ORIGINAL ARTICLE

Brigatinib Versus Alectinib in *ALK*-Positive NSCLC After Disease Progression on Crizotinib: Results of Phase 3 ALTA-3 Trial

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ABSTRACT

Introduction: This open-label, phase 3 trial (ALTA-3; NCT03596866) compared efficacy and safety of brigatinib versus alectinib for *ALK*+ NSCLC after disease progression on crizotinib.

Methods: Patients with advanced *ALK*+ NSCLC that progressed on crizotinib were randomized 1:1 to brigatinib 180 mg once daily (7-d lead-in, 90 mg) or alectinib 600 mg twice daily, aiming to test superiority. The primary end point was blinded independent review committee–assessed progression-free survival (PFS). Interim analysis for efficacy and futility was planned at approximately 70% of 164 expected PFS events.

Results: The population (N = 248; brigatinib, n = 125; alectinib, n = 123) was notable for long median duration of prior crizotinib (16.0–16.8 mo) and low rate of *ALK* fusion in baseline circulating tumor DNA (ctDNA; 78 of 232 [34%]). Median blinded independent review committee–assessed PFS was 19.3 months with brigatinib and 19.2 months with alectinib (hazard ratio = 0.97 [95% confidence interval: 0.66–1.42], $p = 0.8672$]). The study met futility criterion. Overall survival was immature (41 events [17%]). Exploratory analyses pooled across the treatment groups revealed median PFS of 11.1 versus 22.5 months in patients with versus without ctDNA-detectable *ALK* fusion at baseline (hazard ratio: 0.48 [95% confidence interval: 0.32–0.71]). Treatment-related adverse events in more than 30% of patients (brigatinib, alectinib) were elevated levels of blood creatine phosphokinase (70%, 29%), aspartate aminotransferase (53%, 38%), and alanine aminotransferase (40%, 36%).

Conclusions: Brigatinib was not superior to alectinib for PFS in crizotinib-pretreated *ALK*+ NSCLC. Safety was consistent with the well-established and unique profiles of each drug. The low proportion of patients with ctDNA-detectable *ALK* fusion may account for prolonged PFS with both drugs in ALTA-3.

Keywords: Alectinib; Anaplastic lymphoma kinase; Brigatinib; Non–small cell lung cancer; Tyrosine kinase inhibitor

Introduction

ALK rearrangements occur in approximately 3% to 8% of patients with NSCLC and drive oncogenic transformation.[1–4] Crizotinib, the first ALK tyrosine kinase inhibitor (TKI) approved for treatment of metastatic *ALK*+ NSCLC,[5] became standard of care by demonstrating superiority over chemotherapy.[6,7] Nevertheless, most, if not all, patients eventually develop treatment resistance and disease progression often in the central nervous system (CNS).[8–11] In addition to inadequate CNS penetration, acquired resistance can occur from secondary mutations in the ALK kinase domain, amplification of the *ALK* fusion gene, and activation of bypass signaling pathways.[12,13] To address these shortcomings, newer ALK TKIs were developed with improved CNS activity and more potent ALK kinase inhibitory activity against several acquired resistance mutations. Subsequent approvals of these agents in the post-crizotinib setting were based on single-arm nonrandomized trials, as development rapidly focused on evaluating their activity in the frontline setting.[14–17]

Alectinib and brigatinib are CNS-active, potent ALK TKIs with differing selectivity against acquired resistance mutations in *ALK*.[13,18–21] In studies of patients with *ALK*+ NSCLC that progressed on crizotinib, median progression-free survival (PFS) was 8.1 to 10.9 months with alectinib[20,22,23] and 14.7 to 16.8 months with brigatinib.[24,25]

We aimed to test the superiority of brigatinib over alectinib for improving PFS after crizotinib failure in this head-to-head trial (ALTA-3), which compared the efficacy and safety of brigatinib with that of alectinib in patients with advanced *ALK*+ NSCLC that progressed on crizotinib. Here, we report the results of the preplanned interim analysis.

Materials and Methods

Study Design and Patients

ALTA-3 was a randomized, phase 3, open-label, multicenter, international trial (ClinicalTrials.gov identifier: NCT03596866) in patients with *ALK*+ NSCLC that progressed on crizotinib. The study was conducted in the People's Republic of China (15 sites), Russia (10 sites), South Korea (nine sites), Spain (six sites), Hong Kong

(five sites), Taiwan (five sites), Italy (four sites), France (three sites), United States (three sites), Argentina (two sites), Canada (two sites), Germany (two sites), Greece (two sites), Romania (two sites), Chile (one site), Mexico (one site), and Sweden (one site). Eligible patients were adults with histologically or cytologically confirmed locally advanced or metastatic NSCLC with documented *ALK* rearrangement by Vysis ALK Break-Apart fluorescence in situ hybridization Probe Kit, Ventana ALK (D5F3) CDx Assay, or Foundation Medicine's FoundationOne CDx. Patients with documented *ALK* rearrangement by a different test could be enrolled if a tumor sample was available for central testing (central testing results were not required before randomization). Patients were also required to have at least one measurable lesion per Response Evaluation Criteria in Solid Tumors (RECIST) version (v) 1.1, Eastern Cooperative Oncology Group performance status of less than or equal to two, adequate organ function, treatment with prior crizotinib for at least 4 weeks before disease progression, and no more than two prior regimens of systemic anticancer therapy other than crizotinib. No other prior ALK TKIs were permitted. Key exclusion criteria were participation in ALTA-1L (NCT02737501); history or presence of pulmonary interstitial disease, drug-related pneumonitis, or radiation pneumonitis; uncontrolled hypertension; symptomatic CNS metastases at screening; and spinal cord compression. Patients who had asymptomatic brain metastases or stable symptoms that did not require an increased dose of corticosteroids to control symptoms in the 7 days before randomization were allowed. If a patient had worsening neurologic symptoms or signs of CNS metastasis, the patient was required to complete local therapy and be neurologically stable (with no requirement for an increasing dose of corticosteroids or use of anticonvulsants) for at least 7 days before randomization. Complete eligibility criteria are provided in the Supplementary Methods.

