MACH-EGFR

Meta-Analysis in locally advanced Cancers of Head & neck on anti-EGFR therapy

Meta-Analysis in locally advanced squamous cell Cancers of Head and neck on anti-EGFR therapy

Initiated by the Institut Gustave Roussy

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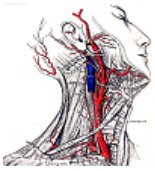

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1. INTRODUCTION AND BACKGROUND

Cancers of the head and neck represent a major burden worldwide. In the United States, 49,670 new cases and 9,700 deaths are expected in 2017 (1). Worldwide and in Europe, WHO's International Agency for Research on Cancer estimates that respectively 452,208 and 106,968 new cases will occur in 2017 (2). Most cases are diagnosed at an advanced stage and are treated with a combination of surgery, radiotherapy and chemotherapy. Previous individual patient data meta-analyses performed by our group under the auspices of the MACH-NC (meta-analysis of chemotherapy in head and neck cancer) or MARCH (meta-analysis of radiotherapy in carcinomas of the head and neck) cooperative groups have previously demonstrated that the addition of chemotherapy to local treatment (3,4) or the modification of radiotherapy fractionation (5) have led to improved survival, mostly by the means of improved locoregional control. Other ways of improving survival have also been pursued, among them the inhibition of the epidermal growth factor pathway.

Oncogenic tyrosine kinases have proved to be promising targets for the development of highly effective anticancer drugs. Among them, the epidermal growth factor and its receptor, the EGFR, are crucial components of tumor growth for squamous cell carcinomas of the head and neck (SCCHN). EGFR is a transmembrane receptor with tyrosine kinase activity and belongs to the human epidermal growth factor receptor (HER) family. The HER family includes EGFR (also named as c-erbB1 / HER1) and three other closely related members: HER2 (c-erbB2), HER3 (c-erbB3) and HER4 (c-erbB4). Activation of HER receptors transmit the extra cellular growth signals by controlling functions such as proliferation, differentiation, migration and apoptosis. Targeting HER, and specifically EGFR is therefore a rationale strategy to improve efficacy of current anticancer treatment of SCCHN. Indeed, high EGFR signaling occurs in the majority of cases generally due to EGFR overexpression, and less frequently to mutation at its extracellular domain. This constitutively activates major signaling pathways promotes unconstrained cellular proliferation and survival, enhanced invasion and angiogenesis, and evasion of apoptosis (6).

Two main strategies have been employed to block EGFR signaling in SCCHN, either using monoclonal antibodies (mAbs) to block receptor–ligand binding and prevent EGFR dimerization; or using tyrosine kinase inhibitors (TKIs) to inhibit EGFR downstream intracellular signaling, through the competing within the ATP-binding site of the intracellular tyrosine kinase domain. The blockade of EGFR with cetuximab a chimeric monoclonal anti body was demonstrated as an efficient strategy in the treatment of SCCHN, either in combination with radiotherapy for locally advanced disease (7) or in combination with platinum-5FU chemotherapy in the recurrent/metastatic setting (8). This allowed to establish a new standard of care for SCCHN (7–10). After these seminal studies, multiple randomized trials have been conducted testing other EGFR targeting (+/- HER2) agents, either as a single agent combined to radiotherapy, or compared to chemotherapy or in addition to

chemotherapy. Interestingly cetuximab has been the only EGFR targeting agent that was clinically approved but cetuximab is a chimeric MAB, not only targeting EGFR but also retaining a native Fc-region that can engage the innate immune system and may induce antibody-dependent cell-mediated cytotoxicity (ADCC) which is supposed to be a key determinant of its anti-tumor activity. Indeed cetuximab is able to activate the immune system and recruit effector cells (natural killer, macrophages) through interactions with its IgG1.
Multiple trials have been conducted using these agents, either as a single agent combined to radiotherapy, or compared to chemotherapy or in addition to chemotherapy. Currently only cetuximab is approved for clinical use in the locally advanced and metastatic settings. Although there is heterogeneity in the compounds used and their mechanisms of action, they share the common goal of blocking the EGFR pathway. The goals of the present individual patient data meta-analysis is therefore to combine and analyze the results of these trials to detect effects that would have been too small to detect in each individual trials, as well as investigating differences related to the type of anti-EGFR agent, the type of comparison or the type of combination, or according to patient or tumor characteristics.

2. OBJECTIVES

Primary objective

The **main purpose** is to assess the impact of either **adding or comparing anti-EGFR therapy to the standard treatment of locally advanced SCCHN** on **overall survival** based on individual data from randomized trials.

First comparison: adding anti-EGFR therapy to chemo-RT or to RT

Loco-regional treatment (radiotherapy and/or surgery) ± chemotherapy

vs.

Loco-regional treatment (radiotherapy and/or surgery) ± the same chemotherapy + **anti-EGFR**

Second comparison: replacing chemotherapy by anti-EGFR therapy, when combined with RT

Loco-regional treatment (radiotherapy and/or surgery) + chemotherapy

vs.

Loco-regional treatment (radiotherapy and/or surgery) + **anti-EGFR**

Trials with the same chemotherapy in both arms (e.g. induction chemotherapy are eligible if they compare another timing (e.g. concomitant) of chemotherapy to anti-EGFR with the same timing. Trials with an anti-EGFR given at more than one timing (e.g concomitant and adjuvant) as well as those adding a second timing (e.g. adjuvant) with the first one given in both arms (for instance concomitant) are eligible.

Secondary objectives

- To assess the effect of anti-EGFR therapy on event-free survival[1], time to loco-regional progression/recurrence , time to distant progression/recurrence, second primaries cumulative rate (if available), head and neck cancer mortality and non-head and neck cancer mortality
- To compare compliance to protocol treatment dose and schedule , acute toxicity and late toxicity between the two treatment modalities.
- To investigate the interaction between treatment's effect and the type of anti-EGFR therapy (subset analysis, indirect comparison).
- To investigate the interaction between treatment's effect and the prognostic factors and patients characteristics (subgroup analyses).
- The trials will be included on the study of the value of event-free survival as surrogate endpoint for overall survival.
- To set up a large network based meta-analysis to compare the different treatment strategies and rank them in terms of efficacy based on the data of this meta-analysis and the updated data of MACH-NC and MARCH. A separate protocol will be prepared for the network meta-analysis. Some trials including arms with anti-EGFR therapy will be included only to complete the network.

[1] Event-free survival is a mixt of disease-free survival for the patients who have complete (R0) surgery and progression-free survival for those who have incomplete surgery or radical radiotherapy.

3. TRIALS SELECTION CRITERIA

All trials must satisfy the following criteria:

Trials must

- Assess the impact of adding anti-EGFR therapy to loco-regional treatment (LRT) combined or not with chemotherapy OR compare anti-EGFR therapy to chemotherapy
- Be randomized in a way which precludes prior knowledge of treatment assignment.
- Be unconfounded for the comparison of the two treatments, except changes of the radiotherapy in the experimental arm (dose or fractionation modification that remain an accepted standard of care) or small difference in chemotherapy dose between the two arms.
- Have completed accrual before 31st December 2015.
- Include patients with squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx or larynx.
- Not include patients with recurrent or metastatic disease.
- Have at least 30 patients in each treatment arm.

Patients should

- Not have a second tumor.
- Not have received prior surgery, except for those enrolled in trials of postoperative treatment.
- Not have received prior radiotherapy.
- Not have received prior chemotherapy, except if induction chemotherapy in both arms and randomization after induction chemotherapy.
- Not have received prior anti-EGFR therapy.
- Undergo a potentially curative loco-regional treatment.

4. TRIAL SEARCH

Data from all published and unpublished randomized trials making the above comparisons in HNSCC patients will be sought using electronic database searching for the period 2000-2016 (trials previously published or presented were included in the previous rounds of the meta-analysis) (Medline, Cancerlit, DARE, Embase, CCT meta-register), hand searching (review articles, meeting proceedings) and by contacting experts in the field.

The search strategy and trials flow chart are detailed in **Appendix A.**

5. DESCRIPTION OF THE TRIALS INCLUDED

Appendix B1 describes trials comparing loco-regional treatments ± chemotherapy with or without anti-EGFR in HSCC which are eligible for the meta-analysis. In all trials loco-regional treatment turned out to be radiotherapy only, except in one trial (11) in which radiotherapy was postoperative. Among the 24 trials (5802 patients) identified (9,11–33),18 (4293 patients) focused on the effect of anti-EGFR in addition to radiotherapy or chemoradiation. The others six trials (1509 patients) compared chemotherapy to anti-EGFR. Because of trials with more than two arms or factorial design, the number of treatment comparisons is higher than the number of trials. For the same reason, the number of patients may also increase artificially because of the need to duplicate the control group in multi-arms trials. In 20 trials, only one timing of treatment was evaluated: concomitant for 18 trials, induction for one and adjuvant for another one. In 3 trials, a combination of timing was evaluated: induction + concomitant (16); concomitant + adjuvant (26). In the last trial (21), a multiple arms trial, the timing evaluated were concomitant alone, adjuvant alone or both. For the descriptions below, the trial was separated in two parts: one adjuvant (with 50% of the patients of the control arm), one concomitant (including the concomitant + adjuvant and 50% of the patients of the control arm).

Below and in Table 1, the trials were classified according to the *first timing of treatment randomized* (except for *Harrington, 2015* which was considered as a concomitant trial).

Anti-EGFR have been assessed as:

- Induction treatment in 2 trials (199 patients)
- Concomitant treatment in 21 trials (5426 patients): 18 trials with concomitant anti-EGFR only; one with induction + concomitant; one with concomitant + adjuvant; one with concomitant or concomitant + adjuvant
- Adjuvant treatment in 2 trials (177 patients): one trial with adjuvant anti-EGFR only; and a part of a trial with adjuvant only.

Table 1: Number of patients (trials) according to the timing of anti-EGFR and comparison type

Timing	Number of patients (Trials)		
	(RT±CT) ± Anti-EGFR	**RT-CT vs RT-Anti-EGFR**	**Total**
Induction	199 (2)	0	199 (2)
Concomitant	3917 (15)	1509 (6)	5426 (21)
Adjuvant	177 (2)	0	177 (2)
Total	**4293 (18)***	**1509 (6)**	**5802 (24)**

*One trial (21) randomizing both for concomitant and adjuvant anti-EGFR timing is counted in the concomitant and adjuvant timing line explaining why the total of the number of trials for the three timing in the column (RT±CT) ± Anti-EGFR is 19 when the total is only 18, and 25 instead of 24 for the column total.

Regarding the type of anti-EGFR used, trials assessed either monoclonal antibodies or tyrosine-kinase inhibitors. When considering both comparisons together, trials and patients were distributed the following manner:

Chimeric MAB anti-EGFR :

- Cetuximab:10 trials (2844 patients)

Humanised MAB anti-EGFR :

- Nimotuzumab: 2 trials (198 patients)
- Panitumumab: 3 trials (625 patients)
- Zalutumumab: 1 trial (619 patients)

TK inhibitors anti-EGFR

- Gefitinib: 4 trials (450 patients)
- Erlotinib: 1 trial (204 patients)

TK inhibitors anti- EGFR & HER2

- Lapatinib: 3 trials (862 patients)
- Afatinib (irreversible inhibition) (no trial currently completed)

Table 2 shows the repartition of patients (trials) by anti-EGFR drug for each comparison group.

