

**A SPECIAL MEETING REVIEW EDITION**

## Highlights in NSCLC From the 2014 American Society of Clinical Oncology Annual Meeting

A Review of Selected Presentations From the 2014 American Society of Clinical Oncology Annual Meeting • May 30-June 3, 2014 • Chicago, Illinois

### Special Reporting on:

- Overall Survival (OS) in Patients With Advanced Non-Small Cell Lung Cancer (NSCLC) Harboring Common Epidermal Growth Factor Receptor Mutations (EGFR M+): Pooled Analysis of Two Large Phase III Studies (LUX-Lung 3 [LL3] and LUX-Lung 6 [LL6]) Comparing Afatinib With Chemotherapy (CT)
- REVEL: A Randomized, Double-Blind, Phase III Study of Docetaxel (DOC) and Ramucirumab (RAM; IMC-1121B) Versus DOC and Placebo (PL) in the Second-Line Treatment of Stage IV Non-Small Cell Lung Cancer (NSCLC) Following Disease Progression After One Prior Platinum-Based Therapy
- Antiangiogenic-Specific Adverse Events (AEs) in Patients With Non-Small Cell Lung Cancer (NSCLC) Treated With Nintedanib (N) and Docetaxel (D)
- LUX-Lung 5: A Randomized, Open-Label, Phase III Trial of Afatinib (A) Plus Paclitaxel (P) Versus Investigator's Choice of Chemotherapy (ICC) in Patients (pts) With Metastatic Non-Small Cell Lung Cancer (NSCLC) Who Had Progressed on Erlotinib/Gefitinib (E/G) and Afatinib
- Onartuzumab Plus Erlotinib Versus Erlotinib in Previously Treated Stage IIIb or IV NSCLC: Results From the Pivotal Phase III Randomized, Multicenter, Placebo-Controlled METLung (OAM4971g) Global Trial

### PLUS Meeting Abstract Summaries

#### With Expert Commentary by:

Mark A. Socinski, MD  
Professor of Medicine and Thoracic Surgery  
Director, Lung Cancer Section, Division of Hematology/Oncology  
Clinical Associate Director, Lung SPORE  
Co-Director, UPMC Lung Cancer Center of Excellence  
Co-Director, Lung and Thoracic Malignancies Program  
University of Pittsburgh  
Pittsburgh, Pennsylvania

ON THE WEB:  
[hematologyandoncology.net](http://hematologyandoncology.net)

Indexed through the National Library of Medicine  
(PubMed/MEDLINE), PubMed Central (PMC), and EMBASE

FOR 1ST-LINE TREATMENT

## Prescribe GILOTRIF for mNSCLC with common EGFR mutations

Identify common EGFR mutations (Del19 and L858R). Treat with GILOTRIF and support patients through the Solutions Plus™ program.



EGFR=epidermal growth factor receptor; FDA=US Food and Drug Administration; mNSCLC=metastatic non-small cell lung cancer.

### INDICATION AND LIMITATION OF USE

**Indication:** GILOTRIF is indicated for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution 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 other EGFR mutations.

### SELECTED IMPORTANT SAFETY INFORMATION

#### WARNINGS AND PRECAUTIONS

##### Diarrhea

- Diarrhea has resulted in dehydration with or without renal impairment; some of these cases were fatal. In the pivotal study, diarrhea occurred in 96% of patients treated with GILOTRIF (n=229), of which 15% was Grade 3 in severity and occurred within the first 6 weeks. Renal impairment as a consequence of diarrhea occurred in 6.1% of patients treated with GILOTRIF, out of which 3 (1.3%) were Grade 3.
- For patients who develop prolonged Grade 2 diarrhea lasting more than 48 hours or greater than or equal to Grade 3 diarrhea, withhold GILOTRIF until diarrhea resolves to Grade 1 or less, and resume GILOTRIF with appropriate dose reduction. 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 therapy until loose bowel movements cease for 12 hours.

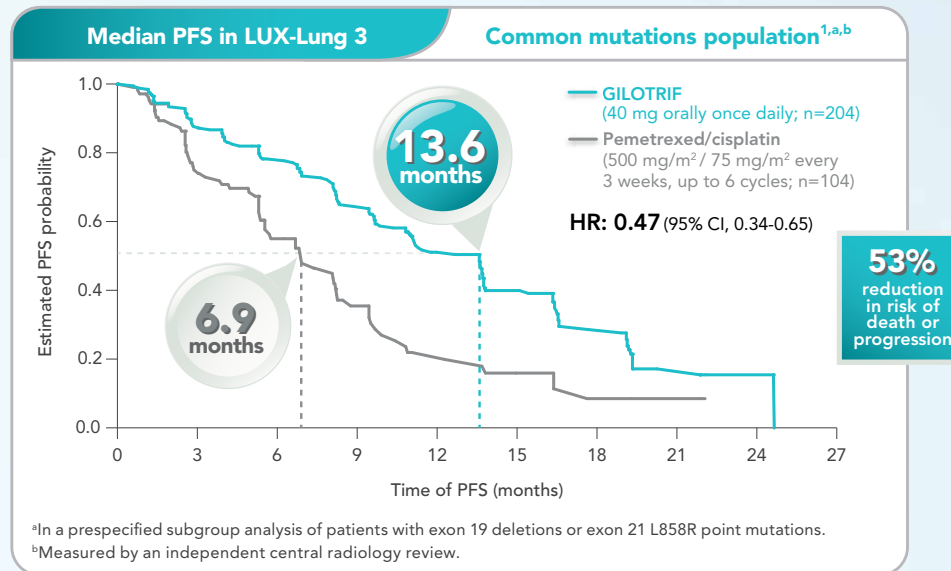
##### Bullous and Exfoliative Skin Disorders

- Grade 3 cutaneous reactions characterized by bullous, blistering, and exfoliating lesions occurred in 6 (0.15%) of the 3865 patients who received GILOTRIF across clinical trials. In the pivotal study, the overall incidence of cutaneous reactions consisting of rash, erythema, and acneiform rash was 90%, and the incidence of Grade 3 cutaneous reactions was 16%. In addition, the incidence of Grade 1-3 palmar-plantar erythrodysesthesia syndrome was 7%. Discontinue GILOTRIF in patients who develop life-threatening bullous, blistering, or exfoliating lesions. For patients who develop prolonged Grade 2 cutaneous adverse reactions lasting more than 7 days, intolerable Grade 2, or Grade 3 cutaneous reactions, withhold GILOTRIF until the adverse reaction resolves to Grade 1 or less, and resume GILOTRIF with appropriate dose reduction.

IN THE INDICATED POPULATION OF PATIENTS WITH COMMON MUTATIONS\*

# GILOTRIF: Nearly double the PFS vs pemetrexed/cisplatin<sup>1</sup>

Progression-free survival (PFS) by independent review (common mutations\*)<sup>1</sup>



## Overall survival (OS)

- 30.3 months OS with GILOTRIF vs 26.2 months with pemetrexed/cisplatin in patients with common EGFR mutations (HR: 0.82; 95% CI, 0.59-1.14)<sup>2,3</sup>
- More than 70% of patients in LUX-Lung 3 received subsequent treatment at progression<sup>4</sup>

**LUX-Lung 3:** A randomized, multicenter, open-label trial that assessed the efficacy and safety of GILOTRIF 40 mg orally once daily (n=230) vs up to 6 cycles of pemetrexed/cisplatin (n=115) as 1st-line therapy in patients with EGFR mutation-positive mNSCLC. Randomization was stratified according to EGFR mutation status (exon 19 deletion vs exon 21 L858R vs other) and race (Asian vs non-Asian). The primary endpoint was PFS (assessed by independent review).<sup>2</sup>

CI=confidence interval; HR=hazard ratio.  
\*Common mutations=Del19 and L858R.

## • Common EGFR mutations (n=308)<sup>2-4</sup>

### – Del19 (n=170)

- 13.7 months median PFS for GILOTRIF vs 5.6 months for pemetrexed/cisplatin (HR: 0.28; 95% CI, 0.18-0.44)
- 31.6 months median OS for GILOTRIF vs 21.1 months for pemetrexed/cisplatin (HR: 0.55; 95% CI, 0.36-0.85)

### – L858R (n=138)

- 10.8 months median PFS for GILOTRIF vs 8.1 months for pemetrexed/cisplatin (HR: 0.73; 95% CI, 0.46-1.17)
- 27.2 months median OS for GILOTRIF; pemetrexed/cisplatin not estimable (HR: 1.30; 95% CI, 0.76-2.23)

## • Limitation of Use: Safety and efficacy of GILOTRIF have not been established in patients whose tumors have other EGFR mutations

### – Uncommon mutations (n=37)<sup>2,3,5</sup>

- There were 26 GILOTRIF-treated patients in the "other" (uncommon) EGFR mutations subgroup, which consisted of 9 unique mutation patterns
- Median PFS: 2.8 months with GILOTRIF vs 9.9 months with pemetrexed/cisplatin (HR: 1.89; 95% CI, 0.84-4.28)
- Median OS: 15.9 months with GILOTRIF; pemetrexed/cisplatin not estimable (HR: 3.08; 95% CI, 1.04-9.15)

## SELECTED IMPORTANT SAFETY INFORMATION

### WARNINGS AND PRECAUTIONS

#### Interstitial Lung Disease (ILD)

- ILD or ILD-like adverse reactions (e.g., lung infiltration, pneumonitis, acute respiratory distress syndrome, or alveolitis allergic) occurred in 1.5% of the 3865 patients who received GILOTRIF across clinical trials; of these, 0.4% were fatal. The incidence of ILD appeared to be higher in patients of Asian ethnicity (2.1%) as compared to non-Asians (1.2%). In the pivotal study, the incidence of Grade  $\geq 3$  ILD was 1.3% and resulted in death in 1% of GILOTRIF-treated patients.
- Withhold GILOTRIF during evaluation of patients with suspected ILD, and discontinue GILOTRIF in patients with confirmed ILD.

Please see full Important Safety Information and brief summary of full Prescribing Information on adjacent pages.

Learn more at [www.GILOTRIF.com](http://www.GILOTRIF.com).

**References:** 1. Sequist LV, Yang JC, 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. doi:10.1200/JCO.2012.44.2806. 2. Gilotrif® (afatinib) tablets Prescribing Information. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc.; November 2013. 3. Data on file. Boehringer Ingelheim. OS tables. 4. Data on file. Boehringer Ingelheim. CTR. 5. Data on file. Boehringer Ingelheim. Other mutations PFS table.

 **GILOTRIF<sup>®</sup>**  
(afatinib) tablets  
**TEST. IDENTIFY. TREAT.**

# Indication and Important Safety Information

## INDICATION AND LIMITATION OF USE

GILOTRIF is indicated for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution 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 other EGFR mutations.

## WARNINGS AND PRECAUTIONS

### Diarrhea

- Diarrhea has resulted in dehydration with or without renal impairment; some of these cases were fatal. In the pivotal study, diarrhea occurred in 96% of patients treated with GILOTRIF (n=229), of which 15% was Grade 3 in severity and occurred within the first 6 weeks. Renal impairment as a consequence of diarrhea occurred in 6.1% of patients treated with GILOTRIF, out of which 3 (1.3%) were Grade 3.
- For patients who develop prolonged Grade 2 diarrhea lasting more than 48 hours or greater than or equal to Grade 3 diarrhea, withhold GILOTRIF until diarrhea resolves to Grade 1 or less, and resume GILOTRIF with appropriate dose reduction. 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 therapy until loose bowel movements cease for 12 hours.

### Bullous and Exfoliative Skin Disorders

- Grade 3 cutaneous reactions characterized by bullous, blistering, and exfoliating lesions occurred in 6 (0.15%) of the 3865 patients who received GILOTRIF across clinical trials. In the pivotal study, the overall incidence of cutaneous reactions consisting of rash, erythema, and acneiform rash was 90%, and the incidence of Grade 3 cutaneous reactions was 16%. In addition, the incidence of Grade 1-3 palmar-plantar erythrodysesthesia syndrome was 7%. Discontinue GILOTRIF in patients who develop life-threatening bullous, blistering, or exfoliating lesions. For patients who develop prolonged Grade 2 cutaneous adverse reactions lasting more than 7 days, intolerable Grade 2, or Grade 3 cutaneous reactions, withhold GILOTRIF until the adverse reaction resolves to Grade 1 or less, and resume GILOTRIF with appropriate dose reduction.

### Interstitial Lung Disease (ILD)

- ILD or ILD-like adverse reactions (e.g., lung infiltration, pneumonitis, acute respiratory distress syndrome, or alveolitis allergic) occurred in 1.5% of the 3865 patients who received GILOTRIF across clinical trials; of these, 0.4% were fatal. The incidence of ILD appeared to be higher in patients of Asian ethnicity (2.1%) as compared to non-Asians (1.2%). In the pivotal study, the incidence of Grade  $\geq 3$  ILD was 1.3% and resulted in death in 1% of GILOTRIF-treated patients.
- Withhold GILOTRIF during evaluation of patients with suspected ILD, and discontinue GILOTRIF in patients with confirmed ILD.

### Hepatic Toxicity

- In 3865 patients who received GILOTRIF across clinical trials, 10.1% had liver test abnormalities, of which 7 (0.18%) were fatal. In the pivotal study, liver test abnormalities of any grade occurred in 17.5% of the patients treated with GILOTRIF.
- Obtain periodic liver testing in patients during treatment with GILOTRIF. Withhold GILOTRIF in patients who develop worsening of liver function. In patients who develop severe hepatic impairment while taking GILOTRIF, treatment should be discontinued.

### Keratitis

- Keratitis, characterized as acute or worsening eye inflammation, lacrimation, light sensitivity, blurred vision, eye pain, and/or red eye occurred in 0.8% of patients treated with GILOTRIF among 3865 patients across clinical trials. Keratitis was reported in 5 (2.2%) patients in the pivotal study, with Grade 3 in 1 (0.4%). Withhold GILOTRIF during evaluation of patients with suspected keratitis, and 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.

