Clinical trial results:
Prospective Trial for the diagnosis and treatment of children, adolescents and young adults with Intracranial Germ Cell Tumours

Summary

EudraCT number	2009-018072-33
Trial protocol	DE SE GB FR AT IT
Global end of trial date	30 June 2020

Results information

Result version number	v1 (current)
This version publication date	07 January 2021
First version publication date	07 January 2021

Trial information

Trial identification

Sponsor protocol code	UKM08_0057

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Universitätsklinikum Münster
Sponsor organisation address	Albert-Schweitzer-Campus 1, Gebäude D5, Münster, Germany, 48149
Public contact	SIOP CNS GCT II-Studienleitung, Universitätsklinikum Münster, 0049 15144048563, Gabriele.Calaminus@ukmuenster.de
Scientific contact	SIOP CNS GCT II-Studienleitung, Universitätsklinikum Münster, 0049 15144048563, Gabriele.Calaminus@ukmuenster.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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	10 November 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 June 2020
Global end of trial reached?	Yes
Global end of trial date	30 June 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Germinoma:
-To maintain current high event-free survival (EFS) rates using a risk adapted approach
-In localised germinoma: to omit whole brain and spinal irradiation by using combined treatment with standard chemotherapy and ventricular irradiation (+/- boosts)
-In bifocal tumours (pineal + suprasellar): to treat as non-metastatic disease and to omit whole brain and spinal irradiation by using combined treatment with standard chemotherapy and ventricular irradiation (+/- boosts)
-In metastatic disease: to maintain current excellent EFS in metastatic germinoma with craniospinal irradiation
Malignant non-germinoma:
-To improve EFS in high risk patients by intensifying treatment
-by dose escalation of chemotherapy in patients identified as high risk at diagnosis
-by standardising the surgical approach for residual disease after treatment
Teratoma:
-To register patients and collect data regarding diagnostics, treatment and outcome in order to develop future treatment strategies

Protection of trial subjects:

This study was 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). Prior to recruitment of subjects, the relevant authorities and ethics committees had to approve and authorize this clinical trial. Amendments were only implemented after approval. Before the procedures mentioned in the protocol were performed, the subject or his/her parent/legal guardian had to sign and date the approved informed consent form according to the requirements of national law.

Background therapy:

Supportive care during chemotherapy
Diabetes Insipidus (DI) is a common complication encountered in the treatment of malignant CNS GCTs. DI should be controlled prior to starting chemotherapy, and particular attention should be paid to sodium and fluid balance throughout treatment in all cases. Clinicians were advised to work closely with their colleagues in endocrinology.
Anti-emetic treatment should have included a 5HT antagonist. Administration of steroids (e.g. dexamethasone) during chemotherapy should be avoided if at all possible, and only used for anti-emesis if other therapies had failed. If symptoms of raised intracranial pressure developed during treatment, the cause (e.g. hydrocephalus) should be actively sought. Steroids should only be used as a short-term measure prior to definitive treatment of raised pressure. In patients with raised intracranial pressure at the time of the first chemotherapy course, particular care should be taken about hyperhydration. In such cases therapy modifications should be discussed with the co-ordinator.
The prophylactic use of cotrimoxazole (sulfamethoxazole/trimethoprim) was optional and should be based on local practice, as no case of pneumocystis carinii infection had been reported in the SIOP CNS GCT 96 series. Prophylactic antibiotic/antifungal decontamination could be used if it is the normal practice in the treating hospital. The choice of antibiotics used during episodes of febrile neutropenia should be based on local guidelines.

Evidence for comparator: -

Actual start date of recruitment	06 October 2011
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	Sweden: 18
Country: Number of subjects enrolled	United Kingdom: 83
Country: Number of subjects enrolled	Austria: 8
Country: Number of subjects enrolled	France: 128
Country: Number of subjects enrolled	Germany: 140
Country: Number of subjects enrolled	Italy: 3
Country: Number of subjects enrolled	Norway: 5
Country: Number of subjects enrolled	Switzerland: 9
Worldwide total number of subjects	394
EEA total number of subjects	385

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	5
Infants and toddlers (28 days-23 months)	5
Children (2-11 years)	134
Adolescents (12-17 years)	156
Adults (18-64 years)	94
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The patients were recruited from 100 trial sites in 8 countries. The recruitment period was from 06 October 2011 to 01 July 2018. The first patient was enrolled on the 07 February 2012 and the last one was diagnosed on the 26 June 2018.

