JAMA Oncology | Original Investigation

Afatinib vs Placebo as Adjuvant Therapy After Chemoradiotherapy in Squamous Cell Carcinoma of the Head and Neck
A Randomized Clinical Trial

Barbara Burtness, MD; Robert Haddad, MD; José Dinis, MD; José Trigo, MD; Tomoya Yokota, MD; Luciano de Souza Viana, MD; Ilya Romanov, MD; Jan Vermorken, MD; Jean Bourhis, MD; Makoto Tahara, MD; José Getulio Martins Segalla, MD; Amanda Psyrri, MD; Irina Vasilevskaya, MD; Chaitali Singh Nangia, MD; Manuel Chaves-Conde, MD; Naomi Kiyota, MD; Akihiro Homma, MD; Petra Holeckova, MD; Josep Maria Del Campo, MD; Nirav Asarawala, MD; Ulisses Ribaldo Nicolau, MD; Daniel Rauch, MD; Caroline Even, MD; Bushi Wang, PhD; Neil Gibson, PhD; Eva Ehrnrooth, MD; Kevin Harrington, PhD; Ezra E. W. Cohen, MD; for the LUX-Head & Neck 2 investigators

IMPORTANCE Locoregionally advanced head and neck squamous cell cancer (HNSCC) is treated curatively; however, risk of recurrence remains high among some patients. The ERBB family blocker afatinib has shown efficacy in recurrent or metastatic HNSCC.

OBJECTIVE To assess whether afatinib therapy after definitive chemoradiotherapy (CRT) improves disease-free survival (DFS) in patients with HNSCC.

DESIGN, SETTING, AND PARTICIPANTS This multicenter, phase 3, double-blind randomized clinical trial (LUX-Head & Neck 2) studied 617 patients from November 2, 2011, to July 4, 2016. Patients who had complete response after CRT, comprising radiotherapy with cisplatin or carboplatin, with or without resection of residual disease, for locoregionally advanced high- or intermediate-risk HNSCC of the oral cavity, hypopharynx, larynx, or oropharynx were included in the study. Data analysis was of the intention-to-treat population.

INTERVENTIONS Patients were randomized (2:1) to treatment with afatinib (40 mg/d) or placebo, stratified by nodal status (N0-2a or N2b-3) and Eastern Cooperative Oncology Group performance status (0 or 1). Treatment continued for 18 months or until disease recurrence, unacceptable adverse events, or patient withdrawal.

MAIN OUTCOMES AND MEASURES The primary end point was DFS, defined as time from the date of randomization to the date of tumor recurrence or secondary primary tumor or death from any cause. Secondary end points were DFS at 2 years, overall survival (defined as time from the date of randomization to death), and health-related quality of life.

RESULTS A total of 617 patients were studied (mean [SD] age, 58 [8.4] years; 528 male [85.6%]). Recruitment was stopped after a preplanned interim futility analysis on July 4, 2016, on recommendation from an independent data monitoring committee. Treatment was discontinued. Median DFS was 43.4 months (95% CI, 37.4 months to not estimable) in the afatinib group and not estimable (95% CI, 40.1 months to not estimable) in the placebo group (hazard ratio, 1.13; 95% CI, 0.81-1.57; stratified log-rank test $P = .48$). The most common grade 3 and 4 drug-related adverse effects were acneiform rash (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%] in the afatinib group vs 1 [0.5%] in the placebo group), and diarrhea (32 [7.8%] in the afatinib group vs 1 [0.5%] in the placebo group).

CONCLUSIONS AND RELEVANCE This study's findings indicate that treatment with afatinib after CRT did not improve DFS and was associated with more adverse events than placebo in patients with primary, unresected, clinically high- to intermediate-risk HNSCC. The use of adjuvant afatinib after CRT is not recommended.

TRIAL REGISTRATION ClinicalTrials.gov identifier: NCT01345669

JAMA Oncol. 2019;5(8):1170-1180. doi:10.1001/jamaoncol.2019.1146
Published online June 13, 2019.

Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: The LUX-Head & Neck 2 investigators are listed at the end of this article.

Corresponding Author: Barbara Burtness, MD, Department of Internal Medicine and Yale Cancer Center, Yale University School of Medicine, 333 Cedar St, New Haven, CT 06520 (barbara.burtness@yale.edu).

© 2019 American Medical Association. All rights reserved.

Downloaded From: https://jamanetwork.com/ by a Bashkir State Medical University User on 12/09/2020

Head and neck squamous cell carcinoma (HNSCC) is the sixth most common cancer worldwide.[1] Approximately 50% of patients present with locoregionally advanced disease,[2] and many patients receive definitive concurrent chemoradiotherapy (CRT) as primary therapy. Outcomes for patients treated with primary CRT are comparable to those for surgery, and many patients treated with surgery require combined-modality postoperative therapy.[3] Risk of recurrence remains high among some subsets of patients, even among those who attain a complete response with CRT or who have no evidence of disease after surgery to resect residual disease.[4] Strategies to reduce recurrence and death have largely focused on intensification of conventional treatment, with limited success for altered fractionation radiotherapy together with chemotherapy[5] or induction chemotherapy.[6,7]

The epidermal growth factor receptor (EGFR) has an important role in progression and treatment resistance in HNSCC[8]; targeting of EGFR with the monoclonal antibody cetuximab improves chemotherapy and radiotherapy responsiveness and improves survival in the locoregionally advanced and metastatic settings.[9-11] However, the small-molecule inhibitors of EGFR tyrosine kinase activity, gefitinib and erlotinib, have limited activity in HNSCC.[12,13] Other members of the ERBB receptor family may also be aberrantly expressed in HNSCC, may contribute to resistance to EGFR targeting, and may be targets themselves.[14] Afatinib, an irreversible ERBB family inhibitor, has demonstrated efficacy in recurrent or metastatic HNSCC after failure of platinum-based therapy.[15] Targeting of EGFR and other ERBB family members has been explored as maintenance or adjuvant therapy after definitive treatment.[16,17] Thus, this study examines whether the orally available, active, tolerable, irreversible ERBB family inhibitor afatinib could prevent or delay recurrence in patients with clinical features of intermediate- to high-risk disease.

Key Points

Question Does afatinib as adjuvant therapy after definitive chemoradiotherapy improve disease-free survival in head and neck cancer?

Findings This randomized clinical trial of 617 patients found that afatinib therapy after definitive chemoradiotherapy in patients with intermediate- to high-risk unresected head and neck cancer did not improve disease-free survival vs placebo. In addition, afatinib therapy did not confer any health-related quality-of-life benefit, and changes over time in global health status and pain scores favored placebo.

Meaning These study findings indicate that use of adjuvant afatinib therapy after concurrent chemoradiotherapy is not recommended in head and neck cancer.

Methods

Study Design and Participants

In this double-blind, placebo-controlled, phase 3 randomized clinical trial (LUX-Head & Neck 2), eligible patients had histologically or cytologically confirmed, locoregionally advanced HNSCC. Unfavorable risk was defined as a nonoropharyngeal primary site or oropharyngeal cancer in heavy smokers (>10 pack-years). Patients had unresected disease before CRT. Definitive CRT must have been completed no longer than 24 weeks before randomization. Previous treatment with EGFR-targeted agents was not permitted. Patients with primary tumor of the base of tongue and/or tonsil together with a smoking history of 10 pack-years or less were ineligible. Full eligibility criteria are listed in the eMethods in Supplement 1. The study protocol was designed in accordance with the Declaration of Helsinki,[18] the International Conference on Harmonization Guideline for Good Clinical Practice, and applicable region-specific regulatory requirements and was approved by independent ethics committees at each center. All patients provided written informed consent. An independent data monitoring committee (DMC) monitored study conduct. The trial protocol can be found in Supplement 2.

Randomization and Masking

Between November 2, 2011, and July 4, 2016, a total of 617 patients were randomized 2:1 to receive afatinib or placebo and stratified based on nodal status (N0-N2a vs N2b-N3) and Eastern Cooperative Oncology Group (ECOG) performance status (0 vs 1). The randomization list was generated using a validated pseudorandom number generator (block size, 3). Patient assignment to a treatment group was by an interactive voice or web-based response system. Patients, investigators, and the sponsor trial team were blinded to the randomized treatment until database lock.

Procedures

Patients received oral afatinib, 40 mg once daily; the dose was escalated to 50 mg after 4 weeks or more with no treatment-related adverse events (AEs) other than grade 1 rash. In the event of grade 3 or higher treatment-related AEs, grade 2 or higher diarrhea, nausea and/or vomiting, or grade 1 or higher reduced renal function, treatment was interrupted until severity reduced to grade 1 or lower. Tolerability-guided dose reduction was then permitted in 10-mg decrements to a minimum of 20 mg. Patients who required further reductions were removed from therapy. Treatment continued for 18 months or until disease recurrence or secondary primary tumor, unacceptable AEs, or patient withdrawal.

