Original Study

Efficacy and Safety of Brigatinib Compared With Crizotinib in Asian vs. Non-Asian Patients With Locally Advanced or Metastatic ALK–Inhibitor-Naive *ALK*+ Non–Small Cell Lung Cancer: Final Results From the Phase III ALTA-1L Study

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Abstract

We evaluated brigatinib efficacy and safety compared with crizotinib in an analysis of Asian (n = 108) and non-Asian (n = 167) subgroups from the phase III ALTA-1L study. Brigatinib showed better BIRC-assessed PFS over crizotinib in Asians and non-Asians (HR [95% CI], log-rank: Asians, 0.35 [0.20-0.59], *P* = .0001; non-Asians, 0.56 [0.38-0.84], *P* = .0041). Overall safety was similar between groups.

Background: Brigatinib is a next-generation anaplastic lymphoma kinase (ALK) inhibitor with demonstrated efficacy in locally advanced and metastatic non–small cell lung cancer (NSCLC) in crizotinib-refractory and ALK inhibitor-naive

Abbreviations: AE, adverse event; ALK, anaplastic lymphoma kinase; *ALK*+, anaplastic lymphoma kinase rearrangement–positive; ALT, alanine aminotransferase; ALTA-1L, ALK in Lung Cancer Trial of brigAtinib in 1st Line; AST, aspartate aminotransferase; BIRC, blinded independent review committee; BMI, body mass index; CI, confidence interval; CNS, central nervous system; CPK, creatine phosphokinase; CR, complete response; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; FDA, US Food and Drug Administration; HR, hazard ratio; iPFS, intracranial progression-free survival; NE, not evaluable; NR, not reached; NSCLC, non–small cell lung cancer; OR, odds ratio; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetic; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; TEAE, treatment-emergent adverse event; TKI, tyrosine kinase inhibitor.

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Submitted: May 25, 2022; Revised: Jul 8, 2022; Accepted: Jul 16, 2022; Epub: xxx

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https://doi.org/10.1016/j.cllc.2022.07.008

Please cite this article as: Myung J. Ahn et al, Efficacy and Safety of Brigatinib Compared With Crizotinib in Asian vs. Non-Asian Patients With Locally Advanced or Metastatic ALK–Inhibitor-Naive ALK+ Non–Small Cell Lung Cancer: Final Results From the Phase III ALTA-1L Study, Clinical Lung Cancer,

settings. This analysis assessed brigatinib in Asian vs. non-Asian patients from the first-line ALTA-1L trial. **Patients and Methods:** This was a subgroup analysis from the phase III ALTA-1L trial of brigatinib vs. crizotinib in ALK inhibitor–naive *ALK*+ NSCLC. The primary endpoint was progression-free survival (PFS) as assessed by blinded independent review committee (BIRC). Secondary endpoints included confirmed objective response rate (ORR) and overall survival (OS) in the overall population and BIRC-assessed intracranial ORR and PFS in patients with brain metastases. **Results:** Of the 275 randomized patients, 108 were Asian. Brigatinib showed consistent superiority in BIRC-assessed PFS vs. crizotinib in Asian (hazard ratio [HR]: 0.35 [95% CI: 0.20-0.59]; log-rank $P = .0001$; median 24.0 vs. 11.1 months) and non-Asian (HR: 0.56 [95% CI: 0.38-0.84]; log-rank $P = .0041$; median 24.7 vs. 9.4 months) patients. Results were consistent with investigator-assessed PFS and BIRC-assessed intracranial PFS. Brigatinib was well tolerated. Toxicity profiles and dose modification rates were similar between Asian and non-Asian patients. **Conclusion:** Efficacy with brigatinib was consistently better than with crizotinib in Asian and non-Asian patients with locally advanced or metastatic ALK inhibitor-naive *ALK*-+ NSCLC. There were no clinically notable differences in overall safety in Asian vs. non-Asian patients.

Clinical Lung Cancer, Vol. 000, No.xxx, 1–11
Keywords: ALK TKI-naive, Anaplastic lymphoma kinase, Clinical trial, First line, Tyrosine kinase inhibitor

Introduction

Anaplastic lymphoma kinase (*ALK*) receptor tyrosine kinase rearrangements occur in approximately 3% to 5% of patients with non–small cell lung cancer (NSCLC) and occur at similar rates among Asian and non-Asian populations.[1-4] A number of ALK inhibitors, including crizotinib, alectinib, ceritinib, brigatinib, and lorlatinib, have reported efficacy in treatment of patients with ALK TKI-naive anaplastic lymphoma kinase–positive (*ALK*+) NSCLC.[5-12] Crizotinib, the first approved ALK inhibitor, demonstrated efficacy superior to pemetrexed plus platinum chemotherapy in previously untreated patients.[6] Studies of the efficacy and safety of crizotinib and of alectinib have demonstrated similar efficacy between Asian and non-Asian patients.[4,8,13-16]

Brigatinib (ARIAD Pharmaceuticals, Inc., Cambridge, MA) is a next-generation ALK inhibitor that targets a broad range of *ALK* resistance mutations.[17-19] The phase III ALK in Lung Cancer Trial of brigAtinib in 1st Line (ALTA-1L; NCT02737501) trial compared the efficacy and safety of brigatinib and crizotinib in ALK inhibitor-naive advanced *ALK*+ NSCLC.[9-11] The primary endpoint, blinded independent review committee (BIRC)-assessed progression-free survival (PFS), was met at the first interim analysis and confirmed at the second interim analysis.[9,10] At the final analysis, with median follow-up for brigatinib of 40.4 months, brigatinib maintained superiority in BIRC-assessed PFS (hazard ratio [HR]: 0.48 [95% CI: 0.35-0.66]; $P < .0001$), with median PFS of 24.0 months vs. 11.0 months, respectively.[11]

At the first interim analysis of ALTA-1L, a subgroup analysis in Asian and non-Asian patients reported longer BIRC-assessed PFS with brigatinib compared with crizotinib in both populations (HR for disease progression or death, Asian: 0.41 [95% CI: 0.20-0.86]; non-Asian: 0.54 [95% CI: 0.33-0.90]).[9] Here, we report final efficacy and safety results of ALTA-1L in Asian and non-Asian patients.