Pre-assignment

Screening details:

The study included patients with Intracranial Germ Cell tumours of any histology and intracranial site and dissemination.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Mal. Non-Germinoma

Arm description:

Study patients with a malignant non-germinoma GCT. In this diagnostic group, patients received the following treatment:
- Patients with standard risk received standard chemotherapy consisting of four courses of cisplatin, etoposide and ifosfamide. High risk patients received 2 cycles of standard chemotherapy followed by two dose intensified courses of cisplatin, etoposide and ifosfamide with stem cell support.
- After 3 courses of chemotherapy, resection of the residual tumor was performed (if indicated), If viable cells were found in the resected tumour specimen, the patients were transferred to the high risk arm.
- Chemotherapy was followed by radiotherapy for both risk groups.

Arm type	Experimental
Investigational medicinal product name	Cisplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Cisplatin was administered on days 1 to 5 of 21-day cycles 1 to 4 at a dose of 20 mg/m²/day.

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

Dosage and administration details:

Standard risk: Etoposide was administered on days 1 to 3 of 21-day cycles 1 to 4 at a dose of 100 mg/m²/day.
High risk: Etoposide was given on days 1 to 3 of the first two 21-day cycles at a dose of 100 mg/m²/day. On cycles 3 and 4, Etoposide was administered on days 1 to 5 at a dose of 300 mg/m²/day (high dose).

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

Dosage and administration details:

Standard risk: Ifosfamide was administered on days 1 to 5 of 21-day cycles 1 to 4 at a dose of 1500 mg/m²/day.
High risk: Ifosfamide was given on days 1 to 5 of the first two 21-day cycles at a dose of 1500 mg/m²/day. On cycles 3 and 4, Ifosfamide was administered on days 1 to 5 at a dose of 2000 mg/m²/day (high dose).

Arm title	Germinoma

Arm description:

Study patients with a germinoma GCT. In this diagnostic group, patients received the following treatment:
- Non-metastatic fully staged germinoma (± teratoma): Chemotherapy consisting of two courses (1 and 3) of carboplatin and etoposide, alternating with two courses (2 and 4) of ifosfamide and etoposide. Chemotherapy was followed by radiotherapy.
- Metastatic or incompletely staged germinomas (± teratoma): Received only radiotherapy.

Arm type	Experimental
Investigational medicinal product name	Carboplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Carboplatin was given on day 1 of 21-day cycles 1 and 3 at a dose of 600 mg/m²/day.

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

Dosage and administration details:

Ifosfamide was administered on day 1 to 5 of 21-day cycles 2 and 4 at a dose of 1800 mg/m²/day.

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

Dosage and administration details:

Etoposide was given on days 1 to 3 of 21-day cycles 1 to 4 at a dose of 100 mg/m²/day.

Arm title	Teratoma

Arm description:

Study patients with intracranial teratomas were registered in order to obtain better information regarding the epidemiology and biology of this rare disease. Teratoma were treated by surgery as main treatment option and additional treatment according to histology and resection status. Treatment for mature and immature teratoma had to be individualised, based on the age of the patient, clinical status, tumour stage and histology. Thus, no overall therapeutic strategy was outlined in the protocol but recommendations were given on an individual basis.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 1	Mal. Non-Germinoma	Germinoma	Teratoma
Started	112	261	21
Completed	97	260	20
Not completed	15	1	1
Tumor-related death	15	1	1

Baseline characteristics

Reporting groups

Reporting group title	Mal. Non-Germinoma

Reporting group description:

Study patients with a malignant non-germinoma GCT. In this diagnostic group, patients received the following treatment:
- Patients with standard risk received standard chemotherapy consisting of four courses of cisplatin, etoposide and ifosfamide. High risk patients received 2 cycles of standard chemotherapy followed by two dose intensified courses of cisplatin, etoposide and ifosfamide with stem cell support.
- After 3 courses of chemotherapy, resection of the residual tumor was performed (if indicated), If viable cells were found in the resected tumour specimen, the patients were transferred to the high risk arm.
- Chemotherapy was followed by radiotherapy for both risk groups.

