Afatinib versus placebo as adjuvant therapy after chemoradiation in squamous cell carcinoma of the head and neck: a randomised, double-blind, phase 3 trial (LUX-Head & Neck 2)

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Summary [Word count: 300/300 words]

Background Locally advanced squamous cell cancer of the head and neck (HNSCC) is treated curatively; however, risk of recurrence remains high among some patients. The ERBB family blocker, afatinib, has shown efficacy in recurrent/metastatic HNSCC. LUX-Head&Neck 2 assessed whether afatinib after definitive concurrent chemoradiation (CCRT) improved disease-free survival (DFS).

Methods This randomised, phase 3 double-blind trial enrolled patients who had complete response after CCRT, comprising radiotherapy with cisplatin or carboplatin for loco-regionally advanced high-/intermediate-risk HNSCC of the oral cavity, hypopharynx, larynx, or oropharynx. Patients were randomised (2:1) to afatinib (40 mg/day) or placebo, stratified by nodal status (N0-2a/N2b-3) and Eastern Cooperative Oncology Group performance status (0/1). Treatment continued for 18 months or until disease recurrence, unacceptable adverse events (AEs) or other reasons necessitating withdrawal. The primary endpoint was DFS. This study is registered with ClinicalTrials.gov: NCT01345669.

Findings Between November 2, 2011 and July 4, 2016, 617 patients were randomised (afatinib: 411; placebo: 206). Recruitment was stopped after a pre-planned interim futility analysis on July 4, 2016 upon recommendation from an independent data monitoring committee. Treatment was discontinued. Median DFS was 43·4 months (95% confidence interval [CI] 37·4–not estimable) in the afatinib group and not estimable (95% CI 40·1-not estimable) with placebo (hazard ratio 1·13, 95% CI 0·81-1·57; stratified log-rank test p=0·48). The most common grade 3/4 drug-related AEs were rash/acne (61 [14·8%] of 411 patients in the afatinib group *vs* 1 [0·5%] of 206 patients in the placebo group), stomatitis (55 [13·4%] *vs* 1 [0·5%]) and diarrhoea (32 [7·8%] *vs* 1 [0·5%]).

Interpretation Afatinib after CCRT did not improve DFS versus placebo in patients with primary unresected, clinically high-/intermediate-risk HNSCC. The utility of ERBB family inhibition as adjuvant therapy in HNSCC will depend on further refinement of risk stratification and a better understanding of predictive biomarkers.

Funding: Boehringer Ingelheim

Panel: **RESEARCH IN CONTEXT**

Evidence before this study

We performed a review of the literature published up to October 30, 2017, using PubMed, and of trials presented as abstracts at key oncology meetings (such as the annual meeting of the American Society of Clinical Oncology and the European Society for Medical Oncology). Using the search terms 'HNSCC', 'locally advanced', and 'chemoradiotherapy', we reviewed manuscripts and abstracts investigating strategies to reduce recurrence and death in high- or intermediate-risk patients with locally advanced HNSCC. This review showed that strategies have largely focussed on intensification of conventional treatment (radiation and chemotherapy); targeting of the EGFR family has also been investigated as maintenance therapy, with limited success. Overall, there remains an unmet need for prevention of recurrence among high- or intermediate-risk patients with locally advanced HNSCC.

Added value of this study

This study shows that the irreversible ERBB family blocker, afatinib, did not improve disease-free survival compared with placebo when used as adjuvant therapy after definitive CCRT in patients with primary unresected locally advanced high-/intermediate-risk HNSCC. Consistent with results shown in a trial assessing afatinib in patients with recurrent/metastatic HNSCC (LUX-Head & Neck 1), non-significant trends towards increased benefit from afatinib were apparent among patients with tumours which were p16-negative and/or had high PTEN expression.

Implications of all the available evidence

Broad inhibition of ERBB family receptors as adjuvant therapy in HNSCC has not been shown to improve outcome when compared with placebo, consistent with observations for other EGFR-targeted therapy. Based on findings among biomarker subgroups in this study, assessment of ERBB inhibition in molecularly enriched populations may be warranted for future trials.

[Word limit for manuscript text: 4500 words; currently 4141 words]

Introduction

Squamous cell carcinoma of the head and neck (HNSCC) is the sixth most common cancer worldwide, with an annual global incidence of approximately 650,000 cases.[1] Among the common causes of HNSCC are environmental exposures, such as habitual use of tobacco and alcohol, and infection with high-risk human papillomavirus (HPV). HPV-associated cancers arise predominantly in the oropharynx.[2] Approximately 50% of patients with HNSCC present with loco-regionally advanced (LA) disease,[3] and many patients, even if formally resectable, receive definitive concurrent chemoradiation (CCRT) as primary therapy because of functional considerations. Outcomes for patients treated with primary CCRT are comparable to those for surgery, and many patients treated with surgery require combined modality post-operative therapy.[4] Risk of recurrence remains high among some subsets of patients, even among those who attain a complete response to CCRT, or who have no evidence of disease following surgery to resect residual disease.[5] Patients with HPV-related oropharynx cancer who are lifetime light (≤10 pack-years) or never smokers have the most favourable outcomes after CCRT,[6] while patients with a more significant smoking history and bulky or HPV-unrelated disease are more likely to recur.[6] A recursive partitioning analysis of the R0129 chemoradiotherapy trial indicated 3-year overall survival (OS) of 46·2% for high-risk (HPV-negative and either >10 pack-years or ≤10 pack-years and T4 tumours) and 70·8% for intermediate-risk patients (HPV-negative, ≤10 pack-years and T2–3 tumours or HPV-related, >10 pack-years and N2b–N3 cancer).[6] Strategies to reduce recurrence and death in such high- or intermediate-risk patients have largely focussed on intensification of conventional treatment, with limited success for altered fractionation radiation together with chemotherapy[6] or induction chemotherapy.[7,8]

The epidermal growth factor receptor (EGFR) has been shown to play an important role in progression and treatment resistance in HNSCC;[9] targeting of EGFR with the monoclonal antibody cetuximab improves chemotherapy and radiotherapy responsiveness

and improves survival in the LA and metastatic settings.[10-12] However, the small-molecule inhibitors of EGFR tyrosine kinase activity, gefitinib and erlotinib, have limited activity in HNSCC.[13,14] Other members of the ERBB receptor family – human epidermal growth factor receptor 2 (HER2 [ERBB2]), HER3 (ERBB3), and HER4 (ERBB4) – may also be aberrantly expressed in HNSCC, may contribute to resistance to EGFR-targeting, and may be targets in themselves.[15] Furthermore, EGFR may be translocated to the nucleus in both HPV-related and -unrelated HNSCC, constituting a mechanism of resistance to antibody-based therapy which is amenable to targeting with small-molecule inhibitors.[16,17] Thus, dual- or pan-HER tyrosine kinase inhibitors have promise in HNSCC because of the potential to overcome resistance due to HER2/HER3 signaling and nuclear translocation of EGFR. Afatinib, an irreversible ERBB family inhibitor, has demonstrated efficacy in recurrent or metastatic HNSCC after failure of platinum-based therapy.[18] EGFR and other HER-family member targeting has been explored as a target for maintenance or adjuvant therapy following definitive treatment. Single-arm studies have included post-radiation courses of cetuximab or gefitinib.[19,20] Moreover, the advent of oral agents provides therapy that is suitable for prolonged administration. Gefitinib or lapatinib could be safely administered with chemoradiotherapy and as maintenance therapy in locally advanced HNSCC.[21-23]

Thus, we wished to study whether the orally available, active and tolerable, irreversible ERBB family inhibitor, afatinib could prevent or delay recurrence in patients with clinical features of intermediate- to high-risk disease.

Methods

Study design and participants

Patients were randomised in 136 centres in 29 countries worldwide in this double-blind, placebo-controlled, phase 3 trial. Eligible patients were aged ≥18 years and had histologically or cytologically confirmed LA HNSCC (Stage III, IVa or IVb SCC of the oral cavity, oropharynx or hypopharynx, or Stage IVa or IVb SCC of the larynx). As HPV status was not determined for eligibility, unfavourable risk was defined as non-oropharynx primary site or oropharynx cancer in heavy smokers (>10 pack-years). Patients were required to have unresected disease prior to CCRT. Definitive CCRT must have been completed no longer than 24 weeks prior to randomisation, comprising radiotherapy with curative intent to a minimum dose of 66 Gy in 33 fractions, and cisplatin (minimum cumulative dose of 200 mg/m^2) or carboplatin (minimum cumulative area under the concentration-time curve of 9). Patients were required to have no evidence of disease after CCRT, based on clinical and radiographic examination (defined as no residual tumour after CCRT, or no residual tumour after CCRT followed by R0 tumour resection, or no evidence of nodal disease after CCRT followed by neck dissection). An Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1 was also required.

Previous treatment with EGFR-targeted small molecules, EGFR-targeted antibodies and/or any investigational agents for HNSCC was not permitted. Patients with a smoking history of ≤10 pack-years and tumour site of base of tongue and/or tonsil were not eligible for enrolment. Additional key exclusion criteria were: primary cancer of the nasopharynx, sinuses and/or salivary glands; any other malignancy (except for simultaneous HNSCC primaries, appropriately treated superficial basal cell skin cancer and surgically cured cervical cancer in situ) unless free of disease for ≥5 years; known pre-existing interstitial lung disease; clinically relevant cardiovascular abnormalities; cardiac left ventricular dysfunction with resting ejection fraction of <50%; significant or recent acute gastrointestinal disorders

with diarrhoea; and laboratory values of absolute neutrophil count <1·5 x 10^9 cells/L, platelet count <75 x 10^9 cells/L, calculated creatinine clearance <50 mL/min, total bilirubin >1·5 x upper limit of normal (ULN), and aspartate aminotransferase or alanine aminotransferase >3 x ULN.

The study protocol was designed in accordance with the Declaration of Helsinki, the International Conference on Harmonisation Guideline for Good Clinical Practice, and applicable region-specific regulatory requirements, and was approved by independent ethics committees at each centre. All patients provided written informed consent for trial participation. Patients who volunteered for assessment of tumour biomarkers provided separate informed consent for collection and analysis of tissue samples in accordance with local ethical and regulatory requirements.

Randomisation and masking

Patients were randomised 2:1 to receive afatinib or placebo, and stratified based on nodal status (N0–N2a *vs* N2b–N3), and ECOG PS (0 *vs* 1). The randomisation list was generated using a validated pseudo-random number generator (block size: 3). The assignment of a patient to a treatment group was determined by means of an interactive voice or web-based response system. Patients, investigators, and the sponsor trial team were blinded to the randomised treatment until database lock.

Procedures

Oral afatinib was given at an initial dose of 40 mg once daily and the dose was escalated to 50 mg after at least 4 weeks in the absence of any treatment-related adverse events (AEs) other than grade 1 skin rash. In the event of any grade ≥3 treatment-related AE, grade ≥2 diarrhoea for 2 or more consecutive days or grade ≥2 nausea and/or vomiting for 3 or more consecutive days despite supportive care, or grade ≥1 reduced renal function, treatment was interrupted for up to 21 days until severity reduced to grade ≤1 or baseline. After recovery to

grade ≤1, the afatinib dose was reduced by 10 mg decrements (e.g. to 30 mg once daily for those previously receiving afatinib 40 mg). Dose reduction to a minimum of afatinib 20 mg once daily was permitted. Patients who required further dose reduction were removed from therapy. Treatment continued for 18 months or until disease recurrence/second primary tumour, unacceptable AEs or other reasons necessitating withdrawal.

Images of the head, neck and chest were assessed by the investigator and by independent central review. Assessment of tumour recurrence or second primary tumour was performed using computed tomography (CT), magnetic resonance imaging or positron emission tomography (PET)-CT every 16 weeks during the first 2 years, and every 24 weeks thereafter, until recurrence of disease, loss to follow-up or completion of the trial. Radiotherapy data were sent to a central quality assurance unit (EQUAL-ESTRO) for independent review. Health-related quality of life (HRQoL) was assessed using the following patient-reported outcome measures: European Organisation for the Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ-C30) and its associated Head and Neck cancer-specific module (QLQ-H&N35), and the EuroQoL (EQ-5D) health status questionnaire. The incidence and severity of AEs were evaluated according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 3·0. Tumour biomarker assessment of p16 status, PTEN and HER3 expression was conducted on archival tumour tissue samples from all patients who voluntarily provided separate consent (see online appendix).

Outcomes

The primary endpoint was disease-free survival (DFS), defined as the number of days from the date of randomisation to the date of tumour recurrence/second primary tumour or death from any cause. The definition of recurrence or second primary tumour was the appearance of any new lesion without any evident benign aetiology, as determined by investigator and independent central assessment of images of the head, neck and chest.

Tumour recurrence was further classified into local, regional or distant subtypes. The primary analysis of DFS was based on investigator assessment. Prespecified subgroup analyses of DFS included: nodal status (N0–N2a *vs* N2b-N3), baseline ECOG PS (0 *vs* 1), gender (male *vs* female), age (<65 *vs* ≥65 years), region (Asia *vs* Europe *vs* North/Latin America *vs* Other), induction chemotherapy (yes *vs* no), primary tumour site (oropharynx *vs* non-oropharynx), smoking history (<10 pack-years *vs* ≥10 pack-years), p16 status as a surrogate for HPV association (positive *vs* negative *vs* no result) and neck dissection before CCRT (yes *vs* no).

Secondary endpoints were DFS at 2 years, OS (defined as the time from the date of randomisation to death) and HRQoL. Additional endpoints included time to loco-regional failure, time to distant failure, occurrence of second primary tumour and safety. Analysis of HRQoL focussed on the pain and swallowing scale from QLQ-H&N35 and the global health status/QoL scale from QLQ-C30. For each of these scales, the following analyses were performed: the distribution of patients improved, stable or worsened; time to deterioration (defined as the time from randomisation to the first 10-point worsening on the 0–100 point scale) and mean difference in symptom scores over time.

Statistical analyses

The trial was powered to detect a prolonged median DFS with afatinib of 48 months compared to the assumed DFS of 34 months with placebo.[23] Randomisation of 669 patients was required to detect a difference in DFS (with a hazard ratio [HR] of 0·71) at a power of 80% with a one-sided type-I error of α=0·025.

Efficacy analyses included all randomised patients (intent-to-treat population). Safety analyses included all treated patients (those who received at least one dose of study drug). DFS was analysed using a stratified log-rank test, with stratification factors of nodal status (N0–N2a *vs* N2b–N3) and ECOG PS (0 *vs* 1). The Kaplan–Meier method was used to

estimate DFS for each treatment group, and HRs were derived using a stratified Cox proportional hazards model.

The difference in DFS at 2 years was calculated as the difference between the Kaplan–Maier estimates for each treatment. OS was analysed in the same manner as DFS. An independent data monitoring committee (DMC) was appointed to monitor study conduct. A futility analysis was planned for when approximately 40% of DFS events had occurred. SAS version 9·4 was used for all statistical analyses. This study is registered with ClinicalTrials.gov, number NCT01345669.

Role of the funding source

The trial was designed by the LUX-Head & Neck 2 steering committee in collaboration with Boehringer Ingelheim. Data were collected by the investigators and analysed by the Boehringer Ingelheim trial team. All authors, including those from Boehringer Ingelheim, were responsible for data interpretation and the development of the article and approved the final version. BB had full access to all data in the study and had final responsibility for the decision to submit for publication.

Results

Patients and treatment exposure

Between November 2, 2011 and July 4, 2016, 799 patients were screened and 617 patients were randomised (411 to afatinib and 206 to placebo; figure 1). All randomised patients received their assigned study treatment. A pre-planned futility analysis, performed by the DMC at approximately 40% of DFS events, showed the study was unlikely to demonstrate a significant advantage with afatinib. There were no major safety concerns, but more treatment-related AEs were observed with afatinib. Therefore, based on the recommendation of the independent DMC, the trial was halted on July 4, 2016. Patients were discontinued from treatment, and follow-up for disease recurrence and survival was stopped. At the time the trial was halted, 171 patients (27·7%) were receiving study treatment (111 patients [27·0%] in the afatinib group and 60 [29·1%] in the placebo group), while 211 (34·2%) had completed 18 months of treatment (124 [30·2%] in the afatinib group and 87 [42·2%] in the placebo group). Thus, a lower percentage of patients in the afatinib arm completed study treatment compared with the placebo group. Discontinuations due to other reasons are shown in figure 1. Overall, patient demographics and tumour characteristics at baseline were well balanced between the two treatment groups (table 1).

Median treatment duration was 300.0 days (IQR 92·0–559·0) with afatinib and 455·5 days (IQR 228·0–560·0) with placebo. The percentage of patients taking at least 80% of the planned study medication was numerically lower for the afatinib group (85·3%) than the placebo group (98·5%). Eighty (19·5%) afatinib-treated patients were escalated to 50 mg (32 subsequently reduced to 40 mg, six of these had a further reduction to 30 mg and one had a further reduction to 20 mg). Among those who did not escalate (331 patients), 188 patients had a dose reduction to 30 mg and 88 of these patients had a further dose reduction to 20 mg. In the placebo arm, 166 (80·6%) patients escalated to 50 mg (nine subsequently reduced to 40 mg and one had a further reduction to 30 mg). Among those in the placebo

arm who did not escalate (n=40 [19·4%]), two had a dose reduction to 30 mg and there were no further dose reductions.

Efficacy

Data cut-off for analysis of DFS was 25 October, 2016, after a median follow-up of 21·9 months (IQR 11·0–31·3). At the time of analysis, 109 (26·5%) of 411 patients in the afatinib group and 52 (25·2%) of 206 patients in the placebo group had experienced a DFS event. Median DFS by investigator review was 43·4 months (95% CI 37·4–not estimable) with afatinib versus not estimable (95% CI 40·1–not estimable) with placebo (HR 1·13, 95% CI 0·81–1·57; stratified log-rank test p=0·48; figure 2A). The effect of afatinib versus placebo on DFS was explored in pre-planned subgroup analyses, and the results were generally consistent with the primary analysis. There was no clear trend of benefit with either placebo or afatinib in any subgroup except patients with nodal status N0–N2a, where there was an apparent benefit with placebo (HR 2·23, 95% CI 1·18–4·22; figure 2B). Conversely, a non-significant benefit was apparent with afatinib in patients with nodal status N2b–N3 (HR 0·82, 95% CI 0·55–1·21). In the biomarker-based analyses, a non-significant trend in favour of afatinib was apparent in patients with centrally confirmed p16-negative status (HR 0·75, 95% CI 0·44–1·26) and also potentially among those with tumours expressing high levels of PTEN (‘PTEN-high’; HR 0·89, 95% CI 0·42–1·88; figure 3). There was no apparent difference between afatinib and placebo treatment based on tumour expression of HER3 levels (appendix figure 1).

The DFS rate at 2 years was evaluated using the Kaplan–Meier method; the probability of being disease-free at 2 years was 67·2% in the afatinib group and 73·5% in the placebo group (estimated difference: -6·3%, 95% CI -15·0–2·5; p=0·16). At the time of data cut-off for the futility analysis, OS data were immature; 62 (15·1%) of 411 patients in the afatinib group and 23 (11·2%) of 206 patients in the placebo group had died. Median OS was not estimable for either treatment group. The further endpoints, which included time to

loco-regional failure and time to distant failure (distant recurrence or distant second primary tumour), were also immature: loco-regional failure occurred in 52 (12·7%) of 411 patients receiving afatinib and 20 (9·7%) of 206 patients receiving placebo; distant failure was reported in 43 (10·5%) of patients in the afatinib group and 28 (13·6%) in the placebo group.

HRQoL

Among patients in the randomised population, 97·1% and 96·1% of afatinib- and placebo-treated patients completed QLQ-C30 questionnaires at baseline (97·1% and 95·1%, respectively, completed QLQ-HN35 questionnaires at baseline). Participation remained high during the treatment visits (around 90%), declining to 50–60% for the end of treatment visit (appendix table 1).

There was no significant difference in the proportions of patients with either improving or worsening global health status/QoL between the two groups (odds ratio [OR] for improved *vs* not improved [95% CI] 0·8 [0.58–1.16]; p=0·26) or for subscales of overall health or QoL rate. Similarly, there were no significant differences between afatinib and placebo in the proportions of patients with improving or worsening overall pain score (OR [95% CI] for improved *vs* not improved 1·4 [1.0–2.10]; p=0·052) or swallowing score (OR 1·4 [0.99–2.07]; p=0·056).

Time to deterioration was significantly shorter in the afatinib group than in the placebo group for global health status/QoL and pain (figure 4). There was no significant difference in time to deterioration in swallowing scale scores for afatinib versus placebo (figure 4). Changes in global health status (mean difference = -3·4; p=0·0005) and pain scores (mean difference =3·2, p=0·0028) over time significantly favoured placebo, while there was no significant difference in swallowing scores between treatment arms (mean difference = 1·3; p=0·22; appendix table 2).

Safety

Treatment-related AEs were reported in 396 (96·4%) of 411 patients in the afatinib group and 114 (55·3%) of 206 patients in the placebo group. The most common grade 3/4 treatment-related AEs with afatinib were rash/acne (61 [14.8%]), diarrhoea (32 [7.8%]) and stomatitis (55 [13.4%]) (table 2; appendix table 3).

AEs leading to dose reduction occurred in 217 (52·8%) patients receiving afatinib and 10 (4·9%) receiving placebo. The most frequent AEs leading to dose reduction were diarrhoea (afatinib 83 [20·2%], *vs* placebo one [0·5%]), rash/acne (72 [17·5%] *vs* one [0·5%]) and stomatitis (53 [12·9%] *vs* two [1·0%]). Sixty-nine (16·8%) afatinib-treated patients had an AE leading to permanent treatment discontinuation. The most common reasons for discontinuations with afatinib were diarrhoea (14 [3·4%]), stomatitis (14 [3·4%]) and rash/acne (nine [2·2%]). Fourteen (6·8%) patients in the placebo group had an AE leading to discontinuation (neoplasm recurrence in two patients [not considered related to treatment]; other AEs occurred in one patient each).

Serious AEs (SAEs) occurred in 80 (19·5%) patients in the afatinib group and 51 (24·8%) in the placebo group. SAEs that occurred in >1% of patients in either treatment group were laryngeal oedema (afatinib: eight [1·9%] patients *vs* placebo: eight [3·9%] patients), neoplasm recurrence (five [1·2%] *vs* three [1·5%]), dyspnoea (two [0·5%] *vs* three [1·5%]), pneumonia (one [0·2%] *vs* five [2·4%]) and osteonecrosis (0 *vs* three [1·5%]). Treatment-related SAEs occurred in 22 (5·4%) patients in the afatinib group and three (1·5%) patients in the placebo group. The most common treatment-related SAEs were anaemia, decreased appetite, interstitial lung disease (each affecting three patients [0·7%]) with afatinib and ischaemic stroke, pulmonary alveolar haemorrhage, respiratory tract infections (each affecting one patient [0·5%]) with placebo. During the treatment period, nine (2·2%) patients in the afatinib group and six (2·9%) patients in the placebo group had a fatal AE. One fatal AE in the afatinib group was considered treatment-related: the patient had

cachexia at baseline and weight loss was reported as an AE (day 61). The patient collapsed and died suddenly at home (day 69). No autopsy was performed; the relationship to study treatment was reported as probable as there was no evidence for another cause.

Discussion

LUX-Head & Neck 2 is, to our knowledge, the first and largest trial to assess broad ERBB family blockade versus placebo as adjuvant therapy after definitive CCRT in patients with primary unresected LA high-/intermediate-risk HNSCC. The trial was closed early following a pre-planned futility analysis which suggested the study was unlikely to demonstrate a significant efficacy advantage with afatinib. At trial cessation, a lower percentage of patients in the afatinib group (approximately 30%) had completed the planned treatment period than in the placebo group (approximately 42%); early termination of the study will have likely limited the number of patients who completed the planned 18-month treatment period. Median exposure to study treatment was markedly shorter in the afatinib group than in the placebo group (300 *vs* 456 days, respectively). Given a study population of patients who were free of disease and in complete remission at study entry, patients may have been less motivated to tolerate AEs associated with adjuvant treatment. Overall, the study showed that afatinib following definitive CCRT in intermediate- to high-risk unresected HNSCC did not improve DFS versus placebo, but nor did afatinib have a detrimental effect on survival in the overall population. Analyses of DFS by subgroups showed no statistically significant benefits with afatinib, although there was a non-significant trend towards slight benefit for afatinib among patients with nodal status N2b–3. Premature closure of the trial makes any interpretation of subgroup results difficult due to the high level of censoring. Additionally, afatinib did not confer any HRQoL benefit, in terms of global health status, pain or swallowing. Given that patients enrolled in the trial had undergone definitive CCRT, were disease-free at the start of the study, and that afatinib did not impact recurrence, the lack of HRQoL benefit with afatinib is not unexpected.

In oropharyngeal squamous cell carcinoma (OPSCC), evidence of HPV association correlates with improved prognosis in the curative and recurrent/metastatic settings.[24,25] p16 protein is a surrogate marker for HPV infection in OPSCC.[26] As such, DFS events would be

expected to occur less frequently in p16/HPV-positive patients. This study was enriched for high- and intermediate-risk patients (i.e. p16/HPV-negative patients) by excluding patients with a smoking history of ≤10 pack-years with an oropharyngeal primary tumour site. However, p16 status was unknown for approximately half of the patients (223 afatinib patients and 104 placebo patients, based on central assessments), as biomarker testing was not mandatory. Nevertheless, for patients with known negative p16 status (central testing), the DFS HR was 0·75 (95% CI 0·44–1·26). This is consistent with data from the phase 3 LUX-Head & Neck 1 trial, which compared afatinib with methotrexate in patients with recurrent or metastatic HNSCC.[18] Analysis of tumour biomarkers from LUX-Head & Neck 1 showed patients with p16-negative disease derived increased benefit from afatinib.[27] Patients with tumours which were EGFR amplified, HER3-low or PTEN-high also had increased benefit from afatinib in the LUX-Head & Neck 1 trial. In the current study (LUX-Head & Neck 2), we also found a suggestion that high PTEN expression may be associated with benefit for afatinib over placebo (albeit a relatively weak signal), while there was no apparent difference between treatments based on HER3 expression. It should be noted that analysis of subgroups in LUX-Head & Neck 2 are limited by the early closure of the trial.

Treatment of high- and intermediate-risk LA HNSCC remains challenging, but to date adjuvant and maintenance therapies have not demonstrated improvements in DFS or OS when used in unselected or clinically selected patients. While blockade of ERBB family members in HNSCC has strong scientific rationale and has demonstrated efficacy in platinum-refractory, recurrent or metastatic HNSCC, these results have not translated into the adjuvant setting. The addition of lapatinib, an EGFR/HER2 inhibitor, to post-operative chemoradiotherapy and as long-term maintenance did not improve outcome when compared with placebo in patients with surgically treated high-risk HNSCC.[23] Similarly, the addition of panitumumab, an EGFR antibody, to CCRT in patients with unresected locally advanced HNSCC did not confer any benefit versus CCRT alone.[28] While there are differences in the designs of these studies, this does suggest the role of ERBB inhibition in the adjuvant setting

may need to be reassessed. Differences between antibody- and tyrosine kinase inhibition-sensitive cancers may emerge from the biomarker characterisation of these cancers, and future studies in molecularly enriched populations may be warranted if the current observations are confirmed. For example, for afatinib, it would appear the p16-negative, PTEN highly-expressing patients with high nodal stage would be most appropriate for future trials of adjuvant afatinib. Immunotherapy agents, including nivolumab and pembrolizumab, have recently demonstrated efficacy in the recurrent and/or metastatic setting, following chemotherapy failure and are now approved in this indication.[29,30] Early phase trials assessing these agents in a locally advanced setting are underway, and results are awaited to see if they may be able to impact treatment outcomes (NCT02841748; NCT02764593).

In the present study, the safety profile of afatinib was in line with that reported previously.[18] Common treatment-related AEs included rash/acne, diarrhoea, stomatitis, and paronychia, which are related to the inhibition of EGFR by afatinib. No unexpected safety findings were observed during the median afatinib treatment period of 300 days. As might be expected in a placebo-controlled trial, the frequency of AEs was higher in patients receiving active treatment; however, in general, afatinib could be tolerated with appropriate dose adjustment and management of AEs.

In conclusion, afatinib did not improve DFS compared with placebo in patients with primary unresected, clinically high-/intermediate-risk HNSCC, and was associated with more treatment-related AEs. The utility of ERBB family inhibition as adjuvant therapy in HNSCC will require refinement of risk stratification, predictive biomarkers, and a larger therapeutic window for this strategy to be successful and improve survival.

Contributors

BB was involved in study design, patient enrolment and treatment, data collection, data analysis, data interpretation, and writing of the report. RH, JD, JMT, TY, LdSV, IR, JV, JB, MT, JG, MS, AP, IV, CSN, MC-C, NK, AH, PH, JMDC, NA, URN, DR, CE, KH, EEWC were involved in patient enrolment and treatment, data collection, and manuscript reviewing. CE, BW, NG and EE were involved in study design, data collection, data analysis, data interpretation, and manuscript reviewing. All authors approved the final manuscript for submission.

Declaration of interests

All authors must disclose any financial and personal relationships with other people or organisations that could inappropriately influence (bias) their work. Examples of financial conflicts include employment, consultancies, stock ownership, honoraria, paid expert testimony, patents or patent applications, and travel grants, all within 3 years of beginning the work submitted. If there are no conflicts of interest, authors should state that none exist.
[Section to be completed based on author forms]

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References

1. Ferlay J, Soerjomataram I, Dikshit R*, et al.* Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer* 2015; **136**: E359-386. DOI: 10.1002/ijc.29210.
2. Gillison ML, Koch WM, Capone RB*, et al.* Evidence for a causal association between human papillomavirus and a subset of head and neck cancers. *J Natl Cancer Inst* 2000; **92**: 709-720.
3. Seiwert TY, Salama JK and Vokes EE. The chemoradiation paradigm in head and neck cancer. *Nat Clin Pract Oncol* 2007; **4**: 156-171.
4. Kelly JR, Park HS, An Y*, et al.* Comparison of Survival Outcomes Among Human Papillomavirus-Negative cT1-2 N1-2b Patients With Oropharyngeal Squamous Cell Cancer Treated With Upfront Surgery vs Definitive Chemoradiation Therapy: An Observational Study. *JAMA Oncol* 2017; **3**: 1107-1111. DOI: 10.1001/jamaoncol.2016.5769.
5. Lango MN, Andrews GA, Ahmad S*, et al.* Postradiotherapy neck dissection for head and neck squamous cell carcinoma: pattern of pathologic residual carcinoma and prognosis. *Head Neck* 2009; **31**: 328-337. DOI: 10.1002/hed.20976.
6. Ang KK, Harris J, Wheeler R*, et al.* Human papillomavirus and survival of patients with oropharyngeal cancer. *N Engl J Med* 2010; **363**: 24-35.
7. Cohen EE, Karrison TG, Kocherginsky M*, et al.* Phase III randomized trial of induction chemotherapy in patients with N2 or N3 locally advanced head and neck cancer. *J Clin Oncol* 2014; **32**: 2735-2743. DOI: 10.1200/JCO.2013.54.6309.
8. Haddad R, O'Neill A, Rabinowits G*, et al.* Induction chemotherapy followed by concurrent chemoradiotherapy (sequential chemoradiotherapy) versus concurrent chemoradiotherapy alone in locally advanced head and neck cancer (PARADIGM): a randomised phase 3 trial. *Lancet Oncol* 2013; **14**: 257-264. DOI: 10.1016/S1470-2045(13)70011-1.
9. Ang KK, Berkey BA, Tu X*, et al.* Impact of epidermal growth factor receptor expression on survival and pattern of relapse in patients with advanced head and neck carcinoma. *Cancer Res* 2002; **62**: 7350-7356.
10. Bonner JA, Harari PM, Giralt J*, et al.* Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. *N Engl J Med* 2006; **354**: 567-578.
11. Burtness B, Goldwasser MA, Flood W*, et al.* Phase III randomized trial of cisplatin plus placebo compared with cisplatin plus cetuximab in metastatic/recurrent head and neck cancer: an Eastern Cooperative Oncology Group study. *J Clin Oncol* 2005; **23**: 8646-8654.
12. Vermorken JB, Mesia R, Rivera F*, et al.* Platinum-Based Chemotherapy plus Cetuximab in Head and Neck Cancer. *N Engl J Med* 2008; **359**: 1116-1127. DOI: 10.1056/NEJMoa0802656.
13. Stewart JS, Cohen EE, Licitra L*, et al.* Phase III study of gefitinib compared with intravenous methotrexate for recurrent squamous cell carcinoma of the head and neck [corrected]. *J Clin Oncol* 2009; **27**: 1864-1871. DOI: 10.1200/JCO.2008.17.0530.
14. Bauman JE, Austin MC, Schmidt R*, et al.* ERCC1 is a prognostic biomarker in locally advanced head and neck cancer: results from a randomised, phase II trial. *Br J Cancer* 2013; **109**: 2096-2105. DOI: 10.1038/bjc.2013.576.
15. Wang D, Qian G, Zhang H*, et al.* HER3 Targeting Sensitizes HNSCC to Cetuximab by Reducing HER3 Activity and HER2/HER3 Dimerization: Evidence from Cell Line and Patient-Derived Xenograft Models. *Clin Cancer Res* 2017; **23**: 677-686. DOI: 10.1158/1078-0432.CCR-16-0558.
16. Psyrri A, Yu Z, Weinberger PM*, et al.* Quantitative Determination of Nuclear and Cytoplasmic Epidermal Growth Factor Receptor Expression in Oropharyngeal Squamous Cell Cancer by Using Automated Quantitative Analysis. *Clin Cancer Res* 2005; **11**: 5856-5862. DOI: 10.1158/1078-0432.ccr-05-0420.
17. Li C, Iida M, Dunn EF*, et al.* Nuclear EGFR contributes to acquired resistance to cetuximab. *Oncogene* 2009; **28**: 3801-3813. DOI: 10.1038/onc.2009.234.

18. Machiels JP, Haddad RI, Fayette J*, et al.* Afatinib versus methotrexate as second-line treatment in patients with recurrent or metastatic squamous-cell carcinoma of the head and neck progressing on or after platinum-based therapy (LUX-Head & Neck 1): an open-label, randomised phase 3 trial. *Lancet Oncol* 2015; **16**: 583-594. DOI: 10.1016/S1470-2045(15)70124-5.
19. Argiris A, Heron DE, Smith RP*, et al.* Induction docetaxel, cisplatin, and cetuximab followed by concurrent radiotherapy, cisplatin, and cetuximab and maintenance cetuximab in patients with locally advanced head and neck cancer. *J Clin Oncol* 2010; **28**: 5294-5300. DOI: 10.1200/JCO.2010.30.6423.
20. Chen C, Kane M, Song J*, et al.* Phase I Trial of Gefitinib in Combination With Radiation or Chemoradiation for Patients With Locally Advanced Squamous Cell Head and Neck Cancer. *J Clin Oncol* 2007; **25**: 4880-4886. DOI: 10.1200/jco.2007.12.9650.
21. Cohen EEW, Haraf DJ, Kunnavakkam R*, et al.* Epidermal Growth Factor Receptor Inhibitor Gefitinib Added to Chemoradiotherapy in Locally Advanced Head and Neck Cancer. *J Clin Oncol* 2010; **28**: 3336-3343. DOI: 10.1200/jco.2009.27.0397.
22. Harrington K, Berrier A, Robinson M*, et al.* Randomised Phase II study of oral lapatinib combined with chemoradiotherapy in patients with advanced squamous cell carcinoma of the head and neck: rationale for future randomised trials in human papilloma virus-negative disease. *Eur J Cancer* 2013; **49**: 1609-1618. DOI: 10.1016/j.ejca.2012.11.023.
23. Harrington K, Temam S, Mehanna H*, et al.* Postoperative Adjuvant Lapatinib and Concurrent Chemoradiotherapy Followed by Maintenance Lapatinib Monotherapy in High-Risk Patients With Resected Squamous Cell Carcinoma of the Head and Neck: A Phase III, Randomized, Double-Blind, Placebo-Controlled Study. *J Clin Oncol* 2015; **33**: 4202-4209. DOI: 10.1200/JCO.2015.61.4370.
24. Deng Z, Hasegawa M, Aoki K*, et al.* A comprehensive evaluation of human papillomavirus positive status and p16INK4a overexpression as a prognostic biomarker in head and neck squamous cell carcinoma. *Int J Oncol* 2014; **45**: 67-76. DOI: 10.3892/ijo.2014.2440.
25. Vermorken JB, Psyrri A, Mesia R*, et al.* Impact of tumor HPV status on outcome in patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck receiving chemotherapy with or without cetuximab: retrospective analysis of the phase III EXTREME trial. *Ann Oncol* 2014; **25**: 801-807. DOI: 10.1093/annonc/mdt574.
26. Weinberger PM, Yu Z, Haffty BG*, et al.* Molecular classification identifies a subset of human papillomavirus-associated oropharyngeal cancers with favorable prognosis. *J Clin Oncol* 2006; **24**: 736-747. DOI: 10.1200/JCO.2004.00.3335.
27. Cohen EEW, Licitra LF, Burtness B*, et al.* Biomarkers predict enhanced clinical outcomes with afatinib versus methotrexate in patients with second-line recurrent and/or metastatic head and neck cancer. *Ann Oncol* 2017; **28**: 2526-2532. DOI: 10.1093/annonc/mdx344.
28. Mesia R, Henke M, Fortin A*, et al.* Chemoradiotherapy with or without panitumumab in patients with unresected, locally advanced squamous-cell carcinoma of the head and neck (CONCERT-1): a randomised, controlled, open-label phase 2 trial. *Lancet Oncol* 2015; **16**: 208-220. DOI: 10.1016/S1470-2045(14)71198-2.
29. Ferris RL, Blumenschein GJ, Fayette J*, et al.* Nivolumab for Recurrent Squamous-Cell Carcinoma of the Head and Neck. *N Engl J Med* 2016; **375**: 1856-1867. DOI: 10.1056/NEJMoa1602252.
30. Seiwert TY, Burtness B, Mehra R*, et al.* Safety and clinical activity of pembrolizumab for treatment of recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-012): an open-label, multicentre, phase 1b trial. *Lancet Oncol* 2016; **17**: 956-965. DOI: 10.1016/S1470-2045(16)30066-3.

Table 1: **Patient baseline demographics and tumour characteristics**

Characteristic	**Afatinib (n=411)**	**Placebo (n=206)**
Gender		
Male	350 (85·2)	178 (86·4)
Female	61 (14·8)	28 (13·6)
Age (years)		
Median (range)	58·0 (25·0–83·0)	57·0 (25·0–79·0)
ECOG performance status		
0	267 (65·0)	133 (64·6)
1	144 (35·0)	73 (35·4)
Region		
Asia	71 (17·3)	30 (14·6)
Europe	260 (63·2)	132 (64·1)
North/Latin America	75 (18·2)	41 (19·9)
Other	5 (1·2)	3 (1·5)
Smoking status		
Current smoker	114 (27·7)	45 (21·8)
Current non-smoker	297 (72·3)	161 (78·2)
Smoking pack-years†		
<10	42 (10·2)	18 (8·7)
≥10	368 (89·5)	188 (91·3)
Alcohol consumption		
Non-drinker	256 (62·3)	129 (62·6)
≤7 units/wk	75 (18·2)	37 (18·0)
>7 units/wk	74 (18·0)	39 (18·9)
Primary tumour site		
Oral cavity	35 (8·5)	21 (10·2)
Oropharynx	216 (52·6)	111 (53·9)
Hypopharynx	85 (20·7)	48 (23·3)
Larynx	73 (17·8)	25 (12·1)
More than one site	2 (0·5)	1 (0·5)
T stage for primary tumour		
T0	0 (0·0)	0 (0·0)
T1	26 (6·3)	11 (5·3)
T2	99 (24·1)	55 (26·7)
T3	159 (38·7)	67 (32·5)
T4	127 (30·9)	73 (35·4)
N stage for primary tumour		
N0–N2a	159 (38·7)	83 (40·3)
N2b–N3	252 (61·3)	123 (59·7)
Time since first diagnosis (months)	n=409	n=205
Median (range)	7·8 (3·4–16·1)	7·8 (4·3–80·9)
Clinical stage at diagnosis		
III	72 (17·5)	40 (19·4)
IVa	309 (75·2)	141 (68·4)
IVb	30 (7·3)	25 (12·1)
Differentiation grade		
Well differentiated	50 (12·2)	29 (14·1)
Moderately differentiated	153 (37·2)	74 (35·9)
Poorly differentiated	90 (21·9)	45 (21·8)
Undifferentiated	7 (1·7)	0 (0·0)
Not specified/not assessable	111 (27·0)	58 (28·2)
p16 status (central testing)		
Positive	53 (12·9)	41 (19·9)
Negative	135 (32·8)	61 (29·6)
No result available	223 (54·3)	104 (50·5)

Induction chemotherapy		
Yes	166 (40·4)	84 (40·8)
No	245 (59·6)	122 (59·2)
Chemotherapy type		
Cisplatin-based	311 (75·7)	157 (76·2)
Carboplatin-based	32 (7·8)	19 (9·2)
Both	68 (16·5)	29 (14·1)
Radiotherapy dose, Gy		
Median (range)	70·0 (39·6–74·2)	70·0 (45·0–76·0)
Neck dissection before CCRT		
Yes	10 (2·4)	3 (1·5)
No	401 (97·6)	203 (98·5)
R0 resection and/or neck dissection post-CCRT		
Yes	32 (7·8)	9 (4·4)
No	379 (92·2)	197 (95·6)
Time from CCRT end to randomisation (weeks)		
Median (range)	16·9 (3·9–27·3)	16·9 (4·8–26·0)

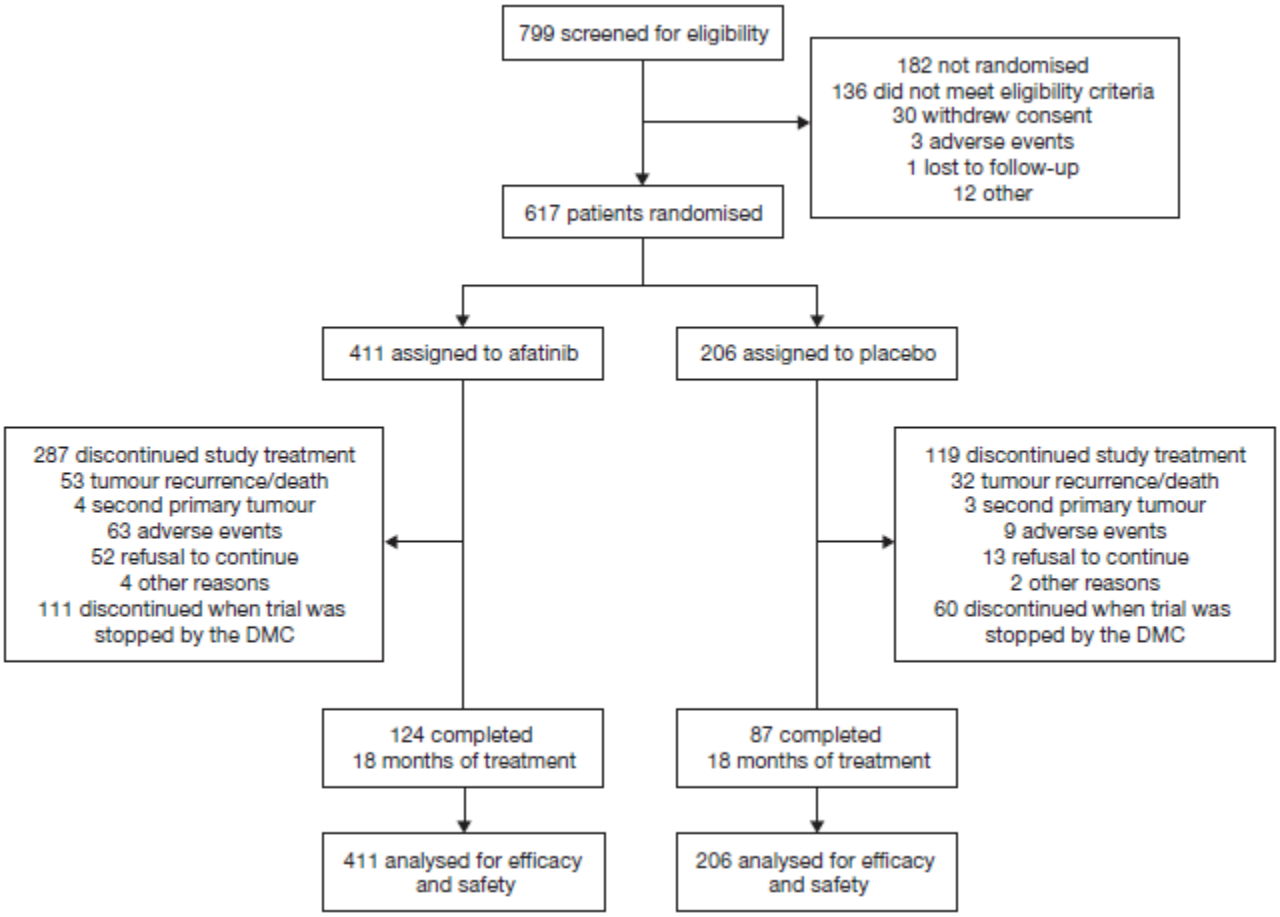
Data are n (%) or median (range)
[†]Smoking pack-years were summarised for ex- and current smokers who reported pack-years at the screening visit. The '<10 pack-years' group includes non-smokers.
CCRT, concurrent chemoradiation; ECOG, Eastern Cooperative Oncology Group; wk, week

***Table 2*: All-grade treatment-related AEs (≥5% incidence in either treatment group)**

Event — n (%)	Afatinib group (n=411)				Placebo group (n=206)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
Total with related AEs	234 (56·9)	154 (37·5)	7 (1·7)	1 (0·2)	105 (51·0)	9 (4·4)	0	0
Rash/acne†	267 (65·0)	60 (14·6)	1 (0·2)	0	43 (20·9)	1 (0·5)	0	0
Diarrhoea	291 (70·8)	32 (7·8)	0	0	26 (12·6)	1 (0·5)	0	0
Stomatitis†	150 (36·5)	55 (13·4)	0	0	22 (10·7)	1 (0·5)	0	0
Paronychia†	73 (17·8)	11 (2·7)	0	0	4 (1·9)	0	0	0
Fatigue†	75 (18·2)	2 (0·5)	0	0	16 (7·8)	1 (0·5)	0	0
Dry skin	65 (15·8)	1 (0·2)	0	0	10 (4·9)	0	0	0
Decreased appetite	48 (11·7)	5 (1·2)	1 (0·2)	0	8 (3·9)	0	0	0
Pruritus	47 (11·4)	4 (1·0)	0	0	9 (4·4)	0	0	0
Nausea	36 (8·8)	0 (0·0)	0	0	11 (5·3)	1 (0·5)	0	0
Epistaxis	34 (8·3)	0 (0·0)	0	0	1 (0·5)	0	0	0
Weight decreased	31 (7·5)	0 (0·0)	0	0	3 (1·5)	0	0	0
Palmar-plantar erythrodysaesthesia syndrome	28 (6·8)	2 (0·5)	0	0	0 (0·0)	0	0	0
Dry mouth	25 (6·1)	1 (0·2)	0	0	2 (1·0)	0	0	0
Vomiting	24 (5·8)	0 (0·0)	0	0	8 (3·9)	2 (1·0)	0	0
Dysgeusia	20 (4·9)	1 (0·2)	0	0	5 (2·4)	0	0	0
Dyspepsia	20 (4·9)	1 (0·2)	0	0	4 (1·9)	0	0	0

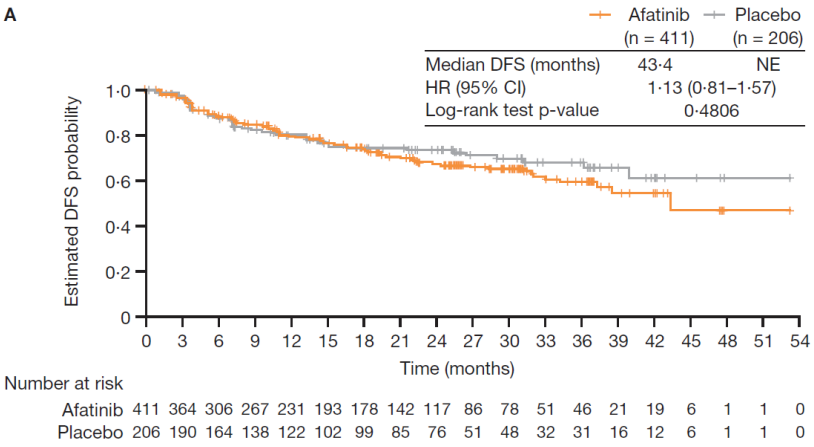
†Grouped term
AE, adverse event

***Figure 1*: CONSORT study design**

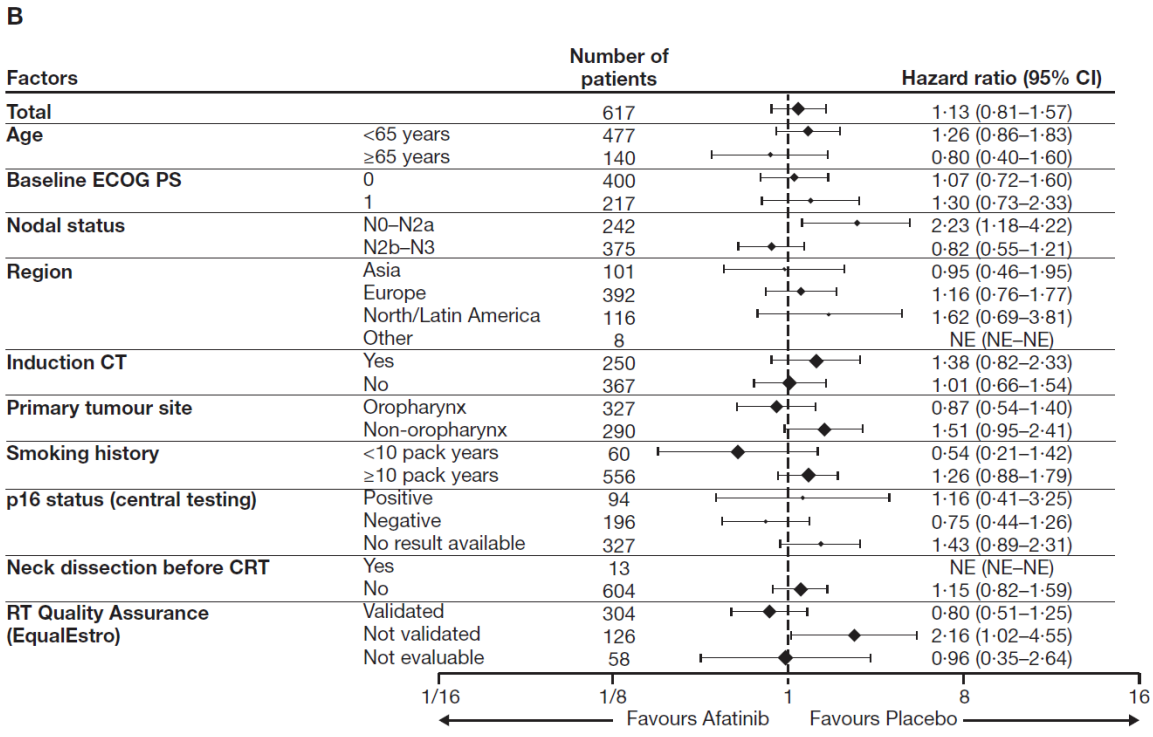


DMC, data monitoring committee

***Figure 2*: (A) Kaplan–Meier estimates of disease-free survival for all randomised patients. (B) Forest plot of disease-free survival according to predefined subgroups**

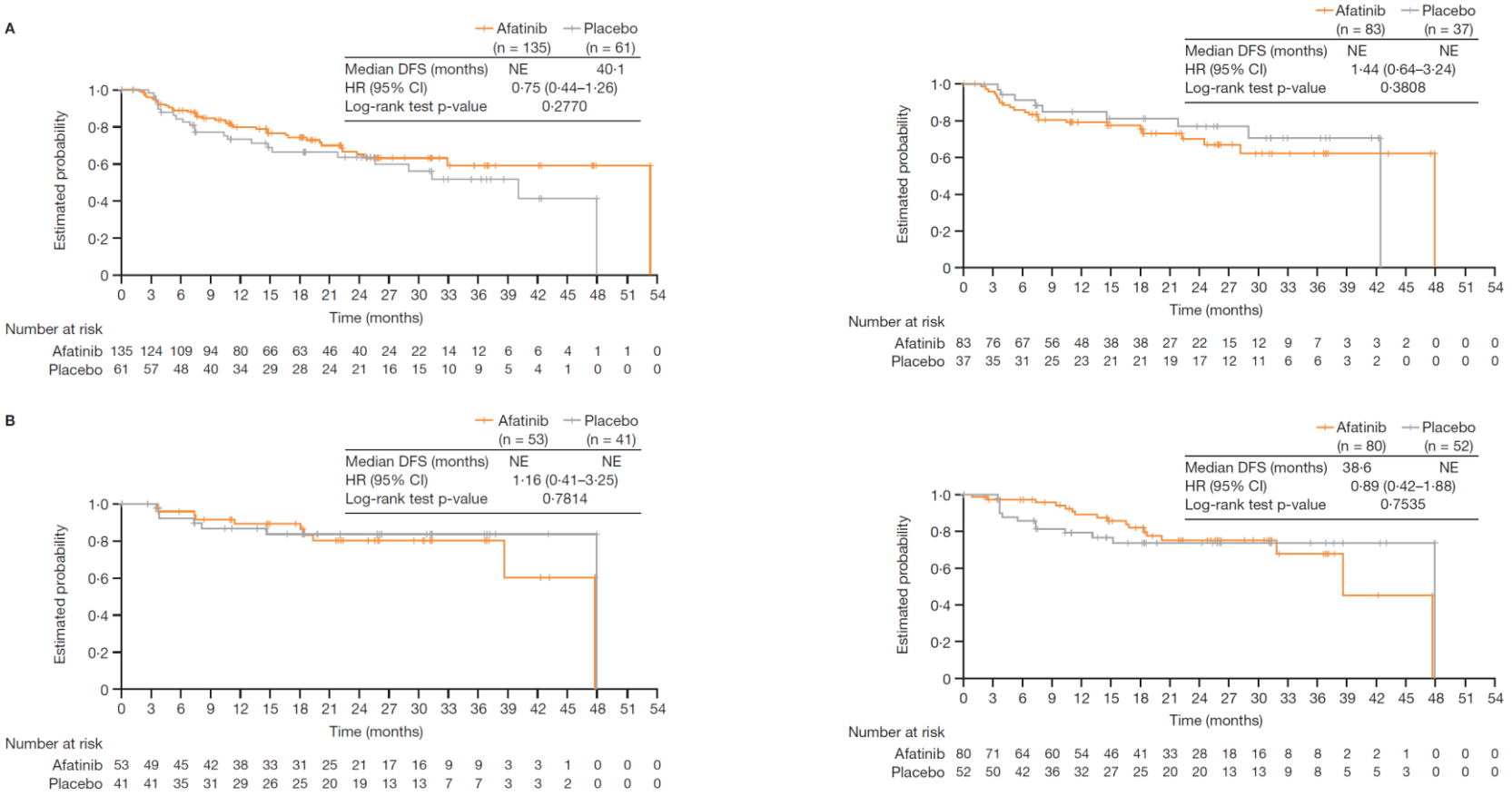


CI, confidence interval; DFS, disease-free survival; HR, hazard ratio; NE, not estimable



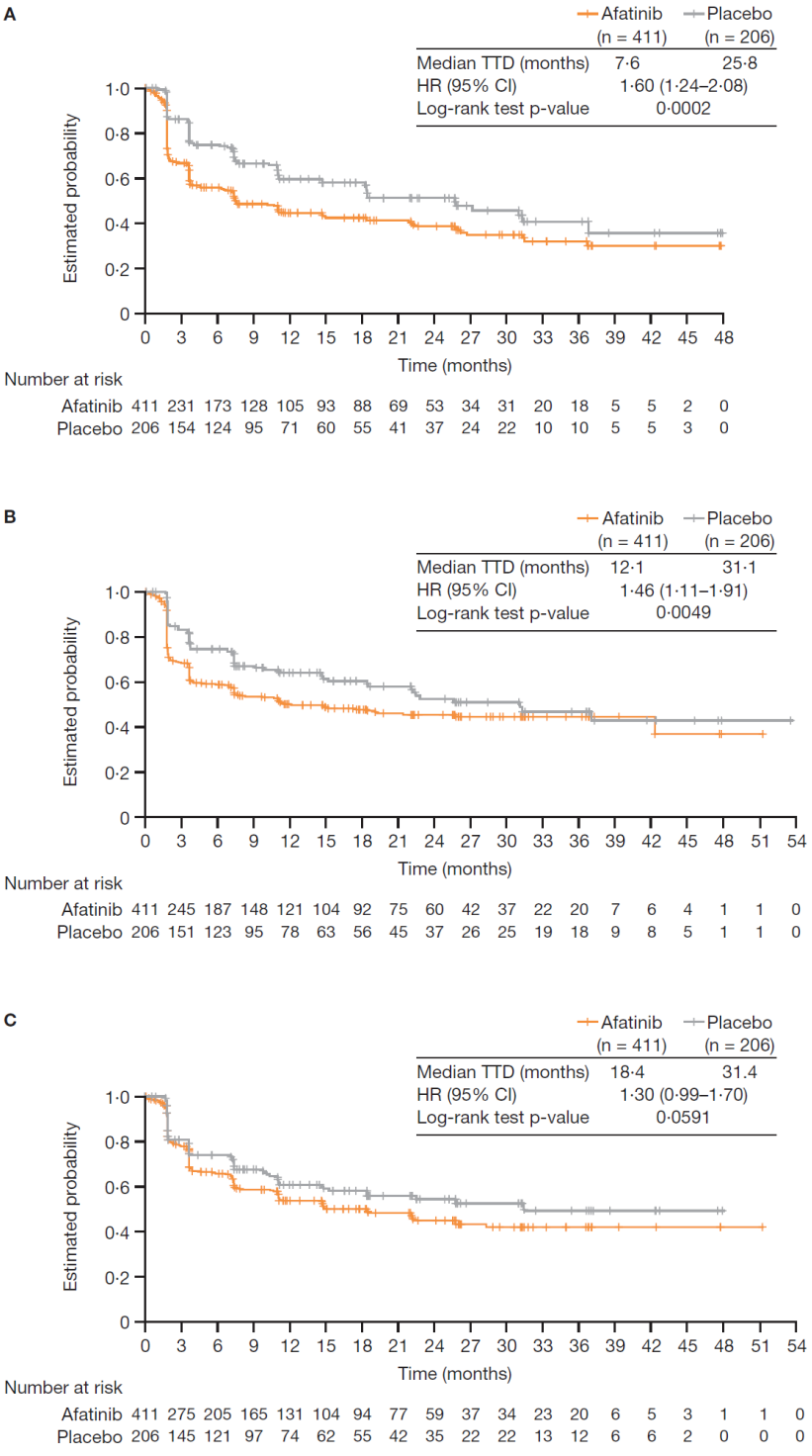
CI, confidence interval; CRT, chemoradiotherapy; CT, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group performance status; RT, radiotherapy

***Figure 3*: Kaplan–Meier estimates of disease-free survival according to p16 status ([A] p16-negative and [B] p16-positive) and PTEN status by central testing ([C] PTEN IHC ≤150 and [D] PTEN IHC >150)**



DFS, disease-free survival; HR, hazard ratio; IHC, immunohistochemistry; NE, not estimable

***Figure 4*: Kaplan–Meier estimates of time to deterioration in (A) EORTC global health status, (B) EORTC pain and (C) in EORTC swallowing**



CI, confidence interval; EORTC, European Organisation for Research and Treatment of Cancer; HR, hazard ratio; TTD, time to deterioration

WEB EXTRA MATERIAL

ANALYSIS OF p16 STATUS AND PTEN/HER3 EXPRESSION IN TUMOURS

p16 status was assessed on archival tumour tissues slides in a central and/or local laboratory. In the central laboratory, p16 status was determined based on immunohistochemistry (IHC) staining of formalin-fixed, paraffin-embedded archival tumour samples using the CINtec® p16 Histology assay (Ventana Medical Systems, Inc., Tucson, Arizona, USA). Most local laboratories also used IHC staining to determine p16 status, while some used standard polymerase chain reaction methodology.

IHC staining of individual tumour cells was evaluated using staining intensity categories from 0 (no staining) to 3 (strong staining). Nuclear and cytoplasmic staining were considered, as localisation of p16 is observed in the nucleus and/or cytoplasm of tumour cells. The percentages of tumour cells within the selected field of view demonstrating the different staining intensity categories were determined, and a histology score (H-score) was calculated based on the following formula:

H = (% no staining [%0] x 0) + (% weak staining [%1] x 1) + (% moderate staining [%2] x 2) + (% strong staining [%3] x 3)

p16-positivity was determined by an H-score of ≥210 (indicating that ≥70% of tumour cells in a sample showed strong p16 nuclear and/or cytoplasmic staining). This cut-off is routinely used in HNSCC clinical trials.[1-3]

PTEN and HER3 expression assessment was carried out in a central laboratory. PTEN status was determined by IHC staining of formalin-fixed, paraffin-embedded archival tumour samples using the antibody clone 138G6 (Cell Signaling Technology, Inc., Danvers, Massachusetts, USA). An H-score of >150 was used to define high PTEN expression, as described previously.[4] HER3 status was also determined by IHC staining of formalin-fixed, paraffin-embedded archival tumour samples using the antibody clone DAK-H3-IC (Dako,

Glostrup, Denmark). An H-score of ≤50 was used to define low HER3 expression, as described previously.[4]

***Table* S1: Questionnaire completion rates for QLQ-C30 and QLQ-HN3**

	Afatinib			Placebo		
Questionnaire collection timepoint	**Expected questionnaires**	**QLQ-C30 received questionnaires, N (%)**	**QLQ-HN35 received questionnaires, N (%)**	**Expected questionnaires**	**QLQ-C30 received questionnaires, N (%)**	**QLQ-HN35 received questionnaires, N (%)**
Randomisation	411	399 (97·1)	399 (97·1)	206	198 (96·1)	196 (95·1)
Visit 6	339	310 (91·4)	309 (91·2)	193	183 (94·8)	179 (92·7)
Visit 8	304	277 (91·1)	277 (91·1)	185	178 (96·2)	178 (96·2)
Visit 12	247	219 (88·7)	217 (87·9)	162	150 (92·6)	149 (92·0)
Visit 16	200	180 (90·0)	178 (89·0)	128	116 (90·6)	116 (90·6)
Visit 20	161	144 (89·4)	141 (87·6)	106	89 (84·0)	90 (84·9)
EOT visit	404	200 (49·5)	199 (49·3)	206	121 (58·7)	120 (58·3)
Second follow-up visit after EOT	266	149 (56·0)	150 (56·4)	130	78 (60·0)	78 (60·0)

***Table S2*: Change in global health status/QoL, pain and swallowing scores over time**

	Afatinib (N=411)	**Placebo (N=206)**
Change in global health status/QoL score over time		
Patients with global health score, N (%)	392 (95·4)	194 (94·2)
Baseline score, mean (SD)	72·4 (17·6)	71·9 (18·7)
Post-baseline score, adjusted mean (SE)	29·6 (2·2)	33·0 (2·3)
Afatinib *vs* placebo		
Adjusted mean (SE); 95% CI; p-value	-3·4 (0·98); -5·33, -1·49; 0·0005	
Change in pain score over time		
Patients with pain score, N (%)	397 (96·6)	195 (94·7)
Baseline score, mean (SD)	20·0 (20·5)	16·8 (19·5)
Post-baseline score, adjusted mean (SE)	13·1 (1·0)	9·9 (1·1)
Afatinib *vs* placebo		
Adjusted mean (SE); 95% CI; p-value	3·2 (1·1); 1·12, 5·36; 0·0028	
Change in swallowing score over time		
Patients with swallowing score, N (%)	397 (96·6)	196 (95·1)
Baseline score, mean (SD)	22·7 (23·6)	19·0 (21·7)
Post-baseline score, adjusted mean (SE)	10·1 (1·0)	8·8 (1·1)
Afatinib *vs* placebo		
Adjusted mean (SE); 95% CI; p-value	1·3 (1·1); -0·81, 3·45; 0·22	