This study was conducted in accordance with the International Council for Harmonization guidelines for good clinical practice, the Declaration of Helsinki, and all applicable local regulations. The protocol and informed consent documents were approved by the local institutional review board or ethics committee at each site. All patients provided written informed consent before screening.

Outcomes

The primary end point was blinded independent review committee (BIRC)–assessed PFS per RECIST v1.1. The key secondary end point was overall survival (OS); other secondary end points included investigator-assessed PFS; BIRC- and investigator-assessed objective response rate (ORR), duration of response (DOR), and time to response; BIRC-assessed intracranial ORR per modified RECIST v1.1; safety and tolerability; and health-related quality of life. Exploratory outcomes included analyses of biomarker determinants of efficacy, such as detection of *ALK* fusion and *TP53* mutations in circulating tumor DNA (ctDNA).

Procedures

Patients were randomized 1:1 to receive brigatinib 180 mg once daily (7-d lead-in at 90 mg) or alectinib 600 mg twice daily with food. Randomization was stratified by presence of brain metastases at baseline (yes versus no) and investigator-assessed best prior response to crizotinib (complete response or partial response versus any other status or unknown). Patients continued the study treatment until occurrence of investigator-assessed disease progression or intolerable toxicity or when any other discontinuation criterion was met. Patients could continue the study treatment beyond disease progression if the investigator determined that there was evidence of continued clinical benefit. Dose reduction or interruption was permitted for management of adverse events (AEs). The initial protocol mandated brigatinib dose interruption or reduction for grade 3 or 4 blood creatine phosphokinase level (CPK) elevations, regardless of the presence of related symptoms. In February 2021, the protocol was revised to require accompanying symptoms (grade $\geq$2 muscle pain or weakness) for dose modifications for grade 3 or 4 CPK elevation.

Disease was assessed by chest and abdomen imaging by computed tomography (CT) or contrast-enhanced magnetic resonance imaging and brain imaging by contrast magnetic resonance imaging or contrast CT at screening and every 8 weeks to cycle 12 and every 12 weeks thereafter. All images were submitted to a central laboratory for BIRC assessment. Target lesion response was confirmed at least 4 weeks after the initial response. Follow-up assessments occurred every 12 weeks after the last dose. Severity of AEs was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03.

Patient-reported outcomes (PROs) included the European Organization for Research and Treatment of Cancer (EORTC) quality of life (QoL) questionnaire (QLQ)-C30 (version 3.0)[26] and its lung cancer-specific module, the EORTC QLQ-LC13,[27] which were administered at baseline, on day 1 of each 4-week cycle, and 30 days after the last dose.

Blood samples for exploratory molecular genetic analyses of ctDNA in the plasma were obtained at

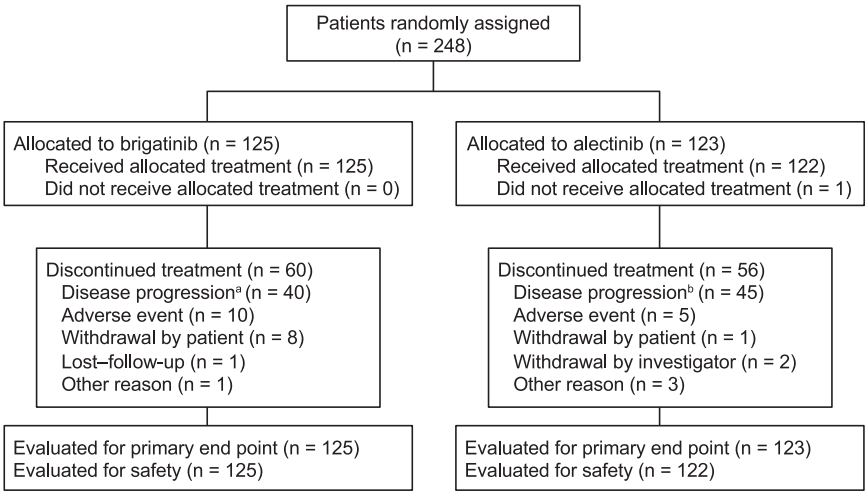


Figure 1. CONSORT diagram for the ALTA-3 trial. Data are reported as of the cutoff date for the interim analysis (February 11, 2022). [a]There were 32 patients who had documented disease progression per RECIST version 1.1, and eight had clinical disease progression. [b]There were 42 patients who had documented disease progression per RECIST version 1.1, and three had clinical disease progression. CONSORT, Consolidated Standards of Reporting Trials; RECIST, Response Evaluation Criteria in Solid Tumors.

screening, cycle 3 day 1, and at the end of treatment visit. Presence of *ALK* fusions, *EML4-ALK* variants, *TP53* mutations, and acquired *ALK* resistance mutations at baseline and time of progression was determined retrospectively by next-generation sequencing (NGS) of plasma ctDNA by Resolution Bioscience (Agilent) or AmoyDx (only patients enrolled in the People's Republic of China). A full list of genes covered by each assay is provided in Supplementary Table 1.

Statistical Analysis

Approximately 246 patients were to be enrolled to provide 90% power to detect a 6-month improvement in PFS (hazard ratio [HR] for disease progression or death = 0.60) after a total of 164 events had occurred, assuming median PFS of 9 months for alectinib[22,23] and 15 months for brigatinib,[28] on the basis of values reported in single-arm trials. An O'Brien-Fleming Lan-DeMets alpha spending function was used to control the two-sided alpha level at 0.05. An interim analysis was planned to occur at approximately 70% of target PFS events (approximately 115 of 164 expected events). The protocol was amended in March 2021 to include a futility test (margin for futility, $p > 0.6948$) for the interim analysis.

Efficacy analyses were based on the intention-to-treat (ITT) population, which included all patients randomized to treatment. The safety analysis population included all patients who received at least one dose of the study drug. The PRO analysis population included all randomized patients who had baseline and more than or equal to one postbaseline PRO measurement.

