A blind randomized multicenter study of accelerated fractionated chemo-radiotherapy with or without the hypoxic radiosensitizer nimorazole (Nimoral), using a 15 gene signature for hypoxia in the treatment of HPV/p16 negative squamous cell carcinoma of the head and neck.

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Collaborative Groups: EORTC Radiation Oncology Group
EORTC Head and Neck Cancer Group

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Attention:
This is an Intergroup study lead by the DAHANCA and coordinated by the EORTC. The present protocol is written according to the EORTC template and is fully applicable to all collaborative groups

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Protocol summary

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<th>A blind randomized multicenter study of accelerated fractionated chemo-radiotherapy with or without the hypoxic cell radiosensitizer nimorazole (Nimoral), using a 15-gene signature for hypoxia in the treatment of HPV/p16 negative squamous cell carcinoma of the head and neck.</th>
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<tr>
<td>Objective(s)</td>
<td>There are two primary objectives in this study: The first of them is to evaluate in a blinded randomized trial, whether the hypoxic cell radiosensitizer nimorazole can improve the effect of primary curative accelerated fractionated concomitant chemo-radiotherapy with concomitant cisplatin given to patients with locally advanced HPV/p16 negative squamous cell carcinoma of the head and neck (HNSCC). The second one is to investigate if the patients and tumors that may have such benefit can be predicted by the use of a hypoxic gene profile, i.e. if the treatment benefit is larger and essentially restricted to the subset of patients who are hypoxic cell signature positive. The secondary objectives will be to evaluate the feasibility and morbidity of such treatment.</td>
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<tr>
<td>Methodology</td>
<td>This is a blind randomized, placebo-controlled, multicenter, phase III study of accelerated fractionated chemo-radiotherapy with or without the hypoxic radiosensitizer nimorazole in the treatment of squamous cell carcinoma of the head and neck (HNSCC).</td>
</tr>
<tr>
<td>Number of patients</td>
<td>This is a randomized superiority trial where the number of patients enrolled is planned as 640, 320 in each treatment arm. <strong>However, should the observed proportion of hypoxic signature positive patients be lower than anticipated, the recruitment will continue until 200 patients are available in the hypoxic signature positive subgroup.</strong></td>
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| Diagnosis and main criteria for inclusion | ♦ Newly diagnosed tumors classified as stage III-IV located in the larynx, oropharynx and hypopharynx (unknown primary and oral cavity are not eligible)  
♦ HPV/p16 negative (≤70% positively stained cells), assessed locally (please refer to chapter 1.2).  
♦ Histopathological diagnosis of invasive squamous cell carcinoma in the primary tumor  
♦ No distant metastasis (M0)  
♦ Age > 18 years  
♦ Before patient registration, written informed consent must be given according to ICH/GCP, and national/local regulations  
♦ Tumor material (7 FFPE sections) available for central testing of the hypoxic gene signature  
♦ WHO performance 0-2  
♦ All hematology and biochemical investigations, should be done within 4 weeks before randomization (maximum 6 weeks before treatment |
Normal bone marrow function based on routine blood samples, i.e. neutrophils ≥ 1.0 x 10^9/L, platelets ≥ 75 x 10^9/L, hemoglobin ≥ 10.0 g/dL or 6.2 mmol/L

Normal kidney function creatinine clearance ≥ 60ml/min (measured or calculated according to the method of Cockcroft and Gault, Appendix D), and Electrolyte balance: calcium ≤ 11.5 mg/dl or 2.9 mmol/l, magnesium ≥ 1.2 mg/dl or 0.5 mmol/l

Normal liver function assessed by routine laboratory examinations, i.e. bilirubin < 1.5 x ULN, ALT< 3 x ULN, alkaline phosphatases < 3 x ULN

No prior or current anticancer treatment to the head and neck area (e.g. radical attempted or tumor reductive surgery, neo-adjuvant chemotherapy, EGFR inhibitors or radiotherapy).

Patients must be candidate for curative intent external beam chemoradiotherapy, and must be expected to complete the treatment.

All patients should have an oral and dental examination including preferably clinical and radiological examination. Whenever indicated, extraction of dental elements should be carried out at least 10 to 14 days before treatment start.

Radiotherapy planned to start within acceptable delay (preferably within 2 weeks and a maximum of 4 weeks from randomization).

Radiotherapy planned to start within 8 weeks from baseline imaging tumor assessment.

Patients should not have symptoms of peripheral neuropathy, assessed by medical history.

Absence of any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule; those conditions should be discussed with the patient before randomization in the trial.

All subjects must:

- Agree to abstain from donating blood while receiving therapy and for four weeks following discontinuation of therapy.
- Agree not to share study medication with another person and to return all unused study drug to the investigator.

### Treatment

| Test product, dose and mode of administration | Accelerated radiotherapy (Therapeutic PTV: 70 Gy, 6 fractions/week, 35 fractions of 2 Gy, prophylactic PTV: 54.25 Gy, 6 fractions/week, 35 fractions of 1.55 Gy) + concomitant cisplatin (either weekly schedule of 40 mg/m^2 (delivered on day 1, 8, 15, 22, 29) or 100 mg/m^2 on day 1 and day 22). Patients will receive nimorazole or placebo (1.2 g/m^2) 90 min prior to each radiotherapy fraction but no more than 5 times a week (If the 6th radiotherapy fraction in a week is given on a separate day from the 5th fraction of radiotherapy, no nimorazole/placebo dose is received that day. If |

| Treatment | Accelerated radiotherapy (Therapeutic PTV: 70 Gy, 6 fractions/week, 35 fractions of 2 Gy, prophylactic PTV: 54.25 Gy, 6 fractions/week, 35 fractions of 1.55 Gy) + concomitant cisplatin (either weekly schedule of 40 mg/m^2 (delivered on day 1, 8, 15, 22, 29) or 100 mg/m^2 on day 1 and day 22). Patients will receive nimorazole or placebo (1.2 g/m^2) 90 min prior to each radiotherapy fraction but no more than 5 times a week (If the 6th radiotherapy fraction in a week is given on a separate day from the 5th fraction of radiotherapy, no nimorazole/placebo dose is received that day. If |
the 6th fraction of radiotherapy is given on the same day as the 5th fraction, nimorazole/placebo is given 90 minutes before the 5th radiotherapy fraction, only).

<table>
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<tr>
<th>Duration of treatment</th>
<th>Concomitant chemo-radiotherapy + nimorazole or placebo will be delivered in 6 weeks (an additional 2 days overall treatment time will be accepted).</th>
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<tr>
<td>Reference therapy, dose and mode of administration</td>
<td>Accelerated radiotherapy (Therapeutic PTV: 70 Gy, 6 fractions/week, 35 fractions of 2 Gy, prophylactic PTV: 54.25 Gy, 6 fractions/week, 35 fractions of 1.55 Gy during 6 weeks starting on a Monday); radiotherapy will be delivered in 6 weeks, however an additional 2 days overall treatment time will be accepted. Cisplatin can be administered as either a weekly schedule of 40 mg/m² (delivered on day 1, 8, 15, 22, 29) or 100 mg/m² on day 1 and day 22.</td>
</tr>
<tr>
<td>Criteria for evaluation</td>
<td>Primary endpoint is: ♦ Locoregional control rate Secondary endpoints are: ♦ Local control (T-site) ♦ Regional control (N-site) ♦ Time to distant metastasis ♦ Overall survival ♦ Disease-free survival ♦ Disease-specific survival ♦ Acute and late morbidity</td>
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</table>
| Statistical methods | Two main analyses will be done in the trial with the same objective of looking at the treatment effect of nimorazole. The first one will be done in the whole population of randomized patients and the second one will be done in the subgroup of randomized patients having a positive hypoxic cell signature as it’s anticipated that the full effect of the nimorazole will be confined in this subgroup. In the whole population, the null hypothesis to be tested is H0: HR=1 versus the alternative hypothesis H1: HR=0.615. In the subgroup of randomized patients having a positive hypoxic cell signature, the null hypothesis to be tested is H0: HR=1 versus the alternative hypothesis H1: HR=0.46. Following a closed testing procedure for those two analyses to preserve the overall type I error at 0.025, the type I error will be 0.015 in the whole population and 0.012 in the positive subgroup. The analyses of the efficacy endpoints (locoregional control rate, disease-free survival, disease-specific survival and overall survival) will be performed on all randomized patients according to the intention to treat principle. The analyses of the safety endpoints will be performed on the safety population defined as all randomized patients who have started their
| Future Translational research | Prospective baseline tumor material collection for future translational research program to address  
1) screening for genetic and cellular determinants of outcome based on FFPE samples  
2) biomarker discovery |
1 Introduction

1.1 Background of the study

Head and neck cancer is the fifth most common malignancy worldwide. The incidence is rising, particularly among socially deprived sections of the community. Squamous cell carcinoma of the head and neck (HNSCC) is linked to a number of risk factors, including smoking and excessive consumption of alcohol, such that many patients have co-morbid conditions. More than 60 percent of patients present with locally advanced (stage III and IV) disease, where the presence of distant metastases are infrequent, and mainly a consequence of locoregional treatment failure. The treatment of such locally advanced HNSCC is predominately radiotherapy, alone or combined with simultaneous chemotherapy, mainly cisplatin-based regimens. Several biological modifications of radiotherapy of HNSCC have markedly improved the outcome in form of both locoregional control and laryngectomy-free, disease specific and overall survival. These modifications include the use of altered fractionation (i.e. accelerated and hyperfractionation), hypoxic modification and concomitant chemo-radiotherapy. All three modifications have been developed through a large number of randomized clinical trials and are consequently supported by large Meta-analyses, including more than 30,000 patients. Thus, all three modifications have level 1A evidence (Ref. 34, Ref. 35, Ref. 36).

Although, intuitively the three modifications do not interact with each other, studies directly comparing the individual modalities against the two others are limited in numbers. The aim of the current study is therefore to investigate the hypoxic modifier nimorazole when combined with accelerated fractionation and concomitant chemo-radiotherapy with weekly cisplatin. Based on the Danish Head and Neck Cancer (DAHANCA) study group’s database, which is a national database mainly built on experience from a large number of clinical trials, the benefits of these three biological modifications in stage III and IV patients, with larynx, pharynx and oral cavity squamous cell carcinoma, have been evaluated. The studies clearly indicate an improved outcome when each of the three biological principles is added successively to the prior modality. Further, a multivariate analysis shows independent prognostic benefits, using both local control and survival as end points of all three modifications (Ref. 3). This strongly indicates that addition of hypoxic modification to chemo-radiotherapy would be beneficial. A similar randomized trial by Trans-Tasman Radiation Oncology Group (TROG) using the hypoxic cytotoxin Tirapazamine, this was found to yield an almost significant (p=0.06) benefit in favor of hypoxic modification, when combined in patients treated with concomitant chemo-radiotherapy (Ref. 4). The lack of conclusive results of this trial was thought at least partly to be due to poor quality of radiotherapy, leaving only a reduced number of patients evaluable for final outcome.

The original DAHANCA 5 trial (Ref. 1) demonstrating the benefit of nimorazole in HNSCC evaluates the hypoxic modifier in a study where the primary treatment was conventionally fractionated radiotherapy (5 fractions/week for 7 weeks). Subsequently, the DAHANCA 7 trial (Ref. 2) demonstrated that adding accelerated fractionation (6 fractions/week for 6 weeks) to that schedule improved the outcome, and the opposite, comparing accelerated fractionation alone with added nimorazole is currently being investigated in a randomized trial (IAEA-HypoX).

There is substantial evidence from randomized trials and a consequent meta-analysis that the treatment of HNSCC can be substantially improved by the use of cisplatin based concomitant chemotherapy due to additive or supra-additive cell killing of the tumor stem-cells leading to improved loco-regional tumor control. In addition, it may theoretically also reduce the risk of distant metastases although this has not been significantly demonstrated (Ref. 11, Ref. 12).
The initially used regimen was cisplatin, 100 mg/m² given three times at three-week intervals during conventional radiotherapy. However, this schedule has been shown to be associated with substantial toxicity and about half of the patients may not comply with the treatment (Ref. 7). Especially the elderly patient group with a higher incidence of comorbidity has great difficulties in tolerating this schedule. The use of accelerated fractionation may further bear a risk of increasing the toxicity (Ref. 12).

The RTOG 0129 randomized study showed an equally effective outcome between treatment with two cycles of 100 mg/m² of cisplatin together with accelerated fractionation vs. three cycles of 100 mg/m² cisplatin together with conventional fractionation (Ref. 13). The interaction between accelerated fractionation and chemo-radiotherapy is however more complex, as the accelerated fractionation especially benefits the T-site with limited or no benefit on the nodal disease, whereas patients with large lymph nodes may benefit from the chemotherapy. The two treatment principles are therefore likely to be at least supra-additive, as it is also shown in data from the DAHANCA database, which demonstrate significant independent importance of the two parameters on both locoregional control and survival (Ref. 3).

In addition to the evidence that a total cisplatin dose of 200 mg/m² in combination with accelerated concomitant radiotherapy may be as effective as a total cisplatin dose of 300 mg/m² concomitant with conventional fractionated radiotherapy, there are good indications suggesting that what matters is the total dose of chemotherapy and not the strength of the individual dose.

The feasibility and tolerance of the combined schedule of nimorazole, accelerated fractionation and concurrent chemo-radiotherapy with weekly cisplatin (40 mg/m² weekly for at least five weeks) has been evaluated in the DAHANCA 18 study (Ref. 5), a Phase II study with more than 300 Stage III and IV patients, and found to be a feasible and acceptable treatment with a compliance to both the hypoxic modifier and chemotherapy in about 80% of patients and an almost 95% compliance to radiotherapy. The treatment has subsequently become routine treatment of Danish head and neck cancer patients and has also been the control arm in a recently completed large randomized trial (DAHANCA 19) (Ref. 6), comparing this treatment schedule with the same schedule, plus the Epidermal Growth Factor (EGF) receptor inhibitor Zalutumumab. Thus, there are abundant data indicating that nimorazole and weekly cisplatin is an acceptable schedule with superior compliance to e.g. that found for the schedule of 100 mg/m² cisplatin every three weeks (Ref. 7). However, the documentation demonstrating that the hypoxic modifier significantly adds to the accelerated chemo-radiotherapy schedule is still indirect and thus the current clinical trial is aiming towards securing that information.

Based on the reality that different cisplatin regimens are applied at different treatment centers and the lack of direct comparisons of the two regimens, the concomitant cisplatin regimen in the current protocol will be optional and be administered as either a weekly schedule of 40 mg/m² (delivered on day 1, 8, 15, 22, 29) or 100 mg/m² on day 1 and day 22, both schedules yielding a total dose of 200 mg/m². Both schedules will secure maximum tolerance and compliance in the current patient group, which is characterized by having Human papillomavirus (HPV) negative tumors who consequently have a higher incidence of comorbidity. It should also be noted that despite the fact that the treatment burden with chemo-radiotherapy is substantially higher than with accelerated fractionation alone, this additional morbidity due to the treatment is associated with acute and late reactions.

Nimorazole, a 5-nitroimidazole was developed in the mid-1980s as a hypoxic radiosensitizer with limited, non-serious toxicity. Thus, in contrast to the more lipophilic 2-nitromidazoles (misonidazole, ethanidazole, etc.) the drug does not have neurotoxicity at therapeutic dose levels, so the main side effects are nausea and vomiting. This is associated with the immediate intake of the drug and ceases immediately when intake of the drug is skipped. Thus, the side effects are purely acute without long lasting symptoms (Ref. 1).

Oral intake of the drug may be difficult for patients in the later part of radiotherapy due to the presence of stomatitis. For that purpose the drug has been formulated as dispersible tablets that can be dispersed in liquid to ease the intake. Similarly, nimorazole can be given to patients via nasogastric (NG) feeding tube
or directly into the stomach via percutaneous endoscopic gastrostomy tube (PEG). There are no indications that the side effects to cisplatin and nimorazole are synergistic, but the combined acute side effects from both drugs may compromise the compliance to treatment.

Many head and neck cancer patients smoke, and smoking during radiotherapy should be strongly discouraged. Recent data have confirmed that patients smoking during radiotherapy treatment have significantly poorer locoregional control due to poor tumor oxygenation, which may render the tumors more hypoxic. In addition such patients suffer from the traditional smoking related problems, such as increased risk of secondary cancer (Ref. 8).

Head and neck carcinoma has changed its pattern due to dramatic variation in epidemiology. A very fast increase in HPV induced oropharyngeal carcinomas has been seen, especially in Western countries – and at the same time, the traditional smoking and alcohol related tumors are on a decline. The HPV/p16 positive tumors are characterized by a substantially better prognosis and although the tumors may express hypoxic features, such as hypoxic gene profiling, low oxygen content by pO2 measurements and expressing hypoxia in PET scans, there seems to be no benefit from hypoxic modification, probably due to increased cellular radiosensitivity compared to HPV/p16 negative tumors. The optimal treatment of such HPV positive tumors is currently discussed and some de-escalation of the therapy is considered, and there is clearly no indication for the use of hypoxic modification (Ref. 37, Ref. 10). For that reason, patients with a HPV/p16 positive profile are not included in the current study, which will solely address the more resistant HPV/p16 negative tumors where hypoxic resistance is a very distinct feature and the tumors benefit from hypoxic modification.

Targeted treatment with hypoxic modification has not yet been possible due to the lack of suitable predictive markers capable of identifying patients and tumors, which may benefit from the treatment. Although the presence of hypoxia can be identified by oxygen sensitive electrodes, various PET imaging modalities or immuno-histochemical markers, these are tedious and expensive procedures that have never been incorporated into routine practice. Recently a hypoxic gene profile has been developed based on tumor oxygen electrode measurements and subsequently independently verified and demonstrated to be highly prognostic for identifying tumors in need of hypoxic modification (specifically nimorazole). This profile, which is found in approximately one third of the HNSCC tumors, can be measured based on RNA extracted from the primary paraffin embedded histopathological biopsy from the diagnostic specimens. Retrospective evaluation in the DAHANCA 5 trial (Ref. 9, Ref. 10) showed a strong ability to predict the need for hypoxic modification for both local regional control and tumor specific deaths. The usefulness of this hypoxic gene profile will, however, be strengthened by being demonstrated in a prospective clinical trial.

### 1.2 Scoring and classification of p16-immunohistochemistry in HPV-related oropharyngeal cancer

Expression of p16 is highly correlated to Human Papillomavirus (HPV) in oropharyngeal cancer (Ref. 24, Ref. 25, Ref. 26, Ref. 27) and the strong prognostic impact of p16-immunohistochemistry (IHC) in radiotherapy of HNSCC has been demonstrated in several clinical trials (Ref. 24, Ref. 27, Ref. 28, Ref. 37).

The recommendations on the scoring and classification p16-IHC are devised on the basis of a revision of DAHANCA-material (Ref. 29) and recommendations set forward by El-Naggar et al (Ref. 30) taking into account both the percentage of p16-positive tumor cells and the characteristic morphological profile of HPV-related HNSCC (Ref. 30, Ref. 31).
1.2.1 Interpretation of p16-IHC

Strong and uniform p16-staining (both cytoplasmatic and nuclear) in > 70% of cancer cells of basaloid non-keratinised/partially keratinised oropharyngeal carcinoma is classified as p16-positive and can be interpreted as HPV-positive.

Absent or weak p16-staining of basaloid non-keratinised/partially keratinised oropharyngeal carcinoma is classified as p16-negative.

Non-uniform/patchy p16-staining in conventional keratinising squamous cell carcinoma of the oropharynx is classified as p16-negative.

Whether additional HPV-testing (in situ hybridisation/PCR-detection) would further optimize the correlation with HPV in the two last-mentioned situations is presently unresolved, and as such not routinely recommended by the DAHANCA.

1.2.2 p16-IHC staining on formalin fixed paraffin embedded (FFPE) tissue

The following protocol represents an example of p16-IHC performed on a BenchMark® XT autostainer (Ventana Medical Systems, Illkirch, France).

FFPE sections are cut at 5 µm on Superfrost® plus charged glass slides (Menzel-Glaser), heated at 60°C for 1 hour and deparaffinised in the instrument with EZ prep solution (Ventana Medical Systems). Antigen retrieval is carried out using Cell Conditioning 1 solution (CC1, Ventana Medical Systems). Sections are incubated with murine anti-p16 antibody clone JC8 (Santa Cruz Biotechnology Inc) diluted 1:25 for 32 minutes. Specific reactions are detected using ultraView™ Universal DAB Detection Kit (Ventana Medical Systems) and the slides counterstained with haematoxylin.

Other commercially available antibodies can be used for incubation, for instance the E6H4 clone (MTM Laboratories) which has been used in several clinical trials and also recommended by NordiQC (Nordic immunohistochemical Quality Control) (Ref. 32).

1.3 Nimorazole: Investigational drug information

1.3.1 General information

Nimorazole belongs to a class of chemicals known as 5-nitroimidazoles. Nitroimidazoles are used therapeutically as anti-infective drugs due to their antiprotozoal, antitrichomonal and antibacterial activity targeting anaerobic bacteria and protozoan infections.

Nimorazole is also a hypoxic radiosensitizer with high electron affinity enabling the drug to mimic the effect of oxygen in rendering hypoxic cells radiosensitive.

Of all nitroimidazoles, nimorazole has been the choice of drug to further pursue as a hypoxic radiosensitizer due to good bioavailability in tumors following oral administration, short half-life and good therapeutic ratio compared to other nitroimidazoles such as misonidazole.

The benefit of hypoxic radiosensitization has been tested in clinical studies in more than 10,000 patients with various solid tumors. The highest benefit was seen in squamous cell cancers – specifically HNSCC but also in uterine cervix cancer.

Nimorazole is presented as dispersible tablets. This oral dosage form provides convenient dosing of patients throughout radiotherapy whether through routine oral administration or through a PEG/NG tube.
1.3.2 Pre-clinical safety and pharmacology

A nimorazole plasma concentration of approximately 50 µg/mL gave a radiotherapy enhancement ratio of ~1.4 in C3H mouse mammary carcinoma. Such plasma levels are equivalent to a dose of 1.2 g/m² nimorazole in humans.

