Original Investigation

First-Line Erlotinib Therapy Until and Beyond Response Evaluation Criteria in Solid Tumors Progression in Asian Patients With Epidermal Growth Factor Receptor Mutation–Positive Non–Small-Cell Lung Cancer
The ASPIRATION Study

Keunchil Park, MD; Chong-Jen Yu, MD; Sang-We Kim, MD; Meng-Chih Lin, MD; Virote Sriuranpong, MD; Chun-Ming Tsai, MD; Jong-Seok Lee, MD; Jin-Hyoung Kang, PhD; K. C. Allen Chan, MD; Pablo Perez-Moreno, MD; Peter Button, MSc; Myung-Ju Ahn, MD; Tony Mok, MD

IMPORTANCE Continuing molecularly targeted treatment beyond disease progression in non–small-cell lung cancer (NSCLC) has appeared promising in retrospective analyses, highlighting the challenge to identify whether progression is the optimal time to switch treatment.

OBJECTIVE To study the efficacy of first-line erlotinib therapy in patients with NSCLC with activating *EGFR* mutations and postprogression erlotinib therapy.

DESIGN, SETTING, AND PARTICIPANTS ASPIRATION (Asian Pacific trial of Tarceva as first-line in *EGFR* mutation) was a phase 2, open-label, single-arm study conducted from 2011 to 2012 in 23 centers in Hong Kong, Korea, Taiwan, and Thailand of adults with stage IV, *EGFR* mutation–positive NSCLC, with ECOG performance status 0 to 2.

INTERVENTIONS Patients received erlotinib 150 mg/d orally until disease progression, after which erlotinib therapy could be continued at patient and/or investigator discretion.

MAIN OUTCOMES AND MEASURES The primary end point was progression-free survival (PFS1; time to Response Evaluation Criteria in Solid Tumours 1.1 progression or death). Secondary end points included PFS2 (time to off-erlotinib progression if erlotinib therapy was extended beyond progression at patient and/or investigator discretion), objective response rate, disease control rate, overall survival, and safety. The use of plasma-based assessment of *EGFR* mutations was also investigated.

RESULTS Of 359 patients screened, 208 were enrolled. Median follow-up was 11.3 (95% CI, 10.9-13.0) months. Of the 207 intent-to-treat patients (62.3% female; median age, 60.8 [range, 28-89] y), 176 had a PFS1 event (171 progression and 5 deaths); of these, 78 discontinued and 93 continued erlotinib therapy following progression. Median PFS1 was 10.8 (95% CI, 9.2-11.1) months. Median PFS1 and PFS2 in the 93 continuing patients was 11.0 (95% CI, 9.2-11.1) and 14.1 (95% CI, 12.2-15.9) months, respectively. Median PFS1 and PFS2 was 11.0 (95% CI, 9.3-12.0) and 14.9 (95% CI, 12.2-17.2) months in patients with exon 19 deletions or L585R mutations. Overall response rate was 66.2%; disease control rate was 82.6%. Median overall survival was 31.0 months (95% CI, 27.3 months to not reached). In the safety population (n = 207) serious adverse events were reported in 27.1%, with events of at least grade 3 experienced by 50.2%. Sensitivity and specificity of plasma-based *EGFR* mutation analysis was 77% and 92%, respectively.

CONCLUSIONS AND RELEVANCE ASPIRATION supports the efficacy of first-line erlotinib therapy in patients with *EGFR* mutation–positive NSCLC and that treatment beyond progression is feasible and may delay salvage therapy in selected patients.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT01310036

JAMA Oncol. 2016;2(3):305-312. doi:10.1001/jamaoncol.2015.4921
Published online December 30, 2015.

Editorial page 300

Supplemental content at jamaoncology.com

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Keunchil Park, MD, Division of Haematology/Oncology, Innovative Cancer Medicine Institute, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81 Irwon-ro, Gangnam-gu, Seoul 135-710, Korea (kpark@skku.edu).

The discovery of epidermal growth factor receptor (*EGFR*) mutations has revolutionized treatment of non–small-cell lung cancer (NSCLC).[1,2] EGFR tyrosine kinase inhibitors (TKIs) including erlotinib hydrochloride, gefitinib, and afatinib are now the standard first-line treatment for *EGFR* mutation–positive NSCLC, based on superior efficacy vs traditional chemotherapy.[3-9]

Almost all patients receiving first-line EGFR TKIs will eventually experience disease progression according to the criteria of Jackman et al[10] that endorse both Response Evaluation Criteria in Solid Tumours (RECIST) and the World Health Organization definition of progression.[11,12] However, the question remains whether these are the most appropriate criteria for stopping EGFR TKI treatment.[10,13] Acquired T790M mutation in exon 20 is the most common cause of resistance to EGFR TKI therapy; however, its occurrence is a heterogeneous process, meaning that not all metastatic tumors behave the same way.[14]

Premature discontinuation of EGFR TKI therapy may result in rapid progression of symptoms and tumor regrowth, with reintroduction of TKI therapy leading to decreased tumor growth.[15] Therefore, clinicians often continue EGFR TKI treatment beyond RECIST progression, based on data from retrospective studies.[16,17] Oxnard et al[16] showed that continuation of EGFR TKI therapy plus locoregional treatment (surgery and radiotherapy), after progression of disease (PD), delayed the need for second-line chemotherapy by 3 months (n = 19). In a retrospective analysis by Nishie et al,[17] continuing EGFR TKI therapy beyond PD significantly extended overall survival (OS) compared with switching to chemotherapy. Continuation of EGFR TKI therapy after PD in *EGFR* mutation-positive disease is recommended in the National Comprehensive Cancer Network guidelines[18]; however, this guidance is based on retrospective data.