Images of the head, neck, and chest were assessed by the investigator and independent central review, a central team independent of the trial investigators. Disease status was assessed using computed tomography, magnetic resonance imaging, or positron emission tomography–computed tomography every 16 weeks for 2 years and every 24 weeks thereafter until disease recurrence, unavailability or loss to follow-up, or trial completion. Radiotherapy data were independently reviewed through a central quality assurance unit (EQUAL-ESTRO). Health-related quality of life (HRQoL) was assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (QLQ-C30) and its associated head and neck cancer–specific module (QLQ-HN35).[19] Incidence and severity of AEs were evaluated according to the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 3.0.[20] Prespecified tumor biomarker assessment of p16 status, PTEN, and ERBB2 expression was conducted on archival tumor tissue samples from patients who provided separate consent (see eMaterial and eMethods in the Supplement).

© 2019 American Medical Association. All rights reserved.

Downloaded From: https://jamanetwork.com/ by a Bashkir State Medical University User on 12/09/2020

Outcomes

The primary end point was investigator-assessed disease-free survival (DFS), defined as time from the date of randomization to the date of tumor recurrence or secondary primary tumor or death from any cause. Secondary end points were DFS at 2 years, overall survival (OS) (time from the date of randomization to death), and HRQoL.

Statistical Analysis

The trial was powered to detect a prolonged median DFS with afatinib of 48 months compared with the assumed DFS of 34 months with placebo. This assumption was based on data from a trial investigating lapatinib vs placebo during CRT and for up to 12 months as maintenance (MAINTYNANCE),[21] which suggested median DFS with placebo was likely to be approximately 34 months. Assuming exponential distribution for the time to tumor recurrence or secondary primary tumor (or death), our trial was powered to detect a prolonged median DFS of 14 months with afatinib. Randomization of 669 patients was therefore required to detect a difference in DFS (with a hazard ratio [HR] of 0.71) at a power of 80% with a 1-sided type I error of $\alpha = .025$. $P < .05$ was considered to be statistically significant.

Efficacy analyses included all randomized patients (intention-to-treat population). Safety analyses included all treated patients (received at least 1 dose of study drug). Disease-free survival was analyzed using a stratified log-rank test (2-sided, .05 significance level), with stratification factors of nodal status (N0-N2a vs N2b-N3) and ECOG performance status (0 vs 1). The Kaplan-Meier method was used to estimate DFS for each treatment group; HRs were derived using a stratified Cox proportional hazards regression model. The SAS statistical software, version 9.4 (SAS Institute Inc) was used for all statistical analyses.

Results

Patients and Treatment Exposure

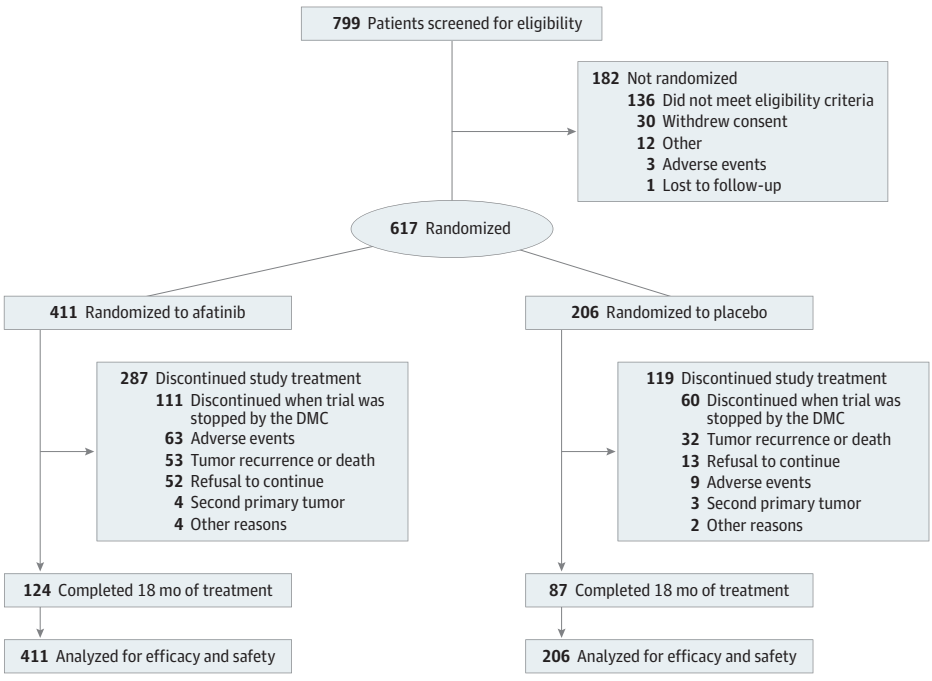
A total of 617 patients were studied (mean [SD] age, 58 [8.4] years; 528 male [85.6%]) (**Figure 1**). A preplanned futility analysis, performed by the DMC at approximately 40% of DFS events, revealed that the study was unlikely to demonstrate a significant advantage with afatinib. There were no major safety concerns, but more treatment-related AEs were observed with afatinib therapy. Therefore, based on the independent DMC recommendation, 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 of trial cessation, 171 patients (27.7%) were receiving study treatment (111 [27.0%] in the afatinib group and 60 [29.1%] in the placebo group); 211 (34.2%) had completed 18 months of treatment (124 [30.2%] in the afatinib group and 87 [42.2%] in the placebo group). Overall, patient demographics and tumor characteristics at baseline were well balanced between groups (**Table 1**).

Median treatment duration was 300.0 days (interquartile range [IQR], 92.0-559.0 days) with afatinib and 455.5 days (IQR, 228.0-560.0 days) with placebo; 85.3% of patients in the afatinib group and 98.5% of patients in the placebo group had taken at least 80% of the planned doses of study medication.

Efficacy

Data cutoff for analysis of DFS was October 25, 2016, after a median follow-up of 21.9 months (IQR, 11.0-31.3 months); 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 was 43.4 months (95% CI, 37.4 months to not es-

Figure 1. CONSORT Study Design



DMC indicates data monitoring committee.

© 2019 American Medical Association. All rights reserved.

Downloaded From: https://jamanetwork.com/ by a Bashkir State Medical University User on 12/09/2020

Table 1. Patient Baseline Demographics and Tumor Characteristics[a]

Characteristic	Afatinib (n = 411)	Placebo (n = 206)
Sex		
Male	350 (85.2)	178 (86.4)
Female	61 (14.8)	28 (13.6)
Age, median (range), y	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 or 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 nonsmoker	297 (72.3)	161 (78.2)
Smoking pack-years[b]		
<10	42 (10.2)	18 (8.7)
≥10	368 (89.5)	188 (91.3)
Alcohol consumption		
Nondrinker	256 (62.3)	129 (62.6)
≤7 Units per week	75 (18.2)	37 (18.0)
>7 Units per week	74 (18.0)	39 (18.9)
Primary tumor 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)
>1 Site	2 (0.5)	1 (0.5)
T stage for primary tumor		
T0	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 tumor		
N0 to N2a	159 (38.7)	83 (40.3)
N2b to N3	252 (61.3)	123 (59.7)
Time since first diagnosis, median (range), mo[c]	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)

(continued)

Table 1. Patient Baseline Demographics and Tumor Characteristics (continued)[a]

Characteristic	Afatinib (n = 411)	Placebo (n = 206)
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
Not specified or 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, median (range), Gy,	70.0 (39.6-74.2)	70.0 (45.0-76.0)
Neck dissection before CRT		
Yes	10 (2.4)	3 (1.5)
No	401 (97.6)	203 (98.5)
R0 resection and/or neck dissection after CRT		
Yes	32 (7.8)	9 (4.4)
No	379 (92.2)	197 (95.6)
Time from CRT end to randomization, median (range), wk	16.9 (3.9-27.3)	16.9 (4.8-26.0)

Abbreviations: CRT, concurrent chemoradiation; ECOG, Eastern Cooperative Oncology Group;

[a] Data are presented as number (percentage) of patients unless otherwise indicated.

[b] Smoking pack-years were summarized for ex- and current smokers who reported pack-years at the screening visit. The less than 10 pack-years group includes nonsmokers.