Studies on in-vitro glycolytic metabolism (via tracer uptake) of hypoxic human squamous cell carcinoma cell line UT-SCC-5 exposed to increasing levels of hypoxia indicated that nimorazole was moderately toxic for hypoxic cells, whereas nimorazole only exerted a moderate effect on the survival of fully oxygenated cells. This indicates some bioreductive activity of nimorazole.

In mice and rats, nimorazole has shown only slight and transient effect on CNS (reduced activity, reduced reactivity to stimuli, hypothermia) after high doses.

Nimorazole has no effect on intestinal transit time in mice mirroring the lack of effect on in vitro intestinal contraction. Nimorazole has no effect on blood pressure in cats or rabbits. Although no determination of effects on ECG has been studied this lack of effect on blood pressure adds to the assumption that nimorazole has no or only insignificant effect on heart and circulation. Furthermore, no signs (neither clinical nor at autopsy) in the toxicology studies raise a suspicion of such an effect.

The pharmacokinetics of nimorazole has not been extensively studied in animals, through data available confirm what is known from other nitroimidazoles such as: wide distribution in the body, high renal excretion after metabolism in the liver, relatively low protein-binding, a short half-life and a good tissue-penetration into tumors are characteristics for nimorazole among nitroimidazoles which together with that the two main metabolites of nimorazole maintain the radio-sensitizing ability of nimorazole making the compound a valuable adjuvant in radio-therapy of cancer.

The acute toxicity in rodents is low with a LD₅₀ of about 2 g/kg or higher.

Toxicity studies with duration of three months in rats and dogs revealed no significant findings after daily doses of up to 250 mg/kg in rats and after 120 mg/kg in dogs, apart from a reduced number of spermatocytes in male dogs of the high dose only (120 mg/kg). However this effect is not reflected in the study of male fertility in rabbits.

Teratogenicity studies in as many as three species (mice, rats and rabbits) have been undertaken showing nimorazole to be devoid of teratogenic properties.

Fertility studies in male rabbits did not show any effect of nimorazole. However the duration of the administration period does only cover the last half of the spermatogenesis.

Apart from an Ames’ test with several nitroimidazoles where nimorazole showed mutagenic activity in some of the strains of salmonella Typhimurium used (standard strains for this type of test) no specific assays of the mutagenic properties of nimorazole has been retrieved, though nimorazole has been included in several studies of the mutagenic properties of nitroimidazoles. As the anti-microbial activity goes hand in hand with the mutagenic activity of nitroimidazoles and that nimorazole has a poor anti-microbial activity, a low mutagenic potential is assumed.

Nitroimidazoles (in particular metronidazole) are suspected to be genotoxic carcinogens. However no specific studies of the carcinogenic potential of nimorazole have been performed it can be assumed that such a potential may be low due to the low mutagenicity of nimorazole.

Regarding the similarities in many respects between nimorazole and metronidazole which has a long record of favorable use in anti-microbial therapy it is considered that the risk of use of nimorazole for the indication proposed is comparable to or better than that for use of metronidazole.
1.3.3 Previous clinical experience with nimorazole

Hypoxic modification of radiotherapy has shown clinical benefit in the treatment of HNSCC and to some extent in uterine cervix cancer.

At dose levels up to 2.5 g/day, 5 days a week during 6–7 weeks (total dose of approximately 75 g), nimorazole showed significant benefit in terms of improved locoregional control and disease specific survival in patients with loco-regionally advanced head and neck cancer over patients treated with conventional radiotherapy.

With this dosing regimen the side effect profile was acceptable with the most predominant side effects being nausea and vomiting.

Studies have also showed the benefit of accelerated radiotherapy versus conventional radiotherapy, i.e. acceleration defined as six fractions per week instead of five but at the same total dose of irradiation. This benefit was statistically significant for locoregional control and disease specific survival when radiotherapy was given alone or concurrently with nimorazole.

Studies suggest that patients with HPV positive HNSCC may respond less favorably to nimorazole.

Studies suggest that patients with more rather than less hypoxic HNSCC tumors respond more favorably to nimorazole.

The current protocol will be the first randomized study addressing the importance of using an hypoxic radiosensitizer to improve the outcome of accelerated chemo-radiotherapy in locally advanced HNSCC, and the first study to specifically address the issue of targeting patients with hypoxic tumors through a molecular signature.

2 Objectives of the trial

2.1 Primary objectives

There are two primary objectives in this study:

The first primary objective is to evaluate in a blinded randomized trial, whether the hypoxic cell radiosensitizer nimorazole can improve the effect of primary curative accelerated fractionated concomitant chemo-radiotherapy with cisplatin given to patients with locally advanced HPV/p16 negative (HNSCC).

The second primary objective is to investigate if patients who may have such benefit can be predicted by the use of a hypoxic gene profile, i.e. if the treatment benefit is larger and essentially restricted to the subset of patients who are hypoxic cell signature positive.

2.2 Secondary objective

The secondary objective will aim to evaluate the feasibility and morbidity of such a treatment strategy.
2.3 End-points

Primary endpoint
♦ Locoregional control rate

Secondary endpoints:
♦ Local control (T-site)
♦ Regional control (N-site)
♦ Time to distant metastasis
♦ Overall survival
♦ Disease-free survival
♦ Disease-specific survival
♦ Acute and late morbidity

3 Patient selection criteria

To be eligible the patient has to meet all inclusion criteria and must not violate any of the exclusion criteria.

3.1 Registration step

3.1.1 Inclusion criteria
♦ Before patient registration, written informed consent must be given according to ICH/GCP, and national/local regulations
♦ Newly diagnosed tumors classified as stage III-IV located in the larynx, oropharynx and hypopharynx (unknown primary and oral cavity are not eligible).
♦ HPV/p16 negative (≤70% positively stained cells), assessed locally (please refer to chapter 1.2).
♦ Histopathological diagnosis of invasive squamous cell carcinoma in the primary tumor.
♦ No distant metastasis (M0).
♦ Age ≥ 18 years.
♦ Tumor material (7 FFPE sections) available for central testing of the hypoxic gene signature
3.2 Randomization step

3.2.1 Inclusion criteria

♦ WHO performance 0-2.

♦ All hematology and biochemical investigations, should be done within 4 weeks before randomization (maximum 6 weeks before treatment starts)

   ♦ Normal bone marrow function based on routine blood samples, i.e. neutrophils ≥ 1.0 x 10^9/L, platelets ≥ 75 x 10^9/L, hemoglobin ≥ 10.0 g/dL or 6.2 mmol/L

   ♦ Normal kidney function creatinine clearance ≥ 60 mL/min (measured or calculated according to the method of Cockcroft and Gault, Appendix D), and Electrolyte balance: calcium ≤ 11.5 mg/dl or 2.9 mmol/L, magnesium ≥ 1.2 mg/dl or 0.5 mmol/L

   ♦ Normal liver function assessed by routine laboratory examinations, i.e. bilirubin < 1.5 x ULN, ALT< 3 x ULN, alkaline phosphatases < 3 x ULN

♦ No prior or current anticancer treatment to the head and neck area (e.g. radical attempted or tumor reductive surgery, neo-adjuvant chemotherapy, EGFR inhibitors or radiotherapy).

♦ Patients must be candidate for curative intent external beam chemo-radiotherapy, and must be expected to complete the treatment.

♦ All patients should have an oral and dental examination including preferably clinical and radiological examination. Whenever indicated, extraction of dental elements should be carried out at least 10 to 14 days before treatment start.

♦ Radiotherapy planned to start within acceptable delay (preferably within 2 weeks and a maximum of 4 weeks from randomization).

♦ Radiotherapy planned to start within 8 weeks from baseline imaging tumor assessment.

♦ Patients should not have symptoms of peripheral neuropathy, assessed by medical history.

♦ Absence of any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule; those conditions should be discussed with the patient before randomization in the trial.

♦ All subjects must:

   ♦ Agree to abstain from donating blood while receiving therapy and for four weeks following discontinuation of therapy.

   ♦ Agree not to share study medication with another person and to return all unused study drug to the investigator.
3.2.2 Exclusion criteria

♦ Patients who have received treatment with any investigational drug substance within 4 weeks prior to randomization.

♦ Current participation in any other interventional clinical study.

♦ Pregnant or breast-feeding female patient. Pregnancy test should be done within 72 hours from treatment start.

♦ Female subjects of childbearing potential (defined as a sexually mature woman who 1) has not undergone a hysterectomy or bilateral oophorectomy or 2) has not been naturally post-menopausal (amenorrhoea following cancer therapy does not rule out childbearing potential) for at least 12 consecutive months (i.e. has had menses at any time in the preceding 12 consecutive months) not willing to use adequate contraception during study and for 6 month after last dose of study drug.

♦ Male subjects not willing to use condoms throughout study drug therapy, and for 6 months after cessation of study therapy if their partner is of childbearing potential and has no contraception.

♦ Known or suspected HIV infection.

♦ Second malignancies in the 3 years prior to study entry with the exception of surgically cured carcinoma in situ of the cervix, in situ breast cancer, incidental finding of stage T1a or T1b prostate cancer, and basal/squamous cell carcinoma of the skin.

♦ Uncontrolled or chronic bacterial, fungal or viral infection.

♦ Known or suspected hypersensitivity to component(s) of investigational product or cisplatin contraindication.

All indicated timelines and absolute values requested by the eligibility criteria must be adhered to. However, a maximum of +/- 10% of the reference value for laboratory parameters and a maximum of +/- 2 days for timelines may be acceptable. Discussion with EORTC Headquarters and study coordinator is encouraged.

4 Trial design

This is a blinded, randomized, placebo-controlled, multicenter, phase III study of accelerated fractionated chemo-radiotherapy with or without the hypoxic radiosensitizer nimorazole in the treatment of squamous cell carcinoma of the head and neck.

4.1 Blinding

The patient, the investigator and study team at site and the EORTC Headquarters study team will remain blinded to treatment allocation up to the database lock for the final analysis of the primary endpoint.

However, at any time during the trial, in case of a safety concern affecting an individual patient, the site investigator can request the unblinding of that patient. The unblinding requests should be made by the site investigator through the ORTA randomization system (see section 12).
4.2 Design

Patients will be first registered into the EORTC ORTA system (registration = step 1) after signing the informed consent form. The site will immediately send the FFPE samples for hypoxic gene signature to the central lab (within 24 hours if possible). Once the results are assessed and entered in ORTA by the central lab (step 2), the site will be notified that they can further proceed to patient randomization in the EORTC ORTA system. Patients will be randomized (step 3) after verification of the eligibility criteria to receive one of the following: chemoradiotherapy (CRT) + nimorazole, or chemoradiotherapy (CRT) + placebo. Maximum time elapsed between registration and randomization should be three weeks. Maximum time elapsed between randomization and treatment start should be 4 weeks.

Step 1 = registration, step 2 = central lab enters hypoxic gene signature result in ORTA, site is notified, step 3 = randomization (R); trt = treatment; CRT = chemoradiotherapy.

CRT will consist of accelerated radiotherapy (therapeutic PTV: 70 Gy, 6 fractions/week, 35 fractions of 2 Gy, prophylactic PTV: 54.25 Gy, 6 fractions/week, 35 fractions of 1.55 Gy) + concomitant cisplatin (weekly schedule of 40 mg/m² (delivered on day 1, 8, 15, 22, 29) or 100 mg/m² on day 1 and day 22). Nimorazole/placebo (1.2 g/m²) 90 min prior to each radiotherapy fraction (no more than 5 times a week). Note: 2 or 5 total dose administration of Cisplatin will be given (maximum total dose to be given 200 mg/m²) while Nimorazole/Placebo will continue thereafter with the radiotherapy fractions.

The first day of CRT + nimorazole/placebo will be counted as "day 1" (of "week 1").
5 Therapeutic regimens, expected toxicity, dose modifications

5.1 Treatment Allocation
Patients will be randomized in a 1:1 ratio.

5.2 Investigational Medicinal Product

5.2.1 Drug supply
Nimorazole and placebo will be supplied free of charge by Azanta A/S, Denmark. To request investigational product, please refer to the procedure described in the guidelines for drug supply and handling.

5.2.2 Packaging, dispensing and storage
Investigational product tablets are supplied in 100 mL Duma HDPE bottles with 150 tablets of nimorazole 500 mg or placebo. The drugs are packed in bottles labeled with a number. The label will not display any information on the treatment arm. A blank space will allow the hospital pharmacist to indicate the seqID of the patient. It should be underlined that the patient seqID and the bottle number is different.

If necessary, the tablets can be dispersed in a glass of water or in a bottle with 200 mL of water to form a fine particulate suspension for drinking or for dispensing through a NG/PEG tube.

5.2.3 Drug reconciliation procedures
Accountability of the investigational study drug(s) is under the responsibility of the investigator and can be delegated to an appropriately qualified person.

Study drug accountability should be maintained by each site. Accountability records should include receipt date, batch numbers, bottles number, expiry dates, patient SeqID, use by subject, dispensing dates, quantities (lowest unit) and stock balance.

In addition to internal accountability documentation on site, EORTC study-specific accountability and drug destruction forms will be supplied for this purpose, if site-specific forms are deemed not sufficiently detailed or do not provide enough information, according to EORTC Quality Assurance criteria.

The drug accountability and destruction forms will be verified during monitoring visits.

At the end of study, when all patients have stopped protocol treatment, complete drug reconciliation per batch should be available at the site for verification by EORTC in order to allow drug return procedure.

Both the unused and the expired study medication must be returned to Azanta, upon authorization of the EORTC, according to guidelines for drug handling.

The medication provided for this trial is to be used only as indicated in this protocol and only for the patients entered in this study.
5.2.4 Initial dose and schedule

5.2.4.1 Dosage of Investigational Medicinal Product

Nimorazole/placebo is to be administered in doses of approximately 1.2 g/m² body surface area prior to daily irradiation treatments (first daily irradiation treatment if there are 2 given on that day). Total dose over the entire irradiation period should be approximately 36 g/m² and must not exceed 40 g/m² or a total of 75 g. This dose level provides maximum radiotherapy enhancement ratio and is the maximum tolerated dose level.

Nimorazole/placebo dose will be prescribed as follow:

<table>
<thead>
<tr>
<th>Body surface¹</th>
<th># tablets per intake</th>
<th>Dose of nimorazole/placebo per intake</th>
<th>Total dose of nimorazole/placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1.6 m²</td>
<td>3</td>
<td>1.5 g</td>
<td>45 g</td>
</tr>
<tr>
<td>1.6–1.9 m²</td>
<td>4</td>
<td>2.0 g</td>
<td>60 g</td>
</tr>
<tr>
<td>&gt; 1.9 m²</td>
<td>5</td>
<td>2.5 g</td>
<td>75 g</td>
</tr>
</tbody>
</table>

¹ Nomogram for calculation of body surface area (see Appendix F)

In the case of 2 fractions of radiotherapy per day, nimorazole/placebo will be taken only once before the 1st daily fraction.

In case of 6 fractions per week on 6 different days (e.g. on Saturday), nimorazole/placebo will only be taken the first 5 times a week.

At each treatment, the nurse or the physician must check with the patient that the drug has been taken and any missed dose should be reported in the CRFs. The drug is to be given 90 minutes prior to the first daily irradiation treatment, no more than 5 times a week.

Nimorazole/placebo is provided as dispersible tablets. For patients who have difficulties swallowing, the tablets can be dispersed in a glass of water or a bottle with 200 mL of water to form a fine particulate suspension. This provides convenient dosing of patients throughout radiotherapy whether through routine oral administration or through naso-gastric - or percutaneous gastrostomy feeding tube.

5.2.4.2 Pre-medication

With the dose regimen that will be used, the side effect profile of nimorazole has been acceptable with the predominant side effects being nausea and vomiting.

The use of antiemetics such as metoclopramide, metopimazine or ondansetron is recommended.

5.2.5 Deviations from nimorazole/placebo treatment

Deviations from the nimorazole/placebo treatment must be registered in the weekly CRF. Examples of this may be:

♦ Radiotherapy not given after intake of the drug (e.g. machine breakdown): continue the planned treatment.
♦ Nimorazole/placebo not taken before radiotherapy (e.g. the patient forgot): continue radiotherapy as scheduled.
♦ Vomiting of the drug: do not repeat the nimorazole/placebo treatment on the same day but maintain the radiotherapy dose. Give antiemetics for nausea/vomiting the following days to alleviate symptoms from treatment.
♦ If drug is discontinued because of side effects: continue the radiotherapy. All deviations from the planned drug treatment should be recorded.

Deviations or discontinuations of the planned treatment do not exclude the patient from the study, but the patient should follow the treatment protocol as closely as possible.

5.2.6 Nimorazole/placebo overdosage

Neurotoxic effects, including transient seizures (epileptiform), paresthesia and peripheral neuropathy, have been reported with nimorazole after 5 to 7 days of doses of 6 to 10.4 g every other day.

If any of these events occur, temporary or permanent interruption of nimorazole/placebo treatment is recommended.

5.3 Radiotherapy

The following guidelines apply to all investigators participating in the trial.

5.3.1 Facility and equipment

All patients participating to the study will be treated by 6 to 10 MV photons using Simultaneous Integrated Boost Intensity Modulated Radiation Therapy (SIB-IMRT) delivered by static or dynamic techniques. Linear accelerator or Tomotherapy based equipment are allowed.

Participating institutions must comply with the Quality Assurance of Radiotherapy requirements and procedures described in detail in the Quality Assurance in Radiotherapy chapter 15.4.1. Sites that do not conform to the requirements of the audit will not be allowed to participate.

A Quality Assurance check will be performed prospectively on the first 5 patients enrolled at each site before the start of treatment to check conformity to the radiotherapy protocol. In addition all remaining patients will be checked retrospectively. If possible, this retrospective check will be performed during the first 3 weeks of treatment to allow for major corrections if needed.

5.3.2 Dental examination

All patients receiving radiotherapy should have an oral and dental examination including clinical and radiological examination.

When indicated, extraction of dental elements should be carried out. The interval between extractions and start of chemo-radiotherapy should be at least 10 to 14 days.

Adequate dental care (including daily fluorine application) should be recommended to all patients, at least during follow-up.
5.3.3 Patient position and data acquisition

All patients will be irradiated in supine position. Immobilization devices such as customized masks have to be used to secure the accuracy and reproducibility of patients positioning during radiotherapy.

Preferably, mask immobilization of the head, neck and shoulders will be used.

For all patients, Planning Computed Tomography (Planning-CT), using a set of slices extending from the level of the base of skull to the lower border of the clavicle, will be required. Slice thickness of preferably 2-3 mm will be used.

To enhance vascular and soft tissue contrast and to facilitate delineation of both target volumes and organs at risk (OAR’s), the use of intravenous contrast enhancement is mandatory (except if allergies).

Images will be constructed with at least 512 x 512 pixel matrices.

Co-registration with MRI to delineate the target volumes and/or OAR is left to the discretion of the investigator. The use of FDG-PET-CT for target volume delineation will not be allowed in the study.

5.3.4 Volume definition

The definition of volumes will be in accordance with ICRU Reports #50, #62 and #83 (Ref. 14, Ref. 15, Ref. 16).

The first clinical target volume (CTV) (so-called prophylactic dose CTV) will include the primary tumor Gross Tumor Volume (GTV) with a security margin, the involved nodal area(s) if any, and all nodal areas at risk for microscopic infiltration.

The second CTV (so-called therapeutic dose CTV) will include the primary tumor GTV and the involved nodes with a security margin around both.

5.3.4.1 Selection of the nodal Clinical Target Volume

The selection of the nodal levels will be done according to the following guidelines. These guidelines are valid irrespective of the primary tumor T-stage.

Oropharyngeal carcinomas

<table>
<thead>
<tr>
<th>Nodal stage (AJCC 7th edition)</th>
<th>Levels to be included in the CTV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ipsilateral neck</td>
</tr>
<tr>
<td>N0 - N1 (in level II, III or IV)</td>
<td>II-III-IV + RP(^1) for post. pharyngeal wall tumor</td>
</tr>
<tr>
<td>N2a - N2b</td>
<td>(Ib), II, III, IV, V + RP</td>
</tr>
<tr>
<td>N2c</td>
<td>According to N stage on each side of the neck</td>
</tr>
<tr>
<td>N3</td>
<td>I, II, III, IV, V + RP ± adjacent structures according to clinical and radiological data</td>
</tr>
</tbody>
</table>

\(^1\)retropharyngeal nodes
Specificities:

**Inclusion of level Ib**: any tumor with extension to the oral cavity, e.g. to retromolar trigone, mobile tongue, inferior gum, oral side of anterior tonsilar pillar.

**Unilateral neck treatment**: localized tumor of the tonsil (e.g. T1 or small T2) without frank involvement of the soft palate (i.e. tumor extension beyond the intersection of the tonsilar pillars) or the base of tongue.

**Retropharyngeal nodes**: systematic irradiation of retropharyngeal lymph nodes irrespective of the N stage for transfixing soft palate tumors is recommended.

**Retro-styloid nodes**: systematic irradiation of retro-styloid lymph nodes in case of upper level II nodal infiltration is recommended.

**Medial Supra-clavicular fossa nodes**: systematic irradiation of the supra-clavicular fossa lymph nodes in case of level IV nodal infiltration is recommended.

### Hypopharyngeal carcinomas

<table>
<thead>
<tr>
<th>Nodal stage (AJCC 7th edition)</th>
<th>Ipsilateral neck</th>
<th>Contralateral neck</th>
</tr>
</thead>
<tbody>
<tr>
<td>N0</td>
<td>II-III-IV + Rp(^1) for post pharyngeal wall tumor + VI for apex of piriform sinus or esophageal extension</td>
<td>II-III-IV + Rp(^1) for post pharyngeal wall tumor + VI for esophageal extension</td>
</tr>
<tr>
<td>N1 - N2a - N2b</td>
<td>(Ib), II, III, IV, V + Rp(^1) + VI for piriform sinus or esophageal extension</td>
<td>II-III-IV + Rp(^1) for post pharyngeal wall tumor + VI for esophageal extension</td>
</tr>
<tr>
<td>N2c</td>
<td>According to N stage on each side of the neck</td>
<td>According to N stage on each side of the neck</td>
</tr>
<tr>
<td>N3</td>
<td>I, II, III, IV, V + Rp(^1) + VI for piriform sinus or for esophageal extension ± adjacent structures according to clinical and radiological data</td>
<td>II-III-IV + Rp(^1) for post pharyngeal wall tumor + VI for esophageal extension</td>
</tr>
</tbody>
</table>

\(^1\)retropharyngeal nodes

Specificities:

**Retro-styloid nodes**: systematic irradiation of retro-styloid lymph nodes in case of upper level II nodal infiltration is recommended.

