Protocol TPExtreme

GORTEC 2014-01

under the aegis of Head and Neck Intergroup GORTEC-GETTEC-GERCOR
in collaboration with UNICANCER H&N group

Title :	**Randomized, controlled trial of Platinum-Cetuximab combined either with Docetaxel (TPEx) or with 5FU (Extreme) in patients with recurrent/metastatic squamous cell cancer of the head and neck**
Acronym	**TPExtreme**
N° EudraCT	**2014-000048-14**
Study Phase	Phase II
Date / Version	22/12/2016 - Version 5.0
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Investigators and study administrative structure

- The Groupe d'Oncologie Radiothérapie Tête et Cou (GORTEC, President Prof Jean Bourhis) is the sponsor of this clinical study which will be carried out at approximately 80 centers in France, Spain and Germany. The Investigator coordinator is Prof. Joel Guigay, M.D. The data center is localized at the unit of Biostatistics and Epidemiology, Gustave Roussy, Villejuif, France which will perform data management and statistical analysis under the leadership of Dr Anne AUPERIN.
- Regulatory submissions to competent authorities and ethics committees in France will be performed by the GORTEC and in Germany and Spain by ASCOPHARM NOVASCO Group.
- Pharmacovigilance will be performed by PV Unit of Gustave Roussy, France. ASCOPHARM together with the GORTEC will supervise safety and the timely reporting of adverse events (AEs) and serious adverse events (SAEs).
- An Independent Data and Safety Monitoring Committee (IDSMC) will be established to monitor safety data. The IDSMC charter will provide further details.

- Quality assurance will be supervised by the sponsor. This multinational trial requires a significant logistic and administrative structure for its efficient execution. All site initiation visits in the 3 countries will be performed by ASCOPHARM NOVASCO Group, France. Spanish sites coordination, monitoring and, close out visits will be performed by ASCOPHARM NOVASCO Group, France. German sites coordination, monitoring and, close out visits will be performed by AIO Studien gGmbH. Coordination and monitoring of French sites will be assured by GORTEC in cooperation with ASCOPHARM. ASCOPHARM NOVASCO Group SOPs will be used for monitoring visits in all countries.
- The GORTEC will supply the docetaxel medication which is the investigational medicinal product (IMP). Docetaxel will be distributed by a third party provider under the supervision of the GORTEC. IMP supply procedures will provide further details.

SIGNATURE PAGE

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

EudraCT Number: 2014-000048-14

Version n° 5.0 of 22 December 2016

This protocol version has been approved by:	**Date and Signature:**
The Sponsor: GORTEC The President : Professor Jean Bourhis	
Coordinating Investigator : Professor Joel Guigay	

I, …….., principal investigator, certify that I have read the protocol named « TPExtreme » and I declare to conduct this study in accordance with the approved protocol, the principles of Good Clinical Practice, and the European and French regulatory requirements laid down, respectively, by the clinical trials directive (2001/20/EC) and the Public Health Law of August 9, 2004.

I declare to:

- **explicitly inform patient and obtain his/her written informed consent after his/her acquaintance with the patient information sheet;**
- **declare all SAE to the Sponsor or its designee immediately, i.e. within 24 hours of awareness of the event(s);**
- **respect all inclusion and exclusion criteria as well as the start and the end of study dates;**
- **enter all study data required in the eCRF;**
- **fully answer all queries regarding eCRF;**
- **accept all the regular monitoring visits;**
- **ensure study documents archiving for at least 15 years beyond the end of this clinical trial.**

Principal Investigator:

Center Number/Institution name:

Date: __ __ / __ __/ 20__ __ **Signature:**

Listing of Acronyms and Abbreviations

AE	Adverse event
AIO	Arbeitsgemeinschaft Internistische Onkologie (German Association of Medical Oncology group)
ALT	Alanine Aminotransferase (SGPT: Serum Glutamate-Pyruvate Transferase)
ANC	Absolute Neutrophil Count
AP	Alkaline Phosphatase
aPTT	activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase (SGOT: Serum Glutamate-Oxalate Transferase)
BSA	Body Surface Area
BUN	Blood Urea Nitrogen
C	Cycle
CBC	Complete Blood Count
CI	Confidence Interval
CR	Complete Remission
CRA	Clinical Research Assistant
eCRF	Electronic Case Report Forms
CT	Computed tomography
D	Day
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal Growth Factor Receptor
EMA	European Medicines Agency
EORTC	European Organization for Research and Treatment of Cancer
EXTREME	Erbitux in First-Line Treatment of Recurrent or Metastatic Head & Neck Cancer
FFS	Failure Free Survival
FPG	Fasting Plasma Glucose
GCP	Good Clinical Pratice
G-CSF	Granulocyte – Colony Stimulating Factor
GGT	γ-Glutamyl Transferase
h	hour
GORTEC	Groupe d'Oncologie Radiothérapie Tête et Cou (French Radiation and Oncology Group for Head and Neck)
HIV	Human Immunodeficiency Virus
HN	Head and Neck
HNSCC	Head and Neck Squamous Cell Carcinoma
HPV	Human Papilloma Virus
IB	Investigator's Brochure
ICH	International Conference on Harmonization
ICRU	International Commission on Radiation Units and Measurements
IDSMC	Independant Data and Safety Monitoring Committee
IMP	Investigational Medicinal Product
INR	International Normalized Ratio
LDH	Lactate Dehydrogenase
min	Minute

MDRD	Modification of Diet in Renal Disease
MRI	Magnetic Resonance Imaging
NCI	National Cancer Institute
NCI-CTCAE v4.0	NCI – Common Terminology Criteria for Adverse Events version 4.0
NYHA	New York Heart Association
OS	Overall Survival
PD	Progressive Disease
PET	Positron Emission Tomography
PFS	Progression Free Survival
PR	Partial Response
PS	Performance Status
PT	Prothrombin Time
QoL	Quality of life
RECIST	Response Evaluation Criteria In Solid Tumours
R/M	Recurrent and/or Metastatic
SAE	Serious Adverse Event
SBP	Systolic Blood Pressure
SADR	Serious adverse drug reaction
SCC	Squamous Cell Carcinoma
SPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TPEx	TaxoterePlatineErbitux
TPF	TaxoterePlatinum-Fluorouracil
TTCC	Tratamiento de Tumores de Cabeza y Cuello (Spanish Head and Neck Cancer Cooperative Group)
TTP	Time to progression
ULN	Upper limit of Normal value
UFPV	Unité Fonctionnelle de Pharmacovigilance
vs	*Versus*
W	Week
WBC	White Blood Cell

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1 Synopsis

EudraCT Number	2014-000048-14
Title	Randomized, controlled trial of Platinum-Cetuximab combined either with Docetaxel (TPEx) or with 5FU (Extreme) in patients with recurrent/metastatic squamous cell cancer of the head and neck
Sponsor	GORTEC (Groupe d'Oncologie Radiothérapie Tête et Cou) CHU Bretonneau - CORAD 2 Boulevard Tonnellé, 37044 Tours cedex 9, France
Coordinating Investigator	Pr Joël Guigay, Centre Antoine-Lacassagne, Nice
Type of study	Phase II multicentric randomized,,open trial
Background	• Cetuximab combined with platinum and 5FU according to the EXTREME regimen is currently the standard of care in first line recurrent metastatic HNSCC (Vermorken et al NEJM 2011). The overall response rate was 36%, and the progression free survival (PFS) 5.6 months with a median OS of 10.1 months. Over the last 40 years, this EXTREME regimen has been the only treatment which was able to improve survival of patients with recurrent metastatic HNSCC, as compared to conventional chemotherapy. • Other new therapeutic approaches have been tested recently to challenge this standard platinum-5FU-cetuximab EXTREME regimen in recurrent metastatic HNSCC, but failed to demonstrate significant improvement as compared to the EXTREME regimen. These new treatments included the use of panitumumab (Spectrum phase III), of Pemetrexed, or Cilengitide combined with EXTREME. Other regimens are under investigation (Bevacizumab + chemotherapy, ongoing phase III ECOG or the combination of Sorafenib + paclitaxel-carboplatin). • On the other hand, the combination of cetuximab and taxane has shown interesting signs of efficacy in previous phase II trials. • The combination of Docetaxel - cisplatine (75mg/m^2 / 3 weekly) appeared easier to deliver compared to conventional cisplatin 5FU. • The docetaxel–cisplatin-cetuximab regimen (TPEx) with 4 cycles of chemotherapy followed by maintenance with cetuximab every 2 weeks has been tested in a phase II GORTEC trial (J Guigay, ASCO 2012 and Annals of Oncol 2015) demonstrating a very good efficacy of this combination as first-line treatment in a series of 54 patients with recurrent / metastatic HNSCC. Toxicity was manageable with G-CSF support. This TPEx regimen showed an overall response rate of 53.8% and a median OS of 14 months which are very promising as compared to the EXTREME regimen (response rate 36% and median OS 10.1 months). OS reached 16.7 months for patients who could start maintenance cetuximab therapy. • This TPEx regimen seems more efficient and also more convenient than the standard cisplatin–5FU-cetuximab EXTREME regimen. The TPEx regimen might then be a relevant substitute for EXTREME as first-line treatment in fit patients with recurrent metastatic HNSCC, and justify further direct comparison in the frame of this randomized study.
Center(s) / Countries	• France 52 centers, 186 patients • Germany 15 centers, 120 patients • Spain 14 centers, 110 patients

Objectives	**Primary objective :** to compare in terms of overall survival the TPEx and EXTREME regimens as first line treatment of patients with recurrent / metastatic HNSCC
	Secondary Objectives: The secondary objectives of the trial are to compare the TPEx and EXTREME regimens in terms of: - Objective response rate (complete response (CR) or partial response (PR) according to RECIST 1.1 criteria) at 12 weeks (centralized review) - Best overall response rate (PR or CR or SD with confirmation of CR or PR by a second assessment 6 weeks later) - Progression free survival (PFS) - Time to progression (TTP) - Toxicity (all grades, according to NCI CTCAE V4.0) - Compliance with chemotherapy and cetuximab - Health-related quality of life (QL) assessed by EORTC QLQ-C30 questionnaire Ancillary objectives: - A multinational cost-effectiveness study will be performed alongside the trial to determine the most efficient regimen. - Study of the impact of p16 / HPV tumour status on the efficacy difference of the 2 regimens in patients with oropharyngeal initial tumour
Methodology	Prospective, randomized, controlled, open, multicentric phase II trial
Number of patients	Total number of patients: 540, 270/arm

Inclusion criteria	• Histologically confirmed diagnosis squamous cell carcinoma of head and neck: oral cavity, oropharynx, hypopharynx, larynx (histological confirmation is mandatory at least for initial diagnosis) • Recurrence and/or metastatic disease not suitable for local therapy • At least one measurable lesion (RECIST) by CT or MRI • PS < 2 • Age ≥ 18 years and < 71 years • Clearance of creatinine > 60ml/mn (MDRD) • Haematological function as follows: absolute neutrophil count > 1.5 x 10^9/l, platelet > 100 x 10^9/l, hemoglobin ≥ 9.5 g/dl • Hepatic function as followed: bilirubin ≤ Upper limit of normal (ULN); SGOT/SGPT < 1.5 ULN; AP < 2.5 ULN • Estimated life expectancy > 12 weeks • Informed Consent Form signed • Affiliation to an health insurance • Negative pregnancy test in women of childbearing potential within 14 days prior to treatment initiation (premenopausal or less than 12 months of amenorrhea post-menopause, and who have not undergone surgical sterilization). Both men and women (of childbearing potential) who are sexually active must use adequate contraception, during and for at least 6 months post-treatment.

Exclusion criteria	• Patients with nasopharyngeal cancer, paranasal sinus cancer or unknown primary • Prior systemic chemotherapy for the head and neck carcinoma, except if given as part of a multimodal treatment for locally advanced disease which was completed more than 6 months prior to study entry • Surgery (excluding diagnostic biopsy) or radiotherapy (excluding antalgic radiotherapy out of upper aerodigestive tract) within 6 weeks before study entry • Contra-indication to receive cisplatin • Known dihydropyrimidine dehydrogenase (DPD) deficiency • Administration of prophylactic phenytoin • Recent or planed yellow fever vaccination • Prior dose of cisplatin > 300 mg/m² (a patient who received prior RT + 3 cycles of cisplatin or 3 cycles induction TPF, i.e. total dose of cisplatin ≤ 300 mg/m², for locally advanced primary HN cancer can be included) • Prior anti-EGFR treatment received less than 12 months before enrolment in the trial • Known hypersensitivity reaction to 5FU, cisplatin, carboplatin, docetaxel or cetuximab • Documented or symptomatic brain or leptomeningeal metastasis • Clinically significant cardiovascular disease, e.g. cardiac failure of New York Heart Association classes III-IV, uncontrolled coronary artery disease, cardiomyopathy, uncontrolled arrhythmia, uncontrolled hypertension, or history of myocardial infarction in the last 12 months • Other malignancies within 5 years prior to randomization, with the exception of adequately treated basal skin cancer and carcinoma in situ of the cervix**.** • Active infection (infection requiring IV antibiotics), including active tuberculosis and known and declared human immunodeficiency virus (HIV). • Significant disease which, in the judgment of the investigator, would make the patient inappropriate for entry into the trial. • Any social, personal, medical and/or psychologic factor(s) that could interfere with the observance of the patient to the protocol and/or the follow-up and/or the signature of the informed consent. • Pregnant or breast feeding women • Individual deprived of liberty by judicial or administrative decision, or under any kind of guardianship • Individual with hierarchical relationship to Sponsor or Investigator or clinical trial site staff

Treatment	• **Standard treatment (EXTREME)** **6 cycles every 3 weeks** Cisplatin: 100 mg/m² iv on Day1 ; 5FU: 4000 mg/m² total dose starting on day 1 and during 96h in continuous infusion Cetuximab: 400 mg/m² iv on Day1 (loading dose), then 250 mg/m² iv weekly. If Cisplatin is not tolerated and/or when the total cumulative dose of cisplatin (including prior administration) reaches 600 mg/m², cisplatin has to be replaced by carboplatin, AUC 5, except in the case of bleeding tumour. **Maintenance:** Cetuximab continuation (according to current recommendations (Peyrade et al., 2013)) will begin only if at least disease stabilization is observed at the end of chemotherapy. • **Experimental treatment (TPEx)** **4 cycles every 3 weeks** Cisplatin: 75 mg/m² iv on Day1 Docetaxel: 75 mg/m² iv on Day1 Cetuximab: 400 mg/m² iv on Day1 (loading dose) then 250 mg/m² iv weekly. If Cisplatin is not tolerated, cisplatin has to be replaced by carboplatin, AUC 5, except in the case of bleeding tumour Primary prophylactic administration of GCSF must be administered systematically after each cycle of chemotherapy **Maintenance**: Cetuximab continuation (according to current recommendations (Peyrade et al., 2013)) will begin only if at least disease stabilization is observed at the end of chemotherapy.
Duration of treatments	In both arms, maintenance with cetuximab is only started if at least disease stabilization is observed and will be given until progression or unacceptable toxicity
Primary endpoint	Overall survival (OS)
Statistical analysis	In the EXTREME trial, the median OS was 10.1 months (Vermorken NEJM 2008). In the TPEx trial, the median OS was 14.0 months (Guigay ASCO 2012). This difference corresponds to a hazard ratio (HR) of 0.72. Assuming a two sided type I error of 0.05, observing 374 deaths will provide a 88% power to detect this HR of 0.72. 374 deaths are expected out of a total of 540 patients randomized in the 2 arms within 36 months and a study duration (enrolment + follow-up) of 44 months, assuming that the lost-to-follow-up rate per month is not higher than 0.5% in each treatment arm. A futility analysis will be performed when 163 deaths have been observed. Randomization will assign the 2 arms with a 1:1 ratio by minimization on the following factors: - Performance Status (ECOG 0 versus 1) - Type of disease evolution (loco regional recurrence alone versus metastasis) - Previous cetuximab (yes / no) - Country (France, Germany, Spain)

Duration of the trial & timelines	Duration of inclusion	36 months
	Duration of follow-up	Until patient death or until the target number of deaths (n=374) is achieved. However, each alive patient must be followed at least one year after the end of study treatment, even if the 374 deaths are observed before one-year follow-up of the last randomized patient.
	2014 Q1 Q2-3 Q4 **2015** Q1-Q4 **2016-2017** Q1-Q3 Q4 **2018** **Q1** Q1-Q4 **2019**	Protocol + CRF Submission to competent authorities + Sites Initiation / Enrolment Enrolment Enrolment / Follow-up Enrolment / Follow-up Follow-up Futility interim analysis Follow-up Main analysis of primary end-point when 374 deaths are observed Publication

Trial flowchart is available in section 12.1.

2 Rational of the study

2.1 Recurrent and/or metastatic HNSCC

Worldwide more than 500,000 new cases of Head and Neck Squamous Cell Carcinoma (HNSCC) are projected annually and approximately 77,000 new cases are diagnosed each year in Europe. Alcohol and tobacco are the main etiological factors that are responsible for the frequent comorbidities. When diagnosed early (stage I or II), HNSCC can be cured with surgery and/or radiotherapy, and relapses are uncommon. Unfortunately, up to 75% of HNSCC patients present with locally advanced disease and are mainly treated with radiotherapy and in some cases surgery. Newer strategies such as induction chemotherapy or chemoradiotherapy could provide better survival; however, the 5-year survival rate remains around 30% and 60% of subjects will experience a loco-regional or distant relapse within 2 years of initial treatment. Furthermore, about 10% of patients present with distant metastases at initial diagnosis (1).

Recurrent and/or metastatic HNSCC are then a common clinical situation and although this group of patients has very heterogeneous disease characteristics, they share a dismal prognosis with a median survival time around 6–11 months and a relatively poor quality of life.

Several therapeutic strategies may be used depending on the time and the type of relapse, the previous treatments, and the patient's condition (performance status and comorbidities). Best supportive care remains a possible option in patients who present with severe comorbidities and a poor performance status. Selected patients can also benefit from re-irradiation (external or brachytherapy) or salvage surgery (2-5). However, the majority of these patients receive palliative chemotherapy as it has been shown to lead to increased survival time and better quality of life compared to best supportive care (6, 7).

2.2 Standard treatment in recurrent and/or metastatic HNSCC

The standard chemotherapeutic treatments for recurrent and/or metastatic HNSCC include several drugs such as methotrexate, bleomycin, 5-fluorouracil (5-FU), and platinum compounds. New agents such as taxanes have shown promising results in phase II studies (8-13). However, these results have not been confirmed in phase III studies (14, 15). Cisplatin is the most widely used drug for the treatment of recurrent and/or metastatic HNSCC and, as such, is considered the standard treatment in this indication. Cisplatin treatment for recurrent and/or metastatic HNSCC has been shown to have a median objective response rate as a single agent of 28% (range 14–41%) and a well-defined safety profile (16). The combination of cisplatin and 5-FU has shown higher response rates than cisplatin alone, and several phase III studies have been performed to investigate whether this translates into improved survival. Jacobs (17) compared cisplatin or 5-FU as monotherapy to the cisplatin + 5-FU combination in 249 subjects with recurrent and/or metastatic HNSCC and observed a similar median survival time of 5.7 months for the 3 arms.

However, the objective response rates for the 3 arms were significantly different (cisplatin 17%, 5-FU 13%, cisplatin + 5-FU combination 32%). Forastiere et al (18) reported a phase III study comparing cisplatin + 5-FU to carboplatin + 5-FU and to methotrexate alone, in 277 subjects with recurrent and/or metastatic HNSCC. Although the overall response rate was significantly better for the cisplatin + 5-FU arm (32%, 21% and 10% respectively), the median response duration and survival time was similar for all 3 groups.

Similarly, the European Organization for Research on Treatment of Cancer (EORTC) group initiated a phase III study in 282 subjects with recurrent and/or metastatic HNSCC comparing cisplatin alone to the cisplatin + 5-FU combination and a third combination arm (cisplatin + bleomycin + methotrexate + vincristine) (19). Although the objective response rate was significantly superior for the combination arms (31% for cisplatin + 5-FU, 34% for cisplatin + bleomycin + methotrexate + vincristine, and 15% for cisplatin alone), no significant difference in overall survival was observed between the 3 treatment groups (29 weeks).

Similarly, the cisplatin + paclitaxel combination has been compared to cisplatin + 5-FU in 194 subjects with recurrent and/or metastatic HNSCC (15). There were no significant differences in terms of response rate (28% and 22%, respectively), median survival time (9 and 8 months, respectively), or 1-year survival rates (30% and 41%, respectively). Overall, all published randomized trials suggest that cisplatin and 5-FU in combination produced higher response rates compared to single agents and most of the other combinations, but with higher hematological and non-hematological toxicities. Regarding survival time, the combination of cisplatin plus 5-FU produced a small but questionable improvement over monotherapy with a median survival of 6 to 8 months. Carboplatin + 5-FU containing regimens are also frequently used because of their good safety profile (lower renal, otologic, neurologic, and gastrointestinal toxicity than cisplatin) (18, 20). Response rates and survival are not statistically different from cisplatin-based regimens (18).

The EMR 62202-008 phase I/II study investigated the tolerance and efficacy of the cisplatin or carboplatin AUC 5 + 5-FU regimen in combination with cetuximab as first-line therapy for recurrent and/or metastatic HNSCC (21). The overall and disease response rate was 33.3% and 59.3% in the cisplatin arm, versus 38.5% and 80.8%, respectively. Median overall survival time was lower with carboplatin (8.5 versus 10.6 months). The results demonstrated that full doses of cisplatin or carboplatin and 5-FU can be combined with the recommended dose of cetuximab with only a minimal increase in grade 3 toxicity and promising improvements in efficacy.

The carboplatin- and 5-FU combination has also been confirmed by the EXTREME (Erbitux in First-Line Treatment of Recurrent or Metastatic Head & Neck Cancer) regimen (22). Thirty-three to thirty-nine percent of patients have received carboplatin instead of cisplatin. Carboplatin is therefore approved for the treatment of HNSCC in several European countries.

Thus, a major improvement has been observed by adding cetuximab to platinum and 5FU according to the EXTREME regimen. Cetuximab was added to platinum-5FU during the 6 cycles of treatment and continued as maintenance in patients with stable disease. Cetuximab, a

chimerized antibody of the IgG1 subclass, was originally derived from a mouse myeloma cell-line resulting in chimerization of the murine monoclonal antibody M225 developed at the University of California, San Diego (23). Cetuximab was constructed by cloning the heavy and light chains of M225 and adapting them for expression together with the constant regions of the human kappa light chain and human gamma 1 heavy chain. The chimerization process resulted in an antibody with binding affinity to EGFR greater than the natural ligand, EGF (24). Cetuximab blocks binding of EGF and TGFα to EGFR and inhibits ligand-induced activation of this tyrosine kinase receptor. Cetuximab also stimulates EGFR internalization, in effect, removing the receptor from the cell surface and thereby preventing interaction with its ligand (25). The safety profile of cetuximab has proven to be acceptable in a large number of clinical trials, and approval was obtained in different types of cancers, including head and neck.
Over the past 40 years, the EXTREME has been the only regimen able to improve survival of patients with recurrent metastatic HNSCC, as compared to conventional chemotherapy. This regimen was indeed tested in a large randomized study and compared to 5FU and platinum (22). The overall response rate was 36%, the median progression free survival (PFS) 5.6 months and the median OS 10.1 months versus 20%, 3.3 months and 7.4 months respectively for the conventional arm. The PFS (5.8 months) and OS (10.6 months) were slightly better for the patients having received cisplatin (instead of carboplatin). The EXTREME regimen is currently considered as the standard of care in first line recurrent metastatic HNSCC, with use of carboplatin for patients not able to receive cisplatin.
Other new therapeutic approaches have been tested more recently to challenge this standard platinum-5FU-cetuximab EXTREME regimen, but failed to demonstrate significant improvement. These new treatments included the use of panitumumab combined with 5FU and platinum (phase III), Pemetrexed cisplatin based regimen, or Cilengitide combined with EXTREME. Results coming from phase II studies testing new combinations including mToR inhibitors, bevacizumab combined with chemotherapy (ongoing phase III ECOG) or the combination of sorafenib + paclitaxel-carboplatin need to be confirmed.

On the other hand, the combination of cetuximab and taxane has shown interesting signs of anti-tumour efficacy in phase II trials **(**26-28**)**, and Docetaxel combined with cisplatin (75mg/m² / 3 weeks) appeared easier to deliver compared to conventional combination of cisplatin and 5FU. This led to the design of a new regimen including Taxotere-Cisplatin and cetuximab, so called the TPEx (Taxotere-Platinum-Erbitux) regimen. This TPEx regimen of 4 cycles of Docetaxel–cisplatin-cetuximab followed by maintenance with cetuximab every 2 weeks has been tested in a phase II GORTEC trial (29) demonstrating a very good efficacy of this combination as first-line treatment in a series of 54 patients with recurrent / metastatic HNSCC. Toxicity was manageable with G-CSF support. This TPEx regimen showed an overall response rate of 53.8% and a median OS of 14 months which are very promising as compared to the EXTREME regimen (response rate 36% and median OS 10.1 months). OS reached 16.7 months for patients who could start maintenance cetuximab therapy. This TPEx regimen might be a relevant substitute for

EXTREME as first-line treatment in fit patients with recurrent metastatic HNSCC. These considerations justify further direct comparison in the frame of this randomized study.

3 Benefit/risk ratio

Studies EMR 62202-008 and EMR 62202-002 showed that therapeutic doses of cisplatin can be safely combined with the recommended dose of cetuximab. In the Phase III trial EMR 62202-002, first-line treatment with the combination of cisplatin, 5-FU and cetuximab (EXTREME regimen) resulted in a significant prolongation of PFS and median overall survival time in patients with locally recurrent/metastatic HNSCC, as compared to conventional chemotherapy, and creating EXTREME as the new standard of care for this category of patients.

Indeed, the EXTREME regimen has a good benefit risk ratio which has been previously evaluated and led to an approval (EMA and FDA) and the generalisation of the use of this regimen as standard treatment in first line treatment in recurrent / metastatic HNSCC patients.
The preclinical, clinical-pharmacological, and current clinical data on cetuximab indicate that the benefit/risk ratio is considered positive and that a combination of cetuximab with cisplatin and docetaxel (TPEx regimen) might be effective in patients with HNSCC potentially resulting in a prolongation of the progression-free survival time.
The benefit/risk relationship has been carefully considered in the preparation of this study protocol. A prior Phase II trial of the TPEx regimen has been designed to guarantee optimal patient care.
From our previous experience, the TPEx regimen seems more efficient (overall survival) and also more convenient than the standard cisplatin–5FU-cetuximab EXTREME regimen (4 cycles of chemotherapy instead of 6 cycles and no i.v. continuous infusion). In addition, the toxicity / efficacy profile also seems favourable as suggested by the excellent dose intensity achieved and the high rate of patients (78%) who were able to start maintenance therapy.
Taking together all these considerations, the TPEx regimen might be a good substitute for EXTREME as first-line treatment in patients with recurrent metastatic HNSCC, and it is justified and necessary to perform a direct comparison in a randomized trial to further test this hypothesis.
The trial will be discontinued in case of new findings indicating that a relevant deterioration of the risk-benefit relationship is probable. Therefore, potential risks of the combination treatment will be recognized immediately allowing appropriate measures to be taken. This trial will be monitored by an Independent Data and Safety Monitoring Committee and will be conducted in compliance with the protocol, International Conference on Harmonisation (ICH) Note for Guidance on Good Clinical Practice (GCP) (ICH, Topic E6, 1996) and applicable regulatory requirements.

4 Study objectives

4.1 Primary objective

The primary objective is to compare in terms of overall survival the TPEx and EXTREME regimens as first line treatment of patients with recurrent / metastatic HNSCC

4.2 Secondary objectives

The secondary objectives of the trial are to compare the TPEX and EXTREME regimens in terms of:

- Objective response rate (complete response (CR) or partial response (PR) according to RECIST 1.1 criteria) at 12 weeks (centralized review)
- Best overall response rate (PR or CR or SD with confirmation of CR or PR by a second assessment 6 weeks later)
- Progression free survival (PFS)
- Time to progression (TTP)
- Toxicity (all grades, according to NCI-CTCAE V4.0)
- Compliance with chemotherapy and cetuximab
- Health related quality of life (QL) assessed by the EORTC QLQ-C30 questionnaire

Ancillary studies:

- A multinational cost-effectiveness study will be performed alongside the trial to determine the most efficient regimen
- Study of the impact of p16 / HPV tumour status on the efficacy difference of the 2 regimens in patients with oropharyngeal initial tumour

5 Investigational plan

5.1 Overall study design and plan

This open-label, randomized, controlled, multicenter phase II study will randomize 540 patients with recurrent and/or metastatic HNSCC who had not received previous chemotherapy for this setting (first line treatment).

Approximately 80 study centers in Europe (France, Germany, Spain) will participate.

Eligible patients will have a diagnosis of recurrent and/or metastatic squamous cell carcinoma of the head and neck.

Randomization will assign the 2 treatment arms with a 1:1 ratio, by minimization on the following factors:

- Performance status (ECOG, *Appendix 3*): 0 vs 1

- Type of evolution: locoregional progression alone vs metastatic evolution with or without locoregional progression
- Previous treatment by cetuximab (yes/no)
- Country (France, Germany, Spain)

5.2 Treatment groups

Group A: Combination of cetuximab plus cisplatin and 5-FU: **EXTREME**

Group B: Combination of cetuximab plus cisplatin and docetaxel: **TPEx**

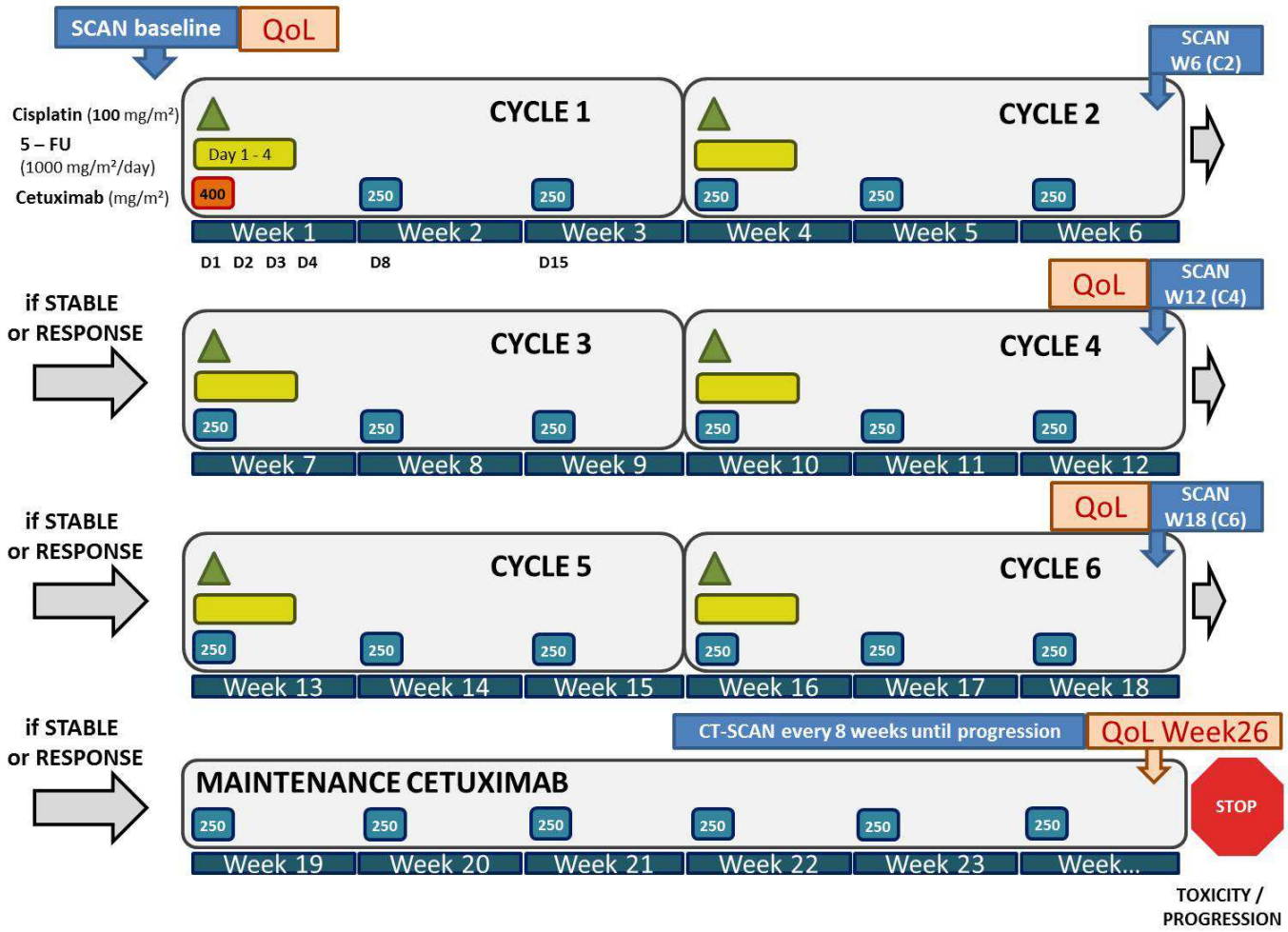
5.2.1 Group A: STANDARD TREATMENT: EXTREME

6 cycles every 3 weeks of:

Cisplatin: 100 mg/m² iv on Day1
5FU: 4000 mg/m² total dose starting on day 1 and during 96h in continuous infusion
Cetuximab: 400 mg/m² iv on Day1 (loading dose), then 250 mg/m² iv weekly.

If cisplatin is not tolerated and/or when the total cumulative dose of cisplatin (including prior administration) reaches 600 mg/m², cisplatin has to be replaced by carboplatin, AUC 5 (but not exceeding 750 mg), except in the case of bleeding tumour.

Maintenance cetuximab continuation (according to current recommendations (Peyrade et al.,



2013 (30)) will begin only if at least disease stabilization is observed, at the end of chemotherapy, and will be continued until PD or unacceptable toxicity.

Fig. 1. EXTREME Scheme

Duration of treatment for patients in the EXTREME arm**:** Patients with absence of progression disease (PD) and unacceptable toxicity will receive a maximum of 6 cycles of chemotherapy plus cetuximab. Patients who demonstrate at least stable disease (SD), at the end of chemotherapy, will continue treatment with cetuximab until PD or occurrence of unacceptable toxicity. A minimum number of 2 cycles of chemotherapy must have been received in order to start cetuximab maintenance. Patients with unacceptable toxicity due to one of the study drugs will receive the tolerated drug(s) until PD or up to a maximum of 6 cycles of chemotherapy. Study treatment will be discontinued earlier in case of PD and/or unacceptable toxicity. If treatment with cetuximab is delayed because of related toxicity, the 21-day rhythm of chemotherapy is retained. Cetuximab can be delayed for a maximum of 14 days. If treatment with chemotherapy is delayed because of related toxicity, the weekly rhythm of cetuximab is retained. Chemotherapy can be delayed for a maximum of 14 days.

5.2.2 Group B: EXPERIMENTAL TREATMENT: TPEx

4 cycles every 3 weeks of:

Cisplatin: 75 mg/m² iv on Day1

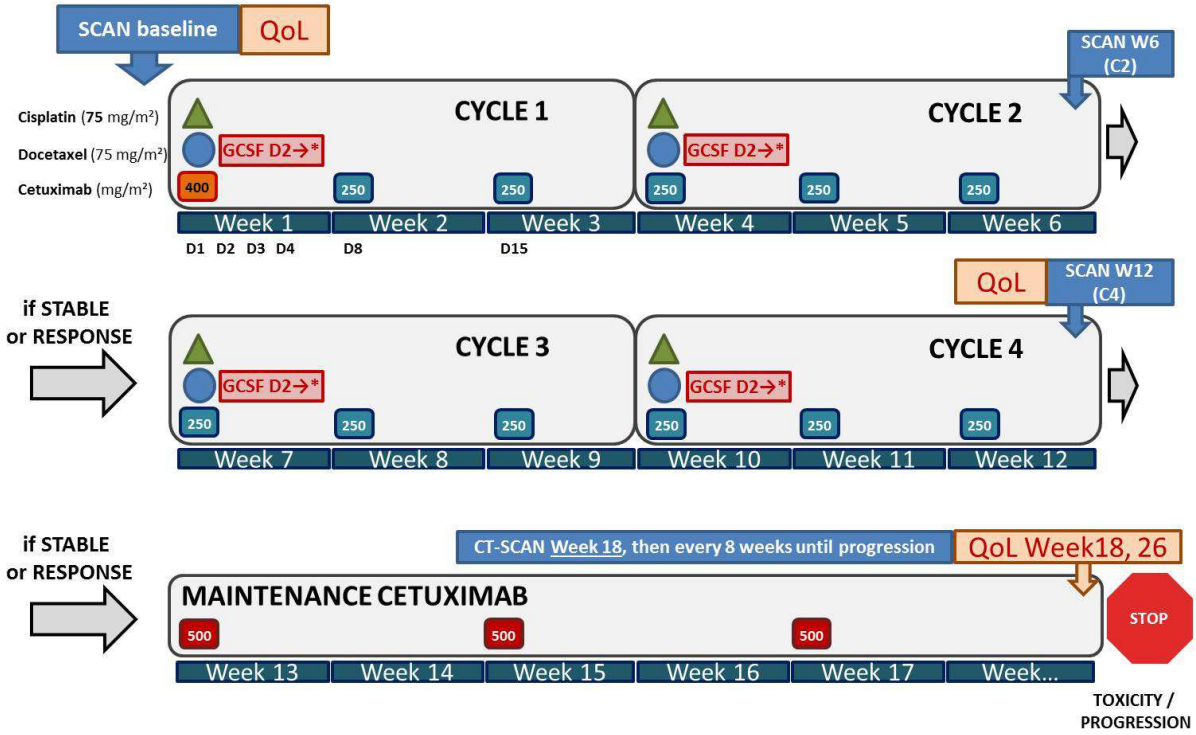
Docetaxel: 75 mg/m² iv on Day1

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

If cisplatin is not tolerated, cisplatin is replaced by carboplatin, AUC 5 (but not exceeding 750 mg), except in the case of bleeding tumour.

Primary prophylactic administration of GCSF must be administered systematically after each cycle of chemotherapy (see concomitant medication section).

Maintenance cetuximab: cetuximab continuation (according to current recommendations (Peyrade et al., 2013)) will begin only if at least disease stabilization is observed at the end of chemotherapy.



* GCSF until normalization of ANC (>1.5 10^9/L), usually during 5 days

Fig. 2. TPEx Scheme

Duration of treatment for patients in TPEx group: Patients with absence of PD and unacceptable toxicity will receive up to a maximum of 4 cycles of chemotherapy. Patients who demonstrate at least stable disease (SD) will continue treatment with cetuximab until PD or occurrence of unacceptable toxicity. A minimum number of 2 cycles of chemotherapy must have been received in order to start cetuximab maintenance. Patients with unacceptable toxicity due to one of the study drugs will receive the tolerated drug(s) until PD or up to a maximum of 4 cycles of chemotherapy. Study treatment will be discontinued earlier in case of PD and for occurrence of unacceptable toxicity. If treatment with cetuximab is delayed because of related toxicity, the 21-day rhythm of chemotherapy is retained. Cetuximab can be delayed for a maximum of 14 days. If treatment with chemotherapy is delayed because of related toxicity, the weekly rhythm of cetuximab is retained. Chemotherapy can be delayed for a maximum of 14 days.

5.3 Follow up during treatment

The following follow up evaluations will be performed weekly during chemotherapy treatment and every two weeks during maintenance cetuximab treatment: clinical examination (PS, weight, physical examination), AE and concomitant medications recording, and biologic exams (hematology and blood chemistry).

Evaluation of lesions should be performed at baseline, every 6 weeks after treatment start until Week18, and then every 8 weeks until PD **in both arms regardless of number of performed chemotherapy cycles and even in case of chemotherapy administration delay**, in order to assure the same follow-up of the patients in both arms (although the number of cycles between them is different):

- at Week 6 (corresponding to the end of cycle 2 in both arms),
- at Week 12 (corresponding to the end of and cycle 4 in both arms), accompanied by EORTC QLQ-C30 and EQ-5D Quality of Life assessments
- at Week 18 (corresponding to the end of cycle 6 in the EXTREME arm and 6-weeks of the maintenance period in the TPEx arm), accompanied by EORTC QLQ-C30 and EQ-5D Quality of Life assessments
- After Week 18, evaluation of lesions should be performed every 8 weeks until PD in both arms. EORTC QLQ-C30 and EQ-5D Quality of Life assessments must be performed at Weeks 18 and 26 in both arms then every 8 weeks for EQ5D only.
- A CT scan or MRI should be performed at the end of treatment/withdrawal visit (within 7 days) if there was no PD documented by imaging at the previous evaluation. Imaging exams should be performed whenever disease progression is suspected.

5.4 Follow-up after treatment

After the end of maintenance or chemotherapy (if maintenance could not be started), follow-up evaluations will be performed in all patients every 8 weeks. If a patient is withdrawn from study treatment (Section 8.1), EORTC QLQ-C30 and EQ-5D Quality of Life assessments must be performed at Week 12, Week 18 and Week 26, then every 8 weeks for EQ-5D only. Patients will be followed until death or until the target number of deaths (n=374) is reached. However, each alive patient must be followed at least one year after the end of study treatment, even if the 374 deaths are observed before one-year follow-up of the last randomized patient.

6 Selection of the study population

6.1 Inclusion criteria

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

- Histologically confirmed diagnosis squamous cell carcinoma of head and neck: oral cavity, oropharynx, hypopharynx, larynx (histological confirmation is mandatory at least for initial diagnosis)
- Recurrence and/or metastatic disease not suitable for local therapy
- At least one measurable lesion (RECIST) by CT or MRI
- PS < 2
- Age ≥ 18 years and < 71 years
- Clearance of creatinine > 60ml/mn MDRD (Modification of Diet in Renal Disease (appendix 4)
- Haematological function as follows: absolute neutrophil count > 1.5 x 10^9/l, platelet > 100 x 10^9/l, hemoglobin ≥ 9.5 g/dl
- Hepatic function as followed: bilirubin ≤ Upper limit of normal (ULN); SGOT/SGPT < 1.5 ULN; AP < 2.5 ULN
- Estimated life expectancy > 12 weeks.
- Informed Consent form signed
- Affiliation to a health insurance
- Negative pregnancy test in women of childbearing potential within 14 days prior to treatment initiation (premenopausal or less than 12 months of amenorrhea post-menopause, and who have not undergone surgical sterilization). Both men and women (of childbearing potential) who are sexually active must use adequate contraception, during and for at least 6 months post-treatment.

6.2 Exclusion criteria

Patients are not eligible for this study, if they fulfill 1 or more of the following exclusion criteria:

- Patients with nasopharyngeal cancer, paranasal sinus cancer or unknown primary
- Prior systemic chemotherapy for the head and neck carcinoma, except if given as part of a multimodal treatment for locally advanced disease which was completed more than 6 months prior to study entry
- Surgery (excluding diagnostic biopsy) or radiotherapy (excluding antalgic radiotherapy out of upper aerodigestive tract) within 6 weeks before study entry.
- Contra-indication to receive cisplatin.
- Known dihydropyrimidine dehydrogenase (DPD) deficiency
- Administration of prophylactic phenytoin
- Recent or planned yellow fever vaccination

- Prior dose of cisplatin for locally advanced primary HN cancer > 300mg/m² (a patient who received prior RT + 3 cycles of cisplatin or 3 cycles induction TPF, i.e. total dose of cisplatin ≤ 300 mg/m², for locally advanced primary HN cancer can be included)
- Prior anti-EGFR treatment received less than 12 months before enrolment in the study
- Known hypersensitivity reaction to 5FU, cisplatin, carboplatin, docetaxel or cetuximab
- Documented or symptomatic brain or leptomeningeal metastasis
- Clinically significant cardiovascular disease, e.g. cardiac failure of New York Heart Association classes III-IV, uncontrolled coronary artery disease, cardiomyopathy, uncontrolled arrhythmia, uncontrolled hypertension, or history of myocardial infarction in the last 12 months
- Other malignancies within 5 years prior to randomization, with the exception of adequately treated basal skin cancer and carcinoma in situ of the cervix**.**
- Active infection (infection requiring IV antibiotics), including active tuberculosis and known and declared human immunodeficiency virus (HIV).
- Significant disease which, in the judgment of the investigator, would make the patient inappropriate for entry into the trial
- Any social, personal, medical and/or psychologic factor(s) that could interfere with the observance of the patient to the protocol and/or the follow-up and/or the signature of the informed consent.
- Pregnant or breast feeding women
- Individual deprived of liberty by judicial or administrative decision, or under any kind of guardianship
- Individual with hierarchical relationship to Sponsor or Investigator or clinical trial site staff

7 Randomization

Randomization of patients will occur following initial work-up and before start of treatment. Randomization will be done using TenAlea software (NKI, Amsterdam) via internet and the two arms will be assigned with a 1:1 ratio, by minimization. To avoid deterministic minimisation and assure allocation concealment, the treatment which minimises the imbalance will be assigned with a probability of 0.80. The minimization factors are:

- Performance status (ECOG): 0 vs 1
- Type of evolution: locoregional recurrence alone vs metastatic evolution with or without locoregional recurrence
- Previous treatment with cetuximab (yes/no)
- Country (France, Germany, Spain)

The definition of the randomization parameters will be implemented by the Biostatistic and Epidemiology Unit of Gustave Roussy, France.

The investigators and delegated site staff can perform randomisation directly by internet (username and password will be given to the investigators) or by faxing the randomization form to the Biostatistic and Epidemiology Unit of Gustave Roussy, France.

The system will check the eligibility criteria and will register the minimization factors. If the patient is eligible, the randomisation by minimization will be done. A registration number and randomization assignment (TPEx or EXTREME) will be sent by return by email to the physician and to the pharmacist of the center.

8 Removal of patients from the study or from the study treatment and study discontinuation

8.1 Patient discontinuation

Study discontinuation:

Patients are free to discontinue the study at any time without giving any reason. The patient must be withdrawn from the entire study in case of withdrawal of consent to participate in the study and withdrawal of consent to data collection.

Treatment discontinuation:

The patient must discontinue the study treatment in the event of any of the following but must be followed for progression, quality of life, survival:

- Withdrawal of the patient's consent to receive study treatment without withdrawal of consent to data collection
- Occurrence of a clinical event that affects patient's safety, if discontinuation is considered necessary by the investigator and/or by the GORTEC
- Occurrence of AEs, if discontinuation of study drug is desired or considered necessary by the investigator and/or the patient
- Unacceptable toxicity attributed to treatment
- Occurrence of pregnancy
- Occurrence of PD

Additionally, cetuximab must be discontinued in case of:

- Grade 3 or 4 allergic/hypersensitivity (infusion related) reaction to cetuximab
- Occurrence of a second allergic/hypersensitivity reaction, with a slower infusion rate
- Occurrence of grade 3 skin toxicity despite appropriate dose reductions
- Occurrence of grade 4 skin toxicity

In case of premature discontinuation of therapy in a patient for any reason, the patient should continue to attend the scheduled assessments.

In case of withdrawal from all treatments due to occurrence of unacceptable toxicity, the patient will remain under the supervision of the investigator until the toxicities have resolved and /or stabilized and will remain in the study.

If a patient has failed to attend scheduled assessments in the study, the investigator must determine the reasons and the circumstances as completely and accurately as possible.

After the end of the study treatment, regardless of the reason for discontinuation, the follow-up visit schedule must be followed in all patients until death or until the target number of deaths (n=374) is achieved. However, each alive patient must be followed at least one year after the end of study treatment, even if the 374 deaths are observed before one-year follow-up of the last randomized patient (except for those patients who have withdrawn their consent for data collection).

8.2 Study discontinuation

Study discontinuation is at the discretion of the sponsor in any of the following events:

– Medical reasons :

  - Clinically significant cardiovascular disease
  - Active infection (infection requiring IV antibiotics), including active tuberculosis and known and declared human immunodeficiency virus (HIV).
  - Unexpected high rates of Serious Adverse Drug Reaction (SADR) or toxic deaths in the experimental arm (TPEx)

- Financial or ethical reasons affecting the continued performance of the study
- Difficulties in the recruitment of patients

Safety data from the study will be reviewed by the GORTEC and also by the independent DSMC on an ongoing basis in order to ensure that it is appropriate to continue the study.

9 Treatments

9.1 Treatments administered

Cetuximab, cisplatin, carboplatin, docetaxel and 5-FU will all be administered as IV infusions. All study treatments are commercially available and will be provided by the Investigation site, except for docetaxel that will be provided by the sponsor GORTEC (via a third-party partner).

9.1.1 Cetuximab

9.1.1.1 General guidelines for all cetuximab administrations

1. Before the first cetuximab administration, appropriate antiallergic prophylaxis with a corticosteroid (at a dose equivalent to ≥ 8mg dexamethasone intravenous or oral) and an appropriate antihistamine (standard H1 blocker, intravenous or oral, at standard dosage) is mandatory. The same pretreatment is also recommended before all subsequent infusions of cetuximab.

2. Infusions will be given via an infusion pump or gravity drip. Cetuximab must not be mixed with any other substance and therefore requires a separate infusion line. When other IV administration is required concomitant to cetuximab administration (e.g. hydration) a second line must be used.

3. Infusions will be given via an infusion pump or gravity drip, whereby the infusion rate is not to exceed 5 mg/min (1 mL/min) for the first 400 mg/m² infusion and 10 mg/min (2 mL/min) for all subsequent 250 mg/m² infusions. Saline 0.9% solution is used to flush the line at the end of infusion.

4. A physician must be present during the first administration of cetuximab (i.e. initial dose) and resuscitation equipment and agents to treat anaphylactic reactions must always be at hand. Vital signs are checked pre-, mid-, post- and 1 hour post-infusion. A close monitoring of patients, particularly during the first administration for at least two hours, is required. The patient is observed over 1 hour post-infusion.

5. The cetuximab infusion must end 1 hour before the start of chemotherapy. Cisplatin or carboplatin should be administered after a 1 hour observation period following the cetuximab infusion.

6. The dose and volume of cetuximab to be infused are dependent upon the patient's body surface area (BSA). The maximum BSA accepted for cetuximab dose calculation is $2m^2$.

9.1.1.2 Administration of cetuximab during chemotherapy

The dosage for cetuximab is as follows:

I. The **initial dose** (first infusion) is 400 mg/m² (80 mL/m²) should be administered slowly and the speed must not exceed 5 mg/min whilst all vital signs are closely monitored for at least two hours (maximum infusion rate 5 mg/min = 1 mL/min). If during the first infusion, an infusion-related reaction occurs within the first 15 minutes, the infusion should be stopped. A careful benefit/risk assessment should be undertaken including consideration whether the patient may have preformed IgE antibodies before a subsequent infusion is given.

II. The subsequent **weekly dose** (all further infusions) is 250 mg/m² (50 mL/m²) and is administered with maximum infusion rate of 10 mg/min = 2 mL/min.

Documentation of the actual dose, date, infusion start time and infusion end time is mandatory.

9.1.1.3 Administration of maintenance cetuximab

Cetuximab is administered by IV infusion at a dose of 250 mg/m^2 weekly in EXTREME arm or at a dose of a 500 mg/m^2 every 2 weeks in TPEx arm. The infusion rate is not to exceed 10 mg/min (2 mL/min). Maintenance with Cetuximab is given until progression, unacceptable AEs or other reason necessitating withdrawal.

9.1.2 Cisplatin

Cisplatin is a commercially available antineoplastic agent for the treatment of patients with HNSCC.

9.1.2.1 Administration of cisplatin in the EXTREME arm

Cisplatin will be administered as a dose of 100 mg/m² (infusion duration 1mg/min, at least 120 minutes) on the first day of each treatment cycle. Administration of cisplatin will be repeated every 21 days (one cycle) **for a maximum of 6 cycles**. The number of cycles has to take into account if the patient received cisplatin during initial previous treatment for locally advanced disease, and the maximal cumulative total dose can be only 600 mg/m². After 600 mg/m², it is mandatory to replace Cisplatin by Carboplatin AUC 5 (but not exceeding 750 mg total dose of carboplatin per cycle), except in the case of bleeding tumour.

Cisplatin can be administered according to procedures in common use at the study centers. Nevertheless, the drug administration sequence, 1 mg/min maximum infusion rate and minimum 120 min infusion duration must be strictly respected. The maximum body surface area accepted for dose calculation is 2m^2.

The following procedure is given as example:

Antiemetic premedication which includes a 5-HT3 antagonist prior and after cisplatin administration.

Hydration and mannitol diuresis (IV bolus of 12.5 g of mannitol just before cisplatin administration and IV infusion of 25 g of mannitol in 1 L of fluid over 4 hours starting after cisplatin infusion)

In both cases the sequence of administration will be as follows:

> **t = 0 hours to t = 3 hours**: IV pre-hydration with 1 to 2 L of fluids.
>
> **t = 3 hours to t = 6 hours**: cisplatin 100 mg/m² diluted in a minimum of 250 mL normal saline.
>
> **Post t = 6**: post-hydration with 2 to 4 additional liters of specified fluid per IV or oral route over 24 hours.

There must be at least 1 hour between the end of the cetuximab infusion and the start of the cisplatin infusion. IV pre-hydration can be performed concomitant to cetuximab administration

but a separate line must be used. Cisplatin infusions will be given via an infusion pump or gravity drip.

9.1.2.2 Administration of cisplatin in the TPEx arm

Cisplatin will be administered after docetaxel infusion, at a dose of 75 mg/m² (infusion duration 1mg/min, at least 120 minutes) on the first day of each treatment cycle. Administration of cisplatin will be repeated every 21 days (one cycle) **for a maximum of 4 cycles**.

Cisplatin can be administered according to procedures in common use at the study centers or according to the procedure given previously as an example. Nevertheless, the drug administration sequence, 1 mg/min maximum infusion rate and minimum 120 min infusion duration must be strictly respected. The maximum body surface area accepted for dose calculation is $2m^2$.

9.1.3 Carboplatin

Carboplatin is a commercially available antineoplastic agent for the treatment of patients with HNSCC.

Carboplatin is used when Cisplatin is not tolerated or when the total cumulative dose of cisplatin reaches 600 mg/m². Carboplatin is contra-indicated in patients with bleeding tumours.

Carboplatin will be administered intravenously as a dose of AUC 5 (infusion duration 60 minutes) on the first day of each treatment cycle. The dose of carboplatin will be calculated considering the patient's renal function as described by the glomerular filtration rate using the Calvert formula or the Chatelut formula, given that the target AUC is 5 (appendix 5). The dose should not exceed 750 mg per cycle due to current recommendations (http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm228974.htm). There must be at least 1 hour between the end of cetuximab infusion and the start of the carboplatin infusion. Carboplatin infusions will be given via an infusion pump or gravity drip.

9.1.4 Fluorouracil

5-FU is a commercially available cytotoxic agent (pyrimidine analogue) used for the treatment of several cancers.

5-FU will be administered as a dose of 1000 mg/m^2/day as a continuous IV infusion from day 1 to day 4 of each treatment cycle. Administration of 5-FU is to start upon completion of cisplatin or carboplatin administration and may be performed via the same infusion line. 5-FU infusions will be given via an infusion pump or gravity drip. There must be at least 1 hour between the end of cetuximab infusion and the start of the 5-FU infusion. The maximum body surface area accepted for dose calculation is $2m^2$.

9.1.5 Docetaxel

Docetaxel is a commercially available antineoplastic agent for the treatment of patients with locally advanced HNSCC as part of induction chemotherapy.

In this study in R/M HNSCC patients, it is considered as the investigational product, and it will be provided by the sponsor GORTEC. A company will be in charge of preparation and delivery of Docetaxel to the study centers. The drug supply procedures are specified in a separate document.

Docetaxel will be administered intravenously at day 1, one hour after Cetuximab infusion and before platin infusion, at a dose of 75 mg/m² (infusion duration 60 minutes) every 21 days for 4 cycles. Each cycle of chemotherapy will last 21 days. The maximum body surface area accepted for dose calculation is $2m^2$.

A premedication will be given to all patients in order to prevent the onset of hypersensitivity reaction (HSR) and to reduce and /or delay the occurrence of skin toxicity and fluid retention related to docetaxel. Premedication with corticosteroids (for example dexamethasone as a dose of 16 mg by day *ie* 8 mg twice a day) is recommended during 3 days, starting the day before the infusion of docetaxel. At day 1, as a premedication is administered before the cetuximab infusion, it is not necessary to deliver again just before the infusion of docetaxel.

9.2 Premedications and concomitant medication for EXTREME and TPEx regimens

All premedications and concomitant medications necessary for EXTREME and TPEx regimens are commercially available and will be provided by Investigation sites.

9.2.1 Medications allowed

Treatments considered by the investigator as necessary for the good health of the patient may be administered and will be registered in the CRF.

9.2.2 Premedication with cetuximab

Before the first cetuximab administration, appropriate anti-allergic prophylaxis with both a corticosteroid and an appropriate antihistamine is mandatory (see details section above). This premedication is also recommended before all subsequent infusions of cetuximab.

9.2.3 Premedications and adjuvant treatments with chemotherapy

Antiemetic premedication which includes a 5-HT3 antagonist is mandatory prior and after chemotherapy, adapted to each patient, as well as mouthwashes and other symptomatic treatments (nutrition, analgesics, helmet, cooled gloves,..).

Premedication with oral and IV corticosteroids is recommended to prevent hypersensitivity reaction and toxicity of docetaxel (see section above).

Hydration is mandatory with administration of cisplatin (see section 9.1.2)

9.2.4 Recombinant Granulocyte Colony Stimulating Factor (GCSF)

Primary prophylactic administration of GCSF will be administered **systematically** after each cycle of chemotherapy **in TPEX Arm.** A subcutaneous administration of lenograstim is recommended after each cycle as a dose of 150 micrograms/m²/day (34 MUI if body surface < 1.80 m²). Dose equivalent of filgrastim is 5 micrograms/kg/day. To start 24 to 72 h after the completion of chemotherapy, until normalization of ANC (>1.5 10^9/L), usually during 5 days.

GCSF will be provided by Investigation sites who are responsible for assuring its availability on site during the entire study. In case of difficulties in obtaining GCSF by the Investigation site, the site should contact the Sponsor GORTEC.

No primary prophylactic administration of GCSF is recommended **in EXTREME** arm.

9.2.5 Treatments not allowed

No other anticancer treatment such as chemotherapy, hormone therapy, immunotherapy or molecular targeted therapies is allowed during the study treatment. However antalgic radiotherapy on bone metastases out of target lesions is allowed.

Yellow fever vaccine is strictly contraindicated for patients treated with cisplatin because of the risk of fatal systemic vaccinal disease. In view of the risk of generalized illness, it is advisable to use an inactive vaccine if available.

Vaccination with any weakened live vaccine should be avoided in immunocompromised patients treated with cisplatin and 5FU.

Brivudin, sorivudin and analogues are not allowed in patients treated with 5FU.

9.2.6 Interactions with other medications

9.2.6.1 Interactions with cetuximab

No interaction with other medication has been demonstrated at now.

9.2.6.2 Interactions with docetaxel

In vitro studies have shown that docetaxel metabolism can be modified by concomitant administration of compounds which are inducer, inhibitor of, or metabolized by, cytochrome P450-3A (ciclosporin, terfenadin, ketoconazole, erythromycin, troleandomycin).

9.3 Dose modifications and treatment alterations for Cetuximab

9.3.1 Cetuximab dose modification/treatment alterations for infusion reactions

Severe infusion-related reactions have been reported in patients treated with cetuximab, in some cases with fatal outcome. Some of these reactions may be anaphylactic or anaphylactoid in nature or represent a cytokine release syndrome (CRS). Symptoms usually occurred during the first infusion and up to 1 hour after the end of infusion, but may have occurred after several hours or with subsequent infusions. It is recommended to warn patients of the possibility of such a late onset and instruct them to contact their physician if such symptoms of an infusion-related reaction occur. Occurrence of a severe infusion-related reaction requires immediate and permanent discontinuation of cetuximab therapy and may necessitate emergency treatment. Special attention is recommended for patients with pre-existing cardiopulmonary disease.

Anaphylactic reactions may occur as early as within a few minutes of the first infusion e.g. due to preformed IgE antibodies cross-reacting with cetuximab. These reactions are commonly associated with bronchospasm and urticaria. They can occur despite the use of premedication. The risk for anaphylactic reactions is much increased in patients with a history of allergy to red meat or tick bites or positive results of tests for IgE antibodies against cetuximab (α-1-3-galactose). In these patients cetuximab should be administered only after a careful assessment of benefit/risk, including alternative treatments, and only under close supervision of well-trained personnel with resuscitation equipment ready.

In each case of an allergic/hypersensitivity reaction, the investigator should implement treatment measures according to the best available medical practice.

The first dose should be administered slowly and the speed must not exceed 5 mg/min whilst all vital signs are closely monitored for at least two hours. If during the first infusion, an infusion-related reaction occurs within the first 15 minutes, the infusion should be stopped. A careful benefit/risk assessment should be undertaken including consideration whether the patient may have preformed IgE antibodies before a subsequent infusion is given.

If an infusion-related reaction develops later during the infusion or at a subsequent infusion further management will depend on its severity:

a) Grade 1: continue slow infusion under close supervision

b) Grade 2: continue slow infusion and immediately administer treatment for symptoms

c) Grade 3 and 4: stop infusion immediately, treat symptoms vigorously and contraindicate further use of cetuximab

A cytokine release syndrome (CRS) typically occurs within one hour after infusion and is less commonly associated with bronchospasm and urticaria. CRS is normally most severe in relation to the first infusion.

Mild or moderate infusion-related reactions are very common comprising symptoms such as fever, chills, dizziness, or dyspnea that occur in a close temporal relationship mainly to the first cetuximab infusion.

If the patient experiences a mild or moderate infusion-related reaction, grade 1, the infusion rate will be decreased by 50% *e.g.* infusion will be done during 4 hours if a reaction occurred during the first infusion. It is recommended to maintain this lower infusion rate in all subsequent infusions.

Based on previous experience with cetuximab allergic/hypersensitivity reactions, the treatment guidelines as described in the following table 1 may be applicable.

Table 1: Treatment guidelines for cetuximab allergic/hypersensitivity reactions

CTCAE V4.0 grades/symptoms Infusion related reaction	**Action**
Grade 1 Mild transient reaction (transient flushing or rash, drug fever < 38°C)	Decrease the cetuximab infusion rate by 50% and monitor closely for any worsening, decrease further if reactions persists as applicable: 1st dose: · decrease infusion rate by 50% resulting in an infusion duration 4 hours 2nd dose (500mg/m^2 only): · decrease infusion rate by 50% resulting in an infusion duration of 3 hours, if allergic/hypersensitivity reaction persists decrease infusion rate by another 25% to an infusion duration of 4 hours Subsequent doses: · decrease infusion rate by 50% resulting in an infusion duration of 2 hours, if allergic/hypersensitivity reaction persists decrease infusion rate by another 50% to an infusion duration of 4 hours The total infusion time for cetuximab at 500mg/m² should not exceed 4 hours.

Grade 2 Rash, flushing, urticaria, dyspnea, drug fever ≥ 38°C. Promptly responsive to interruption of infusion and symptomatic treatment.	Stop cetuximab infusion Administer bronchodilators, oxygen, etc. as medically indicated Resume infusion at 50% of previous rate once allergic/hypersensitivity reaction has resolved or decreased to grade 1 in severity, and monitor closely for any worsening. Prolongation of infusion duration should be performed as described for grade 1 reactions, as applicable. The total infusion time for cetuximab at 500mg/m² should not exceed 4 hours.
Grade 3 or Grade 4 Grade 3: Symptomatic bronchospasm, allergy-related edema/angioedema, hypotension. Not rapidly responsive to brief interruption of infusion and/or to symptomatic medication; recurrence of symptoms following initial improvement; hospitalization, indicated for clinical sequelae. Grade 4: Anaphylaxis. Life-threatening consequences; urgent intervention indicated.	Stop cetuximab infusion immediately and disconnect infusion tubing from the patient Administer epinephrine, bronchodilators, antihistamines, glucocorticoids, intravenous fluids, vasopressor agents, oxygen, etc., as medically indicated Patients have to be withdrawn immediately from treatment and must not receive any further cetuximab treatment

Re-treatment following allergic/hypersensitivity reactions

Once a cetuximab infusion rate has been decreased due to an allergic/hypersensitivity reaction, it will remain decreased for all subsequent infusions. If the patient has another allergic/hypersensitivity reaction with the slowest infusion rate, the infusion should be stopped, and the patient has to be withdrawn from cetuximab treatment and must not receive any further cetuximab treatment.

If a patient experiences a Grade 3 or 4 allergic/hypersensitivity reaction at any time, cetuximab should be discontinued. The patient must not receive any further cetuximab treatment.

9.3.2 Cetuximab dose reduction for skin reactions

Skin reactions are very common and treatment interruption or discontinuation may be required. According to clinical practice guidelines prophylactic use of oral tetracyclines (6 - 8 weeks) and topical application of 1% hydrocortisone cream with moisturiser should be considered.

If a patient experiences a severe skin reaction (grade 3 or more; according to NCI-CTCAE v4.0), cetuximab therapy must be interrupted. Treatment may only be resumed if the reaction

has resolved to grade 2. If the severe skin reaction occurred for the first time, treatment may be resumed without any change in dose level. With the second and third occurrences of severe skin reactions, cetuximab therapy must again be interrupted. Treatment may only be resumed at a lower dose level, if the reaction has resolved to grade 2. If severe skin reactions occur a fourth time or do not resolve to grade 2 during interruption of treatment, permanent discontinuation of cetuximab treatment is required.

Treatment guidelines for skin reactions are summarized in Figures 3 and 4.

Figure 3: Treatment guidelines for skin reactions with weekly cetuximab

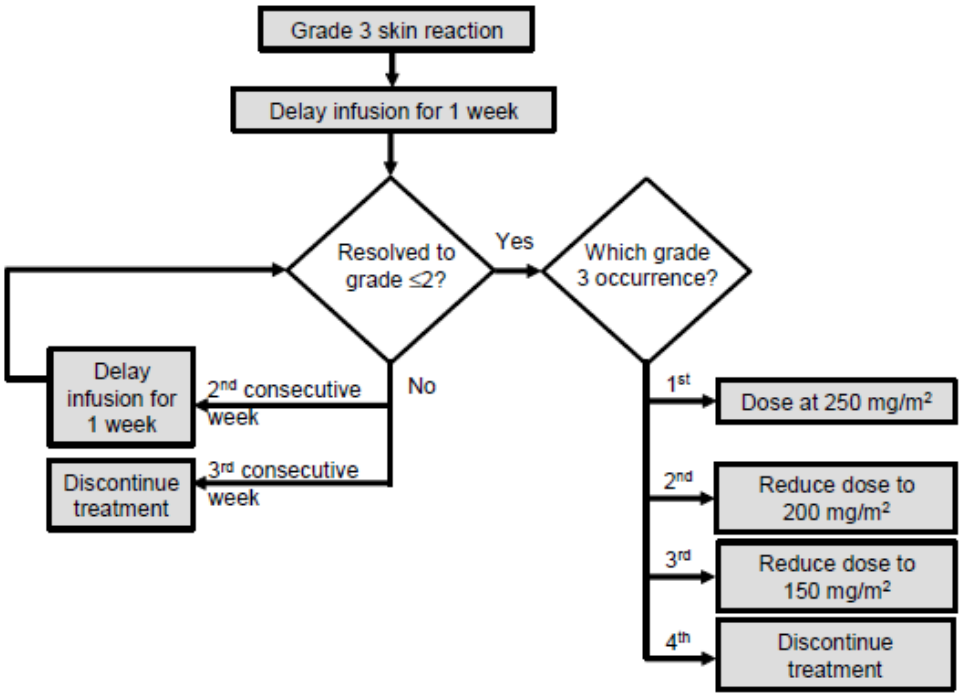
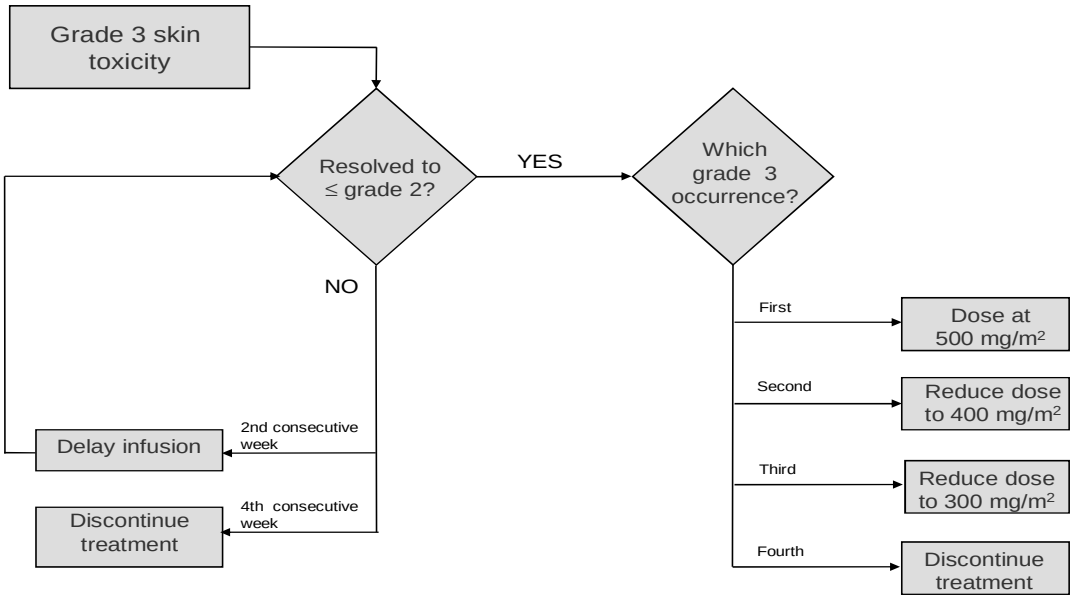


Figure 4: Treatment guidelines for skin reactions with cetuximab every 2 weeks



9.3.3 Electrolyte disturbances

Progressive decreasing serum magnesium levels occur frequently and may lead to severe hypomagnesaemia. Treatment of any hypomagnesaemia should be as clinically indicated according to local standards and cetuximab therapy should be continued unless the treating Investigator has any related safety concern. Hypomagnesaemia is reversible following discontinuation of cetuximab.

In addition, hypokalaemia may develop as a consequence of diarrhoea.

Hypocalcaemia may also occur; in particular in combination with platinum-based chemotherapy the frequency of severe hypocalcaemia may be increased.

Determination of serum electrolyte levels is recommended prior to and periodically during cetuximab treatment. Electrolyte repletion is recommended, as appropriate.

9.3.4 Other reasons for cetuximab discontinuation

If a patient develops an intercurrent illness (e.g. infection) that, in the opinion of the investigator and/or the sponsor, mandates interruption of therapy, this intercurrent illness must

resolve within a time frame such that no more than 2 consecutive cetuximab infusions are withheld. In any case of delayed cetuximab treatment, there will be no new 400 mg/m² initial dose at the restart of treatment, and all subsequent treatments will be at the assigned dose level including any previous dose reductions.

Cetuximab therapy will not be delayed for chemotherapy-related toxicity. Therefore, if the infusion of chemotherapy is delayed, the patient will continue to receive weekly infusions of cetuximab. If the chemotherapy is terminated for chemotherapy-related toxicity, cetuximab may be continued as monotherapy, and no other anti-cancer treatment will be given to patients in either group until PD. Patients in both groups will continue to receive scheduled evaluation visits until PD. **In case of cetuximab-related toxicity, chemotherapy will not be delayed and the planned schedule for administration should be maintained.** If the cetuximab therapy is permanently stopped for cetuximab-related toxicity, chemotherapy may be continued if clinically indicated.

9.4 Dose modifications and treatment alterations for chemotherapy

9.4.1 General recommendations

Every effort will be made to administer the full doses of cisplatin, docetaxel and 5-FU. Dose modifications are always based on the dose of the previous cycle. Only 2 dose-modifications described in *Tables 2, 3 and 4* are permitted. If further toxicity occurs or the criteria for resuming treatment are not met, the patient must be withdrawn from chemotherapy.

Dose adjustments are to be made according to the system showing the greatest degree of toxicity experienced during the previous cycle. Toxicities will be graded using the NCI CTCAE, Version 4.0.

If a patient experiences several toxicities and there are conflicting recommendations, please follow the most conservative dose adjustment recommended (dose reduction appropriate to the most severe toxicity).

Patients in group A (cetuximab + cisplatin + 5FU) will, in absence of either PD or unacceptable toxicity, receive 6 cycles of study treatment. Patients who demonstrate at least SD at the end of up to 6 cycles of chemotherapy will continue treatment with cetuximab until PD or occurrence of unacceptable toxicity. Patients with unacceptable toxicity due to one of the study drugs will receive the tolerated drug(s) until PD or up to a maximum of 6 cycles of chemotherapy.

Patients in group B (cetuximab + cisplatin + docetaxel) will, in absence of PD and unacceptable toxicity, receive 4 cycles of chemotherapy. Patients who demonstrate at least SD at the end of up to 4 cycles of chemotherapy will continue treatment with cetuximab until PD or occurrence of unacceptable toxicity. Patients with unacceptable toxicity due to one of the study drugs will receive the tolerated drug(s) until PD or up to a maximum of 4 cycles of chemotherapy.

Note that dosages, which have been reduced for toxicity, must not be re-escalated.

9.4.2 Potential toxicities

9.4.2.1 Potential toxicities observed with cisplatin

Nephrotoxicity; ototoxicity; myelodepression with leucopenia, thrombopenia and anemia; infectious complications; nausea and vomiting; and peripheral neuropathies.

9.4.2.2 Potential toxicities observed with carboplatin

Myelodepression with thrombopenia, leucopenia, neutropenia and anemia; infectious complications; nausea and vomiting; ototoxicity; and peripheral neuropathies.

9.4.2.3 Potential toxicities observed with 5-FU

Cardiac toxicity: The typical signs of cardiac toxicity under treatment with 5-FU are ischemic pain occurring a few hours after a bolus or after the start of a continuous infusion, together with characteristic electrocardiogram (ECG) changes. Silent ECG alterations may also occur. Myocardial infarction has been reported. Thus, treatment with 5-FU must be stopped in patients who develop such symptoms or have any other cardiac events of unclear origin during or after treatment with 5-FU.

Hand-foot syndrom: Patients treated with 5-FU may develop hand-foot syndrome, characterized by redness and swelling of the palms and soles of the feet. Mild hand-foot syndrome is painless but in 10–15% of cases it can be painful and is usually associated with blisters, ulcerations, cracks and desquamation. 100–150 mg pyridoxine (vitamin B6) per day may be helpful.

Diarrhea and mucositis: Patients treated with 5-FU may develop mucositis, or more commonly diarrhea. In these cases, symptomatic treatment with loperamide is recommended. The following guideline outlines the dose adjustments for chemotherapy in response to different toxic effects and the criteria for restarting treatment.

9.4.2.4 Potential toxicities observed with docetaxel

Myelosuppression, colitis, diarrhea, hypersensitivity reaction, fluid retention, alopecia, skin and ungueal toxicity, neuropathies.

9.4.3 Doses adjustments

Modifications to the doses of chemotherapy are based on: Chemotherapy-induced hematological changes or Non-hematological toxicity during the previous cycle.

9.4.3.1 Hematological toxicities

Febrile neutropenia

Febrile neutropenia is defined as follows:

Grade 2 fever (temperature > 38.1°C) concomitant with grade 4 neutropenia (absolute neutrophil count (ANC) <500/mm^3) requiring IV antibiotics and/or hospitalization. Fever should be graded using the NCI-CTC grading system. The reported temperature should be the oral or equivalent temperature.

In cases of febrile neutropenia, the following approach is recommended:

- Hospital admission except where outpatient care may be suitable
- Pre-antibiotic evaluation (e.g. antibiogram)
- White Blood cell count with differential and blood culture should be performed
- Dose reductions and commencement of an antibiotic therapy

In case of febrile neutropenia, blood counts must be done every 2 days until recovery to ANC ≥500/mm³ or temperature <38.1°C.

Table 2: Treatment Adjustment for Febrile Neutropenia

Adverse Event	**Treatment**
Febrile neutropenia Documented infection	1) The first episode of febrile neutropenia or documented infection will result in antibiotic treatment and reduction by 20% of all the cisplatin, docetaxel and 5-FU doses while maintaining the duration of 5-FU infusion of 4 days (or dose reduction of carboplatin to AUC4 if applicable) 2) If there is a second episode despite dose reduction, the patient must receive prophylactic antibiotics (quinolone) during the subsequent cycles and a 2nd dose reduction by 20% of all the cisplatin, docetaxel and 5-FU doses (or dose reduction of carboplatin to AUC3 if applicable) 3) If there is a third episode, the patient will be withdrawn from chemotherapy

Neutropenia and Thrombopenia

- **EXTREME Arm**

Table 3: Criteria for Modifications based on Hematological results on the Schedule Day of treatment

Neutropenia	Grade 3 (500–999/mm³)	Chemotherapy treatment delay until ≤ Grade 1 (1500–1999/mm³)
	Grade 4	Chemotherapy treatment delay until ≤ Grade1; dose reduction of all further doses of cisplatin and 5-FU by 20% (or dose reduction of carboplatin to AUC4 if applicable)
Thrombopenia	Grade 1	Chemotherapy treatment delay until thrombocytes >100 000/mm³
	≥Grade 2	Chemotherapy treatment delay until thrombocytes >100 000/mm³; dose reduction of all further doses of cisplatin and 5-FU by 20% (or dose reduction of carboplatin to AUC4 if applicable)

➢ **TPEx Arm**

Docetaxel

If neutropenia and/or thrombopenia grade 3/4 without fever, docetaxel is stopped until normalization ANC > $1x10^9$/L and thrombocytes > $100x10^9$/L). A stop of chemotherapy during 7 days is usual in case of fever > 38.5 °C or grade 3/4 complication. Further doses of docetaxel are reduced by 20 %. Study treatment will be definitively stopped in case of absence of normalization at day 36 despite a previous decrease of docetaxel doses.

In combination with cisplatin:

To adjust doses of cisplatin, refer to the Summary of product characteristics of cisplatin.

9.4.3.2 Non-hematological toxicities

➢ **EXTREME Arm**

In case of cisplatin related nephrotoxicity grade ≥1, ototoxicity grade ≥ 3, or neurotoxicity ≥ grade 3, cisplatin may be replaced by carboplatin AUC5 in the following cycles, except in the case of bleeding tumour. This decision needs to be discussed with the study coordinator on a case-by-case basis.

Dose modifications of carboplatin for non-hematologic toxicities will be done according to the recommendations given in Table 4.

Table 4: Dose Modifications and Treatment Alterations to be Performed if Toxicities are Present on the Day of Scheduled Treatment

Toxicity	NCI-CTCAE grade	Action to be taken
Hypercreatinemia	≥ Grade 1*	Delay chemotherapy treatment until Grade 0 and switch to Carboplatin AUC5**
Ototoxicity	≥ Grade 3	Stop Cisplatin and switch to Carboplatin AUC5**
	> Grade 3	Stop Carboplatin
Sensory neuropathy	≥ Grade 3	Stop Cisplatin and switch to Carboplatin AUC5**
	> Grade 3	Stop Carboplatin
Oral Mucositis	Grade 2	Delay chemotherapy treatment until Grade 0
	> Grade 2	Delay chemotherapy treatment until Grade 0; dose reduction of all further doses of 5-FU only by 20%
Diarrhea	Grade 1	Delay chemotherapy treatment until Grade 0
	> Grade 1	Delay chemotherapy treatment until Grade 0; dose reduction of all further doses of 5-FU only by 20%
Hand-foot syndrome	Grade 2	Delay chemotherapy treatment until Grade 0
	> Grade 2	Delay chemotherapy treatment until Grade 0; dose reduction of all further doses of 5-FU only by 20%
Other organ toxicity	Grade 2	Delay chemotherapy treatment until ≤Grade 1
	> Grade 2	Delay chemotherapy treatment until ≤Grade 1; dose

		reduction of all further doses of platinum-based therapy and 5-FU by 20% (or dose reduction of Carboplatin to AUC4 if applicable)

* Grade 1: >ULN - 1.5 x ULN regardless of baseline value
** except in the case of bleeding tumour. Any switch to Carboplatin AUC5 needs to be discussed with the study coordinator

- **TPEx Arm**

Non-hematological chemotherapy related toxicities:

They have to be resolved to grade 0 (excluding skin reactions, paronychia, alopecia, fatigue, ototoxicity, or neurotoxicity which must have resolved to ≤grade 2)

In case of cisplatin related nephrotoxicity grade ≥1, ototoxicity grade ≥ 3, or neurotoxicity ≥ grade 3, cisplatin may be replaced by carboplatin AUC5 in the following cycles, except in the case of bleeding tumour. This decision needs to be discussed with the Study Coordinator on a case-by-case basis.

However, as according to the exclusion criteria, patients should be able to receive 4 cycles of cisplatin, a switch to carboplatin should be exceptional in TPEx arm. Every toxicity requiring a switch from cisplatin to carboplatin will be well documented and will be discussed with the study coordinator.

9.4.3.3 Practical advice concerning specific toxicities of docetaxel

Nausea and vomiting

Despite their low incidence and usually low intensity an antiemetic premedication is allowed at first cycle. If symptoms are grade ≥ 3 despite premedication or antiemetic treatment, dose of docetaxel will be reduced from 75 mg/m² to 65 mg/m².

Gastro-intestinal (GI) toxicity

Abdominal pain, fever, diarrhea, with or without neutropenia, may be early signs of severe GI toxicity and must be evaluated and quickly treated.

Mucositis

Grade 1 or 2: neither modification of dose nor stop of docetaxel. Symptomatic treatment (corticosteroids, analgesic, mouthwashes,…).

Grade 3 or 4: dose reduction of docetaxel to 65 mg/m².

Other adverse effects

In case of grade 3 or 4 clinical and biological hepatic toxicities, treatment must be delayed for 2 weeks maximum until grade ≤ 1 then further doses of docetaxel will be: 65 mg/m² then if relapse 50 mg/m²

Hypersensitivity reaction (HSR)

- Moderate symptoms: local skin reactions (pruritus, rash, flush): Decrease the infusion rate monitor closely for any worsening once allergic/hypersensitivity reaction has resolved, then finish docetaxel infusion at initial rate

- Intermediate symptoms: pruritus, flush, generalized rash, dyspnea, hypotension with Systolic Blood Pressure (SBP) > 80 mmHg: Stop docetaxel infusion, administer intravenous antihistamines and glucocorticoids. Resume infusion once symptoms have completely resolved.

At next cycle, premedication will be strengthened with intravenous corticosteroids and antihistamines.

- Severe symptoms: bronchospasm, generalized urticaria, hypotension with SBP < 80 mmHg: Stop docetaxel infusion, administer antihistamines, glucocorticoids, epinephrine, bronchodilators, intravenous fluids, vasopressor agents, oxygen, etc., as medically indicated. Patients who have presented severe hypersensitivity reactions should not be rechallenged with docetaxel.

Fluid retention

No reduction of dose is recommended. The decision to continue or not docetaxel, in case of edema, is of the only choice of the investigator.

9.4.4 Treatment compliance

Since the intravenous infusion is administered in a hospital or in an outpatient setting, compliance can be easily supervised.

The study medication will be administered by the investigator, or under his/her direct supervision.

The date and time of the start and end of infusion, the exact amount of cetuximab, cisplatin or carboplatin, docetaxel and 5-FU given at each infusion and the initials of the person administering the drug will be documented in the patient medical record. In case the treatment has to be interrupted during infusion, the clinical staff must make an estimate of the percentage of dose received by the patient and document this in the CRF. Reason for non-compliance must be reported in the CRF. Insufficient compliance for cetuximab is defined as a patient missing more than 2 consecutive infusions of cetuximab for reasons other than toxicity. Insufficient compliance for chemotherapy is defined as a patient missing more than 2 consecutive infusions of chemotherapy for reasons other than toxicity.

10 Tumour response assessments

Tumour response will be evaluated according to RECIST 1.1 (Appendix 1). CR, PR, stable disease (SD) or progressive disease (PD) will be assessed by the investigator and also by an independent central review (see Section 10.2).

10.1 Tumour imaging

Measurable disease requires the presence of at least one bi-dimensionally measurable lesion.
The assessments should include imaging by computed tomography (CT) or magnetic resonance imaging (MRI) of the head and neck, chest and abdomen and, if clinically indicated, imaging of any other known or suspected sites of disease using an appropriate method according to clinical practice at the site. If no metastasis is identified on the first abdominal CT, the subsequent work-up could explore only upper abdominal section in addition to head and neck and chest.

Imaging studies must be performed at baseline in order to survey potential metastasis. All baseline evaluations should be performed as close as possible to the treatment start (≤28 days before randomization). At baseline, the organs with metastatic disease should be documented.

Evaluation of lesions should be performed at baseline and every 6 weeks after treatment start until Week18 **in both arms regardless of number of performed chemotherapy cycles**: during chemotherapy, imaging exams must be done at Week 6 (corresponding to the end of cycle 2 in both arms), Week 12 (corresponding to the end of cycle 4 in both arms), and at Week 18 (corresponding to the end of cycle 6 in the EXTREME arm). The evaluation at Week 18 must also be done in the TPEx arm, as the follow-up of the patients must be the same in the two groups although the number of cycles is different between the two arms. **In any case (chemotherapy administration delay, end of treatment because of unacceptable toxicity,…) imaging exams must be done at W6, W12 and W18. After Week 18, evaluation of lesions should be performed every 8 weeks until PD in both arms.** A CT scan or MRI should be performed at the end of treatment/withdrawal visit (within 7 days) if there was no PD documented by imaging at the previous evaluation. Imaging exams should be performed whenever disease progression is suspected. No imaging is required after PD.

Evaluation of lesions should be based on images obtained by either CT scan or MRI. The same method of assessment and the same technique must be used to characterize each identified and reported lesion at baseline and during the study. In cases where CT scan or MRI are not feasible for medical reasons, with clear evidence of PD on the chest X-ray (i.e. under exceptional circumstances), chest X-rays alone may be taken for documentation of PD. All measurements should be recorded in metric notation. In case of skin lesions, clinical evaluation should be made with a caliper and photos must be taken and made available.

The investigational site should strive to objectively evaluate tumour response and confirm tumour progression with radiological tumour imaging for all patients who enter into the trial, including those who discontinue prematurely.

Patients will be evaluated for response according to the RECIST version 1.1 criteria (Appendix 1).

As per RECIST (version 1.1), one to five target lesion(s), not exceeding two lesions per organ, should be identified at screening by CT or MRI. Lesions will be individually recorded in the eCRF at screening and the size of the target lesions will be recorded in millimeters. The lesions must be followed up with the same method(s) used at screening. If a patient develops an allergy to contrast media, CT scans may be performed without contrast media or may be substituted by MRI.

Target lesions should be selected based on their size according to RECIST (1.1) and suitability for accurate repeated measurements. All other lesions should be identified as nontarget lesions and will be recorded at baseline. The non-target lesions need to be followed during the patient's scheduled imaging and will be taken into consideration when determining the patient's response.

In the event of a delay, interruption or discontinuation of treatment, tumour assessment should continue to follow the original schedule, until progressive disease is confirmed by imaging. In case patients who have no progression commence other anti-cancer therapies, tumour imaging should be performed in close proximity to the start of this other therapy.

10.2 Central image review

All image data from baseline, week 6 and week 12 assessments will be sent to a blinded central image review committee composed by head and neck specialized radiologists to obtain an independent systematic interpretation of radiographic image data for all images.

Upon receipt, the central review committee will log all image data into a tracking system and perform quality control of radiographic images. For each patient an independent review of radiographic images including radiological response assessment will be performed by one independent radiologist, who is blinded with regard to patient and treatment.

All procedures will be done according to the specifications provided in the central image review charter.

The results of the central image review will not be communicated to the investigator. Patient management including treatment decision will be based on the assessment of disease by the investigator.

11 Quality of life assessments

11.1 EORTC QLQ-C30 questionnaire

The EORTC QLQ-C30 questionnaire will be used to assess cancer-specific QoL (see *Appendix 7*). This questionnaire has been extensively validated and is available in French, German and Spanish.

The GORTEC will ask the EORTC for the User's agreement between academic sponsors and EORTC will provide the Quality of Life questionnaires in the official languages of the countries

of the participating centers (French, German and Spanish). The Quality of Life questionnaires are paper questionnaires with copyright and that are filled in directly by the patients.

The EORTC questionnaires are an integrated system for assessing the health-related QoL of cancer patients participating in clinical studies. The EORTC QLQ-C30 questionnaire comprises 30 items.

The questionnaire will be completed at baseline before treatment, at Week 12, Week 18 and at Week 26 for all patients whatever the treatment arm and number of chemotherapy cycles performed.

The questionnaires will be handed to the patient and should be completed at the investigational site prior to the initiation of any other study activities or treatments and prior to any contact with the investigator. Patients will be asked to fill in the questionnaires as completely and accurately as possible. The patient must complete the questionnaires with no assistance from family/friends, although the investigator's staff may provide limited assistance, if necessary.

11.2 EuroQol-5D questionnaire

Patients will rate their health status with the EuroQol-5D (EQ-5D) questionnaire (*Appendix 8*). This questionnaire contains five questions. It is available in French, German and Spanish. This questionnaire will be completed at baseline before treatment, at Week 12, Week 18 , Week 26 for all patients whatever the treatment arm and number of chemotherapy cycles performed, and then every 8 weeks.

12 Work up and visit schedule

All investigations are summarized in the study flowchart

12.1 STUDY FLOWCHART

	Before Inclusion	**During Chemotherapy Treatment**			**Maintenance Treatment**		**End of study treatment (within 7 days)**	**Follow up after treatment stop**
Study Week	**Week -4 to 0**	**Weekly**	**Every 3 weeks**	**Every 6 weeks** (Disease Assessment)	**Every 2 weeks**	**Every 8 weeks**		**At least every 8 weeks** (until the target number of deaths (n=374) is achieved#.
Cycle (3 weeks)		**C1 to C4/C6**	**Before every cycle**	**At the end of W6, W12 and W18**				
Informed Consent signed	X							
Inclusion/Exclusion criteria	X*							
Demographics Medical/ Disease History	X							
HPV tumour status (1)	X							
Concomitant Treatments	X*	X	X	X	X		X	
CLINICAL EXAMINATION								
PS / Body Weight / Height (only at D1)	X*	X	X	X	X		X	
Physical examination / Signs and symptoms (2)	X*	X	X	X	X**		X	X
AE assessment (3)		X	X	X	X		X	X
BIOLOGY (4)								
Hematology	X*	X	X	X	X		X	
Blood chemistry	X*	X	X	X	X		X	
Coagulation	X*							
IMAGING (5) AND PARACLINICAL EXAMINATIONS								
CT-scan and/or MRI of the H&N	X			X (also end of W18 in TPEx arm)		X	X***	**<u>Every 8 weeks until progression</u>**
CT thorax-abdomen	X			X (also end of W18 in TPEx arm)		X	X***	
PET Scanner (optional)	X			X		X	X***	
12-lead ECG	X*		X					
QUALITY OF LIFE								
QLQ-C30	X*			W12 and W18				W26
EQ-5D	X*			W12 and W18				W26 and then every 8 weeks

* Must be done between W-2 and D0

** During maintenance, physical exam with check of vital signs must be done before each cetuximab administration, i.e. weekly in the EXTREME arm.
*** if there was no PD documented by imaging at the previous evaluation
# However, each alive patient must be followed at least one year after the end of study treatment, even if the 374 deaths are observed before one-year follow-up of the last randomized patient.

1. HPV status analysis will be done only in patients with oropharyngeal initial tumour.

2. Physical examination will include:
- vital signs (temperature, blood pressure (systolic/diastolic, after 5 minutes of rest, heart rate (after 5 minutes of rest), respiration rate)
- examination of major body systems including cardiovascular, pulmonary, neurological, gastrointestinal (including liver and spleen), genitourinary, musculoskeletal system, lymphatic, dermatological,
- weight,
- performance status

Except weight and performance status, the results of physical examinations carried out do not need to be recorded on the CRF unless abnormalities are discovered which should then be reported as AEs.

3. AE assessment: Toxicity (according to CTC-NCI V4): grade 1 to 4 toxicity by type of toxicity (hematological, digestive, oral mucositis, cutaneous, infusion reaction, infection, renal, metabolic, fatigue, other). Assessment of AEs at 30±2 days after last study treatment administration.

4. Biology:

- Hematology: Hemoglobin, WBC with differential, platelet count. If grade 4 neutropenia, assess ANC every 2-3 days until ANC > 0.5 x 10^9/L and at least weekly thereafter until ANC > 1.0 x 10^9/L.

- Blood chemistry: Liver function tests: SGOT (AST), SGPT (ALT), total bilirubin, conjugated bilirubin, Alkaline Phosphatase, GGT. Renal function tests: Sodium, potassium, calcium, phosphate, bicarbonate, urea, creatinine and estimated creatinine clearance, uric acid. Others: Glycemia, magnesium, LDH, albumin and total protein.

- Coagulation: Prothrombin time, INR, activated partial thromboplastin time (aPTT)

- Additional tests will be performed when clinically appropriate.

5. Tumour Assessment (RECIST criteria): CT-scan and/or MRI of the H&N, chest and abdomen to be performed at baseline (screening) and every 6 weeks after treatment start and until W19: during chemotherapy, as the follow-up of the patients must be the same in the two groups although the number of cycles is different between the two groups, imaging exams must be done at W6 and W12 (end of C2 and C4 in both arms) and W18 or the beginning of W19 (end of C6 in the EXTREME arm and after 6 weeks of maintenance in the TPEx arm). Evaluation times must be W6, W12 and W18 even in case of chemotherapy administration delay. Afterwards, evaluation of lesions should be performed every 8 weeks until PD. A CT scan or MRI should be performed at the end of treatment/withdrawal visit (within 7 days) if there was no PD documented by imaging at the previous evaluation. Imaging exams should be performed whenever disease progression is suspected. PET-CT is optional. If no metastasis is identified on the first abdominal CT, the subsequent work-up could explore only upper abdominal section in addition to head and neck and chest.

12.2 Screening visit

The screening visit (baseline) has to take place within 15 days of the start of treatment. Exams for tumour assessment should be done within 28 days of the start of treatment.

Quality of life questionnaires QLQ-C30 and EQ-5D must be filled in at baseline before treatment start.

Randomization/Inclusion forms (signed/dated by an Investigator) can be used as source documents.

12.3 Visits during chemotherapy

12.3.1 Start of cycle visit (Day 1 of each cycle)

The following procedures and investigations will be performed at the start of each cycle of chemotherapy administration:

- Weight and BSA, Performance status (*Appendix 3*)
- Physical examination and check of vital signs but not recorded in the eCRF unless abnormalities are discovered which should then be reported as AEs
- 12-lead ECG
- Blood sampling for safety laboratory (hematology and biochemistry) assessments
- Documentation of AEs and concomitant medication

12.3.2 Weekly cetuximab visits during chemotherapy

The following procedures and investigations will be performed at weekly intervals before cetuximab administration:

- Physical examination and check of vital signs but not recorded in the CRF unless abnormalities are discovered which should then be reported as AEs
- Blood sampling for safety laboratory (hematology and biochemistry) assessments
- Documentation of AEs and concomitant medications

12.3.3 Every 6 weeks during chemotherapy and until end of Week 18: Tumour assessment

CT- and/or MRI-scans of the H&N, chest and abdomen need to be performed. The same method must be used for each assessment. PET-CT is optional. If no metastasis is identified on the first abdominal CT, the subsequent work-up could explore only upper abdominal section in addition to head and neck and chest.

Tumour assessment must be done at the end of **Week 6, Week 12, and Week 18 in both arms regardless of the number of performed chemotherapy cycles and even in case of chemotherapy administration delay**.

12.3.4 At Week 12 and Week 18: QLQ-C30 and EQ-5D questionnaires

The EORTC QLQ-C30 questionnaire and the EQ-5D questionnaire must be filled in at the end of **Week 12 and Week 18 in both arms regardless of the number of performed chemotherapy cycles and even in case of chemotherapy administration delay**.

12.4 Visits during maintenance:

12.4.1 Before each cetuximab administration

– Physical examination and check of vital signs

12.4.2 Every 2 weeks

Every 2 weeks

- Weight, BSA, Performance status
- Physical examination and check of vital signs but not recorded in the eCRF unless abnormalities are discovered which should then be reported as AEs
- Blood sampling for safety laboratory (hematology and biochemistry) assessments
- Documentation of AEs and concomitant medications

12.4.3 Every 8 weeks during maintenance after W18: tumour assessment

CT- and/or MRI-scans of the H&N, chest and abdomen need to be performed. The same method must be used for each assessment. If no metastasis was identified on the first abdominal CT, the subsequent work-up could explore only upper abdominal section in addition to head and neck and chest. PET-CT is optional. Tumour assessment must be done every 8 weeks until progression.

12.4.4 At Week 18 and Week 26: QLQ-C30 and EQ-5D questionnaires

The EORTC QLQ-C30 questionnaire and the EQ-5D questionnaire must be filled in at W18 (before start of maintenance if 6 cycles of EXTREME have been given or during maintenance) and at W26 (i.e. during maintenance or, after maintenance if stopped before W26).

12.5 End of study treatment visit

Within the 7 days of the end of the study treatment (maintenance or chemotherapy if no maintenance could be done), the following procedures and investigations will be performed:

- Weight and BSA, Performance status
- Physical examination and check of vital signs but not recorded in the CRF unless abnormalities are discovered which should then be reported as AEs
- Blood sampling for safety laboratory (hematology and biochemistry) assessments
- Documentation of AEs (additional assessment of AEs should be done at 30±2 days after last study treatment administration) and concomitant medications

- Tumour assessment if there was no PD documented by imaging at the previous evaluation:

CT-scan and/or MRI of the H&N, chest and abdomen (same method as used for previous assessments). PET-CT is optional.

12.6 Follow-up after treatment stop

Follow up of all patients will continue until the target number of deaths (n=374) is achieved. However, each alive patient must be followed at least one year after the end of study treatment, even if the target number of death is observed before one-year follow-up of the last randomized patient. The survival status, the EuroQol-5D (EQ-5D) and any further anticancer treatments will be documented every 8 weeks.

Tumour assessment must be done every 8 weeks until progression if the treatment was stopped for another reason than progression.

QLQ-C30 questionnaires must be filled at Week 26. The questionnaires can be filled in by the patient when he/her comes for the follow-up visits every 8 weeks. The “26 weeks” questionnaires can be filled in between 22 and 30 weeks if there is no planned follow-up visit exactly 26 weeks after the start of treatment.

13 HPV analysis

This analysis will be done only in patients with oropharyngeal initial tumour.

HPV status: centralised analysis on formalin fixed initial biopsy or surgical specimen blocks. Four unstained slides should be addressed to Gustave Roussy Morphological pathology service according to procedures provided in the central HPV analysis charter.

Pathological evaluation of the tumour tissue to confirm histology (histological type – squamous cell carcinoma – and degree of differentiation) will be performed. Unstained slides will be prepared for evaluation of p16 expression by immunohistochemistry (IHC) and for the assessment of presence of HPV16, 18 and 33 by Chromogenic In Situ Hybridization (CISH) within tumour tissue; p16 IHC and HPV CISH will be conducted in the Gustave Roussy translational research laboratory as it has been already setup for other large scale studies. IHC p16 analysis will be performed on BenchMark ULTRA automated slide staining system using Ultra View technique, pre-diluted CINTEC antibody and CC1 buffer for antigen retrieval. Confirmation of histological diagnosis, evaluation of p16 expression by IHC and of presence of HPV16, 18 and 33 by CISH within tumour tissue will be performed by Dr Odile CASIRAGHI (Gustave Roussy Morphological pathology service).

14 Assessment of safety

14.1 Definitions

14.1.1 Adverse event (AE)

An adverse event (AE) is any untoward medical occurrence in a patient or clinical trial patient administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding) symptom, or disease temporally associated with the use of a medicinal product whether or not considered related to the medicinal product.

14.1.2 Serious Adverse event (SAE)

is any untoward medical occurrence that any dose:

- Results in death;
- Is life-threatening *
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity;
- Results in congenital anomaly/birth defect or abortion.
- Or is otherwise considered medically significant by the Investigator**

* A life-threatening event is one where the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if more severe.

****** Medical judgement should be exercised in deciding whether an AE is serious in other situations. AEs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the SAE definition above.

An SAE judged as potentially related to a study drug qualifies as Serious Adverse Drug Reaction (SADR).

The following events are not considered as SAEs and **ARE EXCLUDED from EXPEDITED REPORTING**

- A visit to the emergency room or other hospital department for less than 24 hours that does not result in admission (unless considered an “important medical event” or a life-threatening event)
- Outpatient or same-day hospital service or ambulatory procedures
- Clinical observation or short-stay units
- Hospitalization due to standard supportive care (e.g. implant of central venous catheter)

- A pre-planned hospitalization for a condition which existed at the start of study drug and which did not worsen during the course of study drug treatment
- Social hospital admission (e.g., patient has no place to sleep; hospice facilities)
- Administrative hospital admission (e.g., for yearly physical examinations)
- Protocol-specified hospital admission during a clinical trial (e.g., for a procedure required by the study protocol or for clinical research)
- Optional hospital admission not associated with a precipitating clinical AE (e.g., for elective cosmetic surgery)
- Death caused by disease progression more than 30 days after the end of study treatment.

14.1.3 Expected Serious Adverse Event

An expected SAE is an event already mentioned in the most recent version of the investigator's brochure or in the summary of product characteristics for drugs with a market authorization.

14.2 Intensity criteria

Intensity criteria must not be confused with criteria for seriousness, which serve as guidelines for definition of reporting obligations.

Intensity of events will be estimated according to the NCI-CTC classification, version 4.0 (toxicity score grade 1 to 5). Intensity of adverse events not listed in this classification will be evaluated according to the following terms:

Mild (grade 1): does not affect the patient's usual daily activity

Moderate (grade 2): perturbs the patient's usual daily activity

Severe (grade 3): prevents the patient carrying out his usual daily activities

Very severe (grade 4): necessitates intensive care or is life-threatening

Death (grade 5)

14.3 SAEs Reporting

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

Any late serious adverse event (occurring after this period of 30 days) considered as reasonably related to study drug(s) should be reported to the sponsor; regardless of time elapsed since last study drug dose.

The investigator must fill in immediately the SAE Form (*Appendix 6*) then send it signed and dated, within 24 hours of learning of its occurrence, even if it does not appear to be treatment-related, **by fax to: + 33 (0)1 42 11 61 50**

Phone: 33 (0)1 42 11 61 00 (9 a.m. - 6 p.m. from Monday to Friday, except bank holidays)

E-mail: phv@gustaveroussy.fr

Information collected in the SAE form is crucial to assess the case. For this reason diligence in collecting as much verifiable and reliable information is needed: both, quality and timelines are key factors. The local investigator should not wait for full details prior to making the initial report. The initial report should be promptly followed up with the full details.

If known, the diagnosis of the underlying illness or disorder should be recorded, rather than its individual symptoms. The following information should be captured for all SAEs: onset, duration, intensity, seriousness, relationship to study drugs, action taken and treatment required.

The investigator must also attach the following wherever possible:

- a copy of the summary of hospitalization or prolongation of hospitalization
- a copy of the post-mortem report (if applicable)
- a copy of all relevant laboratory examinations and the dates on which these examinations were carried out, including relevant negative results as well as normal laboratory ranges
- all other document that are judged useful and relevant

All these documents will remain anonymous.

14.4 Follow-up information

The investigator is responsible for the appropriate medical follow-up of patients until resolution or stabilization of the adverse event or until the patient's death. This may mean that follow-up should continue once the patient has left the trial. Follow up information about a previously reported SAE must be reported by the investigator within 24 hours of receiving it (at latest on the next working day).

The investigator also transmits the final report at the time of resolution or stabilization of the SAE. The investigator retains the documents concerning the serious adverse event so that previously transmitted information can be completed if necessary.

14.5 SUSAR reporting

SUSARs will be identified by the Pharmacovigilance Unit of Gustave Roussy and validated by the sponsor.

The SPC of Docetaxel will be used as reference Documents to determine if an event is expected or not.

The Pharmacovigilance Unit will report the SUSARs to all the concerned competent authorities and ethics committees as required by national laws of participating countries. In addition, the SUSARs will also be transmitted to the EMA Pharmacovigilance database (EUDRAVIGILANCE).

Timelines:

- ➔ Fatal or life-threatening SUSARs: no later than 7 calendar days after the sponsor has first knowledge.
- ➔ Non-fatal and non-life-threatening SUSARs: no later than 15 calendar days.

In addition, all SUSARs reports and all reports involving expected serious adverse drug reaction that are fatal will additionally be forwarded to all study investigators and the IDSMC, for information.

14.6 Exposure to drug during pregnancy/lactation:

In the event of a pregnancy occurring during the course of the study, the patient must be withdrawn from study drug immediately.

The Pharmacovigilance Unit of Gustave Roussy must be notified within 24 hours if a pregnancy occurred during the study or within 90 days following the last administration of study drugs and the patient followed during the entire course of the pregnancy and postpartum period. Parental and neonatal outcomes must be recorded even if they are completely normal and without AEs. The “pregnancy report form” should be used.

15 Statistical considerations

15.1 Endpoints

15.1.1 Primary endpoint

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

15.1.2 Secondary endpoints

- Objective response rate (complete response (CR) or partial response (PR) according to RECIST 1.1 criteria and assessed by central imaging review) at 12 weeks. For the statistical analysis of this endpoint, patients not evaluable (whatever the reason, including death) will be considered as failure (i.e. no CR, no PR) for this endpoint.
- Best overall tumour response rate (RECIST 1.1 criteria) during chemotherapy and maintenance: CR or PR or SD confirmed for CR or PR by a second assessment 6 weeks later
- Progression free survival (PFS): minimum time from randomization to progression as defined by RECIST 1.1 criteria or to death from any cause. Patients who don't have any of these events are censored at the date of last follow-up.
- Time to Progression (TTP): minimum time from randomization to progression as defined by RECIST 1.1 criteria. In case of death from other cause than cancer and no prior progression, the patient will be censored at the time of death. In case of death related to cancer without an accurate date of progression before death, the patient will be considered in progression at the time of death. In the event of no progression and no death, the patient will be censored at the date of last follow-up.
- Toxicity (according to CTC-NCI V4): all grades
- Compliance: Insufficient compliance for cetuximab is defined as a patient missing more than 2 consecutive infusions of cetuximab, even if the missed infusions are due to toxicity. Insufficient compliance for chemotherapy is defined as a patient missing more than 2 consecutive infusions of chemotherapy, even if the missed infusions are due to toxicity.
- Health related quality of life (QoL) assessed by EORTC QLQ-C30. The primary endpoint of the QoL study is the global health status/quality of-life scale of the QLQ-C30 questionnaire.
- Quality-adjusted life-years (QALYs) based on Euroqol EQ-5D measurements
- Net monetary benefit

15.2 Sample size calculation

In the EXTREME trial, the median OS was 10.1 months (Vermorken NEJM 2008). In the TPEx trial, the median OS was 14.0 months (Guigay ASCO 2012). This difference corresponds to a hazard ratio (HR) of 0.722.
Assuming a two sided type I error of 0.05, observing 374 deaths will provide a 88% power to detect this HR of 0.722. 374 deaths are expected out of a total of 540 patients randomized in the 2 arms within 36 months and a study duration (enrolment + follow-up) of 44 months and assuming that the lost-to-follow-up rate per month is not higher than 0.5% in each treatment arm.

This number of patients will allow a 90% power to detect a 14% absolute difference in best objective response rate (from 36% to 50%, OR=0.563) with type I error of 0.05 (2-sided). The

objective response rates were 36% in the EXTREME trial (Vermorken NEJM 2008) and 51.9% in the TPEx trial (Guigay Ann Oncol 2015).

15.3 Interim analysis for futility

The trial was initially designed with 80% power, requiring the inclusion of 416 patients. In this design, the end of inclusion was expected to occur during the first quarter of 2017. In order to increase the power of the trial to 88%, the number of patients is increased to 540 patients. However, to avoid continuing the trial if the probability to show that TPEx is superior to EXTREME is weak, a futility interim analysis is planned at the point when the 416 patients initially planned will be included.

One interim analysis for OS will be performed to allow early stopping of the trial for futility (rejection of the alternative hypothesis). We will use a one-sided futility rule, i.e. consideration for stopping the trial at interim analysis will be given if the interim results suggest that the final results will not significantly favor the TPEx arm. The trial is designed to have one interim futility analysis and the final analysis based on the primary OS endpoint. Futility boundary is constructed by using the spending function of Lan-DeMets. The futility boundary is non-binding. The interim futility analysis of OS will be performed when the 416 patients initially planned will be included, i.e. when approximately 44% of the deaths have occurred (163 deaths). Consideration for stopping the trial for futility will be given if the observed HR at that time is higher than 1. The beta error spent at this first analysis will be 0.019 and the probability of boundary crossing under H0 will be 0.50. Since the observed number of deaths at the interim analysis may not be exactly equal to the planned number of deaths, the boundary will be updated based on the actual number of observed deaths using the pre-specified β-spending functions.

15.4 Statistical analyses

The main analysis of overall survival will be done when the required total number of 374 deaths is reached.

An interim futility analysis is planned (section 15.3).

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

OS will be estimated with the Kaplan Meier method. The 95% confidence intervals (95% CI) of the survival rates will be calculated with the Rothman method. The main comparison of OS between the two arms will be done by Cox's models that included the minimization factors at randomization (stratification by country and adjustment for performance status, type of evolution

and previous cetuximab) (main analysis of the primary endpoint). Univariate analysis by logrank will also be performed.

The same analyses will be done for PFS and TTP.

The rate of objective response (complete and partial response assessed by central review) at 12 weeks will be compared between the 2 arms by logistic regression taking into account minimization factors at randomization (main analysis of this endpoint). Not evaluable or not evaluated patients (whatever the reason, including death, lost to follow up) will be considered as failure (i.e. no CR, no PR) for this endpoint. A sensitivity analysis will be done based on the evaluable patients only. Univariate analysis by chi square test will also be performed.

The analysis of the best overall response rate will present a description of the 4 response categories (CR, PR, Stable, Progression) in the 2 arms without formal statistical test between the arms. Comparison of Disease Control (CR+PR+Stable) between the 2 arms will be done in the same way as for objective response. Comparison of 3 response categories CR+PR / Stable / Progression will be done using ordinal logistic regression taking into account minimization factors. Not evaluable or not evaluated patients (whatever the reason, including death, lost to follow up) will be considered as failure (i.e. progression) for these analyses.

Subgroup analyses:
The efficacy analyses will also be done according to several characteristics of patients and tumours by testing interaction between arm of treatment and the following characteristics: age (<60y vs ≥60y), sex, performance status (0 vs 1), tumour location (oropharynx / larynx-hypopharynx / oral cavity), type of evolution (locoregional only vs distant metastasis). Among patients with oropharynx initial tumour, the interaction analyses will also study HPV tumour status (oropharynx positive vs oropharynx negative) and p16 tumour status (oropharynx positive vs oropharynx negative). The interaction analysis of tumour classified by HPV (or p16) status and localisation will also be done (oropharynx positive / oropharynx negative / larynx-hypopharynx / oral cavity).

Toxicity will be described by cycle of chemotherapy and during maintenance. In the comparison of the toxicity of 2 arms during chemotherapy, the maximal toxicity grade observed during chemotherapy cycles will be used. In the comparison of the toxicity of 2 arms during maintenance, the maximal toxicity grade observed during maintenance will be used. In the comparison of the toxicity of 2 arms at any time, the maximal toxicity grade observed during chemotherapy cycles and maintenance will be used. The toxicity will be analysed in 3 categories: grade 0 vs grade 1-2 versus grade 3-4. The rate of all types of toxicity will be compared between the two arms for chemotherapy courses and during maintenance and all together. The rates of grade 0 vs grade 1-2 versus grade 3-4 toxicity by type of toxicity (hematological, digestive, mucositis, cutaneous, infusion reaction, infection, renal, metabolic, fatigue, other) will also be compared between the two arms in the same way.

Compliance will be described and compared between the 2 arms. The rate of insufficient compliance will be compared between the 2 arms using chi square test and by logistic regression taking potential confounding factors into consideration. Reasons for insufficient compliance will be classified as toxicity and other.

All p-values will be two-sided at a significance level of 0.05, except for the futility interim analysis. Only the comparison of OS is considered a confirmatory statistical test, while all other statistical tests are supportive and/or of explorative nature. For this reason, no alpha adjustment for multiple testing is applied.

15.5 Quality of life study

The quality of life study will be done in all centers and all randomized patients will be included in the QoL study.

Health-related quality of life (HRQoL) will be assessed using the EORTC QLQ-C30 (Aaronson et al. JNCI 1993) questionnaire.

The EORTC QLQ-C30 is composed of 30 questions. Twenty-four questions participate in nine multi-item scales and six questions are single-item measures. There are five functional scales (physical, role, cognitive, emotional, and social), three symptom scales (fatigue, pain, nausea/vomiting), and a global health status/quality of-life scale. There are five single item measures assessing additional symptoms commonly reported by cancer patients (dyspnea, loss of appetite, insomnia, constipation, and diarrhea) and a single item concerning perceived financial impact of the disease.

The primary endpoint of the quality of life study will be the **global health status/quality of-life scale of the QLQ-C30 questionnaire.**

Patient-reported outcomes of QoL and disease/treatment-related symptoms scales will be scored according to the EORTC recommendations, as described in the EORTC QLQ-C30 Scoring Manual (standardized scores). When at least half the items of a score are completed, the missing items will be ignored when making the calculation of the scale score. When more than half the items of a score are missing, the scale score will not be calculated and the score will be missing.

QLQ-C30 subscales and single-item subscores will be summarized by means (standard deviation) and median for each treatment arm and presented graphically using boxplots by treatment and time. The single-item scales will also be presented as row scores in 4 or 2 categories.

The scores of the different scales of the QLQ-C30 questionnaire will be compared between the 2 arms using mixed models for repeated measures taking into account the repetitive assessments of QoL and the initial value before treatment. In order to take into account the fact that QoL data could be missing mainly because of disease progression, a dummy variable indicating at each measure whether or not it is the last will be included in the model. The conclusion of the

comparison of quality of life between the 2 arms will be based on the analysis of global health status/quality of-life scale of the QLQ-C30 questionnaire. Treatment effect and time effect will be tested.

In case of floor and ceiling effects in QoL data, normality cannot be assumed and a multinomial distribution in 4 classes will be used for each scale. Repeated measures will then be analyzed with a generalized estimating equation (gee) model for multinomial data.

15.6 Cost-effectiveness study

A multinational cost-effectiveness study will be performed alongside the clinical trial TPExtreme to determine the most efficient regimen between TPEx and Extreme as first line treatment in patients with recurrent / metastatic HNSCC. The rational for conducting a multinational economic evaluation is to take into account the variability of treatment patterns and intercountry differences in unit costs [Polsky].

In each country, a health economist correspondent will participate to the design of a common case report form suitable for all 3 of the healthcare systems respectively France, Germany and Spain. The collection and management of the economic data will be fully integrated into the clinical data.

15.6.1 Costs measurement

15.6.1.1 Type of costs

We will consider only direct medical costs. We will focus on all hospital stays (inpatient and outpatient) in the investigator centers (30 - 50 centers in France, 16 in Germany and 15 in Spain) and eventually hospitalisation in a palliative care unit in other hospitals. We will also collect information to estimate the costs incurred for G-CSF administration. Resource use will be collected prospectively for each patient from the date of randomization until the end of follow-up (patient death or 1 year after the end of the study treatment, including maintenance). This will ensure a common time horizon for costs and outcomes.

15.6.1.2 Perspective and unit costs

Costs will be assessed from the public payer perspective. In each country, the hospital public sector is the major provider of hospital care for the patient population targeted in this trial. Expenditures for hospitalizations will be valued according to diagnoses related groups (DRGs) codes assigned on the patient's discharge abstract. DRGs prices/cost weights within each country (national GHS-groupe homogènes de séjours in France, national G-DRGs in Germany and All Patient-DRGs in Spain) will be used. Supplementary fees for expensive drugs will be added according to the reimbursement rules in each country. For instance, in France, cetuximab is among the drugs paid outside the activity based payment (liste en sus, special list of expensive drugs delivers in hospitals and reimbursed separately from the DRG price for chemotherapy). Since March 2012, docetaxel is available as a generic medicine and is no longer on the list en

sus. The cost of docetaxel from the payer perspective is therefore covered by the DRG price in France.

15.6.2 Outcomes measurement

Two criteria will be used: the number of life years (LYs) gained and the number of quality-adjusted life-years (QALYs).

15.6.2.1 Measurement of life years

LYs will be computed from overall survival using the restricted mean survival method [Royston] at 1.5 year after randomization.

15.6.2.2 Measurement of QALYs

This protocol addresses the impact on patient health related quality of live (HRQoL) of being randomized to TPEx vs. Extreme. We will use the EuroQol-5D (EQ-5D) questionnaire which is available in French, German and Spanish [Cheung; Krabbe; Pickard]. It is a validated measure with several domains of health status. The EQ-5D contains five dimensions, each with three levels of severity. The five dimensions are: mobility, self-care, usual activities, pain / discomfort, and anxiety / depression. Severity is stated as: no problems, moderate problems, or severe problems. Patients will rate their health status with the EQ-5D at baseline before treatment, at Week 12, Week 18, Week 26 and then every 8 weeks.

Population-based preference weights have been derived for each EQ-5D domain that permit translation of functional status scores to utility weights that may be used to derive QALYs. QALYs will be obtained directly from the study population combining the health states collected from the patient population and the EQ-5D tariffs obtained by the time trade-off technique in each one of the country [www.euroqol.org].

Survival estimates for patients in each trial arm will be combined with utility weights to determine QALYs for the arms of the study. To create uniform periods of utility and survival, patient survival rates will be computed for each observation period covered the EQ-5D [Billingham]. QALYs will be adjusted for potential baseline mean utility imbalance [Manca 2005].

15.6.3 Cost-effectiveness analysis

An intention-to-treat analysis will be used for the cost-effectiveness analyses. Outcomes (number of life-years gained and QALYs gained) will be measured over a time horizon of 1.5 year (within-trial analysis). No extrapolation beyond the time horizon of the trial is planned. Discounting of the cost and the outcomes is not necessary given the short-term horizon of the trial (1.5 years).

Incremental costs and outcomes will be measured as differences in arithmetic means. Mean difference in costs and QALYs and their 95% confidence interval (CI) will be estimated using the non-parametric bootstrap method. For the cost-effectiveness analysis (both LYs and QALYs), the net monetary benefit approach (mean and 95% CI) will be used varying the willingness-to-pay for a life year or a QALY. To estimate the mean incremental net monetary benefit taking into account potential differences between countries, we will use an adequate statistical method (pooled estimate resulting from the average of estimates in each country weighted by the inverse of variance or shrinkage estimator from a hierarchical model).

Fixed parameters (unit costs for docetaxel and G-CSF, unit costs for main hospital stays) uncertainty will be addressed through a univariate and a multivariate sensitivity analysis.

16 Ethical and regulatory aspects

16.1 Responsibilities of the Investigator

The investigator shall be responsible for ensuring that the clinical study is performed in accordance with the protocol, the ethical principles that have their origin in the Declaration of Helsinki as well as with the International Conference on Harmonization (ICH) Note for Guidance on GCP (ICH, Topic E6, 1995) and applicable regulatory requirements. These documents state that the informed consent of patients is an essential precondition for participation in the clinical study.

16.2 Patient information

An unconditional prerequisite for a patient participating in the study is his/her written informed consent. Adequate information must therefore be given to the patient by the investigator before informed consent is obtained. A person designated by the investigator may give the information, if permitted by local regulations. A patient information sheet in the local language and prepared in accordance with the Note for Guidance on GCP (ICH, Topic E6, 1995) will be provided by the sponsor for the purpose of obtaining informed consent. In addition to this written information, the investigator or his/her designate will inform the patient verbally. In doing so, the wording used will be chosen so that the information can be fully and readily understood by laypersons. The patient information sheet will be revised whenever important new information becomes available that may be relevant to the consent of patients.

16.3 Patient consent

The written informed consent of the patient to participate in the clinical study has to be given before any trial driven activities are carried out. It must be signed and personally dated by the patient and by the investigator/person designated by the investigator to conduct the informed consent discussion.

Signed informed consent form must be obtained from all patients before any trial driven procedures are carried out. Provision of consent will be confirmed in the inclusion form of the eCRF by the investigator. The signed and dated declaration of informed consent will remain at the investigator's site and must be safely archived by the investigator so that the forms can be retrieved at any time for monitoring, auditing and inspection purposes. A copy of the signed and dated information and consent should be provided to the patient prior to participation.

16.4 Patient Insurance

Insurance coverage shall be provided in accordance with the regulations of each individual country for all patients enrolled in the study from the time of patient's inclusion into the study i.e. from the time consent is given. GORTEC is covered by a legal liability insurance policy:

In France: Société Hospitalière d'Assurances Mutuelles (SHAM, 18 rue Edouard Rochet, 69372 LYON Cedex 08, Tél. +33 (0)4 72 75 50 25), legal liability insurance policy n° 141352.

In Spain:

HDI-Gerling Industrie Versicherung AG,Sucursal en Espana, C/Luchana, 23-5e Planta

28010, Madrid

Tel : +34 914 442 000 Fax : +34 914 442 019

Contract number : 130/001/009464

In Germany:

HDI-Gerling Industrie Versicherung AG, Bernhard Hoppe, Am Schönenkamp 45

40599, Düsseldorf

Tel : 0211- 74 82 54 04 Fax : 0511- 64 51 15 00 23

Versicherungs-Nr.: 48157572 03010 (number of the client, AIO-Studien-gGmbH)

Anmelde-Nr.: 0003 2014 07 (registration number of the contract)

17 Study management

17.1 Data collection

The main objective is to obtain those data required by the study protocol in a complete, accurate, legible and timely fashion. The data in the eCRF should be consistent with the relevant source documents.

The data recorded in the course of this study must be documented in the eCRF. The Biostatistics and Epidemiology Unit of Gustave Roussy will implement electronic CRF (eCRF) using MACRO software (InferMed Ltd), thus allowing secure online data collection. MACRO software is validated to comply with 21 CFR Part 11. Each user will have personal identifiers (user ID / password) and data access will be strictly limited.

The eCRF will be used for recording all data for each patient. It is the responsibility of the Investigator to ensure that the eCRF is properly and completely filled in. The e-CRF must be completed for all patients who have given informed consent and have been randomized in the study. Except weight and performance status, the results of physical examinations carried out do not need to be recorded on the eCRF unless abnormalities are discovered which should then be reported as AEs.

Source documentation for patients should be the physician's patient records, and as such, will be maintained at the study site.

17.2 Source data and patient files

The investigator has to keep a written or electronic patient file for every patient participating in the clinical study. In this patient file, the available demographic and medical information of a patient has to be documented, in particular the following: name, date of birth, sex, height, weight, patient history, concomitant diseases and concomitant medication (including changes during the study), statement of entry into the study, study identification, randomization number, the date of informed consent, all study visit dates, predefined performed examinations and clinical findings, observed AEs, and reason for withdrawal from the study (if applicable). It should be possible to verify the inclusion and exclusion criteria for the study from the available data in this file. It must be possible to identify each patient by using this patient file. Additionally, any other documents with source data, especially original printouts of data that were generated by technical equipment have to be filed. This includes ECG tracings, X-ray films, CT and MRI scans, laboratory value listings, and if applicable pregnancy test results. All these documents have to bear at least the patient number and the printing date printed by the recording device to indicate to which patient and to which study procedure the document belongs. Computerized patient files will be printed whenever source data verification is performed by the monitor.

17.3 Investigator Site File and archiving

The investigator will be provided with an Investigator Site File at the start of the study. This file contains all relevant documents necessary for the conduct of the study. This file must be safely archived after termination of the study. It is the responsibility of the investigator to ensure that the patient identification sheets are stored for at least 15 years beyond the end of the clinical study. All original patient files must be stored for the longest possible time permitted by the regulations at the hospital, research institute, or practice in question. If archiving can no longer be maintained at the site, the investigator will notify the sponsor.

17.4 Monitoring, Quality Assurance

In order to guarantee the authenticity and the credibility of the data in conformity with good clinical practices, the Sponsor has installed a quality assurance system which includes:

- Trial management in accordance with the GORTEC procedures,

- Quality control of data at the investigating site by the ASCOPHARM, AIO and GORTEC CRAs according to ASCOPHARM procedures,

- Possible auditing of investigating centers.

Quality control on site will be ensured by the ASCOPHARM, AIO and GORTEC CRAs.

The CRA must check that the investigator's file exists and that it is updated.

The CRA must verify the consent forms, that patients fulfil eligibility criteria, the validity of evaluation criteria and treatment toxicity with the help of source documents and the sending of imaging exams for central review and the sending of material for p16 and HPV study if necessary.

The CRA will check drug accountability and ensure that the drug accountability forms are validated and signed by the in-house pharmacist before any request for destruction.

17.5 Changes to the study protocol

Changes to, or formal clarifications of the study protocol must be documented in writing. Major changes to the protocol will be described in a "Protocol Amendment". It will be submitted to the relevant EC(s)/IRB(s) and to authorities, where required. Approval/favorable opinion from the relevant EC(s)/IRB(s) will be required prior to implementation of the amendment except for amendment performed for urgent safety concern.

Any amendment affecting the patient requires the patient's informed consent prior to implementation.

