Overall survival (OS) in patients with EGFR mutation-positive NSCLC receiving sequential afatinib and osimertinib: updated analysis of the observational GioTag study[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.

Study design[1,2]

- GioTag is a real-world, global, multicenter, noninterventional, observational study of 204 adult patients with EGFR M+ NSCLC (Del19/L858R)
- The study used existing data from medical records or electronic health records (US only)
- Patients had T790M-positive disease following first-line afatinib and had started on osimertinib treatment ≥10 months prior to data entry
- The primary outcome was median time to treatment failure, also referred to as time on treatment (defined as the time from the first dose of afatinib to the time of the last dose of osimertinib or death)
- The secondary outcome was the type and proportion of acquired resistance mechanisms after osimertinib treatment
- Although OS was not a primary outcome of the study and was not mature at the time of analysis, it was measured and included as a part of the statistical analysis plan
- For the interim analysis presented here, updated data were collected from 94 US patients with available electronic health records; final analysis, incorporating data from manual chart reviews of a further 29 patients, is anticipated in early 2020

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.

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

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%).

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.

EGFR M+=epidermal growth factor receptor mutation positive; NSCLC=non-small cell lung cancer; OS=overall survival.

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

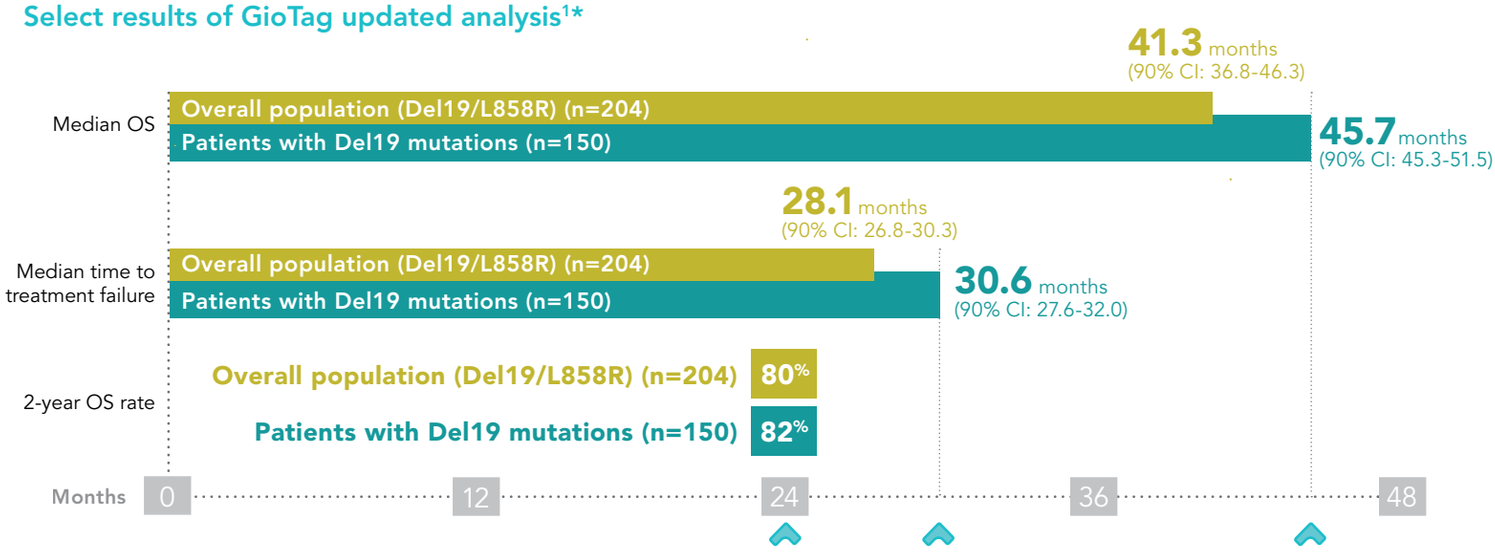
GILOTRIF® (afatinib) tablets

GIOTAG: UPDATED ANALYSIS

Real-world data showed GILOTRIF® (afatinib) tablets followed by osimertinib delivered median time to treatment failure of 30.6 months and median OS of 45.7 months in Del19 patients with EGFR M+ NSCLC[1]

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.

Select results of GioTag updated analysis[1]*



- In the LUX-Lung 3 study, GILOTRIF achieved nearly 3 years median OS in patients with a Del19 mutation (33.3 months vs 21.1 months for pemetrexed-cisplatin; 95% CI: 0.36-0.79; *p*=0.0015)[3,4†]
- Up to 73% of patients with Del19 mutations may develop T790M mutations[5,6]
- Patients with T790M mutations may be treated with osimertinib, the only approved T790M inhibitor, in second-line therapy[7]

GILOTRIF first-line may offer patients with a Del19 mutation the opportunity of a targeted treatment sequence[1,2]

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.[3,4]

GioTag Study: A real-world, global, multicenter, retrospective, observational study of 204 adult patients with EGFR M+ mNSCLC (Del19/L858R) using 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. At the start of GILOTRIF treatment, 150 (73.5%) patients had a Del19 mutation, 53 (26.0%) had the L858R mutation, and one patient had both Del19 and L858R. Primary endpoint was median time to treatment failure defined as time from the first dose of GILOTRIF to that of the last dose of osimertinib or death. For this interim analysis, updated data were collected from 94 US patients with available electronic health records. Final analysis, incorporating data from manual chart reviews of a further 29 patients, is anticipated in early 2020.[1,2]

SELECTED IMPORTANT SAFETY INFORMATION FOR GILOTRIF® (afatinib) TABLETS

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.

GF PROF ISI 10.21.19

EGFR M+=epidermal growth factor receptor mutation positive; NSCLC=non-small cell lung cancer; OS=overall survival; HR=hazard ratio; CI=confidence interval; mNSCLC=metastatic non-small cell lung cancer; PFS=progression-free survival.
*Primary endpoint: Time to treatment failure. OS maturity: 42%.
†In a prespecified subgroup analysis of patients with Del19 mutations for the secondary endpoint of OS.

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

References: 1. Hochmair MJ, et al. *Future Oncol.* (2019). [In press.] **2.** Hochmair MJ, Morabito A, Hao D, et al. *Future Oncol.* 2018;14(27):2861-2874. **3.** GILOTRIF [prescribing information]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc. **4.** Yang JCH, Wu YL, Schuler M, et al. *Lancet Oncol.* 2015;16(2):141-151. **5.** Ke EE, Zhou Q, Zhang QY, et al. *J Thorac Oncol.* 2017;12(9):1368-1375. **6.** Jenkins S, Yang JC, Jänne PA, et al. *J Thorac Oncol.* 2017;12(8):1247-1256. **7.** Girard N. *Future Oncol.* 2018;14 (11):1117-1132.

Boehringer Ingelheim

GILOTRIF® (afatinib) tablets