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Afatinib as second-line treatment in patients with recurrent/metastatic squamous cell carcinoma of the head and neck: Subgroup analyses of treatment adherence, safety and mode of afatinib administration in the LUX-Head and Neck 1 trial

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ABSTRACT

Objectives: Patients with head and neck squamous cell carcinoma (HNSCC) can experience severe symptom burden and/or difficulty swallowing, leading to problems with treatment adherence/administration. In LUX-Head and Neck 1 (LH&N1; NCT01345682), second-line afatinib improved progression-free survival (PFS) versus methotrexate in patients with recurrent/metastatic HNSCC. We report adherence and safety across pre-specified and additional subgroups potentially linked to afatinib PFS benefit in LH&N1 (p16 status, smoking history), and afatinib adherence, safety and efficacy by administration (oral versus feeding tube; post-hoc analysis).

Methods: Patients were randomized (2:1) to afatinib (40 mg/day) or intravenous methotrexate (40 mg/m^2/week).

Results: Among 320 afatinib-treated and 160 methotrexate-treated patients, 83–92% and 76–92% (of patients with data available) across all subgroups took ≥80% of treatment. Across p16 status and smoking history

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subgroups, the most common treatment-related adverse events (AEs) were diarrhea (70–91%), rash/acne (72–84%), stomatitis (34–73%) with afatinib; and included stomatitis (39–100%), fatigue (22–50%), nausea (19–36%) with methotrexate. Dose reduction decreased AE incidence/severity. Baseline characteristics were generally similar between oral/feeding tube (n = 276/n = 46) groups. 89%/89% (of patients with data available) took ≥80% of assigned afatinib. Median PFS was 2.6 versus 2.7 months (hazard ratio: 0.997; 95% confidence interval: 0.72–1.38). The most common afatinib-related AEs were: rash/acne (74% versus 74%), diarrhea (73% versus 65%), stomatitis (40% versus 30%).

Conclusion: Subgroup analyses of LH&N1 demonstrate that afatinib has predictable and manageable safety across patient subgroups, with high treatment adherence, and is effective via oral and feeding tube administration.

Introduction

There are a number of potential challenges in the management of locally recurrent and metastatic head and neck squamous cell carcinoma (HNSCC). Common challenges for patients include severe symptom burden, and, specifically, impaired swallowing function caused by previous treatment (e.g. surgical resection, radiotherapy) and local tumor morbidity, and associated with an overall poor prognosis [1,2]. These issues can lead to a poor quality of life (QoL), as well as problems with treatment administration and adherence, particularly in patients with locally recurrent disease [3]. Ideally, any emerging treatment option for HNSCC should not increase the morbidity of these common challenges.

In the Phase III LUX-Head and Neck 1 trial (LH&N1; NCT01345682), afatinib, an oral irreversible ErbB family blocker, significantly improved progression-free survival (PFS) compared with methotrexate as second-line treatment for patients with recurrent/metastatic (R/M) HNSCC who had progressed on or after platinum-based therapy. PFS was improved with afatinib in the overall study population (median 2.6 versus 1.7 months, hazard ratio [HR]: 0.80 [95% confidence interval (CI): 0.65–0.98], p = 0.030) and across most patient subgroups, particularly in patients who had not previously been treated with an epidermal growth factor receptor (EGFR)-targeted antibody [4]. In post-hoc analyses, marked improvements in PFS were observed with afatinib in patients with baseline characteristics potentially linked to human papillomavirus (HPV) negativity, including p16 negative disease (afatinib versus methotrexate, HR [95% CI]: 0.69 [0.50–0.96]) and smoking history ≥10 pack-years (HR [95% CI]: 0.71 [0.56–0.90]) [4]. Further, in combined analyses of tumor biomarkers, marked differences in objective response rates were observed with afatinib versus methotrexate in patients with p16-negative and *EGFR*-amplified HNSCC (17.7% versus 0%) and also in those with p16-negative and EGFR monoclonal antibody (mAb)-naïve HNSCC (27.5% versus 4.8%) [5]. With regard to QoL in the overall LH&N1 afatinib population, time to deterioration curves of global health status, pain and swallowing were representative of the PFS curves, suggesting an association between prolonged control of QoL and symptoms, and PFS [4].

The treatment adherence rate with afatinib in LH&N1 (89% of patients took ≥80% of the assigned afatinib treatment) [4] was encouraging given the generally poor adherence to oral anticancer treatment in this setting [6]. This was likely, in part, owing to the predictable and manageable safety profile of afatinib. The most common afatinib-related adverse events (AEs) in LH&N1 were rash/acne and diarrhea (primarily of grade 1–2) [4]. A total of 103 (32%) patients had a dose reduction due to afatinib-related AEs, facilitated by the availability of multiple different doses of afatinib, and the established dose-reduction protocol for afatinib. Afatinib dose reduction has been assessed among patients with *EGFR* mutation-positive non-small cell lung cancer (NSCLC) in the Phase III LUX-Lung 3 and 6 studies. In these studies, tolerability-guided dose reduction from 40 mg, which was found to be more likely in patients with higher afatinib plasma concentrations, reduced the incidence and severity of AEs without compromising efficacy [7]. The impact of afatinib dose reduction on AEs and efficacy has not, however, been assessed in HNSCC.

Keeping in mind the impact that HNSCC can have on a patient's QoL, and the subgroup-specific improvements in PFS observed in LH&N1 [4], it is important to consider whether other clinical outcomes with afatinib may differ across HNSCC patient subgroups. Of clear interest are subgroups that have a specific relevance to HNSCC, such as those defined by: p16 status, given the association between p16-negativity and poor prognosis in oropharyngeal squamous cell carcinoma (SCC) [8–11]; smoking history (smoking being a well-known independent risk factor) [12]; and mode of afatinib administration. The latter is of particular importance to patients with locally recurrent HNSCC and an impaired swallowing mechanism. This is often the result of the location of the tumor, and radiation- and chemoradiation therapy-induced tissue damage [13,14], resulting in a reliance on a feeding tube (gastric tube) for the drug delivery.