Reporting group title	Germinoma

Reporting group description:

Study patients with a germinoma GCT. In this diagnostic group, patients received the following treatment:
- Non-metastatic fully staged germinoma (± teratoma): Chemotherapy consisting of two courses (1 and 3) of carboplatin and etoposide, alternating with two courses (2 and 4) of ifosfamide and etoposide. Chemotherapy was followed by radiotherapy.
- Metastatic or incompletely staged germinomas (± teratoma): Received only radiotherapy.

Reporting group title	Teratoma

Reporting group description:

Study patients with intracranial teratomas were registered in order to obtain better information regarding the epidemiology and biology of this rare disease. Teratoma were treated by surgery as main treatment option and additional treatment according to histology and resection status. Treatment for mature and immature teratoma had to be individualised, based on the age of the patient, clinical status, tumour stage and histology. Thus, no overall therapeutic strategy was outlined in the protocol but recommendations were given on an individual basis.

Reporting group values	Mal. Non-Germinoma	Germinoma	Teratoma
Number of subjects	112	261	21
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	5
Infants and toddlers (28 days-23 months)	1	0	4
Children (2-11 years)	42	83	9
Adolescents (12-17 years)	50	104	2
Adults (18-64 years)	19	74	1
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	13.45	15.79	5.32
standard deviation	± 4.87	± 6.35	± 5.94
Gender categorical Units: Subjects			
Female	23	52	7
Male	89	209	14

Reporting group values	Total		
Number of subjects	394		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	5		
Infants and toddlers (28 days-23 months)	5		
Children (2-11 years)	134		
Adolescents (12-17 years)	156		
Adults (18-64 years)	94		
From 65-84 years	0		
85 years and over	0		
Age continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical Units: Subjects			
Female	82		
Male	312		

End points

End points reporting groups

Reporting group title	Mal. Non-Germinoma

Reporting group description:

Study patients with a malignant non-germinoma GCT. In this diagnostic group, patients received the following treatment:
- Patients with standard risk received standard chemotherapy consisting of four courses of cisplatin, etoposide and ifosfamide. High risk patients received 2 cycles of standard chemotherapy followed by two dose intensified courses of cisplatin, etoposide and ifosfamide with stem cell support.
- After 3 courses of chemotherapy, resection of the residual tumor was performed (if indicated), If viable cells were found in the resected tumour specimen, the patients were transferred to the high risk arm.
- Chemotherapy was followed by radiotherapy for both risk groups.

Reporting group title	Germinoma

Reporting group description:

Study patients with a germinoma GCT. In this diagnostic group, patients received the following treatment:
- Non-metastatic fully staged germinoma (± teratoma): Chemotherapy consisting of two courses (1 and 3) of carboplatin and etoposide, alternating with two courses (2 and 4) of ifosfamide and etoposide. Chemotherapy was followed by radiotherapy.
- Metastatic or incompletely staged germinomas (± teratoma): Received only radiotherapy.

Reporting group title	Teratoma

Reporting group description:

Study patients with intracranial teratomas were registered in order to obtain better information regarding the epidemiology and biology of this rare disease. Teratoma were treated by surgery as main treatment option and additional treatment according to histology and resection status. Treatment for mature and immature teratoma had to be individualised, based on the age of the patient, clinical status, tumour stage and histology. Thus, no overall therapeutic strategy was outlined in the protocol but recommendations were given on an individual basis.

Primary: 3-year Event Free Survival probability - ITT

End point title	3-year Event Free Survival probability - ITT

End point description:

The probability of Event Free Survival (pEFS) at 3 years was estimated according to the Kaplan-Meier method. The analysis was performed using the "intention to treat" (ITT) principle for all study patients of the respective diagnostic groups (Germinoma, Non-Germinoma and Teratoma).

End point type	Primary

End point timeframe:

From date of diagnosis to first event (death from any cause, relapse, progressive disease on therapy or second malignancy).