Patients and Methods

ALTA-1L is an open-label, randomized, international, phase III trial. The trial was conducted in accordance with the ethical standards of the Declaration of Helsinki and the International Council for Harmonization guideline for Good Clinical Practice and was approved by local institutional review boards. All patients provided written informed consent. The detailed methods for this study have been previously published.[9]

Briefly, eligible patients were adults ≥ 18 years of age who had locally advanced or metastatic NSCLC with at least 1 measurable lesion according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1[20] and had not previously received ALK-targeted therapy. Patients must have been *ALK*+ based on locally determined testing. Asymptomatic or stable central nervous system (CNS) metastases were permitted. Patients who had received more than 1 prior systemic anticancer regimen, or radiation therapy within 14 days before the first dose of trial drug, were excluded.

Patients were randomized 1:1 to receive oral brigatinib 180 mg once daily (with 7 days lead-in period at 90 mg once daily) or oral crizotinib 250 mg twice daily in 28 days cycles; they were further stratified according to the presence or absence of brain metastases at baseline and the completion of at least 1 full cycle of chemotherapy for locally advanced or metastatic disease (Yes vs. No). Treatment was continued until disease progression, as assessed by BIRC, unacceptable toxicity, or other discontinuation criteria were met. The intracranial BIRC reviewers were independent from the systemic BIRC reviewers. Crossover from the crizotinib arm to the brigatinib arm was permitted following disease progression, after a 10-day washout period. Brigatinib could be continued after disease progression at the investigator's discretion. Dose interruptions or reductions were permitted for treatment-related adverse events (TEAEs).

The primary endpoint was PFS according to RECIST v1.1 as assessed by the BIRC. Secondary endpoints included the confirmed objective response rate (ORR), confirmed intracranial ORR, intracranial PFS, overall survival (OS), duration of response, and safety. Disease assessments were performed every 8 weeks through cycle 14 and then every 12 weeks until the end of treatment. Responses were confirmed at least 4 weeks after the initial response. Adverse events (AEs) were categorized using the National Cancer Institute Common Terminology Criteria for Adverse Events, v4.03.

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Table 1 Demographics and Baseline Characteristics

	Asian		Non-Asian	
	Brigatinib (n = 59)	Crizotinib (n = 49)	Brigatinib (n = 78)	Crizotinib (n = 89)
Median age, years (range)	55 (32-80)	56 (30-89)	60 (27-86)	60 (29-83)
Female, n (%)	31 (53)	26 (53)	38 (49)	55 (62)
Median weight, kg (range)[a]	60 (43-96)	60 (40-85)	70 (46-111)	70 (46-117)
Median BMI, kg/m^2 (range)[b]	23 (16-31)	23 (16-32)	26 (18-41)	26 (18-44)
ECOG performance status, n (%)				
0	18 (31)	13 (27)	36 (46)	40 (45)
1	39 (66)	33 (67)	37 (47)	45 (51)
2	2 (3)	3 (6)	5 (6)	4 (4)
Disease stage at study entry				
IIIB	2 (3)	5 (10)	6 (8)	7 (8)
IV	57 (97)	44 (90)	72 (92)	82 (92)
ALK status assessed by locally FDA-approved test, n (%)[c]	54 (92)	41 (84)	69 (88)	71 (80)
Baseline brain metastases, n (%)[d]	21 (36)	16 (33)	19 (24)	25 (28)
Prior radiotherapy to the brain, n (%)	7 (12)	8 (16)	11 (14)	11 (12)
Prior chemotherapy in the locally advanced or metastatic setting, n (%)[e]	19 (32)	12 (24)	17 (22)	25 (28)

ALK = anaplastic lymphoma kinase; BMI = body mass index; ECOG = Eastern Cooperative Oncology Group; FDA = Food and Drug Administration; ; FISH, fluorescence in situ hybridization; IHC, immunohistochemistry
[a] Asian crizotinib arm, n = 48. Non-Asian arms: brigatinib, n = 77; crizotinib, n = 87
[b] Asian crizotinib arm, n = 48. Non-Asian arms: brigatinib, n = 71; crizotinib, n = 82
[c] Patients whose *ALK*+ status was tested locally by Vysis FISH or Ventana IHC
[d] As assessed by investigator
[e] Prior chemotherapy defined as completion of ≥ 1 full cycle of chemotherapy in the locally advanced or metastatic setting

The final analysis was conducted following the last patient last visit in January, 2020, approximately 3.5 years after last patient first enrollment. This prespecified subgroup analysis of outcomes in Asian vs. non-Asian patients was conducted following the final analysis. Asian patients included all patients whose race was self-reported as native Asian. Efficacy was evaluated in the intention-to-treat population, in Asian and non-Asian patients separately. PFS was compared between the 2 arms using a 2-sided stratified log-rank test (stratification factors: presence of intracranial CNS metastases at baseline [Yes vs. No], and prior chemotherapy for locally advanced or metastatic disease [Yes vs. No]); ethnicity was not a stratification parameter. Median time to efficacy events and 95% CIs were estimated for each treatment arm using the Kaplan-Meier method. The safety population included all patients who received at least 1 dose of study drug. Statistical analyses were performed using Base 9.4 SAS/STAT 13.1 software (SAS Institute, Cary, NC). Data are reported as of the data cutoff date for the final analysis of January 29, 2021.[11]

Results

Patients

A total of 275 patients were randomized, with 108 (39%) Asian patients and 167 (61%) non-Asian patients. The median age, weight, and body mass index of Asian patients were slightly less than those of non-Asian patients (Table 1). Numerically more Asian patients had Eastern Cooperative Oncology Group performance status 1 compared with the non-Asian population (Table 1). There were no other substantial differences between populations or between brigatinib- and crizotinib-treated patients. At study completion, no patient in either arm remained on treatment. Median follow-up was similar between the Asian and non-Asian cohorts; 40.7 months (range 0.7-49.9 months) and 39.8 months (range 0-52.4 months) in the brigatinib arm, respectively, and 13.6 months (range 0.1-47.0 months) and 15.5 months (range 0.3-51.7 months), respectively, in the crizotinib arm.

Efficacy

Systemic Progression-free Survival. Consistent with results from the overall population, brigatinib demonstrated better BIRC-assessed PFS over crizotinib in both Asian and non-Asian patients. In Asian patients, the HR for PFS was 0.35 [95% CI: 0.20-0.59]; $P = .0001$ by log-rank test; Figure 1A). In non-Asian patients, the HR was 0.56 [95% CI: 0.38-0.84]; $P = .0041$ by log-rank test; Figure 1B). Investigator-assessed PFS supports BIRC assessment, continuing to show improvements with brigatinib in Asian and in non-Asian patients vs. crizotinib (Figure 1C, D).

