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Real-world use of and clinical outcomes with dacomitinib as first-line therapy in Asian patients with *EGFR* mutation–positive locally advanced or metastatic non-small cell lung cancer: Final analysis of the ARIA study

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ABSTRACT

Background: Dacomitinib, a second-generation, irreversible tyrosine kinase inhibitor of epidermal growth factor receptor (EGFR), showed statistically significant progression-free survival improvement over gefitinib in patients with treatment-naive *EGFR* mutation–positive advanced non-small cell lung cancer (NSCLC) in the phase 3 ARCHER 1050 study (NCT01774721). We report results from the final analysis of ARIA (NCT04609319), a noninterventional study of dacomitinib's real-world utilization and associated clinical outcomes in Asian patients with *EGFR* mutation–positive advanced NSCLC.

Methods: This longitudinal, multicenter cohort study collected prospective and retrospective data from patients with *EGFR* mutation–positive locally advanced or metastatic NSCLC who were treated with first-line dacomitinib. Study objectives were to describe clinical and disease characteristics, therapeutic patterns of dacomitinib use, and clinical outcomes.

Results: 299 patients located in China (n = 261), India (n = 24), and Malaysia (n = 14) were enrolled and included in the analysis. Starting dose was 30 mg once daily in 159 (53.2 %) patients, 45 mg once daily in 138 (46.2 %), and other doses in 2 (0.7 %). As of May 28, 2024, 95 patients (31.8 %) had dose reductions, 47 (15.7 %) had dose increases, 41 (13.7 %) had dose interruptions, and 223 (74.6 %) had permanently discontinued dacomitinib. Median duration of treatment was 17.2 months (IQR, 19.2). Median time to treatment failure was 17.0 months (95 % CI, 14.5–19.8). Median progression-free survival was 20.1 months (95 % CI, 17.4–22.4). 148 (49.5 %) patients had treatment-related adverse events; most common were rash (n = 93 [31.1 %]), diarrhea (n = 81 [27.1 %]), and paronychia (n = 57 [19.1 %]).

Conclusions: To our knowledge, ARIA is the largest real-world study of dacomitinib's efficacy and safety. Final analysis of this study showed substantial clinical efficacy of dacomitinib and revealed treatment patterns, such as starting dose, in the real world. Safety data were consistent with dacomitinib's known safety profile. These results support first-line dacomitinib use in Asian patients with *EGFR* mutation–positive advanced NSCLC.
ClinicalTrials.gov NCT04609319.

1. Introduction

Non-small cell lung cancer (NSCLC) accounts for approximately 85 % of all lung cancer cases, of which adenocarcinoma, squamous cell carcinoma, and large cell carcinoma are the most common subtypes [1]. Epidermal growth factor receptor *(EGFR)* is an important driver oncogene in NSCLC, with the exon 19 deletion and exon 21 L858R substitution mutations being the most common activating mutations [2,3]. Based on a recent systematic review and *meta*-analysis that included 456 studies and 115,815 patients with NSCLC, the overall pooled prevalence of *EGFR* mutations was 32.3 % (95 % CI, 30.9 %–33.7 %) [4]. The prevalence of *EGFR* mutations in patients with NSCLC was higher in Asia (51.4 %) than in North and South America (24.4 %) and Europe (14.1 %) [4,5]. Recent clinical guidelines across Asia, the United States, and Europe recommend that all patients with NSCLC undergo *EGFR* mutation testing before treatment decisions are made [6,7].

The identification of specific *EGFR*-activating mutations led to the development of targeted EGFR–tyrosine kinase inhibitors (TKIs). This marked a revolutionary milestone in the management of NSCLC and signaled the dawn of precision medicine use in lung cancer. EGFR-TKI therapy is currently regarded as a standard-of-care first-line treatment for *EGFR* mutation–positive NSCLC [8,9]. Current guidelines recommend using EGFR-TKIs alone or in combination with vascular endothelial growth factor (VEGF) inhibitors or VEGF receptor inhibitors such as bevacizumab or ramucirumab. First-, second-, and third-generation EGFR-TKIs are all approved to treat *EGFR* mutation–positive locally advanced or metastatic NSCLC [7]. First-generation EGFR-TKIs (e.g., gefitinib and erlotinib) showed improvements in progression-free survival (PFS) over platinum-based doublet chemotherapy by inhibiting EGFR through competitive binding with ATP at the ATP-binding site of EGFR [9]. Second-generation EGFR-TKIs (afatinib and dacomitinib) and the third-generation EGFR-TKI osimertinib have shown significant improvements in PFS over first-generation EGFR-TKIs [10–12].

Dacomitinib, a second-generation irreversible EGFR-TKI, offers high potency due to its irreversible inhibition of EGFR and inhibition of the entire ErbB family of tyrosine kinases (EGFR, ERBB2, ERBB3, ERBB4) [13,14]. Dacomitinib was approved by the US Food and Drug Administration in 2018 and by China's National Medical Products Administration in 2019 for the first-line treatment of patients with locally advanced or metastatic NSCLC with *EGFR* exon 19 deletion or exon 21 L858R substitution mutations [15,16]. Between January 2019 and July 2020, dacomitinib received approval in several other countries and regions in Europe and Asia [17–22]. In the phase 3 ARCHER 1050 study (NCT01774721), dacomitinib improved median PFS compared with gefitinib according to blinded independent central review (14.7 vs 9.2 months; hazard ratio [HR], 0.59; 95 % CI, 0.47–0.74; $P < 0.0001$) and improved median overall survival (OS; 34.1 vs 26.8 months; HR, 0.76; 95 % CI, 0.582–0.993; $P = 0.0438$) in patients with treatment-naive *EGFR* mutation–positive locally advanced or metastatic NSCLC [11,23]. In Asian patients enrolled in ARCHER 1050, dacomitinib was associated with significantly longer median PFS (16.5 vs 9.3 months; HR, 0.509; 95 % CI, 0.391–0.662; $P < 0.0001$) and median OS (37.7 vs 29.1 months; HR, 0.759; 95 % CI, 0.578–0.996) compared with gefitinib [24].

Currently, information is lacking on the real-world utilization of dacomitinib as first-line therapy and its associated clinical outcomes in Asian patients with *EGFR* mutation–positive locally advanced or metastatic NSCLC. The overall objectives of the ARIA study (NCT04609319) were to understand and describe the clinical and disease characteristics, therapeutic patterns of dacomitinib use, and clinical outcomes in this patient population treated with first-line dacomitinib. The findings from this study represent an important step toward addressing the existing knowledge gaps (i.e., real-world dosing, therapeutic patterns, and clinical outcomes) regarding dacomitinib therapy.

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2. Patients and methods

2.1. Study design

ARIA is a longitudinal, multicenter cohort study with prospective, retrospective, and mixed (a combination of prospective and retrospective) clinical and demographic data collected from eligible patients located in 3 Asian countries: China, India, and Malaysia. This is an observational real-world study; thus, no investigative drug or intervention was administered to patients. Physicians provided treatment with dacomitinib to eligible patients based on their routine practices and in the best interests of the patients under their care. Data were collected from patients from the date of advanced NSCLC diagnosis to the date of death, loss to follow-up, withdrawal of consent, or end of study, whichever occurred first. Here, we present the results of the final analysis of the data collected in ARIA through the cutoff date of May 28, 2024.

2.2. Patient population and selection

Patients were selected from 14 tertiary cancer-treating hospitals: 9 in China, 2 in India, and 3 in Malaysia. Patients were eligible for inclusion in this study if they were aged ≥18 years, had histologically confirmed *EGFR* mutation–positive locally advanced or metastatic NSCLC, and were treated with dacomitinib as first-line therapy for advanced NSCLC after confirmation of *EGFR* mutation status. *EGFR* mutation–positive was defined as the presence of any *EGFR*-activating mutation (exon 19 deletion or exon 21 L858R substitution) or other uncommon *EGFR* mutations prior to dacomitinib treatment. Patients must have had ≥1 follow-up visit after dacomitinib initiation and no enrollment in any interventional clinical study. Patients enrolled in China must have received dacomitinib after the marketing authorization date in China; patients enrolled in India and Malaysia must have received dacomitinib after the initiation of the compassionate use program in these countries. From the last patient's first visit, the study mandated 20 months of follow-up to ensure a minimum follow-up of 20 months for all patients in the study.

2.3. Data collection

Study data were collected both prospectively and retrospectively. Unstructured prospective and/or retrospective data from patients' hospital medical records were abstracted manually by trained research personnel and subsequently entered into a study-specific electronic data capture system via a standardized electronic case report form.

2.4. Study objectives

The primary objectives were to describe the demographics and clinical characteristics of patients; the starting dose of dacomitinib as first-line therapy; any dose modification(s); the related timing and reason(s) for dose modification, interruption, or discontinuation; the duration of treatment; and the real-world time to treatment failure (TTF). The secondary objectives were to describe the real-world PFS and characterize adverse events (AEs). In addition, real-world TTF, real-world PFS, real-world OS, AEs, starting dose, and dose modification of dacomitinib were described in 2 subgroups of patients with a common *EGFR* mutation (i.e., exon 19 deletion or exon 21 L858R substitution) enrolled in China. The exploratory objectives were to describe real-world OS, prevalence of *EGFR* T790M mutation emergence at disease progression, and subsequent treatments and associated clinical outcomes after permanent discontinuation of dacomitinib.

2.5. Statistical analysis

Results were summarized using descriptive statistics with no statistical hypotheses; categorical variables were summarized using frequencies (counts) and percentages, and continuous variables were summarized using means, standard deviations, medians, and interquartile ranges. Time-to-event data such as real-world OS, real-world PFS, and real-world TTF were analyzed using the Kaplan-Meier method; medians and their 2-sided 95 % CIs were estimated. The CIs for the median were calculated according to the Brookmeyer and Crowley method.

2.6. Ethical considerations

For patients with prospective and mixed data, written informed consent was obtained from the patients or their representatives. For some patients with retrospective data, an informed consent waiver was obtained from the institutional review board or independent ethics committee. All other patients with retrospective data were required to sign informed consent forms.