[c] Sample sizes are 409 for the afatinib group and 205 for the placebo group.

timable) with afatinib therapy and could not be estimated (95% CI, 40.1 months to not estimable) with placebo (HR, 1.13; 95% CI, 0.81-1.57; stratified log-rank test $P = .48$) (**Figure 2**A). Preplanned subgroup analyses of median DFS (Figure 2B) suggested that afatinib resulted in a worse DFS in patients with nodal status N0 to N2a (HR, 2.23; 95% CI, 1.18-4.22) and no benefit in patients with nodal status N2b to N3 (HR, 0.82; 95% CI, 0.55-1.21). In the biomarker-based analyses, the DFS HR for afatinib vs placebo was 0.75 (95% CI, 0.44-1.26) in patients with centrally confirmed p16-negative status and 0.89 (95% CI, 0.42-1.88) among those with tumors expressing high levels of PTEN (**Figure 3**). There was no difference between afatinib therapy and placebo based on ERBB3 expression levels (HR, 0.94; 95% CI, 0.32-2.80) (eFigure 1 in Supplement 1). Time from CRT to randomization was balanced between arms (Table 1) and did not affect DFS (HR, 0.94 [95% CI, 0.51-1.72] for patients with time from CRT to randomization ≤3 months and 1.24 [95% CI, 0.84-1.85] for those with time from CRT to randomization of >3 months; Cox proportional hazards regression model $P = .43$).

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 to 2.5; $P = .16$). At data cutoff, OS data were immature (only approximately 15% of the expected OS events had occurred); 62 patients (15.1%) had died in the afatinib group and 23 (11.2%) in the placebo group. Median OS could not be estimated for either group.

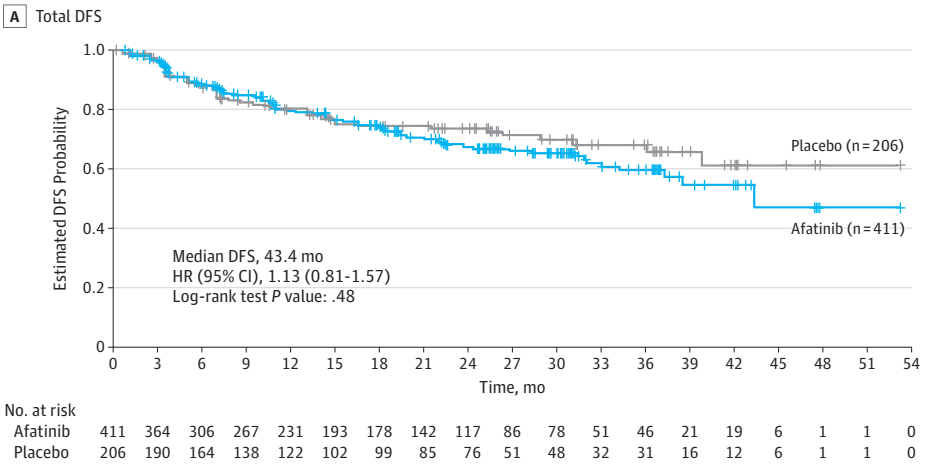
Health-Related Quality of Life

Among patients in the randomized population, QLQ-C30 and QLQ-HN35 questionnaire completion rates were high during the

© 2019 American Medical Association. All rights reserved.

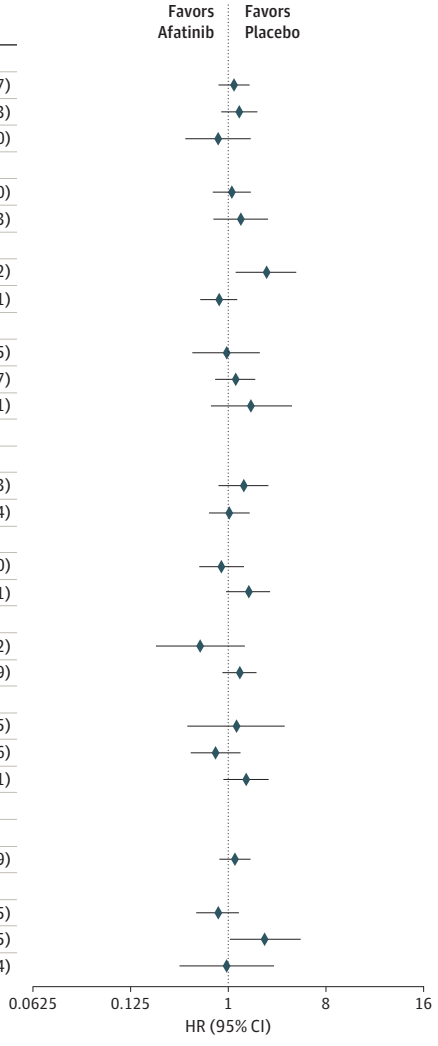
Downloaded From: https://jamanetwork.com/ by a Bashkir State Medical University User on 12/09/2020

Figure 2. Analysis of Disease-Free Survival (DFS)



B Subgroup DFS

Source	No. of Patients	Hazard Ratio (95% CI)
Total		
Age, y	617	1.13 (0.81-1.57)
<65	477	1.26 (0.86-1.83)
≥65	140	0.80 (0.40-1.60)
Baseline ECOG PS		
0	400	1.07 (0.72-1.60)
1	217	1.30 (0.73-2.33)
Nodal status		
N0-N2a	242	2.23 (1.18-4.22)
N2b-N3	375	0.82 (0.55-1.21)
Region		
Asia	101	0.95 (0.46-1.95)
Europe	392	1.16 (0.76-1.77)
North or Latin America	116	1.62 (0.69-3.81)
Other	8	NE (NE-NE)
Induction CT		
Yes	250	1.38 (0.82-2.33)
No	367	1.01 (0.66-1.54)
Primary tumor site		
Oropharynx	327	0.87 (0.54-1.40)
Nonoropharynx	290	1.51 (0.95-2.41)
Smoking history		
<10 Pack-years	60	0.54 (0.21-1.42)
≥10 Pack-years	556	1.26 (0.88-1.79)
p16 status (central testing)		
Positive	94	1.16 (0.41-3.25)
Negative	196	0.75 (0.44-1.26)
No result available	327	1.43 (0.89-2.31)
Neck dissection before CRT		
Yes	13	NE (NE-NE)
No	604	1.15 (0.82-1.59)
RT quality assurance (Equal-Estro)		
Validated	304	0.80 (0.51-1.25)
Not validated	126	2.16 (1.02-4.55)
Not evaluable	58	0.96 (0.35-2.64)

