (Per Protocol)	R3 Treo-Mel (Per protocol)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	46	41		
Units: Events	35	31		

Statistical analyses

Statistical analysis title	Final analysis

Statistical analysis description:

Because the number of the initially planned number of events (n=155) could not be reached, an adaptive design change was performed based on the data from the 1st interim analysis, according to which only an additional analysis is planned. The conditional rejection error probability (CREP) (Müller & Schäfer 2001) was calculated for the one-sided null hypothesis, resulting in +=0.0116. The CREP was used as new local significance level for the final analysis of the remaining trial.

Comparison groups	R3 Treo-Mel v R3 VAC
Number of subjects included in analysis	109
Analysis specification	Pre-specified
Analysis type	superiority[9]
P-value	= 0.1195 [10]
Method	Increment of the logrank test statistic
Parameter estimate	Hazard ratio (HR)
Point estimate	0.821
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.532
upper limit	1.268

Notes:

[9] - In the final analysis the one-sided null hypothesis was tested by calculating the approximately normally distributed independent increment of the logrank test statistic (Wassmer 2006). The final analysis was performed on data from 30th June 2019.

[10] - The independent increment of the logrank test statistic was -0.889, leading to the one-sided single-stage p-value p_end+=0.1195> 0.0116=+

Statistical analysis title	First interim analysis

Statistical analysis description:

The primary endpoint is event-free survival (EFS) starts at the date of randomization and ends at the date of first compound event (progression of disease, relapse of disease, diagnosis of secondary malignancy, or death of the patient irrespective of its cause) or at the date of the patient's most recent consultation. The EFS was analyzed using the intention-to-treat principle in the full-analysis set. A multiple type 1 error rate (significance level) of α = 2.5% (one-sided) was controlled.

Comparison groups	R3 VAC (First interim analysis) v R3 Treo-Mel (First interim analysis)
Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	superiority[11]
P-value	= 0.4737 [12]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.979

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.52
upper limit	1.842

Notes:

[11] - An adaptive one-sided group sequential design with four stages using an inverse normal combination function, O'Brien & Fleming boundaries, and equally spaced weights was applied (Wassmer 2006, O'Brien & Fleming 1979).
[12] - Stage I one-sided p-value is reported. The hypotheses that the randomization arm 'R3: Treo-Mel' differs in the full-analysis set from the randomization arm 'R3: VAC' with respect to EFS could not be rejected.

Statistical analysis title	Final analysis (Per protocol)
Comparison groups	R3 VAC (Per Protocol) v R3 Treo-Mel (Per protocol)
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4463
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.51
upper limit	1.35

Secondary: R1 trial: Overall survival (OS)

End point title	R1 trial: Overall survival (OS)[13]

End point description:

Overall survival time (OS) starts at the date of randomisation and ends at the date of death of the patient (irrespective of its cause) or at the date of the patient's most recent consultation. Patients lost to follow-up are censored at the date of their last consultation.

End point type	Secondary

End point timeframe:

From randomisation to death.

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The R2 randomization of the EURO-E.W.I.N.G. 99 trial was continued in the EWING2008 Trial. The EWING2008 R2 data were transferred to the EURO-E.W.I.N.G. 99 data center and was analyzed by the EURO-E.W.I.N.G. Group. The results were already published (see online references).

End point values	R1 Add-on	R1 No Add-on	R1 Add-on (Per protocol)	R1 No Add-on (Per protocol)
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	142	142	101	135
Units: Deaths	13	12	9	10

Statistical analyses

Statistical analysis title	R1 trial: OS (full analysis set)
Statistical analysis description:	
Comparision of overall survival between R1: Add-on and R1: No Add-on in the full analysis set (ITT principle).	
Comparison groups	R1 Add-on v R1 No Add-on
Number of subjects included in analysis	284
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8445
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.49
upper limit	2.37

Statistical analysis title	R1 trial: OS (Per protocol)
Comparison groups	R1 Add-on (Per protocol) v R1 No Add-on (Per protocol)
Number of subjects included in analysis	236
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7441
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.47
upper limit	2.86

Secondary: R3 trial: Overall survival (OS)

End point title	R3 trial: Overall survival (OS)[14]

End point description:

Overall survival time (OS) starts at the date of randomisation and ends at the date of death of the patient (irrespective of its cause) or at the date of the patient's most recent consultation. Patients lost to follow-up are censored at the date of their last consultation.

End point type	Secondary

End point timeframe:

From randomisation to death or last follow-up.

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The R2 randomization of the EURO-E.W.I.N.G. 99 trial was continued in the EWING2008 Trial. The EWING2008 R2 data were transferred to the EURO-E.W.I.N.G. 99 data center and was analyzed by the EURO-E.W.I.N.G. Group. The results were already published (see online references).

End point values	R3 VAC	R3 Treo-Mel	R3 VAC (Per Protocol)	R3 Treo-Mel (Per protocol)
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	54	55	46	41
Units: Deaths	31	30	23	23

Statistical analyses

Statistical analysis title	R3 trial: OS (full analysis set)

Statistical analysis description:

Comparision of overall survival between R3: Treo-Mel and R3: VAC in the full analysis set (ITT principle).

Comparison groups	R3 VAC v R3 Treo-Mel
Number of subjects included in analysis	109
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.868
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.58
upper limit	1.58

Statistical analysis title	R3 trial: OS (Per protocol)
Comparison groups	R3 VAC (Per Protocol) v R3 Treo-Mel (Per protocol)
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8779
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.05

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.59
upper limit	1.87

Adverse events

Adverse events information

Timeframe for reporting adverse events:

from treatment initiation until 3 months following completion of active oncological therapy.