Systemic Response Rate and Duration of Response. Among Asian patients, the BIRC-assessed confirmed ORR (n/N; 95% CI) was 80% (47/59; 67%-89%) in the brigatinib arm and 71% (35/49; 57%-83%) in the crizotinib arm (Table 2). In non-Asian patients, confirmed ORR was 71% (55/78; 59%-80%) with brigatinib and 57% (51/89; 46%-68%) with crizotinib. Disease control rates were similar across treatment groups in Asian and non-Asian patients. The duration of response among confirmed responders was longer with brigatinib treatment, with a median duration of 22.2 months

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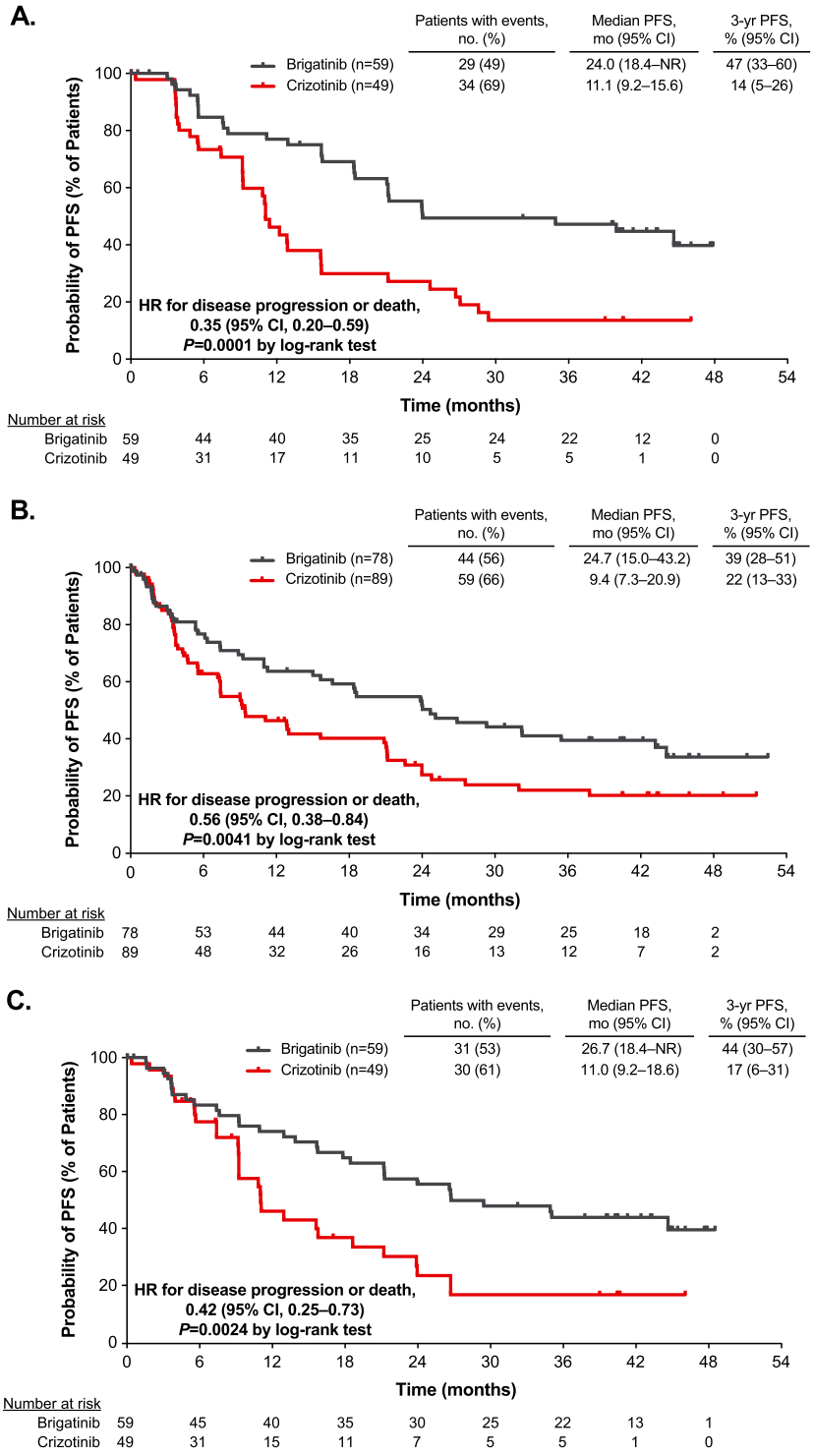
Figure 1 **Efficacy of brigatinib and crizotinib in Asian and non-Asian patients with TKI-naive *ALK*-+ NSCLC. Kaplan-Meier–estimated BIRC-assessed PFS for (A) Asian and (B) non-Asian patients in the intention-to-treat population; Kaplan-Meier–estimated investigator-assessed PFS for (C) Asian and (D) non-Asian patients in the intention-to-treat population; overall survival for (E) Asian and (F) non-Asian patients in the intention-to-treat population.**



ALK = anaplastic lymphoma kinase gene; BIRC = blinded independent review committee; CI = confidence interval; HR = hazard ratio; NR = not reached; NSCLC = non–small cell lung cancer; OS = overall survival; PFS = progression-free survival; TKI = tyrosine kinase inhibitor.