Table 2: Number of patients (trials) in each comparison group for each anti-EGFR drug

Anti-EGFR	Number of patients (Trials)		
	(RT±CT) ± Anti-EGFR	**RT-CT vs RT-Anti-EGFR**	**Total**
Monoclonal antibody			
Cetuximab	1807 (6)	1037 (4)	2844 (10)
Nimotuzumab	198 (2)	0	198 (2)
Panitumumab	153 (1)	472 (2)	625 (3)
Zalutumumab	619 (1)	0	619 (1)
Subtotal	*2777 (10)*	*1509 (6)*	*4286 (16)*
Tyrosine-Kinase Inhibitor			
Gefitinib	450 (4)	0	450 (4)
Erlotinib	204 (1)	0	204 (1)
Lapatinib	862 (3)	0	862 (3)
Subtotal	*1516 (8)*	*0*	*1516 (8)*
Total	**4293 (18)**	**1509 (6)**	**5802 (24)**

6. EVALUATION CRITERIA

6.1 ENDPOINTS

The main endpoint will be **overall survival**, because of its importance and because of the reliability of the measurement. Cause of death will be studied, if possible.
Secondary endpoints such as time to locoregional failure (or local failure and regional failure separately, according to the quality of data collected), distant failure, or second primaries cumulative rate as well as event-free survival and specific survival (head and neck cancer mortality and non-head and neck cancer mortality), treatment compliance, early and late toxicity will be also considered. Event-free survival is defined as the time from randomization to local, regional or distant failure or death from any cause. Second primary are not considered an event for this endpoint.

6.2 PROGNOSTIC FACTORS

The prognostic factors (groups) that will be considered are:

- Age (50 or less, 51-60, 61-70, 71+).
- Sex (male, female).
- Performance status (WHO or equivalent, 0, 1, 2+).
- Site of the primary tumor (oral cavity, oropharynx, larynx, hypopharynx, other).
- Stage (I-II, III, IV), for opharyngeal HPV+ patients the new staging system will be used if information is available (especially uni or bi laterality of lymph nodes)
- Smoking status (never, former, current)
- HPV status, when available
- EGFR expression, when available
- Acneiform rash post EGFR treatment, keeping in mind that it is a post randomization factor (intent to treat not possible)

7. DATA COLLECTION AND QUALITY CONTROL

For each eligible trial, the main investigator will be asked to provide the following basic data for survival and prognostic factors for **all** randomized patients.

- Date of birth[2] or age.
- Sex.
- Performance status
- Site of the primary.
- TNM staging (if not available stage ; in any case, provide information on classification used).
- Smoking status (never, former, current; pack-year)
- p16 status, if available
- HPV , if available
- Type of HPV test (ISH,…)
- EGFR status, if available
- Type of EGFR markers (protein expression, mutation, copy number…)
- Allocated treatment.
- Date of randomization or anonymized[3] date derivated from this date.
- Number of cycles (or injection) of induction, concomitant or adjuvant chemotherapy received, if any.
- Tumor surgery before RT (no/yes)
- Radiotherapy started / not started
- Date first day radiotherapy
- Date last day radiotherapy
- Total administered dose of radiotherapy on tumor
- Total number of fractions of radiotherapy
- Type of radiotherapy (2D, 3D, IMRT)
- Dose of administered anti-EGFR. (number of injections for monoclonal antibody, treatment duration for tyrosine kinase inhibitor)
- Treatment's administration (specify whether patients received their full per protocol treatment, had a dose reduction, or interrupted their treatment)
- Acute toxicity (neutropenia, thrombocytopenia, anemia, kidney failure, diarrhea, allergy/anaphylaxis, acneiform rash, other cutaneous, liver toxicity (elevated transaminases), mucositis, hearing loss, neurotoxicity, need for feeding tube)

  + Specification of toxicity grading system used (if NCI-CTC specify the version)
- Late toxicity (cutaneous fibrosis, xerostomia, bone necrosis, persistence of feeding tube after one year of treatment)

  + Specification of toxicity grading system used

[2] In cases where communicating patients-related dates (e.g: patient's date of birth, date of randomization…) is forbidden by local legislation, anonymized dates will be welcomed. Anonymization can be done by adding a random number to all the dates provided in the database.

[3] In cases where communicating patients-related dates (e.g: patient's date of birth, date of randomization…) is forbidden by local legislation, anonymized dates will be welcomed. Anonymization can be done by adding a random number to all the dates provided in the database.

- Date of last follow-up.
- Survival status.
- Cause of death.
- Date of tumor progression/recurrence, date of nodal progression/recurrence
- Date of distant progression/recurrence
- Date and type of second primary
- Whether excluded from trial analysis.
- Reason for exclusion (if applicable).

Appendix D gives the suggested format and coding to send the data to the Secretariat. All data will be checked for internal consistency and consistency with trial protocol and published report. Quality of the trials will be checked according to the Cochrane Working group on IPD meta-analysis (Stewart LA, et al. Stat Med 14:2057–2079, 1995). Range checks will be performed and extreme values will be checked with the trialists. Each trial will be analyzed individually, and the resulting survival analyses and trial data will be sent to the trialists for verification.

8. STATISTICAL ANALYSIS PLAN

With 5500 patients (3700 deaths) it would be possible using a two-sided test at a 5% significance level to detect, with a 98% power, an absolute improvement in overall survival from 30 % to 35 % at 5-years. Therefore, the study would have enough power to detect the small but clinically important difference which is likely to occur in clinical oncology.

Trial characteristics will be reported in tabular form, information will include patient numbers, period of recruitment, population description, treatment details and median follow-up. Median follow-up will be computed using the reverse Kaplan-Meier method (34).

SURVIVAL ANALYSIS

The main analysis will be performed on the endpoint of overall survival separately for the two comparisons: loco-regional treatment (radiotherapy and/or surgery) ± chemotherapy with or without anti-EGFR therapy and chemotherapy versus anti-EGFR therapy. Additional analyses will be conducted on the endpoints of event-free survival, loco-regional progression/recurrence rate, distant progression/recurrence rate, head and neck cancer mortality and non head and neck cancer mortality, if sufficient data are available, separately for the two treatment comparisons.

All analyses will concern every randomized patients and will be performed on an **intent-to-treat basis.** Therefore patients will be analyzed according to the allocated treatment, irrespective of whether they have actually received it or not. **Survival analyses will be stratified by trial**, and the log-rank expected number of deaths and variance will be used to compute individual (i.e. by trial) and overall pooled hazard ratios by the fixed-effect model (35,36). Thus, the time to death for each patient will be used within trials to calculate the hazard ratio, which represents the overall risk of death for patients to whom anti-EGFR therapy has been allocated compared to that of the other patients. To compare compliance or toxicity rates, overall pooled odds ratio stratified by trials will be calculated by a fixed-effect model.

Head and neck cancer and non-head and neck cancer mortality using method similar to that used in the Meta-Analysis of Radiotherapy in Carcinoma of Head and neck (MARCH) (5) will be studied. The term head and neck cancer correspond here to primary head and neck cancer. In that Meta-Analysis, an unbiased, although potentially diluted, logrank analysis of head and neck cancer mortality was obtained indirectly by subtracting the logrank statistic for non-head and neck cancer mortality from the logrank statistic for mortality from all causes (i.e., the two observed values, the two expected values, and the two variances are each subtracted from each other). Non-head and neck cancer mortality was defined as death of known cause without recurrence and not considered as a head and neck cancer death. Head and neck cancer mortality included death of any cause with prior recurrence or progression, death from head and neck cancer and death from unknown cause if occurring within 5 year after randomization. Deaths from unknown cause will be consired as non cancer death if occurring after 5 year, as it is unlikely to have a cancer related death after that time point without a recurrence.

Heterogeneity between trials will be investigated by performing a Cochran test, and the I^2 statistic (37) will be used as a measure of consistency among trials. A random effects model will be carried out in case of important and unexplained heterogeneity. Stratified survival curves will be estimated for control and experimental groups using annual death rates and hazard ratios. They will be used to calculate absolute benefit at 5-years with its 95% confidence intervals (35). The difference, between arms, in restricted mean survival time (RmstD) will be also estimated at 5-years. The RmstD can be defined graphically as the area between the survival curves of two treatment arms up to 5 years. It can have positive or negative value: when it’s positive, it means that the experimental treatment is associated with a life year gain, and when it’s negative, with a life year loss (38–40). In addition, a multivariate Cox model will be used as exploratory analysis to investigate the potential impact of prognostiv factors on survival. All p-values will be two-sided. A test with a value inferior to 5% will be considered significant, but when it comes to heterogeneity test, a 10 % threshold will be used.

SUBGROUP AND SUBSET ANALYSES

To explore whether the treatment effect varies according to trial (e.g. timing of anti-EGFR therapy, type of anti-EGFR…) or patient characteristics (e.g. age, performance status, p16/HPV status…), an analysis of the interaction (or trend) between these characteristics and the treatment effect will be conducted for both comparisons. To avoid bias, only within trial information will be used for subgroup analyses, as described by Fisher *et.* al (41).

- **Subgroup Analyses (based on patients characteristics)**

For both comparisons, if sufficient data is available, treatment effect's consistency will be assessed across the pre-defined subroups of patients based on all the prognostic factors listed below using Cox model with interaction term.

- Age (50 or less, 51-60, 61-70, 71+).
- Sex (male, female).
- Smoking status (never, former, current)
- Performance status (WHO or equivalent, 0, 1, 2+).
- Site of the primary tumor (oral cavity, oropharynx, larynx, hypopharynx, other).
- Stage (I-II, III, IV).
- p16, when available (for oropharyngeal cancers only)
- HPV status, when available
- EGFR status, when available
- Acneiform rash post EGFR treatment
- Type of radiotherapy (2D/3D/IMRT)

The analyses will be stratified by trial. In case of heterogeneity of the treatment effect between trials overall, or within a subset, the analysis won't be performed in the corresponding population. Patients' categories will be combined if the number of patients per category is not sufficient. Heterogeneity of the interaction between trials will be investigated.

- **Subset Analyses (based on trials characteristics)**

Subset analyses correspond to the study of the interaction between trial characteristics and treatment effect. Several comparisons of the results of anti-EGFR therapy in **groups of trials** classified according to the type of anti-EGFR, the timing of anti-EGFR or the timing of chemotherapy are planned as exploratory analyses. Residual heterogeneity within trial subgroups was computed by subtracting the χ^2 statistic of the heterogeneity test between groups from the χ^2 statistic of the overall heterogeneity test. The main results will be presented globally and according to the different trial groups which will be defined for each comparison as follows:

Addition of Anti-EGFR therapy to Loco-Regional Treatment combined or not with Chemotherapy

Subset	Number of patients (Trials)
Types of Anti-EGFR	
Cetuximab	1807 (6)
Other Monoclonal antibody	970 (4)
Tyrosine kinase inhibitor	1516 (8)
Timing of Anti-EGFR therapy[a]	
Concomitant ± Adjuvant[1]	3917 (15)
Induction ± Concomitant ± Adjuvant[2]	199 (2)
Adjuvant only[3]	177 (2)
Timing of Chemotherapy	
No Chemotherapy	773 (5) [b]
Concomitant only	3248 (11)
Induction ± Concomitant	272 (2)

[a] *The timing of the first randomized administration was considered, one trial* (21) *was included in two timings;*
[b] *Include two trials in which patients received or not chemotherapy based on stage or general condition.*
[1] *12 trials randomized only concomitant anti-EGFR, 2 trials randomized concomitant plus adjuvant* (11,24)*, and one concomitant or both concomitant and adjuvant* (21)*;*[2] *one trial on induction only* (25)*, one on induction + concomitant* (16)*;*[3] *one trial randomized adjuvant only* (12) *and the other adjuvant anti-EGFR with the same anti-EGFR given concomitantly in both arms*(21)*.*

Comparison of Anti-EGFR therapy to Chemotherapy

Subset	Number of patients (Trials)
Anti-EGFR agent	
Cetuximab	1037 (4)
Panitumumab	472 (2)
Timing of Chemotherapy*	
Concomitant only	702 (4)
Induction ± Concomitant	807 (3)

** 7 trials instead of 6 trials as one trial with 2 x 2 design (induction chemotherapy yes/no, concomitant chemotherapy vs. concomitant cetuximab*

In the comparison of anti-EGFR therapy to chemotherapy, an indirect comparison of the trials will be performed according to anti-EGFR therapy timing if there are enough trials for each anti-EGFR timing, otherwise this comparison will be conducted as a sensitivity analysis.