In further analyses of the LH&N1 study, we evaluate adherence to and safety of afatinib in the LH&N1 study population across pre-specified and additional subgroups of interest. Further, we evaluate the impact of dose reduction on the incidence of common AEs. In a post-hoc analysis, we also compare treatment adherence, efficacy and safety in patients who received afatinib via oral administration compared with via feeding tube in LH&N1.

Materials and methods

Study design and patients

In this global, Phase III, open-label trial, which enrolled patients with second-line R/M HNSCC progressing following ≥2 cycles of platinum-based therapy, patients were randomized (2:1) to oral afatinib (40 mg/day) or intravenous methotrexate (40 mg/m^2/week), stratified by Eastern Cooperative Oncology Group performance status (ECOG PS) of 0/1 and prior EGFR mAb therapy (yes/no). Dose adjustment schemes were permitted for both afatinib and methotrexate [4]. For afatinib-treated patients, in the event of drug-related grade ≥3 or selected grade ≥1–2 AEs, treatment was paused until the AE returned to grade ≤1, returned to the grade present at baseline, or completely resolved. Providing the AE returned to the appropriate grade or resolved within 14 days, afatinib was resumed at a lower dose. Afatinib dose reductions were permitted in 10-mg decrements to a minimum of 20 mg. In both study arms, treatment continued until disease progression, unacceptable toxicity or other reasons necessitating withdrawal. Full details of the LH&N1 (NCT01345682) trial design have been published [4].

Afatinib tablets could be swallowed (with ~250 ml of water or following dispersion) or administered via a feeding tube (e.g. gastrostomy-tube [G-tube]) following dispersion. Afatinib tablets were dispersed as follows: the tablet was placed in a ~100 ml glass of non-carbonated drinking water or isotonic sodium chloride solution, stirred occasionally until the tablet was broken up into very small particles and then immediately drunk or administered via feeding tube. Another 100 ml of water was used to rinse the glass and allow the patient to

Table 1
Treatment adherence by subgroup.

	Age		Gender		Alcohol consumption		Prior EGFR-mAb treatment		Prior CRT		p16 status		Smoking history	
Afatinib[a]														
	< 65 years	≥65 years	Male	Female	≤7 units/week	> 7 units/week	Yes	No	Yes	No	Positive	Negative	< 10 pack-years	≥10 pack-years
	(n = 228)	(n = 78)	(n = 262)	(n = 44)	(n = 238)	(n = 54)	(n = 180)	(n = 126)	(n = 165)	(n = 141)	(n = 30)	(n = 133)	(n = 55)	(n = 240)
Percentage of medication taken														
< 80%	25 (11)	10 (13)	28 (11)	7 (16)	25 (11)	9 (17)	23 (13)	12 (10)	13 (8)	22 (16)	4 (13)	11 (8)	5 (9)	29 (12)
80–100%	201 (88)	67 (86)	231 (88)	37 (84)	210 (88)	45 (83)	154 (86)	114 (90)	150 (91)	118 (84)	25 (83)	121 (91)	49 (89)	209 (87)
> 100%	2 (< 1)	1 (1)	3 (1)	0	3 (1)	0	3 (2)	0	2 (1)	1 (< 1)	1 (3)	1 (< 1)	1 (2)	2 (< 1)
Methotrexate														
	< 65 years	≥65 years	Male	Female	≤7 units/week	> 7 units/week	Yes	No	Yes	No	Positive	Negative	< 10 pack-years	≥10 pack-years
	(n = 116)	(n = 44)	(n = 136)	(n = 24)	(n = 123)	(n = 33)	(n = 98)	(n = 62)	(n = 73)	(n = 87)	(n = 18)	(n = 67)	(n = 31)	(n = 125)
Percentage of medication taken														
< 80%	17 (15)	8 (18)	23 (17)	2 (8)	19 (15)	6 (18)	10 (10)	15 (24)	13 (18)	12 (14)	4 (22)	11 (16)	4 (13)	20 (16)
80–100%	94 (81)	35 (80)	109 (80)	20 (83)	100 (81)	26 (79)	84 (86)	45 (73)	58 (79)	71 (82)	13 (72)	53 (79)	24 (77)	102 (82)
> 100%	5 (4)	1 (2)	4 (3)	2 (8)	4 (3)	1 (3)	4 (4)	2 (3)	2 (3)	4 (5)	1 (6)	3 (4)	3 (10)	3 (2)

CRT, chemoradiation therapy; EGFR, epidermal growth factor receptor; mAb, monoclonal antibody.
[a] Adherence data were not available for 14 patients treated with afatinib.

receive any remaining drug [15]. The investigator or other study personnel monitored treatment compliance by counting the pills remaining in each patient's current bottle when a new bottle was dispensed. Treatment adherence was calculated based on pill count, days since last pill count, and cumulative number of treatment interruption days due to AEs.

The study was conducted in accordance with the Declaration of Helsinki and International Conference on Harmonisation guidelines on Good Clinical Practice. The protocol was approved by local ethics committees at each center. Written informed consent was obtained for each patient.

Objectives of this analysis

This analysis of the LH&N1 study had several objectives. Firstly, we aimed to evaluate adherence to and safety of afatinib in the LH&N1 study population across pre-specified and additional subgroups of interest: age (< 65 or ≥65 years), gender (male or female), alcohol consumption (> 7 or ≤7 units/week), prior EGFR-mAb treatment (yes or no), prior CRT (yes or no), p16 status (positive or negative), and smoking history (< 10 or ≥10 pack-years).

To evaluate the safety of afatinib, any-cause AEs and treatment-related AEs (i.e. AEs considered related to the administration of each study drug) were analyzed. In addition, we investigated the impact of dose reduction on the incidence of common any-cause AEs (diarrhea, rash/acne and stomatitis). Finally, we conducted a post-hoc analysis to compare treatment adherence, efficacy and safety in patients who received afatinib via oral administration compared with via feeding tube.