End point values	Mal. Non-Germinoma	Germinoma	Teratoma	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	112	261	21	
Units: percent				
number (confidence interval 95%)	69.7 (59.6 to 77.7)	96.2 (92.9 to 98.0)	80.7 (56.3 to 92.3)	

Statistical analyses

Statistical analysis title	Final analysis (Intention to treat)

Statistical analysis description:

The log-rank test was used to compare the groups.

Comparison groups	Germinoma v Teratoma v Mal. Non-Germinoma
Number of subjects included in analysis	394
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Logrank

Primary: 3-year Event Free Survival probability - PP

End point title	3-year Event Free Survival probability - PP

End point description:

The probability of event-free survival (pEFS) at 3 years was estimated according to the Kaplan-Meier method. The analysis was performed using the "per protocol" (PP) principle for all study patients of the respective diagnostic groups (Germinoma, Non-Germinoma and Teratoma). Patients for the PP analysis were all patients with complete diagnostic procedures, administration of all blocks of chemotherapy required by the protocol and radiotherapy delivered according to the protocol with dosage deviations less than 10%. Patients, who died during treatment were analysed in the PP analysis.

End point type	Primary

End point timeframe:

From date of diagnosis to first event (death from any cause, relapse, progressive disease on therapy or second malignancy).

End point values	Mal. Non-Germinoma	Germinoma	Teratoma	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	71	215	20	
Units: percent				
number (confidence interval 95%)	67.6 (54.0 to 78.0)	97.0 (93.3 to 98.6)	85.0 (60.4 to 94.9)	

Statistical analyses

Statistical analysis title	Final analysis (Per Protocol)

Statistical analysis description:

The log-rank test was used to compare the groups.

Comparison groups	Mal. Non-Germinoma v Germinoma v Teratoma
Number of subjects included in analysis	306
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Logrank

Secondary: 3-year Survival probability - ITT

End point title	3-year Survival probability - ITT

End point description:

The probability of Survival at 3 years was estimated according to the Kaplan-Meier method. The analysis was performed according to the "intention to treat" (ITT) principle for all study patients of the respective diagnostic groups (Germinoma, Non-Germinoma and Teratoma).

End point type	Secondary

End point timeframe:

From date of diagnosis to death from any cause.

End point values	Mal. Non-Germinoma	Germinoma	Teratoma	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	112	261	21	
Units: percent				
number (confidence interval 95%)	81.0 (71.5 to 87.6)	99.6 (97.1 to 99.9)	95.2 (70.7 to 99.3)	

Statistical analyses

Statistical analysis title	Final analysis (Intention to treat)

Statistical analysis description:

The log-rank test was used to compare the groups.

Comparison groups	Mal. Non-Germinoma v Germinoma v Teratoma
Number of subjects included in analysis	394
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Logrank

Secondary: 3-year Survival probability - PP

End point title	3-year Survival probability - PP

End point description:

The probability of Survival (pEFS) at 3 years was estimated according to the Kaplan-Meier method. The analysis was performed according to the "per protocol" (PP) principle for all study patients of the respective diagnostic groups (Germinoma, Non-Germinoma and Teratoma). Patients for the PP analysis were all patients with complete diagnostic procedures, administration of all blocks of chemotherapy required by the protocol and radiotherapy delivered according to the protocol with dosage deviations less than 10%. Patients, who died during treatment were analysed in the PP analysis.

End point type	Secondary

End point timeframe:

From date of diagnosis to death from any cause.

End point values	Mal. Non-Germinoma	Germinoma	Teratoma	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	71	215	20	
Units: percent				
number (confidence interval 95%)	84.4 (72.4 to 91.4)	99.5 (96.6 to 99.9)	95.0 (69.5 to 99.3)	

Statistical analyses

Statistical analysis title	Final analysis (Per Protocol)
Statistical analysis description: The log-rank test was used to compare the groups.	
Comparison groups	Mal. Non-Germinoma v Germinoma v Teratoma
Number of subjects included in analysis	306
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Logrank

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first day of study treatment until end of study follow-up (2 years after treatment initiation).

Adverse event reporting additional description:

SAEs were reported in compliance with the law. In the eCRF, however, only toxicities according to CTCAE were documented without information on whether they were serious. Therefore, severe toxicities (CTC grade >=3, hematologic: CTC grade 4) were reported here as SAE and non-severe toxicities (CTC grade 1-2, hematologic: CTC grade 1-3) as non-SAE.