### Embryofetal Toxicity

- GILOTRIF is Pregnancy Category D. Based on its mechanism of action, GILOTRIF can cause fetal harm when administered to a pregnant woman. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.
- Advise females of reproductive potential to use highly effective contraception during treatment, and for at least 2 weeks after the last dose of GILOTRIF. Advise patients to contact their healthcare provider if they become pregnant, or if pregnancy is suspected, while taking GILOTRIF.

### Combination with Vinorelbine in HER2 Positive Metastatic Breast Cancer

- An early interim overall survival analysis of a randomized Phase 3 trial in HER2 positive metastatic breast cancer showed an increased mortality in patients receiving GILOTRIF in combination with vinorelbine compared to trastuzumab and vinorelbine. The combination of GILOTRIF and vinorelbine was also associated with a higher rate of adverse events (such as diarrhea, rash) and fatal events related to infections and cancer progression. GILOTRIF combined with vinorelbine should not be used in patients with HER2 positive metastatic breast cancer.

## ADVERSE REACTIONS

- In GILOTRIF-treated patients (n=229) the most common adverse reactions in the pivotal study ( $\geq 20\%$  all grades & vs pemetrexed/cisplatin-treated patients (n=111)) were diarrhea (96% vs 23%), rash/dermatitis acneiform (90% vs 11%), stomatitis (71% vs 15%), paronychia (58% vs 0%), dry skin (31% vs 2%), decreased appetite (29% vs 55%), pruritus (21% vs 1%).
- 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%; n=5) experienced ventricular dysfunction (defined as diastolic dysfunction, left ventricular dysfunction, or ventricular dilation; all < Grade 3) compared to chemotherapy-treated patients (0.9%; n=1).

## DRUG INTERACTIONS

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

- Concomitant taking 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 taking 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

### Nursing Mothers

- It is not known whether afatinib is present in human milk. Because many drugs are present in human milk and because of the potential for serious adverse reactions in nursing infants from GILOTRIF, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

### Renal Impairment

- GILOTRIF has not been studied in patients with severely impaired renal function. Closely monitor patients with moderate (CLcr 30-59 mL/min) to severe (CLcr <30 mL/min) renal impairment and adjust GILOTRIF dose if not tolerated.

### 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 APR 2014

Please see brief summary of full Prescribing Information on adjacent pages.



Copyright © 2014. Boehringer Ingelheim Pharmaceuticals, Inc.  
All rights reserved. (4/14) GF613003PROF





# GILOTRIF® (afatinib) tablets, for oral use

Initial U.S. Approval: 2013

## BRIEF SUMMARY OF PRESCRIBING INFORMATION

Please see package insert for full Prescribing Information.

**INDICATIONS AND USAGE:** GILOTRIF is indicated for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution 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 other EGFR mutations.

**DOSAGE AND ADMINISTRATION: Patient Selection:** Select patients for the first-line treatment of metastatic NSCLC with GILOTRIF based on the presence of EGFR exon 19 deletions or exon 21 (L858R) substitution mutations in tumor specimens [see *Indications and Usage*]. Information on FDA-approved tests for the detection of EGFR mutations in NSCLC is available at: <http://www.fda.gov/CompanionDiagnostics>. **Recommended Dose:** The recommended dose of GILOTRIF is 40 mg orally once daily until disease progression or no longer tolerated by the patient. Take GILOTRIF at least 1 hour before or 2 hours after a meal. Do not take a missed dose within 12 hours of the next dose. **Dose Modification:** Withhold GILOTRIF for any drug-related adverse reactions of: NCI CTCAE\* Grade 3 or higher; Diarrhea of Grade 2 or higher persisting for 2 or more consecutive days while taking anti-diarrheal medication [see *Warnings and Precautions*]; Cutaneous reactions of Grade 2 that are prolonged (lasting more than 7 days) or intolerable [see *Warnings and Precautions*]; Renal dysfunction of Grade 2 or higher. Resume treatment when the adverse reaction fully resolves, returns to baseline, or improves to Grade 1. Reinstigate GILOTRIF at a reduced dose, i.e., 10 mg per day less than the dose at which the adverse reaction occurred. Permanently discontinue GILOTRIF for: Life-threatening bullous, blistering, or exfoliative skin lesions [see *Warnings and Precautions*]; Confirmed interstitial lung disease (ILD) [see *Warnings and Precautions*]; Severe drug-induced hepatic impairment [see *Warnings and Precautions*]; Persistent ulcerative keratitis [see *Warnings and Precautions*]; Symptomatic left ventricular dysfunction; Severe or intolerable adverse reaction occurring at a dose of 20 mg per day. **P-gp Inhibitors:** For patients who require therapy with a P-glycoprotein (P-gp) inhibitor, reduce GILOTRIF daily dose by 10 mg if not tolerated. Resume the previous dose after discontinuation of the P-gp inhibitor as tolerated [see *Drug Interactions*]. **P-gp Inducers:** For patients who require chronic therapy with a P-gp inducer, increase GILOTRIF daily dose by 10 mg as tolerated. Resume the previous dose 2 to 3 days after discontinuation of the P-gp inducer [see *Drug Interactions*].

**CONTRAINDICATIONS:** None

**WARNINGS AND PRECAUTIONS: Diarrhea:** Diarrhea has resulted in dehydration with or without renal impairment; some of these cases were fatal. In Study 1, diarrhea occurred in 96% of patients treated with GILOTRIF (n=229), of which 15% was Grade 3 in severity and occurred within the first 6 weeks [see *Adverse Reactions*]. Renal impairment as a consequence of diarrhea occurred in 6.1% of patients treated with GILOTRIF, out of which 3 (1.3%) were Grade 3. For patients who develop prolonged Grade 2 diarrhea lasting more than 48 hours or greater than or equal to Grade 3 diar-

rhea, withhold GILOTRIF until diarrhea resolves to Grade 1 or less, and resume GILOTRIF with appropriate dose reduction [see *Dosage and Administration*]. 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 therapy until loose bowel movements cease for 12 hours. **Bullous and Exfoliative Skin Disorders:** Grade 3 cutaneous reactions characterized by bullous, blistering, and exfoliating lesions occurred in 6 (0.15%) of the 3865 patients who received GILOTRIF across clinical trials [see *Adverse Reactions*]. In Study 1, the overall incidence of cutaneous reactions consisting of rash, erythema, and acneiform rash was 90%, and the incidence of Grade 3 cutaneous reactions was 16%. In addition, the incidence of Grade 1-3 palmar-plantar erythrodysesthesia syndrome was 7%. Discontinue GILOTRIF in patients who develop life-threatening bullous, blistering, or exfoliating lesions [see *Dosage and Administration*]. For patients who develop prolonged Grade 2 cutaneous adverse reactions lasting more than 7 days, intolerable Grade 2, or Grade 3 cutaneous reactions, withhold GILOTRIF until the adverse reaction resolves to Grade 1 or less, and resume GILOTRIF with appropriate dose reduction [see *Dosage and Administration*]. **Interstitial Lung Disease (ILD):** ILD or ILD-like adverse reactions (e.g., lung infiltration, pneumonitis, acute respiratory distress syndrome, or alveolitis allergic) occurred in 1.5% of the 3865 patients who received GILOTRIF across clinical trials; of these, 0.4% were fatal. The incidence of ILD appeared to be higher in patients of Asian ethnicity (2.1%) as compared to non-Asians (1.2%). In Study 1, the incidence of Grade  $\geq 3$  ILD was 1.3% and resulted in death in 1% of GILOTRIF-treated patients. Withhold GILOTRIF during evaluation of patients with suspected ILD, and discontinue GILOTRIF in patients with confirmed ILD [see *Dosage and Administration*]. **Hepatic Toxicity:** In 3865 patients who received GILOTRIF across clinical trials, 10.1% had liver test abnormalities, of which 7 (0.18%) were fatal. In Study 1, liver test abnormalities of any grade occurred in 17.5% of the patients treated with GILOTRIF. Obtain periodic liver testing in patients during treatment with GILOTRIF. Withhold GILOTRIF in patients who develop worsening of liver function [see *Dosage and Administration*]. In patients who develop severe hepatic impairment while taking GILOTRIF, treatment should be discontinued. **Keratitis:** Keratitis, characterized as acute or worsening eye inflammation, lacrimation, light sensitivity, blurred vision, eye pain, and/or red eye occurred in 0.8% of patients treated with GILOTRIF among 3865 patients across clinical trials. Keratitis was reported in 5 (2.2%) patients in Study 1, with Grade 3 in 1 (0.4%). Withhold GILOTRIF during evaluation of patients with suspected keratitis, and if diagnosis of ulcerative keratitis is confirmed, treatment with GILOTRIF should be interrupted or discontinued [see *Dosage and Administration*]. 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 [see *Adverse Reactions*]. Contact lens use is also a risk factor for keratitis and ulceration. **Embryo-fetal Toxicity:** Based on its mechanism of action, GILOTRIF can cause fetal harm when administered to a pregnant woman. Afatinib was embryotoxic and, in animals with maternal toxicity, led to abortions at late gestational stages in rabbits at doses of 5 mg/kg (approximately 0.2 times the human exposure at the recommended dose of 40 mg daily) or greater. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus [see *Use in Specific Populations*]. Advise females of reproductive potential to use highly effective contraception during treatment, and for at least 2

weeks after the last dose of GILOTRIF. Advise patients to contact their healthcare provider if they become pregnant, or if pregnancy is suspected, while taking GILOTRIF [see *Use in Specific Populations*]. **Combination with Vinorelbine in HER2 Positive Metastatic Breast Cancer:** An early interim overall survival analysis of a randomized Phase 3 trial in HER2 positive metastatic breast cancer showed an increased mortality in patients receiving GILOTRIF in combination with vinorelbine compared to trastuzumab and vinorelbine. The combination of GILOTRIF and vinorelbine was also associated with a higher rate of adverse events (such as diarrhea, rash) and fatal events related to infections and cancer progression. GILOTRIF combined with vinorelbine should not be used in patients with HER2 positive metastatic breast cancer.

**ADVERSE REACTIONS:** The following adverse reactions are discussed in greater detail in other sections of the labeling: Diarrhea [see *Warnings and Precautions*]; Bullous and Exfoliative Skin Disorders [see *Warnings and Precautions*]; Interstitial Lung Disease [see *Warnings and Precautions*]; Hepatic Toxicity [see *Warnings and Precautions*]; Keratitis [see *Warnings and Precautions*]; **Clinical Trials Experience:** Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The safety evaluation of GILOTRIF is based on the data from more than 3800 patients, including 2135 NSCLC patients receiving GILOTRIF monotherapy at or above the recommended dose. **Controlled Study:** The data in Tables 1 and 2 below reflect exposure of 229 EGFR-TKI naïve GILOTRIF-treated patients with EGFR mutation-positive, metastatic, non-squamous, NSCLC enrolled in a randomized, multicenter, open-label trial (Study 1). Patients received GILOTRIF 40 mg daily until documented disease progression or intolerance to the therapy. A total of 111 patients were treated with pemetrexed/cisplatin. Patients were treated with pemetrexed 500 mg/m<sup>2</sup> followed after 30 minutes by cisplatin 75 mg/m<sup>2</sup> every three weeks for a maximum of six treatment courses. The median exposure was 11.0 months for patients treated with GILOTRIF and 3.4 months for patients treated with pemetrexed/cisplatin. The overall trial population had a median age of 61 years; 61% of patients in the GILOTRIF arm and 60% of patients in the pemetrexed/cisplatin arm were younger than 65 years. A total of 64% of patients on GILOTRIF and 67% of pemetrexed/cisplatin patients were female. More than two-thirds of patients were from Asia (GILOTRIF 70%; pemetrexed/cisplatin 72%). 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 in Study 1 included pulmonary toxicity/ILD-like adverse reactions (1.3%), sepsis (0.43%), and pneumonia (0.43%). Dose reductions due to adverse reactions were required in 57% of GILOTRIF-treated patients. The most frequent adverse reactions that led to dose reduction in the patients treated with GILOTRIF were diarrhea (20%), rash/acne (19%), paronychia (14%), and stomatitis (10%). Discontinuation of therapy in GILOTRIF-treated patients for adverse reactions was 14.0%. The most frequent adverse reactions that led to discontinuation in GILOTRIF-treated patients were diarrhea (1.3%), ILD (0.9%), and paronychia (0.9%). Clinical trials of GILOTRIF excluded patients with an abnormal left ventricular ejection fraction (LVEF), i.e., below the institutional lower limit of normal. In Study 1, all patients were evaluated for LVEF at screening and every 9 weeks thereafter in the GILOTRIF-treated group and as needed in the pemetrexed/cisplatin group. More GILOTRIF-treated patients (2.2%; n=5) experienced

\*National Cancer Institute Common Terminology Criteria for Adverse Events, v 3.0

ventricular dysfunction (defined as diastolic dysfunction, left ventricular dysfunction, or ventricular dilation; all < Grade 3) compared to chemotherapy-treated patients (0.9%; n=1).

**Table 1 Adverse Reactions Reported in ≥10% of GILOTRIF™ (afatinib) tablets-Treated Patients in Study 1**

Adverse Reaction	GILOTRIF n=229		Pemetrexed/ Cisplatin n=111	
	All Grades (%)	Grade 3* (%)	All Grades (%)	Grade 3* (%)
<b>Gastrointestinal disorders</b>				
Diarrhea	96	15	23	2
Stomatitis <sup>1</sup>	71	9	15	1
Cheilitis	12	0	1	0
<b>Skin and subcutaneous tissue disorders</b>				
Rash/Dermatitis acneiform <sup>2</sup>	90	16	11	0
Pruritus	21	0	1	0
Dry skin	31	0	2	0
<b>Infections and infestations</b>				
Paronychia <sup>3</sup>	58	11	0	0
Cystitis	13	1	5	0
<b>Metabolism and nutrition disorders</b>				
Decreased appetite	29	4	55	4
<b>Respiratory, thoracic and mediastinal disorders</b>				
Epistaxis	17	0	2	1
Rhinorrhea	11	0	6	0
<b>Investigations</b>				
Weight decreased	17	1	14	1
<b>General disorders and administration site conditions</b>				
Pyrexia	12	0	6	0
<b>Eye disorders</b>				
Conjunctivitis	11	0	3	0

\*None of the adverse reactions in this table except stomatitis (one patient on GILOTRIF [0.4%]) were Grade 4 in severity.

<sup>1</sup>Includes stomatitis, aphthous stomatitis, mucosal inflammation, mouth ulceration, oral mucosa erosion, mucosal erosion, mucosal ulceration

<sup>2</sup>Includes group of rash preferred terms, acne, acne pustular, dermatitis acneiform

<sup>3</sup>Includes paronychia, nail infection, nail bed infection

**Table 2 Adverse Reactions of Laboratory Abnormalities from the Investigations SOC Reported in ≥5% of GILOTRIF-Treated Patients in Study 1**

Adverse Reaction	GILOTRIF n=229		Pemetrexed/ Cisplatin n=111	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Alanine aminotransferase increased	11	2	4	0
Hypokalemia <sup>1</sup>	11	4	5	4
Aspartate aminotransferase increased	8	2	2	1

<sup>1</sup>Includes hypokalemia, blood potassium decreased  
SOC=system organ class

**DRUG INTERACTIONS:** *Effect of P-glycoprotein (P-gp) Inhibitors and Inducers:* Oral administration of a P-gp inhibitor (ritonavir at 200 mg twice daily) 1 hour before administration of GILOTRIF increased systemic exposure to afatinib by 48%. There was

no change in afatinib exposure when ritonavir was administered simultaneously with or 6 hours after GILOTRIF. Concomitant taking of P-gp inhibitors (including but not limited to ritonavir, cyclosporine A, itraconazole, itraconazole, erythromycin, verapamil, quinidine, tacrolimus, nelfinavir, saquinavir, and amiodarone) with GILOTRIF can increase exposure to afatinib [see *Dosage and Administration*]. Co-administration with oral dose of a P-gp inducer (rifampicin at 600 mg once daily for 7 days) decreased exposure to afatinib by 34%. Concomitant taking 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 [see *Dosage and Administration*].

**USE IN SPECIFIC POPULATIONS: Pregnancy:**

Pregnancy Category D. *Risk Summary:* Based on its mechanism of action, GILOTRIF can cause fetal harm when administered to a pregnant woman. Afatinib was embryotoxic and, in animals with maternal toxicity, led to abortions at late gestational stages in rabbits at doses of 5 mg/kg (approximately 0.2 times the exposure by AUC at the recommended human dose of 40 mg daily) or greater. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus [see *Warnings and Precautions*]. *Animal Data:* Administration of afatinib to pregnant rabbits at doses of 5 mg/kg (approximately 0.2 times the exposure by AUC at the recommended human dose of 40 mg daily) or greater during the period of organogenesis caused increased post implantation loss and, in animals showing maternal toxicity, abortion at late gestational stages. In the same study, at the high dose level of 10 mg/kg (approximately 0.7 times the exposure by AUC at the recommended human dose of 40 mg daily) there were reduced fetal weights, and increases in the incidence of runts, as well as visceral and dermal variations. In an embryofetal development study in rats, there were skeletal alterations consisting of incomplete or delayed ossifications and reduced fetal weight at a dose of 16 mg/kg (approximately twice the exposure at the recommended human dose of 40 mg daily).

**Nursing Mothers:** It is not known whether afatinib is present in human milk. Afatinib was present in the milk of lactating rats at concentrations 80-150 times higher than those found in plasma from 1 to 6 hours after administration. Because many drugs are present in human milk and because of the potential for serious adverse reactions in nursing infants from GILOTRIF, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. **Pediatric Use:** Safety and effectiveness of GILOTRIF in pediatric patients have not been established. **Geriatric Use:** Of the 3865 patients in the clinical studies of GILOTRIF, 32% of patients were 65 years and older, while 7% were 75 years and older. No overall differences in safety were observed between patients 65 years and over and younger patients. In Study 1, 39% of the 345 patients were 65 years of age or older and 4% were 75 years or older. No overall differences in effectiveness were observed between patients 65 years and older and younger patients. **Females and Males of Reproductive Potential:**

*Contraception: Females:* Counsel patients on pregnancy planning and prevention. Advise female patients of reproductive potential to use highly effective contraception during treatment with GILOTRIF, and for at least 2 weeks after the last dose of GILOTRIF. Advise patients to contact their healthcare provider if they become pregnant, or if pregnancy is suspected, while taking GILOTRIF [see *Use in Specific Populations*]. **Renal Impairment:** GILOTRIF has not been studied in patients with severely impaired renal function (creatinine clearance [CLCr] <30 mL/min). Adjustments to the starting dose of

GILOTRIF are not considered necessary in patients with mild (CLCr 60-89 mL/min) renal impairment. Closely monitor patients with moderate (CLCr 30-59 mL/min) to severe (CLCr <30 mL/min) renal impairment and adjust GILOTRIF dose if not tolerated. **Hepatic Impairment:** GILOTRIF has not been studied in patients with severe (Child Pugh C) hepatic impairment. Adjustments to the starting dose of GILOTRIF are not considered necessary in patients with mild (Child Pugh A) or moderate (Child Pugh B) hepatic impairment. Closely monitor patients with severe hepatic impairment and adjust GILOTRIF dose if not tolerated.

**OVERDOSAGE** Overdose was reported in 2 healthy adolescents each of whom ingested 360 mg of GILOTRIF (as part of a mixed-drug ingestion) resulting in nausea, vomiting, asthenia, dizziness, headache, abdominal pain, and elevated amylase (<1.5 times upper limit of normal [ULN]). Both subjects recovered.

**PATIENT COUNSELING INFORMATION:** See FDA-approved patient labeling (*Patient Information*).

**Diarrhea:** Advise patients that diarrhea occurs in nearly all patients who receive GILOTRIF. Inform patients that diarrhea may result in dehydration and renal impairment if not treated. Advise patients to notify their physician if diarrhea develops and to seek medical attention promptly for severe or persistent diarrhea [see *Warnings and Precautions (5.1) and Adverse Reactions*]. **Bullous and Exfoliative Skin Disorders:** Advise patients to minimize sun exposure with protective clothing and use of sunscreen while taking GILOTRIF [see *Warnings and Precautions*].

**Interstitial Lung Disease:** Advise patients to immediately report any new or worsening lung symptoms, or any combination of the following symptoms: trouble breathing or shortness of breath, cough, fever [see *Warnings and Precautions*]. **Hepatic Toxicity:** Advise patients that they will need to undergo liver function monitoring periodically. Advise patients to immediately report any symptoms of a liver problem (e.g., skin or the whites of eyes turn yellow, urine turns dark or brown (tea colored), pain on the right side of stomach, bleed or bruise more easily than normal, lethargy) [see *Warnings and Precautions*].

**Keratitis:** Advise patients to immediately report eye problems (e.g., eye pain, swelling, redness, blurred vision, or other vision changes) [see *Warnings and Precautions*]. **Left Ventricular Dysfunction:** Advise patients to contact a healthcare professional immediately for any of the following: new onset or worsening shortness of breath or exercise intolerance, cough, fatigue, swelling of the ankles/legs, palpitations, or sudden weight gain [see *Dosage and Administration and Adverse Reactions*].

**Instructions for Taking GILOTRIF:** Advise patients to take GILOTRIF on an empty stomach at least 1 hour before or 2 hours after eating [see *Dosage and Administration*]. Advise patients not to take a missed dose within 12 hours of the next dose. **Embryofetal Toxicity:** Counsel patients on pregnancy planning and prevention. Advise females of reproductive potential to use highly effective contraception during treatment, and for at least 2 weeks after taking the last dose of GILOTRIF [see *Warnings and Precautions and Use in Specific Populations*]. **Nursing Mothers:** Advise patients to discontinue nursing while taking GILOTRIF [see *Use in Specific Populations*].

Copyright © 2014 Boehringer Ingelheim International GmbH

ALL RIGHTS RESERVED

Revised: April 2014

GF-BS (4-14)

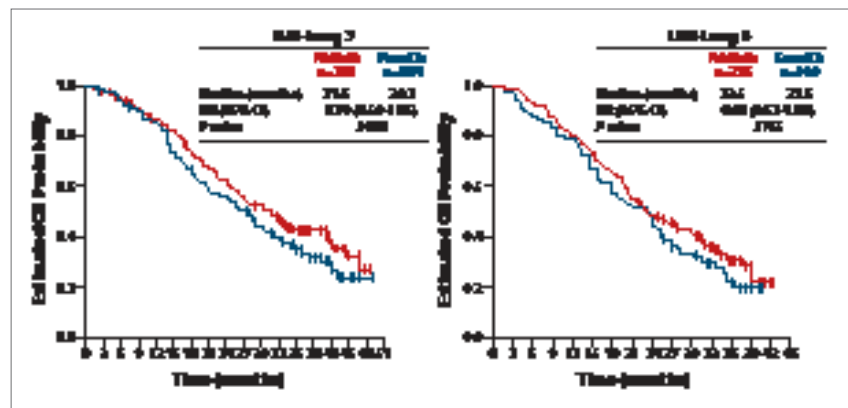
GF612024PROF

Rx only



# Overall Survival (OS) in Patients With Advanced Non-Small Cell Lung Cancer (NSCLC) Harboring Common Epidermal Growth Factor Receptor Mutations (EGFR M+): Pooled Analysis of Two Large Phase III Studies (LUX-Lung 3 [LL3] and LUX-Lung 6 [LL6]) Comparing Afatinib With Chemotherapy (CT)

The epidermal growth factor receptor (EGFR) is a common driver molecule in non-small cell lung cancer (NSCLC), making it an attractive target for the development of novel therapies in the current era of personalized medicine. Mutations located in the EGFR tyrosine kinase domain confer increased sensitivity to tyrosine kinase inhibitors (TKIs) that attenuate EGFR activity, such as erlotinib and gefitinib. They are more common in certain patient subsets. *EGFR* mutations have been reported in approximately 40% of Asian NSCLC patients compared with 10% of white patients.<sup>1</sup> Activating mutations are also more common in patients with adenocarcinoma histology, women, and people who never smoked. Two types of mutations account for 90% of sensitizing mutations in NSCLC tumors. The most common type of activating *EGFR* mutation—representing nearly half of these mutations in NSCLC tumors—is in-frame deletion in exon 19 (del19), which encodes part of the kinase domain.<sup>2</sup> The L858R point mutation in exon 21 is the second most common mutation, accounting for another 40% of *EGFR* mutations in NSCLC tumors.<sup>2</sup> Uncommon mutations account for the rest.<sup>2</sup> First-generation TKIs showed an improvement in progression-free survival (PFS) and overall response rate (ORR) over platinum-doublet chemotherapy in 7 randomized, controlled trials.<sup>3-9</sup> However, the reversible TKIs did not improve overall survival (OS), in part



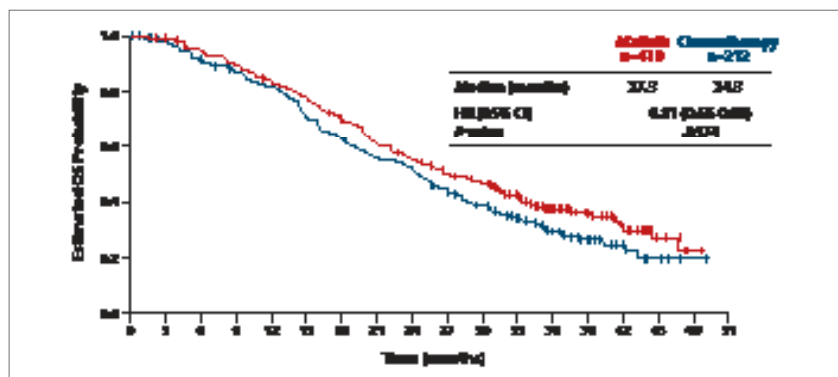
**Figure 1.** In an analysis of mature overall survival data for patients with metastatic NSCLC harboring the exon 19 deletion or the exon 21 L858R *EGFR* mutation in the LUX-Lung 3 and LUX-Lung 6 trials, afatinib was associated with a numerically superior median overall survival vs standard chemotherapy in LUX-Lung 3 but not LUX-Lung 6. Neither comparison was statistically significant. Cis, cisplatin; Gem, gemcitabine; HR, hazard ratio; NSCLC, non-small cell lung cancer; Pem, pemetrexed. Adapted from Yang JCH et al. ASCO abstract 8004. *J Clin Oncol.* 2014;32(5 suppl).<sup>20</sup>

because patients who failed treatment were allowed to cross over to the other treatment arm.<sup>10-16</sup>

The second-generation, irreversible TKI afatinib inhibits the kinase activity of the ErbB family of receptors.<sup>17</sup> Two large, phase 3 studies compared afatinib monotherapy vs standard chemotherapy as first-line treatment for NSCLC patients with *EGFR* mutations. In both LUX-Lung 3, conducted worldwide, and LUX-Lung 6, conducted in Asia, afatinib demonstrated superior PFS, ORR, and patient-reported outcomes compared with chemotherapy.<sup>18,19</sup> In the United States, afatinib is approved for first-line treatment of patients with metastatic NSCLC harboring the exon 19 deletion or the exon 21 L858R *EGFR* mutation. Yang and colleagues presented

mature OS data on patients with these mutations from the LUX-Lung 3 and LUX-Lung 6 trials.<sup>20</sup>

Both of the trials enrolled treatment-naïve patients with stage IIIB/IV adenocarcinoma of the lung as well as *EGFR* mutations that were detected by central laboratory testing. Patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Patients were stratified based on mutation type and then randomized 2:1 to receive either afatinib (400 mg daily) or up to 6 cycles of cisplatin plus either pemetrexed (in LUX-Lung 3) or gemcitabine (in LUX-Lung 6). In both studies, the primary endpoint was PFS by independent review, and OS was a secondary endpoint. LUX-Lung 3 randomized 345 patients to treatment;



**Figure 2.** In a supplementary analysis of the LUX-Lung 3 and LUX-Lung 6 trials that combined data from patients with common mutations, afatinib monotherapy yielded a superior median overall survival vs standard chemotherapy. HR, hazard ratio. Adapted from Yang JCH et al. ASCO abstract 8004. *J Clin Oncol.* 2014;32(5 suppl).<sup>20</sup>

62% of events had occurred at a median follow-up of 41 months. LUX-Lung 6 randomized 364 patients to treatment; 68% of events had occurred at a median follow-up of 33 months. Both arms in LUX-Lung 3 yielded a median OS of 28.2 months (hazard ratio [HR], 0.88;  $P=.3850$ ). LUX-Lung 6 yielded a median OS of 23.1 months for afatinib vs 23.5 months for chemotherapy (HR, 0.93;  $P=.6137$ ).

