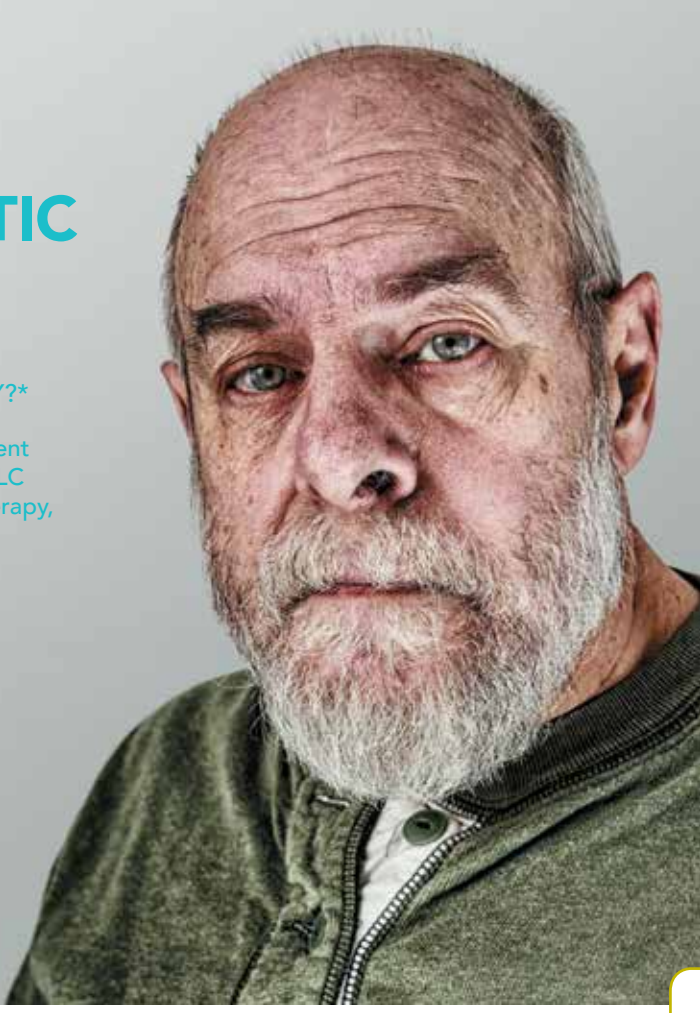
WHAT ARE THE TREATMENT OPTIONS FOR

PATIENTS WITH METASTATIC SQUAMOUS NSCLC AFTER PROGRESSING

ON PLATINUM-BASED CHEMOTHERAPY?*

GILOTRIF is the only FDA-approved oral agent for patients with metastatic squamous NSCLC progressing after platinum-based chemotherapy, regardless of mutation status.[1,2]



*Not an actual patient.

INDICATIONS AND USAGE

GILOTRIF is indicated for the first-line treatment of 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.

Limitations of Use: Safety and efficacy of GILOTRIF have not been established in patients whose tumors have resistant EGFR mutations.

GILOTRIF is indicated for the treatment of patients with metastatic squamous NSCLC progressing after platinum-based chemotherapy.

SELECTED IMPORTANT SAFETY INFORMATION FOR GILOTRIF® (afatinib) TABLETS

WARNINGS AND PRECAUTIONS

Diarrhea

- GILOTRIF can cause diarrhea which may be severe and can result in dehydration with or without renal impairment. In clinical studies, some of these cases were fatal.

Please see Important Safety Information continued on the following pages and full Prescribing Information, including Patient Information.

GILOTRIF® (afatinib) tablets

Consider GILOTRIF® (afatinib) tablets as early as second line for patients progressing after platinum-based chemotherapy, regardless of mutation status[1,2]

No biomarker testing required[1,2]

Treatment options in later lines of therapy[1,3]:

GILOTRIF

ADDITIONAL LINES OF CHEMOTHERAPY*

BEST SUPPORTIVE CARE

*Not an actual patient.