Adverse event reporting additional description:

Expected toxicities, both severe (CTC grade >=3, hematologic: CTC grade = 4) and non-severe (CTC grade 1-2, hematologic: CTC grade 1-3), were recorded as pre-specified items according to CTCAE in the CRF. Severe toxicities were documented as SAE and non-severe toxicities as non-SAE. Toxicities collected as free text in the CRF were not documented.

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	3.0

Reporting groups

Reporting group title	Safety: R1 Add-on

Reporting group description:

All randomized patients who received R1 add-on treatment (Safety set, as-treated). In this reporting group, 11 deaths occurred with the following causes: Cancer = 9, Secondary malignancy = 1, Pneumonia = 1. Because the deaths could not be assigned to any specific toxicity, 0 was entered under „Serious adverse event details and values" for both „Fatalities number" and „Fatalities causally related to treatment number".

Reporting group title	Safety: R1 no Add-on

Reporting group description:

All randomized patients who received R1 no Add-on treatment (Safety set, as-treated). In this reporting group, 14 deaths occurred with the following causes: Cancer = 14. Because the deaths could not be assigned to any specific toxicity, 0 was entered under „Serious adverse event details and values" for both „Fatalities number" and „Fatalities causally related to treatment number".

Reporting group title	Safety: R2loc VAI

Reporting group description:

All randomized patients who received R2loc VAI treatment (Safety set, as-treated). In this reporting group, 2 deaths occurred with the following causes: Cancer = 2. Because the deaths could not be assigned to any specific toxicity, 0 was entered under „Serious adverse event details and values" for both „Fatalities number" and „Fatalities causally related to treatment number".

Reporting group title	Safety: R2loc Bu-Mel

Reporting group description:

All randomized patients who received R2loc Bu-Mel treatment (Safety set, as-treated). In this reporting group, 1 death occurred with the following cause: Cancer = 1. Because the deaths could not be assigned to any specific toxicity, 0 was entered under „Serious adverse event details and values" for both „Fatalities number" and „Fatalities causally related to treatment number".

Reporting group title	Safety: R2pulm VAI

Reporting group description:

All randomized patients who received R2pulm VAI treatment (Safety set, as-treated). In this reporting group, 4 deaths occurred with the following causes: Cancer = 4. Because the deaths could not be assigned to any specific toxicity, 0 was entered under „Serious adverse event details and values" for both „Fatalities number" and „Fatalities causally related to treatment number".

Reporting group title	Safety: R2pulm Bu-Mel

Reporting group description:

All randomized patients who received R2pulm Bu-Mel treatment (Safety set, as-treated). In this reporting group, 2 deaths occurred with the following causes: Cancer = 1, Pulmonary veno-occlusive disease (Treatment-related) = 1. Because the deaths could not be assigned to any specific toxicity, 0 was entered under „Serious adverse event details and values" for both „Fatalities number" and „Fatalities causally related to treatment number".

Reporting group title	Safety: R3 VAC

Reporting group description:

All randomized patients who received R3 VAC treatment (Safety set, as-treated). In this reporting group, 35 deaths occurred with the following causes: Cancer = 34, Acute pulmonary embolism = 1.

Because the deaths could not be assigned to any specific toxicity, 0 was entered under „Serious adverse event details and values" for both „Fatalities number" and „Fatalities causally related to treatment number".

Reporting group title	Safety: R3 Treo-Mel

Reporting group description:

All randomized patients who received R3 Treo-Mel treatment (Safety set, as-treated). In this reporting group, 25 deaths occurred with the following causes: Cancer = 24, Secondary malignancy = 1. Because the deaths could not be assigned to any specific toxicity, 0 was entered under „Serious adverse event details and values" for both „Fatalities number" and „Fatalities causally related to treatment number".

Serious adverse events	Safety: R1 Add-on	Safety: R1 no Add-on	Safety: R2loc VAI
Total subjects affected by serious adverse events			
subjects affected / exposed	124 / 124 (100.00%)	157 / 160 (98.13%)	18 / 18 (100.00%)
number of deaths (all causes)	11	14	2
number of deaths resulting from adverse events			
Investigations			
Hemoglobin			
subjects affected / exposed	66 / 124 (53.23%)	85 / 160 (53.13%)	8 / 18 (44.44%)
occurrences causally related to treatment / all	145 / 145	180 / 180	14 / 14
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukocytes			
subjects affected / exposed	123 / 124 (99.19%)	155 / 160 (96.88%)	15 / 18 (83.33%)
occurrences causally related to treatment / all	1337 / 1337	1390 / 1390	125 / 125
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Granulocytes			
subjects affected / exposed	114 / 124 (91.94%)	148 / 160 (92.50%)	15 / 18 (83.33%)
occurrences causally related to treatment / all	1307 / 1307	1334 / 1334	107 / 107
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Platelets			
subjects affected / exposed	107 / 124 (86.29%)	136 / 160 (85.00%)	11 / 18 (61.11%)
occurrences causally related to treatment / all	652 / 652	711 / 711	62 / 62
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fever			
subjects affected / exposed	9 / 124 (7.26%)	19 / 160 (11.88%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	10 / 10	28 / 28	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Creatinine			

