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.

Study number: **TTCC-2007-01**

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CONFIDENCIAL All information and data included in this protocol contains trade secrets and privileged or confidential information. These limitations will also apply to all information considered privileged or confidential that will be provided in the future. This material may be disclosed and used by your team and collaborators, as necessary for the conduct of the clinical study.

I agree to carry out the study in accordance with the protocol described in this document and in accordance with Good Clinical Practice, as well as the applicable legal requirements.

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List of abbreviations and definition of terms

5-FU	5-Fluorouracil
AE	Adverse event
AEMPS	Spanish Agency of Medicines and Medical Devices
AJCC	American Joint Commission for Cancer
ARF	Serious adverse event alert report form
ASCO	American Society of Clinical Oncology
BSA	Body surface area
BMI	Body mass index
BMS	Bristol-Myers Squibb
CDK	Cyclin-dependent protein kinase
CR	Complete response
CREC	Clinical Research Ethics Committee
CRC	Colorectal cancer
CRF	Case report form
CRO	Contract Research Organisation
CTC	Common toxicity criteria
C225	Chimeric monoclonal antibody C225, Cetuximab, ErbituxTM
DP	Disease progression
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EGF	Epidermal growth factor
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency
EMR	E. Merck Research
EORTC	European Organization for Research and Treatment of Cancer
FDA	Food and Drug Administration
GCP	Good clinical practice
CI	Confidence interval
C_{max}	Mean of the maximum serum concentration
CT	Computed tomography
CTV	Clinical target volume
EU	European Union
FND	Functional neck dissection
GOT	Glutamic oxaloacetic transaminase
GPT	Alanine aminotransferase
HIV	Human Immunodeficiency Virus
HNSCC	Head and Neck Squamous Cell Carcinoma
HR	Hazard ratio
ICH	International Conference on Harmonisation
ICRU	International Commission on Radiation Units
IEC	Independent Ethics Committee
NMR	Nuclear magnetic resonance
PET-TC	Positron emission tomography – Computed tomography
ORR	Overall response rate
OS	Overall survival
PF	Cisplatin + 5-FU
PFS	Progression-free survival
PR	Partial response

PTV	Planning target volume
QoL	Quality of life
RECIST	Response Evaluation Criteria in Solid Tumours
RT	Radiotherapy
RTOG	Radiation Therapy Oncology Group
SAE	Serious adverse event
SGOT	Serum glutamic oxaloacetic transaminase (=ALT = alanine transaminase)
SGPT	Serum glutamic pyruvic transaminase (=AST = aspartate transaminase)
TFS	Trial Form Support
TGFα	Transforming growth factor alpha
TNM	Tumour-lymph node-metastasis classification
TPF	Docetaxel, cisplatin, 5-fluorouracil
UNL	Upper normal limit
USA	United States of America
SD	Stable disease
TTP	Time to progression
USAN	United states adopted names
VAP	Visit after progression
Vss	Steady-state volume of distribution
WHO	World Health Organization
WHO-DRL	World Health Organization's Reference list of drugs
β-HCG	Human chorionic gonadotropin beta

1. Summary

Title:	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.
Study Code:	TTCC-2007-01
Sponsor:	Grupo Español de Tratamiento de Tumores de Cabeza y Cuello (TTCC) [Spanish Group for Head and Neck Tumour Treatment]
Coordinating Investigators:	Dr Ricardo Hitt Prof Juan Jesús Cruz
Sites:	43 Spanish sites approximately
Ethics Committees:	Ethical Committees of the Participating Centres
Planned duration of the study:	• November 2007 – October 2015 • Total: 96 months. • Recruitment period: 53 months. • Estimated date of the closing of the clinical phase: 36 months since the inclusion of the last patient.
Study phase:	Study phase III, open, randomized and multi-centre
Objectives:	This is a phase III study designed to assess the non-inferiority of the experimental arm compared with the standard arm in terms of overall survival (OS) in patients with locally advanced and unresectable squamous cell carcinoma in the head and neck that responded to induction chemotherapy with the docetaxel, cisplatin, 5-fluorouracil (TPF) regimen. Primary objective: • To show that the induction chemotherapy followed by radiotherapy (RT) + Cetuximab is at least non-inferior to chemotherapy with TPF followed by RT + cisplatin compared with OS in patients with unresectable HNSCC. Secondary objectives: • To evaluate the activity and safety of TPF treatment.

	• To evaluate the reasons for study non-continuation (possibility of complying with randomisation criteria) after induction treatment with TPF. • To evaluate and compare efficacy in the 2 treatment groups (experimental arm versus standard arm): - Disease-free survival - Specific survival - Time to locoregional control of disease • To evaluate and compare the safety activity and safety profiles of the 2 treatment groups (experimental versus standard): - Response rate - Acute and chronic toxicity rates • To evaluate and compare the patient perceptions using quality-of-life questionnaires. • To evaluate the treatment compliance rate with RT plus Cetuximab and RT plus cisplatin, after combination with induction and TPF.
Design and population of the study	Phase III, open-label, randomised and multicentre study in patients with unresectable locally advanced HNSCC. Before the start of protocol-specific procedures, written informed consent must be obtained. All patients will start treatment with 3 cycles of induction chemotherapy with the TPF regimen: 1. Patients who progress with the treatment with TPF will be excluded from the study and will be treated according to each site's protocol. 2. Patients with TPF toxicity that may not follow a treatment that includes cisplatin, will be excluded from the study and treated according to each site's protocol and in accordance with international guidelines. 3. Patients who are unable to receive at least two cycles of induction will be excluded from the study and will be treated according to each site's protocol and in accordance with international guidelines. 4. Patients who respond to or are stabilised with TPF and who may follow treatment with cisplatin, will be randomised to receive normofractionated RT plus cisplatin (Group A) versus the combination of cetuximab and normofractionated RT

(Experimental Group B). Patients will be stratified according to location (oral cavity, versus oropharynx, versus larynx versus hypopharynx), to ensure a homogeneous distribution.

As a result, there are 2 separate parts of the study:

- Part 1 of the study: the period from the signing of informed consent form until the response and toxicity assessment of induction chemotherapy with TPF.
- Part 2 of the study: the period from randomisation following induction chemotherapy with TPF until the end of study.

The assignment of patients to any of the populations mentioned below will be made before closing the database.

Part 1 of the study (period between the signing of informed consent to the evaluation of response and toxicity to induction chemotherapy with TPF):

A. *Safety population 1*: all patients who have signed the informed consent form and who have received at least one dose of chemotherapy with TPF.

B. *Intention-to-treat population 1*: all patients enrolled who have received at least one dose of TPF chemotherapy.

Part 2 of the study (period from randomisation after TPF chemotherapy and until the end of study):

C. Safety population 2: all randomised patients who have initiated the assigned radical treatment.

D. Intention-to-treat population 2: all randomised patients who have at least began their assigned radical treatment.

The following table outlines the foreseen moments of tumour evaluation from the beginning of the study:

SCHEME	CLINICAL EVALUATION OF TUMOR*	TUMOR IMAGE TECHNIQUES**	THORAX RADIOGRAPHY
Pre-treatment	X	X	X
At the end of the 3rd TPF cycle	X	X	
4 weeks post-RT	X		
6-8 weeks post-	X	X	

	<table><tr><td>RT</td><td></td><td></td><td></td></tr><tr><td>During years 1 and 2</td><td>/ 3 months</td><td>/ 6 months***</td><td>/ 12 months***</td></tr><tr><td>During years 3 and 4</td><td>/ 6 months</td><td>/ 6 months***</td><td>/ 12 months***</td></tr><tr><td>During year 5</td><td>/ 12 months</td><td>/ 12 months*** (optional)</td><td>/ 12 months***</td></tr></table> * It will include direct and/or indirect optical examinations of the tumour that they consider necessary. The exception would be the assessment at 4 weeks after the end of RT ** CT, PET-CT or MRI of the head and neck (always the same technique) *** or at the time of suspected progression and/or recurrence Abdominal ECHO, PET-CT and bone scan only if there is a suspicion of metastasis in these locations.
Methodology	The main analysis of the study will be carried out with the intention – to-treat (ITT) population that has been randomized to the standard branch or to the experimental branch. It will be proved, by means of the following hypotheses, if the experimental treatment group is, at least, not inferior to the standard group: - H0: Experimental Arm / Standard Arm ≥1.3 - H1: Experimental Arm / Standard Arm <1.3 It will be concluded that the experimental group is at least not inferior to the standard group if the unilateral confidence interval (CI) of 95% of the hazard ratio (HR) calculated by the Cox method does not contain the 1.3. In the analysis of OS, which is the primary endpoint proposed in this study, the Cox proportional hazards regression model will be used. Calculation of sample size is based on an assumed exponential distribution, using the following parameters: o Unilateral testing with an alpha of 0.05 and 80% power. o A recruitment phase of 53 months. o A follow-up phase of 36 months. o A HR of 0.0231 for the standard arm (median progression-free survival of 30 months) o $HR_{\text{Experimental arms / Standard arms}} = 0.938$ (this assumes a median of 32 months for the experimental arm) o Competing risk of 0.01.

	The total number of randomised and evaluable patients is 398. We also have to add the 15% of patients who will progress with TPF or will be lost to this total number. Total number of patients: 469.
Evaluation criteria:	**Evaluation of efficacy, safety and compliance:** OVERALL SURVIVAL (OS): the time from the start of induction chemotherapy with TPF to death due to any cause or to the last check-up in the case of living patients. OVERALL RESPONSE RATE (ORR): this is defined as the response rate (complete + partial) measured according to the solid tumour response endpoints (RECIST) 1.0 modified. ADVERSE EVENT (AE) RATE AND LABORATORY PARAMETERS: defined as the AE rate, including abnormal laboratory parameters, which occurred during the study period, according to the following criteria: 1. Common Toxicity Criteria (CTC) from the National Cancer Institute (NCI), version 3.0 during the induction treatment 2. CTC from the NCI, version 3.0 and CTC from the RTOG during chemotherapy/RT or Cetuximab/RT treatment and up to 90 days after completion of RT. If in doubt, the criteria that assess the AE at the highest level will be used. 3. Late CTC from the RTOG/EORTC from 90 days after completion of RT, which will be basically used to gather chronic toxicity associated with radio-chemotherapy All abstracts and lists of AE and laboratory data will be based on the safety population. EARLY STUDY WITHDRAWALS: this is defined as exclusion from the study, for any reason, before the end of treatment and before the first expected response assessment, at 6-8 weeks after completion of RT. Lists and summary tables will be provided, giving the reason for the end of the study and when it occurred. These summaries and lists will be based on the safety population. Part 2 of the study will be separated by assigned treatment arm. INCIDENCE AND TIME WHEN DOSE REDUCTION OR DISCONTINUATION OCCURRED: this is defined as any significant variation in the planned treatment dose (modifications greater than 10% of the planned dose), modification of the expected treatment day (changes of more than 2 working days) or

	discontinuations of planned treatment. Details and summary tables will be provided, providing the incidence of reductions or treatment discontinuations and giving the reason. These summaries and lists will be based on the safety population. Part 2 of the study will be separated by assigned treatment arm. PROGESSION-FREE SURVIVAL (PFS): time since the start date of treatment with TPF induction chemotherapy until the time when disease progression occur or death occur due to any cause. Patients who show no progression or death will be censored on the date of the last check-up. Patients for whom no tumour assessments are available after the baseline evaluation will be censored on day 1. Patients who show no progression and begin a cancer treatment other than that of the study will be censored on the start date of the other treatment. DISEASE-SPECIFIC SURVIVAL: time elapsed from the start date of treatment with TPF induction chemotherapy to date of death due to disease or related to the treatment of the disease. Deaths caused by other reasons will be considered "censored" data on the date of death. Patients who does not die will be censored on the date of the last check-up. TIME TO LOCOREGIONAL CONTROL OF DISEASE: locoregional control: defined as permanent and complete resolution of the disease in terms of its initial site and lymph nodes (T and N categories). If the disease last (regardless of size) or the tumour recur or a second tumour appear in the field RT, it will be recorded as a therapeutic failure. This allows for surgical rescue on the lymph nodes if, after the evaluation at the end of RT, the cervical adenopathy remain but the primary tumour will be under control (indicated as part of the first treatment). Locoregional failure will be considered in cases of patients who have rescue surgery on the primary tumour (T surgery) because of its persistence. Lymph node recurrence after a complete cervical lymph node remission will also be considered a therapeutic failure. In some cases, residual tumours may have persisted, consisting of areas of fibrosis or scarring, which may have remained stable or resolved gradually over time and which are not accompanied by evidence of locoregional disease progression or clinical deterioration. We define locoregional control time of the disease as time from the start of TPF induction chemotherapy to tumour recurrence or the appearance of a second tumour within the RT field. Patients who do not achieve complete remission at any of the points of the analysis will be considered therapeutic failures from day 1 (start of TPF chemotherapy). SATISFACTION WITH TREATMENT. QUALITY OF LIFE ANALYSIS: EORTC quality-of-life questionnaires is chosen for this study. QLQ-C30 version 3.0 is a basic questionnaire with 30 items

	and the QLQ-H&N35 module, made up of 35 items. These questionnaires are self-completed by the patients when they are at the site. They have to complete them before starting TPF induction chemotherapy, after 3 cycles of TPF, just before the patient knows the radical treatment arm to which they've been assigned, and then 6-8 weeks after completion of RT (evaluation visit following radical treatment) and every 6 months during the follow-up visits for the first and second year. If the time for completing the questionnaire coincides with an assessment of the tumour, the patient will fil it in before knowing the results of the tumour study. Overall scores and those per field in the total population and per treatment group will be described. A comparative analysis will be performed on the different scales according to the treatment assigned by the randomisation. OTHER VARIABLES: continuous variables will summarised using descriptive statistics, i.e. the mean, median, standard deviation, minimum, and maximum and two-sided CI of 95%, when appropriate. The qualitative variables will be summarised using counts, percentages, and 95% two-sided CI, when appropriate. The differences between means or percentages will be accompanied by 95% two-sided CI or will be compared using the corresponding statistical test.
Statistical Methods:	Efficacy and safety analyses will be performed using descriptive and/or comparative statistical techniques that are suited to each situation.

Patients selection:	**Inclusion criteria**: 1. Before beginning the specific procedures of the protocol, informed written consent has to be obtained and documented. 2. Locally advanced cancer of the head and neck (oral cavity, oropharynx, larynx and hypopharynx), stage III-IV, with no evidence of metastasis. 3. The tumour has to be classified as inoperable according to Northern California Oncology Group [5] criteria after assessment by a multidisciplinary team, which include, at least, a specialist in oncological surgery from the Ears, Nose and Throat Department or a specialist in maxillofacial surgery (as applicable), a specialist in Medical Oncology and a specialist in Radiotherapy oncology. The reason for inoperability will be noted on the CRF. NCOG inoperability criteria: - Technically nonresectable (Includes: Evidence of mediastinal dissemination; tumour fixed to the clavicle, base of the cranium or cervical vertebrae; involvement of the nasopharynx). - Medical criteria based on a low surgical curability. - Medical contraindication for surgery. 4. Anatomically and pathologically proven epidermoid carcinoma. 5. Disease measurable according to the modified RECIST 1.0 criteria. 6. Men or women aged 18 to 70 inclusive. 7. ECOG performance status: 0 or 1 8. Patients in a medical condition to be able to receive induction treatment with TPF followed by normofractionated RT with cetuximab or cisplatin. 9. Patients with adequate haematological function: neutrophils $\geq 2x10^9$ platelets $\geq 100x10^9$, haemoglobin ≥ 9 g/dL and no symptoms related to anaemia.

	10. Adequate liver function: Bilirubin ≤ 1.5×Upper Normal Limit (UNL), and some of the following parameters: GOT ≤ 2.5 UNL or GPT ≤ 2.5 UNL or alkaline phosphatase < 2 UNL; however, if all of these are present, their value should not exceed the UNL. 11. Adequate kidney function: serum creatinine < 1.4 mg/dL (120 μmol/L); if the values were > 1.4 mg/dL, creatinine clearance has to be > 60 mL/min (real or calculated by the Cockcroft–Gault method). 12. Adequate nutritional status: Body mass index > 18.5% or albumin ≥ 30 g/L. 13. Patients have to be accessible for treatment and follow-up.

	Exclusion criteria: 1. Metastatic disease. 2. Previous treatment by surgery, with radiotherapy and/or chemotherapy for the disease being studied. 3. Other tumour locations in the head and neck area, other than the oral cavity, oropharynx, larynx and hypopharynx. 4. Stages other than stage III or IVM0. 5. A previous and/or synchronous squamous cell carcinoma. 6. Diagnosis of another neoplasia in the past 5 years except properly treated cervical carcinoma in situ and/or basal cell carcinoma. 7. Active infection (infection that requires intravenous antibiotics), including diagnosed active tuberculosis and HIV. 8. Uncontrolled hypertension defined as systolic blood pressure ≥ 180 mm Hg and/or diastolic blood pressure ≥ 130 mm Hg at rest. 9. Pregnancy (its absence should be confirmed by a serum β-HCG test) or lactation. 10. Systemic, chronic and concomitant immune therapy or hormone therapy for cancer. 11. Other concomitant antineoplastic treatments. 12. Clinically significant coronary artery disease or a history of myocardial infarction in the past 12 months or high risk of uncontrolled arrhythmia or uncontrolled heart failure. 13. Chronic obstructive pulmonary disease that required ≥ 3 hospitalisations in the previous 12 months. 14. Uncontrolled active peptic ulcer. 15. Presence of a psychological or medical illness that would prevent the patient from taking part in the study or from providing written informed consent. 16. Known drug abuse (except for heavy drinking). 17. Known allergic reaction to any of the ingredients of the study treatment. 18. Previous treatment with monoclonal antibodies or other inhibitors of signal transduction or EGFR inhibitors. 19. Any experimental treatment in the 30 days prior to study entry.

2. Index

3. Justification and objectives

3.A Justification for cetuximab

As of 28 April 1999, the USAN adopted the name cetuximab for the chimeric monoclonal antibody C225. On 8 May 2000, cetuximab obtained the proposed qualifying status of the International Nonproprietary Names (INN).

Cetuximab (Erbitux®) was developed jointly by Bristol-Myers Squibb (BMS), ImClone Systems Incorporated and Merck KGaA. In February 2004 the Food and Drug Administration (FDA) authorised in the United States of America (USA) the commercial use of Erbitux™ combined with irinotecan in the treatment of metastatic colorectal carcinoma (CRC) expressing epidermal growth factor receptor (EGFR) in patients refractory to irinotecan-based chemotherapy and alone for patients intolerant to irinotecan. In June 2004 the European Medicines Agency (EMA) approved the use of cetuximab (Erbitux®) in the European Union (EU) (as well as in Norway and Iceland) combined with irinotecan in the treatment of patients with CRC expressing EGFR after treatment failure with cytotoxic agents, including irinotecan. In Spain, the Spanish Agency of Medicines and Medical Devices (AEMPS) authorised the marketing of Erbitux® on 18 January 2005. On 30 November 2004, marketing authorisation for cetuximab (Erbitux®) was also approved in Argentina, Chile and Mexico for the treatment of metastatic CRC expressing EGFR in patients refractory to irinotecan, either alone or combined with irinotecan.

In December 2005 cetuximab (Erbitux®) was approved for the treatment of locally advanced head and neck squamous cell carcinoma (HNSCC) combined with radiotherapy (RT), in Switzerland, and in March 2006 it was approved in the EU by the EMA. In Spain, the AEMPS authorised the use of Erbitux® in the treatment of head and neck cancers on 31 May 2006. In Argentina, the Philippines, Chile, Israel and Mexico, Erbitux® was also authorised as monotherapy in patients with recurrent and/or metastatic HNSCC where previous chemotherapy had failed. On 1 March 2006, Erbitux® was approved in the USA for use in combination with RT for the treatment of locally advanced HNSCC, and as a single agent in recurrent or metastatic HNSCC where platinum-based chemotherapy had failed.

In the Investigator's Brochure, version 10.0, dated May 2004 [6] further information about the relevant pre-clinical pharmacological, pharmacokinetic and toxicological data can be found.

3.A.1 Epidermal growth factor receptor in cancer

EGFR is a transmembrane glycoprotein that is expressed under normal conditions and is a member of the tyrosine kinase receptor family. EGFR is expressed in many human tissues, and the activation of the proto-oncogene, which encodes it, results in the overexpression seen in many types of tumour. EGFR has an extracellular domain that constitutes a ligand-binding site for the epidermal growth factor (EGF) and for tumour growth factor alpha (TGFα). After ligand-binding, the intracellular domain of EGFR is activated, which triggers the signal-transduction pathway of EGFR-mediated tyrosine

kinase, and consequently various cell mechanisms that regulate cell growth and division are activated [7].

The *in vitro* analysis performed with cell lines that not only express EGFR in large amounts but also produce a ligand for these receptors has shown that EGFR may be activated by an autocrine pathway, causing cell proliferation in cultures [8]. In order to inhibit the cell proliferation that expresses EGFR, EGFR antagonists have been synthesised that block the ligand-binding site.

Table 3.1 shows the prevalence of EGFR expression in some of the most common tumours [9].

Table 3.1 Prevalence of EGFR expression in the most common tumours.

Type of tumour	Percentage of EGFR expression
Oesophageal cancer	92%
Head and neck squamous cell carcinoma (HNSCC)	90%
Pancreatic cancer	89%
Colorectal cancer (CRC)	82%
Prostate cancer	65%
Bladder cancer	65%
Ovarian epithelial cancer	60%
Cervical cancer	60%
Renal cell carcinoma	50%
Non-small cell lung cancer (NSCLC)	50%

EGFR: Epidermal growth factor receptor

3.A.1.1 EGFR inhibition and cell cycle

The effects of EGFR blockade on cell-cycle progression have been studied in several human cell lines, including the colorectal cancer cell line (DiFi), the mammary epithelial cell line (MCF10A), the epidermoid carcinoma cell line (A-431) and the prostate cancer cell line (DU145). These studies suggest that the EGFR blockade with monoclonal antibodies like cetuximab cause the cell cycle to stop in G1, which is accompanied by decreased activity of cyclin-dependent kinases (CDKs) 2 and increased expression of the cyclin-CDK inhibitor p27K1P1 [10,11]. In addition to stopping the G1 phase, it has also been shown to block the EGFR that induces cell death through apoptosis in the DiFi human colorectal cancer cell line [12].

3.A.2 Cetuximab

Cetuximab, a chimeric antibody in subclass IgG1, was originally obtained from a mouse myeloma cell line. The chimerization process produces an antibody with an affinity for binding to EGFR that is greater than that of the natural ligand EGF [13]. Cetuximab blocks the binding of EGF and TGF-α to EGFR, thereby inhibiting the activation of this receptor tyrosine kinase caused by the ligand binding. Cetuximab also stimulates EGFR internalisation, thus effectively removing the cell-surface receptor and preventing it

from interacting with the ligand [14]. Cetuximab was created by chimerization of the murine monoclonal antibody (M225), developed at the University of California, San Diego [6]. Cetuximab was constructed genetically by cloning the heavy and light chains of M225 and adapting them for expression with the constant domains of the human light chain k and heavy chain γ 1.

In an *in vitro* study to establish the biological activity of cetuximab and its specificity to human EGFR compared with that of a murine antibody against EGFR (M225), both cetuximab as well as M225 inhibited the growth of A431 cells to a similar extent, i.e. 30% of the control [13].

3.A.2.1 Binding cetuximab ligands to tissue *in vitro*

In a series of immunohistochemical studies to characterise the binding of cetuximab to human and animal tissues, it was shown that cetuximab reacted positively and specifically to human placental epithelium [6]. Specific staining was also observed in the normal epithelia of skin, gastrointestinal tract, urogenital system and tonsillar crypts, and in squamous cell carcinoma and small-cell lung cancer. There was no specific staining in cancers in other organs, in melanomas or in lymphoid tumours. In a cross-species study, the control human placental tissues showed positive staining for cetuximab; however, no staining was observed in monkey liver tissues (*Cynomolgus and Rhesus*), baboons, rodents and dogs. In the Investigator's Brochure, version 10.0, dated May 2004, specific details of these studies can be found [6].

3.A.2.2 Criteria for dose selection and clinical pharmacokinetic parameters of cetuximab

When the clinical development of cetuximab was started, the objective was to administer doses of the antibody which were safe and which would maintain serum concentrations of cetuximab above the doses needed to saturate the binding of EGFR associated with the tumour obtained in preclinical mouse models (approximately 20 nM). In this early stage of clinical development, this dose-selection criterion was revised considering in the hypothesis that binding to EGFR not associated with the tumour (especially in the liver and the skin) could cause a considerable loss of cetuximab, which might limit the availability of antibody for the tumour-associated receptors. Expanding this hypothesis, it was thought that the binding of cetuximab to targets other than the tumour and the subsequent internalisation of the receptor represented a major route of elimination of cetuximab, which could theoretically become saturated. Thus, at some point the systemic clearance of cetuximab could become saturated, which might be detected by estimating serum pharmacokinetic parameters in subjects (total body clearance and half-life). Based on this hypothesis the criteria used to select the dose were revised to find the dose at which systemic clearance (as determined by serum pharmacokinetic parameters) becomes saturated.

The initial clinical development programme for cetuximab was composed of 14 studies, 13 of which contributed to the pharmacokinetic database. In dose-finding studies, where the dose of cetuximab was increased from 5 to 500 mg/m^2, a trend towards decreased clearance of cetuximab was described. At doses above 200 mg/m^2, cetuximab clearance appeared to stabilise and was maintained at approximately 0.02 L/h/m^2 up to the highest dose studied, 500 mg/m^2. The estimated mean terminal half-life of cetuximab in serum increased from 14 to 97 hours in the dosage range from 5 to 300 mg/m^2 after which the

half-life seemed to stabilise. The mean of the steady-state volume of distribution (Vss) of cetuximab in serum was not cetuximab dose-dependent; it was from 1.96 to 2.52 L/m^2, which suggests that cetuximab is distributed in an equal or slightly higher volume in the vascular space. Based on the foregoing and on the finding of an increased incidence of skin toxicity at 500 mg/m^2, the cetuximab regimen chosen for the phase II clinical trials was an initial dose of 400 mg/m^2 followed by repeated doses every week of 250 mg/m^2. It has been suggested that on this regimen patients might maintain EGFR activity and drug activity.

When cetuximab was administered alone to subjects with solid tumours at an initial dose of 400 mg/m^2 followed by weekly maintenance doses of 250 mg/m^2 (n=7 subjects), the mean of the maximum serum concentration (C_{max}) of cetuximab at week 3 was 153 µg/mL (range from 112 to 225 µg/mL). The mean elimination half-life at week 3 was 119 h (range from 82 to 188 hours). The mean Vss at week 3 was 3.6 L (range from 2.2 to 4.5 L). Concomitant administration of irinotecan (350 mg/m^2) at week 4 did not change the pharmacokinetic characteristics of cetuximab, given that the relationships (expressed as a percentage) of all the pharmacokinetic parameters of cetuximab at week 4 versus week 3 were from 87% to 123% (EMR 62 202-012 study by Merck).

3.A.2.3 Response of anti-cetuximab antibodies

The presence of anti-cetuximab antibodies was evaluated in a total of 614 patients treated with cetuximab up to 30 November 2002, analysing the baseline and subsequent serum concentrations. The overall incidence of an anti-cetuximab immune response in these patients was 3.7%. When there was an anti-cetuximab response, in general it was found to be weak. The anti-cetuximab antibodies were analysed in two patients who had greater reactivity (4,670 and 6,516 ng/mL) in an *in vitro* trial to determine neutralising activity. The serum concentrations analysed did not interfere with the ability of cetuximab to inhibit proliferation in a cell line sensitive to cetuximab, thus suggesting that the antibodies of these sera were not neutralising. The levels of serum reactivity in the other subjects were not high enough to perform this kind of analysis. To determine the specificity of the antibody response, the sera of 15 patients who had a positive response to anti-cetuximab were then studied using as a competitor unlabelled cetuximab in an immunoradiometric double-antigen assay. This analysis showed that the sera of 14 of the 15 patients contained antibodies specific to anti-cetuximab.

3.A.2.4 Clinical experience with cetuximab

Clinical experience with cetuximab is detailed in the Investigator's Brochure for cetuximab, version 10.0, dated 20 May 2004 [6]. Clinical trials with cetuximab started in 1994. Cetuximab has been administered in phase I-III clinical trials as a single agent or in combination with chemotherapy and RT. Those trials have shown anti-tumour activity in metastatic colorectal cancer, HNSCC, non-small cell lung cancer and pancreatic cancer. The clinical experience with cetuximab in head and neck cancers is detailed in section 3.A.2.6.

3.A.2.5 Clinically significant adverse events related to cetuximab at the time of the study design

The database includes safety data from 2,127 patients treated with cetuximab in 33 clinical trials up to 30 November 2003 [6]. Adverse events (AEs) were reported in 90.3% of patients. A total of 1,378 patients (64.8%) reported at least one AE of grade 3 or 4. In all, 1,817 patients (85.4%) had AEs related to cetuximab. In total, 31.7% of patients reported cetuximab-related AEs of grade 3 or 4. The most common AE with cetuximab was acneiform rash.

The Investigator's Brochure [6] summarises the safety data in table format for all phase I studies, by indication for phase II studies and by study for each phase III study.

The incidence of the most common cetuximab-related AEs (all grades) is given in Table 3.2.

Table 3.2 Most common cetuximab-related AEs (all grades, n=2127, up to 30 November 2003).

Adverse event	Frequency		
	N	Grade ≤1 (%)	Grade 3-4 (%)
Skin reaction[a]	1621	76.2	11.1
Fatigue/Malaise/Lethargy	640	30.1	4.2
Nausea/Vomiting	510	24.0	2.2
Mucositis/Stomatitis	372	17.5	2.3
Diarrhoea	321	15.1	2.4
Nail irritation	229	10.8	0.3
Allergic reactions or hypersensitivity[b]	112	5.3	2.4

Data from 2127 patients in 33 trials who received cetuximab alone or in combination with chemotherapy or radiotherapy.

[a] Includes the COSTART terms acne, rash, maculopapular rash, pustular rash, dry skin or exfoliative dermatitis.

[b] Includes the COSTART terms allergic reaction or anaphylactoid reaction.

Skin reactions are the most common AEs related to cetuximab (76.2% grades 1-4, 11.1% grades 3 or 4). They usually occur as an acne-like rash or, less often, as nail disorders. The aetiology of acneiform rash is thought to be the result of cetuximab binding to the EGFR of the cells of the epidermis, thus interfering with the homeostasis of the epidermis, hair follicles and sebaceous glands, as well as with the regulation of skin inflammation.

Acneiform rash (72.4% grades 1-4) usually occur during the first three weeks of treatment on the face, upper part of the chest and the back, although sometimes it extends to the limbs. It appears as multiple pustular or follicular lesions, histologically characterised as lymphocytic perifolliculitis or superficial suppurative folliculitis. It tends to resolve over time without after-effects after stopping treatment. In patients who received cetuximab in doses under 100 mg/m^2, there were few cases of acneiform rash reported, and they were limited to grades 1 and 2. For treatment guidelines, see section 7.A.1.4.1.

A clear correlation has been established between the onset of skin toxicity and the efficacy of treatment, both in response and in time to progression (TTP) and survival [15,16].

Nail disorders are another typical, but less common skin manifestation (10.8% grades 1-4, 0.3% grades 3 or 4 = 0.3%) that occur at different pain levels and sensitivity, as does cracked skin on the distal end of the fingers and toes. These patients developed paronychia associated with swelling of the lateral nail folds of the fingers or toes. The digits most commonly affected are the big toes and the thumbs. In one patient, the middle finger was also affected. In some cases, swelling of the lateral nail folds was associated with friable pyogenic granuloma that bled but with only minor trauma. Cleaning and padding the areas affected provided the greatest relief from symptoms. From the information provided by the investigators, nail disorders have been known to last up to 2 months after discontinuing cetuximab.

Allergic or hypersensitivity reactions: grade 3 or 4 reactions have been observed (including allergic and anaphylactic reactions), characterised by rapid onset of airway obstruction (bronchospasm, stridor, hoarseness), urticaria and/or hypotension, in 2.4% of patients treated with cetuximab. Approximately 80% of all allergic or hypersensitivity reactions occurred during the first infusion of cetuximab and were observed during the infusion or one hour after completing it.

Before the first administration of cetuximab, patients should be pre-treated with an antihistamine and a corticosteroid (see section 7.A.1.3). This pretreatment is also recommended prior to all subsequent infusions of cetuximab, as some patients experienced their first serious hypersensitivity or allergic reaction during later infusions. To date, in studies with cetuximab, patients who experienced serious reactions received conventional treatment, all but one recovered without after-effects, and they were removed from the corresponding studies. This patient died due to angioedema after completion of the cetuximab infusion, which was reported because of a grade 4 reaction. The appearance of allergic or hypersensitivity reactions does not appear to be related to monotherapy or combination therapy, underlying disease or previous exposure to murine monoclonal antibodies.

Mild to moderate allergic or hypersensitivity reactions can usually be controlled by slowing the infusion rate of cetuximab (see section 7.A.1.4.2).

After the approval of cetuximab by regulatory agencies and subsequent marketing, several cases of hypomagnesaemia have been reported, possibly associated with the administration of cetuximab, whether combined or not with chemotherapy. Most have been described as mild and/or moderate hypomagnesaemia, and so in general this is not a clinically significant finding; it is usually associated with secondary hypocalcaemia and/or hypokalaemia [17,18]. Preliminary data from three randomised trials (E5397, NCIC CO.17 and BMS CA225014) have confirmed that magnesium levels may fall in patients on cetuximab, whether combined or not with chemotherapy, compared with patients included in a control arm without cetuximab. Current data are insufficient for establishing the frequency of this finding. In the cases described, there was a quick response with magnesium supplementation, where it was considered necessary to replace it, and the condition was able to be reversed, as the hypomagnesaemia resolved within a few weeks of stopping treatment with cetuximab.

3.A.2.6 Clinical experience with cetuximab in head and neck cancers

Cetuximab has been evaluated in locally advanced disease and in metastatic and/or recurrent HNSCC, both in first-line and salvage therapy.

3.A.2.6.1 As salvage therapy in recurrent and/or metastatic disease

An extensive development programme for cetuximab in HNSCC has been carried out, which includes several phase II studies examining the efficacy and safety of cetuximab combined with a platinum-based agent (cisplatin or carboplatin) or cetuximab alone in patients with metastatic and/or recurrent HNSCC, in whom disease progression was confirmed during administration of platinum-based chemotherapy [19–21]. In studies investigating cetuximab combined with a platinum-based agent, the overall response rate (ORR) was 11-13%, the disease control rate 51%, median TTP 2.2-2.8 months, and median survival 5.2-6 months [19,20]. In a study investigating cetuximab alone in the same patient population (EMR 62 202-016 study), the ORR was 13%, the disease control rate 45%, median TTP 2.3 months, and median survival 5.9 months [21].

These results indicate that cetuximab given alone provides the same benefit as the combination of cetuximab with a platinum-based agent in patients who have progressed on a previous regimen of platinum-based chemotherapy. The results obtained in these 3 studies are superior to historical results observed in these patients: 3.4% with objective responses and a median survival of 3.5 months [22,23].

3.A.2.6.2 As first-line treatment in recurrent and/or metastatic disease

The most extensive study in first-line treatment of recurrent and/or metastatic HNSCC was done by the Eastern Cooperative Oncology Group (ECOG), and it compared cisplatin + cetuximab versus cisplatin + placebo in 121 patients (E5397) [24]. The ORR was higher in the group treated with cetuximab (26.3% vs 9.8%, p=0.03), while the efficacy values based on time were also better in the group treated with cetuximab, though there were no statistically significant differences (overall survival [OS]: 9.2 months vs 7.9 months; progression-free survival [PFS]: 4.2 months vs 2.7 months). Cetuximab did not change the safety profile of cisplatin.

A phase I/II study (EMR 62 202-008) has also been conducted to investigate the tolerability and efficacy of the cisplatin or carboplatin regimen + 5-fluorouracil (5-FU) combined with cetuximab as first-line treatment for recurrent and/or metastatic HNSCC. The results showed that cetuximab did not alter the known safety profile of chemotherapy, and vice versa; full doses were therefore able to be given. The efficacy data were encouraging with an ORR of 36%, a disease control rate of 74%, a median TTP of 5.1 months and a median OS of 9.9 months [25].

At the 2007 American Society of Clinical Oncology (ASCO) he results of the phase III study (EMR 62 202-002 EXTREME) [26] were presented, in patients with recurrent and/or metastatic HNSCC, in which the efficacy of the combination of cetuximab was compared with the regimen of cisplatin or carboplatin + 5-FU in first-line treatment versus the same chemotherapy regimen alone. The results have shown a statistically significant increase in median survival, from 7.4 months in the chemotherapy-alone arm to 10.1 months with the chemotherapy-plus-cetuximab combination, with no major

changes in the toxicity profile of the platinum-based regimen. At that same ASCO, the *Grupo Español de Tratamiento de Tumores de Cabeza y Cuello* (TTCC, Spanish Group for Head and Neck Tumour Treatment) presented a phase II study [27] with excellent results in tumour response with the combination of weekly paclitaxel and cetuximab (60% of responses in the same population of patients with recurrent and metastatic disease).

3.A.2.6.3 As treatment combined with RT in locally advanced disease

There are many preclinical studies showing that the cetuximab-induced inhibition of EGFR increases the effectiveness of RT, as it decreases the number of cells in the S phase and increases them in the G1 phase, facilitates apoptosis, decreases the ability of DNA repair, and has a clear antiangiogenic effect [28–32].

Based on this scientific justification, a phase Ib/IIa trial was conducted at the University of Alabama, Birmingham in patients with locally advanced HNSCC [33]. In this dose-escalation trial, 8 patients were administered weekly infusions of cetuximab combined with normofractionated or hyperfractionated RT. Tolerance was excellent and toxicities associated with radiation did not increase by adding cetuximab to RT, and the full dose of cetuximab was therefore able to be given. Of the 15 evaluable patients in this study, 13 (87%) complete responses were seen, based on physical and endoscopic exams. These results were very encouraging compared with historical controls, and so a phase III study was designed for patients with locally advanced HNSCC to compare the combination of cetuximab and RT versus RT alone, which was the standard treatment accepted by the FDA when the study was started in 1999 [34,35].

In this study, 424 patients with locally advanced HNSCC were enrolled: oropharynx 60%, larynx 25% and hypopharynx 15%. A total of 208 patients received the combination of cetuximab and RT (accelerated with concomitant overprint 56%; normofractionated 26%; hyperfractionated 18%), and 212 had RT alone (accelerated with concomitant overprint 56%; normofractionated 27%; hyperfractionated 17%). Median follow-up was 54 months. The combination of cetuximab and RT provided a significant improvement in survival and locoregional disease control (Table 3.3). Median survival was 49 months for combined and 29.3 months in the RT-alone arm (p=0.02). There were no significant differences in studied quality of life (QoL) parameters between treatment arms [34–36].

Table 3.3 Combined cetuximab and RT versus RT alone.

	Combined cetuximab and RT	RT alone	P-value	Relative risk reduction
Overall Survival				
At 2 years	62%	55%	0.02	0.74 (0.57-0.97)
At 3 years	55%	45%	0.05	
Locoregional control				
At 2 years	63%	55%	0.02	
At 3 years	50%	41%	<0.001	0.68 (0.52-0.89)

The administration of cetuximab determined the presence of the usual related toxicity, but did not increase the toxicity related to RT (Table 3.4).

Table 3.4 Most common side effects in the study.

Toxicity	Radiotherapy (n=212)		Cetuximab + Radiotherapy (n=208)	
	All Grades	Grade 3-4	All Grades	Grade 3-4
Acneiform rash	10%	1%	87%	17%
Radiation dermatitis	90%	18%	86%	23%**
Mucositis, stomatitis	94%	52%	93%	56%
Dysphagia	63%	30%	65%	26%
Xerostomia	71%	3%	72%	5%
Asthenia	49%	5%	56%	4%
Infusion-related reactions* **	2%	0%	15%**	3%*

* p <0.05; ** p <0.001; *** Recorded due to relationship to cetuximab.

The magnitude of the improvement in survival provided by the combination of cetuximab and RT is comparable to that associated with chemoradiotherapy treatment, but with much lower toxicity [35,37,38]. The multivariate analysis confirmed that the administration of cetuximab was an independent prognostic factor for the improvement in survival.

Based on these results, the regulatory agencies authorised the use of cetuximab in the treatment of head and neck cancers. Since March 2006, Erbitux in combination with RT is indicated for the treatment of locally advanced HNSCC.

3.B Study rationale

HNSCC represent 5% of cancers diagnosed de novo in the total adult population. This is a potentially curable malignant neoplasia if diagnosed at an early stage, but unfortunately two-thirds of cases are diagnosed at an advanced locoregional stage, or stages III and IV M0 [39]. Despite the fact that in recent years there have been important advances in the treatment of HNSCC, with confirmation of the efficacy of radiochemotherapy programmes with cisplatin [37,38], locally advanced unresectable HNSCCs have a very poor prognosis, with a median survival of less than 20-24 months, and only 25-30% of patients living at 5 years [40–42]. Approximately 60-70% of these patients will develop a locoregional failure and 20-30% will develop distant metastasis.

With these results, it is clear that an effort should be made to investigate and integrate the new therapeutic options available for the treatment of HNSCC, in order to try to improve the prognosis of patients with unresectable locally advanced HNSCC.

3.B.1. Induction chemotherapy with TPF (docetaxel, cisplatin, 5-fluorouracil)

Induction chemotherapy programmes, which are basically the a continuous infusion of combined cisplatin and 5-FU (PF), and which during the 1990s led to the development of strategies for organ preservation [43,44] and reducing the incidence of distant metastases [45], were questioned by the meta-analysis published in 2000 (MACH-NC:

Meta-Analysis of Chemotherapy in Head and Neck Cancer) and updated in 2004 [37,38]. The MACH-NC established the role of radiochemotherapy programmes with cisplatin as a new standard treatment for locally advanced HNSCC, because the improvement in survival was superior to that provided by the treatments with induction chemotherapy followed by RT and/or surgery [37,38].

A subsequent specific meta-analysis of the efficacy of induction chemotherapy with PF confirmed that absolute 5-year survival was active and increased by 5% [46]. Its efficacy was lower than radiochemotherapy programmes with cisplatin; therefore, its integration in sequential programmes with subsequent chemoradiotherapy should also be improved and studied.

The introduction of the taxanes (docetaxel or paclitaxel) which are demonstrated to be active in HNSCC without presenting cross-resistance with cisplatin, and with a minimally-overlapping toxicity profile with PF, made it possible to design combination chemotherapy regimens with 3 drugs (PF + paclitaxel, PF + docetaxel). These regimens were shown to be highly active in the first phase I-II studies with response rates of up to 90% and a significant percentage of complete responses [47–49]. These good results with an acceptable toxicity profile led to the conduct of phase III studies to compare these new induction chemotherapy regimens with the "classic" PF. In the past 2 years, results of 4 phase III studies have been presented, and these have definitively established the efficacy of induction docetaxel, cisplatin and 5-FU (TPF) in locally advanced HNSCC.

Hitt et al. published the results of a phase III study with 382 patients with locally advanced unresectable and resectable HNSCC, which showed that the sequence of the combination of PF with paclitaxel followed by radiochemotherapy with cisplatin provides better survival than the PF sequence followed by chemoradiotherapy: 43 months versus 37 months; p=0.06. In contrast to what was expected, the PF combination with paclitaxel was less toxic than PF [50].

A phase III study by the European Organization for Research and Treatment of Cancer (EORTC 24971) with 358 patients with unresectable advanced HNSCC was presented at the 2004 ASCO and was updated at the 2006 ASCO. This study showed that administration of 4 cycles of induction TPF followed by radical RT provides a significant improvement in survival compared with the PF induction sequence followed by radical RT: 18.6 months versus 14.2 months; hazard ratio (HR): 0.73 [0.56-0.90]; p=0.0052. The TPF regimen was better tolerated and provided a better QoL in all studied parameters, compared with the PF regimen [51–53].

At the 2006 ASCO, the results of two new phase III trials with TPF were presented. A first study included 501 patients with locally advanced resectable and unresectable HNSCC, and compared TPF administration followed by non-standard radiochemotherapy (normofractionated RT carboplatin, 1.5 area under the curve (AUC)/weekly), followed by the same radiochemotherapy regimen. With a median follow-up of 42 months, the TPF regimen provided a significant improvement in survival: +70.6 months versus 30.1 months with 62% of the patients alive after 3 years versus 48%, HR: 0.70 [0.54-0.90], p=0.0058 [54].

The second phase III study included 205 patients with carcinoma of the larynx or hypopharynx, who required surgical treatment involving a laryngectomy. The

possibility of preserving the larynx was investigated by comparing TPF versus PF followed by radical RT when a response was confirmed or radical surgery when no response was confirmed. TPF provided a high objective and complete response (CR) rate, greater therapeutic compliance, a higher rate of larynx preservation and larynx function, as well as a clear trend towards improved survival [55].

With the results provided by TPF in the trials described, regulatory agencies (EMA and FDA) have approved administration of TPF as an effective induction regimen, especially in patients with unresectable locally advanced HNSCC and good overall condition, as established at ASCO 2006 [54,55]. In Spain, the AEMPS approved administration of TPF for patients with unresectable locally advanced HNSCC, from 8 June 2007.

3.B.2. Sequential treatment with TPF

The first phase II studies with TPF induction chemotherapy followed with RT indicated that TPF was a highly active regimen that reduced the incidence of distant metastases, but locoregional control of disease could continue to be a problem for a group of patients [56]. Therefore, from a conceptual and biological perspective, following TPF induction, the most effective locoregional treatment possible should be offered.

Currently, there are two studies, a randomised phase II and a randomised phase II-III study by the TTCC, that suggest a greater efficacy of TPF followed by standard chemoradiotherapy with cisplatin 100 mg/m^2 than when standard chemoradiotherapy was administered without previous induction [57,58]. These preliminary results reinforce the work line of TTCC in the sense that after an effective induction chemotherapy the most effective locoregional treatment possible must be administered [48,58], in order to be able to control the metastatic spread without jeopardising the results of locoregional control, which can be brought about by the reduction in the tumour volume prior to administration of locoregional treatment.

Thus, in unresectable disease, the combination of induction chemotherapy with TPF followed by the best locoregional treatment is being established as a new standard in order to improve poor results obtained with chemoradiotherapy alone. The results of the Spanish group on unresectable disease [58] showing a significant improvement in the TTP favouring the induction chemotherapy arms, support sequential therapy followed by chemoradiotherapy with cisplatin as the new standard for this group of patients.

3.B.3. Radiotherapy combined with cisplatin for treatment following induction chemotherapy with TPF

In the 1990s, no randomised study with induction chemotherapy had demonstrated that it could increase the OS rate when used against a local treatment only, this being either surgery or RT. Only one Italian study [59] in the analysis of the subgroup with unresectable disease found that patients who had received 4 cycles of induction chemotherapy with PF at full doses had a lower rate of local and metastatic recurrence, resulting in increased survival.

As well as the poor survival results in the induction regimens, the meta-analysis [37] was published, which suggested that the only way of increasing survival versus single

locoregional treatment was through the use of concomitant treatments, and several randomised trials were published in the same period [40,60–64] that demonstrated that treatment with chemoradiotherapy has much greater locoregional control and survival than RT alone. As a result of these events, therapeutic regimens started to be based on concomitant treatment. The normofractionated RT regimen (70 Gy) with cisplatin at doses of 100 mg/m^2 on days 1, 22 and 43 of RT was chosen as the concomitant regimen with the best balance between acute toxicity and therapeutic efficacy, and as a result, since the beginning of the 2000s, it has been the standard regimen, which is still the case.

At ASCO 2006, the new sequential therapeutic approach was strengthened for unresectable disease [55,57,58], but a major concern arose due to the toxicity of the administration of radiochemotherapy with cisplatin after induction chemotherapy. Particularly since the scientific community is aware of having underestimated the incidence and severity of chronic toxicity caused by radiochemotherapy programmes with cisplatin that can be responsible for up to 6% of deaths and a significant deterioration in the QoL of these patients [65,66]. In this regard a larger randomised study with TPF (the TAX324 study), which showed that treatment with TPF is superior to PF, used a sequential treatment with carboplatin radiochemotherapy, which is not a therapeutic programme with proven efficacy [34,35,54]. In fact, there was a phase III randomised study with 124 patients with locally advanced HNSCC, which compared normofractionated RT versus RT + cisplatin (100 mg/m^2/3 weeks) versus RT + carboplatin (7 AUC/3 weeks): median TTP was 6.3 months versus 45.2 months versus 17.7 months p=0.0002; and median survival of 12.2 months versus 48.6 months versus 24.5 months p=0.0003 [67].

When acute toxicity is analysed in randomised studies [40,60–64] which have compared chemoradiotherapy versus RT alone, there is only a significant increase against concomitant regimens, which is shown in Table 3.5. The most significant increase occurs in mucositis, which increases in both severity and duration. This is a key factor in chemoradiotherapy treatments, which results in a series of complications for patients, which will involve greater support requirements by hospitals where they are treated (over half will need enteral feeding tubes, there is a significant increase in medical and nursing visits, greater antibiotic treatment requirements, etc.). Due to increasing support requirements, HNSCC need to be restructured if they want to keep offering adequate treatment, a key factor in recovery.

Table 3.5 Comparison of the increase in severe acute toxicity in concomitant chemoradiotherapy compared to RT alone in 6 randomised studies [40,60–64]

Toxicity	Increase
Grade 3-4 mucositis	13-30%
Grade 3-4 Radiodermatitis	5-10%
Grade 3-4 vomiting	10-15%
Grade 3-4 neutropenia	30-40%
Risk of infection	4-15%

Weight loss > grade 1	10%
Toxic mortality	2%

Although it is difficult to know the increase in chronic toxicity due to a lack of published data, there is indirect data that may help us to get an idea of the magnitude of the problem. In patients who have received chemoradiotherapy, the main cause of death not related to disease, during the first year, is treatment-related toxicity [65]. Argiris analysed the causes of death in the first few years in more than 300 patients treated at his institution with concomitant chemoradiotherapy, as part of clinical trials: 45% were due to disease progression, 15% had treatment complications (9% acute + 6% late), 9% to secondary neoplasias (in particular in lung cancer) and 21% for the comorbidity associated with these patients. It is possible that the increase in toxicity caused by more aggressive treatment regimens determines these high mortality rates due to the patient's base co-morbidity. In this same regard, an update was presented to ASCO 2006 for the study of the US Intergroup trial RTOG 91-11 in the conservative treatment of the larynx [68]. It is supported that concomitant treatment is superior to induction chemotherapy with PF (and to RT alone) in locoregional control and larynx preservation rate, but this does not lead to an impact on survival. In fact, when the OS curve was analysed with close follow-up after 7 years, the curves start to be separated from the fifth year in favour of induction chemotherapy and while it is not yet reached a difference of statistical significance, the curve of concomitant treatment is clearly lowering, at the same level as the RT alone curve. It is interesting to note that the causes of death vary according to the treatment arm: patients in the RT alone arm died mainly from a recurrence their disease, whereas patients with concomitant chemoradiotherapy had a high rate of deaths unrelated to cancer. In other words, concomitant treatment with chemoradiotherapy in conservative treatment achieves better control of the neoplastic disease. However, it does not produce any impact on survival as it favours death due to other causes, most probably related to the impact of the increase in chronic toxicity on cardiovascular underlying disease in these patients.

In conclusion, for unresectable disease, the best treatment option in terms of anti-tumour efficacy is the combination of induction chemotherapy with TPF followed by chemoradiotherapy with cisplatin. However, the toxicity associated with this treatment regimen (assumes a total of 6 cycles of cisplatin) is making it necessary to search for alternative treatments that control to disease just as well, but with a lower potential acute and chronic toxicity profile.

3.B.4. Radiotherapy combined with cetuximab for treatment following induction chemotherapy with TPF

The combination of cetuximab and RT is a treatment option approved by regulatory agencies (the FDA and EMA), which has been shown to increase locoregional control and survival without increasing acute and chronic toxicity. This can provide effective and well-tolerated treatment for patients with locally advanced HNSCC who have had TPF as induction treatment [34]. Its excellent tolerance allows for the maintenance of planned treatment times, both between induction chemotherapy and RT and during RT, which is essential for achieving good therapeutic outcomes. Furthermore, the

combination with RT does not alter the QoL parameters compared to RT alone [36]. For more information on this treatment arm, see section 3.A.2.6.3.

3.C. Rationale for a randomised study

Despite all the therapeutic advances described, patients with unresectable locally advanced HNSCC continue to have a poor prognosis -18.6 months- when they are treated with TPF in the updated, more extensive study [50–52]. The TPF regimen must constitute the therapeutic basis upon which new biological treatments are added, while also trying to improve results without significantly increasing toxicity [53].

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 HNSCC, without increasing the acute and/or chronic toxicity associated with RT (see section 3.A.2.6.3).

This is why this phase III, randomised study has been designed. All patients with unresectable locally advanced HNSCC will start treatment with induction chemotherapy with the TPF regimen. Patients with progression in this chemotherapy regimen will be withdrawn from the study, as it is known that the possibility of a cure from these patients is practically negligible and therefore each site will decide which is the best therapeutic procedure for them, with the aim of not causing excessive toxicity. Patients with a response to induction chemotherapy or a stable disease (SD) will be randomised to a control arm (chemoradiotherapy with cisplatin), which is considered standard by the Spanish group for treatment of HNSCC, or they will be assigned the treatment arm receiving a treatment considered investigational (RT in combination with cetuximab). The study aims to evaluate the non-inferiority of the experimental arm versus the standard arm in terms of OS in patients with HNSCC who have responded to induction chemotherapy with the TPF regimen. Moreover, the acute and chronic toxicity of both treatment arms will be carefully compared, as well as the QoL of subjects subject to these treatments.

This study will be conducted according to this protocol, the good clinical practice (GCP) guidelines and applicable regulations.

4. Study objectives

4.A Primary objective

- 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 HNSCC.

4.B Secondary Objectives

The secondary objectives are:

- To evaluate the activity and safety of TPF treatment.
- To evaluate the reasons for study non-continuation (possibility of complying with randomisation criteria) after induction treatment with TPF.
- To evaluate and compare efficacy in the 2 treatment groups (experimental arm versus standard arm):
  - Disease-free survival
  - Specific survival
  - Time to locoregional control of disease
- To evaluate and compare the safety activity and safety profiles of the 2 treatment groups (experimental versus standard):
  - Response rate
  - Acute and chronic toxicity rates
- To evaluate and compare the patient perceptions using QoL questionnaires.
- To evaluate the treatment compliance rate with RT plus Cetuximab and RT plus cisplatin, after combination with induction and TPF.

5. Investigational plan

5.A Study design

Phase III, open-label, randomised and multicentre clinical trial in patients with unresectable locally advanced HNSCC.

5.B Randomisation

Patients will have signed the informed consent form to participate in the study at the time they have been recognised as candidates, following diagnosis of unresectable locally advanced HNSCC, and always before starting treatment with TPF induction chemotherapy. Patients with stage III and IV squamous cell carcinoma of the oropharynx, larynx, hypopharynx or oral cavity considered as unresectable by a committee for head and neck tumours and with no evidence of distant metastasis, will be eligible for the study.

However, only those patients that present objective response or stabilization after induction chemotherapy with TPP, and do not have a contraindication to continue treatment with cisplatin, will be randomized to two groups to continue with the radical treatment (randomized population):

Group A (standard): Concomitant RT with Cisplatin
Group B (experimental): Concomitant RT with Cetuximab

Patients will be randomized according to a scheme generated by a computer program that will be used to ensure that patients are distributed equally between the two treatment groups and will be performed after the 3 cycles of TPF, only in patients in response or stabilization after induction chemotherapy and who are able to continue receiving cisplatin.

A stratified randomization will be performed according to the primary location of the disease (oral cavity, versus oropharynx, versus larynx, versus hypopharynx). Each stratum will be randomized in a 1:1 ratio to one of the two treatment groups, group A (standard RT concomitant with Cisplatin and group B (experimental: RT with Cetuximab).

The randomization will be made in the DCTrials 2.5 application (electronic CRF) that will be used to collect the data of the patients included in the trial. DCTrials 2.5 is a web-based application and accessible via the Internet.

Only the randomization of patients from authorized investigators will be accepted and once the list of registration criteria has been verified, which includes having received a minimum of 2 cycles of induction TPF, having had a stable response or disease to that treatment and not having a contraindication to being able to continue treatment with cisplatin.

Randomization:

Randomization will be stratified according to primary location of the disease (oral cavity, versus oropharynx versus larynx versus hypopharynx), each stratum will be randomised at a 1:1 ratio to one of the two treatment groups, group A (standard concomitant RT with cisplatin and group B (experimental: RT with Cetuximab).

Patients who have signed informed consent will not be randomized, will not be part of the main analysis of the study, although they will be followed similarly to randomized patients and descriptive information on their treatment and evolution will be obtained.

5.C Study design

5.C.1 Overall design

Patients must sign the informed consent form to participate in the study at the time they will be recognized as candidates, following diagnosis of unresectable locally advanced HNSCC, and always before starting treatment with TPF induction chemotherapy.

All patients will start treatment with 3 cycles of induction chemotherapy with the TPF regimen.

1.- Patients who progress with the treatment with TPF will be excluded from the study and will be treated according to each Site's protocol.

2.- Patients with TPF toxicity, which mean that they cannot follow a treatment that include cisplatin, will be excluded from the study and treated according to each site's protocol and in accordance with international guidelines.

3.- Patients who are unable to receive at least two cycles of induction will be excluded from the study and will be treated according to each site's protocol and in accordance with international guidelines.

4.- Patients who respond to or are stabilized with TPF and who can follow treatment with cisplatin, will be randomised to receive normofractionated RT plus cisplatin (Group A) versus the combination of cetuximab and normofractionated RT (Experimental Group B). Patients will be stratified by tumour location (oral cavity, versus oropharynx versus larynx versus hypopharynx), to ensure homogeneous distribution.

As a result, there are two separate parts of the study:

- *Part 1 of the study*: the period from the signing of the informed consent form until the response and toxicity assessment of induction chemotherapy with TPF (standard group)

- *Part 2 of the study*: the period from randomisation following induction chemotherapy with TPF until the end of study (experimental group)

The objective of the trial is to demonstrate the non-inferiority of the experimental arm compared to the standard arm in terms of OS, using time to death due to any case as the primary endpoint.

In the analysis of OS, which is the primary endpoint proposed in this study, the Cox proportional hazards regression will be used. The general formula of the hypothesis to at least prove non-inferiority was as follows:

$$H_0: HR_{\text{Experimental Arm / Standard Arm}} \geq 1.3$$
$$H_1: HR_{\text{Experimental Arm / Standard Arm}} < 1.3$$

Calculation of sample size is based on an assumed exponential distribution, using the following parameters:

- Unilateral testing with an alpha of 0.05 and 80% power.
- A recruitment phase of 53 months.
- A follow-up phase of 36 months.
- A HR of 0.0231 for the standard arm (median PFS of 30 months).
- $HR_{\text{Experimental arms / Standard arms}} = 0.938$ (this assumes a median of 32 months for the experimental arm).
- Competing risk of 0.01.

The total number of randomised and evaluable patients is 398. At this size, we also have to add 15% of the patients who will progress with TPF or will be lost (dropouts or TPF toxicity that provide continued cisplatin administration), so the patients total is 469.

5.C.2 Study planning

Around 43 sites from the Spanish TTCC Group will participate in the study. Patients with stage III and IV squamous cell carcinoma of the oropharynx, larynx, hypopharynx or oral cavity considered as unresectable by a committee for head and neck tumours and with no evidence of distant metastasis, will be eligible for the study.

All the patients included in the study will receive a combination of TPF chemotherapy every 3 weeks for 3 cycles, followed by RT combined with cetuximab (experimental arm) or cisplatin (standard arm) depending on the randomisation arm.

Neoadjuvant treatment will be given according to the regimen in Table 5.1.

Table 5.1 Diagram of the induction chemotherapy combination.

Drugs	Daily dose	Administration	Days
Docetaxel	75 mg/m^2/d	IV 1 hour	1
Cisplatin	75 mg/m^2/d	IV 1 hour	1
5-FU	750 mg/m^2/d	24-hour infusion	1-5
Dexamethasone	16 mg	8 mg/12 hours	-1, 1 and 2
Ciprofloxacin (or equivalent)	1 g	500 mg/12 hours	D 7-15
G-CSF*	150 µg/m^2/d	SC	D 7-12

IV: intravenous; SC: subcutaneous

*Lenograstim (Granocyte®) is recommended. If another granulocyte-colony stimulating factor (G-CSF) will be used, it has to be administered according to the summary of product characteristics.

Patients who present an objective response or stabilisation to the TPF treatment, who receive at least 2 cycles of induction therapy and do not have any contraindications to continued cisplatin treatment will be randomised into 2 radical treatment groups:

- **Group A** (standard): Concomitant RT with cisplatin**:** at 3-4 weeks (5 weeks at most) from the beginning of the 3rd TPF cycle, treatment begin with concomitant normofractionated RT with chemotherapy (cisplatin 100 mg/m^2 IV).

Drugs	**Daily dose**	**Administration**	**Days**
Cisplatin	100 mg/m^2/d	IV 1 hour	1, 22 and 43 of the RT

- Cisplatin will be administered every three weeks from the first day of RT.

- **Group B** (experimental): Concomitant RT with cetuximab**:** at 3-4 weeks (5 weeks at most) from the beginning of the 3rd TPF cycle, treatment begin with normofractionated RT. Cetuximab will have be started the week before.

Drugs	**Daily dose**	**Administration**	**Days**
Cetuximab*	250 mg/m^2/d	IV 1 hour	1, 8, 15, 22, 29, 36, 43 and 50**

*Initial dose of 400 mg/m^2/day in the first infusion for 120 minutes

** Or to the end of the RT if there is any delay

- **Cetuximab will be administered continuously weekly, from one week before the start of RT (loading dose).**

5.C.2.1. Intervention due to unacceptable TPF toxicity

If a patient has unacceptable toxicity to one of the study drugs, treatment with the drug will be discontinued but the patient will continue to receive the other study drugs and treatments. In the case of the TPF regimen, if a patient has unacceptable toxicity to two of the study drugs, neoadjuvant treatment will be discontinued.

- If a **minimum of 2 cycles** was received, the response to the treatment will be evaluated: if a response or stabilisation and ability to be continue cisplatin treatment is shown, the patient will be randomised to assign him to the radical treatment arm.

- However, if **a minimum of two TPF cycles was not received** or toxicity caused **prevented the continuation of cisplatin treatment,** the patient has to leave the study and will be treated according to the protocol for each site and according to international recommendations.

5.C.2.2. Evaluation of response to TPF

2-3 weeks after the administration of the 3rd cycle of induction chemotherapy, a CR assessment study will be conducted with computed axial tomography (CAT), Positron

Emission Tomography and Computed Tomography (PET-CT) or magnetic resonance imaging (MRI) and a clinical assessment of the tumour that include direct and/or indirect eye exams as necessary, as well as a biopsy of suspicious areas if that would be accurate.

If the investigator suspects disease progression at any time, the disease will have to be assessed using both clinical and imaging techniques before the indicated date.

If disease progression is detected, the scheduled treatment will be discontinued and the visit after progression (VAP) will be conducted, and the patient will receive the treatment that the investigator considers most appropriate outside the study. From the trial perspective, the patients will enter into the follow-up phase and the information on all subsequent treatments and survival will be collected. **If a patient receive any anti-cancer treatment other than that of the study design before disease progression is confirmed, the patient information will be censored from this point on and the case will be analysed individually to establish the possibility that this is a disease progression.**

At 3-4 weeks (5 weeks at most) from the start of the 3rd TPF cycle, patients who have not progressed and have no contraindication to continue receiving treatment with cisplatin will receive the second part of the treatment according to randomisation: arm A (RT combined with cisplatin) or arm B (RT combined with cetuximab). In exceptional individual cases, and with prior contact with the study coordinators, a 5th week of delay will be permitted to start RT.

RADIOTHERAPY REGIMEN (same for arm A and arm B)

Radiotherapy	Total dose	Dose per fraction
Normofractionated	70 Gy	2 Gy per fraction 35 fractions 1 fraction a day

4-6 MV Lineal accelerators as well as electrons with different energy levels are recommended, if overprinting is necessary in some areas with tumours or those at risk.

The total dose in the tumour and lymph node areas affected will be 70 Gy. Doses in the lymph node areas at high-risk of microscopic disease will be 55-60 Gy and in low-risk elective areas, 45-50 Gy.
PTV1 = CTVt + CTVn + CTVn elective plus 45-50 Gy margins
PTV11= CTVt + CTVn of maximum risk plus 60 Gy margins
PTV111= CTVt plus 70 Gy margins
Maximum dose in marrow 45 Gy.

5.C.2.3. Evaluation of response after radical treatment

The response in all patients will be evaluated at 6-8 weeks after completing RT with cisplatin or cetuximab (same for both radical treatment arms). See section 8.B.2.2.

5.C.3 Discussion of the study design

The TPF chemotherapy regimen has been proved very effective, both in the treatment of squamous cell carcinomas of the head and neck as well as in gastric adenocarcinomas. In HNSCC it has been shown to be superior to conventional treatment with PF, and in unresectable disease there is evidence that using an induction chemotherapy improves the survival outcomes of these patients. The standard continuation of induction chemotherapy is concomitant RT with cisplatin. However, the total administration of 6 cycles of cisplatin involves considerable toxicity to the patient. Moreover, cetuximab can be combined with RT to increase its efficacy without increasing associated toxicity, and so combining it with RT after 3 cycles of TPF is an interesting and promising area to be studied in HNSCC. The study aim to demonstrate the non-inferiority of the combination of RT plus cetuximab compared to the combination of RT plus cisplatin after 3 cycles of TPF induction chemotherapy.

5.C.4 End of trial

The study duration is determined at the time when there are 282 deaths. A 53-month continuous recruitment period, 36-month follow-up after the inclusion of the last patient and also a median survival of 30 months are considered.

5.D Blinding

Not applicable.

5.E Study periods

It is planned that the deadline of the clinical phase of the study be 36 months after inclusion of the last patient. The planned overall duration of the study for a total of 469 patients is 96 months (53 months for recruitment plus 36 months of follow-up since the last patient).

The schedule foreseen for this study is from November 2007 to October 2015.

6. Study population screening

6.A Selection criteria

6.A.1 Inclusion criteria

For inclusion in the study, all of the following inclusion criteria must be met:

1. Before beginning the specific procedures of the protocol, informed written consent have to be obtained and documented.

2. Locally advanced cancer of the head and neck (oral cavity, oropharynx, larynx and hypopharynx), stage III-IV, with no evidence of metastasis.

3. The tumour have to be classified as inoperable according to Northern California Oncology Group [5] criteria after assessment by a multidisciplinary team, which includes, at least, a specialist in oncological surgery from the Ears, Nose and Throat Department or a specialist in maxillofacial surgery (as applicable), a specialist in Medical Oncology and a specialist in Radiotherapy oncology. The reason for inoperability will be recorded on the case report form (CRF).

NCOG inoperability criteria:

   - Technically nonresectable (includes: evidence of mediastinal dissemination; tumour fixed to the clavicle, base of the cranium or cervical vertebrae; involvement of the nasopharynx).

   - Medical criteria based on a low surgical curability.

   - Medical contraindication for surgery.

4. Anatomically and pathologically proven epidermoid carcinoma.

5. Disease measurable according to the modified RECIST 1.0 criteria.

6. Men or women aged 18 to 70 inclusive.

7. ECOG performance status: 0 or 1

8. Patients in a medical condition to be able to receive induction treatment with TPF followed by normofractionated RT with cetuximab or cisplatin.

9. Patients with adequate haematological function: neutrophils $\geq 2 \times 10^9$, platelets $\geq 100 \times 10^9$, haemoglobin ≥ 9 g/dL and no symptoms related to anaemia.

10. Adequate liver function: Bilirubin ≤ 1.5 x upper normal limit (UNL), and some of the following parameters: glutamic oxaloacetic transaminase (GOT) ≤ 2.5 UNL or alanine aminotransferase (GPT) ≤ 2.5 ULN or alkaline phosphatase <

UNL; however, if all of these are present, their value should not exceeded the UNL.

11. Adequate kidney function: serum creatinine < 1.4 mg/dL (120 μmol/L); if the values are > 1.4 mg/dL, creatinine clearance has to be > 60 mL/min (real or calculated by the Cockcroft–Gault method).

12. Adequate nutritional status: Body mass index (BMI) > 18.5% or albumin ≥ 30 g/L.

13. Patients have to be accessible for treatment and follow-up.

6.A.2 Exclusion criteria

Patients cannot be included in the study if they meet any of the following criteria:

1. Metastatic disease.

2. Previous treatment by surgery, with RT and/or chemotherapy for the disease being studied.

3. Other tumour locations in the head and neck area, other than the oral cavity, oropharynx, larynx and hypopharynx.

4. Stages other than stage III or IVM0.

5. A previous and/or synchronous squamous carcinoma.

6. Diagnosis of another neoplasia in the past 5 years except properly treated cervical carcinoma in situ and/or basal cell carcinoma.

7. Active infection (infection that required intravenous antibiotics), including diagnosed active tuberculosis and HIV.

8. Uncontrolled hypertension defined as systolic blood pressure ≥ 180 mmHg and/or diastolic blood pressure ≥ 130 mmHg at rest.

9. Pregnancy (its absence must be confirmed by a serum β-HCG test) or lactation.

10. Systemic, chronic and concomitant immune therapy or hormone therapy for cancer.

11. Other concomitant antineoplastic treatments.

12. Clinically significant coronary artery disease or a history of myocardial infarction in the past 12 months or high risk of uncontrolled arrhythmia or uncontrolled heart failure.

13. Chronic obstructive pulmonary disease that required ≥ 3 hospitalisations in the previous 12 months.

14. Uncontrolled active peptic ulcer.

15. Presence of a psychological or medical illness that would prevent the patient from taking part in the study or from granting informed consent.

16. Known drug abuse (except for heavy drinking).

17. Known allergic reaction to any of the ingredients of the study treatment.

18. Previous treatment with monoclonal antibodies or other inhibitors of signal transduction or EGFR inhibitors.

19. Any experimental treatment in the 30 days prior to study entry.

6.B Patients number

The objective of the trial is to demonstrate the non-inferiority of the experimental arm compared to the standard arm in terms of OS, using time to death due to any case as the primary endpoint.

In the analysis of OS, which is the primary endpoint proposed in this study, the Cox proportional hazards regression will be used. The general formula of the hypothesis to at least prove non-inferiority is as follows:

$$H_0: HR_{\text{Experimental Arm / Standard Arm}} \geq 1.3$$
$$H_1: HR_{\text{Experimental Arm / Standard Arm}} < 1.3$$

Calculation of sample size is based on an assumed exponential distribution, using the following parameters:

- Unilateral testing with an alpha of 0.05 and 80% power.
- A recruitment phase of 53 months.
- A follow-up phase of 36 months.
- A HR of 0.0231 for the standard arm (median PFS of 30 months).
- $HR_{\text{Experimental arms / Standard arms}} = 0.938$ (this assumes a median of 32 months for the experimental arm).
- Competing risk of 0.01.

The total number of randomised and evaluable patients is 398. At this size, we also have to add 15% of the patients who will progress with TPF or will be lost (dropouts or TPF toxicity that provide continued cisplatin administration), so the patient total is 469.

6.C Withdrawal criteria

6.C.1 Patients withdrawal

Patients can freely withdraw from the study at any time without having to provide any reason.

Subjects have to be withdrawn from the study when any of the following situations occurred:

- Withdrawal of the informed consent.
- Disease progression. When disease progression is detected, the patient will be withdrawn from the study and will receive the treatment considered most suitable by the investigator.
- Patients who are not considered to be in a suitable condition to receive cisplatin-based treatment at the time of randomization
- Patients who have not been able to receive at least 2 cycles of induction and therefore whose response to it cannot be assessed.
- Appearance of any exclusion criterion that is clinically relevant and that may affect patient safety.
- If treatment is discontinued permanently without confirming disease progression, but the patient's investigator considers it necessary to administer a salvage therapy other than that envisioned in the trial.
- Pregnancy.
- Administration of any concomitant medication that is not permitted, as detailed in the section 7.B when the result described is withdrawal from the study.
- Failure to fulfil the protocol.

If a patient have not attended the scheduled study evaluations, the investigator have to determine the reasons and circumstances as completely and accurately as possible.

If a patient is withdrawn early from the study, if possible all scheduled tests have to be performed to evaluate the tumour fully (indirect and/or direct optical exam of the tumour and a diagnostic imaging technique, particularly CTT and/or PET-CT and/or MRI). In any case, the “End of treatment sheet" section of the case report form have to be completed.

If there is a medical reason for the withdrawal, the patient have to remain under the supervision of the investigator until the AEs will be resolved.

A patient may be replaced by another only if the patient leaves the study before the first infusion of cetuximab, cisplatin or the start of the first RT fraction.

Information will be collected on subsequent treatments administered and the survival of all patients, regardless of the reason for withdrawal, at the same frequency as the post-treatment visits.

6.C.2 Study discontinuation

The study may be discontinued if the principal investigator and sponsor consider it necessary in the following cases:

- Medical or ethical reasons affecting the continuation of the study.
- Difficulties in recruiting patients.
- Ineffectiveness of the study medication.
- Onset of adverse reactions to cetuximab that are unacceptable and unknown to date with regard to their nature, severity and duration; or an unexpected incidence of any unacceptable adverse reaction.

The principal investigator, the study coordinator and sponsor will supervise the drug safety data on a regular basis to ensure that it is appropriate to continue with the study.

Note: Patients who have adverse reactions to TPF induction chemotherapy, which prevent them from continuing to receive cisplatin will not be randomised, will be withdraw from the study at that time although they will have similar follow-up in order to obtain data on their treatment and evolution, which will be treated descriptively.

6.C.3 Recruitment period

The planned recruitment period is 53 months.

7. Treatment description

7.A Treatments administered and therapeutic regimen

All the patients included in the study will receive 3 cycles of TPF chemotherapy upon entry and subsequently, if there is no disease progression, they will be randomised to receive:

Arm A (standard): will receive conventional RT combined with cisplatin.

No other cancer treatment will be administered before confirming disease progression or persistence after radical treatment.

Arm B (experimental): will receive conventional RT combined with cetuximab.

No other cancer treatment will be administered before confirming disease progression or persistence after radical treatment.

If a patient has unacceptable toxicity to one of the study drugs during concomitant treatment (cisplatin or cetuximab), treatment with this drug will be discontinued but the patient will continue to receive the RT planned in the trial:

Group A (standard): **Cisplatin** must be discontinued permanently but without withdrawing the patient from the study in cases of:

- Appearance of serious AEs (SAEs) (see section 7.A.2), if the investigator and/or the patient want or consider withdrawal of the study medication necessary.

The patient will finish treatment with RT alone if the investigators believe this to be possible.

Group B (experimental): **Cetuximab** must be suspended definitively but without withdrawing the patient from the study in case of:

- Repeated appearance of Grade 3 dermal toxicity in spite of an appropriate dose reduction (see section 7.A.3.4.1). In this situation, the investigator may consult

the principal investigator and/or study coordinator to assess the possibility of individualised measures that allow the patient to continue receiving cetuximab.
- Grade 3-4 cetuximab-related hypersensitivity reaction.
- Suspension of 4 consecutive cetuximab infusions. In this situation, the investigator may consult the principal investigator and/or study coordinator to consider the reasons and assess the possibility of individualised measures that allow the patient to continue receiving cetuximab.
- Appearance of AEs, if the investigator and/or the patient wants or considers withdrawal of the study medication necessary.

The patient will finish treatment with RT alone, if the investigators believe this to be possible.

If there is a toxicity caused by the TPF regimen:

- If the unacceptable toxicity is clearly attributable to one of the TPF drugs (docetaxel or 5-FU), this drug will be discontinued for the following treatment cycles (provided that it is not toxicity to cisplatin, which will lead to withdrawal from the study).
- If a patient suffers unacceptable toxicity due to cisplatin or there is toxicity linked to least two drugs in the combination, induction treatment with TPF will be suspended, with matters being conducted as follows:

1. If such toxicity occurs after then 1st cycle, the patient will be withdraw from the study.
2. If this toxicity occurs after the 2nd or 3rd cycle, the patient may be randomised if there have been tumour response or stabilisation and, if there are no contraindications to treatment with cisplatin. If the patient cannot follow cisplatin treatment, they will be withdrawn from the study and will not be randomised.
3. If the patient cannot be randomised due to toxicity preventing continued treatment with cisplatin, the patient will be withdrawn from the study and will be treated according to each site's protocol and according to international recommendations.

7.A.1 Induction treatment (Part 1): Docetaxel in combination with cisplatin and 5-FU (TPF)

7.A.1.1 Therapeutic programme

The patients will receive docetaxel 75 mg/m^2, followed by cisplatin 75 mg/m^2 on day 1. The 5-FU will be administered after the end of cisplatin infusion as a continuous infusion of 750 mg/m^2/day for 5 days.

Treatment with docetaxel
Dose: 75 mg/m^2
Route: IV infusion of 1 hour. For the first 5 minutes, the infusion will be administered very slowly.
Regimen: Day 1 and then every 3 weeks.

Treatment with cisplatin
Dose: 75 mg/m^2
Route: IV infusion of 1 hour.

Regimen: Day 1 and then every 3 weeks.

Adequate hydration will be ensured during administration of cisplatin.

Treatment with 5-FU
Dose: 750 mg/m^2/day
Route: IV continuous infusion over 24 hours for 5 days.
Regimen: Days 1-5 and then every 3 weeks.

The sequence of the drugs recommended will be the following:

Day 1:

- **Start, t = 0 to t = 2h**: Infusion of 1 L of normal saline or of 5% glucose in 0.45% saline, con KCl (20 mmol/L) and $MgSO_4$ (2 g/L).
- **From t = 2h to t = 3h**: Infusion of docetaxel in 250 mL of 5% glucose or 0.9% NaCl.
- **Immediately before the infusion of cisplatin:** 12.5 g mannitol in the IV bolus
- **From t = 3h to t = 4h:** cisplatin 75 mg/m^2 in 500 mL of normal saline
- **From t = 4h to 8h**: infusion of 25 g mannitol in 1 L of normal saline or of 5% glucose in 0.45% saline, con KCl (20 mmol/L) and $MgSO_4$ (2 g/L).
- **From t = 8h:** start of continuous IV infusion of 5-FU, 750 mg/m^2, using an infusion pump.

Days 2, 3, 4, 5:

- 5-FU, 750 mg/m^2/day, on the following days, up to a total of 5 consecutive days of treatment.

7.A.1.2 Prophylactic medication of TPF

7.A.1.2.1 Antiemetic pre-medication

All patients have to receive a prophylactic antiemetic medication that will include a serotonin receptor (5-HT3) antagonist, such as ondansetron or granisetron, before and after the administration of cisplatin.

7.A.1.2.2 Pre-medication with corticosteroids

The next pre-medication will be administered to all patients to prevent a hypersensitivity reaction and to reduce and/or delay the presentation of skin toxicity and fluid retention in relation to docetaxel.

Dexamethasone 8 mg orally with a total of 6 doses

- The night before chemotherapy.
- Immediately on waking up on the morning of chemotherapy.
- One hour before the docetaxel infusion (might be IV during administration of the treatment)
- The night of docetaxel.
- The morning of the day following docetaxel.
- The afternoon after docetaxel.

If dexamethasone administration is not possible, the medication equivalent to 8 mg of dexamethasone is:

- methylprednisolone at a dose of 40 mg orally
- prednisolone at a dose of 50 mg orally

7.A.1.2.3 Recombinant granulocyte colony-stimulating factor (G-CSF)

It is necessary to administer prophylactic administration from the first cycle on.

Dose*: Lenograstim (Granocyte) 150 μg/m^2/day from day 7 until day 12.

Route: Subcutaneous.

Regimen: Starting after the end of chemotherapy (day 7). Lenograstim will be administered once a day for 6 days, i.e. from day 7 to day 12, both included.

*Lenograstim is recommended. If another granulocyte-colony stimulating factor will be used, it will be administered according to the summary of product characteristics.

7.A.1.2.4 Prophylactic antibiotic therapy

All patients have to be given prophylactic antibiotic therapy with ciprofloxacin at a dose of 500 mg orally twice daily for 9 days from day 7 of each cycle, or their equivalent (for example levofloxacin) according to the investigator's normal practice.

7.A.1.3 Dose adjustment

The dose will be modified in the case of severe toxic and/or non-haematological toxic effects. The dose adjustments will be performed according to the type of toxicity that showed the highest grade of toxicity. Toxic effects will be graded according to NCIC-CTG criteria, version 3.0.

The main toxic dose-limiting effect of docetaxel in monotherapy is neutropenia. Other toxic effects that can be seen are anaphylactoid-type reactions and cutaneous reactions, toxic effects on the digestive system (nausea, vomiting, oral mucositis, diarrhoea), reversible paraesthesia, alopecia, asthenia and minor local venous reactions (phlebitis) at the injection site and fluid retention/oedema. The standards given below show the dose adjustments to be adopted in the event of several of these toxic effects.

The main toxic effects observed with cisplatin in monotherapy are nausea and vomiting, peripheral neuropathy, nephrotoxicity and ototoxicity.

The main toxic effects observed with 5-FU in monotherapy are mucositis, myelosuppression and diarrhoea.

If a patient experience several toxic effects and the recommendations give conflict with one another, the most conservative dose adjustment of those recommended must be followed, involving a reduction in doses that is suitable for the most severe toxicity. Once the doses have been reduced because of toxicity they must not be re-escalated.

7.A.1.3.1 Docetaxel dose adjustments

Haematological toxicity and/or complications

Fever will be classified in grades using the NCI-CTC system, version 3.0. The temperature reported has to be oral or equivalent. In the case of febrile neutropenia, the following strategy is recommended:

- Hospitalisation
- Pre-antibiotic evaluation
- Complete blood count and blood cultures
- Start of empirical antibiotic therapy

FEBRILE NEUTROPENIA OR DOCUMENTED INFECTION

Adverse event	Action to be taken in subsequent cycles
▪ Febrile neutropenia ▪ Documented infection	The first episode of febrile neutropenia and/or documented infection will remain with G-CSF and ciprofloxacin (or their equivalent) and the docetaxel dose will be reduced from 75 to 60 mg/m^2. If a second episode occurs, the patient will remain with ciprofloxacin (or its equivalent) and G-CSF, and the dose of docetaxel will be reduced from 60 to 50 mg/m^2

BLOOD COUNT ON DAY 21

	Action to be taken
Neutrophils $\geq 1.0 \times 10^9$/L Platelets $\geq 100 \times 10^9$/L	Treatment at the scheduled date
Neutrophils $<1.0 \times 10^9$/L	Delay over 1 week and repetition of the complete blood count on day 28 ▪ If ANC $\geq 1.0 \times 10^9$/L, administer chemotherapy by reducing the dose of docetaxel from 75 to 60 mg/m^2 (*). In a second episode, this should be repeated and the docetaxel dose would be reduced to 50 mg/m^2. ▪ If ANC is $<1.0 \times 10^9$/L. There was a new 1-week delay and repeat haematology count on day 35: - If ANC $\geq 1.0 \times 10^9$/L, administer chemotherapy by reducing the dose of docetaxel from 75 to 60 mg/m^2 (*). In a second episode, this should be repeated and the docetaxel dose would be lowered to 50 mg/m^2. - If there is no recovery by day 35 (ANC $<1.0 \times 10^9$/L), the patient will abandon the induction chemotherapy and will be treated according to each site's protocol, and in accordance with international recommendations. (*) Maintain G-CSF and ciprofloxacin (or their equivalent) according to the regimen defined in points 7.A.2.2.3 and 7.A.2.2.4 of the Study Protocol.

Platelets <100 x 10^9/L	Delay over 1 week and repetition of the complete blood count on day 28 ▪ If the platelet count ≥100 × 10^9/L, administration of chemotherapy but the dose of docetaxel will be reduced from 75 to 60 mg/m^2. In a second episode, this should be repeated and the docetaxel dose would be lowered to 50 mg/m^2. ▪ If platelet count <100 x 10^9/L. perform a complete blood count on day 35: o If the platelet count ≥100 x 10^9/L, administer chemotherapy, reducing the dose from 75 to 60 mg/m^2. In a second episode, this should be repeated and the docetaxel dose would be lowered to 50 mg/m^2. o If there is no recovery by day 35 (platelet count <100 x 10^9/L), the patient abandon the induction chemotherapy and proceed as established in section 7.A for unacceptable toxicity due to the TPF regimen.

Skin reactions

Docetaxel tends to induce erythematous maculopapular rash that is sometimes itchy, which particularly affects hands, forearms and feet, but also on the chest and face. It may occur in up to 50% of patients during the first week. Hand-foot syndrome and nail disorders have also been reported. Skin and nail disorders are usually more prominent in patients treated with a high cumulative dose and/or weekly administration. Therefore, patients included in the trial are not expected to have extraordinary problems managing this toxicity.

Grades 0, 1 and 2: no changes.

Grade 3: delay up to ≤ 1 and treat again with a reduction in the docetaxel dose from 75 to 60 mg/m^2. If there is no recovery at grade ≤ 1 within a 2-week delay, the patient should discontinue treatment with docetaxel.

Grade 4: treatment with docetaxel will be discontinued.

Nail disorders do not change dose modification.

Nausea and/or vomiting

An antiemetic regimen with 5-HT3 antagonists will be administered from the first cycle as well as corticosteroids that will be administered for 3 days as prophylaxis for fluid retention, which work together to reduce the incidence and severity of emesis. Patients with persistent nausea and/or vomiting despite these measures will be able to receive other antiemetic regimens.

Bilirubin and impaired liver function

In case of abnormal bilirubin levels during the study, the next cycle will be delayed for a maximum of 2 weeks. If there is no recovery, treatment with docetaxel will be discontinued.

If AST and/or ALT and/or ALP levels are altered, the following had to be performed:

AST / ALT values	ALP values	Dose modification
≤1.5 x UNL	≤5 x UNL	No dose change
>1.5 x UNL - ≤2.5 x UNL	≤2.5 x UNL	No dose change
>2.5 x UNL - ≤5 x UNL	≤2.5 x UNL	Reduction of docetaxel dose from 75 to 60 mg/m^2
>1.5 x UNL - ≤5 x UNL	>2.5 x UNL - ≤5 x UNL	Reduction of docetaxel dose from 75 to 60 mg/m^2
>5 x UNL	or >5 x UNL	Delay a maximum of 2 weeks. If recovery to previous values have not occurred within this period, docetaxel will be discontinued.

AST: aspartate transaminase; ALP: alkaline phosphatase; ALT: alanine transaminase UNL: upper normal limit

If there is a deterioration of these parameters after initial dose reduction, treatment with docetaxel will be definitively suspended.

7.A.1.3.2 Cisplatin dose adjustments

Peripheral sensory and motor neurotoxicity

A neurological examination will be performed before study entry, and then when the patient have symptoms suggestive of neuropathy and/or 2 cycles of induction TPF chemotherapy.

The following dose modifications will be applied:

Grade 0.1: no changes.
Grade 2: cisplatin reduction to 50 mg/m^2
Grade ≥3: treatment with cisplatin will be discontinued

Ototoxicity

In the case of grade 3 or 4, treatment with cisplatin will be discontinued.

Nephrotoxicity

In case of elevated serum creatinine (≥ 1.5 x patient initial value) despite adequate hydration, creatinine clearance will be determined and the following dose reductions will be considered:

- If creatinine clearance (CCl) is ≥ 60 mL/min: the full dose of cisplatin will be administered and CCl will repeated before each cycle.

- If CCl is ≥ 40 mL/min <60 mL/min: the cisplatin dose will be reduced to 50 mg/m^2 in the subsequent cycles and the CCl will be repeated in the remaining cycles.

- If CCl is < 40 mL/min: cisplatin will be suspended in the remaining cycles.

Thrombocytopenia

If grade 4 thrombocytopenia occurs (<25 x 10^9/L), the dose of cisplatin will be reduced to 25% (from 75 to 60 mg/m^2).

7.A.1.3.3 5-FU dose adjustment

Mucositis

For grade 3 mucositis, the dose of 5-FU will be reduced by 20%, from 750 to 600 mg/m^2/day. In case of grade 4 mucositis, treatment with 5-FU will be discontinued.

Diarrhoea

If diarrhoea is observed, maintenance therapy is allowed to be administered. If grade 3 diarrhoea occur, the 5-FU dose will be lowered by 20% from 750 to 600 mg/m^2/day. In case of grade 4 diarrhoea, treatment with 5-FU will be discontinued.

7.A.1.3.4 Other toxicities

For the other grade 3 and 4 toxic effects not covered by the preceding sections, with the exception of hair loss and nail disorders, chemotherapy will be discontinued for a maximum of two weeks from the planned administration date until resolution to grade ≤ 1. The possibility of administering chemotherapy again will be assessed in each case, with the necessary changes and modifications to the doses.

7.A.1.4. Management of the specific toxic effects of docetaxel, which do not require dose modifications

7.A.1.4.1. Hypersensitivity reactions

During the first and second infusions, the patient's overall status will be assessed as well as, if possible, blood pressure and heart rate, for at least the first 10 minutes, with a view to immediate intervention in case of a hypersensitivity reaction. The patients receive the infusions in an area where resuscitation equipment and other drugs (adrenaline, prednisone equivalents, etc.) are available. If a hypersensitivity reaction occurs, it will be treated according to the best available medical practice.

HYPERSENSITIVITY REACTIONS TO DOCETAXEL

NCI-CTC grade, version 3	Treatment
Grade 1	Decrease in infusion rate until the symptoms disappear, close observation of the patient. Subsequently, complete the docetaxel infusion into the initially planned rate. In

	the following cycles, use the same pre-medication indicated in section 7.A.1.2.2.
Grade 2	Discontinue docetaxel infusion Administer antihistamines and corticosteroids intravenously Resume docetaxel infusion once symptoms have disappeared. In subsequent cycles, administer antihistamines and corticosteroids intravenously, one hour before the infusion as well as the pre-medication established in section 7.A.2.2.2.
Grade 3	Discontinue docetaxel infusion Administer antihistamines and corticosteroids intravenously. Add adrenaline and/or bronchodilators and/or fluids and/or IV macromolecules if indicated. Once the signs and/or symptoms of the hypersensitivity reaction have disappeared, you may resume the infusion of docetaxel within 24 hours of discontinuation, if medically suitable and possible. The premedication regimen described in section 7.A.2.2.2 is only recommended when docetaxel is reinfused over 3 hours after discontinuation. In subsequent cycles, dexamethasone will be administered at a dose of 20 mg orally in the evening before chemotherapy, the morning of chemotherapy and one hour before the docetaxel infusion. Diphenhydramine (or equivalent) will also be administered at the 50 mg IV 1 hour dose before the docetaxel infusion. If a severe reaction occurs again, docetaxel is permanently suspended.
Grade 4	Appropriate urgent treatment (see description in grade 3) and docetaxel suspended permanently.

7.A.1.4.2. Peripheral oedemas and/or effusions

If there have been fluid retention during treatment despite premedication with corticosteroids, its symptoms and signs have to be graded according to NCIC-CTG criteria. Dose reduction is not planned. Weight will be recorded as often as possible to document a possible weight gain that may be due to oedema.

The recommended treatment -spironolactone 100 mg/day orally- will be initiated when the patient develop grade 2 or 3 in an attempt to continue treatment with docetaxel.

If symptoms may not be adequately controlled, adding furosemide at doses of 20-40 mg/day orally will be assessed. The clinical tolerance of the patient, the overall response and the investigator's medical opinion determine whether it is better in the patient's interest to continue with docetaxel or suspend it.

7.A.2 Radical treatment (Part 2 – arm A): Cisplatin (during concomitant treatment with radiotherapy)

Patients will receive cisplatin 100 mg/m^2 on day 1, coinciding with the first day of RT, and subsequently on days 22 and 43 of RT:

Dose: 100 mg/m^2

Route: IV infusion of 1 hour.

Regimen: Day 1 and then every 3 weeks.

Adequate hydration will be ensured during administration of cisplatin. The sequence of the drugs recommended is the following:

Day 1:

- **Start, t = 0 to t = 2h**: Infusion of 1 L of normal saline or of 5% glucose in 0.45% saline, with KCl (20 mmol/L) and MgSO4 (2 g/L).
- **From t = 2h to t = 3h**: Infusion of docetaxel in 250 mL of 5% glucose or 0.9% NaCl.
- **Immediately before the infusion of cisplatin**: 12.5 g mannitol in the IV bolus
- **From t = 3h to t = 4h**: cisplatin 100 mg/m^2 in 500 mL of normal saline
- **From t = 4h to 8h**: infusion of 25 g mannitol in 1 L of normal saline or of 5% glucose in 0.45% saline, with KCl (20 mmol/L) and MgSO4 (2 g/L).

7.A.2.1 Prophylactic medication of cisplatin

7.A.2.1.1 Antiemetic pre-medication

All patients have to receive a prophylactic antiemetic medication that includes a 5-HT3 antagonist, such as ondansetron or granisetron, before and after the administration of cisplatin. The adjuvant use of dexamethasone is recommended.

7.A.2.2 Dose adjustment

The dose will be modified in the case of severe toxic and/or non-haematological toxic effects. The dose adjustments are performed according to the type of toxicity that showed the highest grade of toxicity.

If a patient experiences several toxic effects and the recommendations give conflict with one another, the most conservative dose adjustment of those recommended must be followed, involving a reduction in doses that is suitable for the most severe toxicity. Once the doses have been reduced because of toxicity they must not be re-escalated.

7.A.2.2.1 Cisplatin dose adjustments

Haematological toxicity and/or complications

Fever will be classified in grades using the NCI-CTC system, version 3.0. The temperature reported will be oral or equivalent. In the case of febrile neutropenia, the following strategy is recommended:

- Hospitalisation
- Pre-antibiotic evaluation
- Complete blood count and blood cultures
- Start of empirical antibiotic therapy

FEBRILE NEUTROPENIA OR DOCUMENTED INFECTION

Adverse event	Action to be taken in subsequent cycles
▪ Febrile neutropenia ▪ Documented infection	The first episode of febrile neutropenia and/or documented infection, the dose of cisplatin is reduced from 100 to 75 mg/m^2. If a second episode occurs, the third dose of cisplatin is suspended.

BLOOD COUNT ON DAY 21

	Action to be taken
Neutrophils ≥ 1.0×10^9/L Platelets ≥ 100x10^9/L	Treatment at the scheduled date
Neutrophils <1.0 x 10^9/L	Delay over 1 week and repetition of the complete blood count on day 28 ▪ If ANC ≥1.0 x 10^9/L, administer chemotherapy by reducing the dose of cisplatin from 100 to 75 mg/m^2. If there is a second episode, the 3rd cisplatin cycle should be discontinued. ▪ If ANC is <1.0 x 10^9/L. There was a new 1-week delay and repeat haematology count on day 35: - If ANC ≥1.0 x 10^9/L, administer chemotherapy by reducing the dose of cisplatin from 100 to 75 mg/m^2. When this happens, there is no space to administer the 3rd cycle of cisplatin, so this 3rd cycle is suspended. - If there is no recovery on day 35 (ANC <1.0 x 10^9/L), the patient will discontinue chemotherapy with cisplatin and will continue radiotherapy treatment.
Platelets <100 x10^9/L	Delay over 1 week and repetition of the complete blood count on day 28 ▪ If the platelet count ≥100 × 10^9/L, administer chemotherapy but the dose of cisplatin will be reduced from 100 to 75 mg/m^2. If there is a second episode, the 3rd cisplatin cycle is suspended. ▪ If platelet count <100 x 10^9/L perform a complete blood count on day 35: ○ If the platelet count ≥100 x 10^9/L, administer cisplatin, reducing the dose from 100 to 75 mg/m^2. If there is a second episode, treatment with cisplatin should be suspended.

	○ If there is no recovery on day 35 (Platelet count <100 x 10^9/L), the patient will discontinue chemotherapy with cisplatin and will continue radiotherapy treatment.

Nausea and/or vomiting

An antiemetic regimen with 5-HT3 antagonists will be administered from the first cycle as well as corticosteroids that will be administered for 3 days as prophylaxis for fluid retention, which work together to reduce the incidence and severity of emesis. Patients with persistent nausea and/or vomiting despite these measures will be able to receive other antiemetic regimens.

Peripheral sensory and motor neurotoxicity

A neurological examination will be performed before study entry and then when the patient have symptoms suggestive of neuropathy.

The following dose modifications will be applied:

Grade 0, 1: no changes.
Grade 2: cisplatin reduction to 50 mg/m^2
Grade ≥ 3: treatment with cisplatin is suspended

Ototoxicity

In the case of grade 3 or 4, treatment with cisplatin will be discontinued.

Nephrotoxicity

In case of elevated serum creatinine (≥1.5 x patient initial value) despite adequate hydration, creatinine clearance have to be determined and the following dose reductions will be considered:

- If CCl is ≥ 60 mL/min: the full dose of cisplatin will be administered and CCl will be repeated before each cycle.
- If CCl is ≥ 40 mL/min <60 mL/min: the cisplatin dose will be reduced to 50 mg/m^2 in the subsequent cycles and the CCl will be repeated in the remaining cycles.
- If CCl is < 40 mL/min: cisplatin will be suspended in the remaining cycles.

7.A.2.2.2 Other toxicities

For the other grade 3 and 4 toxic effects not covered by the preceding sections, with the exception of hair loss and nail disorders, cisplatin will be discontinued for a maximum of two weeks from the planned administration date until resolution to grade ≤ 1. The possibility of administering cisplatin again will be assessed in each case, with the necessary changes and modifications to the doses.

Under no circumstances will a dose of cisplatin be administered once RT treatment have been completed. If due to the successive delays of cisplatin administration, the cisplatin

doses that have not yet been administered coincided with the end of treatment with RT; these will not be recovered.

7.A.3 Radical treatment (Part 2 – Arm B): Cetuximab (during concomitant treatment with radiotherapy) Dose and fractionation

The dose and procedure for the administration of cetuximab will be as follows:

- The initial dose (first infusion) is 400 mg/m^2 (= 80 mL/m^2). For safety reasons, it is mandatory to treat patients with a suitable antihistamine and corticosteroid (as prophylactic treatment in order to reduce the risk of an allergic reaction). The required volume will be administered in a 2-hour period (maximum velocity of 2 mL/min) and a saline solution (0.9%) will be used to wash the route at the end of the infusion. Vital signs will be checked before the administration of cetuximab and then during infusion and for one hour after infusing the volume.

This initial dose or load will be administered one week before the first day of RT, then 2-4 weeks after the 3rd cycle of TPF.

- The weekly dose (the remaining infusions) is 250 mg/m^2 (= 50 mL/m^2). Patients should be treated in advance with a suitable antihistamine and corticosteroid. The required volume will be administered in a 1-hour period (maximum velocity of 2 mL/min) and a saline solution (0.9%) will be used to wash the route at the end of the infusion. Although no vital signs checks are necessary, careful observation of the patient (up to one hour after infusion) is required to monitor the possible appearance of AEs (specifically, allergic reactions).

The weekly dose will be maintained until the RT programme is completed. The last week of cetuximab coincided with the last week in which the patient received RT.

7.A.3.1 Dose modifications and cetuximab treatment changes

7.A.3.1.1 Skin reaction

If a patient experience grade 3 skin toxicity, treatment with cetuximab will be delayed. The investigator will be able to establish concomitant treatment with moisturising creams and/or oral and/or topical antibiotics and/or topical corticosteroids (a specific manual for the management of skin toxicity will be distributed). Treatment may only be resumed if the reaction is repeated to grade 2, which may be delayed by up to four consecutive infusions.

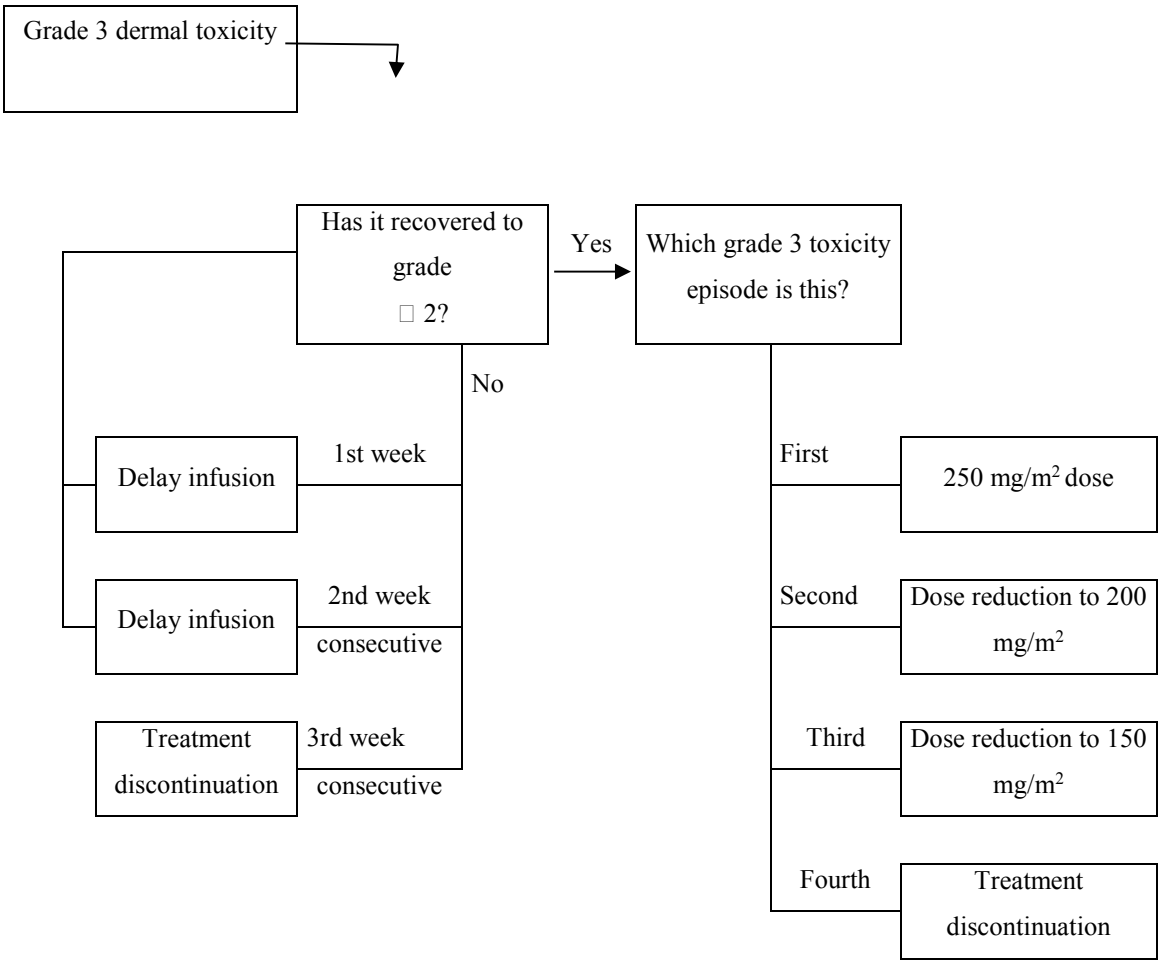
If the serious skin reaction occurs for the first time, the treatment may be resumed without changes in the dose. If they present severe skin reactions for the second or third time, the treatment with cetuximab will be again discontinued and may resume with a lower dose (200 mg/m^2 body surface area after the second time, and 150 mg/m^2 days after the third time) only if the reaction remit to grade 2.

If severe skin reactions occur for a fourth time, or they do not recover to grade 2 during treatment interruption, the treatment with cetuximab have to be suspended permanently.

If the patient have Grade 4 dermal toxicity, treatment with cetuximab will be discontinued.

If the infusion of cetuximab will be discontinued for 4 weeks due to cetuximab toxicity or due to an intercurrent condition (e.g. infection) that require treatment discontinuation, treatment with cetuximab will be discontinued. In each case, the principal investigator and/or study coordinator may have assessed the possibility of the patient continuing to receive cetuximab (Figure 7.1).

Figure 7.1 Adjustment of treatment in case of dermal toxicity caused by cetuximab.



7.A.3.1.2 Allergic reaction

If a hypersensitivity reaction occurs, the investigator have to establish therapeutic measures according to the best available medical practices. Based on previous experience with hypersensitivity reactions, the following treatment guidelines may be applied (Table 7. 1):

Table 7. 1 Adjustment of treatment in case of allergic or hypersensitivity reactions caused by cetuximab.

CTC grade of allergic reactions or hypersensitivity	Treatment
Grade 1	Reduce the cetuximab infusion rate by 50% and closely monitor for worsening. The total infusion time for cetuximab should not exceed 4 hours.
Grade 2	Interrupt the infusion of cetuximab. Administer bronchodilators, oxygen, etc. as medically indicated. Resume the infusion at 50% of the previous rate after it has disappeared or decreased to a Grade 1 allergic/hypersensitivity reaction and closely monitor for worsening.
Grade 3 or Grade 4	Stop cetuximab infusion immediately and remove the infusion route from the patient. Administer adrenaline, bronchodilators, antihistamines, corticosteroids, intravenous fluids, vasopressors, oxygen, etc. when medically indicated. **Patient treatment should immediately be discontinued and treatment with cetuximab should not subsequently be restarted.**

New administration of treatment after a hypersensitivity reaction

Once the rate of infusion of cetuximab is reduced due to the onset of an allergic or hypersensitivity reaction, the reduction will continue for later infusions. If a subject has a second allergic or hypersensitivity reaction to the slower infusion rate, the treatment with cetuximab have to be discontinued definitively. If at any time, a patient experiences an allergic or hypersensitivity reaction of Grade 3 or 4, cetuximab treatment will be suspended. If there is any doubt as to whether the subject's reaction is a Grade 1-4 allergic or hypersensitivity reaction, the study coordinator and/or principal investigator have to be immediately contacted for consultation and for assignment of a grade.

7.A.3.1.3 Management of radiodermatitis concomitant with cetuximab-induced skin rash

One of the side effects associated with RT is radiodermatitis, which occurs in head and neck tumours in the area of the cheek, retroauricular area and neck. In other words, it coincides with one of the areas with the most skin disorders caused by cetuximab. In patients treated with RT and concomitant cetuximab, both skin toxicities coincide within the irradiation field, and therefore some patients may have severe skin disorders in this area that require specific support measures.

The management of this toxicity will be performed according to the grade of dermatitis as specified in section 8.B.7. It is summarised in the following table:

Grade of radiation dermatitis	Grade 1	Grade 2	Grade 3	Grade 4
General measures	The general measures are those belonging to each site. ***Topical application of protective substances or dressings, gels, and emulsions should not be applied immediately before treatment with radiotherapy, as it can cause a bolus effect, thus increasing the dose of radiation on the epidermis. The skin within the irradiation field must be cleaned and dried appropriately just before being irradiated.***			
Measurements based on the degree of toxicity	Keep the area irradiated clean. Subsequent use of a protective dressing is optional.	To keep the area treated with clean, even when ulcerated.		Check that the irradiation dose and distribution is correct.
	If anti-infectious measurements are required, anti-infective dressings may occasionally be used (e.g. triclosan or chlorhexidine).	When infection is not suspected, one of the following topical measures can be used: o Shower gels, possibly with the addition of antiseptics (e.g. chlorhexidine-based creams) o Hydrophilic dressings were applied after radiotherapy to the cleaned irradiated area, they may improve the topical symptoms. o An anti-inflammatory emulsion, such as triethanolamine. o Hyaluronic acid cream. o Zinc oxide paste, if it is considered possible to break them before starting each radiotherapy fraction. o Silver sulfadiazine or beta glucan cream can be used after radiation (preferably in the afternoon) after cleaning the irradiated area.		It requires a specialised treatment on wounds with the support of the radiation oncologist, dermatologist and nurse, and should be treated individually.
		When infection is suspected: o The person tasked with treated the lesion must rule out the presence of an infection, if they require a culture to identify the infectious agent. o Topical antibiotics (they are not recommended to be used prophylactically) o Doxycycline is not recommended in this stage.		
Cetuximab	Continue with treatment	Continue with treatment		Suspend radiotherapy and cetuximab

7.A.3.1.4 Modifications or delay of cetuximab dose

If a patient presents a concomitant condition (e.g. infection) that in the opinion of the investigator and/or study coordinator requires interruption of treatment, the concomitant condition has to be cured within a period of time that does not prevent more than four consecutive infusions of cetuximab from being administered. If treatment with cetuximab will be delayed, another loading dose will not be administered and all subsequent treatments will be administered at the allocated dose. If the administration of cetuximab suspends for a period of time, the study investigator and/or coordinator may assess the possibility of the patient continuing to receive cetuximab or withdrawing them from the study.

7.A.4. Radical treatment (part 2 both arms): RADIOTHERAPY

Normofractionated RT combined with cisplatin or cetuximab

The RT administration regimen for RT is shown in Table 7.2. It will be started at 3-4 weeks (5 weeks at most) from the start of the administration of the 3rd cycle of induction chemotherapy, with the aim of minimising the effect that treatment stops have on the cell repopulation. In individual – exceptional – cases, and previous contact with the study coordinators, a 5th week of delay will be allowed for the start of RT. In no case there will remain weeks without treatment with cetuximab.

The sequence, interval and hours compared to the administration of cisplatin (standard arm) or cetuximab (experimental arm) and RT will be the most suitable for the site and the patient.

Table 7.2 Radiotherapy administration regimen for radiotherapy.

Radiotherapy	Total radiotherapy	Dose per fraction
Normofractionated	Total 70 Gy, divided into 35 fractions	2 Gy / fraction 1 fraction per day 35 fractions for 7 weeks

7.A.4.1 Planning

Treatment planning with radiation will be done before any treatment. If there are anthropometric variations in the patients after having received chemotherapy, it is not due to a decrease in adenopathies (N3) or by weight loss; a new planning will be performed to adjust the dosimetry to the current volume. Re-planning will be performed after the third induction chemotherapy. The initial volume of the disease have to be what is treated. RT will be performed using three-dimensional analysis with a CAT scan. This will be done with contrast if possible. The distance between the cuts in the planning CT scan will be 5 mm.

The patient have to be immobilised with a thermoplastic mask and carbon-fibre support, where possible for the use of subsequent fields.

7.A.4.2. Determination of volumes

To design the volumes and the specification of the dose, it is recommended to follow the International Commission on Radiation Units (ICRU) 50 recommendations. To determine the clinical target volume (CTV) of the primary tumour, it is recommended to follow the general considerations published by Eisbruch et al. [1]. To determine the CTV of the lymph node chains, we followed the recommendations and consensus published by the DAHANCA, EORTC, GORTEC and RTOG for the negative lymph nodes, and the recommendations of Grégoire et al. [2,3] for the positive lymph nodes.

The determination of the volumes will be always performed by taking into account the initial disease volume, and not just the disease that lasted after chemotherapy. This is intended to improve the dosimetric study of the treatment and reduce the doses in healthy tissues.

The margins added to the gross tumour volume (GTV) to reach the CTV will be 5 mm plus the margin of organ and patient movement, and the technical inaccuracies that will be specific to each site.

They defined 2 or 3 planning target volumes (PTVs) according to the initial disease, tumour size and lymph node extension.

To restrict the dose to healthy tissues, the values published by Emami et al. will be used [4].

7.A.4.3. Method, dose and fractioning

Accelerators with 4-6 MV as well as electrons with different energy levels are recommended, in case overprinting is necessary in some areas with tumours or those at risk.

The total dose in the tumour and lymph node areas affected will be 70 Gy. Doses in the lymph node areas at high-risk of microscopic disease will be 55-60 Gy and in low-risk elective areas, 45-50 Gy.

PTV1 = CTVt + CTVn + CTVn elective plus 45-50 Gy margins
PTV11= CTVt + CTVn of maximum risk plus 60 Gy margins
PTV111= CTVt plus 70 Gy margins
Maximum dose in marrow 45 Gy.

7.A.4.4. In the case of treatment discontinuation

In the case of treatment, discontinuation, due either to malfunction or revision of the treatment machine, continued treatment have to be ensured, and so the use of another unit is recommended. For units that have different energy levels, it is recommended to perform the dosimetry on an alternative device.

7.A.4.5. Check of the treatment

In technically complex cases, treatment simulation is recommended. Testing the treatment will be performed by X-ray of all fields or at least portal-vision at baseline and technical changes.

A linear accelerator will be used, 4-6 MV which have different types of electrons for proper radiation of the posterior cervical lymph nodes.

7.A.4.6 Management of acute radiation toxicity

If skin or mucosa grade 4 toxicity occurs, the possibility of temporary suspension of treatment is assessed. For any other degree of minor toxicity, with the necessary support measures have to be taken to guarantee treatment continuity. Given that it is an accelerated diagram, prolongation of total treatment time seems to lower the benefits of this type of therapeutic regimen.

The protocol for each site will be followed in terms of prophylaxis and dental hygiene and management of skin and mucosal toxicity.

Analgesics: it is recommended to use a rapid analgesic scale going through a first step with a non-steroidal anti-inflammatory drugs (NSAIDs) and analgesics, a second step with opioids, followed by a third step with morphine or fentanyl.

Skin toxicity: it is recommended to hydrate and clean the skin.

- In the case of G I dermatitis: hydration
- In case of G II-III dermatitis: topical corticosteroids
- In case of G-IV dermatitis: topical corticosteroids, epithelializing creams and dressings

Mucositis: The following recommendations will be considered:

- Analgesics: rapid escalation using the WHO cancer pain relief ladder
- Nutritional support: according to the protocol of each site. Oral nutritional support was recommended for oral administration if there was weight loss of ≥ 5%. If the weight loss was ≥ 10%, the use of nasogastric or gastrostomy tube is recommended for feeding.

Nasogastric or gastrostomy tube for feeding: recommended to use in the following situations:

1. Weight loss ≥ 10% (assess it from weight loss ≥ 5% of initial weight).
2. Grade 3 functional mucositis
3. Pain in oral cavity and/oropharyngeal pain poorly controlled with morphine.
4. Risk of aspiration: appearance of cough and/or choking during intake.
5. Swallowing disorder initially attributed to the tumour and/or spreading of the tumour into the supraglottis.

Interruption of radiotherapy: it will be considered in the following clinical situations:

1. Mucositis measured by physical examination and/or functional, grade 4.
2. Mucositis measured by physical examination and/or functional, grade 3, when it is associated with weight loss ≥ 20% with respect to the initial weight or a decrease in Karnofsky index score ≥ 40% compared to baseline.
3. Grade 4 Radiodermatitis

The discontinuation of RT due to toxicity do not prevent the treatment of RT in 8 weeks. It is always attempted to finish within this time, if the delay requires finishing for the ninth week, before exceeding 8 weeks, it is required to consult the study coordinators whether to consider these patients as evaluable. If the treatment is completed after a period of 9 weeks, the patient have to be withdrawn from the study.

The discontinuation of RT due to toxicity do not involve the discontinuation of cetuximab treatment, which continues to be administered during this interruption and will be suspended only if the patient withdraw from the study.

Radiotherapy report:

It is recommended that the following be included in the external RT report:

- Definition of GTV, CTV, PTV and organs at risk.
- Positioning of the patient and immobilisation.
- Technique used: number of beams, energy of the beams.
- Description of interruptions: number of days and cause.
- Dose specifications: maximum and minimum dose in each PTV, mean and median in each PTV, dose in organs at risk
- Toxicity: grade of epithelitis, grade of clinical and functional mucositis.
- A copy of the complete dosimetry, including dose-volume histograms of the defined volumes and risk organs had to be included.
- Provide images of the cross-sections representative of the delimited volumes as well as digitally reconstructed radiographic (DRR) images from each of the treatment fields used.

7.A.3.4 Cisplatin at the same time as radiotherapy (Arm A, conventional)

Cisplatin will be administered 1st day of the RT and subsequently every 21 days (days 22 and 43 of the RT), irrespective of the duration of the RT. The discontinuation of RT due to toxicity involves discontinuation of cisplatin treatment that may be restarted if it will be decided to continue with the RT treatment. Cisplatin will be administered while the patient is undergoing RT, and the last day possible will be the last day of administration of RT.

7.A.3.5 Cetuximab at the same time as radiotherapy (arm B, experimental)

Cetuximab will be administered throughout the entire RT, regardless of its duration. The discontinuation of RT due to toxicity do not involve the discontinuation of cetuximab treatment, which continues to be administered during this interruption and will be suspended only if the patient withdraw from the study. Cetuximab will be maintained until the last week in which the patient completed RT.

7.A.5 Dissection of the neck after radiotherapy

For those patients in whom a persistent cervical adenopathy is observed but with control of the primary tumour during the definitive treatment assessment (a complete extension study at 6-8 weeks after the RT has finished), it is assessed whether to carry out a neck

dissection. The decision on the type of neck dissection depend on the head and neck surgeon, and will be discussed in detail with the multidisciplinary treatment team.

In patients where the initial lymph node condition is resectable, the type of dissection depends on the location, size and relationship to the cervical structures. In cases of N1 and some cases of N2, the procedure to be performed will be a functional neck dissection (FND), preserving important neck structures such as the internal jugular vein, the spinal nerve and the sternocleidomastoid muscle. In cases where the size or location of the cervical adenopathies make this technique impossible, a radical FND will be performed - without preserving the aforementioned cervical structures. There is also the possibility, depending on the surgical findings, of performing a modified FND, with the preservation of some of the aforementioned cervical structures. The use of this technique depends on the surgical findings. In general, irrespective of the technique used, the neck dissection levels must include lymph node areas I to IV or II to IV.

In patients whose initial lymph node condition is classified as unresectable (N3), the most advisable technique to be performed will be a Radical RND.

The performance of selective FNDs, which involve the removal of one or two lymph node levels, without the performance of a regulated neck dissection, will be left to the discretion of each Tumour Committee. Its advantage comes from a lower post-operative morbidity; its disadvantage is that it involves the incomplete removal of all the cancer.

Lymph node surgical rescue due to the persistence of cervical adenopathies with primary tumour control is considered an integral part of the therapeutic programme, which is why it is not considered a therapeutic failure or a serious event.

If the lymph node persistence is accompanied by a local disease persistence, this will be considered a therapeutic failure, and in this case, the performance of the most suitable salvage therapy have to be evaluated.

Note: Prophylactic neck surgery after the end of the complete treatment, irrespective of the final response to treatment, for all patients with N2/N3 initially, is optional for each site.

7.B Previous and concomitant medicine

All patients in this study will be offered supportive measures for disease-related symptoms and treatment-associated toxicity. Any concomitant medication (e.g. antibiotics, analgesics, antihistamines, anti-emetics, steroids), procedures (e.g. paracentesis, thoracentesis) or blood products (e.g. erythrocyte, platelet or frozen fresh plasma transfusions) administered during the study and in the 2 weeks prior to its start will be recorded the CRF, indicating the date, indication, procedure description and clinical observations, if any. The generic name of the medication will be specified together with the total daily dose and duration of the treatment. In the case of medications containing more than two active substances, the brand name may be used.

The patients have to be premedicated with antihistamines and corticosteroids before they receive the first dose of cetuximab. Similarly, the patients also have to be premedicated with dexamethasone before the administration of docetaxel. It is

recommended that the patients be premedicated with antihistamines and corticosteroids before the subsequent cetuximab infusions.

Palliative RT may not be administered for pain management or other non-curative purposes.

Surgery to remove tumours is not permitted during the study. The study patient will be withdrawn if this surgery is carried out. If, at the end of the study, tumour persistence, relapse or progression (exit from the study) is observed, the investigator may obviously then make a decision regarding the appropriateness or not of performing rescue and/or palliative surgery.

Permitted concomitant medication

Sedatives, antiemetics, antibiotics, analgesics, antihistamines, steroids, red blood cell concentrates, erythropoietin, or fresh-frozen plasma or platelet transfusions may 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 may be administered for curative purposes. Only the administration of haematopoietic growth factors is accepted.

Erythropoietin is only administered in patients with a haemoglobin value below 10 g/dL and at the lowest possible dose to avoid a transfusion. Furthermore, the administration of erythropoietin will be stopped if, after 8 weeks of treatment, the patient's haemoglobin levels do not recover to the levels necessary or if they still require transfusions.

Prophylactic treatment with an antihistamine and a corticosteroid is administered before the initial dose of cetuximab will be administered. Similarly, the patients have to be premedicated with corticosteroids before all the docetaxel doses. Prophylactic treatment with an antihistamine and a corticosteroid before the following weekly doses of cetuximab is recommended.

Non-permitted concomitant medication

Patients in this study may not be administered any other concomitant chronic systemic immunotherapies, chemotherapy not indicated in the study protocol, RT not indicated by the study, hormone therapy for cancer (the administration of corticosteroids at low doses as antiemetics and progestogens for the tumour cachexia is allowed), amifostine or any other investigational drugs. If it is necessary to administer a concomitant drug or procedure that is not permitted, the patient will be withdrawn from the study.

7.C Material management

The drugs in this study are approved for the study indication, and therefore, the normal supply methods and the handling instructions specified in their respective summaries of product characteristics are followed.

7.D Assessment of treatment compliance

The study medication will be administered by the investigator or under their direct supervision. Given that the IV infusions will be administered in a hospital or in an outpatient environment, compliance with the treatment may be easily monitored.

The date and the exact quantity of the drug administered at each infusion will be recorded in the study CRF/medication form. The date and the start and end time of the infusion, as well as the exact quantity of cetuximab, cisplatin and TPF administered at each infusion, will be recorded in the patient's medical record. If the treatment have to be modified, the medical staff have to evaluate the percentage of the dose received by the patient and record this in the CRF. All the reasons have to be recorded.

In the event of insufficient compliance by the patient, the principal investigator and the study coordinator decide together, on a case-by-case basis, on the possible withdrawal of the patient from the study.

8. Efficacy and safety measurements and study outline

8.A Efficacy evaluations

The variables of the study are shown in section 12.A. The main objective of the study is to determine the non-inferiority in OS of the experimental branch (TPF followed by RT + Cetuximab) versus the standard branch (TPF followed by RT + cisplatin).

8.B Description of the methods used

The following table summarizes the evaluations to be made during the periods of selection, treatment and follow-up of the study. The descriptions of the methodology to be followed are included in the following sections.

Table 8.1 Diagram of the valuations to be made during the study

Assessment	Include
Informed consent	• Written informed consent to participate in the study will be made before the start of induction chemotherapy with TPF.
Register	• Assignment of patient number
Demographic data	• Age (date of birth) • Sex • Ethnic origin
Tumour diagnosis	• Date of initial diagnosis • Histological type and degree of differentiation • Tumour, ganglion (node), metastasis (TNM) classification • Staging according to the *American Joint Commission for Cancer* (AJCC) criteria; 6th edition • It will be recorded if both the primary tumour and the lymph node involvement are resectable or unresectable
Medical history and previous treatments	• Malignant and non-malignant diseases of previous interest • Treatments administered in the two weeks prior to the start of the study
Inclusion and exclusion criteria	• Comprehensive review of all criteria
Physical exploration	• Height, weight, BMI, and body surface area (BSA) • General aspect • Cardiovascular system • Pulmonary • Neurological • Digestive system • Genitourinary device • Locomotor apparatus • Lymphatic system • Dermatological • Eyes • Extremities • Detailed physical examination of the head and neck area, to rule out a second neoplasia

Vital signs	• Temperature • Resting heart rate • Blood pressure at rest (systolic and diastolic)
Activity degree	• ECOG - PS
Dental evaluation	• It is recommended to remove seriously damaged parts before therapy, trying to preserve or restore them when possible.
Nutritional assessment	• A minimum intake of 1700 calories per day should be guaranteed, but if it is possible orally, the use of nasogastric tube and/or jejunostomy will be assessed.
Direct optical examinations of the tumour	• It is advisable to perform a panendoscopy under general anaesthesia with the necessary biopsies. When this is not possible or is not considered necessary, an indirect laryngoscopy with an evaluation of the oropharynx, hypopharynx and larynx will be accepted.
Diagnostic imaging techniques (within 5 weeks before inclusion)	• CT, PET-CT or head and neck nuclear magnetic resonance (NMR) • Chest X-ray • Bone scintigraphy and a bone radiology directed only in cases where bone metastasis is suspected • Ultrasonography or CT scan/PET-CT scan in the case of suspected liver metastases and/or relevant abnormalities of liver function.
Laboratory analysis (2 weeks before inclusion)	• Haematology: haemoglobin, white blood cell count, absolute neutrophil count, and platelet count • Biochemistry: alanine aminotransferase [SGOT], aspartate aminotransferase [SGPT], lactate dehydrogenase [LDH], total protein, serum creatinine, urea, alkaline phosphatase, total bilirubin, albumin, and electrolytes-sodium, potassium, calcium, and magnesium- • Creatinine clearance, optional or if creatinine > 120 µmol/L (1.4 mg/dL) • Pregnancy test, if applicable
Cardiovascular tests	• Electrocardiogram (ECG)
Adverse events	• On all visits and according to what is specified in section 9.A.1
Concomitant medication	• On all visits and according to what is specified in section 9.A.1
Survival and other antineoplastic treatments	• With the same frequency as post-treatment visits

8.B.1 Valuations to be made during the study

8.B.1.1 Informed consent of the patient

Patients must sign an informed consent before undergoing any specific protocol evaluation and before receiving treatment (induction chemotherapy with TPF) (Appendix 1).

8.B.1.2 Demographic data

Demographic data should include the assigned patient number, date of birth, gender and ethnic origin, which will only be recorded at the baseline visit.

8.B.1.3 Clinic history

The clinical history should include the date of diagnosis, the main diagnosis including the histological or pathological documentation of the neoplasm, other pathologies and the related treatments when these have been administered in the 14 days prior to the start of the assigned treatment.

The clinical history will only be collected at the baseline visit.

8.B.1.4 Inclusion and exclusion criteria

To be included in the study, patients must meet all the inclusion criteria and none of exclusion (section 6.A).

8.B.1.5 Physical exploration

The full physical examination includes height, weight, BMI, body surface area (BSA) and a complete evaluation of the cardiovascular, respiratory, nervous, gastrointestinal, hepatic, renal, and cardiovascular systems and equipment. Dermatological and musculoskeletal, extremities and a complete and detailed physical examination of the head and neck area.

A complete physical examination will be performed at the baseline visit, at each visit before the administration of TPF-type chemotherapy, at each response assessment visit and at the post-progression visit except for the BSA, which will not be necessary to calculate the post-progression visit. Height will only be recorded at the baseline visit.

8.B.1.6 Vital signs

Vital signs include heart rate (after 5 minutes at rest), blood pressure (systolic and diastolic, after 5 minutes at rest) and temperature (measured using the same method in the same patient).

The vital signs will be monitored and recorded before, during, immediately after and 1 hour after the administration of the first infusion of cetuximab. The following weekly visits should not be documented in the CRF unless the results are anomalous and are reported as an AE.

8.B.1.7 Dental evaluation

It is advisable to carry out an extraction of the pieces seriously damaged before the therapy, trying to preserve or restore them when possible. At least a period of 10 days should be allowed for the healing of the gums after extraction.

8.B.1.8 Functional status according to the ECOG scale

Functional status will be assessed using the ECOG scale at the baseline visit, at each visit and at the end of the study visit.

8.B.1.9 Clinical evaluation of the tumour

The measurement of the tumour will be made through a complete physical examination of the oral cavity, pharynx and the cervical and supraclavicular ganglionic areas that will include physical measurements of the affected tumour areas, emphasizing the following characteristics:

- Lesion location, size and mobility.
- Presence of trismus or decreased mobility of the tongue.
- Alteration of functionalism of cranial nerves V, VII, IX, X, XI and XII.
- Number, location, size and characteristics of cervical adenopathies.

It is advisable to perform a **panendoscopy** under general anaesthesia, which allows a better evaluation and localization of the structures invaded by the tumour, performing the necessary biopsies in the correct location and ruling out the presence of second primary tumours. It includes therefore the evaluation of the nasopharynx, the oropharynx, the oral cavity, the larynx, the hypopharynx and the oesophagus.

When this is not possible or is not considered necessary, an **indirect laryngoscopy** with an evaluation of the oropharynx, hypopharynx and larynx with the necessary biopsies will be accepted.

The location and size of the primary tumour and lymph node involvement should be identified in representative diagrams.

In case of skin lesions of ≥ 20 mm, clinical evaluation will be carried out by means of a calibrator and photographs will be taken.

All determinations will be recorded in the metric system.

8.B.1.10 Evaluation by tumour image

A computed tomography (CT) or MRI of the head and neck will be performed, allowing a complete study of the locoregional tumour disease and the evaluation of more complicated areas such as the base of the skull, the base of the tongue, the parapharyngeal space, the mandible and the structures cervical vessels. These baseline and subsequent radiological studies should be performed using identical techniques (type and volume of contrast, times, cuts, apparatus, etc.) to ensure the comparability of the images obtained and to evaluate the efficacy correctly.

If the patient has a PET-CT scan of the head and neck, if the CT scan performed on the hybrid equipment (PET-CT) is low dose, it is not useful for the morphological measurements required by the RECIST 1.0. However, if CT is performed with contrast, intravenous and oral, and with adequate parameters to be of diagnostic quality, then PET-CT can be used in the baseline assessment and to assess response to treatment.

A baseline chest radiograph will be performed and every 12 months thereafter, but it will not be necessary to perform this radiograph if the patient has a chest CT or PET-CT within the stipulated times for the chest radiograph.

Only in cases where bone metastasis is suspected, a bone scan and a directed bone radiology, or a PET-CT, will be requested; and an abdominal ultrasound or CT scan/PET-CT scan in the case of suspected liver metastases and/or significant liver function abnormalities.

8.B.1.11 Safety laboratory evaluations

Sites will have to provide a list of the normal ranges to the study promoter and the CRO, who should be informed of all changes in normal values that are made during the study.

At the baseline visit a **haematological study** should be performed, which will include the determination of leukocytes, neutrophils, platelets, haemoglobin; and a **biochemical**

study that will include sodium, potassium, calcium, magnesium, LDH, SGOT, SGPT, alkaline phosphatase, total bilirubin, total proteins, albumin, creatinine and urea.

If the creatinine values are > 120 μmol/L (1.4 mg/dL), a creatinine clearance will be requested. With lower values, it is optional.

Serum pregnancy test (only in women with the possibility of pregnancy). All patients (men and women) must use medically accepted methods of contraception throughout the study and up to 6 months after the end of treatment.

8.B.1.12 Cardiac tests

An electrocardiogram will be performed in the 21 days prior to the start of treatment.

8.B.1.13 Assignment of the stage and resectability

With the information from sections 8.B.1.9 and 8.B.1.10 the tumour will be classified according to the Tumour-Ganglion-Metastasis (TGM) and a stage will be assigned according to the criteria of the *American Joint Commission for Cancer* (AJCC) 6th edition.

It will be recorded in all cases if the lymph node disease is unresectable or unresectable (in the evaluation of the Committees of each Site); with the objective of facilitating the decision to perform the rescue cervical evacuation adequate for each case, in the event of persistence of adenopathies at 6-8 weeks after completing RT (see section 7.A.5).

The criterion of surgically unresectable disease will be defined in the different Interdisciplinary Committees of the Head and Neck of the Institutions participating in the study. The tumour should be considered inoperable according to the criteria of the Northern California Oncology Group [5] after evaluation by a multidisciplinary team, which will include, at least, a specialist in oncological surgery of the O.R.L. or maxillo-facial surgery (as appropriate), a specialist in Medical Oncology and a specialist in Radiation Oncology. The reason for inoperability will be noted in the CRF.

NCOG inoperability criteria:

1. Technically nonresectable (Includes: Evidence of mediastinal dissemination; tumour fixed to the clavicle, base of the cranium or cervical vertebrae; involvement of the nasopharynx).
2. Medical criteria based on a low surgical curability.
3. Medical contraindication for surgery.

In cases considered unresectable due to the characteristics of the primary tumour, a ganglionic surgical rescue will be offered in the case of complete response of the primary tumour to treatment with persistent cervical disease.

In cases considered unresectable due to the characteristics of both the primary tumour and cervical disease, a ganglionic surgical rescue will be offered in the case of complete response of the primary tumour to treatment with persistent cervical disease.

In cases considered unresectable due to the characteristics of the cervical disease, being the primary tumour resectable, a ganglionic surgical rescue will be offered in the case of complete response of the primary tumour to treatment with persistent cervical disease.

8.B.2 Response evaluation

8.B.2.1 Response evaluation after 3 cycles of TPF

The assessment of the response to neoadjuvant treatment with the TPF will be made 2-3 weeks after the start of the 3rd cycle of TPF.

The assessment of the response will be based on an integrated evaluation of the multidisciplinary treatment team that will include:

- A clinical evaluation of the tumour (see section 8.B.1.9)
- An evaluation of the tumour by imaging techniques (see section 8.B.1.10)

If the investigator suspects a progression of the disease, a clinical and imaging assessment should be done before the dates indicated.

In cases where CT, PET-CT or MRI scans are not indicated for medical reasons and there is clear evidence of disease progression on chest radiography, optical techniques and/or physical examination (ie, in exceptional circumstances), documentation of progressive disease can be based only on chest radiography, optical techniques and/or physical examination.

In case of progression of the disease, the visit after progression (VAP) visit will be carried out and the patient will be removed from the study. The investigator will be able to decide which is the most appropriate treatment strategy for the patient.

8.B.2.2 Response evaluation at the end of treatment (same for both arms of radical treatment)

The evaluation of the response after 3 cycles of neoadjuvant treatment with the TPF regimen followed by concomitant RT with cisplatin or cetuximab will be carried out 6-8 weeks post-radiotherapy.

This assessment will be based on the integrated evaluation of the multidisciplinary treatment team that will include:

- A clinical evaluation of the tumour (see section 8.B.1.9)
- An evaluation of the tumour by imaging techniques (see section 8.B.1.10)

From this moment, the patient will enter the follow-up phase (see section 8.C.6).

8.B.2.3 Response evaluation criteria

Response will be evaluated using the modified RECIST 1.0 criteria. These criteria includes confirmation of tumour response in a second observation performed at least 4 weeks after the initial assessment. In this specific trial, the responses (CR or partial response [PR]) observed after the third and last cycle of TPF will not be re-evaluated 4

weeks after assessment of the initial response, since RT begin as soon as possible after the end of the neoadjuvant treatment.

The lesions will be assessed based on physical examination of the tumour and in the images obtained using CAT, PET-CT* or MRI scan. The same method and evaluation technique will be used to characterise each of the lesions identified and reported in the baseline period and during the study.

* "If the CT is performed with contrast, intravenous and oral, and with the appropriate parameters to be of diagnostic quality".

Lesions will be assessed at baseline and 2-3 weeks after administration of the 3rd cycle of TPF, at 6-8 weeks post-RT, and in the first 6 months in the first, the second, second and fourth year and every 12 months thereafter. If the investigator suspects disease progression, the disease will be assessed using both clinical and imaging techniques before the indicated dates.

If a CT, PET-CT MRI scan are not indicated for medical reasons and there is clear evidence of disease progression on chest X-ray, optical techniques and/or physical examination (in other words, in exceptional circumstances), disease progression documentation may be based on chest X-ray, optical techniques and/or physical examination.

An assessment of the disease will be carried out on the VAP visit if there is no documented disease progression by imaging techniques, in prior assessments.

Local radiologists assessed the plates of the CAT scan, PET-CT or the MRI according to the modified RECIST 1.0 criteria. The outcome of the assessments will be carefully documented in the CRF and tumour progression was assessed and documented as described as follows:

Definitions

To assess the objective response, the tumour mass at the baseline visit will be estimated, to be compared with subsequent assessments. Tumour lesions will be classified at the baseline visit as follows:

- **Measurable**: the lesion can be accurately measured in at least one dimension (the greater diameter should be measured) such as ≥ 20 mm using conventional techniques or as ≥ 10mm using conventional MRI or CT scan.

- **Non-measurable**: the other lesions, including small lesions (longest diameter < 20 mm using conventional techniques or < 10 mm using conventional MRI/spiral CT scan/PET-CT) and truly non-measurable lesions. The lesions considered truly non-measurable include the following: bone lesions, leptomeningeal disease, ascites, pleural/skin/lung/skin or abdominal masses that have not been confirmed or followed by imaging techniques, cystic lesions, pericardial effusion, inflammatory disease in the breast, and lymphangitis. Tumours located in pre-irradiated tumours areas are not be considered measurable either.

All the baseline assessments will be performed as close as possible to the start of treatment (≤ 35 days before the start of treatment).

Lesions will be assessed based on images obtained using CAT, PET-CT or MRI. The same method and the same assessment technique have to be used to characterise the lesions identified at the baseline visit and subsequent visits. All measurements will be recorded using the metric system and using rulers or calibrators.

Baseline evaluation

All measurable lesions must be identified, up to a maximum of 10 lesions in total, as recorded and measured target lesions at the baseline visit. The target lesions will be selected for their size (lesions with the largest diameter) and suitability for repeatedly conducting precise measurements. These lesions have to be assigned numbers in the CRF that could not be changed for every patient throughout the study. The sum of all the largest diameters of all the target lesions will be calculated, recorded as the sum of largest diameters at the baseline visit. This sum of larger diameters will be used as a reference, used to characterise the tumour's objective responses, while progression is diagnosed based on the smallest sum of the smallest of the largest diameters taken during the study treatment.

The rest of the lesions will be identified as non-target lesions and will also be recorded at the baseline visit. It is not necessary to measure these lesions, but their status will be monitored throughout the study.

Evaluation of response at consecutive visits

The overall response will be defined according to the assessment of target and non-target lesions, also taking into account the appearance of new lesions. The definitions are:

Evaluation of the target lesions:

Complete response (CR):	**Disappearance of all target lesions**
Partial response (PR):	Reduction of at least 30% in the sum of the largest diameter of all target lesions, using the sum of larger diameters at the baseline visit as a reference.
Stable disease (SD):	There is neither sufficient reduction to classify it as PR nor sufficient increase to classify it as DP; in other words, a decrease in the sum of the greatest diameter of all target lesions less than 30%, taking the baseline measurement as the reference or an increase of this diameter by less than 20%, using the smallest sum of larger diameters after the start of treatment as the reference.
Disease progression (DP)	An increase of 20% or more of the sum of the largest diameter of all target lesions, using the smallest sum of larger diameters since the treatment started as the reference.

Evaluation of non-target lesions:

Complete response (CR):	**Disappearance of all non-target lesions**
Incomplete response (IR) /stable disease (SD)	Persistence of one or more non-target lesions
Disease progression (DP)	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions (although a clear progression of non-target

	lesions is exceptional, in these circumstances, the physician's opinion must prevail).

Patients with a global deterioration in their health that require discontinuation of treatment without objective evidence of disease progression at that time will be classified as "symptomatic deterioration". Every effort have to be made to document progression even after discontinuing treatment.

The overall response will be obtained from the values taken from the target and non-target lesions, and taking into account the appearance or lack thereof of new lesions. Table 8.2 shows all overall responses of potential combinations of tumour responses. The overall response assessments will be carried out on each visit in which a response evaluation is scheduled.

Table 8.2 Assessment of overall response

Target lesions:	Non-target lesions.	New lesions	Overall response
CR	CR	No	CR
CR	IR/SD_1	No	PR
PR	No-DP	No	PR
SD	No-DP	No	SD
DP	Any	Yes or no	DP
Any	DP	Yes or no	DP
Any	Any	Yes	DP

Notification of results

The investigator will check the response to the treatment in all the patients included in the study according to the screening visit's findings. All patients will be classified into one of the following groups:

- Complete Response
- Partial Response
- Stable disease
- Disease progression
- Death from cancer
- Early death due to toxicity
- Early death due to another cause
- Unknown (not assessable, data insufficient)

Patients who die before any of the post-treatment assessments of response may be conducted will be considered “premature deaths”. For the response analysis, they will be considered to have had a “progressive disease”.

Patients who have experienced symptomatic deterioration without objective evidence of progression will be classified within the “progressive disease” group.

8.B.3 Quality of life assessment

The importance of evaluating the QoL in head and neck cancer, which can affect some of the most basic functions of life, is recognized. In the study of EORTC-24971 [53] the

TPF administration was shown to improve the QoL in relation to patients who had received FP. In this study, it is expected that the experimental arm (RT plus cetuximab) is superior to the control arm (RT plus cisplatin) in the reduction of acute and chronic adverse effects.

For this comparative study, the QoL questionnaires of the EORTC have been chosen. The questionnaire QLQ-C30 version 3.0 [69] is a basic questionnaire of 30 items. The module QLQ-H & N35 [70], consisting of 35 items, will also be used, with the authorization of Kristin Bjordal.

These questionnaires will be self-completed by the patients when they will be in the site. They will have to complete them before starting TPF induction chemotherapy, after 3 cycles of TPF, just before the patient know the radical treatment arm to which they have been assigned, and then 6-8 weeks after completion of RT and every 6 months during the follow-up visits for the first and second year. If the time for completing the questionnaire coincide with an assessment of the tumour, the patient will fill it in before knowing the results of the tumour study.