SELECTED IMPORTANT SAFETY INFORMATION FOR GILOTRIF® (afatinib) TABLETS

WARNINGS AND PRECAUTIONS

Diarrhea (cont'd)

- For patients who develop Grade 2 diarrhea lasting more than 48 hours or Grade 3 or greater diarrhea, withhold GILOTRIF until diarrhea resolves to Grade 1 or less, and then resume at a reduced dose.
- Provide patients with an anti-diarrheal agent (e.g., loperamide) for self-administration at the onset of diarrhea and instruct patients to continue anti-diarrheal until loose stools cease for 12 hours.

Bullous and Exfoliative Skin Disorders

- GILOTRIF can result in cutaneous reactions consisting of rash, erythema, and acneiform rash. In addition, palmar-plantar erythrodysesthesia syndrome was observed in clinical trials in patients taking GILOTRIF.
- Discontinue GILOTRIF in patients who develop life-threatening bullous, blistering, or exfoliating skin lesions. For patients who develop Grade 2 cutaneous adverse reactions lasting more than 7 days, intolerable Grade 2, or Grade 3 cutaneous reactions, withhold GILOTRIF. When the adverse reaction resolves to Grade 1 or less, resume GILOTRIF with appropriate dose reduction.

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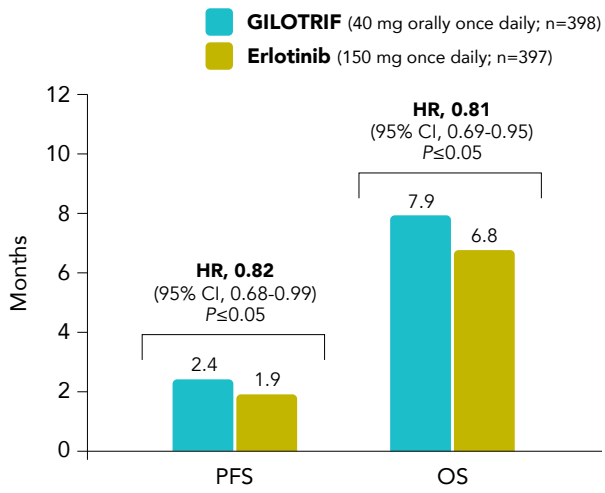
Significant improvements in PFS and OS vs erlotinib in LUX-Lung 8[1]*

Median PFS and median OS[1]



(201/398) ACHIEVED DISEASE CONTROL[2†]

- Approximately 37% of patients (146/398) treated with GILOTRIF® (afatinib) tablets achieved stable disease or objective response, based on a post hoc analysis[2]
- Median duration of objective response: 7.3 months (95% CI, 3.7-16.5) with GILOTRIF vs 3.7 months (95% CI, 2.6-10.2) with erlotinib[2]

*In LUX-Lung 8, a head-to-head trial of GILOTRIF 40 mg once daily vs erlotinib 150 mg once daily in patients with metastatic squamous NSCLC with disease progression following ≥4 cycles of platinum-based chemotherapy; primary endpoint was PFS; key secondary endpoint was OS.[2]

†Disease control was defined as complete response, partial response, stable disease, or non-complete response and non-progressive disease.[2]

CI=confidence interval; HR=hazard ratio; OS=overall survival; PFS=progression-free survival.

Bullous and Exfoliative Skin Disorders (cont'd)

- Postmarketing cases of toxic epidermal necrolysis (TEN) and Stevens Johnson syndrome (SJS) have been reported in patients receiving GILOTRIF. Discontinue GILOTRIF if TEN or SJS is suspected.

Interstitial Lung Disease

- Interstitial Lung Disease (ILD) or ILD-like adverse reactions (e.g., lung infiltration, pneumonitis, acute respiratory distress syndrome, or alveolitis allergic) occurred in patients receiving GILOTRIF in clinical trials. In some cases, ILD was fatal. The incidence of ILD appeared to be higher in Asian patients as compared to white patients.
- Withhold GILOTRIF during evaluation of patients with suspected ILD, and discontinue GILOTRIF in patients with confirmed ILD.