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Figure 1 Continued

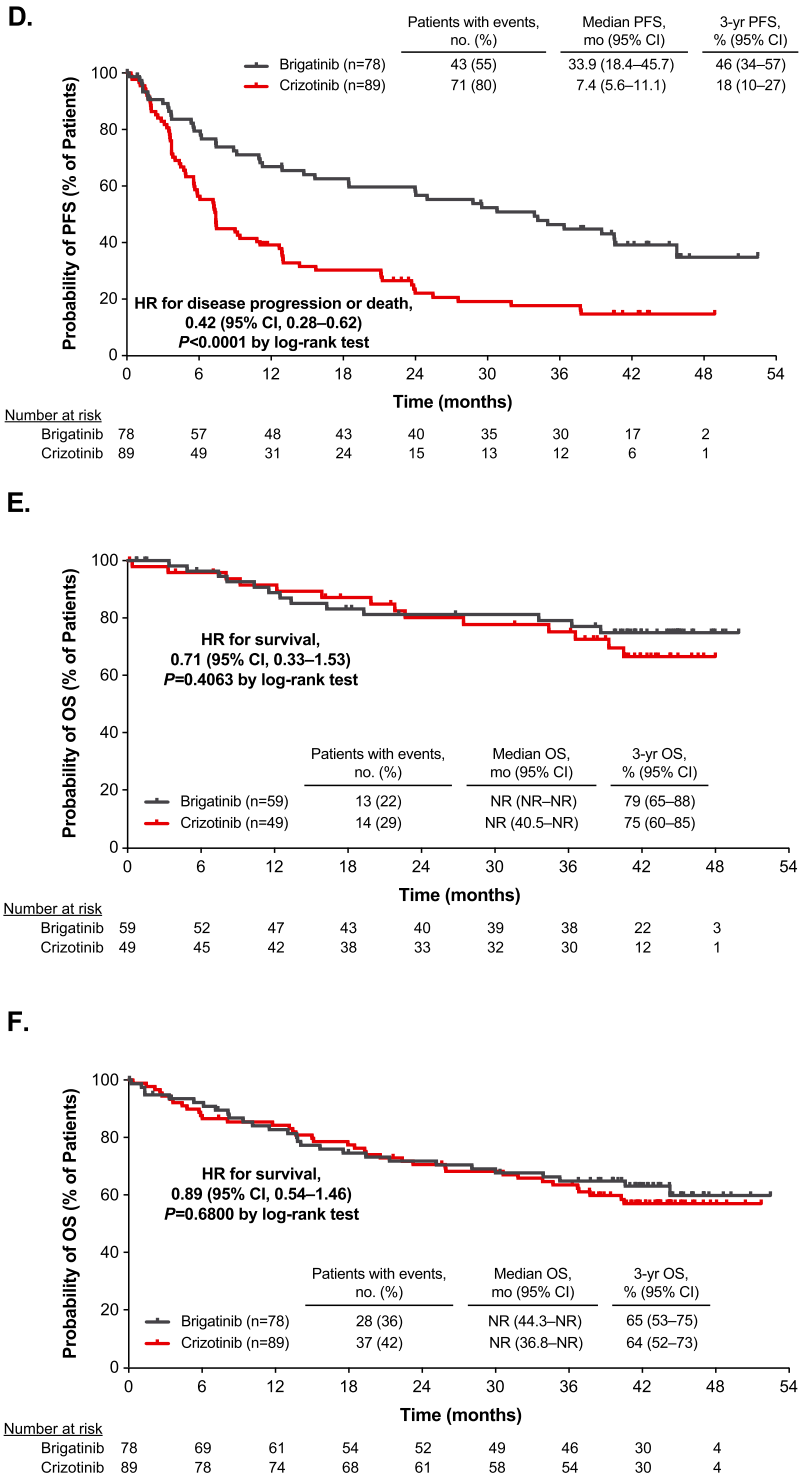

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Table 2 BIRC-Assessed Objective Response Rate (Intent-to-treat Population)

	Asian			Non-Asian		
	Brigatinib	Crizotinib	OR (95% CI)[a]	Brigatinib	Crizotinib	OR (95% CI)[a]
Intention-to-treat population						
No. of patients	59	49		78	89	
Confirmed ORR, n (%) (95% CI)	47 (80) (67-89)	35 (71) (57-83)	1.70 (0.69-4.18); $P = .2546$	55 (71) (59-80)	51 (57) (46-68)	1.77 (0.93-3.36); $P = .0783$
Disease control rate, n (%) (95% CI)	53 (90) (79-96)	45 (92) (80-98)		64 (82) (72-90)	74 (83) (74-90)	
Median DOR in confirmed responders, months (95% CI)	22.2 (16.6-NE)	11.0 (9.1-19.3)		41.4 (22.2-NE)	19.4 (11.1-35.8)	
Probability of maintaining response, % (95% CI)						
1 year	76 (61-86)	46 (28-63)		79 (66-88)	63 (47-75)	
2 years	48 (33-62)	25 (11-41)		60 (45-72)	42 (27-56)	
3 years	46 (31-60)	14 (4-29)		52 (37-64)	33 (19-48)	
Patients with any brain metastases at baseline (as assessed by the BIRC[b])						
No. of patients	21	18		26	31	
Confirmed intracranial ORR, % (95% CI)	13 (62) (38-82)	6 (33) (13-59)	7.24 (1.22-42.87); $P = .0212$	18 (69) (48-86)	1 (3) (0-17)	71 (6.86-734.32); $P < .0001$
Intracranial CR, n (%)	11 (52)	0		10 (38)	1 (3)	
Intracranial PR, n (%)	2 (10)	6 (33)		8 (31)	0	

BIRC = blinded independent review committee; CI = confidence interval; CR = complete response; DOR = duration of response; NE = not evaluable; NR = not reached; OR = odds ratio; ORR = objective response rate; PR = partial response
[a] ORs (brigatinib vs. crizotinib) and *P* values are from a Cochran-Mantel-Haenszel test stratified by presence of brain metastases at baseline and prior chemotherapy for locally advanced or metastatic disease
[b] Intracranial reviewers were independent from systemic reviewers

and 11.0 months among Asian patients treated with brigatinib and crizotinib, respectively. Median duration of response was 41.4 months for brigatinib compared with 19.4 months in the crizotinib group in the non-Asian group (Table 2).

Overall Survival. A total of 92 patients died as of the data cutoff date (January 29, 2021). In both the Asian and non-Asian subgroups, more patients died in the crizotinib arm (Asian patients: brigatinib, 13 [22%]; crizotinib, 14 [29%]; non-Asian patients: brigatinib, 28 [36%]; crizotinib, 37 [42%]). OS trended in favor of brigatinib in both the Asian and non-Asian populations (HR for OS, Asian patients: 0.71 [95% CI: 0.33-1.53]; $P = .4063$ by log-rank test (Figure 1E); non-Asian patients: 0.89 [95% CI: 0.54-1.46]; $P = .6800$ by log-rank test (Figure 1F).

Efficacy in Patients With Brain Metastases. A total of 96 patients had baseline brain metastases as assessed by BIRC (Asian patients: brigatinib, 21, crizotinib, 18; non-Asian patients: brigatinib, 26, crizotinib, 31). There was a better intracranial ORR in both Asian and non-Asian patients treated with brigatinib than with crizotinib. Confirmed intracranial ORR (n/N; 95% CI) in Asian patients was 62% (13/21; 38%-82%) for brigatinib and 33% (6/18; 13%-59%) for crizotinib (odds ratio [OR] for brigatinib vs. crizotinib, 7.24 [95% CI: 1.22-42.87]; $P = .0212$; Table 2). In non-Asian patients, confirmed intracranial ORR was 69% (18/26; 48%-86%) for brigatinib and 3% (1/31; 0%-17%) for crizotinib (OR: 71.00 [95% CI: 6.86-734.32]; $P < .0001$). Among all patients, regardless of whether brain metastases were present at baseline, BIRC-assessed intracranial PFS was better in patients treated with brigatinib vs. crizotinib (Figure 2A, 2B).

