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# Afatinib versus methotrexate as second-line treatment for patients with R/M HNSCC progressing on or after platinum-based therapy: LUX-Head & Neck 3 Phase III trial

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Ye Guo,[1*] Myung-Ju Ahn,[2] Anthony Chan,[3] Cheng-Hsu Wang,[4] Jin Hyoung Kang,[5] Sung-Bae Kim,[6] Maximino Bello III,[7] Rajendra Singh Arora,[8] Qingyuan Zhang,[9] Xiaohui He,[10] Ping Li,[11] Arunee Dechaphunkul,[12] Vijay Kumar,[13] Krishna Kamble,[14] Wie Li,[15] Alaa Kandil,[16] Ezra Cohen,[17] Yuan Geng,[18] Eleftherios Zografos,[19] Ping Zhang Tang[20]

[1]Shanghai East Hospital, Tongji University, Shanghai, China; [2]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea; [3]Chinese University of Hong Kong, Prince of Wales Hospital, Hong Kong, China; [4]Chang Gung Memorial Hospital, Keelung and Chang Gung University, College of Medicine, Keelung, Taiwan; [5]Seoul St. Mary's Hospital, Seoul, South Korea; [6]Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea; [7]St. Luke's Medical Center, Quezon City, Philippines; [8]Sujan Surgical Cancer Hospital and Amravati Cancer Foundation, Amravati, India; [9]Harbin Medical University Cancer Hospital, Harbin, China; [10]Cancer Hospital, Chinese Academy of Medical Science, Beijing, China; [11]West China Hospital, Sichuan University, Chengdu, China; [12]Prince of Songkla University, Songkhla, Thailand; [13]King George's Medical University, Lucknow, India; [14]Government Medical College and Hospital, Nagpur, India; [15]First Hospital Affiliated to Jilin University, Jilin, China; [16]Alexandria University Hospital, Alexandria, Egypt; [17]San Diego Moores Cancer Center, University of California, San Diego, CA, USA; [18]Boehringer Ingelheim (China) Investment Co., Ltd, China; [19]Boehringer Ingelheim Ltd, Bracknell, Berkshire, UK; [20]Cancer Hospital Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China


## Introduction

- Second-line treatment options are limited for patients with recurrent and/or metastatic (R/M) squamous cell carcinoma of the head and neck (HNSCC), particularly in Asian countries[1,2]
- In the global, randomized, Phase III LUX-Head & Neck 1 study, the ErbB family blocker, afatinib, was superior to methotrexate (MTX) in patients with R/M HNSCC[3]
  - Notable benefit with afatinib was seen in patients:
    - with p16-negative disease (surrogate for human papillomavirus [HPV]-negative disease)[4]
    - not pretreated with an anti-epidermal growth factor receptor (EGFR) antibody
- HNSCC is particularly prevalent in Asian countries; moreover, p16-negative disease is more common in Asian countries[5,6]
- LUX-Head & Neck 3 (NCT01856478) compared the efficacy and safety of afatinib versus MTX in Asian patients with R/M HNSCC after platinum-based therapy

## Methods

- Randomized, multi-center, open-label Phase III study
  - 53 centers in 8 countries (China, India, Korea, Thailand, Egypt, Taiwan, Hong Kong, and the Philippines)

**Key inclusion criteria**

- Aged ≥18 years
- Histologically/cytologically confirmed SCC of the oral cavity, oropharynx, hypopharynx, or larynx
- Not amenable to salvage surgery or radiotherapy
- ECOG PS 0/1
- Documented PD after platinum-based therapy*

**Key exclusion criteria**

- Primary site of nasopharynx, sinuses, and/or salivary glands
- More than 1 previous platinum-based systemic regimen for R/M disease, except immunotherapy before or after platinum-based treatment
- PD within 3 months of curatively intended treatment for LA/M HNSCC
- Pre-existing ILD or clinically relevant CV abnormalities

- Patients were randomized (2:1) to a starting dose of 40 mg/day afatinib (feeding tube or oral) or 40 mg/m$^2$/week iv MTX
- Tolerability-guided dose adjustments were permitted