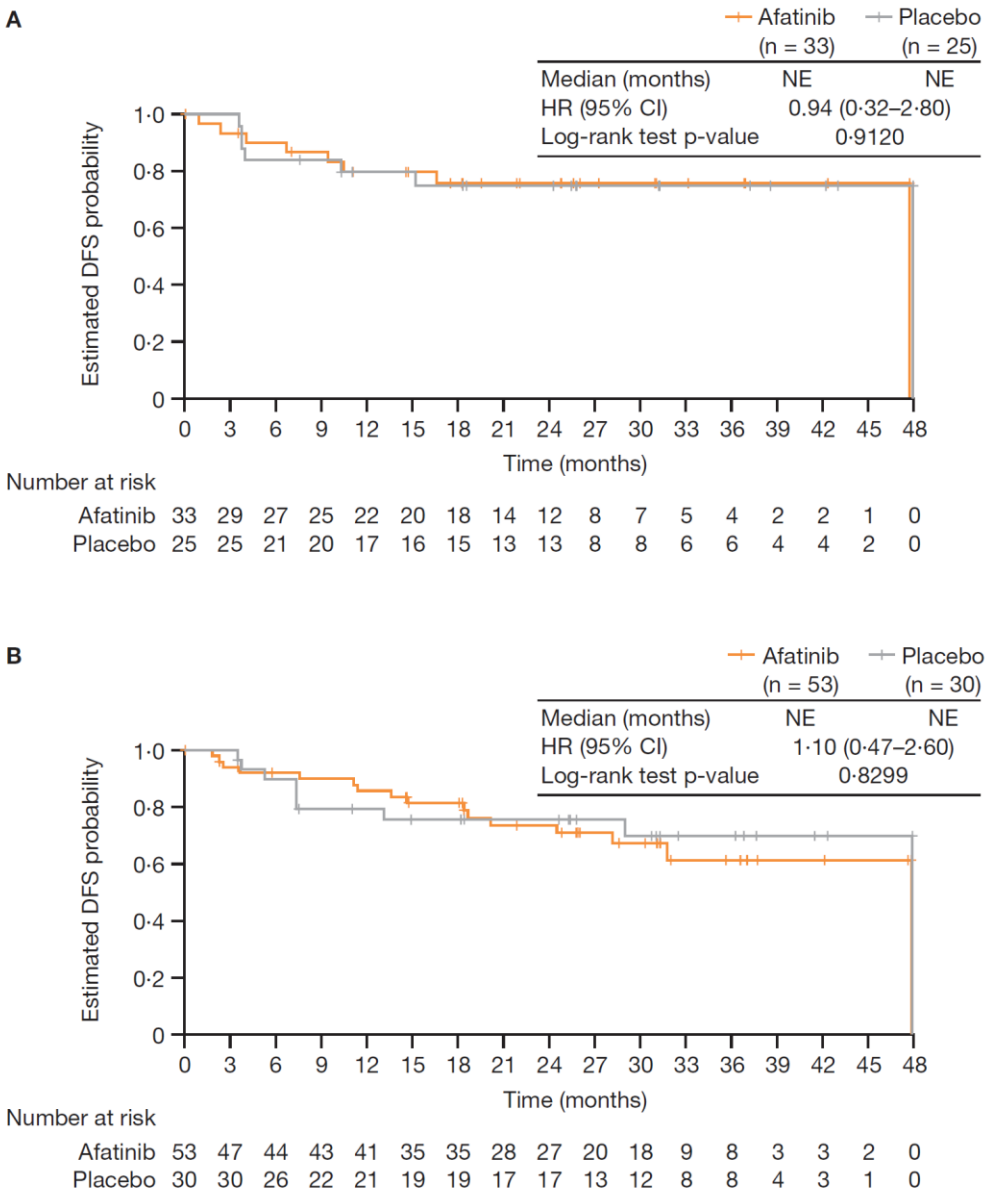
***Table S3*: All-grade treatment-related AEs (≥5% incidence in either treatment group)**

	Afatinib group (n=411)				Placebo group (n=206)			
Event — n (%)	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
Total with related AEs	234 (56·9)	154 (37·5)	7 (1·7)	1 (0·2)	105 (51·0)	9 (4·4)	0	0
Rash/acne†	267 (65·0)	60 (14·6)	1 (0·2)	0	43 (20·9)	1 (0·5)	0	0
Diarrhoea	291 (70·8)	32 (7·8)	0	0	26 (12·6)	1 (0·5)	0	0
Stomatitis†	150 (36·5)	55 (13·4)	0	0	22 (10·7)	1 (0·5)	0	0
Paronychia†	73 (17·8)	11 (2·7)	0	0	4 (1·9)	0	0	0
Fatigue†	75 (18·2)	2 (0·5)	0	0	16 (7·8)	1 (0·5)	0	0
Dry skin	65 (15·8)	1 (0·2)	0	0	10 (4·9)	0	0	0
Decreased appetite	48 (11·7)	5 (1·2)	1 (0·2)	0	8 (3·9)	0	0	0
Pruritus	47 (11·4)	4 (1·0)	0	0	9 (4·4)	0	0	0
Nausea	36 (8·8)	0	0	0	11 (5·3)	1 (0·5)	0	0
Epistaxis	34 (8·3)	0	0	0	1 (0·5)	0	0	0
Weight decreased	31 (7·5)	0	0	0	3 (1·5)	0	0	0
Palmar-plantar erythrodysaesthesia syndrome	28 (6·8)	2 (0·5)	0	0	0 (0·0)	0	0	0
Dry mouth	25 (6·1)	1 (0·2)	0	0	2 (1·0)	0	0	0
Vomiting	24 (5·8)	0	0	0	8 (3·9)	2 (1·0)	0	0
Dysgeusia	20 (4·9)	1 (0·2)	0	0	5 (2·4)	0	0	0
Dyspepsia	20 (4·9)	1 (0·2)	0	0	4 (1·9)	0	0	0
Cheilitis	18 (4·4)	1 (0·2)	0	0	0	0	0	0
Oral pain	13 (3·2)	1 (0·2)	0	0	3 (1·5)	0	0	0
Dysphagia	9 (2·2)	2 (0·5)	1 (0·2)	0	2 (1·0)	0	0	0
Blood creatinine phosphokinase increased	6 (1·5)	2 (0·5)	1 (0·2)	0	1 (0·5)	0	0	0
Oral candidiasis	8 (1·9)	1 (0·2)	0	0	1 (0·5)	0	0	0
Anaemia	7 (1·7)	0	1 (0·2)	0	1 (0·5)	0	0	0
Odynophagia	6 (1·5)	1 (0·2)	0	0	3 (1·5)	0	0	0
Gamma-glutamyl transferase increased	5 (1·2)	0	1 (0·2)	0	0	0	0	0

Glossitis	5 (1·2)	1 (0·2)	0	0	1 (0·5)	0	0	0
Left ventricular dysfunction	4 (1·0)	2 (0·5)	0	0	2 (1·0)	0	0	0
Nasal inflammation	5 (1·2)	1 (0·2)	0	0	0	0	0	0
Aspartate aminotransferase increased	4 (1·0)	1 (0·2)	0	0	1 (0·5)	0	0	0
Dehydration	4 (1·0)	1 (0·2)	0	0	0	0	0	0
Lymphopenia	4 (1·0)	1 (0·2)	0	0	2 (1·0)	0	0	0
Interstitial lung disease	4 (1·0)	2 (0·5)	1 (0·2)	0	0	0	0	0
Dyspnoea	2 (0·5)	1 (0·2)	0	0	1 (0·5)	0	0	0
Electrocardiogram QT prolonged	2 (0·5)	1 (0·2)	0	0	0	1 (0·5)	0	0
Hyponatremia	1 (0·2)	1 (0·2)	1 (0·2)	0	0	0	0	0
Leukopenia	2 (0·5)	1 (0·2)	0	0	0	0	0	0
Nail pitting	1 (0·2)	2 (0·5)	0	0	0	0	0	0
Blood bilirubin increased	1 (0·2)	0	1 (0·2)	0	0	0	0	0
Cellulitus	1 (0·2)	1 (0·2)	0	0	1 (0·5)	0	0	0
Oedema	1 (0·2)	1 (0·2)	0	0	0	0	0	0
Otitis media	1 (0·2)	1 (0·2)	0	0	0	0	0	0
Acute kidney injury	0	1 (0·2)	0	0	0	0	0	0
Chapped lips	0	1 (0·2)	0	0	0	0	0	0
Cranial nerve disorder	0	1 (0·2)	0	0	0	0	0	0
Death	0	0	0	1 (0·2)	0	0	0	0
Ear pain	0	1 (0·2)	0	0	0	0	0	0
Eyelid infection	0	1 (0·2)	0	0	0	0	0	0
Intestinal haemorrhage	0	1 (0·2)	0	0	0	0	0	0
Lipase increased	0	1 (0·2)	0	0	0	0	0	0
Neutropenic infection	0	1 (0·2)	0	0	0	0	0	0
Oropharyngeal candidiasis	0	1 (0·2)	0	0	0	0	0	0
Osteoradionecrosis	0	1 (0·2)	0	0	0	0	0	0
Pneumonia	0	1 (0·2)	0	0	1 (0·5)	0	0	0
Tooth loss	1 (0·2)	0	0	0	0	1 (0·5)	0	0
Trigeminal nerve disorder	0	1 (0·2)	0	0	0	0	0	0
Urticaria	0	1 (0·2)	0	0	1 (0·5)	0	0	0
Vulvovaginal mycotic infection	0	1 (0·2)	0	0	0	0	0	0
Dental caries	0	0	0	0	1 (0·5)	1 (0·5)	0	0

Ischaemic stroke	0	0	0	0	0	1 (0·5)	0	0
Polyneuropathy	0	0	0	0	0	1 (0·5)	0	0
Pulmonary alveolar haemorrhage	0	0	0	0	0	1 (0·5)	0	0
Vertigo	0	0	0	0	1 (0·5)	1 (0·5)	0	0

***Figure S1*: Kaplan–Meier estimates of disease-free survival according to HER3 status by central testing. (A) HER3 IHC ≤50 and (B) HER3 IHC >50**



DFS, disease-free survival; HR, hazard ratio; IHC, immunohistochemistry; NE, not estimable

References

1. Vermorken JB, Psyrri A, Mesia R*, et al.* Impact of tumor HPV status on outcome in patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck receiving chemotherapy with or without cetuximab: retrospective analysis of the phase III EXTREME trial. *Ann Oncol* 2014; **25**: 801-807.

2. Ang KK, Zhang Q, Rosenthal DI*, et al.* Randomized phase III trial of concurrent accelerated radiation plus cisplatin with or without cetuximab for stage III to IV head and neck carcinoma: RTOG 0522. *J Clin Oncol* 2014; **32**: 2940-2950. DOI: 10.1200/JCO.2013.53.5633.

3. Singhi AD and Westra WH. Comparison of human papillomavirus in situ hybridization and p16 immunohistochemistry in the detection of human papillomavirus-associated head and neck cancer based on a prospective clinical experience. *Cancer* 2010; **116**: 2166-2173. DOI: 10.1002/cncr.25033.

4. Cohen EEW, Licitra LF, Burtness B*, et al.* Biomarkers predict enhanced clinical outcomes with afatinib versus methotrexate in patients with second-line recurrent and/or metastatic head and neck cancer. *Annals of Oncology* 2017; **28**: 2526-2532. DOI: 10.1093/annonc/mdx344.