The primary end point of BIRC-assessed PFS was evaluated using a two-sided log-rank test stratified by the presence or absence of baseline brain metastases and best response to prior crizotinib therapy. For time-to-event analyses, Kaplan-Meier methods estimated median values and associated two-sided 95% confidence intervals (CIs). HRs were calculated using the stratified Cox regression model with stratification factors. PRO scale scores were summarized using descriptive statistics; changes from baseline were analyzed using linear mixed models that included treatment group, visit, interaction between treatment group and visit, baseline score, and stratification factors as covariates. A change of at least 10 points was considered a clinically meaningful worsening or improvement. Time to worsening was defined as time from the date of randomization to the earliest date at which the patient's score had at least a 10-point deterioration from baseline. Statistical analyses were performed with SAS version 9.4 (SAS Institute, Cary, NC).

Results

Patients

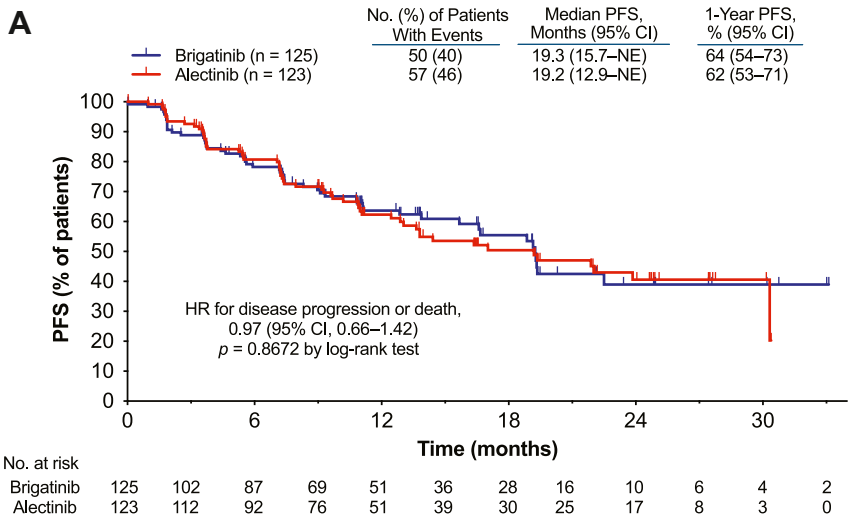
From May 2019 to June 2021, 248 patients were randomized (brigatinib, n = 125; alectinib, n = 123; Fig. 1). One patient allocated to alectinib who did not receive the treatment was included in the ITT population. Baseline demographics and disease characteristics were balanced between the treatment arms (Table 1). Across the arms, 30% of the patients had received one prior line of chemotherapy for systemic disease and 3% had

Table 1. Patient Demographics and Baseline Characteristics

Characteristic	Brigatinib (n = 125)	Alectinib (n = 123)
Median age, y (range)	54.0 (22-83)	53.0 (28-82)
Sex, female, n (%)	67 (54)	68 (55)
Race, n (%)		
Asian	74 (59)	66 (54)
White	50 (40)	52 (42)
Other	1 (1)	5 (4)
Region, n (%)		
Asia Pacific	70 (56)	62 (50)
Europe	43 (34)	41 (33)
South America	7 (6)	13 (11)
North America	2 (2)	5 (4)
Missing data	3 (2)	2 (2)
Median time since initial diagnosis, mo (range)	22.2 (2.3-161.8)	21.3 (2.4-266.2)
Median time since end date of most recent prior systemic anticancer therapy, mo (range)	0.5 (0.03-24.2)	0.5 (0.03-12.3)
Disease stage at study entry, n (%)		
IIIB	5 (4)	2 (2)
IV	120 (96)	121 (98)
Organ involvement at study entry, n (%)[a]		
Lung	101 (81)	108 (88)
Brain	80 (64)	75 (61)
Lymph nodes	60 (48)	58 (47)
Bone	36 (29)	34 (28)
Pleura	30 (24)	36 (29)
Effusion or ascites	20 (16)	24 (20)
ECOG performance status at study entry, n (%)		
0	42 (34)	51 (41)
1	80 (64)	70 (57)
2	3 (2)	2 (2)
ALK rearrangement detected by local testing at study entry, n (%)	120 (96)	114 (93)
ALK status assessed locally by FDA-approved test, n (%)	99 (79)	101 (82)
Smoking history, n (%)		
Never	82 (66)	85 (69)
Current	4 (3)	6 (5)
Former	39 (31)	32 (26)
Prior chemotherapy for systemic disease, n (%)	39 (31)	43 (35)
One line of prior chemotherapy	35 (28)	40 (33)
Two lines of prior chemotherapy	4 (3)	3 (2)
Median duration of prior crizotinib treatment, mo (range)	16.0 (1.3-85.9)	16.8 (1.0-83.8)
Best response to prior crizotinib, n (%)		
CR or PR	84 (67)	86 (70)
Other response or unknown	41 (33)	37 (30)
Brain metastases at baseline, n (%)	80 (64)	75 (61)
Measurable brain metastases at baseline, n (%)	30 (24)	31 (25)
Prior radiotherapy to the brain, n (%)	34 (27)	28 (23)
Whole brain radiation therapy	5 (4)	5 (4)
Stereotactic radiosurgery	3 (2)	3 (2)
Other	27 (22)	21 (17)
Best response to most recent prior radiotherapy to the brain, n (%)[b]		
CR or PR	7 (21)	7 (25)
Other response or unknown	27 (79)	21 (75)

[a]Other sites of tumor involvement (≤20% of patients): adrenal, head and neck, kidney, liver, ovary, pericardium, soft tissue, and spleen.
[b]Denominator is the number of patients who received prior radiotherapy to the brain (brigatinib, n = 34; alectinib, n = 28).
CR, complete response; ECOG, Eastern Cooperative Oncology Group; FDA, Food and Drug Administration; PR, partial response.