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	3.0

Reporting groups

Reporting group title	Mal. Non-Germinoma

Reporting group description:

All study patients with a malignant non-germinoma GCT who received study treatment. In this reporting group, 15 tumor-related deaths occurred.
Because the causal relationship between treatment and the occurrence of toxicity was not recorded in the eCRF, 0 is entered here under „Serious adverse events" for „Occurrences causally related to treatment".

Reporting group title	Germinoma

Reporting group description:

All study patients with a germinoma GCT who received study treatment. In this reporting group, one tumor-related death occurred.
Because the causal relationship between treatment and the occurrence of toxicity was not recorded in the eCRF, 0 is entered here under „Serious adverse events" for „Occurrences causally related to treatment".

Serious adverse events	Mal. Non-Germinoma	Germinoma	
Total subjects affected by serious adverse events			
subjects affected / exposed	99 / 112 (88.39%)	170 / 261 (65.13%)	
number of deaths (all causes)	15	1	
number of deaths resulting from adverse events	0	0	
Investigations			
Hemoglobin			
subjects affected / exposed	24 / 112 (21.43%)	15 / 261 (5.75%)	
occurrences causally related to treatment / all	0 / 34	0 / 18	
deaths causally related to treatment / all	0 / 0	0 / 0	
WBC			
subjects affected / exposed	89 / 112 (79.46%)	110 / 261 (42.15%)	
occurrences causally related to treatment / all	0 / 256	0 / 203	
deaths causally related to treatment / all	0 / 0	0 / 0	

Neutrophils			
subjects affected / exposed	90 / 112 (80.36%)	149 / 261 (57.09%)	
occurrences causally related to treatment / all	0 / 271	0 / 405	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelets			
subjects affected / exposed	66 / 112 (58.93%)	56 / 261 (21.46%)	
occurrences causally related to treatment / all	0 / 129	0 / 80	
deaths causally related to treatment / all	0 / 0	0 / 0	
Creatinine			
subjects affected / exposed	1 / 112 (0.89%)	1 / 261 (0.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glomerular filtration			
subjects affected / exposed	1 / 112 (0.89%)	3 / 261 (1.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tubular phosphate r.			
subjects affected / exposed	3 / 112 (2.68%)	2 / 261 (0.77%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypernatremia			
subjects affected / exposed	14 / 112 (12.50%)	11 / 261 (4.21%)	
occurrences causally related to treatment / all	0 / 27	0 / 16	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatremia			
subjects affected / exposed	28 / 112 (25.00%)	34 / 261 (13.03%)	
occurrences causally related to treatment / all	0 / 55	0 / 44	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalemia			
subjects affected / exposed	10 / 112 (8.93%)	2 / 261 (0.77%)	
occurrences causally related to treatment / all	0 / 12	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalemia			

subjects affected / exposed	18 / 112 (16.07%)	10 / 261 (3.83%)	
occurrences causally related to treatment / all	0 / 26	0 / 15	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypophosphatemia			
subjects affected / exposed	19 / 112 (16.96%)	1 / 261 (0.38%)	
occurrences causally related to treatment / all	0 / 31	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypermagnesemia			
subjects affected / exposed	22 / 112 (19.64%)	11 / 261 (4.21%)	
occurrences causally related to treatment / all	0 / 42	0 / 15	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypomagnesemia			
subjects affected / exposed	1 / 112 (0.89%)	1 / 261 (0.38%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcemia			
subjects affected / exposed	3 / 112 (2.68%)	1 / 261 (0.38%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypocalcemia			
subjects affected / exposed	7 / 112 (6.25%)	2 / 261 (0.77%)	
occurrences causally related to treatment / all	0 / 8	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acidosis			
subjects affected / exposed	12 / 112 (10.71%)	6 / 261 (2.30%)	
occurrences causally related to treatment / all	0 / 20	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Headache			
subjects affected / exposed	6 / 112 (5.36%)	6 / 261 (2.30%)	
occurrences causally related to treatment / all	0 / 6	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral neurotox.			

subjects affected / exposed	8 / 112 (7.14%)	6 / 261 (2.30%)	
occurrences causally related to treatment / all	0 / 9	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Central neurotox.			
subjects affected / exposed	5 / 112 (4.46%)	2 / 261 (0.77%)	
occurrences causally related to treatment / all	0 / 6	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Hemorrhage			
subjects affected / exposed	4 / 112 (3.57%)	1 / 261 (0.38%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fever			
subjects affected / exposed	6 / 112 (5.36%)	3 / 261 (1.15%)	
occurrences causally related to treatment / all	0 / 7	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	23 / 112 (20.54%)	10 / 261 (3.83%)	
occurrences causally related to treatment / all	0 / 37	0 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	13 / 112 (11.61%)	12 / 261 (4.60%)	
occurrences causally related to treatment / all	0 / 15	0 / 13	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	10 / 112 (8.93%)	1 / 261 (0.38%)	
occurrences causally related to treatment / all	0 / 15	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhea			
subjects affected / exposed	3 / 112 (2.68%)	3 / 261 (1.15%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			

subjects affected / exposed	1 / 112 (0.89%)	0 / 261 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Hearing			
subjects affected / exposed	3 / 112 (2.68%)	1 / 261 (0.38%)	
occurrences causally related to treatment / all	0 / 6	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Audiometry			
subjects affected / exposed	2 / 112 (1.79%)	0 / 261 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Allergic reaction/hypersensitivity			
subjects affected / exposed	0 / 112 (0.00%)	1 / 261 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Liver			
subjects affected / exposed	4 / 112 (3.57%)	1 / 261 (0.38%)	
occurrences causally related to treatment / all	0 / 7	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Changes in the skin			
subjects affected / exposed	0 / 112 (0.00%)	1 / 261 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erythema multiform.			
subjects affected / exposed	1 / 112 (0.89%)	0 / 261 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Proteinuria			

subjects affected / exposed	1 / 112 (0.89%)	0 / 261 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal			
subjects affected / exposed	1 / 112 (0.89%)	0 / 261 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Endocrine			
subjects affected / exposed	1 / 112 (0.89%)	1 / 261 (0.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Infection			
subjects affected / exposed	24 / 112 (21.43%)	21 / 261 (8.05%)	
occurrences causally related to treatment / all	0 / 37	0 / 23	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Mal. Non-Germinoma	Germinoma	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	110 / 112 (98.21%)	255 / 261 (97.70%)	
Investigations			
Hemoglobin			
subjects affected / exposed	82 / 112 (73.21%)	201 / 261 (77.01%)	
occurrences (all)	387	726	
WBC			
subjects affected / exposed	16 / 112 (14.29%)	119 / 261 (45.59%)	
occurrences (all)	174	553	
Neutrophils			
subjects affected / exposed	13 / 112 (11.61%)	64 / 261 (24.52%)	
occurrences (all)	107	265	
Platelets			

subjects affected / exposed	32 / 112 (28.57%)	138 / 261 (52.87%)	
occurrences (all)	197	316	
Creatinine			
subjects affected / exposed	35 / 112 (31.25%)	33 / 261 (12.64%)	
occurrences (all)	68	65	
Glomerular filtration			
subjects affected / exposed	23 / 112 (20.54%)	18 / 261 (6.90%)	
occurrences (all)	39	32	
Tubular phosphate r.			
subjects affected / exposed	5 / 112 (4.46%)	9 / 261 (3.45%)	
occurrences (all)	5	10	
Hypernatremia			
subjects affected / exposed	32 / 112 (28.57%)	42 / 261 (16.09%)	
occurrences (all)	78	90	
Hyponatremia			
subjects affected / exposed	33 / 112 (29.46%)	46 / 261 (17.62%)	
occurrences (all)	96	115	
Hyperkalemia			
subjects affected / exposed	29 / 112 (25.89%)	39 / 261 (14.94%)	
occurrences (all)	54	59	
Hypokalemia			
subjects affected / exposed	36 / 112 (32.14%)	47 / 261 (18.01%)	
occurrences (all)	93	79	
Hypophosphatemia			
subjects affected / exposed	37 / 112 (33.04%)	53 / 261 (20.31%)	
occurrences (all)	98	94	
Hypermagnesemia			
subjects affected / exposed	33 / 112 (29.46%)	27 / 261 (10.34%)	
occurrences (all)	82	51	
Hypomagnesemia			
subjects affected / exposed	28 / 112 (25.00%)	29 / 261 (11.11%)	
occurrences (all)	49	53	
Hypercalcemia			
subjects affected / exposed	13 / 112 (11.61%)	17 / 261 (6.51%)	
occurrences (all)	26	33	
Hypocalcemia			

