Clinical trial results:
Induction chemotherapy with cetuximab-docetaxel-cisplatin-fluorouracil (ETPF) in patients with resectable stage III or IV squamous cell carcinoma of the oropharynx

Summary

EudraCT number	2007-002116-25
Trial protocol	FR
Global end of trial date	30 October 2013

Results information

Result version number	v1 (current)
This version publication date	23 July 2016
First version publication date	23 July 2016

Trial information

Trial identification

Sponsor protocol code	O 07-1

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00665392
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	GERCOR
Sponsor organisation address	151 rue du faubourg Saint Antoine, PARIS, France, 75011
Public contact	Regulatory Affairs, GERCOR, 33 1 49 29 85 00, regulatory.affairs@gercor.com.fr
Scientific contact	Coordinating investigator - Tenon Hospital - Paris, Pr Jean Lacau St Guily , 33 1 40 29 85 00, regulatory.affairs@gercor.com.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	30 October 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 April 2013
Global end of trial reached?	Yes
Global end of trial date	30 October 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the clinical and radiological complete response (crCR) of the primary tumor at 3 months after cetuximab-TPF combination (ETPF) induction therapy in the treatment of patients with locally advanced resectable SCCHN of the oropharynx.

Protection of trial subjects:

Pre and concomitant medication consisted of IV hydration and infusion of diphenhydramine hydrochloride and dexamethasone, oral corticoid, antiemetic and IV antihistaminic.
Primary prophylaxis with granulocyte colony stimulating factor (G-CSF) was required.
In case of allergic reaction to cetuximab, or hematological events or other adverse events, doses were to be reduced. Dose adjustments were to be made according to the system showing the greatest degree of toxicity.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	18 July 2008
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: 42
Worldwide total number of subjects	42
EEA total number of subjects	42

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)	37
From 65 to 84 years	5

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

From July 2008 to April 2013, 42 were included in 9 french centers were active (APHP : Tenon, HEGP, Bichat - Paris; Centre René Huguenin - Saint Cloud; Hôpital Foch - Suresnes; GH Saint Joseph - Paris; Hôpital Simone Veil - Montmorency; CH Lyon Sud - Lyon ; Hôpital Delafontaine - Saint Denis.

Pre-assignment

Screening details:

The main inclusion criteria : Previously untreated, resectable stage III (T3 or T1-2N1-2M0) to IVB (T4 or T1-3N3M0) SCCHN of the oropharynx, measurable or evaluable disease, WHO performance status ≤1, adequate hematologic, renal and liver functions.
The main exclusion criteria: Uncontrolled cardiac or other disease, Hearing impairment

Period 1

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

Arms

Arm title	ETPF administration

Arm description:

Erbitux with concomitant anti-tumor therapy : TPF (Taxotere, Cisplatin, 5FU)
3 cycles (one cycle = 21 days)

Arm type	Experimental
Investigational medicinal product name	Cetuximab
Investigational medicinal product code	
Other name	Erbitux
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

cetuximab : IV infusion during 120 min
dosage: 400 mg/m² Day 1, 250 mg/m² Day 8 and Day 15.

Investigational medicinal product name	Docetaxel
Investigational medicinal product code	
Other name	Taxotere
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Taxotere :IV infusion 1h
Dosage : 75mg/m² Day 1

Investigational medicinal product name	Cisplatin
Investigational medicinal product code	
Other name	Cisplatine
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Cisplatin: IV infusion 1h
dosage: 75mg/m² Day 1

Investigational medicinal product name	5 FU
Investigational medicinal product code	
Other name	Fluoro-uracile
Pharmaceutical forms	Solution for injection/infusion

Routes of administration	Intravenous use

Dosage and administration details:

5FU : IV infusion on 5 days
Dosage : 750mg/m²/day = 3750mg/m² total dose

Number of subjects in period 1	ETPF administration
Started	42
Completed	40
Not completed	2
toxic death	1
Protocol deviation	1

Baseline characteristics

Reporting groups	
Reporting group title	Overall Period
Reporting group description:	
ETPF administration	

Reporting group values	Overall Period	Total	
Number of subjects	42	42	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	37	37	
From 65-84 years	5	5	
85 years and over	0	0	
Age continuous Units: years			
median	56.1		
standard deviation	± 6.8	-	
Gender categorical Units: Subjects			
Female	8	8	
Male	34	34	
grade of differentiation Units: Subjects			
Well	17	17	
Moderate	18	18	
Poor or undifferentiated	4	4	
Missing	3	3	
Primary tumor localization Units: Subjects			
Anterior	3	3	
Lateral (tonsillar area)	37	37	
Posterior	1	1	
Superior	1	1	
T-stage Units: Subjects			
T2	13	13	
T3	24	24	
T4	5	5	
N-stage Units: Subjects			