Type of radiotherapy (2D/3D/IMRT) will be also studied. Depending of the structure of the data, subset (if RT technique is homogeneous per trial) or subgroup (if within trials patients can have different RT techniques) analysis will be used.

SENSITIVITY ANALYSES

Hazard ratios for overall survival will also be calculated excluding any trials that are clear outliers (i.e. trials whose 95% CI did not overlap with the 95% CI of the global HR) or particular, e.g. trials that are confounded (for instance different dose of chemotherapy between arms). The impact of the exclusion of these trials on the results will be studied, as in our previous analyses (3–5). The following sensitivity analyses will be performed:

- Exclusion of small trials (<100 patients or 50 patients by arms)
- Exclusion of trials for which dose of chemotherapy or equivalent dose of radiotherapy (*i.e.* dose taking into account duration) are different between treatment arms (confounded trials).
- Exclusion of trials with a follow-up shorter than 5 years
- Exclusion of trials for which date of randomization and events are not available, as data checking will be incomplete in this case.
- Exclusion of trials with more than one timing of anti-EGFR and only one being randomized (e.g. anti-EGFR given concomitantly to all patients and adjuvant treatment being randomized) or randomizing anti-EGFR given for more than one timing (e.g. induction + concomitant).

SURROGATE ENDPOINT VALIDATION

Michiels *et al.*, showed that event-free survival could be used as a surrogate of overall survival since it was a better correlate with overall survival than loco-regional control when it comes to assessing the treatment effect of radiotherapy and chemotherapy in randomised trials of locally advanced HNSCC (42). In the wake of these findings, we will investigate whether loco-regional control and event-free survival are good surrogate endpoints of overall survival in the context of the evaluation of the effect of anti-EGFR therapy. Therefore, data will be analyzed at both individual and trial levels. A specific protocol will be prepared. Both patient-level correlation (i.e correlation between two survival times) and trial level correlation (correlation between two harzard ratios) will be studied as in the previous study (42).

NETWORK META-ANALYSIS

The data of these meta-analyses will be used to update the **network meta-analysis** on the treatment of non metastatic squamous cell carcinoma which will include updated data from MACH-NC and MARCH (43). A specific protocol will be prepared. Some trials not eligible for the current meta-analysis will be included in the network meta-analysis and their individual patient data collected (see table 8 **appendix C1**).

9. WORKING PARTIES IN THE META-ANALYSIS

In order to complete the meta-analysis successfully, three groups with specific functions have been created : 1) the Secretariat 2) the Advisory Board 3) the MACH-EGFR Trialists' Collaborative Group.
The Secretariat is in charge of the coordination of the meta-analysis. It is responsible for completing the trial register and for inviting investigators to provide data available on patients. The Secretariat is also in charge of checking, processing and analyzing the data. Finally, the Secretariat is responsible for preparing reports, publications and works in close collaboration with the Advisory Board.

The Advisory Board will include international experts in the field of medical oncology, radiotherapy, and surgery involved in head and neck cancer, and experts in meta-analysis. The list of its members is given on the page 2. The Advisory Board will support the Secretariat with medical and methodological expertise, help determine trials relevant to the overview, and promote contact between investigators and all the collaborators.

The MACH-EGFR Trialists' Collaborative Group will include the investigators responsible for trials included in the meta-analysis. The members of the Secretariat and the Advisory Board will also be included in this group. It will be responsible for providing the Secretariat with data on patients and for discussing the reports prepared by the Advisory Board and the Secretariat.

An investigator meeting will be organized by the Secretariat to discuss the preliminary results of the meta-analysis and to plan additional analyses.

10. PRACTICAL CONSIDERATIONS

The Secretariat, located in the Biostatistics Unit at Gustave Roussy, will be responsible for liaising with trialists. The main database will be run by the Secretariat. All data, updating and correction should be sent there. All supplied data will remain confidential and used exclusively for the meta-analysis.

11. PUBLICATION POLICY

Any publication arising from this project will be made on behalf of the Meta-Analysis in locally advanced Cancers of Head and neck on anti-EGFR therapy (MACH-EGFR) Collaborative Group, and will include a list of all collaborators.

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APPENDIX A: Trial search strategy

The search strategy used in July 2015 and repeated in August 2016 was :

1) for MEDLINE from PubMed

((laryngeal neoplasms[MeSH Terms]) OR mouth neoplasms[MeSH Terms]) OR nose neoplasms[MeSH Terms]) OR pharyngeal neoplasms[MeSH Terms]) OR salivary gland neoplasms[MeSH Terms]) OR (head and neck)) OR laryngeal) OR larynx) OR glottis) OR glottic) OR subglottis) OR subglottic) OR supraglottis) OR supraglottic) OR oral) OR mouth) OR lip) OR gingiva) OR gingival) OR tongue) OR palate) OR palatal) OR buccal) OR nose) OR nasal) OR sinonasal) OR paranasal) OR sinus) OR pharyngeal) OR pharynx) OR hypopharyn*) OR nasopharyn*) OR oropharyn*)) AND (((((((((cancer*) OR carcinom*) OR adenocarcinom*) OR malignan*) OR tumor*) OR tumour*) OR neoplasm*) OR (squamous OR epidermoid OR undifferentiated carcinoma)) OR Carcinoma, squamous cell[MeSH Terms])) AND ((drug therapy[MeSH Subheading]) OR chemotherapy) OR chemoradiation) OR chemoradiotherapy) OR radiochemotherapy) OR radio-chemotherapy) OR radiation*) OR radiotherap*) OR pharmacotherapy) OR taxane*) OR docetaxel) OR paclitaxel) OR taxoid) OR taxotere) OR cisplatin) OR platin*) OR carboplatin) OR fluorouracil) OR 5-fluorouracil) OR fluoro-uracil) OR 5FU) OR hydroxyurea) OR tegafur-uracil) OR leucovorin) OR target therapy) OR anti-egfr) OR egfr-inhibitors) OR egfr) OR EGF) OR zalutumumab) OR cetuximab) OR bevacizumab) OR panitumumab) OR gefitinib) OR erlotinib) OR lapatinib) OR nimotuzumab) OR gemcitabine) OR mitomycin) OR methotrexate)) AND (((((((randomized controlled trial[Publication Type]) OR clinical trial, phase iii[Publication Type]) OR clinical trial, phase iv[Publication Type]) OR clinicaltrials.gov[Secondary Source ID]) OR isrctn[Secondary Source ID]) OR randomized controlled trials as topic[MeSH Terms])) AND ((((random OR randomised OR randomized OR rct OR rcts OR single-blind OR double-blind)) AND (trial* OR study OR studies)))))) AND ("2009"[Date - Publication] : "2015"[Date - Publication]))

2) For Web of Science

#6	#5 AND #4 AND #3 AND #2 AND #1 *DocType=All document types; Language=All languages;*
#5	(TS=(random*)) *AND* **DOCUMENT TYPES:** (Article) *DocType=All document types; Language=All languages;*
#4	(TS=(squamous)) *AND* **DOCUMENT TYPES:** (Article) *DocType=All document types; Language=All languages;*
#3	(TS=(chemotherapy OR chemoradiation OR chemoradiotherapy OR radiochemotherapy OR radio-chemotherapy OR pharmacotherapy)) *AND* **DOCUMENT TYPES:** (Article) *DocType=All document types; Language=All languages;*
#2	(TS=(cancer* OR carcinoma* OR adenocarinoma* OR malignan* OR tumor* OR tumour* OR neoplasm)) *AND* **DOCUMENT TYPES:** (Article) *DocType=All document types; Language=All languages;*
#1	(TS=((head AND neck) OR laryngeal OR larynx OR glottis OR glottic OR subglottis OR subglottic OR supraglottis OR supraglottic OR oral OR mouth OR lip OR gingiva OR gingival OR tongue OR palate OR palatal OR buccal OR nose OR nasal OR sinonasal OR paranasal OR sinus OR pharyngeal OR pharynx OR hypopharyn* OR nasopharyn*

	OR oropharyn*)) *AND* **DOCUMENT TYPES:** (Article) *DocType=All document types; Language=All languages;*

3) For Scopus

TITLE-ABS-KEY (**"head and neck"** OR **laryngeal** OR **larynx** OR **glottis** OR **glottic** OR **subglottis** OR **subglottic** OR **supraglottis** OR **supraglottic** OR **oral** OR **mouth** OR **lip** OR **gingiva** OR **gingival** OR **tongue** OR **palate** OR **palatal** OR **buccal** OR **nose** OR **nasal** OR **sinonasal** OR **paranasal** OR **sinus** OR **pharyngeal** OR **pharynx** OR **hypopharyn*** OR **nasopharyn*** OR **orophayn***) AND TITLE-ABS-KEY (**cancer*** OR **carcinoma*** OR **adenocarcinoma*** OR **malignan*** OR **tumor*** OR **tumour*** OR **neoplasm***) AND TITLE-ABS-KEY (**squamous** OR **epidermoid** OR **"undifferentiated carcinoma"**) AND TITLE-ABS-KEY (**chemotherapy** OR **chemoradiation** OR **chemoradiotherapy** OR **radiochemotherapy** OR **radio-chemotherapy** OR **pharmacotherapy** OR **taxane*** OR **docetaxel** OR **paclitaxel** OR **taxoid** OR **taxotere** OR **cisplatin** OR **platin*** OR **carboplatin** OR **fluorouracil** OR **5-fluorouracil** OR **fluoro-uracil** OR **5fu** OR **hydroxyuera** OR **tegarfur-uracil** OR **leucovorin** OR **"target therapy"** OR **anti-egfr** OR **"EGFR inhibitors"** OR **egfr** OR **egf** OR **zalutumumab** OR **cetuximab** OR **bevacizumab** OR **panitumumab** OR **gefitinib** OR **erlotinib** OR **lapatinib** OR **nimotuzumab** OR **gemcitabine** OR **mitomycin** OR **methotrexate**) AND ((TITLE-ABS-KEY (**random** OR **randomise** OR **randomize** OR **randomised** OR **randomized** OR **rct** OR **rcts** OR **single-blind** OR **double-blind**) AND TITLE-ABS-KEY (**trial** OR **trials** OR **study** OR **studies**))) AND (LIMIT-TO (PUBYEAR , **2015**) OR LIMIT-TO (PUBYEAR , **2014**) OR LIMIT-TO (PUBYEAR , **2013**) OR LIMIT-TO (PUBYEAR , **2012**) OR LIMIT-TO (PUBYEAR , **2011**) OR LIMIT-TO (PUBYEAR , **2010**) OR LIMIT-TO (PUBYEAR , **2009**))