3. Results

3.1. Patient population

Initially, 307 patients were enrolled in the study, but 8 were excluded from the analysis: 5 did not initiate dacomitinib as first-line treatment, 2 did not follow up after dacomitinib initiation, and 1 was enrolled twice (Fig. S1). Of the 299 patients who were included in the analysis, 261 were enrolled in China, 24 were enrolled in India, and 14 were enrolled in Malaysia. In the total population, the median age was 59.0 years (interquartile range [IQR], 14.0), 161 (53.8 %) patients were female, 165 (55.2 %) were never smokers, 170 (56.9 %) had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1, 6 (2.0 %) had an ECOG PS of 2, and 3 (1.0 %) had an ECOG PS of 3 (Table 1). Most patients were diagnosed with stage IV NSCLC (n = 279 [93.3 %]), and the most common histopathologic subtype was adenocarcinoma (n = 291 [97.3 %]). At baseline, 54 (18.1 %) patients had central nervous system metastases, 192 (64.2 %) had an exon 21 L858R substitution mutation, and 91 (30.4 %) had an exon 19 deletion mutation.

3.2. Dacomitinib use and treatment patterns

The starting dose of dacomitinib was 30 mg once daily (QD) in 159 (53.2 %) patients, 45 mg QD in 138 (46.2 %), and other doses in 2 (0.7 %). The 2 patients who received other doses received either 15 mg QD or 30 mg twice daily. At the time of data cutoff, 95 (31.8 %) patients had dose reductions, 47 (15.7 %) had dose increases, and 41 (13.7 %) had dose interruptions (Table 2). The most common reasons for the first dose reduction were rash or dermatitis (14.7 %), diarrhea (7.4 %), and mouth ulceration (7.0 %). In patients with a starting dose of 30 mg QD, 23 (14.5 %) had dose reductions and 23 (14.5 %) had dose increases. Among patients with a starting dose of 45 mg QD, 71 (51.4 %) had dose reductions and 23 (16.7 %) had dose increases. Dose increases occurred only after a patient's first dose reduction, so that their dose did not exceed 45 mg QD. Overall, 223 (74.6 %) patients had permanently discontinued first-line dacomitinib (Table S1). The most common reasons for permanent discontinuation were disease progression (45.2 %), death (12.7 %), and AEs (2.3 %).

3.3. Efficacy of dacomitinib

Median duration of first-line dacomitinib treatment was 17.2 months (IQR, 19.2) in all patients and 17.8 months (IQR, 19.5) in patients enrolled in China. Due to small sample sizes, the efficacy results from patients enrolled in India and Malaysia were not reported separately, as they were for patients enrolled in China. Median real-world TTF with dacomitinib was 17.0 months (95 % CI, 14.5–19.8) in all patients

Table 1
Demographics and baseline characteristics of patients.

	Dacomitinib starting dose			Total (N=299)
	30 mg QD (n=159)	45 mg QD (n=138)	Other[a] (n=2)	
Age, mean (SD), years	61.5 (9.8)	57.6 (9.3)	70.5 (12.0)	59.8 (9.8)
Age, median (IQR), years	61.5 (14.0)	58.0 (12.0)	70.5 (17.0)	59.0 (14.0)
Sex, n (%)				
Female	101 (63.5)	59 (42.8)	1 (50.0)	161 (53.8)
Male	58 (36.5)	79 (57.2)	1 (50.0)	138 (46.2)
Ethnicity, n (%)				
Chinese	145 (91.2)	125 (90.6)	2 (100)	272 (91.0)
Indian	12 (7.5)	13 (9.4)	0	25 (8.4)
Malay	1 (0.6)	0	0	1 (0.3)
Unknown	1 (0.6)	0	0	1 (0.3)
Body mass index, mean (SD), kg/m^2	22.6 (3.6)	23.1 (3.4)	26.4 (NA)	22.9 (3.5)
Smoking status, n (%)				
Never	93 (58.5)	71 (51.4)	1 (50.0)	165 (55.2)
Former	24 (15.1)	41 (29.7)	1 (50.0)	66 (22.1)
Current	2 (1.3)	11 (8.0)	0	13 (4.3)
ECOG performance status, n (%)				
0	20 (12.6)	11 (8.0)	0	31 (10.4)
1	59 (37.1)	80 (58.0)	0	139 (46.5)
2	0	5 (3.6)	1 (50.0)	6 (2.0)
3	2 (1.3)	1 (0.7)	0	3 (1.0)
Unknown	73 (45.9)	40 (29.0)	1 (50.0)	114 (38.1)
Missing	5 (3.1)	1 (0.7)	0	6 (2.0)
NSCLC stage, n (%)				
IIIB	6 (3.8)	8 (5.8)	2 (100)	16 (5.4)
IIIC	0	4 (2.9)	0	4 (1.3)
IVA	56 (35.2)	46 (33.3)	0	102 (34.1)
IVB	97 (61.0)	80 (58.0)	0	177 (59.2)
NSCLC histopathologic subtype, n (%)				
Adenocarcinoma	157 (98.7)	133 (96.4)	1 (50.0)	291 (97.3)
Squamous cell carcinoma	2 (1.3)	3 (2.2)	1 (50.0)	6 (2.0)
Large cell carcinoma	0	1 (0.7)	0	1 (0.3)
Other	0	1 (0.7)	0	1 (0.3)
Type of first *EGFR* mutation, n (%)[b]				
Exon 21 L858R substitution	102 (64.2)	89 (64.5)	1 (50.0)	192 (64.2)
Exon 19 deletion	54 (34.0)	36 (26.1)	1 (50.0)	91 (30.4)
T790M mutation	0	2 (1.4)	0	2 (0.7)
Other	22 (13.8)	37 (26.8)	0	59 (19.7)
Site of metastasis, n (%)[c]				
Bone	82 (51.6)	70 (50.7)	0	152 (50.8)
CNS	25 (15.7)	29 (21.0)	0	54 (18.1)
Liver	14 (8.8)	15 (10.9)	0	29 (9.7)
Adrenal gland	13 (8.2)	12 (8.7)	0	25 (8.4)
Other	95 (59.7)	87 (63.0)	0	182 (60.9)

CNS, central nervous system; **ECOG**, Eastern Cooperative Oncology Group; **EGFR**, epidermal growth factor receptor; **IQR**, interquartile range; **NA**, not available; **NSCLC**, non-small cell lung cancer; **QD**, once daily.
[a] Refers to 15 mg QD or 30 mg twice daily. Starting dose and treatment patterns were based on the individual physician's routine practices.
[b] A patient may have had > 1 mutation.
[c] A patient may have had > 1 site of metastasis.

Table 2
Dacomitinib dose modifications and reasons for dose reduction.

	Dacomitinib starting dose			**Total (N=299)**
	30 mg QD (n=159)	**45 mg QD (n=138)**	**Other[a] (n=2)**	
Patients with any dose reduction, n (%)	23 (14.5)	71 (51.4)	1 (50.0)	95 (31.8)
Patients with any dose increase, n (%)	23 (14.5)	23 (16.7)	1 (50.0)	47 (15.7)
Patients with any dose interruption, n (%)	17 (10.7)	23 (16.7)	1 (50.0)	41 (13.7)
Patients with first dose modification, n (%)[b]	31 (19.5)	71 (51.4)	1 (50.0)	103 (34.4)
With first dose reduction	18 (11.3)	71 (51.4)	0	89 (29.8)
Reason for first dose reduction[c]				
Rash or dermatitis (including dermatitis acneiform, rash, and maculopapular rash)	8 (5.0)	36 (26.1)	0	44 (14.7)
Diarrhea	3 (1.9)	19 (13.8)	0	22 (7.4)
Mouth ulceration	2 (1.3)	19 (13.8)	0	21 (7.0)
Paronychia	5 (3.1)	15 (10.9)	0	20 (6.7)
Nausea or vomiting	1 (0.6)	1 (0.7)	0	2 (0.7)
Decreased appetite	1 (0.6)	0	0	1 (0.3)
Interstitial lung disease	0	1 (0.7)	0	1 (0.3)
Electrolyte abnormalities	0	1 (0.7)	0	1 (0.3)
With first dose increase	13 (8.2)	0	1 (50.0)	14 (4.7)
Patients with second dose modification, n (%)	15 (9.4)	30 (21.7)	1 (50.0)	46 (15.4)
With second dose reduction (from modified dose)	5 (3.1)	7 (5.1)	1 (50.0)	13 (4.3)
With second dose increase (from modified dose)	10 (6.3)	23 (16.7)	0	33 (11.0)

QD, once daily.
[a] Refers to 15 mg QD or 30 mg twice daily.
[b] Dose modification refers to either dose reduction or dose increase.
[c] A patient may have had > 1 reason for dose reduction.

(Fig. 1A) and 17.6 months (95 % CI, 15.3–20.6) in patients enrolled in China (Fig. 1B). In the total population with a median duration of follow-up of 20.1 months (IQR, 32.7), PFS events occurred in 183 (61.2 %) patients and the median real-world PFS in all patients was 20.1 months (95 % CI, 17.4–22.4) (Fig. 2A). The median real-world PFS was 18.3 months (95 % CI, 15.5–26.5) in patients with a starting dose of 30 mg QD and 21.0 months (95 % CI, 17.4–24.2) in patients with a starting dose of 45 mg QD. In patients enrolled in China with a median duration of follow-up of 20.9 months (IQR, 37.5), median real-world PFS was 20.9 months (95 % CI, 18.1–24.6), with PFS events occurring in 152 (58.2 %) patients (Fig. 2B). In patients with exon 21 L858R substitution mutations (n = 192), median real-world PFS was 19.3 months (95 % CI, 17.3–22.5), with PFS events occurring in 59.9 % of patients (Fig. 2C). In patients with exon 19 deletion mutations (n = 91), median real-world PFS was 21.0 months (95 % CI, 15.8–29.9), with PFS events occurring in 58.2 % of patients (Fig. 2D). At first disease progression, *EGFR* T790M mutation was found to be the most common resistance mutation and was reported in 26 of 50 (52.0 %) patients who had a mutation test (Fig. S2).

At the time of this final analysis, real-world OS data were immature. OS events occurred in 64 (21.4 %) patients with median real-world OS not reached (NR) (95 % CI, NR-NR) (Fig. S3). The estimated 12-, 24-, and 36-month OS rates were 95.3 % (95 % CI, 92.9 %-97.8 %), 82.2 % (95 % CI, 77.5 %-86.9 %), and 72.5 % (95 % CI, 66.2 %-78.8 %), respectively.

3.4. Safety of dacomitinib

Overall, treatment-related adverse events (TRAEs) occurred in 148 (49.5 %) patients treated with first-line dacomitinib (Table 3). Among patients with TRAEs, 76 (25.4 %) had dose reductions, 17 (5.7 %) had

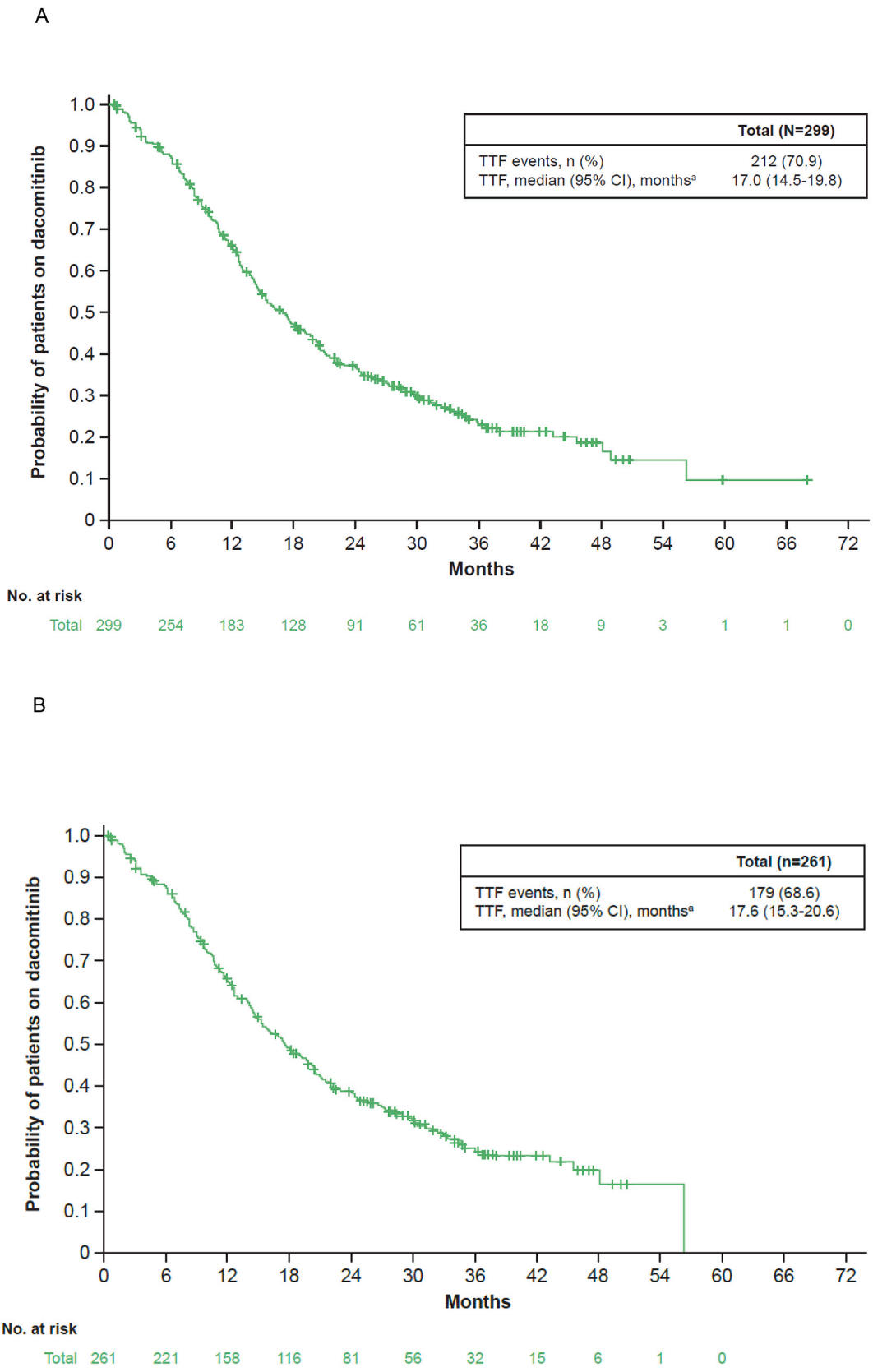

Fig. 1. Real-world TTF. Kaplan-Meier curve of real-world TTF in (A) all patients and (B) patients enrolled in China. The number of TTF events and median real-world TTF in each group are shown in the table inset. **TTF**, time to treatment failure. [a]Calculated using the Brookmeyer and Crowley method to obtain 95% CI.

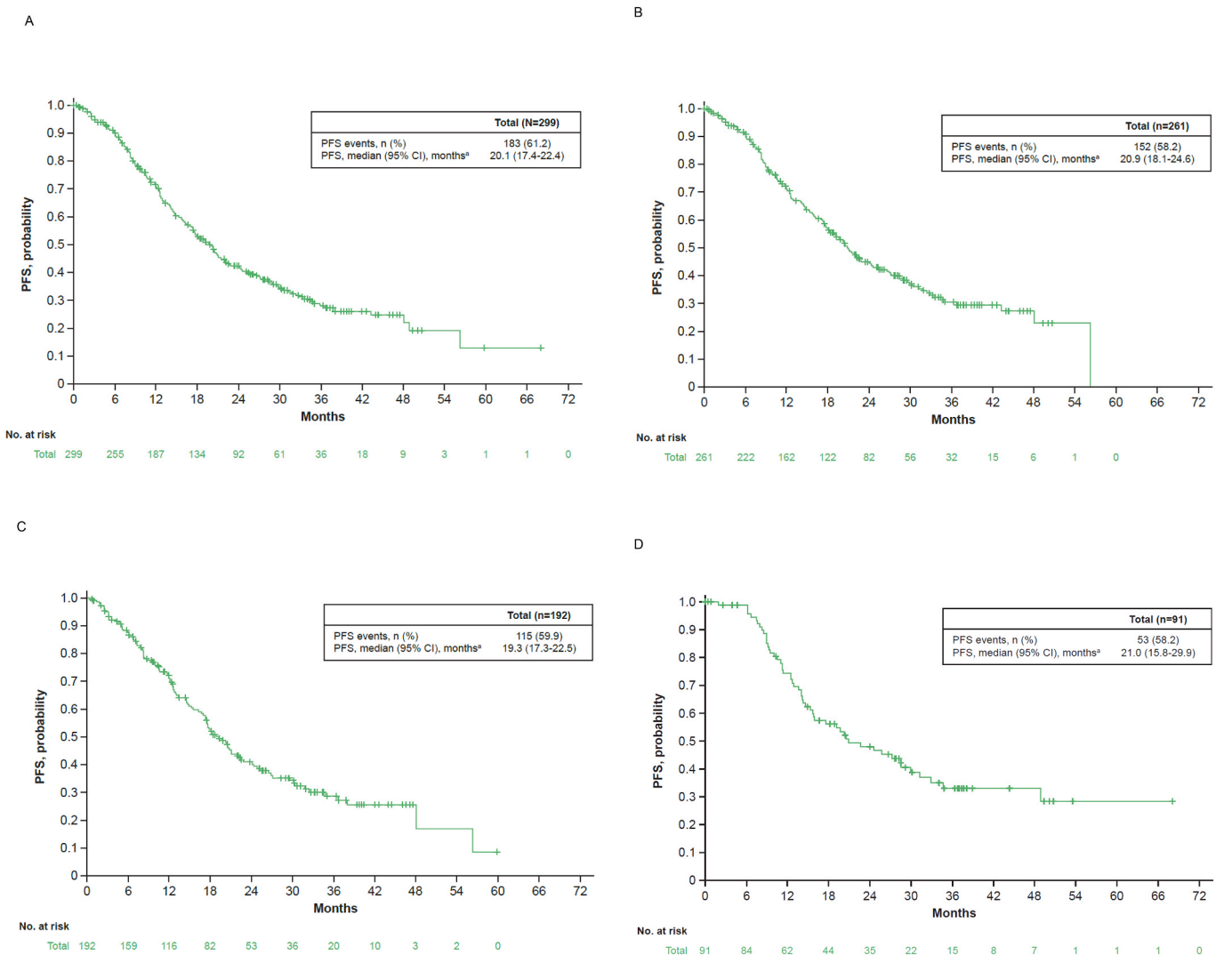

Fig. 2. Real-world PFS. Kaplan-Meier curve of real-world PFS in (A) all patients, (B) patients enrolled in China, (C) patients with exon 21 L858R substitution mutations, and (D) patients with exon 19 deletion mutations. The number of PFS events and median real-world PFS in each group are shown in the table inset. **NR**, not reached; **PFS**, progression-free survival. [a]Calculated using the Brookmeyer and Crowley method to obtain 95% CI.

dose interruptions, and 7 (2.3 %) permanently discontinued dacomitinib. The most common TRAEs were rash (31.1 %), diarrhea (27.1 %), and paronychia (19.1 %).

4. Discussion

To our knowledge, ARIA is the largest real-world study of dacomitinib as first-line treatment in Asian patients with *EGFR* mutation–-positive locally advanced or metastatic NSCLC. ARIA is a multicenter observational study using prospective and retrospective real-world data from patients in 3 Asian countries. The baseline demographic, clinical, and disease characteristics of patients in ARIA were comparable to those of patients with *EGFR* mutation–positive NSCLC from China, India, and Malaysia in prior clinical and real-world studies [25–27]. Additionally, the median age of patients in ARIA (59 years) was similar to the median age of patients in the dacomitinib-treated group (n = 227) in the pivotal ARCHER 1050 study (62 years [11]).

According to the China prescribing information, the recommended starting dose of dacomitinib is 45 mg QD, and treatment should be continued until disease progression or unacceptable toxicity [16]. Reduced doses of dacomitinib can be used to manage treatment-related toxicity and maintain efficacy. In ARCHER 1050, all 227 patients received dacomitinib at a starting dose of 45 mg QD and among them, 150 (66.1 %) received a dose reduction [11]. In our study, in the real-world setting, more than half of the patients (n = 159 [53.2 %]) started dacomitinib at a dose of 30 mg QD, and 138 (46.2 %) patients started at a dose of 45 mg QD. In another real-world study in 99 patients from 7 hospitals in China, the starting dose of dacomitinib was 30 mg QD in 82.8 % of patients and 45 mg QD in 17.2 % of patients [28]. The use of a lower starting dose of dacomitinib in real-world studies in China may be attributed to a pragmatic approach to potentially avoid severe toxicity. In addition, the patient population in real-world studies tends to be different from the patient population enrolled in clinical trials, as patients with poor PS and multiple comorbidities typically are not enrolled in most clinical trials.

Multiple studies have shown that AEs related to dacomitinib are managed by dose modifications, which allow efficacy to be retained and quality of life to be maintained [29–31]. In this real-world study, 103 (34.4 %) patients had dose modifications, with 95 (31.8 %) requiring dose reductions and 47 (15.7 %) requiring dose increases. Some patients had both dose reductions and dose increases during their treatment with dacomitinib. Patients with a starting dose of 45 mg QD had a greater frequency of dose reductions (51.4 %) than patients with a starting dose of 30 mg QD (14.5 %). In the aforementioned real-world study in 99

Table 3
Safety outcomes in patients receiving first-line dacomitinib.

	Dacomitinib starting dose			Total (N=299)
	30 mg QD (n=159)	45 mg QD (n=138)	Other[a] (n=2)	
Patients with any TRAEs, n (%)	68 (42.8)	79 (57.2)	1 (50.0)	148 (49.5)
Action taken for dacomitinib	68 (42.8)	79 (57.2)	1 (50.0)	148 (49.5)
Dose reduction	18 (11.3)	57 (41.3)	1 (50.0)	76 (25.4)
Dose interruption	6 (3.8)	10 (7.2)	1 (50.0)	17 (5.7)
Permanent discontinuation	4 (2.5)	3 (2.2)	0	7 (2.3)
TRAEs occurring in ≥1 % of patients				
Rash	41 (25.8)	52 (37.7)	0	93 (31.1)
Diarrhea	44 (27.7)	36 (26.1)	1 (50.0)	81 (27.1)
Paronychia	26 (16.4)	30 (21.7)	1 (50.0)	57 (19.1)
Mouth ulceration	14 (8.8)	26 (18.8)	0	40 (13.4)
Stomatitis	9 (5.7)	3 (2.2)	0	12 (4.0)
Pruritus	5 (3.1)	1 (0.7)	0	6 (2.0)
Dry skin	3 (1.9)	2 (1.4)	1 (50.0)	6 (2.0)
Dermatitis acneiform	4 (2.5)	0	0	4 (1.3)
Palmar-plantar erythrodysesthesia syndrome	4 (2.5)	0	0	4 (1.3)
Conjunctivitis	2 (1.3)	1 (0.7)	0	3 (1.0)
Decreased appetite	3 (1.9)	0	0	3 (1.0)
Dry eye	1 (0.6)	1 (0.7)	1 (50.0)	3 (1.0)
Skin exfoliation	1 (0.6)	2 (1.4)	0	3 (1.0)

QD, once daily; **TRAE**, treatment-related adverse event.
[a] Refers to 15 mg QD or 30 mg twice daily.

Chinese patients, 16.2 % had a dose modification while receiving dacomitinib [28]. The Asian subgroup analysis of ARCHER 1050 reported 67.6 % of patients with dose reductions [24]. Overall, the rates of dose modification varied in the aforementioned studies, likely due to the differences in administered dose levels, limitations of data collection in real-world studies, and variation in physicians' experience and knowledge of managing adverse reactions to dacomitinib in real-world usage compared with clinical trials.

In the total population of ARIA, the median real-world PFS was 20.1 months (95 % CI, 17.4–22.4), which is slightly longer than the median PFS in the Asian subgroup of ARCHER 1050 (16.5 months; 95 % CI, 12.9–18.4) [24]. This may be due to differences in clinical management during the different time periods that the two studies were conducted, or varying starting doses, more flexible dose modifications, less frequent or less stringent progression assessments, and ethnic or regional variations in the patient population in ARIA.

The median real-world PFS was numerically similar between dosing groups in ARIA: 18.3 months in patients with a starting dose of 30 mg and 21.0 months in patients with a starting dose of 45 mg. However, this real-world observational study was not designed to compare the results of these 2 starting doses, so conclusions cannot be made about the optimal starting dose based on the PFS results. In the prospective phase 2 ATORG-003 study (NCT04027647), which used a 30 mg dacomitinib starting dose, the median PFS was 16.1 months (95 % CI, 12.1–19.2) and the 12-month PFS rate was 60 % [32]. While trials directly comparing the efficacy of different EGFR-TKIs have not been performed, the median real-world PFS results with dacomitinib observed in the present study show the robust efficacy of this second-generation EGFR-TKI in a real-world setting.

The subset of patients with exon 21 L858R substitution mutations is commonly thought to be harder to treat than the subset with exon 19 deletion mutations, based on better response and survival rates in the latter group [33–36]. In ARCHER 1050, median PFS according to blinded independent central review was 12.3 and 16.5 months in patients with exon 21 L858R substitution mutations and exon 19 deletion mutations, respectively. At the final analysis of ARIA, median real-world PFS was 19.3 months in patients with exon 21 L858R substitution mutations and 21.0 months in those with exon 19 deletion mutations, indicating that dacomitinib is effective in patients with either mutation in the real-world setting. In ARCHER 1050, dacomitinib showed an OS benefit compared with gefitinib in patients with exon 21 L858R substitution mutations: median OS, 32.5 months (95 % CI, 25.5–39.5) versus 23.2 months (95 % CI, 19.6–28.9); HR, 0.665 (95 % CI, 0.470–0.941) [37]. Although OS data were immature in ARIA, the estimated probability of being alive at 36 months was 72.5 % (95 % CI, 66.2 %-78.8 %).

In addition, ARIA analyzed the mutation profile and found *EGFR* T790M to be the most common mutation at disease progression, present in 26 of the 50 (52.0 %) patients tested. While this is a small dataset, the finding aligns with previous studies showing that the T790M mutation developed in approximately half of all patients with *EGFR* mutation–-positive advanced NSCLC whose tumors progressed on first- or second-generation EGFR-TKIs [38,39]. This is an important observation, as patients with T790M-positive tumors could subsequently receive third-generation EGFR-TKIs at the time of progression [12].

