Clinical trial results:
Randomized, controlled trial of Platinum-Cetuximab combined either with Docetaxel (TPEx) or with 5FU (Extreme) in patients with recurrent/metastatic squamous cell cancer of the head and neck

Summary

EudraCT number	2014-000048-14
Trial protocol	ES DE
Global end of trial date	31 December 2021

Results information

Result version number	v1 (current)
This version publication date	19 November 2023
First version publication date	19 November 2023
Summary attachment (see zip file)	summary of report (2014-000048-14_Résumé rapport_TPextreme.pdf)

Trial information

Trial identification

Sponsor protocol code	TPEXTREME

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02268695
WHO universal trial number (UTN)	-
Other trial identifiers	TPExtreme: GORTEC 2014-01

Notes:

Sponsors

Sponsor organisation name	GORTEC
Sponsor organisation address	4 Bis Rue Emile Zola, TOURS, France, 37000
Public contact	Laura Sinigaglia, GORTEC, laura.sinigaglia@gortec.fr
Scientific contact	Pr Joël GUIGAY, GORTEC, joel.guigay@gortec.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	20 December 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	31 December 2021
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

to compare in terms of overall survival the TPEx and EXTREME regimens as first line treatment of patients with recurrent / metastatic HN SCC

Protection of trial subjects:

Follow-up of patients according to the protocol calendar, adaptation of treatment or discontinuation of treatment according to toxicities

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	10 October 2014
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	12 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 68
Country: Number of subjects enrolled	France: 409
Country: Number of subjects enrolled	Germany: 64
Worldwide total number of subjects	541
EEA total number of subjects	541

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)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	438
From 65 to 84 years	103

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study is presented to patients during a standard visit by theinvestigator. If the patient agrees to participate and meets the eligibility criteria, then they can be included in the trial.

Pre-assignment

Screening details:

- Histologically confirmed diagnosis squamous cell carcinoma of head and neck: oral cavity, oropharynx, hypopharynx, larynx (histological confirmation is mandatory at least for initial diagnosis).
- Recurrence and/or metastatic disease not suitable for local therapy.
- At least one measurable lesion (RECIST) by CT or MRI.

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	Standard treatment (EXTREME)

Arm description:

6 cycles every 3 weeks
- Cisplatin: 100 mg/m² iv on Day1
- 5FU: 4000 mg/m² total dose starting on day 1 and during 96h in continuous infusion
- Cetuximab: 400 mg/m² iv on Day1 (loading dose), then 250 mg/m² iv weekly.
- If Cisplatin is not tolerated and/or when the total cumulative dose of cisplatin (including prior administration) reaches 600 mg/m², cisplatin has to be replaced by carboplatin, AUC 5, except in the case of bleeding tumor.

Arm type	Active comparator
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:

100 mg/m² iv on Day1

Investigational medicinal product name	5-Fluorouracil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion, Concentrate for solution for injection
Routes of administration	Infusion , Injection

Dosage and administration details:

4000 mg/m² total dose starting on day 1 and during 96h in continuous infusion

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

Dosage and administration details:

400 mg/m² iv on Day1 (loading dose), then 250 mg/m² iv weekly.

Arm title	Experimental treatment (TPEx)

Arm description:

- 4 cycles every 3 weeks
- Cisplatin: 75 mg/m² iv on Day1
- Docetaxel: 75 mg/m² iv on Day1
- Cetuximab: 400 mg/m² iv on Day1 (loading dose) then 250 mg/m² iv weekly.
- If cisplatin is not tolerated, cisplatin has to be replaced by carboplatin, AUC 5, except in the case of bleeding tumor. Primary prophylactic administration of GCSF was administered systematically after each cycle of chemotherapy.

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:

75mg/m² iv on Day1

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

Dosage and administration details:

75 mg/m² iv on Day1

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

Dosage and administration details:

400 mg/m² iv on Day1 (loading dose) then 250 mg/m² iv weekly.

