



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 BE |
| 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 (\pm 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 (\pm 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 (\pm 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 (\pm 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 | \pm 4.87 | \pm 6.35 | \pm 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 (\pm 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 (\pm 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 occurrences (all) | 51 / 112 (45.54%) 132 | 51 / 261 (19.54%) 93 | |
| Acidosis subjects affected / exposed occurrences (all) | 17 / 112 (15.18%) 33 | 19 / 261 (7.28%) 34 | |
| Cardiac disorders Cardiac function subjects affected / exposed occurrences (all) | 2 / 112 (1.79%) 4 | 3 / 261 (1.15%) 3 | |
| Nervous system disorders Headache subjects affected / exposed occurrences (all) | 64 / 112 (57.14%) 132 | 122 / 261 (46.74%) 186 | |
| Peripheral neurotox. subjects affected / exposed occurrences (all) | 22 / 112 (19.64%) 31 | 23 / 261 (8.81%) 30 | |
| Central neurotox. subjects affected / exposed occurrences (all) | 35 / 112 (31.25%) 59 | 40 / 261 (15.33%) 52 | |
| General disorders and administration site conditions Hemorrhage subjects affected / exposed occurrences (all) | 1 / 112 (0.89%) 3 | 8 / 261 (3.07%) 10 | |
| Fever subjects affected / exposed occurrences (all) | 69 / 112 (61.61%) 158 | 97 / 261 (37.16%) 165 | |
| Nausea subjects affected / exposed occurrences (all) | 68 / 112 (60.71%) 254 | 182 / 261 (69.73%) 471 | |
| Vomiting subjects affected / exposed occurrences (all) | 84 / 112 (75.00%) 254 | 133 / 261 (50.96%) 292 | |
| Stomatitis subjects affected / exposed occurrences (all) | 22 / 112 (19.64%) 37 | 28 / 261 (10.73%) 38 | |
| Diarrhea | | | |

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

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

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 17 December 2015 | <ul style="list-style-type: none">- 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 | <ul style="list-style-type: none">- 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