**Medial Supra-clavicular fossa nodes**: systematic irradiation of the supra-clavicular fossa lymph nodes in case of level IV nodal infiltration is recommended.
Laryngeal carcinomas

<table>
<thead>
<tr>
<th>Nodal stage (AJCC 7th edition)</th>
<th>Levels to be included in the CTV</th>
<th>Ipsilateral neck</th>
<th>Contralateral neck</th>
</tr>
</thead>
<tbody>
<tr>
<td>N0 - N1 (in level II, III or IV)</td>
<td>II-III-IV + VI for trans- or sub-glottis extension</td>
<td>II-III-IV + VI for trans- or sub-glottis extension</td>
<td></td>
</tr>
<tr>
<td>N2a - N2b</td>
<td>II, III, IV, V + VI for trans- or sub-glottis extension</td>
<td>II-III-IV + VI for trans- or sub-glottis extension</td>
<td></td>
</tr>
<tr>
<td>N2c</td>
<td>According to N stage on each side of the neck</td>
<td>According to N stage on each side of the neck</td>
<td></td>
</tr>
<tr>
<td>N3</td>
<td>Ib, II, III, IV, V + VI for trans- or sub-glottis extension ± adjacent structures according to clinical and radiological data</td>
<td>II-III-IV + VI for trans- or sub-glottis extension</td>
<td></td>
</tr>
</tbody>
</table>

Specificities:

*Retro-styloid nodes*: systematic irradiation of retro-styloid lymph nodes in case of upper level II nodal infiltration is recommended.

*Medial Supra-clavicular fossa nodes*: systematic irradiation of the supra-clavicular fossa lymph nodes in case of level IV nodal infiltration is recommended.

5.3.4.2 **Delineation of the Gross Tumor Volume (GTV)**

The primary tumor volume and the positive lymph nodes (i.e. any nodes with a smaller diameter above 1 cm and/or a necrotic center) will be delineated on the planning CT. The use of fused MRI is left to the discretion of the radiation oncologist. No delineation on FDG-PET is allowed. However FDG-PET can be used to help visualize the primary tumor at the discretion of the treating radiation oncologist.

5.3.4.3 **Delineation of the nodal Clinical Target Volume (nodal CTV)**

The neck node levels will be delineated on each CT slices according to the updated guidelines defined by a consensus panel for the node-negative and the node-positive neck (Ref. 22, Ref. 23). In case of infiltration (or suspicion of infiltration) of the sterno-cleido-mastoid muscle, the muscle will be included in the prophylactic nodal CTV.

Radiological boundaries of the various neck node levels are presented in Appendix G.

The therapeutic nodal CTV will be delineated by adding a margin of 7 mm around the nodal GTV. The therapeutic CTV should however always remain within the prophylactic dose nodal CTV.

5.3.4.4 **Delineation of the primary tumor Clinical Target Volume (primary tumor CTV)**

For the primary tumor prophylactic CTV, a security margin taking into account the compartmentalization of the head and neck area (e.g. parapharyngeal space, pre-epiglottic space), and the presence of weak (e.g. epiglottis) or strong (e.g. hyo-epiglottic ligament, bone cortex) barriers limiting these spaces will be added to the GTV. For the primary tumor therapeutic CTV, an 8 mm margin around the GTV is typically recommended (with correction for air cavities). Further tumor specific recommendations can be found in Appendix H. The therapeutic CTV should however be included into the prophylactic CTV.
5.3.4.5 Delineation of the Planning Target Volume (PTV)

A set-up margin will be implemented around each CTV to take into account patient set-up uncertainties. This margin will have to be selected by each participating center depending on their equipment, irradiation techniques and experiences. Typically, for patients immobilized with a head-neck and shoulder fixation device, a 3-5 mm margin appears adequate. Reduction of the CTV to PTV margin in the skin direction is allowed to reduce skin toxicity. It is left to the discretion of the treating physician. Dose calculations should be made in the PTV within the body.

5.3.4.6 Delineation of Organs at Risk (OAR) and Planning Organ at Risk Volume (PRV)

The spinal cord (from base of skull to level of Th2) and the brain stem should be outlined. Both parotid glands should be routinely outlined. If possible, mandible will be outlined as well. In patients with oropharyngeal tumors, the larynx (from the ary-epiglottic folds cranially to the sub-glottis caudally, and from the thyroid cartilage anteriorly to the arytenoid cartilage posteriorly) may be delineated as an OAR as well. For pharyngo-laryngeal tumors, the oral cavity (from the hard palate cranially to the hyoid bone caudally, and from the lip anteriorly to the anterior tonsil pillar posteriorly) may be delineated as an OAR. Additional normal structures or 'avoidance structures' may be delineated as an aid to the optimization process in particular to avoid hot spots outside of the PTV. This will be left to the discretion of the treating physicians and their medical physicists.

A set-up margin will be added to the spinal cord and the brain stem to take into account patient set-up uncertainties. This margin will have to be selected by each participating center depending on their equipment, irradiation techniques and experiences. Typically, for patients immobilized with a head-neck and shoulder fixation device, a 3-5 mm margin appears adequate.

5.3.5 Dose prescription, specification and reporting in the PTV

Dose prescription, specification and reporting will be done according to ICRU report 83 recommendations (Ref. 16).

Patients will be treated by SIB-IMRT with the first fraction given on a Monday. A median dose of 70 Gy will be prescribed to the therapeutic dose PTV in 35 fractions of 2 Gy. A median dose of 54.25 Gy will be prescribed to the prophylactic dose PTV in 35 fractions of 1.55 Gy. Six fractions per week will be delivered over an overall treatment time of 6 weeks. Patients will be treated 6 days a week, or 5 days a week with two fractions delivered on one particular day according to institutional policy. When 2 fractions per day are given, the time interval between the 2 fractions should at least be 7h.

Dose-volume constraints will be used for both dose specification and dose reporting in PTV and PRV/OAR.

5.3.6 Treatment planning

Patients will be treated by IMRT using 6 to 10 MV photons. For linear accelerators, field arrangements are left to the discretion of the medical physicists to produce an optimal dose distribution matching the dose-volume constraints for PTV, PRV and OAR. Non-coplanar field arrangements are allowed, but beam directions through the eyes, are not allowed unless really unavoidable. All field entrance and exits should be within the planning CT range, in order to avoid any inadequate dose calculations.

Treatment plans will be computed using modern type B dose calculation algorithms, such as convolution/superposition, Monte Carlo, collapsed cone or equivalent algorithms. The dose calculation matrix to be used must be below 4 mm. Dose calculations will be performed using density heterogeneity corrections.
The following dose-volume objectives will be used for planning, dose specification and dose reporting in PTV, PRV and OAR:

<table>
<thead>
<tr>
<th>PTV OAR / PRV</th>
<th>D$_{95}$% $^1$</th>
<th>D$<em>{near-min}$ or D$</em>{98}$%</th>
<th>D$<em>{near-max}$ or D$</em>{2%}$</th>
<th>D$_{5%}$</th>
<th>Median dose or D$_{50%}$</th>
<th>Mean dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTV-70 Gy</td>
<td>≥ 95 % of planned dose</td>
<td>≥ 90 % of planned dose</td>
<td>-</td>
<td>≤ 107 % of planned dose</td>
<td>70 Gy +/- 2%</td>
<td>-</td>
</tr>
<tr>
<td>PTV-54.25 Gy</td>
<td>≥ 95 % of planned dose</td>
<td>≥ 90 % of planned dose</td>
<td>-</td>
<td>-</td>
<td>54.25 Gy +/- 2%</td>
<td>-</td>
</tr>
<tr>
<td>PRV spinal cord</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>≤ 45 Gy</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>PRV brain stem</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>≤ 50 Gy</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Contralateral parotid</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>≤ 24 Gy</td>
<td>-</td>
</tr>
<tr>
<td>Ipsilateral parotid</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>25-27 Gy</td>
<td>-</td>
</tr>
<tr>
<td>Oral cavity</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>≤ 30 Gy</td>
<td>-</td>
</tr>
<tr>
<td>Larynx</td>
<td>-</td>
<td>-</td>
<td>≤ 44 Gy</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Mandible</td>
<td>-</td>
<td>-</td>
<td>≤ 70 Gy</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

$^1$ D$_{v}$: Dose in v% of the volume

Individual QA will be performed for all patients included in this clinical trial, see 15.4.1 for details. The main goal will be to evaluate the delineation of the target volumes and organs at risk, the dose distributions and dose volume histograms, using the DICOM data visualization platform VODCA (Visualization and Organization of Data for Cancer Analysis). A panel of experts (radiation oncologists and medical radiation physicists) from the EORTC Radiation Oncology Group will be identified to perform the reviews.

Details of how acceptable (minor) and unacceptable (major) protocol deviations are classified can be found in Appendix H.

5.3.7 Treatment verification and accuracy

Daily patient set-up shall be performed using laser alignment to reference marks on the mask of the patient.

Portal films, EPID, kVCT or MVCT will be obtained for all fields on the first day of treatment and at the time of each field modification.

During treatment, as a minimum requirement, an off-line set-up correction protocol that requires imaging at least once a week must be put in place. It is highly advised to adhere to the adapted "shrinking action level" (SAL) or "extended no action level" (eNAL) off-line protocols as described in the literature. Daily on-line set-up verification and correction is also allowed but not mandatory. Alternatively, set-up
corrections may be done according to local validated correction protocols. All protocols used shall be based on bony anatomy.

If the total dose used for imaging is expected to exceed 2% of the prescribed dose (1.5 Gy), a correction should be performed during the treatment planning.

5.3.8 Side effects of head and neck radiotherapy

Radiation-induced head and neck toxicity is well known and has been well described. It is expected to vary according to the total dose and the concomitant use of chemotherapy. Loco-regional toxicity will be monitored during treatment using the CTCAE scaling system and will be reported in the CRFs.

Reversible mucositis and pharyngitis is expected, and supportive care will be initiated (e.g. pain killers, mouth wash, adaptation of the diet, use of a naso-gastric or percutaneous endoscopic gastrostomy feeding tube). In very rare cases of severe grade 4 mucositis (e.g. bleeding), it may be necessary to interrupt radiotherapy for a few days. However, it is mandatory to limit the break to a strict minimum.

Various degrees of skin reaction (typically grade 2, less frequently grade 3) are expected in the treated area. Other expected acute reactions include xerostomia, dysgeusia, ageusia and dysphagia.

Central nervous system events in terms of nausea and vomiting are expected.

Late effects include some degree of xerostomia and occasionally persistent dysphagia.

Mandibular osteoradionecrosis may occur in less than 5% of the patients. Thorough dental evaluation and, if necessary, adequate care performed before the start of radiotherapy will substantially decrease this risk.

5.3.9 Treatment interruptions / modifications

No modifications will be permitted with regard to the target volume selection and delineation, the radiation dose prescriptions and the overall treatment time (major deviations).

Local investigators will carefully follow their patients during treatment and take all adequate measures (e.g. use of pain killer, use of a naso-gastric feeding tube or percutaneous gastrostomy) to avoid any interruption and/or modification of the total dose. It is however the responsibility of the local investigator to interrupt the treatment delivery if deemed appropriate in the best interest of the patient. Such interruption will be recorded in the CRF.

In case of machine breakdown or bank holidays, all measures will be taken to avoid prolonging the overall treatment time, e.g. adding an extra fraction a day with at least a 7 hour interval. However, no more than seven 2-Gy fractions will be delivered per week.

5.4 Cisplatin treatment (standard treatment)

Cisplatin is considered a non-IMP as it is a standard background treatment received by all patients in the trial.

5.4.1 Dosage of cisplatin

Chemotherapy will include one of the two cisplatin regimens specified in this protocol at the discretion of the participating centers. The centers must however treat all the patients they will recruit with one of the two regimens chosen before site activation. Chemotherapy should start on the first day of radiotherapy. Cisplatin should be infused before radiation therapy delivery.
The 2 options are:

♦ Cisplatin 100 mg/m² i.v. on day 1 and 22 of radiotherapy

or

♦ Cisplatin 40 mg/m² i.v. on day 1, 8, 15, 22, 29 of radiotherapy.

Before and after administration of cisplatin, adequate hydration is required and can be given as normally used in each institution. For the 100 mg/m² option, it is recommended to hospitalize the patient for 24h to allow optimal hydration before and after drug injection. For the 40 mg/m² option, administration of cisplatin on an out-patient basis is acceptable.

5.4.2 Administration of cisplatin

The first course of cisplatin should begin on the first Monday of radiotherapy.

Before starting the treatment with cisplatin, the following criteria must be met:

♦ Neutrophils >1.0 x10⁹/L
♦ Platelets >75 x10⁹/L
♦ Creatinine clearance >60 mL/min (Cockcroft formula)

For the 100 mg/m² three-weekly regimen (day 1 and day 22), the following recommendations are proposed:

♦ Encourage the patient to drink 2-3 liters of water per day during the days preceding and following cisplatin infusion.
♦ Any pre-existing dehydration must be corrected before starting the hydration related to cisplatin administration.
♦ Antiemetic medications should include:
  ♦ 5-HT3 antagonist (i.e. granisetron 1-3 mg IV or ondansetron 8-32 mg IV or palonosetron IV 0.25 mg IV; 30 minutes before cisplatin infusion),
  ♦ aprepitant* : 125 mg p.o. (30 minutes before cisplatin infusion) and 80 mg/day p.o. during the two following days,
  ♦ corticosteroids (i.e. dexamethasone 12 mg, 30 minutes before cisplatin infusion and dexamethasone 8 mg/day p.o. during the three following days). Another equivalent corticosteroid regimen is allowed according to local practice,
  ♦ any "as-needed" antiemetics according to each institutional guideline (metoclopramide, alizapride, additional steroids…).

* If aprepitant is not given, dexamethasone dosage should be increased to 20 mg on day 1 and ondansetron or granisetron and corticoseroids may be given during 3 days to control delayed nausea and vomiting according to local practice.

♦ Intravenous pre and post-hydration: 2 liters of sodium chloride 0.9% over 2 hours prior to cisplatin infusion. Following cisplatin infusion, an overnight additional hydration is also advised with two liters of saline solution.
♦ Cisplatin infusion: mannitol before cisplatin infusion is allowed according to local practice. Cisplatin should be prepared according to local practice and should be infused over 30 minutes.
Urinary output: >100 mL/hour before starting cisplatin infusion and also after cisplatin infusion during at least 4-6 hours (400 mL/4 hours). If this level is not reached, furosemide (Lasix®) 20 mg iv should be given.

Weigh patient before and after cisplatin infusion, if weight gain is > 1.5 kg, furosemide (Lasix®) 20 mg iv should be given.

Replace potassium (K) and magnesium (Mg) as needed.

Check for presence of ototoxicity.

For the 40 mg/m² weekly regimen, the following recommendations are proposed:

Encourage the patient to drink 2-3 liters of water during the days preceding and following cisplatin infusion.

Any pre-existing dehydration must be corrected before starting the hydration related to cisplatin administration.

Antiemetic medications should include:

- 5-HT3 antagonist (i.e. granisetron 1-3 mg IV or ondansetron 8-32 mg IV or palonosetron IV 0.25 mg IV; 30 minutes before cisplatin infusion).*
- corticosteroids according to local practice i.e. dexamethasone 10-20 mg before cisplatin infusion. Another equivalent corticosteroid is allowed.*
- any "as-needed" antiemetics according to each institutional guideline (metoclopramide, alizapride, additional steroids...).

* Ondansetron or granisetron and corticosteroids may be given during 3 days to control delayed nausea and vomiting according to local practice.

Intravenous pre-hydration: 2 liters of sodium chloride 0.9% over 2 hours prior to cisplatin infusion.

Cisplatin infusion: mannitol before cisplatin infusion is allowed according to local practice. Cisplatin should be prepared according to local practice and should be infused over 15 minutes.

Urinary output: >100 mL/hour before starting cisplatin infusion and also after cisplatin infusion during at least 4-6 hours (400 mL/4 hours). If this level is not reached give furosemide (Lasix®) 20 mg IV or p.o.

Replace potassium (K) and magnesium (Mg) as needed.

Check for presence of ototoxicity.

5.4.3 Cisplatin-related toxicity

The major dose limiting toxicities observed with single agent cisplatin are the following:

- Gastrointestinal toxicity: nausea and vomiting;
- Nephrotoxicity: renal function impairment associated with tubular damage and manifested with elevation in serum creatinine and urea and decrease in creatinine clearance. It is also associated with serum electrolyte disturbances, like hypomagnesaemia, hypocalcaemia, hyponatraemia, hypokaliaemia and hypophosphatemia;
- Ototoxicity: cumulative and not reversible damage, manifesting with hearing loss in the high frequency;
- Haemotoxicity: neutropenia, thrombocytopenia, anemia;
Neurotoxicity: manifesting with peripheral neuropathy and paresthesia in both upper and lower extremities.

### 5.4.4 Dose adjustment for cisplatin

Every treatment infusion, cisplatin full dose will be given if neutrophils are $\geq 1.0 \times 10^9$/L and platelets $\geq 75 \times 10^9$/L. If these levels are not reached, then in both treatment arms a maximum delay of 2 weeks is allowed and blood counts should be performed at the investigator's judgment but at least weekly to document recovery. If hematological toxicity has not resolved after 2 weeks, the patients should not receive further cisplatin. The patient will continue with radiation treatment and will be followed-up according to study protocol.

The following dose reductions of chemotherapy should be applied and should be carried over through all subsequent infusions. In the event that cisplatin treatment is stopped, no substitution with, for example, carboplatin will be allowed. Cessation of cisplatin therapy is not, in itself, a reason for discontinuing the patient from the study.

#### 5.4.4.1 Dose reductions for neutropenia

In the case of treatment delay due to delayed neutrophil recovery, the following policies are recommended:

- if the neutrophil count has resolved to $\geq 1.0 \times 10^9$/L in $\leq 1$ week, administer full dose of cisplatin;
- if the neutrophil count has resolved to $\geq 1.0 \times 10^9$/L in $> 1$ week but $\leq 2$ weeks, proceed with a 20% dose reduction of cisplatin.

#### 5.4.4.2 Dose reductions for febrile neutropenia

In case of any febrile neutropenia (at least CTCAE 4.0 Grade 3: absolute neutrophil count <1000/mm³ with a single temperature of $\geq 38.3$ degrees C (101 degrees F) or a sustained temperature of $\geq 38$ degrees C (100.4 degrees F) for more than one hour), it is recommended that the patient is hospitalized and treated with antibiotics as appropriate. After a period of febrile neutropenia, additional precautions have to be taken for the subsequent infusions. It is recommended to reduce the cisplatin dose by 20%.

No growth factor support such as erythropoietin or granulocyte-colony stimulating factor is allowed.

#### 5.4.4.3 Dose reductions for thrombocytopenia

If complicated thrombocytopenia $\geq$ grade 3, with hemorrhage and/or requiring prophylactic/therapeutic platelet transfusions (recommended at $<10 \times 10^9$/L, but dependent upon local transfusion policy) occurs at any point during the treatment, appropriate supportive care should be given and cisplatin treatment should be delayed until platelets are $>75 \times 10^9$/L, but no more than 2 weeks of interruption is allowed. Over this time, treatment will be discontinued.

In any case at the occurrence of grade 4 thrombocytopenia at nadir ($<25 \times 10^9$/L), 20% cisplatin dose reduction should take place in the subsequent infusion.
5.4.4.4 Dose reduction for renal toxicity

In case of renal toxicity, cisplatin dose should be reduced as followed:

<table>
<thead>
<tr>
<th>Creatinine Clearance</th>
<th>Cisplatin dose for the three-weekly regimen (day 1 and day 22)</th>
<th>Cisplatin dose for the weekly regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 60 mL/min</td>
<td>100 mg/m²</td>
<td>40 mg/m²</td>
</tr>
<tr>
<td>50-60 mL/min</td>
<td>80 mg/m²</td>
<td>30 mg/m²</td>
</tr>
<tr>
<td>40-50 mL/min</td>
<td>50 mg/m²</td>
<td>20 mg/m²</td>
</tr>
<tr>
<td>&lt; 40 mL/min</td>
<td>Discontinue</td>
<td>Discontinue</td>
</tr>
</tbody>
</table>

5.4.4.5 Dose reduction for peripheral neuropathy

A neurological examination must be performed before the second cisplatin injection, and every subsequent injection. In case of symptoms or signs experienced by the patient, more frequent examinations should be performed and the following dose modification are recommended:

♦ Grade 0, 1 (CTCAE 4.0): no change.
♦ Grade 2 (CTCAE 4.0): cisplatin will be reduced to 60 mg/m² in case of 100 mg/m² schedule and to 20 mg/m² in case of the weekly schedule.
♦ Grade ≥ 3 (CTCAE 4.0 scaling system): cisplatin will be discontinued.

5.4.4.6 Dose reduction for ototoxicity

Cisplatin is known to cause high frequency hearing loss. The following dose modifications are recommended:

♦ If grade 1 or 2 hearing loss (CTCAE 4.0 scaling system) occurs, the risk of additional hearing loss versus the potential benefit of continuing cisplatin chemotherapy should be made.
♦ Grade 3 and 4 hearing loss (CTCAE 4.0 scaling system) is an indication to discontinue cisplatin.

5.5 Concomitant therapy

5.5.1 Therapy allowed during study

Antiemetics as described in Section 5.4.2.