received two prior lines. Approximately two-thirds of the patients had investigator-reported brain metastases at screening (brigatinib, 64%; alectinib, 61%). Similar percentages of patients had received prior radiotherapy to the brain in the brigatinib (27%) and alectinib (23%) arms. Median (range) duration of prior crizotinib



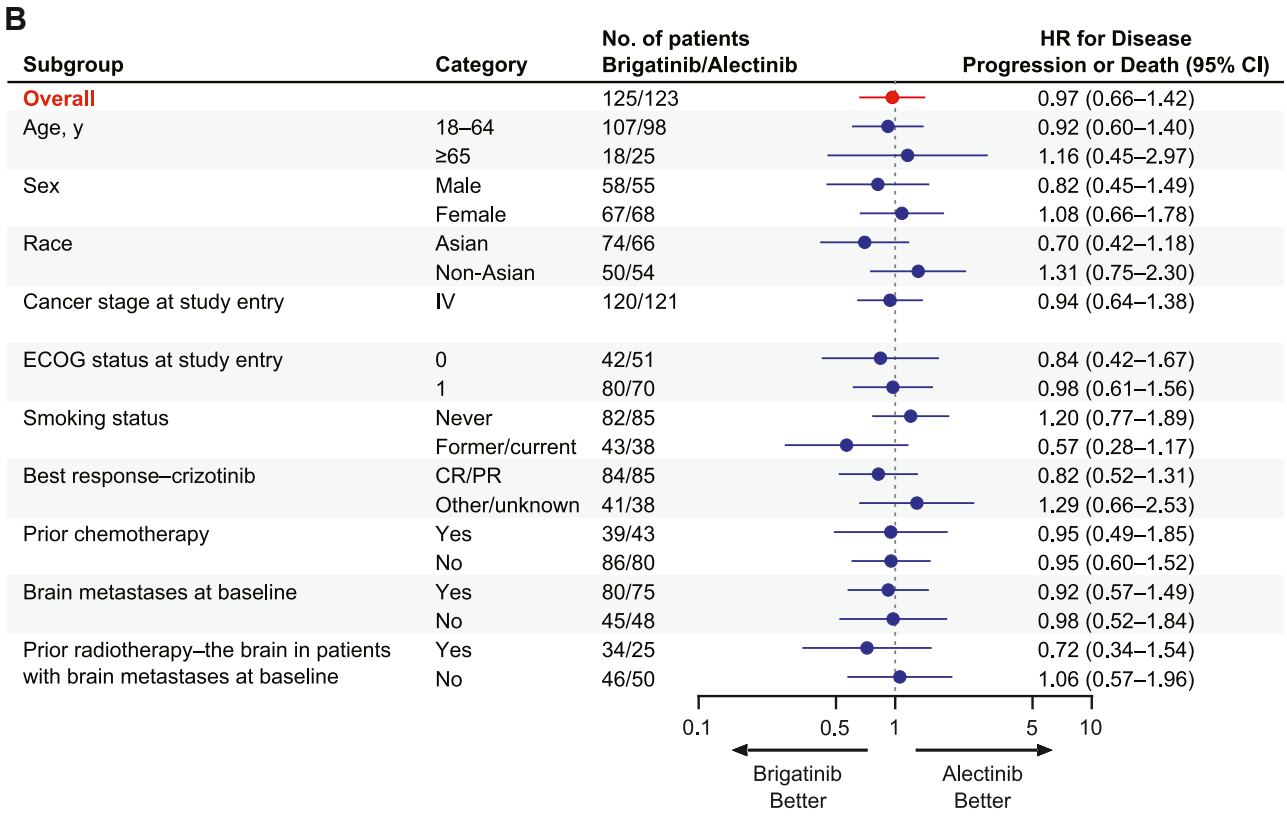


Figure 2. Efficacy of brigatinib and alectinib in patients with *ALK*+ NSCLC that had progressed on crizotinib. Kaplan-Meier-estimated (*A*) BIRC-assessed PFS in the ITT population. (*B*) Forest plot of HRs for BIRC-assessed PFS across patient subgroups. HRs were not calculated for patients with < stage IV cancer (brigatinib, n = 5; alectinib, n = 2) or for patients with an ECOG performance status score of 2 at study entry (brigatinib, n = 3; alectinib, n = 2) because of insufficient patient numbers. (*C*) Best change from baseline in the sum of target lesions by BIRC assessment. The dotted line at −30% represents the threshold for partial response, per RECIST version 1.1. Bar colors indicate the best overall response and not the target lesion response. BIRC, blinded independent review committee; CI, confidence interval; CR, complete response; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; ITT, intention-to-treat; NE, not estimable; PFS, assessed progression-free survival; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors.

treatment was 16.0 months in the brigatinib arm and 16.8 months in the alectinib arm; 67% and 70% of the patients, respectively, had a response to prior crizotinib.

At data cutoff (February 11, 2022), 65 patients (52%) in the brigatinib arm and 66 patients (54%) in the alectinib arm remained on the study treatment. The