Number of subjects in period 1	Standard treatment (EXTREME)	Experimental treatment (TPEx)
Started	270	271
Completed	118	191
Not completed	152	80
Adverse event, serious fatal	21	10
Physician decision	4	2
Consent withdrawn by subject	17	6
Adverse event, non-fatal	36	20
no treatment received	6	8
other toxicity	-	17
Lost to follow-up	2	1
missing reason	-	1
Tumor progression	34	13
other reason	32	2

Baseline characteristics

Reporting groups	
Reporting group title	Standard treatment (EXTREME)
Reporting group description:	
6 cycles every 3 weeks - Cisplatin: 100 mg/m² iv on Day1 - 5FU: 4000 mg/m² total dose starting on day 1 and during 96h in continuous infusion - Cetuximab: 400 mg/m² iv on Day1 (loading dose), then 250 mg/m² iv weekly. - If Cisplatin is not tolerated and/or when the total cumulative dose of cisplatin (including prior administration) reaches 600 mg/m², cisplatin has to be replaced by carboplatin, AUC 5, except in the case of bleeding tumor.	
Reporting group title	Experimental treatment (TPEx)
Reporting group description:	
- 4 cycles every 3 weeks - Cisplatin: 75 mg/m² iv on Day1 - Docetaxel: 75 mg/m² iv on Day1 - Cetuximab: 400 mg/m² iv on Day1 (loading dose) then 250 mg/m² iv weekly. - If cisplatin is not tolerated, cisplatin has to be replaced by carboplatin, AUC 5, except in the case of bleeding tumor. Primary prophylactic administration of GCSF was administered systematically after each cycle of chemotherapy.	

Reporting group values	Standard treatment (EXTREME)	Experimental treatment (TPEx)	Total
Number of subjects	270	271	541
Age categorical			
Age ≥ 18 years and < 71 years.			
Units: Subjects			
Adults (18-64 years)	223	215	438
From 65-71 years	47	56	103
Age continuous			
Units: years			
median	60	60	
full range (min-max)	23 to 71	38 to 70	-
Gender categorical			
Units: Subjects			
Female	39	31	70
Male	231	240	471

End points

End points reporting groups

Reporting group title	Standard treatment (EXTREME)

Reporting group description:

6 cycles every 3 weeks
- Cisplatin: 100 mg/m² iv on Day1
- 5FU: 4000 mg/m² total dose starting on day 1 and during 96h in continuous infusion
- Cetuximab: 400 mg/m² iv on Day1 (loading dose), then 250 mg/m² iv weekly.
- If Cisplatin is not tolerated and/or when the total cumulative dose of cisplatin (including prior administration) reaches 600 mg/m², cisplatin has to be replaced by carboplatin, AUC 5, except in the case of bleeding tumor.

Reporting group title	Experimental treatment (TPEx)

Reporting group description:

- 4 cycles every 3 weeks
- Cisplatin: 75 mg/m² iv on Day1
- Docetaxel: 75 mg/m² iv on Day1
- Cetuximab: 400 mg/m² iv on Day1 (loading dose) then 250 mg/m² iv weekly.
- If cisplatin is not tolerated, cisplatin has to be replaced by carboplatin, AUC 5, except in the case of bleeding tumor. Primary prophylactic administration of GCSF was administered systematically after each cycle of chemotherapy.

Primary: Overall survival

End point title	Overall survival[1]

End point description:

Overall survival (OS): defined as the time to death from any cause measured from randomization. Patients with disease progression may be treated with off protocol therapy but will be followed for overall survival evaluation.

End point type	Primary

End point timeframe:

At the end of study

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: The analysis of efficacy endpoints was done in the Intent to Treat (ITT) population. The toxicity analysis was done in the population of patients who received at least one administration of chemotherapy or cetuximab.

End point values	Standard treatment (EXTREME)	Experimental treatment (TPEx)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	243	234		
Units: Survival rate				
number (confidence interval 95%)	13.4 (12.2 to 15.8)	14.5 (12.5 to 15.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Objective response rate

End point title	Objective response rate

End point description:

Objective response rate (complete response (CR) or partial response (PR) according to RECIST 1.1 criteria and assessed by central imaging review) at 12 weeks, by local assessment and by centralized review.

End point type	Secondary

End point timeframe:

At the end of trial

End point values	Standard treatment (EXTREME)	Experimental treatment (TPEx)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	270	269		
Units: Survival rate				
number (confidence interval 95%)	5.9 (5.3 to 6.3)	5.1 (4.6 to 6.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Best overall tumor response rate

End point title	Best overall tumor response rate

End point description:

Best overall tumor response rate (RECIST v.1.1 criteria) during treatment by local assessment

End point type	Secondary

End point timeframe:

During the treatment

End point values	Standard treatment (EXTREME)	Experimental treatment (TPEx)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	270	269		
Units: Survival rate				
number (confidence interval 95%)	5.9 (5.3 to 6.3)	5.1 (4.6 to 6.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression free survival (PFS)

End point title	Progression free survival (PFS)

End point description:

Progression free survival (PFS): minimum time from randomization to progression as defined by RECIST v. 1.1 criteria or to death from any cause. Patients who did not have any of these events were censored at the date of last follow-up.