5.5.2 Prohibited therapy procedures during study

Some drugs interact with nimorazole. These should be avoided. It includes especially other nitroimidazoles (e.g. metronidazole, tinidazole) and aminoglycosides (e.g., netilmicine and gentamycin). However, no particular drug-drug interaction studies have been performed with nimorazole.

For metronidazole, another 5-nitroimidazole drug, the following interactions are described, which may also apply to nimorazole. These drugs should be avoided.

Metronidazole has been reported to potentiate the anticoagulant effect of warfarin and other oral coumarin anticoagulants, resulting in a prolongation of prothrombin time. The simultaneous administration of drugs that induce microsomal liver enzymes, such as phenytoin or phenobarbital, may accelerate the elimination of metronidazole, resulting in reduced plasma levels; impaired clearance of phenytoin has also been reported.
The simultaneous administration of drugs that decrease microsomal liver enzyme activity, such as cimetidine, may prolong the half-life and decrease plasma clearance of metronidazole.

In patients stabilized on relatively high doses of lithium, short-term Flagyl therapy has been associated with elevation of serum lithium and, in a few cases, signs of lithium toxicity. Serum lithium and serum creatinine levels should be obtained several days after beginning metronidazole to detect any increase that may precede clinical symptoms of lithium intoxication.

For cisplatin contraindications, please refer to SmPc.

5.6 Withdrawal criteria

Irrespective of the disease status, the treatment will always be discontinued in case of patient’s refusal or excessive toxicity precluding further therapy, at the discretion of the responsible physician. Patients discontinuing therapy in the absence of progression should not receive any other anti-cancer treatment before their disease progresses, unless this is clearly in the interest of the patient.

Patients should, whenever possible, irrespective of the reason for withdrawal, be examined as soon as possible. All relevant assessments should be completed according to the last scheduled visit. All study drug-related adverse events should be followed until resolved or until the Investigator assesses them as chronic or stable i.e ≤ Grade 1.

After progression, the treatment will be left to the discretion of the treating physician.

6 Clinical evaluation, laboratory tests and follow-up

6.1 Before treatment start

♦ Informed consent for the clinical trial and, if consented, for the biological translational studies.
♦ Complete medical history: including age, smoking habits, alcohol habits, use of recreational drugs, concurrent illnesses, use of adequate contraception, history of past oncological or chronic diseases, assessment of symptoms suggestive of peripheral neuropathy and weight loss during the past 6 months.
♦ Assessment of concomitant medications
♦ AE assessment (CTCAE 4.0) according to standard practice.
♦ Complete physical examination: including height, weight, vital signs and WHO/ECOG performance status and presence/absence feeding tube, gastrostomy or tracheostomy.
♦ Fiberoptic examination and endoscopy under general anesthesia of the upper-aerodigestive track with biopsies of the primary lesion(s). Photograph of the lesion(s) and/or drawing of the finding(s) should be routinely performed to ease Gross Tumor Volume delineation.
♦ Oral and dental check-up including radiological examination with teeth extraction if needed should be performed ideally before the loco-regional imaging to avoid dental feeling artifacts.
♦ Imaging of the loco-regional primary disease with contrast enhanced CT-scan or MRI of the head and neck. The choice between CT and MRI is left to the discretion of the investigator, but will have to be use consistently for response evaluation, primary endpoint and follow-up.
♦ Documentation of the absence of distant metastases with FDG-PET-CT, or CT-scan of the chest.
♦ Documentation of the pathologic examination of the biopsy specimen confirming the diagnosis of HPV-negative squamous cell carcinoma. HPV positivity will be evaluated by p16-immunohistochemistry (please refer to chapter 1.2).
Three unstained paraffin-embedded tumor sections for the molecular signature assessment of hypoxia. This test is mandatory for all patients participating to the study.

Three unstained paraffin-embedded tumor sections for optional prospective biological collection

Blood tests including white blood cells count (WBC), absolute neutrophil count (ANC), hemoglobin, platelets count, bilirubin, ALT, AST, alkaline phosphatase, gamma-GT, LDH, sodium, potassium, calcium, magnesium, phosphate, urea and serum creatinine.

If clinically indicated, HIV test.

Baseline pregnancy test for women of child bearing potential within 72 hours before treatment start

6.2 During treatment (i.e. from week 1 to 6)

Weekly physical examination with WHO/ECOG performance status, vital signs, weight according to standard practice and need for feeding tube, gastrostomy or tracheostomy positioning.

AE weekly assessment (CTCAE 4.0) according to standard practice.

Assessment of concomitant medications.

Blood tests taken weekly including absolute neutrophil count (ANC), hemoglobin, platelets count, urea and serum creatinine, sodium, potassium, calcium, magnesium and phosphate according to standard practice.

Neurological examination before the second cisplatin injection, and every subsequent injection.

6.3 After the end of treatment (follow-up)

6.3.1 During the 2nd and 4th weeks after the end of treatment (early follow-up)

Physical examination with WHO/ECOG performance status, vital signs, weight and need for feeding tube, gastrostomy or tracheostomy positioning.

AE assessment (CTCAE 4.0).

Neurological examination.

Assessment of concomitant medications.

Blood tests including absolute neutrophil count (ANC), hemoglobin, platelets count, urea and serum creatinine, sodium, potassium, calcium, magnesium and phosphate according to standard practice.

6.3.2 At three months (± 2 weeks) after the end of treatment (disease evaluation)

Complete physical examination including weight, vital signs, WHO/ECOG performance status assessment and need for feeding tube, gastrostomy or tracheostomy positioning.

AE assessment (CTCAE 4.0) if not yet resolved.

Fiberoptic examination and if deemed useful endoscopy under general anesthesia of the upper-aerodigestive track with biopsies of any suspicious lesion(s).

Blood tests including absolute neutrophil count (ANC), hemoglobin, platelets count, urea and serum creatinine, sodium, potassium, calcium, magnesium and phosphate according to standard practice.
Contrast enhanced CT-scan or MRI of the head and neck. The examination should be similar to the one performed during the work-up procedure.

In case of residual neck nodes, patients should be considered for a selective neck node dissection to be performed between 3 and 4 months after the end of treatment.

Neurological examination.

6.3.3 Subsequent follow-up visits

Every 2 months for subsequent 2 years (at 5, 7, 9, 11, 13, 15, 17, 19, 21, 23 months) then every 4 months for next 3 visits (at 27, 31, 35 months) and every 6 months thereafter up to year 5 (at 41, 47, 53, 59 months).

Complete physical examination including weight, vital signs and WHO/ECOG performance status and need for feeding tube, gastrostomy or tracheostomy positioning.

Treatment related AE assessment (CTCAE version 4.0).

Fiberoptic examination and if deemed useful endoscopy under general anesthesia of the upper-aerodigestive track with biopsies of any suspicious lesion(s).

Blood tests including absolute neutrophil count (ANC), hemoglobin, platelets count, urea and serum creatinine, sodium, potassium, calcium, magnesium and phosphate according to standard practice.

On a yearly basis (±1 month) up to 5 years after end of treatment, or in case of clinical suspicion of relapse or residual disease:

Contrast enhanced CT-scan or MRI of the head and neck. The examination should be similar to the one performed during the work-up procedure.

Chest CT or FDG-PET.

A dental work up is recommended twice a year.
### 6.4 Summary table

<table>
<thead>
<tr>
<th>Timing</th>
<th>Before treatment start</th>
<th>Treatment</th>
<th>Early follow-up</th>
<th>Disease evaluation</th>
<th>Late follow-up</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Before Registration</td>
<td>Before Randomization</td>
<td>Week 1 to 6 (weekly)</td>
<td>2nd and 4th weeks after EoT</td>
<td>3 months after EoT</td>
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<tr>
<td>Informed consent</td>
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<td></td>
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<td>Eligibility criteria</td>
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<td>7-unstained FFPE sections for hypoxic signature</td>
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<tr>
<td>4 FFPE sections for optional future TR (if applicable)</td>
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<td>Medical history</td>
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<td>♥ Smoking history</td>
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<td>♥ Alcohol Consumption</td>
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<tr>
<td>♥ Concurrent illness</td>
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<tr>
<td>♥ symptoms suggestive of peripheral neuropathy</td>
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<td>♥ weight loss during the past 6 months</td>
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<td>X</td>
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</table>
### Before treatment start

<table>
<thead>
<tr>
<th>Timing</th>
<th>Physical examination</th>
<th>Dental check up</th>
<th>Neurological examination</th>
<th>Fiberoptic examination</th>
<th>Biopsy/selective neck node dissection/fine needle aspirate</th>
<th>Endoscopy (+biopsy if required)</th>
<th>Loco-regional scan CT/MRI</th>
<th>Chest CT or FDG-PET</th>
<th>Pregnancy test</th>
<th>Hematology and biochemical tests</th>
<th>Adverse events</th>
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<tbody>
<tr>
<td>Before Registration</td>
<td>♦ Body weight</td>
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<td>Before Randomization</td>
<td>♦ Height (baseline only)</td>
<td>X</td>
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<td>♦ Vital signs</td>
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<td>♦ WHO/ECOG performance status</td>
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<td></td>
<td>♦ Need for feeding tube, gastrostomy or tracheostomy</td>
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<td></td>
<td>Physical examination</td>
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<td>Dental check up</td>
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<td>Neurological examination</td>
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<td>Fiberoptic examination</td>
<td>X</td>
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<td></td>
<td>Biopsy/selective neck node dissection/fine needle aspirate</td>
<td>X</td>
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<td></td>
<td>Endoscopy (+biopsy if required)</td>
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<td></td>
<td>Loco-regional scan CT/MRI</td>
<td>X</td>
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<td>Chest CT or FDG-PET</td>
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<td>Pregnancy test</td>
<td>X</td>
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<td>Hematology and biochemical tests</td>
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<td></td>
<td>Adverse events</td>
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### Treatment

<table>
<thead>
<tr>
<th>Before treatment start</th>
<th>Treatment</th>
<th>Early follow-up</th>
<th>Disease evaluation</th>
<th>Late follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before Registration</td>
<td></td>
<td>Week 1 to 6 (weekly)</td>
<td>2nd and 4th weeks after EoT</td>
<td>3 months after EoT</td>
</tr>
<tr>
<td>Before Randomization</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Early follow-up

- X
- X
- X
- X
- X
- X

### Disease evaluation

- X
- X
- X
- X
- X
- X

### Late follow-up

- X (not yet resolved AE only)
- X (late toxicity)

**Note:** Treatment should start within 8 weeks from baseline imaging assessment

EoT=End of treatment
*: Follow up: Every 2 months for subsequent 2 years (at 5, 7, 9, 11, 13, 15, 17, 19, 21, 23 months) then every 4 months for next 3 visits (at 27, 31, 35 months) and every 6 months thereafter up to year 5 (at 41, 47, 53, 59 months).

1: Age, Disease stage (Stage III or IV with no distant metastasis), disease localization, squamous cell pathology and HPV negativity (please refer to chapter 1.2)

2: Vital Signs: Blood Pressure and Temperature

3: Dental work up at baseline and twice a year thereafter (recommended)

4: before the second cisplatin injection, and every subsequent injection

5: If needed in case of clinical suspicion of relapse or residual disease (see chapter 7.1)

6: In case of residual lymph node, patients should be considered for selective neck node dissection (see chapter 7.1)

7: using the same imaging method and done on a yearly basis up to 5 years or in case of clinical suspicion of relapse or residual disease (see chapter 7.1)

8: Pregnancy test for women of childbearing potential within 72 hours prior to treatment start

9: At randomization, blood tests including white blood cells count (WBC), absolute neutrophil count (ANC), hemoglobin, platelets count, bilirubin, ALT, AST, alkaline phosphatase, gamma-GT, LDH, sodium, potassium, calcium, magnesium, phosphate, urea and serum creatinine.

10: Blood tests taken including absolute neutrophil count (ANC), hemoglobin, platelets count, urea, serum creatinine, sodium, potassium, calcium, magnesium and phosphate

See also Appendix I (Study timelines overview).
7 Criteria of evaluation

7.1 Evaluation of efficacy

7.1.1 Locoregional control

The diagnosis of a local or regional recurrence requires histological documentation and imaging of the head and neck region, including CT-scan and/or MRI. In case a pathological confirmation of the recurrence cannot be obtained, the diagnosis will be accepted based on clinical judgment. The imaging examination should be similar to the one performed during the work-up procedure.

The recurrence will be considered:

♦ local if the recurrence is documented in the area of the tumor bed,
♦ regional if the recurrence occurs in the form of positive nodes in the ipsilateral or contra-lateral neck.

During the follow-up (see section 6.3), patients may have two types of visits:

♦ complete with physical examination, fiberoptic examination and imaging
♦ partial with physical examination and fiberoptic examination

The diagnostic of locoregional recurrence will be assessed as follow:

<table>
<thead>
<tr>
<th>Visit</th>
<th>Conclusion</th>
<th>Action</th>
<th>Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete: physical* + imaging evaluations</td>
<td>If ONLY one of the examinations shows abnormality (suspicious tissue, oedema, post RT changes or no clear conclusion)</td>
<td>Next subsequent follow-up visit</td>
<td>No Recurrence</td>
</tr>
<tr>
<td></td>
<td>If at least one of the examinations shows abnormality AND with strong suspicion of recurrence (residual tumor mass, suspicious mass palpated)</td>
<td>Pathological examination (through elective neck node dissection if regional or endoscopy if local)</td>
<td>No Recurrence</td>
</tr>
<tr>
<td></td>
<td>Next subsequent follow-up visit</td>
<td>Negative pathological examination (i.e. no tumor in sample) =&gt; next subsequent follow-up visit</td>
<td>No Recurrence</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Positive pathological examination (i.e. tumor in sample)</td>
<td>Recurrence at the date of the first examination showing abnormality</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Not possible to have pathological examination</td>
<td>Recurrence (based on clinical assessment) at the date of the first examination showing abnormality</td>
</tr>
<tr>
<td>Partial: only physical* evaluation</td>
<td>If NO abnormality</td>
<td>Next subsequent follow-up visit</td>
<td>No Recurrence</td>
</tr>
<tr>
<td></td>
<td>If any abnormality</td>
<td>Imaging +/- pathological examination (through elective neck node dissection if regional or endoscopy if local)</td>
<td>No Recurrence</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Negative pathological examination =&gt; next subsequent follow-up visit</td>
<td>No Recurrence</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Positive pathological examination</td>
<td>Recurrence at the date of the first examination showing abnormality</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No confirmation possible</td>
<td>Recurrence (based on clinical assessment) at the date of the first examination showing abnormality</td>
</tr>
</tbody>
</table>

* Physical evaluation includes fiberoptic examination for local assessment of tumor recurrence

Time to locoregional recurrence is counted from the day of randomization to the day of the first record of appearance of local or regional progression (clinical examination, imaging assessment showing suspicion or pathological confirmation).

Distant recurrence/progression and second cancers diagnosed before locoregional recurrence and death in absence of locoregional recurrence are not considered events of interest, but will be considered as competing risk events in the analysis of this endpoint.
Patients without any of the listed events (i.e. events of interest or competing risks events) are censored at the date of the last follow-up examination.

### 7.1.2 Distant recurrence/progression

Diagnosis of distant recurrence/progression can only be made when one of the criteria defined below is met:

- Obvious radiological evidence of distant metastases on imaging (CT scan, MRI scan as indicated by the clinical picture).
- Positive biopsy (in case of doubt on radiological imaging or clinically suspected recurrence, e.g. subclavicular lymph node or skin metastasis or any palpable mass).

The documented date of distant recurrence/progression will be the date of confirmation of the distant recurrence/progression using these methods for diagnosis. At the time of distant recurrence/progression, the investigator should clearly indicate the site of tumor recurrence/progression and the method of diagnosis. In the absence of obvious radiological evidence of recurrence/progression, positive biopsy must be obtained.

Time to distant-metastases is counted from the day of randomization to the day of the first record of appearance of distant recurrence/progression. "Locoregional-only" progression or second cancers diagnosed before the distant metastases and death in absence of distant metastases are not considered events of interest for this endpoint.

Patients without any of the events of interest are censored at the date of the last follow-up examination. Death in absence of distant-metastases is considered as a competing risk event in the analysis of this endpoint.

### 7.1.3 Second cancer

The diagnosis of a second head and neck cancer requires histological proof of a new tumor mass outside of the tumor bed, which is not compatible with the diagnosis of regional lymphatic metastasis.

The diagnosis of a second cancer outside of the head and neck region requires histological proof of a new tumor mass outside of the head and neck region, which is not compatible with the diagnosis of distant metastasis.

### 7.1.4 Disease-free survival

Disease specific free survival will be measured from the date of randomization to the date of first occurrence of any of the following events:

- any locoregional recurrence (i.e. local recurrence in the tumor bed or any positive node in the contralateral or ipsilateral neck).
- distant recurrence/progression.
- death due to any cause.

Patients alive and free of disease recurrence/progression (as defined above) are censored at the date of the most recent follow-up examination.
7.1.5 Disease-specific survival

Disease-specific survival will be measured from the date of randomization to the date of death due to primary HNSCC. Patients alive are censored at the date of the most recent follow-up examination. Death from causes other than primary HNSCC is considered as a competing risk event in the analysis of this endpoint.

7.1.6 Overall survival

Overall survival will be measured from the date of randomization to the date of death whatever the cause of death. Patients who are alive are censored at the date of the most recent follow-up examination.

7.2 Safety monitoring

7.2.1 General evaluation of adverse events

This study will use the International Common Terminology Criteria for Adverse Events (CTCAE), version 4.0, for toxicity and adverse event reporting. A copy of the CTCAE can be accessed from the CTEP homepage (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev4.pdf). A link to this page is provided on the EORTC website http://www.eortc.org/investigators-area/ctc.

All adverse events will be recorded; the investigator will assess whether those events are drug related (reasonable possibility, no reasonable possibility) and this assessment will be recorded in the database for all adverse events.

Only the worst grade per CTCAE category will be recorded.

The collection period will start after registration. Events with onset before the start of treatment will be considered as baseline and will be used as a reference to interpret Adverse Event occurring during or after the treatment period.

7.2.2 Serious adverse events

Serious adverse events are defined by the Good Clinical Practice Guideline.

Serious adverse events should be immediately reported according to the procedure detailed in this protocol (see chapter 14 on Reporting of Serious Adverse Events).

7.2.3 Toxic deaths

Toxic death is defined as death due to toxicity (defined as adverse events that are not confirmed as "No reasonable possibility"). The cause of death must be reported as "toxicity".

The evaluation of toxic deaths is performed independently of the evaluation of locoregional control. (patients can die from toxicity after a complete assessment of the response to therapy).

7.2.4 Evaluability for safety

All patients who have started the treatment will be included in overall safety analyses.

For hematological events, the medical review team may decide that blood counts have not been performed and/or reported according to the protocol and are therefore inadequate for the evaluation of one/several hematological parameters in some patients.

Patients who have discontinued treatment because of toxicity will always be included in the safety analyses.
7.2.5 Evaluation of specific toxicities

Hematological toxicity will be assessed during treatment and after treatment during a 30-days recovery period on the basis of blood counts. The nadir count should be computed and graded according to the International CTCAE 4.0. The nadir in a given treatment week is the lowest laboratory value in that treatment week; the overall nadir for a patient is the lowest laboratory value among all treatment weeks.

Toxicity that appears within 90 days of the last treatment will be regarded as acute toxicity.

Toxicity that appears > 90 days after last treatment administration will be regarded as late toxicity.

Acute and late treatment toxicity will be evaluated and graded according to the CTCAE version 4.0.

Particular attention will be paid to the assessment of the following items that will be used for monitoring the acute toxicity related to the protocol treatments:

- Oral or pharyngeal mucositis grade ≥ 3.
- Skin toxicity inside radiation field (in ‘radiation dermatitis’) grade ≥ 3.
- Neutropenia grade 4 lasting ≥ 7 days.
- Thrombocytopenia grade 4 lasting ≥ 7 days.
- Any CTCAE 4.0 of the category "infection" grade ≥ 3.
- Renal toxicity (in “investigations”, “creatinine increased”) grade ≥ 3.
- Death due to toxicity (i.e. any grade 5 adverse event related to treatment).

Particular attention will be paid to the assessment of the following items that will be used for monitoring the late toxicity related to the protocol treatments:

- Gastrointestinal disorders - Mucositis.
- Gastrointestinal disorders - Dysphagia.
- Gastrointestinal disorders - Dry mouth (xerostomia).
- Skin and subcutaneous tissue disorders - Telangiectasia.
- Skin and subcutaneous tissue disorders - Skin induration.
- Musculoskeletal and connective tissue disorders - Osteonecrosis of jaw.
- Respiratory, thoracic and mediastinal disorders - Voice alterations, hoarseness, aphonia.
- Nervous system disorders - Peripheral sensory neuropathy.
- Any CTCAE 4.0 grade ≥ 3.

8 Statistical considerations

8.1 Statistical design

8.1.1 Sample size

The study is designed as a blinded randomized phase III trial. The reference arm is the arm with concomitant chemo-radiotherapy (accelerated radiotherapy + cisplatin) + placebo. The experimental arm is the arm with concomitant chemo-radiotherapy + nimorazole. The primary endpoint of the study is locoregional control rate (see chapter 7.1.1 for definition).

The two co-primary objectives of this trial are:
♦ To evaluate whether the hypoxic cell radiosensitizer nimorazole can improve the effect of primary curative accelerated fractionated concomitant chemo-radiotherapy with cisplatin on the locoregional control rate in the whole group (1-sided alpha=0.015).

♦ To investigate if the hypoxic gene profile is a predictive factor for benefit of hypoxic sensitization. This will be done by testing for a large treatment benefit in the subset of patients who are hypoxic cell signature positive (1-sided alpha=0.012).

In a secondary analysis, the treatment effect of nimorazole will also be investigated in the subgroup of patients who are hypoxic cell signature negative.

In consequence, the treatment effect of nimorazole will be mainly evaluated in the whole population and also in the population of patients with hypoxic cell signature positive. In order to preserve an overall type I error of 0.025, a closed testing procedure (according to Song & Chi, Ref. 17) will be used. It means that in the whole population the type I error level is set at 0.015 and in the hypoxic cell signature positive subgroup, the type I error level is set at 0.012.

