Lung and bronchus cancer is the second most common form of cancer in the United States. In 2018, lung cancer was newly diagnosed in 234,030 individuals, representing 13.5% of all new cancer cases. Lung cancer remains the leading cause of cancer mortality in men and women, accounting for more than 25% of all cancer deaths, which translated to 154,050 deaths in 2018. The relative 5-year survival rate for metastatic lung cancer is only 4.7%. Lung cancer has a substantial impact on the patient’s quality of life, particularly in advanced stages, when the patient may have a high symptom burden, accompanied by fatigue, dyspnea, pain, and depression. In addition, lung cancer has a profound economic impact, accounting for a cost of $13.9 billion to the US healthcare in 2017.

Of the 2 main types of lung cancer, non–small-cell lung cancer (NSCLC) is responsible for 80% to 85% of all cases, and small-cell lung cancer accounts for 10% to 15%. The treatment of metastatic NSCLC generally includes chemotherapy, targeted therapy, immunotherapy, or a combination of these therapies.

The epidermal growth factor receptor (EGFR), a tyrosine kinase found on the surface of epithelial cells, is overexpressed in certain malignant tumors. EGFR mutations are common in nonsmokers with adenocarcinoma-type NSCLC. Moreover, a high frequency of EGFR mutations has been identified in Asian patients with advanced (stage IIIB or IV) NSCLC (ie, adenocarcinoma).

The most common EGFR mutations are exon 19 deletions (accounting for 45% of EGFR mutations) and exon 21 L858R substitutions (40% of EGFR mutations). In general, patients with NSCLC with these mutations receive the newer EGFR tyrosine kinase inhibitors, including afatinib (Gilotrif), erlotinib (Tarceva), gefitinib (Iressa), or osimertinib (Tagrisso). Recently, another targeted kinase inhibitor became available for this patient population.

On September 27, 2018, the US Food and Drug Administration (FDA) approved dacomitinib (Vizimpro; Pfizer), an oral EGFR kinase inhibitor, for the first-line treatment of patients with metastatic NSCLC and EGFR exon 19 deletion or exon 21 L858R substitution mutations, as detected by an FDA-approved test.

The approval of dacomitinib was based on results from the ARCHER 1050 phase 3 clinical study. Dacomitinib was granted a priority review by the FDA, indicating the drug's potential as a significant treatment advance for this patient population.

The FDA granted dacomitinib an orphan drug designation, indicating it is the first and only drug approved for the treatment of metastatic NSCLC that harbors these specific EGFR mutations.

Commenting on the approval of dacomitinib, Tony Mok, MD, Chief Investigator and Chair, Department of Clinical Oncology, Chinese University of Hong Kong, said, “The findings from ARCHER 1050 suggest that Vizimpro should be considered as a new first-line treatment option for patients with EGFR-mutated non-small cell lung cancer exon 19 deletion or exon 21 L858R substitution mutations.”

Mechanism of Action
Dacomitinib is an oral kinase inhibitor that irreversibly inhibits the activity of EGFR proteins, including EGFR/HER1, HER2, and HER4, and specific EGFR-activating mutations, including exon 19 deletion or the exon 21 L858R substitution mutation. In preclinical studies, dacomitinib demonstrated antitumor activity and dose-dependent inhibition of EGFR and HER2 autophosphorylation and tumor growth.

Dosing and Administration
The recommended dose of dacomitinib is 45 mg orally once daily; dacomitinib can be taken without regard
to meals. Dacomitinib is available as 15-mg, 30-mg, and 45-mg tablets.9

**Pivotal Clinical Trial: ARCHER 1050**

The efficacy of dacomitinib was demonstrated in the ARCHER 1050 study, a randomized, multinational, multicenter, open-label, phase 3 clinical trial that included patients with unresectable, metastatic NSCLC with an EGFR exon 19 deletion or exon 21 L858R substitution mutation.9,10 Eligible patients had to have an Eastern Cooperative Oncology Group performance status of 0 or 1, no previous therapy for metastatic disease, or recurrent disease with a minimum of 12 months disease-free after completing systemic therapy. Overall, 92% of the patients had stage IV NSCLC, and 8% had stage IIIB disease.9

The patients who received treatment with dacomitinib had a significant improvement in progression-free survival (PFS) compared with gefitinib, as determined by an Independent Radiologic Central review (the primary end point); the group receiving dacomitinib achieved a 5.5-month longer PFS than the group receiving gefitinib (Table).9,10

<table>
<thead>
<tr>
<th>Efficacy parameter</th>
<th>Dacomitinib (N = 227)</th>
<th>Gefitinib (N = 225)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS, based on IRC review</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with event, N (%)</td>
<td>136 (59.9)</td>
<td>179 (79.6)</td>
</tr>
<tr>
<td>Median PFS, mo</td>
<td>14.7 (95% CI, 11.1-16.6)</td>
<td>9.2 (95% CI, 9.1-11.0)</td>
</tr>
<tr>
<td>Hazard ratio&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.59 (95% CI, 0.47-0.74)</td>
<td></td>
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<tr>
<td>P value&lt;sup&gt;b&lt;/sup&gt;</td>
<td>&lt;.0001</td>
<td></td>
</tr>
<tr>
<td>Overall response rate, based on IRC review</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall response rate, %</td>
<td>75 (95% CI, 69-80)</td>
<td>72 (95% CI, 65-77)</td>
</tr>
<tr>
<td>P value&lt;sup&gt;c&lt;/sup&gt;</td>
<td>.39</td>
<td></td>
</tr>
<tr>
<td>Median duration of response, based on IRC review, mo</td>
<td>14.8 (95% CI, 12.0-17.4)</td>
<td>8.3 (95% CI, 7.4-9.2)</td>
</tr>
</tbody>
</table>

<sup>a</sup>From stratified Cox regression.  
<sup>b</sup>Based on the stratified log-rank test.  
<sup>c</sup>Based on the stratified Cochran-Mantel-Haenszel test.  
CI indicates confidence interval; IRC, Independent Radiologic Central; NSCLC, non–small-cell lung cancer; PFS, progression-free survival.  

Dacomitinib has no contraindications.9

**Drug Interactions**

Dacomitinib should not be used concomitantly with proton pump inhibitors, because these drugs can reduce the efficacy of dacomitinib. Instead, locally acting antacids or H<sub>2</sub> receptor antagonists can be used with dacomitinib. Dacomitinib should be administered at least 6 hours before or 10 hours after an H<sub>2</sub> receptor antagonist.9

The concomitant use of dacomitinib with cytochrome (CY) P2D6 substrates should be avoided in situations where minimal increases in the concentration of CYP2D6 substrates may lead to serious or life-threatening adverse events.9

**Use in Specific Populations**

Women should be advised not to breastfeed during treatment with dacomitinib and for at least 17 days after the last dose.9

In older patients aged ≥65 years, treatment with dacomitinib resulted in a higher incidence of grade 3 and 4 adverse reactions (67% vs 56%, respectively), more frequent dose interruptions (53% vs 45%, respectively), and more frequent discontinuations (24% vs 10%, respectively) compared with patients aged <65 years.9

No dose adjustments of dacomitinib are required for patients with mild or moderate renal impairment or mild hepatic impairment. The recommended dose of dacomitinib has not been established for patients with severe renal impairment or severe hepatic impairment.9
Warnings and Precautions

Patients receiving dacomitinib should be monitored for pulmonary symptoms of interstitial lung disease or pneumonitis. Dacomitinib should be withheld if patients show worsening of respiratory symptoms indicative of interstitial lung disease. If interstitial lung disease is confirmed, dacomitinib should be permanently discontinued.9

Severe and fatal diarrhea occurred with dacomitinib treatment. Dacomitinib should be withheld if patients have grade ≥2 diarrhea until it recovers to grade ≤1 severity; then dacomitinib can be resumed at the same or a reduced dose, depending on the severity of diarrhea. Antidiarrheal treatment should be initiated promptly.9

Dacomitinib can cause fetal harm; women of reproductive potential should use effective contraception during dacomitinib treatment and for at least 17 days after the final dose.9

Rash and exfoliative skin reactions occurred with dacomitinib treatment. Dacomitinib should be withheld if the patient has persistent grade 2 or any grade 3 or 4 dermatologic adverse reaction until it recovers to grade ≤1 severity; then dacomitinib can be resumed at the same or a reduced dose, depending on the severity of the dermatologic reaction. Oral antibiotics should be initiated for grade ≥2 severe dermatologic adverse reactions.9

Conclusion

The FDA approval of dacomitinib provides a new once-daily oral treatment option that may improve outcomes for patients with metastatic NSCLC associated with EGFR mutations, including exon 19 deletion or L858R substitution mutations. Patients who received treatment with dacomitinib had a significantly longer PFS duration than patients who received gefitinib treatment.

References