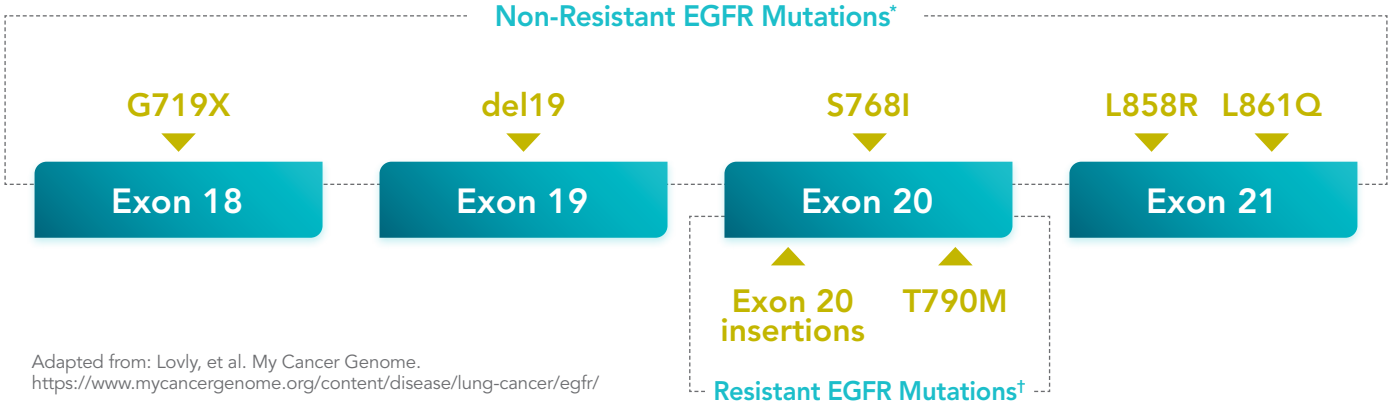
Identify non-resistant EGFR mutations to determine the appropriate first-line treatment[1,2]

Overview of prevalent non-resistant and resistant EGFR mutations[3]



Adapted from: Lovly, et al. My Cancer Genome. https://www.mycancergenome.org/content/disease/lung-cancer/egfr/

*As per GILOTRIF prescribing information.

†Limitation of use: Safety and efficacy of GILOTRIF have not been established in patients whose tumors have resistant mutations; resistant mutations may include others besides T790M and exon 20 insertions.

GILOTRIF has the broadest first-line indication of any TKI in EGFR M+ mNSCLC[4,5]

Mutations covered by EGFR TKIs indicated in 1st-line

Mutations	GILOTRIF® (afatinib) tablets*	TAGRISSO® (osimertinib)§
del19	✓	✓
L858R	✓	✓
L861Q	✓	¶
G719X	✓	¶
S768I	✓	¶

EGFR=epidermal growth factor receptor; EGFR M+=epidermal growth factor receptor mutation positive; FDA=US Food and Drug Administration; mNSCLC=metastatic non-small cell lung cancer; TKI=tyrosine kinase inhibitor.

*GILOTRIF (afatinib) is a kinase inhibitor indicated for 1st-line treatment of patients with mNSCLC whose tumors have non-resistant EGFR mutations as detected by an FDA-approved test.

§TAGRISSO is a kinase inhibitor indicated for the first-line treatment of patients with metastatic NSCLC whose tumors have epidermal growth factor (EGFR) exon 19 deletions or exon 21 L858R mutations, as detected by an FDA-approved test.

¶Not indicated.

GILOTRIF® (afatinib) tablets

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.

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.
- 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.
- 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.
- 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.
- 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.
- 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.

ADVERSE REACTIONS

Adverse Reactions observed in clinical trials were as follows:

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

- In GILOTRIF-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.

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 accompanying full Prescribing Information, including Patient Information.

Proven efficacy in non-resistant EGFR mutations

- Among the 75 GILOTRIF-treated patients with uncommon EGFR mutations, 32 patients had a non-resistant EGFR mutation[4*]
- The confirmed overall response rate, as assessed by independent radiology review, was 66% (95% CI, 47%–81%)[4,7]
- At the time of the assessment, among the 21 responders, 52% of patients had a response duration of ≥12 months and 33% had a response duration of ≥18 months[7]

Activity of GILOTRIF in additional mutations (single or in combination)[4*]

EGFR mutation	Number of patients treated with GILOTRIF (n=32)	Number of confirmed responses (n=21)	Duration of response, mo (n=21)
S768I	1	1	37.3
S768I and G719X	5	4	4.1, 13.2, 15.2, 29.5†
S768I and L858R	2	1	34.5†
G719X	8	6	5.7,† 8.1, 9.6, 23.5,† 25.2, 31.8†
G719X and L861Q	3	2	2.8,† 6.8
L861Q	12	7	2.8, 4.0, 4.1, 8.3,† 12.9, 15.2, 20.6
L861Q and del19	1	0	N/A

*Data from a pooled analysis of LUX-Lung 2, 3, and 6.‡

†Response ongoing at time of censoring.

Additional efficacy data by mutation[4,6]

Objective response, progression free survival, and overall survival‡

Mutation	Objective Response	PFS (months)	OS (months)
G719X (n=18)	14 (77.8%, 52.4–93.6)	13.8 (6.8–NE)	26.9 (16.4–NE)
L861Q (n=16)	9 (56.3%, 29.9–80.2)	8.2 (4.5–16.6)	17.1 (15.3–21.6)
S768I (n=8)	8 (100.0%, 63.1–100.0)	14.7 (2.6–NE)	NE (3.4–NE)

Data are n (%, 95% CI) or median (95% CI).

- Tumor response (ORR and PFS) was assessed prospectively by RECIST in a central independent radiology review as part of the original study design

NE=not evaluable; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; RECIST=Response Evaluation Criteria in Solid Tumors.

‡Efficacy data are from a pooled analysis of LUX-Lung 2, 3, and 6. LUX-Lung 2: a single arm, multicenter study of afatinib 40 or 50 mg orally once daily until disease progression or intolerable side effects. EGFR status was determined by bi-directional Sanger sequencing of tumor tissue. LUX-Lung 3: a randomized, multicenter study comparing treatment with afatinib 40 mg orally once daily to intravenous cisplatin 75 mg/m^2 plus pemetrexed 500 mg/m^2 every 21 days for up to 6 cycles. EGFR status was determined by the therascreen® EGFR RGQ PCR Kit. LUX-Lung 6: a randomized, multicenter study comparing treatment with afatinib 40 mg to intravenous gemcitabine 1000 mg/m^2 on day 1 and day 8 plus cisplatin 75 mg/m^2 on day 1 of a 3-week schedule for up to 6 cycles. EGFR status was determined by the therascreen® EGFR RGQ PCR Kit.

References 1. Kris MG, Johnson BE, Berry LD, et al. Using multiplexed assays of oncogenic drivers in lung cancers to select targeted drugs. *JAMA*. 2014;311(19): 1998-2006. **2.** Cheema PK, Raphael S, El-Maraghi R, et al. Rate of EGFR mutation testing for patients with nonsquamous non-small-cell lung cancer with implementation of reflex testing by pathologists. *Curr Oncol*. 2017;24(1):16-22. **3.** Lovly, C., L. Horn, W. Pao. 2015. EGFR in Non-Small Cell Lung Cancer (NSCLC). My Cancer Genome https://www.mycancergenome.org/content/disease/lung-cancer/egfr/ Accessed Nov. 26, 2019 **4.** GILOTRIF [prescribing information]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc. **5.** Tagrisso [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP. **6.** Yang JC, Sequist LV, Geater SL, et al. Clinical activity of afatinib in patients with advanced non-small-cell lung cancer harbouring uncommon EGFR mutations: a combined post-hoc analysis of LUX-Lung 2, LUX-Lung 3, and LUX-Lung 6. *Lancet Oncol*. 2015;16(7):830-838. **7.** U.S. Food & Drug Administration (FDA). FDA broadens afatinib indication to previously untreated, metastatic NSCLC with other non-resistant EGFR mutations (press release). https://www.fda.gov/drugs/informationondrugs/approveddrugs/ucm592558.htm. Accessed 3.13.2019.

Please see accompanying full Prescribing Information, including Patient Information.

Boehringer Ingelheim

GILOTRIF® (afatinib) tablets