Assessments

Treatment adherence and safety of afatinib and methotrexate were assessed in pre-specified subgroups of interest (as described above); post-hoc analysis in additional subgroups of interest (according to p16 status and smoking pack-years) was also conducted.

In the afatinib treatment arm, post-hoc analysis compared the impact of dose reduction on the incidence and severity of AEs of special interest before and after dose reduction from 40 mg. Further, post-hoc analyses of treatment adherence, efficacy (PFS, overall survival [OS], response rate and tumor shrinkage) and safety were conducted for oral versus feeding tube groups.

Safety was monitored weekly, with the incidence and intensity of AEs graded according to the National Cancer Institute-Common Terminology Criteria for Adverse Events (version 3.0). Tumor response was assessed by the investigators and independent central review (RECIST v1.1) every 6 weeks for the first 24 weeks, and every 8 weeks thereafter [4]. Tumor shrinkage was defined as the maximum decrease in the sum of diameters of the target lesions.

Statistical analyses

Detailed methods for statistical analyses (SAS, version 9.2) for LH&N1 have been reported [4]. Treatment adherence and safety data for all groups were characterized using descriptive statistics. The percentage of medication taken was defined as: (total doses of medication taken)/(total prescribed) × 100%. For afatinib, medication taken/missed/prescribed was counted as the number of tablets or days, and for methotrexate, as the number of infusions or weeks. PFS and OS for oral and feeding tube groups were estimated using Kaplan–Meier analysis, and HRs were derived using a Cox proportional hazards model.

Results

Treatment adherence and safety across patient subgroups

Of 320 patients treated with afatinib and 160 patients treated with methotrexate, 306 and 160 patients, respectively, were included in treatment adherence analyses (14 patients in the afatinib group did not have data available for calculation of adherence). Treatment adherence by patient subgroup is presented in Table 1. The proportion of patients who took ≥80% of the assigned medication was 83–92% across all subgroups in the afatinib arm, and 76–92% across all subgroups in the methotrexate arm.

p16-negativity and a smoking history of ≥10 pack-years are potentially linked to HPV-negativity [16,17], and in LH&N1, patients with these baseline characteristics exhibited particularly pronounced PFS benefit with afatinib (afatinib versus methotrexate, p16 negative: HR [95% CI]: 0.69 [0.50–0.96]; smoking history ≥10 pack years: 0.71 [0.56–0.90]) [4]. Samples for p16 analysis could not be obtained for almost half of all randomized patients in both arms of the study. In general, patient baseline characteristics were balanced between the known and unknown p16 status subgroups, although there were some differences in race, geographical region, Veristrat status and best response to prior platinum-based therapy (known vs unknown p16 status: Caucasian 143 [56%] vs 178 [79%]; West Europe 195 [76%] vs 133 [59%]; Veristrat good 142 [55%] vs 54 [24%]; CR/PR/SD 157 [61%] vs 104 [46%]). In both the afatinib and methotrexate treatment arms, there were fewer patients with p16-positive disease (n = 31 and n = 18) than p16-negative disease (n = 140 and n = 67; Table 2), and with a smoking history of < 10 pack-years (n = 56 and n = 31) than

Table 2
Treatment-related AEs according to p16 status (≥20% incidence in any subgroup).

	Afatinib (N = 320)						Methotrexate (N = 160)					
	All grades			Grade ≥3			All grades			Grade ≥3		
p16 status	Positive (n = 31)	Negative (n = 140)	Missing (n = 149)	Positive (n = 31)	Negative (n = 140)	Missing (n = 149)	Positive (n = 18)	Negative (n = 67)	Missing (n = 75)	Positive (n = 18)	Negative (n = 67)	Missing (n = 75)
Any related AE, n (%)	30 (97)	134 (96)	139 (93)	7 (23)	60 (43)	60 (40)	18 (1 0 0)	57 (85)	62 (83)	7 (39)	18 (27)	32 (43)
Rash/acne[a]	26 (84)	101 (72)	111 (74)	1 (3)	10 (7)	20 (13)	3 (17)	3 (4)	7 (9)	0	0	0
Diarrhea	27 (87)	99 (71)	105 (70)	2 (6)	13 (9)	15 (10)	3 (17)	8 (12)	8 (11)	1 (6)	1 (1)	1 (1)
Stomatitis[a]	17 (55)	54 (39)	54 (36)	1 (3)	6 (4)	13 (9)	13 (72)	27 (40)	29 (39)	2 (11)	5 (7)	6 (8)
Paronychia[a]	8 (26)	20 (14)	18 (12)	0	1 (< 1)	2 (1)	0	0	0	0	0	0
Nausea	6 (19)	36 (26)	22 (15)	1 (3)	0	4 (3)	4 (22)	15 (22)	17 (23)	0	0	1 (1)
Fatigue[a]	5 (16)	46 (33)	28 (19)	2 (6)	10 (7)	6 (4)	4 (22)	26 (39)	21 (28)	0	1 (1)	4 (5)
AST increased	2 (6)	1 (< 1)	1 (< 1)	0	0	0	4 (22)	6 (9)	5 (7)	1 (6)	1 (1)	2 (3)
Anemia	1 (3)	15 (11)	6 (4)	0	3 (2)	1 (< 1)	3 (17)	11 (16)	16 (21)	1 (6)	3 (4)	6 (8)
Neutropenia	0	0	1 (< 1)	0	0	1 (< 1)	3 (17)	12 (18)	16 (21)	0	1 (1)	10 (13)

AE, adverse event; AST, aspartate aminotransferase.
[a] Grouped terms.