*Previous treatment with EGFR-targeted antibody therapy (but not EGFR TKIs) allowed

CV, cardiovascular; ECOG PS, Eastern Cooperative Oncology Group performance status; ILD, interstitial lung disease; iv, intravenous; LA, locally advanced; PD, progressive disease; SCC, squamous cell carcinoma

## Methods (cont'd)

| | |
|---|---|
| Primary endpoint | • PFS by independent review |
| Secondary endpoints | • OS, ORR, PROs |
| Other endpoints | • Tumor shrinkage, DCR (PR+CR+SD) |

- Response was assessed by investigator and independent review per RECIST v1.1, Q6W for the first 24 weeks and Q8W thereafter
- PROs were assessed with QLQ-C30 and QLQ-H&N35
- AEs were assessed according to NCI CTCAE v3
- Tumor biomarker analysis of p16 status was assessed by IHC

AE, adverse event; CR, complete response; DCR, disease control rate; IHC, immunohistochemistry; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; PROs, patient-reported outcomes; QLQ-C, EORTC quality of life core module; QLQ-H&N, EORTC quality of life head and neck module; Q6W, every 6 weeks; Q8W, every 8 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease

## Results

### Patients and treatment

- 340 patients randomized (afatinib n=228; MTX n=112; **Table 1**) and 332 were treated (excludes 8 patients in the MTX arm)
- Median (range) duration of treatment was 3.0 (<0.1–35.9) and 1.4 (<0.1–8.8) months, respectively

**Table 1. Patient demographics and baseline characteristics**

| Characteristic | Afatinib (n=228) | MTX (n=112) |
|---|---|---|
| Male, n (%) | 193 (85) | 99 (88) |
| Median age, years (range) | 55·5 (28–83) | 58.0 (27–76) |
| ≥65 years, n (%) | 31 (14) | 16 (14) |
| Asian, n (%) | 215 (94) | 107 (96) |
| East Asian*, n (%) | 131 (58) | 78 (70) |
| ECOG PS 0/1, n (%) | 47 (21)/181 (79) | 24 (21)/88 (79) |
| p16 status†, n (%) | | |
| Positive | 9 (4) | 1 (<1) |
| Negative | 79 (35) | 30 (27) |
| No result available | 140 (61) | 81 (72) |
| Prior use of anti-EGFR mAb for R/M disease‡, n (%) | 30 (13) | 13 (12) |
| Smoking pack-years, n (%) | | |
| <10 | 107 (47) | 46 (41) |
| ≥10 | 120 (53) | 66 (59) |
| Localization of recurrence, n (%) | | |
| Locoregional only | 114 (50) | 59 (53) |
| Distant metastases only | 17 (8) | 7 (6) |
| Both | 96 (42) | 46 (41) |
| Best response to prior platinum-based therapy, n (%) | | |
| CR/PR | 9 (4)/29 (13) | 5 (4)/11 (10) |
| SD/PD | 29 (13)/135 (59) | 11 (10)/67 (60) |
| Unknown/missing | 10 (4)/16 (7) | 5 (4)/13 (12) |

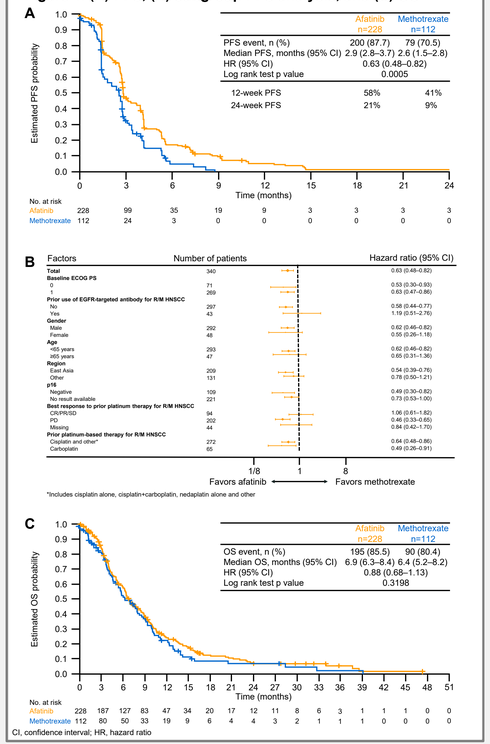
*China, Hong Kong, Korea, Taiwan; †Based on central test results; ‡9 patients received nimotuzumab and the rest received cetuximab; mAb, monoclonal antibody