Safety

Brigatinib was well tolerated in both Asian and non-Asian populations (Table 3). The most common (> 25% of patients overall) any-grade TEAEs were gastrointestinal events, increased blood creatine phosphokinase, cough, increased aminotransferases, and peripheral edema. There were no remarkable differences in AE profiles between the Asian and non-Asian populations. The incidence of increased aspartate aminotransferase (31% vs. 22%), increased alanine aminotransferase (31% vs. 17%), and constipation (25% vs. 16%) was numerically higher in Asian patients treated with brigatinib than in non-Asian patients. Diarrhea (64% vs. 51%), nausea (40% vs. 24%), and peripheral edema (13% vs. 5%) were more frequent in non-Asian patients treated with brigatinib than in Asian patients treated with briga-

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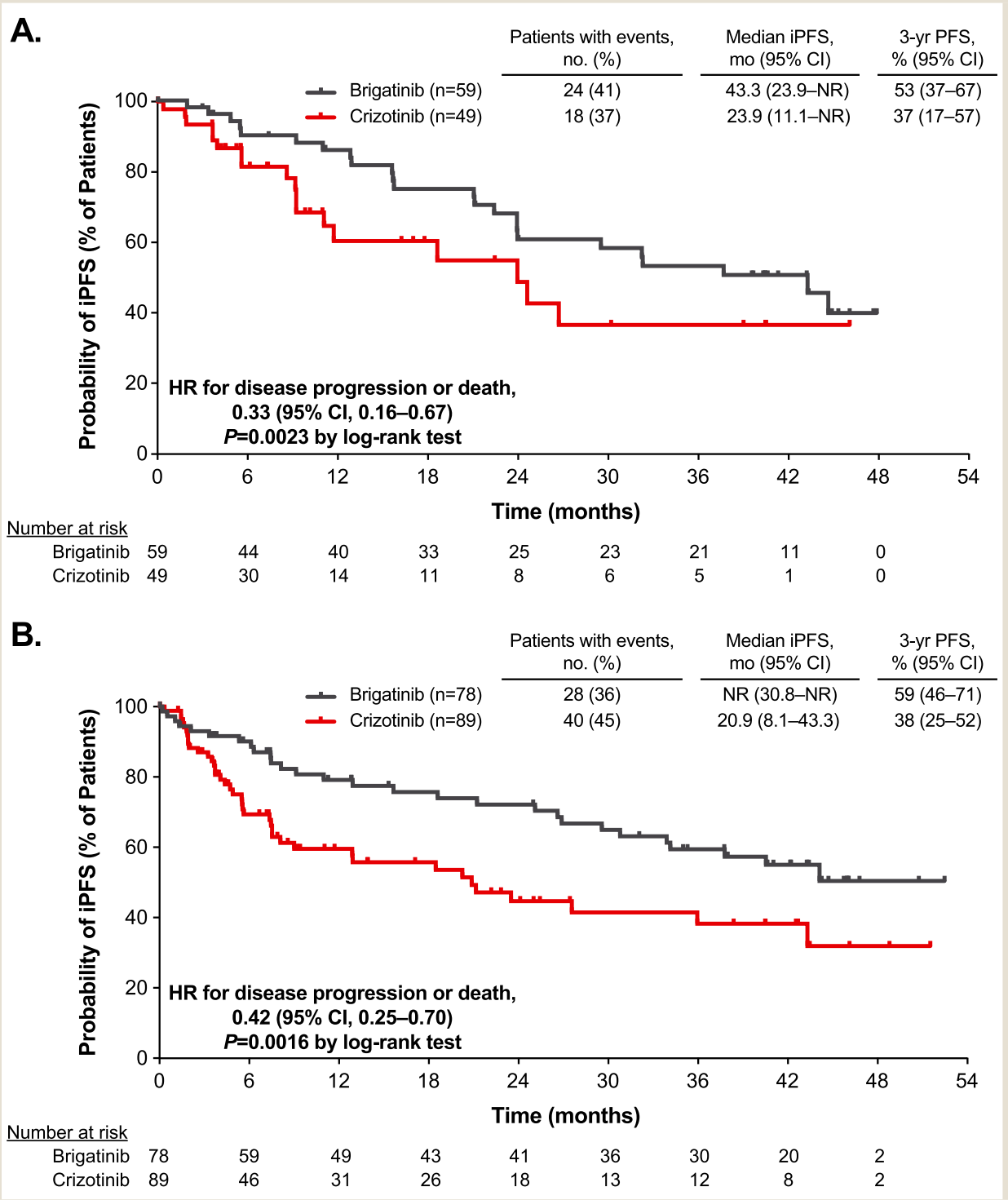
Figure 2 Intracranial efficacy of brigatinib and crizotinib in (A) Asian and (B) non-Asian patients with TKI-naive *ALK*-+ NSCLC regardless of brain metastases at baseline. Kaplan-Meier–estimated BIRC-assessed PFS for the intention-to-treat population. Intracranial reviewers were independent from systemic reviewers.[11]



ALK = anaplastic lymphoma kinase gene; BIRC = blinded independent review committee; CI = confidence interval; HR = hazard ratio; iPFS = intracranial progression-free survival; NR = not reached; NSCLC = non–small cell lung cancer; PFS = progression-free survival; TKI = tyrosine kinase inhibitor.