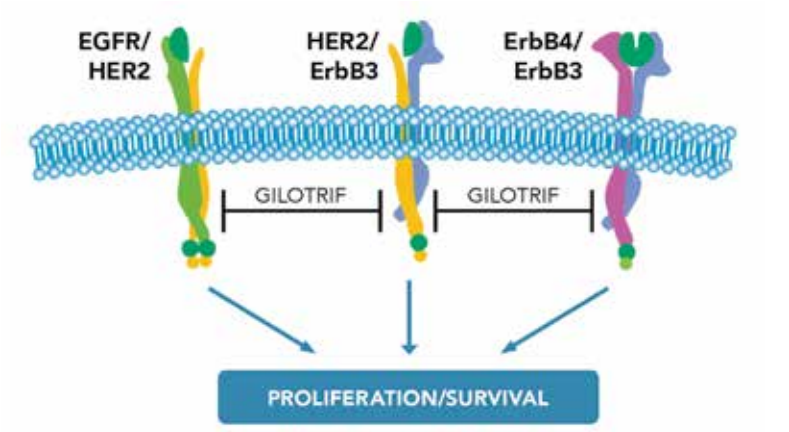
Hepatic Toxicity

- Hepatic toxicity as evidenced by liver function tests abnormalities has been observed in patients taking GILOTRIF. In 4257 patients who received GILOTRIF across clinical trials, 9.7% had liver test abnormalities, of which 0.2% were fatal.

ErbB proteins, including EGFR, are frequently altered in patients with squamous NSCLC[4]

- ErbB family proteins drive oncogenesis and can be mutated or overexpressed in patients with NSCLC[4-6]
  - 21.6% of patients with squamous NSCLC had tumors with 1 or more ErbB mutations in an exploratory, retrospective analysis of tumor specimens from 245 patients eligible for next-generation sequencing in LUX-Lung 8[4]
- GILOTRIF® (afatinib) tablets irreversibly block signaling from all homo- and heterodimers formed by select ErbB family members EGFR (ErbB1), HER2 (ErbB2), and ErbB4[1,7]

Irreversible inhibition of select ErbB receptor family signaling by GILOTRIF[1,7,8]



Adapted with permission from Hirsch V. *BioDrugs*. 2015;29(3):171.

The clinical significance of the mechanism of action has not been established.

Hepatic Toxicity (cont'd)

- Obtain periodic liver testing in patients during treatment with GILOTRIF. Withhold GILOTRIF in patients who develop worsening of liver function. Discontinue treatment in patients who develop severe hepatic impairment while taking GILOTRIF.

Gastrointestinal Perforation

- Gastrointestinal (GI) perforation, including fatal cases, has occurred with GILOTRIF. GI perforation has been reported in 0.2% of patients treated with GILOTRIF among 3213 patients across 17 randomized controlled clinical trials.
- Patients receiving concomitant corticosteroids, nonsteroidal anti-inflammatory drugs (NSAIDs), or anti-angiogenic agents, or patients with increasing age or who have an underlying history of GI ulceration, underlying diverticular disease, or bowel metastases may be at an increased risk of perforation.
- Permanently discontinue GILOTRIF in patients who develop GI perforation.