subjects affected / exposed	2 / 124 (1.61%)	2 / 160 (1.25%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	2 / 2	7 / 7	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Proteinuria			
subjects affected / exposed	0 / 124 (0.00%)	2 / 160 (1.25%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	4 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hematuria			
subjects affected / exposed	2 / 124 (1.61%)	0 / 160 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Glumerular filtration rate			
subjects affected / exposed	1 / 124 (0.81%)	1 / 160 (0.63%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tubular phosphate reabsorption			
subjects affected / exposed	19 / 124 (15.32%)	5 / 160 (3.13%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	71 / 71	15 / 15	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bilirubin			
subjects affected / exposed	2 / 124 (1.61%)	1 / 160 (0.63%)	2 / 18 (11.11%)
occurrences causally related to treatment / all	3 / 3	1 / 1	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
S-GOT/S-GPT			
subjects affected / exposed	16 / 124 (12.90%)	24 / 160 (15.00%)	3 / 18 (16.67%)
occurrences causally related to treatment / all	41 / 41	45 / 45	6 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac function test			
subjects affected / exposed	1 / 124 (0.81%)	2 / 160 (1.25%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	1 / 1	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ECHO: LV-SF			

subjects affected / exposed	6 / 124 (4.84%)	4 / 160 (2.50%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	7 / 7	9 / 9	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mucous membrane			
subjects affected / exposed	0 / 124 (0.00%)	0 / 160 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Salivary gland			
subjects affected / exposed	1 / 124 (0.81%)	0 / 160 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pharynx and oesophagus			
subjects affected / exposed	1 / 124 (0.81%)	2 / 160 (1.25%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	1 / 1	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Larynx			
subjects affected / exposed	0 / 124 (0.00%)	0 / 160 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal tract			
subjects affected / exposed	0 / 124 (0.00%)	1 / 160 (0.63%)	2 / 18 (11.11%)
occurrences causally related to treatment / all	0 / 0	1 / 1	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung			
subjects affected / exposed	0 / 124 (0.00%)	0 / 160 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Central neurotoxicity			
subjects affected / exposed	3 / 124 (2.42%)	4 / 160 (2.50%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	3 / 3	4 / 4	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			

subjects affected / exposed	6 / 124 (4.84%)	7 / 160 (4.38%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	6 / 6	8 / 8	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral neurotoxicity			
subjects affected / exposed	2 / 124 (1.61%)	5 / 160 (3.13%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	8 / 8	14 / 14	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
General physical condition			
subjects affected / exposed	26 / 124 (20.97%)	43 / 160 (26.88%)	4 / 18 (22.22%)
occurrences causally related to treatment / all	81 / 81	106 / 106	7 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	0 / 124 (0.00%)	1 / 160 (0.63%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stomatitis			
subjects affected / exposed	39 / 124 (31.45%)	50 / 160 (31.25%)	3 / 18 (16.67%)
occurrences causally related to treatment / all	87 / 87	137 / 137	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	20 / 124 (16.13%)	30 / 160 (18.75%)	2 / 18 (11.11%)
occurrences causally related to treatment / all	27 / 27	69 / 69	4 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	7 / 124 (5.65%)	15 / 160 (9.38%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	10 / 10	17 / 17	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Changes in the skin			
subjects affected / exposed	7 / 124 (5.65%)	9 / 160 (5.63%)	3 / 18 (16.67%)
occurrences causally related to treatment / all	10 / 10	13 / 13	6 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Infections and infestations			
Infection			
subjects affected / exposed	45 / 124 (36.29%)	67 / 160 (41.88%)	8 / 18 (44.44%)
occurrences causally related to treatment / all	97 / 97	122 / 122	12 / 12
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Safety: R2loc Bu-Mel	Safety: R2pulm VAI	Safety: R2pulm Bu-Mel
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 7 (100.00%)	12 / 12 (100.00%)	9 / 9 (100.00%)
number of deaths (all causes)	1	4	2
number of deaths resulting from adverse events			
Investigations			
Hemoglobin			
subjects affected / exposed	3 / 7 (42.86%)	7 / 12 (58.33%)	5 / 9 (55.56%)
occurrences causally related to treatment / all	3 / 3	13 / 13	9 / 9
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukocytes			
subjects affected / exposed	7 / 7 (100.00%)	12 / 12 (100.00%)	9 / 9 (100.00%)
occurrences causally related to treatment / all	41 / 41	86 / 86	58 / 58
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Granulocytes			
subjects affected / exposed	5 / 7 (71.43%)	10 / 12 (83.33%)	9 / 9 (100.00%)
occurrences causally related to treatment / all	25 / 25	81 / 81	57 / 57
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Platelets			
subjects affected / exposed	6 / 7 (85.71%)	11 / 12 (91.67%)	9 / 9 (100.00%)
occurrences causally related to treatment / all	23 / 23	41 / 41	33 / 33
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fever			
subjects affected / exposed	0 / 7 (0.00%)	0 / 12 (0.00%)	1 / 9 (11.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Creatinine			

subjects affected / exposed	0 / 7 (0.00%)	0 / 12 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Proteinuria			
subjects affected / exposed	0 / 7 (0.00%)	0 / 12 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hematuria			
subjects affected / exposed	1 / 7 (14.29%)	0 / 12 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Glumerular filtration rate			
subjects affected / exposed	1 / 7 (14.29%)	0 / 12 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tubular phosphate reabsorption			
subjects affected / exposed	0 / 7 (0.00%)	0 / 12 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bilirubin			
subjects affected / exposed	0 / 7 (0.00%)	0 / 12 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
S-GOT/S-GPT			
subjects affected / exposed	2 / 7 (28.57%)	2 / 12 (16.67%)	1 / 9 (11.11%)
occurrences causally related to treatment / all	2 / 2	6 / 6	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac function test			
subjects affected / exposed	0 / 7 (0.00%)	0 / 12 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ECHO: LV-SF			

