GILOTRIF: Brodest 1st-line indication of any TKI in EGFR M+ mNSCLC1-3

Mutations covered by EGFR TKIs in 1st-line

<table>
<thead>
<tr>
<th>Mutations</th>
<th>GILOTRIF*</th>
<th>Tarceva†</th>
<th>Iressa‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>del19</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>L858R</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>L861Q</td>
<td>✓</td>
<td>NEW</td>
<td>_§</td>
</tr>
<tr>
<td>G719X</td>
<td>✓</td>
<td>NEW</td>
<td>_§</td>
</tr>
<tr>
<td>S768I</td>
<td>✓</td>
<td>NEW</td>
<td>_§</td>
</tr>
</tbody>
</table>

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.
† TARCEVA (erlotinib) is a kinase inhibitor indicated for the treatment of patients with mNSCLC whose tumors have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test receiving 1st-line, maintenance, or 2nd- or greater-line treatment after progression following at least one prior chemotherapy regimen.
‡ IRESSA (gefitinib) is a TKI indicated for the 1st-line treatment of patients with mNSCLC whose tumors have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test.
§ Not indicated.

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.

Limitation 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
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 click here for full Prescribing Information, including Patient Information.
GILOTRIF can help even more patients in 1st-line EGFR M+ mNSCLC

- Efficacy in GILOTRIF is well established in EGFR M+ mNSCLC patients with del19 or L858R mutations
- GILOTRIF also has proven efficacy in additional mutations: L861Q, G719X, and S768I
- As a result, GILOTRIF is now approved in 1st-line to help even more EGFR M+ mNSCLC patients

Approval based on analysis of 3 clinical trials

<table>
<thead>
<tr>
<th>LUX-Lung 2</th>
<th>LUX-Lung 3</th>
<th>LUX-Lung 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>A single-arm study exploring the anti-tumor efficacy of GILOTRIF in EGFR M+ NSCLC patients with stage IIIB/IV disease and ECOG PS 0-2</td>
<td>A randomized, open-label, global trial comparing 1st-line GILOTRIF versus chemotherapy in EGFR M+ mNSCLC patients</td>
<td>A randomized, open-label study comparing 1st-line GILOTRIF versus chemotherapy</td>
</tr>
<tr>
<td>Patients were treated with GILOTRIF 50 mg orally once daily (n=99) or 40 mg once daily (n=30)</td>
<td>Patients were randomized 2:1 to receive either GILOTRIF 40 mg orally once daily (n=230) or IV cisplatin 75 mg/m² and pemetrexed 500 mg/m² once every 21 days up to a maximum of 6 cycles (n=115)</td>
<td>Patients were randomized 2:1 to receive either GILOTRIF 40 mg orally once daily (n=242) or IV gemcitabine 1000 mg/m² (on days 1 and 8) plus cisplatin 75 mg/m² (on day 1) once every 21 days up to a maximum of 6 cycles (n=122)</td>
</tr>
<tr>
<td>Primary endpoint was the proportion of patients with a confirmed objective response, as determined by RECIST 1.0 based on an independent review of imaging</td>
<td>Primary endpoint was PFS as assessed by independent blinded review, and secondary endpoints included OS</td>
<td>Primary endpoint was PFS as assessed by independent review, and key secondary endpoints included the proportion of patients who achieved an overall response</td>
</tr>
</tbody>
</table>

ECOG PS=Eastern Cooperative Oncology Group performance status; OS=overall survival; PFS=progression-free survival; RECIST=Response Evaluation Criteria in Solid Tumors.

SELECTED IMPORTANT SAFETY INFORMATION WARNING 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 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. Treatment should be discontinued in patients who develop severe hepatic impairment while taking GILOTRIF.

Please see Important Safety Information continued on the following pages and click here for full Prescribing Information, including Patient Information.
Proven efficacy in even more EGFR mutations

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

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

*Efficacy data from a pooled analysis of LUX-Lung 2, 3, and 6.
†Response ongoing at time of censoring.

Based on the responses outlined in the above table
- The confirmed overall response rate, as assessed by independent radiology review, was 66% (95% confidence interval, 47%-81%)†.
- 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.

SELECTED IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

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, treatment with GILOTRIF should be interrupted or discontinued. 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%).

Please see Important Safety Information continued on the following pages and click here for full Prescribing Information, including Patient Information.
Now even more EGFR M+ mNSCLC patients can benefit with GILOTRIF 1st-line1

GILOTRIF is
- Established with efficacy in EGFR M+ mNSCLC patients with del19 and L858R mutations
- The only agent with proven OS in del19 patients (for 1st-line EGFR M+ mNSCLC vs chemotherapy)
- Now the only FDA-approved TKI for non-resistant EGFR mutations including L861Q, G719X, and S768I

SELECTED IMPORTANT SAFETY INFORMATION

ADVERSE REACTIONS

Adverse Reactions observed in clinical trials were as follows: (continued)

First-line treatment of EGFR mutation-positive, metastatic NSCLC
- 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%), 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 includedILD (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, 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 nursing infants from GILOTRIF, lactating women should not 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 m²) 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 m² 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.