Keratitis

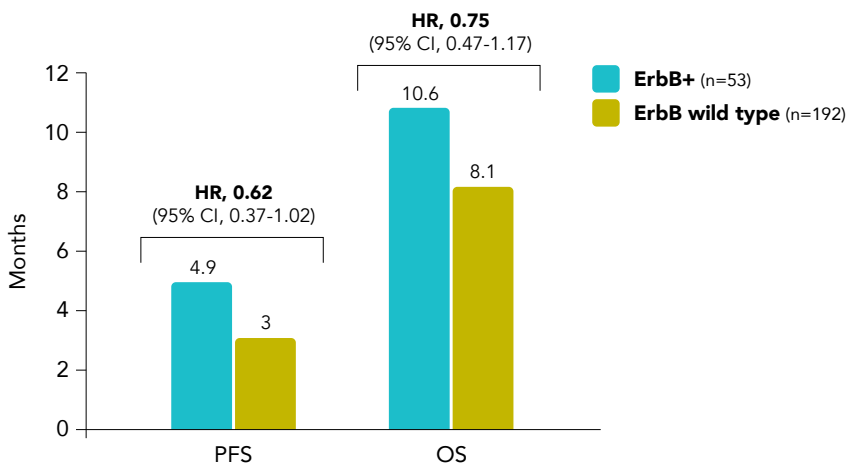
- Keratitis has been reported in patients taking GILOTRIF.

Observed benefits of GILOTRIF were more pronounced in squamous NSCLC patients with ErbB mutations[4]

The efficacy of GILOTRIF in squamous NSCLC may be due to suppression of compensatory signaling through ErbB family members[9]

- In an ad hoc analysis, 245 patients had tissue samples available for next-generation sequencing, and 53 patients had ErbB mutations (EGFR, HER2, ErbB4)[4]

Median PFS and median OS in patients with and without ErbB mutations[4]



In an exploratory retrospective analysis of LUX-Lung 8, researchers developed a hypothesis that may explain differential responses seen in this patient population.[2]

The specimens for tumor genetic analysis (TGA) were retrospectively selected and enriched for patients with PFS of more than 2 months (149/245 [60.8%] of patients with specimens used for TGA had PFS of more than 2 months vs 341/795 [42.9%] of patients in the overall LUX-Lung 8 population) to ensure that the data set reflected a range of responsiveness to EGFR-targeted TKIs.[2]

TKI=tyrosine kinase inhibitor.

Keratitis (cont'd)

- Withhold GILOTRIF during evaluation of patients with suspected keratitis. If diagnosis of ulcerative keratitis is confirmed, interrupt or discontinue GILOTRIF. If keratitis is diagnosed, the benefits and risks of continuing treatment should be carefully considered. GILOTRIF should be used with caution in patients with a history of keratitis, ulcerative keratitis, or severe dry eye. Contact lens use is also a risk factor for keratitis and ulceration.

Embryo-Fetal Toxicity

- GILOTRIF can cause fetal harm when administered to a pregnant woman. Advise pregnant women and females of reproductive potential of the potential risk to a fetus.

GILOTRIF® (afatinib) tablets

Similar occurrence of serious adverse reactions vs erlotinib[2]

In LUX-Lung 8,*

- 44% of patients in each treatment arm experienced serious adverse reactions[2]

Adverse reactions reported in ≥10% of GILOTRIF-treated patients[1]

Adverse reaction	GILOTRIF (n=392) Grade 3-4, %	Erlotinib (n=395) Grade 3-4, %	GILOTRIF (n=392) All grades, %	Erlotinib (n=395) All grades, %
Gastrointestinal disorders				
Diarrhea	11	3	75	41
Stomatitis†	4	1	30	11
Nausea	2	1	21	16
Vomiting	1	1	13	10
Skin and subcutaneous tissue disorders				
Rash/acneiform dermatitis‡	7	11	70	70
Pruritus	0	0	10	13
Infections				
Paronychia§	1	0	11	5
Metabolism and nutrition disorders				
Decreased appetite	3	2	25	26

*In the LUX-Lung 8 phase 3 study (N=795), GILOTRIF was compared with erlotinib for second-line treatment of patients with squamous NSCLC.[2]

†Includes stomatitis, aphthous stomatitis, mucosal inflammation, mouth ulceration, oral mucosa erosion, mucosal erosion, mucosal ulceration.[1]

‡Includes acne, dermatitis, acneiform dermatitis, eczema, erythema, exfoliative rash, folliculitis, rash, rash generalized, rash macular, rash maculo-papular, rash pruritic, rash pustular, skin exfoliation, skin fissures, skin lesion, skin reaction, skin toxicity, skin ulcer.[1]

§Includes paronychia, nail infection, nail bed infection.[1]

Treatment-related discontinuation due to any adverse reactions was similar in both arms (20% vs 17% for GILOTRIF® [afatinib] vs erlotinib). The most frequent adverse reactions that led to discontinuation in GILOTRIF-treated patients were diarrhea (4.1%) and rash/acne (2.6%).[1,2]

MORE THAN 13,000 PATIENTS HAVE BEEN TREATED WITH GILOTRIF SINCE ITS APPROVAL[10]

SELECTED IMPORTANT SAFETY INFORMATION FOR GILOTRIF® (afatinib) TABLETS

WARNINGS AND PRECAUTIONS

Embryo-Fetal Toxicity (cont'd)

- Advise females of reproductive potential to use effective contraception during treatment, and for at least 2 weeks after the last dose of GILOTRIF. Advise female patients to contact their healthcare provider with a known or suspected pregnancy.

Please see Important Safety Information continued on the following pages and full Prescribing Information, including Patient Information.

SELECTED IMPORTANT SAFETY INFORMATION FOR GILOTRIF® (afatinib) TABLETS

ADVERSE REACTIONS

Adverse Reactions observed in clinical trials were as follows:

First-line treatment of EGFR mutation-positive, metastatic NSCLC

- In GILOTRIF® (afatinib)-treated patients (n=229) the most common adverse reactions (≥20% all grades & vs pemetrexed/cisplatin-treated patients (n=111)) were diarrhea (96% vs 23%), rash/acneiform dermatitis (90% vs 11%), stomatitis (71% vs 15%), paronychia (58% vs 0%), dry skin (31% vs 2%) and pruritus (21% vs 1%). Other clinically important adverse reactions observed in patients treated with GILOTRIF include: decreased appetite (29%), nausea (25%), and vomiting (23%).
- Serious adverse reactions were reported in 29% of patients treated with GILOTRIF. The most frequent serious adverse reactions reported in patients treated with GILOTRIF were diarrhea (6.6%); vomiting (4.8%); and dyspnea, fatigue, and hypokalemia (1.7% each). Fatal adverse reactions in GILOTRIF-treated patients included pulmonary toxicity/ILD-like adverse reactions (1.3%), sepsis (0.43%), and pneumonia (0.43%).
- More GILOTRIF-treated patients (2.2%) experienced ventricular dysfunction (defined as diastolic dysfunction, left ventricular dysfunction, or ventricular dilation; all < Grade 3) compared to chemotherapy-treated patients (0.9%).

Previously Treated, Metastatic Squamous NSCLC

- In GILOTRIF-treated patients (n=392) the most common adverse reactions (≥20% all grades & vs erlotinib-treated patients (n=395)) were diarrhea (75% vs 41%), rash/acneiform dermatitis (70% vs 70%), stomatitis (30% vs 11%), decreased appetite (25% vs 26%), and nausea (21% vs 16%).
- Serious adverse reactions were reported in 44% of patients treated with GILOTRIF. The most frequent serious adverse reactions reported in patients treated with GILOTRIF were pneumonia (6.6%), diarrhea (4.6%), and dehydration and dyspnea (3.1% each). Fatal adverse reactions in GILOTRIF-treated patients included ILD (0.5%), pneumonia (0.3%), respiratory failure (0.3%), acute renal failure (0.3%), and general physical health deterioration (0.3%).

DRUG INTERACTIONS

Effect of P-glycoprotein (P-gp) Inhibitors and Inducers

- Concomitant use of P-gp inhibitors (including but not limited to ritonavir, cyclosporine A, ketoconazole, itraconazole, erythromycin, verapamil, quinidine, tacrolimus, nelfinavir, saquinavir, and amiodarone) with GILOTRIF can increase exposure to afatinib.
- Concomitant use of P-gp inducers (including but not limited to rifampicin, carbamazepine, phenytoin, phenobarbital, and St. John's wort) with GILOTRIF can decrease exposure to afatinib.

USE IN SPECIFIC POPULATIONS

Lactation

- Because of the potential for serious adverse reactions in breastfed infants from GILOTRIF, advise women not to breastfeed during treatment with GILOTRIF and for 2 weeks after the final dose.

Females and Males of Reproductive Potential

- GILOTRIF may reduce fertility in females and males of reproductive potential. It is not known if the effects on fertility are reversible.

What are the treatment options for patients with metastatic squamous NSCLC after progressing on platinum-based chemotherapy?

Consider GILOTRIF after progression on a platinum-based chemotherapy

- GILOTRIF is the only oral agent approved in metastatic squamous NSCLC regardless of mutation status[1,2]
- Median PFS and OS were significantly longer with GILOTRIF vs erlotinib[1,2]
- Similar occurrence of serious adverse reactions vs erlotinib[2]

SELECTED IMPORTANT SAFETY INFORMATION FOR GILOTRIF® (afatinib) TABLETS

USE IN SPECIFIC POPULATIONS

Renal Impairment

- Patients with severe renal impairment (estimated glomerular filtration rate [eGFR] 15 to 29 mL/min/1.73 m^2) have a higher exposure to afatinib than patients with normal renal function. Administer GILOTRIF at a starting dose of 30 mg once daily in patients with severe renal impairment. GILOTRIF has not been studied in patients with eGFR <15 mL/min/1.73 m^2 or who are on dialysis.

Hepatic Impairment

- GILOTRIF has not been studied in patients with severe (Child Pugh C) hepatic impairment. Closely monitor patients with severe hepatic impairment and adjust GILOTRIF dose if not tolerated.

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Please see Important Safety Information above and on the previous pages and full Prescribing Information, including Patient Information.

References: 1. GILOTRIF [prescribing information]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc. **2.** Soria JC, Felip E, Cobo M, et al. Afatinib versus erlotinib as second-line treatment of patients with advanced squamous cell carcinoma of the lung (LUX-Lung 8): an open-label randomised controlled phase 3 trial. *Lancet Oncol*. 2015;16(8):897-907. **3.** Paik PK, Pillai RN, Lathan CS, Velasco SA, Papadimitrakopoulou V. New treatment options in advanced squamous cell lung cancer. *Am Soc Clin Oncol Educ Book*. 2019;39:e198-e206. **4.** 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*. 2018;4(9):1189-1197. **5.** Engelman JA, Cantley LC. The role of the ErbB family members in non-small cell lung cancers sensitive to epidermal growth factor receptor kinase inhibitors. *Clin Cancer Res*. 2006;12(14 Pt 2):4372s-4376s. **6.** Pillai RN, Behera M, Berry LD, et al. HER2 mutations in lung adenocarcinomas: a report from the Lung Cancer Mutation Consortium. *Cancer*. 2017;123(21):4099-4105. **7.** Solca F, Dahl G, Zoephel A, et al. Target binding properties and cellular activity of afatinib (BIBW 2992), an irreversible ErbB family blocker. *J Pharmacol Exp Ther*. 2012;343(2):342-350. **8.** Hirsh V. Next-generation covalent irreversible kinase inhibitors in NSCLC: focus on afatinib. *BioDrugs*. 2015;29(3):167-183. **9.** Xu Y, Ding VW, Zhang H, et al. Spotlight on afatinib and its potential in the treatment of squamous cell lung cancer: the evidence so far. *Ther Clin Risk Manag*. 2016;12:807-816. **10.** Data on file.

Boehringer Ingelheim

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