



Clinical trial results:

OSSII-TTP Evaluation chez l'enfant et l'adulte présentant une rechute d'ostéosarcome de l'efficacité et de la tolérance d'un traitement adjuvant par Thiotépa® haute dose associé à une chimiothérapie conventionnelle
OSII-TTP A multicentric randomized phase II clinical trial evaluating high-dose thiotepa as adjuvant treatment to standard chemotherapy in patients with resectable relapsed osteosarcoma

Summary

| | |
|--------------------------|-----------------|
| EudraCT number | 2009-009899-12 |
| Trial protocol | FR |
| Global end of trial date | 23 October 2018 |

Results information

| | |
|-----------------------------------|--|
| Result version number | v1 (current) |
| This version publication date | 13 March 2021 |
| First version publication date | 13 March 2021 |
| Summary attachment (see zip file) | Publication OSII-TTP (10.1016j.ejca.2019.11.007.pdf) |

Trial information

Trial identification

| | |
|-----------------------|------------|
| Sponsor protocol code | ET2008-044 |
|-----------------------|------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT00978471 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Centre Léon Bérard |
| Sponsor organisation address | 28 rue Laennec, LYON, France, 69008 |
| Public contact | Dr Perrine MAREC-BERARD, Centre Léon Bérard, 33 478782828, DRCIreglementaire@lyon.unicancer.fr |
| Scientific contact | Dr Perrine MAREC-BERARD, Centre Léon Bérard, 33 478782828, DRCIreglementaire@lyon.unicancer.fr |

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 | 23 October 2018 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 23 October 2018 |
| Global end of trial reached? | Yes |
| Global end of trial date | 23 October 2018 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The primary endpoint was overall survival (OS), defined as the time from randomisation until death from any cause

Protection of trial subjects:

follow-up will be performed at the end of the 2nd and 4th courses of conventional chemotherapy, following the administration of thiotepa (if applicable), 8 weeks after the end of the therapeutic program, 3 months and 6 months after the end of the treatment, then every 6 months until the end of the study (3 years after inclusion of the last patient). Beyond this period, monitoring will be carried out according to the habits of each center.

Background therapy: -

Evidence for comparator: -

| | |
|---|-------------------|
| Actual start date of recruitment | 16 September 2009 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|------------|
| Country: Number of subjects enrolled | France: 44 |
| Worldwide total number of subjects | 44 |
| EEA total number of subjects | 44 |

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) | 10 |
| Adolescents (12-17 years) | 20 |
| Adults (18-64 years) | 14 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Randomization will be carried out following the second course of conventional chemotherapy, after the radiological evaluation of the targets scheduled between D14 and D21 after the 2nd course. It will be stratified on the criterion "single lesion" "multiple lesions" at the time of the relapse.

Pre-assignment

Screening details:

Inclusion will be made at the time of diagnosis of the relapse, after operability has been confirmed (immediate or delayed).

Period 1

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

Arms

| | |
|------------------------------|--------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Experimental |

Arm description:

4 courses of conventional chemotherapy followed by high-dose chemotherapy with thiotepa associated with autologous PSC. Resection surgery of all tumor locations will be performed as soon as it is deemed possible.

| | |
|--|---|
| Arm type | Experimental |
| Investigational medicinal product name | THIOTEPA |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate and solvent for concentrate for solution for infusion |
| Routes of administration | Intravascular use |

Dosage and administration details:

The reconstituted solution is hypotonic and must be diluted before administration in 500 ml of 9 mg / ml (0.9%) sodium chloride solution for injections.