subjects affected / exposed	0 / 7 (0.00%)	1 / 12 (8.33%)	2 / 9 (22.22%)
occurrences causally related to treatment / all	0 / 0	1 / 1	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mucous membrane			
subjects affected / exposed	0 / 7 (0.00%)	0 / 12 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Salivary gland			
subjects affected / exposed	0 / 7 (0.00%)	0 / 12 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pharynx and oesophagus			
subjects affected / exposed	0 / 7 (0.00%)	0 / 12 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Larynx			
subjects affected / exposed	0 / 7 (0.00%)	0 / 12 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal tract			
subjects affected / exposed	0 / 7 (0.00%)	0 / 12 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung			
subjects affected / exposed	0 / 7 (0.00%)	0 / 12 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Central neurotoxicity			
subjects affected / exposed	0 / 7 (0.00%)	0 / 12 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			

subjects affected / exposed	0 / 7 (0.00%)	0 / 12 (0.00%)	1 / 9 (11.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral neurotoxicity			
subjects affected / exposed	0 / 7 (0.00%)	0 / 12 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
General physical condition			
subjects affected / exposed	0 / 7 (0.00%)	2 / 12 (16.67%)	5 / 9 (55.56%)
occurrences causally related to treatment / all	0 / 0	2 / 2	8 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	0 / 7 (0.00%)	0 / 12 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stomatitis			
subjects affected / exposed	5 / 7 (71.43%)	4 / 12 (33.33%)	6 / 9 (66.67%)
occurrences causally related to treatment / all	6 / 6	8 / 8	15 / 15
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	1 / 7 (14.29%)	1 / 12 (8.33%)	1 / 9 (11.11%)
occurrences causally related to treatment / all	2 / 2	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	1 / 7 (14.29%)	1 / 12 (8.33%)	3 / 9 (33.33%)
occurrences causally related to treatment / all	1 / 1	1 / 1	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Changes in the skin			
subjects affected / exposed	0 / 7 (0.00%)	1 / 12 (8.33%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Infections and infestations			
Infection			
subjects affected / exposed	1 / 7 (14.29%)	5 / 12 (41.67%)	6 / 9 (66.67%)
occurrences causally related to treatment / all	2 / 2	6 / 6	8 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Safety: R3 VAC	Safety: R3 Treo-Mel	
Total subjects affected by serious adverse events			
subjects affected / exposed	62 / 64 (96.88%)	44 / 44 (100.00%)	
number of deaths (all causes)	35	25	
number of deaths resulting from adverse events			
Investigations			
Hemoglobin			
subjects affected / exposed	31 / 64 (48.44%)	31 / 44 (70.45%)	
occurrences causally related to treatment / all	64 / 64	66 / 66	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukocytes			
subjects affected / exposed	58 / 64 (90.63%)	44 / 44 (100.00%)	
occurrences causally related to treatment / all	504 / 504	425 / 425	
deaths causally related to treatment / all	0 / 0	0 / 0	
Granulocytes			
subjects affected / exposed	55 / 64 (85.94%)	40 / 44 (90.91%)	
occurrences causally related to treatment / all	459 / 459	393 / 393	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelets			
subjects affected / exposed	54 / 64 (84.38%)	42 / 44 (95.45%)	
occurrences causally related to treatment / all	269 / 269	256 / 256	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fever			
subjects affected / exposed	5 / 64 (7.81%)	5 / 44 (11.36%)	
occurrences causally related to treatment / all	5 / 5	5 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Creatinine			

subjects affected / exposed	1 / 64 (1.56%)	7 / 44 (15.91%)	
occurrences causally related to treatment / all	1 / 1	10 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proteinuria			
subjects affected / exposed	0 / 64 (0.00%)	2 / 44 (4.55%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hematuria			
subjects affected / exposed	1 / 64 (1.56%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glumerular filtration rate			
subjects affected / exposed	0 / 64 (0.00%)	2 / 44 (4.55%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tubular phosphate reabsorption			
subjects affected / exposed	2 / 64 (3.13%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bilirubin			
subjects affected / exposed	1 / 64 (1.56%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
S-GOT/S-GPT			
subjects affected / exposed	12 / 64 (18.75%)	6 / 44 (13.64%)	
occurrences causally related to treatment / all	19 / 19	10 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac function test			
subjects affected / exposed	1 / 64 (1.56%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ECHO: LV-SF			

subjects affected / exposed	3 / 64 (4.69%)	3 / 44 (6.82%)	
occurrences causally related to treatment / all	7 / 7	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucous membrane			
subjects affected / exposed	1 / 64 (1.56%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Salivary gland			
subjects affected / exposed	0 / 64 (0.00%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharynx and oesophagus			
subjects affected / exposed	1 / 64 (1.56%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Larynx			
subjects affected / exposed	0 / 64 (0.00%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal tract			
subjects affected / exposed	0 / 64 (0.00%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung			
subjects affected / exposed	1 / 64 (1.56%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Central neurotoxicity			
subjects affected / exposed	1 / 64 (1.56%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			

subjects affected / exposed	2 / 64 (3.13%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	2 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral neurotoxicity			
subjects affected / exposed	1 / 64 (1.56%)	2 / 44 (4.55%)	
occurrences causally related to treatment / all	1 / 1	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
General physical condition			
subjects affected / exposed	18 / 64 (28.13%)	18 / 44 (40.91%)	
occurrences causally related to treatment / all	24 / 24	43 / 43	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	0 / 64 (0.00%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	19 / 64 (29.69%)	21 / 44 (47.73%)	
occurrences causally related to treatment / all	35 / 35	40 / 40	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	13 / 64 (20.31%)	5 / 44 (11.36%)	
occurrences causally related to treatment / all	19 / 19	10 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	7 / 64 (10.94%)	5 / 44 (11.36%)	
occurrences causally related to treatment / all	9 / 9	7 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Changes in the skin			
subjects affected / exposed	3 / 64 (4.69%)	7 / 44 (15.91%)	
occurrences causally related to treatment / all	3 / 3	10 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	

