

David S. Ettinger, M.D., FACP, FCCP
Skip Viragh Outpatient Cancer Building
201 North Broadway
Viragh 9154, Box 6
Baltimore, MD 21287

July 24, 2018

Re: NCCN Guidelines Panel: Non-Small Cell Lung Cancer

Dear Dr. Ettinger,

Barbara Moehring, PharmD, MBA
Director, Clinical Development Medical
Affairs Oncology - Specialty Care

900 Ridgebury Rd/P.O. Box 368
Ridgefield, CT 06877-0368
Telephone (203) 778-7858
[barbara.moehring@boehringer-
ingelheim.com](mailto:barbara.moehring@boehringer-ingelheim.com)

On behalf of Boehringer Ingelheim Pharmaceuticals, Inc., I respectfully request that the NCCN Non-Small Cell Lung Cancer Guidelines Panel review and consider the inclusion of afatinib (GILOTRIF®) for treatment of advanced squamous cell carcinoma of the lung following progression on or after platinum-based chemotherapy based on the data described below.

Specific Change Requested: Add afatinib for subsequent therapy for the treatment of patients with advanced squamous cell carcinoma of the lung (SqCC) following progression on or after platinum-based chemotherapy.

Rationale:

Despite the FDA approval of afatinib for patients with SqCC in 2016,¹ many payers still deny access to afatinib because it is not recommended for second-line or beyond in the NCCN guidelines. This leads to instances where appropriate patients are not able to receive treatment with afatinib, despite the therapy decision already made with their physician. Some payers have decided to only include therapies on their formulary if recommended in the NCCN guidelines.

Afatinib was approved based on results from the phase 3 LUX-Lung 8 trial which randomized erlotinib or afatinib in patients with advanced squamous cell carcinoma of the lung following platinum based chemotherapy (N=795). The results of this study showed that treatment with afatinib significantly improved both overall survival (OS; median, 7.9 vs 6.8 months; hazard ratio [HR] 0.81; 95%CI, 0.69-0.95; P=.008) and progression free survival (PFS; median, 2.6 vs 1.9 months; HR, 0.81; 95% CI 0.69-0.96; P=.01) as compared to treatment with erlotinib. Afatinib was also associated with modest improvements in disease control rate, patient related outcomes, and disease-related symptoms versus erlotinib. The pattern of adverse events was similar between treatments and consistent with their already established safety profiles.^{1,2}

In a recently published article by Goss et al., the investigators conducted an ad hoc secondary analysis of LUX-Lung 8 to determine if outcomes were associated with *ERBB* family member aberrations. Tumor specimens from 245 patients who had PFS > 2 months were eligible for next generation sequencing (NGS). Among afatinib treated patients (n=132), PFS (median, 4.9 vs 3.0 months; HR, 0.62; 95%CI, 0.37-1.02; P=0.06) and OS (median, 10.6 vs 8.1 months; HR, 0.75, 95% CI 0.47-1.17; P=.21) were longer among those with *ERBB* mutation-positive disease than among those without. The authors concluded that afatinib is a second-line treatment option for lung SqCC and may be particularly suitable for patients whose tumors carry at least one *ERBB* mutation.³

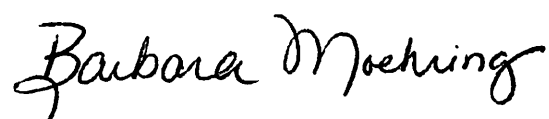
In addition, in a retrospective analysis of the phase 3 LUX-Lung 8 trial the ability of the VeriStrat serum protein test to predict differential clinical benefit with afatinib versus erlotinib, and the association of VeriStrat status with clinical outcomes irrespective of EGFR-TKI used, were assessed. Pretreatment plasma samples were analyzed using matrix-assisted laser desorption ionization time-of-flight mass spectrometry. Spectra were evaluated to assign a VeriStrat 'Good' (VS-G) or VeriStrat 'Poor' (VS-P) classification. Overall survival (OS), progression-free survival, and other endpoints were assessed with respect to pretreatment VeriStrat status. OS was the primary efficacy variable. VS-G classification was strongly associated with favorable survival outcomes with either afatinib or erlotinib compared with VS-P classification. In VS-G patients, survival outcomes with afatinib were superior to those with erlotinib.⁴

EGFR+ mNSCLC

The most recent Supplemental NDA approval (January 12, 2018) from the FDA for GILOTRIF® (afatinib) tablets broadens GILOTRIF's indication as a first-line treatment for patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have non-resistant epidermal growth factor receptor (EGFR) mutations as detected by an FDA-approved test. The product label for GILOTRIF now includes the following uncommon non-resistant EGFR mutations: G719X, L861Q, and S768I. FDA initially approved GILOTRIF in 2013 for the treatment of patients with metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test.¹

Thank you for taking the time to consider the request in this letter. Please let me know if you have any questions or require additional information.

Sincerely,



Barbara Moehring, PharmD, MBA
Director, Clinical Development Medical Affairs (CDMA) Oncology – Specialty Care

References:

1. GILOTRIF® (afatinib) [package insert]; Ridgefield, CT USA, 2018.
2. Soria JC, Felip E, Cobo M et al. Afatinib (A) vs erlotinib (E) as second-line therapy of patients (pts) with advanced squamous cell carcinoma (SC) of the lung (LUX-Lung 8); open-label randomized controlled phase 3 trial. *Lancet Oncol.* 2015;16(8):897-907.
3. Goss GD, Felip E, Cobo M et al. Association of ERBB mutations with clinical outcomes of afatinib-or erlotinib-treated patients with lung squamous cell carcinoma. Secondary analysis of the LUX-Lung 8 randomized clinical trial. *JAMA Oncol.* Published online June 14, 2018.
4. Gadgeel S, Goss G, Soria JC, et al. Evaluation of the VeriStrat® serum protein test in patients with advanced squamous cell carcinoma of the lung treated with second-line afatinib or erlotinib in the phase III LUX-Lung 8 study. *Lung Cancer.* 2017;109:101-108. Free full text available at: <https://www.ncbi.nlm.nih.gov/pubmed/28577938>.