In the experimental arm, thiotepa will be administered 3 to 4 weeks after the last course of conventional chemotherapy (within a period of 8 weeks maximum), 3 days in a row, by an intravenous infusion over two hours at a dose of 300 mg/ m²/day, i.e. a total dose of 900 mg/m² for one treatment.

| | |
|--|---|
| Arm title | Conventional chemotherapy |
| Arm description: 4 courses of conventional chemotherapy. Surgery resection of all tumor locations will be performed as soon as it is deemed possible. | |
| Arm type | Active comparator |
| Investigational medicinal product name | Adriamycin, ifosfamide, cisplatin, etoposide |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate and solvent for solution for injection/infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

It will include 4 courses spaced 21 days apart, according to a scheme therapy optimized according to the first-line treatment protocol and the histological response to the initial treatment. This optimization will make it possible to maintain the cumulative doses of A, I, P and E at 450 mg, 120 g, 600 mg and 3000 mg, respectively. The regimens proposed below are recommended depending on the 1st line treatments, but each investigator can adapt this treatment on a case-by-case basis, respecting the number of cures, the interval between each course and the maximum cumulative doses.

| Number of subjects in period 1 | Experimental | Conventional chemotherapy |
|---------------------------------------|--------------|---------------------------|
| Started | 22 | 22 |
| Completed | 22 | 22 |

Baseline characteristics

End points

End points reporting groups

| | |
|--|---------------------------|
| Reporting group title | Experimental |
| Reporting group description: 4 courses of conventional chemotherapy followed by high-dose chemotherapy with thiotepa associated with autologous PSC. Resection surgery of all tumor locations will be performed as soon as it is deemed possible. | |
| Reporting group title | Conventional chemotherapy |
| Reporting group description: 4 courses of conventional chemotherapy. Surgery resection of all tumor locations will be performed as soon as it is deemed possible. | |

Primary: Primary end point

| | |
|--|----------------------------------|
| End point title | Primary end point ^[1] |
| End point description: The primary endpoint was overall survival (OS), defined as the time from randomisation until death from any cause. | |
| End point type | Primary |
| End point timeframe: Month | |

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: OS, PFS, and PR-S were estimated with the KaplanMeier method and were described in terms of median and survival rates (at 1- and 2-year) in each arm, along with the associated two-sided 95% confidence intervals (CIs) for the estimates. Survival distributions were compared between the two study arms using a logrank test, supported by a Cox regression to estimate the HR and its 95% CIs. Median follow-up (minemax) was calculated using the reverse KaplanMeier method.

| End point values | Experimental | Conventional chemotherapy | | |
|-----------------------------|-----------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 22 | 22 | | |
| Units: Month | 22 | 22 | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information^[1]

Timeframe for reporting adverse events:

The investigator collects (spontaneous patient report or questioning) and immediately notifies the sponsor of all SAEs, in a written report, whether or not they are deemed to be attributable to research and which occur during the study.

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|--------------------|--------|
| Dictionary name | MedDRA |
| Dictionary version | 21.0 |

Frequency threshold for reporting non-serious adverse events: 5 %

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.

Justification: The majority of patients in both treatment arms experienced AEs (17 [77.3%] patients in arm A; 19

[86.4%] patients in arm B), including at least one grade ≥ 3 AE (A: 16 [72.7%]; B: 18 [81.8%]). Nine patients experienced serious AEs (A: 5; B: 4). To note, several unexpected serious adverse events occurred in Arm A in

one patient (pancytopenia grade 4, gastrointestinal disorders, including stomatitis grade 3, oesophagitis grade

3, anal inflammation grade 4); no toxic death was observed.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|--|
| 04 June 2009 | Modification of 2 inclusion and randomization criteria |
| 08 February 2011 | Collection of intercurrent AEs and SAEs at randomization and those occurring following randomization Collection only of AEs of grade ≥ 2 according to NCI-CTCAE V4 |
| 12 September 2011 | Extension of the duration of inclusions by 24 months |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date | Interruption | Restart date |
|------------------|---|-----------------|
| 08 November 2011 | Temporary stop of inclusions following the withdrawal of Thiotépa from the market on 13/10/11. Awaiting new lots. | 26 October 2012 |

Notes:

Limitations and caveats

None reported