The reasons for the selection of the indicated time points are as follows:

- Before induction chemotherapy: to find out the patient's baseline condition.
- After 3 cycles of induction chemotherapy: to determine the changes after chemotherapy and just before randomisation.
- 6-8 weeks after finishing RT: To determine the patient's condition in light of recent RT and at the time the first tumour response assessment is conducted.
- At 6, 12, 18 and 24 months after RT, to allow the patient to have recovered from the RT toxicity.

The QoL questionnaires will be completed before the patient know the results of the tumour study. The patient have to complete the questionnaires themselves, in their own language, at the site.

8.B.3.1. Quality of life dimensions

For the QLQ-C30, 15 scales are taken from the 30 initial items: 5 functional scales (physical, role played, emotional, cognitive and social function), 3 symptoms scales (fatigue, nausea and vomiting, pain), 6 individual symptom scales (dyspnoea, insomnia, loss of appetite, constipation, diarrhoea and financial difficulties) and 1 overall health/QoL status scale.

18 scales of the 35 initial items are taken for the QLQ-H&N35: 7 multi-item symptoms scales (pain, swallowing, feeling, speech, eating from a social perspective, social interactions and sexuality) and 11 individual symptom scales (condition of teeth, mouth opening, salivation, cough, sensation of illness, use of analgesic medication, nutritional supplements, feeding tubes, weight loss and weight gain).

The scores for all scales are calculated according to the procedures defined in the EORTC Scoring Manual, ranging from 0 to 100 following linear transformation (72). The highest scores on the functional and overall health/QoL status scales indicate a high level of functioning and a better QoL, respectively, while higher scores on symptom scales represent a higher level of symptoms.

8.B.4 TPF administration

TPF (docetaxel, cisplatin, 5-FU) should be administered under the supervision of the investigator, as described in section 7.A.1.

The date of TPF administration should be reflected in the CRF.

8.B.5 Administration of cisplatin concomitant with radiotherapy

Cisplatin should be administered under the supervision of the investigator, as described in section 7.A.2.

The date of cisplatin administration should be reflected in the CRF.

8.B.6 Administration of cetuximab concomitant with radiotherapy

Cetuximab should be administered under the supervision of the investigator as described in section 7.A.3 in an area where resuscitation equipment and other drugs are available (adrenaline, prednisolone equivalents, etc.)

Cetuximab will be administered from one week before starting the RT program until the week of its termination, or if before a progression of the disease, an unacceptable toxicity or withdrawal of consent by the patient is observed.

In the CRF should be reflected the date of administration of cetuximab, the time of start and end of all infusions.

8.B.7 Adverse events

An assessment of toxicity and/or AEs should be made at each visit.

All AEs must be reported in the manner described in section 9.A.1 .

All AEs related to treatment, both with induction chemotherapy (TPF) and with RT plus cisplatin or RT plus cetuximab, should be classified according to the **following criteria**:

1. NCI CTC, version 3.0 during the induction treatment (Appendix 3)
2. NCI common toxicity criteria (CTC), version 3.0 (Appendix 3) and CTC of the RTOG during Chemotherapy/RT or Cetuximab/RT and 90 days after completion of the RT (Appendix 4). In case of doubt, the criteria that assessed the AE to be the highest grade were used.
3. Late CTC from the RTOG/EORTC from 90 days after completion of RT, which were basically used to gather chronic toxicity associated with radio-chemotherapy (Appendix 5)

Special precautions must be taken with:

Allergic reactions

During or after infusion with cetuximab and/or docetaxel allergic reactions may occur. It is therefore recommended to pre-treat patients with an adequate antihistamine (it is

mandatory at the visit of the first infusion). As a routine precaution, the patients included in this study will remain under close observation for possible AE, from the start of the infusion until one hour after the infusion is finished, in an area with resuscitation equipment and emergency agents (adrenaline, prednisone equivalents, etc.).

In the event of an allergic reaction or reaction to infusion with cetuximab and/or docetaxel, the patient should be treated with the best available means (see section 7.A.1.4.1). The patient should be instructed to notify the investigator immediately of any delayed reaction.

Interstitial pneumonitis

In the recent literature, severe acute interstitial pneumonitis has been described in patients treated with another agent against EGFR, gefitinib. In case a patient in this study develops a severe pulmonary toxicity that manifests with dyspnoea and/or hypoxia, it is advisable to consult an appropriate specialist (pulmonologist). In addition, the promoter must be notified through the Serious Adverse Event Alert Report Form (ARF) in order to make a timely decision on the case. Tests that are considered medically appropriate, such as a high-resolution chest CT, should be performed. If the result of these tests indicates interstitial disease, more tests should be seriously considered, if not contraindicated by the patient's condition. These tests are bronchoscopy with transbronchial biopsy for pathological anatomy and cultures and, if the bronchoscopic studies are negative, lung biopsy for pathological anatomy (for evidence of malignancy or infection). Patients with any severe toxicity (grade 3 or 4), including pulmonary toxicity, should not be re-treated with cetuximab until the severe toxicity is resolved.

8.B.8 Concomitant medication

The concomitant medication, dosage, route of administration, start date and duration of all treatments should be reflected in the CRF. After the post-progression visit, only the subsequent treatment lines for head and neck cancer will be collected.

8.B.9 Survival status

When a death occurs due to an unknown cause, the principal investigator/promoter recommends carrying out an autopsy in order to adequately document the cause of the death.

8.C Conduct of the study

The schedule of visits, procedures and evaluations required is described in the study schedule (see Appendix 2). It may be necessary to study other parameters and/or increase the frequency of the examinations depending on the findings discovered during the study.

The methodology of the studies and activities is described in section 8.B.

For safety and efficacy reasons, the investigator have to comply with the schedule as closely as possible.

8.C.1 Screening/baseline visit

The baseline visit have to be performed within 21 days prior to the scheduled start date of TPF induction chemotherapy treatment.

Patients have to sign the informed consent form before carrying out the specific assessments of the protocol and before receiving treatment (see Appendix 2).

The following assessments prior to treatment will be performed in the three weeks prior to study entry except the β-HCG pregnancy test, which will be carried out within seven days prior to inclusion of the patient in the study.

The following assessments prior to treatment will be performed in the previous 3 weeks:

- Informed consent (consent to participate in the study).
- Diagnosis of the primary tumour.
- Inclusion and exclusion criteria.
- Demographic data.
- Medical history.
- Physical examination including weight, height, BMI and BSA.
- Dental examination.
- ECOG-PS Performance Status.
- Assessment of the tumour through a complete physical examination and a direct visual examination, preferably via panendoscopy or direct laryngoscopy, (previous 28 days). A diagram of the lesions and lymph nodes will be made.
- Radiological examinations using a CAT, a PET-CT scan or MRI scan of the head and neck. A chest X-ray will also be performed, which may not be performed if there is a chest CAT/PET-CT scan. It is accepted up to 35 days prior to the planned start date of treatment.
- Definitive assignment of the stage, with description of the primary tumour and whether or not lymph node involvement is resectable from entry.
- An electrocardiogram.
- Bone scan if the alkaline phosphatase ≥ 1.5 x UNL or clinical suspicion of bone metastases.
- Blood draw for haematology study, clinical chemistry. The determination of β-hCG should be performed within 7 days prior to the inclusion of a patient of childbearing age in the study.
- QoL questionnaires (QLQ-C30 and QLQ-H&N35).
- Concomitant medication
- Patient recruitment form.

Based on the findings, the investigator will include patients in the study, sending an inclusion sheet by fax to the CRO/study coordinator.

8.C.2 Evaluation visits during neoadjuvant treatment with TPF

Visits will be made every 3 weeks during treatment with TPF, which will coincide on the day of the next cycle of TPF:

- Collection of blood samples for the complete laboratory safety, haematology and clinical chemistry analyses every 3 weeks, coinciding with the administration of chemotherapy. The extraction may occur in the previous 48 hours, but the results will have to be available before administration of chemotherapy.
- Physical examination including weight (this will be determined every week during full treatment, at the investigator's discretion), performance status based on ECOG - PS and calculation of BSA every 3 weeks, coinciding with the administration of chemotherapy.
- Clinical assessment of the tumour to rule out progression during treatment with TPF. If progression is suspected, radiological assessment will be brought forward using CAT, PET-CT or MRI scan to document progression.
- Documentation of AEs and concomitant treatments (weekly).

8.C.3 Response assessment visit after neoadjuvant treatment with TPF

The following assessments and procedures will be performed 2-3 weeks after the administration of the 3rd cycle of TPF:

- Physical examination, weight and BSA.
- ECOG-PS performance status assessment.
- Clinical assessment of the tumour, including direct and/or indirect optical exams of the tumour as considered necessary, as well as a biopsy of suspicious areas if that would be accurate.
- Radiological studies using a CAT, a PET-CT or MRI scan (always the same technique) of the head and neck 2-3 weeks after the administration of the 3rd cycle of TPF.
- Complete laboratory tests with blood count and biochemistry
- QoL questionnaires (QLQ-C30 and QLQ-H&N35).
- Documentation of AEs and concomitant treatments.

When treatment will be discontinued for reasons other than disease progression, efforts will be made to carry out a response assessment before starting an alternative treatment For example, if a patient can only receive 2 cycles of TPF, the response will be assessed to decide whether they can be randomised.

PATIENT RANDOMISATION:

All patients will receive 3 cycles of induction chemotherapy with the TPF regimen. Treatment will be organised according to the evaluation of the response to TPF chemotherapy:

1.- Patients who progressed with the treatment with TPF will be excluded from the study and will be treated according to each Site’s protocol.

2.- Patients with a response or stabilisation when treated with TPF but with toxicity that contraindicated the continuation of treatment with cisplatin will be excluded from the study and will continue treatment according to each site's protocol and according to international guidelines. These patients will then analysed as a population with intention-to-treat (ITT).

3.- Patients who are unable to receive at least two cycles of induction will be excluded from the study and will be treated according to each site's protocol and in accordance with international guidelines.

4.- Patients who respond to or are stabilised with TPF and who have not shown toxicity that prevented the continuation of treatment with cisplatin, will be randomised to receive normofractionated RT plus cisplatin (Group A - standard) versus the combination of cetuximab and normofractionated RT (Group B - experimental).

STRATIFICATION: to ensure a homogeneous distribution, patients will be stratified according to:

- Tumour location (oral cavity, versus oropharynx versus larynx versus hypopharynx).

8.C.4 Evaluation visits during radical treatment (concomitant radiotherapy with cisplatin [Arm A] or cetuximab [arm B])

Weekly visits will be conducted during concomitant treatment in the same way in both treatment arms.

8.C.4.1. Concomitant radiotherapy with cisplatin

- Physical examination, performance status based on ECOG–PS and weight.
- Complete blood count and clinical chemistry profile (sodium, potassium, magnesium, calcium, LDH, SGOT, SGPT, alkaline phosphatase, total bilirubin, total proteins, albumin, creatinine and urea). This will be performed just before starting combined treatment and coinciding with each administration of cisplatin. A blood test will be repeated at 3 weeks after the last cisplatin dose and only if a grade 3/4 analytical alteration persists until it has resolved, or at the investigator's discretion. In addition, a blood count will be performed every 15 days.
- Documentation of AEs and concomitant treatments.

8.C.4.2. Concomitant radiotherapy with cetuximab

It will coincide with the day cetuximab is administered:

- Administration of cetuximab
- Physical examination, performance status based on ECOG–PS and weight.
- Complete blood count and clinical chemistry profile (sodium, potassium, magnesium, calcium, LDH, SGOT, SGPT, alkaline phosphatase, total bilirubin, total proteins, albumin, creatinine and urea). It will be performed just before the

start of the combined treatment and every 3 weeks. The latest blood test will be performed when RT has been completed and subsequently, and only in the event of a grade 3/4 analytical alteration until resolution, or at the investigator's discretion. In addition, a blood count will be performed every 15 days.

- Documentation of AEs and concomitant treatments.

8.C.5 Evaluation visit during the first 8 weeks after completion of radiotherapy and definitive end of the radical treatment (identical for both treatment arms)

Two assessments will be conducted, one at 4 weeks and another at 6-8 weeks after having completed RT.

THE EVALUATION AT 4 WEEKS will consist of a complete physical examination including weight, performance status according to ECOG-PS, a haematological and clinical chemistry profile, a clinical assessment of the tumour (which included direct and/or indirect optical exams of the tumour, as considered necessary) and an evaluation of the AEs that may appear since the completion of the RT. Due to post-RT local inflammatory problems, a clinical assessment of the tumour may be impossible during this visit.

THE EVALUATION AT 6-8 WEEKS will be the same as that at 4 weeks but with a CAT scan, a PET-CT scan or MRI of the head and neck to establish the definitive assessment of locoregional disease control; and, if necessary, with biopsy of suspected disease persistence areas, and assessment of the QoL test.

In the assessment at 6-8 weeks the decision will be made concerning the necessity of performing a cervical lymph node dissection (see section 7.A.5).

8.C.6 Evaluation visits during the follow-up period

Table 8.5 shows the tests and assessments that should be performed on all patients included in the study during the follow-up period starting from 6-8 weeks after completion of RT.

Patients with toxicity associated with cisplatin or cetuximab will be adequately monitored until the toxicity is resolved.

An abdominal ultrasound or CAT/PET-CT scan and/or a bone scan or a PET/CT scan is only considered if there is suspected metastases at these sites.

The QoL questionnaires (QLQ-C30 and QLQ-H&N35) will be undertaken every 6 months during the follow-up visits for the first and second year.

Table 8.3 Evaluations during the follow-up period

Regimen	During years 1 and 2	During years 3 and 4	During year 5
Clinical assessment of the tumour*	Every 3 months	Every 6 months	Every 12 months

Physical examination with weight and ECOG performance status assessments	Every 3 months	Every 6 months	Every 12 months
Assessment of late radiotherapy toxicity	Every 3 months	Every 6 months	Every 12 months
Complete blood count and clinical biochemistry	Every 3 months	Every 6 months	Every 12 months
Tumour imaging methods**	Every 6 months***	Every 6 months***	Every 12 months***
Chest X-ray	Every 12 months***	Every 12 months***	Every 12 months***

* Will include direct and/or indirect optical exams of the tumour as deemed necessary, as well as a biopsy of suspicious areas if accurate
** CAT, PET-CT or MRI of the head and neck (always the same technique).
*** Or at the time of suspected progression and/or recurrence.

When recurrence and/or progression at any level is significant, complete the study in order to be able to study the therapeutic failure pattern: locoregional and/or distant.

With this follow-up, there is a complete tumour assessment of the disease at 12 months after starting treatment (1st cycle of TPF), at 24 months, and at 36 months.

Follow-up after 5 years will be performed according to the protocol for each site.

8.C.7 Visit after progression

Patients will be required to attend a VAP visit once DP occurred.

The following additional procedures and tests will be performed at this visit:

- Physical examination.
- ECOG performance status assessment.
- Collection of blood samples for laboratory safety analyses (haematology and biochemistry).
- Assessment on the need for lymph node dissection.
- Documentation of the AEs and concomitant medication in accordance with that specified in section 9.A.1 .
- A CAT, a PET-CT or MRI scan of the head and neck when the last took place more than 4 weeks ago, and have not shown recurrence and/or progression.
- Clinical assessment of the tumour (which included direct and/or indirect eye exams of the tumour considered as necessary), when the latter have been performed more than 4 weeks ago, and have not shown recurrence and/or progression.
- Chest X-ray when the last have been done over 4 weeks ago, and recurrence and/or progression have not been demonstrated.
- Survival status.

8.C.8 Follow-up visits following the visit after progression

After the visit after progression, data will be collected on the subsequent therapy lines with the same frequency as the post-treatment visits. When hospital visits are not required, survival data may be obtained by phone.

9. Adverse events

9.A Brief summary of adverse events and serious adverse events

9.A.1 Adverse events (AE)*

An AE is defined as any unfavourable medical experience that affects a patient or a subject that participates in a clinical investigation to which a pharmaceutical product has been administered, and that does not necessarily have a causal relationship with this treatment. Therefore, an AE can be a sign (including an anomalous laboratory data, for example), symptom or unfavourable and unintended disease, associated chronologically with the use of a pharmaceutical specialty, whether or not it is related to the pharmaceutical specialty.

Due to regulatory standards, events that occur before and after the treatment period should also be designated as AE. Therefore, safety surveillance (notification of AEs) begin when the patient is included in the study (date of signing the informed consent) and will continue until the evaluation visit after the RT treatment has been made in combination with cisplatin or cetuximab.

After 90 days post-treatment of RT in combination with cisplatin or cetuximab, only data on chronic toxicity associated with radio-chemotherapy will be collected and following the Common Criteria for Late Toxicity of the RTOG/EORTC (Appendix 5). This procedure complies with the requirements of the authorities and the request of the insurance companies of the patients.

9.A.2 Adverse events or serious adverse events (SAE)*

SAEs (experiences) or severe reactions are any unfavourable medical experience that occurs during any phase of the study (from the inclusion of the patient to the evaluation visit after RT treatment in combination with cisplatin or cetuximab), at any dose of the product in investigation, and that it meets one or more of the following criteria:

- Produces the death of the subject,
- Threatens life,

  NOTE: The term "life threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically could have caused death had it been more severe.
- Requires the hospitalization of the patient or the extension of an existing income,
- Result in a persistent or significant disability/disability
- It is a birth defect or congenital anomaly in the offspring of the patient
- It is an important medical event

The medical and scientific criteria will be used to decide whether immediate notification is appropriate in each situation, such as important medical events that may not be

*Management of clinical safety data: "Definitions and Standards for Expedited Reporting - ICH Topic E 2ª, 1995

immediately life threatening or result in death or hospitalization but may endanger the patient or require intervention for prevent any of the consequences mentioned in the previous definitions. These situations or in case of doubt will usually be considered serious.

Examples of such events include intensive treatment in an emergency department or at home because of allergic bronchospasm; blood dyscrasias or seizures that do not involve hospitalization; appearance of drug dependence or drug addiction; or presence of malignant tumours that are anatomopathologically different from the primary tumour.

Other events considered as SAE

Overdose should always be considered and treated as a SAE.

Pregnancy and breastfeeding are criteria for exclusion. In case pregnancy occurs during the course of the study, the patient should be withdrawn from the treatment under study immediately. The Promoter must be notified immediately and the patient will be observed throughout the pregnancy and the post-partum period. All the data of the mother and the new-born must be recorded, even if they are completely normal and do not present any adverse event. The ARF form must be used, although pregnancy is not considered a SAE. No "severity criteria" box should be checked. ARF is only used to guarantee immediate communication.

9.A.3 Events not considered as SAE

The progression of the disease is not considered a SAE. Due to the seriousness of the disease under study, certain situations will be considered as SAEs excluded from immediate notification:

- Elective hospitalization and surgery for the treatment of the disease,
- Elective hospitalization to simplify treatment or study procedures
- Hospitalization that is unequivocally due to disease progression

9.B Methods of registration and evaluation of adverse events.

All AEs must be documented in the corresponding section of the data collection notebook. In addition, all SAEs must be documented in the ARF (for an "initial" SAE or for "follow-up" information from a previous SAE).

The following information will be recorded for each event in the CRF:

- A description of the AE in medical terms, not as the patient refers;
- The start date;
- The date of recovery (end date);
- The degree/severity according to investigator's assessment according to the definitions of the **following criteria**:
    1. National Cancer Institute (NCI) CTC, version 3.0 during the induction treatment (Appendix 3)
    2. NCI CTC, version 3.0 (Appendix 3) and CTC of the Radiation Therapy Oncology Group (RTOG) during the treatment of QT/RT or Cetuximab/RT

and up to 90 days after the completion of radiation therapy (Appendix 4). In case of doubt, the criteria that assess the adverse event in the highest degree will be used.

3. RTOG/EORTC Common Criteria for Late Toxicity from 90 days after the completion of RT, which will basically serve to collect the chronic toxicity associated with radio-chemotherapy (Appendix 5)

- The causal relationship with the study medication according to the investigator; the most important factor in the documentation is the chronological relationship between the AE and the study medication. The following criteria should be used about the causal relationship of AE with the drug or study procedures:
  - Not related = there is no temporal relationship with the administration of the drug (too early, too late, or the study drug was not taken) or there is a reasonable causal relationship with another drug, breakthrough disease or other circumstance and the SAE.
  - Unlikely = there is a temporal relationship with the administration of the drug, but there is no reasonable causal relationship between the study drug and the SAE.
  - Possible = there is a reasonable causal relationship between the study drug and the SAE. There is no information about the interruption of the drug or it is not clear.
  - Probable = there is a reasonable causal relationship between the study drug and the SAE. The event responds to the interruption of the drug, it is not necessary to re-expose it.
  - Safe/Definitive = There is a reasonable causal relationship between the study drug and the SAE. The event responds to the interruption of the drug and reappears when it is re-exposed, if it is clinically feasible.
- The action taken with the drug (none, interruption of the medication, reduction of the dose, delay of the medication, reduction of the speed of the infusion)
- Other actions (none, concomitant medication administered new hospitalization or prolongation thereof, surgical intervention, etc.)
- The result of the AE according to the following definitions:
  - Recovery with sequelae
  - Recovery without sequelae
  - Continue, without treatment
  - Continue, with treatment
  - Death
  - Change in the degree of toxicity
- Gravity: yes or no

If one of the patients experiences the same AE on several occasions, the AE in question must be documented and evaluated each time it occurs.

9.C Procedure for reporting serious adverse events

Any AE or abnormal value in laboratory parameters that is considered serious or medically significant occurred during the course of the study or during the post-treatment period, regardless of the treatment received by the patient, should be immediately reported by the investigator by telephone or fax. The names, addresses and telephone and fax numbers are listed in the ARF.

After a phone notification, the information must be sent in writing by fax or mail. To make the written notification, the ARF must be used (for an "initial" SAE or for "follow-up" information from a previous SAE).

As a general rule, the investigator must document and medically assess the AE, and describe its evolution, in the ARF as well as in the AE section of the CRF. When necessary, the ARF sent by fax must be accompanied by some relevant pages of the CRF, for example, clinical history, AEs and concomitant medication.

The promoter and/or study coordinator may request additional information, if necessary, to ensure that the initial notification of SAE is made to the health authorities within the required times. For the follow-up report to the authorities, the sponsor and/or study coordinator may be asked to obtain more information in order to have a detailed description and a final evaluation of the case, including copies of hospital reports, autopsy reports and other relevant documents.

If there is incomplete or inconsistent SAE information directly affecting the communication obligation of the promoter to the health authorities, the Corporate Pharmacovigilance Group can contact the investigator directly to clarify it.

Investigator must notify the Clinical Research Ethics Committee (CREC), if applicable, in accordance with international and local laws and regulations.

9.D Monitoring of patients with adverse events

The following (S)AE must be notified or followed up as specified in section 9.A.1 :

- All new AEs must be registered in the CRF.
- All new SAEs must be notified through the ARF.

All AEs assessed as possible, probably or definitely related to the study medication, and which were still present at the time of the post-progression visit, should be followed (ie, these AEs should be evaluated until their final evolution in the first follow-up visit of survival).

It is the responsibility of the promoter and the investigator to ensure that the necessary additional therapeutic measures are taken, and that appropriate follow-up is carried out.

10. Ethical aspects

10.A General considerations

10.A.1 Notification to the authorities

The study protocol and any other applicable documentation (information for the patient, informed consent, etc.) will be presented to the health authorities in accordance with the regulations in force at the time of presenting the study.

10.A.2 Ethics committee of clinical investigation

Before commencing the study, the protocol and other documents (patient information sheet and informed consent form, investigator's brochure) will be submitted to the corresponding Independent Ethics Committee (IEC) with the aim of obtaining a favourable opinion/approval. The favourable opinion/approval will be filed in the investigator's file, with a copy being kept in the general study file.

The study will only be started once the favourable report/approval have been obtained in writing. The sponsor will request the documentation relating to the date of the IEC meeting, the composition of the committee and the voting members present at the meeting. The sponsor also will require a written approval that clearly identified the clinical trial, the protocol version and the consent documents that will be reviewed. As far as possible, a copy of the minutes of the meeting will be obtained from the meeting in which the protocol was evaluated.

Any amendment to the protocol will be submitted to the IECs; they will also be informed of SAEs, according to current legislation.

10.B Patient information and informed consent

10.B.1 Information for the patient

An essential requirement for a patient's participation in the clinical trial is written informed consent. The investigator have to provide adequate patient information before obtaining his/her consent. Local legislation permitting, the investigator will be able to designate a person to provide the information. A patient information sheet will be provided in the local language according to Conference on Harmonisation (ICH) GCP standards (ICH Topic E6, 1995). In addition to the written information, the investigator will inform the patient verbally. Terms will be used such that the content will be completely legible and understandable for the layperson. The information sheet will be updated whenever important new information is available that may be relevant for patient consent.

10.B.2 Patient consent

The patient have to give written informed consent to participate in the clinical study before any study-related procedure will be carried out (see Appendix 1). This consent form will be signed and dated personally by the patient and by the investigator or the person designated to explain and discuss the informed consent form with the patient.

The investigator will confirm that the patient granted his/her consent in the CRF. The signed and dated informed consent form will remain at the site and will be kept by the investigator in a safe place so that it can be available at any time for monitoring, inspection or audit. The patient will be given a signed and dated copy of the patient information and informed consent form before being included in the study.

Illiterate patients

If the patient or his or her legal representative cannot read, an independent and reliable witness have to be present, that is say, a person not related to the site or to the study, throughout the discussion of the informed consent form. The choice of witness have to not affect the right to patient confidentiality. Family members and friends will be considered suitable independent witnesses. Once the patient or his or her legal representative have consented verbally and signed, if able, the witness signed and dated the consent form personally, thus attesting that the information is accurate and that the patient or his or her legal representative have fully understood the content of the agreement in the informed consent form and that consent will be actually granted.

10.C Confidentiality

See section 11.B.1.

10.D Patient insurance

The promoter will provide mandatory insurance coverage for all patients participating in the study from the time of their inclusion in the study (ie date of patient consent). The insurance coverage will comply with the legal requirements and GCP guidelines and in accordance with Spanish regulations. In the file of the investigator of each site, a certificate of the insurance policy must be kept together with the insurance conditions.

11. Practical considerations

11.A Participants' responsibilities

11.A.1 Administrative structure of the study

The study will be monitored through regular visits and telephone calls to the investigator. During visits to the site, the monitor should review the patients' original records, medication stock records, and document preservation. In addition, the monitor should evaluate the study procedures and discuss any problems with the investigator. During the course of the study, audits can be carried out in the participating sites. The investigator will allow direct access to the source data/documents for the tasks of monitoring, auditing, review of the CREC and inspection by the health authorities.

11.A.2 Investigator's responsibilities

The investigator will be responsible for ensuring that the study is being conducted in accordance with the protocol, the Declaration of Helsinki and in accordance with the Standards of GCP (CPMP/ICH/135/95) approved on July 17, 1996, as well as to the relevant legal requirements. These documents explain that informed consent of patients is an essential condition for participation in the clinical trial.

11.A.3 Monitoring, quality assurance and inspections by the authorities

This study will be conducted in accordance with the Standards of GCP (CPMP/ICH/135/95) dated July 17, 1996. The clinical monitor of the study will arrange visits with certain regularity in the sites of the study to verify the development of the same one.

During monitoring visits, the monitors will:

- Help solve any problem
- Examine all the CRFs to check if there are data that have been omitted, as well as compliance with the protocol and possible AEs
- Discuss the inconsistencies of the study data
- Ensure that all study material is properly stored and is properly dispensed
- Check the compliance of the investigator's obligations
- Review the consents of the patients, in particular the date and the signature of the consent.
- Complete the Verification of Original Data record as described below

According to the International ICH guidelines on PCBs, monitoring will include verification of the data collected in the CRF against the original records of patients. This verification will be done through direct access to the patient's medical history. It is guaranteed that the patient's confidentiality will be respected at all times. Participation in the study will be interpreted as an acceptance to allow verification of the original data.

The promoter and/or principal investigator may decide to conduct audits to verify the validity of the study data.

11.A.4 Modifications to the study protocol

Changes in the study protocol should be made in the form of modifications to the written protocol. These will need the approval of all signatories on page 2 of the final version of the protocol. The signature of the modification of the study protocol by the principal investigator will be considered sufficient if it has authorization on behalf of the other investigators.

Any amendment to the protocol that could affect the patient, for example, changes in procedures/evaluations or issues related to patient safety, will require a favourable report/approval of the CREC of each site, before its implementation. Purely administrative changes should be notified to the CREC, but do not require formal approval. Any amendment that affects patients requires an additional informed consent for each patient before its implementation.

11.A.5 Study protocol deviations

Deviations from the protocol are not allowed -especially the prescription of doses not programmed in the protocol-, other forms of administration, other indications or treatment periods longer than those established.

11.B Conditions for archiving and handling data

11.B.1 Handling of the Data Record Collection

An electronic CRF (eCRF) will be created on-line in which investigators will record the integrity of the data directly through a web page.

The eCRF will be developed based on a standard application: DCTrials 2.5. This is a web-based application and accessible via the Internet through browsers: Internet Explorer 5.0 or higher and Netscape 8.0 or higher.

DCTrials 2.5 includes the functionalities module of the investigator and module of the monitor/study manager.

A data management plan will be made before the start of the study. A validation of the functions of the eCRF application will be performed by entering simulated data prior to the start of the data entry process.

11.B.1.1 Data accessibility

Access to the database will be restricted to the system administrator (design and data entry), to the Data Manager, who will be the investigators who will perform the data transcription (data entry) and the monitors (reading data and editing queries). Any entry in the database must be registered, identified and dated. Any modification of the data will be traceable (registered, identified, dated and the old value retained).

At user level: security is guaranteed by the application, which encrypts communications between the server and the user.

11.B.1.2 Security

At user level: security is guaranteed by the application that encrypts communications between the server and the user.

At server level: the current legislation in relation to the control and restriction of physical access to the data is applied.

11.B.1.3 Password Management

It is guaranteed that the only person with access to a password is its owner:

- Any password transmission is done through a secure environment.
- At the beginning of the study, the user will be assigned a temporary password. When accessing the application for the first time, you will be obliged to modify this password and enter a password of 5 characters or more.
- In case of loss of password, the user must inform the help desk service of the study and the latter will provide another temporary password that must be modified the first time he/she returns to access the application.

This guarantees, at a technical level, the security of the access codes.

11.B.1.4 Data management

The data will be entered by the same investigator, connecting to a portal that will give access to an on-line database, through a user and its corresponding exclusive password, to ensure the confidentiality and security of the data.

In order to guarantee the confidentiality of the data of the patients participating in the study, only the investigator and his team of collaborators will have access to them, the representative of the promoter who will perform the monitoring tasks, the auditor in case the study was subject to an audit, the CREC and the Health Authorities.

The content of the electronic records of data collection, as well as the documents generated during the study, will be protected against use by people outside the research, will be considered strictly confidential and will not be disclosed to third parties except those specified in the previous section. The treatment of the personal data required in this study is governed by the Organic Law 15/1999.

Prior to the declaration of the definitive database, a verification of the consistency of the values of the inclusion/non-inclusion criteria, of the clinical evaluations, of the results of complementary explorations, of the dates of visit, of compliance, of concomitant medication, AEs, information about dropouts and evaluation of efficacy. A queries management will be carried out, to clarify the inconsistencies.

The queries management allows the user to identify possible omissions or errors in the entered data.

The queries system requires the definition of the conditions of data entry and indicate the mandatory data.

The application will identify on the data entry forms the fields that have some incidence and that the user must resolve.

The user can consult the list of queries in their cases and directly access the data form to make the necessary corrections.

Any subsequent change in the database will be done leaving a traceable record of it (Audit Trail). The Audit Trail (or audit of modifications) will record all operations performed on the database:

- Connections (correct and incorrect)
- Data query
- High cases
- Cases modifications
- Etc...

In addition, the user will be registered and the date and time in which a certain operation was performed. So that it is possible to fully monitor the evolution of the database.

The Audit Trail will also incorporate a recovery system that allows restoring a previous state of the database eliminating all the modifications made from a certain date.

The content of the eCRF database will be transferred to SAS data sets for statistical analysis. All statistical analyses will be performed using the statistical package SAS® system version 8.2 for Windows 2000 or later available.

11.B.2 Original data and patient file

The investigator must keep a file of each patient who participates in the study either on paper or electronically. In this patient file, the demographic and medical information available must be recorded, in particular the following information: name, date of birth, sex, height, weight, patient's history, concomitant diseases and concomitant medication (including changes during the study), report of inclusion in the study, identification of the study, date of informed consent, date of all study visits, explorations made and clinical findings, AEs observed (if applicable), and, if applicable, the reasons for the withdrawal of the study. With the data available in this file, it should be possible to verify the inclusion and exclusion criteria of the study.

It should be possible to identify all the patients in the study using this file.

In addition, any other document that contains original data, especially the reports generated by technical devices, must be archived. All these documents must have at least the identification of the patient and the date printed by the registration device, to indicate to which patient and to which study procedure that document belongs.

The printed copies of the patient files that are computerized must be signed and dated by the investigator, endorsed by the monitor and stored in the patient's medical record as a source document.

The medical information relevant to the evaluation of efficacy and safety will be transcribed to the e-CRF specifically designed for the study and collected in the clinical history.

During the monitoring visits, the consistency between the patient's medical records and the e-CRF data, that is, the verification of the original data will be checked.

The e-CRF data that come from original documents should be consistent with them, in case there is any discrepancy should be justified.

The study will be carried out in accordance with the Organic Law of Protection of Personal Data 15/1999 and RD 994/99 of security measures for automated files containing personal data.

11.B.3 Investigator's file, data conservation and record handling

The investigator will be provided with a study file at the beginning of the study. This file contains all the relevant documents necessary to carry out the study. Once the study is finished, this file should be kept in a safe place.

It is the responsibility of the investigator to ensure that the patient's identification sheets are kept for at least 15 years after the end of the clinical trial. The original files of patients should be kept for as long as possible allowed by the regulations of the hospital, research institute or the doctor in question. If the file cannot be kept at the site, the investigator must notify the promoter.

The data required for the analysis will be recorded and electronically transferred to a central database, through an electronic data report collection (eCRF). The system works on the Internet, with a system of data recording in real time (online). The data, introduced by investigators, are transferred directly via the Internet to a central database, without being registered on the investigator's local computer.

High security standards for the transfer and storage of study data are guaranteed by the use of technologies such as an encrypted data transfer, firewall and a daily backup to protect centrally stored data. Write access to the system will be limited to authorized personnel, and the system will automatically maintain a trail for the audit of all entries and corrections of the eCRF.

The electronic report collection is operated under an electronic signature, which consists of the combination of an identification code and a password. Each investigator will be provided with these codes of strictly personal and non-transferable use. Investigator can change his access password as many times as he wishes. The codes will be used to enter, modify or visualize the study data.

It is the responsibility of the investigators to keep their passwords secret, that is, not to reveal them to third parties.

Once the study in the sites is finished, the database will be sent to the biometrics department of the company TFS, responsible for the statistical analysis of the same. Before carrying out any analysis, the populations in a meeting between the promoter and TFS (Clean File Meeting) will be defined and all the populations and deviations

will be reflected in a report to be signed by the promoter and the persons responsible for TFS (Clean File Protocol).

11.B 4 Quality control

During the course of the study, the monitor will be responsible for ensuring that the study will be conducted in compliance with GCP and the current legislation. Verifying, among other procedures, the informed consent of all patients will be obtained correctly, that study procedures will be followed as detailed in the protocol and that data collection will be conducted accurately, for which purpose they will compare the information available in medical records (source documents) with the data recorded in the e-CRF.

In case of lack of information or partial or imprecise information, discrepancy reports will be generated by the data-handling department of TFS responsible for this task so that the investigator can resolve them.

The data generated in this clinical trial will be handled in accordance with the standard operating procedures of the company TFS, which is responsible for data handling.

11.C Final report and publication

TTCC undertakes to comply with current Spanish legislation on clinical trials, and specifically article 38 of Royal Decree 223/2004, which establishes the obligation to publish the results, both positive and negative, in scientific journals, with mention to the CREC that approved the study, and to the funding source. By signing this protocol, principal investigator accepts the terms of the TTCC's publication policy and undertakes to respect them as a member of the Spanish Treatment Group of Head and Neck Tumours.

12. Statistical analysis

12.A Efficacy and safety endpoints

The **study's primary endpoint** is OS defined as time between the start of treatment with TPF and death due to any cause.

The *secondary endpoints* of the study are:

- ORR (according to the modified RECIST 1.0 criteria), will be measured for induction chemotherapy and also for both radical treatment arms after TPF (RT + Cisplatin and RT + Cetuximab).
- Incidence and time when dose reductions or suspensions will be carried out (rate of compliance with the protocol in both treatment arms).
- PFS.
- Specific survival.
- Time to locoregional control of disease.
- Satisfaction with treatment. Analysis of QoL in both treatment arms.

12.B Analysis populations

The assignment of patients to any of the populations mentioned below will be made before closing the database.

Part I of the study (period between the signature of the informed consent form until the evolution of the response and toxicity to induction chemotherapy with TPF)

A. *Safety population 1* (SP 1): all patients who have signed the informed consent form and who received at least one dose of chemotherapy with TPF.

B. *Intention-to-treat population 1* (ITT 1): all patients enrolled who have signed the informed consent form and who have received at least one dose of TPF chemotherapy.

Part II of the study (period from randomisation after induction chemotherapy with TPF and until the end of the study)

A. *Safety population 2* (SP 2): all randomised patients who have initiated the assigned radical treatment.

B. *Intention-to-treat population 2* (ITT 2): all randomised patients who have at least started the assigned radical treatment.

12.C Efficacy and safety analysis

12.C.1 Primary efficacy analysis: overall survival

OS is defined as: the time from the start of induction chemotherapy with TPF to death due to any cause or to the last check-up in the case of living patients.

The study's primary analysis will be performed on the ITT population that will be randomised into the standard arm or the experimental arm. It will be tested using the following hypotheses, if the experimental treatment group is, at least, non-inferior to the standard group:

H0: $HR_{\text{Experimental arm / Standard arm}} \geq 1.3$.
H1: $HR_{\text{Experimental arm / Standard arm}} < 1.3$

The one-sided alpha level specified in the study protocol is 0.05. Thus, non-inferiority can be concluded if the upper limit of the two-sided 90% CI for the HR is below 1.3.

Patients who have signed an informed consent form but have not been randomised will not be included in the primary study primary analysis, although they will be monitored in a similar way to randomised patients and descriptive information will be taken from their treatment and evolution.

12.C.2 Secondary analysis

12.C.2.1 Overall Survival

OS is defined as: the time from the start of induction chemotherapy with TPF to death due to any cause or to the last check-up in the case of living patients.

The analysis will be performed on the ITT population of part 2 and ITT of part 1.

The results of a proportional hazards regression model, which includes the factors used for stratification and/or prognostic factors in this disease, will also be presented in the ITT populations, in order to evaluate the sensitivity of the main analysis.

In addition to the risk reasons and their corresponding one-sided 95% CIs, the results of these analyses will be summarised for each treatment group, with data in the form of Kaplan-Meier graphs and median survival rates at 2, 3 and 5 years, with the corresponding 95% unilateral CI.

12.C.2.2 Overall response rate

The ORR is defined as the response rate (CR + PR) measured using the RECIST 1.0 method.

The populations analysed will be in part 1 after induction therapy, ITT population, and in part 2 also the ITT PP population.

The results on part 1 will be presented in absolute and relative frequency tables and the corresponding 95% CI.

The results from part 2, as well as the absolute and relative frequency tables with a 95% CI for each treatment group, the response rates will be compared using the chi-squared test (or the corresponding non-parametric test) with a 95% CI.

Using the ITT population 1, exploratory analyses will be performed to search for prognostic factors in the response rate.

12.C.2.3 Adverse events rate and laboratory parameters

All the AEs that appear will be recorded in the case report form according to the following criteria:

1. NCI CTC, version 3.0 during the induction treatment (Appendix 3)
2. NCI CTC, version 3.0 (Appendix 3) and CTC of the RTOG during Chemotherapy/RT or Cetuximab/RT and 90 days after completion of the RT (Appendix 4). In case of doubt, the criteria that assessed the AE to be the highest grade will be used.
3. Late CTC from the RTOG/EORTC from 90 days after completion of RT, which will be basically used to gather chronic toxicity associated with radio-chemotherapy (Appendix 5)

AEs will be presented in the form of lists and summarised by absolute and relative frequency tables. A table for part 1 (induction therapy) and another for the part 2 treatment assigned by the randomisation group will be presented. In both the AEs will be separated according to whether they are related to the study medication or not. When classification of the relationship with the study medication will be lacking, it will be deemed to be related to the study medication.

Laboratory data will be presented by the incidence of toxicities according to the corresponding criteria and changes from the baseline to the highest degree of toxicity, according to the given criteria, as described during treatment.

All abstracts and lists of AEs and laboratory data will be based on the safety population.

12.C.2.4 Early withdrawals from the study

The main reason for withdrawal from the study will be recorded in the case report form. Lists and summary tables will be provided, giving the reason for the end of the study and when it occurred.

These summaries and lists will be based on the safety population. Part 2 of the study will be separated by assigned treatment arm.

12.C.2.5 Incidence and time when dose reductions or suspensions were carried out

Details and summary tables will be provided, providing the incidence of reductions or treatment discontinuations and giving the reason.

These summaries and lists will be based on the safety population. Part 2 of the study will be separated by assigned treatment arm.

12.C.2.6 Progression-free survival

For the PFS analysis, we defined TTP as the time since the start date of treatment with TPF induction chemotherapy until the time when DP occurred or death occurred due to any cause. Patients who show no progression or die will be censored on the date of the last check-up. Patients for whom no tumour assessments are available after the baseline

evaluation will be censored on day 1. Patients who show no progression and begin a cancer treatment other than that of the study will be censored on the start date of the other treatment.

This analysis will be performed on the ITT populations in both parts of the study.

In part 2, the study have no power to show statistical differences or equivalences between the two treatment groups after randomisation. Using the Cox proportional hazards regression, the risk ratio will be presented together with its 95% CI, as well as the Kaplan-Meier estimations of the survival curves for each treatment group (including and survival rates and medians at 2, 3 and 5 years, with their corresponding 95% CI). The regression model will also include the factors used for stratification and/or prognostic factors of this disease in order to assess the robustness of the primary analysis.

12.C.2.7 Disease-free specific survival

For the disease-specific survival analysis, we defined TTP as time elapsed from the start date of treatment with TPF induction chemotherapy to date of death due to disease or related to the treatment of the disease. Deaths caused by other reasons will be considered "censored" data on the date of death. Patients who do not die will be censored on the date of the last check-up.

This analysis will be performed on the ITT populations in both parts of the study. In part 2, the study have no power to show statistical differences or equivalences between the two treatment groups after randomization. Using the Cox proportional hazards regression, the risk ratio will be presented together with its 95% CI, as well as the Kaplan-Meier estimations of the survival curves for each treatment group (including and survival rates and medians at 2, 3 and 5 years, with their corresponding 95% CI). The regression model will also include the factors used for stratification and/or prognostic factors of this disease in order to assess the robustness of the primary analysis.

12.C.2.8 Time to locoregional control of disease

Locoregional control: defined as permanent and complete resolution of the disease in terms of its initial site and lymph nodes (T and N). If the disease lasts (regardless of size) or the tumour recur or a second tumour appear in the field RT, it will be recorded as a therapeutic failure. This allows for surgical rescue on the lymph nodes if after the evaluation at the end of RT the cervical adenopathy will remain but the primary tumour will be under control (indicated as part of the first treatment). Locoregional failure will be considered in cases of patients who have rescue surgery on the primary tumour (T surgery) because of its persistence. Lymph node recurrence after a complete cervical lymph node remission will also be considered a therapeutic failure. In some cases, residual tumours may persist, consisting of areas of fibrosis or scarring, which may remain stable or resolved gradually over time and which is not accompanied by evidence of locoregional disease progression or clinical deterioration.

We define disease locoregional control time as time from the start of TPF induction chemotherapy to tumour recurrence or the appearance of a second tumour within the RT field. Patients who do not achieve complete remission at any of the points of the analysis will be considered therapeutic failures from day 1 (start of TPF chemotherapy).

This analysis will be performed on the ITT populations in both parts of the study.

In part 2, the study have no power to show statistical differences or equivalences between the two treatment groups after randomisation. Using the Cox proportional hazards regression, the risk ratio will be presented together with its 95% CI, as well as the Kaplan-Meier estimations of the survival curves for each treatment group (including and survival rates and medians at 2, 3 and 5 years, with their corresponding 95% CI). The regression model will also include the factors used for stratification and/or prognostic factors of this disease in order to assess the robustness of the primary analysis.

12.C.2.9 Satisfaction with treatment. Quality-of-life analysis in both treatment arms

EORTC QoL questionnaires are chosen for this study. QLQ-C30 version 3.0 [1], which is a basic questionnaire with 30 items and the QLQ-H&N35 module [2], which is made up of 35 items.

These questionnaires will be self-completed by the patients when they will be in the site. They have to complete them before starting TPF induction chemotherapy, after 3 cycles of TPF, just before the patient knew the radical treatment arm to which they have been assigned, and then 6-8 weeks after completion of RT and every 6 months during the follow-up visits for the first and second year. If the time for completing the questionnaire coincide with an assessment of the tumour, the patient will fill it in before knowing the results of the tumour study.

Overall scores and those per field in the total population and per treatment group will be described. A comparative analysis will be performed on the different scales according to the treatment assigned by the randomisation. The QoL population (patients who complete the questionnaires) that is explained in section 12.B will be used for these analyses.

12.C.2.10 Other endpoints

Continuous variables will be summarised using descriptive statistics, i.e. the mean, median, standard deviation, minimum, and maximum and two-sided 95% CI, when appropriate. The qualitative variables will be summarised using counts and percentages and 95% two-sided CI, when appropriate. The differences between means or percentages will be accompanied by 95% two-sided CI or will be compared using the corresponding statistical test.

12.D Sample size

The calculation of the sample size will be performed on the primary objective of determining non-inferiority in terms of OS of the experimental arm (TPF followed by RT + Erbitux) compared to the control arm (TPF followed by RT + cisplatin).

Calculation of sample size will be based on an assumed exponential distribution, using the following parameters:

- Unilateral testing with an alpha of 0.05 and 80% power.
- A recruitment phase of 53 months.
- A follow-up phase of 36 months.
- A risk rate for the standard 0.0231 arm (median OS of 30 months)

- A $HR_{\text{Experimental arm/Standard arm}} = 0.938$ (this assumes a median of 32-months for the experimental arm).
- Competing risk of 0.01.

The total number of randomised and evaluable patients will be 398. We also have to add the 15% of patients who will progress with TPF or will be lost to this total number. Total number of patients: 469.

The study duration will be determined at the time when there will be 282 deaths. A 53-month continuous recruitment period, 36-month follow-up after the inclusion of the last patient and also a median survival of 30 months will be considered.

12.E Intermediate analysis

A review committee will perform periodic analyses to monitor the safety of both treatment branches and the evaluability of the patients included.

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