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AZD9291 in EGFR Inhibitor–Resistant Non–Small-Cell Lung Cancer

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ABSTRACT

BACKGROUND

The *EGFR* T790M mutation is the most common mechanism of drug resistance to epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors in patients who have lung cancer with an *EGFR* mutation (*EGFR*-mutated lung cancer). In preclinical models, the EGFR inhibitor AZD9291 has been shown to be effective against both EGFR tyrosine kinase inhibitor–sensitizing and T790M resistance mutations.

METHODS

We administered AZD9291 at doses of 20 to 240 mg once daily in patients with advanced lung cancer who had radiologically documented disease progression after previous treatment with EGFR tyrosine kinase inhibitors. The study included dose-escalation cohorts and dose-expansion cohorts. In the expansion cohorts, prestudy tumor biopsies were required for central determination of *EGFR* T790M status. Patients were assessed for safety, pharmacokinetics, and efficacy.

RESULTS

A total of 253 patients were treated. Among 31 patients enrolled in the dose-escalation cohorts, no dose-limiting toxic effects occurred at the doses evaluated. An additional 222 patients were treated in five expansion cohorts. The most common all-cause adverse events were diarrhea, rash, nausea, and decreased appetite. The overall objective tumor response rate was 51% (95% confidence interval [CI], 45 to 58). Among 127 patients with centrally confirmed *EGFR* T790M who could be evaluated for response, the response rate was 61% (95% CI, 52 to 70). In contrast, among 61 patients without centrally detectable *EGFR* T790M who could be evaluated for response, the response rate was 21% (95% CI, 12 to 34). The median progression-free survival was 9.6 months (95% CI, 8.3 to not reached) in *EGFR* T790M–positive patients and 2.8 months (95% CI, 2.1 to 4.3) in *EGFR* T790M–negative patients.

CONCLUSIONS

AZD9291 was highly active in patients with lung cancer with the *EGFR* T790M mutation who had had disease progression during prior therapy with EGFR tyrosine kinase inhibitors. (Funded by AstraZeneca; ClinicalTrials.gov number, NCT01802632.)

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SOMATIC MUTATIONS IN THE GENE encoding epidermal growth factor receptor (EGFR) are detected in approximately 30 to 40% of non-small-cell lung cancers (NSCLCs) from Asian patients and in 10% of NSCLCs from white patients.¹⁻³ EGFR mutations lead to constitutive activation of EGFR signaling and oncogenic transformation both in vitro and in vivo.^{4,5} Cancers with EGFR mutations (EGFR-mutated cancers) depend on EGFR signaling for growth and survival and are often sensitive to treatment with EGFR tyrosine kinase inhibitors.⁶ Among patients with advanced EGFR-mutated NSCLC, treatment with EGFR tyrosine kinase inhibitors (e.g., gefitinib, erlotinib, and afatinib) is associated with response rates of 56 to 74% and a median progression-free survival of 10 to 14 months; both outcomes are superior to those with platinum-based chemotherapy.⁷⁻¹⁰

Despite initial responses to EGFR tyrosine kinase inhibitors, the majority of patients will have disease progression within 1 to 2 years after treatment initiation (acquired resistance).⁷⁻¹⁰ In approximately 60% of patients, the mechanism of acquired resistance is the development of an additional EGFR mutation, EGFR T790M.¹¹ This mutation leads to an enhanced affinity for ATP, thus reducing the ability of ATP-competitive reversible EGFR tyrosine kinase inhibitors, including gefitinib and erlotinib, to bind to the tyrosine kinase domain of EGFR.¹² One strategy to overcome this mechanism of resistance is through the use of irreversible EGFR inhibitors.¹³ Although the irreversible EGFR inhibitors afatinib and dacomitinib have been shown to be effective in preclinical models, they are associated with response rates of less than 10% and a progression-free survival of less than 4 months in patients with NSCLC who have received previous treatment with gefitinib or erlotinib, probably owing to an inability of afatinib or dacomitinib to inhibit EGFR T790M at clinically achievable doses.¹⁴⁻¹⁷ In addition, the potent inhibition of wild-type EGFR by these agents is associated with skin and gastrointestinal toxic effects.^{18,19} Treatment options after the failure of an EGFR tyrosine kinase inhibitor are thus limited and include cytotoxic chemotherapy or supportive care.²⁰

AZD9291 (AstraZeneca) is an oral, potent, irreversible EGFR tyrosine kinase inhibitor that is selective for EGFR tyrosine kinase inhibitor-sensitizing mutations and the T790M resistance

mutation (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).²¹ As compared with previous EGFR inhibitors, AZD9291 shows significantly less in vitro activity against wild-type EGFR.²¹ In studies involving genetically engineered mouse models of EGFR-mutated NSCLC, AZD9291 had antitumor activity in EGFR L858R tumors that was similar to that of afatinib, but AZD9291 was significantly more effective than afatinib in EGFR L858R tumors that had a concurrent T790M mutation.²¹ This suggests that AZD9291 may be effective in patients with EGFR-mutated NSCLC in whom T790M-mediated resistance to EGFR inhibitors had developed. We conducted a phase 1 study to determine the safety and efficacy of AZD9291 in patients with advanced EGFR-mutated NSCLC in whom resistance to treatment with EGFR tyrosine kinase inhibitors had developed.

METHODS

PATIENTS

Patients were eligible for inclusion in the study if they had locally advanced or metastatic NSCLC, if they had a known EGFR tyrosine kinase inhibitor-sensitizing mutation or had had prior clinical benefit (as defined by the Jackman criteria in Table S1 in the Supplementary Appendix²²) from treatment with an EGFR tyrosine kinase inhibitor, and if they had radiologically documented disease progression while still receiving such treatment. There was no upper limit for the number of prior EGFR-inhibitor or systemic therapies. Details regarding testing for EGFR T790M and inclusion and exclusion criteria are provided in the Supplementary Appendix.

STUDY OVERSIGHT

This study was conducted in accordance with the principles of the Declaration of Helsinki and the Good Clinical Practice guidelines of the International Conference on Harmonisation. The protocol, which is available at NEJM.org, was approved by the local institutional review board at each participating site. All patients provided written informed consent before being screened.

The study was designed by the sponsor (AstraZeneca) together with the study investigators. The sponsor collected the data and analyzed them in conjunction with the authors. The first author wrote the first draft of the manuscript. Editorial support funded by the sponsor was

provided by iMed Communications. The pharmacokinetic variables were calculated by BAST (Loughborough, United Kingdom) under the paid supervision of the sponsor. All the authors reviewed and provided input to the manuscript and made the decision to submit it for publication. The authors had access to the data and vouch for the validity of the trial results reported here and adherence to the protocol.

STUDY DESIGN

The primary objective was to determine the safety and efficacy of AZD9291. Key secondary objectives included determination of the maximum dose associated with an acceptable level of adverse events as well as determination of the pharmacokinetics and antitumor activity of the agent. The study included dose-escalation and dose-expansion cohorts. Patients in the dose-escalation cohorts received a single dose of AZD9291 (in capsule form) followed by a pharmacokinetic evaluation period; after 7 days, they received the same oral dose daily for the remainder of the study, with additional pharmacokinetic assessment after daily continuous dosing. Each cycle of AZD9291 treatment was 21 days long. The first dose tested was 20 mg daily. Each subsequent dose cohort represented a 100% increase from the previous dose, with the exception of the final dose escalation, which was from 160 mg once daily to 240 mg once daily. Further details are available in the Supplementary Appendix.

If any evidence of clinical activity was observed in an escalation cohort, a dose-expansion cohort for that dose could be opened. Expansion cohorts were opened at a particular dose only after that dose had been determined to have an acceptable side-effect profile in the escalation cohort to permit dose escalation to the next dose level. In the expansion cohorts, daily continuous dosing commenced immediately, with pharmacokinetic assessments after continuous dosing. To be included in the dose-expansion cohorts, patients had to undergo a tumor biopsy after disease progression during the most recent line of therapy to test for *EGFR* T790M. Patients continued AZD9291 until disease progression, the development of unacceptable adverse events, or withdrawal of consent. Continuation of AZD9291 after disease progression was allowed at the discretion of the treating physician in consultation with the sponsor.

The first patient was enrolled on March 6,

2013. The data-cutoff date was August 1, 2014, and the study was ongoing. Enrollment into additional cohorts, including patients who have not received prior treatment, and a phase 2 extension were ongoing (Fig. S2 in the Supplementary Appendix).

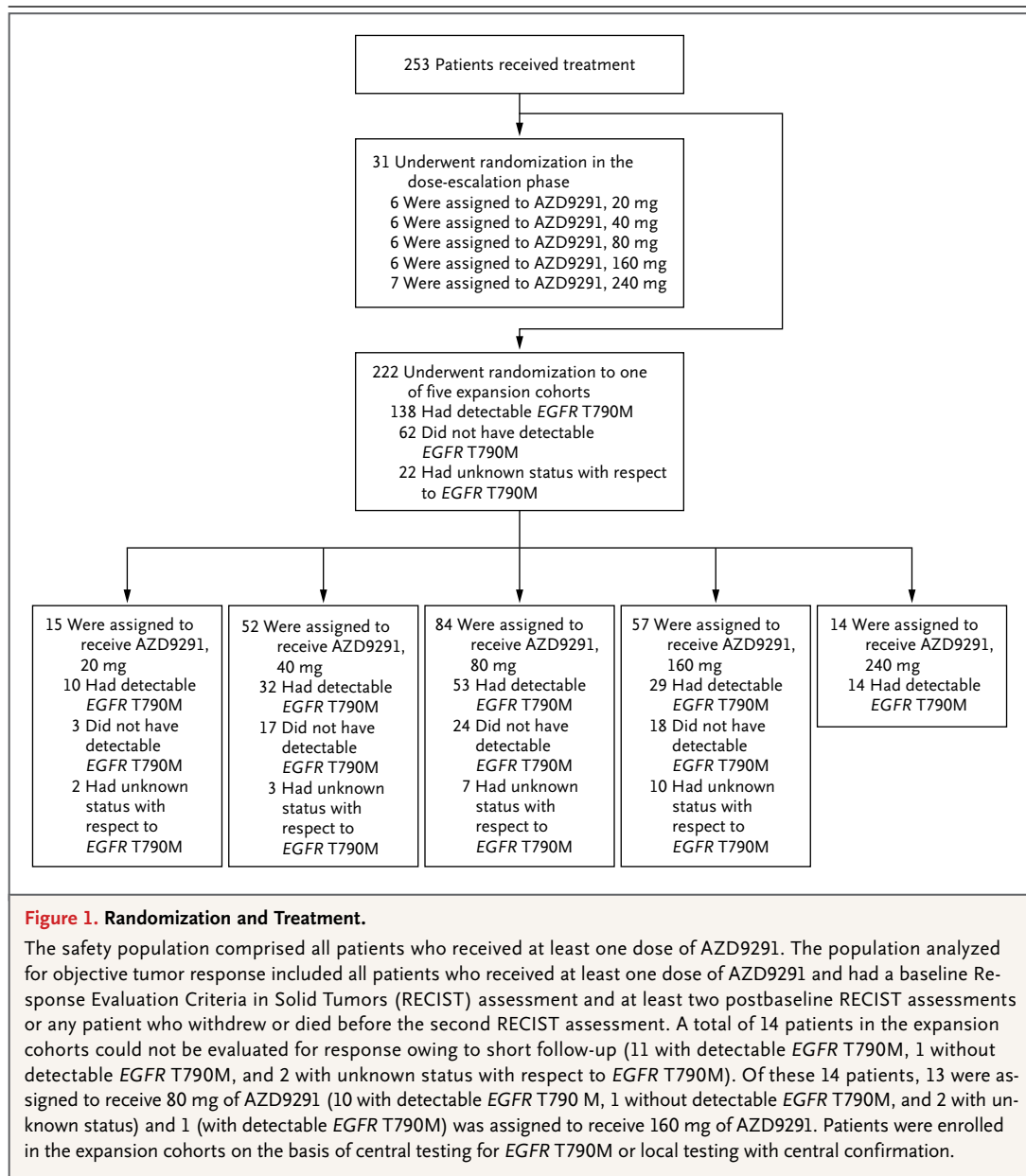
STUDY ASSESSMENTS

Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0 (http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf). Blood samples for pharmacokinetic assessments were obtained in both the dose-escalation and dose-expansion phases of the study; further details are available in the Supplementary Appendix. In the expansion cohorts, pretreatment tumor-biopsy specimens were tested for *EGFR* T790M status in a central laboratory with the use of the cobas *EGFR* Mutation Test (Roche Molecular Systems).

At baseline, all patients underwent tumor imaging, which included either computed tomography or magnetic resonance imaging of the chest and abdomen. Brain imaging was required only in patients with known or suspected brain metastases. Restaging scans were obtained at 6-week intervals during treatment and were assessed by investigators and independent central review, according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1 (Table S2 in the Supplementary Appendix). The objective response rate was defined as the percentage of patients with at least one confirmed response before any evidence of progression.

STATISTICAL ANALYSIS

For the dose-escalation cohorts, the dose levels were chosen after review of all available emerging safety and pharmacokinetic data. For the secondary efficacy and safety end points, data from patients in the dose-escalation and dose-expansion cohorts were pooled. Safety data are summarized for all patients who received at least one dose of AZD9291. Efficacy data are summarized for all patients and for patients in expansion cohorts whose *EGFR* T790M status was known on the basis of central testing. For this analysis, the population that could be evaluated for response included all patients who received at least one dose of AZD9291 and who had a baseline RECIST assessment and at least two postbaseline RECIST assessments or any patient who with-



drew or died before the second RECIST assessment. Duration of response and median progression-free survival were calculated with the use of the Kaplan–Meier technique.

RESULTS

PATIENTS

A total of 253 patients received at least one dose of AZD9291, 31 in the dose-escalation cohorts and 222 in the expansion cohorts (Fig. 1), across 33 sites in Japan, South Korea, Taiwan, France, Spain, Germany, Australia, the United Kingdom,

and the United States. A total of 62% of the patients (156 of 253) were women, 62% (156 of 253) were Asian, and 96% (242 of 253) had adenocarcinoma on histologic analysis (Table 1). All the patients had received at least one prior *EGFR* tyrosine kinase inhibitor (Table 1), and 80% had received prior cytotoxic chemotherapy (Table S3 in the Supplementary Appendix). *EGFR* T790M was detected in tumors from 138 of the 222 patients (62%) in the expansion cohorts and was not detected in tumors from 62 patients in those cohorts (28%); the status was unknown for 22 patients (10%).

Table 1. Baseline Demographic and Clinical Characteristics in the Safety Population.

Characteristic	Escalation (N=31)	Expansion (N=222)
Sex — no. (%)		
Male	11 (35)	86 (39)
Female	20 (65)	136 (61)
Age — yr		
Median	61	60
Range	39–81	28–88
Race — no. (%) [*]		
White	8 (26)	82 (37)
Asian	22 (71)	134 (60)
Other	1 (3)	5 (2)
Missing data	0	1 (<0.5)
Histologic type — no. (%)		
Adenocarcinoma	29 (94)	213 (96)
Squamous-cell carcinoma	1 (3)	2 (1)
Other	1 (3)	5 (2)
Missing data	0	2 (1)
No. of prior EGFR tyrosine kinase inhibitors at baseline — median (range)	1 (1–4)	2 (1–5)
EGFR mutation type by central test — no. (%) [†]		
Exon 19		112 (50)
L858R		65 (29)
Other [‡]		10 (5)
None		13 (6)
Unknown		22 (10)
T790M status by central test — no. (%) [†]		
Positive		138 (62)
Negative		62 (28)
Unknown		22 (10)

^{*} Race was determined by the investigator.

[†] Central testing was not performed for the escalation cohort.

[‡] Other mutation types were exon 18 G719X (in seven patients), exon 18 G719X and exon 20 S768I (in two patients), and exon 20 insertion (in one patient).

ADVERSE EVENTS

Patients in the dose-escalation phase of the study received 20 to 240 mg of AZD9291 daily. No dose-limiting toxic effects were observed during the 28-day evaluation period (7 days after administration of a single dose plus 21 days of daily dosing) at any dose level, and therefore a maximum dose that is associated with an acceptable level of adverse events has not been defined. Table 2 summarizes adverse events (those occurring in ≥10% of patients overall) of any grade and of grade 3 or higher. The most common adverse events were

diarrhea (47% of patients), rash (grouped term; 40%), nausea (22%), and decreased appetite (21%). Adverse events of diarrhea and rash increased in frequency in a dose-dependent manner. Any event of grade 3 or higher was observed in 32% of the patients. Adverse events leading to dose reduction or drug discontinuation were observed in 7% and 6%, respectively, of all patients. Serious adverse events were observed in 22% of the patients (Table S4 in the Supplementary Appendix); serious adverse events that were considered to be treatment-related, as assessed by the site

investigator, were observed in 6% of the patients. There were no significant differences in the severity or frequency of adverse events between Asian and non-Asian patients.

We noted 6 cases of potential pneumonitis-like events: 2 occurred in non-Japanese Asian patients and 4 in non-Asian patients. All 6 patients discontinued AZD9291, and the event either had resolved or was resolving at the time

of data cutoff; further details are provided in the Supplementary Appendix. Only 6 patients had an adverse event of hyperglycemia, and 11 patients had an adverse event of prolongation of the corrected QT interval; none of these events resulted in reduction or discontinuation of the drug. There were 7 fatal adverse events, one of which (pneumonia) was reported as being possibly drug-related.

Table 2. Adverse Events According to Daily Dose of AZD9291.*

Event	20 mg (N=21)	40 mg (N=58)	80 mg (N=90)	160 mg (N=63)	240 mg (N=21)	Total (N=253)
	<i>number of patients (percent)</i>					
Any adverse event	21 (100)	56 (97)	83 (92)	63 (100)	21 (100)	244 (96)
Any adverse event that was considered to be drug-related	14 (67)	38 (66)	71 (79)	59 (94)	21 (100)	203 (80)
Any adverse event of grade 3–5	6 (29)	21 (36)	26 (29)	24 (38)	5 (24)	82 (32)
Any adverse event of grade 3–5 that was considered to be drug-related	2 (10)	2 (3)	10 (11)	16 (25)	3 (14)	33 (13)
Any adverse event leading to dose reduction	0	1 (2)	0	10 (16)	6 (29)	17 (7)
Any adverse event leading to drug discontinuation	3 (14)	1 (2)	4 (4)	4 (6)	2 (10)	14 (6)
Any adverse event leading to drug discontinuation that was considered to be drug-related	2 (10)	0	1 (1)	3 (5)	1 (5)	7 (3)
Serious adverse event	4 (19)	13 (22)	20 (22)	16 (25)	3 (14)	56 (22)
Serious adverse event that was considered to be drug-related	3 (14)	1 (2)	4 (4)	6 (10)	1 (5)	15 (6)
Most common events†						
Diarrhea						
Any grade	5 (24)	24 (41)	30 (33)	43 (68)	16 (76)	118 (47)
Grade 3–5	0	1 (2)	1 (1)	1 (2)	1 (5)	4 (2)
Rashes and acne‡						
Any grade	5 (24)	13 (22)	29 (32)	40 (63)	15 (71)	102 (40)
Grade 3–5	0	0	0	2 (3)	0	2 (1)
Nausea						
Any grade	3 (14)	10 (17)	16 (18)	19 (30)	7 (33)	55 (22)
Grade 3–5	1 (5)	0	0	0	0	1 (<0.5)
Decreased appetite						
Any grade	7 (33)	11 (19)	14 (16)	16 (25)	6 (29)	54 (21)
Grade 3–5	1 (5)	0	1 (1)	0	0	2 (1)
Dry skin						
Any grade	2 (10)	9 (16)	10 (11)	25 (40)	5 (24)	51 (20)
Grade 3–5	0	0	0	0	0	0
Pruritus						
Any grade	2 (10)	11 (19)	15 (17)	12 (19)	7 (33)	47 (19)
Grade 3–5	0	0	0	0	0	0

Table 2. (Continued.)

Event	20 mg (N=21)	40 mg (N=58)	80 mg (N=90)	160 mg (N=63)	240 mg (N=21)	Total (N=253)
	<i>number of patients (percent)</i>					
Fatigue						
Any grade	4 (19)	15 (26)	9 (10)	11 (17)	5 (24)	44 (17)
Grade 3–5	1 (5)	0	0	0	1 (5)	2 (1)
Paronychia						
Any grade	2 (10)	5 (9)	11 (12)	18 (29)	6 (29)	42 (17)
Grade 3–5	0	0	0	1 (2)	0	1 (<0.5)
Constipation						
Any grade	1 (5)	13 (22)	15 (17)	10 (16)	1 (5)	40 (16)
Grade 3–5	0	0	0	0	0	0
Cough						
Any grade	3 (14)	9 (16)	12 (13)	13 (21)	0	37 (15)
Grade 3–5	0	0	0	0	0	0
Stomatitis						
Any grade	1 (5)	5 (9)	9 (10)	13 (21)	3 (14)	31 (12)
Grade 3–5	0	0	0	0	0	0
Vomiting						
Any grade	3 (14)	4 (7)	9 (10)	7 (11)	6 (29)	29 (11)
Grade 3–5	0	0	0	0	0	0
Anemia						
Any grade	0	6 (10)	11 (12)	9 (14)	2 (10)	28 (11)
Grade 3–5	0	1 (2)	3 (3)	0	0	4 (2)
Dyspnea						
Any grade	2 (10)	8 (14)	9 (10)	8 (13)	0	27 (11)
Grade 3–5	0	4 (7)	1 (1)	0	0	5 (2)
Upper respiratory tract infection						
Any grade	5 (24)	5 (9)	9 (10)	5 (8)	1 (5)	25 (10)
Grade 3–5	0	0	0	0	0	0
Headache						
Any grade	0	6 (10)	9 (10)	9 (14)	1 (5)	25 (10)
Grade 3–5	0	0	0	0	0	0

* Calculations were based on 253 patients who received at least one dose of the study treatment. Events were considered to be drug-related on the basis of assessment by the site investigator. The grade of adverse event was defined on the basis of the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.

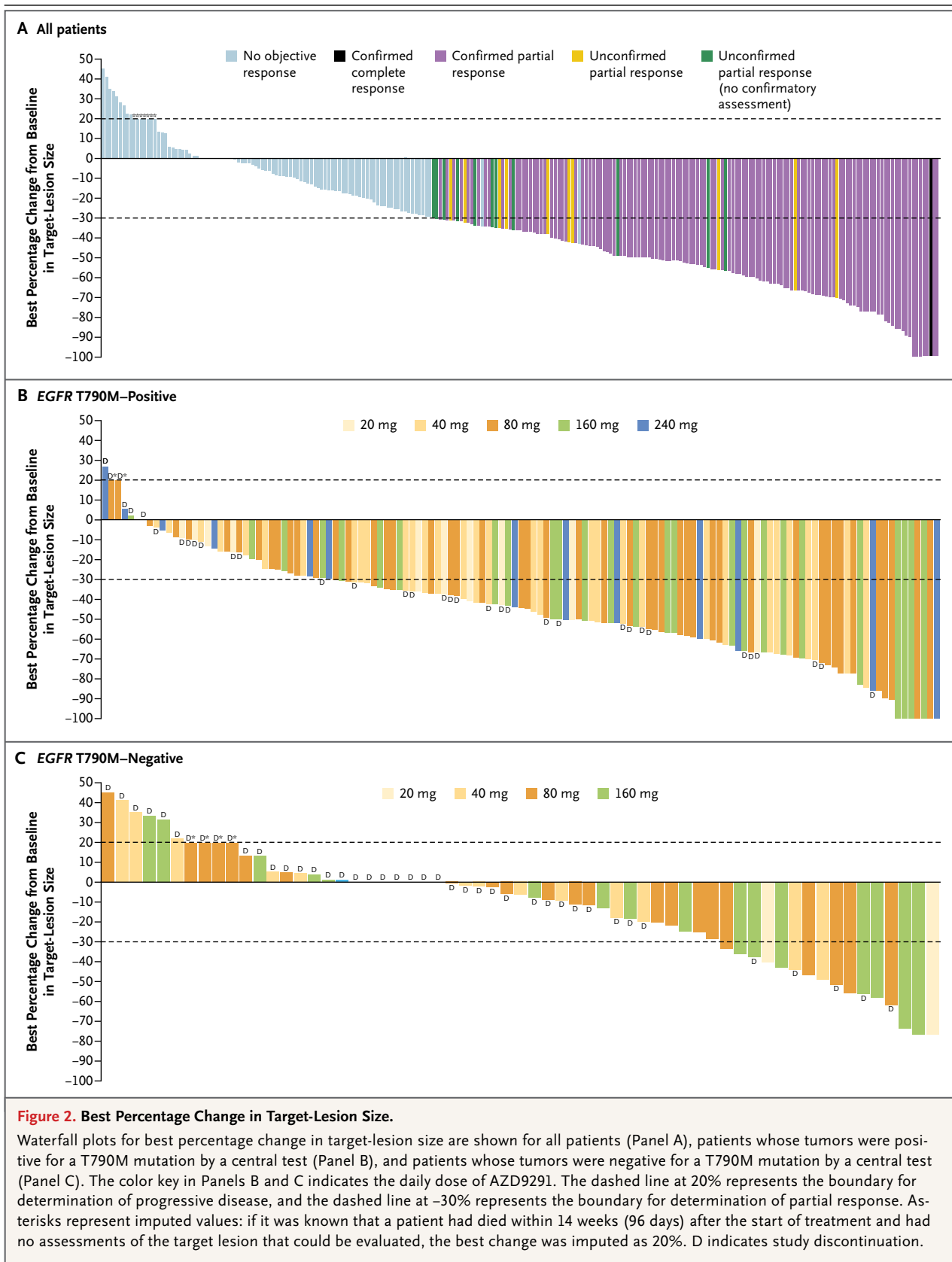
† Shown are events that occurred in at least 10% of patients.

‡ This is a group term (sum of high-level and preferred terms, according to the definitions in the *Medical Dictionary for Regulatory Activities*).

PHARMACOKINETICS

Pharmacokinetic analyses showed that AZD9291 exposure, maximal plasma concentration, and area under the plasma concentration–time curve increased in a dose-proportional manner

across the range from 20 to 240 mg after single and multiple doses (Table S5 and Fig. S3 in the Supplementary Appendix). Further details are provided in the Supplementary Appendix.



EFFICACY

Tumor Response

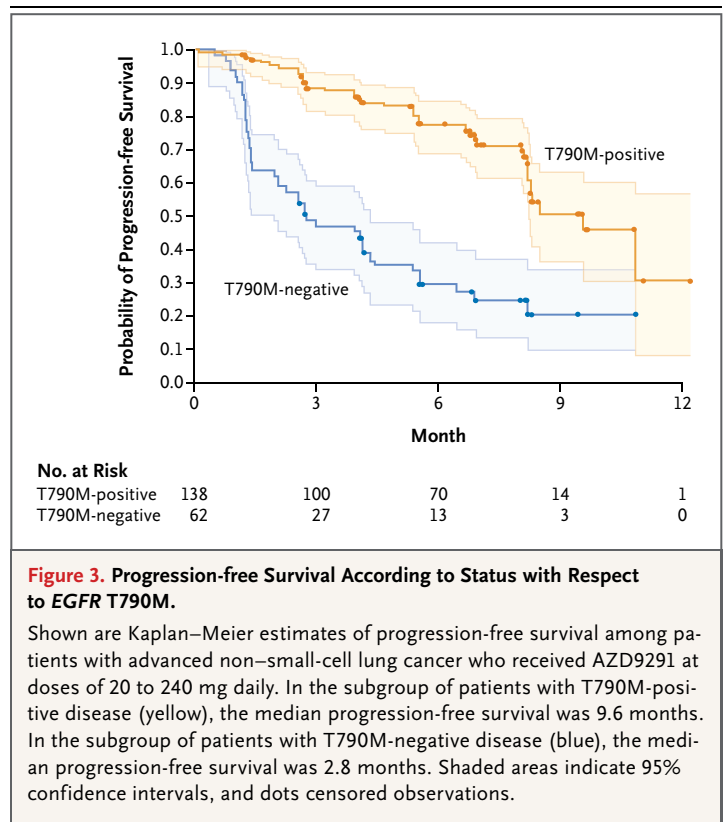
Of the 253 patients treated across all dose levels, 239 could be evaluated for response. Of the 239 patients, 123 (51%; 95% confidence interval [CI], 45 to 58) had a confirmed partial response (122 patients) or a complete response (1 patient), 78 (33%) had stable disease, 34 (14%) had progressive disease, and 4 (2%) could not be assessed for response (Fig. 2A). The rate of disease control (complete response, partial response, or stable disease) was 84% (95% CI, 79 to 88). There was not a substantial difference in the objective response rate between the 150 Asian patients (50%; 95% CI, 42 to 58) and the 89 non-Asian patients (54%; 95% CI, 43 to 65). The response rate was similar at each of the dose levels of AZD9291 (Table S6 in the Supplementary Appendix).

Of 138 patients with *EGFR* T790M confirmed by central testing, 127 could be evaluated for response. The objective response rate was 61% (78 of the 127 patients; 95% CI, 52 to 70), and the disease control rate was 95% (121 of the 127 patients; 95% CI, 90 to 98) (Fig. 2B, and Table S6 in the Supplementary Appendix). Of 62 patients with no detectable *EGFR* T790M by central testing, 61 could be evaluated for response. The objective response rate was 21% (13 of the 61 patients; 95% CI, 12 to 34), and the disease control rate was 61% (37 of the 61 patients; 95% CI, 47 to 73) (Fig. 2C, and Table S6 in the Supplementary Appendix). Response rates according to prior therapy with *EGFR* tyrosine kinase inhibitors and *EGFR* activating mutations and among patients with no detectable *EGFR* mutation are shown in Figures S4, S5, and S6 and Tables S7 and S8 in the Supplementary Appendix.

Duration of Response and Progression-free Survival

Among the 105 patients in the expansion cohorts who had a confirmed response, 85% had a response duration of 6 months or longer. However, data for 79% (83 of the 105 patients) were censored at the time of the data cutoff. The median progression-free survival was 8.2 months (41% maturity [92 events in 222 patients]).

In the subgroup of patients with detectable *EGFR* T790M, 88% of the patients had an estimated response duration of 6 months or longer, with a median progression-free survival of 9.6 months (95% CI, 8.3 to not reached; 30% maturity) among all 138 patients with that mutation (Fig. 3). Among patients with no detectable *EGFR* T790M,



69% of the patients had an estimated response duration of 6 months or longer, with a median progression-free survival of 2.8 months (95% CI, 2.1 to 4.3; 71% maturity) among all 62 patients without the mutation. Treatment durations for patients with detectable T790M and those with undetectable T790M are shown in Figure S7 in the Supplementary Appendix.

DISCUSSION

The development of drug resistance is a major barrier to the successful long-term treatment of patients with *EGFR*-mutated NSCLC. Strategies to treat patients with *EGFR* T790M, the most common cause of acquired drug resistance, have been hampered by both lack of efficacy and dose-limiting toxic effects.^{16,17} Among the most effective strategies to date, the combination of afatinib and cetuximab is associated with a response rate of 29% (32% among patients with *EGFR* T790M and 25% among patients without it) but is associated with substantial skin toxic effects (20% of grade 3 or higher) and gastrointestinal toxic effects (6% of grade 3 or higher).²³ In contrast, we found that AZD9291 as monotherapy

was associated with a response rate of 61%, with limited skin and gastrointestinal adverse effects, among patients with *EGFR* T790M. This suggests that a structurally distinct *EGFR* inhibitor, one that is selective for the mutated form of *EGFR*, can be clinically effective and has a side-effect profile that is not dose-limiting in the majority of patients in whom T790M-mediated drug resistance had developed. It has long been recognized that *EGFR* T790M is a drug-resistance mechanism, but our study provides clinical evidence that the presence of T790M causes resistance to *EGFR* tyrosine kinase inhibitors.

The primary objective of this study was to assess the safety and efficacy of AZD9291. The 20-mg starting dose was selected on the basis of preclinical toxicology data and xenograft models that predicted that this dose would be sufficient to inhibit *EGFR* T790M, whereas doses equivalent to 80 mg or more were expected to lead to more profound inhibition of tumor growth.²¹ AZD9291 treatment led to similar response rates among patients with detectable *EGFR* T790M across all dose levels. As suggested by the preclinical studies, AZD9291 treatment was associated with limited skin and gastrointestinal adverse effects. At the 160-mg and 240-mg dose levels, there was an increase in the incidence and severity of adverse events associated with inhibition of non-mutant *EGFR*, including rash, dry skin, pruritus, and diarrhea. This suggests that at these dose levels, AZD9291 is starting to inhibit wild-type *EGFR* more significantly in patients. The dose of 80 mg once daily is being evaluated further as a single agent in patients with detectable *EGFR* T790M (ClinicalTrials.gov numbers, NCT02094261 and NCT0215198).

Our study was designed to investigate AZD9291 in cohorts of patients with T790M-mediated resistance to *EGFR* tyrosine kinase inhibitors and patients with non-T790M-mediated resistance. AZD9291 was associated with a higher objective response rate and longer progression-free survival in patients with T790M-mediated drug resistance than in those with non-T790M-mediated resistance. Although the data are still immature (30% maturity), the current median progression-free survival in patients with detectable *EGFR* T790M (9.6 months) is encouraging. *EGFR* T790M has been recognized as a prognostic biomarker, but our findings show that it is also a predictive biomarker for the efficacy of AZD9291.

Acquired resistance to *EGFR* tyrosine kinase inhibitors is mediated by non-T790M mechanisms in approximately 40% of cancers.¹¹ Although the mechanisms are not fully understood, known mechanisms include activation of non-*EGFR* bypass signaling pathways and histologic transformation (epithelial-to-mesenchymal transformation or transformation to small-cell lung cancer); in some instances, these mechanisms may be due to tumor heterogeneity. AZD9291 was associated with a response rate of 21% among patients without detectable *EGFR* T790M and a lower rate (11%) among patients who were T790M-negative and had received an *EGFR* tyrosine kinase inhibitor as the last treatment regimen before study entry. Thus, one reason for the activity of AZD9291 in patients without detectable *EGFR* T790M may be a retreatment effect after a “holiday” from treatment with an *EGFR* tyrosine kinase inhibitor, as reported previously in some studies of gefitinib.²⁴

Current approaches to address cancers that are resistant to *EGFR* tyrosine kinase inhibitors with non-T790M-dependent resistance mechanisms include investigation of the combination of an *EGFR* inhibitor and a *MET* inhibitor; this combination, however, has been limited by both toxic effects and a lack of efficacy.^{25,26} The activity of AZD9291 coupled with its safety profile may provide the opportunity to evaluate combination treatment strategies, including with *MET* inhibitors, to further improve clinical outcomes in patients with resistance to *EGFR* tyrosine kinase inhibitors.

In summary, AZD9291 was associated with tumor responses in the majority of patients with advanced NSCLC in whom T790M-mediated drug resistance had developed.

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