subjects affected / exposed	51 / 112 (45.54%)	51 / 261 (19.54%)	
occurrences (all)	132	93	
Acidosis			
subjects affected / exposed	17 / 112 (15.18%)	19 / 261 (7.28%)	
occurrences (all)	33	34	
Cardiac disorders			
Cardiac function			
subjects affected / exposed	2 / 112 (1.79%)	3 / 261 (1.15%)	
occurrences (all)	4	3	
Nervous system disorders			
Headache			
subjects affected / exposed	64 / 112 (57.14%)	122 / 261 (46.74%)	
occurrences (all)	132	186	
Peripheral neurotox.			
subjects affected / exposed	22 / 112 (19.64%)	23 / 261 (8.81%)	
occurrences (all)	31	30	
Central neurotox.			
subjects affected / exposed	35 / 112 (31.25%)	40 / 261 (15.33%)	
occurrences (all)	59	52	
General disorders and administration site conditions			
Hemorrhage			
subjects affected / exposed	1 / 112 (0.89%)	8 / 261 (3.07%)	
occurrences (all)	3	10	
Fever			
subjects affected / exposed	69 / 112 (61.61%)	97 / 261 (37.16%)	
occurrences (all)	158	165	
Nausea			
subjects affected / exposed	68 / 112 (60.71%)	182 / 261 (69.73%)	
occurrences (all)	254	471	
Vomiting			
subjects affected / exposed	84 / 112 (75.00%)	133 / 261 (50.96%)	
occurrences (all)	254	292	
Stomatitis			
subjects affected / exposed	22 / 112 (19.64%)	28 / 261 (10.73%)	
occurrences (all)	37	38	
Diarrhea			

subjects affected / exposed	35 / 112 (31.25%)	40 / 261 (15.33%)	
occurrences (all)	63	59	
Pain			
subjects affected / exposed	4 / 112 (3.57%)	13 / 261 (4.98%)	
occurrences (all)	9	15	
Ear and labyrinth disorders			
Hearing			
subjects affected / exposed	29 / 112 (25.89%)	13 / 261 (4.98%)	
occurrences (all)	60	23	
Audiometry			
subjects affected / exposed	26 / 112 (23.21%)	9 / 261 (3.45%)	
occurrences (all)	49	15	
Hepatobiliary disorders			
Liver			
subjects affected / exposed	11 / 112 (9.82%)	19 / 261 (7.28%)	
occurrences (all)	24	35	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	78 / 112 (69.64%)	192 / 261 (73.56%)	
occurrences (all)	228	490	
Changes in the skin			
subjects affected / exposed	46 / 112 (41.07%)	82 / 261 (31.42%)	
occurrences (all)	68	94	
Erythema multiform.			
subjects affected / exposed	12 / 112 (10.71%)	18 / 261 (6.90%)	
occurrences (all)	16	19	
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	19 / 112 (16.96%)	19 / 261 (7.28%)	
occurrences (all)	31	31	
Hematuria			
subjects affected / exposed	33 / 112 (29.46%)	21 / 261 (8.05%)	
occurrences (all)	54	30	
Endocrine disorders			
Endocrine			
subjects affected / exposed	2 / 112 (1.79%)	3 / 261 (1.15%)	
occurrences (all)	4	6	

Infections and infestations Infection subjects affected / exposed occurrences (all)	 47 / 112 (41.96%) 101	 66 / 261 (25.29%) 103	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 December 2015	- Additional information on the management of certain toxicities has been added. - Evaluation time points were adapted. - Further details on the administration of chemotherapy were provided. - The SAE chapter has been amended. - New side effects of the study therapy were added and explained.
26 April 2018	- Additional information about replacement of cisplatin with carboplatin were added (Chemotherapy in malignant non-germinoma). - Information on time management in case of SAE were amended. - The extension of the recruitment period for the study by two years was added.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported