Lung cancer is the leading cause of cancer-related mortality worldwide. As much as 85% of primary lung cancers are non-small cell lung cancers (NSCLC) (1). A major characteristic of NSCLC is aberrant signaling pathways, including those mediated by the human epidermal growth factor receptor (HER) family of receptor tyrosine kinases, HER1 (epidermal growth factor receptor; EGFR), HER2, HER3 and HER4. At least one member of the HER family of receptors are expressed in 90% of solid tumors with 60% of these tumors containing abnormalities in a HER family member contributing to tumor development (2). EGFR overexpression is a common event in NSCLC. Estimates indicate that approximately 10-15% of Caucasian and 20-30% of Asian NSCLC patient tumors contain gain-of-function mutations in the EGFR gene. The most common EGFR mutations include deletions in exon 19 (45-50% of mutations) and the L858R point mutation in exon 21 (40-45% of mutations) (3-5). Presence of these mutations can make the NSCLC cells more dependent on EGFR for growth and more sensitive to EGFR tyrosine kinase inhibitors (TKIs), including gefitinib and erlotinib, the only two currently approved EGFR-targeted therapies for advanced NSCLC. Both agents are orally active, reversible, competitive inhibitors that mimic ATP binding to the kinase domain of EGFR. Despite the effectiveness of these drugs against mutant EGFR, most mutant EGFR-carrying NSCLC patients that initially respond to gefitinib/erlotinib acquire resistance to these inhibitors within 14 months leading to disease progression (6). The primary mechanism for the observed resistance to gefitinib/erlotinib was found to be the presence of a secondary mutation in EGFR (T790M) that is present in approximately 50% of patients with acquired resistance to gefitinib/erlotinib (7,8). This secondary point mutation alters the structure of the EGFR kinase domain with two consequences: (I) decreased binding of gefitinib/erlotinib to EGFR kinase domain, and (II) enhanced affinity of ATP for the EGFR kinase domain. These consequences ultimately mediate resistance to gefitinib/erlotinib in preclinical studies and patients (5,7,9-11).

These discoveries have made it necessary for developing second-generation EGFR TKIs, which led to irreversible TKIs such as dacomitinib, neratinib, and canertinib. Dacomitinib (PF00299804) is a pan-HER family, orally active inhibitor that has activity toward EGFR, HER2, and HER4. Whereas reversible EGFR TKIs compete with ATP in the kinase domain of EGFR, dacomitinib also competes for ATP binding but then covalently binds at the edge of the ATP binding cleft on Cys773 of EGFR via the Michael mechanism (addition of nucleophile to an α,β unsaturated carbonyl) (12). The result of this covalent binding is that the inhibitor irreversibly blocks binding of ATP to the kinase, rendering it inactive (12). Dacomitinib has been shown to be more potent than reversible EGFR inhibitors in cell-based assays (9). Due to its irreversible nature, dacomitinib has a low off-rate when compared to reversible inhibitors and its pharmacodynamics will be determined by its target (EGFR) half-life, meaning it can only be overcome by synthesis of new protein (9,13). Results of several preclinical studies demonstrated that dacomitinib displayed the ability to inhibit several different EGFR mutants, including the commonly found primary EGFR mutants (i.e. exon 19 deletion or L858R mutation) and the secondary EGFR T790M mutant (9,10). It has been shown that dacomitinib was effective at reducing the growth of gefitinib-resistant NSCLC xenografts (9).

Building upon the promising preclinical results, dacomitinib has undergone two Phase I clinical trials in patients with advanced solid tumor types (14,15). In these trials, patients with NSCLC comprised 47% (14) and 69% (15) of the study population with other tumor types comprising primarily breast and colorectal cancers. Maximum tolerated dose in these trials was established at 45 mg once daily and patients had manageable adverse events at this dosage. There was indication of a positive clinical response in both trials as one trial observed 4/110
patients had a partial response while 44/110 patients had stable
disease (14). The other observed 1/13 patients had a partial
response while 9/13 patients had stable disease ≥6 weeks while
4/8 NSCLC patients showed tumor shrinkage (15). NSCLC
patients with EGFR mutations had either a partial response
(2/29; 7%) or stable disease (12/29; 41%) in one trial (14)
while the other found tumor shrinkage was 85% less in tumors
with WT EGFR compared to mutant EGFR (15). These results
suggested a potential clinical benefit to NSCLC patients leading
to Phase II trials.

The potential clinical benefit of dacomitinib has been
further tested in a Phase II clinical trial recently published
by Ramalingam et al. in the Journal of Clinical Oncology (16).
Patients treated in this trial had advanced NSCLC with disease
progression following at least one chemotherapy regimen with
no prior EGFR-targeted therapy. Investigators recruited 188
patients that were randomly assigned to either dacomitinib
(45 mg once daily) or erlotinib (150 mg once daily) treatment.
This is the first clinical trial published to directly compare
dacomitinib (irreversible EGFR TKI) to erlotinib (reversible
EGFR TKI) in any cancer type. There was a similar prevalence of
EGFR mutations (16%) and KRAS mutations (16.4%) between
groups. However, there was an imbalance in the amount of
EGFR mutant patients receiving dacomitinib (20.2%) versus
those receiving erlotinib (11.7%). Results showed a statistically
significant difference in progression-free survival (PFS) in
patients receiving dacomitinib (2.86 months) compared to
erlotinib (1.91 months). The difference in PFS was even greater
in patients with the molecular subset of KRAS-WT/EGFR any
status (3.71 months for dacomitinib vs. 1.91 months for erlotinib).

A significantly greater objective response rate for dacomitinib
was also observed (17%) compared to erlotinib (5.3%). The
clinical benefit response rate (complete response plus partial
response plus stable disease ≥24 weeks) was significantly
greater for dacomitinib (29.8%) compared to erlotinib (14.9%).
Differences may be related to the observation that dacomitinib
had a longer duration of response compared to erlotinib (16.56
versus 9.23 months, respectively).

Results of this Phase II trial are in agreement with dacomitinib
performance in two earlier Phase I trials published to date (14,15).
These trials observed dacomitinib administration resulted in
stable disease for at least six weeks in up to 70% (15) of patients.
One Phase I study suggested patients with EGFR mutations
appear to respond more favorably to dacomitinib than other
patients (15). However, Ramalingam et al. (16) did not find
dacomitinib had a greater response in EGFR mutant patients
compared to EGFR-WT patients. This is in contrast to erlotinib
as previous trials clearly showed enhanced PFS and overall
survival (OS) in EGFR-mutant NSCLC patients compared to
EGFR-WT patients (Table 1) (16,26). Also, the higher PFS
with dacomitinib observed by Ramalingam et al. (16) may have been
due to an imbalance of patients with EGFR mutations (20% in
dacomitinib group, 12% in erlotinib group). However, PFS was
also improved in patients receiving dacomitinib with KRAS-
WT/EGFR-WT, suggesting the inequality of EGFR mutants in
this population did not entirely drive the differences in overall
PFS. Dacomitinib also inhibits HER2 and HER4 in addition
to EGFR. The improved PFS with dacomitinib may be due to
simultaneous inhibition of all three HER family members.

<p>| Table 1. Survival in trials involving erlotinib and/or dacomitinib in NSCLC. |
|----------------|----------------|----------------|----------------|</p>
<table>
<thead>
<tr>
<th>Reference</th>
<th>Patients</th>
<th>Phase</th>
<th>Treatment</th>
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<th>EGFR-Mut</th>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>N</td>
<td>PFS*</td>
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<td>Erlotinib</td>
<td>44</td>
<td>2.6</td>
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<tr>
<td>(18)</td>
<td>No Chemo + EGFR Mut</td>
<td>III</td>
<td>Erlotinib</td>
<td>—</td>
<td>—</td>
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<tr>
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<td>Erlotinib</td>
<td>31</td>
<td>2.1</td>
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<td>Erlotinib</td>
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<tr>
<td>(23)</td>
<td>No Chemo + EGFR Mut</td>
<td>III</td>
<td>Erlotinib</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
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<td>Erlotinib</td>
<td>152</td>
<td>—</td>
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</tbody>
</table>

* in months; Chemo, chemotherapy; Mut, mutation; Ther, therapy; PD, progressive disease; N, patient number; PFS, progression-free survival; OS, overall survival.
administration are manageable and clinical improvements are often observed. Phase I trials to determine safety of dacomitinib in patients primarily found AEs that were gastrointestinal or dermatological (14,15). These events primarily consisted of diarrhea, rash, dermatitis aciform, and fatigue and were largely grade 1 or 2 in severity. Ramalingam et al. (16) found similar AEs in their study, although AEs were more common in patients receiving dacomitinib compared to erlotinib. Despite AEs being more common in the dacomitinib group, there were clinically meaningful improvements in disease symptoms such as cough, dyspnea, and chest pain among others. Together, these trials suggest dacomitinib does indeed cause mild to moderate AEs but also reduces disease symptoms.

There are several clinical trials ongoing to evaluate the efficacy of dacomitinib in the treatment of NSCLC. Several Phase I trials are ongoing to establish the safety of dacomitinib administration in combination with inhibitors that target mediators of gefitinib/erlotinib resistance (e.g., c-MET, IGF-1R). There are also multiple Phase II/III trials aimed at determining whether dacomitinib is better used as first-line therapy prior to gefitinib/erlotinib and whether it has efficacy in patients refractory to gefitinib/erlotinib. Phase III trials are also ongoing to extend the findings of Ramalingam et al. (16) comparing dacomitinib to erlotinib with the primary outcome of PFS. Results of these trials will have a large impact on whether dacomitinib has significant clinical use and will determine if it will be approved for broad clinical use in NSCLC patients.

These early trials using dacomitinib suggest potential benefits; however, its utility in patients is still unclear. This is suggested by the fact that dacomitinib did not yield significantly enhanced overall survival compared to erlotinib (16). Regardless, the prolonged PFS with dacomitinib over erlotinib in patients with WT EGFR may suggest usefulness in patients with amplified WT EGFR. In addition to genetic status of EGFR, other aspects of the complex EGFR signaling may play a role in NSCLC response to dacomitinib, such as, EGFR subcellular localization (27-29). Lastly, the enhancement in PFS by dacomitinib observed by Ramalingam et al. (16) could be due to inhibition of other HER family members, suggesting these tumors are dependent on not only EGFR but also HER2 and HER4, a topic preclinical studies have yet to fully address. Future preclinical and clinical studies should address these issues.

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References