Infections and infestations			
Infection			
subjects affected / exposed	27 / 64 (42.19%)	23 / 44 (52.27%)	
occurrences causally related to treatment / all	45 / 45	39 / 39	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Safety: R1 Add-on	Safety: R1 no Add-on	Safety: R2loc VAI
Total subjects affected by non-serious adverse events			
subjects affected / exposed	124 / 124 (100.00%)	160 / 160 (100.00%)	18 / 18 (100.00%)
Investigations			
Hemoglobin			
subjects affected / exposed	58 / 124 (46.77%)	75 / 160 (46.88%)	10 / 18 (55.56%)
occurrences (all)	1900	1865	207
Leukocytes			
subjects affected / exposed	1 / 124 (0.81%)	4 / 160 (2.50%)	3 / 18 (16.67%)
occurrences (all)	807	662	91
Granulocytes			
subjects affected / exposed	6 / 124 (4.84%)	5 / 160 (3.13%)	1 / 18 (5.56%)
occurrences (all)	461	403	51
Platelets			
subjects affected / exposed	17 / 124 (13.71%)	22 / 160 (13.75%)	6 / 18 (33.33%)
occurrences (all)	867	913	90
Fever			
subjects affected / exposed	109 / 124 (87.90%)	131 / 160 (81.88%)	15 / 18 (83.33%)
occurrences (all)	875	991	73
Creatinine			
subjects affected / exposed	28 / 124 (22.58%)	34 / 160 (21.25%)	4 / 18 (22.22%)
occurrences (all)	100	83	7
Proteinuria			
subjects affected / exposed	61 / 124 (49.19%)	60 / 160 (37.50%)	3 / 18 (16.67%)
occurrences (all)	238	194	5
Hematuria			

subjects affected / exposed	59 / 124 (47.58%)	65 / 160 (40.63%)	5 / 18 (27.78%)
occurrences (all)	186	143	5
Glumerular filtration rate			
subjects affected / exposed	30 / 124 (24.19%)	26 / 160 (16.25%)	2 / 18 (11.11%)
occurrences (all)	104	92	3
Tubular phosphate reabsorption			
subjects affected / exposed	20 / 124 (16.13%)	29 / 160 (18.13%)	2 / 18 (11.11%)
occurrences (all)	141	67	3
Bilirubin			
subjects affected / exposed	28 / 124 (22.58%)	40 / 160 (25.00%)	2 / 18 (11.11%)
occurrences (all)	84	79	12
S-GOT/S-GPT			
subjects affected / exposed	97 / 124 (78.23%)	120 / 160 (75.00%)	15 / 18 (83.33%)
occurrences (all)	1071	996	104
ECHO: LV-SF			
subjects affected / exposed	13 / 124 (10.48%)	17 / 160 (10.63%)	1 / 18 (5.56%)
occurrences (all)	33	45	1
ureter and bladder			
subjects affected / exposed	1 / 124 (0.81%)	2 / 160 (1.25%)	0 / 18 (0.00%)
occurrences (all)	1	2	0
Mucous membrane			
subjects affected / exposed	5 / 124 (4.03%)	7 / 160 (4.38%)	1 / 18 (5.56%)
occurrences (all)	5	8	1
Salivary gland			
subjects affected / exposed	1 / 124 (0.81%)	1 / 160 (0.63%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Pharynx and oesophagus			
subjects affected / exposed	2 / 124 (1.61%)	7 / 160 (4.38%)	1 / 18 (5.56%)
occurrences (all)	2	8	1
Larynx			
subjects affected / exposed	2 / 124 (1.61%)	3 / 160 (1.88%)	0 / 18 (0.00%)
occurrences (all)	2	3	0
Upper gastrointestinal tract			
subjects affected / exposed	4 / 124 (3.23%)	7 / 160 (4.38%)	1 / 18 (5.56%)
occurrences (all)	5	7	1
Lower gastrointestinal tract including			

pelvis			
subjects affected / exposed	1 / 124 (0.81%)	5 / 160 (3.13%)	0 / 18 (0.00%)
occurrences (all)	1	5	0
Lung			
subjects affected / exposed	2 / 124 (1.61%)	4 / 160 (2.50%)	0 / 18 (0.00%)
occurrences (all)	4	5	0
Cardiac disorders			
Cardiac function test			
subjects affected / exposed	13 / 124 (10.48%)	18 / 160 (11.25%)	1 / 18 (5.56%)
occurrences (all)	32	40	2
Nervous system disorders			
Cantral neurotoxicity			
subjects affected / exposed	19 / 124 (15.32%)	20 / 160 (12.50%)	2 / 18 (11.11%)
occurrences (all)	53	48	4
Seizure			
subjects affected / exposed	12 / 124 (9.68%)	8 / 160 (5.00%)	0 / 18 (0.00%)
occurrences (all)	17	9	0
Peripheral neurotoxicity			
subjects affected / exposed	63 / 124 (50.81%)	50 / 160 (31.25%)	9 / 18 (50.00%)
occurrences (all)	290	144	51
General disorders and administration site conditions			
General physical condition			
subjects affected / exposed	89 / 124 (71.77%)	108 / 160 (67.50%)	13 / 18 (72.22%)
occurrences (all)	1404	1443	173
Headache			
subjects affected / exposed	3 / 124 (2.42%)	2 / 160 (1.25%)	1 / 18 (5.56%)
occurrences (all)	4	2	1
Stomatitis			
subjects affected / exposed	63 / 124 (50.81%)	83 / 160 (51.88%)	8 / 18 (44.44%)
occurrences (all)	407	469	45
Vomiting			
subjects affected / exposed	91 / 124 (73.39%)	98 / 160 (61.25%)	9 / 18 (50.00%)
occurrences (all)	672	634	41
Diarrhoea			
subjects affected / exposed	72 / 124 (58.06%)	66 / 160 (41.25%)	7 / 18 (38.89%)
occurrences (all)	214	199	12

