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Clinical Trial Results

Phase II Study of Afatinib as Third-Line Treatment for Patients in Korea With Stage IIIB/IV Non-Small Cell Lung Cancer Harboring Wild-Type *EGFR*

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Author Summary

Abstract

Background. This phase II single-arm trial evaluated afatinib, an irreversible inhibitor of the ErbB receptor family as third-line treatment of Korean patients with advanced non-small cell lung cancer (NSCLC) and tumors with wild-type *EGFR*. Currently, no standard therapy exists for these patients.

Methods. Eligible patients had stage IIIB/IV wild-type *EGFR* lung adenocarcinoma and had failed to benefit from two previous lines of chemotherapy but had not received anti-EGFR treatment. Patients received oral afatinib at 40 mg per day until disease progression or occurrence of intolerable adverse events (AEs). The primary endpoint was confirmed objective tumor response (OR) rate (confirmed complete response [CR] or partial response [PR]). Secondary endpoints included disease control rate (DCR; OR or stable disease for ≥6 weeks), progression-free survival (PFS), and safety.

Results. Forty-two patients received afatinib treatment, and 38 of those were included in efficacy analyses. No confirmed CRs or PRs were reported. DCR was 24% (9 of 38 patients), with a median disease control duration of 19.3 weeks. Median PFS was 4.1 weeks (95% confidence interval: 3.9–8.0). Frequently reported AEs (mainly grades 1 and 2) were rash/acne (88%), diarrhea (62%), and stomatitis (57%).

Conclusion. Heavily pretreated patients with wild-type *EGFR* NSCLC treated with afatinib monotherapy did not experience an objective response and only 24% had disease stabilization lasting more than 6 weeks. AEs were manageable and consistent with the expected safety profile. ***The Oncologist*** 2014;19:702–703

Discussion

Although well established for lung cancer patients with molecular targets such as activating *EGFR* mutations or *ALK* rearrangement, there is no standard targeted therapy for those patients without identified molecular drivers. In these patients, there are no standard treatment options following failure of two previous lines of standard chemotherapy.

Preclinical studies demonstrated that afatinib conferred greater antitumor activity than reversible EGFR tyrosine kinase inhibitors in wild-type *EGFR* cancer models. Hence, this study was designed to investigate the efficacy of afatinib monotherapy in heavily pretreated NSCLC patients whose tumors have wild-type *EGFR.* Overall, 9 of 38 evaluable patients (24%) experienced stabilization of their disease for ≥6 weeks with afatinib monotherapy for a median duration of 19.3 weeks (range: 11.6–28.0 weeks), whereas no patients achieved an objective tumor response (Fig. 1). Median progression-free survival, a secondary endpoint, was 4.1 weeks (95% confidence interval: 3.9–8.0) (Fig. 2). These limited efficacies in this population are consistent with existing evidence.

All treated patients had at least one AE, the majority of which were mild (grade 1) or moderate (grade 2). The most common AEs were rash/acne (37 patients, 88%), followed by diarrhea (26 patients, 62%) and stomatitis (24 patients, 57%)—all known characteristics of EGFR inhibition and consistent with the known safety profile of afatinib. Seventeen patients (40%) had at least one serious AE (SAE); nine had fatal events, but none of the SAEs was considered to be

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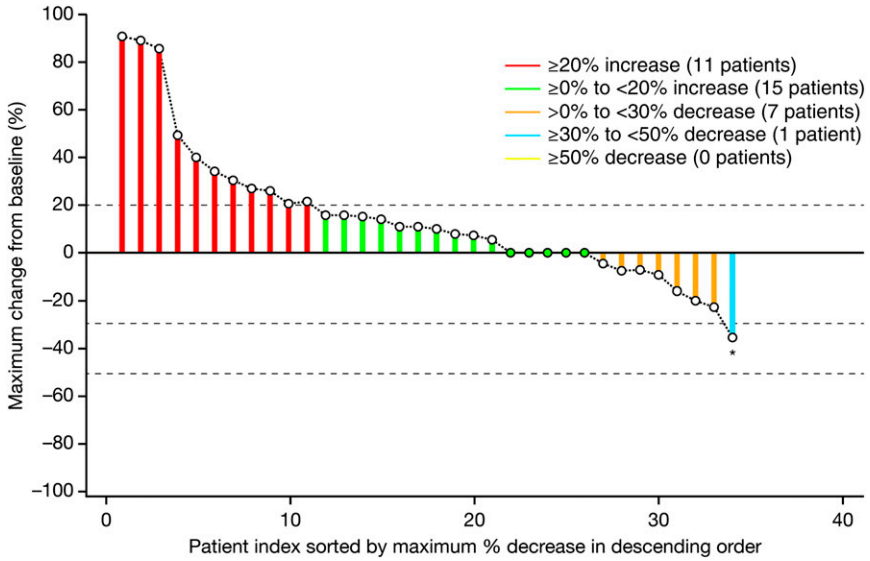

Figure 1. Maximum change in tumor size (target lesions) from baseline in patients with wild-type epidermal growth factor receptor ($n = 34$). The maximum mean change from baseline is +15% (range: −35 to 91). *This patient had a partial response after 3.7 weeks; however, the response was not confirmed at the subsequent scan (week 8), which showed progressive disease.

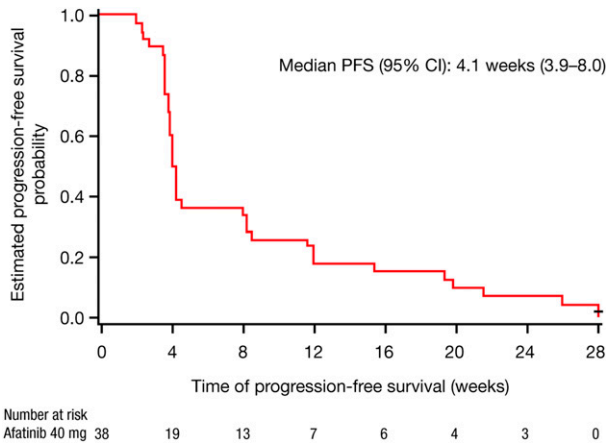

Figure 2. Progression-free survival.

Abbreviations: CI, confidence interval; PFS, progression-free survival.

treatment related. There were no events of interstitial lung disease or pneumonitis.

The absence of a comparator arm restricts, to some extent, the conclusions that can be drawn from this study. Because tissue samples were available from only 19 patients, the central laboratory was unable to confirm wild-type *EGFR* status for the total population, although eligible patients should have been identified as wild-type *EGFR* by a local laboratory. Four patients were excluded from the efficacy analysis because they tested positive for *EGFR* mutations by the central laboratory; three of these derived benefit (two with partial response and one with stable disease).

In conclusion, 24% of heavily pretreated NSCLC patients with wild-type *EGFR* experienced disease stabilization for ≥6 weeks with afatinib. Third-line afatinib was tolerable, and AEs were manageable.

Author disclosures available online.