Clinical trial results:
A Phase II Trial With Radiotherapy Plus Cetuximab to Evaluate Specific Survival Free of Laryngectomy in Patients With Resectable and Locally Advanced Larynx Cancer, After Treatment With TPF Chemotherapy

Summary

EudraCT number	2008-000332-40
Trial protocol	ES
Global end of trial date	12 June 2015

Results information

Result version number	v1 (current)
This version publication date	11 April 2019
First version publication date	11 April 2019

Trial information

Trial identification

Sponsor protocol code	TTCC-2007-02

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00765011
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Grupo Español de Tratamiento de Tumores de Cabeza y Cuello (TTCC)
Sponsor organisation address	C/ Velázquez, 7 – 3º , Madrid, Spain, 28001
Public contact	Dr Ricard Mesia Nin, Grupo Español de Tratamiento de Tumores de Cabeza y Cuello (TTCC), 0034 93 335 70 11, rmesia@iconcologia.net
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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	14 October 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 May 2015
Global end of trial reached?	Yes
Global end of trial date	12 June 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate survival - with larynx function after 3 years in patients with response evaluated based on the primary tumour (T category) after induction TPF and treated with RT + Cetuximab

Protection of trial subjects:

The study medication was administered by the investigator or under their direct supervision. Given that the intravenous infusions were administered in a hospital or in an outpatient environment, compliance with the treatment could be easily monitored. The date and the start and end time of the infusion, as well as the exact quantity of cetuximab and TPF (docetaxel, cisplatin, 5-fluorouracil) administered at each infusion were recorded in the patient's medical record. If the treatment was modified, the medical staff had to evaluate the percentage of the dose received by the patient and record this in the CRF. All the reasons for non-compliance had to be recorded. As a standard precaution, the patients included in the study were under observation from the start of the infusion of cetuximab until at least 1 hour after the end of the cetuximab infusion in a quiet area with resuscitation equipment and other drugs required in case of an emergency (epinephrine, prednisolone and equivalent medicinal products). In the event that the treatment had to be interrupted during the infusion, the staff responsible for the procedure had to estimate the percentage of the dose received by the patient and record this in the CRF. The reasons for any lack of therapeutic compliance had to be recorded. Inadequate compliance with the cetuximab administration regimen was defined as missing more than 2 consecutive infusions for reasons other than toxicity. In the event of insufficient compliance by the patient, the principal investigator and the study coordinator decided together, on a case by case basis, regarding the possible withdrawal of the patient from the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 October 2008
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	36 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 94
Worldwide total number of subjects	94
EEA total number of subjects	94

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)	76
From 65 to 84 years	18
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

94 patients were included.
Part I: 93 patients received at least one dose of chemotherapy with TPF (ITT 1)
Part II: 72 patients received RT+cetuximab treatment(ITT 2)
This was a national study with all patients being included at 15 Spanish sites

Pre-assignment

Screening details:

Key inclusion criteria: 18-70 years of age, life expectancy >3 months, histologically demonstrated larynx squamous carcinoma , to be able to receive TPF treatment followed by normofractionated radiotherapy with cetuximab, adequate hepatic and renal function.
1 patient did not meet all the study inclusion criteria and did not started TPF treatment

Period 1

Period 1 title	Part I + Part II (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Not applicable

Arms

Arm title	Arm 1

Arm description:

The response obtained for the primary tumour after induction TPF determined the subsequent measures and treatments:
-Complete or partial response of the T category: Three to five weeks after the administration of the 3rd cycle of TPF, normofractionated RT was started. Cetuximab had to be administered at one week prior to the start of RT and maintained weekly until the end of the RT.
-T stabilisation or disease progression (T and/or N): These patients had to be offered rescue surgery at the earliest date possible.

Arm type	Experimental
Investigational medicinal product name	TPF
Investigational medicinal product code	
Other name	Docetaxel, cisplatin, 5-fluorouracil
Pharmaceutical forms	Infusion
Routes of administration	Intravascular use

Dosage and administration details:

Treatment is initiated with 3 cycles of TPF (docetaxel, cisplatin, 5-fluorouracil) every 3 weeks with G-CSF (lenograstim was recommended) and ciprofloxacin.