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Table 3 Safety Overview and Treatment-Emergent Adverse Events[a] of Any Grade Reported in ≥ 25% of All Patients (Safety Population[b])

	Asian				Non-Asian			
	Brigatinib (n = 59)		Crizotinib (n = 48)		Brigatinib (n = 77)		Crizotinib (n = 89)	
	Any	Grade ≥ 3	Any	Grade ≥ 3	Any	Grade ≥ 3	Any	Grade ≥ 3
Overview of adverse events, n (%)								
Any adverse event	59 (100)	42 (71)	48 (100)	25 (52)	77 (100)	53 (69)	89 (100)	52 (58)
Adverse event leading to dose reduction	27 (46)	–	9 (19)	–	33 (43)	–	25 (28)	–
Adverse event leading to treatment interruption	43 (73)	–	21 (44)	–	55 (71)	–	44 (49)	–
Adverse event leading to treatment discontinuation	5 (8)	–	3 (6)	–	13 (17)	–	9 (10)	–
Adverse events reported in ≥ 25% of all patients, n (%)								
Diarrhea	30 (51)	1 (2)	23 (48)	0	49 (64)	2 (3)	54 (61)	4 (4)
Increased blood CPK	30 (51)	20 (34)	7 (15)	1 (2)	38 (49)	16 (21)	16 (18)	1 (1)
Cough	22 (37)	0	6 (13)	0	27 (35)	0	23 (26)	0
Increased AST	18 (31)	4 (7)	17 (35)	1 (2)	17 (22)	2 (3)	19 (21)	8 (9)
Increased ALT	18 (31)	4 (7)	21 (44)	3 (6)	13 (17)	2 (3)	28 (31)	11 (12)
Constipation	15 (25)	0	16 (33)	0	12 (16)	1 (1)	41 (46)	0
Nausea	14 (24)	0	27 (56)	2 (4)	31 (40)	3 (4)	54 (61)	2 (2)
Vomiting	11 (19)	0	20 (42)	1 (2)	19 (25)	2 (3)	41 (46)	2 (2)
Peripheral edema	3 (5)	0	19 (40)	0	10 (13)	1 (1)	44 (49)	1 (1)

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CPK = creatine phosphokinase
[a] AEs starting or worsening on or after the first dose of study treatment and no later than the earliest of (1) 30 days after the last dose of treatment to which the patient was assigned, or (2) the day before the start of brigatinib therapy in patients who crossed over
[b] Patients treated with ≥ 1 dose of study medication

tinib. It is notable that this trend of slight differences in AE frequency was also generally observed in patients treated with crizotinib.

Grade ≥ 3 TEAEs occurred at similar rates in Asian (71%) vs. non-Asian patients (69%) treated with brigatinib. More Asian than non-Asian patients treated with brigatinib experienced grade ≥ 3 increases in creatinine phosphokinase (34% vs. 21%). In this study, disease progression was required to be reported as an AE unless it was asymptomatic radiological progression alone. Twenty-two patients had AEs leading to death, most attributed to lung cancer progression. None were deemed related to study treatment by the investigator. Among Asian patients, interstitial lung disease/pneumonitis at any time occurred in 7% of patients (4/59) in the brigatinib arm and no patients in the crizotinib arm, with grade 3 or 4 interstitial lung disease occurring in 3% of patients (2/59) treated with brigatinib. Any-grade interstitial lung disease/pneumonitis with early onset (defined as within 14 days of treatment initiation) was observed in 3% of patients (2/59) in the brigatinib arm. Among non-Asian patients, interstitial lung disease/pneumonitis at any time was reported in 5% of patients (4/77) in the brigatinib arm, similar to that in Asian patients, and 3% of patients (3/89) in the crizotinib arm. Grade 3 or 4 pneumonitis occurred in 3% of patients (2/77) treated with brigatinib and 1% of patients (1/89) treated with crizotinib. Any-grade early-onset pneumonitis was reported in 3% of patients (2/77) treated with brigatinib; no early-onset interstitial lung disease was reported in non-Asian patients.

The dose modification rate was similar between both populations treated with brigatinib (Table 3). Median brigatinib dose intensity was 150.0 mg/d for Asian patients and 165.6 mg/d for non-Asian patients. In the crizotinib arm, the median dose intensity was 496.9 mg/d and 494.5 mg/day for Asian and non-Asian patients, respectively. Dose reduction due to AEs was mandated by investigator or protocol in 46% and 19% of Asian patients in the brigatinib and crizotinib arms, respectively, and in 43% and 28% of non-Asian patients, respectively. Fewer Asian patients (brigatinib, 8%; crizotinib, 6%) than non-Asian patients (brigatinib, 17%; crizotinib, 10%) discontinued treatment due to TEAEs. There was no remarkable difference in the profile of AEs that led to drug discontinuation in Asian vs. non-Asian patients.

Discussion

Results from a phase I ethnobridging study (data on file) demonstrated a lack of race effects on the pharmacokinetic (PK) profile of brigatinib in healthy Asian and white volunteers. These results were supported by a population PK model–based analysis of patients in ALTA-1L that showed consistent brigatinib systemic exposures in Asian and non-Asian patients.[21]

In this ALTA-1L final analysis, brigatinib showed sustained improvement in systemic and intracranial efficacy compared with crizotinib in both Asian and non-Asian patients with ALK inhibitor–naive *ALK*+ NSCLC, consistent with the analyses of the overall population[9-11,22] and with the report based on the first interim analysis.[9] Asian patients show a trend of better PFS with brigatinib over crizotinib than non-Asian patients; however, the HRs had overlapping 95% CIs and the median PFS was similar for both treatment arms in Asian and Non-Asian populations. One limitation of our analysis is that the Cox proportional regression

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analysis did not account for covariates other than the 2 stratification factors, which have slightly, but not significantly, different distributions in the Asian and non-Asian populations. To avoid any potential impact from these 2 randomization factors, they were included in the regression model for adjustment. The median PFS is a point estimate of survival, while HR describes the overall distribution. The Kaplan-Meier curves show that the separation in BIRC-assessed PFS between brigatinib and crizotinib is more obvious in Asians than in non-Asians without considering the impact of any covariate and can explain the lower HR in the Asian population.

Previous studies have demonstrated similar efficacy between Asian and non-Asian patients treated with crizotinib and alectinib.[4,8,13-15] In an analysis of previously treated (1 prior platinum-based regimen) and untreated patients from PROFILE 1007 and 1014, comparable benefits were observed in Asian and non-Asian patients.[4] In Asian patients, the HR for PFS was 0.53 (95% CI: 0.36-0.76; $P < .001$; median PFS: crizotinib 8.1 months, chemotherapy 2.8 months); in non-Asian patients, the HR for PFS was 0.45 (95% CI: 0.30-0.66; $P < .001$; median PFS: crizotinib 7.1 months vs. chemotherapy 3.2 months).[4] In the ALEX study comparing alectinib and crizotinib in patients with TKI-naive NSCLC, PFS subgroup analyses showed similar benefit in Asian (HR: 0.46 [95% CI: 0.280-0.75]) and non-Asian (HR: 0.49 [95% CI: 0.32-00.75]) patients.[8,15] With longer follow-up of ALTA-1L, this study strengthens the observation that second-generation ALK TKIs improve PFS and intracranial efficacy compared with crizotinib in patients with advanced *ALK*+ NSCLC, regardless of ethnicity.