Hepatobiliary disorders			
VOD Bearman			
subjects affected / exposed	0 / 124 (0.00%)	0 / 160 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Changes in the skin			
subjects affected / exposed	80 / 124 (64.52%)	85 / 160 (53.13%)	9 / 18 (50.00%)
occurrences (all)	263	221	36
Infections and infestations			
Infection			
subjects affected / exposed	75 / 124 (60.48%)	83 / 160 (51.88%)	9 / 18 (50.00%)
occurrences (all)	667	788	52

Non-serious adverse events	Safety: R2loc Bu-Mel	Safety: R2pulm VAI	Safety: R2pulm Bu-Mel
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 7 (100.00%)	12 / 12 (100.00%)	9 / 9 (100.00%)
Investigations			
Hemoglobin			
subjects affected / exposed	4 / 7 (57.14%)	5 / 12 (41.67%)	4 / 9 (44.44%)
occurrences (all)	47	130	55
Leukocytes			
subjects affected / exposed	0 / 7 (0.00%)	0 / 12 (0.00%)	0 / 9 (0.00%)
occurrences (all)	12	55	12
Granulocytes			
subjects affected / exposed	1 / 7 (14.29%)	0 / 12 (0.00%)	0 / 9 (0.00%)
occurrences (all)	12	32	4
Platelets			
subjects affected / exposed	1 / 7 (14.29%)	1 / 12 (8.33%)	0 / 9 (0.00%)
occurrences (all)	21	78	23
Fever			
subjects affected / exposed	7 / 7 (100.00%)	11 / 12 (91.67%)	8 / 9 (88.89%)
occurrences (all)	19	52	42
Creatinine			
subjects affected / exposed	2 / 7 (28.57%)	4 / 12 (33.33%)	0 / 9 (0.00%)
occurrences (all)	3	9	0
Proteinuria			

subjects affected / exposed	2 / 7 (28.57%)	5 / 12 (41.67%)	4 / 9 (44.44%)
occurrences (all)	2	9	8
Hematuria			
subjects affected / exposed	1 / 7 (14.29%)	5 / 12 (41.67%)	4 / 9 (44.44%)
occurrences (all)	4	9	6
Glumerular filtration rate			
subjects affected / exposed	1 / 7 (14.29%)	2 / 12 (16.67%)	1 / 9 (11.11%)
occurrences (all)	6	2	4
Tubular phosphate reabsorption			
subjects affected / exposed	2 / 7 (28.57%)	3 / 12 (25.00%)	1 / 9 (11.11%)
occurrences (all)	2	4	1
Bilirubin			
subjects affected / exposed	1 / 7 (14.29%)	3 / 12 (25.00%)	3 / 9 (33.33%)
occurrences (all)	1	6	3
S-GOT/S-GPT			
subjects affected / exposed	3 / 7 (42.86%)	10 / 12 (83.33%)	8 / 9 (88.89%)
occurrences (all)	29	78	58
ECHO: LV-SF			
subjects affected / exposed	0 / 7 (0.00%)	0 / 12 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	2
ureter and bladder			
subjects affected / exposed	0 / 7 (0.00%)	0 / 12 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Mucous membrane			
subjects affected / exposed	0 / 7 (0.00%)	0 / 12 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Salivary gland			
subjects affected / exposed	0 / 7 (0.00%)	0 / 12 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Pharynx and oesophagus			
subjects affected / exposed	0 / 7 (0.00%)	0 / 12 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Larynx			
subjects affected / exposed	0 / 7 (0.00%)	1 / 12 (8.33%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Upper gastrointestinal tract			

subjects affected / exposed	0 / 7 (0.00%)	2 / 12 (16.67%)	0 / 9 (0.00%)
occurrences (all)	0	2	0
Lower gastrointestinal tract including pelvis			
subjects affected / exposed	0 / 7 (0.00%)	2 / 12 (16.67%)	1 / 9 (11.11%)
occurrences (all)	0	2	1
Lung			
subjects affected / exposed	0 / 7 (0.00%)	0 / 12 (0.00%)	2 / 9 (22.22%)
occurrences (all)	0	0	2
Cardiac disorders			
Cardiac function test			
subjects affected / exposed	0 / 7 (0.00%)	2 / 12 (16.67%)	2 / 9 (22.22%)
occurrences (all)	0	2	2
Nervous system disorders			
Cantral neurotoxicity			
subjects affected / exposed	2 / 7 (28.57%)	0 / 12 (0.00%)	0 / 9 (0.00%)
occurrences (all)	7	0	0
Seizure			
subjects affected / exposed	0 / 7 (0.00%)	0 / 12 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Peripheral neurotoxicity			
subjects affected / exposed	2 / 7 (28.57%)	5 / 12 (41.67%)	3 / 9 (33.33%)
occurrences (all)	9	17	6
General disorders and administration site conditions			
General physical condition			
subjects affected / exposed	6 / 7 (85.71%)	9 / 12 (75.00%)	4 / 9 (44.44%)
occurrences (all)	34	106	50
Headache			
subjects affected / exposed	0 / 7 (0.00%)	0 / 12 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Stomatitis			
subjects affected / exposed	2 / 7 (28.57%)	5 / 12 (41.67%)	3 / 9 (33.33%)
occurrences (all)	16	35	8
Vomiting			
subjects affected / exposed	3 / 7 (42.86%)	8 / 12 (66.67%)	7 / 9 (77.78%)
occurrences (all)	15	54	23
Diarrhoea			