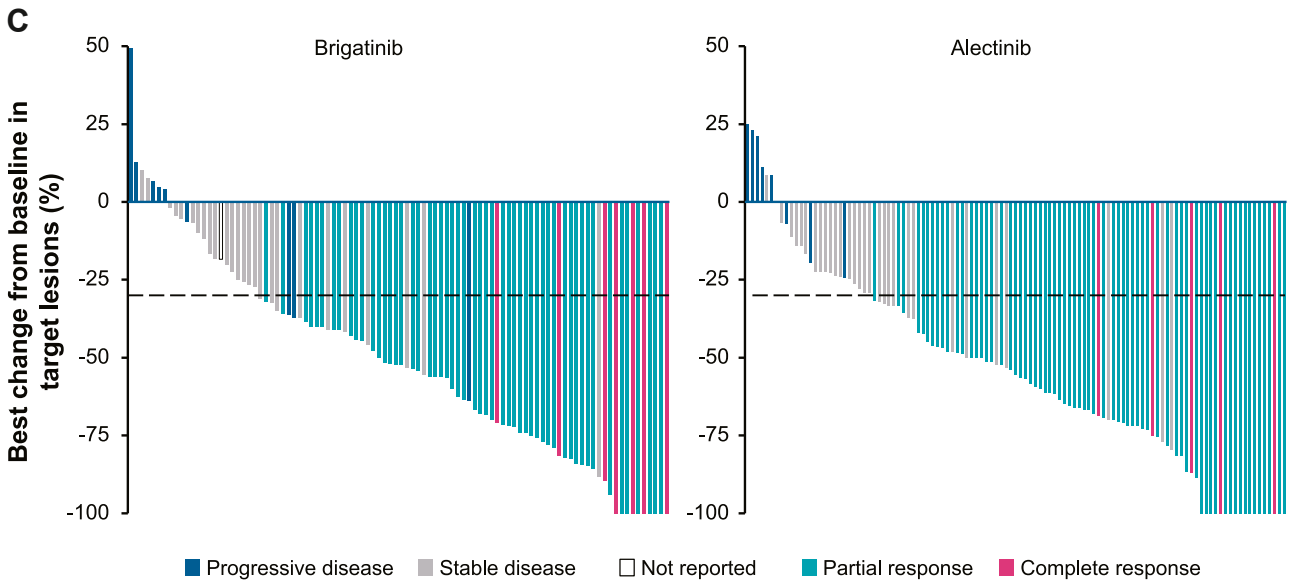


Figure 2. Continued.

median (range) follow-up was 15.9 (1.1–33.2) months for brigatinib and 16.9 (0.2–32.7) months for alectinib. The median (range) duration of treatment was 12.9 (0.1–33.1) months for brigatinib and 13.6 (1.1–32.6) months for alectinib.

Efficacy

Primary End Point: PFS by BIRC Assessment. A total of 107 BIRC-assessed events of disease progression or death had occurred at data cutoff (brigatinib: 50 of 125 patients [40%]; alectinib: 57 of 123 [46%]). Median PFS (95% CI) was 19.3 months (15.7–not estimable [NE]) for brigatinib and 19.2 months (12.9–NE) for alectinib (HR = 0.97 [95% CI: 0.66–1.42], log-rank $p = 0.8672$; Fig. 2*A*). An independent data monitoring committee determined that the study met the predefined futility criterion on the basis of the p value threshold ($p > 0.6948$) for HR of PFS and recommended study closure. Investigator-assessed PFS was similar between the groups (median [95% CI]: brigatinib, 16.8 mo [10.9–19.4]; alectinib, 16.6 mo [13.6–27.6]; HR = 1.23 [95% CI: 0.86–1.76]; Supplementary Fig. 1), consistent with BIRC assessment. Subgroup analyses revealed no difference between the groups in BIRC-assessed PFS (Fig. 2*B*).

Overall Survival. At the time of analysis, OS was not mature, with events occurring in 41 of 248 patients (17%; brigatinib: 27 [22%]; alectinib: 14 [11%]). Kaplan-Meier estimates of 12-month survival were 89% (95% CI: 81%–93%) for brigatinib and 96% (95% CI: 90%–98%) for alectinib.

Subsequent Therapy. A total of 59 patients received subsequent systemic anticancer therapy (brigatinib, n = 25; alectinib, n = 34; Supplementary Table 2). In the brigatinib arm, 21 of 25 patients (84%) who received subsequent anticancer treatment received another ALK TKI at any time after discontinuing brigatinib, most frequently alectinib (40% [10 of 25]) and lorlatinib (36% [nine of 25]). In the alectinib arm, 28 of 34 patients (82%) with subsequent anticancer treatment received an ALK TKI, most frequently lorlatinib (47% [16 of 34]) and brigatinib (24% [eight of 34]). Subsequent chemotherapy was given to 44% of the patients (11 of 25) in the brigatinib arm and 41% (14 of 34) in the alectinib arm, most frequently pemetrexed-based chemotherapy (brigatinib, 40% [10 of 25]; alectinib, 32% [11 of 34]).

Systemic Response Rate and Durability of Response. The confirmed ORR by BIRC assessment was 52% (95% CI: 43%–61%) for brigatinib and 61% (95% CI: 52%–70%) for alectinib (Supplementary Table 3). Median time to response was 1.9 (range: 1.6–16.5) months for brigatinib and 1.8 (range: 1.4–16.6) months for alectinib. Median DOR was 17.5 months (95% CI: 14.8–NE) for brigatinib and 20.2 months (95% CI: 12.6–NE) for alectinib. Best change from baseline in the target lesions is found in Figure 2*C*.

Intracranial Efficacy. Among the patients with measurable brain lesions at baseline, BIRC-assessed confirmed intracranial ORR was 73% (22 of 30 patients; 95% CI:

Table 2. TRAEs of Any Grade That Were Reported in at Least 10% of Patients in Either Arm or That Differed by at Least 5% Between Arms

	Brigatinib (n = 125)		Alectinib (n = 122)	
TRAE	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Any TRAE	115 (92)	55 (44)	108 (89)	22 (18)
Laboratory-related TRAEs				
Increased blood CPK	88 (70)	33 (36)	35 (29)	2 (2)
Increased AST	66 (53)	1 (1)	46 (38)	6 (5)
Increased ALT	50 (40)	4 (3)	44 (36)	7 (6)
Lipase increased	27 (22)	9 (7)	15 (12)	3 (2)
Increased blood LDH	21 (17)	0	10 (8)	0
Anemia	17 (14)	1 (1)	31 (25)	3 (2)
Increased amylase	17 (14)	3 (2)	7 (6)	3 (2)
Increased blood alkaline phosphatase	13 (10)	0	19 (16)	0
Increased blood creatinine	9 (7)	0	13 (11)	0
Increased alpha hydroxybutyrate dehydrogenase	8 (6)	0	0	0
Increased bilirubin conjugated	2 (2)	0	10 (8)	0
Increased blood bilirubin	3 (2)	0	35 (29)	2 (2)
Nonlaboratory TRAEs				
Hypertension	28 (22)	7 (6)	1 (1)	0
Rash	13 (10)	1 (1)	5 (4)	0
Interstitial lung disease	7 (6)	0	0	0
Myalgia	6 (5)	0	13 (11)	0
Fatigue	5 (4)	1 (1)	11 (9)	0
Constipation	3 (2)	0	28 (23)	0
Peripheral edema	2 (2)	0	16 (13)	0

Note: Data are reported as number of patients (%).
ALT, alanine aminotransferase; AST, aspartate aminotransferase; CPK, creatine phosphokinase; LDH, lactate dehydrogenase; TRAE, treatment-related adverse event.