The sample size and the analysis plan of the trial are based on numerous assumptions for which there is a limited amount of supporting material. It is essential to monitor the parameters regularly as they have the potential to directly impact the sample size of the trial, the timelines for the analyses and possibly the statistical power.

The parameters of concern are:

♦ a) the **locoregional control rates expected in the reference arm (whole group)**. These were assumed to follow a piecewise exponential distribution with locoregional control rates of 80% at 1 year, 68% at 2 years, 65% at 3 years and that essentially no patients have locoregional failures after 3 years.

♦ b) the **HR for treatment effect** (nimorazole/placebo) in whole group. We target a HR of 0.615 (b=0.615). (Ref. 1)

♦ c) the **proportion of patients effectively classified hypoxic signature** + (this parameter relates to % test failures and to true prevalence of very hypoxic patients). For the present design we assume 5% test failure overall and 1/3 of all assessable patients being classified positive for the hypoxic signature. Thus in our case c=0.316. (Ref. 9, Ref. 10)

♦ d) the **misclassification rate** (+ classed – or – classed +). This mixture results from the patients for whom the genetic signature is close to the threshold. As this factor was already present in the Dahanca 5 analysis by gene-signature profile on which we based the assumptions to an amount of approximately 10%, we did not included further dilution to this factor in the calculations. Thus d=0 in our calculations

♦ e) the **effect of the signature in the reference arm (which we call prognostic effect)**. This was taken to be a hazard ratio of 2.0 (Ref. 10). In this design, as it is assumed that the patients in the positive hypoxic signature subgroup who receive nimorazole and all negative hypoxic signature patients have a same outcome. The prognostic effect of the signature is very close to the target treatment effect expected in the hypoxic signature positive subgroup.(e=2.0)

♦ f) the **HR for treatment effect (nimorazole/placebo) in positive hypoxic signature subgroup**. In this study we target a treatment effect of HR=0.46 in the subgroup (f=0.46). (Ref. 9, Ref. 10)

♦ g) the **patient accrual rate in the whole group**. We assume that the recruitment will start slowly and that it will take approximately one year after first patient in (FPI) to reach a full speed recruitment of 150 patients / year after year 1, which corresponds to a monthly recruitment of 12.5. During the 1st year of recruitment, we expect that the monthly recruitment rate will be on average 3.15 pts/months during Q1, 5.16 pts/months during Q2, 7.25/month during Q3 and 9.45/ month during Q4.

♦ h) the **dropout rate** (that includes patients who die or have distant metastases or have second cancer or drop out without having had locoregional failure). We estimated this rate to 5% (h=0.05)
i) we also anticipate that a small proportion of patients entering the study will be staged T2N1. These are unlikely to contribute many events given their better prognosis.

The evaluation and the monitoring of those parameters are described in chapter 9.

8.1.1.1 In the subgroup of patients with positive hypoxic gene signature

Based on the anticipated prognostic effect of the signature (parameter e above) and the anticipated locoregional control rates in the unselected group (parameter a above), the anticipated locoregional control rates for the positive hypoxic cell signature subgroup has been estimated to be of 71.5% at 1 year, 56.0% at 2 years and 52.3% at 3 years without nimorazole.

We also anticipate that the full effect of the experimental treatment will be essentially confined in this subgroup whereas the treatment effect in the negative hypoxic signature subgroup is very modest (HR=0.90) (Ref. 9, Ref. 10). Based on this, the expected treatment benefit in the results bringing the locoregional control rate of the subgroup to 85.7% at 1y, 76.6% at 2y, and 74.2% at 3 years when patients are treated with nimorazole (HR=0.46) (Ref. 9, Ref. 10). To achieve 80% power for testing this hypothesis in the subgroup, at a one-sided type I error rate of 0.012 requires 64 events of locoregional failures.

Accounting for a 5% drop out rate (parameter h above) requires that a very minimum of 200 evaluable patients be entered in this group. Using these assumptions, we expect that this number would be recruited in 4.8 years.

8.1.1.2 Sample size for the whole group of patients

In the present study, it is assumed a locoregional control rates as specified under g) above.

Based on those assumptions and in order to detect HR = 0.615 (equivalent to an increase in locoregional control rate of 11.7% increase at 3 years from 65% without nimorazole to 76.7% with nimorazole), with 80% power using a one-sided 0.015 alpha level test, a total of 154 events is required.
Accounting for a 5% drop out rate (parameter h above) requires that a very minimum of 610 evaluable patients be entered in the full group of patients. In order to cover for a possible rate of ineligible patients or undefined hypoxic gene signature, we will target the recruitment of 640 patients in total for the full group of patients. We expect that this number would be recruited in 4.8 years.

The final analysis will be conducted when both criteria are met: 64 events observed in the subgroup of patients with positive hypoxic gene signature and 154 events observed in the full group of patients. Both criteria are expected to happen approximately 7 months after entry of the last patient.

Thus the expected time from first patient in (FPI) to final analysis within this subgroup is 5.4 years.

As we assumed that of the 95% of patients in whom the signature will be assessable, 1/3 will be classed hypoxic signature positive, 640 patients should in theory be sufficient to guarantee that 200 patients are available in the subset (as this subgroup represents 31.6% of the whole group).

However, should the observed proportion of hypoxic signature positive patients be lower than anticipated, the recruitment will continue until 200 patients are available in the hypoxic signature positive subgroup.

8.1.1.3 In the subgroup of patients with negative hypoxic gene signature

In the previous DAHANCA-5 study, the observed treatment effect in that subgroup was HR=0.86 (95%CI: 0.35-1.05). This study is not sized for detecting the expected very modest treatment effect expected in this subgroup which we assume in this study to be in the order of HR=0.90.
With 405 patients recruited in this subgroup (2/3*0.95 of 640), we expect around 88 events of locoregional failure at the planned time of final analysis. With 88 events, the study has 4.7% power (see above figure) to reject H0 under the alternative hypothesis (HR=0.90) with a 1-sided type I error rate of 0.015.

8.2 Interim evaluation

No formal interim analysis for the efficacy endpoints is planned for this study. However, some of the previously cited parameters (in 8.1.1) will be regularly monitored, see details in section 9. In addition, after 450 patients recruited (approximately at 3.5 years), IDMC will be asked to review parameters (except the one evaluating treatment effect) that may lead to blinded adaptions of the sample size calculation including timing of final analysis. Accrual will not be stopped during this evaluation of parameters.

8.3 Randomization and stratifications

Patients will be centrally randomized (for practical details, see chapter on registration / randomization procedure). A minimization technique will be used for random treatment allocation between the two treatment arms concomitant chemo-radiotherapy + nimorazole and concomitant chemo-radiotherapy + placebo using a 1:1 ratio and stratifying by

- Institution
- Tumor localization (larynx vs. hypopharynx vs. oropharynx)
- Tumor classification (T1-2 vs. T3-4)
- Nodal classification (N0-1 vs. N2-3)
- WHO performance status (0-1 vs. 2)
- Hypoxic gene-profile (positive vs. negative vs. undetermined at time of randomization)
8.4 Statistical analysis plan

8.4.1 Primary and secondary endpoints

The endpoints that will be used in the statistical analysis are defined in chapter 7 and listed in chapter 2.

8.4.2 Analysis populations

The following analysis populations will be used for the analysis of the trial:

♦ Intention-to-treat population: All randomized patients will be analyzed in the arm they were allocated by randomization.

♦ Per protocol population: All randomized patients who are eligible and have started their allocated treatment

♦ Safety population: All randomized patients who have started their allocated treatment

A patient will be considered to be eligible if he/she did not have any deviation from the patient entry criteria listed in chapter 3 of the protocol. Potential eligibility problems will be assessed during the medical review meetings.

8.4.3 Statistical methods

For each efficacy endpoint, results will be presented in the whole population and in each subgroup of patients (positive and negative hypoxic gene signatures).

8.4.3.1 Analyses methods for the primary endpoint

The following section will detailed the statistical analysis of the locoregional control rate (primary endpoint). The primary analysis will be performed in the intention-to-treat population and will be used to conclude on the efficacy of the treatment in the whole population and also in the subgroup of patients with the positive hypoxic gene signature.

The one-sided significance level is 0.015 in the whole group of patients and 0.012 in the subgroup of patients with the positive hypoxic gene signature. As the statistical analyses will also be conducted in the negative hypoxic gene signature, the treatment effect will be tested at the one sided significance level 0.0015 in that subgroup, according to Song&Chi. The two-sided confidence intervals will therefore be calculated at the 97% and at the 97.6% confidence levels, respectively. The 95% confidence intervals will be provided as supplementary information.

In studies of radiation, we expect a local effect of the treatment explaining the choice of locoregional control rate as primary endpoint. However, a patient may develop distant disease or a second cancer and die before a locoregional relapse is observed. In this case the observation of distant disease hinders the observation of local disease. Furthermore, the occurrence of locoregional relapse after distant disease or second cancer may not be of much interest since treatment of the distant disease may alter the chances of locoregional disease recurring. Therefore, the competing risks methodology (Ref. 20) will be used for the primary analysis of the locoregional control rate.

First of all, a tabulation of the type of first event considered in the primary endpoint will be provided:

♦ locoregional recurrence

♦ competing risks events: distant recurrence/progression, second cancers or death without any prior locoregional recurrence

♦ alive without any disease recurrence/progression (loco-regional or distant) or second cancer
A descriptive table of the location of the locoregional recurrence (T-site and N-site) will be given as well.

In competing risks analysis, distant recurrence/progression, second cancers or death without any prior locoregional recurrence will be considered as competing risk at the time of the occurrence of the competing event.

The cumulative incidence of the event of interest (locoregional recurrence) will be plotted (Ref. 18, Ref. 20) in each treatment group, the 2-year cumulative incidence rates will be estimated from the curves and its associated 95% confidence intervals will be calculated.

Time to locoregional recurrence will be compared with a Fine&Gray model (Ref. 18, Ref. 33) adjusted for the stratification factors (specified in 8.3 except the institution and the hypoxic gene signature). The hazard ratio will be estimated with its confidence intervals. The significance of the treatment effect will be evaluated by means of a score test.

Before fitting the Fine&Gray model, a substantial evidence for non-proportional treatment hazards of the cumulative incidence function in the form of a qualitative change over time will be explored. If severe deviation from proportionality of hazards is found (e.g. crossing hazards) this will be taken into account in the interpretation and the analysis of the treatment effect will be conducted by applying the Gray test which is the equivalence of Log-rank test in presence of competing risks. If there is substantial evidence for non-proportional hazards for one of the stratification factor, this one will be removed from the adjusted Fine&Gray model but will be used as a stratification factor.

The interaction between the treatment effect (nimorazole/placebo) and the hypoxic gene signature effect (positive/negative) will also be tested for exploratory purpose. Assuming that 600 patients with known hypoxic gene signature will be used for the interaction test and 154 events will be observed at the time of the analysis, the power of an interaction test at the 10% 2-sided type I error rate, according to Peterson and Georges, is 65%.

8.4.3.2 Analyses methods for the other efficacy endpoints

♦ As for the primary endpoint, the primary analysis of the other efficacy endpoints (Overall Survival, Time to distant metastasis, Disease-free survival and Disease-specific survival) will be performed in the intention-to-treat population.

The two-sided significance level is 0.05 in the whole group of patients and in the subgroup of patients with the positive hypoxic gene signature. The two-sided confidence intervals will therefore be calculated at the 95% confidence level.

♦ Overall survival rates will be estimated by the Kaplan-Meier method (Ref. 19). The median survival time and its associated non-parametric confidence interval will be calculated. The median survival time and its associated non-parametric confidence interval will be calculated. Survival rates at 2 year will be estimated using the log-log transformation of the survival rate estimate and the standard deviation of the Kaplan Meier estimate based on the Greenwood formula (Ref. 20, Ref. 21).

♦ A Cox proportional hazard regression model adjusted for the stratification factors will also be fitted to estimate the effect size using hazard ratios (HR) and the associated 95% confidence interval.

♦ As for the primary endpoint, the following efficacy endpoints (disease-free survival, disease-specific survival, time to distant metastasis and time to second cancer) will follow the same statistical methodology taking into account competing risk events (see section 8.4.3.1).
8.4.3.3 Analyses methods for safety endpoints

All the analyses of the safety endpoints will be performed in the safety population and will be presented overall and separately in acute and late toxicity (as defined in 7.2.5).

The safety assessments include hematological toxicity, laboratory measurements and adverse events. Only the safety assessments performed before progression or within 7 days of progression and before start of any further anti-cancer therapy will be included in the analysis.

Acute and late toxicity will be tabulated (worst CTCAE 4.0 grade per patient). A second tabulation of adverse events related to treatment (excluding no reasonable possibility event, but including relationship not assessable) will be made.

For items suggesting a > 5% difference in the rate of severe (grade 3-4) toxicity between the two treatment arms, a chi-square test may be applied to assess whether the difference is beyond random fluctuations.

8.4.3.4 Pre-planned sensitivity or exploratory analyses

A first sensitivity analysis will be done on all efficacy endpoints specified in chapter 7 where the treatment comparisons will not be adjusted for the stratification factors.

A second sensitivity analysis will be done on all efficacy endpoints (except overall survival) using a "classical" statistical methodology. All efficacy endpoint will be described using Kaplan-Meier curves (Ref. 19) by treatment arm, where patients having a competing event will be censored at the time of the occurrence of the competing event. The median survival time and its associated non-parametric 95% confidence interval will be calculated. Time to event rates at 2 year will be estimated using the log-log transformation of the survival rate estimate and the standard deviation of the Kaplan Meier estimate based on the Greenwood formula (Ref. 20, Ref. 21).

Each efficacy endpoints will be compared by treatment arm with the Cox’s proportional hazards model adjusted for the stratification factors (specified in 8.3 except the institution and the hypoxic gene signature) (Ref. 21). The hazard ratio will be estimated with its confidence intervals. The significance of the treatment effect will be evaluated by means of a score test.

Before fitting the Cox model, a substantial evidence for non-proportional treatment hazards in the form of a qualitative change over time will be explored. If severe deviation from proportionality of hazards is found (e.g. crossing hazards) this will be taken into account in the interpretation and the analysis of the treatment effect will be conducted by applying the Logrank test which is free of the proportionality assumption. If there is substantial evidence for non-proportional hazards for one of the stratification factor, this one will be removed from the adjusted model but will be used as a stratification factor in the Cox model.

A third sensitivity analysis will be done if 10% of the patients have been excluded from the per-protocol population. In such case, the statistical analyses of the efficacy endpoints will be repeated in the per protocol population.

8.4.4 Data recoding and display

Frequency tables will be tabulated (by treatment group or otherwise) for all categorical variables by the levels of the variables as they appear on the CRF (with %). Categories with a text field specification will be tabulated as categories and then supplemented by a listing with the following information for the patients fulfilling the condition for the specification (patient id, institution, treatment group, value of the item and text field contents).

Dates relating to events prior to entry will be presented as the delay in days (or weeks, months, or years) between the past event and the date of entry (date of randomization – date of past event + 1) and presented using the median and range. For example, on the randomization checklist, the date of last administration of
prior treatment (or the date of first diagnosis of the cancer) will be presented as the time elapsed (in days, weeks, months or years, as appropriate) since the day of the last administration and the date of entry on study (date of randomization – last administration/diagnosis +1).

Other delays (e.g. re-treatment delays) are presented as continuous variables using the median and range. Continuous variables for which a coding system exists (such as for laboratory data) will be recoded into categories (for adverse events, the grading scale specified in the protocol will be used). Whenever no specific scale exists, lab data will be categorized based on the normal range: for example, below the lower normal limit (when appropriate), within the normal range, above the upper normal limit (ULN) and the degree to which it is above the ULN (for example > 2.5 x ULN, > 5 x ULN, > 10 x ULN). For laboratory data, the nadir is generally displayed. The nadir in a given cycle is the lowest laboratory value in that cycle; the overall nadir for a patient is the lowest laboratory value among all cycles.

Other continuous variables (for example age, dose ...) are presented using the median and range (minimum, maximum).

If appropriate, continuous data may also be presented in categories (for example, age may also be grouped in decades).

Dose intensity for cisplatin will be calculated on the full duration of the chemoradiation, adding up the administered doses of cisplatin in mg/m². This will be compared to 200 mg/m² for the 6-weeks period.

The total dose of radiotherapy will be calculated adding up the administered doses in Gy and compared to 70 Gy.

The total dose of nimorazole / placebo for the whole treatment period will be calculated adding up the administered doses in g/m² and compared to 5x6x1.2 = 36 g/m² for nimorazole and to 0 g/m² for placebo.

Treatment compliance is defined as receiving 80 to 120% of the planned treatment dose.

8.5 End of study

End of study occurs when all of the following criteria have been satisfied:

1. Ninety days after all patients have stopped protocol treatment
2. The trial is mature for the analysis of the primary endpoint as defined in the protocol
3. The database has been fully cleaned and frozen for this analysis

9 Data Monitoring

No efficacy results will be presented at EORTC Group meetings or elsewhere before the trial is closed to recruitment and the data are mature for the analysis of the primary endpoint, unless recommended otherwise by the EORTC IDMC.

As a blind trial, some data will be monitored by the blind study team and some will be only assessed by the unblind team (Clinical Research Physician and Statistician) who will present the data to the IDMC.

The table below summarizes the design parameters (listed also in section 8.1.1) and safety to be monitored. The sections 9.1 and 9.2 describe how and when the data will be monitored.
9.1 Blind monitoring during medical review meetings

Safety data are reviewed within the EORTC Headquarters by the blind study team (Clinical Research Physician, Statistician, Data manager, Project Manager) on a regular basis as part of the Medical Review process. Problems which are identified will be discussed with the Study Coordinators who will take appropriate measures. Safety information will also be included in trial status reports which serve as a basis of discussion during EORTC Group meetings. These reports will be made available to investigators participating in the study.

In addition, the medical review will assess for this study the parameters c), g), h) and i) (see above table) pertaining to the statistical design that do not relate to the treatment differences and do not require unblind. The medical review will be performed with treatment allocation blinded. Trial Status Reports will contain no information on the individual treatment allocation and summary tables will be presented with all treatments arms pooled together.

In case of a safety concern detected at a global study population level or if the monitoring of design parameters requires a major change to the statistical design of the trial, the study team will seek advice from the EORTC Independent Data Monitoring Committee (IDMC) at any time during the course of the study.

9.2 Monitoring by the independent data monitoring committee

The EORTC Independent Data Monitoring Committee (IDMC) will review all safety problems or other issues identified during the blind medical review and for an advice is sought. Experts on the IDMC performing this review will be selected to have the relevant early trials/drug development expertise and will provide a review process independent of that of the Medical Review. In principle, no access to outcome data is necessary for safety reviews. The IDMC may request unblinding for their review.

Once 450 patients (70% of accrual) were recruited in the trial, the EORTC IDMC is also charged with the review of the parameters c), g), h), i) (as for the medical review) plus parameters a) and e) that require unblinding (see above table).

Those reviews will be done in accordance with the EORTC Policy 004 on “Independent Data Monitoring Committees and Interim Analyses”. Unblinding for global safety reasons and unblinding after 450 patients recruited will be performed according to EORTC SOP CM-011-SOP “Blind Studies”. The unblinded Statistician, an independent Statistician at the EORTC Headquarters not involved in the conduct of the trial and the Pharmacovigilance Physician will write the unblinded report and will present it to the IDMC.
The results are confidential and are discussed by the EORTC IDMC. The IDMC will subsequently recommend to the EORTC Group and Sponsors whether any changes should be made to the study design. In case the review of the design parameters lead to blinded adaptions (not based on treatment differences) of the sample size or timing of analyses, the blind study statistician will receive from IDMC the new parameters which are different from the assumptions made in 8.1.1 and will propose adaption of the study design.

10 Translational research

10.1 Introduction

Samples will be collected for two purposes in this trial:

♦ 7 unstained paraffin-embedded tumor sections (mandatory) will be collected for determination of the 15 gene hypoxic signature

♦ 4 additional unstained paraffin-embedded tumor sections (optional) if available on site, will be collected for future translational research. If any, left overs of the 4 unstained paraffin-embedded tumor sections sent to central lab for hypoxic gene signature determination will also be used for the same future translational research

More details about sample preparation/shipment will be described in the “Human Biological Material Management Guidelines” available for sites before their activation.

10.2 15 gene hypoxic signature

This translational research program is an integral part of the trial as patient's tumor will need to be classified prior to entry and hypoxic gene signature result is to be used as a stratification criterion. Three unstained paraffin-embedded tumor sections are needed for the molecular signature assessment of hypoxia.

The classifier was developed based on 30 candidate genes which are all upregulated by low levels of oxygen, thereby reflecting the physiological condition in tumors that is responsible for increased resistance to radiotherapy, and which can be overcome by the hypoxic sensitizer, Nimorazole. The 30 genes were selected from in vitro array studies on human head and neck cancer cell lines exposed to variable levels of oxygen, and selected for their pH independence and uniform upregulation across different cell lines line. The upregulation was confirmed in vivo with the same cell lines grown as xenografts in mice using a hypoxic tracer to identify hypoxic regions of the tumors (Ref. 9).

One Way ANOVA principles were used to develop the final classifier based on comparisons of gene expression values measured by uniplex RT-qPCR with multiplex target gene pre-amplification in a unique clinical dataset of 58 head and neck cancer patients (Ref. 9). These patients could be divided in two groups ('more' or 'less' hypoxic) based on direct pO2 measurements using oxygen electrode measurements. Fifteen genes were identified, which provide a robust classification, both regarding biological variability and regarding the issue of potential missing values. The genes are correlated and show similar expressions patterns between patients, i.e. all genes are either high or low in a given tumor sample. There is some biological heterogeneity, and a few genes may differ from the overall pattern of expression in a given sample. There is no clear pattern as to which genes may differ.