Both trials enrolled patients with the common mutations del19 and L858R, as well as uncommon mutations. The trial population reflected the incidence of mutations in the overall population: 49% to 51% of patients in each of the 4 arms had del19 tumors, 38% to 41% had the L858R mutation, and 10% to 12% had uncommon *EGFR* mutations. Afatinib binds with high specificity to the tyrosine kinase domain, and therefore different types of *EGFR* mutations may be associated with different responses to afatinib. As earlier analyses revealed, among the patients with common *EGFR* mutations, afatinib demonstrated a superior median PFS in both LUX-Lung 3 (13.6 months vs 6.9 months; HR, 0.47;  $P<.0001$ ) and LUX-Lung 6 (11.0 months vs 5.6 months; HR, 0.25;  $P<.0001$ ).<sup>18,19</sup> The current analysis also yielded a numerically superior median OS for afatinib in LUX-Lung 3 (31.6 months vs 28.2 months; HR, 0.78; 95% CI, 0.58-1.06;  $P=.1090$ ) but not in LUX-Lung 6 (23.6

months vs 23.5 months; HR, 0.83; 95% CI, 0.62-1.09;  $P=.1756$ ), and neither comparison was statistically significant (Figure 1).

A Forest plot subgroup analysis identified 1 factor that was associated with superior outcome from afatinib treatment: the presence of the del19 *EGFR* mutation. Moreover, Kaplan-Meier analysis showed that, in LUX-Lung 3, the subset of patients with del19 yielded a median OS of 33.3 months after treatment with afatinib ( $n=112$ ) vs 21.1 months with chemotherapy ( $n=57$ ; HR, 0.54; 95% CI, 0.36-0.79;  $P=.0015$ ). Similarly, in LUX-Lung 6, del19 patients yielded a median OS of 31.4 months with afatinib ( $n=124$ ) vs 18.4 months with chemotherapy ( $n=62$ ; HR, 0.64; 95% CI, 0.44-0.94;  $P=.0229$ ). To discern other factors that affect OS, a supplementary analysis combined patients with common mutations from both trials ( $n=631$ ). Afatinib monotherapy yielded a superior median OS (27.3 months vs 24.3 months; HR, 0.81; 95% CI, 0.66-0.99;  $P=.0374$ ; Figure 2). Forest plot analysis again pinpointed del19 as the only factor associated with superior OS, and Kaplan-Meier analysis revealed an improved median OS for the del19 patients who received afatinib in either trial (31.7 months vs 20.7 months; HR, 0.59; 95% CI, 0.45-0.77;  $P=.0001$ ). However, no significant difference in median OS emerged for patients with L858R (22.1

months with afatinib vs 26.9 months with chemotherapy; HR, 1.25; 95% CI, 0.92-1.71;  $P=.1600$ ).

Subsequent treatment was the most important confounding factor. In LUX-Lung 3, 71% of patients randomized to afatinib subsequently received chemotherapy, and 75% of patients randomized to cisplatin plus pemetrexed received subsequent *EGFR* TKI therapy. In LUX-Lung 6, 59% of the afatinib patients later received chemotherapy, and 56% of chemotherapy patients later received an *EGFR* TKI. Because the studies included patients from several countries, the authors examined the influence of insurance reimbursement on subsequent treatment. In countries with universal reimbursement policies, including Japan, Taiwan, Korea, Germany, and France, 81% of patients initially on afatinib subsequently received chemotherapy, and 91% of patients initially received chemotherapy with subsequent *EGFR* TKI treatment. In countries without universal reimbursement policies, mainly represented by China, Thailand, Russia, the Philippines, and Malaysia, 57% of patients received afatinib followed by chemotherapy, and 52% of patients received chemotherapy followed by afatinib. However, differences in crossover did not appear to alter the superior outcome observed with afatinib. In countries with universal reimbursement policies, 91% of patients crossed over from chemotherapy to *EGFR* TKI therapy, and del19 was associated with an HR of 0.50 (95% CI, 0.31-0.81). In countries without universal reimbursement policies, 52% of patients received chemotherapy followed by an *EGFR* TKI, and del19 was associated with an HR of 0.59 (95% CI, 0.42-0.82). In Japan, 100% of patients crossed over, and del19 was associated with an HR of 0.34 (95% CI, 0.13-0.87). In contrast, the subsets of patients with L858R mutations yielded HRs greater than 1, with the lowest HR observed for Japanese patients (HR, 1.13; 95% CI, 0.40-3.21).

Dr Yang concluded that, based on the analysis of patients from these 2 large



### ABSTRACT SUMMARY A Randomized, Double-Blind Phase 3 Trial of Adjuvant Erlotinib (E) Versus Placebo (P) Following Complete Tumor Resection With or Without Adjuvant Chemotherapy in Patients (pts) With Stage IB-IIIa EGFR Positive (IHC/FISH) Non-Small Cell Lung Cancer (NSCLC): RADIANT Results

Exploratory analyses of the BR.21 trial suggested that treatment with an EGFR TKI may be more effective in patients with increased EGFR protein expression or gene amplification (Tsao MS et al. *N Engl J Med.* 2005;353[2]:133-144). The phase 3 RADIANT (Randomized Double-Blind Trial in Adjuvant NSCLC With Tarceva) trial investigated whether adjuvant erlotinib could improve disease-free survival in patients with completely resected NSCLC with EGFR protein overexpression or gene amplification (Abstract 7501). The trial enrolled patients with stage IB to IIIa NSCLC whose tumors were EGFR-positive based on IHC or fluorescence in situ hybridization. Patients had undergone complete surgical resection; those without adjuvant chemotherapy were enrolled within 90 days of resection, and those who had received adjuvant platinum doublet therapy were enrolled within 180 days. The 973 enrolled patients were randomized 2:1 to receive either erlotinib (150 mg daily) or matching placebo. The trial failed to meet its primary endpoint; erlotinib did not improve median disease-free survival vs placebo (50.5 months vs 48.2 months, respectively; HR, 0.90; 95% CI, 0.741-1.104;  $P=$ .3235). At a median follow-up of 47 months, immature median OS data showed a similar outcome (not reached in both arms; HR, 1.13; 95% CI, 0.881-1.448;  $P=$ .3350). The median treatment duration was reduced in the erlotinib arm (11.9 months vs 21.9 months with placebo), and patients receiving erlotinib experienced more drug-related AEs (93.6% vs 52.8% with placebo). A subset analysis examined outcomes in the 161 patients with *EGFR* del19 or L858R mutations (Abstract 7513). The 102 patients who received erlotinib showed an improved median disease-free survival over the 59 patients who received placebo (46.4 months vs 28.5 months; HR, 0.61; 95% CI, 0.384-0.981;  $P=$ .0391). However, the difference was considered nonsignificant based on the hierarchical testing protocol directing that if the primary endpoint was not met, all subsequent endpoints would be deemed nonsignificant. Immature data showed no difference in median OS for the patients with *EGFR* mutations ( $P=$ .8153).

phase 3 studies, first-line afatinib significantly improved OS compared with chemotherapy in patients with the *EGFR* del19 mutation. The results suggest that del19 patients and L858R patients respond differently to the same EGFR TKI; therefore, these 2 patient subsets should be studied separately in the future.

### References

- Roengvorahoj M, Tsongalis GJ, Dragnev KH, Rigas JR. Epidermal growth factor receptor tyrosine kinase inhibitors as initial therapy for non-small cell lung cancer: focus on epidermal growth factor receptor mutation testing and mutation-positive patients. *Cancer Treat Rev.* 2013;39(8):839-850.
- Mitsudomi T, Yatabe Y. Epidermal growth factor receptor in relation to tumor development: *EGFR* gene and cancer. *FEBS J.* 2010;277(2):301-308.

- Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. *N Engl J Med.* 2009;361(10):947-957.
- Maemondo M, Inoue A, Kobayashi K, et al; North-East Japan Study Group. Gefitinib or chemotherapy for non-small-cell lung cancer with mutated *EGFR*. *N Engl J Med.* 2010;362(25):2380-2388.
- Mitsudomi T, Morita S, Yatabe Y, et al; West Japan Oncology Group. Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial. *Lancet Oncol.* 2010;11(2):121-128.
- Rosell R, Carcereny E, Gervais R, et al; Spanish Lung Cancer Group in collaboration with Groupe Français de Pneumo-Cancérologie and Associazione Italiana Oncologia Toracica. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced *EGFR* mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. *Lancet Oncol.* 2012;13(3):239-246.
- Zhou C, Wu YL, Chen G, et al. Erlotinib versus chemotherapy as first-line treatment for patients with advanced *EGFR* mutation-positive non-small-cell lung cancer (OPTI-

- MAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study. *Lancet Oncol.* 2011;12(8):735-742.
- Wu YL, Liang CK, Zhou C, et al. First-line erlotinib versus cisplatin/gemcitabine (GP) in patients with advanced *EGFR* mutation-positive non-small-cell lung cancer (NSCLC): interim analyses from the phase 3, open-label, ENSURE study [WCLC abstract P1.11-021]. *J Thorac Oncol.* 2013;8(suppl 2).
- Han JY, Park K, Kim SW, et al. First-SIGNAL: first-line single-agent irressa versus gemcitabine and cisplatin trial in never-smokers with adenocarcinoma of the lung. *J Clin Oncol.* 2012;30(10):1122-1128.
- Fukuoka M, Wu YL, Thongprasert S, et al. Biomarker analyses and final overall survival results from a phase III, randomized, open-label, first-line study of gefitinib versus carboplatin/paclitaxel in clinically selected patients with advanced non-small-cell lung cancer in Asia (IPASS). *J Clin Oncol.* 2011;29(21):2866-2874.
- Wu Y, Fukuoka M, Mok TSK, et al. Tumour response, skin rash and health-related quality of life (HRQoL)—post-hoc data from the IPASS study [ECCO/ESMO/ESTRO abstract 9134]. *Eur J Cancer.* 2011;47(suppl 1):S633-S634.
- Inoue A, Kobayashi K, Maemondo M, et al; North-East Japan Study Group. Updated overall survival results from a randomized phase III trial comparing gefitinib with carboplatin-paclitaxel for chemo-naïve non-small cell lung cancer with sensitive *EGFR* gene mutations (NEJ002). *Ann Oncol.* 2013;24(1):54-59.
- Mitsudomi T, Morita S, Yatabe Y, et al. Updated overall survival results of WJTOG 3405, a randomized phase III trial comparing gefitinib (G) with cisplatin plus docetaxel (CD) as the first-line treatment for patients with non-small cell lung cancer harboring mutations of the epidermal growth factor receptor (*EGFR*) [ASCO abstract 7521]. *J Clin Oncol.* 2012;30(15 suppl).
- Tarceva [package insert]. Northbrook, IL: OSI Pharmaceuticals, LLC; 2012.
- Zhou C, Wu YL, Liu X, et al. Overall survival (OS) results from OPTIMAL (CTONG0802), a phase III trial of erlotinib (E) versus carboplatin plus gemcitabine (GC) as first-line treatment for Chinese patients with *EGFR* mutation-positive advanced non-small cell lung cancer (NSCLC) [ASCO abstract 7520]. *J Clin Oncol.* 2012;30(15 suppl).
- Yoshioka H, Mitsudomi T, Morita S, et al. Final overall survival results of WJTOG 3405, a randomized phase 3 trial comparing gefitinib (G) with cisplatin plus docetaxel (CD) as the first-line treatment for patients with non-small cell lung cancer (NSCLC) harboring mutations of the epidermal growth factor receptor (*EGFR*) [ASCO abstract 7520]. *J Clin Oncol.* 2014;32(5 suppl).
- Li D, Ambrogio L, Shimamura T, et al. BIBW2992, an irreversible *EGFR*/*HER2* inhibitor highly effective in preclinical lung cancer models. *Oncogene.* 2008;27(34):4702-4711.
- Sequist LV, Yang JC, 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.
- Wu YL, Zhou C, Hu CP, et al. Afatinib versus cisplatin plus gemcitabine for first-line treatment of Asian patients with advanced non-small-cell lung cancer harbouring *EGFR* mutations (LUX-Lung 6): an open-label, randomised phase 3 trial. *Lancet Oncol.* 2014;15(2):213-222.
- Yang JCH, Sequist LV, Schuler MH, et al. Overall survival (OS) in patients (pts) with advanced non-small cell lung cancer (NSCLC) harboring common (Del19/L858R) epidermal growth factor receptor mutations (*EGFR* mut): pooled analysis of two large open-label phase III studies (LUX-Lung 3 [LL3] and LUX-Lung 6 [LL6]) comparing afatinib with chemotherapy (CT) [ASCO abstract 8004]. *J Clin Oncol.* 2014;32(5 suppl).

## REVEL: A Randomized, Double-Blind, Phase III Study of Docetaxel (DOC) and Ramucirumab (RAM; IMC-1121B) Versus DOC and Placebo (PL) in the Second-Line Treatment of Stage IV Non-Small Cell Lung Cancer (NSCLC) Following Disease Progression After One Prior Platinum-Based Therapy

Advancements in genomics have led to the identification of many predictive biomarkers in patients with NSCLC, including the *EGFR* mutations and *ALK* rearrangements. Yet targeted therapies have remained irrelevant for the majority of patients with NSCLC of squamous cell histology, and chemotherapy remains the treatment backbone. Additionally, targeted therapies are unavailable for approximately half of NSCLC patients with nonsquamous histology. In the United States, second-line therapies are associated with a median OS of approximately 7 to 8 months.<sup>1-3</sup> In the past decade, none of the trials assessing the addition of a new agent to standard second-line chemotherapy have demonstrated an improvement in OS for patients with NSCLC. Clearly, new options are needed for patients in the second-line setting.

Angiogenesis is a critical target in NSCLC and is largely mediated by the vascular endothelial growth factor (VEGF)-A/VEGF receptor-2 axis. In order to grow beyond a few millimeters in diameter, tumors must generate their own vasculature to assimilate nutrients and remove cellular waste. Many targeted therapies have been focused on preventing the growth of tumor vasculature. Ramucirumab is a human immunoglobulin G1 monoclonal antibody that binds specifically to the extracellular domain of VEGF receptor-2, preventing its activation by all VEGF ligands. Preclinical and phase 1/2 studies demonstrated antiangiogenic and antitumor activity.<sup>4</sup> A phase 3 study in second-line

### ABSTRACT SUMMARY A Randomized, Multicenter, Open-Label, Phase III Study of Gemcitabine-Cisplatin (GC) Chemotherapy Plus Necitumumab (IMC-11F8/LY3012211) Versus GC Alone in the First-Line Treatment of Patients (pts) With Stage IV Squamous Non-Small Cell Lung Cancer (sq-NSCLC)

Little progress has been made in improving the treatment of NSCLC patients with squamous cell histology, largely owing to a lack of common oncogenic drivers that can be used to guide targeted drug development. In a phase 3 trial, the addition of the anti-EGFR antibody cetuximab to platinum-based first-line therapy significantly improved efficacy in NSCLC patients, with the greatest benefit seen in the SCC subpopulation (Pirker R et al. *Lancet*. 2009;373[9674]:1525-1531). The SQUIRE (First-Line Treatment of Participants With Stage IV Squamous Non-Small Cell Lung Cancer With Necitumumab and Gemcitabine-Cisplatin) trial investigated the addition of necitumumab, a human immunoglobulin G1 anti-EGFR antibody, to gemcitabine plus cisplatin, standard treatment for patients with advanced or metastatic, treatment-naive, NSCLC of squamous cell histology (Abstract 8008). The study enrolled 1093 patients with stage IV squamous cell NSCLC. Patients were randomized to receive 6 cycles of gemcitabine (1250 mg/m<sup>2</sup> on days 1 and 8) plus cisplatin (75 mg/m<sup>2</sup> on day 1) with or without necitumumab (800 mg on days 1 and 8). Patients who achieved a complete response, partial response, or stable disease in the necitumumab arm received maintenance antibody therapy until disease progression. Patients received a median relative dose intensity of 86% for gemcitabine, 95% for cisplatin, and 94% for necitumumab. The study met its primary endpoint, demonstrating an improved median OS with the addition of necitumumab at a median follow-up of 25 months (11.5 months vs 9.9 months; HR, 0.84; 95% CI, 0.74-0.96; *P*=.012). A preplanned Forest plot analysis demonstrated a benefit for several subgroups, including smokers (HR, 0.85; 95% CI, 0.74-0.98). The SQUIRE trial also showed an improvement in median PFS with the addition of necitumumab to gemcitabine plus cisplatin (5.7 months vs 5.5 months; HR, 0.85; 95% CI, 0.74-0.98; *P*=.020). AEs of grade 3 or higher were more frequent in the necitumumab arm (72.1% vs 61.6%), as were the AEs that led to death (12.3% vs 10.5%). Rates of hematologic toxicities were similar in both arms. Grade 3 or higher AEs of interest that were more common with the antibody therapy included hypomagnesemia (9.3% vs 1.1%), skin rash (7.1% vs 0.4%), and venous thromboembolic events (5.0% vs 2.6%).

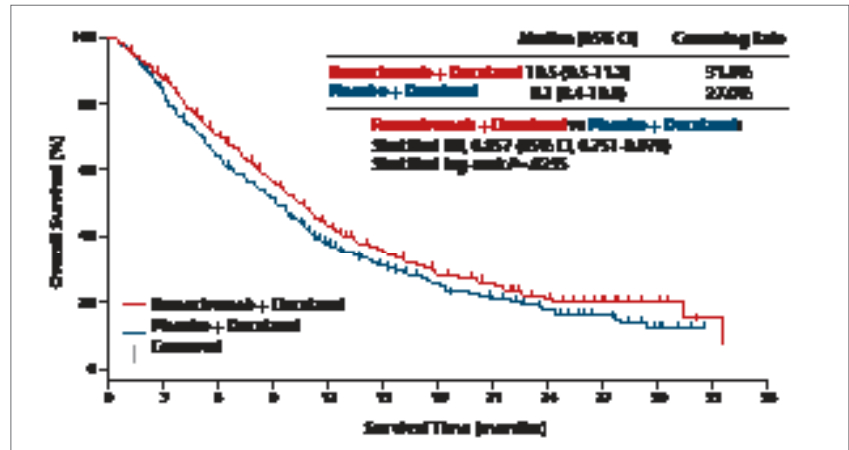
gastric cancer demonstrated that ramucirumab monotherapy can prolong OS, and ramucirumab monotherapy has been recently approved by the US Food

and Drug Administration for second-line treatment of gastric cancer.<sup>5</sup>

Dr Maurice Pérol presented mature data from REVEL (A Study of Chemo-

therapy and Ramucirumab vs. Chemotherapy Alone in Second Line Non-Small Cell Lung Cancer Participants Who Received Prior First Line Platinum Based Chemotherapy), the first study in a decade to show an improvement in OS over standard second-line treatment for patients with metastatic NSCLC.<sup>6</sup> The REVEL study was a double-blind, randomized, placebo-controlled, phase 3 trial assessing the impact of adding ramucirumab to docetaxel as second-line treatment for patients with stage IV NSCLC. Enrolled patients with advanced or metastatic disease had experienced disease progression during or after treatment with 1 first-line, platinum-based agent, with or without maintenance therapy. Eligibility was not predicated on specific tumor histology, and therefore enrollment included patients with squamous and nonsquamous tumor histologies. Patients with prior exposure to bevacizumab were also eligible. All patients had an ECOG performance status of 0 or 1. Exclusion criteria included major blood vessel invasion or significant intratumor cavitation, evidence of bleeding disorders, and related factors that might indicate increased sensitivity to an antiangiogenic agent.

After stratification for ECOG performance status, sex, prior maintenance therapy, and geographic region, patients were randomized in a 1:1 ratio to receive either ramucirumab (10 mg/kg) plus docetaxel (75 mg/m<sup>2</sup>) once every 3 weeks or placebo plus docetaxel at the same dosage. Treatment was continued until disease progression or toxicity. The primary endpoint was OS. Secondary endpoints included PFS, ORR, safety, and quality-of-life assessments (which will be reported at a later date). The study had a planned enrollment of 1242 patients. It required 869 events for an 85% power to detect a reduction in the risk of death with a targeted HR of 0.816 and a 2-sided  $\alpha$ -level of less than 0.05 using the stratified log-rank test. These outcomes correspond to



**Figure 3.** In the phase 3 REVEL study of patients receiving second-line therapy for stage IV NSCLC, the addition of ramucirumab to docetaxel was associated with a significant improvement in overall survival as compared with docetaxel monotherapy. HR, hazard ratio; NSCLC, non-small cell lung cancer; REVEL, A Study of Chemotherapy and Ramucirumab vs. Chemotherapy Alone in Second Line Non-Small Cell Lung Cancer Participants Who Received Prior First Line Platinum Based Chemotherapy. Adapted from Pérol M et al. ASCO abstract 8006. *J Clin Oncol.* 2014;32(5 suppl).<sup>6</sup>

an increase in median OS from 7.5 months in the control arm to 9.2 months in the investigational arm.

The intent-to-treat population included 625 patients in the placebo arm and 628 in the ramucirumab-plus-docetaxel arm. Patient characteristics and baseline demographics were well balanced between the 2 arms. Patients had a median age of 62 years (range, 21-86 years), two-thirds were male, and more than 80% were white. Approximately one-fourth of patients had squamous cell histology. Wild-type *EGFR* was identified in one-third of patients; in the majority of patients, *EGFR* mutation status was unknown. Nearly one-fourth of patients had received prior taxane therapy, 14% had received prior bevacizumab, and two-thirds had benefitted from first-line platinum treatment.

The antiangiogenic treatment yielded a significant improvement in ORR over placebo (22.9% vs 13.6%;  $P < .001$ ). Similarly, the disease control rate was superior (64.0% vs 52.6%;  $P < .001$ ). Ramucirumab also yielded an improved median PFS over placebo (4.5 months vs 3.0 months; HR, 0.762; 95% CI, 0.677-0.859;  $P < .0001$ ). In the Kaplan-Meier curve

of PFS, the 2 arms separated early and remained separate for the study duration. Forest plot analysis showed a PFS benefit with ramucirumab for most subgroups, including patients with squamous histology (24% risk reduction) and those with nonsquamous histology (23% risk reduction).

The REVEL study also met its primary endpoint, showing a median OS of 10.5 months among patients who received ramucirumab plus docetaxel vs 9.1 months among those who received placebo plus docetaxel (HR, 0.857; 95% CI, 0.751-0.979;  $P = .0235$ ; Figure 3). Again, the Kaplan-Meier plot showed clear separation between the 2 arms for the study duration. A Forest plot analysis of OS showed a benefit in most subgroups, particularly patients who had received prior maintenance therapy (HR, 0.69). Squamous or nonsquamous cell tumor histologies were associated with HRs of 0.88 and 0.83, respectively. Nearly half of the patients received systemic therapy after discontinuation from the study, with approximately 20% of patients receiving an EGFR TKI and the remainder receiving gemcitabine (12%), vinorelbine (10%), or pemetrexed (9%). An

approximately equal proportion of patients in each arm received the same treatment after discontinuation from the study, suggesting a minimal impact on the differences in outcomes.

Among all patients who discontinued treatment, the majority did so because of progressive disease (investigational arm, 56%; placebo arm, 70%). Discontinuation owing to an adverse event (AE) was more common in the investigational arm compared with the placebo arm (15% vs 9%). More patients in the investigational arm experienced a treatment-emergent AE of grade 3 or higher (78.9% vs 71.8%); however, serious treatment-emergent AEs occurred at a similar rate in both arms (43% vs 42%, respectively). Moreover, the majority of

toxicities were attributed to docetaxel. The most common grade 3/4 AEs that occurred with greater frequency in the antibody arm included neutropenia (48.8% vs 39.8%), febrile neutropenia (15.9% vs 10.0%), and fatigue (14.0% vs 10.5%); no deaths were associated with these AEs. Grade 1/2 bleeding was more frequent in the ramucirumab arm (26.5% vs 12.9%), with the majority of episodes consisting of epistaxis (18.2% for ramucirumab plus docetaxel vs 6.3% for placebo).

## References

1. Shepherd FA, Dancy J, Ramlau R, et al. Prospective randomized trial of docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy. *J Clin Oncol.* 2000;18(10):2095-2103.

2. Shepherd FA, Rodrigues Pereira J, Ciuleanu T, et al; National Cancer Institute of Canada Clinical Trials Group. Erlotinib in previously treated non small-cell lung cancer. *N Engl J Med.* 2005;353(2):123-132.

3. Scagliotti G, Hanna N, Fossella F, et al. The differential efficacy of pemetrexed according to NSCLC histology: a review of two Phase III studies. *Oncologist.* 2009;14(3):253-263.

4. Krupitskaya Y, Wakelee HA. Ramucirumab, a fully human mAb to the transmembrane signaling tyrosine kinase VEGFR-2 for the potential treatment of cancer. *Curr Opin Investig Drugs.* 2009;10(6):597-605.

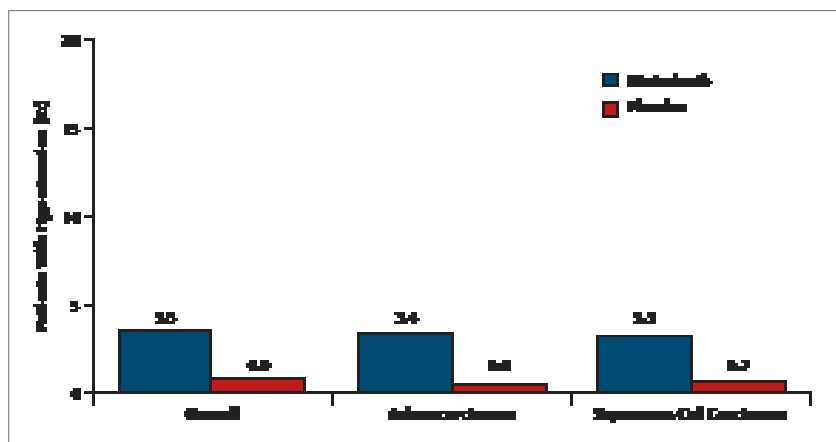
5. Fuchs CS, Tomasek J, Yong CJ, et al; REGARD Trial Investigators. Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): an international, randomised, multicentre, placebo-controlled, phase 3 trial. *Lancet.* 2014;383(9911):31-39.

6. Pérol M, Ciuleanu TE, Arrieta O, et al. REVEL: a randomized, double-blind, phase III study of docetaxel (DOC) and ramucirumab (RAM; IMC-1121B) versus DOC and placebo (PL) in the second-line treatment of stage IV non-small cell lung cancer (NSCLC) following disease progression after one prior platinum-based therapy [ASCO abstract 8006]. *J Clin Oncol.* 2014;32(5 suppl).

## Antiangiogenic-Specific Adverse Events (AEs) in Patients With Non-Small Cell Lung Cancer (NSCLC) Treated With Nintedanib (N) and Docetaxel (D)

Antiangiogenic treatments, such as monoclonal antibodies and TKIs, have shown activity in several tumor types; however, their use is limited by their characteristic AEs, such as bleeding, thrombosis, perforation, and hypertension. Bevacizumab is the only antiangiogenic agent currently approved for treating NSCLC. Its indication is restricted to nonsquamous histology, and it is contraindicated for patients with a history of clinically significant hemorrhage or hemoptysis associated with an increased risk of bleeding.<sup>1</sup> Nintedanib is a new oral inhibitor of angiogenesis. It blocks activation of the VEGF receptors 1 through 3, the fibroblast growth factor receptors 1 through 3, and the platelet-derived growth factor receptors  $\alpha$  and  $\beta$ , leading to apoptosis of the cells in the vasculature.

LUME-Lung 1 (BIBF 1120 Plus Docetaxel as Compared to Placebo Plus Docetaxel in 2nd Line Non Small Cell



**Figure 4.** The phase 3 LUME-Lung 1 trial added nintedanib to docetaxel in patients with advanced NSCLC after failure of first-line chemotherapy. Rates of hypertension of any grade were higher among patients who received nintedanib. LUME-Lung 1, BIBF 1120 Plus Docetaxel as Compared to Placebo Plus Docetaxel in 2nd Line Non Small Cell Lung Cancer; NSCLC, non-small cell lung cancer. Adapted from Reck M et al. ASCO abstract 8100. *J Clin Oncol.* 2014;32(5 suppl).<sup>3</sup>

Lung Cancer) is a randomized, placebo-controlled, phase 3 trial that investigated the addition of nintedanib to docetaxel in patients with advanced NSCLC after

failure of first-line chemotherapy.<sup>2,3</sup> The study enrolled 1314 patients in 27 countries with stage IIIB/IV, recurrent NSCLC that progressed after first-line



chemotherapy. Patients were randomized to receive docetaxel (75 mg/m<sup>2</sup>) on day 1 plus either nintedanib (200 mg twice daily) or matching placebo on days 2 to 21 of a 3-week cycle until disease progression or unacceptable toxicity. After a median follow-up of 7.1 months, the study met its primary endpoint, showing an improved PFS among patients who received nintedanib plus docetaxel compared with those who received placebo plus docetaxel (3.4 months vs 2.7 months; HR, 0.79; 95% CI, 0.68-0.92; *P*=.0019). PFS improved regardless of histology. Patients with adenocarcinoma who received the nintedanib combination showed a benefit in median OS (12.6 months vs 10.3 months; HR, 0.83; 95% CI, 0.70-0.99; *P*=.0359).

To fully elucidate the AE profile of this new antiangiogenic drug, the incidence and intensity of antiangiogenesis-associated AEs were assessed according to the Common Terminology Criteria for Adverse Events (version 3.0) in all

patients who received at least 1 dose of nintedanib, docetaxel, or placebo.<sup>3</sup> Nongastrointestinal perforations of any grade occurred at low rates in the overall population (1.2% with nintedanib vs 0.2% with placebo), in patients with adenocarcinoma (1.3% vs 0.3%, respectively), and in patients with squamous cell carcinoma (SCC; 0.7% vs 0%, respectively). The highest rates of gastrointestinal perforation were observed in SCC patients (0.4% with nintedanib vs 1.1% with placebo). Hypertension of any grade occurred in a small proportion of patients in both arms, but was higher with nintedanib compared with placebo among the overall population (3.5% vs 0.9%, respectively), patients with adenocarcinoma (3.4% vs 0.6%, respectively), and patients with SCC (3.3% vs 0.7%, respectively; Figure 4). Bleeding events of any grade were most frequent in SCC patients and were higher with nintedanib than placebo (17.1% vs 10.8%). In contrast, patients with adenocarcinoma

had similar rates of bleeding regardless of treatment (10.9% with nintedanib vs 11.1% with placebo). Among SCC patients, the most frequent bleeding events of any grade were pulmonary (10.9% with nintedanib vs 8.6% with placebo). Bleeding events of grade 3 or greater were also highest among patients with SCC in the nintedanib arm (2.9% vs 2.6% for placebo). Fatal bleeding events were rare and occurred at similar rates in the 2 treatment arms.

## References

1. Avastin [package insert]. South San Francisco, CA; Genentech Inc; 2013.
2. Reck M, Kaiser R, Mellemegaard A, et al; LUME-Lung 1 Study Group. Docetaxel plus nintedanib versus docetaxel plus placebo in patients with previously treated non-small-cell lung cancer (LUME-Lung 1): a phase 3, double-blind, randomised controlled trial. *Lancet Oncol*. 2014;15(2):143-155.
3. Reck M, Mellemegaard A, Orlov SV, et al. Antiangiogenic-specific adverse events (AEs) in patients with non-small cell lung cancer (NSCLC) treated with nintedanib (N) and docetaxel (D) [ASCO abstract 8100]. *J Clin Oncol*. 2014;32(5 suppl).

# LUX-Lung 5: A Randomized, Open-Label, Phase III Trial of Afatinib (A) Plus Paclitaxel (P) Versus Investigator's Choice of Chemotherapy (ICC) in Patients (pts) With Metastatic Non-Small Cell Lung Cancer (NSCLC) Who Had Progressed on Erlotinib/Gefitinib (E/G) and Afatinib

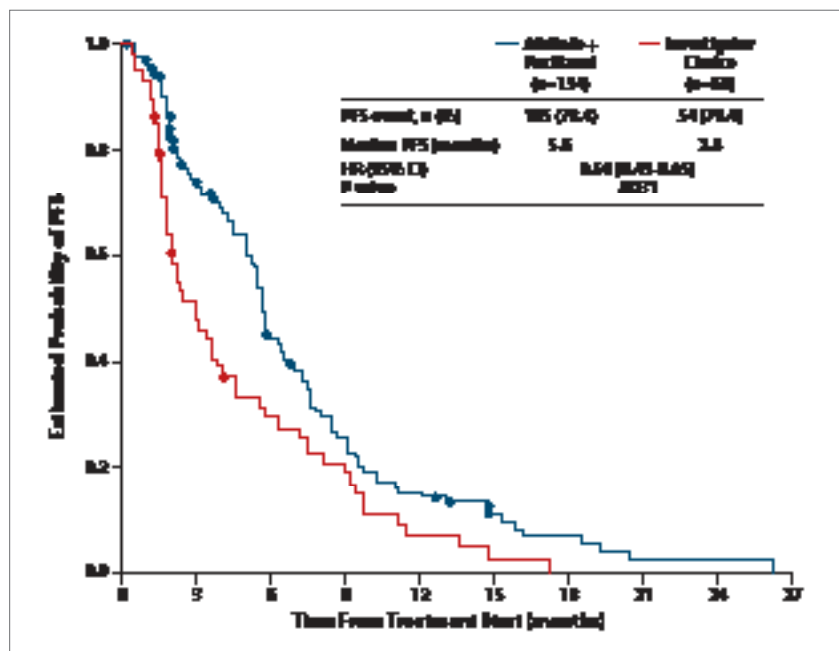
**A**lthough EGFR TKIs can successfully treat NSCLC, patients eventually develop resistance.<sup>1,2</sup> In many tumor types, patients have benefitted when inhibition of driver pathways is maintained with targeted agents after disease progression. Retrospective and nonrandomized studies in NSCLC have suggested that maintenance of EGFR inhibition improves disease control over chemotherapy alone,<sup>3,4</sup> but this approach has not been studied prospectively. Afatinib is an oral, irreversible ErbB family blocker that inhibits the EGFR/ErbB1, HER2/

ErbB2, and ErbB4 receptor kinases.<sup>5,6</sup> TKIs have demonstrated efficacy in treatment-naïve NSCLC patients harboring *EGFR* activating mutations, as well as in patients with acquired resistance to erlotinib and gefitinib, 2 reversible EGFR TKIs.<sup>7-10</sup>

The randomized, open-label, phase 3 LUX-Lung 5 trial was designed to prospectively investigate the efficacy of afatinib plus paclitaxel in NSCLC patients who progressed after receiving at least 1 line of chemotherapy and then subsequently progressed while on afatinib.<sup>11</sup> The trial enrolled 1154

patients from 115 centers in 23 countries. Eligible patients had stage IIIB/IV NSCLC that had failed at least 1 line of chemotherapy that included a platinum and pemetrexed. The patients had achieved a clinical benefit from erlotinib or gefitinib that lasted for at least 12 weeks but was followed by progression.

The trial consisted of 2 parts. In part A, all patients received treatment with afatinib (50 mg daily). Patients who exhibited a complete response, partial response, or stable disease with afatinib followed by progression after



**Figure 5.** In the phase 3 LUX-Lung 5 trial, the combination of afatinib plus paclitaxel yielded a significant improvement in median PFS compared with chemotherapy. HR, hazard ratio; PFS, progression-free survival. Adapted from Schuler MH et al. ASCO abstract 8019. *J Clin Oncol.* 2014;32(5 suppl).<sup>11</sup>

12 weeks on treatment proceeded to part B, in which they were randomized 2:1 to receive either afatinib (40 mg daily) plus paclitaxel (80 mg/m<sup>2</sup> weekly) or the treating physician's choice of single-agent chemotherapy.

The primary endpoint was PFS, with secondary endpoints including ORR, OS, and safety. Patients were randomized to afatinib plus paclitaxel (n=134) or chemotherapy (n=68), which consisted of paclitaxel (37%), pemetrexed (29%), docetaxel (15%), or other agents (19%). Baseline characteristics were well balanced between the 2 arms. Patients had a median age of 60 years, and half were male. More than two-thirds of patients had received at least 2 lines of prior chemotherapy, and fewer than 10% of patients had SCC.

The combination of afatinib plus paclitaxel yielded a significant improvement in median PFS compared with chemotherapy (5.6 months vs 2.8 months; HR, 0.60; 95% CI, 0.43-0.85;  $P=.0031$ ; Figure 5). The ORR was higher with afatinib plus paclitaxel than with chemotherapy (32.1% vs 13.2%, respectively; odds ratio, 3.1; 95% CI, 1.4-6.8;  $P=.0049$ ), as was the disease control rate (74.6% vs 45.6%, respectively; odds ratio, 3.4; 95% CI, 1.9-6.3;  $P<.0001$ ). Subgroup analysis suggested a benefit from the afatinib combination for patients with SCC. No difference in median OS emerged (12.2 months for both arms; HR, 1.00; 95% CI, 0.70-1.43;  $P=.9936$ ). The most common treatment-related AEs in the afatinib plus paclitaxel arm compared with

chemotherapy were diarrhea (53.8% vs 6.7%), alopecia (32.6% vs 15.0%), and asthenia (27.3% vs 28.3%).

## References

- Goldberg SB, Oxnard GR, Digumarthy S, et al. Chemotherapy with Erlotinib or chemotherapy alone in advanced non-small cell lung cancer with acquired resistance to EGFR tyrosine kinase inhibitors. *Oncologist.* 2013;18(11):1214-1220.
- Jackman D, Pao W, Riely GJ, et al. Clinical definition of acquired resistance to epidermal growth factor receptor tyrosine kinase inhibitors in non-small-cell lung cancer. *J Clin Oncol.* 2010;28(2):357-360.
- Katakami N, Atagi S, Goto K, et al. LUX-Lung 4: a phase II trial of afatinib in patients with advanced non-small-cell lung cancer who progressed during prior treatment with erlotinib, gefitinib, or both. *J Clin Oncol.* 2013;31(27):3335-3341.
- Li D, Ambrogio L, Shimamura T, et al. BIBW2992, an irreversible EGFR/HER2 inhibitor highly effective in pre-clinical lung cancer models. *Oncogene.* 2008;27:4702-4711.
- Miller VA, Hirsh V, Cadranel J, et al. Afatinib versus placebo for patients with advanced, metastatic non-small-cell lung cancer after failure of erlotinib, gefitinib, or both, and one or two lines of chemotherapy (LUX-Lung 1): a phase 2b/3 randomised trial. *Lancet Oncol.* 2012;13(15):528-538.
- Paz-Ares L, Soulières D, Melezinek I, et al. Clinical outcomes in non-small-cell lung cancer patients with EGFR mutations: pooled analysis. *J Cell Mol Med.* 2010;14(1-2):51-69.
- Sequist LV, Yang JC, 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.
- 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.
- Wu YL, Zhou C, Hu CP, et al. Afatinib versus cisplatin plus gemcitabine for first-line treatment of Asian patients with advanced non-small-cell lung cancer harbouring EGFR mutations (LUX-Lung 6): an open-label, randomised phase 3 trial. *Lancet Oncol.* 2014;15(2):213-222.
- Yoshimura N, Okishio K, Mitsuoka S, et al. Prospective assessment of continuation of erlotinib or gefitinib in patients with acquired resistance to erlotinib or gefitinib followed by the addition of pemetrexed. *J Thorac Oncol.* 2013;8(1):96-101.
- Schuler MH, Yang CH, Park K, et al. Continuation of afatinib beyond progression: results of a randomized, open-label, phase III trial of afatinib plus paclitaxel (P) versus investigator's choice chemotherapy (CT) in patients (pts) with metastatic non-small cell lung cancer (NSCLC) progressed on erlotinib/gefitinib (E/G) and afatinib—LUX-Lung 5 (LL5) [ASCO abstract 8019]. *J Clin Oncol.* 2014;32(5 suppl).

## Onartuzumab Plus Erlotinib Versus Erlotinib in Previously Treated Stage IIIb or IV NSCLC: Results From the Pivotal Phase III Randomized, Multicenter, Placebo-Controlled METLung (OAM4971g) Global Trial

The MET receptor tyrosine kinase is overexpressed in a subset of NSCLC tumors. Dysregulation of the MET receptor can occur through numerous mechanisms, including gene amplification; the introduction of activating mutations; and dysregulation of its ligand, hepatocyte growth factor. These aberrant events have been implicated in numerous oncogenic processes, including increased cell survival, motility, proliferation, and invasion.<sup>1</sup> In NSCLC, MET overexpression is associated with early recurrence and a poor prognosis, even in early-stage disease.<sup>2</sup> The combined targeting of EGFR and MET is of interest in NSCLC. Although the exact relationship between the expression, activation, and dysregulation of these 2 receptors has not been elucidated, MET and EGFR are often coexpressed in solid tumors. In lung cancer, MET increases the expression of EGFR ligands, and MET amplification has been observed in tumors with acquired resistance to EGFR TKIs.<sup>3,4</sup>

Onartuzumab is a humanized, single-arm antibody that prevents ligand binding to the MET receptor.<sup>5</sup> In contrast, most antibodies contain 2 antigen-binding sites; when these antibodies bind to a target receptor, dimerization may occur, thus inducing activation. Onartuzumab was designed with only 1 target-binding site to prevent this potential activation of the MET pathway. A phase 2 study examined the combination of onartuzumab plus erlotinib vs erlotinib monotherapy in 137 patients with refractory NSCLC and found no difference in median PFS for the overall study population ( $P=.69$ ).<sup>6</sup> In a predefined subset analysis, however, 66 patients

with MET overexpression based on immunohistochemistry (IHC) showed a significant increase in median PFS from treatment with the onartuzumab/erlotinib combination vs erlotinib alone (2.9 months vs 1.5 months; HR, 0.53; 95% CI, 0.28-0.99;  $P=.04$ ). In addition, these patients showed a striking increase in median OS with the combination treatment (12.6 months vs 3.8 months; HR, 0.37; 95% CI, 0.19-0.72;  $P=.002$ ). Although the onartuzumab combination was superior in patients with MET receptor overexpression by IHC, no such difference was observed for patients with *MET* gene amplification as assessed by fluorescence in situ hybridization.

Based on these promising phase 2 results, a larger trial was undertaken to compare the combination therapy vs erlotinib monotherapy in patients with MET overexpression. The randomized, placebo-controlled, phase 3 METLung (A Study of Onartuzumab [MetMab] in Combination With Tarceva [Erlotinib] in Patients With Met Diagnostic-Positive Non-Small Cell Lung Cancer Who Have Received Chemotherapy for Advanced or Metastatic Disease [MetLung]) trial enrolled patients with an ECOG performance status of 0 or 1 and refractory, stage IIIB or IV NSCLC of any histology with centrally confirmed MET overexpression based on IHC.<sup>7</sup> *EGFR* mutation status was also determined but was not a criterion for trial entry. Patients were stratified based on *EGFR* status (mutated vs wild-type), MET expression level (2+ vs 3+), number of prior treatments, and tumor histology. Patients were then evenly randomized to receive erlotinib (150 mg daily) plus either onartuzumab (15 mg/kg every 3 weeks) or placebo. The primary endpoint was

OS; therefore, no crossover to the other treatment arm was allowed. Secondary endpoints included PFS, ORR, quality of life, safety, and pharmacokinetics. The final analysis was planned after 364 OS events, with 1 interim analysis planned after 67% of OS events had occurred. The interim analysis rejection boundaries defined superior efficacy by an HR of 0.73 or lower, with futility defined as an HR of 0.94 or greater.

The METLung study enrolled 499 patients. Patient demographics and baseline characteristics were well balanced between the 2 treatment arms. Patients had a median age of 63 years, and 56% were male. Nonsquamous tumor histology was present in 86% of patients, and nearly one-third had received 2 prior lines of therapy. MET IHC 2+ expression was reported in 79% of patients, and the remaining patients had 3+ expression. Approximately 11% of patients in each arm had a mutated *EGFR*.

The study failed to reach its primary endpoint, yielding a median OS of 9.1 months for the control arm vs 6.8 months for the onartuzumab-plus-erlotinib arm (HR, 1.27; 95% CI, 0.98-1.65;  $P=.07$ ). Subgroup analysis failed to demonstrate a benefit with the onartuzumab combination vs erlotinib monotherapy. Moreover, for the subset of patients with MET IHC 3+ overexpression, the onartuzumab combination yielded a shorter median OS compared with the control arm (9.1 months vs 6.4 months, respectively; HR, 1.02; 95% CI, 0.59-1.75). Similarly, median PFS was no different for the onartuzumab-plus-erlotinib arm vs the control arm (2.7 months vs 2.6 months; HR, 0.99; 95% CI, 0.81-1.20;  $P=.92$ ). Again, subgroup analysis

failed to identify a definitive benefit from the combined inhibition of MET and EGFR.

The combination therapy was generally well tolerated. The most common AEs of any grade were rash (39% in the combination arm vs 37% with monotherapy), diarrhea (39% vs 47%, respectively), and dermatitis acneiform (32% vs 26%, respectively). AEs of any grade that were considered related to the inhibition of MET included peripheral edema (22% vs

8%, respectively) and hypoalbuminemia (17% vs 4%, respectively).

## References

1. Sadiq AA, Salgia R. MET as a possible target for non-small-cell lung cancer. *J Clin Oncol*. 2013;31(8):1089-1096.
2. Cheng TL, Chang MY, Huang SY, et al. Overexpression of circulating c-met messenger RNA is significantly correlated with nodal stage and early recurrence in non-small cell lung cancer. *Chest*. 2005;128(3):1453-1460.
3. Matsubara D, Ishikawa S, Sachiko O, Aburatani H, Fukuyama M, Niki T. Co-activation of epidermal growth factor receptor and c-MET defines a distinct subset of lung adenocarcinomas. *Am J Pathol*. 2010;177(5):2191-2204.

4. Engelman JA, Janne PA. Mechanisms of acquired resistance to epidermal growth factor receptor tyrosine kinase inhibitors in non-small cell lung cancer. *Clin Cancer Res*. 2008;14(10):2895-2899.

5. Merchant M, Ma X, Maun HR, et al. Monovalent antibody design and mechanism of action of onartuzumab, a MET antagonist with anti-tumor activity as a therapeutic agent. *Proc Natl Acad Sci USA*. 2013;110(32):E2987-E2996.

6. Spigel DR, Ervin TJ, Ramlau RA, et al. Randomized phase II trial of Onartuzumab in combination with erlotinib in patients with advanced non-small-cell lung cancer. *J Clin Oncol*. 2013;31(32):4105-4114.

7. Spigel DR, Edelman MJ, O'Byrne K, et al. Onartuzumab plus erlotinib versus erlotinib in previously treated stage IIIb or IV NSCLC: results from the pivotal phase III randomized, multicenter, placebo-controlled METLung (OAM4971g) global trial [ASCO abstract 8000]. *J Clin Oncol*. 2014;32(5 suppl).

# Highlights in NSCLC From the 2014 ASCO Meeting

Mark A. Socinski, MD

Professor of Medicine and Thoracic Surgery

Director, Lung Cancer Section, Division of Hematology/Oncology

Clinical Associate Director, Lung SPORE

Co-Director, UPMC Lung Cancer Center of Excellence

Co-Director, Lung and Thoracic Malignancies Program

University of Pittsburgh

Pittsburgh, Pennsylvania

The 2014 meeting of the American Society of Clinical Oncology (ASCO) offered many important presentations on the management of patients with non-small cell lung cancer (NSCLC). Some of the most interesting studies involved third-generation epidermal growth factor receptor (EGFR) inhibitors in patients with EGFR mutations and resistance to agents such as erlotinib and gefitinib. In patients with *ALK* fusion proteins, a second-generation *ALK* inhibitor was of particular interest. Novel agents under evaluation included the antibodies necitumumab and ramucirumab in combination with standard therapies. In addition, data were presented from a trial evaluating consolidation chemotherapy in patients with stage III NSCLC.

## Patients With EGFR Mutations

Dr James Chih-Hsing Yang evaluated survival outcomes in a pooled analysis

of the LUX-Lung 3 and LUX-Lung 6 trials, which compared afatinib to chemotherapy.<sup>1-3</sup> These 2 trials are the largest in this setting. The analysis showed a survival advantage in the *EGFR*-mutant population for afatinib vs cisplatin plus pemetrexed (in LUX-Lung 3)<sup>2</sup> and vs cisplatin plus gemcitabine (in LUX-Lung 6).<sup>3</sup> Interestingly, the most dramatic survival advantage was seen in patients with the *EGFR* exon 19 deletion, whose overall survival improved by an impressive 11 months with afatinib over chemotherapy. Unfortunately, patients with the exon 21 *EGFR* mutation did not show a significant improvement in median overall survival. These different survival outcomes confirm that *EGFR* mutations vary in their sensitivity to EGFR TKIs.

The data from this analysis reinforce the use of afatinib as first-line treatment and lend support for this agent as the "drug of choice" for those patients with an exon 19 *EGFR* mutation. Other tyrosine kinase inhibitors in this setting

may have a similar effect, but these data advance afatinib to the forefront of these agents, particularly among patients with the *EGFR* exon 19 deletion mutation.

Data were presented for the phase 3 LUX-Lung 5 trial, which compared afatinib plus paclitaxel vs the investigator's choice of chemotherapy in patients who had progressed during treatment with erlotinib/gefitinib and afatinib.<sup>4</sup> Those patients who received the afatinib/paclitaxel combination had a significant improvement in median progression-free survival (PFS) compared with chemotherapy (5.6 months vs 2.8 months;  $P=.0031$ ). However, the treatment in this trial was mostly administered in the fourth-line setting, and the results have limited applicability in clinical practice because few patients remain fit enough for fourth-line therapy.

Dr Terufumi Kato presented results from a randomized trial that evaluated the addition of bevacizumab to erlotinib vs erlotinib alone in NSCLC patients with *EGFR* mutations.<sup>5</sup> The



study showed an impressive difference in the primary endpoint of PFS, which nearly doubled with the addition of bevacizumab. The PFS curves separated quickly. Bevacizumab was associated with no surprising toxicities in this population of patients with *EGFR* mutations, who tend to be healthier than the average lung cancer patient. These data provide some optimism that PFS can be improved in this patient population. An ongoing trial is evaluating the same treatment, and results are eagerly awaited.<sup>6</sup> The study presented by Dr. Kato was relatively small (N=152), and it will be important to see if the results can be replicated. The data from the ongoing trial will also be analyzed in combination with the data from Dr. Kato and colleagues.

Dr. David R. Spigel presented results from the phase 3 METLung (A Study of Onartuzumab [MetMab] in Combination With Tarceva [Erlotinib] in Patients With Met Diagnostic-Positive Non-Small Cell Lung Cancer Who Have Received Chemotherapy for Advanced or Metastatic Disease [MetLung]) trial, which compared onartuzumab plus erlotinib with erlotinib alone in previously treated stage IIIb or IV NSCLC patients.<sup>7</sup> The study failed to demonstrate a benefit from the onartuzumab combination over erlotinib monotherapy in overall survival or PFS. Subset analysis failed to identify any groups that benefited from the combination treatment. These findings are a disappointment following the promising results demonstrated in a previous phase 2 trial.<sup>8</sup> Although the phase 2 trial showed no difference in PFS among the overall population, patients with high expression of MET seemed to derive great benefit from the addition of onartuzumab to erlotinib vs erlotinib alone; among these patients, overall survival was 12.6 months with the onartuzumab/erlotinib combination vs 3.8 months with erlotinib alone (hazard ratio [HR], 0.37; 95% CI, 0.19-0.72;  $P=.002$ ). The population in the phase

3 METLung trial was enriched for patients with high expression of MET,<sup>7</sup> and it seemed that this population had a high likelihood of benefitting from the combination of onartuzumab plus erlotinib. Unfortunately, the results of METLung were frankly negative. In fact, patients who received onartuzumab plus erlotinib were slightly disadvantaged compared with the control arm of patients who received erlotinib alone. The METLung trial is a reminder that the great test of any new agent is the phase 3 trial, and that it is possible to be misled by smaller, randomized phase 2 trials. At the ASCO presentation, there was much discussion about why the results were negative, but there is no good explanation at this time.

### Novel Antibodies

Dr. Nick Thatcher presented results of the SQUIRE (First-Line Treatment of Participants With Stage IV Squamous Non-Small Cell Lung Cancer With Necitumumab and Gemcitabine-Cisplatin) study, a phase 3 trial that examined the addition of necitumumab to cisplatin and gemcitabine in patients with stage IV squamous cell carcinoma NSCLC.<sup>9</sup> Necitumumab is a fully humanized anti-EGFR antibody,<sup>10</sup> in contrast to cetuximab, which contains approximately 30% murine protein.<sup>11</sup> Enrollment in this trial was not based on EGFR expression. The trial met its primary endpoint by showing a statistically significant improvement in overall survival with the addition of necitumumab (11.5 months vs 9.9 months; HR, 0.84; 95% CI, 0.74-0.96;  $P=.01$ ).<sup>9</sup> This improvement in overall survival is clinically important for the population of patients with squamous cell histology. There have been no treatment advances in the squamous cell population in the past 2 decades. We have no other targeted agent offering any hope of prolonged survival, and the standard of care remains a platinum-based doublet such as carboplatin/paclitaxel

and albumin-bound paclitaxel/gemcitabine.<sup>12</sup> In contrast, patients with adenocarcinoma have options such as pemetrexed and bevacizumab, and there is also the possibility they have an actionable genotype such as the *EGFR* mutation or *ALK* translocation, which are exceedingly unusual in patients with squamous histology. The results of the SQUIRE trial offer hope for improved survival in the squamous population. Among the entire study population, the improvement in overall survival was modest, but some patients gained substantial benefit. Because necitumumab is an antibody with a specific target, there is hope that a biomarker can be developed to identify patients most likely to benefit from this agent. In the SQUIRE trial, the initial evaluation using immunohistochemistry and the H-score was not revealing. I would caution against reaching final conclusions regarding the SQUIRE trial until a more detailed analysis of the H-score data is available.

The second-line REVEL (A Study of Chemotherapy and Ramucirumab vs. Chemotherapy Alone in Second Line Non-Small Cell Lung Cancer Participants Who Received Prior First Line Platinum Based Chemotherapy) trial explored the use of the antiangiogenic antibody ramucirumab, which is an antibody to the vascular endothelial growth factor receptor 2.<sup>13,14</sup> A key point concerning this trial is that it accepted all histologies, so patients with squamous cell carcinomas were well represented. The control arm was docetaxel, and the treatment arm consisted of ramucirumab added to docetaxel. The trial met its primary endpoint of improvement in overall survival. The addition of ramucirumab to docetaxel improved median overall survival to 10.5 months compared with 9.1 months for docetaxel alone (HR, 0.857; 95% CI, 0.751-0.979;  $P=.0235$ ). Ramucirumab also improved PFS and the overall response rate. Ramucirumab is currently approved for use in gastric cancer.<sup>15</sup> It is not

### ABSTRACT SUMMARY Erlotinib Plus Bevacizumab (EB) Versus Erlotinib Alone (E) as First-Line Treatment for Advanced *EGFR* Mutation-Positive Nonsquamous Non-Small Cell Lung Cancer (NSCLC): An Open-Label Randomized Trial

A phase 2 study evaluated whether NSCLC patients with *EGFR* mutations might benefit from dual VEGF/*EGFR* inhibition in the first-line setting (Abstract 8005). The trial enrolled chemotherapy-naïve NSCLC patients with nonsquamous, stage IIIB/IV or recurring disease and an activating *EGFR* mutation (del19 or L858R). Patients had a performance status of 0 or 1 and no brain metastases. They were randomized evenly to receive erlotinib (150 mg daily) or erlotinib plus bevacizumab (15 mg/kg every 3 weeks). The primary endpoint was PFS by independent review. Secondary endpoints included OS, tumor response, safety, quality of life, and symptom improvement. The study recruited 154 patients from 30 institutions, although 2 patients in the combination arm withdrew before they received treatment. At the time of data cutoff, 103 PFS events had been observed. Baseline characteristics were well balanced between the 2 arms. Patients had a median age of 67 years, and nearly two-thirds were female. More than half of the patients had never smoked, and approximately 53% had the del19 *EGFR* mutation. The study met its primary endpoint, demonstrating a significant improvement in median PFS with the addition of bevacizumab to erlotinib (16.0 months vs 9.7 months; HR, 0.54; 95% CI, 0.36-0.79;  $P=.0015$ ). For the group of patients with del19, bevacizumab plus erlotinib yielded a median PFS of 18.0 months vs 10.3 months for erlotinib alone (HR, 0.41; 95% CI, 0.24-0.72). For patients with the L858R mutation in exon 21, combination treatment yielded a median PFS of 13.9 months compared with 7.1 months for erlotinib alone (HR, 0.67; 95% CI, 0.38-1.18). AEs of grade 3 or higher were more common in patients receiving the combination treatment than erlotinib monotherapy (91% vs 53%, respectively). However, serious AEs occurred in approximately one-fourth of patients in each arm. AEs of grade 3 or greater that occurred at a significantly higher rate with the combination treatment vs placebo included hypertension (60% vs 10%, respectively) and proteinuria (8% vs 0%, respectively).

known whether data from REVEL will extend the indication of ramucirumab to include use in combination with docetaxel in second-line NSCLC.

The REVEL trial is notable for several reasons. As mentioned, it accepted all NSCLC histologies. It evaluated use of an antiangiogenic agent, which is important because the only antiangiogenic agent currently approved in lung cancer is bevacizumab, which is not indicated in squamous NSCLC owing to the risk of toxicity.<sup>16</sup> There were no toxicity concerns in the REVEL trial. In addition, monotherapy was established as second-line treatment more than a decade ago; the REVEL trial is the first to demonstrate that 2 drugs are better than 1 in the second-line setting. The REVEL

trial also reinforces the concept that the angiogenic pathway is an important target, although the benefits are still modest.

The phase 3 LUME-Lung 1 (BIBF 1120 Plus Docetaxel as Compared to Placebo Plus Docetaxel in 2nd Line Non Small Cell Lung Cancer) trial investigated the addition of nintedanib to docetaxel in patients with advanced NSCLC after failure of first-line chemotherapy.<sup>17</sup> The study met its primary endpoint; the addition of nintedanib improved PFS (3.4 months vs 2.7 months; HR, 0.79; 95% CI, 0.68-0.92;  $P=.0019$ ).

### Adjuvant Therapy

The RADIANT (Randomized Double-Blind Trial in Adjuvant NSCLC

With Tarceva) trial examined the use of adjuvant erlotinib vs placebo in the postsurgical setting.<sup>18</sup> The design included early-stage patients (IB to IIIA) who were *EGFR*-positive according to protein expression testing using immunohistochemistry or fluorescence in situ hybridization. The use of adjuvant cisplatin-based chemotherapy was permitted. Patients were randomized in a placebo-controlled fashion. In the intent-to-treat population, the results were negative; no benefit was seen with adjuvant erlotinib vs placebo. A subset analysis of the patients with *EGFR* mutations (17%) showed an improvement in median disease-free survival with erlotinib vs placebo (46.4 months vs 28.5 months;  $P=.0391$ ),<sup>19</sup> although this difference was not considered statistically significant per the study protocol. Overall survival was not significantly impacted by treatment in patients with *EGFR* mutations.

The RADIANT trial raises some important issues. There is the temptation to treat *EGFR*-mutant disease in the adjuvant setting with an *EGFR* tyrosine kinase inhibitor, but the data for this approach are inconclusive. There does not appear to be an overall survival advantage, despite the improvement in disease-free survival. The duration of therapy in the RADIANT trial is another consideration. The intent was to deliver 2 years of therapy with erlotinib, but many patients received a shorter duration. An interesting finding of this study concerns brain recurrences, which were more frequent in the erlotinib arm than in the placebo arm (21.7% vs 17.8%, respectively). The pattern of recurrence may have therefore shifted under the influence of the *EGFR* tyrosine kinase inhibitor. It is important to be aware of this potential effect.

### Stage III Disease

Dr Keunchil Park presented results from a phase 3 trial exploring the role of consolidation therapy after

concurrent chemoradiation in patients with stage III NSCLC.<sup>20</sup> This area is controversial. The established duration of therapy in advanced-stage disease, as well as in the adjuvant setting, is 4 cycles. In patients with stage III disease receiving induction or consolidation therapy, no survival differences have been seen with the addition of chemotherapy beyond the time of radiotherapy—or even before. The results of this trial reinforced that concept. There was no hint from the survival or PFS curves that 2 cycles of consolidation therapy, in this case with cisplatin and docetaxel, made a difference.

Although trials like this one do not necessarily change practice, they remind us that some of our routine treatment approaches are not necessarily supported by clinical trial data. One concern in this setting is that the benefit associated with administering chemotherapy beyond the chemoradiotherapy portion may be minimal, much like what is seen in the adjuvant chemotherapy setting. Four cycles of cisplatin-based therapy might be prescribed to obtain a 5% advantage at 5 years, and it took several thousand patients to statistically show that improvement.<sup>21</sup> All of the trials in stage III disease that address this issue have ranged in size from 300 to 500 patients, so they are underpowered to show very minor differences that may be real and clinically relevant, but perhaps not statistically significant.<sup>22</sup> Trial data from several thousand patients would be needed to show that the benefit is real and might provide a curative advantage in a small proportion of patients, much like adjuvant chemotherapy. Although Dr Park's trial provided interesting data, it will not change clinical practice at this point.

### Disclosure

*Dr Socinski has no real or apparent conflicts of interest to report.*

### References

1. Yang JCH, Sequist LV, Schuler MH, et al. Overall survival (OS) in patients (pts) with advanced non-small cell lung cancer (NSCLC) harboring common (Del19/L858R) epidermal growth factor receptor mutations (*EGFR* mut): pooled analysis of two large open-label phase III studies (LUX-Lung 3 [LL3] and LUX-Lung 6 [LL6]) comparing afatinib with chemotherapy (CT) [ASCO abstract 8004]. *J Clin Oncol*. 2014;32(5 suppl).
2. Sequist LV, Yang JC, 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.
3. Wu YL, Zhou C, Hu CP, et al. Afatinib versus cisplatin plus gemcitabine for first-line treatment of Asian patients with advanced non-small-cell lung cancer harbouring *EGFR* mutations (LUX-Lung 6): an open-label, randomised phase 3 trial. *Lancet Oncol*. 2014;15(2):213-222.
4. Schuler MH, Yang CH, Park K, et al. Continuation of afatinib beyond progression: results of a randomized, open-label, phase III trial of afatinib plus paclitaxel (P) versus investigator's choice chemotherapy (CT) in patients (pts) with metastatic non-small cell lung cancer (NSCLC) progressed on erlotinib/gefitinib (E/G) and afatinib—LUX-Lung 5 (LL5) [ASCO abstract 8019]. *J Clin Oncol*. 2014;32(5 suppl).
5. Kato T, Seto T, Nishio M, et al. Erlotinib plus bevacizumab (EB) versus erlotinib alone (E) as first-line treatment for advanced *EGFR* mutation-positive nonsquamous non-small cell lung cancer (NSCLC): an open-label randomized trial [ASCO abstract 8005]. *J Clin Oncol*. 2014;32(5 suppl).
6. ClinicalTrials.gov. Erlotinib with or without bevacizumab in treating patients with stage IV non-small cell lung cancer with *EGFR* mutations. <http://clinicaltrials.gov/ct2/show/NCT01532089>. Identifier: NCT01532089. Accessed September 15, 2014.
7. Spigel DR, Edelman MJ, O'Byrne K, et al. Onartuzumab plus erlotinib versus erlotinib in previously treated stage IIIb or IV NSCLC: results from the pivotal phase III randomized, multicenter, placebo-controlled METLung (OAM4971g) global trial [ASCO abstract 8000]. *J Clin Oncol*. 2014;32(5 suppl).
8. Spigel DR, Ervin TJ, Ramlau RA, et al. Randomized phase II trial of Onartuzumab in combination with erlotinib in patients with advanced non-small-cell lung cancer. *J Clin Oncol*. 2013;31(32):4105-4114.
9. Thatcher N, Hirsch FR, Szczesna A, et al. A randomized, multicenter, open-label, phase III study of gemcitabine-cisplatin (GC) chemotherapy plus necitumumab (IMC-11F8/LY3012211) versus GC alone in the first-line treatment of patients (pts) with stage IV squamous non-small cell lung cancer (sq-NSCLC) [ASCO abstract 8008]. *J Clin Oncol*. 2014;32(5 suppl).
10. Dienstmann R, Tabernero J. Necitumumab, a fully human IgG1 mAb directed against the *EGFR* for the potential treatment of cancer. *Curr Opin Investig Drugs*. 2010;11(12):1434-1441.
11. Wadlow RC, Hezel AF, Abrams TA, et al. Panitumumab in patients with KRAS wild-type colorectal cancer after progression on cetuximab. *Oncologist*. 2012;17(1):14. doi:10.1634/theoncologist.2011-0452.
12. Pennell NA. Selection of chemotherapy for patients with advanced non-small cell lung cancer. *Cleve Clin J Med*. 2012;79(electronic suppl 1):eS46-eS50. doi: 10.3949/ccjm.78.s2.10.
13. Pérol M, Ciuleanu TE, Arrieta O, et al. REVEL: a randomized, double-blind, phase III study of docetaxel (DOC) and ramucirumab (RAM; IMC-1121B) versus DOC and placebo (PL) in the second-line treatment of stage IV non-small cell lung cancer (NSCLC) following disease progression after one prior platinum-based therapy [ASCO abstract 8006]. *J Clin Oncol*. 2014;32(5 suppl).
14. Clarke JM, Hurwitz HI. Targeted inhibition of VEGF receptor 2: an update on ramucirumab. *Expert Opin Biol Ther*. 2013;13(8):1187-1196.
15. FDA approves Cyramza for stomach cancer. US Food and Drug Administration. <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm394107.htm>. Updated April 22, 2014. Accessed September 2, 2014.
16. Johnson DH, Fehrenbacher L, Novotny WF, et al. Randomized phase II trial comparing bevacizumab plus carboplatin and paclitaxel with carboplatin and paclitaxel alone in previously untreated locally advanced or metastatic non-small-cell lung cancer. *J Clin Oncol*. 2004;22(11):2184-2191.
17. Reck M, Mellemegaard A, Orlov SV, et al. Antiangiogenic-specific adverse events (AEs) in patients with non-small cell lung cancer (NSCLC) treated with nintedanib (N) and docetaxel (D) [ASCO abstract 8100]. *J Clin Oncol*. 2014;32(5 suppl).
18. Kelly K, Altorki NK, Eberhardt WEE, et al. A randomized, double-blind phase 3 trial of adjuvant erlotinib (E) versus placebo (P) following complete tumor resection with or without adjuvant chemotherapy in patients (pts) with stage IB-IIIA *EGFR* positive (IHC/FISH) non-small cell lung cancer (NSCLC): RADIANT results [ASCO abstract 7501]. *J Clin Oncol*. 2014;32(5 suppl).
19. Shepherd FA, Altorki NK, Eberhardt WEE, et al. Adjuvant erlotinib (E) versus placebo (P) in non-small cell lung cancer (NSCLC) patients (pts) with tumors carrying *EGFR*-sensitizing mutations from the RADIANT trial [ASCO abstract 7513]. *J Clin Oncol*. 2014;32(5 suppl).
20. Park K, Ahn YC, Ahn JS, et al. A multinational phase III randomized trial with or without consolidation chemotherapy using docetaxel and cisplatin after concurrent chemoradiation in inoperable stage III non-small cell lung cancer (CChelN) [ASCO abstract 7500]. *J Clin Oncol*. 2014;32(5 suppl).
21. Pignon JP, Tribodet H, Scagliotti GV, et al; LACE Collaborative Group. Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE Collaborative Group. *J Clin Oncol*. 2008;26(21):3552-3559.
22. Okawara G, Mackay JA, Evans WK, Ung YC; Lung Cancer Disease Site Group of Cancer Care Ontario's Program in Evidence-based Care. Management of unresected stage III non-small cell lung cancer: a systematic review. *J Thorac Oncol*. 2006;1(4):377-393.