4) For Cochrane

ID	Search	Hits
#1	MeSH descriptor: [Laryngeal Neoplasms] explode all trees	283 / 304
#2	MeSH descriptor: [Mouth Neoplasms] explode all trees	513 / 553
#3	MeSH descriptor: [Nose Neoplasms] explode all trees	34 / 36
#4	MeSH descriptor: [Pharyngeal Neoplasms] explode all trees	510 / 559
#5	MeSH descriptor: [Salivary Gland Neoplasms] explode all trees	67 / 74
#6	#1 or #2 or #3 or #4 or #5	1125 / 1229
#7	cancer*:ti,ab,kw (Word variations have been searched)	68705 / 76662
#8	carcinoma*:ti,ab,kw (Word variations have been searched)	20974 / 22905
#9	adenocarcinoma*:ti,ab,kw (Word variations have been searched)	4051 / 4571
#10	malignan*:ti,ab,kw (Word variations have been searched)	8939 / 9850
#11	tumor*:ti,ab,kw (Word variations have been searched)	24326 / 27941
#12	tumour*:ti,ab,kw (Word variations have been searched)	5329 / 5954
#13	neoplasm*:ti,ab,kw (Word variations have been searched)	51357 / 56767
#14	squamous:ti,ab,kw (Word variations have been searched)	4597 / 5053
#15	epidermoid:ti,ab,kw (Word variations have been searched)	140 / 144
#16	undifferentiated carcinoma:ti,ab,kw (Word variations have been searched)	108 / 128

#17 squamous cell carcinoma:ti,ab,kw (Word variations have been searched) 3881 / 5
#18 {or #7-#17} 101793 / 112526
#19 "drug therapy":ti,ab,kw (Word variations have been searched) 98573 / 110975
#20 chemotherapy:ti,ab,kw (Word variations have been searched) 35299 / 38588
#21 chemoradiation:ti,ab,kw (Word variations have been searched) 762 / 881
#22 chemoradiotherapy:ti,ab,kw (Word variations have been searched) 1703 / 2081
#23 radiochemotherapy:ti,ab,kw (Word variations have been searched) 407 / 449
#24 radio-chemotherapy:ti,ab,kw (Word variations have been searched) 132 / 139
#25 radiation*:ti,ab,kw (Word variations have been searched) 11244 / 14964
#26 radiotherap*:ti,ab,kw (Word variations have been searched) 13630 / 14964
#27 pharmacotherapy:ti,ab,kw (Word variations have been searched) 4882 / 5170
#28 taxane:ti,ab,kw (Word variations have been searched) 707 / 842
#29 docetaxel:ti,ab,kw (Word variations have been searched) 2545 / 3023
#30 paclitaxel:ti,ab,kw (Word variations have been searched) 3842 / 4392
#31 taxoid:ti,ab,kw (Word variations have been searched) 20 / 25
#32 taxotere:ti,ab,kw (Word variations have been searched) 181 / 185
#33 cisplatin:ti,ab,kw (Word variations have been searched) 7709 / 8275
#34 platin*:ti,ab,kw (Word variations have been searched) 2340 / 2674
#35 carboplatin*:ti,ab,kw (Word variations have been searched) 2896 / 3197
#36 fluorouracil:ti,ab,kw (Word variations have been searched) 6971 / 7500
#37 5-fluorouracil:ti,ab,kw (Word variations have been searched) 3416 / 3599
#38 fluoro-uracil:ti,ab,kw (Word variations have been searched) 29 / 31
#39 5FU:ti,ab,kw (Word variations have been searched) 488 / 533
#40 hydroxyuera:ti,ab,kw (Word variations have been searched) 0 / 0
#41 tegafur-uracil:ti,ab,kw (Word variations have been searched) 46 / 49
#42 leucovorin:ti,ab,kw (Word variations have been searched) 1682 / 1812
#43 "target therapy":ti,ab,kw (Word variations have been searched) 509 / 20
#44 anti-egfr:ti,ab,kw (Word variations have been searched) 129 / 169
#45 egfr-inhibitors:ti,ab,kw (Word variations have been searched) 78 / 55
#46 egfr:ti,ab,kw (Word variations have been searched) 1612 / 2155
#47 egf:ti,ab,kw (Word variations have been searched) 203 / 237
#48 zalutumumab:ti,ab,kw (Word variations have been searched) 13 / 14
#49 cetuximab:ti,ab,kw (Word variations have been searched) 694 / 852
#50 bevacizumab:ti,ab,kw (Word variations have been searched) 1572 / 2048
#51 panitumumab:ti,ab,kw (Word variations have been searched) 169 / 230
#52 gefitinib:ti,ab,kw (Word variations have been searched) 300 / 357
#53 erlotinib:ti,ab,kw (Word variations have been searched) 498 / 0
#54 lapatinib:ti,ab,kw (Word variations have been searched) 273 / 357
#55 nimotuzumab:ti,ab,kw (Word variations have been searched) 33 / 44
#56 gemcitabine:ti,ab,kw (Word variations have been searched) 1987 / 2303
#57 mitomycin:ti,ab,kw (Word variations have been searched) 2088 / 2184
#58 methotrexate:ti,ab,kw (Word variations have been searched) 6159 / 6593
#59 {or #19-#58} 152970 / 169601
#60 clinical trial phase3:ti,ab,kw or clinical trial phase 4:ti,ab,kw Publication Year from 2009 to 2015 (Word variations have been searched) 8333 / 42255 (without date restriction)
#61 random*:ti,ab,kw or rct:ti,ab,kw or rcts:ti,ab,kw or single-blind:ti,ab,kw or double-blind:ti,ab,kw (Word variations have been searched) 542986 / 597096
#62 trial*:ti,ab,kw or study:ti,ab,kw or studies:ti,ab,kw Publication Year from 2009 to 2015 (Word variations have been searched) 235645 / 744675 (without date restriction)

#63 {and #61-#62} 192923 / 556878
#64 #60 or #63 193602 / 563387
#65 #6 and #18 and #59 and #64 91 / 42 (Publication Year from 2014 to 2016)

5) Embase

#70 ('larynx tumor'/exp OR 'mouth tumor'/exp OR 'nose tumor'/exp OR 'pharynx cancer'/exp OR 'salivary gland tumor'/exp OR 'head cancer'/exp OR 'neck cancer'/exp) AND (cancer* OR carcinoma* OR adenocarcinoma* OR malignan* OR tumor* OR tumour* OR neoplasm* OR ((squamous OR 'epidermoid'/exp OR epidermoid OR 'undifferentiated carcinoma'/exp OR 'undifferentiated carcinoma') OR ('squamous cell carcinoma'/exp OR 'squamous cell carcinoma'))) AND (('drug therapy'/exp OR 'drug therapy') OR ('chemotherapy'/exp OR 'chemotherapy') OR ('chemoradiation'/exp OR 'chemoradiation') OR ('chemoradiotherapy'/exp OR 'chemoradiotherapy') OR ('radiochemotherapy'/exp OR 'radiochemotherapy') OR 'radio chemotherapy' OR ('pharmacotherapy'/exp OR pharmacotherapy) OR 'taxane' OR 'docetaxel'/exp OR 'paclitaxel'/exp OR 'taxoid'/exp OR 'taxotere'/exp OR 'cisplatin'/exp OR platin* OR 'carboplatin'/exp OR 'fluorouracil'/exp OR '5 fluorouracil':ab,ti OR 'fluoro uracil':ab,ti OR 5fu:ab,ti OR 'hydroxyurea'/exp OR 'tegafur uracil'/exp OR 'leucovorin'/exp OR 'targeted therapy' OR 'anti egfr':ab,ti OR (egfr AND inhibitors:ab,ti) OR 'egfr' OR 'egf' OR 'zalutumumab'/exp OR 'cetuximab'/exp OR 'bevacizumab'/exp OR 'panitumumab'/exp OR 'gefitinib'/exp OR 'erlotinib'/exp OR 'lapatinib'/exp OR 'nimotuzumab'/exp OR 'gemcitabine'/exp OR 'mitomycin'/exp OR 'methotrexate'/exp) AND (('randomized controlled trial'/exp OR 'randomized controlled trial') OR ('phase 3 clinical trial'/exp OR 'phase 3 clinical trial') OR ('phase 4 clinical trial'/exp OR 'phase 4 clinical trial') OR 'clinicaltrials gov' OR 'isrctn' OR ('randomized controlled trial (topic)'/exp OR 'randomized controlled trial (topic)') OR ((random OR randomise OR randomize OR randomised OR randomized OR rct OR rcts OR 'single blind' OR 'double blind':ab,ti) AND (trial OR trials OR 'study'/exp OR study OR studies:ab,ti))) AND [2009-2015]/py 1088
#69 ('larynx tumor'/exp OR 'mouth tumor'/exp OR 'nose tumor'/exp OR 'pharynx cancer'/exp OR 'salivary gland tumor'/exp OR 'head cancer'/exp OR 'neck cancer'/exp) AND (cancer* OR carcinoma* OR adenocarcinoma* OR malignan* OR tumor* OR tumour* OR neoplasm* OR ((squamous OR 'epidermoid'/exp OR epidermoid OR 'undifferentiated carcinoma'/exp OR 'undifferentiated carcinoma') OR ('squamous cell carcinoma'/exp OR 'squamous cell carcinoma'))) AND (('drug therapy'/exp OR 'drug therapy') OR ('chemotherapy'/exp OR 'chemotherapy') OR ('chemoradiation'/exp OR 'chemoradiation') OR ('chemoradiotherapy'/exp OR 'chemoradiotherapy') OR ('radiochemotherapy'/exp OR 'radiochemotherapy') OR 'radio chemotherapy' OR ('pharmacotherapy'/exp OR pharmacotherapy) OR 'taxane' OR 'docetaxel'/exp OR 'paclitaxel'/exp OR 'taxoid'/exp OR 'taxotere'/exp OR 'cisplatin'/exp OR platin* OR 'carboplatin'/exp OR 'fluorouracil'/exp OR '5 fluorouracil':ab,ti OR 'fluoro uracil':ab,ti OR 5fu:ab,ti OR 'hydroxyurea'/exp OR 'tegafur uracil'/exp OR 'leucovorin'/exp OR 'targeted therapy' OR 'anti egfr':ab,ti OR (egfr AND inhibitors:ab,ti) OR 'egfr' OR 'egf' OR 'zalutumumab'/exp OR 'cetuximab'/exp OR 'bevacizumab'/exp OR 'panitumumab'/exp OR 'gefitinib'/exp OR 'erlotinib'/exp OR 'lapatinib'/exp OR 'nimotuzumab'/exp OR 'gemcitabine'/exp OR 'mitomycin'/exp OR 'methotrexate'/exp) AND (('randomized controlled trial'/exp OR 'randomized controlled trial') OR ('phase 3 clinical trial'/exp OR 'phase 3 clinical trial') OR ('phase 4 clinical trial'/exp OR 'phase 4 clinical trial') OR 'clinicaltrials gov' OR 'isrctn' OR ('randomized controlled trial (topic)'/exp OR 'randomized controlled trial (topic)') OR ((random OR randomise OR randomize OR randomised OR randomized OR rct OR rcts OR 'single blind' OR 'double blind':ab,ti) AND (trial OR trials OR 'study'/exp OR study OR studies:ab,ti))) 1839

#68 ('randomized controlled trial'/exp OR 'randomized controlled trial') OR ('phase 3 clinical trial'/exp OR 'phase 3 clinical trial') OR ('phase 4 clinical trial'/exp OR 'phase 4 clinical trial') OR 'clinicaltrials gov' OR 'isrctn' OR ('randomized controlled trial (topic)'/exp OR 'randomized controlled trial (topic)') OR ((random OR randomise OR randomize OR randomised OR randomized OR rct OR rcts OR 'single blind' OR 'double blind':ab,ti) AND (trial OR trials OR 'study'/exp OR study OR studies:ab,ti)) 957672
#67 (random OR randomise OR randomize OR randomised OR randomized OR rct OR rcts OR 'single blind' OR 'double blind':ab,ti) AND (trial OR trials OR 'study'/exp OR study OR studies:ab,ti) 910989
#66 trial OR trials OR 'study'/exp OR study OR studies:ab,ti 13502644
#65 random OR randomise OR randomize OR randomised OR randomized OR rct OR rcts OR 'single blind' OR 'double blind':ab,ti 982118
#64 'randomized controlled trial (topic)'/exp OR 'randomized controlled trial (topic)' 76318
#63 'isrctn' 7506
#62 'clinicaltrials gov' 70044
#61 'phase 4 clinical trial'/exp OR 'phase 4 clinical trial' 2440
#60 'phase 3 clinical trial'/exp OR 'phase 3 clinical trial' 36071
#59 'randomized controlled trial'/exp OR 'randomized controlled trial' 457044
#58 ('drug therapy'/exp OR 'drug therapy') OR ('chemotherapy'/exp OR 'chemotherapy') OR ('chemoradiation'/exp OR 'chemoradiation') OR ('chemoradiotherapy'/exp OR 'chemoradiotherapy') OR ('radiochemotherapy'/exp OR 'radiochemotherapy') OR 'radio chemotherapy' OR ('pharmacotherapy'/exp OR pharmacotherapy) OR 'taxane' OR 'docetaxel'/exp OR 'paclitaxel'/exp OR 'taxoid'/exp OR 'taxotere'/exp OR 'cisplatin'/exp OR platin* OR 'carboplatin'/exp OR 'fluorouracil'/exp OR '5 fluorouracil':ab,ti OR 'fluoro uracil':ab,ti OR 5fu:ab,ti OR 'hydroxyurea'/exp OR 'tegafur uracil'/exp OR 'leucovorin'/exp OR 'targeted therapy' OR 'anti egfr':ab,ti OR (egfr AND inhibitors:ab,ti) OR 'egfr' OR 'egf' OR 'zalutumumab'/exp OR 'cetuximab'/exp OR 'bevacizumab'/exp OR 'panitumumab'/exp OR 'gefitinib'/exp OR 'erlotinib'/exp OR 'lapatinib'/exp OR 'nimotuzumab'/exp OR 'gemcitabine'/exp OR 'mitomycin'/exp OR 'methotrexate'/exp 4525373
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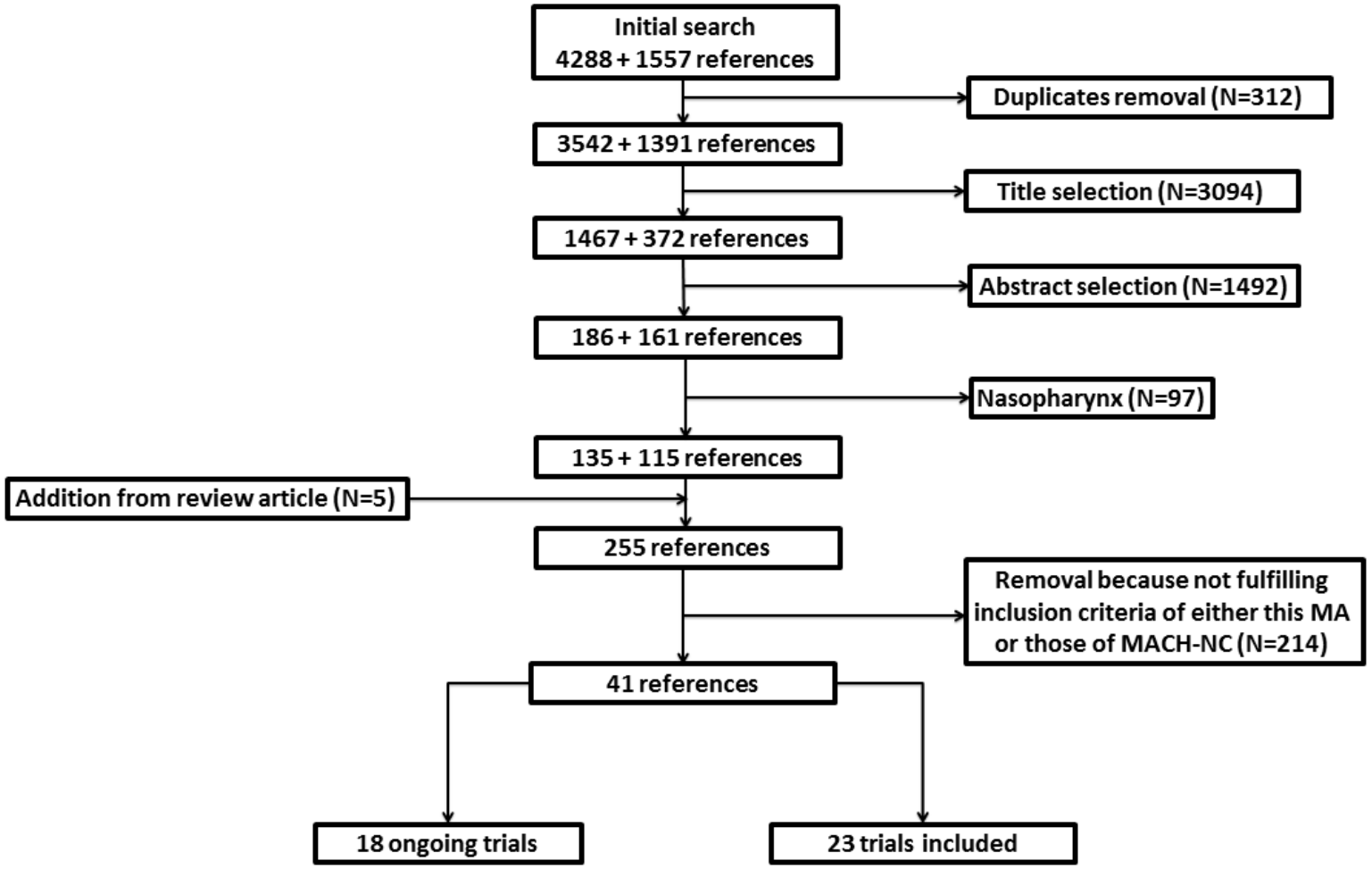
#55 'gemcitabine'/exp 36918
#54 'nimotuzumab'/exp 745
#53 'lapatinib'/exp 8088
#52 'erlotinib'/exp 18149
#51 'gefitinib'/exp 17208
#50 'panitumumab'/exp 5360
#49 'bevacizumab'/exp 36023
#48 'cetuximab'/exp 18631
#47 'zalutumumab'/exp 181
#46 'egf' 34410
#45 'egfr' 57733
#44 egfr AND inhibitors:ab,ti 10653
#43 'anti egfr':ab,ti 3568
#42 'targeted therapy' 28851
#41 'leucovorin'/exp 28441
#40 'tegafur uracil'/exp 3359
#39 'hydroxyurea'/exp 20970
#38 5fu:ab,ti 3364
#37 'fluoro uracil':ab,ti 263
#36 '5 fluorouracil':ab,ti 31473

#35 'fluorouracil'/exp 110836
#34 'carboplatin'/exp 48312
#33 platin* 69141
#32 'cisplatin'/exp 134660
#31 'taxotere'/exp 38592
#30 'taxoid'/exp 2041
#29 'paclitaxel'/exp 73159
#28 'docetaxel'/exp 38592
#27 'taxane' 15350
#26 'pharmacotherapy'/exp OR pharmacotherapy 2014742
#25 'radio chemotherapy' 1656
#24 'radiochemotherapy'/exp OR 'radiochemotherapy' 22577
#23 'chemoradiotherapy'/exp OR 'chemoradiotherapy' 28139
#22 'chemoradiation'/exp OR 'chemoradiation' 25876
#21 'chemotherapy'/exp OR 'chemotherapy' 683524
#20 'drug therapy'/exp OR 'drug therapy' 4190081
#19 cancer* OR carcinoma* OR adenocarcinoma* OR malignan* OR tumor* OR tumour* OR neoplasm* OR ((squamous OR 'epidermoid'/exp OR epidermoid OR 'undifferentiated carcinoma'/exp OR 'undifferentiated carcinoma') OR ('squamous cell carcinoma'/exp OR 'squamous cell carcinoma')) 4283987
#18 (squamous OR 'epidermoid'/exp OR epidermoid OR 'undifferentiated carcinoma'/exp OR 'undifferentiated carcinoma') OR ('squamous cell carcinoma'/exp OR 'squamous cell carcinoma') 182590
#17 'squamous cell carcinoma'/exp OR 'squamous cell carcinoma' 135872
#16 squamous OR 'epidermoid'/exp OR epidermoid OR 'undifferentiated carcinoma'/exp OR 'undifferentiated carcinoma' 181974
#15 neoplasm* 755811
#14 tumour* 285768
#13 tumor* 2307642
#12 malignan* 619565
#11 adenocarcinoma* 194843
#10 carcinoma* 911655
#9 cancer* 2860570
#8 'larynx tumor'/exp OR 'mouth tumor'/exp OR 'nose tumor'/exp OR 'pharynx cancer'/exp OR 'salivary gland tumor'/exp OR 'head cancer'/exp OR 'neck cancer'/exp 134269
#7 'neck cancer'/exp 3106
#6 'head cancer'/exp 1439
#5 'salivary gland tumor'/exp 17411
#4 'pharynx cancer'/exp 27451
#3 'nose tumor'/exp 18351
#2 'mouth tumor'/exp 90913
#1 'larynx tumor'/exp 30481

Trial Flow Chart
(search initiated in August 2015 and completed in August 2016)



APPENDIX B1: Description of the trials assessing addition of Anti-EGFR to loco-regional treatment with or without chemotherapy

Table 1: Addition of anti-EGFR (Monoclonal antibody) to radiotherapy or chemoradiation

(See Appendix B3 for abbreviations)

First author	NCT	Inclusion period	Sites	Stage	Treatment	Timing	Anti-EGFR drug and dose	CT drug and dose	RT regimen	Analyzed / Randomized
Bonner[4] (9) (2006)	NCT00004227	1999-2002	OP, HP, L	III, IV	RT ± Conc Cetux	Conc	**Cetux** Loading: 400 mg/m² then 250 mg/m² qw for 7 wks	/	**70 Gy** : 2 Gy/d for 6-7 wks **72-76.8 Gy** : 1.2 Gy bid for 6-6.4 wks **72 Gy**: 1.8 Gy/d for 3.6 wks then 1.8 + 1.5 Gy/d for 2.4 wks	424/424
Mesia (12) (2013)	NA	2005-2007	OP	III, IV	RT + Conc Cetux ± Adj Cetux	Adj	**Cetux** Loading: 400 mg/m² then 250 mg/m² qw Adj: 250 mg/m² qw, 12 wks	/	**69.9 Gy** : 1.8 Gy/d, 5 d pw, for 3 wks then 1.8 + 1.5 Gy/d, 5d pw, for 2.4 wks	91/91
RTOG 0522 Ang[5] (13) (2014)	NCT00265941	2005-2009	OP, HP, L	III, IV	RT + Conc C ± Conc Cetux	Conc	**Cetux** Loading: 400 mg/m² then 250 mg/m² qw for 6 wks	**C:** 100 mg/m² q3w, 2c	**72 Gy (no IMRT)** : 1.8 Gy/d (18 d) then 1.8 + 1.5 Gy/d the last 12 d for 6 wks overall **70 Gy (IMRT)** : 2 Gy/d (4 d pw) + 2 Gy bid (1 d pw) for 6 wks	891/940
DeLOS-II Dietz (14) (2014)	NCT00508664	2007-2012	HP, L	III, IV	Induc CDF[6] + RT ± Conc Cetux	Conc	**Cetux** Loading : 400 mg/m² then 250 mg/m² qw for 16 wks	Induc (3c) **C:** 75 mg/m² (d 1) **D:** 75 mg/m² (d 1) **F:** 750 mg/m² (d 1-5)	**69.6 Gy:** Not detailed	174/180
Andreadis (15) (2011)[7]	NCT01301248	2008-2011	NA	III, IV	RT + Conc C ± Conc Cetux	Conc	**Cetux** Loading: 400 mg/m² then 250 mg/m² qw for 7.2-7.8 wks	**C:** 40 mg/m² qw for 7.2-7.8 wks	**65-70 Gy** 1.8 Gy/d for 7.2-7.8 wks	NA/80

[4] RT regimens was one of the factor of stratification of the randomization

[5] RT regimens were not randomized, it's fair to assume that it was center dependent.