In ALTA-1L, Asian patients had a trend toward better survival in both arms compared with non-Asian patients, with numerically higher 3-year OS rates for both brigatinib and crizotinib. In subgroup analyses of Asian and non-Asian patients from the PROFILE 1014 trial of crizotinib vs. chemotherapy, the HR (95% CI) for OS was 0.93 (0.58-1.49) in Asian patients and 0.72 (0.47-1.11) in non-Asians.[16] In the ALEX trial of alectinib vs. crizotinib, the HR for OS was 0.74 (0.40-1.36) for Asians and 0.69 (0.43-1.10) for non-Asians.[15]

The safety profile of brigatinib in Asian and non-Asian patients was consistent with the established safety profile of brigatinib from multiple studies.[11,19,23] Brigatinib was well tolerated in both Asian and non-Asian patients, reflected by similar rates of dose modifications between the 2 subpopulations. Certain toxicities, such as nausea and vomiting, were more frequent in the non-Asian population in both treatment arms. A similar finding was observed for alectinib in a subgroup analysis of the ALEX study.[24] The underlying reason is unknown and may be related to dietary habits or reporting bias. With longer follow-up, the pneumonitis rate did not significantly differ in Asian vs. non-Asian patients who received brigatinib.

Conclusion

Results from the final analysis of the ALTA-1L trial demonstrate brigatinib to be better in terms of efficacy compared with crizotinib in both Asian and non-Asian patients. Brigatinib is well tolerated and represents a once-daily, single-tablet, promising first-line treatment option in both Asian and non-Asian patients with ALK inhibitor-naive locally advanced or metastatic *ALK*+ NSCLC.

Clinical Practice Points

- Brigatinib is a second-generation ALK TKI approved for treatment of advanced *ALK*+ NSCLC. In the phase III ALTA-1L trial, brigatinib demonstrated superior efficacy vs. crizotinib in patients with ALK TKI-naive *ALK*+ NSCLC and was well tolerated. We conducted a planned analysis in Asian and non-Asian subgroups from ALTA-1L to determine the effects of ethnicity on efficacy and tolerability of brigatinib.
- Consistent with overall ALTA-1L results, brigatinib demonstrated consistently better BIRC-assessed PFS compared with crizotinib in both Asian and non-Asian patients (HR, Asian: 0.35 [95% CI: 0.20-0.59], $P = .0001$; HR, non-Asian: 0.56 [0.38-0.84], $P = .0041$). Patients in the brigatinib arm also had numerically better overall ORR (OR [Asian/non-Asian]: 1.70/1.77), intracranial ORR (OR: 7.24/71.00), and trend to longer OS (HR: 0.71/0.89) vs. crizotinib. Brigatinib was well tolerated in both groups. Higher percentages of increased creatinine phosphokinase, aspartate aminotransferase, alanine aminotransferase, and constipation reported in Asian patients were not clinically meaningful, and dose modification rates were similar between Asian and non-Asian patients.
- These results are supported by a phase I PK study in healthy Asian and white volunteers that demonstrated a lack of race effects on the brigatinib PK profile (data on file). A population PK model-based analysis of patients in ALTA-1L also showed comparable systemic exposures to brigatinib in Asian and non-Asian patients.
- This subgroup analysis from long-term follow-up demonstrates the consistent efficacy and tolerability of brigatinib in Asian and non-Asian patients. Brigatinib represents a first-line treatment option in Asian patients with ALK inhibitor-naive advanced *ALK*+ NSCLC.

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Validation (*Verification, whether as a part of the activity or separate, of the overall replication/ reproducibility of results/experiments and other research outputs)*: M.J. Ahn, M.J. Hochmair, G.C. Chang, M.R. García Campelo, A.I. Spira, R. Califano, F. Griesinger, E. Felip, Y. Liu, P. Zhang, S. Popat, D.R. Camidge

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Writing - review & editing: All authors

Data Sharing Statement

The data sets, including the redacted study protocol, redacted statistical analysis plan, and individual participant data supporting the results reported in this article, will be made available within 3 months from initial request, to researchers who provide a methodologically sound proposal. The data will be provided after de-identification, in compliance with applicable privacy laws, data protection, and requirements for consent and anonymization.

ClinicalTrials.gov registration

NCT02737501

Acknowledgments

The authors would like to thank the patients, their families, and their caregivers; the ALTA-1L investigators and their team members at each study site; and colleagues from Millennium Pharmaceuticals, Inc., Cambridge, MA, USA, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited. Professional medical writing assistance was provided by Lauren Gallagher, RPh, PhD, of Peloton Advantage, LLC, an OPEN Health company, Parsippany, NJ, USA, and funded by Millennium Pharmaceuticals, Inc. Teodor G. Paunescu, PhD (Takeda Pharmaceuticals U.S.A., Inc.) is acknowledged for editorial assistance.

This study was supported by ARIAD Pharmaceuticals, Inc., Cambridge, MA, USA, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited. The sponsor designed and conducted the study and collected the data together with the authors. The sponsor managed and analyzed the data. Data were interpreted by the authors and the sponsor. The sponsor together with the authors prepared, reviewed, and approved the manuscript and made the decision to submit the manuscript for publication.

