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 KaplaneMeier 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 logank test, supported by a Cox regression to estimate the HR and its 95% CIs. Median follow-up (minemax) was calculated using the reverse KaplaneMeier 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 questionning) and immediately notifies the sponsor of all SAEs, in a written report, wether or not theay are deemed to be attributable to research and wich 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