Stay ahead of your patients

Models are for illustrative purposes only.

GioTag: an observational study

First retrospective, global, real-world study that assessed total treatment duration of GILOTRIF® (afatinib) tablets followed by osimertinib[1]

Limitations: The main limitations of this study were its retrospective nature and potential for selection bias. The other main limitation of the study was a lack of a comparator arm, which limits interpretation of the results.[1]

INDICATION 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.

SELECTED IMPORTANT SAFETY INFORMATION

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.

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

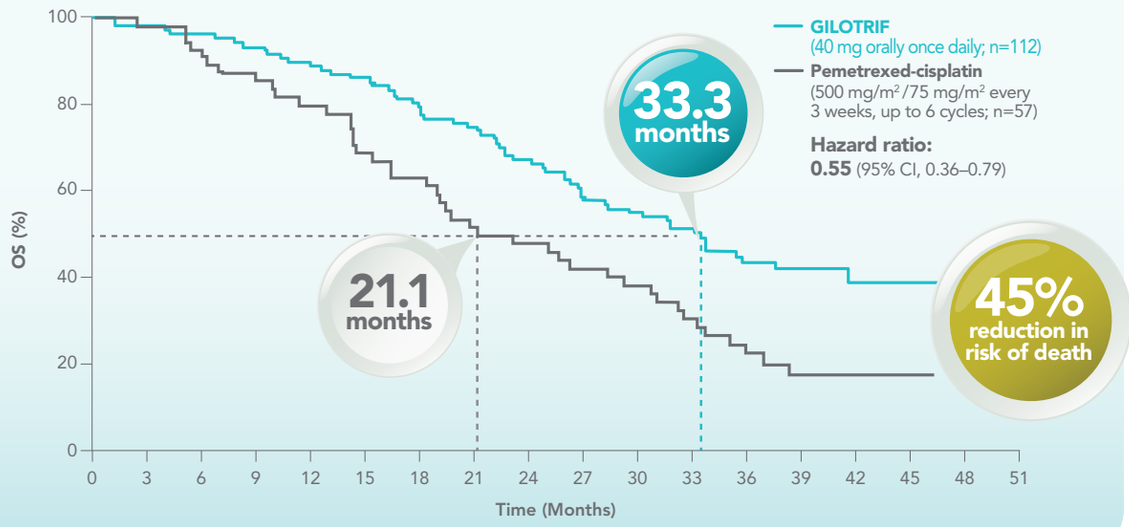
GILOTRIF® (afatinib) tablets

GILOTRIF® (afatinib) tablets: Foundational clinical trial results

GioTag data should be considered in context of results from GILOTRIF clinical trials.

In the LUX-Lung 3 trial, GILOTRIF achieved nearly 3 years overall survival (OS) in patients with del19 mutations[2,3]

Median OS in LUX-Lung 3: del19 mutations population[2,3*†]



*In a prespecified subgroup analysis of patients with del19 mutations for the secondary endpoint of OS.

†LUX-Lung 3: GILOTRIF 40 mg orally once daily (n=230) vs up to 6 cycles of pemetrexed-cisplatin (n=115) as first-line therapy in patients with EGFR M+ mNSCLC; primary endpoint was PFS; key secondary endpoint was OS.

Median PFS in del19: 13.7 months with GILOTRIF vs 5.6 months with pemetrexed-cisplatin (HR=0.28; 95% CI, 0.18–0.44) in a prespecified subanalysis of the primary endpoint[2,4†]

Adverse reactions (ARs) in LUX-Lung 3

Common ARs in LUX-Lung 3[2]

- In GILOTRIF-treated patients (n=229) the most common ARs (≥20% all grades and 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 ARs observed in patients treated with GILOTRIF include decreased appetite (29%), nausea (25%), and vomiting (23%)

Serious ARs reported in LUX-Lung 3[2]

- Serious ARs were reported in 29% of patients treated with GILOTRIF. The most frequent serious ARs reported in patients treated with GILOTRIF were diarrhea (6.6%), vomiting (4.8%), and dyspnea, fatigue, and hypokalemia (1.7% each). Fatal ARs in GILOTRIF-treated patients included pulmonary toxicity/ILD-like ARs (1.3%), sepsis (0.43%), and pneumonia (0.43%)

Discontinuations in LUX-Lung 3[2]

- Discontinuation of therapy in GILOTRIF-treated patients for ARs was 14%
- The most frequent ARs that led to discontinuation in GILOTRIF-treated patients were diarrhea (1.3%), ILD (0.9%), and paronychia (0.9%)

CI=confidence interval; EGFR M+=epidermal growth factor receptor mutation positive; HR=hazard ratio; ILD=interstitial lung disease; mNSCLC=metastatic non-small cell lung cancer; PFS=progression-free survival.