54%–88%) with brigatinib and 68% (21 of 31; 95% CI: 49%–83%) with alectinib (Supplementary Table 3). Median time to intracranial response was 1.9 (range: 1.6–7.4) months in the brigatinib arm and 3.5 (range: 1.6–9.2) months in the alectinib arm. Median duration of intracranial response was not mature (intracranial progression or death events among the responders: brigatinib, 7 [32%]; alectinib, 6 [29%]).

Safety

The most common treatment-related AEs (TRAEs; more than 30% of the patients) in the brigatinib arm were increased blood CPK (70%), increased aspartate aminotransferase (AST; 53%), and increased alanine aminotransferase (ALT; 40%) levels and in the alectinib arm were increased AST (38%) and increased ALT (36%) levels (Table 2). TRAEs that were at least 10 percentage points more common with brigatinib than alectinib were all laboratory abnormalities (brigatinib, alectinib: increased CPK, 70%, 29%; increased AST, 53%, 38%) and hypertension (22%, 1%); events that were at least 10 percentage points more common with alectinib were increased blood bilirubin level (alectinib, brigatinib: 29%, 2%), constipation (23%, 2%), anemia (25%, 14%), and peripheral edema (13%, 2%). Grade 3 or 4 TRAEs occurred in 44% of the patients treated with brigatinib and 18% treated with alectinib (Table 2). No deaths were treatment related.

Interstitial lung disease (ILD) within the first 14 days of treatment (i.e., early onset ILD) occurred in three patients (2%; all grade 2) in the brigatinib arm and no patient in the alectinib arm. Two patients with early onset ILD recovered within 10 days after dose interruption and were successfully reintroduced to brigatinib; one patient discontinued the treatment.

TRAEs resulted in dose reduction in 26 patients (21%) treated with brigatinib and 14 patients (11%) treated with alectinib and dose interruption in 54 patients (43%) and 18 patients (15%), respectively. Most dose reductions were protocol mandated owing to laboratory abnormalities (brigatinib arm, 16 of 26 patients [62%]; alectinib arm, seven of 14 patients [50%]; Supplementary Table 4). Six patients (5%) in the brigatinib arm and three (2%) in the alectinib arm discontinued the study treatment because of TRAEs (Supplementary Table 5).

Health-related Quality of Life

Least squares mean EORTC QLQ-C30 global health status score improved from baseline in the brigatinib

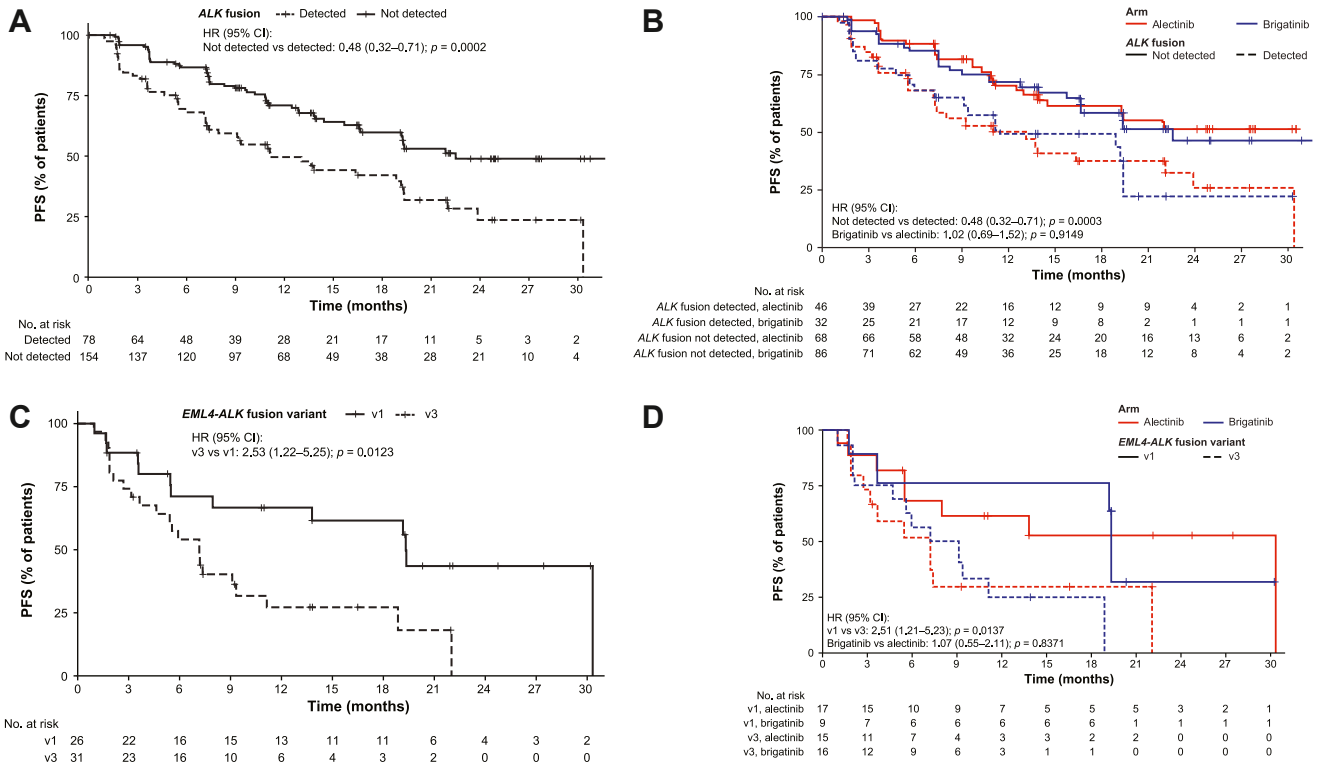


Figure 3. Efficacy by baseline molecular variables in plasma ctDNA. Kaplan-Meier plot of BIRC-assessed PFS in patients with versus without detectable *ALK* fusion at baseline (*A*) pooled by treatment group and (*B*) separated by treatment group and in patients with *EML4-ALK* fusion v1 versus v3 (*C*) pooled by treatment group and (*D*) separated by treatment group. BIRC, blinded independent review committee; CI, confidence interval; ctDNA, circulating tumor DNA; HR, hazard ratio; PFS, progression-free survival; V1, variant 1; V3, variant 3.

