TARGETED DRUG THERAPY

# Pilot Study of Dacomitinib for Patients With Metastatic *EGFR*-Mutant Lung Cancers With Disease Progression After Initial Treatment With Osimertinib

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abstract

**PURPOSE** Patients with *EGFR*-mutant lung cancer have no approved targeted therapies after disease progression on first-line osimertinib, a third-generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI). Preclinical studies suggest that tumors with both *EGFR*-sensitizing alteration and acquired second-site EGFR resistance alterations after treatment with osimertinib retain sensitivity to second-generation EGFR TKIs. We hypothesized that dacomitinib, a pan-human epidermal growth factor receptor TKI, may be effective in this setting.

**METHODS** In this phase II study, patients who had progressed on first-line osimertinib were treated with dacomitinib 45 mg orally daily until disease progression or intolerability. The primary end point was objective response rate.

**RESULTS** We enrolled 12 patients. Two partial responses were documented (17% objective response rate; 95% CI, 5 to 45). The median progression-free survival was 1.8 months (95% CI, 1.6 to not reached). One patient with an original sensitizing EGFR G719A mutation and one patient without molecular testing available had partial responses, whereas 0 of the 3 patients with second-site acquired *EGFR* resistance mutations (two C797S and one G724S) met the response criteria. The patient with EGFR G719A has an ongoing response at 17 months, which exceeds prior time on osimertinib (11 months).

**CONCLUSION** In the first trial evaluating a second-generation EGFR TKI after first-line third-generation osimertinib, we found that dacomitinib after disease progression on osimertinib has limited benefit.

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## INTRODUCTION

Twenty percent of lung adenocarcinomas harbor sensitizing alterations in *epidermal growth factor receptor* (*EGFR*).[1] When used as initial therapy, the third-generation EGFR tyrosine kinase inhibitor (TKI) osimertinib produces an 80% response rate and median progression-free survival (PFS) of 19 months[2] in patients with these lung cancers,[1] but the development of resistance is ultimately universal. There are no approved EGFR TKIs after osimertinib although on-target resistance typically with acquisition of a second-site EGFR mutation is a recognized phenomenon.[3,4] *EGFR* C797S is a second-site mutation that confers resistance to osimertinib[5-7] and is estimated to occur in 7% of patients treated with first-line osimertinib.[3,8] Additional second-site *EGFR* mutations including G718X and G724X also render lung cancers resistant to osimertinib but may retain sensitivity to earlier-generation EGFR TKIs.[9,10]

Dacomitinib is a second-generation, irreversible pan-human epidermal growth factor receptor TKI. First-line treatment with dacomitinib resulted in prolonged PFS[11] and overall survival[12] compared with treatment with gefitinib. In vitro studies demonstrate that *EGFR*-mutant cell lines that harbor an *EGFR*-sensitizing alteration such as L858R or exon 19 deletion (del 19) plus a second-site *EGFR* alteration such as C797S in the absence of T790M are resistant to osimertinib but retain sensitivity to quinazoline-based EGFR inhibitors such as dacomitinib.[13] This finding supports the hypothesis that dacomitinib may be effective after disease progression on osimertinib in patients with acquired second-site *EGFR* mutations or human epidermal growth factor receptor family–mediated resistance, but this has not been investigated in a prospective study.

To our knowledge, we conducted the first phase II study of dacomitinib in patients with metastatic

ASSOCIATED CONTENT

**Protocol**

Author affiliations and support information (if applicable) appear at the end of this article.

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## CONTEXT

**Key Objective**

Patients with advanced epidermal growth factor receptor (EFGR)-mutant lung cancer have no approved targeted therapies after first-line osimertinib, a third-generation EGFR tyrosine kinase inhibitor (TKI). This phase II study investigated whether dacomitinib, an irreversible, second-generation pan-human EGFR TKI, may be effective in patients after disease progression on initial osimertinib.

**Knowledge Generated**

Among 12 treated patients, the objective response rate was 17% (95% CI, 5 to 45). The median progression-free survival was 1.8 months (95% CI, 1.6 to not reached). One patient with a baseline EGFR G719A alteration had an ongoing partial response lasting over 17 months. Three patients had second-site acquired *EGFR* alterations, and none of these patients had a response.

**Relevance**

To our knowledge, this is the first prospective trial investigating a second-generation EGFR TKI after initial osimertinib. Dacomitinib after disease progression on initial osimertinib is not effective as a general treatment strategy.

*EGFR*-mutant lung cancer with disease progression after initial osimertinib.