New samples are classified based on the distance from the new sample to the two means of the training samples ('more' or 'less' hypoxic groups, respectively) and the variance. This is done for each of the 15 genes. The mean and variance values for each of the 15 genes are locked and classification is performed as defined in Reference 9. The procedure for classification of samples in the current trial is the same as used for the validation in the DAHANCA 5 trial, i.e. each individual sample is classified qualitatively as being either 'more' or 'less' hypoxic (Ref. 9, Ref. 10).
The EORTC applies a risk-based approach for implementation of diagnostic biomarkers. This risk scale is described here under:

<table>
<thead>
<tr>
<th>Class</th>
<th>Impact Level</th>
<th>Explanation and examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Low individual risk</td>
<td>Correlative TR on HBM collected within clinical studies. This is for research purposes only and does not influence or determine the patient's treatment in any way.</td>
</tr>
<tr>
<td>B</td>
<td>Moderate individual risk</td>
<td>Integral TR:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1) The biomarker is only one of several determinants for guiding therapy decisions e.g. assay results are combined with clinical assessments to guide decisions (i.e. the test result is not the sole deterrent of treatment decision or the test result requires follow-up laboratory testing). Example: trial endpoint is a combination of both PSA recurrence and clinically observed recurrence in prostate cancer.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2) Biomarker testing forms an integral part of the trial, with all patients in the trial being assessed. The test is critical for the scientific objectives of the study.</td>
</tr>
<tr>
<td>C</td>
<td>High individual risk</td>
<td>Integral TR: High individual risk for patients in the case of erroneous results. This includes monitoring the level of medicines leading to patient management decisions and screening for selection of patients for selective therapy &amp; management. Example: 70 gene signature in MINDACT trial.</td>
</tr>
<tr>
<td>D</td>
<td>High individual risk/ high risk to public health</td>
<td>Assays that detect the presence of transmissible agents that causes life-threatening diseases with a high risk of propagation.</td>
</tr>
</tbody>
</table>

This trial has been assessed as class B2, which drives the level of quality assurance applied to the assay.

### 10.3 Future translational research projects

If the patient consents to participate to the optional sub-study, 4 additional FFPE sections, if available on site, will be sent to the biobank in addition to the mandatory 7 FFPE sections used for the hypoxic gene signature determination.

Left over from the 7 FFPE sections used for the hypoxic gene signature determination as well as the 4 additional FFPE sections will be biobanked in Aarhus, Denmark, for future research.

The study steering committee, in accordance with the EORTC biobank policy POL 020, will decide on the use of biological material for projects not defined in the present protocol. Any future research on left over tissue samples would have to be scientifically valid and approved by the EORTC Translational Research Advisory Committee (TRAC) and relevant Ethics Committees, according to applicable legislation (see “Access to HBM” process described in chapter 13.3). Further in depth analysis may involve screening for genetic and cellular determinants of outcome, biomarker discovery, using the available biological samples and appropriate molecular technologies.
10.4 General principles for human biological material (HBM) collection

Human biological material (HBM) collection involves the collection and storage of biological material, residual biological material or derivatives in compliance with ethical and technical requirements.

Biobanking refers to the chain of procedures that encompass the life cycle of the biological material, e.g. from collection, shipping to long term storage and use, and may also be subject to local regulation and/or national/international legislation.

In this study, biological material will be centralized and stored in the Department of Experimental Clinical Oncology at the Aarhus University Hospital, Noerrebrogade 44, DK-800 Aarhus C, Denmark.

The following principles apply to storage of HBM:

♦ The biobank will have a designated manager responsible for collection and will act as a communication point with the EORTC

♦ The collected HBM should be documented, i.e. the amount remaining and its location.

♦ The Study Steering Committee (SSC) will be responsible for TR project review and prioritization, including the consideration of newly proposed TR projects not specified in the protocol. In the absence of the SSC, responsibilities of the SSC are transferred to the Study Coordinators and/or EORTC HQ as applicable.

♦ Final decisions on the use of HBM will be determined by a majority vote of the SSC. Additional expertise may be sought through advisory non-SSC members.

Access to HBM (see EORTC Biobanking Policy POL020): HBM may be used for another purpose for which it was originally collected, subject to meeting ethical principles and is covered by informed consent/ethics approval. In the case of secondary use of HBM, (i.e. for new TR projects that are not specified in the clinical study protocol and that were not foreseen at the time of protocol writing) interested parties may apply for the use of HBM and will follow the next steps:

♦ A short description of the new TR projects will be written and submitted to EORTC HQ for coordination with the appropriate SSC.

♦ The SSC will prioritize the TR projects. Access procedures defined by the SSC will build on the following key points:

  ♦ Project prioritization

  ♦ should be strongly based on scientific merit,

  ♦ should consider the contribution of the different investigators to the trial and TR project,

  ♦ will take into consideration if the applicant is an EORTC member or not (whilst maintaining the principle of access to the wider scientific community and commitments owed to study participants and ethical committees).

♦ Protection of confidentiality must be respected.

♦ An EORTC HQ feasibility check, including recommendations for regulatory and ethical matters and other restrictions on the use of the HBM, will take place. If in the event the HBM collections are still retained at individual clinical sites, the TR project leader and the involved EORTC Group are responsible for collecting and providing information on availability of HBM for the feasibility assessment.
♦ Prioritized TR projects will then be reviewed by the Translational Research Advisory Committee (TRAC).

♦ Once SSC prioritization, the EORTC HQ feasibility assessment, and TRAC review are complete and when all applicable competent Ethics Committees approvals are in place and ethical principles are met, the TR project can be activated and HBM release and analysis can commence.

♦ The EORTC Board will mediate any disagreements of opinion between TRAC, the EORTC HQ feasibility assessment, the SSC and the TR project leader(s), as needed.

10.5 Data storage, transfer and development of technical appendices

The translational projects will be the result of the work of collaborating institutions and EORTC HQ. Separate technical appendices will be jointly developed for each project. These appendices will be written before starting any analysis and will specify the analytical and methodological details. Clinical and patient-reported outcome data will be stored in the EORTC clinical database and biological investigational data will be stored in respective collaborating institutions. Transfer of data will be realized according to applicable procedures in each organization.

11 Investigator authorization procedure

Investigators will be authorized to register and randomize patients in this trial only once they have returned the following documents to the EORTC Headquarters:

♦ The updated signed and dated curriculum vitae of the Principal Investigator.

♦ The (updated) list of normal ranges for the investigator’s institution signed and dated by the head of the laboratory. Please make sure normal ranges are provided also for those tests required by the protocol but not routinely done at the investigator’s institution.

♦ A Confirmation of interest form and Study Agreement between EORTC and Principal Investigator, stating that the investigator will fully comply with the protocol. This must include an estimate of yearly accrual and a statement on any conflict of interest that may arise due to trial participation.

NB: A signed conflict of interest disclosure form will be required only if a possible conflict is declared on the Confirmation of interest form.

♦ A copy of the favorable opinion of the local or national (whichever is applicable) ethics committee mentioning the documents that were reviewed (including the version numbers and version dates of all documents). A list of all members of the ethics committee is also requested.

♦ A copy of the translated and adapted (according to all national requirements) Patient Information / Informed Consent sheet. Version numbers and dates must be clearly stated on each page.

♦ The signature log-list of the staff members with a sample of each authorized signature and the indication of the level of delegations. In case patients receive treatment at a satellite institution, i.e. outside the authorized institution, details on the satellite institution, including the CV of the local investigator, normal lab ranges and the approval of an ethics committee will have to be transmitted to the EORTC Headquarters. Please keep in mind that all communication is done ONLY between the primary institution and the EORTC Headquarters.

♦ The full name, address, phone numbers and e-mail address of the local pharmacist who will be responsible for the trial medication (for any trial where the drug will be provided).

♦ An accreditation, a certification, an established quality control / external quality assessment or another validation should be provided for the own laboratory.

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Radiation Therapy Quality Assurance (RTQA) documents requested prior to site authorization, as defined in chapter 15.4.1.

The center specific list of required documents will be included in the protocol activation package, with proper instructions as required by this protocol, your group and/or the applicable national law.

The new investigator will be added to the “authorization list”, and will be allowed to register/randomize patients in the trial as soon as

♦ All the above mentioned documents are available at the EORTC Headquarters.
♦ All applicable national legal and regulatory requirements are fulfilled.

Patient registration/randomization from centers not (yet) included on the authorization list will not be accepted.

12 Patient registration & randomization procedure

12.1 General procedure

Patient registration/randomization will only be accepted from authorized investigators (see chapter on “investigator authorization procedure”).

Patients should be registered/randomized directly on the EORTC online randomization system (ORTA = online randomized trials access), accessible 24 hours a day, 7 days a week, through the internet.

To access the interactive randomization program, the investigator needs a username and a password (which can be requested at http://orta.eortc.be/).

In case of problems investigators can phone the EORTC Headquarters from 9.00 am to 5.00 pm (Belgian local time) from Monday through Friday in order to randomize patients via the EORTC call center. Randomization via the phone is not available on Belgian holidays. A list of these holidays is available on the EORTC web site (http://orta.eortc.be/) and it is updated annually.

<table>
<thead>
<tr>
<th>Through Internet:</th>
<th><a href="http://orta.eortc.be/">http://orta.eortc.be/</a></th>
</tr>
</thead>
<tbody>
<tr>
<td>In case of problems randomization by phone:</td>
<td>+32 2 774 16 00</td>
</tr>
</tbody>
</table>

12.2 Registration procedure (step 1)

A patient can only be registered after signature of the Patient Informed Consent.

STANDARD INFORMATION REQUESTED:

♦ institution number
♦ protocol number (1219)
♦ step number: 1
♦ name of the responsible investigator
♦ patient's code (maximum 4 alphanumerics)
♦ patient's birth date (day/month/year)
PROTOCOL SPECIFIC QUESTIONS:

♦ Some eligibility criteria will be checked:
  ♦ Biological material availability for hypoxic signature testing procedure
  ♦ Classification and localization of newly diagnosed tumors
  ♦ HPV/p16 test result
  ♦ Histopathological diagnosis of invasive squamous cell carcinoma in the primary tumor
  ♦ No distant metastasis (M0)
  ♦ Age > 18 years
  ♦ Date of written informed consent (day/month/year)

Once these data have been verified, the EORTC sequential patient identification number (“seqID”) will be allocated to the patient. This number will allow the identification of the patients in the VISTA/Remote Data Capture system (VISTA/RDC) that will be used to complete the Case Report Forms.

After this registration step, the material for testing the hypoxic signature should be send IMMEDIATELY to the central laboratory (within 24 hours if possible). All SAMPLE SHIPMENTS and REPORTS must be identified with the EORTC Id (seqID) attributed at registration.

12.3 Central laboratory testing of the hypoxic signature (step 2)

After registration and shipment of the sample, the central laboratory will assess the patient’s hypoxic gene signature status. The assessment results will be entered by the central laboratory in the ORTA system (step 2). This step is performed by the central laboratory in a blinded way: result of this testing will not be provided to the investigators.

At the end of this step, the site will be informed by a notification that they can now randomize the patient in the ORTA system (step 3). Hypoxic gene signature result will be used for stratification at randomization.

In case (exceptional) of failure of the hypoxic gene signature analysis in the 3 weeks period between registration and randomization, the status of the signature entered by the central lab will be considered as "unknown". The site will be informed by a notification that they can randomize the patient in the ORTA system, and the status will be rectified later on for the statistical analysis.
12.4 Randomization procedure (blinded, step 3)

A patient can only be randomized after verification of eligibility. Both the eligibility check and randomization must be done before the start of the protocol treatment.

STANDARD INFORMATION REQUESTED:
♦ institution number
♦ protocol number (1219)
♦ step number: 3
♦ name of the responsible investigator
♦ patient's code (maximum 4 alphanumerics)
♦ patient's birth date (day/month/year)

PROTOCOL SPECIFIC QUESTIONS:
♦ all eligibility criteria will be checked one by one
♦ actual values for the eligibility parameters will be requested when applicable
♦ stratification factors
♦ date foreseen for protocol treatment start

Once eligibility has been verified, treatment will be randomly allocated to the patient by the electronic system.

As this is a blind trial, neither the treatment arm nor its description will be provided. Only the number of the bottle containing the drug to be administered to the patient will be provided.

12.5 Description of the blind procedure

To blind the treatment allocation after the randomization procedure, the EORTC Headquarters uses the concept of “treatment bottle”. The drugs are packed in bottles displaying only a number. The program used for registering patients and running the minimization algorithm is identical to the one used for open label studies. The computer chooses a treatment dynamically, based on the other patients randomized in the study and the stratification factors defined in the protocol.

A bottle containing the allocated treatment available at the institution is subsequently identified, and its number is displayed by the randomization program. Please refer to the drug supply management guidelines for further details.

12.6 Stock management process

The stock of treatment bottles is maintained in each participating institution in the protocol by the company.

Each institution will initially be provided with a batch of treatment bottles. The first patient randomized by this institution will be allocated one of the bottles included in the initial set.

When part of the available bottles has been allocated, additional batches of treatment bottles are sent to the institution to maintain the number of bottles available for new randomizations. As described in guidelines for drug supply & handling, the institution needs to confirm the reception of each batch of additional bottles before they can be allocated to new patients. This system avoids the allocation of a treatment bottle not yet available in the institution.
Reception of treatment bottles must be confirmed to the company by e-mail or fax.

12.7 Unblinding procedure

Single patient unblinding by the investigator during the course of the study:

At any time during the trial, in case of a safety concern affecting an individual patient, the site investigator can request the unblinding of that patient.

The unblinding requests should be made through the ORTA randomization system. The unblinding procedure can be run any time. Investigators should log on to the system and fill in the identification screen with the standard questions (same as during the randomization step). To run the unblinding program, step 4 should be selected. The system will ask a series of justification questions, describing the reason why the treatment needs to be unblinded. If the answers to these questions justify unblinding, an automatic email describing the unblinded treatment will be sent to the investigator.

Unblinding at final analysis:

The patient, the investigator and the site team and the EORTC HQ study team will be unblinded only after database lock for the final analysis of the primary endpoint. At unblinding for final analysis, the project manager will inform investigators that the allocated treatment of their patients is available upon request.

Other unblinding during the course of the study:

Unblinding for global safety reasons are described in chapter 9.

13 Forms and procedures for collecting data

13.1 Case report forms and schedule for completion

Data will be reported on the forms specifically designed by the EORTC Headquarters for this study. Forms should be electronically sent to the EORTC Headquarters through the VISTA/RDC (Remote Data Capture) system, with the exception of the SAE form and the Pregnancy notification form which are paper CRFs.

SERIOUS ADVERSE EVENTS SHOULD BE IMMEDIATELY REPORTED ACCORDING TO THE PROCEDURE DETAILED IN THIS PROTOCOL (see chapter on Reporting Serious Adverse Events).

A. Before the treatment starts:

♦ The patient must be registered/randomized in the trial by INTERNET or in case of problems by phone.

The electronic CRFs to be completed for a patient are available on the VISTA/RDC website one day after the registration/randomization on http://rdc.eortc.be/ or on http://www.eortc.org in the section for investigators.

The paper CRF(s) will be made available to the institution at the time the institution is authorized.

B. During/after treatment

The list of forms to be completed for this study and their submission schedule are available on the VISTA/RDC website and are also described in the "guidelines for completion of case report forms" that are provided to each participating investigator.

ALL Forms must be electronically approved and sent by the responsible investigator or one of his/her authorized staff members
13.2 Data flow

The forms must be completed electronically, with the exception of the paper forms (the SAE form and the pregnancy notification form), according to the schedule defined in the guidelines for completion of Case Report Forms.

The list of staff members authorized to enter data (with a sample of their signature) must be identified on the signature log and sent to the EORTC Headquarters by the responsible investigator before the start of the study. To enter the RDC system, the investigator or authorized staff member needs to use the same username and password that are used to access the interactive randomization program (ORTA).

In all cases, it remains the responsibility of the principal investigator to check that data are entered in the database as soon as possible and that the electronic forms are filled out completely and correctly.

The EORTC Headquarters will perform extensive consistency checks on the received data and will issue queries in case of inconsistent data. The queries for the electronic forms will appear in the VISTA/RDC system and must be answered there directly.

The EORTC data manager will subsequently apply the corrections into the database.

When satellite institutions are involved, all contact is made exclusively with the primary institution, for purposes of data collection and all other study related issues.

If an investigator (or an authorized staff member) needs to modify a CRF after the form has been electronically sent to the EORTC Headquarters, he/she should create a request for data correction in the VISTA/RDC system.

13.3 HBM* sample registration and tracking

Once the patient is registered, this procedure might take up to one day, the investigator or his/her authorized staff must log on "Samples" website at http://samples.eortc.be/ or by clicking on the link "Samples Website" at the bottom of the page http://rdc.eortc.be

"Samples" is a web based tracking tool designed to register, manage and track Human Biological Materials collected in the frame of EORTC clinical trials.

Details about access the "Samples" Website, register samples and tracking shipments are described on the guidelines of HBM* management.

(*) Human Biological Material

14 Reporting of Serious Adverse Events

ICH GCP and the EU Directive 2001/20/EC require that both investigators and sponsors follow specific procedures when notifying and reporting adverse events/reactions in clinical trials. These procedures are described in this section of the protocol.

14.1 Definitions

These definitions reflect the minimal regulatory obligations; specific protocol requirements might apply in addition.

AE: An Adverse Event is defined as “any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment”. An adverse event can therefore be any unfavorable and unintended signs (such as rash or enlarged liver), symptoms (such as nausea or chest pain), an abnormal laboratory
finding (including results of blood tests, x-rays or scans) or a disease temporarily associated with the use of the protocol treatment, whether or not considered related to the investigational medicinal product.

**AR:** An Adverse reaction of an investigational medicinal product is defined as “any noxious and unintended response to a medicinal product related to any dose administered”.

All adverse events judged by either the reporting investigator or the sponsor as having a reasonable causal relationship to a medicinal product qualify as adverse reactions. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.

**UAR:** An Unexpected Adverse Reaction is “any adverse reaction, the nature, or severity of which is not consistent with the applicable product information” (e.g. investigator's brochure for an unapproved investigational product or summary of product characteristics (SmPC) for a marketed product).

When the outcome of the adverse reaction is not consistent with the applicable product information this adverse reaction should be considered as unexpected.

**Severity:** The term “severe” is often used to describe the intensity (severity) of a specific event (as in mild, moderate or severe, or as described in CTC grades); the event itself, however, may be of relative minor medical significance (such as severe headache). This is not the same as “serious,” which is based on patient/event outcome or action criteria usually associated with events that pose a threat to patient’s life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

**SAE:** A Serious Adverse Event is defined as any untoward medical occurrence or effect in a patient, whether or not considered related to the protocol treatment, that at any dose:

- results in death
- is life-threatening (i.e. an event in which the subject was at risk of death at the time of event; it does not refer to an event which hypothetically might have caused death if it was more severe)
- requires inpatient hospitalization or prolongation of existing patient hospitalization
- results in persistent or significant disability or incapacity
- is a congenital anomaly or birth defect
- is a medically important event or reaction.

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious such as important medical events that might not be immediately life-threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

**SAR:** A Serious Adverse Reaction is defined as any SAE which is considered related to the protocol treatment.

**SUSAR:** Suspected Unexpected Serious Adverse Reaction.

SUSARs occurring in clinical investigations qualify for expedited reporting to the appropriate Regulatory Authorities within the following timeframes:

- Fatal or life-threatening SUSARs within 7 calendar days
- Non-fatal or non-life-threatening SUSARs within 15 calendar days

**Inpatient hospitalization:** a hospital stay equal to, or greater than, 24 hours.

**Second primary malignancy** is one unrelated to the treatment of a previous malignancy (and is NOT a metastasis from the previous malignancy).
Secondary malignancy is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the previous malignancy.

14.2 Exceptions

The following situations do not need to be reported as SAEs:

♦ Elective hospitalization for pre-existing conditions that have not been exacerbated by trial treatment.
♦ A hospitalization which was planned before the patient consented for study participation and where admission did not take longer than anticipated.
♦ A hospitalization planned for protocol related treatment or protocol related procedure as per institutional standard timelines.
♦ Social and/or convenience admission to a hospital
♦ Medical or surgical procedure (e.g. endoscopy, appendectomy); the condition that leads to the procedure is an (S)AE.
♦ Situations where an untoward medical occurrence did not occur (palliative care, rehabilitation, overdose without occurrence of an adverse event).
♦ Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

By EORTC convention, clinical events related to the primary cancer being studied or to the primary cancer progression are not to be reported as SAEs, even if they meet any of the seriousness criteria from the standard SAE definition, unless the event is more severe than expected and therefore the investigator considers that their clinical significance deserves reporting.

14.3 Severity assessment

The severity of all AEs (serious and non-serious) in this trial should be graded using CTCAE v4.0

www.eortc.org/investigators-area/ctc

14.4 Causality assessment

The investigator is obligated to assess the relationship between protocol treatment and the occurrence of each SAE following the definitions in this table:

<table>
<thead>
<tr>
<th>Relationship to the protocol treatment</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reasonable possibility</td>
<td>There is a reasonable possibility that the protocol treatment caused the event</td>
</tr>
<tr>
<td>No reasonable possibility</td>
<td>There is no reasonable possibility that the protocol treatment caused the event</td>
</tr>
</tbody>
</table>

The investigator will use clinical judgment to determine the relationship. Alternative causes, such as natural history of the underlying diseases, medical history, concurrent conditions, concomitant therapy, other risk factors, and the temporal relationship of the event to the protocol treatment will be considered and investigated.
The decision will be recorded on the SAE form and if necessary the reason for the decision will also be recorded.

### 14.5 Expectedness assessment

The expectedness assessment is the responsibility of the sponsor of the study. The expectedness assessment will be performed against the following reference documents:

- Nimorazole: Investigator's Brochure
- Cisplatin: Summary of Product Characteristics (SmPC).
- Placebo: Safety Data sheet

### 14.6 Reporting procedure for investigators

This procedure applies to all Serious Adverse Events (SAEs) occurring from the time a subject is registered until 30 days after last protocol treatment and to any SAE that occurs outside of the SAE detection period (after the 30-days period), if it is considered to have a reasonable possibility to be related to the protocol treatment or study participation.