N0	5	5	
N1	9	9	
N2	27	27	
N3	1	1	
Staging Units: Subjects			
III	32	32	
IV	10	10	
ECOG status Units: Subjects			
PS 0	33	33	
PS 1	8	8	
Missing	1	1	
Lip mobility Units: Subjects			
Normal	40	40	
Decreased	2	2	
Trismus Units: Subjects			
Yes	5	5	
No	37	37	
Creatinine clearance (ml/min) Units: Subjects			
< 60	1	1	
60 - 120	31	31	
> 120	8	8	
Missing	2	2	
Albuminemia (g/L) Units: Subjects			
< 40	8	8	
≥60	14	14	
Missing	20	20	
Life style risk factor Units: Subjects			
Alcohol	3	3	
Tobacco	8	8	
Alcohol + Tobacco	25	25	
None	6	6	
HPV16 status Units: Subjects			
Positive	17	17	
Negative	25	25	

End points

End points reporting groups

Reporting group title	ETPF administration
Reporting group description:	
Erbitux with concomitant anti-tumor therapy : TPF (Taxotere, Cisplatin, 5FU) 3 cycles (one cycle = 21 days)	
Subject analysis set title	Tumor response rate - Tumor
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
At 3 months	
Subject analysis set title	Tumor response rate - Node
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
At 3 months	
Subject analysis set title	Tumor response rate - Tumor and node
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
At 3 months	
Subject analysis set title	HPV16-positive
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
17 patients/42 were HPV16-positive	
Subject analysis set title	HPV-16 negative
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
25 patients/42 were HPV-16 negative	

Primary: Clinical and radiological complete response (crCR) of the primary tumor at 3 months

End point title	Clinical and radiological complete response (crCR) of the primary tumor at 3 months[1]
End point description:	
Analyses were performed in a modified intent-to-treat (mITT) population. Patients were considered evaluable for tumor response if they had received at least one dose of ETPF combination.	
End point type	Primary
End point timeframe:	
At 3 months after end of 3 cycles EPTF combination	

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: Response rate presented with corresponding 95% CI was calculated using the binomial distribution

End point values	Tumor response rate - Tumor	Tumor response rate - Node	Tumor response rate - Tumor and node	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	41	41	41	
Units: Subject				
complete (crCR)	9	8	4	

incomplete	29	27	31	
progression	0	0	0	
not evaluable	3	6	6	

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Response (cR)

End point title	Clinical Response (cR)

End point description:

Clinical complete response (cCR) is defined by:
- Disappearance of all clinical evidence of visible tumor,
- Disappearance of all palpable residual infiltration,
- Disappearance of all evidence of residual visible tumor on CT scan in pharynx and parapharyngeal space,
- Complete symmetric remobilization of the tongue and amygdala.
- Disappearance of pre-existing trismus.
- Negative control biopsy.

End point type	Secondary

End point timeframe:

at 3 months after end of 3 cycles ETPF combination

End point values	Tumor response rate - Tumor	Tumor response rate - Node	Tumor response rate - Tumor and node	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	41	41	41	
Units: number				
complete (cCR)	17	15	13	
incomplete	21	23	25	
progression	0	0	0	
not evaluable	3	3	3	

Statistical analyses

No statistical analyses for this end point

Secondary: Radiological response (rR)

End point title	Radiological response (rR)

End point description:

Radiological response is defined according to RECIST 1.0 criteria:
- Complete response (CR): disappearance of all target lesions
- Partial response (PR): at least a 30% decrease in the sum of the longest diameter of target lesions, taking as reference the baseline sum longest diameter,
- Progressive disease (PD): at least a 20% increase in the sum of the longest diameter of target

lesions, taking as reference the smallest sum longest diameter recorded since the treatment started or the appearance of one or more new lesions,
• Stable disease (SD): neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum longest diameter since the treatment started

End point type	Secondary

End point timeframe:

At 3 months after end of 3 cycles ETPF combination

End point values	Tumor response rate - Tumor	Tumor response rate - Node	Tumor response rate - Tumor and node	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	41	41	41	
Units: number				
complete (rCR)	14	8	4	
Major Partial Response (≥50%)	10	14	11	
Minor Partial Response (<50%)	0	3	3	
Stable disease	6	6	10	
Progression	0	0	0	
Not evaluable	11	10	13	

Statistical analyses

No statistical analyses for this end point

Secondary: 2-year estimated PFS

End point title	2-year estimated PFS

End point description:

After a median of 23.9 months (95% CI, 15.4-28.6), median PFS was 37.6 months (95% CI, 19.1-NA)

End point type	Secondary

End point timeframe:

2-year

End point values	ETPF administration			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: percentage				
median (standard error)	63.6 (± 8.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: 2-year estimated overall survival (OS)

End point title	2-year estimated overall survival (OS)

End point description:

Median OS was not achieved

End point type	Secondary

End point timeframe:

2-year

End point values	ETPF administration			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: percentage				
median (standard error)				
2-year estimated OS	82.4 (± 6.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pathological response

End point title	Pathological response

End point description:

A pathological complete response is defined as no viable tumour cells detected on histological examination post surgery.

End point type	Secondary

End point timeframe:

Pathological response is evaluable in patients with tumour surgical resection only.

End point values	ETPF administration			
Subject group type	Reporting group			
Number of subjects analysed	22			
Units: number				
pathological complete response	9			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Biomarkers analysis - EGFR pathway components

End point title	Biomarkers analysis - EGFR pathway components

End point description:

Biomarker levels analysis according to crCR in the patients for whom pre-treatment formalin-fixed, paraffin-embedded tumor tissue block and cryopreserved tumor blocks were available

End point type	Other pre-specified

End point timeframe:

Correlative studies investigating EGFR-related biomarkers and HPV status in tumor and blood samples obtained prior to and after induction therapy were done for exploratory purposes as planned in the protocol

End point values	ETPF administration			
Subject group type	Reporting group			
Number of subjects analysed	38			
Units: number				
median (full range (min-max))	0 (0 to 0)			

Attachments (see zip file)	ECHO 07_Biomarker levels analysis.pdf

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Biomarkers analysis - distribution of alcohol and tobacco use according to HPV status

End point title	Biomarkers analysis - distribution of alcohol and tobacco use according to HPV status

End point description:

End point type	Other pre-specified

End point timeframe:

HPV status in tumor and blood samples obtained prior to and after induction therapy were done for exploratory purposes as planned in the protocol.

End point values	HPV16-positive	HPV-16 negative		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	17	25		
Units: number				
Alcohol only	2	1		
Tobacco only	5	3		
Both Alcohol and Tobacco	8	17		

None	2	4		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Until 1 month after the last administration	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	15.1

Reporting groups	
Reporting group title	ETPF administration
Reporting group description:	
Erbitux with concomitant anti-tumor therapy : TPF (Taxotere, Cisplatin, 5FU)	

Serious adverse events	ETPF administration		
Total subjects affected by serious adverse events			
subjects affected / exposed	13 / 41 (31.71%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	1		
Vascular disorders			
Hypovolaemia			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Orthostatic hypotension			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac arrest			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	1 / 1		
Gastrointestinal disorders			
Vomiting			

subjects affected / exposed	2 / 41 (4.88%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Diarrhoea	Additional description: grade 3		
subjects affected / exposed	3 / 41 (7.32%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Acute pancreatitis			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Febrile aplasia			
subjects affected / exposed	2 / 41 (4.88%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Febrile neutropenia			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infection at the portacath site			
subjects affected / exposed	2 / 41 (4.88%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	ETPF administration		
Total subjects affected by non-serious adverse events subjects affected / exposed	41 / 41 (100.00%)		
Nervous system disorders Neuropathy peripheral subjects affected / exposed occurrences (all)	4 / 41 (9.76%) 0		
Blood and lymphatic system disorders Neutropenia subjects affected / exposed occurrences (all) Anemia subjects affected / exposed occurrences (all) Thrombocytopenia subjects affected / exposed occurrences (all) Creatinine subjects affected / exposed occurrences (all)	18 / 41 (43.90%) 0 33 / 41 (80.49%) 0 9 / 41 (21.95%) 0 9 / 41 (21.95%) 0		
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all) Stomatitis subjects affected / exposed occurrences (all) Diarrhoea	16 / 41 (39.02%) 0 13 / 41 (31.71%) 0 14 / 41 (34.15%) 0		

subjects affected / exposed occurrences (all)	27 / 41 (65.85%) 0		
Skin and subcutaneous tissue disorders Acne subjects affected / exposed occurrences (all)	 18 / 41 (43.90%) 0		
Infections and infestations Febrile neutropenia subjects affected / exposed occurrences (all)	 8 / 41 (19.51%) 0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Some data which reported as "not available" in the clinical study report have been reported as "0" in this register.

Notes: