Clinical trial results:
Open Label Randomized, Multi-centre Phase III Trial of TPF Plus Concomitant Treatment With Cisplatin and Radiotherapy Versus Concomitant Cetuximab and Radiotherapy in Locally Advanced, Unresectable Head and Neck Cancer

Summary

EudraCT number	2007-005540-24
Trial protocol	ES
Global end of trial date	23 December 2016

Results information

Result version number	v1 (current)
This version publication date	28 November 2019
First version publication date	28 November 2019

Trial information

Trial identification

Sponsor protocol code	TTCC-2007-01

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Grupo Español de Tratamiento de Tumores de Cabeza y Cuello (TTCC)
Sponsor organisation address	SEOM, Calle Velázquez, 7-3º, Madrid, Spain, 28001
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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	05 July 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	05 July 2013
Global end of trial reached?	Yes
Global end of trial date	23 December 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate that induction (TPF) chemotherapy followed by RT + Cetuximab is at least non-inferior to chemotherapy with TPF followed by RT + Cisplatin in terms of OS in patients with unresectable SCCHN.

Protection of trial subjects:

All patients were offered supportive measures for disease-related symptoms and treatment-associated toxicity. Any concomitant medication, procedures or blood products administered during the study and in the 2 weeks prior to its start were recording the CRF. The patients had to be premedicated with: antihistamines and corticosteroids before they received the first dose of cetuximab, dexamethasone before the administration of docetaxel. Palliative RT could not be administered for pain management or other non-curative purposes. Surgery to remove tumours was not permitted. The study patient was withdrawn if this surgery was carried out. If, at the end of the study, tumour persistence, relapse or progression (exit from the study) was observed, the investigator could then make a decision regarding the appropriateness or not of performing rescue and/or palliative surgery.Sedatives, antiemetics, antibiotics, analgesics, antihistamines, steroids, red blood cell concentrates, or fresh-frozen plasma or platelet transfusions could be administered to help the treatment of pain, infection or other complications of the neoplasia. In the case of documented febrile neutropenia or infection, IV antibiotics could be administered for curative purposes. Only the administration of haematopoietic growth factors was accepted. Erythropoietin was only administered in patients with a haemoglobin value below 10 g/dL and at the lowest possible dose so as to avoid a transfusion. Furthermore, the administration of erythropoietin was stopped if, after 8 weeks of treatment, the patient's haemoglobin levels did not recover to the levels necessary or if they still required transfusions. Prophylactic treatment with an antihistamine and a corticosteroid was administered before the initial dose of cetuximab was administered. Similarly, the patients had to be premedicated with corticosteroids before all the docetaxel doses.

Background therapy:

The combination of TPF induction chemotherapy followed by concomitant chemoradiotherapy with cisplatin currently appears to be the new standard treatment in unresectable cancer. However, increased acute and particularly chronic toxicity lead us to reconsider continuing a chemoradiotherapy regimen after induction chemotherapy. In particular, due to the onset of cetuximab and the finding that cetuximab has been shown to increase the efficacy of RT with a significant increase in locoregional disease control and survival in locally advanced SCCHN, without increasing the acute and/or chronic toxicity associated with RT.

Evidence for comparator: -

Actual start date of recruitment	15 July 2008
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, 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: 519
Worldwide total number of subjects	519
EEA total number of subjects	519

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)	434
From 65 to 84 years	85
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

In total, 530 patients with locally advanced, unresectable head and neck cancer were recruited at 43 sites in Spain between 2008-2013.

Pre-assignment

Screening details:

Prior to start date of the TPF induction chemotherapy treatment, the patients signed informed consent and were assessed for e.g. diagnosis and inclusion/exclusion critera. Eligible patients were recruited to an induction period (ITT1). Those still eligible after this period were randomized to either of the two radical treatment arms (ITT2).

Period 1

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

Arms

Arm title	Induction treatment following Radical treatment

Arm description:

- Induction treatment (ITT1): Chemotherapy with TPF (docetaxel, cisplatin, 5-fluorouracil)
- Radical treatment (ITT2) - Group A: Cisplatin + Radiotherapy
- Radical treatment (ITT2) - Group B: Cetuximab + Radiotherapy

Arm type	Experimental
Investigational medicinal product name	TPF (docetaxel, cisplatin, 5-fluorouracil)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

The treatment was started with 3 cycles of TPF (docetaxel, cisplatin and 5-fluorouracil) every 3 weeks supported with G-CSF and ciprofloxacin (or its equivalent).

Docetaxel (75 mg/m2/d; IV 1 hour; 1 day)
Cisplatin (75 mg/m2/d; IV 1 hour; 1 day)
5-FU (750 mg/m2/d; 24-hour infusion; 1-5 day)

Investigational medicinal product name	Cisplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

At 3-4 weeks (5 weeks at most) from the end of the 3rd TPF cycle, conventionally fractionated RT concomitant with chemotherapy was started (cisplatin 100 mg/m2). Patients received cisplatin 100 mg/m2 on day 1 (IV infusion of 1 hour), coinciding with the first day of RT, and subsequently on days 22 and 43 of RT.

Investigational medicinal product name	Cetuximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

At 3-4 weeks (5 weeks at most) from the end of the 3rd TPF cycle, conventionally fractionated RT

started. Cetuximab was administered at an initial dose of 400 mg/m2/day in the first infusion for 120 minutes, followed by weekly doses of 250 mg/m2/day for 60 minutes.

Number of subjects in period 1	Induction treatment following Radical treatment
Started	519
Completed	407
Not completed	112
Consent withdrawn by subject	4
Physician decision	6
Adverse event, non-fatal	42
Death	15
Lost to follow-up	2
Progressive disease	23
Protocol deviation	13
Not treated	7

Baseline characteristics

Reporting groups	
Reporting group title	Induction treatment following Radical treatment
Reporting group description:	
- Induction treatment (ITT1): Chemotherapy with TPF (docetaxel, cisplatin, 5-fluorouracil) - Radical treatment (ITT2) - Group A: Cisplatin + Radiotherapy - Radical treatment (ITT2) - Group B: Cetuximab + Radiotherapy	

Reporting group values	Induction treatment following Radical treatment	Total	
Number of subjects	519	519	
Age categorical Units: Subjects			
Adults (18-64 years)	434	434	
From 65-84 years	85	85	
Age continuous Units: years			
arithmetic mean	56.9		
full range (min-max)	29.4 to 72.7	-	
Gender categorical Units: Subjects			
Female	56	56	
Male	463	463	
ECOG Units: Subjects			
ECOG 0	135	135	
ECOG 1	383	383	
ECOG NA	1	1	
Anatomic location Units: Subjects			
Oropharynx	222	222	
Larynx	88	88	
Hypopharynx	120	120	
Oral cavity	89	89	
Tumour category Units: Subjects			
T 1-3	183	183	
T4	333	333	
UK	3	3	
Nodule Status Units: Subjects			
N0/1	126	126	
N2	329	329	
N3	62	62	
UK	2	2	
Smoking history Units: Subjects			
Smoker	399	399	

Non smoker	120	120	
Alcohol Units: Subjects			
Drinker	349	349	
Non drinker	170	170	
Race Units: Subjects			
Caucasic/white	518	518	
Asiatic	1	1	
Squamous Carcinoma grade Units: Subjects			
Grade I	40	40	
Grade II	142	142	
Grade III	67	67	
UNK	270	270	
Stage Units: Subjects			
III	44	44	
IVA	372	372	
IVB	102	102	
UK	1	1	
TNM (Clinical+Radiological) Units: Subjects			
T1-3N0/1	28	28	
T1-3N2	118	118	
T1-3N3	37	37	
T4N0/1	99	99	
T4N2	210	210	
T4N3	25	25	
UK	1	1	
N2	1	1	
Scintigraphy Units: Subjects			
Abnormal	2	2	
Normal	12	12	
UKN	505	505	
Dental evaluation Units: Subjects			
Abnormal	192	192	
Normal	66	66	
UKN	261	261	
X-ray Units: Subjects			
Abnormal	42	42	
Normal	390	390	
UKN	87	87	
Physical condition - head and neck - primary lesion Units: Subjects			
Oropharynx	196	196	
Larynx	75	75	

Hypopharynx	110	110	
Oral cavity	67	67	
UKN	71	71	
Height			
Units: cm			
arithmetic mean	166.9		
standard deviation	± 8.33	-	
Theorical weight			
Units: kg			
arithmetic mean	69.5		
standard deviation	± 13.99	-	
Body surface			
Units: m2			
arithmetic mean	1.76		
standard deviation	± 0.22	-	
Weight			
Units: kilogram(s)			
arithmetic mean	67.8		
standard deviation	± 14.9	-	
Exposure G-CSF			
Units: Subjects			
arithmetic mean	0		
standard deviation	± 0	-	

Subject analysis sets	
Subject analysis set title	Cisplatin+RT (Standard arm)
Subject analysis set type	Full analysis
Subject analysis set description:	
After randomization: Cisplatin + Radiotherapy	
Subject analysis set title	Cetuximab+RT (Experimental arm)
Subject analysis set type	Full analysis
Subject analysis set description:	
After randomization: Cetuximab + Radiotherapy	

Reporting group values	Cisplatin+RT (Standard arm)	Cetuximab+RT (Experimental arm)	
Number of subjects	205	202	
Age categorical			
Units: Subjects			
Adults (18-64 years)	181	168	
From 65-84 years	25	40	
Age continuous			
Units: years			
arithmetic mean	56.1	57.4	
full range (min-max)	39.6 to 72.7	29.4 to 70.7	
Gender categorical			
Units: Subjects			
Female	19	25	
Male	186	177	

ECOG Units: Subjects			
ECOG 0	49	61	
ECOG 1	155	141	
ECOG NA	1	0	
Anatomic location Units: Subjects			
Oropharynx	90	86	
Larynx	38	38	
Hypopharynx	43	43	
Oral cavity	34	35	
Tumour category Units: Subjects			
T 1-3	71	85	
T4	133	116	
UK	1	1	
Nodule Status Units: Subjects			
N0/1	46	47	
N2	130	130	
N3	29	24	
UK	0	1	
Smoking history Units: Subjects			
Smoker	168	160	
Non smoker	37	42	
Alcohol Units: Subjects			
Drinker	139	143	
Non drinker	66	59	
Race Units: Subjects			
Caucasic/white	205	201	
Asiatic	0	1	
Squamous Carcinoma grade Units: Subjects			
Grade I	18	16	
Grade II	48	58	
Grade III	27	20	
UNK	112	108	
Stage Units: Subjects			
III	17	13	
IVA	147	149	
IVB	41	39	
UK	0	1	
TNM (Clinical+Radiological) Units: Subjects			
T1-3N0/1	0	1	
T1-3N2	1	0	
T1-3N3	9	12	

T4N0/1	44	58	
T4N2	18	15	
T4N3	37	35	
UK	85	72	
N2	11	9	
Scintigraphy Units: Subjects			
Abnormal	1	2	
Normal	3	8	
UKN	198	397	
Dental evaluation Units: Subjects			
Abnormal	77	80	
Normal	28	24	
UKN	100	98	
X-ray Units: Subjects			
Abnormal	13	12	
Normal	160	155	
UKN	32	35	
Physical condition - head and neck - primary lesion Units: Subjects			
Oropharynx	83	75	
Larynx	35	33	
Hypopharynx	40	41	
Oral cavity	26	25	
UKN	21	28	
Height Units: cm			
arithmetic mean	167.7	166.6	
standard deviation	± 7.8	± 8.5	
Theorical weight Units: kg			
arithmetic mean	69.5	69.7	
standard deviation	± 13.6	± 13.9	
Body surface Units: m2			
arithmetic mean	1.8	1.8	
standard deviation	± 0.2	± 0.2	
Weight Units: kilogram(s)			
arithmetic mean	68.0	68.3	
standard deviation	± 14.1	± 14.6	
Exposure G-CSF Units: Subjects			
arithmetic mean	48.0	47.9	
standard deviation	± 33.8	± 22.8	

End points

End points reporting groups

Reporting group title	Induction treatment following Radical treatment
Reporting group description: - Induction treatment (ITT1): Chemotherapy with TPF (docetaxel, cisplatin, 5-fluorouracil) - Radical treatment (ITT2) - Group A: Cisplatin + Radiotherapy - Radical treatment (ITT2) - Group B: Cetuximab + Radiotherapy	
Subject analysis set title	Cisplatin+RT (Standard arm)
Subject analysis set type	Full analysis
Subject analysis set description: After randomization: Cisplatin + Radiotherapy	
Subject analysis set title	Cetuximab+RT (Experimental arm)
Subject analysis set type	Full analysis
Subject analysis set description: After randomization: Cetuximab + Radiotherapy	

Primary: Overall survival

End point title	Overall survival
End point description: Overall survival defined as time between the start of treatment with TPF (induction) and death due to any cause, or to the last check-up in the case of living patients.	
End point type	Primary
End point timeframe: Measured from induction until death or time of last check-up.	

End point values	Cisplatin+RT (Standard arm)	Cetuximab+RT (Experimental arm)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	205	202		
Units: month				
median (confidence interval 95%)	63.6 (42.2 to 75.1)	42.9 (33.6 to 72.2)		

Statistical analyses

Statistical analysis title	Overall survival
Statistical analysis description: Cox proportional hazards regression model to prove non-inferiority.	
Comparison groups	Cisplatin+RT (Standard arm) v Cetuximab+RT (Experimental arm)

Number of subjects included in analysis	407
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Cox proportional hazard
Point estimate	0.05
Confidence interval	
level	90 %
sides	1-sided
upper limit	1.3

Secondary: Progression-free survival

End point title	Progression-free survival

End point description:

End point type	Secondary

End point timeframe:

From start of induction treatment until the date of progression or death from any cause, whichever occurred first.

End point values	Induction treatment following Radical treatment	Cisplatin+RT (Standard arm)	Cetuximab+RT (Experimental arm)	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	519	205	202	
Units: months				
median (confidence interval 95%)	22.6 (17.6 to 31.1)	39.9 (26.1 to 62.8)	20.2 (15.2 to 31.1)	

Statistical analyses

No statistical analyses for this end point

Secondary: Disease specific survival

End point title	Disease specific survival

End point description:

End point type	Secondary

End point timeframe:

From start of induction treatment until the date of progression.

End point values	Cisplatin+RT (Standard arm)	Cetuximab+RT (Experimental arm)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	205	202		
Units: months				
median (confidence interval 95%)	75.1 (63.8 to 82)	85.3 (47.1 to 100.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall response rate (RECIST criteria)

End point title	Overall response rate (RECIST criteria)

End point description:

End point type	Secondary

End point timeframe:

During the induction and radical treatment periods.

End point values	Induction treatment following Radical treatment	Cisplatin+RT (Standard arm)	Cetuximab+RT (Experimental arm)	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	519	205	202	
Units: percent				
number (confidence interval 95%)	72.3 (68.2 to 76.1)	76.1 (69.7 to 81.8)	79.7 (73.5 to 85.0)	

Statistical analyses

No statistical analyses for this end point

Secondary: Overall response rate (Investigator criteria)

End point title	Overall response rate (Investigator criteria)

End point description:

End point type	Secondary

End point timeframe:

During the induction and radical treatment periods.

End point values	Induction treatment following Radical treatment	Cisplatin+RT (Standard arm)	Cetuximab+RT (Experimental arm)	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	519	205	202	
Units: percent				
number (confidence interval 95%)	73.2 (69.2 to 77.0)	76.1 (69.7 to 81.8)	80.2 (74.0 to 85.5)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
AEs collected during radical treatment period.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups	
Reporting group title	Cisplatin+RT (Standard arm)
Reporting group description:	
Comprised of patients that received the standard treatment (Cisplatin), in the Radical treatment part (ITT2).	
Reporting group title	Cetuximab+RT (Experimental arm)
Reporting group description:	
Comprised of patients that received the experimental treatment (Cetuximab), in the Radical treatment part (ITT2).	

Serious adverse events	Cisplatin+RT (Standard arm)	Cetuximab+RT (Experimental arm)	
Total subjects affected by serious adverse events			
subjects affected / exposed	58 / 205 (28.29%)	48 / 202 (23.76%)	
number of deaths (all causes)	110	115	
number of deaths resulting from adverse events	8	12	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour haemorrhage			
subjects affected / exposed	0 / 205 (0.00%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 205 (0.49%)	2 / 202 (0.99%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infarction			
subjects affected / exposed	0 / 205 (0.00%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Phlebitis			

subjects affected / exposed	1 / 205 (0.49%)	0 / 202 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis			
subjects affected / exposed	0 / 205 (0.00%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 205 (0.49%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device deployment issue			
subjects affected / exposed	0 / 205 (0.00%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucosal inflammation			
subjects affected / exposed	28 / 205 (13.66%)	26 / 202 (12.87%)	
occurrences causally related to treatment / all	27 / 32	33 / 34	
deaths causally related to treatment / all	0 / 0	2 / 2	
Pyrexia			
subjects affected / exposed	4 / 205 (1.95%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	1 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 205 (0.00%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute pulmonary oedema			

subjects affected / exposed	0 / 205 (0.00%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Dyspnoea			
subjects affected / exposed	1 / 205 (0.49%)	2 / 202 (0.99%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Laryngeal stenosis			
subjects affected / exposed	1 / 205 (0.49%)	0 / 202 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	1 / 205 (0.49%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	1 / 205 (0.49%)	0 / 202 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 205 (0.49%)	0 / 202 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress			
subjects affected / exposed	0 / 205 (0.00%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	0 / 205 (0.00%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Confusional state			

subjects affected / exposed	1 / 205 (0.49%)	0 / 202 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disorientation			
subjects affected / exposed	1 / 205 (0.49%)	0 / 202 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 205 (0.00%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight decreased			
subjects affected / exposed	1 / 205 (0.49%)	0 / 202 (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			
Hip fracture			
subjects affected / exposed	0 / 205 (0.00%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radiation skin injury			
subjects affected / exposed	1 / 205 (0.49%)	0 / 202 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shunt thrombosis			
subjects affected / exposed	0 / 205 (0.00%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Pyloric stenosis			

subjects affected / exposed	0 / 205 (0.00%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheo-oesophageal fistula			
subjects affected / exposed	0 / 205 (0.00%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 205 (0.00%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Bradycardia			
subjects affected / exposed	1 / 205 (0.49%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	0 / 205 (0.00%)	2 / 202 (0.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Prinzmetal angina			
subjects affected / exposed	0 / 205 (0.00%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus tachycardia			
subjects affected / exposed	0 / 205 (0.00%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	0 / 205 (0.00%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			

Headache			
subjects affected / exposed	0 / 205 (0.00%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sciatic nerve neuropathy			
subjects affected / exposed	1 / 205 (0.49%)	0 / 202 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 205 (0.00%)	2 / 202 (0.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	0 / 205 (0.00%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 205 (0.98%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	2 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone marrow failure			
subjects affected / exposed	1 / 205 (0.49%)	0 / 202 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Febrile neutropenia			
subjects affected / exposed	24 / 205 (11.71%)	24 / 202 (11.88%)	
occurrences causally related to treatment / all	3 / 24	1 / 28	
deaths causally related to treatment / all	1 / 1	0 / 0	
Neutropenia			
subjects affected / exposed	4 / 205 (1.95%)	7 / 202 (3.47%)	
occurrences causally related to treatment / all	1 / 4	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

Abdominal pain			
subjects affected / exposed	1 / 205 (0.49%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aphagia			
subjects affected / exposed	1 / 205 (0.49%)	0 / 202 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	3 / 205 (1.46%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis			
subjects affected / exposed	0 / 205 (0.00%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	1 / 205 (0.49%)	0 / 202 (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 / 205 (0.49%)	0 / 202 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	0 / 205 (0.00%)	2 / 202 (0.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic enteritis			
subjects affected / exposed	1 / 205 (0.49%)	0 / 202 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nausea			

subjects affected / exposed	1 / 205 (0.49%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic colitis			
subjects affected / exposed	0 / 205 (0.00%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Odynophagia			
subjects affected / exposed	1 / 205 (0.49%)	0 / 202 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			
subjects affected / exposed	0 / 205 (0.00%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumoperitoneum			
subjects affected / exposed	0 / 205 (0.00%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Stomatitis			
subjects affected / exposed	2 / 205 (0.98%)	0 / 202 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	3 / 205 (1.46%)	4 / 202 (1.98%)	
occurrences causally related to treatment / all	2 / 3	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Skin toxicity			
subjects affected / exposed	0 / 205 (0.00%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			

Haematuria			
subjects affected / exposed	0 / 205 (0.00%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prerenal failure			
subjects affected / exposed	1 / 205 (0.49%)	0 / 202 (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	7 / 205 (3.41%)	3 / 202 (1.49%)	
occurrences causally related to treatment / all	4 / 7	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abscess neck			
subjects affected / exposed	1 / 205 (0.49%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal abscess			
subjects affected / exposed	1 / 205 (0.49%)	0 / 202 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	0 / 205 (0.00%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Diverticulitis			
subjects affected / exposed	1 / 205 (0.49%)	0 / 202 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	1 / 205 (0.49%)	0 / 202 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			

subjects affected / exposed	1 / 205 (0.49%)	0 / 202 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
peritonitis			
subjects affected / exposed	0 / 205 (0.00%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumonia			
subjects affected / exposed	6 / 205 (2.93%)	2 / 202 (0.99%)	
occurrences causally related to treatment / all	0 / 6	0 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Respiratory tract infection			
subjects affected / exposed	4 / 205 (1.95%)	2 / 202 (0.99%)	
occurrences causally related to treatment / all	1 / 4	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Sepsis			
subjects affected / exposed	2 / 205 (0.98%)	0 / 202 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Septic shock			
subjects affected / exposed	1 / 205 (0.49%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	1 / 1	0 / 1	
Toxic shock syndrome			
subjects affected / exposed	1 / 205 (0.49%)	0 / 202 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 205 (0.00%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Cachexia			

subjects affected / exposed	0 / 205 (0.00%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decreased appetite			
subjects affected / exposed	1 / 205 (0.49%)	0 / 202 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	2 / 205 (0.98%)	0 / 202 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malnutrition			
subjects affected / exposed	2 / 205 (0.98%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 1	1 / 1	

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

Non-serious adverse events	Cisplatin+RT (Standard arm)	Cetuximab+RT (Experimental arm)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	188 / 205 (91.71%)	185 / 202 (91.58%)	
Injury, poisoning and procedural complications			
Skin toxicity			
subjects affected / exposed	89 / 205 (43.41%)	94 / 202 (46.53%)	
occurrences (all)	117	185	
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	37 / 205 (18.05%)	16 / 202 (7.92%)	
occurrences (all)	74	39	
Neurotoxicity			
subjects affected / exposed	26 / 205 (12.68%)	6 / 202 (2.97%)	
occurrences (all)	46	19	
General disorders and administration site conditions			

Mucosal inflammation			
subjects affected / exposed	152 / 205 (74.15%)	161 / 202 (79.70%)	
occurrences (all)	453	541	
Asthenia			
subjects affected / exposed	152 / 205 (74.15%)	161 / 202 (79.70%)	
occurrences (all)	270	219	
Pyrexia			
subjects affected / exposed	7 / 205 (3.41%)	24 / 202 (11.88%)	
occurrences (all)	31	44	
Xerosis			
subjects affected / exposed	2 / 205 (0.98%)	12 / 202 (5.94%)	
occurrences (all)	4	15	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	38 / 205 (18.54%)	13 / 202 (6.44%)	
occurrences (all)	125	63	
Neutropenia			
subjects affected / exposed	47 / 205 (22.93%)	2 / 202 (0.99%)	
occurrences (all)	97	36	
Leukopenia			
subjects affected / exposed	18 / 205 (8.78%)	2 / 202 (0.99%)	
occurrences (all)	36	20	
Ear and labyrinth disorders			
Ototoxicity			
subjects affected / exposed	22 / 205 (10.73%)	8 / 202 (3.96%)	
occurrences (all)	31	21	
Gastrointestinal disorders			
Odynophagia			
subjects affected / exposed	83 / 205 (40.49%)	72 / 202 (35.64%)	
occurrences (all)	144	138	
Dry mouth			
subjects affected / exposed	58 / 205 (28.29%)	60 / 202 (29.70%)	
occurrences (all)	78	88	
Dysphagia			
subjects affected / exposed	58 / 205 (28.29%)	54 / 202 (26.73%)	
occurrences (all)	99	91	
Nausea			

subjects affected / exposed	45 / 205 (21.95%)	13 / 202 (6.44%)	
occurrences (all)	130	94	
Vomiting			
subjects affected / exposed	36 / 205 (17.56%)	18 / 202 (8.91%)	
occurrences (all)	121	100	
Constipation			
subjects affected / exposed	24 / 205 (11.71%)	19 / 202 (9.41%)	
occurrences (all)	59	47	
Diarrhoea			
subjects affected / exposed	10 / 205 (4.88%)	14 / 202 (6.93%)	
occurrences (all)	103	150	
Stomatitis			
subjects affected / exposed	16 / 205 (7.80%)	16 / 202 (7.92%)	
occurrences (all)	47	31	
Cheilitis			
subjects affected / exposed	1 / 205 (0.49%)	14 / 202 (6.93%)	
occurrences (all)	11	28	
Respiratory, thoracic and mediastinal disorders			
Dysphonia			
subjects affected / exposed	11 / 205 (5.37%)	6 / 202 (2.97%)	
occurrences (all)	17	11	
Skin and subcutaneous tissue disorders			
Skin toxicity			
subjects affected / exposed	13 / 205 (6.34%)	44 / 202 (21.78%)	
occurrences (all)	17	79	
Rash			
subjects affected / exposed	1 / 205 (0.49%)	70 / 202 (34.65%)	
occurrences (all)	1	131	
Erythema			
subjects affected / exposed	4 / 205 (1.95%)	12 / 202 (5.94%)	
occurrences (all)	10	17	
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	17 / 205 (8.29%)	3 / 202 (1.49%)	
occurrences (all)	28	10	
Infections and infestations			

Oral candidiasis subjects affected / exposed occurrences (all)	7 / 205 (3.41%) 13	11 / 202 (5.45%) 17	
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	41 / 205 (20.00%) 137	23 / 202 (11.39%) 106	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 January 2008	This amendment reported the request for clarifications from the IECs (there was no body of the amendment as a result).
03 March 2008	This amendment reported the inclusion of 23 new sites to the study in order to achieve the objective of 398 randomised and evaluable patients for a total of 458 included. The change in Principal Investigator at Hospital Clínico Lozano Blesa in Zaragoza, and the update to the study coordinators was also notified.
02 May 2008	•The toxicity rating criteria were changed to achieve a more precise evaluation during the different study periods based on the treatment the patient was receiving, specifically during the RT and for late toxicity.•The name of "end of study visit" was replaced by "VAP". •The assessment schedule of the tumour for the assessment visit was modified after radical treatment (which went from 10-12 weeks post-RT to 6–8 weeks) and the schedule for post-treatment visits for better monitoring of the patient was also changed (increasing the frequency of visits and exams during the 5 years of follow-up).•A dental assessment was added to the response assessment visit after the induction treatment.•An assessment of weight for every week of treatment (induction and radical) was added.•Fortnightly blood tests were added while radical treatment to better monitor the patient.•The schedule for assessing QoL was changed (every 6 months during years 1 and 2, instead of only every 4 months for 1 year). It was also clarified that once the patient progressed, it would not be necessary to complete these questionnaires.•Visual exams of the tumour during the assessment visits for induction treatment were removed.•The documentation of concomitant AEs and treatment during the different study treatments was clarified. From 90 days post-radiochemotherapy treatment, only data on chronic toxicity associated with this treatment was collected, following the RTOG/EORTC late CTC.•The study schedule was changed in accordance with the aforementioned changes.•The inclusion of 5 new sites in the study was requested so that the sample size (458 patients) could be achieved.•The non-participation of one of the already approved sites (Instituto Oncológico de Guipúzcoa) was reported.•Various typing errors were corrected and the use of CSFs, and the use of colony-stimulating factors and CRF management was written more clearly, as for this study an online or e-CRF (non paper-based)
19 June 2008	• The Patient Information Sheet and Informed Consent Form were adapted according to the submitted and approved changes, in amendment No 3 of 2 May 2008. After evaluation and approval of protocol amendment 3 by the IECs involved, the sponsor was requested to change the patient information sheet and informed consent form according to the changes in the proposed schedule in this amendment. Furthermore, according to the request from another two IECs who assessed the protocol during the evaluation of amendment 2, and in order to have a single version of the patient information sheet and informed consent form for all sites, a couple of aspects of this document were also changed. • Sections of previous and concomitant medication were updated. Specifically, amifostine (Ethyol®) was included as non-permitted medication due to possible serious dermatological adverse reactions and erythropoietin was removed as a non-permitted concomitant medication as its use was part of clinical practice in many sites and it appeared erroneously. • The dental evaluation in the evaluation visit following neoadjuvant treatment with TPF was removed, with dental assessment only at baseline. • Various typographic errors were corrected.

01 September 2008	• The change in Principal Investigator in one of the already approved sites was reported (H. Clínico de Santiago de Compostela). • A typographical error in the footer of the approved version of the Patient Information Sheet and Informed Consent Form (version No.3 dated 19/06/08) was reported to the IECs. This footer requested the patient's dated signature for all sheets. In order to facilitate the process for obtaining Informed Consent, the IECs were informed that the signature and date of the patient would only be requested in the Informed Consent Form, while the footer would be removed in the information sheets.
30 October 2008	•The diagnosis of epidermoid carcinoma was clarified. •The section on allowed concomitant medication was updated. • Medication prior to cetuximab infusion was updated. •Typing errors were corrected. •Statistical errors were corrected (1. The terms "equivalence/equivalent" were corrected by "non-inferior / non-inferiority" in some sections of the protocol. The term "equivalent" was not correct in this study, whose main objective was to demonstrate non-inferiority; 2. The number of patients to be included in the study was corrected according to the expected withdrawal rate (15% who progressed with TPF or were lost). The initial calculation of 458 patients to be included to obtain 398 assessable was not correct when taking this 15% into account. The re-calculation showed that 469 patients were needed to obtain 398 evaluable patients; 3.The definitions of the first and second part of the study were corrected and the definitions of the different study populations in both of these were corrected. The existence of at least one post-baseline evaluable CT scan was added in the protocol population. The population was removed for QoL analysis, since ICH guidelines did not include this type of population. Tables with the data obtained from the quality-life questionnaires used in this study were produced; 4.Some typographical errors were corrected).
27 April 2009	• Reported the inclusion of a new site (Hospital Clínico de Valencia). • Reported a change in Principal Investigator in the Hospital Arnau de Vilanova Hospital in Lleida. • Reported a change in Principal Investigator in the Hospital Universitario de Salamanca. • Typing errors were corrected.
21 September 2009	• The change in Principal Investigator at the Hospital La Paz. • The change in Principal Investigator at the Hospital Virgen de las Nieves.
26 November 2009	This amendment reported the change of principal investigator in Hospital de Sagunto.
30 August 2010	• The change in Principal Investigator at the Hospital Morales Meseguer. • The change of CRM in Trial Form Support.
30 September 2010	This amendment reported the change of principal investigator at Hospital Clínico de Santiago.

30 April 2012	•The change of study Sponsor and the national Coordinator contact details. •Change in Principal Investigator in Hospital Universitario 12 de Octubre. •The change in Principal Investigator in the Hospital Arnau de Vilanova in Valencia. •The change in inclusion criteria 9, 10, 12 and 13 (1. Number 9: it was requested to replace "haemoglobin >10 g/dL" with "haemoglobin >9 g/dL and no symptoms related to anaemia". 2. Number 10: it was requested to replace "bilirubin ≤1 x UNL, GOT and GPT ≤ 2.5 UNL, alkaline phosphatase <5 UNL" with "Bilirubin ≤1.5 x UNL, and some of the following values: GOT ≤2.5 ULN or GPT ≤2.5 UNL or alkaline phosphatase <2 UNL; however, if all of these are present, their value should not exceed the UNL". 3.Number 12: it was requested to remove the inclusion criterion no. 12 blood calcium ≤1.25 x UNL. 4. Number 13: replacing "Suitable nutritional status: weight loss <20% compared to theoretical weight and albumin ≥35 g/L" with "Adequate nutritional status: BMI >18.5% or albumin ≥30 g/L").•Modification to the induction treatment. •Change in the duration of the trial and the number of sites. •Change in the Tumour Assessment Imaging Techniques and the periods when it is carried out. • The change in the non-therapeutic visit regimen during neoadjuvant treatment.
04 October 2012	The change in Principal Investigator at Hospital Lucus Augusti was requested via this amendment.
13 October 2014	This amendment requested: • A change in Principal Investigator at Hospital de Sagunto. • A change in Principal Investigator at the Hospital Central de Asturias.
22 January 2015	This amendment reported the performance of a genetic sub-study to gain an in-depth knowledge of the genetic mechanisms of epidermoid head and neck cancer by identifying mutations in tumour tissue, in order to define prognostic subtypes and molecular predictive factors of response that allow the best therapeutic strategy to be established for each patient. In order to be able to investigate these molecular characteristics in the TTCC-2007-01 trial, in this additional protocol (GEN-TTCC-2007-01 Project), the baseline tumour samples were requested from the subjects included in the study. The DNA from the tumour samples was obtained with prior consent of the subjects included in the study, and were stored at the Centro de Investigación del Cáncer de Salamanca-IBSAL for analysis and research into genes in association with this trial.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported