Synopsis

Title:	**PHASE III TRIAL TESTING THE BENEFIT OF INTENSITY-MODULATED RADIOTHERAPY WITH WEEKLY REPLANIFICATIONS VERSUS INTENSITY MODULATED RADIOTHERAPY WITH ONLY ONE PLANIFICATION IN LOCALLY ADVANCED OROPHARYNX CARCINOMA FOR DECREASING XEROSTOMIA**

EUDRACT N°	
ACRONYM	**ARTIX (Adaptative Radiotherapy to Decrease Xerostomia in Oropharynx Carcinoma)**
SPONSOR	**Centre Eugene Marquis – Rennes - France**
STUDY COORDINATORS	Principal investigator: Pr Renaud de Crevoisier, Eugène Marquis Cancer Center, Rennes, France
TYPE OF STUDY	Randomized group-parallel multicentre phase 3 study

Hypothesis	The use of weekly replanning (adaptive radiotherapy) will decrease the xerostomia at 1 year, compared to standard IMRT
Primary Objective	To evaluate adaptive radiotherapy for locally advanced oropharynx cancer to improve salivary flow at 12 months after the end of radiotherapy
Secondary Objectives	- To evaluate the xerostomia and functional symptoms specific for head and neck - To evaluate early and late toxicities - To evaluate the excretory function of salivary gland (measured by scintigraphy). - To evaluate the local control, the disease-free survival and the overall survival.
Primary endpoint	Xerostomia rate measured by salivary flow after stimulation by parafilm before treatment and 12 months after the end of radiotherapy
Secondary endpoint	- Xerostomia rate measured by salivary flow after stimulation by parafilm before treatment and 6, 18 and 24 months after the end of radiotherapy - Excretory function measured by scintigraphy, before treatment and 12 months after the end of radiotherapy - Xerostomia specific questionnaire before treatment, and 3, 6, 12, 18 and 24 months after the end of radiotherapy - Functional questionnaire (MD Anderson Symptom Inventory Head Neck)c questionnaire before treatment, and 3, 6, 12, 18 and 24 months after the end of radiotherapy - Toxicities: Early (weekly during radiotherapy and at 3 months) and late at 6, 12, 18 and 24 months (based on CTCAE V4.0) - Local control rate at 2 years (based on T and N stage, and HPV status) - 2-year overall survival and 2-year overall specific survival - 1-year locoregional recurrence rate
Study design	The ARTIX trial is a randomised, parallel-group, multicentre study comparing systematic weekly replanning (ART) with standard IMRT (where a single replanning was left to the physician's appreciation) for patients with locally advanced oropharyngeal cancer.
Study Treatments	Patients will be randomly assigned in 2 arms, stratified by 4 factors (1:1, stratified by staging, HPV status, concomitant treatment and IMRT technic): - Standard arm: standard IMRT, with one initial planning - Experimental arm: Adaptive radiotherapy: IMRT with systematic weekly replanning to spare the parotid gland Radiotherapy: RT will be performed using IMRT (intensity modulated RT), based on CT. The following target volumes and organs at risk will be defined: - CTV 1 high risk (macroscopic tumor and immediate area): 70 Gy (2Gy/day) corresponding to GTV (Gross Tumor Volume) plus 5-10 mm margin. - CTV 2 intermediate: 63 Gy (1.8 Gy/day), corresponding to area of high risk of microscopic involvement (close to the tumor or immediate lymph node close to

	the GTV) - CTV 3 low risk : 56 Gy (1.6 Gy/day) corresponding to low risk area (N0 neck) The following dose will be delivered, in 35 fractions, 5 days per week, during 7 weeks, using simultaneous integrated boost technic: - PTV 1 (CTV 1 + 5mm) : 70 Gy (2 Gy/day) - PTV 2 (CTV 2 + 5 mm) : 63 Gy (1.8 Gy/day) - PTV 3 (CTV 3 + 5 mm): 56 Gy (1.6 Gy/day) Image guided radiotherapy will be used, with daily Kv2D or MV3D. Replanning will be performed based on a weekly CT (without IV contrast) from 2nd week to 6th week, to spare the parotid gland. Concomitant treatment: The following treatment will be administered during radiotherapy: - CDDP: 100mg/m², IV, J1-J22-J43 Or - Cetuximab: 400mg/m² IV at J-7, then 250 mg/m² IV weekly during the 7 weeks of RT Or - Carboplatin: 70 mg/m²/day J1-J4 and 5FU 600 mg/m² J1-J4 at week 1, 4 and 7 of RT,
Inclusion criteria	• Squamous cell carcinoma oropharynx histologically proven, T3-T4 or N2-N3, with an indication of chemo-radiotherapy, previously untreated • Age > 18 and ≤ 75 years. • Performance Status ECOG 0-2 • Biological parameters compatible with concomitant treatment • proper stomatological care • Written informed consent
Exclusion Criteria	• Both parotids included in target volume • T1 or T2 with N1 stage • Induction chemotherapy • Surgery (with curative intent) before radiotherapy • History of other malignancy within the last 5 years (exception of in situ carcinoma, skin carcinomas) • Not eligible for concomitant treatment • Significant disease which, in the judgment of the investigator, as a result of the medical interview, physical examinations, or screening investigations would make the patient inappropriate for entry into the trial