ASPIRATION (Asian Pacific trial of Tarceva as first-line in *EGFR* mutation; ML25637; NCT01310036) (Supplement 1) was an open-label, single-arm, phase 2 study with the primary objective of studying the efficacy of first-line erlotinib therapy in patients with activating *EGFR* mutations. The concept of treatment beyond RECIST 1.1 progression and the use of plasma-based DNA for detection of *EGFR* mutations were also investigated. At the investigators' discretion, patients with PD by RECIST 1.1 (progression-free survival 1 [PFS1]) were allowed to continue erlotinib therapy until investigator decision, with off-erlotinib PD in this subgroup defined as progression-free survival 2 (PFS2) (**Figure 1**). The primary end point was PFS1; however, one of the learning objectives relevant to clinical practice is the extension of PFS with treatment beyond progression (the difference between PFS1 and PFS2, which was conducted as a post hoc analysis).

At a Glance

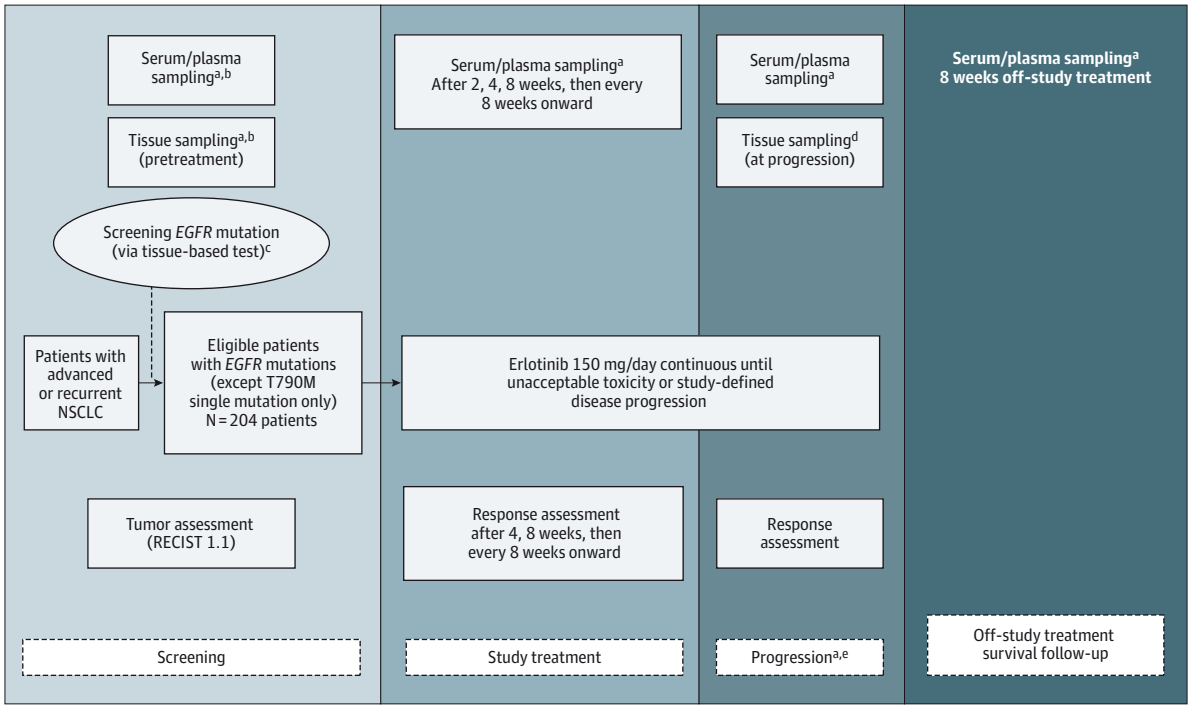
- The ASPIRATION trial was designed to assess first-line erlotinib therapy in patients with *EGFR* mutation–positive non–small-cell lung cancer (NSCLC) and the concept of treatment beyond disease progression.
- Patients received erlotinib 150 mg/d orally until progression. At initial progression (progression-free survival 1 [PFS1]), erlotinib therapy could be continued at patient and/or investigator discretion to assess whether treatment beyond progression was feasible (progression-free survival 2 [PFS2]).
- In the overall population (n = 207), median PFS1 was 10.8 months (95% CI, 9.2-11.1), which was similar to previously reported PFS results in Asian patients with *EGFR* mutation–positive NSCLC. Median PFS1 and PFS2 in the subgroup that continued to receive erlotinib following progression (n = 93) was 11.0 and 14.1 months, respectively, giving an additional 3.1 months of PFS.
- ASPIRATION supports the efficacy of first-line erlotinib therapy in *EGFR* mutation–positive NSCLC and suggests the feasibility of erlotinib treatment beyond progression, although validation in a randomized setting is warranted.

Methods

Patients with *EGFR* mutation–positive NSCLC received first-line erlotinib 150 mg/d orally. At the time of PFS1 determined by RECIST 1.1, erlotinib therapy could be continued (stopping at the investigators' discretion or patient decision). Whereas precise guidance was not given, the protocol suggested patients with symptomatic extracranial progression, rapid progression, worsening Eastern Cooperative Oncology Group (ECOG) performance status (PS), or life-threatening complications as examples of those who may not be suitable for continued erlotinib therapy; however, the final decision was at the treating physician's discretion. ASPIRATION was conducted at 23 centers across Hong Kong, Korea, Taiwan, and Thailand. Inclusion criteria were patients at least 18 years old with confirmed stage IV or recurrent NSCLC (TNM 7th edition) with activating *EGFR* mutations, measurable disease, and ECOG PS 0 to 2. Key exclusion criteria included T790M mutations at baseline, prior chemotherapy, prior treatment with anti-human epidermal growth factor receptor agents, uncontrolled medical conditions, preexisting pulmonary fibrosis, and warfarin sodium use.