≥10 pack-years (n = 253 and n = 125; Table 3). In this analysis, the incidence of any treatment-related AE was similar across the p16 status and smoking history subgroups (range across subgroups, all grades [grade ≥3], afatinib: 91–97% [23–43%]; methotrexate: 83–100% [0–43%]; Tables 2 and 3).

Consistent with the primary analysis of the overall afatinib population [4], the most common afatinib-related AEs across all p16 status and smoking history subgroups were diarrhea (range across subgroups, all grades [grade ≥3]: 70–91% [4–27%]), rash/acne (72–84% [0–13%]) and stomatitis (34–73% [0–9%]). Afatinib-related diarrhea, rash/acne, stomatitis and paronychia (of any grade) were more common in the p16-positive group, and fatigue was more common in the p16-negative group; grade ≥3 diarrhea, rash/acne, and stomatitis were only very marginally more common in the p16-negative group. While afatinib-related rash/acne (of any grade) was more common in the < 10 pack-year group, and fatigue was more common in the ≥10 pack-year group, the incidence of grade ≥3 common AEs was not notably different between the smoking history groups.

In the methotrexate arm, stomatitis (range across subgroups, all grades [grade ≥3]: 39–100% [0–11%]), fatigue (22–50% [0–5%]) and nausea (19–36% [0–1%]) were among the most common treatment-related AEs in all subgroups analyzed, in addition to increased aspartate transaminase (AST) in p16-positive patients, and anemia and neutropenia in patients with a known smoking history. Methotrexate-related stomatitis, rash/acne and increased AST were found to be more common in p16-positive patients, whereas fatigue was more common in the p16-negative group. Methotrexate-related nausea and rash/acne were more common in the patients with a < 10 pack-year smoking history. There were however, no notable differences in the incidence of these grade ≥3 AEs across the p16 status or smoking history subgroups.

In the primary analysis [4], the incidence of treatment-related tumor hemorrhage and interstitial lung disease was low in both the afatinib and methotrexate arms, and this was also the case in all p16 status and smoking history subgroups (data not shown).

The overall frequency of any-cause AEs was generally similar across all pre-specified subgroups, and the p16 and smoking status subgroups in both the afatinib (range across subgroups, all grades [grade ≥3]: 98%–100% [58–82%]) and methotrexate (97%–100% [42–68%]) treatment arms (Supplementary Tables 1–7). However, of note, there was a lower incidence of any-cause grade ≥3 AEs among female patients (42%) in the methotrexate arm, when compared with other subgroups (Supplementary Table 2).

Dose reductions and treatment discontinuations with afatinib for AEs of special interest

Across all patient subgroups assessed, three of the most frequently occurring any-cause and treatment-related AEs in afatinib-treated patients were diarrhea, rash/acne and stomatitis (Supplementary Tables 1–7, Tables 2 and 3). These AEs were further investigated as AEs of special interest.

Diarrhea

A total of 249 afatinib-treated patients had diarrhea of any causality. Diarrhea led to dose reduction of afatinib in 34 (14%) of these patients and to treatment discontinuation in 3 (1%) of these patients. All 3 patients who discontinued treatment were < 65-year old males and current/ex-smokers with ≥10 pack-years smoking history, who received afatinib via oral administration. For one of these patients, a protocol violation was recorded, and two patients had gastrointestinal disorders at baseline.

In LH&N1, 95 afatinib-treated patients had a dose reduction from 40 mg. Of these, 81 patients had diarrhea before dose reduction (17 with grade ≥3), and 45 patients had diarrhea after dose reduction (5 with grade ≥3; Fig. 1).

Rash/acne

A total of 247 afatinib-treated patients had rash/acne of any causality. Rash/acne led to dose reduction in 32 (13%) of these patients. There were no treatment discontinuations due to rash/acne.

Of the 95 patients in LH&N1 who had a dose reduction to afatinib < 40 mg, 72 patients had rash/acne before dose reduction (18 with grade ≥3) and 54 patients had rash/acne after dose reduction (8 with grade ≥3; Fig. 1).

Stomatitis

A total of 143 afatinib-treated patients had stomatitis of any causality. Stomatitis led to dose reduction in 14 (10%) of these patients and to treatment discontinuation in 5 (3%) patients. Two of the patients who discontinued treatment had a protocol violation, including the one described above under diarrhea. All patients who discontinued treatment were current/ex-smokers with ≥10 pack-years smoking history.

Of the 95 patients in LH&N1 who had a dose reduction of afatinib, 48 patients had stomatitis before dose reduction (10 with grade ≥3) and 27 patients had stomatitis after dose reduction (6 with grade ≥3; Fig. 1).

Table 3
Treatment-related AEs according to smoking history (≥20% in any subgroup).

	Afatinib (N = 320)[a]				Methotrexate (N = 160)[b]			
	All grades		Grade ≥3		All grades		Grade ≥3	
Smoking pack-years*	< 10 (n = 56)	≥10 (n = 253)	< 10 (n = 56)	≥10 (n = 253)	< 10 (n = 31)	≥10 (n = 125)	< 10 (n = 31)	≥10 (n = 125)
Any related AE, n (%)	51 (91)	242 (96)	17 (30)	106 (42)	27 (87)	106 (85)	10 (32)	47 (38)
Rash/acne[c]	46 (82)	183 (72)	5 (9)	26 (10)	6 (19)	6 (5)	0	0
Diarrhea	42 (75)	179 (71)	2 (4)	25 (10)	2 (7)	17 (14)	1 (3)	2 (2)
Stomatitis[c]	19 (34)	98 (39)	3 (5)	17 (7)	13 (42)	52 (42)	0	13 (10)
Nausea	10 (18)	52 (21)	1 (2)	4 (2)	11 (36)	24 (19)	0	1 (< 1)
Fatigue[c]	8 (14)	65 (26)	3 (5)	14 (6)	10 (32)	39 (31)	1 (3)	4 (3)
Anemia	1 (2)	19 (8)	0	4 (2)	5 (16)	25 (20)	3 (10)	7 (6)
ALT increased	0	1 (< 1)	0	0	2 (7)	12 (10)	0	3 (2)
Neutropenia	0	1 (< 1)	0	1 (< 1)	4 (13)	26 (21)	2 (7)	9 (7)

AE, adverse event; ALT, alanine aminotransferase.
[a] Data missing for 11 patients.
[b] Data missing for 4 patients.
[c] Grouped terms.