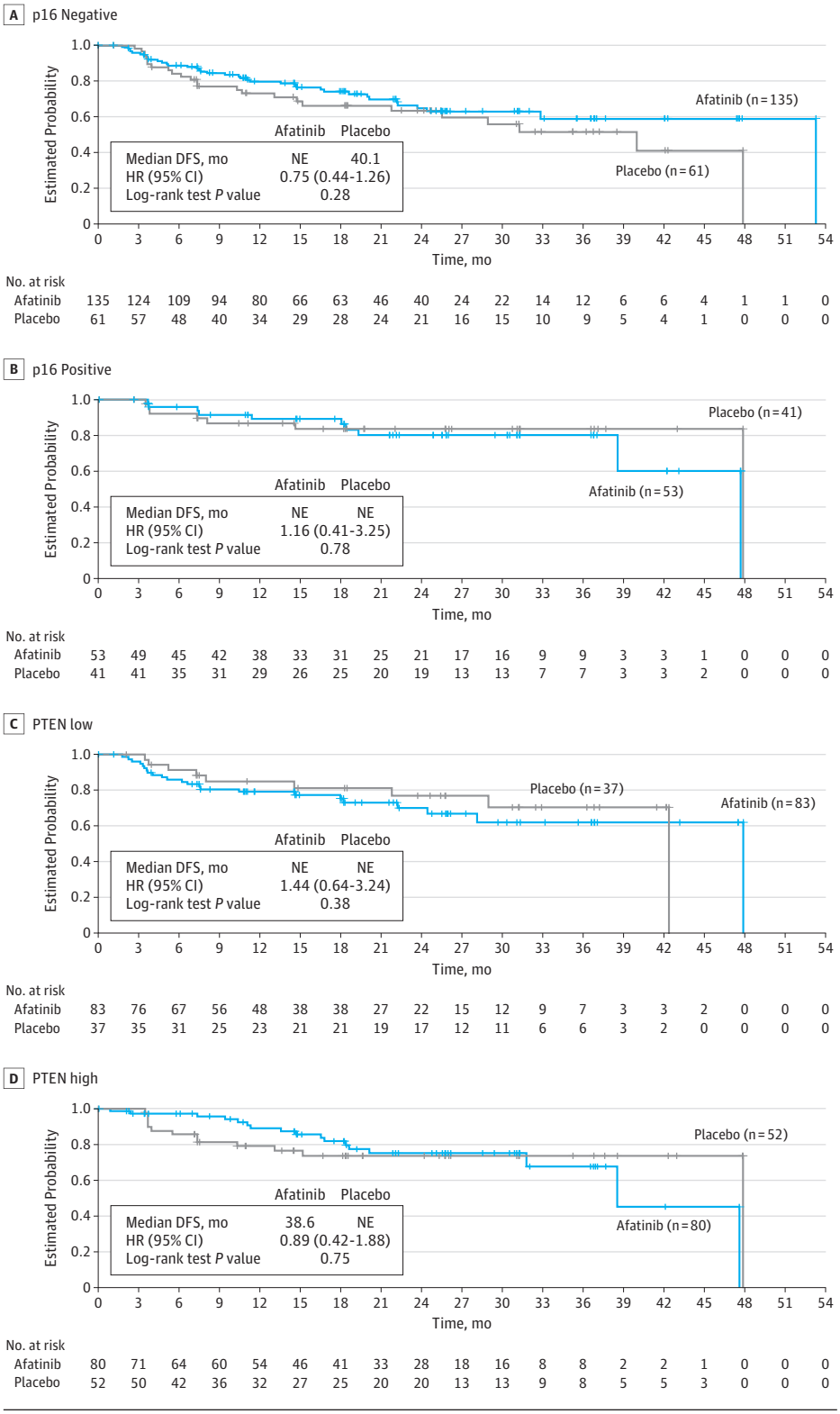


A, Kaplan-Meier estimates of DFS for all randomized patients. B, Forest plot of DFS according to predefined subgroups. CRT indicates chemoradiotherapy; CT, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; NE, not estimable; and RT, radiotherapy.

© 2019 American Medical Association. All rights reserved.

Downloaded From: https://jamanetwork.com/ by a Bashkir State Medical University User on 12/09/2020

Figure 3. Disease-Free Survival (DFS) According to p16 Status and PTEN Status by Central Testing



Kaplan-Meier estimates of DFS in patients with p16-negative tumors (A), patients with p16-positive tumors (B), patients with tumors expressing low levels of PTEN (immunohistochemistry [IHC] H score ≤150), and patients with tumors expressing high levels of PTEN (IHC H score >150). HR indicates hazard ratio; NE, not estimable.

treatment visits (approximately 90%), decreasing from 50% to 60% for the end of treatment visit (eTable 1 in Supplement 1).

No significant difference was found in the proportions of patients with improving or worsening global health status or QoL between the 2 groups (odds ratio [OR] for improved vs not improved, 0.8; 95% CI, 0.58-1.16; P = .26) or for subscales of overall health or QoL. Similarly, no significant differences were found in the proportions of patients with an improving or wors-

© 2019 American Medical Association. All rights reserved.

Downloaded From: https://jamanetwork.com/ by a Bashkir State Medical University User on 12/09/2020

ening overall pain score (OR for improved vs not improved, 1.4; 95% CI, 1.0-2.10; P = .052) or swallowing score (OR, 1.4; 95% CI, 0.99-2.07; P = .06).

Time to deterioration (time to a ≥10-point worsening in score from baseline[22]) was significantly shorter in the afatinib group than in the placebo group for global health status and QoL as well as pain (eFigure 2 in Supplement 1). No significant difference was found in time to deterioration in swallowing scores for afatinib vs placebo. Changes in global health status (mean [SE] difference = −3.4 [0.98]; P < .001) and pain scores (mean [SE] difference = 3.2 [1.08], P = .003) over time significantly favored placebo, whereas no significant difference was found in swallowing scores (mean [SE] difference = 1.3 [1.08]; P = .22) (eTable 2 in Supplement 1).

Safety

Treatment-related AEs were reported in 396 patients (96.4%) in the afatinib group and 114 patients (55.3%) in the placebo group. The most common grade 3 to 4 treatment-related AEs with afatinib were rash or acne (61 [14.8%]), diarrhea (32 [7.8%]), and stomatitis (55 [13.4%]) (**Table 2** and eTable 3 in Supplement 1).

Adverse events leading to dose reduction occurred in 217 patients (52.8%) receiving afatinib therapy and 10 (4.9%) receiving placebo; the most common AEs were diarrhea (83 [20.2%] in the afatinib group vs 1 [0.5%] in the placebo), rash or acne (72 [17.5%] in the afatinib group vs 1 [0.5%] in the placebo group), and stomatitis (53 [12.9%] in the afatinib group vs 2 [1.0%] in the placebo group). Sixty-nine afatinib-treated patients (16.8%) had an AE leading to permanent treatment discontinuation; the most common were diarrhea (14 [3.4%]), stomatitis (14 [3.4%]), and rash or acne (9 [2.2%]). Fourteen patients (6.8%) in the placebo group had an AE that led to treatment discontinuation (neoplasm recurrence in 2 patients [not considered treatment related]; other AEs occurred in 1 patient each).

Serious AEs occurred in 80 patients (19.5%) in the afatinib group and 51 patients (24.8%) in the placebo group; treatment-related serious AEs occurred in 22 patients (5.4%) in the afatinib group and 3 patients (1.5%) in the placebo group. The most common treatment-related serious AEs were anemia, decreased appetite, and interstitial lung disease (each affecting 3 patients [0.7%]) receiving afatinib therapy and ischemic stroke, pulmonary alveolar hemorrhage, and respiratory tract infections (each affecting 1 patient [0.5%]) receiving placebo. Nine patients (2.2%) in the afatinib group and 6 (2.9%) in the placebo group had a fatal AE. One in the afatinib group was considered treatment related: the patient had cachexia at baseline, and weight loss was reported as an AE.

Discussion

To our knowledge, LUX-Head & Neck 2 is the first trial to assess broad ERBB family blockade vs placebo as adjuvant therapy after definitive CRT in patients with primary unresected, locoregionally advanced high- to intermediate-risk HNSCC. The trial failed to demonstrate superiority in terms of DFS at a preplanned futility analysis and was closed prematurely. 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 will have likely limited the number of patients who completed the planned

Table 2. All-Grade Treatment-Related AEs (≥5% Incidence in Either Treatment Group)

	No. (%) of AEs							
	Afatinib Group (n = 411)				Placebo Group (n = 206)			
Event	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 or acne[a]	267 (65.0)	60 (14.6)	1 (0.2)	0	43 (20.9)	1 (0.5)	0	0
Diarrhea	291 (70.8)	32 (7.8)	0	0	26 (12.6)	1 (0.5)	0	0
Stomatitis[a]	150 (36.5)	55 (13.4)	0	0	22 (10.7)	1 (0.5)	0	0
Paronychia[a]	73 (17.8)	11 (2.7)	0	0	4 (1.9)	0	0	0
Fatigue[a]	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 erythrodysesthesia syndrome	28 (6.8)	2 (0.5)	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

Abbreviation: AE, adverse event.

[a] Grouped term.

© 2019 American Medical Association. All rights reserved.

Downloaded From: https://jamanetwork.com/ by a Bashkir State Medical University User on 12/09/2020

18-month treatment. Median exposure to study treatment was markedly shorter in the afatinib group than in the placebo group.

Overall, the study found that afatinib after definitive CRT in patients with intermediate- to high-risk unresected HNSCC did not improve DFS vs placebo. Subgroup analyses of DFS found no significant benefits with afatinib, although the premature trial closure limits any interpretation of these results because of the high level of censoring. Afatinib did not confer any HRQoL benefit, and changes over time in global health status and pain scores favored placebo. Given that patients had undergone definitive CRT, that patients were disease free at the start of the study, and that afatinib therapy did not affect recurrence, a negative effect on HRQoL with afatinib treatment is not unexpected.

In oropharyngeal squamous cell carcinoma, evidence of human papillomavirus (HPV) association correlates with improved prognosis in the curative and recurrent or metastatic settings.[23,24] p16 Protein is a surrogate marker for HPV infection in oropharyngeal squamous cell carcinoma.[25] As such, DFS events would be expected to occur less frequently in p16/HPV-positive patients. At the time of study design, no validated p16 assay was available; hence, the study was enriched for high- and intermediate-risk patients (ie, p16/HPV-negative patients) by excluding patients with a smoking history of 10 pack-years or less with an oropharyngeal primary tumor site. However, p16 status was unknown for approximately half of the patients because biomarker testing was not mandatory. Nevertheless, for patients with known p16-negative status, the DFS HR was 0.75 (95% CI, 0.44-1.26; $P = .28$). This finding is consistent with data from the phase 3 LUX-Head & Neck 1 trial, which compared treatment with afatinib vs methotrexate in patients with recurrent or metastatic HNSCC.[15] Analysis of tumor biomarkers from LUX-Head & Neck 1 found that patients with p16-negative disease derived increased benefit from afatinib.[26] Patients with tumors that were EGFR amplified, ERBB3 low, or PTEN high also had increased benefit from afatinib in LUX-Head & Neck 1. In the present study (LUX-Head & Neck 2), although the early trial termination limited interpretation of subgroup analyses, we also found a suggestion (albeit a relatively weak signal) that preserved PTEN expression may be associated with a benefit of afatinib over placebo; however, there was no apparent difference between treatments based on ERBB3 expression.

The DFS observed in the control group was prolonged relative to our estimates, which may have limited the ability of our study to show a benefit for the afatinib group. It is possible that HPV status could have influenced the median DFS if our study included a higher proportion of HPV-positive patients, for whom prognosis is usually more favorable. However, in the MAINTYNANCE study, 82% of patients in the placebo group were HPV positive (unknown status in only 5%),[21] whereas in our study, only 19.9% of patients were known to be HPV positive, with 50.5% of patients having unknown status. This finding suggests that the differences in expected vs observed DFS were unlikely to be a result of HPV status.

Treatment of high- and intermediate-risk, locoregionally advanced HNSCC remains challenging; however, to date, adjuvant and maintenance therapies have not demonstrated improvements in DFS or OS when used in unselected or clinically selected patients. Although blockade of ERBB family members in HNSCC has strong scientific rationale and demonstrated efficacy in platinum-refractory, recurrent or metastatic HNSCC, these results have not translated into the adjuvant setting. The addition of lapatinib therapy, an EGFR/ERBB2 inhibitor, to postoperative CRT and as long-term maintenance did not improve outcomes when compared with placebo in patients with surgically treated high-risk HNSCC.[21] Similarly, the addition of panitumumab therapy, an EGFR antibody, to CRT in patients with unresected, locoregionally advanced HNSCC did not confer any benefit vs CRT alone.[27] Although there are differences in study designs, the consistency of results suggests 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 characterization of these cancers, and future studies in molecularly enriched populations may be warranted. For example, for afatinib, the p16-negative, PTEN-expressing patients with high nodal stage may be most appropriate for future trials of adjuvant afatinib. Preclinical studies have recently identified potential approaches to enhance ERBB3 blockade in HNSCC, for example, via agents that lock ERBB3 in the inactive conformation,[28] via dual targeting of ERBB3 and Trop2,[29] or via targeting of cetuximab and bromodomain-containing protein 4.[30] However, more work is required to assess these approaches in the clinic.

In the present study, the afatinib safety profile was in line with previous reports.[15] No unexpected safety findings were observed during the median treatment period. 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 AE management.

Limitations

This study has a number of limitations, not least the premature termination, which limit the conclusions that can be drawn. In addition, at the time of study design, HPV biomarkers were still being debated; hence, HPV status was not included as a stratification factor in randomization. Patients may also have harbored additional phosphoinositide 3-kinases pathway mutations that affected EGFR inhibition and therefore outcome. Furthermore, patients were eligible for enrollment up to 24 weeks after completion of CRT, during which time many high-risk patients may have relapsed, possibly leading to a selection bias toward favorable-risk patients.

Conclusions

In this study, treatment with afatinib did not improve DFS compared with placebo in patients with primary unresected, clinically high- to intermediate-risk HNSCC and was associated with more treatment-related AEs and reduced QoL. Afatinib maintenance therapy in this setting is not recommended based on these results.

© 2019 American Medical Association. All rights reserved.

Downloaded From: https://jamanetwork.com/ by a Bashkir State Medical University User on 12/09/2020

ARTICLE INFORMATION

Accepted for Publication: February 19, 2019.

Published Online: June 13, 2019. doi:10.1001/jamaoncol.2019.1146

Author Affiliations: Department of Medicine and Yale Cancer Center, Yale University School of Medicine, New Haven, Connecticut (Burtness); Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, Massachusetts (Haddad); Instituto Português de Oncologia, Porto, Portugal (Dinis); Department of Medical Oncology, Hospital Virgen de la Victoria, IBIMA, Malaga, Spain (Trigo); Division of Gastrointestinal Oncology, Shizuoka Cancer Centre, Shizuoka, Japan (Yokota); Department of Medical Oncology, Hospital Marcio Cunha, Ipatinga, Brazil (de Souza Viana); Russian Oncological Research Centre, Moscow, Russia (Romanov); Department of Medical Oncology, Antwerp University Hospital, Edegem, Belgium (Vermorken); Department of Oncology, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland (Bourhis); Department of Head and Neck Medical Oncology, National Cancer Centre Hospital East, Kashiwa, Japan (Tahara); Department of Clinical Oncology, Hospital Amaral Carvalho, Jau, Brazil (Martins Segalla); Department of Internal Medicine, National Kapodistrian University of Athens, Attikon University Hospital, Athens, Greece (Psyrri); Oncology Centre of Moskovskiy, St Petersburg, Russia (Vasilevskaya); Comprehensive Cancer Centre, University of California at Irvine, Orange (Nangia); Department of Oncology, Hospital Virgen del Rocio, Sevilla, Spain (Chaves-Conde); Department of Medical Oncology and Hematology, Kobe University Hospital Cancer Center, Kobe, Japan (Kiyota); Faculty of Medicine and Graduate School of Medicine, Hokkaido University, Sapporo, Hokkaido, Japan (Homma); Department of Oncology and Radiotherapy, Hospital Na Bulovce and 1st Medical Faculty of Charles University, Prague, Czech Republic (Holeckova); Department of Oncology, Vall d'Hebron University Hospital, Barcelona, Spain (Del Campo); Shree Krishna Hospital and Medical Research Centre, Gujarat, India (Asarawala); Department of Clinical Oncology, AC Camargo Cancer Center, São Paulo, Brazil (Nicolau); Inselspital, University Hospital Bern, Bern, Switzerland (Rauch); Department of Head and Neck Cancer, Gustave Roussy, Villejuif, France (Even); Boehringer Ingelheim Pharmaceuticals Inc, Ridgefield, Connecticut (Wang); Boehringer Ingelheim Pharma GmbH & Co KG, Biberach, Germany (Gibson); Boehringer Ingelheim, Danmark A/S, Denmark (Ehrnrooth); Division of Radiotherapy and Imaging, The Royal Marsden Hospital/The Institute of Cancer Research, National Institute for Health Research Biomedical Research Centre, London, United Kingdom (Harrington); Department of Translational Science, Moores Cancer Centre, University of California at San Diego, La Jolla (Cohen).

Author Contributions: Drs Harrington and Cohen contributed equally to this work. Dr Burtness had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Burtness, Haddad, Yokota, Romanov, Vermorken, Bourhis, Kiyota, Wang, Ehrnrooth, Cohen.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Haddad, Yokota, Romanov, Bourhis, Tahara, Psyrri, Nangia, Kiyota, Harrington, Cohen.
Critical revision of the manuscript for important intellectual content: Burtness, Haddad, Dinis, Trigo, Yokota, de Souza Viana, Romanov, Vermorken, Bourhis, Martins Segalla, Vasilevskaya, Nangia, Chaves-Conde, Kiyota, Homma, Holeckova, Maria Del Campo, Asarawala, Nicolau, Rauch, Even, Wang, Gibson, Ehrnrooth, Harrington, Cohen.
Statistical analysis: Haddad, Yokota, Romanov, Bourhis, Wang.
Obtained funding: Yokota, Romanov, Bourhis, Holeckova.
Administrative, technical, or material support: Dinis, Bourhis, Psyrri, Nicolau, Harrington.
Supervision: Burtness, Trigo, Bourhis, Nangia, Kiyota, Holeckova, Rauch, Harrington, Cohen.

Conflict of Interest Disclosures: Dr Burtness reported receiving grants and personal fees from Boehringer Ingelheim, Bristol-Myers Squibb, and Merck and personal fees from Medimmune. Dr Haddad reported receiving grants and personal fees from Merck, Bristol-Myers Squibb, Pfizer, Genentech, and AstraZeneca; personal fees from Loxo and Celgene; and grants from Boehringer Ingelheim. Dr Yokota reported receiving grants from Boehringer Ingelheim; personal fees from Merck Serono, Bayer, and Eisai; grants from MSD, Novartis, Nanocarrier, and Pfizer; and grants and personal fees from AstraZeneca, Bristol-Myers Squibb, and ONO Pharmaceutical Co Ltd. Dr Vermorken reported a paid advisory role for Merck KGaA. Dr Tahara reported receiving grants from Boehringer Ingelheim; personal fees from MSD, Otsuka, and Bayer; grants and personal fees from Eisai, AstraZeneca, Pfizer, Ono Pharmaceuticals, and Bristol-Myers Squibb; and grants from Novartis and NanoCarrier. Dr Martins Segalla reported receiving honoraria from Roche and Amgen. Dr Nangia reported receiving personal fees from Merck and Novartis. Dr Kiyota reported receiving research funding from Nippon Boehringer Ingelheim Co Ltd, ONO Pharmaceutical Co Ltd, Bristol-Myers Squibb, AstraZeneca, and Pfizer. Dr Asarawala reported receiving research funding from Boehringer Ingelheim. Drs Wang, Gibson, and Ehrnrooth reported employment with Boehringer Ingelheim. Dr Harrington reported receiving travel support from Boehringer Ingelheim and grants, personal fees, and a paid advisory role from AstraZeneca, MSD, Merck Serono, BMS, and Pfizer. Dr Cohen reported a paid consultancy/advisory role with Merck, Pfizer, AstraZeneca, Bristol-Myers Squibb, and Human Longevity Inc. No other disclosures were reported.

Funding/Support: The study was funded by Boehringer Ingelheim.

Role of the Funder/Sponsor: The trial was designed by the LUX-Head & Neck 2 Steering Committee in collaboration with Boehringer Ingelheim. Data were collected by the investigators and analyzed by the Boehringer Ingelheim trial team. Together with the sponsor, Drs Burtness, Even, Wang, and Gibson were involved in study design. An independent data monitoring committee was responsible for study conduct and management. All authors, including those from the sponsor, were responsible for data interpretation, article development, and approval of the final version. The lead author had full access to all study data and had final responsibility for the decision to submit for publication.

Group Members: The LUX-Head & Neck 2 investigators include the following: *Argentina:* Raul Eduardo Giglio, MD, Instituto de Oncologia Angel H. Roffo, Universidad de Buenos Aires, Buenos Aires; Cesar Raul Blajman, MD, Isis Centro Especializado de Luce SA, Urquiza, Santa Fe; Jose Mario Freue, MD, Centro, de Estudio y Tratamiento de Efermedades Neoplásicas, Brandsen, Villa Dominico; Norma Graciela Pilnik, MD, Clínica Colombo, Duarte Quiros, Cordoba; and Felipe Salvador Palazzo, MD, Centro Oncologico CAIPO, San Miguel de Tucuman. *Austalia:* Margaret McGrath, MBBS, FRACP, Division of Cancer Service, Princess Alexandra Hospital, Wooloongabba. *Austria:* Thorsten Füreder, MD, and Gabriela Kornek, MD, Medizinische Universität Wien, AKH, Universitäts-Klinik für Innere Medizin I, Wien; Angelika Pichler, MD, Thomas Bauernhofer, MD, and Christoph Tinchon, MD, LKH Leoben-Eisenerz, Abteilung für Innere Medizin, Leoben; Richard Greil, MD, LKH Salzburg, Universitäts-Klinik für Innere Medicine III, Salzburg; Martin Burian, MD, Krankenhaus der Barmherzigen, Schwestern Linz, Abteilung Hals-Nasen-Ohren, Linz; and Heinz Kienzer, MD, SMZ Süd, Wien. *Belgium:* Pol Specenier, MD, UZA, Dienst Medische Oncologie, Edegem; Brieuc Sautois, MD, Centre Hospitalier Universitaire de Liège, Liège; Philip Debruyne, MD, Az Groeninge Campus, Kortrijk, Marie-Pascale Graas; MD, Cliniques St Joseph, Médecine Interne, Liège; Annelies Maes, MD, Jessa Ziekenhuis Hasselt, Hasselt; Christophe Lonchay, MD, Grand Hôpital de Charleroi–Centre Hospitalier Notre Dame, Service d'Oncologie, Charleroi, Belgium; Jean-François Daisne, MD, Cliniques et Maternité Sainte-Elisabeth Namur, Service Oncologie, Namur; Christel Fontaine, MD, UZ Brussel, Oncologie, Brussels. *Brazil:* Gilberto Castro Junior, MD, ICESP–Instituto do Cancer do Estado de Sao Paulo Octavio, Frias de Oliveira, Setor de Pesquisa Clinica, Sao Paulo; Rodrigo Perez Pereira, MD, Irmandade Santa Casa de Misericordia de Porto Alegre, Porto Alegre; Pedro Rafael Martins De Marchi, MD, Fundacao Pio XII–Hospital do Cancer de Barretos, Pesquisa Clinica, Barretos; Luciano de Souza Viana, MD, Fundacao Pio XII–Hospital do Cancer de Barretos, Pesquisa Clinica, Barretos; Jose Getulio Martins Segalla, MD, Hospital Amaral Carvalho, Jau; Ulisses Ribaldo Nicolau, MD, Hospital A. C. Camargo, Departamento de Oncologia, Sao Paulo; and Nicolas Silva Lazaretti, MD, Hospitalda Cidade de Passo Fundo, Centro de Pesquisa em Oncologia, Passo Fundo. *Canada:* Swati Kulkarni, MD, and Yasmin Alam, MD, Windsor Regional Cancer Program, Clinical Trials Department, Windsor, Ontario; Cheryl Ho, MD, BC Cancer Agency–Vancouver Centre, Clinical Trials Unit, Vancouver, British Columbia; George Shenouda, MD, Montreal General Hospital, McGill University Health Centre (MUHC), Cedars Cancer Centre, Montreal, Quebec; Denis Soulieres, MD, Hematologiste et oncologue medical CHUM–Hopital Notre-Dame, Montreal, Quebec; Khalil Sultanem, MD, Jewish General Hospital, MUHC, Montreal, Quebec; and Simron Singh, MD, Sunnybrook Health Sciences Centre, Odette Cancer Centre, Toronto, Ontario. *Chile:* Pablo Gonzalez Mella, MD, Instituto Oncologico

© 2019 American Medical Association. All rights reserved.

Downloaded From: https://jamanetwork.com/ by a Bashkir State Medical University User on 12/09/2020