[6] Until Feb 2009 patients received 3 cycles of CDF (called also TPF) induction, afterwards only CD (TP); randomization appears to be before induction.

[7] Trial info only available on *clinicaltrial.gov* (estimated sample size only available, last status active not recruiting at the date of the planned completion date)

First author	NCT	Inclusion period	Sites	Stage	Treatment	Timing	Anti-EGFR drug and dose	CT drug and dose	RT regimen	Analyzed / Randomized
Lee/Koh (16) (2015)	NCT00623558	2008-NA	OC, OP, HP, L	NA	Induc (C+D) + RT + Conc C vs Induc (C+D+Cetux) + RT + Conc (C+Cetux)	Induc + Conc	**Cetux** 250 mg/m² qw	Induc (q3w, 3c) **C:** 75mg/m² **D:** 75 mg/m² Conc **C:** 30 mg/m² qw	NA	NA/92
Rodriguez (17) (2010)	NA	2002-2007	OC, OP, HP, L	III, IV	RT + Conc placebo vs RT + Conc Nimo	Conc	**Nimo** 200 mg qw for 6-7 wks	/	**60-66 Gy**: 2 Gy/d for 6-7 wks	NA/106
Reddy (18) (2014)[8]	NA		OC, OP, HP, L	III, IV	RT (+/- Conc) vs RT (+/- Conc) + Nimo	Conc	**Nimo** 200 mg qw for 6-7 wks	**C: 5**0 mg/m² qw	**60-66 Gy**: 2 Gy/d for 6-7 wks	92/92
CONCERT-1[9] Mesia (19) (2015).	NCT00500760	2007-2009	OC, OP, HP, L	III, IV-A, IV-B	RT + Conc C ± Conc Pani	Conc	**Pani** 9 mg/kg q3w	**C** (q3w) Alone : 100 mg/m² With Pani:75 mg/m²	**70 Gy:** 2 Gy/d for 7 wks	150/153
DAHANCA 19 Eriksen (20) (2014)	NCT00496652	2007-2012	OC, OP, HP, L	III, IV, other	RT + Conc C[10] ± Conc Zalu	Conc	**Zalu** 8 mg/kg qw for 5.5 wks	**C:** 40 mg/m² qw for 5.5 wks (only for stage III-IV)	**66-68 Gy:** 2 Gy/d, 6 d pw + Nimorazole qd for 5.5 wks	NA/619

[8] Concomitant cisplatin is delivered in non-frail patients ; randomization was stratified according to concomitant treatment

[9] Cisplatin dose reduced when combined to Panitumumab.
Randomization in favor of the Panitumumab arm with a 2:3 ratio and stratified on Radiotherapy modality (3D *vs.* IMRT)

[10] Patients with stage III-IV carcinomas (89% of the total patient population) received Cisplatin

Table 2: Addition of Anti-EGFR (Tyrosine-Kinase Inhibitor) to radiotherapy or chemoradiation

(See Appendix B3 for abbreviations)

First author	NCT	Inclusion period	Sites	Stage	Treatment	Timing	Anti-EGFR drug and dose	CT drug and dose	RT regimen	Analyzed / Randomized
Gregoire (21) (2011)	NCT00229723	2004-2008	OC, OP, HP, L, Other	III, IV	Seven arms[11]: RT + Conc (C+placebo) + Adj (placebo vs $Gefi_{250\ mg}$ vs $Gefi_{500\ mg}$) vs RT + Conc (C+$Gefi_{250mg}$) + Adj (placebo vs $Gefi_{250mg}$) vs RT + Conc (C+$Gefi_{500\ mg}$) + Adj (placebo vs $Gefi_{500\ mg}$)	Conc ± Adj	**Gefi** 250 or 500 mg/d Conc: for 8-9 wks Adj: for up to 2 yrs post-randomization	**C:** 100 mg/m² q3w, 3c	**70 Gy :** 2 Gy/d for 7 wks	226/226
Nandwani (22) (2010)	NA	2007-2008	NA	NA	RT + Conc C ± Conc Gefi	Conc	**Gefi** 250 mg/d qw for 7 wks	**C:** 30 mg/m² qw for 7 wks	**70 Gy :** 2 Gy/d for 7 wks	NA/100
Singh (23) (2013)	NA	2008-2010	OC	III, IV	RT ± Conc Gefi	Conc	**Gefi** 250 mg/d for 7 wks	/	**70 Gy :** 2 Gy/d for 7 wks	60/60
Bhattacharya (24) (2014)	NA	2011-2012	OC, OP, HP, L	III, IV-A, IV-B	RT + Conc C ± Conc Gefi	Conc	**Gefi** 250 mg/d for 7 wks	**C:** 30 mg/m² qw for 7 wks	**66 Gy :** 2 Gy/d for 7 wks	61/64
Del Campo (25) (2011)	NA	2006-2007	OC, OP, HP, L	III, IV-A, IV-B	Induc placebo + RT + Conc C vs Induc Lapa + RT + Conc C	Induc	**Lapa** 1500 mg/d for 2-6 wks	**C:** NA	**66-70 Gy:** 2 Gy/d for 6-7 wks	107/107
Harrington (26) (2013)	NCT00387127	2006-2009	OC, OP, HP, L	III, IV-A, IV-B	RT + Conc C+ Conc placebo + Adj placebo vs RT + Conc C+ Conc Lapa + Adj Lapa	Conc + Adj	**Lapa** 1500 mg/d	**C:** 100 mg/m² q3w, 3c	**65 Gy (IMRT) or 70 Gy (2D, 3D):** <2.5 Gy/d for 6.5-7 wks	67/67
Harrington (11) (2015)[12]	NCT00424255	NA	OC, OP, HP, L	II, III, IV-A	Induc placebo + RT + Conc (C+ placebo) + Adj placebo vs Induc Lapa + RT + Conc (C +Lapa) + Adj Lapa	Induc + Conc + Adj	**Lapa** 1500 mg/d Induc: 3-7 d before RT Conc: for 6-7 wks Adj: for 1 yr	**C:** 100 mg/m² q3w, 3c	**66 Gy po:** 2 Gy/d for 7 wks	688/688

[11] Arm1: Conc (C+placebo) + Adj placebo; Arm 2: Conc (C+ $Gefi_{250\ mg}$) + Adj $Gefi_{250\ mg}$; Arm 3: Conc (C+ $Gefi_{500\ mg}$) + Adj $Gefi_{500\ mg}$; Arm 4: Conc (C+ $Gefi_{250\ mg}$) + Adj placebo; Arm 5: Conc (C+ $Gefi_{500\ mg}$) + Adj placebo; Arm 6: Conc (C+ placebo) + Adj $Gefi_{250\ mg}$; Arm 7: Conc (C+ placebo) + Adj $Gefi_{500\ mg}$; randomization 2:1:1:1:1:1:1. This trial may be considered as a 2x 2 factorial design with randomization on concomitant gefitinib yes/no and adjuvant gefitinib yes/no.

[12] Resected tumor with surgical margin < 5 mm and/or extra-capsular extension

First author	NCT	Inclusion period	Sites	Stage	Treatment	Timing	Anti-EGFR drug and dose	CT drug and dose	RT regimen	Analyzed / Randomized
Martins (27) (2013)	NCT004 10826.	2006-2011	OC, OP, HP, L, NP	III, IV	RT + Conc C ± Conc Erlo	Conc	**Erlo** 150 mg/d for 7 wks	**C:** 100 mg/m² q3w , 3c	**70 Gy :** 2 Gy/d for 7 wks	204/204

APPENDIX B2: Description of the trials comparing Anti-EGFR to chemotherapy

Table 3: Comparing Anti-EGFR to chemotherapy

(See Appendix B3 for abbreviations)

First author	NCT	Inclusion period	Sites	Stage	Treatment	Timing	Anti-EGFR drug and dose	CT drug and dose	RT regimen	Analyzed / Randomized
TREMPLIN Lefebvre (28) (2013)[13]	NCT00169247	2006-2008	HP, L	III, IV	Induc CDF + RT + Conc C vs Induc CDF + RT + Conc Cetux	Conc	**Cetux** Loading: 400 mg/m² then 250 mg/m² qw	Induc: (q3w, 3c) **C:** 75 mg/m² **D:** 75 mg/m² **F:** 750 mg/m²/d (d 1-5) Conc : (q3w, 3c) **C:** 100 mg/m²	**70 Gy:** 2 Gy/d for 7 wks	116/116
GTTC Ghi (29) (2015)	NCT01086826	2008-NA	OC, OP, HP	III, IV	2x2 Factorial design: • RT + Conc (C+F) vs RT + Conc Cetux • Induc CDF + RT+ Conc (C+F) vs Induc CDF + RT+ Conc Cetux	Conc	**Cetux** Loading: 400 mg/m² then 250 mg/m² qw for 7 wks	Induc: (q3w, 3c) **C:** 80 mg/m² **D:** 75 mg/m² **F:** 800 mg/m²/d (d1-4) Conc: (q5w, 2c) **C:** 20mg/m²/d (d 1-4) **D:** 800 mg/m²/d for 4 d	**70 Gy:** 2 Gy/d for 7 wks	415/421[14]
Hitt (30) (2014)[15]	NCT00716391	NA	OC, HP, L	III, IV	Induc CDF + RT + Conc C vs Induc CDF + RT + Conc Cetux	Conc	**Cetux** Loading: 400 mg/m² then 250 mg/m² qw	Induc: (q3w) **C:** 75 mg/m² d1 **D:** 75 mg/m² d1 **F:** 750 mg/m²/d (d 1-5) Conc **C:** 100 mg/m²/d q3w	**70 Gy:** 2 Gy/d for 7 wks	516/531
Magrini (31) (2015)	NCT01216020.	2011-2014	OC, OP, HP, L	III, IV-A, IV-B	RT + Conc C vs RT + Conc Cetux	Conc	**Cetux** Loading: 400 mg/m² then 250 mg/m² qw	**C:** 40 mg/m² qw for 7 wks	**70 Gy:** 2 Gy/d for 7 wks	66/70
CONCERT-2 Giralt[16] (32) (2015)	NCT00547157	2007-2009	OC, OP, HP, L	III, IV-A, IV-B	RT + Conc C vs RT + Conc Pani	Conc	**Pani** 9 mg/kg q3w, 3c	**C:** 100 mg/m² (d 1 + 22)	**70-72 Gy:** 1-2 f/d for 6-6.5 wks	151/152

[13] Randomization after induction complete or good partial response)

[14] 101 patients of the Phase II trial which compared TPF+Chemoradiation to chemoradiation, are not eligible and won't be included in the comparison of Cetuximab with Chemotherapy which included 320 patients. The two randomization were: TPF induction yes/no and concomitant CF vs Cetux.

[15] Randomizatoin after induction

[16] Randomization in favor of Panitumumab with a 2:3 ratio and stratified on Radiotherapy modality (3D *vs.* IMRT). Two types of IMRT were used: a concomitant boost technique or a simultaneous boost technique.