End point type	Secondary

End point timeframe:

from randomization until progression

End point values	Standard treatment (EXTREME)	Experimental treatment (TPEx)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	255	248		
Units: Survival rate				
number (confidence interval 95%)	6.2 (5.8 to 6.7)	6.0 (5.7 to 6.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Progression (TTP)

End point title	Time to Progression (TTP)

End point description:

Time to Progression (TTP): minimum time from randomization to progression as defined by RECIST v.1.1 criteria. In case of death from other cause than cancer and no prior progression, the patient was censored at the time of death. In case of death related to cancer without an accurate date of progression before death, the patient was considered in progression at the time of death. In the event of no progression and no death, the patient was censored at the date of last follow-up.

End point type	Secondary

End point timeframe:

from randomization to progression

End point values	Standard treatment (EXTREME)	Experimental treatment (TPEx)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	235	232		
Units: Survival rate				
median (confidence interval 95%)	6.6 (6.1 to 7.3)	6.2 (5.9 to 7.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Health related quality of life (QoL)

End point title	Health related quality of life (QoL)

End point description:

Health related quality of life (QoL) assessed by EORTC QLQ-C30. The primary endpoint of the QoL study was the global health status/quality of-life scale of the QLQ-C30 questionnaire.

End point type	Secondary

End point timeframe:

During the treatment

End point values	Standard treatment (EXTREME)	Experimental treatment (TPEx)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	270	269		
Units: Survival rate				
arithmetic mean (confidence interval 95%)	57 (55 to 60)	60 (57 to 63)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events (AEs) were described during chemotherapy and during maintenance

Adverse event reporting additional description:

Any SAE which occurs or comes to the attention of the investigator at any time during the study, since study treatment is started and within 30 days after the last administration of study drugs independent of the circumstances or suspected cause, must be reported immediately, within 24 hours of knowledge (at latest on the next working day).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	EXTREME
Reporting group description: -	
Reporting group title	TPEX

Reporting group description: -

Serious adverse events	EXTREME	TPEX	
Total subjects affected by serious adverse events			
subjects affected / exposed	143 / 265 (53.96%)	118 / 263 (44.87%)	
number of deaths (all causes)	243	234	
number of deaths resulting from adverse events	23	16	
Blood and lymphatic system disorders			
Febril neutropenia			
subjects affected / exposed	10 / 265 (3.77%)	21 / 263 (7.98%)	
occurrences causally related to treatment / all	10 / 10	21 / 21	
deaths causally related to treatment / all	6 / 6	3 / 3	
General disorders and administration site conditions			
General physical health deterioration			
subjects affected / exposed	17 / 265 (6.42%)	10 / 263 (3.80%)	
occurrences causally related to treatment / all	17 / 17	10 / 10	
deaths causally related to treatment / all	3 / 3	2 / 2	
Allergic reaction			
subjects affected / exposed	10 / 265 (3.77%)	5 / 263 (1.90%)	
occurrences causally related to treatment / all	10 / 10	5 / 5	
deaths causally related to treatment / all	3 / 3	2 / 2	

Fever			
subjects affected / exposed	6 / 265 (2.26%)	7 / 263 (2.66%)	
occurrences causally related to treatment / all	6 / 6	7 / 7	
deaths causally related to treatment / all	2 / 2	1 / 1	
Fatigue			
subjects affected / exposed	8 / 265 (3.02%)	3 / 263 (1.14%)	
occurrences causally related to treatment / all	8 / 8	3 / 3	
deaths causally related to treatment / all	1 / 1	0 / 0	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	20 / 265 (7.55%)	7 / 263 (2.66%)	
occurrences causally related to treatment / all	20 / 20	7 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucositis oral			
subjects affected / exposed	9 / 265 (3.40%)	8 / 263 (3.04%)	
occurrences causally related to treatment / all	9 / 9	8 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	8 / 265 (3.02%)	4 / 263 (1.52%)	
occurrences causally related to treatment / all	8 / 8	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	4 / 265 (1.51%)	8 / 263 (3.04%)	
occurrences causally related to treatment / all	4 / 4	8 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnea			
subjects affected / exposed	2 / 265 (0.75%)	7 / 263 (2.66%)	
occurrences causally related to treatment / all	2 / 2	7 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Infection (any type)			

subjects affected / exposed	41 / 265 (15.47%)	37 / 263 (14.07%)	
occurrences causally related to treatment / all	41 / 41	37 / 37	
deaths causally related to treatment / all	9 / 9	8 / 8	