subjects affected / exposed	2 / 7 (28.57%)	9 / 12 (75.00%)	3 / 9 (33.33%)
occurrences (all)	3	23	12
Hepatobiliary disorders			
VOD Bearman			
subjects affected / exposed	1 / 7 (14.29%)	0 / 12 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Skin and subcutaneous tissue disorders			
Changes in the skin			
subjects affected / exposed	5 / 7 (71.43%)	5 / 12 (41.67%)	4 / 9 (44.44%)
occurrences (all)	11	18	7
Infections and infestations			
Infection			
subjects affected / exposed	5 / 7 (71.43%)	7 / 12 (58.33%)	3 / 9 (33.33%)
occurrences (all)	18	52	25

Non-serious adverse events	Safety: R3 VAC	Safety: R3 Treo-Mel	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	63 / 64 (98.44%)	44 / 44 (100.00%)	
Investigations			
Hemoglobin			
subjects affected / exposed	32 / 64 (50.00%)	13 / 44 (29.55%)	
occurrences (all)	675	494	
Leukocytes			
subjects affected / exposed	5 / 64 (7.81%)	0 / 44 (0.00%)	
occurrences (all)	204	137	
Granulocytes			
subjects affected / exposed	3 / 64 (4.69%)	0 / 44 (0.00%)	
occurrences (all)	113	69	
Platelets			
subjects affected / exposed	8 / 64 (12.50%)	2 / 44 (4.55%)	
occurrences (all)	282	219	
Fever			
subjects affected / exposed	55 / 64 (85.94%)	38 / 44 (86.36%)	
occurrences (all)	322	284	
Creatinine			
subjects affected / exposed	6 / 64 (9.38%)	12 / 44 (27.27%)	
occurrences (all)	10	38	

Proteinuria			
subjects affected / exposed	28 / 64 (43.75%)	18 / 44 (40.91%)	
occurrences (all)	62	52	
Hematuria			
subjects affected / exposed	26 / 64 (40.63%)	19 / 44 (43.18%)	
occurrences (all)	80	63	
Glumerular filtration rate			
subjects affected / exposed	2 / 64 (3.13%)	6 / 44 (13.64%)	
occurrences (all)	14	36	
Tubular phosphate reabsorption			
subjects affected / exposed	7 / 64 (10.94%)	6 / 44 (13.64%)	
occurrences (all)	17	8	
Bilirubin			
subjects affected / exposed	17 / 64 (26.56%)	12 / 44 (27.27%)	
occurrences (all)	41	23	
S-GOT/S-GPT			
subjects affected / exposed	48 / 64 (75.00%)	37 / 44 (84.09%)	
occurrences (all)	318	248	
ECHO: LV-SF			
subjects affected / exposed	1 / 64 (1.56%)	3 / 44 (6.82%)	
occurrences (all)	6	8	
ureter and bladder			
subjects affected / exposed	2 / 64 (3.13%)	2 / 44 (4.55%)	
occurrences (all)	2	4	
Mucous membrane			
subjects affected / exposed	3 / 64 (4.69%)	1 / 44 (2.27%)	
occurrences (all)	5	1	
Salivary gland			
subjects affected / exposed	0 / 64 (0.00%)	0 / 44 (0.00%)	
occurrences (all)	0	0	
Pharynx and oesophagus			
subjects affected / exposed	3 / 64 (4.69%)	1 / 44 (2.27%)	
occurrences (all)	4	2	
Larynx			
subjects affected / exposed	0 / 64 (0.00%)	0 / 44 (0.00%)	
occurrences (all)	0	0	

Upper gastrointestinal tract			
subjects affected / exposed	9 / 64 (14.06%)	8 / 44 (18.18%)	
occurrences (all)	15	14	
Lower gastrointestinal tract including pelvis			
subjects affected / exposed	8 / 64 (12.50%)	7 / 44 (15.91%)	
occurrences (all)	16	14	
Lung			
subjects affected / exposed	3 / 64 (4.69%)	1 / 44 (2.27%)	
occurrences (all)	3	1	
Cardiac disorders			
Cardiac function test			
subjects affected / exposed	6 / 64 (9.38%)	6 / 44 (13.64%)	
occurrences (all)	12	9	
Nervous system disorders			
Cantral neurotoxicity			
subjects affected / exposed	17 / 64 (26.56%)	7 / 44 (15.91%)	
occurrences (all)	36	10	
Seizure			
subjects affected / exposed	8 / 64 (12.50%)	2 / 44 (4.55%)	
occurrences (all)	9	2	
Peripheral neurotoxicity			
subjects affected / exposed	22 / 64 (34.38%)	18 / 44 (40.91%)	
occurrences (all)	85	75	
General disorders and administration site conditions			
General physical condition			
subjects affected / exposed	44 / 64 (68.75%)	23 / 44 (52.27%)	
occurrences (all)	598	410	
Headache			
subjects affected / exposed	2 / 64 (3.13%)	3 / 44 (6.82%)	
occurrences (all)	2	5	
Stomatitis			
subjects affected / exposed	33 / 64 (51.56%)	22 / 44 (50.00%)	
occurrences (all)	172	149	
Vomiting			
subjects affected / exposed	38 / 64 (59.38%)	37 / 44 (84.09%)	
occurrences (all)	226	214	

Diarrhoea subjects affected / exposed occurrences (all)	31 / 64 (48.44%) 90	27 / 44 (61.36%) 87	
Hepatobiliary disorders VOD Bearman subjects affected / exposed occurrences (all)	0 / 64 (0.00%) 0	0 / 44 (0.00%) 0	
Skin and subcutaneous tissue disorders Changes in the skin subjects affected / exposed occurrences (all)	38 / 64 (59.38%) 126	29 / 44 (65.91%) 98	
Infections and infestations Infection subjects affected / exposed occurrences (all)	32 / 64 (50.00%) 220	20 / 44 (45.45%) 216	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 February 2011	- Member states were added: Belgium, Czech Republic and Spain joined study participation - Member state withdrawl trial participation: Slovenia - Changes in Datamanagement: Electronic data capture system is established. - Note regarding treatment with Treosulfan was added: In small children <20 kg BW the dose of treosulfan should be calculated per kg BW. 1 m² BSA = 30 kg BW - Changes in drug supply: In Germany study sites will be supplied with commercial drug from Novartis until 31 Dec 2011 - Changes in dosing of obese patients to ensure safety: In patients with BSA >2 m² dosing of chemotherapy may have to be adjusted to the individual patient's requirements and tolerance. Note: Observe maximum single dose for vincristine: 2 mg. - Changes (due to typing error) in reportable AEs: Adverse Events not reportable on an SAE form are to be reported on the appropriate CRF (toxicity check list). This include: Neutropenia and neutropenic fever (CTCAE°1-4). Haematological toxicity: haemoglobin, WBC, granulocytes, platelets (CTCAE°1-4).
23 April 2013	- Changes in inclusion of patients: The option of registering patients to be observed is added into study design. These patients do not meet all inclusion criteria or meet one or more exclusion criteria. - Member states were added to participate in trial for recruiting patients to the R2 arm oft he trial: France, UK, USA - Member state was added: Hungary joined trial participation - Changes in Tresulfan IV administration: Infusion time was extended to 2 h - Changes in drug supply: In Germany study sites will be supplied with commercial drug from Novartis until 30 Sep 2013 - Clarification of drug administration which is relevant for patient safety: If SF remains below 29% then omit DOX and substitute ACT 0.75 mg/m2/d (d1, d2) (IV push) (1.5 mg/m2/cycle) (max. single dose/d: 1.5 mg/d).
18 September 2013	- Member states were added: Autralia and New Zealand joined trial participation. - Transformation of the original group sequential design into the corresponding inverse normal design: For the randomized risk groups R1 and R3 will be conducted, with 3 planned interim analyses and early stopping rules using the O'Brien and Fleming Design. For risk groups R2loc and R2pulm three interim analyses are intended to be performed using an inverse normal design corresponding to an equally spaced four step group sequential design according to O'Brien & Fleming (Wassmer 2006, O'Brien & Fleming 1979). After each interim analysis a data dependent sample size recalculation may be performed. Then, the accrual period, the observation time and the schedule of the next interim and final analysis (required number of events) can be adapted. If no adaptions are performed, the inverse normal design coincides with the underlying group sequential design. - Recommendation added for dose modifications of elderly patients to enhance paintent's safety: Chemotherapy may have to be adjusted indivudual patient's requirements. In these cases the EWING2008 Head Office should be contacted. - Recommandation added for dose medoifications in case of significant toxicities to enhance patient's safety. Dose modicfications for ifosmamide, cyclophosphamide and actinomycin D

08 December 2014	- Member state was added: Finland joined trial participation. - Member state withdrawl trial participation: Spain - Changes in sample size, anticipated accrual time and recruitment period for risk groups: Recalculation of R2 (R2loc and R2pulm) with respect to conditional power was performed. - Clarification for patients who are not randomised and do not recieve the standard treatment was added: additional information for was provided each risk group in a guideline - Changes in drug supply: In Germany study sites will be supplied with commercial drug from Novartis until 31 Dec 2016 - SPC for all drugs are updated
19 February 2016	- Changes in study organisation: Retirement of Prof. Juergens; Prof. Dirksen is the new Coordinating Ivestigator - Changes in plannes study period: The overall study duration (incl. follow-up) was extended by one year as the accrual rate into the trials was slightly lower as expected. - Member state was added: Lithuania joined trial participation - Member state withdrawl trial participation: Slovakia - Changes in recruitment cohort: The study committee decided to close the R2loc arm and the R2pulm arm because of low accrual rate into the randomized arms. The study will be analyzed. - Changes in medication of Standard Risk R1 patients: Fenretinide will not be available, therefore the arm, that included fenretinide was deleted from the protocol for clarification. This results also on changes of the primary and secondary objecitves and oft he sample size. - Changes in inclusion criteria: for Germany patients either sex, age <48 months may be included. - Changes in Key time points: Response evaluation prior to add-on in R1 was changed to optional at the respective time points. - Changes in the staticital analysis: Transformation of the original group sequential design into the corresponding inverse normal design.
06 July 2018	- Update if trial conduct: R1 and R3 accrual was discontinued on April 1st 2018 - Statistical design has been adapted for final analysis: Adaption of the statistical analysis strategy for the final analysis of the primary endpoint, because the required number of events for the upcoming interim/final analyses cannot be reached. Due to the statistical design change, no further interim analyses will be performed. In the R1 and R3 trial the final analysis will be performed at the end of the trial. - Changes in drug supply: Zoledronic acid is no longer supplied by Novartis - Prophylaxis of ifosfamide-induced encephalopathy was changed: Methylene blue (50mg) should be given 4 times daily

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/30188789

http://www.ncbi.nlm.nih.gov/pubmed/31553693