Ltda, Vina del Mar; and Jose Antonio Solis Campos, MD, Hospital Clinico Vina del Mar, Vina del Mar. *Czech Republic:* Petra Holeckova, MD, Hospital Na Bulovce, Department of Radiation Oncology, Praha; Jana Prausova, MD, Teaching Hospital Motol, Oncology Clinic, Praha; and Radka Obermannova, MD, Masarykuv Memorial Cancer Institute, Comprehensive Oncologic Care Clinic, Brno. *Denmark:* Jeppe Friborg, MD, and Lena Specht, MD, Rigshospitalet, Onkologisk afd., Sektion 5073, Finsenscentret, København. *Egypt:* Amr Abdelaziz Elsaid, MD, Alexandria Clinical Research Center, New Alexandria University Hospital, Alexandria. *Finland:* Heikki Minn, MD, TYKS, Syöpätautien klinikka, Turku. *France:* Laurent Martin, MD, Centre de Radiothérapie Guillaume le Conquérant, Oncologie Option Radiothérapie, Le Havre; Frédéric Rolland, MD, Centre René Gauducheau, CLCC Nantes Atlantique, Service d'oncologie Médicale, Saint Herblain Cedex; Philippe Ceruse, MD, Centre Hospitalier Lyon Sud, Pierre-Bénite; Gilles Calais, MD, Hôpital Bretonneau CHRU de Tours, Tours; Caroline Even, MD, and Joë Guigay, MD, Institut Gustave Roussy, Service d'hospitalisation du département de Cancérologie Cervico Faciale, Villejuif Cedex; Charles Ferte, MD, Institut Gustave Roussy, Villejuif Cedex; Frédéric Peyrade, MD, Centre Antoine Lacassagne–CRLCC Nice–Côte d'Azur, Nice; Florence Duffaud, MD, AP-HM Hôpital de la Timone, Marseille; Elise Champeaux-Orange, MD, CHR Orléans La Source, Cellule Essais Cliniques, Orléans; Alexandre Coutte, MD, CHU Amiens Hôpital, Sud Bâtiment, Oncologie RDC, Salouel; Florian Clatot, MD, Centre Hospitalier Becquerel Rouen, Rouen; Pierre Fournel, MD, Institut de Cancérologie Lucien Neuwirth, Saint Priest en Jarez; and Laurence Bozec Le Moal, MD, Centre de Lutte contre le Cancer René Huguenin, Saint Cloud. *Germany:* Andreas Dietz, MD, Universitätsklinikum Leipzig, Leipzip; Viktor Grünwald, MD, Medizinische Hochschule Hannover, Hannover; Thomas Gauler, MD, Universitatsklinikum Essen, Essen; Orlando Guntinas-Lichius, MD, Universitätsklinikum Jena, HNO-Klinik, Jena; Guido Hildebrandt, MD, and Thomas Kuhnt, MD, Universitätsklinikum Rostock, Rostock; Horst-Jürgen Schmidt, MD, Westpfalz-Klinikum, HNO-Klinik, Kaiserslautern; Michael Henke, MD, Universitätsklinikum Freiburg, Freiburg; Anja Rückert, MD, Schwarzwald-Baar Klinikum, Villingen-Schwenningen; Wolfram Brugger, MD, Schwarzwald-Baar Klinikum, Klinik für Hämatologie, Onkologie, Infektiologie, und Immunologie, Villingen-Schwenningen; Nicole Rotter, MD, Universitätsklinik und Hochschulambulanz für HNO-Heilkunde, Ulm; and Rolf Mahlberg, MD, Klinikum Mutterhaus der Borromäerinnen gGmbH, Innere Medizin I, Trier. *Greece:* Vasilios Karavasilis, MD, and Georgios Fountzilas, MD, General Hospital of Thessaloniki "Papageorgiou," Aristoteleio University of Thessaloniki, Thessaloniki; and Diamanto Psyrri, MD, General Hospital of Athens "Attiko B," Chaidari. *Hungary:* Istvan Lang, MD, PhD, National Institute of Oncology "B" Internal Medicine, Budapest; Andras Boer, MD, National Institute of Oncology, Budapest; Judit Kocsis, MD, University of Debrecen, Debrecen; Gabor Pajkos, MD, PhD, Bacs-Kiskun County Hospital, Kecskemet; and Laszlo Tamas, MD, Semmelweis University, Budapest. *India:* A. L. Anand, MBBS, MD, Max Superspeciality Hospital, Max Cancer Centre, New Delhi; Ajay Sharma, MBBS, MD, and Sharma, MBBS, MD, Acharya Tulsi Regional Cancer Treatment & Research Institute, Sardar Patel Medical College & Associated Group of Hospitals, Bikaner, Rajasthan; Murali Voona, MBBS, MS, Mch, Mahatma Gandhi Cancer Research Institute, Vishakapatnam; Ananda Selvakumar Pandy, MBBS, MD, DNB, and Kirushna Kumar, MBBS, MD, Meenakshi Mission Hospital & Research centre, Madurai, Tamil Nadu; Raj Kumar Poovna Nathan, MBBS, DNB, MS, Mch, and Venkatesan Srinivasan, MBBS, MCCP, MDRT, FIPM, Kamakshi Memorial Hospital, Chennai, Tamil Nadu; Bhooshan Zade, MBBS, MD, DNB, and Minish Jain, MBBS, MD, Ruby Hall Clinic, Pune; B. J. Srinivasa MBBS, MD, DNB, and Radheshyam Naik, MBBS, MD, DNB, HCG Bangalore Institute of Oncology, c/o Triesta Sciences, Bangalore, Karnataka; B. K. Mohanty, MBBS, MD, Fortis Memorial Research Institute, Department of Radiation Oncology, Gurgaon, Punjab; and Nirav Asarawala, MBBS, MD , DM, MS Patel Cancer Center, Shree Krishna Hospital Medical Research Centre, Karamsad, Anand. *Israel:* Tomer Charas, MD, and Salem Billan, MD, Rambam Medical Center, Oncology Institute, Haifa; and Aron Popovtzer, MD, Beilinson Medical Center, Davidoff Center, Petach Tikva. *Italy:* Lisa Licitra, PhD, Dipartimento di Medicina-SS, Trattamento Tumori Testa e Collo, Istituto Nazionale dei Tumori, Milan; Daris Ferrari, PhD, and Paolo Fao, MD, Oncologia Medica, Azienda Ospedaliera S. Paolo, Milan; Marco Merlano, MD, S.C. Oncologia Medica, A. O. "S. Croce e Carle," Confreria; Maria Cossu Rocca, PhD, Istituto Europeo Oncologico, Unita' di Cure Mediche, Milan. *Japan:* Akihiro Homma, MD, Hokkaido University Hospital, Hokkaido; Hirofumi Fujii, MD, Jichi Medical University Hospital, Tochigi; Makoto Tahara, MD, National Cancer Center Hospital East, Kashiwa; Syujiro Minami, MD, and Masato Fujii, MD, National Hospital Organization Tokyo Medical Center, Tokyo; Tomoya Yokota, MD, Shizuoka Cancer Center, Shizuoka; Shigenori Kadowaki, MD, and Kei Muro, MD, Aichi Cancer Center Hospital, Aichi; Naomi Kiyota, MD, Kobe University Hospital, Kobe; Kenji Okami, MD, Tokai University Hospital, Kanagawa; Toshinari Yagi, MD, and Kunitoshi Yoshino, MD, Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka; Koji Matsumoto, MD, Hyogo Cancer Center, Hyogo; Shunji Takahashi, MD, Japanese Foundation for Cancer Research, Tokyo; and Kazuto Matsuura, MD, Miyagi Cancer Center, Miyagi. *Mexico:* Miguel Angel Alvarez Avitia, MD Instituto Nacional de Cancerologia, and Hector Jorge Gonzalez Riestra, MD, Central Medico Quirurgica de Aguascalientes S. A. de C. V. CMG Grupo Oncologico, Aguascalientes. *The Netherlands:* E. van Meerten, MD, Erasmus Medical Center, Rotterdam; J. Buter, MD, VU Medisch Centrum, Amsterdam; and A. J. Gelderblom, MD, Leids Universitair Medisch Centrum Klinische Oncologie, Leiden. *Poland:* Andrzej Kawecki, MD, PhD, M. Sklodowska-Curie Oncology Institute, Warsaw, and Wojciech Golusinski, MD, PhD, Wielkopolskie Oncology Centre, Poznan. *Portugal:* José Dinis, MD, Instituto Português de Oncologia do Porto Francisco Gentil, Serviço de Medicina Oncológica, Porto; Rui Dinis, MD, Hospital do Espírito Santo, Evora; Leonor Ribeiro, MD, Centro Hospitalar Lisboa Norte,Hospital de Santa Maria, Lisboa; Regina Silva, MD, Instituto Português de Oncologia Coimbra Francisco Gentil Serviço Oncologia Médica, Coimbra; and Hélder Mansinho, MD, Hospital Garcia de Orta, Almada. *Russia:* Irina Selezneva, DMedSc, and Mikhail Biakhov, MD, N. A. Semashko Central Clinical Hospital No. 2, Moscow; Rinat Galiulin, PhD, Clinical Oncology Center, Omsk; Adel Izmailov, PhD, Bashkiria State Medical University, Sterlitamak; Ilya Romanov, PhD, Russian Oncological Research Centre, Moscow; Vladimir Vladimirov, MD, GUZ Pyatigorsky Oncological Dispensary, Pyatigorsk; Valery Vinogradov, MD, Russian Research Center for Radiology and Surgical Technologies, St Petersburg; Fagim Mufazalov, MD, Republican Clinical Oncology Center, Ufa; and Irina Vasilevskaya, PhD, Oncology Centre of Moskovskiy, St Petersburg. *Spain:* Neus Baste, MD, and Josep Mª del Campo, MD, Vall d'Hebron University Hospital, Barcelona; Ricard Mesía Nin, MD, Hospitalet de Llobregat, Llobregat; Antonio López Pousa, MD, Servicio de Oncologia Medica, Barcelona; Juan Jose Grau de Castro, MD, and Oscar Reig, MD, Hospital Clinic i Provincial de Barcelona, Barcelona; Ruth Vera, MD, Complejo Hospitalario de Navarra, Pamplona; JoseManuel Trigo, MD, IBIMA, Malaga; Lara Iglesias, MD, Hospital 12 de Octubre, Madrid; Javier Martínez Trufero, MD, Hospital Miguel Servet, Zaragoza; Sergio Vázquez, MD, Hospital Universitario Lucus Augusti, Lugo; Belén Rubio, MD, Hospital Universitario Quirón, Madrid; José Enrique Alés, MD, Hospital Nuestra Señora de Sonsoles, Avila; Esther Villar, MD, Hospital Regional Universitario Carlos Haya, Malaga; Jordi Rubió, MD, Institut Català d'Oncologia, Girona; Yolanda Escobar, MD, Hospital Gregorio Marañón, Madrid; Ainara Soria, MD, Hospital Ramón y Cajal, Madrid; and Mauel Chaves, MD, Hospital Virgen del Rocio, Sevilla. *Sweden:* Gun Wickart Johansson, MD, Signe Friesland, MD, and Roger Tell, MD, Karolinska Universitetssjukhuset, Stockholm; and Jan Nyman, MD, Sahlgrenska Universitetssjukhuset, Göteborg. *Switzerland:* Sacha Rothschild, MD, and Alfred Zippelius, MD, Universitätsspital Basel, Basel; and Daniel Rauch, MD, and Nurguel Usluoglu, MD, Inselspital Bern, Bern. *Ukraine:* Inna Gogunska, MD, PhD, and Dmytro Zabolotniy, MD, PhD, O. S. Kolomiychenko Institute of Otolaryngology of National Academy of Medical Science of Ukraine, Kiev; Yuriy Vinnyk, MD PhD, Kharkiv Regional Clinical Oncology Center, Kharkiv; and Oleksandr Burian, MD, Kharkiv Regional Clinical Oncology Center, Kharkiv. *United Kingdom:* Kevin Harrington, MD, The Royal Marsden Hospital/The Institute of Cancer Research, National Institute for Health Research Biomedical Research Centre, London; Andrew Sykes, MD, The Christie NHS Foundation Trust, Manchester; David Peel, MD, University Hospitals of Leicester NHS Hospital Trust, Leicester Royal Infirmary, Leicester; James Lester, MD, and Martin Robinson, MD, Sheffield Teaching Hospitals NHS Foundation Trust, Weston Park Hospital, Sheffield; Devraj Srinivasan, MD, Ioanna Fragkandrea-Nixon, MD, and Elizabeth Junor, MD, NHS Lothian Western General Hospital, Edinburgh Cancer Centre, Edinburgh; Simon Gollins, MD, Glan Clwyd Hospital North Wales Cancer Treatment Centre, Rhyl; Mererid Evans, MD, Velindre NHS Trust, Velindre Cancer Centre, Cardiff; Kate Newbold, MD, The Royal Marsden NHS Foundation Trust, Sutton; David Hwang, MD, Royal Devon & Exeter NHS Foundation Trust, Royal Devon & Exeter Hospital, Exeter; and Stefano Schipani, MD, and Mohammed Rizwanullah, MD, Beatson West of Scotland Cancer Centre, Glasgow. *United States:* Omar Atiq, MD, and Konstantinos Arnaoutakis MD, University of Arkansas for Medical Sciences, Little Rock, Arkansas; Jessica Bauman, MD, Barbara Burtness, MD, and Ranee Mehra, MD, Fox Chase Cancer Center, Philadelphia,