## METHODS

This trial was a prospective, single-center phase II study in patients with *EGFR*-mutant lung cancers with disease progression on initial osimertinib. This study is exploratory in nature. The primary end point of the trial was to obtain preliminary estimates of the objective response rate (ORR), defined as partial and complete responses, which could be used to design future phase II studies with a primary efficacy end point. Sample size was selected as one reasonably large enough to estimate the ORR. Secondary objectives included PFS, overall survival, and safety and tolerability of dacomitinib after osimertinib. Correlative analyses included identification of pretreatment somatic alterations associated with response to dacomitinib and identification of mechanisms of resistance to dacomitinib. The trial was conducted after approval of the institutional review board at Memorial Sloan Kettering Cancer Center. The study was registered at ClinicalTrials.gov identifier: NCT03755102.

**TABLE 1.** Baseline Patient and Disease Characteristics

| Characteristic | Patients (N = 12) |
|---|---|
| Age, median (range), years | 62 (49-82) |
| Sex | |
| Female | 5 |
| Male | 7 |
| KPS, % | |
| ≥ 90 | 5 |
| 80 | 6 |
| 70 | 1 |
| Smoking status | |
| Former (pack-year range) | 6 (3-25) |
| Never | 6 |
| Brain metastases | |
| No | 7 |
| Yes (treated) | 5 (4) |
| *EGFR*-sensitizing mutation | |
| L858R | 6 |
| Exon 19 del | 5 |
| G719A | 1 |
| *EGFR* second-site mutations | |
| C797S | 2 |
| G724S | 1 |
| Median time on osimertinib (range), months | 17 (8-38) |

Abbreviation: KPS, Karnofsky performance status.

### Patients

Patients had stage IV or recurrent lung cancers with a somatic activating mutation in *EGFR*. Patients demonstrated radiologic progression during treatment with first-line osimertinib and were required to have had a repeat biopsy after osimertinib progression. No previous treatment with a first-generation or second-generation EGFR TKI or chemotherapy was permitted. Stable brain metastases were allowed. All patients had to have adequate organ function, Karnofsky performance status of 70% of higher, and measurable disease per RECIST 1.1.

### Study Design

This was a single-institution, single-arm, open-label phase II study. All patients were treated with dacomitinib 45 mg orally daily until disease progression or intolerability. This study was initially planned to enroll 24 patients, 12 with *EGFR* second-site mutations such as C797S and 12 without a second-site mutation.

### Study Assessment

Treatment cycles were 4 weeks in duration. Patients were assessed every 2 weeks for the first cycle and every 4 weeks

subsequently. Patients had history, physical examination, complete blood count, and serum chemistry studies performed at every visit. Toxicity was graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 4.0. Response to therapy was assessed by interval imaging every 8 weeks with response evaluated per RECIST 1.1.

### Statistical Analysis

Safety and tolerability were summarized using descriptive statistics. Response rates were calculated using binomial proportions and exact 95% CIs. PFS was estimated using the Kaplan-Meier method and defined as the time from start of dacomitinib treatment until progression or death. Patients who did not experience either event were censored at the date on which they left the study or date of last assessment if they were still receiving dacomitinib.

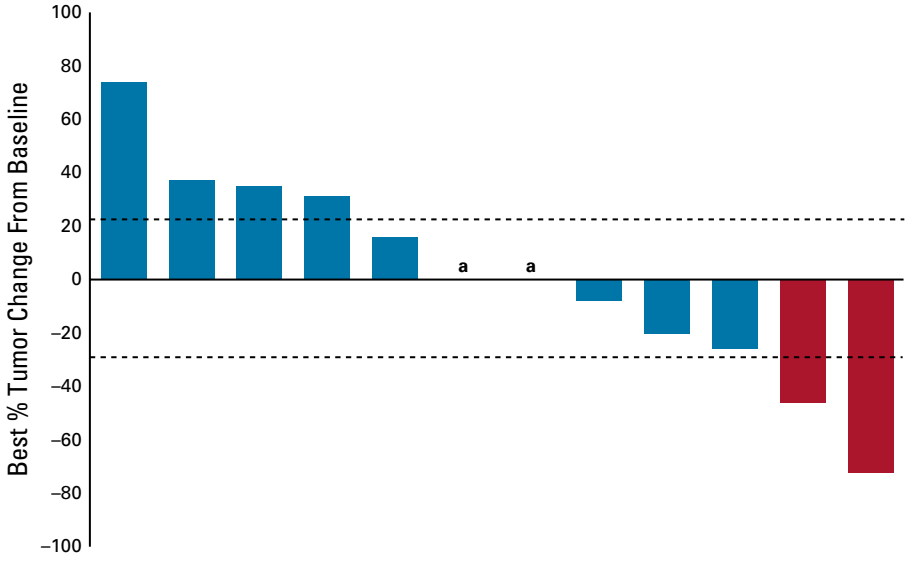
### Next-Generation Sequencing

Patients with available pre- and post-treatment tumor specimens underwent next-generation sequencing with MSK-IMPACT[14] or MSK-ACCESS on cell-free DNA collected from peripheral blood. Somatic variants were called as described previously.[14]

## RESULTS

### Patients

From November 2018 to August 2020, 12 patients were enrolled (Table 1). Ten patients discontinued treatment for disease progression, one withdrew because of toxicity, and one patient continues on study. Given slow accrual and low




| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ***EGFR*-Activating Alteration** | | Del 19 | Del 19 | L858R | Del 19 | L858R | L858R | L858R<br>A871G | L858R | Del 19 | L858R | G719A | Del 19 |
| Predacomitinib | ***EGFR*** | 4x Amp | None found | None found[c] | C797S (6%) | None found | None found | None found | None found | G724S (19%) | C797S (87%)<br>12X Amp | None found | ND |
| Predacomitinib | **Non-*EGFR*** | TP53<br>2.7x *MET* amp | TP53 | None found | TP53 | TP53 | None found | TP53 | TP53 | TP53 | TP53 | TP53 | ND |
| **Postdacomitinib** | | ND | ND | ND | C797S (11%)[c] | ND | None found | None found | None found | T790M (11%) | None found[c] | ND | T790M (6%)[c] |
| Treatment time (months) | **Osimertinib** | 17 | 19 | 19 | 17 | 8 | 21 | 38 | 8 | 16 | 21 | 11 | 8 |
| Treatment time (months) | **Dacomitinib** | 2 | 2 | 2 | 2 | 2 | 2[b] | 2 | 1 | 5 | 2 | 17+ | 11 |

**FIG 1.** Dacomitinib clinical efficacy. Best responses of target lesions (RECIST 1.1). Although samples may have had other alterations found on sequencing, only alterations with known prognostic or therapeutic implications are shown in the non-*EGFR* and postdacomitinib rows. None found indicates sample underwent sequencing, but no alterations with prognostic or therapeutic implications were found. [a]Indicates no change in tumor measurements per RECIST criteria, [b]indicates that the patient withdrew from the study because of toxicity. ND indicates sequencing not done because no sample was available. [c]Indicates plasma cfDNA sequencing with MSK-ACCESS. All sequencing not marked with "[c]" was performed on tissue. cfDNA, cell-free DNA.

response rate observed among the first 12 patients enrolled, the Protocol was terminated early.

### Efficacy

All 12 patients had baseline and on-treatment radiologic assessments. Two patients had confirmed partial responses for an ORR of 17% (95% CI, 5 to 45) (Fig 1). Zero of three patients with acquired second-site *EGFR* alterations met the response criteria. The median PFS was 1.8 months (95% CI, 1.6 to not reached) with a range of 0.9-17 months. The median survival from time of treatment initiation was not reached, with a median follow-up 13 months.

### Tolerability

All 12 patients were evaluable for toxicity. The most frequent (≥ 10%) treatment-related adverse events were diarrhea, rash, dry skin, weight loss, fatigue, paronychia, and nail changes (Table 2). There were four grade 3 treatment-related adverse events (two diarrhea, hypokalemia, and pneumothorax), but no grade 4 events and no deaths. One patient underwent dose reduction from 45 to 30 mg for grade 2 maculopapular rash. One patient held study drug for grade 3 diarrhea and later withdrew for grade 2 weight loss and grade 2 rash.

### Pre- and Post-Treatment Genomic Analysis

All patients had a pretreatment biopsy performed within 8 weeks of starting dacomitinib. Ten biopsies were sufficient for targeted exome sequencing with MSK-IMPACT; one patient with an insufficient biopsy sample underwent predacomitinib plasma cfDNA sequencing with MSK-ACCESS. Of the two responders, one harbored an *EGFR* G719A–sensitizing alteration and the other patient did not have a sufficient pretreatment tissue or plasma sample available but had a known *EGFR* exon 19 deletion from previous testing. Three patients had acquired second-site *EGFR* alterations after initial osimertinib: two with C797S (one with concurrent 12-fold *EGFR* amplification) and one with G724S. Because C797S and G724S are on different exons from the *EGFR*-sensitizing alterations, we could not determine whether they were cis or trans to the sensitizing alterations. In total, 9 of the 11 (82%) patients had pretreatment *TP53* alterations and one patient had 2.7-fold *MET* amplification (Fig 1). Seven patients had post-dacomitinib tissue or plasma cfDNA sequencing. Two of these patients (29%), including one responder, acquired *EGFR* T790M during treatment with dacomitinib.

**TABLE 2.** Treatment-Related Adverse Events in At Least 10% of Patients or ≥ Grade 3

| CTCAE Term | Grade 1 | Grade 2 | Grade 3 | Total (%) |
|---|---|---|---|---|
| Rash | 4 | 3 | 0 | 7 (58) |
| Diarrhea | 2 | 3 | 2 | 7 (58) |
| Dry skin | 2 | 2 | 0 | 4 (33) |
| Weight loss | 3 | 1 | 0 | 4 (33) |
| Fatigue | 3 | 0 | 0 | 3 (25) |
| Paronychia | 1 | 2 | 0 | 3 (25) |
| Nail changes | 2 | 0 | 0 | 2 (17) |
| Hypokalemia | 0 | 0 | 1 | 1 (8) |
| Pneumothorax | 0 | 0 | 1 | 1 (8) |

Abbreviation: CTCAE, Common Terminology Criteria for Adverse Events.

Among the three patients with predacomitinib *EGFR* second-site alterations, two patients had tumor shrinkage not meeting the response criteria. Both cancers with minor tumor shrinkage were notable for higher variant allele frequencies (VAFs) of G724S/C797S before dacomitinib (19% and 87%), which were not detected on post-treatment sampling. The third patient with a low pre-dacomitinib C797S VAF of 6% had primary disease progression on dacomitinib; C797S remained detectable at 11% in plasma after progression on dacomitinib. Of note, pre- and post-treatment VAFs for this patient may be difficult to compare directly because post-treatment sequencing was performed on plasma.

## DISCUSSION

Given the lack of approved targeted therapies after disease progression on osimertinib, this trial aimed to ascertain whether dacomitinib, a second-generation EGFR TKI, could be a fruitful strategy for patients with *EGFR*-mutant lung cancer after disease progression on initial osimertinib. In practice, it is common to attempt sequencing of EGFR inhibitors after first-line osimertinib despite no supporting prospective data. There were two PRs observed among treated patients with an ORR of 17% and median PFS of 1.8 months. The toxicities seen with dacomitinib are consistent with expected toxicities of EGFR inhibition, with diarrhea and rash as the most common treatment-related adverse events.

Molecular characterization of treated patients demonstrated several genomic alterations among treated patients, which may have affected treatment outcomes. Eighty-two percent of pretreatment samples harbored *TP53* mutations, which are associated with shortened response to EGFR TKIs and worse prognosis in lung cancer with *EGFR* alterations.[15] *MET* amplification was also discovered retroactively in one patient's pretreatment biopsy, likely explaining the patient's primary disease progression on dacomitinib.

A patient with EGFR G719A, an atypical *EGFR* exon 18 mutation, achieved a confirmed partial response and has an ongoing response at 17 months, exceeding the 11 months she had been on osimertinib. Previous studies have shown that the second-generation EGFR TKI afatinib can effectively treat patients with atypical *EGFR* alterations, including G719A.[16,17] Clinical evaluation of dacomitinib in rare atypical *EGFR* alterations is limited. In a phase II trial of

dacomitinib after disease progression on erlotinib and chemotherapy, one patient with EGFR G719C had an objective response.[18] Further investigation is needed to determine whether upfront treatment with a second-generation TKI such as dacomitinib or afatinib may be superior to osimertinib for patients with atypical *EGFR* alterations.

*EGFR* second-site mutations are rare after first-line osimertinib treatment.[3] We aimed to compare responses among patients with *EGFR* second-site alterations with those without, but only two patients with acquired EGFR C797S and one with EGFR G724S were enrolled. None of the patients with *EGFR* second-site mutations met the response criteria. It is possible that dacomitinib may have differential activity toward the various *EGFR* second-site alterations because afatinib had enhanced inhibitory activity against C797S compared with G724S in in vitro studies.[9] On the basis of the limited number of patients with second-site alterations enrolled, we were not able to investigate whether specific second-site alterations may be more sensitive to dacomitinib and we did not enroll patients with other second-site acquired alterations, such as EGFR L718Q or L844V.

Pre- and postdacomitinib analysis of *EGFR* second-site alteration VAFs suggests that higher pretreatment VAFs may be associated with greater tumor shrinkage, with low VAFs of the second-site alteration suggesting the second-site alteration is subclonal. In this setting, therapy targeting the second-site alteration is less likely to be effective. A previous study similarly showed that patients with higher pretreatment VAFs of *EGFR* T790M had great tumor shrinkage when treated with rociletinib, a third-generation EGFR TKI.[19]

In summary, dacomitinib had limited benefit after disease progression after initial treatment on osimertinib. Accrual to this study was overall lower than expected, likely because of the low frequency of *EGFR* second-site alterations after first-line osimertinib, estimated to be 7% compared with 30% in patients treated with early-generation EGFR TKIs.[3] Given the low ORR observed among the first 12 patients in this study, the study was terminated early. Future studies investigating treatment strategies in patients with acquired second-site *EGFR* alterations will likely require multi-institutional enrollment. As there is tumor heterogeneity in the lung cancers with *EGFR* second-site alterations, we hypothesize that combination treatment with dacomitinib and osimertinib may be a more promising strategy. A follow-up trial of dacomitinib plus osimertinib solely in patients with acquired *EGFR* second-site mutations after osimertinib is ongoing.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