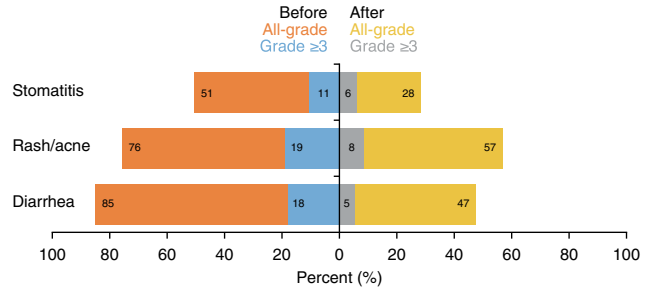

Fig. 1. Proportion of patients with adverse events of special interest before versus after dose reduction of afatinib from 40 mg.

Treatment adherence, efficacy and safety by afatinib mode of administration (oral versus feeding tube)

A total of 276 patients randomized to the afatinib treatment arm received afatinib via oral administration and 46 patients randomized to afatinib received the drug via feeding tube (all via G-tube). Baseline characteristics were generally similar between the two groups (Supplementary Table 8).

Median (range) time on treatment for 274 patients who received afatinib via oral administration was 83.5 days (2.0–546.0) and for 46 patients treated via feeding tube was 74.5 days (15.0–512.0). Treatment adherence data were available for 261 patients in the oral administration group and 45 patients in the feeding tube group; of these patients, 89% of patients in each group took ≥80% of the afatinib doses assigned.

Eighty-three (30%) patients who received treatment via oral administration had afatinib dose reduction, compared with 12 (26%) patients who received treatment via feeding tube. In the oral administration group, median (range) exposure to the reduced dose of 30 mg/day (n = 81) was 28.0 days (1.0–428.0) and to 20 mg/day (n = 18) was 29.0 days (7.0–165.0). In the feeding tube group, median (range) exposure to 30 mg/day (n = 12) was 71.5 days (7.0–489.0) and to 20 mg/day (n = 2) was 250.0 days (110.0–390.0).

Median PFS was similar between the oral administration and feeding tube subgroups (2.62 [95% CI: 1.77–2.73] versus 2.66 [95% CI: 1.54–3.65] months; HR: 0.997 [95% CI: 0.72–1.38]; Fig. 2A). Median OS was longer in the oral administration subgroup compared with the feeding tube subgroup (7.46 [95% CI: 6.74–8.28] versus 5.16 [95% CI: 3.81–6.05] months; HR: 1.41 [95% CI: 1.03–1.95]; Fig. 2B). Within both administration groups, landmark OS rates were generally higher in patients with baseline ECOG PS 0, compared with ECOG PS 1 (at all time-points in the feeding tube group, and until ~21 months in the oral administration group; Fig. 2C). However, very few patients with ECOG PS 0 at baseline received afatinib via feeding tube (n = 6). Response rates were comparable between the subgroups (Table 4). In the oral administration subgroup, 28 (10%) patients achieved an objective

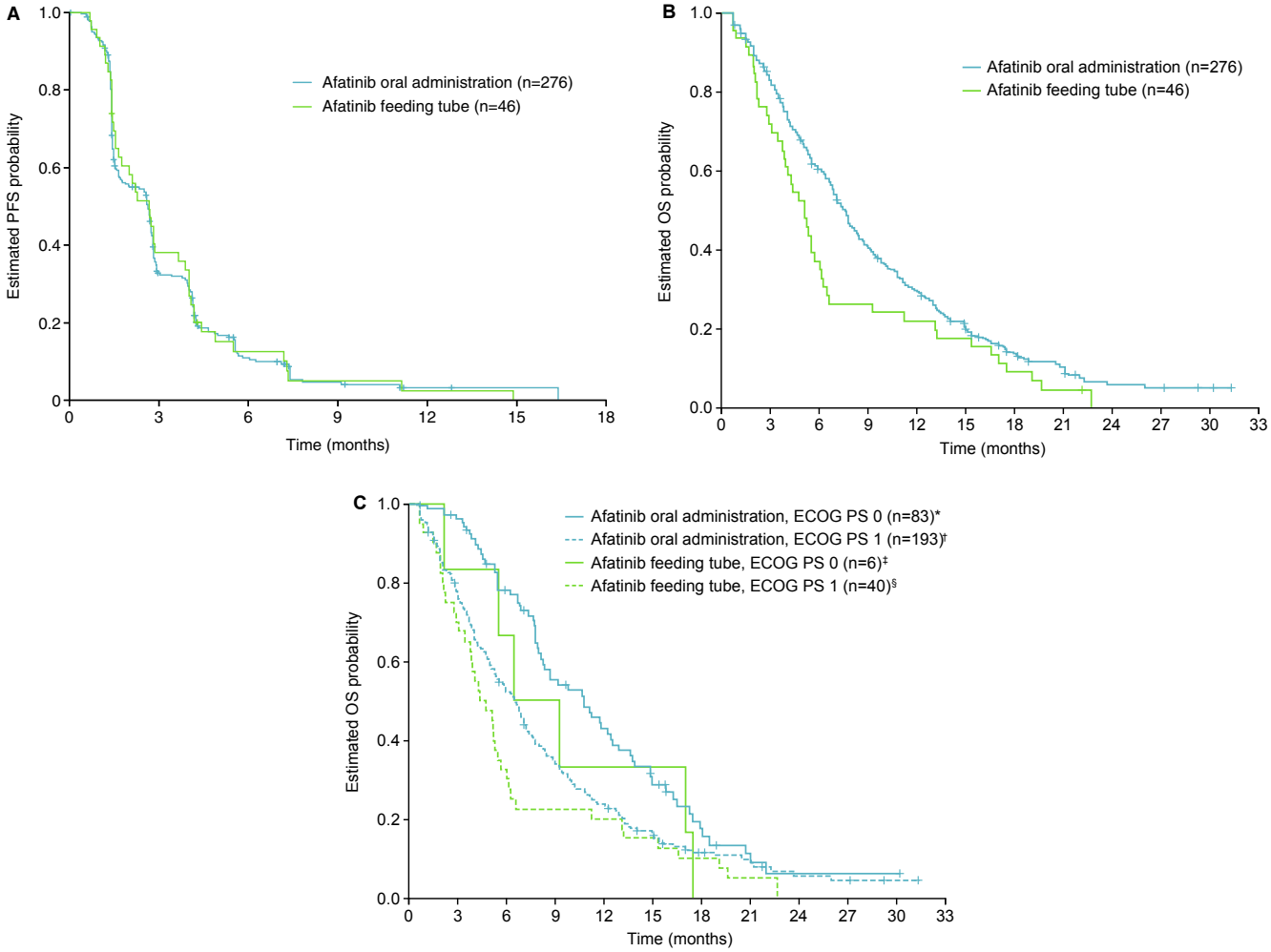

Fig. 2. (A) PFS, (B) OS and (C) OS according to ECOG PS by independent review in the afatinib oral and feeding tube groups. ECOG PS, Eastern Cooperative Oncology Group Performance Status; NA, not applicable; OS, overall survival; PFS, progression-free survival. *Median (95% CI): 10.8 months (8.2–12.9); †Median (95% CI): 6.6 months (5.3–7.4); ‡Median (95% CI): 7.9 months (5.5–NA); §Median (95% CI): 4.6 months (3.8–6.0).

Table 4
Best overall response to afatinib by independent review according to mode of administration.

	Feeding tube (N = 46)	Oral administration (N = 276)
Disease control, n (%)	25 (54)	133 (48)
Objective response (PR only)	5 (11)	28 (10)
SD	14 (30)	84 (30)
Non-CR/Non-PD[a]	6 (13)	21 (8)
PD, n (%)	15 (33)	113 (41)
Not evaluable, n (%)	6 (13)	30 (11)
Durable PR, SD or non-CR/non-PD (PFS > 12 weeks), n (%)	20 (43)	104 (38)

CR, complete response; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.
[a] Applicable to patients who did not have target lesions at baseline.

response (all partial responses [PRs]) and 84 (30%) patients had stable disease (SD). In the feeding tube subgroup, 5 (11%) patients achieved an objective response (all PRs) and 14 (30%) patients had SD. Overall a similar benefit with regard to tumor shrinkage was observed for the oral administration and feeding tube subgroups (Supplementary Fig. 1).

AEs of any cause occurred in 272 (99%) patients who received afatinib via oral administration (181 [66%] grade ≥3) and 46 (100%) patients treated with afatinib via feeding tube (34 [74%] grade ≥3). The most common AEs in both administration subgroups were rash/acne (oral versus feeding tube; 78% versus 74%), diarrhea (79% versus 70%), fatigue (45% versus 41%) and stomatitis (46% versus 35%), and the majority of cases were grade 1–2.

Treatment-related AEs occurred in 260 (95%) patients treated with afatinib via oral administration (108 [40%] grade ≥3) and 43 (93%) patients treated with afatinib via feeding tube (19 [41%] grade ≥3; Table 5). In both oral and feeding tube groups, the most common treatment-related any-grade AEs were rash/acne (75% and 74%), diarrhea (73% and 65%) and stomatitis (40% and 30%), and the majority were grade 1–2. Thirty-seven (13%) patients in the oral group experienced a treatment-related serious AE (32 [12%] grade ≥3) and 7 (15%) patients in the feeding tube group (5 [11%] grade ≥3). Discontinuations due to treatment-related AEs were observed in 18 (7%) patients in the oral group versus 5 (11%) patients in the feeding tube group.

Discussion

In this additional analysis of patients with R/M HNSCC from LH&N1 [4], the proportion of patients who took ≥80% of medication across pre-specified subgroups (age, gender, alcohol consumption, prior EGFR mAb use and prior CRT) and additional subgroups of interest (p16 status and smoking history) ranged between 83 and 92% for afatinib and 76–92% for methotrexate. As adherence with oral medication can be a challenge for cancer patients [18], the high percentage of patients across these subgroups who took ≥80% of the assigned afatinib is noteworthy.

In subgroup analyses of safety, three of the most frequently occurring any-cause and treatment-related AEs across all pre-specified and additional subgroups assessed were diarrhea, rash/acne and stomatitis with afatinib, and stomatitis, fatigue and nausea with methotrexate. These findings are consistent with those reported for the overall afatinib- and methotrexate-treated populations [4]. We observed only small differences in the incidence and severity of individual any-cause AEs across the pre-specified subgroups.

p16 status and smoking history were selected as additional subgroups of interest for this analysis based on the relevance in HNSCC, and the increased PFS benefit seen among patients in LH&N1 with baseline p16-negativity and smoking history of ≥10 pack years [4]. The p16 protein is a surrogate biomarker for HPV infection, and increasing data in oropharyngeal SCC suggest it is associated with improved prognosis in the curative and R/M settings [8–11]. It is also well known that smoking is an independent risk factor for head and neck cancer [12], and a history of heavy smoking has been linked to HPV negativity [17]. Retrospective analyses of patients with oropharyngeal SCC have also reported differences in oncological treatment tolerability according to smoking history and p16 status of the disease, with HPV-positivity and no smoking history correlating with more severe oral mucositis [19,20]. In this analysis of LH&N1, while several afatinib-related AEs, including diarrhea and rash/acne, were more common overall in patients with p16-positive disease, conversely, there were no notable differences in such grade ≥3 occurrences across p16 status subgroups. In the methotrexate arm, stomatitis and fatigue were most common in patients with p16-positive and p16-negative disease, respectively, but there were no notable differences between the p16-positive and -negative groups in grade ≥3 frequency of these AEs.

In addition, while there were differences in the overall incidence of some treatment-related AEs across smoking history subgroups (e.g. with both afatinib and methotrexate, treatment-related rash/acne was more common in patients with a smoking history of < 10 pack-years), there were no notable differences across the smoking history groups in grade ≥3 occurrences of these AEs. It should be noted that, in both the afatinib and methotrexate treatment arms, patient numbers were much lower in both the p16-positive and < 10 pack-year smoking history groups than in the p16-negative and ≥10 pack-year groups.

Diarrhea, rash/acne and stomatitis were identified as AEs of special interest in the afatinib arm due to the frequent occurrence (any-cause and treatment-related) across the investigated patient subgroups. Tolerability-guided dose reductions of afatinib from the recommended starting dose of 40 mg reduced the incidence and severity of each of these AEs. Further, few patients discontinued treatment due to these AEs (diarrhea, < 1%; rash/acne, 0%; stomatitis, 2%) and, among those who did, there were no particular patterns in patient characteristics, except that all were current or ex-smokers with a ≥10 pack-years smoking history; some protocol violations were also noted. These findings demonstrate that, consistent with studies of afatinib in *EGFR* mutation-positive NSCLC [7], protocol-defined tolerability-guided dose adjustment of afatinib is an effective strategy in the management of AEs

Table 5
Treatment-related AEs in patients who received afatinib via oral administration versus feeding tube (≥5% in any treatment arm).

	Oral administration (n = 274)		Feeding tube (n = 46)	
	All grades	Grade ≥3	All grades	Grade ≥3
Any treatment-related AE, n (%)	260 (95)	108 (39)	43 (93)	19 (41)
Rash/acne[a]	204 (74)	26 (9)	34 (74)	5 (11)
Diarrhea	201 (73)	28 (10)	30 (65)	2 (4)
Stomatitis[a]	109 (40)	16 (6)	14 (30)	3 (7)
Nausea	54 (20)	5 (2)	10 (22)	0
Paronychia[a]	36 (13)	3 (1)	10 (22)	0
Fatigue[a]	70 (26)	15 (5)	9 (20)	3 (7)
Vomiting	32 (12)	4 (1)	9 (20)	0
Anemia	15 (5)	3 (1)	7 (15)	1 (2)
Dry skin	29 (11)	0	7 (15)	0
PPE syndrome	11 (4)	2 (< 1)	6 (13)	0
Conjunctivitis[a]	14 (5)	1 (< 1)	4 (9)	1 (2)
Abdominal pain	10 (4)	1 (< 1)	3 (7)	1 (2)
Dyspepsia	20 (7)	0	3 (7)	0
Epistaxis	14 (5)	0	3 (7)	0
Headache	3 (1)	0	3 (7)	0
Decreased appetite	41 (15)	10 (4)	2 (4)	0
Pruritus	25 (9)	3 (1)	1 (2)	1 (2)
Weight decreased	25 (9)	2 (< 1)	1 (2)	0

AE, adverse event; PPE, palmar–plantar erythrodysesthesia.
[a] Grouped terms.

across patient subgroups. With regard to QoL, published data for the overall LH&N1 population demonstrated significantly improved patient-reported outcomes of disease-related symptoms and QoL with afatinib compared with methotrexate [4].

In LH&N1, around half of patients treated with afatinib had received previous curatively intended CRT [4]. Patients undergoing radiation or chemoradiation therapy for head and neck cancer may experience an impaired swallowing mechanism due to the location of the targeted tumor, and may therefore receive enteral nutrition by means of a feeding tube [13,14]. This is a particularly relevant challenge for patients with locally recurrent HNSCC, and data suggest that enteral feeding can induce long-term tube dependence, continuing after CRT [21]. There are limited data available comparing oral versus feeding tube administration of oral anticancer therapies in HNSCC. Findings from a Phase II trial of the oral kinase inhibitor, dasatinib, in patients with R/M advanced HNSCC after platinum-based therapy, showed greater drug exposure, decreased half-life and greater maximum concentration of dasatinib in the feeding tube versus oral administration group [22]. Conversely, in a Phase II study in which patients with R/M HNSCC were randomized to receive afatinib 40 mg/day or cetuximab 250 mg/m^2/week, afatinib plasma concentrations were similar across different administration routes (oral tablet, gastric feeding tube and dispersion) [23].

In this analysis of afatinib administration mode in LH&N1, treatment adherence was similar between patients who received afatinib via oral administration versus feeding tube (89% of patients with data available in both groups took ≥80% of the assigned afatinib, respectively). Safety findings based on either method (oral versus feeding tube) were consistent with those of the overall study population [4], with diarrhea, rash/acne and stomatitis as the most commonly reported any-cause and treatment-related AEs, regardless of the route of administration. Similarly, the incidence and severity of other treatment-related AEs was generally consistent between administration routes and resulted in few patients discontinuing treatment (oral versus feeding tube; 7% versus 11%).

The safety findings for afatinib across pre-specified and additional patient subgroups, as well as mode of administration groups, are consistent with those previously reported with afatinib for the treatment of lung cancer. The safety profile of afatinib has been explored extensively across its approved settings in first-line *EGFR* mutation-positive NSCLC and second-line advanced SCC of the lung following platinum-based chemotherapy. In the LUX-Lung studies, rash/acne and diarrhea were the most frequently observed afatinib-related AEs, along with stomatitis and paronychia [24–26].

With regard to efficacy in patients who received afatinib via oral administration versus feeding tube, we observed no difference in PFS, response rate or tumor shrinkage between the groups, which is perhaps not surprising given the small size of the feeding tube subgroup and the post-hoc nature of the analysis. Regardless, the finding of comparable treatment efficacy in patients receiving afatinib via feeding tube suggests that it may be prudent to permit patients who are experiencing difficulty taking afatinib orally to transition to a feeding tube (specifically, a G-tube) in future clinical trials.

In contrast, OS was lower in patients who received afatinib via feeding tube compared with oral administration. It should be noted that in the primary analysis, afatinib did not improve OS compared with methotrexate [4], and that the difference observed between afatinib administration groups in the current analysis may be explained by the worse health status of the feeding tube patients at baseline. For example, 30% versus 13% of patients in the oral versus feeding tube groups had an ECOG PS of 0. Furthermore, in both the feeding tube and oral administration groups, landmark OS rates were generally higher in patients with baseline ECOG PS 0, compared with ECOG PS 1. A key limitation of this analysis however, is that only a very small number of patients had ECOG PS 0 at baseline and received afatinib via feeding tube (n = 6). Nevertheless, these data may have implications for survival estimates in future studies that enroll patients with feeding tubes, since such patients appear to have a generally worse prognosis at baseline.

Taken together, the findings from this analysis demonstrate that afatinib has a predictable and manageable safety profile that is consistent across key patient subgroups, and is an effective treatment option via both oral and feeding tube administration. Dose reduction of afatinib effectively reduced the incidence and severity of key AEs, suggesting that this strategy is effective in helping to limit the impact of treatment-related AEs in patients for whom high symptom burden is a common challenge.

Author contributions

All authors approved the final draft for submission. Robert Haddad and Ezra E. W. Cohen contributed towards study design; data acquisition, analysis and interpretation; and manuscript preparation, editing and review. Joel Guigay, Ulrich Keilholz, Jérôme Fayette, Lisa Licitra, Daniel Rauch and Thomas Gauler contributed towards data acquisition, analysis and interpretation; and manuscript review. Paul M. Clement, Lionnel Geoffrois, Gabriela Kornek and Sylvie Zanetta-Devauges contributed towards data acquisition and manuscript review. Luciano de Souza Viana contributed towards data acquisition, manuscript review and quality control of data and algorithms. Frédéric Rolland, Jan Vermorken contributed towards data analysis and interpretation; and manuscript review. Didier Cupissol contributed towards data acquisition, manuscript review and quality control of data and algorithms. Ulisses Ribaldo Nicolau contributed towards data acquisition, analysis and interpretation; manuscript editing and review; and quality control of data and algorithms. Jean-Pascal Machiels contributed towards study design; data analysis and interpretation; manuscript preparation and review. Makoto Tahara and Bohuslav Melichar contributed towards data acquisition, analysis and interpretation; and manuscript editing and review. Yuan Geng contributed towards study design; data acquisition, analysis and interpretation; manuscript preparation and review; statistical analysis and quality control of data and algorithms. Eleftherios Zografos contributed towards data analysis and interpretation; and manuscript preparation, editing and review.

Declaration of Competing Interest

Robert Haddad reports advisory council or committee participation for the National Comprehensive Cancer Network; consulting fees from Bristol-Myers Squibb, Merck, Bayer, Pfizer, Genentech, AstraZeneca and Loxo; and grants or funds from Bristol-Myers Squibb, Merck, Pfizer, Boehringer Ingelheim, Genentech, Kura and AstraZeneca. Joel Guigay reports advisory council or committee participation for AstraZeneca, Bristol-Myers Squibb, Innate Pharma, Merck KGaA, and Nanobiotix; and grants or funds from Bristol-Myers Squibb and Merck KGaA. Ulrich Keilholz reports honoraria and consulting fees from AstraZeneca, Bristol-Myers Squibb, MSD, Merck KGaA, Novartis and Pfizer; and grants or funds from AstraZeneca. Paul M. Clement reports consulting fees from Bristol-Myers Squibb, MSD, AbbVie, Vifor, Leo, Merck and AstraZeneca; and grants or funds from AstraZeneca. Jérôme Fayette reports honoraria from Bristol-Myers Squibb, MSD, AstraZeneca, Innate Pharma, Biogen and Merck Serono. Lisa Licitra reports advisory board participation (expert opinion) for Bayer, GlaxoSmithKline, MSD, Kura Oncology, Ipsen, Health & Life srl, Merck–Serono, Doxa Pharma srl; consulting fees for public speaking/teaching in medical meetings from Eisai, Bristol-Myers Squibb, MSD, Merck–Serono, Boehringer Ingelheim, Novartis, AstraZeneca, Roche, Bayer, Debiopharm, Sobi, Kura Oncology, Health & Life srl, Ipsen Innovation, Immuno-Oncology Hub, Incyte Biosciences Italy srl, Doxa Pharma srl, Amgen and Nanobiotics Sa; and grants or funds to her institution from Eisai, MSD, Merck–Serono, Boehringer Ingelheim, Novartis, AstraZeneca, Roche, Bristol-Myers Squibb, Celgene International, Exelixis inc, Hoffmann-La

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Data sharing statement

To ensure independent interpretation of clinical study results, Boehringer Ingelheim grants all external authors access to all relevant material, including participant-level clinical study data, and relevant material as needed by them to fulfill their role and obligations as authors under the ICMJE criteria.

Furthermore, clinical study documents (e.g. study report, study protocol, statistical analysis plan) and participant clinical study data are available to be shared after publication of the primary manuscript in a peer-reviewed journal and if regulatory activities are complete and other criteria met per the BI Policy on Transparency and Publication of Clinical Study Data: https://trials.boehringer-ingelheim.com/transparency_policy.html

Prior to providing access, documents will be examined, and, if necessary, redacted and the data will be de-identified, to protect the personal data of study participants and personnel, and to respect the boundaries of the informed consent of the study participants.

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Researchers should use https://clinicalstudydatarequest.com to request access to study data.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.oraloncology.2019.08.004.

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