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

GioTag: Study design[1]

Limitations: The main limitations of this study were its retrospective nature and potential for selection bias. The other main limitation of the study was a lack of a comparator arm, which limits interpretation of the results.[1]

Global study across 10 countries[1]

204 patients*

73.5% (n=150) had a del19 mutation†

>15% (n=31) had an ECOG performance status (PS) of ≥2‡

- Real-world, global, multicenter, retrospective, observational study of 204 adult patients with EGFR M+ mNSCLC (del19 or L858R)
- 169 (83.7%) and 200 (98.0%) patients received starting doses of 40 mg/day GILOTRIF and 80 mg/day osimertinib, respectively
- The study used existing data from medical records or electronic health records (US only)
- Patients had T790M-positive disease following first-line GILOTRIF and had started on osimertinib treatment ≥10 months prior to data entry to avoid early censoring and ensure mature data
- The predominant reason for discontinuation of GILOTRIF was progressive disease (n=190, 93.1%). At the time of database lock (June 29, 2018), 106 patients (52.0%) had discontinued osimertinib, with progressive disease being the most common reason for discontinuation (n=98, 92.5%); 98 patients were continuing on osimertinib. Half of all patients (50.5%) started GILOTRIF therapy before 2016
- Patients who died on GILOTRIF or were unfit or unwilling for second-line therapy were excluded by the study design, which potentially introduced an immortal time bias. Long-term responders to first-line GILOTRIF were excluded due to the study design and thus may be underrepresented

Primary endpoint: Time on treatment

ECOG=Eastern Cooperative Oncology Group.

*Patients had diverse ethnicity with 120 (58.8%) Caucasians, 50 (24.5%) Asians, 18 (8.8%) African Americans, and 16 (7.8%) with no data/unknown.
†At the start of GILOTRIF treatment, 150 (73.5%) patients had a del19 mutation and 53 (26.0%) had the L858R mutation. One patient had both del19 and L858R.
‡At the start of GILOTRIF treatment, ECOG PS was 0, 1, or ≥2 in 43 (21.1%), 110 (53.9%), and 31 (15.2%) patients, respectively.

Results are not intended for direct comparison with clinical trials, because the real-world study was an observational trial with no comparator arm. Differences in study designs, patient populations, and definitions of safety or efficacy outcomes, as well as data collection methods, make it difficult to compare real-world studies with clinical trials.

SELECTED IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Bullous and Exfoliative Skin Disorders

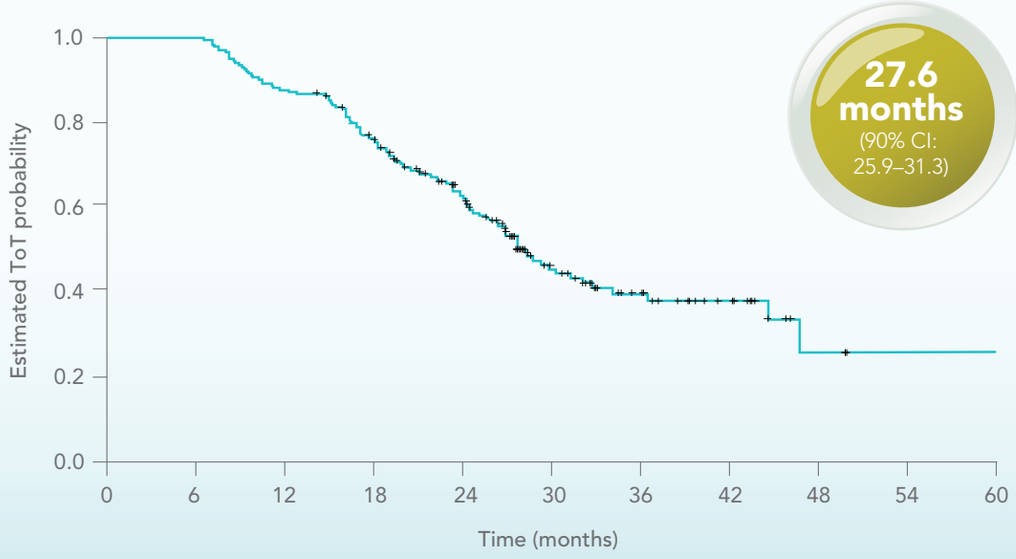
- GILOTRIF can result in cutaneous reactions consisting of rash, erythema, and acneiform rash. In addition, palmar-plantar erythrodysesthesia syndrome was observed in clinical trials in patients taking GILOTRIF.
- Discontinue GILOTRIF in patients who develop life-threatening bullous, blistering, or exfoliating 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.

GILOTRIF® (afatinib) tablets

GioTag: Median time on treatment

In the overall population, median time on treatment (ToT) for GILOTRIF® (afatinib) tablets followed by osimertinib was 27.6 months[1]

GioTag: Overall median time on treatment with sequential GILOTRIF and osimertinib in patients with common mutations



Adapted from Hochmair MJ, Morabito A, Hao D, et al. Sequential treatment with afatinib and osimertinib in patients with *EGFR* mutation-positive non-small-cell lung cancer: an observational study. *Future Oncol.* 2018;14(27):2861-2874.

In a subgroup analysis of patients with ECOG PS ≥2 (n=31) and stable brain metastases (n=21), the sequence of oral targeted therapy with GILOTRIF® (afatinib) tablets followed by osimertinib resulted in a median time on treatment of 22.2 months (90% CI: 16.0–27.0) and 19.4 months (90% CI: 16.0–NR), respectively[1]

NR=not reached.

SELECTED IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

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

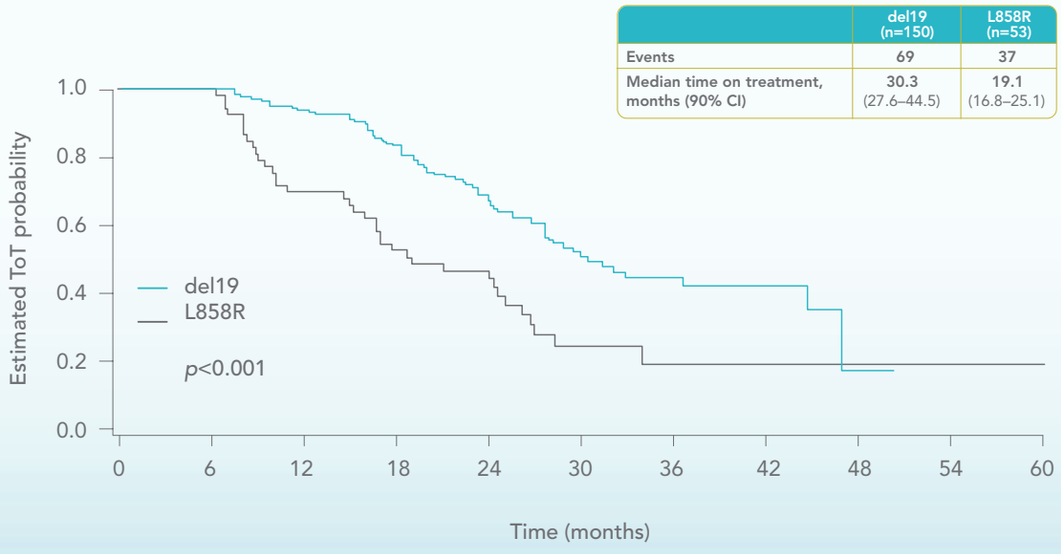
- Hepatic toxicity as evidenced by liver function tests abnormalities has been observed in patients taking GILOTRIF. In 4257 patients who received GILOTRIF across clinical trials, 9.7% had liver test abnormalities, of which 0.2% were fatal.
- Obtain periodic liver testing in patients during treatment with GILOTRIF. Withhold GILOTRIF in patients who develop worsening of liver function. Discontinue treatment in patients who develop severe hepatic impairment while taking GILOTRIF.

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

Patient subgroup analysis

Median time on treatment in patients with a del19 mutation was 30.3 months[1]

GioTag: Time on treatment in patients with del19 vs L858R mutations[1]



	del19 (n=150)	L858R (n=53)
Events	69	37
Median time on treatment, months (90% CI)	30.3 (27.6–44.5)	19.1 (16.8–25.1)

del19: 30.3 months

Adapted from Hochmair MJ, Morabito A, Hao D, et al. Sequential treatment with afatinib and osimertinib in patients with *EGFR* mutation-positive non-small-cell lung cancer: an observational study. *Future Oncol*. 2018;14(27):2861-2874.

- The majority (up to 73%) of del19 patients may develop a T790M resistance mutation after treatment with a first- or second-generation EGFR TKI[1,5,6]
- Patients with T790M mutations may be treated with osimertinib, the only approved T790M inhibitor in second-line therapy[7]

EGFR=epidermal growth factor receptor; TKI=tyrosine kinase inhibitor.

SELECTED IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

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.

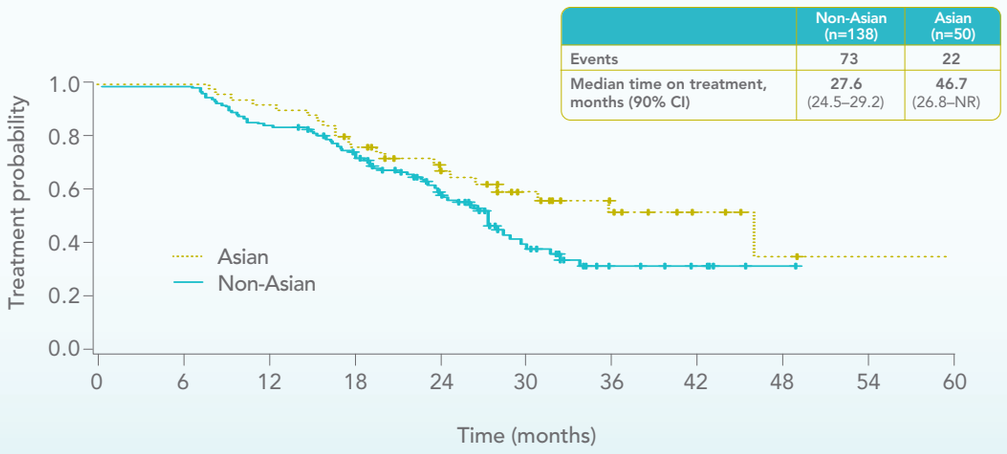
GILOTRIF® (afatinib) tablets

GioTag: Median time on treatment (cont'd)

Patient subgroup analysis

Median time on treatment in patients with Asian ethnicity was 46.7 months[1]

Time on treatment for the sequence - by ethnicity[1]



	Non-Asian (n=138)	Asian (n=50)
Events	73	22
Median time on treatment, months (90% CI)	27.6 (24.5–29.2)	46.7 (26.8–NR)

Patients at risk											
Non-Asian	138	138	117	99	70	22	9	6	1	0	0
Asian	50	50	46	38	29	18	13	6	2	1	1

Asian patients: 46.7 months

Adapted from Hochmair MJ, Morabito A, Hao D, et al. Sequential treatment with afatinib and osimertinib in patients with *EGFR* mutation-positive non-small-cell lung cancer: an observational study. *Future Oncol.* 2018;14(27):2861-2874.

- The estimated prevalence of EGFR mutations in patients of Asian ethnicity with pulmonary adenocarcinoma is approximately 50% to 60%[8]

NR=not reached.

SELECTED IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

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

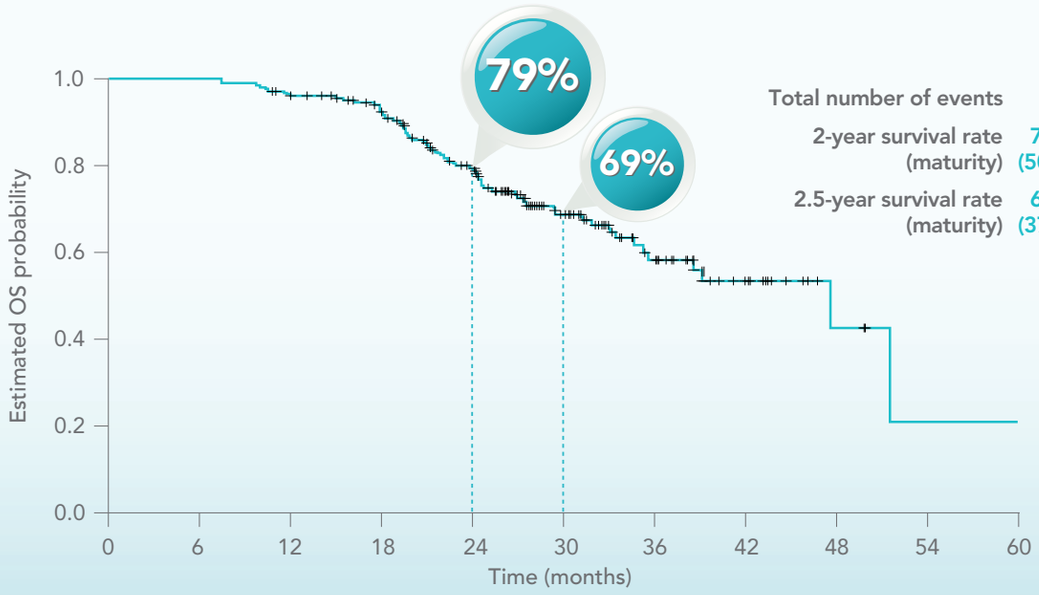
- In GILOTRIF-treated patients (n=229) the most common adverse reactions (≥20% all grades & vs pemetrexed/cisplatin-treated patients (n=111)) were diarrhea (96% vs 23%), rash/acneiform dermatitis (90% vs 11%), stomatitis (71% vs 15%), paronychia (58% vs 0%), dry skin (31% vs 2%) and pruritus (21% vs 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%).

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

GioTag: Overall survival rate

In this real-world study, the 2-year overall survival rate was 79% for those treated with sequential GILOTRIF and osimertinib therapy[1]

GioTag: Overall survival in patients with common mutations treated with sequential GILOTRIF and osimertinib therapy[1]



2-year OS in patients with common mutations using sequential therapy: 79%

Adapted from Hochmair MJ, Morabito A, Hao D, et al. Sequential treatment with afatinib and osimertinib in patients with *EGFR* mutation-positive non-small-cell lung cancer: an observational study. *Future Oncol.* 2018;14(27):2861-2874.

References:

1. Hochmair MJ, Morabito A, Hao D, et al. Sequential treatment with afatinib and osimertinib in patients with *EGFR* mutation-positive non-small-cell lung cancer: an observational study. *Future Oncol.* 2018;14(27):2861-2874.
2. GILOTRIF [prescribing information]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc.
3. Yang JCH, Wu YL, Schuler M, et al. Afatinib versus cisplatin-based chemotherapy for EGFR mutation-positive lung adenocarcinoma (LUX-Lung 3 and LUX-Lung 6): analysis of overall survival data from two randomised, phase 3 trials. *Lancet Oncol.* 2015;16(2):141-151.
4. Sequist LV, Yang JCH, Yamamoto N, et al. Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. *J Clin Oncol.* 2013;31(27):3327-3334.
5. Jenkins S, Yang JC, Jänne PA, et al. EGFR mutation analysis for prospective patient selection in two phase II registration studies of osimertinib. *J Thorac Oncol.* 2017;12(8):1247-1256.
6. Ke EE, Zhou Q, Zhang QY, et al. A higher proportion of the EGFR T790M mutation may contribute to the better survival of patients with Exon 19 deletions compared with those with L858R. *J Thorac Oncol.* 2017;12(9):1368-1375.
7. Girard N. Optimizing outcomes in EGFR mutation-positive NSCLC: which tyrosine kinase inhibitor and when? *Future Oncol.* 2018;14(11):1117-1132.
8. Steuer CE, Behera M, Berry L, et al. Role of race in oncogenic driver prevalence and outcomes in lung adenocarcinoma: results from the Lung Cancer Mutation Consortium. *Cancer.* 2016;122(5):766-772.

SELECTED IMPORTANT SAFETY INFORMATION

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.

GILOTRIF® (afatinib) tablets

Start with GILOTRIF® (afatinib) tablets as first-line treatment[1]

In the LUX-Lung 3 trial, GILOTRIF achieved nearly 3 years OS in patients with del19 mutations[2,3]

- In the del19 population, median OS was 33.3 months vs 21.1 months (HR=0.55; 95% CI, 0.36–0.79)

In the real-world, retrospective, observational GioTag study, the sequence of GILOTRIF followed by osimertinib achieved median time on treatment of 27.6 months (90% CI: 25.9–31.3)[1]

- In the overall population of patients with common mutations (del19 or L858R), median time on treatment was 27.6 months (90% CI: 25.9–31.3)
- Median time on treatment among patients with del19 mutations (n=150) was 30.3 months (90% CI: 27.6–44.5)
- Median time on treatment among patients with Asian ethnicity (n=50) was 46.7 months (90% CI: 26.8–NR)—almost 4 years

Results are not intended for direct comparison with clinical trials, because the real-world study was an observational trial with no comparator arm. Differences in study designs, patient populations, and definitions of safety or efficacy outcomes, as well as data collection methods, make it difficult to compare real-world studies with clinical trials.

SELECTED IMPORTANT SAFETY INFORMATION

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 Important Safety Information starting on the front cover and accompanying full Prescribing Information, including Patient Information.

Boehringer Ingelheim

GILOTRIF® (afatinib) tablets