The primary end point was PFS1 (time from first study dose to first RECIST 1.1-defined PD or death). Secondary end points were PFS2 (time from first study dose to off-erlotinib PD in the subset of patients who continued erlotinib therapy beyond RECIST 1.1 PD). Other secondary end points included objective response rate (ORR; complete or partial response by RECIST 1.1), disease control rate (DCR; stable disease for ≥8 weeks or complete or partial response), PFS1 in the exon 19 deletion/L858R subsets, OS, and safety. These end points were based on investigator assessment and were not subjected to additional central review. Correlation between *EGFR* mutations in plasma and outcomes was also a secondary end point. Tissue *EGFR* mutation status was assessed by local laboratories and further confirmed by central testing if feasible using the cobas 4800 *EGFR* tissue test (Roche). Baseline blood samples were used where available to detect activating *EGFR* mutations (exon 19 and 21) in plasma using digital polymerase chain reaction (eAppendix 1 in Supplement 2). The effects of demographic and baseline characteristics on PFS were also examined as a prespecified exploratory end point. An unplanned exploratory post hoc end point was the difference between PFS1

Figure 1. Study Design



EGFR indicates epidermal growth factor receptor; NSCLC, non–small-cell lung cancer; RECIST, Response Evaluation Criteria in Solid Tumors.
[a]Mandatory.
[b]Tissue, serum, and plasma samples were to be collected for all patients; tissue samples were used for testing at local laboratories, and any remaining samples were sent to the central laboratory with serum/plasma samples for central testing.
[c]Tissue-based *EGFR* screening test must be performed at one of the designated local laboratories.
[d]Optional.
[e]Progression was defined as either RECIST disease progression or off-erlotinib disease progression (only for those patients who continued erlotinib therapy after RECIST disease progression).

and PFS2. Depth of response (the maximum percentage decrease from baseline in the sum of diameters of target lesions) was also assessed as a post hoc analysis.

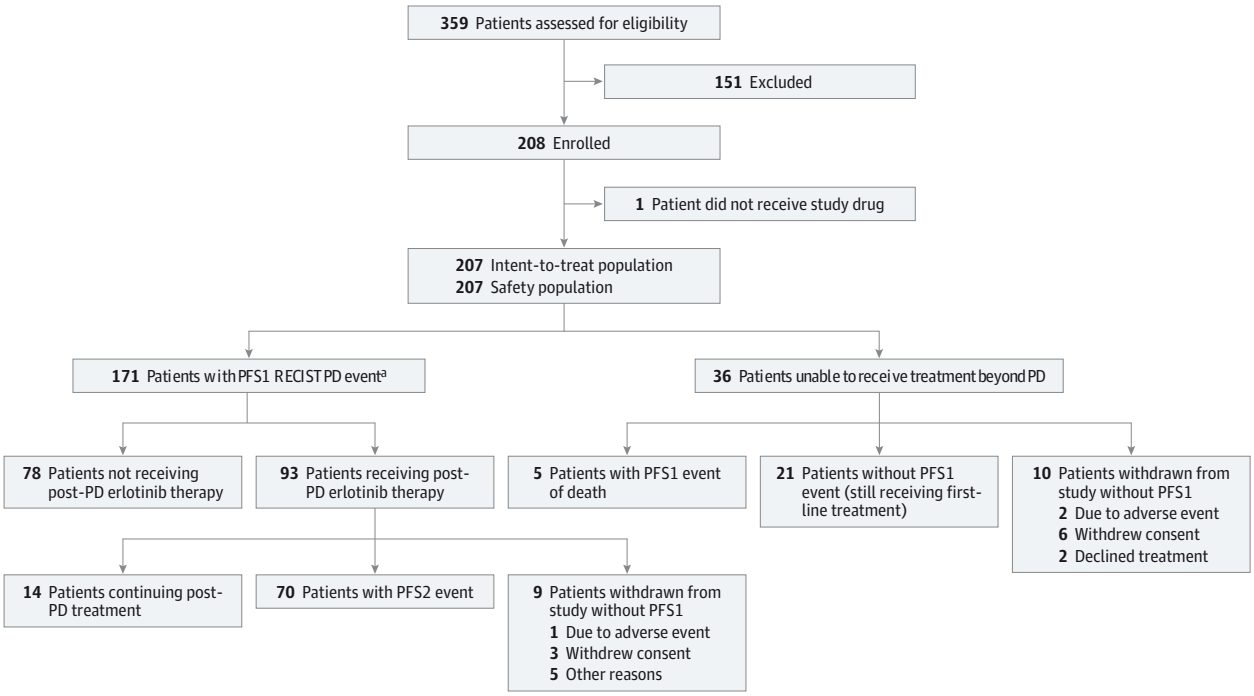
With an assumed median PFS of 13 months, 204 patients were planned for enrollment, with an expectation of 143 events in the follow-up period. This was based on a goal of having 95% confidence intervals (CIs) for the median PFS of plus or minus 2.5 months. Evaluation of PFS1 results was planned to occur after a minimum of 143 PFS1 events had been observed. We analyzed PFS1, PFS2, and OS using Kaplan-Meier methodology. The per-protocol population (PPP) comprised all patients who had *EGFR* mutations according to central laboratory analysis. The intent-to-treat (ITT) population was defined as all patients enrolled who received study medication. The safety population comprised all patients who received at least 1 dose of study medication with at least 1 postbaseline safety assessment. Adverse events (AEs) were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. The primary efficacy analysis set was the PPP (eAppendix 2 in Supplement 2). The efficacy data presented here are from the ITT analysis because this larger population was considered more clinically relevant. The research protocol was approved by the relevant ethics committees, and the study was conducted according to the Declaration of Helsinki and Good Clinical Practice guidelines. Patients gave written informed consent to participate in the trial.

Results

Patients

Between April 2011 and March 2012, 359 patients were screened, with 208 enrolled. The ITT population comprised 207 patients because 1 patient did not receive study medication. The PPP comprised 148 patients. A planned primary analysis was conducted when 155 PFS events had occurred; the present results are from the final updated analysis (cutoff date, February 14, 2014) in which 176 PFS events, including 171 PD events and 5 deaths, had occurred (**Figure 2**). Of the 171 patients with PD, 93 (54%) continued to receive erlotinib following PD and were included in the PFS2 analysis, while 78 did not receive erlotinib following PD. Baseline characteristics of the ITT population are presented in **Table 1**. Briefly, 62.3% of patients were female, 72.9% were never smokers, 97.1% had adenocarcinoma histologic subtype, and 91.8% had ECOG PS 0 or 1. *EGFR* mutation–positive status was centrally confirmed in 148 patients (84 had exon 19 deletions, 60 had L858R mutations; the remaining 4 patients had other

Figure 2. Patient Disposition



Data cutoff was February 14, 2014. PD indicates disease progression; PFS1, progression-free survival; PFS2, time to off-erlotinib PD; RECIST, Response Evaluation Criteria in Solid Tumors.

[a] Total number of PFS events is 176 (includes 5 patients with event of death).

less common *EGFR* mutations) out of 160 with central test results, giving a concordance rate between local and central testing of 92.5%. Poststudy treatments are presented in eTable 1 in Supplement 2.

Efficacy

Median time from first erlotinib dose to last observation and/or follow-up was 25.6 (95% CI, 23.3-25.9) months. The primary end point of median PFS1 was 10.8 (95% CI, 9.2-11.1) months (**Figure 3**A) in the ITT population (n = 207). For patients with a PFS1 event of RECIST progression (n = 171; 5 additional patients had a PFS1 event of death), 35 had new lesions at PD, 72 had an increase in the size of target lesions from baseline at PFS1 as a reason for progression, and 27 had both new and increased lesions. A total of 37 patients had reasons other than changes in target lesions for RECIST PD (including symptomatic PD [n = 6] and other [n = 31, including PD of nontarget lesions {n = 19}, PD of target and nontarget lesion {n = 9}, and PD at follow-up {n = 3}]). The PPP efficacy analysis is presented in eAppendix 2 in Supplement 2.

Secondary end points included median PFS1 in patients with centrally confirmed exon 19 deletions or L858R mutations (n = 144), which was 11.0 (95% CI, 9.3-12.0) months (11.0 [95% CI, 9.4-14.8] months for those with exon 19 deletions and 9.2 [95% CI, 7.3-11.2] months for those with L858R mutations). In the 93 patients who continued erlotinib therapy following PD, median PFS2 was 14.1 (95% CI, 12.2-15.9) months. Of the 93 patients, 79 had ceased taking erlotinib and 14 were still taking erlotinib at the analysis cutoff (PFS2). Of the 79 who ceased erlotinib treatment, 70 had a PFS event (69 were due to PD [64 radiologic, 5 symptomatic progression], 1 was due to death); of the remaining 9 patients, 1 ceased erlotinib therapy because of an AE, 3 withdrew consent, and 5 ceased erlotinib therapy because of administrative or other reasons. For PFS2 assessment, all lesions at PFS1 (target and nontarget) were considered for determining progression. In patients with centrally confirmed exon 19 deletions or L858R mutations, median PFS2 was 14.9 (95% CI, 12.2-17.2) months (15.1 [95% CI, 12.2-20.4] months for exon 19 deletions and 14.0 [95% CI, 8.3-17.2] months for L858R mutations).

Median OS of the ITT population was 31.0 months (95% CI, 27.3 months to not reached; 94 deaths [45.4%]) (Figure 3B). The ORR was 66.2%, with a DCR of 82.6% (complete response, n = 2; partial response, n = 135; stable disease, n = 34). Median time from baseline to best overall response (BOR) was 56 (95% CI, 54-60) days and time from BOR to PFS1 was 141 (95% CI, 112-169) days. Median depth of response was −46.6% (95% CI, −41.98% to 50.41%).

Mutation testing was conducted on baseline plasma samples for the predefined secondary end points. Matched plasma and tumor data from baseline were available for 159 patients; 113 patients were *EGFR* mutation positive by plasma assessment (n = 54 *EGFR* exon 19 deletions, n = 49 L858R mutations, n = 10 exon 19 and L858R) and 46 patients were negative for *EGFR* mutations from plasma samples. Sensitivity and specificity were 77% and 92%, respectively. Concordance rate

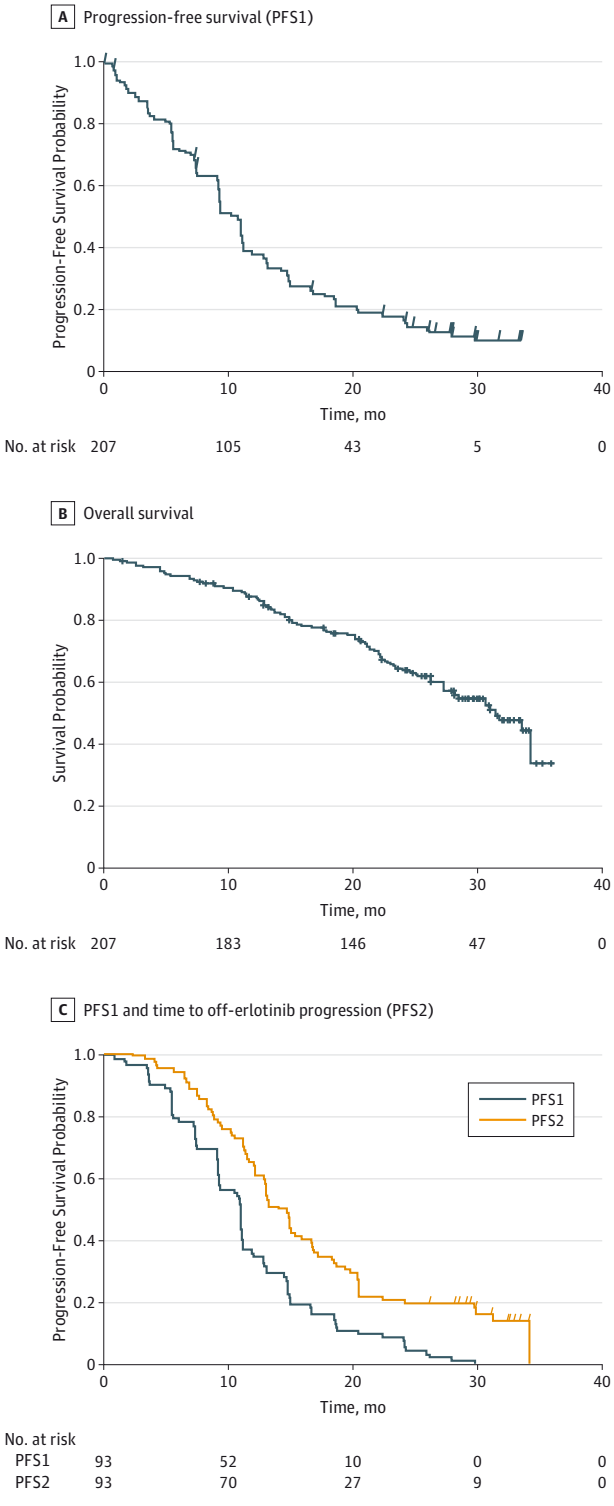
Table 1. Baseline Characteristics in the Intent-to-Treat Population

Characteristic	Patients (n = 207)
Age, median (range), y	60.8 (28-89)
Sex, No. (%)	
Male	78 (37.7)
Female	129 (62.3)
Smoking status, No. (%)	
Never	151 (72.9)
Former	37 (17.9)
Current	19 (9.2)
EGFR mutation, No. (%)	
Exon 19 deletion	109 (52.7)
Exon 21 L858R mutation	87 (42.0)
Other (exon 18/20)	11 (5.3)
Histologic subtype, No. (%)[a]	
Adenocarcinoma	201 (97.1)
Squamous cell	1 (0.5)
Other	5 (2.4)
Disease stage, No. (%)	
Stage IV	175 (84.5)
Recurrent	32 (15.5)
Eastern Cooperative Oncology Group performance status, No. (%)	
0	35 (16.9)
1	155 (74.9)
2	17 (8.2)

Abbreviation: *EGFR*, epidermal growth factor receptor.

[a] Identified by histologic assessment, n = 189; by cytologic assessment, n = 18.

Figure 3. Progression-Free Survival and Overall Survival



with centralized testing of tumor tissue was 78% (eTable 2 in Supplement 2). Median PFS1 was 11.0 (95% CI, 9.2-11.2) months in patients with *EGFR* mutation–positive plasma results vs 12.0 (95% CI, 7.3-15.0) months for patients with a negative plasma digital polymerase chain reaction result (eFigure A in Supplement 2). Median PFS2 was 13.3 (95% CI, 12.2-16.7) and 18.6 (95% CI, 11.5-24.2) months (eFigure B in Supplement 2), respectively, for plasma *EGFR*-positive (n = 46) and *EGFR*-negative subgroups (n = 21). The ORR was 74.1% for patients with *EGFR*-positive plasma assessment and 63.0% for patients with *EGFR*-negative plasma assessment.

Post hoc exploratory analyses showed that the median PFS1 of the 93 patients who had treatment beyond PD was 11.0 (95% CI, 9.2-11.1) months, giving a difference between PFS1 and PFS2 of 3.1 months (Figure 3C). Another post hoc exploratory analysis showed that median OS in these patients was 33.6 (95% CI, 27.3-34.3) months, compared with 22.5 (95% CI, 20.1-27.0) months for the 78 patients who did not continue erlotinib treatment. The differences in characteristics between those who continued erlotinib therapy and those who did not continue erlotinib therapy after PD were also assessed to identify whether there was a particular patient population that would benefit from erlotinib therapy beyond PD. Significantly more patients with recurrent disease at baseline ($P = .009$) and patients with ECOG PS 0 or 1 at PFS1 ($P < .001$) continued to received erlotinib following PD (eTable 3 in Supplement 2). Those who continued erlotinib treatment following PD also had significantly longer median PFS1 ($P = .01$), improved depth of response ($P = .04$), and longer median time from BOR to PFS1 ($P = .005$) than those who did not continue erlotinib treatment. There was also a nonsignificant finding that patients who

Table 2. Adverse Events (Any Grade) in More Than 5% of the Safety Population

Adverse Event	No. (%) (n = 207)
Diarrhea	123 (59.4)
Rash	109 (52.7)
Pruritus	71 (34.3)
Paronychia	62 (30.0)
Dermatitis acneiform	55 (26.6)
Dry skin	52 (25.1)
Cough	51 (24.6)
Stomatitis	44 (21.3)
Decreased appetite	43 (20.8)
Alopecia	33 (15.9)
Back pain	30 (14.5)
Mucosal inflammation	28 (13.5)
Alanine aminotransferase level increased	26 (12.6)
Nausea	25 (12.1)
Dry eye	25 (12.1)
Constipation	23 (11.1)
Vomiting	23 (11.1)
Headache	23 (11.1)
Acne	20 (9.7)
Rhinorrhea	20 (9.7)
Aspartate aminotransferase level increased	20 (9.7)
Chest pain	19 (9.2)
Dyspnea	19 (9.2)
Productive cough	17 (8.2)
Insomnia	17 (8.2)
Anemia	16 (7.7)
Oropharyngeal pain	15 (7.2)
Dizziness	15 (7.2)
Mouth ulceration	14 (6.8)
Pyrexia	14 (6.8)
Musculoskeletal pain	14 (6.8)
Pain in extremity	14 (6.8)
Skin exfoliation	13 (6.3)
Hypokalemia	13 (6.3)
Blood bilirubin level increased	13 (6.3)
Nail disorder	12 (5.8)
Conjunctivitis	12 (5.8)
Eczema	11 (5.3)
Upper abdominal pain	11 (5.3)
Arthralgia	11 (5.3)

were receiving erlotinib for longer durations following PD had increased time from BOR to initial RECIST 1.1 PD. Patients treated with post-PD erlotinib had more new brain lesions at PFS1 than those who did not receive erlotinib following PD (4.3% vs 1.3%, respectively) (eTable 4 in Supplement 2). In the 78 patients who did not continue erlotinib therapy following PD, 82.1% received further off-study drug therapies, compared with 66.7% of the post-PD erlotinib-treated population (eTable 5 in Supplement 2). A total of 7 patients underwent radiotherapy between PFS1 and PFS2; however, because of the low number, we believe that this would not affect the PFS2 data reported.

Safety

A total of 99.5% of patients reported an AE of any grade, with 7.2% of patients discontinuing therapy as a result of AEs. The most common AEs (all grades) were rash (52.7%) and diarrhea (59.4%); all AEs reported in more than 5% of the safety population are shown in **Table 2**. Serious AEs were reported in 27.1% of patients. Adverse events of at least grade 3 were experienced by 50.2% (3.4% [n = 7] were grade 5, 1 was considered treatment related), with 26.1% of patients reporting treatment-emergent grade 3 or 4 AEs.

Discussion

ASPIRATION supports the efficacy of first-line erlotinib in Asian patients with activating *EGFR* mutations. The median PFS1 from ASPIRATION (10.8 months) is consistent with previous studies of first-line single-agent erlotinib therapy in *EGFR* mutation–positive NSCLC both in Asian and white patients (OPTIMAL, 13.1 months; EURTAC, 10.4 months).[7,8] The median OS of 31 months and the ORR and DCR of 66.2% and 82.6%, respectively, are also in line with previous reports of first-line erlotinib treatment.[7,8]

Despite initial response to EGFR TKIs, most patients will experience disease progression. In clinical practice, it is not uncommon for physicians to continue EGFR TKI treatment beyond RECIST PD in clinically well patients.[18] Several retrospective analyses have suggested that molecularly targeted treatment beyond PD may be feasible and of benefit.[16,17,19] Preclinical data indicate the coexistence of *EGFR*-dependent and *EGFR*-independent clones arising in vitro from the same environmental stress.[20] On removal of selective pressure by discontinuation of EGFR TKI therapy, the TKI-sensitive clones may regrow and result in rapid PD with the potential risk of flare-up of symptoms. ASPIRATION is the first study to our knowledge that confirms the feasibility prospectively of continuing erlotinib therapy in selected patients following RECIST PD without undue toxic effects. ASPIRATION also demonstrated a potential improvement in median OS with treatment beyond progression, but this observation could be biased by patient selection. This provides further foundation for the current National Comprehensive Cancer Network clinical guidelines of recommending continuation of EGFR TKI with or without local therapy following either asymptomatic progression or symptomatic but oligometastasis.[18]

By extending the duration of treatment with erlotinib, the introduction of salvage cytotoxic chemotherapy could be delayed. This strategy of continuation of use of targeted agents beyond PD in oncogene-addicted tumors has also been reported by Ou et al[19] in a retrospective analysis of the anaplastic lymphoma kinase inhibitor crizotinib. The ASPIRATION data are also complementary to IMPRESS, in which patients who had experienced PD following first-line treatment with gefitinib were randomized to receive cisplatin, pemetrexed diso-

dium, and gefitinib vs cisplatin, pemetrexed disodium, and placebo; median PFS was 5.4 months for both arms.[21] Results from ASPIRATION and IMPRESS need further support from randomized trial data; however, they encourage discussion of whether continuation of single-agent TKI therapy beyond RECIST PD until evidence of significant systemic PD would be a suitable new treatment paradigm. As the benefit of continuing erlotinib use following PD and "rechallenging" with TKIs both link to the heterogeneity of tumor cells, it would be of interest to compare these 2 strategies to assess the optimum treatment paradigm.

Our exploratory data suggest that continuing erlotinib therapy may be most beneficial in patients with good response to first-line erlotinib, longer time from BOR to PD, or good ECOG PS at PD. In brief, it is conceivable that patients with slow PD could benefit from continuation of EGFR TKI therapy beyond RECIST PD (>50% of patients with PD continued erlotinib therapy in ASPIRATION). With the development of TKIs that target T790M mutations, the optimal strategy and timing for switching treatment will be an important topic for future investigation.

There are some limitations to the present study, especially the fact that the decision to continue erlotinib therapy at PD was at the investigators' or patients' discretion rather than being mandated as part of a randomized design. This may have resulted in selection bias favoring patients with best tumor response, which may mean that the post-PD results are confounded by these factors and are therefore less robust than if the results had been adjusted for the potential bias. However, patients with rapid symptomatic deterioration are clinically distinct from patients with slow asymptomatic PD. Reasons for continuing erlotinib treatment that were specified in addition to investigator or patient decision included slow or minimal progression, progression only to bone, asymptomatic progression, stable primary tumor, good radiologic response, and long disease-control duration. Reasons for not continuing treatment included patient or investigator decision, rapid progression, worsening symptoms, new treatment options or regimen change, and new lesions. The authors concur that it would be inappropriate to consider continuing erlotinib treatment for patients with rapid progression. A further limitation was having the difference between PFS1 and PFS2 as an exploratory end point; on reflection, this would have been a more appropriate definition of PFS2 (time from PD to second PD).

Another limitation of the study was that repeated biopsy at the time of PD was not mandatory, and therefore changes in mutation status that may affect treatment decisions (such as acquisition of T790M mutations) could not be analyzed. The presence of T790M among patients with acquired resistance to EGFR TKIs defines a unique clinical subset with a relatively favorable prognosis.[22] In future studies it is recommended to investigate whether T790M mutation status or other molecular predictors could help guide the decision whether to continue the EGFR TKI therapy on RECIST PD.

ASPIRATION reconfirmed that testing of *EGFR* mutation status using baseline plasma samples is feasible. The potential advantage of this method is that plasma testing could be timely and feasible irrespective of tumor tissue status, as lack of high-quality tumor samples is 1 reason for low testing rates in tissue.[23] ASPIRATION had an interesting observation of longer PFS1 and PFS2 in patients with negative plasma (and positive tumor result) compared with patients with positive plasma results, although we cannot exclude bias because this could be related to tumor burden. An exploratory study of plasma samples from FASTACT-2,[23] a randomized study comparing intercalated chemotherapy and erlotinib with chemotherapy alone, has shown that *EGFR* mutation in plasma correlates with efficacy.[24] Our present findings are in line with the aforementioned results and support the hypothesis of a correlative relationship between plasma *EGFR* mutation status and treatment efficacy.

Conclusions

The prospective ASPIRATION study supports the efficacy of first-line erlotinib therapy in Asian patients with *EGFR* mutation–positive NSCLC and that continuing erlotinib therapy beyond PD is feasible and may be of benefit in delaying salvage anticancer therapy with no undue toxic effects in selected patients; however, validation in a randomized trial would be beneficial.

ARTICLE INFORMATION

Accepted for Publication: October 3, 2015.

Published Online: December 30, 2015. doi:10.1001/jamaoncol.2015.4921.

Author Affiliations: Division of Haematology-Oncology, Samsung Medical Centre, Sungkyunkwan University School of Medicine, Seoul, Korea (Park, Ahn); Department of Internal Medicine, National Taiwan University Hospital, Taipei City, Taiwan (Yu); Department of Oncology, Asan Medical Centre, University of Ulsan College of Medicine, Seoul, South Korea (Kim); Department of Internal Medicine, Kaohsiung Chang Gung Memorial Hospital, Kaohsiung City, Taiwan (Lin); Chang Gung University College of Medicine, Kaohsiung City, Taiwan (Lin); Division of Medical Oncology, Chulalongkorn University, Bangkok, Thailand (Sriuranpong); Department of Chest Medicine, Taipei Veteran General Hospital, Taipei, Taiwan (Tsai); School of Medicine, National Yang-Ming University, Taipei, Taiwan (Tsai); Department of Haematology and Medical Oncology, Seoul National University Bundang Hospital, Bundang, Korea (Lee); Seoul St Mary's Hospital, Seoul, Korea (Kang); Department of Chemical Pathology, Chinese University of Hong Kong, Hong Kong (Chan); F. Hoffmann–La Roche Ltd, Basel, Switzerland (Perez-Moreno); Roche Products Pty Ltd, Dee Why, Australia (Button); State Key Laboratory of South China, Hong Kong Cancer Institute, Chinese University of Hong Kong, Sha Tin, Hong Kong (Mok).

Author Contributions: Profs Park and Mok had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Park, Kim, Sriuranpong, Chan, Perez-Moreno, Ahn, Mok.
Acquisition, analysis, or interpretation of data: Park, Yu, Lin, Tsai, Lee, Kang, Chan, Perez-Moreno, Button, Ahn, Mok.
Drafting of the manuscript: Park, Yu, Sriuranpong, Perez-Moreno, Ahn, Mok.
Critical revision of the manuscript for important intellectual content: Park, Kim, Lin, Tsai, Lee, Kang, Chan, Perez-Moreno, Button, Ahn, Mok.
Statistical analysis: Park, Chan, Button, Mok.
Obtained funding: Ahn, Mok.
Administrative, technical, or material support: Yu, Kim, Lin, Tsai, Kang.
Study supervision: Park, Tsai, Kang, Perez-Moreno, Ahn, Mok.

Conflict of Interest Disclosures: Prof Park has received advisor fees and writing assistance from F. Hoffmann–La Roche; Prof Tsai has received personal fees from Pfizer, F. Hoffmann–La Roche,

Eli Lilly, Boehringer Ingelheim, and AstraZeneca; Dr Chan has received a grant from the Hong Kong Research Grants Council, holds equities in Xcelom Ltd and Sequenom Ltd, is director of Sanomics Ltd, and holds patents issued in molecular diagnostics of cancer; Dr Perez-Moreno is an employee of F. Hoffmann–La Roche and owns stock in F. Hoffmann–La Roche; Mr Button is an employee of Roche Products Pty Ltd; Prof Mok has received personal fees from AstraZeneca, F. Hoffmann–La Roche, Eli Lilly, Merck Serono, Eisai, Bristol-Myers Squibb, AVEO, Pfizer, Boehringer Ingelheim, Novartis, GlaxoSmithKline, Clovis Oncology, Amgen, Janssen, and BioMarin Pharmaceuticals. No other disclosures are reported.

Funding/Support: This trial was funded by F. Hoffmann–La Roche Ltd. Third-party medical writing assistance was funded by F. Hoffmann–La Roche Ltd. We thank the Research Grants Council of Hong Kong (RGC 471012) for supporting the *EGFR* mutation analysis from plasma circulating free DNA.

Role of the Funder/Sponsor: The study was designed, managed, conducted, and monitored by F. Hoffmann–La Roche. F. Hoffmann–La Roche participated in collection, management, analysis, and interpretation of the data; and preparation, review, and approval of the manuscript; however, the authors made the decision to submit the manuscript for publication.

Additional Contributions: Third-party writing assistance was provided by Joanna Musgrove, MRes, of Gardiner-Caldwell Communications, which was compensated for this contribution.

REFERENCES

1. Lynch TJ, Bell DW, Sordella R, et al. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. *N Engl J Med*. 2004;350(21):2129-2139.

2. Paez JG, Jänne PA, Lee JC, et al. EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. *Science*. 2004;304(5676):1497-1500.

3. Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. *N Engl J Med*. 2009;361(10):947-957.

4. Han JY, Park K, Kim SW, et al. First-SIGNAL: first-line single-agent iressa versus gemcitabine and cisplatin trial in never-smokers with adenocarcinoma of the lung. *J Clin Oncol*. 2012;30(10):1122-1128.

5. 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.

6. 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.

7. 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 (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study. *Lancet Oncol*. 2011;12(8):735-742.

8. Costa C, Molina MA, Drozdowskyj A, et al. The impact of EGFR T790M mutations and BIM mRNA expression on outcome in patients with EGFR-mutant NSCLC treated with erlotinib or chemotherapy in the randomized phase III EURTAC trial. *Clin Cancer Res*. 2014;20(7):2001-2010.

9. 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.

10. 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.

11. Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. *Cancer*. 1981;47(1):207-214.

12. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumours. *J Natl Cancer Inst*. 2000;92(3):205-216.

13. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45(2):228-247.

14. Yun CH, Mengwasser KE, Toms AV, et al. The T790M mutation in EGFR kinase causes drug resistance by increasing the affinity for ATP. *Proc Natl Acad Sci U S A*. 2008;105(6):2070-2075.

15. Riely GJ, Kris MG, Zhao B, et al. Prospective assessment of discontinuation and reinitiation of erlotinib or gefitinib in patients with acquired resistance to erlotinib or gefitinib followed by the addition of everolimus. *Clin Cancer Res*. 2007;13(17):5150-5155.

16. Oxnard GR, Lo P, Jackman DM, et al. Delay of chemotherapy through use of post-progression erlotinib in patients with EGFR mutant lung cancer. *J Clin Oncol*. 2012;30(suppl):abstr 7547.

17. Nishie K, Kawaguchi T, Tamiya A, et al. Epidermal growth factor receptor tyrosine kinase inhibitors beyond progressive disease: a retrospective analysis for Japanese patients with activating EGFR mutations. *J Thorac Oncol*. 2012;7(11):1722-1727.

18. NCCN Guidelines Version 1.2015. Non-Small Cell Lung Cancer. National Comprehensive Cancer Network website. http://www.nccn.org/professionals/physician_gls/f_guidelines.asp. Accessed June 11, 2015.

19. Ou SH, Jänne PA, Bartlett CH, et al. Clinical benefit of continuing ALK inhibition with crizotinib beyond initial disease progression in patients with advanced ALK-positive NSCLC. *Ann Oncol*. 2014;25(2):415-422.

20. Kim Y, Ko J, Cui Z, et al. The EGFR T790M mutation in acquired resistance to an irreversible second-generation EGFR inhibitor. *Mol Cancer Ther*. 2012;11(3):784-791.

21. Soria J, Wu Y, Nakagawa K, et al. Gefitinib plus chemotherapy versus placebo plus chemotherapy in EGFR-mutation positive non-small-cell lung cancer after progression on first-line gefitinib (IMPRESS): a phase 3 randomised trial. *Lancet Oncol*. 2015;16(8):990-998.

22. Oxnard GR, Arcila ME, Sima CS, et al. Acquired resistance to EGFR tyrosine kinase inhibitors in EGFR-mutant lung cancer: distinct natural history of patients with tumors harboring the T790M mutation. *Clin Cancer Res*. 2011;17(6):1616-1622.

23. Wu YL, Lee JS, Thongprasert S, et al. Intercalated combination of chemotherapy and erlotinib for patients with advanced stage non-small-cell lung cancer (FASTACT-2): a randomised, double-blind trial. *Lancet Oncol*. 2013;14(8):777-786.

24. Mok T, Wu YL, Lee JS, et al. Detection and dynamic changes of EGFR mutations from circulating tumour DNA as a predictor of survival outcomes in NSCLC patients treated with first-line intercalated erlotinib and chemotherapy. *Clin Cancer Res*. 2015;21(14):3196-3203.