Treatment regimen, pretreatment and supporting measures:
- Docetaxel and Cisplatin: daily dose of 75 mg/m2 by intravenous infusion over 1 hour on day 1.
-5-FU: daily dose of 750 mg/m2 given over 24-hour infusion between days 1-5.
-Dexamethasone: 16 mg daily dose, 8 mg administered every 12 hours, at days -1, 1 and 2.
-Ciprofloxacin: 1g daily dose, 500 mg administered every 12 hours between days 7-15.
-G-CSF: subcutaneous administration of 150 ug/m2/d between days 7-12

The response obtained for the primary tumour after induction TPF determined the subsequent measures and treatments. The complete evaluation of the response had to be done in the 2 or 3 weeks immediately after the administration of the 3rd cycle of TPF.

Investigational medicinal product name	Cetuximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion

Routes of administration	Intravenous use

Dosage and administration details:

Cetuximab was administered continuously weekly, from one week before the start of RT.
-The initial dose of 400 mg/m2/d in the first infusion for 120 minutes on day 1.
-On days 8, 15, 22, 29, 36, 43 and 50 (or to the end of the RT if any delay of RT) cetuximab was administered at a daily dose of 250 mg/m2 by intravenous infusion over 1 hour.

Number of subjects in period 1	Arm 1
Started	94
Completed	94

Baseline characteristics

Reporting groups	
Reporting group title	Part I + Part II

Reporting group description: -

Reporting group values	Part I + Part II	Total	
Number of subjects	94	94	
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)	76	76	
From 65-84 years	18	18	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	8	8	
Male	86	86	

Subject analysis sets	
Subject analysis set title	ITT 1
Subject analysis set type	Intention-to-treat

Subject analysis set description:

This population included all included patients who received at least one dose of chemotherapy with TPF

Subject analysis set title	ITT 2
Subject analysis set type	Intention-to-treat

Subject analysis set description:

This population included all patients with an evaluated response in the primary tumour (T lesion) following induction with TPF and who started treatment with RT + cetuximab

Subject analysis set title	ITT 3
Subject analysis set type	Intention-to-treat

Subject analysis set description:

This population included all patients who did not show a response in the primary tumour (T lesion) after the induction with TPF

Subject analysis set title	SAF 1
Subject analysis set type	Safety analysis

Subject analysis set description:

All patients who signed the informed consent

Subject analysis set title	SAF 2
Subject analysis set type	Safety analysis

Subject analysis set description:

Included all the patients who started the treatment with cetuximab + radiotherapy

Subject analysis set title	PP1
Subject analysis set type	Per protocol

Subject analysis set description:

Protocol population 1 (PP 1): all patients in the intention-to-treat population 1, excluding those patients who were involved in significant breaches of the inclusion/exclusion criteria or major protocol deviations.

Subject analysis set title	PP2
Subject analysis set type	Per protocol

Subject analysis set description:

Protocol population 2 (PP 2): all patients in the intention-to-treat population 2, excluding those patients who were involved in significant breaches of the inclusion/exclusion criteria or major protocol deviations.

Reporting group values	ITT 1	ITT 2	ITT 3
Number of subjects	93	72	18
Age categorical Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Gender categorical Units: Subjects			
Female	7	5	2
Male	86	67	16

Reporting group values	SAF 1	SAF 2	PP1
Number of subjects	94	73	26
Age categorical Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Gender categorical Units: Subjects			
Female	8	6	1
Male	86	67	25

Reporting group values	PP2		
Number of subjects	15		

Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Gender categorical Units: Subjects			
Female	1		
Male	14		

End points

End points reporting groups

Reporting group title	Arm 1

Reporting group description:

The response obtained for the primary tumour after induction TPF determined the subsequent measures and treatments:
-Complete or partial response of the T category: Three to five weeks after the administration of the 3rd cycle of TPF, normofractionated RT was started. Cetuximab had to be administered at one week prior to the start of RT and maintained weekly until the end of the RT.
-T stabilisation or disease progression (T and/or N): These patients had to be offered rescue surgery at the earliest date possible.

Subject analysis set title	ITT 1
Subject analysis set type	Intention-to-treat

Subject analysis set description:

This population included all included patients who received at least one dose of chemotherapy with TPF

Subject analysis set title	ITT 2
Subject analysis set type	Intention-to-treat

Subject analysis set description:

This population included all patients with an evaluated response in the primary tumour (T lesion) following induction with TPF and who started treatment with RT + cetuximab

Subject analysis set title	ITT 3
Subject analysis set type	Intention-to-treat

Subject analysis set description:

This population included all patients who did not show a response in the primary tumour (T lesion) after the induction with TPF

Subject analysis set title	SAF 1
Subject analysis set type	Safety analysis

Subject analysis set description:

All patients who signed the informed consent

Subject analysis set title	SAF 2
Subject analysis set type	Safety analysis

Subject analysis set description:

Included all the patients who started the treatment with cetuximab + radiotherapy

Subject analysis set title	PP1
Subject analysis set type	Per protocol

Subject analysis set description:

Protocol population 1 (PP 1): all patients in the intention-to-treat population 1, excluding those patients who were involved in significant breaches of the inclusion/exclusion criteria or major protocol deviations.

Subject analysis set title	PP2
Subject analysis set type	Per protocol

Subject analysis set description:

Protocol population 2 (PP 2): all patients in the intention-to-treat population 2, excluding those patients who were involved in significant breaches of the inclusion/exclusion criteria or major protocol deviations.

Primary: Survival with a functional larynx

End point title	Survival with a functional larynx[1]

End point description:

Survival with larynx function is the time from the start of TPF treatment to death caused by the disease or by the treatment of the disease, or even to surgery involving total laryngectomy, or loss of larynx function. Deaths caused by other reasons were considered "censored" data on the date of death.

End point type	Primary

End point timeframe:

From the start of TPF treatment to death

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: No statistical analysis was planned for this primary outcome measure

End point values	ITT 2			
Subject group type	Subject analysis set			
Number of subjects analysed	72			
Units: percent				
number (confidence interval 95%)				
1 year	91.5 (85.1 to 98.0)			
2 years	82.7 (73.8 to 91.6)			
3 years	79.4 (69.8 to 89.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall response rate

End point title	Overall response rate

End point description:

The ORR is defined as the response rate (complete + partial) measured according to the WHO method. Any other response was considered as NO overall response.

End point type	Secondary

End point timeframe:

The secondary endpoints for part I of the study were analysed in the ITT1 population (n=93) and in the ITT2 population (n=72).

End point values	ITT 1	ITT 2		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	93	72		
Units: percent				
number (confidence interval 95%)	78.5 (70.1 to 86.8)	97.2 (93.4 to 100.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: T response rate

End point title	T response rate

End point description:

T response rate for the induction chemotherapy with TPF .

End point type	Secondary

End point timeframe:

In the two or three weeks immediately after the administration of the 3rd cycle of TPF.

End point values	ITT 1	ITT 2		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	93	72		
Units: percent				
number (confidence interval 95%)	81.7 (72.4 to 89.0)	98.6 (95.9 to 100.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall surival

End point title	Overall surival

End point description:

Overall survival was defined as the time from the start of induction chemotherapy with TPF to death due to any cause or to the patient's last check-up. Data was censored if death, the last visit or long-term follow-up did not occur.

End point type	Secondary

End point timeframe:

From the start of induction chemotherapy with TPF to death

End point values	ITT 1	ITT 2	ITT 3	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	93	72	18	
Units: percent				
number (confidence interval 95%)				
1 year	95.7 (91.6 to 99.8)	97.2 (93.4 to 100.0)	88.2 (72.9 to 100.0)	
2 years	82.8 (75.1 to 90.5)	86.1 (78.1 to 94.1)	64.7 (42.0 to 87.4)	
3 years	77.3 (68.9 to 85.9)	81.9 (73.0 to 90.8)	58.8 (35.4 to 82.2)	

Statistical analyses

No statistical analyses for this end point

Secondary: Specific survival free of total laryngectomy

End point title	Specific survival free of total laryngectomy

End point description:

By definition, specific survival free of laryngectomy is the time from the start of TPF treatment to death caused by the disease or by the treatment of the disease, or even to surgery involving total laryngectomy. Deaths caused by other reasons were considered "censored" data on the date of death. By definition an event was considered to be total laryngectomy, death from disease progression, disease-related complications and treatment-related events. The following data were considered censored: death by reasons other than those mentioned above, the latest assessment of larynx function or the latest X-ray.

End point type	Secondary

End point timeframe:

From the start of TPF treatment to death

End point values	ITT 1	ITT 2		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	93	72		
Units: percent				
number (confidence interval 95%)				
1 year	86.5 (79.4 to 93.6)	95.8 (91.1 to 100.0)		
2 years	74.2 (64.9 to 83.6)	84.0 (75.3 to 92.7)		
3 years	71.5 (61.8 to 81.2)	80.8 (71.3 to 90.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Specific disease-free survival

End point title	Specific disease-free survival

End point description:

By definition, specific disease-free survival is the time to disease recurrence at any site, either locoregional and/or metastatic, or to treatment-related death. Deaths caused by other reasons were considered "censored" data on the date of death. When treatment failure was confirmed in the disease assessment 10-12 weeks after the end of radiotherapy, it was recorded as a disease that has lasted since onset, as the patient had never been disease-free. Patients who had no recurrence were censored on the date of the last check-up. The patients for whom no tumour assessments were available after the TPF treatment were censored on the date of the start of RT + CETUXIMAB. Patients who showed no progression and began a cancer treatment other than the study drug were censored on the start date of the other treatment.

End point type	Secondary

End point timeframe:

Until time to disease recurrence

End point values	ITT 1	ITT 2	ITT 3	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	93	72	18	
Units: percent				
number (confidence interval 95%)				
1 year	85.4 (78.1 to 92.7)	90.1 (83.2 to 97.1)	64.3 (39.2 to 89.4)	
2 years	70.8 (61.1 to 80.4)	76.9 (67.0 to 86.9)	29.2 (0.14 to 58.3)	
3 years	69.4 (59.6 to 79.3)	76.9 (67.0 to 86.9)	29.2 (0.14 to 58.3)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The safety monitoring started at the time the patient was included in the study (date of the signing of the informed consent form) and continued until the evaluation visit at 10-12 weeks after the RT+cetuximab treatment had been carried out.

Adverse event reporting additional description:

1. CTC from the NCI, version 3.0 during the induction and cetuximab/RT treatment, and for 90 days after the end of the radiotherapy
2.Common Late Toxicity Criteria from RTOG/EORTC from 90 days after the end of the radiotherapy

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups

Reporting group title	SAF 1

Reporting group description:

Safety population 1 includes all patients who signed the informed consent form (n= 94).

Reporting group title	SAF 2

Reporting group description:

Safety Population 2 includes all the patients who started the treatment with cetuximab + radiotherapy (n=73).

Serious adverse events	SAF 1	SAF 2	
Total subjects affected by serious adverse events			
subjects affected / exposed	29 / 93 (31.18%)	8 / 73 (10.96%)	
number of deaths (all causes)	24	14	
number of deaths resulting from adverse events	2	1	
Investigations			
Blood creatine increased			
subjects affected / exposed	1 / 93 (1.08%)	0 / 73 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Radiation mucositis			
subjects affected / exposed	1 / 93 (1.08%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radiation skin injury			

subjects affected / exposed	1 / 93 (1.08%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	2 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Haemorrhage			
subjects affected / exposed	1 / 93 (1.08%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 1	1 / 1	
Cardiac disorders			
Myocardial ischaemia			
subjects affected / exposed	1 / 93 (1.08%)	0 / 73 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	4 / 93 (4.30%)	3 / 73 (4.11%)	
occurrences causally related to treatment / all	5 / 5	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	3 / 93 (3.23%)	2 / 73 (2.74%)	
occurrences causally related to treatment / all	4 / 4	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	1 / 93 (1.08%)	0 / 73 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 93 (1.08%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucosal inflammation			

subjects affected / exposed	6 / 93 (6.45%)	6 / 73 (8.22%)	
occurrences causally related to treatment / all	7 / 7	7 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	1 / 93 (1.08%)	0 / 73 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	2 / 93 (2.15%)	2 / 73 (2.74%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	5 / 93 (5.38%)	4 / 73 (5.48%)	
occurrences causally related to treatment / all	3 / 5	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	1 / 93 (1.08%)	0 / 73 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal inflammation			
subjects affected / exposed	1 / 93 (1.08%)	0 / 73 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal toxicity			
subjects affected / exposed	1 / 93 (1.08%)	0 / 73 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	1 / 93 (1.08%)	0 / 73 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mouth haemorrhage			

subjects affected / exposed	1 / 93 (1.08%)	0 / 73 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal varices haemorrhage			
subjects affected / exposed	1 / 93 (1.08%)	0 / 73 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Stomatitis			
subjects affected / exposed	1 / 93 (1.08%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	2 / 93 (2.15%)	2 / 73 (2.74%)	
occurrences causally related to treatment / all	2 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 93 (1.08%)	0 / 73 (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			
Prerenal failure			
subjects affected / exposed	1 / 93 (1.08%)	0 / 73 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	1 / 93 (1.08%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Device related infection			
subjects affected / exposed	1 / 93 (1.08%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pneumonia			
subjects affected / exposed	3 / 93 (3.23%)	2 / 73 (2.74%)	
occurrences causally related to treatment / all	1 / 3	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Superinfection			
subjects affected / exposed	1 / 93 (1.08%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	SAF 1	SAF 2	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	91 / 93 (97.85%)	73 / 73 (100.00%)	
Injury, poisoning and procedural complications			
Radiation skin injury			
subjects affected / exposed	48 / 93 (51.61%)	48 / 73 (65.75%)	
occurrences (all)	88	88	
Vascular disorders			
Hypotension			
subjects affected / exposed	5 / 93 (5.38%)	5 / 73 (6.85%)	
occurrences (all)	5	5	
Phlebitis			
subjects affected / exposed	12 / 93 (12.90%)	12 / 73 (16.44%)	
occurrences (all)	18	18	
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	21 / 93 (22.58%)	20 / 73 (27.40%)	
occurrences (all)	26	25	
Headache			
subjects affected / exposed	5 / 93 (5.38%)	5 / 73 (6.85%)	
occurrences (all)	5	5	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	7 / 93 (7.53%)	6 / 73 (8.22%)	
occurrences (all)	12	11	

Neutropenia			
subjects affected / exposed	8 / 93 (8.60%)	7 / 73 (9.59%)	
occurrences (all)	11	10	
Thrombocytopenia			
subjects affected / exposed	5 / 93 (5.38%)	4 / 73 (5.48%)	
occurrences (all)	7	6	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	60 / 93 (64.52%)	55 / 73 (75.34%)	
occurrences (all)	110	105	
Mucosal inflammation			
subjects affected / exposed	77 / 93 (82.80%)	70 / 73 (95.89%)	
occurrences (all)	215	202	
Oedema peripheral			
subjects affected / exposed	9 / 93 (9.68%)	8 / 73 (10.96%)	
occurrences (all)	10	9	
Pyrexia			
subjects affected / exposed	21 / 93 (22.58%)	19 / 73 (26.03%)	
occurrences (all)	23	21	
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	5 / 93 (5.38%)	5 / 73 (6.85%)	
occurrences (all)	6	6	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	13 / 93 (13.98%)	12 / 73 (16.44%)	
occurrences (all)	17	16	
Diarrhoea			
subjects affected / exposed	36 / 93 (38.71%)	29 / 73 (39.73%)	
occurrences (all)	49	42	
Dry mouth			
subjects affected / exposed	27 / 93 (29.03%)	26 / 73 (35.62%)	
occurrences (all)	39	38	
Dysphagia			
subjects affected / exposed	26 / 93 (27.96%)	25 / 73 (34.25%)	
occurrences (all)	38	37	

Nausea			
subjects affected / exposed	29 / 93 (31.18%)	25 / 73 (34.25%)	
occurrences (all)	36	32	
Odynophagia			
subjects affected / exposed	31 / 93 (33.33%)	31 / 73 (42.47%)	
occurrences (all)	61	61	
Vomiting			
subjects affected / exposed	30 / 93 (32.26%)	25 / 73 (34.25%)	
occurrences (all)	40	35	
Respiratory, thoracic and mediastinal disorders			
Dysphonia			
subjects affected / exposed	14 / 93 (15.05%)	14 / 73 (19.18%)	
occurrences (all)	20	20	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	41 / 93 (44.09%)	38 / 73 (52.05%)	
occurrences (all)	51	48	
Skin toxicity			
subjects affected / exposed	11 / 93 (11.83%)	11 / 73 (15.07%)	
occurrences (all)	16	16	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	6 / 93 (6.45%)	6 / 73 (8.22%)	
occurrences (all)	6	6	
Infections and infestations			
Candidiasis			
subjects affected / exposed	10 / 93 (10.75%)	10 / 73 (13.70%)	
occurrences (all)	11	11	
Conjunctivitis			
subjects affected / exposed	7 / 93 (7.53%)	7 / 73 (9.59%)	
occurrences (all)	7	7	
Respiratory infections and disorders			
subjects affected / exposed	6 / 93 (6.45%)	5 / 73 (6.85%)	
occurrences (all)	7	6	
Metabolism and nutrition disorders			

Decreased appetite			
subjects affected / exposed	26 / 93 (27.96%)	23 / 73 (31.51%)	
occurrences (all)	37	33	
Hypokalaemia			
subjects affected / exposed	5 / 93 (5.38%)	4 / 73 (5.48%)	
occurrences (all)	7	6	
Hypomagnesaemia			
subjects affected / exposed	6 / 93 (6.45%)	6 / 73 (8.22%)	
occurrences (all)	8	8	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 March 2008	This amendment responded to the clarifications requested by the IECs
14 May 2008	Among other changes, the following changes to the study protocol were made via this amendment: 1. Updating of the individuals in charge of the study 2. Planned duration of the study 3. Change of the toxicity endpoint criteria 4. Evaluation of the performance status of the head and neck areas 5. PET scan 6. Withdrawal criteria 7. Collection of information following the end of the radiotherapy treatment 8. Management of radiodermatitis concomitant with cetuximab-induced skin rash 9. Non-permitted concomitant medication 10. Handling of clinical trial material and evaluation of treatment compliance 11. Recording of vital signs and weight 12. Nomenclature of response 13. Recording of data when the treatment was suspended for reasons other than disease progression 14. Evaluations during the follow-up 15. Documentation of Adverse Events and Concomitant Treatments 16. Secondary analyses 17. Study chart 18. Inclusion of new sites 19. Correction of typographical errors
28 November 2008	The following changes to the protocol were made via amendment 3 to the protocol: 1. Clarification of the diagnosis of epidermoid carcinoma 2. Update of the PERMITTED concomitant medication section 3. Updating of the medication prior to cetuximab infusion 4. Duration of the radiotherapy 5. Informed consent 6. Assessments of the Evaluation Visit Following the Neoadjuvant Treatment 7. Assessments of the Evaluation Visit 10-12 weeks after RT with cetuximab 8. Assessments of the end of study (EOS) visit 9. Adverse Events 10. Correction of typographical errors 11. Correction of statistical errors 12. Study chart
30 June 2009	1. Change in the evaluation of radiotherapy safety and late toxicity 2. Correction of typographical errors
21 September 2009	The Principal Investigator at two sites participating in the study was changed by this amendment.
04 October 2012	The Principal Investigator at one site participating in the study was changed by this amendment.

05 March 2015	The change of the name of the primary objective of study TTCC-2007-02 was requested via this amendment, because of a typographical error at the time the protocol was prepared, and which was noticed by the sponsor when the initial analyses of the results were being carried out. The protocol had defined "laryngectomy-free survival" as the primary objective, when the protocol was designed to determine survival with a functional larynx. The parameters we used as a basis for calculating the final study sample and, therefore to build the statistics for the study, were always based on the results for survival with functional larynx based on the results from the GORTEC group study (data presented by the group at the ASCO conference in 2006 and later published as Poyntreau Y, y col. J Natl Cancer Inst 2009;101: 498 – 506), which was a study that, like ours, used TPF induction chemotherapy. In reality, the two parameters are not that different: Laryngectomy-free survival is defined as the time from the start of the treatment with TPF until the loss of the larynx for any reason or death caused by laryngeal cancer. Survival with functional larynx is defined as the time from the start of the treatment with TPF until the loss of laryngeal function for any reason or death caused by laryngeal cancer. In other words, the functional larynx parameter does not just include resected larynges, but also larynges that have been preserved but which do not function optimally: in reality, in the literature, the percentage difference between the two variables is usually 5-10%, with the functionality parameter being lower, i.e. we are more demanding when it comes to evaluating the study as positive. Similarly, the change of TFS Clinical Research Manager and change of management for the TTCC Group was notified.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported