original reports

AENEAS: A Randomized Phase III Trial of Aumolertinib Versus Gefitinib as First-Line Therapy for Locally Advanced or Metastatic Non–Small-Cell Lung Cancer With *EGFR* Exon 19 Deletion or L858R Mutations

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abstract

PURPOSE Aumolertinib (formerly almonertinib; HS-10296) is a novel third-generation epidermal growth factor receptor tyrosine kinase inhibitor approved in China. This double-blind phase III trial evaluated the efficacy and safety of aumolertinib compared with gefitinib as a first-line treatment for locally advanced or metastatic *EGFR*-mutated non–small-cell lung cancer (NSCLC; ClinicalTrials.gov identifier: NCT03849768).

METHODS Patients at 53 sites in China were randomly assigned 1:1 to receive either aumolertinib (110 mg) or gefitinib (250 mg) once daily. The primary end point was progression-free survival (PFS) per investigator assessment.

RESULTS A total of 429 patients who were naïve to treatment for locally advanced or metastatic NSCLC were enrolled. PFS was significantly longer with aumolertinib compared with gefitinib (hazard ratio, 0.46; 95% CI, 0.36 to 0.60; $P < .0001$). The median PFS with aumolertinib was 19.3 months (95% CI, 17.8 to 20.8) versus 9.9 months with gefitinib (95% CI, 8.3 to 12.6). Objective response rate and disease control rate were similar in the aumolertinib and gefitinib groups (objective response rate, 73.8% and 72.1%, respectively; disease control rate, 93.0% and 96.7%, respectively). The median duration of response was 18.1 months (95% CI, 15.2 to not applicable) with aumolertinib versus 8.3 months (95% CI, 6.9 to 11.1) with gefitinib. Adverse events of grade ≥ 3 severity (any cause) were observed in 36.4% and 35.8% of patients in the aumolertinib and gefitinib groups, respectively. Rash and diarrhea (any grade) were observed in 23.4% and 16.4% of patients who received aumolertinib compared with 41.4% and 35.8% of those who received gefitinib, respectively.

CONCLUSION Aumolertinib is a well-tolerated third-generation epidermal growth factor receptor tyrosine kinase inhibitor that could serve as a treatment option for *EGFR*-mutant NSCLC in the first-line setting.

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ASSOCIATED CONTENT

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Data Supplement

Protocol

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

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INTRODUCTION

Epidermal growth factor receptor *(EGFR)* mutations are one of the most common oncogenic driver mutations in non–small-cell lung cancer (NSCLC). Osimertinib, a third-generation EGFR tyrosine kinase inhibitor (TKI), was initially approved on the basis of the clinical efficacy demonstrated by the AURA program for the treatment of NSCLC patients with an *EGFR* T790M mutation and was subsequently approved for first-line treatment of patients with advanced NSCLC and *EGFR* exon 19 deletion or L858R mutations.[1-4] In the pivotal FLAURA study, treatment with osimertinib resulted in a 54% reduction in the risk of disease progression or death as compared with treatment with a first-generation EGFR TKI. However, the

CONTEXT

Key Objective

ANEAS is a randomized, double-blind, phase III trial evaluating the efficacy and safety of aumolertinib compared with gefitinib as first-line treatment for locally advanced or metastatic epidermal growth factor receptor–mutated non–small-cell lung cancer (NSCLC; ClinicalTrials.gov identifier: NCT03849768).

Knowledge Generated

Aumolertinib is a novel third-generation epidermal growth factor receptor tyrosine kinase inhibitor that has been approved in China for patients with *EGFR*-mutant NSCLC. The results suggest the possible use of aumolertinib as first-line treatment for *EGFR*-mutant NSCLC, particularly given the encouraging low rates of *EGFR* wild-type–mediated toxicity.

Relevance

This study conducted exclusively in China has findings broadly applicable to this genomically defined, global patient population as the natural history of and approach to evaluation and treatment of patients with *EGFR*-mutant NSCLC are similar worldwide, as evidenced by the guidelines of the National Comprehensive Cancer Network, European Society for Medical Oncology, and The Pan-Asian Guidelines Adaptation.

toxicities of rash and diarrhea are strongly associated with inhibition of wild-type *EGFR*.[3] There is a need for additional third-generation *EGFR* inhibitors that both offer effective first-line treatment of *EGFR*-mutant NSCLC and are well-tolerated.

Aumolertinib (proposed international nonproprietary name; formerly almonertinib; HS-10296) is a novel, irreversible, third-generation EGFR TKI developed by Hansoh Pharmaceutical Group Co, Ltd (Shanghai, China). Aumolertinib demonstrated higher selectivity against both *EGFR*-sensitizing and T790M mutations with less inhibition against wild-type *EGFR* than osimertinib.[5] In March 2020 aumolertinib was approved in China, on the basis of APOLLO (ClinicalTrials.gov identifier: NCT0298110),[6,7] for the treatment of patients with advanced NSCLC and an *EGFR* T790M mutation.

On the basis of the preclinical and promising clinical profile of aumolertinib in the second-line setting, the AENEAS trial, a phase III randomized, double-blind study comparing aumolertinib with gefitinib in the first-line setting for patients with advanced *EGFR*-mutant NSCLC, was initiated and the results of the primary analysis are reported herein.

METHODS

Study Design and Patients

AENEAS was a multicenter, double-blind, randomized phase III trial conducted at 53 study sites in mainland China (Data Supplement, online only). The trial was conducted in accordance with the protocol, applicable local regulations, and the Declaration of Helsinki and International Conference on Harmonisation Guidelines for Good Clinical Practices principles. The Protocol (online only) was approved by each institution's research ethics board, and all patients provided written informed consent before initiating any study-related procedure.

Patients with histologic or cytologic confirmation of locally advanced or metastatic NSCLC harboring an *EGFR* mutation (sensitizing mutations, such as exon 19 deletion and L858R mutations, as detected by a central laboratory using the Cobas *EGFR* Mutation Test [version 2; Roche Molecular Systems Inc, Pleasanton, CA]) were eligible, as detected in tissue (preferred) or blood. No prior systemic therapy was permitted except for treatment in the adjuvant/neoadjuvant setting, and no prior treatment with an EGFR inhibitor was permitted.

At baseline, patients were required to have at least one measurable lesion, defined as ≥ 10 mm. Baseline assessment was performed using RECIST 1.1. Prestudy CNS imaging was mandatory. Patients with asymptomatic, stable CNS metastases that did not require steroids for at least 2 weeks before starting the study drug (ie, aumolertinib or gefitinib) were included.

Study Procedures

An interactive web response system randomly assigned eligible patients 1:1 to receive either 110 mg aumolertinib or 250 mg gefitinib, administered once daily orally, stratified by the type of *EGFR* mutation (exon 19 deletion or L858R) and CNS metastases status (with or without). Treatment with study drug was continued until disease progression, withdrawal of consent, the development of unacceptable side effects, or the fulfillment of other discontinuation criteria. Treatment with study drug beyond disease progression was permitted if the patients continued to derive clinical benefits as assessed by the treating investigator. Upon disease progression, patients in the gefitinib group who acquired an *EGFR* T790M mutation were eligible to crossover to aumolertinib treatment.

Outcomes

The primary end point was progression-free survival (PFS), as determined by investigator assessment. Secondary end

points included overall survival (OS), objective response rate (ORR), duration of response (DoR), disease control rate (DCR), and depth of response.

Systemic response was assessed by the investigators and by blinded independent central review and was classified according to RECIST 1.1. Computed tomography imaging was performed at baseline and every 6 weeks (±7 days) from the start of aumolertinib until the 15-month time point, after which imaging was performed at 12-week intervals. Prestudy CNS imaging was mandatory.

All adverse events (AEs) were evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03 for up to 28 days beyond the last dose of any protocol treatment.

TABLE 1. Demographic and Baseline Disease Characteristics

Characteristic	Aumolertinib (n = 214)	Gefitinib (n = 215)
Age, years		
Median	59	62
Range	32-78	25-81
Sex, No. (%)		
Male	80 (37.4)	80 (37.2)
Female	134 (62.6)	135 (62.8)
Smoking history, No. (%)		
Former	49 (22.9)	64 (29.8)
Current	9 (4.2)	7 (3.3)
No	156 (72.9)	144 (67.0)
Race, No. (%)		
Asian	214 (100)	215 (100)
EGFR mutation, No. (%)		
Exon 19 deletion	140 (65.4)	141 (65.6)
L858R	74 (34.6)	74 (34.4)
Tumor staging, No. (%)		
IIIB	12 (5.6)	17 (7.9)
IV	202 (94.4)	198 (92.1)
Pathologic type, No. (%)		
Adenocarcinoma	210 (98.1)	211 (98.1)
Others	4 (1.9)	4 (1.9)
CNS metastases, No. (%)		
Yes	56 (26.2)	59 (27.4)
No	158 (73.8)	156 (72.6)
ECOG performance score, No. (%)		
0	51 (23.8)	54 (25.1)
1	160 (74.8)	159 (74.0)

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

Statistical Analysis

Approximately 262 events of 410 randomly assigned patients can achieve 90% power to detect a hazard ratio (HR) of 0.67 (median PFS [mPFS] from 10 to 15 months) at a 2-sided alpha level of .05 with an enrollment ratio of 1:1, an accrual time of 8 months, and a longest follow-up time of 23 months.

Primary efficacy analysis was performed on the full analysis set, including all randomly assigned patients who received the study drug at least once. The primary end point of PFS was summarized using the Kaplan-Meier method. A log-rank test that was stratified by *EGFR* mutation type and CNS metastases status was used to detect the statistical difference of PFS between the two groups.

The stratified Cox proportional hazards model, as adjusted by *EGFR* mutation type and CNS metastases status, was used to estimate the PFS HR, along with the two-sided 95% CI of the two treatment groups. The proportional hazards assumption was assessed by the use of the model from the study by Lin et al.[8] Other time-to-event end points were analyzed in a similar manner. Both ORR and DCR were summarized using the point estimate with the two-sided 95% CI. A logistic regression model, stratified by *EGFR* mutation type and CNS metastases status, was used for odds ratio and *P* value calculation to compare ORR and DCR between the two treatment groups. Safety analyses were performed on the safety analysis set, which included all randomly assigned patients who received the study drug at least once. All the statistical analysis was performed using SAS v9.4.

RESULTS

The results herein are presented using the data cutoff date of January 15, 2021.

Study Patients and Study Drug Treatment

Between November 30, 2018, and September 06, 2019, 838 patients were screened at 53 centers in China. A total of 409 patients failed screening, and 429 patients were enrolled and randomly assigned (Data Supplement). Forty-one patients (19.1%) on the gefitinib arm had crossed over and received at least one dose of aumolertinib as of the data cutoff date, the disposition of which is presented in the Data Supplement. All randomly assigned patients received one or more doses of study drug (ie, aumolertinib or gefitinib). All enrolled patients had baseline measurable disease according to RECIST 1.1 assessment. Demographic and baseline characteristics were well-balanced between the groups (Table 1). In the total population, 115 patients (26.8%) had brain metastases at baseline—26.2% in the aumolertinib group and 27.4% in the gefitinib group (Table 1).

At the data cutoff of January 15, 2021, the median duration of drug total exposure was 463.5 (range, 1-715) days for

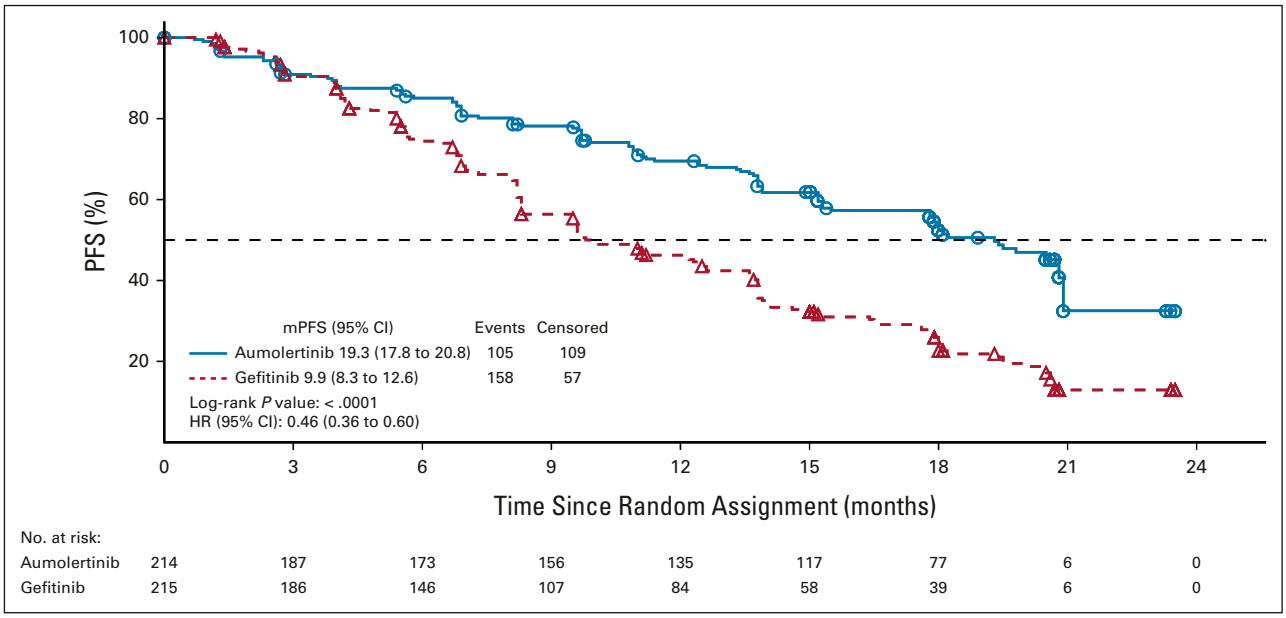

FIG 1. Kaplan-Meier estimates of PFS. The duration of PFS by investigator assessment is estimated via Kaplan-Meier methods. In tandem, hazard in the aumolertinib arm divided by the hazard in the gefitinib arm provided the hazard ratio. For the patients who discontinued study treatment or received new antitumor therapy treatment before progression or death, the patient was censored at the latest evaluable examination date of imaging before the discontinuation date or the date of starting new antitumor therapies. HR, hazard ratio; mPFS, median PFS; PFS, progression-free survival.

aumolertinib and 254.0 (range, 1-714) days for gefitinib. The medication compliance was 99.3% and 98.5% for patients receiving aumolertinib and gefitinib, respectively. A total of 105 patients in the aumolertinib group (data maturity of 49.1%) and 158 patients in the gefitinib group (data maturity of 73.5%) had experienced an event of RECIST-defined progression or death. A total of 93 patients (43.5%) in the aumolertinib group and 34 patients (15.8%) in the gefitinib group had continued to receive study drug treatment as of the data cutoff date.

Efficacy

The median follow-up time in the aumolertinib group was 20.5 months (95% CI, 18.0 to 20.6), compared with 20.7 months (95% CI, 19.3 to 20.8) in the gefitinib group, respectively. The median duration of PFS (as defined by either progressive disease or death) was 19.3 months (95% CI, 17.8 to 20.8) in the aumolertinib group, which was significantly longer ($P < .0001$) than that of the gefitinib group at 9.9 months (95% CI, 8.3 to 12.6; Fig 1). The proportional hazard assumption was not violated per the testing results with a *P* value of .094. The HR between the two groups was 0.46 (95% CI, 0.36 to 0.60; Fig 1). As such, improvements in both 1-year (69.5% *v* 46.3%) and 2-year (32.5% *v* 12.9%) PFS rates were observed for the aumolertinib and gefitinib groups, respectively. Analysis of PFS by blinded independent central review was consistent with these results and is presented in the Data Supplement.

Aumolertinib demonstrated a consistent PFS benefit across all prespecified stratification factors, namely, *EGFR* mutation type and the presence or absence of known or treated CNS metastases (Fig 2).

Among all patients with an *EGFR* exon 19 deletion mutation, the mPFS for the aumolertinib and gefitinib groups was 20.8 months and 12.3 months, respectively (HR, 0.39; $P < .0001$; Fig 3A). Among all patients with *EGFR* L858R, the mPFS for the aumolertinib and gefitinib groups was 13.4 months and 8.3 months, respectively (HR, 0.60; $P = .0102$; Fig 3B). Among all patients with CNS metastases, the mPFS for the aumolertinib and gefitinib groups was 15.3 months and 8.2 months, respectively (HR, 0.38; $P < .0001$; Fig 3C). By comparison, among patients without CNS metastases, the mPFS for both groups was 19.3 months and 12.6 months, respectively (HR, 0.51; $P < .0001$; Fig 3D). Analysis of PFS by other subgroups such as sex, age, smoking history, and baseline ECOG PS is shown in Figure 2.

The summary of secondary efficacy end points is shown in Table 2. Preliminary analysis of OS at the time of the final PFS analysis showed that 123 patients had died (data maturity of 28.7%), including 54 patients (data maturity of 25.2%) in the aumolertinib group and 69 patients (data maturity of 32.1%) in the gefitinib group.

Both ORR and DCR were similar in the aumolertinib and gefitinib groups, respectively, with ORRs of 73.8% (95% CI, 67.4 to 79.6) and 72.1% (95% CI, 65.6 to 78.0),

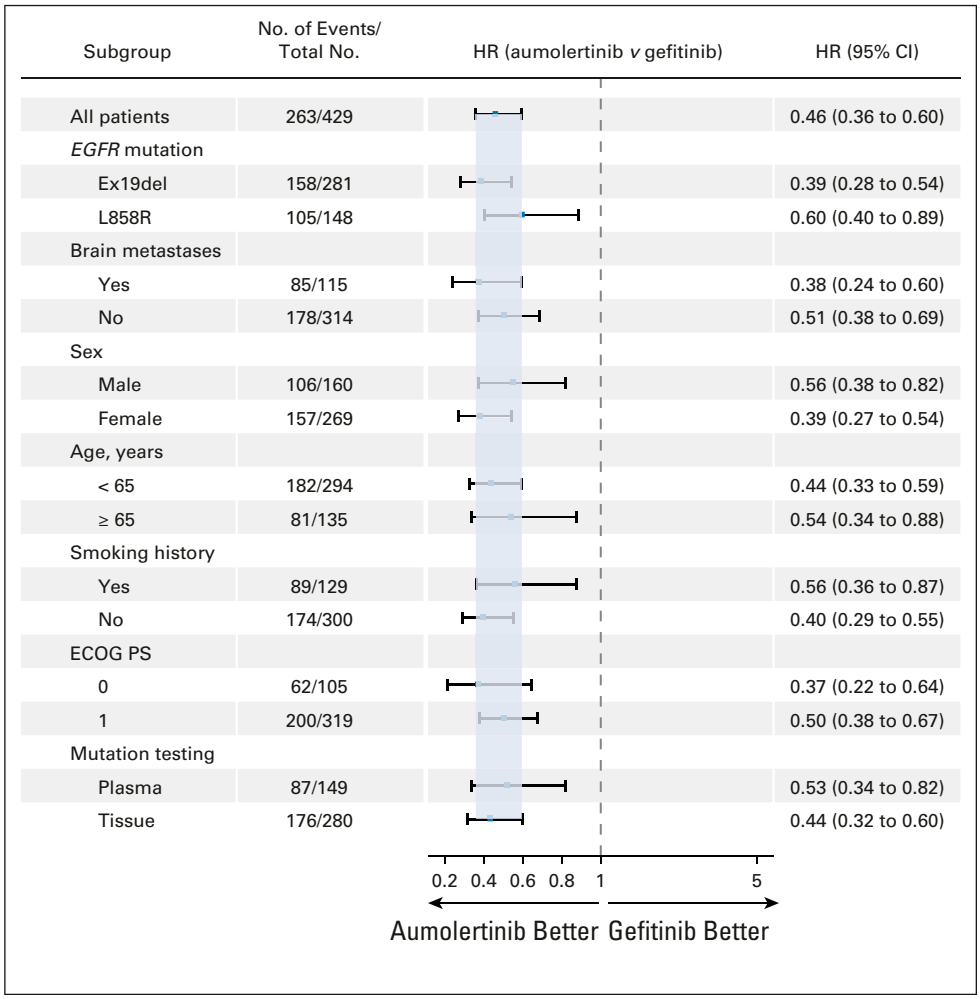

FIG 2. PFS by subgroup analysis. PFS was estimated as shown in Figure 1 for the following prespecified subgroups: *EGFR* mutation type, brain/CNS metastases status, sex, age, smoking history, baseline ECOG PS, and mutation test methods. ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; PFS, progression-free survival.

respectively, and DCRs of 93.0% (95% CI, 88.7 to 96.0) and 96.7% (95% CI, 93.4 to 98.7), respectively.

For both ORR and DCR, there was no statistically significant difference between the two groups ($P = .6939$ and .0884, respectively). The mean percentage of depth of best response of the aumolertinib group was 45% (range, –100 to 50), whereas that of the gefitinib group was 42% (range, –85.5 to 24.4), with no significant difference between the groups ($P = .1688$). The maximum percentage change in sum of the diameters of target lesions compared with baseline for aumolertinib and gefitinib is shown in the Data Supplement.

The median DoR was longer in the aumolertinib group than the gefitinib group at 18.1 months (95% CI, 15.2 to not applicable) versus 8.3 months (95% CI, 6.9 to 11.1; HR, 0.38; 95% CI, 0.28 to 0.51; $P < .0001$). Among patients who had responded to study drug treatment, an event of disease progression or death occurred in 72 of 158 patients (45.6%) in the aumolertinib group and 113 of 155 patients (72.9%) in the gefitinib group as of the data cutoff date.

Safety and AEs

Of the 429 patients, 424 (98.8%) had experienced at least one AE during the study treatment period as of the data cutoff date, January 15, 2021. Of total, 211 patients (98.6%) in the aumolertinib group and 213 patients (99.1%) in the gefitinib group had experienced at least one treatment-emergent adverse event (TEAE; Table 3). TEAEs of grade ≥ 3 were similar in the aumolertinib and gefitinib groups (36.4% *v* 35.8%), respectively (Data Supplement). The most common TEAEs of grade ≥ 3 were ALT increase (2.8% *v* 12.1%) and aspartate transaminase increase (1.4% *v* 9.3%), respectively (Data Supplement). Incidence of serious adverse events was similar in the aumolertinib and gefitinib groups (22.0% *v* 21.4%), respectively (Data Supplement).

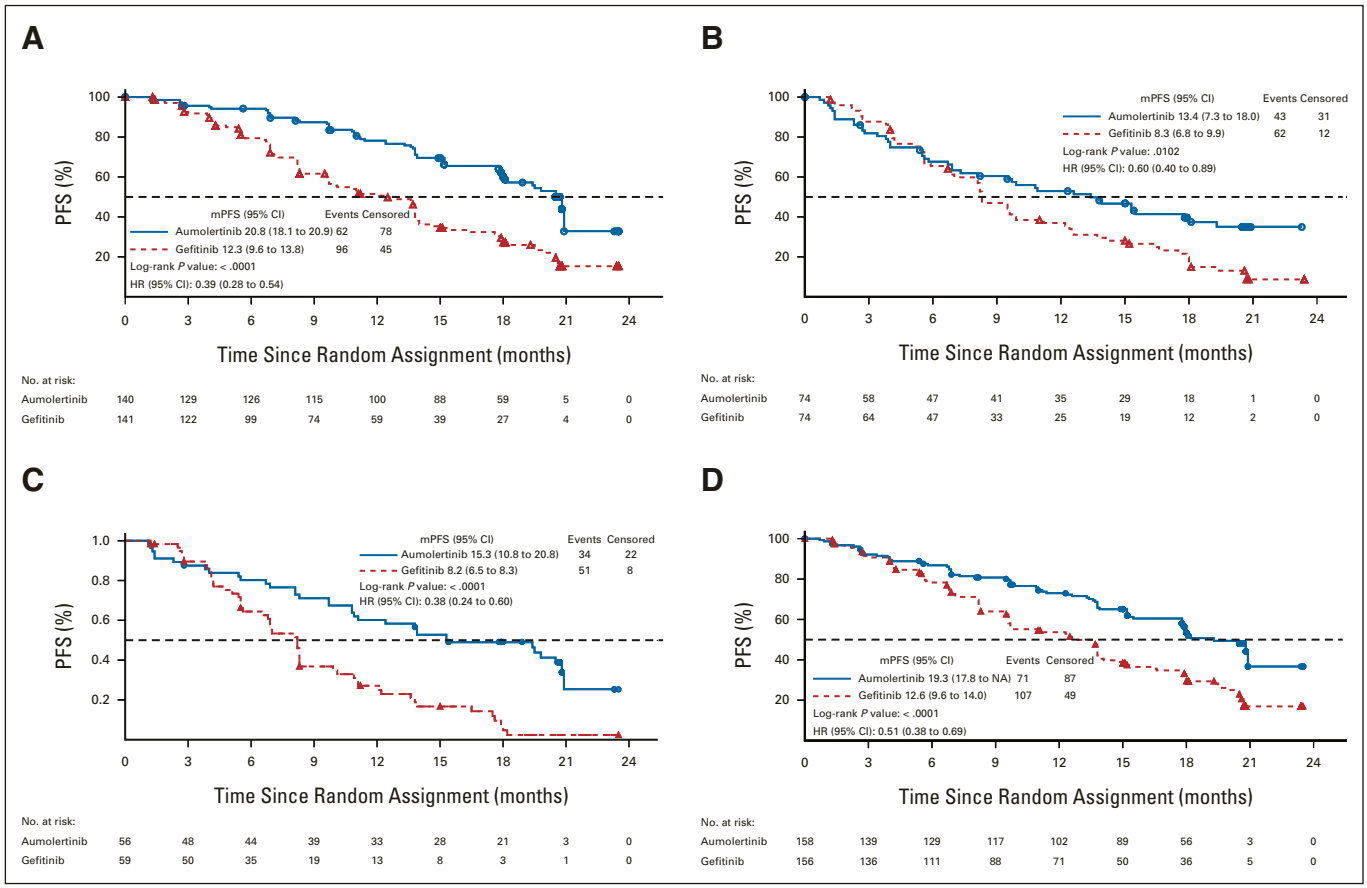

FIG 3. Kaplan-Meier estimates of PFS by stratification factors. PFS was estimated as shown in Figure 1 for the following prespecified groups: (A) patients with *EGFR* exon 19 deletion, (B) patients with *EGFR* L858R, (C) patients with CNS metastases, and (D) patients without CNS metastases. HR, hazard ratio; mPFS, median PFS; NA, not applicable; PFS, progression-free survival.

The most common AEs in the aumolertinib and gefitinib groups were blood creatine phosphokinase (CPK) increase (35.5% *v* 9.3%), aspartate transaminase increase (29.9% *v* 54.0%), ALT increase (29.4% *v* 55.8%), rash (23.4% *v* 41.4%), and diarrhea (16.4% *v* 35.8%; Table 3), respectively. Treatment-related AEs (incidence ≥ 10%) and serious adverse events (any incidence) assessed by the investigator are summarized in the Data Supplement. Two (0.9%) patients in the aumolertinib group experienced interstitial lung disease (which was grade 2) assessed by the investigator as treatment-related, whereas one (0.5%) patient in the gefitinib group had interstitial lung disease.

Aumolertinib was associated with a lower rate of AEs leading to permanent discontinuation (3.7% compared with 5.1% with gefitinib). Dose interruptions were implemented in 36 (16.8%) patients in the aumolertinib group and in 53 (24.7%) patients in the gefitinib group. Nine (4.2%) patients in the aumolertinib group and 10 (4.7%) in the gefitinib group experienced AEs leading to dose reduction.

A total of eight patients—five in the aumolertinib group and three in the gefitinib group—experienced AEs leading to death between the start of initial study drug and up to 28 days after their last dose of study drug treatment. For the five aumolertinib-treated patients, the events leading to death were cardiac arrest (n = 2) and cerebral infarction, cardiogenic pulmonary edema complicated with upper GI hemorrhage, and unexplained (n = 1 each), respectively; the investigator-assessed relationship of the AE to study drug was unrelated in four patients and unable to be determined in one patient. For the three gefitinib-treated patients, the events leading to death were suicide, infectious pneumonia, and unexplained, respectively; the investigator-assessed relationship of the AE to study drug was unrelated in two patients and unable to be determined in one patient.

DISCUSSION

In this article we describe a randomized, phase III trial assessing aumolertinib as an intervention in the context of first-line treatment of patients with advanced *EGFR*-mutant NSCLC using gefitinib as an active comparator. First-generation EGFR inhibitors (eg, gefitinib) were traditionally considered the standard of care for disseminated and recurrent *EGFR*-mutated NSCLC, until the approval of

TABLE 2. Summary of Secondary Efficacy End Points

Efficacy	Aumolertinib (n = 214)	Gefitinib (n = 215)
Best overall response, No. (%)		
CR	1 (0.5)	1 (0.5)
PR	157 (73.4)	154 (71.6)
SD	41 (19.2)	53 (24.7)
PD	12 (5.6)	6 (2.8)
NE	3 (1.4)	1 (0.5)
ORR (95% CI)	73.8 (67.4 to 79.6)	72.1 (65.6 to 78.0)
DCR (95% CI)	93.0 (88.7 to 96.0)	96.7 (93.4 to 98.7)
DoR, months		
Median (95% CI)	18.1 (15.2 to NA)	8.3 (6.9 to 11.1)
Range	0-22.2	0-22.1
12-month response rate (95% CI)	66.2 (57.8 to 73.3)	37.9 (29.7 to 46.0)
15-month response rate (95% CI)	59.2 (50.5 to 66.8)	26.1 (18.9 to 34.0)
18-month response rate (95% CI)	52.4 (43.3 to 60.6)	18.8 (12.2 to 26.5)
OS, months		
Median (95% CI)	NA (NA to NA)	NA (21.8 to NA)
12-month OS rate (95% CI)	86.2 (80.8 to 90.2)	85.3 (79.8 to 89.4)
24-month OS rate (95% CI)	NA (NA to NA)	NA (NA to NA)

NOTE. Data cutoff date: January 15, 2021.

Abbreviations: CR, complete response; DCR, disease control rate; DoR, duration of response; NA, not applicable; NE, not evaluable; ORR, objective response rate; OS, overall survival; PD, progressive disease; PR, partial response; SD, stable disease.

osimertinib by the US Food and Drug Administration in April 2018 for first-line use as demonstrated by the FLAURA trial.[3,9] Subsequently, in December 2020, osimertinib was also approved for use as an adjuvant therapy for resected NSCLC,[10] on the basis of the results of the ADAURA trial. Inherent to this robust progress is the observation that a longer duration of therapy magnifies the importance of tolerability, toxicity, and the cost of component therapy. Given the approval of only one third-generation EGFR inhibitor, there is a standing need for another highly efficacious and well-tolerated agent to diversify the treatment armamentarium.

In AENEAS, aumolertinib met the primary objective of the trial by demonstrating a 9.4-month improvement in mPFS relative to gefitinib. Benefits with aumolertinib were noted across all prespecified stratification factors, including patients stratified by the presence (or absence) of CNS metastases (HR, 0.38). These results were particularly encouraging given that CNS metastases remain a major cause of morbidity and mortality in this population. The superior efficacy observed in patients with exon 19 deletion mutations relative to those with L858R mutations is a consistent feature of the class of third-generation EGFR inhibitors.[3] The median DoR was nearly 10 months longer with aumolertinib, but no significant difference in ORR or DCR was observed.

Toxicities believed to be mediated by the inhibition of wild-type *EGFR* in cutaneous and GI epithelium were observed at lower rates in the aumolertinib group than in the gefitinib group. The rates of both rash and diarrhea were significantly lower in the aumolertinib group than in the gefitinib group (23.4% *v* 41.4% and 16.4% *v* 35.8%, respectively). The observation suggesting less EGFR WT inhibition correlates with preclinical data, including the observation that the primary metabolite of aumolertinib retains comparable selectivity for mutant over wild-type *EGFR* as the parent compound[7]; it also correlates with the toxicity profile noted in APOLLO.[6] Notably, these signals should be interpreted in light of the longer median total exposure time of aumolertinib relative to gefitinib, 464 versus 254 days, respectively.

Blood CPK (skeletal muscle isoform) increase was relatively common with aumolertinib (34% of patients), but this event was predominately mild to moderate in severity. Only 7% of patients had a blood CPK increase of grade ≥ 3 severity. No patient had a CPK increase associated with rhabdomyolysis, and CPK increase did not manifest as a serious adverse event. Thus, CPK increase was a laboratory finding only rarely associated with mild muscle pain. Although CPK increase led to temporary interruption of aumolertinib in 11 patients (5.1%) and to dose reduction in six patients (2.8%), no patients discontinued aumolertinib because of CPK increase.

Importantly, this study was conducted exclusively in China with ethnic Chinese patients. The extrapolation of these study results to patients of other geographic regions is supported by the globally consistent approach to evaluation and treatment of patients with *EGFR*-mutant NSCLC evident in the high similarity of the National Comprehensive Cancer Network, European Society for Medical Oncology, and The Pan-Asian Guidelines Adaptation.[11] Furthermore, multiple studies suggest similar outcomes for this patient population when controlling for widely recognized baseline characteristics such as ECOG PS, *EGFR* mutation type, and sex. Analyses of the outcomes of patients with CNS metastases and CNS progressive disease will be reported in a separate publication. Similarly, given the low maturity of OS, these data along with crossover analyses will be reported in a subsequent publication.

In conclusion, aumolertinib is a well-tolerated third-generation EGFR TKI that is approved in China for the second-line treatment of advanced EGFR T790M mutation-positive NSCLC patients in 2020 and recently for the first-line treatment of locally advanced or metastatic NSCLC harboring TKI sensitizing mutations. The results presented suggest that the use of aumolertinib may be warranted as

TABLE 3. Summary of TEAEs (≥ 10% of patients)

	TEAEs (any severity)		
Event	**Aumolertinib (n = 214), No. (%)**	**Gefitinib (n = 215), No. (%)**	**Total (N = 429), No. (%)**
No. of patients with at least 1 TEAE	211 (98.6)	213 (99.1)	424 (98.8)
System organ class/preferred term			
Investigations	176 (82.2)	183 (85.1)	359 (83.7)
ALT increase	63 (29.4)	120 (55.8)	183 (42.7)
AST increase	64 (29.9)	116 (54.0)	180 (42.0)
Weight decrease	14 (6.5)	35 (16.3)	49 (11.4)
Blood bilirubin increase	18 (8.4)	34 (15.8)	52 (12.1)
WBC count decrease	51 (23.8)	30 (14.0)	81 (18.9)
Gamma-glutamyl transferase increase	19 (8.9)	30 (14.0)	49 (11.4)
Neutrophil count decrease	29 (13.6)	21 (9.8)	50 (11.7)
Blood creatine phosphokinase increase	76 (35.5)	20 (9.3)	96 (22.4)
QT prolongation	23 (10.7)	19 (8.8)	42 (9.8)
Platelet count decrease	47 (22.0)	17 (7.9)	64 (14.9)
Blood lactate dehydrogenase increase	26 (12.1)	14 (6.5)	40 (9.3)
	TEAEs (any severity)		
System Organ Class/Preferred Term	**Aumolertinib (n = 214), No. (%)**	**Gefitinib (n = 215), No. (%)**	**Total (N = 429), No. (%)**
Skin and subcutaneous tissue disorders	76 (35.5)	129 (60.0)	205 (47.8)
Rash	50 (23.4)	89 (41.4)	139 (32.4)
Pruritus	14 (6.5)	26 (12.1)	40 (9.3)
GI disorders	104 (48.6)	120 (55.8)	224 (52.2)
Diarrhea	35 (16.4)	77 (35.8)	112 (26.1)
Mouth ulceration	22 (10.3)	21 (9.8)	43 (10.0)
Nausea	23 (10.7)	20 (9.3)	43 (10.0)
Vomiting	26 (12.1)	11 (5.1)	37 (8.6)
Infections and infestations	107 (50.0)	95 (44.2)	202 (47.1)
Urinary tract infection	46 (21.5)	37 (17.2)	83 (19.3)
Upper respiratory tract infection	41 (19.2)	26 (12.1)	67 (15.6)
Pneumonia	15 (7.0)	12 (5.6)	27 (6.3)
Metabolism and nutrition disorders	91 (42.5)	88 (40.9)	179 (41.7)
Hypokalaemia	19 (8.9)	33 (15.3)	52 (12.1)
Decreased appetite	16 (7.5)	28 (13.0)	44 (10.3)
Hypoalbuminemia	15 (7.0)	23 (10.7)	38 (8.9)
Hepatobiliary disorders			
Hepatic function abnormal	9 (4.2)	26 (12.1)	35 (8.2)
Nervous system disorders	39 (18.2)	33 (15.3)	72 (16.8)
Headache	22 (10.3)	9 (4.2)	31 (7.2)
Blood and lymphatic system disorders	46 (21.5)	21 (9.8)	67 (15.6)
Anemia	43 (20.1)	21 (9.8)	64 (14.9)
Vascular disorders	31 (14.5)	17 (7.9)	48 (11.2)
Hypertension	15 (7.0)	12 (5.6)	27 (6.3)