## Efficacy

### Survival outcomes

- Afatinib reduced the risk of progression or death by 37%; the benefit was consistent across most subgroups (**Figure 1A and B**)
- There was no significant OS difference between arms (**Figure 1C**)

**Figure 1. (A) PFS, (B) subgroup PFS analysis, and (C) OS**

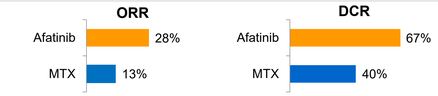



CI, confidence interval; HR, hazard ratio

## Efficacy (cont'd)

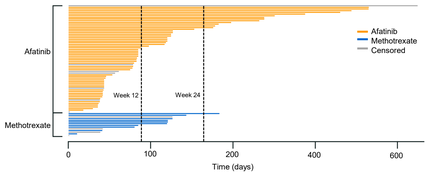
### Tumor response

- Significantly more patients in the afatinib arm had an objective response (odds ratio [OR] 2.76 [95% CI 1.47–5.18], p=0.0016)




- Median duration of response was 2.8 months (95% CI 2.6–3.9) with afatinib and 4.0 months (95% CI 1.4–4.7) with MTX (**Figure 2**)
- 22% and 7% of responding patients in the afatinib and MTX arms, respectively, were still in response at Week 24

**Figure 2. Duration of response**

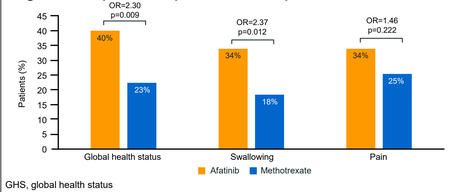



## Health-related quality of life

### PROs

- More patients had clinically relevant improvements in GHS/QoL (40% vs 23%, p<0.01), swallowing (34% vs 18%, p=0.01) and pain (34% vs 25%, p=0.22) with afatinib versus MTX (**Figure 3**)
- Post-baseline change in GHS was more favorable with afatinib versus MTX (22.9 vs 15.0; diff 7.9 [95% CI 3.5–12.4]; p=0.0005)

**Figure 3. Proportion of patients with improvement in PROs**




GHS, global health status

## Safety

- TRAEs (any grade/grade ≥3) were reported in 89/16% (**Table 2**) and 67/23% patients treated with afatinib and MTX

**Table 2. Most common TRAEs (≥10%) with afatinib**

| | Any grade | Grade ≥3 |
|---|---|---|
| Any TRAE, n (%) | 202 (89) | 37 (16) |
| Diarrhea | 153 (67) | 8 (4) |
| Rash/acne* | 126 (55) | 10 (4) |
| Stomatitis* | 86 (38) | 7 (3) |
| Paronychia* | 42 (18) | 2 (<1) |
| Dermatitis acneiform | 28 (12) | 1 (<1) |
| Mouth ulceration | 24 (11) | 1 (<1) |

*Grouped term
TRAE, treatment-related AE

- The most common grade ≥3 TRAEs were rash/acne (4%), diarrhea (4%), and stomatitis (3%) with afatinib, and anemia, leukopenia, and fatigue (all 5%) with MTX
- The tolerability profile of afatinib was in line with previous studies and experience; there were no unexpected safety signals

## Key findings and conclusions

- Afatinib significantly improved PFS and ORR versus MTX, with a manageable safety profile
- Efficacy benefits were complemented by improved QoL with afatinib versus MTX
- These results are consistent with the findings of LUX-Head & Neck 1,[3] and support the efficacy and feasibility of afatinib as a second-line treatment option for certain patients with R/M HNSCC, e.g.:
  - Patients with p16-negative disease
  - EGFR antibody-naïve patients

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*Corresponding author email address: pattrickguo@gmail.com