Changes of administrative or technical nature will be recorded in a document entitled "Administrative change to study protocol". It will be sent for information to the relevant EC(s)/IRB(s) or to authorities, if so required. Amendments and administrative changes will be signed by the study Coordinating Investigator and the Sponsor.

All investigators will acknowledge the receipt and confirm by their signature on the amended protocol signature page or, when applicable, on the amendment signature sheet that they will adhere to the amendment. This sheet/ signature page will be issued in duplicate and after signing one copy will be filed in the Investigator Site File and one in the Study Master File.

17.6 Steering Committee

The Steering Committee will be composed of the 3 national coordinators (J Guigay, U Keilholz, R Mesia), the coordinator of the image review (F Bidault), the study statistician (A Auperin), the

economist (J Bonastre), the person in charge of the pharmacovigilance (S Laghouati), the GORTEC project manager (N Vintonenko) and the sponsor (J Bourhis). The Steering Committee will meet as appropriate, at least once a year, by meeting or conference call, to consider accrual rate, eligibility and safety to ensure the smooth running of the study.

All scientific decisions concerning the study can be made by the Steering Committee, possibly after discussion with the Independent Data and Safety Monitoring Committee (IDSMC).

The final decision concerning premature study termination or protocol amendment will be taken by the sponsor.

17.7 Independent Data and Safety Monitoring Committee

The Independent Data and Safety Monitoring Committee (IDSMC) will be composed of 3 experts: two oncologists and a statistician. The Committee will meet every year (by meeting or conference call) after having received data about inclusion and toxicity. The committee will monitor the progress of the trial on ethical and scientific grounds. The Committee may recommend to the Sponsor some protocol modifications or to stop the trial. The Sponsor will take the final decision.

18 Study report and publication policy

After conclusion of the study, an integrated clinical and statistical study report shall be written by the sponsor in consultation with the coordinating investigator. In this multi-center study, the first publication will be a full publication of all data from all sites. Any publications of the results, either in part or in total (abstracts in journals or newspapers, oral presentations, posters etc.) by investigators or their representatives will require pre-submission review by the sponsor. It should be done at least 45 days before submission for full papers, at least 8 days before abstract submission to congress, at least 15 days before presentation for congress oral presentation or poster. All reasonable comments made by the sponsor in relation to a proposed publication must be incorporated into the publication. The investigator commits him-/herself to forward to the sponsor all papers, manuscripts, or conference abstracts intended for publication or presentation which contain data, or results generated in connection with the study. Papers and abstracts must be available at the sponsor's site in time before the planned submission date to allow for review and comments. Submission for publication requires the expressed written permission from the sponsor. Any publication should follow the publication policy as described below.

The coordinating investigator will have the right to first-time publishing/presentation of the final results of the study at the first congress where this data will be presented, in his capacity of coordinating investigator.

Subsequent authors and the authorship order will be determined in accordance with the « Uniform requirements for manuscripts submitted to biomedical journal » (http://www.icmje.org/) and GORTEC publication rules (http://www.gortec.fr/).

Other publications could be done to report additional results (biological study, specific points concerning quality of life assessment, cost effectiveness study…). The list of authors in any additional publication/presentation of the study, shall be set up based on contribution to the study.

Publications and oral presentations of partial or final results, performed under this agreement, will require appropriate acknowledgement and consent from the sponsor. Investigators wishing to perform analyses of local data will inform the sponsor of any such analyses prior to their initiation. Review and approval by the Steering committee and by the Sponsor will be required for all analyses prior to publication or presentation.

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20 APPENDIX

20.1 APPENDIX 1: RECIST 1.1 CRITERIA

The criteria below are based on RECIST 1.1. (Eur J Cancer 2009 ;45 :228-247)

Measurability of the disease

Measurable disease

Measurable disease requires the presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

Measurable lesions

Lesions that can be accurately measured in at least one dimension with longest diameter ≥ 10 mm (by CT scan, MRI, caliper measurement) or ≥ 20 mm (by chest X-ray). Longest diameter will be recorded.

For a lymph node to be considered pathologically enlarged and measurable, the short axis must be ≥15 mm (by CT scan). The short axis will be recorded.

Non-measurable disease

Non-measurable lesions are all other lesions, including small lesions (longest diameter <10 mm with CT scan, MRI or caliper measurement or <20 mm with chest X-ray or pathological lymph nodes with shortest axis ≥10 and <15 mm) as well as truly non-measurable lesions. Lesions considered truly non-measurable include leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

New lesions in irradiated fields

Previously irradiated lesions should not be used as indicator lesions. However, new lesions occurring in previously irradiated fields can be used to assess the anti-tumour response.

Methods of measurement

All measurements must be recorded in metric notation, using a ruler or calipers. All baseline evaluations must be performed as close as possible to the treatment start and within 4 weeks before the beginning of the treatment. If a lesion is considered too small to measure, a default measurement of 5 mm should be applied. If the lesion is not visible, a default measurement of 0mm should be applied.

The same method of assessment and the same technique must be used to characterise each identified and reported lesion at baseline and during follow-up.

Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules, palpable lymph nodes). In the case of skin lesions, documentation by colour photography including a ruler to estimate the size of the lesion is suggested.

CT and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI should be performed with cuts of 5 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to the chest, abdomen and pelvis.

Ultrasound, endoscopy and laparoscopy should not be used to measure tumour lesions or evaluate tumour response. However, these techniques can be useful to supplement information from other techniques.

Tumour markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalise for a patient to be considered in complete clinical response.

Cytology and histology can be used to differentiate between PR and CR in rare cases (for example, residual lesions in tumour types such as germ cell tumours, where known residual benign tumours can remain).

Baseline Documentation of Target and Non-target Lesions

All measurable lesions up to a maximum of two lesions per organ and five lesions in total, representative of all involved organs should be identified as target lesions and will be recorded, measured and numbered at baseline. The longest diameter will be recorded, except for lymph nodes, which will be measured by their short axis. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repetitive measurements (either by imaging techniques or clinically).

The sum of diameters for all target lesions will be calculated and reported as the baseline sum of diameters. The baseline sum of diameter will be used as reference to further characterize the objective tumour response of the measurable dimension of the disease (see Table 1.1).

Table 1.1: Evaluation of target lesions

Complete Response (CR)	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have a reduction in short axis to <10mm)
Partial Response (PR)	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters
Progression (PD)	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: The

	appearance of one or more new lesions is also considered progression.)
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as "present" or "absent" (see Table 1.2).

Table 1.2: Evaluation of non-target lesions and new lesions

Complete Response (CR)	Disappearance of all non-target lesions and normalisation of tumour marker level. All lymph nodes must be non-pathological in size (<10mm short axis)
Non-CR / Non-PD	Persistence of one or more non-target lesions and/or maintenance of tumour marker level above normal limits
Progression (PD)	Unequivocal progression (see comments below) of existing nontarget lesions. (Note: the appearance of one or more new lesions is also considered progression). Although a clear progression of non-target lesions only is exceptional, in such circumstances, the opinion of the treating physician should prevail and the progression status should be confirmed later by the review panel (or study chair).

In some circumstances it may be difficult to distinguish residual disease from normal tissue.

When the evaluation of complete response depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before confirming the complete response status.

Evaluation of Best Response to Study Treatment

The best response to study treatment (Table 1.3) is the best response recorded from the start of treatment until disease progression or start of further anti-cancer treatment (taking as reference for progressive disease the smallest measurements recorded since the treatment started). In general, the patient's best response assignment will depend on the achievement of both measurements and confirmation criteria.

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration". Every effort should be made to document the objective progression even after discontinuation of treatment.

Table 1.3 Evaluation of overall best response*

Target lesions	**Non-target lesions**	**New lesions**	**Overall response**
CR	CR	No	CR
CR	Non-CR / Non PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	Not evaluated
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

* When SD is believed to be the best response, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of six (6) weeks.

20.2 APPENDIX 2: NCI-CTCAE

The National Cancer Institute - Common Terminology Criteria for Adverse Events

(NCI-CTCAE, Version 4.0) can be uploaded at the following address

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40

Common Terminology Criteria for Adverse Events v4.0 (NCI-CTCAE)

20.3 APPENDIX 3: Performance Status according to the WHO criteria and Karnofsky scale

WHO Scale	Karnofsky Scale %	
0	100	Fully active, able to carry out all normal activity without restriction
1	90-80	Restricted in physically strenuous activity but ambulatory and able to carry out light work.
2	70-60	Ambulatory and capable of all self-care but unable to carry out any work.
3	50-40	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	30-20	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.

20.4 APPENDIX 4: MDRD and Cockroft clearance equations

Modification of Diet in Renal Disease (MDRD) Study equation - 4 variables

Levey et al, Ann. Inter. Med., 1999, 16, 130(6), 461-470

Creatinine Clearance (ml/min) = 186.3 x (creatinine/88.4)$^{-1.154}$ x age$^{-0.203}$ x K x k

K = 1,00 (man) or 0.742 (woman) ; k = 1,212 (african origin)

Weight in Kg, Creatininemia in µmol/l

Cockroft et Gault equation

Cockcroft DW, Gault MH. 1976. Prediction of creatinine clearance from serum creatinine. Nephron 16:31-4.

For serum creatinine concentration in mg/dL:

$$\textbf{CrCl (mL/min)} = \frac{\textbf{(140 – age}^{+}\textbf{)} \times \textbf{(weight)} \times \textbf{0.85 (if woman), or} \times \textbf{1.0 (if man)}}{\textbf{72} \times \textbf{serum creatinine (}\textit{\textbf{mg/dL}}\textbf{)}}$$

For serum creatinine concentration in µmol/L:

$$\textbf{CrCl (mL/min)} = \frac{\textbf{(140 – age}^{+}\textbf{)} \times \textbf{(weight)} \times \textbf{0.85 (if woman), or} \times \textbf{1.0 (if man)}}{\textbf{0.81} \times \textbf{serum creatinine (}\textit{\textbf{µmol/L}}\textbf{)}}$$

+ age in years, weight in kilograms.

20.5 APPENDIX 5: Carboplatin dose calculation using Calvert equation

Carboplatin dose is calculated from creatinine clearance calculated according to Cockcroft and Gault method as mentioned above, using the following Calvert equation:

Calvert Equation:

Dose [mg] = AUC 5 x (calculated creatinine clearance [mL/min] + 25)

AUC = area under the curve

Take into consideration that the resulted dose from Calvert formula is in mg per patient and **not** in mg/m^2

The carboplatin dose **should not exceed 750 mg per cycle** due to current recommendations (http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm228974.htm).

20.6 APPENDIX 6: Severe Adverse Event form

IGR Institut Gustave-Roussy

TPExtreme
Serious Adverse Event Report Form

To be faxed to the Pharmacovigilance unit of IGR under delegation of GORTEC + 33 (0)1 42 11 61 50 or sent via email to phv@gustaveroussy.fr

EudraCT N°: 2014-000048-14 Clinical study N°: GORTEC 2014-01 Country :

1st report | Follow-up report N° | | | Center :

1. PATIENT IDENTIFICATION

Patient Inclusion N° : |_____| | Last Name (3 letters) : |_|_|_| | 1st Name (2 letters) : |_|_| | Date of birth : |_|_| / |_|_| / |_|_|_|_|

Gender :F M | Weight (kg) : |_____| | Height (cm) : |_____| | Treatment arm: |____|

2. EVENT INFORMATION

Date of onset : |_|_| / |_|_| / |_|_| **NCI – CTC V 4 grading toxicity: 1 2 3 4 5**

Diagnosis or main symptom(s) : ....

3. NARRATIVE

....

4. THIS SERIOUS ADVERSE EVENT IS DEFINED AS : (please tick √ all boxes that apply)

Death..... date |_|_| / |_|_| / |_|_|
Life threatening
Requiring or prolonging patient's hospitalization: date |_|_| / |_|_| / |_|_|
Medically significant, specify below : .....
Persistent or significant incapacity/disability
Other cancer : .....
Congenital disorder / birth defect

5. TREATMENTS *(filling the cases, page 2/2)*

6. RELEVANT MEDICAL HISTORY AND/OR CONCOMITANT DISEASES

....

7. CONCOMITANT MEDICATION *(not including medicines for SAE treatment)*

Treatment	Dose/Unit	Route	Indication	First dose	Last dose	Ongoing	Cause/effect relationship yes	no	possible
				|_|_| / |_|_| / |_|_|	|_|_| / |_|_| / |_|_|				
				|_|_| / |_|_| / |_|_|	|_|_| / |_|_| / |_|_|				
				|_|_| / |_|_| / |_|_|	|_|_| / |_|_| / |_|_|				

8. ADVERSE EVENT TREATMENTS

Treatment	Dose/Unit	Route	Indication	First dose	Last dose	Ongoing
				|_|_| / |_|_| / |_|_|	|_|_| / |_|_| / |_|_|	
				|_|_| / |_|_| / |_|_|	|_|_| / |_|_| / |_|_|	
				|_|_| / |_|_| / |_|_|	|_|_| / |_|_| / |_|_|	
				|_|_| / |_|_| / |_|_|	|_|_| / |_|_| / |_|_|	

9. OUTCOME

ongoing
Recovered without after-effects date |_|_| / |_|_| / |_|_|
Recovered with after-effects date |_|_| / |_|_| / |_|_|
Nature of after-effects :
....
Death due to the side effect date |_|_| / |_|_| / |_|_|
Death unconnected with the side effect date |_|_| / |_|_| / |_|_|
Unknown
Date end of the hospitalization : |_|_| / |_|_| / |_|_|

UFPV/ENR/024

5. TREATMENTS

CYCLE N° : DATE FIRST CYCLE : |_|_|/|_|_|/|_|_| ☐ Standard treatment (EXTREME) ☐ Experimental treatment (TPEx)

	ROUTE	DATES		DOSE / UNIT		TREATMENT MODIFICATIONS			TREATMENTS		
		Most recent infusion before SAE		Last dose	cumulative Dose since the 1st administration	(1) No change (2) Delayed (3) Discontinued (4) Dose reduction (5) reduction of infusion rate	if discontinued date of discontinuation	If delayed, stop and restart dates	Did the SAE abate after stopping the treatment 1 : Yes 2 : No 3 : NA	Did the SAE reappear after drug reintroduction 1 : Yes 2 : No 3 : NA	Assessment : 1 : Not related 2 : Unlikely 3 : Possible 4 : Probable 5 : Certain 6 : insufficient data
Cetuximab	IV	From |_|_|/|_|_|/|_|_|	To* |_|_|/|_|_|/|_|_|	|_|_|_|_|	|_|_|_|_|	|_| If dose reduction, new dose :	|_|_|/|_|_|/|_|_|	|_|_|/|_|_|/|_|_| |_|_|/|_|_|/|_|_|	|_|	|_|	|_|
Cisplatin/Carboplatin delete one as appropriate	IV	From|_|_|/|_|_|/|_|_|	To* |_|_|/|_|_|/|_|_|	|_|_|_|_|	|_|_|_|_|	|_| If dose reduction, new dose :	|_|_|/|_|_|/|_|_|	|_|_|/|_|_|/|_|_| |_|_|/|_|_|/|_|_|	|_|	|_|	|_|
5-Fluorouracil	IV	From|_|_|/|_|_|/|_|_|	To* |_|_|/|_|_|/|_|_|	|_|_|_|_|	|_|_|_|_|	|_| If dose reduction, new dose :	|_|_|/|_|_|/|_|_|	|_|_|/|_|_|/|_|_| |_|_|/|_|_|/|_|_|	|_|	|_|	|_|
Docetaxel	IV	From|_|_|/|_|_|/|_|_|	To* |_|_|/|_|_|/|_|_|	|_|_|_|_|	|_|_|_|_|	|_| If dose reduction, new dose :	|_|_|/|_|_|/|_|_|	|_|_|/|_|_|/|_|_| |_|_|/|_|_|/|_|_|	|_|	|_|	|_|

*At onset of the SAE, if treatment is continuing, enter "Cont" under date-to

10. Assessment *(According to you, the SAE is more likely due to)*

☐ Evaluated treatment(s) (which one)..... ☐ Disease progression

☐ Trial protocol ☐ Other concomitant disease(s), pre-existing condition, specify.....

☐ Other concomitant treatment(s), specify..... ☐ Other (including underlying malignancy) :specify.....

11. Reporter

Name and position of the reporter :

Name :
Adress:
Phone :
Fax :
E-mail :

Date |__|__| / |__|__| / |__|__|

Name of the investigator / co-investigator

Signature

20.7 APPENDIX 7: QLQ-C30 questionnaire

ENGLISH

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋

Your birthdate (Day, Month, Year): ⌊ ⌋⌊ ⌋ ⌊ ⌋⌊ ⌋ ⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋

Today's date (Day, Month, Year): 31 ⌊ ⌋⌊ ⌋ ⌊ ⌋⌊ ⌋ ⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋

		Not at All	A Little	Quite a Bit	Very Much
1.	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2.	Do you have any trouble taking a long walk?	1	2	3	4
3.	Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4.	Do you need to stay in bed or a chair during the day?	1	2	3	4
5.	Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:		Not at All	A Little	Quite a Bit	Very Much
6.	Were you limited in doing either your work or other daily activities?	1	2	3	4
7.	Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8.	Were you short of breath?	1	2	3	4
9.	Have you had pain?	1	2	3	4
10.	Did you need to rest?	1	2	3	4
11.	Have you had trouble sleeping?	1	2	3	4
12.	Have you felt weak?	1	2	3	4
13.	Have you lacked appetite?	1	2	3	4
14.	Have you felt nauseated?	1	2	3	4
15.	Have you vomited?	1	2	3	4
16.	Have you been constipated?	1	2	3	4

Please go on to the next page

ENGLISH

During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

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20.8 APPENDIX 8: EuroQol-5D questionnaire

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about ❑
I have some problems in walking about ❑
I am confined to bed ❑

Self-Care

I have no problems with self-care ❑
I have some problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

Usual Activities (*e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities ❑
I have some problems with performing my usual activities ❑
I am unable to perform my usual activities ❑

Pain/Discomfort

I have no pain or discomfort ❑
I have moderate pain or discomfort ❑
I have extreme pain or discomfort ❑

Anxiety/Depression

I am not anxious or depressed ❑
I am moderately anxious or depressed ❑
I am extremely anxious or depressed ❑

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today