<table>
<thead>
<tr>
<th>Registration till 30 days after last protocol treatment:</th>
<th>All SAEs</th>
</tr>
</thead>
<tbody>
<tr>
<td>From day 31 after last protocol treatment:</td>
<td>Only related SAEs</td>
</tr>
</tbody>
</table>

Any secondary malignancy should also be reported in expedited way on a SAE form with the appropriate seriousness criteria!

All reporting must be done by the principal investigator or authorized staff member (i.e. on the signature list) to confirm the accuracy of the report.

All SAE data must be collected on the study-specific SAE form.

All SAEs must be reported immediately and no later than 24 hours from the time the investigator or staff became aware of the event.

All SAE-related information needs to be provided in English.

All additional documents in local language must be accompanied by a translation in English, or the relevant information must be summarized in a follow-up SAE report form.

All SAE-related information must be faxed to:

EORTC Pharmacovigilance Unit:

Fax No. +32 2 772 8027

To enable the Sponsor to comply with regulatory reporting requirements, all initial SAE reports should always include the following minimal information: an identifiable patient (SeqID), a suspect medicinal product if applicable, an identifiable reporting source, the description of the medical event and seriousness criteria, as well as the causality assessment by the investigator. Complete information requested on the SAE form of any reported serious adverse event must be returned within 7 calendar days of the initial report. If the completed form is not received within this deadline, the Pharmacovigilance Unit will make a written request to the investigator.

Queries sent out by the EORTC Pharmacovigilance Unit need to be answered within 7 calendar days.

All forms need to be dated and signed by the principal investigator or any authorized staff member (i.e. on the signature list).
14.7 Reporting responsibilities for EORTC

Unblinding may be required for the reporting of serious adverse events (SAEs) or pregnancies or submission of Development Safety Update Report (DSUR) to Competent Authorities, EudraVigilance Clinical Trial Module (EVCTM) and Ethics Committees.

The EORTC Pharmacovigilance Unit will forward all SAE reports to the appropriate persons.

The EORTC Pharmacovigilance Unit will provide a six-monthly summary which will be added in the Trial Status Report and which will be accessible to all participating investigators.

The EORTC Pharmacovigilance Unit will take in charge the reporting of SUSARs/unexpected events to the Competent Authorities, Ethics committees, EudraVigilance Clinical Trial Module (EVCTM) and all participating investigators whenever applicable.

14.8 Pregnancy reporting

Pregnancy occurring during a patient’s participation in this trial, although not considered an SAE, must be notified to the EORTC Pharmacovigilance Unit within the same timelines as an SAE (within 24 hours) on a Pregnancy Notification Form. The outcome of a pregnancy should be followed up carefully and any adverse outcome to the mother or the child should be reported. This also applies to pregnancies in female partners of a male patient participating in this trial.

- Any pregnancy in a female subject or in a female partner of a male subject diagnosed during the treatment period or within 30 days after last protocol treatment administration must be reported to the EORTC Pharmacovigilance Unit
- This must be reported within 24 hours of first becoming aware of the event by fax, to the Pharmacovigilance Unit on a Pregnancy Notification Form
- If an SAE occurs in conjunction with the pregnancy, please also complete an SAE form as explained in the SAE reporting chapter

15 Quality assurance

15.1 Control of data consistency

Data forms will be entered in the EORTC Headquarters database by using the VISTA/RDC (Remote Data Capture) system. Computerized and manual consistency checks will be performed on newly entered forms; queries will be issued in case of inconsistencies. Consistent forms will be validated by the Data Manager. Inconsistent forms will be kept "pending" until resolution of the inconsistencies.

15.2 On-site quality control

Aarhus University GCP Unit will perform on-site quality control visits, as follows:

The first visit in a participating site will be performed approximately within 3 months after the first patient's randomization at this site. The number of subsequent visits will depend upon site's accrual and quality observed during the first visit. Overall, the average frequency will be around two visits a year per recruiting site.

The aim of these site visits will be:
- to verify that the site facilities remain adequate for performing the trial
- to verify that the principal investigator and site staff involved in the trial are working in compliance with GCP and protocol requirements
to assess the consistency of data reported on the case report forms with the source data
♦ to check that Serious Adverse Events have been properly reported and that follow-up information or queries are correctly fulfilled
♦ to assist the site in resolving any outstanding queries
♦ to control the drug accountability process

15.3 Audits

The EORTC Quality Assurance and Control Unit (QA&C) regularly conducts audits of institutions participating in EORTC protocols. These audits are performed to provide assurance that the rights, safety and wellbeing of subjects are properly protected, to assess compliance with the protocol, processes and agreements, ICH GCP standards and applicable regulatory requirements, and to assess the quality of data.

The investigator, by accepting to participate in this protocol, agrees that EORTC, any third party (e.g. a CRO) acting on behalf of the EORTC, or any domestic or foreign regulatory agency, may come at any time to audit or inspect their site and all subsites, if applicable.

This audit consists of interviews with the principal investigator and study team, review of documentation and practices, review of facilities, equipment and source data verification.

The investigator will grant direct access to paper and/or electronic documentation pertaining to the clinical study (e.g. CRFs, source documents such as hospital patient charts and investigator study files) to these authorized individuals. All site facilities related to the study conduct could be visited during an audit (e.g. pharmacy, laboratory, archives …). The investigator agrees to co-operate and provide assistance at reasonable times and places with respect to any auditing activity.

If applicable, the company(ies) supplying the study drug(s) may have access to anonymized data but will not have access to source documents.

If a regulatory authority inspection is announced, the investigator must inform the EORTC Headquarters QA&C Unit immediately (contact at: QualityAssuranceandControlUnit@eortc.be).

In this way EORTC can provide support in preparing and/or facilitating the inspection. EORTC representatives/delegates may also attend the inspection.

15.4 Other central review procedures

15.4.1 Quality assurance in radiotherapy

All documents pertaining to RTQA procedures will be sent to the centers after receipt of the signed commitment form at the EORTC Headquarters.

The RTQA procedure consists of completing the following prior to site authorization:
♦ Level I: Facility Questionnaire (FQ) and Beam Output Audit (BOA)
♦ Level II: Benchmark Case (Dummy Run)
♦ Level V: Credentialing for the use of IMRT

During the trial, the following RTQA patient-specific procedure must be performed:
♦ Level IV: Extensive Individual Case Review (E-ICR)
15.4.1.1 Prior to authorization

15.4.1.1.1 Facility Questionnaire and Beam Output Audit
All EORTC centers at authorization must have a valid (not older than 2 years) EORTC "Facility Questionnaire" (FQ). This questionnaire must be filled in electronically and submitted online. The web link is on the web page of the Radiation Oncology Group (ROG) http://groups.eortc.be/radio/Qualityassurance.htm under "ROG Facility Questionnaire.”

All centers at authorization must have a valid Beam Output Audit (BOA). If a valid BOA has not already been submitted, this should be sent electronically (pdf) to the following address: rtqa1219@eortc.be.

Further details can be found in the "RTQA Guidelines".

15.4.1.1.2 Benchmark Case (Dummy Run)
All EORTC centers prior to authorization should perform a benchmark case procedure. This is a two-step procedure that contains i) a delineation and ii) planning exercise according to the protocol of a patient case that will be provided. The benchmark case will be centrally reviewed by the Quality Assurance committee of the trial.

Further details can be found in the "RTQA Guidelines".

15.4.1.1.3 Credentialing for the use of IMRT
All EORTC centers prior to authorization must be credentialed for the use of their IMRT technique via the Virtual Phantom Procedure (VPP). This procedure consists of irradiating the site's in-house phantom based on the RT plan created for the Benchmark Case and further details can be found in the "RTQA Guidelines".

15.4.1.2 Patient-specific RTQA program
For all patients, complete treatment plans, including any diagnostic images, must be submitted for central review in DICOM-RT format. The Extensive Individual Case Review (E-ICR) encompasses the following:

♦ All patient digital treatment data must be submitted prior to the start of RT treatment
♦ Prospective evaluation of the first five patients per site
♦ Retrospective evaluation of all the other patients after the first five per site

Should the review result in a “major protocol deviation”, the site might be withdrawn from the authorization list and no longer be in the position to enter patients in the trial, until a resubmission results in an “acceptable – per protocol” review. The same rule will apply in case plans would not be submitted within the requested timelines.

All details about the submission procedure, timelines and supplementary forms are described in the "RTQA Guidelines".

In case of questions or difficulties, please contact the trial RTQA team at the following address: rtqa1219@eortc.be.
16 Ethical considerations

16.1 Patient protection

The responsible investigator will ensure that this study is conducted in agreement with either the Declaration of Helsinki (available on the World Medical Association web site (http://www.wma.net)) and/or the laws and regulations of the country, whichever provides the greatest protection of the patient.

The protocol has been written, and the study will be conducted according to the ICH Harmonized Tripartite Guideline on Good Clinical Practice (ICH-GCP, available online at http://www.ema.europa.eu/pdfs/human/ich/013595en.pdf).

The protocol must be approved by the competent ethics committee(s) as required by the applicable national legislation.

16.2 Subject identification

The name of the patient will neither be asked for nor recorded at the EORTC Headquarters. A sequential identification number will be automatically allocated to each patient registered in the trial. This number will identify the patient and will be included on all case report forms. In order to avoid identification errors, the patient’s code (maximum of 4 alphanumerics) and date of birth will also be reported on the case report forms.

16.3 Informed consent

All patients will be informed about
♦ the aims of the study
♦ the possible adverse events
♦ the procedures and possible hazards to which the patient will be exposed
♦ the mechanism of treatment allocation
♦ strict confidentiality of any patient data
♦ medical records possibly being reviewed for trial purposes by authorized individuals other than their treating physician

The template of the patient’s informed consent statement is given as a separate document dated and version controlled to this protocol.

An adapted translation of the PIS/PIC will be provided by EORTC Headquarters and it is the responsibility of the Coordinating investigators for this trial (sometimes called National Coordinators) to adapt it to national/local requirements where necessary.

The **bold sections of the informed consent document must be reflected in any translation**. The content of these bold sections can either be translated literally or translated in any way that best captures the information given.

The translated informed consent documents are to be submitted to ethics committees for approval. The competent ethics committee for each institution must approve the informed consent documents before the center can join the study. It is the responsibility of the competent ethics committee to ensure that the translated informed documents comply with ICH-GCP guidelines and all applicable national legislation.

It is emphasized in the patient information sheet that participation is voluntary and that the patient is free to refuse further participation in the protocol whenever he/she wants to. This will not have any impact on the
patient’s subsequent care. Documented informed consent must be obtained for all patients included in the study before they are registered and/or randomized at the EORTC Headquarters. The written informed consent form must be signed and personally dated by the patient or by the patient’s legally acceptable representative.

All of the above must be done in accordance with the applicable national legislation and local regulatory requirements.

**17 Administrative responsibilities**

**17.1 The study coordinator**

The Study Coordinator (in cooperation with the EORTC Headquarters) will be responsible for writing the protocol, contributing to the medical review, discussing the contents of the reports with the Data Manager and the Statistician, and for publishing the study results. He will assist the Clinical Research Physician for answering some clinical questions concerning eligibility, treatment, and the medical review of the patients.

**Study coordinator:**

**Jens Overgaard**
Aarhus University Hospital
Noerrebrogade 44, Bfdg 5, 2nd floor
DK-8000 Aarhus C
Denmark
Phone: +45 78 46 26 29
Fax: +45 86 19 71 09
e-mail: jens@oncology.dk

**Study co-coordinator:**

Vincent Grégoire
Cliniques Universitaires St. Luc
Avenue Hippocrate, 10
1200 Brussels
Belgium
Phone: +32 2 764 94 43
Fax: +32 2 764 94 25
e-mail: vincent.gregoire@uclouvain.be

**17.2 The EORTC Headquarters**

The EORTC Headquarters will be responsible for writing the protocol and PIS/IC, reviewing the protocol, setting up the trial, collecting case report forms, controlling the quality of the reported data, organizing the medical review and generating reports and analyses in cooperation with the Study Coordinator. All methodological questions should be addressed to the EORTC Headquarters.

**EORTC HEADQUARTERS**

Avenue E. Mounierlaan 83/11
Brussel 1200 Bruxelles
België - Belgique
Fax: +32 2 7723545
Registration of patients:

http://www.eortc.be/random
Or
Phone (in case of problems): +32 2 774 16 00

17.3 The EORTC group

All questions concerning ongoing membership in the group should be addressed to the chairman and/or secretary of the group.

For new membership contact Membership Committee at membership@eortc.be

ROG EORTC group

Chairman:

Philippe Maingon
Centre Georges-François Leclerc
1, rue du Professeur Marion - B.P. 77980
21079 Dijon CEDEX
France
Phone: +33 380737517
Fax: +33 380362829
e-mail: pmaingon@cgfl.fr

Secretary:

Philippe Poortmans
Dr Bernard Verbeeten Instituut
Brugstraat 10
5042 SB Tilburg
The Netherlands
Phone: +31 13 5947765
Fax: +31 13 4685174
e-mail: poortmans.ph@bvi.nl

18 Trial sponsorship and financing

EORTC is the legal Sponsor for all EORTC participants.

The contact details of the EORTC are:

EORTC Headquarters
Avenue E. Mounierlaan 83/11
Brussel 1200 Bruxelles
België - Belgique
Phone: +32 2 7741611
Fax: +32 2 7723545
e-mail: eortc@eortc.be

An educational grant is provided by Azanta.
19 Trial insurance

A clinical trial insurance has been taken out according to the laws of the countries where the study will be conducted. An insurance certificate will be made available to the participating sites at the time of study initiation.

Clinical trial insurance is only valid in centers authorized by the EORTC Headquarters. For details please refer to the chapter on investigator authorization.

20 Publication policy

All publications must comply with the terms specified in the EORTC Policy 009 “Release of Results and Publication Policy” version 4.02 dated March 2012.

The final publication of the main trial results will be written by the Study Coordinators on the basis of the final analysis performed at the EORTC Headquarters and published in a major scientific journal.

The final publication of associated translational research studies will be written by the Coordinator of the corresponding translational research study.

Authors of the manuscript(s) will include the Study Coordinators, the investigators who have included more than 5% of the eligible patients in the trial (by order of inclusion), and the statistician and clinical research physician in charge of the trial at the EORTC Headquarters. For publication of translational research results, co-authors will also include scientific collaborators who made substantial contribution to the research.

The title of all manuscripts will include “DAHANCA-EORTC”, and all manuscripts will include an appropriate acknowledgment section, mentioning all investigators who have contributed to the trial, the EORTC Headquarters staff involved in the study, as well as supporting bodies (NCI, cancer leagues, supporting company…).

Prior to submission, all publications (papers, abstracts, presentations…) including data pertaining to patients from the present trial will be submitted for review to the EORTC Headquarters, to all co-authors.

The above rules are applicable to publications involving any individual patient registered/randomized in the trial.
Appendix A: References


Ref. 16 ICRU Report 83: Prescribing, Recording and Reporting Photon-Beam Intensity-Modulated Radiation therapy (IMRT). International Commission on Radiation Units and Measurements (2010). 7910 Woodmont Avenue, Bethesda, MD 20814, USA.


Ref. 35 Overgaard J. Hypoxic modification of radiotherapy in squamous cell carcinoma of the head and neck--a systematic review and meta-analysis. Radiother Oncol. 2011; 100: 22-32.


Ref. 38 Peterson, B and George, L (1993): Sample size requirements and length of study for testing interaction in 1 X k factorial design when time to failure is the outcome, Controlled Clinical Trials, (14), pg 511-522.
## Appendix B: Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-HT3</td>
<td>5-hydroxytryptamine type 3</td>
</tr>
<tr>
<td>AE</td>
<td>Adverse Event</td>
</tr>
<tr>
<td>AJCC</td>
<td>American Joint Committee on Cancer</td>
</tr>
<tr>
<td>ALT</td>
<td>Alanine aminotransferase</td>
</tr>
<tr>
<td>ANC</td>
<td>Absolute neutrophil count</td>
</tr>
<tr>
<td>AR</td>
<td>Adverse Reaction</td>
</tr>
<tr>
<td>AST</td>
<td>Aspartate aminotransferase</td>
</tr>
<tr>
<td>BOA</td>
<td>Beam Output Audit</td>
</tr>
<tr>
<td>CNS</td>
<td>Central Nervous System</td>
</tr>
<tr>
<td>CRF</td>
<td>Case Report Form</td>
</tr>
<tr>
<td>CRP</td>
<td>Clinical Research Physician</td>
</tr>
<tr>
<td>CRT</td>
<td>Chemoradiotherapy</td>
</tr>
<tr>
<td>CTCAE</td>
<td>Common Terminology Criteria for Adverse Events</td>
</tr>
<tr>
<td>CTV</td>
<td>Clinical target volume</td>
</tr>
<tr>
<td>DAHANCA</td>
<td>Danish Head and Neck Cancer</td>
</tr>
<tr>
<td>DICOM</td>
<td>Digital Imaging and Communication in Medicine</td>
</tr>
<tr>
<td>DSUR</td>
<td>Development Safety Update Report</td>
</tr>
<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
</tr>
<tr>
<td>ECOG</td>
<td>Eastern Cooperative Oncology Group</td>
</tr>
<tr>
<td>EGF</td>
<td>Epidermal Growth Factor</td>
</tr>
<tr>
<td>E-ICR</td>
<td>Extensive Individual Case Review</td>
</tr>
<tr>
<td>eNAL</td>
<td>extended no action level</td>
</tr>
<tr>
<td>EORTC</td>
<td>European Organisation for Research and Treatment of Cancer</td>
</tr>
<tr>
<td>EoT</td>
<td>End of Trial</td>
</tr>
<tr>
<td>EPID</td>
<td>Electronic portal imaging device</td>
</tr>
<tr>
<td>EVCTM</td>
<td>Eudra Vigilance Clinical Trial Module</td>
</tr>
<tr>
<td>FAZA-PET/CT</td>
<td>Positron emission tomography - Computed Tomography using [18F-fluoroazomycin-arabinoside (FAZA)</td>
</tr>
<tr>
<td>FDG-PET-CT</td>
<td>Positron emission tomography - Computed Tomography using fluorodeoxyglucose</td>
</tr>
<tr>
<td>FFPE</td>
<td>Formalin-Fixed Paraffin-Embedded</td>
</tr>
<tr>
<td>FPI</td>
<td>First patient in</td>
</tr>
<tr>
<td>FQ</td>
<td>Facility Questionnaire</td>
</tr>
</tbody>
</table>
FUP Follow-up period
fx fraction
GTV Gross Tumor Volume
Gy Gray
HBM Human Biological Material
HNCG Head and Neck Cancer Group
HNSCC Squamous cell carcinoma of the head and neck
HPV Human papillomavirus
HQ Headquarters
HR Hazard Ratio
IA Interim Analysis
ICH/GCP International Conference on Harmonisation /Good Clinical Practice
ICRU International Commission on Radiation Units
IDMC Independent Data Monitoring Committee
IHC Immunohistochemistry
IMRT Intensity-Modulated Radiation Therapy
IV Intra Venous
K Potassium
kVCT KiloVolt Computed Tomography
LD Lethal Dose
LDH Lactate dehydrogenase
Mg magnesium
MRI Magnetic Resonance Imaging
MV MegaVolt
MVCT MegaVolt Computed Tomography
NG Nasogastric
nodal CTV Nodal Clinical Target Volume
OAR’s Organs at risk
ORTA Online Randomization Trials Access
PEG Percutaneous endoscopic gastrostomy tube
PET Positron emission tomography
Planning-CT Planning Computed Tomography
pO2 Oxygen Partial Pressure
primary tumor CTV Primary tumor Clinical Target Volume
<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRV</td>
<td>Planning Organ at Risk Volume</td>
</tr>
<tr>
<td>PTV</td>
<td>Planning Target Volume</td>
</tr>
<tr>
<td>QA</td>
<td>Quality assurance</td>
</tr>
<tr>
<td>ROG</td>
<td>Radiation Oncology Group</td>
</tr>
<tr>
<td>RP</td>
<td>Retropharyngeal nodes</td>
</tr>
<tr>
<td>RTOG</td>
<td>Radiation Therapy Oncology Group</td>
</tr>
<tr>
<td>RTQA</td>
<td>Radiation Therapy Quality Assurance</td>
</tr>
<tr>
<td>SAE</td>
<td>Serious Adverse Event</td>
</tr>
<tr>
<td>SAR</td>
<td>Serious Adverse Reaction</td>
</tr>
<tr>
<td>SSC</td>
<td>Study Steering Committee</td>
</tr>
<tr>
<td>SAL</td>
<td>Shrinking action level</td>
</tr>
<tr>
<td>seqID</td>
<td>Sequential patient Identification number</td>
</tr>
<tr>
<td>SIB-IMRT</td>
<td>Simultaneous Integrated Boost Intensity Modulated Radiation Therapy</td>
</tr>
<tr>
<td>SUSAR</td>
<td>Suspected Unexpected Serious Adverse Reaction</td>
</tr>
<tr>
<td>TR</td>
<td>Translational Research</td>
</tr>
<tr>
<td>TRAC</td>
<td>Translational Research Advisory Committee</td>
</tr>
<tr>
<td>TROG</td>
<td>Trans-Tasman Radiation Oncology Group</td>
</tr>
<tr>
<td>ULN</td>
<td>Upper Limit of Normal</td>
</tr>
<tr>
<td>VODCA</td>
<td>Visualization and Organization of Data for Cancer Analysis</td>
</tr>
<tr>
<td>VPP</td>
<td>Virtual Phantom Procedure</td>
</tr>
<tr>
<td>WBC</td>
<td>White blood cells count</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
</tbody>
</table>
# Appendix C: WHO performance status scale

<table>
<thead>
<tr>
<th>Grade</th>
<th>Performance scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Able to carry out all normal activity without restriction</td>
</tr>
<tr>
<td>1</td>
<td>Restricted in physically strenuous activity but ambulatory and able to carry out light work.</td>
</tr>
<tr>
<td>2</td>
<td>Ambulatory and capable of all self-care but unable to carry out any work; up and about more than 50% of waking hours.</td>
</tr>
<tr>
<td>3</td>
<td>Capable of only limited self-care; confined to bed or chair more than 50% of waking hours</td>
</tr>
<tr>
<td>4</td>
<td>Completely disabled; cannot carry on any self-care; totally confined to bed or chair.</td>
</tr>
</tbody>
</table>
Appendix D: Calculation of the glomerular filtration rate (GFR)

COCKCROFT AND GAULT FORMULA

For the calculation of GFR age is measured in years and weight is measured in kilograms.

If serum creatinine is measured in µmol/l, the following formula applies:

**In males:** \[ \text{GFR}[\text{ml/min}] = \frac{1.23 \times (140 - \text{age}) \times \text{weight}}{\text{serum creatinine}} \]

**In females:** \[ \text{GFR}[\text{ml/min}] = \frac{1.05 \times (140 - \text{age}) \times \text{weight}}{\text{serum creatinine}} \]

If serum creatinine is measured in mg/dl, the following formula applies:

**In males:** \[ \text{GFR}[\text{ml/min}] = \frac{(140 - \text{age}) \times \text{weight}}{72 \times \text{serum creatinine}} \]

**In females:** \[ \text{GFR}[\text{ml/min}] = \frac{0.85 \times (140 - \text{age}) \times \text{weight}}{72 \times \text{serum creatinine}} \]
Appendix E: Common Terminology Criteria for Adverse Events

In the present study, adverse events and/or adverse drug reactions will be recorded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0.

At the time this protocol was issued, the full CTC document was available on the NCI web site, at the following address: http://ctep.cancer.gov/reporting/ctc.html.

The EORTC Headquarters web site www.eortc.org\investigators-area\ctc provides a link to the appropriate CTC web site. This link will be updated if the CTC address is changed.
Appendix F: Calculation of body surface area

\[
\text{BSA (m}^2) = \left( \frac{\text{Height(cm)} \times \text{Weight(kg)}}{3600} \right)^{\frac{1}{3}}
\]

Comparison between the TNM atlas of the neck nodes and a proposal of lymph node levels in the neck modified from Robbins.

<table>
<thead>
<tr>
<th>TNM atlas for lymph nodes of the neck</th>
<th>Node levels modified from Robbins</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group number</td>
<td>Level</td>
</tr>
<tr>
<td></td>
<td>Ia</td>
</tr>
<tr>
<td></td>
<td>Ib</td>
</tr>
<tr>
<td>1 submental nodes</td>
<td>I</td>
</tr>
<tr>
<td></td>
<td>II</td>
</tr>
<tr>
<td>2 submandibular nodes</td>
<td>IVa</td>
</tr>
<tr>
<td>3 cranial jugular nodes</td>
<td>IVb</td>
</tr>
<tr>
<td>4 middle jugular nodes</td>
<td>V</td>
</tr>
<tr>
<td>5 caudal jugular nodes</td>
<td>Va</td>
</tr>
<tr>
<td></td>
<td>Vb</td>
</tr>
<tr>
<td>6 dorsal cervical nodes along the spinal accessory nerve</td>
<td>VI</td>
</tr>
<tr>
<td></td>
<td>VIa</td>
</tr>
<tr>
<td></td>
<td>VIb</td>
</tr>
<tr>
<td>8 prelaryngeal and paratracheal nodes</td>
<td>VII</td>
</tr>
<tr>
<td></td>
<td>VIIa</td>
</tr>
<tr>
<td></td>
<td>VIIb</td>
</tr>
<tr>
<td>9 retropharyngeal nodes</td>
<td>VIII</td>
</tr>
<tr>
<td>10 parotid nodes</td>
<td></td>
</tr>
</tbody>
</table>
### TNM atlas group number 1 / modified from Robbins level Ia: submental group

<table>
<thead>
<tr>
<th>Boundaries</th>
<th>Proposal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cranial</td>
<td>mylo-hyoid m</td>
</tr>
<tr>
<td>Caudal</td>
<td>platysma m.</td>
</tr>
<tr>
<td>Anterior</td>
<td>symphysis menti</td>
</tr>
<tr>
<td>Posterior</td>
<td>body of hyoid bone / mylo-hyoid m.</td>
</tr>
<tr>
<td>Lateral</td>
<td>medial edge of ant. belly of digastric m.</td>
</tr>
<tr>
<td>Medial</td>
<td>n.a.</td>
</tr>
</tbody>
</table>

### TNM atlas group number 2 / modified from Robbins level Ib: submandibular group

<table>
<thead>
<tr>
<th>Boundaries</th>
<th>Proposal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cranial</td>
<td>cranial edge of sub-mandibular gland; anteriorly, mylo-hyoid m.</td>
</tr>
<tr>
<td>Caudal</td>
<td>plane through caudal edge of hyoid bone and basilar edge of mandible ; alternatively caudal edge of sub-mandibular gland (whichever is more caudal) / platysma m.</td>
</tr>
<tr>
<td>Anterior</td>
<td>symphysis menti</td>
</tr>
<tr>
<td>Posterior</td>
<td>posterior edge of submandibular gland (caudally) / posterior belly of digastric m. (cranially)</td>
</tr>
<tr>
<td>Lateral</td>
<td>inner side of mandible, down to basilar edge / platysma m. (caudal) / medial pterygoid m. (posteriorly)</td>
</tr>
<tr>
<td>Medial</td>
<td>lateral edge of ant. belly of digastric m. (caudally) / posterior belly of digastric m. (cranially)</td>
</tr>
</tbody>
</table>
### TNM atlas group number 3 / modified from Robbins level II: upper jugular group

<table>
<thead>
<tr>
<th>Boundaries</th>
<th>Proposal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cranial</td>
<td>caudal edge of the lateral process of C1</td>
</tr>
<tr>
<td>Caudal</td>
<td>caudal edge of the body of the hyoid bone</td>
</tr>
<tr>
<td>Anterior</td>
<td>posterior edge of the sub-mandibular gland / posterior edge of posterior belly of digastric m.</td>
</tr>
<tr>
<td>Posterior</td>
<td>posterior edge of sterno-cleido-mastoid m.</td>
</tr>
<tr>
<td>Lateral</td>
<td>Deep (medial) surface of sterno-cleido-mastoid m. / platysma m. / parotid gland / posterior belly of digastric m.</td>
</tr>
<tr>
<td>Medial</td>
<td>medial edge of carotid artery / scalenius mm.</td>
</tr>
</tbody>
</table>

Level II can be divided into level IIa and level IIb by drawing an artificial line at the posterior edge of the internal jugular vein.

### TNM atlas group number 4 / modified from Robbins level III: middle jugular group

<table>
<thead>
<tr>
<th>Boundaries</th>
<th>Proposal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cranial</td>
<td>caudal edge of the body of the hyoid bone</td>
</tr>
<tr>
<td>Caudal</td>
<td>caudal edge of cricoid cartilage</td>
</tr>
<tr>
<td>Anterior</td>
<td>anterior edge of sterno-cleido-mastoid m. / posterior third of thyrohyoid m.</td>
</tr>
<tr>
<td>Posterior</td>
<td>posterior edge of sterno-cleido-mastoid m.</td>
</tr>
<tr>
<td>Lateral</td>
<td>Deep (medial) surface of sterno-cleido-mastoid m.</td>
</tr>
<tr>
<td>Medial</td>
<td>medial edge of carotid artery / scalenius mm.</td>
</tr>
</tbody>
</table>
### TNM atlas group number 5 / modified from Robbins level IVa: lower jugular group

<table>
<thead>
<tr>
<th>Boundaries</th>
<th>Proposal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cranial</td>
<td>caudal edge of cricoid cartilage</td>
</tr>
<tr>
<td>Caudal</td>
<td>2 cm cranial to sternal manubrium</td>
</tr>
<tr>
<td>Anterior</td>
<td>anterior edge of sterno-cleido-mastoid m. (cranially) / body of sterno-cleido-mastoid m. (caudally)</td>
</tr>
<tr>
<td>Posterior</td>
<td>posterior edge of sterno-cleido-mastoid m. (cranially) / scalenius mm. (caudally)</td>
</tr>
<tr>
<td>Lateral</td>
<td>Deep (medial) surface of sterno-cleido-mastoid m. (cranially) / lateral edge of sterno-cleido-mastoid m. (caudally)</td>
</tr>
<tr>
<td>Medial</td>
<td>medial edge of carotid artery / thyroid gland / scalenius mm. (cranially) / medial edge of sterno-cleido-mastoid m. (caudally)</td>
</tr>
</tbody>
</table>

### TNM atlas group number 5 / modified from Robbins level IVb: medial supraclavicular group

<table>
<thead>
<tr>
<th>Boundaries</th>
<th>Proposal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cranial</td>
<td>caudal border of level IVa (2 cm cranial to sternal manubrium)</td>
</tr>
<tr>
<td>Caudal</td>
<td>cranial edge of sternal manubrium</td>
</tr>
<tr>
<td>Anterior</td>
<td>Deep surface of sterno-cleido-mastoid m. / deep aspect of clavicle</td>
</tr>
<tr>
<td>Posterior</td>
<td>anterior edge of scalenius mm. (cranially) / upper lung lobe (caudally)</td>
</tr>
<tr>
<td>Lateral</td>
<td>lateral edge of middle scalenius m.</td>
</tr>
<tr>
<td>Medial</td>
<td>lateral border of level VI (pre-tracheal component) / medial edge of carotid artery</td>
</tr>
</tbody>
</table>
**TNM atlas group number 6 / modified from Robbins level V: posterior triangle group**

<table>
<thead>
<tr>
<th>Boundaries</th>
<th>Proposal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cranial</td>
<td>cranial edge of the body of hyoid bone</td>
</tr>
<tr>
<td>Caudal</td>
<td>plane just below transverse cervical vessels</td>
</tr>
<tr>
<td>Anterior</td>
<td>posterior edge of sterno-cleido-mastoid m.</td>
</tr>
<tr>
<td>Posterior</td>
<td>anterior border of trapezius m.</td>
</tr>
<tr>
<td>Lateral</td>
<td>platysma m / skin</td>
</tr>
<tr>
<td>Medial</td>
<td>levator scapulae m. (cranially) / posterior scalenius m. (caudally)</td>
</tr>
</tbody>
</table>

Surgically, level V is subdivided in two groups of upper (Va) and lower (Vb) nodes according to their respective relationships with the spinal accessory nerve; this division has no real interest for radiotherapy.

**TNM atlas group number 8 / modified from Robbins anterior compartment group: level VIa: prelaryngeal & pretracheal nodes**

<table>
<thead>
<tr>
<th>Boundaries</th>
<th>Proposal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cranial*</td>
<td>caudal edge of the body of the thyroid cartilage</td>
</tr>
<tr>
<td>Caudal</td>
<td>cranial edge of the sternal manubrium</td>
</tr>
<tr>
<td>Anterior</td>
<td>skin / platysma m.</td>
</tr>
<tr>
<td>Posterior</td>
<td>thyroid gland / trachea / infra-hyoid mm. (sterno-hyoid &amp; sterno-thyroid)</td>
</tr>
<tr>
<td>Lateral</td>
<td>anterior edges of the sterno-cleido-mastoid m.</td>
</tr>
<tr>
<td>Medial</td>
<td>n.a.</td>
</tr>
</tbody>
</table>

*for anterior floor of mouth, tip of the tongue and lip tumors, hyoid bone (i.e. caudal limit of level I)
TNM atlas group number 8 / modified from Robbins anterior compartment group: level VIb: paratracheal & recurrent nerve nodes

<table>
<thead>
<tr>
<th>Boundaries</th>
<th>Proposal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cranial</td>
<td>caudal edge of the cricoid cartilage</td>
</tr>
<tr>
<td>Caudal</td>
<td>cranial edge of the sternal manubrium</td>
</tr>
<tr>
<td>Anterior</td>
<td>thyroid gland (cranially) / sterno-thyroid m. (caudally)</td>
</tr>
<tr>
<td>Posterior</td>
<td>pre-vertebral mm. / esophagus</td>
</tr>
<tr>
<td>Lateral</td>
<td>carotid artery</td>
</tr>
<tr>
<td>Medial</td>
<td>trachea / esophagus</td>
</tr>
</tbody>
</table>

TNM atlas group number 9 / modified from Robbins prevertebral compartment group: level VIIa: retropharyngeal nodes

<table>
<thead>
<tr>
<th>Boundaries</th>
<th>Proposal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cranial</td>
<td>upper edge of body of Cl / hard palate</td>
</tr>
<tr>
<td>Caudal</td>
<td>cranial edge of the body of the hyoid bone</td>
</tr>
<tr>
<td>Anterior</td>
<td>posterior edge of the superior or middle pharyngeal constrictor m.</td>
</tr>
<tr>
<td>Posterior</td>
<td>longus capitis m. and longus colli m.</td>
</tr>
<tr>
<td>Lateral</td>
<td>medial edge of the internal carotid artery</td>
</tr>
<tr>
<td>Medial</td>
<td>medial edge of transverse foramen</td>
</tr>
</tbody>
</table>
TNM atlas group number 9 / modified from Robbins prevertebral compartment group: Level VIIb: retro-styloid nodes

<table>
<thead>
<tr>
<th>Boundaries</th>
<th>Proposal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cranial</td>
<td>base of skull (jugular foramen)</td>
</tr>
<tr>
<td>Caudal</td>
<td>caudal edge of the lateral process of C1 (upper limit of level II)</td>
</tr>
<tr>
<td>Anterior</td>
<td>posterior edge of pre-styloid para-pharyngeal space</td>
</tr>
<tr>
<td>Posterior</td>
<td>vertebral body of C1, base of skull</td>
</tr>
<tr>
<td>Lateral</td>
<td>styloid process / deep parotid lobe</td>
</tr>
<tr>
<td>Medial</td>
<td>medial edge of the internal carotid artery</td>
</tr>
</tbody>
</table>

TNM atlas group number 10 / modified from Robbins level VIII: parotid group

<table>
<thead>
<tr>
<th>Boundaries</th>
<th>Proposal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cranial</td>
<td>Zygomatic arch, external auditory canal</td>
</tr>
<tr>
<td>Caudal</td>
<td>angle of the mandible</td>
</tr>
<tr>
<td>Anterior</td>
<td>Posterior edge of mandibular rami &amp; posterior edge of masseter m. (laterally) medial pterygoid muscle (medially)</td>
</tr>
<tr>
<td>Posterior</td>
<td>anterior edge of sterno-cleido-mastoid m. (laterally), posterior belly of digastric m. (medially)</td>
</tr>
<tr>
<td>Lateral</td>
<td>SMAS layer in sub-cutaneous tissue</td>
</tr>
<tr>
<td>Medial</td>
<td>Styloid bone and styloid mm.</td>
</tr>
</tbody>
</table>
Appendix H: Guidelines for Radiotherapy Reviewers

1  Lymph node level selection

1.1 For T3-T4 N0 M0
- Ipsilateral levels II-IV
- Contralateral levels II-IV
- Bilateral retropharyngeal nodes for post. pharyngeal wall tumor
- Level VI for sub-glottic extension, esophageal extension

1.2 For T2-T3-T4 N1 M0
- Ipsilateral levels II-IV
- Contralateral levels II-IV
- Bilateral retropharyngeal nodes for post. pharyngeal wall tumor
- Level VI for sub-glottic extension, esophageal extension
- Ipsilateral retro-styloid area if upper level II node
- Medial supraclavicular nodes if lower neck (level IV) node

1.3 For T2-T3-T4 N2a-N2b-N3 M0
- Ipsilateral levels (Ib), II-V
- Contralateral levels II-IV
- Bilateral retropharyngeal nodes for post. pharyngeal wall tumor
- Unilateral retropharyngeal nodes except for laryngeal tumor
- Level VI for sub-glottic extension, esophageal extension
- Ipsilateral retro-styloid area if upper level II node
- Medial supraclavicular nodes if lower neck (level IV) node

1.4 For T2-T3-T4 N2c M0
- Address the needs on each sides independently, e.g. N1-N2a-N2b-N3 on contralateral side, use N1-N2a-N2b-N3 for that side
2 **Lymph node level delineation**

- For the prophylactic nodal CTV (35 x 1.55 Gy), see the revised atlas on node delineation
- In case of node(s) abutting the SCM muscle (i.e. no fat between the node and the muscle), include at least 1 cm of muscle
- In case of N3 node, extra structures (e.g. parotid gland, para-spinal muscles) may need to be delineated
- For the therapeutic dose nodal CTV (35 x 2.0 Gy), use a GTV to CTV margin of 8 mm, that is contained by the prophylactic dose nodal CTV
- Below are examples of nodal delineation. Further information on a revised neck node atlas can be found in Appendix G and in the Dummy Run 'download' folder.
3 Primary tumor CTV delineation

♦ For laryngeal/hypopharyngeal tumors:
  ♦ Include pre epiglottic space
  ♦ If T3 or T4, include the thyroid cartilage

♦ For oropharyngeal tumors:
  ♦ Include the parapharyngeal space
  ♦ Expand by a margin of 1-1.5cm around any base of tongue GTV

3.1 Laryngeal tumors

3.1.1 Prophylactic dose CTV (35 x 1.55 Gy)
♦ For T2-T4 laryngeal SCC, include the ipsilateral para-laryngeal space, the pre-epiglottic space and the thyroid cartilage (not for T2)
♦ For T2-T4 laryngeal SCC, include ≈1cm of the mucosa from the GTV

3.1.2 Therapeutic dose CTV (35 x 2 Gy)
♦ GTV + 8 mm, but within the prophylactic dose CTV (thus corrected for anatomy)

3.2 Hypopharyngeal tumors

3.2.1 Prophylactic dose CTV (35 x 1.55 Gy)
♦ For T2-T4 piriform sinus SCC, include the thyroid cartilage on the ipsilateral side (not for T2)
♦ For T2-T4 hypopharyngeal SCC, include 1.0-1.5 cm of the mucosa from the GTV

3.2.2 Therapeutic dose CTV (35 x 2 Gy)
♦ GTV + 8 mm, but within the prophylactic dose CTV (thus corrected for anatomy)

3.3 Oropharyngeal tumors

3.3.1 Prophylactic dose CTV (35 x 1.55 Gy)
♦ For T2-T4 lateral wall oropharyngeal SCC, include the ipsilateral para-pharyngeal space
♦ For T2-T4 base of tongue SCC and vallecula, include 1.0-1.5cm of the base of tongue from the GTV
♦ For T2-T4 soft palate SCC, include the full soft palate

3.3.2 Therapeutic dose CTV (35 x 2 Gy)
♦ GTV + 8 mm, but within the prophylactic dose CTV (thus corrected for anatomy)
4 Organs at risk (OAR)

4.1 Delineation
- The following structures are mandatory:
  - Both parotid glands with a 0 mm PRV margin
  - Spinal cord with a 3-5 mm PRV margin
  - Brain stem with a 3-5 mm PRV margin
- “Avoidance structures” such as the oral cavity, the larynx, the constrictor muscles, the skin will be left to the discretion of the investigator

4.2 Dose-volume constraint objectives
- Ipsilateral parotid: $D_{\text{mean}} < 25-27 \text{ Gy}$
- Contralateral parotid: $D_{\text{mean}} \leq 24 \text{ Gy}$
- PRV SC: $D_2 < 45 \text{ Gy}$, and lower if possible
- PRV BS: $D_2 < 50 \text{ Gy}$, and lower if possible
- Avoiding PTV dose compromise should be the main planning priority

5 PTV dose-volume constraint objectives (according to ICRU #83)

5.1 Prophylactic PTV (median dose of 54.25 Gy ± 2%)
- $D_{95\%} \geq 95\%$ of prescribed dose
- $D_{98\%} \geq 90\%$ of prescribed dose
- $D_{5\%} \leq 107\%$ of prescribed dose
- No $D_{5\%}$ constraint in prophylactic PTV on affected side, because of prophylactic PTV overlap with therapeutic dose PTV

5.2 Therapeutic dose PTV (median dose of 70 Gy ± 2%)
- $D_{95\%} \geq 95\%$ of prescribed dose
- $D_{98\%} \geq 90\%$ of prescribed dose
- $D_{5\%} \geq 107\%$ of prescribed dose
Avoiding PTV dose compromise should be the main planning priority
6 Classification of Acceptable ('Minor') and Unacceptable (Major) Protocol Variations

<table>
<thead>
<tr>
<th>PTV/OAR/PRV</th>
<th>Acceptable protocol variation</th>
<th>Unacceptable protocol variation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PTV 70 Gy</strong></td>
<td>$D_{5%} 74.9$ Gy-77 Gy</td>
<td>$D_{5%} &gt;77$ Gy (110 %)</td>
</tr>
<tr>
<td></td>
<td>(107%-110%)</td>
<td>$D_{50%} &lt; 68.6$ Gy or $ &gt; 71.4$ Gy (+/- 2 %)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$D_{95%} &lt; 66.5$ Gy (95%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$D_{98%} &lt; 63$ Gy (90%)</td>
</tr>
<tr>
<td><strong>PTV 54.25 Gy</strong></td>
<td>$D_{5%} 58$ Gy- 59.7 Gy</td>
<td>$D_{95%} &lt; 51.5$ Gy (95%)</td>
</tr>
<tr>
<td></td>
<td>(107%-110%)</td>
<td>$D_{98%} &lt; 48.8$ Gy (90%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$D_{5%}^1 &gt; 59.7$ Gy (110%)</td>
</tr>
<tr>
<td><strong>PRV Spinal Cord</strong></td>
<td>$D_{2%} &gt;45$ Gy and $ \leq 50$ Gy</td>
<td>$D_{2%} &gt;50$ Gy</td>
</tr>
<tr>
<td><strong>PRV Brain Stem</strong></td>
<td>$D_{2%} &gt;50$ and $ \leq 52$ Gy</td>
<td>$D_{2%} &gt;52$ Gy</td>
</tr>
</tbody>
</table>

$^1$ Applies only to contralateral prophylactic PTV in the case of unilateral disease
Appendix I: Study timelines overview