and alectinib arms beginning at cycle 2 with no significant differences between the groups at any time point (Supplementary Fig. 2*A*). Time to worsening (≥10-point deterioration from baseline) in EORTC QLQ-C30 scores was not significantly different between the treatment groups for the global health status score (HR = 1.21 [95% CI: 0.84–1.74], log-rank $p = 0.3126$) or any subscales, with the exception of constipation that favors brigatinib (HR = 0.43 [95% CI: 0.29–0.64], log-rank $p < 0.0001$) and nausea or vomiting (HR = 1.58 [95% CI: 0.99–2.51], log-rank $p = 0.0494$) and appetite loss (HR = 1.58 [95% CI: 1.00–2.52], log-rank $p = 0.0498$), which favor alectinib (Supplementary Fig. 2*B*). Median time to worsening in EORTC QLQ-LC13 composite score for cough, dyspnea, and pain in the chest was similar with brigatinib and alectinib (HR = 0.87 [95% CI: 0.65–1.18], log-rank $p = 0.3582$; Supplementary Fig. 2*C*).

Biomarker Analyses

***ALK* Fusions in Plasma ctDNA.** Among 232 patients with NGS-assessable baseline plasma samples (NGS by Resolution Bioscience in 149 patients and AmoyDx in 83 patients from the People's Republic of China), 78 (34%) had detectable *ALK* fusion in ctDNA (brigatinib, 27% [32 of 118]; alectinib, 40% [46 of 114]; Supplementary Table 6). Patients with undetectable *ALK* fusion in the plasma had longer PFS than those with a detectable *ALK* fusion (Fig. 3*A*), regardless of the treatment group (Fig. 3*B*). In the pooled population, median PFS was 22.5 months (95% CI: 19.2–NE) in the patients without detectable *ALK* fusion versus 11.1 months (95% CI: 8.0–19.3) in the patients with detectable *ALK* fusion (HR = 0.48 [95% CI: 0.32–0.71], $p = 0.0002$). Among the patients with a detectable *EML4-ALK* fusion, variant 3 (v3) was detected at a higher rate in the patients in the brigatinib arm (16 of 28; 57%) than those in the alectinib arm (15 of 44; 34%; Supplementary Table 6). In the pooled population, patients with *EML-ALK* fusion v3 had poorer median PFS (7.2 mo [95% CI: 4.6–NE]) than patients with variant 1 (v1; 19.3 mo [95% CI: 13.8–NE]; HR [v1 versus v3], 2.53 [95% CI: 1.22–5.25], $p = 0.0123$; Fig. 3*C*), with similar outcomes in both treatment arms (Fig. 3*D*).

Among 56 patients with detectable *ALK* fusion and plasma samples evaluated for *TP53* mutations, 20 (36%) had a *TP53* mutation detected, with a similar prevalence in the brigatinib (38% [nine of 24]) and alectinib (34% [11 of 32]) arms. In the pooled population, median PFS

was 7.4 months (95% CI: 5.5–NE) in the patients with a *TP53* mutation and 13.6 months (95% CI: 8.0–NE) in the patients without a *TP53* mutation. Comparison by *TP53* status and treatment group was limited by the small population size.

Results for *ALK* mutations are reported in the Results section of the Supplementary Materials.

Discussion

The phase 3 ALTA-3 trial was the first head-to-head study to compare the efficacy and safety of two next-generation ALK TKIs in patients with *ALK*+ NSCLC post-crizotinib. At interim analysis, median BIRC-assessed PFS was almost identical between the brigatinib (19.3 mo) and alectinib arms (19.2 mo; HR = 0.97 [95% CI: 0.66–1.42], $p = 0.8672$). The study met the prespecified threshold for futility, and the independent data monitoring committee recommended closing the study. Median OS was immature at the time of analysis (overall event rate: 17%) and may be confounded by disproportionate use of subsequent third-generation ALK TKIs in the alectinib arm. Presence of baseline brain metastases (brigatinib, 64%; alectinib, 61%) and use of prior brain radiotherapy (brigatinib, 27%; alectinib, 23%) were equivalent across the treatment groups. Intracranial response was similar in the patients with measurable disease at baseline, with BIRC-assessed confirmed intracranial ORR of 73% and 68% in the brigatinib and alectinib arms, respectively.

Both treatments were associated with the longest PFS reported to date in crizotinib-pretreated *ALK*+ NSCLC. For brigatinib, the median BIRC-assessed PFS in ALTA-3 (19.3 mo) was approximately 3 months longer than in previous reports (14.7–16.8 mo), whereas the confirmed ORR (52%) was consistent with previous observations of 56% to 57%.[24,25] In contrast, median PFS with alectinib in ALTA-3 (19.2 mo) was approximately double that of previous reports (8.1–10.9 mo), and the confirmed ORR (61%) was greater than previously reported unconfirmed ORRs (46%–51%).[20,22,23] None of the subgroups evaluated were associated with differential benefit from brigatinib or alectinib.

The ALTA-3 patient population had some characteristics that may have contributed to better outcomes compared with previous studies. First, patients were not as heavily pretreated as those in prior studies, as 33% of the patients in ALTA-3 had received prior chemotherapy, compared with 72% to 80% in previous post-crizotinib studies.[29] Second, the median duration of prior crizotinib treatment in ALTA-3 (16.8 mo) was longer than in phase 2 studies of post-crizotinib brigatinib (13.2 mo)[28] and alectinib (12.0 mo)[30] and in the phase 3 PROFILE 1014 trial of first-line crizotinib (14.7 mo),[31] suggesting that patients in this trial may have had ALK TKI-sensitive disease and were therefore more likely to have a good prognosis. Nevertheless, it is important to note that time on crizotinib treatment is not the same as PFS, given that patients may have continued crizotinib treatment after disease progression. Third, the proportion of patients with ctDNA-detectable *ALK* fusion in ALTA-3 (34%) was lower than in previous studies in crizotinib-pretreated (brigatinib, 45%[32]; alectinib, 55%)[20] and treatment-naive *ALK*+ NSCLC (alectinib [ALEX]: 70%[33]; brigatinib [ALTA-1L]: 54%).[25] These findings were consistent with a lower tumor burden and possibly smaller tumor volume, suggestive of indolent disease progression on crizotinib. Patients without detectable *ALK* fusions in ctDNA are likely to have improved treatment outcomes, because detectability of *ALK* fusions in the plasma is thought to be associated with more advanced disease stage increasing cell turnover, and therefore increased tumor shedding of ctDNA into the blood.[33,34] In this study, median PFS was doubled in patients without versus with detectable *ALK* fusions (22.5 versus 11.1 mo), confirming an association between ctDNA shedding and prognosis and consistent with previous reports for crizotinib and alectinib.[33,34] Biomarker analyses also confirmed that detection of *EML4-ALK* fusion v3 was prognostic, with poorer PFS in patients with *EML4-ALK* fusion v3 versus v1, consistent with previous findings for brigatinib and alectinib.[25,35] The relative incidence of *EML4-ALK* fusions v1 and v3 was imbalanced between the treatment arms; v3 was more prevalent than v1 in the brigatinib arm but not in the alectinib arm. This difference may have contributed to the unexpectedly longer PFS with alectinib than previously reported in this setting.[20,22,23] Baseline rates of the *TP53* mutation, previously reported to be associated with poorer prognosis,[20,25,36,37] were similar between the arms.

Investigator-assessed PFS was shorter than BIRC-assessed PFS in this study. Patients were initially assessed for PFS events by the investigators, followed by BIRC assessment. The number of patients deemed as having a PFS event was greater for investigator assessment (brigatinib, n = 64; alectinib, n = 60) than for BIRC assessment (brigatinib, n = 50; alectinib, n = 57), leading to different median PFS results. Some level of discordance between BIRC- and investigator-based assessments is common. It is possible that investigators were focused on ensuring that patients received their next therapy as rapidly as possible, potentially resulting in premature assessment of disease progression and underestimation of investigator-assessed PFS compared with the BIRC assessment.

Patient QoL improved with both treatments. Time to worsening in EORTC QLQ-C30 scores was similar between the treatments with respect to most functions and

symptoms, except that brigatinib delayed time to worsening in constipation compared with alectinib, whereas alectinib delayed time to worsening in nausea, vomiting, and loss of appetite compared with brigatinib. These differences are consistent with the AE profile of each drug.

The safety profiles of brigatinib and alectinib were consistent with the well-established and unique profiles for both drugs,[19,25,28,29,38,39] and no new safety concerns were identified. The rate of early onset pneumonitis or ILD with brigatinib (2%) was low and consistent with rates in ALTA-1L (3%) and J-ALTA (1%).[40,41] The higher rate of dose modifications owing to TRAEs in the brigatinib arm was driven by protocol-mandated dose reductions and interruptions for laboratory abnormalities, predominantly increased blood CPK level. A protocol amendment was implemented to require accompanying muscular symptoms for dose modifications owing to elevated CPK, in keeping with current clinical practice and label guidance.[15]

In conclusion, brigatinib was not superior to alectinib and had similar efficacy in this first head-to-head trial of two newer ALK TKIs in patients with *ALK*+ NSCLC that had progressed on crizotinib. The study met the futility criterion for efficacy and is being discontinued. Both brigatinib and alectinib were associated with the longest reported PFS in crizotinib-pretreated *ALK*+ NSCLC. Safety and tolerability were consistent with the well-established and unique profiles of brigatinib and alectinib, and no new safety signals were observed. These data support brigatinib and alectinib as standard treatment options for patients with crizotinib-pretreated *ALK*+ NSCLC. Future follow-up and subgroup analyses from ALTA-3 will provide additional insights into the treatment with second-generation ALK TKIs in patients with *ALK*+ NSCLC post-crizotinib.

CRediT Authorship Contribution Statement

James Chih-Hsin Yang: Study investigator, Enrolled patients, Data interpretation, Manuscript review and revisions, Final approval of manuscript.

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Shun Lu: Study investigator, Enrolled patients, Data interpretation, Manuscript review and revisions, Final approval of manuscript.

Jianxing He: Study investigator, Enrolled patients, Data interpretation, Manuscript review and revisions, Final approval of manuscript.

Mauricio Burotto: Study investigator, Enrolled patients, Data interpretation, Manuscript review and revisions, Final approval of manuscript.

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Sylvie Vincent: Data interpretation, Manuscript review and revisions, Final approval of manuscript.

Jiani Yin: Data interpretation, Manuscript review and revisions, Final approval of manuscript.

Xin Ma: Data interpretation, Manuscript review and revisions, Final approval of manuscript.

Huamao M Lin: Data interpretation, Manuscript review and revisions, Final approval of manuscript.

Sanjay Popat: Study design, Data interpretation, Manuscript review and revisions, Manuscript preparation, Final approval of manuscript.

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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 from the completed study within 3 months from initial request, to researchers who provide a methodologically sound proposal. The data will be provided after deidentification, in compliance with applicable privacy laws, data protection, and requirements for consent and anonymization.

Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of*

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