© 2019 American Medical Association. All rights reserved.

Downloaded From: https://jamanetwork.com/ by a Bashkir State Medical University User on 12/09/2020

Pennsylvania; Hyunseok Kang, MD, and Christine Chung, MD, Johns Hopkins University, Baltimore, Maryland; Thomas Davis, MD, Dartmouth-Hitchcock Medical Center, Lebanon, New Hampshire; Robert Haddad, MD, Dana Farber Cancer Institute, Boston, Massachusetts; Antonio Jimeno, MD, PhD, University of Colorado Cancer Center, Aurora, Colorado; Roger Keresztes, MD, Stony Brook University Cancer Center, Stony Brook, New York; Chaitali Nangia, MD, and Sai-Hong Ignatius Ou, MD, UC Irvine Medical Center, Chao Family Comprehensive Cancer Center, Orange, California; Yungpo Bernard Su, MD, Nebraska Methodist Hospital, Omaha, Nebraska; Lindsay Carol Overton, MD, and Mitchell A. Garrison, MD, Wenatchee Valley Hospitals and Clinics, Wenatchee, Washington; Woondong Jeong, MD, Ahmad Wehbe, MD, and Athanassios Argiris, MD, The University of Texas Health Science Center at San Antonio; Anne Chiang, MD, and Daniel Morgensztern, MD, Yale University Smilow Cancer Hospital at Yale–New Haven, New Haven, Connecticut; Missak Haigentz Jr, MD, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, New York; Danko Martincic, MD, Cancer Care Northwest, Spokane Valley, Washington; and Mercedes Porosnicu, MD, Wake Forest Baptist Health, Winston-Salem, North Carolina.

Data Sharing Statement: See Supplement 3.

Additional Contributions: Flavio Solca, PhD (Boehringer Ingelheim, Vienna, Austria), and Charlotte Lind, PhD (Boehringer Ingelheim Danmark, Copenhagen, Denmark), provided additional analysis as part of their salaried positions. Medical writing assistance was provided by Caroline Allinson, PhD, GeoMed, an Ashfield company, part of UDG Healthcare plc, and was supported financially by Boehringer Ingelheim.

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(5):E359-E386. doi:10.1002/ijc.29210

2. Seiwert TY, Salama JK, Vokes EE. The chemoradiation paradigm in head and neck cancer. *Nat Clin Pract Oncol*. 2007;4(3):156-171. doi:10.1038/ncponc0750

3. 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(8):1107-1111. doi:10.1001/jamaoncol.2016.5769

4. 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(3):328-337. doi:10.1002/hed.20976

5. Ang KK, Harris J, Wheeler R, et al. Human papillomavirus and survival of patients with oropharyngeal cancer. *N Engl J Med*. 2010;363(1):24-35. doi:10.1056/NEJMoa0912217

6. 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(25):2735-2743. doi:10.1200/JCO.2013.54.6309

7. 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(3):257-264. doi:10.1016/S1470-2045(13)70011-1

8. 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(24):7350-7356.

9. 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(6):567-578. doi:10.1056/NEJMoa053422

10. Burtness B, Goldwasser MA, Flood W, Mattar B, Forastiere AA; Eastern Cooperative Oncology Group. 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(34):8646-8654. doi:10.1200/JCO.2005.02.4646

11. Vermorken JB, Mesia R, Rivera F, et al. Platinum-based chemotherapy plus cetuximab in head and neck cancer. *N Engl J Med*. 2008;359(11):1116-1127. doi:10.1056/NEJMoa0802656

12. 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 [published correct appears in *J Clin Oncol*. 2009;27(20):3410]. *J Clin Oncol*. 2009;27(11):1864-1871. doi:10.1200/JCO.2008.17.0530

13. 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(8):2096-2105. doi:10.1038/bjc.2013.576

14. 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(3):677-686. doi:10.1158/1078-0432.CCR-16-0558

15. Machiels JP, Haddad RI, Fayette J, et al; LUX-H&N 1 investigators. 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(5):583-594. doi:10.1016/S1470-2045(15)70124-5

16. 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(36):5294-5300. doi:10.1200/JCO.2010.30.6423

17. 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(31):4880-4886. doi:10.1200/JCO.2007.12.9650

18. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA*. 2013;310(20):2191-2194. doi:10.1001/jama.2013.281053

19. Fayers PM, Aaronson NK, Bjordal K, Groenvold M, Curran D, Bottomley A. *The EORTC QLQ-C30 scoring manual*. 3rd ed. Brussels, Belgium: European Organisation for Research and Treatment of Cancer; 2001.

20. Cancer Therapy Evaluation Program. Common Terminology Criteria for Adverse Events, version 3.0 (CTCAE). National Cancer Institute. https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf. Published August 9, 2006. Accessed May 15, 2019.

21. 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(35):4202-4209. doi:10.1200/JCO.2015.61.4370

22. Osoba D, Rodrigues G, Myles J, Zee B, Pater J. Interpreting the significance of changes in health-related quality-of-life scores. *J Clin Oncol*. 1998;16(1):139-144. doi:10.1200/JCO.1998.16.1.139

23. 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(1):67-76. doi:10.3892/ijo.2014.2440

24. Vermorken JB, Psyrri A, Mesía 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(4):801-807. doi:10.1093/annonc/mdt574

25. 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(5):736-747. doi:10.1200/JCO.2004.00.3335

26. 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(10):2526-2532. doi:10.1093/annonc/mdx344

27. Mesía 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(2):208-220. doi:10.1016/S1470-2045(14)71198-2

28. Lee S, Greenlee EB, Amick JR, et al. Inhibition of ErbB3 by a monoclonal antibody that locks the extracellular domain in an inactive configuration. *Proc Natl Acad Sci U S A*. 2015;112(43):13225-13230. doi:10.1073/pnas.1518361112

29. Redlich N, Robinson AM, Nickel KP, et al. Anti-Trop2 blockade enhances the therapeutic efficacy of ErbB3 inhibition in head and neck squamous cell carcinoma. *Cell Death Dis*. 2018;9(1):5. doi:10.1038/s41419-017-0029-0

30. Leonard B, Brand TM, O'Keefe RA, et al. BET inhibition overcomes receptor tyrosine kinase-mediated cetuximab resistance in HNSCC. *Cancer Res*. 2018;78(15):4331-4343. doi:10.1158/0008-5472.CAN-18-0459

© 2019 American Medical Association. All rights reserved.

Downloaded From: https://jamanetwork.com/ by a Bashkir State Medical University User on 12/09/2020