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

Non-serious adverse events	EXTREME	TPEX	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	264 / 265 (99.62%)	263 / 263 (100.00%)	
Investigations			
Gamma glutamyl transferase increased			
subjects affected / exposed	135 / 265 (50.94%)	115 / 263 (43.73%)	
occurrences (all)	135	115	
Serum albumine decreased			
subjects affected / exposed	133 / 265 (50.19%)	137 / 263 (52.09%)	
occurrences (all)	133	137	
Alcaline phosphatase increased			
subjects affected / exposed	66 / 265 (24.91%)	64 / 263 (24.33%)	
occurrences (all)	66	64	
Alanine aminotransferase increased			
subjects affected / exposed	57 / 265 (21.51%)	58 / 263 (22.05%)	
occurrences (all)	57	58	
Aspartate aminotransferase increased			
subjects affected / exposed	52 / 265 (19.62%)	56 / 263 (21.29%)	
occurrences (all)	52	56	
Creatinine renal clearance increased			
subjects affected / exposed	115 / 265 (43.40%)	64 / 263 (24.33%)	
occurrences (all)	115	64	
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	214 / 265 (80.75%)	201 / 263 (76.43%)	
occurrences (all)	214	201	
Neutropenia			

subjects affected / exposed	121 / 265 (45.66%)	67 / 263 (25.48%)	
occurrences (all)	121	67	
Leucopenia			
subjects affected / exposed	148 / 265 (55.85%)	96 / 263 (36.50%)	
occurrences (all)	148	96	
Febrile leucopenia			
subjects affected / exposed	8 / 265 (3.02%)	15 / 263 (5.70%)	
occurrences (all)	8	15	
Trombocytopenia			
subjects affected / exposed	148 / 265 (55.85%)	96 / 263 (36.50%)	
occurrences (all)	148	96	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	194 / 265 (73.21%)	178 / 263 (67.68%)	
occurrences (all)	194	178	
Fever			
subjects affected / exposed	31 / 265 (11.70%)	30 / 263 (11.41%)	
occurrences (all)	31	30	
General physical health deterioration			
subjects affected / exposed	19 / 265 (7.17%)	11 / 263 (4.18%)	
occurrences (all)	19	11	
Allergic reaction			
subjects affected / exposed	1 / 265 (0.38%)	9 / 263 (3.42%)	
occurrences (all)	1	9	
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	33 / 265 (12.45%)	14 / 263 (5.32%)	
occurrences (all)	33	14	
Hearing impairment or hypo acusia			
subjects affected / exposed	30 / 265 (11.32%)	10 / 263 (3.80%)	
occurrences (all)	30	10	
Gastrointestinal disorders			
Mucositis oral			
subjects affected / exposed	152 / 265 (57.36%)	118 / 263 (44.87%)	
occurrences (all)	152	118	
Nausea			

subjects affected / exposed	173 / 265 (65.28%)	135 / 263 (51.33%)	
occurrences (all)	173	135	
Vomiting			
subjects affected / exposed	116 / 265 (43.77%)	83 / 263 (31.56%)	
occurrences (all)	116	83	
Diarrhoea			
subjects affected / exposed	93 / 265 (35.09%)	116 / 263 (44.11%)	
occurrences (all)	93	116	
Constipation			
subjects affected / exposed	76 / 265 (28.68%)	61 / 263 (23.19%)	
occurrences (all)	76	61	
Dysphagia			
subjects affected / exposed	48 / 265 (18.11%)	33 / 263 (12.55%)	
occurrences (all)	48	33	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	30 / 265 (11.32%)	21 / 263 (7.98%)	
occurrences (all)	30	21	
Skin and subcutaneous tissue disorders			
Rash acneiform			
subjects affected / exposed	166 / 265 (62.64%)	167 / 263 (63.50%)	
occurrences (all)	166	167	
Dry skin			
subjects affected / exposed	72 / 265 (27.17%)	74 / 263 (28.14%)	
occurrences (all)	72	74	
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	36 / 265 (13.58%)	28 / 263 (10.65%)	
occurrences (all)	36	28	
Alopecia			
subjects affected / exposed	31 / 265 (11.70%)	59 / 263 (22.43%)	
occurrences (all)	31	59	
Infections and infestations			
Infection any type			
subjects affected / exposed	72 / 265 (27.17%)	77 / 263 (29.28%)	
occurrences (all)	72	77	
Metabolism and nutrition disorders			