NOTE. Data cutoff date: January 15, 2021. The SOCs and PTs of AEs were coded using MedDRA, version 23.0. AEs were graded according to CTCAE, version 4.03. A patient with two or more AEs in the same SOC or with the same PT was counted only once for that SOC/PT. A patient might have experienced AEs in more than one SOC or with more than one PT.

Abbreviations: AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term; QT, time interval between the start of the Q wave and end of the T wave in the electrical cycle of the heart; SOC, system organ class; TEAE, treatment-emergent adverse event.

the first-line treatment for *EGFR*-mutant NSCLC, particularly given the encouraging rates of *EGFR* wild-type-mediated toxicity. Additional studies of aumolertinib are ongoing in the adjuvant setting (ClinicalTrials.gov identifier: NCT04687241) and in the metastatic setting in combination with chemotherapy (ClinicalTrials.gov identifier: NCT04923906).

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DATA SHARING STATEMENT

Upon request, and subject to certain criteria, conditions, and exceptions, Hansoh will provide access to individual deidentified participant data from Hansoh-sponsored interventional clinical studies conducted for medicines for indications that have been approved. Data requests may be submitted to medical@hspharm.com.

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REFERENCES

1. Mok TS, Wu YL, Ahn MJ, et al: Osimertinib or platinum-pemetrexed in EGFR T790M-positive lung cancer. N Engl J Med 376:629-640, 2017
2. Goss G, Tsai CM, Shepherd FA, et al: Osimertinib for pretreated EGFR Thr790Met-positive advanced non-small-cell lung cancer (AURA2): A multicentre, open-label, single-arm, phase 2 study. Lancet Oncol 17:1643-1652, 2016
3. Soria JC, Ohe Y, Vansteenkiste J, et al: Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. N Engl J Med 378:113-125, 2018
4. Ramalingam SS, Vansteenkiste J, Planchard D, et al: Overall survival with osimertinib in untreated, EGFR-mutated advanced NSCLC. N Engl J Med 382:41-50, 2020
5. Bao R, Zhang F, Tong Z, et al: Discovery of a third-generation EGFR inhibitor, which is highly selective and potent against both resistant and activating EGFR mutations for NSCLC therapy. Cancer Res 76, 2016 (suppl; abstr 3036)
6. Lu S, Wang Q, Zhang G, et al: Efficacy of aumolertinib (HS-10296) in patients with advanced EGFR T790M+ NSCLC: Updated Post-National Medical Products Administration Approval results from the APOLLO registrational trial. J Thorac Oncol 17:411-422, 2022
7. Yang JCH, Camidge DR, Yang CT, et al: Safety, efficacy, and pharmacokinetics of almonertinib (HS-10296) in pretreated patients with EGFR-mutated advanced NSCLC: A multicenter, open-label, phase 1 trial. J Thorac Oncol 15:1907-1918, 2020
8. Lin DY, Wei LJ, Ying Z: Checking the Cox model with cumulative sums of martingale-based residuals. Biometrika 80:557-572, 1993
9. Nagasaka M, Zhu VW, Lim SM, et al: Beyond osimertinib: The development of third-generation EGFR tyrosine kinase inhibitors for advanced EGFR+ NSCLC. J Thorac Oncol 16:740-763, 2021
10. Wu YL, Tsuboi M, He J, et al: Osimertinib in resected EGFR-mutated non-small-cell lung cancer. N Engl J Med 383:1711-1723, 2020
11. Wu YL, Planchard D, Lu S, et al: Pan-Asian adapted clinical practice guidelines for the management of patients with metastatic non-small-cell lung cancer: A CSCO-ESMO initiative endorsed by JSMO, KSMO, MOS, SSO and TOS. Ann Oncol 30:171-210, 2019

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

AENEAS: A Randomized Phase III Trial of Aumolertinib Versus Gefitinib as First-Line Therapy for Locally Advanced or Metastatic Non–Small-Cell Lung Cancer With *EGFR* Exon 19 Deletion or L858R Mutations

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