Disclosure

M. J. Ahn: Honoraria (AstraZeneca, Merck Sharp & Dohme, Roche, Bristol Myers Squibb, Merck KGaA, Alpha Pharmaceuticals) outside of the submitted work. H. R. Kim: Honoraria (Bristol Myers Squibb, AstraZeneca, Merck Sharp & Dohme, Takeda) outside of the submitted work. J. C. H. Yang: Honoraria or advisory role (Boehringer Ingelheim, Eli Lilly, Bayer, Roche/Genentech/Chugai, Astellas, Merck Sharp & Dohme, Merck Serono, Pfizer, Novartis, Celgene, Merrimack, Yuhan Pharmaceuticals, BMS, Ono Pharmaceutical, Daiichi Sankyo, Takeda, AstraZeneca, Hansoh Pharmaceuticals). J. Y. Han: Research grants (Hoffmann-La Roche Ltd, Ono, Pfizer, Takeda); consulting/advisor fees (AstraZeneca, Bristol Myers Squibb, Eli Lilly, Merck Sharp & Dohme, Novartis, Pfizer, Takeda, MedPacto, Abion, Ono); honoraria (AstraZeneca, Bristol Myers Squibb, Hoffmann-La Roche Ltd., Merck Sharp & Dohme, Takeda). M. J. Hochmair: Honoraria (AstraZeneca, Bristol Myers Squibb, Boehringer Ingelheim, Merck Sharp & Dohme, Pfizer, Takeda, Roche); consulting or advisory role (Boehringer Ingelheim, Merck Sharp & Dohme, Pfizer, Novartis, Takeda, Roche). G. C. Chang: Honoraria (F. Hoffmann–La Roche, Ltd, Eli Lilly and Company Oncology, AstraZeneca, Novartis, Pfizer, Boehringer Ingelheim, Bristol Myers Squibb, Merck Sharp & Dohme). A. Delmonte: Consulting/advisory role (AstraZeneca, Boehringer Ingelheim). K. H. Lee: Support of clinical research (Merck), honoraria for advisory board participation (AstraZeneca, Bristol Myers Squibb, Lilly, Merck Sharp & Dohme, Pfizer, Yu-han). M. R. García Campelo: Consulting/advisory role (Merck Sharp & Dohme, Bristol Myers Squibb, Roche, Boehringer Ingelheim, Pfizer, Novartis, AstraZeneca, Lilly, Takeda, Bayer, Sanofi, Janssen); speakers bureau (Merck Sharp & Dohme, Bristol Myers Squibb, Roche, Boehringer Ingelheim, Pfizer, Novartis, AstraZeneca, Lilly, Takeda, Janssen). C. Gridelli: Honoraria as advisory board member or speaker bureau member (AstraZeneca, Roche, Pfizer, Eli Lilly, Merck Sharp & Dohme, Bristol Myers Squibb, Novartis); honoraria as consultant (Menarini, Roche). A. Spira: Consulting/advisory role (ARIAD, AstraZeneca, Clovis Oncology, Roche, Amgen, Mirati, Bristol Myers Squibb, Merck). R. Califano: Honoraria and consulting or advisory role (AstraZeneca, Bristol Myers Squibb, Roche, Merck Sharp & Dohme, Boehringer Ingelheim, Takeda, Novartis). F. Griesinger: Support of scientific research (AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Lilly, Merck Sharp & Dohme, Novartis, Pfizer, Roche, Takeda, Siemens, Amgen, GlaxoSmithKline, Janssen); honoraria for presentations (AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Lilly, Merck Sharp & Dohme, Novartis, Pfizer, Roche, Takeda, ARIAD, AbbVie, Siemens, Amgen, GlaxoSmithKline, Janssen, Sanofi); advisory board participation (AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Lilly, Merck Sharp & Dohme, Novartis, Pfizer, Roche, Takeda, ARIAD, AbbVie, Siemens, GlaxoSmithKline, Janssen, Sanofi). E. Felip: Personal fees (AbbVie, Amgen, AstraZeneca, Bayer, BeiGene, Blue Print Medicines, Boehringer Ingelheim, Bristol Myers Squibb, CME Outfitters, Eli Lilly, GlaxoSmithKline, Janssen, Medical Trends, Medscape, Merck KGaA, Merck Sharp & Dohme, Novartis, PeerVoice, Peptomyc, Pfizer, Prime Oncology, Puma Biotechnology, Regeneron, Roche, Sanofi Genzyme, Springer, Takeda, Touch Medical); grants (Grant for Oncology Innovation [GOI], Fundación Merck Salud); advisory board (Syneos Health); independent member of the board

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(Grífols). D. W. Kim: Research funding (all to institution: Alpha Biopharma, Amgen, AstraZeneca/Medimmune, Boehringer Ingelheim, Daiichi Sankyo, Hanmi, Janssen, Merus, Mirati Therapeutics, Merck Sharp & Dohme, Novartis, Ono Pharmaceutical, Pfizer, Roche/Genentech, Takeda, TP Therapeutics, Xcovery, Yuhan, Chong Kun Dang, Bridge BioTherapeutics, GlaxoSmithKline); travel/accommodation support for advisory board meeting attendance (Amgen, Daiichi-Sankyo). Y. Liu: Employment (Takeda). P. Zhang: Employment (Takeda). S. Popat: NHS funding to the National Institute for Health Research Biomedical Research Centre at the Royal Marsden Hospital/Institute of Cancer Research; honoraria (Boehringer Ingelheim, AstraZeneca, Roche, Takeda, Novartis, Bristol Myers Squibb, Merck Sharp & Dohme, Merck KGaA, Bayer, Blueprint Medicines, Daiichi Sankyo, Guardant Health, Janssen, GlaxoSmithKline, BeiGene, Incyte, Lilly, Amgen); consulting or advisory role (Boehringer Ingelheim, Roche, Novartis, Pfizer, AstraZeneca, Bristol Myers Squibb, Merck Sharp & Dohme, Guardant Health, Takeda, Incyte, Bayer, Blueprint Medicines, Daiichi Sankyo, Janssen, GlaxoSmithKline, BeiGene, Lilly, Merck KGaA, Amgen); research funding (Mirati Therapeutics, Trizell; to institution: Boehringer Ingelheim, Epizyme, Bristol Myers Squibb, Clovis Oncology, Roche; Lilly, Takeda, Celgene, Novartis, ARIAD, Merck Sharp & Dohme, Daiichi Sankyo, Guardant Health, Janssen, GlaxoSmithKline, Turning Point Therapeutics); travel/accommodations/expenses (Boehringer Ingelheim, Merck Sharp & Dohme, Roche). D. R. Camidge: Advisory/consulting role (AbbVie, Apollomics [SRC], AstraZeneca [SRC/SC], Daiichi-Sankyo [ILD adjudication committee], Elevation [SRC], Kestrel [SAB], Nuvalent [SAB], Seattle Genetics, Takeda, Turning Point, Amgen, Anchiano [SAB], BioThera [DSMB], Bristol Myers Squibb, Eisai, EMD Serono, Eli Lilly, GlaxoSmithKline, Helsinn, Janssen, OnKure, Mersana, Pfizer, Qilu, Roche, Sanofi, CBT Pharmaceuticals, G1 Therapeutics [DSMB], Blueprint, Achilles, BeyondSpring, 14ner/Elevation [SRC], Archer, Medtronic, Ribon); research funding (Inivata); PI roles (AbbVie, AstraZeneca, Dizal, Inhibrx, Karyopharm, Pfizer, Phosplatin, PsiOxus, Rain, Roche/Genentech, Seattle Genetics, Takeda, Turning Point). All remaining authors have declared no conflicts of interest.

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