The safety analysis in ARIA found that dacomitinib has a tolerable AE profile. The most common AEs reported (treatment related and all cause) were rash, diarrhea, paronychia, and mouth ulceration, which is consistent with dacomitinib's prescribing information. No new safety signals were observed, suggesting that real-world safety data are consistent with dacomitinib's known safety profile [24,40]. This real-world study showed that efficacy and safety outcomes were generally consistent with prospective trial data [24,32], despite the use of variable starting doses and inclusion of patients less likely to meet clinical trial eligibility.

The limitations of this study were largely typical of real-world studies and should be considered in interpreting these findings. Patient clinical information, such as disease stage, mutation status, death date, AEs, or reasons for dose interruption or permanent treatment discontinuation, was recorded inconsistently or was missing due to loss to follow-up. Since the study was descriptive in nature, it did not provide any comparative analyses of dacomitinib versus other EGFR-TKIs. Additionally, the findings of this study in Asian patients with *EGFR* mutation–positive locally advanced or metastatic NSCLC may not be generalizable to other patient populations. Although the cohort enrolled patients located in 3 different Asian countries, most were of Chinese ethnicity; thus, the results may not fully represent the broader Asian population.

Due to the nature and design of ARIA as a real-world observational study, completion of brain scans at regular intervals was not standardized across treatment sites and central nervous system (CNS)-specific patient data were not consistently collected. Therefore, CNS-specific outcomes with dacomitinib were not available, which is a limitation of ARIA. However, intracranial efficacy of dacomitinib has been reported in other real-world studies and the prospective ATORG-003 study. In a non-interventional, multi-center, ambispective, real-world cohort study of 32 patients treated with first-line dacomitinib (NCT04768491), the intracranial objective response rate (iORR) was 67 % and median intracranial PFS (iPFS) was NR (95 % CI, 12.1 months-NR) [40]. In patients with CNS metastases in ATORG-003, iORR was 54 % and median iPFS was 17.6 months (95 % CI, 7.2–23.1) [32].

Though treatment standards have changed in recent years with osimertinib as the current preferred option and amivantamab plus lazertinib or osimertinib plus platinum-based chemotherapy as other recommended first-line therapies for *EGFR* mutation–positive advanced NSCLC [41,42], dacomitinib is still relevant in real-world settings,

including in countries where newer regimens like osimertinib or amivantamab combination therapies may be unavailable or inaccessible. [43,44] Additionally, patients with contraindications or intolerance to newer agents due to AEs may benefit from other effective first-line options. The real-world data presented here provide valuable evidence for dacomitinib outcomes and safety when in use due to limited access or intolerability to preferred regimens.

In conclusion, to our knowledge, ARIA is the largest real-world study of dacomitinib ever conducted. The results showed that in the real world, the dacomitinib starting dose may be different from the recommended starting dose used in clinical trials based on physicians' choice. The final analysis results showed robust clinical efficacy and supported the use of first-line dacomitinib in Asian patients with *EGFR* mutation–positive locally advanced or metastatic NSCLC in the real-world setting. The safety data for first-line dacomitinib in this real-world patient population were consistent with dacomitinib's known safety profile.

CRediT authorship contribution statement

Lin Wu: Writing – review & editing, Investigation. **Junling Li:** Writing – review & editing, Investigation. **Chong-Rui Xu:** Writing – review & editing, Investigation. **Bivas Biswas:** Writing – review & editing, Investigation. **Somnath Roy:** Writing – review & editing, Investigation. **Ke-Jing Tang:** Writing – review & editing, Investigation. **Huijuan Wang:** Writing – review & editing, Investigation. **Ziling Liu:** Writing – review & editing, Investigation. **Ullas Batra:** Writing – review & editing, Investigation. **Gwo Fuang Ho:** Writing – review & editing, Investigation. **John Low Seng Hooi:** Writing – review & editing, Investigation. **You Lu:** Writing – review & editing, Investigation. **Mingfang Zhao:** Writing – review & editing, Investigation. **Lye Mun Tho:** Writing – review & editing, Investigation. **Jun Zhao:** Writing – review & editing, Investigation. **Shan He:** Writing – review & editing. **Joan Huang:** Writing – review & editing. **Hui Zhang:** Writing – review & editing, Data curation. **Chew Hooi Wong:** Writing – review & editing, Supervision. **Yi-Long Wu:** Writing – review & editing, Investigation.

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Data sharing

Upon reasonable request and subject to review, Pfizer will provide the data that support the findings of this study. Subject to certain criteria, conditions, and exceptions, Pfizer may also provide access to the related individual de-identified participant data. See https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information.

Declaration of competing interest

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Appendix A. Supplementary material

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Glossary

AE: adverse event
CNS: central nervous system
ECOG: Eastern Cooperative Oncology Group
EGFR: epidermal growth factor receptor
HR: hazard ratio
IQR: interquartile range
NCCN: National Comprehensive Cancer Network® (NCCN®)
NR: not reached
NSCLC: non-small cell lung cancer
OS: overall survival
PFS: progression-free survival
PS: performance status
QD: once daily
TKI: tyrosine kinase inhibitor
TRAE: treatment-related adverse event
TTF: time to treatment failure
VEGF: vascular endothelial growth factor