Magnesium metabolism disorder			
subjects affected / exposed	161 / 265 (60.75%)	147 / 263 (55.89%)	
occurrences (all)	161	147	
Potassium disorders			
subjects affected / exposed	162 / 265 (61.13%)	129 / 263 (49.05%)	
occurrences (all)	162	129	
Calcium disorders			
subjects affected / exposed	144 / 265 (54.34%)	145 / 263 (55.13%)	
occurrences (all)	144	145	
Sodium disorders			
subjects affected / exposed	139 / 265 (52.45%)	125 / 263 (47.53%)	
occurrences (all)	139	125	
Phosphorus metabolism disorder			
subjects affected / exposed	137 / 265 (51.70%)	127 / 263 (48.29%)	
occurrences (all)	137	127	
Hyperglycaemia			
subjects affected / exposed	61 / 265 (23.02%)	48 / 263 (18.25%)	
occurrences (all)	61	48	
Anorexia			
subjects affected / exposed	84 / 265 (31.70%)	86 / 263 (32.70%)	
occurrences (all)	84	86	
Weight loss			
subjects affected / exposed	58 / 265 (21.89%)	52 / 263 (19.77%)	
occurrences (all)	58	52	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 August 2014	- Change of principal investigator - Addition of further investigational sites in France
14 January 2015	- Addition of an exclusion criterion concerning concomitant malignancies - Addition of details concerning the commercially availability of the study treatments, premedications, concomitant treatments, and GCSF - Adjustment of the General Guidelines for the cetuximab administration both during chemotherapy and maintenance - Addition of details concerning the cisplatin administration both in the EXTREME arm and in the TPEx arm - Addition of details concerning the 5FUand docetaxel administration - Addition of details concerning the assessments to be performed during the study - Addition of details concerning the QoL assessments to be performed during the study follow-up if a patient was withdrawn from study treatment - Addition of details concerning the QoL assessments to be performed during the study follow-up if a patient was withdrawn from study treatment - Clarification on the definition of the G1 hypercreatinemia according to the NCI CTCAE V4.03 and on the actions to be taken concerning the chemotherapy administration
09 June 2015	- Modification of the Exclusion Criterion concerning the concomitant radiotherapy within 6 weeks before study entry - Addition of two Exclusion Criteria - Addition in the section 2.2 of details concerning the EMR 62202-008 phase I/II study and EXTREME study on standard treatment in recurrent and/or metastatic HNSCC. - Clarification on the use of carboplatin (as part of the EXTREME regimen) for patients not able to receive cisplatin. - Clarifications on the medical, financial, or ethical reasons for study discontinuation - Addition of note in the Flow-Chart clarifying the coagulation tests to be done(Prothrombin time, INR, and aPTT). - Clarification that deaths caused by disease progression more than 30 days after the end ofstudy treatment were not considered as SAEs and were excluded from expedited reporting. -Update of the bibliographic references.
17 January 2017	- Addition of a statistical analysis of futility. -Addition of further 124 patients to be included in the study in order to increase the powerof study from 80% to 88% as consequence of the addition of a statistical analysis of futility

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date

31 December 2021	The sponsor has decided to set the LPLV at 31/12/2021 and to censor the last patients still undergoing treatment on this date. Indeed, the protocol provided for a maintenance period continuing until toxicity or progression. Also, 5 patients were still being treated at this date, making it impossible to perform the final analysis of this trial. The management of these patients continues according to a standard protocol. They will therefore be considered as "long survivors" for this analysis. In addition, the last patient was included in the trial on 13/11/2017, the chosen LPLV therefore ensures a sufficiently long follow-up period, i.e. 4 years. post last inclusion. Furthermore, during this decision, the sponsor was aware that more than 80% of the patients included in the trial had died. The vital status of all patients will be collected on 31/12/2021	-

Notes:

Limitations and caveats

None reported