	• Other severe acute or chronic medical conditions including colitis, inflammatory bowel disease, pneumonitis, pulmonary fibrosis that may increase the risk associated with study participation or study treatment administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for entry into this study. • If Pregnant patients, breastfeeding patients, and female patients of childbearing potential who are unwilling or unable to use a highly effective method of contraception • 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.
Rules for dose modification	• The placement of a nasogastric tube or a medical gastrostomy tube (per endoscopic or interventional radiology) is part of the treatment (>= 2000 Cal/d). • The need for hospitalization for toxicity (usually from the end of the 2nd week) will be evaluated for each patient, depending on the mucosal and general tolerance of the treatment. • The appearance of mucositis with confluent false membranes does not constitute a criterion for stopping treatment, nor does the appearance of WHO grade IV mucositis (oral feeding not possible). On the other hand, severity criteria such as haemorrhagic mucositis, or the occurrence of ulceration would require discontinuation of the treatment. • The appearance of severe radiodermatitis (grade 3) in the radiation field around the 15-20th day of treatment is possible (10% to 30% of cases). This radiation dermatitis is a criterion for stopping Erbitux, if there are severity criteria such as extensive exudative epithelitis in the irradiation field and/or extending beyond the irradiation field and/or when this epithelitis is haemorrhagic, or even when the onset ulceration, this would require discontinuation of Erbitux® and also temporary discontinuation of radiotherapy. The resumption of radiotherapy will be possible when the signs of severity (exudation / haemorrhage) have disappeared. Hematological tolerance: • Systematic transfusion of 2 red blood cells if Hb < 7 g / 100ml. The use of EPO is prohibited, given the potential to stimulate the proliferation of tumour. If, on the scheduled date of chemotherapy, the neutrophil count (PNN) is less than 1500 /mm3 (grade 2) and/or platelets < 100,000/mm3 (grade 1), the cycle is delayed by one week. If the PNN rate is less than 500/mm3 (grade 4) and/or platelets < 25,000/mm3 (grade 4), the cycle is postponed. • If after one week the PNN level remains <1800/mm3 and/or platelets <100,000/mm3, discontinuation of chemotherapy with continuation of radiotherapy alone combined with cetuximab will be considered. Any febrile neutropenia requires hospitalization. The use of haematopoietic growth factors (G-CSF) will only be proposed in the event of profound and/or long-lasting neutropenia. End of treatment : The investigator can also prematurely interrupt the treatment for any reason that would serve the best interests of the person, including the case of an

	intercurrent illness or an adverse event. In the event of premature discontinuation of treatment, at any time and for any reason, the investigator should document the reasons as fully as possible. Patients continue to be monitored according to protocol and follow-up data will be collected until the research is completed.
Reasons for early cessation of trial therapy	The rules for stopping the study are defined in the event of a significant increase in the rate of loco-regional recurrence (> 18%) in the experimental arm of adaptive RT, in comparison with the reference arm (IDMC). This recurrence rate in the 2 treatment arms will be compared and analyzed (with an alpha threshold of 1%) by an independent monitoring committee of the trial, when 50% of the randomized patients will have 1 year of follow-up.
Number of patients	The number of patients was calculated with a comparison test (z-test) for independent groups, with continuity correction and according to a one-sided assumption. Knowing that the risk of xerostomia at 12 months in this indication is 60% with treatment standard (P0), that P1 designates the risk of xerostomia with the adaptive processing, and that it is expected that the strategy adaptive therapy reduces the risk of xerostomia by 25%, assumptions of the calculation of the number of subjects necessary can be written as follows: - Null hypothesis (H0): P0 = P1 = 60% - Alternative hypothesis (H1): P1 < P0. Under these conditions, it is necessary to include at least 132 patients to reject the null hypothesis with a power of 90%. A first kind risk is accepted and set at 5% . An early stopping rule is defined in case of increase of the risk of recurrence (> 18%) in the experimental arm, compared to the standard arm (IDMC). An Independent Data and Safety Monitoring Committee (IDSMC) will be designated and when 50% of the included patients will have a follow up of 1 year, the IDSMC will make a statement on whether the study could continue.
Statistical analysis	Analysis will be performed on the intent-to-treat population, defined by the overall subjects receiving at least one dose of chemotherapy and one radiotherapy session, as assigned by the randomisation procedure. A secondary analysis will be performed on the per protocol population, defined by the intent-to-treat population without major deviation. For main criteria, unilateral test with α =0,025 will be used. Other tests will be performed with α =0,05. For each quantitative parameter, descriptive statistics (number of data available and missing data, mean, standard deviation, mean-deviation, median, min/max, range confidence at 95%) will be presented at each time of measurement as well as for the deviations. For each qualitative parameter, the number and percentage of patients by class/category will be presented at each time of measurement. For the main criterion, the analysis will be carried out on each of the 2 criteria. For the measurement of saliva flow 12 months after the end of radiotherapy, comparison between the 2 treatment arms will be performed with a mixed model with the treatment arm as a fixed factor and the following parameters as covariates: center as well as the 4 stratification factors. For the non-inferiority test on the loco-regional recurrence rate, a survival analysis of time to recurrence as well as survival curves (Kaplan Meier method) will be carried out with as explanatory variables: the arm of treatment, the center and the 4

	stratification factors. The interval 95% confidence level will be calculated and the non-inferiority limit will be 18%. The same test as for measuring saliva flow will be used for the quantification of salivary flow by scintigraphy at each measurement time. For measuring salivary flow after stimulation with paraffin and for quality-of-life scores (Eisbruch Questionnaires and MDASI-HN), analyses of variance with repeated measures will be used to compare the differences in mean according to the time (before treatment and 3, 6, 12, 18, 24 months after the end of radiotherapy) and between the 2 treatment arms. The percentage of patients reporting acute toxicities and late and the loco-regional recurrence rate at 2 years (stage T and N, HPV status) will be compared between the 2 treatment arms using the Chi² test or Fisher's exact test. For 2-year overall survival and specific survival, the comparison between the 2 treatment arms will be made using a survival analysis (Logrank test) and survival curves according to the Kaplan Meier method.
Trial timelines	Inclusion : 5 years 4 months Follow-up : 2 years Total time : 7 years and 6 months