First author	NCT	Inclusion period	Sites	Stage	Treatment	Timing	Anti-EGFR drug and dose	CT drug and dose	RT regimen	Analyzed / Randomized
Siu (33) (2016)	NCT008 20248	2008-2011	OC, OP, HP, L	III, IV	RT + Conc C vs Acc. RT + Conc Pani[17]	Conc	**Pani** 9 mg/kg q3w, 3c	**C:** 100 mg/m² q3w, 3c	**70 Gy (IMRT or 3D):** Standard:2 Gy/d for 7 wks Acc.:2 Gy/d or bid for 6 wks	320/320

[17] CT vs Anti-EGFR but RT regimen differs between treatment groups. MARCH results showed no major differences between Acc RT and standard RT therefore this trial can be included. A sensitivity analysis would be performed without this trial.

APPENDIX B3: Abbreviations used in trial's description tables

Generalities

- **Adj:** adjuvant
- **c:** cycles
- **ci:** continuous infusion
- **Conc:** concomitant
- **CRT:** chemoradiation
- **CT:** chemotherapy
- **d:** days
- **Gy:** Gray
- **IMRT:** intensity modulated radiotherapy
- **Induc:** induction
- **po:** post operative
- **pw:** per week
- **RT:** radiotherapy
- **wks:** weeks
- **yr:** year

Chemotherapy drugs

- **C** : Cisplatin
- **Cb** : Carboplatin
- **CDF (also called TPF)**: Cisplatin + Docetaxel + 5-Fluorouracil
- **D** : Docetaxel
- **F**: 5-Fluorouracil
- **HU**: Hydroxyurea
- **MMC**: Mitomycin C

Anti-EGFR drugs

- **Afa:** Afatinib
- **Cetux**: Cetuximab
- **Erlo:** Erlotinib
- **Gefi:** Gefitinib
- **Lapa:** Lapatinib
- **Nimo**: Nimotuzumab
- **Pani:** Panitumumab
- **Zalu:** Zalutumumab

APPENDIX C1: Description of eligible ongoing or recently closed to accrual trials

Table 5: Addition of anti-EGFR (Monoclonal antibodies) to radiotherapy or chemoradiation

(See Appendix B3 for abbreviations)

First author	NCT	Estimated completion date	Estimated No. patients	Sites	Stage	Treatment	Timing	Anti-EGFR drug and dose	CT drug and dose	RT regimen
Zhong	NCT01434394	2016 (2017)	243	NA	III, IV-A	Induc (C+D+Cetux) + Surgery + Post-op RT vs Surgery +Post-op RT	Induc	**Cetux** Loading: 400 mg/m² then 250 mg/m² qw for 6 wks	Induc: (q3w, 2c) **C:** 75 mg/m² **D:** 75 mg/m²	NA
Riesterer	NCT01435252	2017	68	OP, HP, L	NA	RT + Conc (C + Cetux) ±Adj Cetux	Adj	**Cetux** Conc: 400 mg/m² then 250 mg/m² qw Adj: 500 mg q2w for 12 wks	**C:** 40 mg/m² qw	**Up to 70 Gy** Not detailed
RTOG 1216 Harari	NCT01810913	2020	675	OC, OP, HP, L	III, IV-A, IV-B	RT + Conc C vs RT + Conc D vs RT + Conc (D+Cetux)	Conc	**Cetux** qw for 7 wks	**C:** qw for 6 wks **D:** qw for 6 wks	**IMRT** for 6 wks
ARTFORCE (44) Heukelom (2013)	NCT01504815	2020	268	OC, OP, HP	III, IV	Plan 2x2: • Standard RT + Conc C vs Standard RT + Conc Cetux • Redistributed adaptative RT + Conc C vs Redistributed adaptative RT + Conc Cetux	Conc	**Cetux** Loading: 400 mg/m² then 250 mg/m² qw	**C:** 40 mg/m² qw	**Standard RT** 70 Gy (tumour+ nodes) **R. RT** 70-84 Gy (tumour 50% isocontour PET) + 70 Gy (other tumour + nodes)
RTOG 0920 Machtay	NCT00956007	2021	700	OC, OP, L	III, IV	RT ± Conc Cetux + Adj Cetux	Conc + Adj	**Cetux** qw for 11 wks	/	**IMRT** for 6 wks
Lang	NCT01516996	2018	80	OP, HP	III, IV-B	Induc (C+D) + RT + Conc C ± Conc Nimo	Conc	**Nimo** 200 mg qw for 13-14 wks	Induc (q3w) **C:** 75 mg/m²(d 1-3) **D:** 75 mg/m²(d 1-3) Conc **C:** 75 mg/m² q3w	**68-70 Gy (IMRT) :** 1.8-2 Gy/d for 7 wks

First author	NCT	Estimated completion date	Estimated No. patients	Sites	Stage	Treatment	Timing	Anti-EGFR drug and dose	CT drug and dose	RT regimen
Soo	NCT00957086	2018 (2021)	710	NA	III, IV	RT + Conc placebo +Adj C vs RT + Conc Nimo + Adj C	Conc	**Nimo** 200 mg qw for 8 wks	**C:** NA	NA

Table 6: Addition of Anti-EGFR (Tyrosine-Kinase Inhibitor) to radiotherapy or chemoradiation

(See Appendix B3 for abbreviations)

First author	NCT	Estimated completion date	Estimated No. patients	Sites	Stage	Treatment	Timing	Anti-EGFR drug and dose	CT drug and dose	RT regimen
LUX-Head & Neck 2 (45) Burtness [18]	NCT01345669	Stopped	669 (616)	OC, OP, HP, L	III, IV-A, IV-B	Adj placebo vs Adj Afa	Adj (post CRT)	**Afa** 40-50 mg/d for 18 mths	/	/
LUX-Head & Neck 4 Boehringer Ingelheim	NCT02131155	Stopped	150	NA	III, IV-A, IV-B	Adj placebo vs Adj Afa	Adj (post CRT)	**Afa** NA qd	/	/
GORTEC 2010-02 Racadot Pommier	NCT01427478	2021 (2018)	315	OC, OP, HP	NA	RT + Conc C + Adj placebo vs RT + Conc C + Adj Afa	Adj	**Afa** 40 mg/d for 1 mth then 50 mg/d for 11 mths	**C:** 100 mg/m² q3w	**66 Gy** Not detailed
TRYHARD Wong	NCT01711658	2018	176	OP, HP, L	III, IV	Induc placebo + Conc (C+placebo) + Adj placebo vs Induc Lapa + RT + Conc (C+Lapa) + Adj Lapa	Induc + Conc + Adj	**Lapa** 1500 mg/d Induc : for 1 wk Adj : for 3 mths	**C:** 100 mg/d q3w	**70 Gy (IMRT):** 2 Gy/d for 7 wks
MD Anderson	NCT01927744	End in 2020	100	OC	III, IV-A, IV-B	Induc [(C or Cb) + D + placebo] + surgery vs Induc [(C or Cb) + D+ Erlo][19] + surgery	Induc	**Erlo** 150 mg/d until surgery	**C:** 75 mg/m² q3w, 3c **Cb:** 6 mg.min/ml q3w, 3c **D:** 75 mg/m² q3w, 3c	/

[18] LUX-Head & Neck 2 and 4 have been stopped before being completed. Given the decision has been made in July 2016, we've decided not to include them in the meta-analysis for now since in both studies accrual wasn't completed on December 31st 2014 (see Trial selection criteria)

[19] Every patients received either C or Cb no matter their treatment group

Table 7: Comparing Anti-EGFR to chemotherapy

(See Appendix B3 for abbreviations)

First author	NCT	Estimated completion date	Estimated No. patients	Sites	Stage	Treatment	Timing	Anti-EGFR drug and dose	CT drug and dose	RT regimen
Lukas	NCT02015650	2017	70	OC, OP, HP, L	III, IV	RT + Conc (F + MMC) vs RT + Conc Cetux	Conc.	**Cetux** Loading: 400 mg/m² then 250 mg/m² qw	**F:** 1000-1500 mg/m² (d 8-12 and 43-47) **MMC:** 10-15 mg/m²(d 8 + 43)	for 7 wks
LUX-Head & Neck 4 Boehringer Ingelheim	NCT02131155	Stopped	150	NA	III, IV-A, IV-B	Adj placebo vs Adj Afa	Adj (post CRT)	**Afa** NA qd	/	/
TROG 1201 Matera/ Rischin	NCT01855451	2017	200	OP	III, IV	RT + Conc C vs RT + Conc Cetux	Conc.	**Cetux** Loading: 400 mg/m² then 250 mg/m² qw	**C:** 40 mg/m² qw	**70 Gy :** 2 Gy/d for 7 wks
De-ESCALaTE HPV Mehanna	NA	2017	304	OP	III, IV-A	RT + Conc C vs RT+ Conc Cetux	Conc.	**Cetux** Loading: 400 mg/m² then 250 mg/m² qw	**C:** 100 mg/m² q3w, 3c	for 7 wks
RTOG 1016 Gillison	NCT01302834	2020	706	OP	III, IV	Acc. RT + Conc C vs Acc. RT + Conc Cetux	Conc.	**Cetux** qw for 7 wks	**C:** High dose q3w	**IMRT** qd (d 1-4) + bid (d 5) qw for 6 wks
ARTSCAN III Gebre-Medhin	NCT01969877	2024	618	OC, HP, L	III, IV	T1-T4[20] : RT + Conc C vs RT + Conc Cetux T3-T4 : RT + Conc C vs RT+ Conc Cetux	Conc.	**Cetux** Loading: 400 mg/m² then 250 mg/m² qw	**C:** 40 mg/m²	**68 Gy (T1-T4)** 2 Gy/d **73.1 Gy (T3-T4)** 2.15 Gy/d

[20] Tumor stage

Table 8: Trial which would fit for a network meta-analysis

(See Appendix B3 for abbreviations)

First author	NCT	Estimated completion date	Estimated No. patients	Sites	Stage	Treatment	Timing	Anti-EGFR drug and dose	CT drug and dose	RT regimen
GORTEC 2007-02 (46) Geoffrois L.	NCT01233843	2009-2019	370	NA	NA	RT + Conc (F+Cb) vs Induc TPF + RT+ Conc Cetux	Conc	**Cetux** NA qw	Induc: **C:** 100 mg/m² (d 1) **D:** 100 mg/m² (d 1) **F**: 1000 mg/m² (d 1-5) q3w, 3c Conc: (q3w, 3c) **Cb:** 70 mg/m²/d (d 1-4) **F**: 600 mg/m²/d (d 1-4)	**70 Gy:** 2 Gy/d for 7 wks
INTERCEPTOR (47) Denaro N.	NCT00999700	2018	278	NA	III, IV	RT + Conc (C) vs Induc TPF + RT + Conc Cetux	Conc	**Cetux** Loading: 400 mg/m² then 250 mg/m² qw	Induc: **C:** 75 mg/m² (d 1) **D:** 75 mg/m² (d 1) **F**: 750 mg/m² (d 1-4) q3w Conc: **C:** 100 mg/m² (d 1) q3w, 3c	**Conformal RT or IMRT:** 70 Gy + additional boost if indicated
ICRAT* (48) Stromberger C.	NCT01181401	NA	94	OC, OP, HP	IVA, IVB	RT + Conc (C) vs Induc TPF1 + RT+ Conc Cetux vs Induc TPF2 + RT+ Conc Cetux	Conc	**Cetux** Loading: 400 mg/m² then 250 mg/m² qw x 6	Induc 1: **C:** 75 mg/m² (d 1) **D:** 75 mg/m² (d 1) **F**: 750 mg/m² (d 1-4), q3w, 3c Induc 2: **C:** 40 mg/m² (d 1+8) **D:** **40** mg/m² (d 1+8) **F**: 1500 mg/m² ci (d 1+8), 3w, 3c Conc: (q3w, 3c) **C:** 30 mg/m²/d (d1,8,15,22,29,36) **F**: 600 mg/m²/d (d 1-5)	**72 Gy** Hyperfractionated accelerated radiotherapy IMRT or 3D

** 3-arm trial*

APPENDIX D: How to send data to the Secretariat?

FORMAT FOR THE DATA

The preferred format for the information is described on the following pages. However, if a different format is more convenient for you, this should cause no great difficulty as long as it is clearly specified.

WAYS OF SENDING THE DATA

As long as it will not cause delay, **the easiest way for us to receive the data is by e-mail**[1]. If sending data via email, please encrypt the data and let us know how it has been encrypted in a separate email. We should be able to read any standard CD/DVD[2] if you let us know its specification. Please accompany disk with a printout of its contents.

It is important when trying to achieve a synthesis of the results of many different trials to include all patients ever randomized, whether eligible or not, whether or not they received their allocated treatment, whether properly followed up or not. Please try to get as near as possible to that ideal (or, at least please indicate where post randomization exclusions or losses have occurred), as long as doing so will not delay the sending of the data. If it will cause a delay, then, please send us what you can now, and send the extra information later.

Please, fill out and mail (or fax) the enclosed form to the secretariat to facilitate data processing.

---

[1] Our e-mail address is : jean-pierre.pignon@gustaveroussy.fr

[2] The preferred specification would be PC compatible , CD, ASCII Format.

Suggested coding and format for sending data

	Variable	Format/Coding
Patient/Tumor		
	Patient identifier	10 characters
	Date of birth[21]	dd/mm/yyyy, 99999999=Unknown
	or age	6 blanks (columns 13-18), 2 digits (columns 19-20), 99=Unknown
	Sex	1=Male, 2=Female, 9=Unknown
	Performance Status	For Karnofsky index use 3 digits, for WHO or ECOG index use 2 blanks
	Site of primary	1=Oral cavity, 2=Oropharynx, 3=Larynx, 4=Hypopharynx, 5=Nasopharynx, 6=Cervical node(s) without primary, 7=Others, 9=Unknown
	T[22]	0=T0, 1=T1, 2=T2, 3=T3, 4=T4, 5=TX, 6=Tis, 9=Unknown
	N	0=N0, 1=N1, 2=N2, 3=N3, 4=NX, 9=Unknown
	M	0=M0, 1=M1, 9=Unknown
	or Stage	1 digit (column 34) with blanks in columns 30 & 32, 9=Unknown
	Smoking status	0=Never, 1=Former, 2=Current, 9=Unknown
	if yes, pack-years	3 digits, 999=Unkown
	P16 status	0=Negative, 1=Positive, 9=Unknown
	HPV status	0=Negative, 1=Positive, 9=Unknown
	Methods used to determine HPV status[23]	1=p16, 2=ISH, 3=Other, 9=Unknown
	EGFR status	0=Negative, 1=Positive, 9=Unknown
	Methods used to identify EGFR tumor markers[24]	1=Protein expression, 2=Mutation, 3=Copy number, 4= Other, 9=Unknown

[21] In cases where communicating patients-related dates (e.g: patient's date of birth, date of randomization…) is forbidden by local legislation, anonymized dates will be welcomed. Anonymization can be done by adding a random number to all the dates provided in the database.

[22] T/N/M: if more detailed coding available, please provide with code description.

[23] Specify the methods used in the documents accompanying the data.

[24] Specify the methods used in the documents accompanying the data. If several methods used, please provide results for the different methods.

	Variable	Format/Coding
Treatment		
	Treatment allocated	1=No Anti-EGFR, 2=Anti-EGFR
	Date of randomization	dd/mm/yyyy, 99999999=Unknown
	Number of cycles of induction CT received	1 digit
	Number of cycles of concomitant CT received	1 digit
	Number of cycles of adjuvant CT received	1 digit
	Tumor surgery	0=No, 1=Yes before RT, 2= yes after RT, 4=yes without timing information
	Radiotherapy started	0=No, 1=Yes, 9=Unknown
	Date of first day of radiotherapy	dd/mm/yyyy, 99999999=Unknown
	Date of last day of radiotherapy	dd/mm/yyyy, 99999999=Unknown
	Total administered dose of radiotherapy (Gy)	2 digits + 1 digit separated by a coma (example: 72,2), 99=Unknown
	Total number of fractions of radiotherapy	2 digits, 99=Unknown
	Radiotherapy – technique	1 = 2D, 2 = 3D, 3 = IMRT, 9 = unknown
	Dose of administred anti-EGFR	
	If Monoclonal Antibody:	
	Number of injections (or duration in days)	2 digits, 99=Unknown
	If Tyrosine Kinase Inhibitor[25]:	
	Date of first day of anti-EGFR therapy	dd/mm/yyyy, 99999999=Unknown
	Date of last day of anti-EGFR therapy	dd/mm/yyyy, 99999999=Unknown
	Anti-EGFR administration	1= Full per protocol treatment received, 2=Dose reduction, 3=Treatment interruption

[25] If those dates are unavailable, please provide the duration (in days) of anti-EGFR therapy.

	Variable	Format/Coding
Acute Toxicity		
	Neutropenia	1 digit, 0 to 5 if WHO or NCI-CTC scoring system, 9=Unknown
	Thrombocytopenia	1 digit, 0 to 5 if WHO or NCI-CTC scoring system, 9=Unknown
	Anemia	1 digit, 0 to 5 if WHO or NCI-CTC scoring system, 9=Unknown
	Kidney failure	1 digit, 0 to 5 if WHO or NCI-CTC scoring system, 9=Unknown
	Diarrhea	1 digit, 0 to 5 if WHO or NCI-CTC scoring system, 9=Unknown
	Allergy	1 digit, 0 to 5 if WHO or NCI-CTC scoring system, 9=Unknown
	Acneiform rash	1 digit, 0 to 5 if WHO or NCI-CTC scoring system, 9=Unknown
	Other cutaneous	1 digit, 0 to 5 if WHO or NCI-CTC scoring system, 9=Unknown
	Liver (transaminases) toxicity	1 digit, 0 to 5 if WHO or NCI-CTC scoring system, 9=Unknown
	Mucositis	1 digit, 0 to 5 if WHO or NCI-CTC scoring system, 9=Unknown
	Hearing loss	1 digit, 0 to 5 if WHO or NCI-CTC scoring system, 9=Unknown
	Neurotoxicity	1 digit, 0 to 5 if WHO or NCI-CTC scoring system, 9=Unknwon
	Need for feeding tube	0=No, 1=Yes, 9 =Unknown.
Late Toxicity		
	Cutaneous fibrosis	1 digit, 0 to 5 according to EORTC-RTOG scale, 9=Unknown
	Xerostomia	1 digit, 0 to 5 according to EORTC-RTOG scale, 9=Unknown
	Bone necrosis	1 digit, 0 to 5 according to EORTC-RTOG scale, 9=Unknown
	Persistence of feeding tube after one year of treatment	0=No, 1=Yes, 9=Unknown

	Variable	Format/Coding
Survival		
	Date of last follow-up or death	dd/mm/yyyy, 99999999=Unknown
	Survival status	0=Alive, 1=Dead
	Cause of death	0=Alive, 1=Cancer, 2= Toxicity of anti-EGFR, 3=Toxicity of chemotherapy, 4=Toxicity of radiotherapy, 5=Complication of surgery, 6= Toxicity of the compared treatments (not specified), 7=Secondary malignancy, 8=Other (including death related to second line treatment), 9=Unknown
	Tumor progression/recurrence[26],	0=No, 1=Yes
	Date of tumor progression/recurrence	dd/mm/yyyy, 99999999=Unknown
	Nodal progression/recurrence	0=No, 1=Yes
	Date of nodal progression/recurrence	dd/mm/yyyy, 99999999=Unknown
	Distant progression/recurrence (metastasis)	0=No, 1=Yes
	Date of progression/recurrence failure (metastasis)	dd/mm/yyyy, 99999999=Unknown
	Second primary	0=No, 1=Yes
	Date of second primary	dd/mm/yyyy, 99999999=Unknown
	Type of second primary	1=Lung, 2=Esophagus, 3=Stomach, 4=Colorectal, 5=Liver, 6=Head & Neck, 7=Bladder, 8=Other (specify) 9=Unknown
	Excluded from your analysis	0=No, 1=Yes
	Reasons for exclusion	12 characters

[26] In absence of separate information about tumor and nodal progression/recurrence, please provide information on locoregional progression/recurrence.

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MACH-EGFR

Meta-Analysis in locally advanced Cancers of Head & neck on anti-EGFR therapy

Meta-Analysis in locally advanced Cancers of Head and neck on anti-EGFR therapy

Trial / Protocol number _____

Trial Publication _____

_____

Name of Investigator_____

Address _____

_____

Telephone _____ Fax _____

Email_____

Are you willing to take part in the Meta-analysis? Yes ☐ No ☐

Are the details of your trial correct? Yes ☐ No ☐

Is the most recent publication cited in the publication list? Yes ☐ No ☐

If no, please give correct details _____

_____

Do you know of any other relevant trials not listed in the protocol? Yes ☐ No ☐

If yes, please provide details _____

_____

Is a copy of the trial protocol enclosed? Yes ☐ No ☐

If different from above, please give details of the appropriate contact for the collection of trial data:

Name_____

Address _____

_____

Telephone _____ Fax _____

Email_____

Did the trial have a target for patient accrual? Yes ☐ No ☐ Target: _____

Did the trial reach its target accrual? Yes ☐ No ☐

Date trial opened |__|__| |__|__| |__|__|__|__| Date trial closed |__|__| |__|__| |__|__|__|__|

Meta-Analysis in locally advanced Cancers of Head and neck on anti-EGFR therapy

What method was used to conceal randomisation?

Sealed envelope ☐ Central telephone ☐ Other ☐

What method of randomisation was used in this trial?

Simple ☐ Permuted Blocks ☐ Minimisation ☐ Other ☐

What, if any, stratification factors were used? _____

What proportions was the trial designed to have in each arm? (e.g.1:1) _____

Please list treatments used in the arms of your trial* (including local treatment and drugs given):

Arm 1: _____

Arm 2: _____

** If more than 2 arms give the detail on a separate sheet*

Which TNM or staging classification was used? _____

Which performance status was used? WHO ☐ ECOG ☐ Karnofsky ☐ Other ☐

Which p16 methods and cutoff were used? _____

_____

Which HPV methods and cutoff were used? _____

_____

Which EGFR tumor marker was used? Protein expression ☐ Mutation ☐ Copy number ☐ Other ☐

Specify coding used: _____

Which classification was used for toxicity?

Acute: WHO ☐ NCI-CTC ☐ Other ☐ Specify: _____

Late: RTOG/EORTC ☐ Other ☐ Specify: _____

Will some of the data requested be never available?

Yes ☐ No ☐

If yes, please specify: _____

_____

Any data supplied will remain the property of the trialist(s) who supplied it. These data will remain confidential and will not be used, circulated or distributed in any way that allows access to individual patient data.

Permission for use of the IPD for methodological Research

I agree that an anonymised version of the trial data that I supplied for the meta-analysis can be used in other methodological research projects:

☐ Yes ☐ No

Signed _____ Date _____

Please return to Jean-Pierre Pignon – Institut Gustave Roussy
114 rue Edouard Vaillant – 94805 Villejuif cedex France
- Fax 33 1 42 11 52 58 – e-mail : jean-pierre.pignon@gustaveroussy.fr