Alectinib versus crizotinib in patients with *ALK*-positive non-small-cell lung cancer (J-ALEX): an open-label, randomised phase 3 trial

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Summary

Background Alectinib, a potent, highly selective, CNS-active inhibitor of anaplastic lymphoma kinase (ALK), showed promising efficacy and tolerability in the single-arm phase 1/2 AF-001JP trial in Japanese patients with *ALK*-positive non-small-cell lung cancer. Given those promising results, we did a phase 3 trial to directly compare the efficacy and safety of alectinib and crizotinib.

Methods J-ALEX was a randomised, open-label, phase 3 trial that recruited ALK inhibitor-naive Japanese patients with *ALK*-positive non-small-cell lung cancer, who were chemotherapy-naive or had received one previous chemotherapy regimen, from 41 study sites in Japan. Patients were randomly assigned (1:1) via an interactive web response system using a permuted-block method stratified by Eastern Cooperative Oncology Group performance status, treatment line, and disease stage to receive oral alectinib 300 mg twice daily or crizotinib 250 mg twice daily until progressive disease, unacceptable toxicity, death, or withdrawal. The primary endpoint was progression-free survival assessed by an independent review facility. The efficacy analysis was done in the intention-to-treat population, and safety analyses were done in all patients who received at least one dose of the study drug. The study is ongoing and patient recruitment is closed. This study is registered with the Japan Pharmaceutical Information Center (number JapicCTI-132316).

Findings Between Nov 18, 2013, and Aug 4, 2015, 207 patients were recruited and assigned to the alectinib (n=103) or crizotinib (n=104) groups. At data cutoff for the second interim analysis, 24 patients in the alectinib group had discontinued treatment compared with 61 in the crizotinib group, mostly due to lack of efficacy or adverse events. At the second interim analysis (data cutoff date Dec 3, 2015), an independent data monitoring committee determined that the primary endpoint of the study had been met (hazard ratio 0·34 [99·7% CI 0·17–0·71], stratified log-rank p<0·0001) and recommended an immediate release of the data. Median progression-free survival had not yet been reached with alectinib (95% CI 20·3–not estimated) and was 10·2 months (8·2–12·0) with crizotinib. Grade 3 or 4 adverse events occurred at a greater frequency with crizotinib (54 [52%] of 104) than alectinib (27 [26%] of 103). Dose interruptions due to adverse events were also more prevalent with crizotinib (77 [74%] of 104) than with alectinib (30 [29%] of 103), and more patients receiving crizotinib (21 [20%]) than alectinib (nine [9%]) discontinued the study drug because of an adverse event. No adverse events with a fatal outcome occurred in either treatment group.

Interpretation These results provide the first head-to-head comparison of alectinib and crizotinib and have the potential to change the standard of care for the first-line treatment of *ALK*-positive non-small-cell lung cancer. The dose of alectinib (300 mg twice daily) used in this study is lower than the approved dose in countries other than Japan; however, this limitation is being addressed in the ongoing ALEX study.

Funding Chugai Pharmaceutical Co, Ltd.

Introduction

Non-small-cell lung cancer with anaplastic lymphoma kinase fusion gene-rearrangement (*ALK* positive) is a distinct subset of lung cancer in approximately 5% of patients with advanced adenocarcinoma.[1–3] ALK fusion proteins promote tumour cell growth and survival through the aberrant activation of intracellular signalling.[4,5] Lung cancers harbouring ALK fusion proteins are highly sensitive to ALK tyrosine kinase inhibitors, which efficiently induce apoptosis.[6,7]

The first approved ALK inhibitor, crizotinib, significantly prolonged progression-free survival compared with chemotherapy in patients with untreated and chemotherapy-treated advanced *ALK*-positive non-small-cell lung cancer.[8,9] Crizotinib is approved in Japan (since March, 2012) and the USA (since August, 2011) in any line of treatment, and was approved in the European Union in October, 2012, in the first-line setting.[10–12] However, emergence of resistance to crizotinib is almost inevitable after a median of 10·9 months.[8] This resistance could be due to secondary mutations or amplification of *ALK*, activation of downstream molecules, or poor penetration to the CNS, which is the most common site of progressive disease.[9,13]

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Research in context

Evidence before this study

The selective anaplastic lymphoma kinase tyrosine kinase inhibitor, alectinib, has shown both systemic and CNS efficacy in patients with *ALK*-positive non-small-cell lung cancer. Alectinib showed high activity in patients with chemotherapy-pretreated, *ALK*-positive non-small-cell lung cancer in the phase 1/2 Japanese AF-001JP study, and in crizotinib-refractory patients with *ALK*-positive non-small-cell lung cancer, in two pivotal single-arm phase 2 trials, the global NP28673 study and the North American NP28761 study. No randomised phase 3 trials had been initiated at the design stage of this study. We searched PubMed for English language articles published up to Oct 1, 2016, using the search terms "alectinib", "NSCLC", "*ALK*-rearranged", and "*ALK*-positive", but found no evidence of phase 3 trials reporting clinical data for alectinib.

Added value of this study

This is the first trial, to our knowledge, to directly compare two ALK inhibitors in a predominantly first-line treatment setting, resulting in a favourable progression-free survival for alectinib versus crizotinib. Results of this phase 3 randomised trial showed that alectinib has greater clinical efficacy and better tolerability than the current standard of care, crizotinib, in ALK inhibitor-naive patients with *ALK*-positive non-small-cell lung cancer.

Implications of all the available evidence

Results of this study provide the first head-to-head comparison of alectinib and crizotinib and have the potential to change the standard first-line treatment of *ALK*-positive non-small-cell lung cancer. ALK positivity was confirmed in this study using immunohistochemistry and fluorescence in-situ hybridisation (FISH), or by RT-PCR. Previous studies suggest that concordance between the immunohistochemistry and FISH ALK test is high, thus the results of this study might generalise to patients with ALK positivity confirmed by only immunohistochemistry. The use of immunohistochemistry as a sole diagnostic test will be assessed in the ongoing ALEX study, which will compare the efficacy and safety of alectinib with crizotinib in patients with treatment-naive *ALK*-positive non-small-cell lung cancer.

Alectinib is a selective ALK inhibitor with high CNS penetration;[14,15] it is active against several secondary mutations that confer acquired resistance to crizotinib such as Thr1151_Leu1152insThr, Leu1196Met, Cys1156Tyr, Phe1174Leu, and Gly1269Ala. In a Japanese single-arm, open-label, phase 1/2 study (AF-001JP),[16] alectinib showed high activity in chemotherapy-pretreated, ALK tyrosine kinase inhibitor-naive patients with *ALK*-positive non-small-cell lung cancer. The proportion of patients who achieved an objective response was 93·5% (95% CI 82·1–98·6) with 43 of 46 evaluable patients responding to treatment; the median progression-free survival has not yet been reached, but is anticipated to be longer than 29 months.[16,17] These findings led to the approval of alectinib in Japan in July, 2014.[18] In the USA, alectinib received accelerated approval by the US Food and Drug Administration in 2015 following results from two pivotal single-arm phase 2 trials (the global NP28673[19] and the North American NP28761[20] studies) in patients with disease progression while on crizotinib.[19,20]

Given the promising efficacy and tolerability of alectinib in the AF-001JP study, we did a phase 3 trial (J-ALEX) to directly compare the efficacy and safety of alectinib and crizotinib in Japanese patients with advanced *ALK*-positive non-small-cell lung cancer.

Methods

Study design and participants

J-ALEX is a multicentre, randomised, open-label trial done at 41 study sites in Japan. The trial enrolled ALK inhibitor-naive Japanese patients with *ALK*-positive advanced non-small-cell lung cancer, who were chemotherapy-naive or who had received one previous chemotherapy regimen. Although the favourable safety profile of alectinib was shown by the AF-001JP study,[16] J-ALEX followed an open-label design to ensure safety in individual patients, for whom the doctors had little clinical experience. Also, from an ethical perspective, the study was open label to reduce the burden on patients caused by administering placebo (eight capsules of alectinib need to be taken for each single dose because of the restricted formulation that was available at study initiation, and this would have had to be matched in the crizotinib group).

Eligible patients were aged 20 years or older, with histologically or cytologically confirmed stage IIIB, stage IV, or postoperative recurrent non-small-cell lung cancer that was confirmed to be *ALK*-positive by immunohistochemistry and fluorescence in-situ hybridisation (FISH), or RT-PCR using tissue or cell samples. Patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, and had at least one measurable lesion assessed by physicians based on Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Patients also had to have major organ function within 14 days before enrolment, and consent to use contraception during the study period.

Key exclusion criteria were previous treatment with an ALK inhibitor, meningeal metastases or brain metastases that were symptomatic or required treatment (if palliative treatment, such as with steroids, had been administered after treatment of metastatic brain lesions, then less than 2 weeks must have elapsed since the last dose at enrolment), pleural effusion, ascites, or pericardial effusion requiring drainage, or current or previous radiologically evident interstitial lung disease. For full details

of all inclusion and exclusion criteria, please see the appendix pp 1–2.

The study was done in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice in Japan. The study protocol was reviewed by and approval was obtained from the Institutional Review Board of each study centre, from the perspective of ethical, scientific, and medical validity. All patients provided written informed consent before any study-related procedures were done.

Randomisation and masking

Patients were randomly assigned in a 1:1 ratio, using a stratified permuted-block method, to receive alectinib or crizotinib. Randomisation was done via an interactive web response system (IxRS; EPS Corporation, Tokyo, Japan) using a randomisation code generated independently by the IxRS vendor. Randomisation was stratified by ECOG performance status (0 or 1 *vs* 2), treatment line (first *vs* second), and disease stage (IIIB or IV *vs* postoperative recurrence). Investigators from each study site enrolled patients through IxRS, which provided the treatment assignment information. Participants, people administering the treatment, and those analysing the data were all aware of group assignment. Members of the Independent Review Facility (IRF) who assessed the primary endpoint were masked to treatment and to the investigators' assessment for each patient.

Procedures

Patients received oral alectinib (eight capsules totalling 300 mg; Chugai Pharmaceutical Co, Ltd, Tokyo, Japan) or crizotinib (one capsule totalling 250 mg; Pfizer, Tokyo, Japan) twice daily until progressive disease (unless continuation of treatment was considered clinically meaningful by a physician), unacceptable toxicity, death, or a desire to withdraw. The dose of alectinib was selected on the basis of results of the AF-001JP study,[16,17] which showed high activity and good tolerability with 300 mg twice daily (the approved dose in Japan). Treatment crossover after study withdrawal was allowed in both study groups. Patients initially randomly assigned to the crizotinib group who withdrew from the study because of progressive disease before the approval of alectinib (ie, before September, 2014), were permitted to receive alectinib during the study.

ALK positivity was confirmed centrally by immunohistochemistry and FISH or by RT-PCR, in accordance with published guidelines.[21] ALK protein expression status was determined using high-sensitivity immunohistochemistry with the Histofine ALK iAEP kit (Nichirei Bioscience, Tokyo, Japan).[17] ALK immunohistochemistry results were classified into four categories according to proportion of positive staining: iScore 3, 2, 1, and 0. iScores of 1 (>0% to ≤50% positive), 2 (>50% to ≤80%), or 3 (>80%) were considered *ALK*-positive, and iScores of 0 were considered *ALK*-negative. *ALK* translocations were determined using a Vysis ALK Break Apart FISH Probe kit (Abbott Molecular, Abbot Park, USA). Lesions and tumour markers were assessed at follow-ups until progression was seen, every 4 weeks until week 12, every 8 weeks from week 12 to week 76, and every 12 weeks thereafter until progressive disease or death according to RECIST version 1.1.

See Online for appendix

Outcomes

The primary endpoint was progression-free survival as assessed by the IRF. Secondary endpoints were investigator-assessed progression-free survival, overall survival, proportion of patients who achieved an objective response, duration of response, time to response, time to progression of brain metastatic lesions in patients who had them at baseline, and time to onset of brain metastatic lesions in patients who did not have them at baseline, health-related quality of life (HRQOL), safety, and pharmacokinetics. HRQOL data will be reported separately. Exploratory endpoints were detection of *ALK* genetic mutations and biomarkers associated with efficacy.

IRF-assessed progression-free survival was defined as the time from randomisation to imaging-confirmed progressive disease on the basis of RECIST criteria or death from any cause, whichever occurred first; investigator-assessed progression-free survival was defined as the time from randomisation to confirmed progressive disease on the basis of RECIST, clinical progression based on symptomatic deterioration, or death from any cause, whichever occurred first. Patients without a progression-free survival event at the time of the analysis were censored at the date of their last tumour assessment. Overall survival was defined as the time from randomisation to death from any cause. The proportion of patients with an objective response was defined as the proportion of patients with a complete response or a partial response according to RECIST version 1.1. Duration of response was defined as the time from when the criteria for a complete response or partial response were first met to the occurrence of a progression-free survival event. Time to response was defined as the time from randomisation until the time when the criteria for a complete response or partial response were first met. Time to onset of brain matastatic lesions in patients who did not have them at baseline was defined as the time from randomisation to onset of brain metastatic lesions or death, whichever occurred first; and time to progression of brain metastatic lesions in patients who had them at baseline was the time from randomisation to progression of brain metastatic lesions or death.

We also prespecified a series of sensitivity analyses regarding the definition of progression-free survival to assess the robustness of the primary endpoint results.

Adverse events were recorded and graded according to the National Cancer Institute Common Terminology

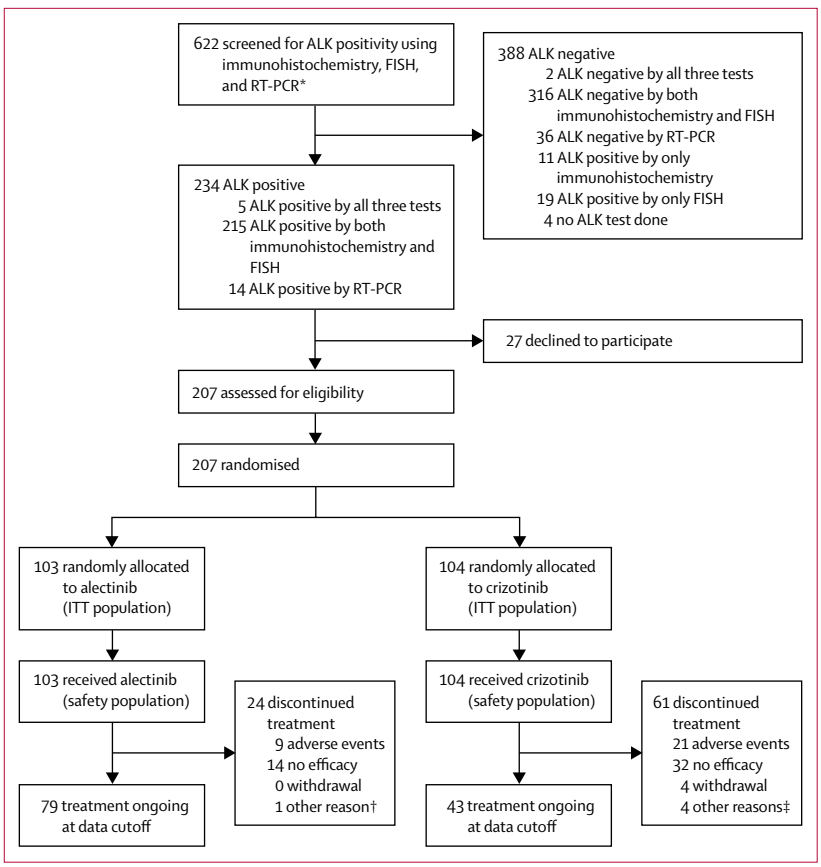

Figure 1: **CONSORT diagram**
ALK=anaplastic lymphoma kinase. FISH=fluorescence in-situ hybridisation. ITT=intention-to-treat. *Patients for ALK retest were included. †One poor compliance. ‡One breast cancer, one patient relocation, and two adverse events.

Criteria for Adverse Events version 4.0 and classified according to the Medical Dictionary for Regulatory Activities.

Statistical analysis

We defined two clinical hypotheses for progression-free survival: the non-inferiority hypothesis (we defined the non-inferiority margin on the hazard ratio [HR] scale as 1·2) and the superiority hypothesis. We applied a hierarchical hypothesis testing procedure and tested the non-inferiority hypothesis first. The superiority hypothesis was tested only if the non-inferiority null hypothesis was rejected.

We planned a target sample size of 200 patients, assuming an enrolment period of 44 months. The time taken to achieve the required 164 progression-free survival events was estimated to be 57 months from the first patient in. This number of events would provide statistical power of 80% for a superiority hypothesis and 97·8% for a non-inferiority hypothesis at a two-sided significance level of 5% under a targeted HR of 0·643, which would correspond to a median progression-free survival of 14·0 months for alectinib and 9·0 months for crizotinib. For overall survival, 150 events would provide 70% statistical power for a superiority hypothesis, under a targeted HR of 0·667, which would correspond to a median overall survival of 30·0 months for alectinib and 20·0 months for crizotinib. Overall survival analyses were only done if the null hypothesis for the superiority in progression-free survival was rejected. Analysis undertaken before reaching the planned number of events was done as an interim analysis using independent O'Brien and Fleming-type alpha spending functions for progression-free survival and overall survival.

We used Kaplan-Meier methods to estimate progression-free survival and other time-to-event endpoints. A stratified Cox regression model was used to estimate the HR and 95% CI of progression-free survival and other time-to-event endpoints using the stratification factors for randomisation; a non-inferiority hypothesis was demonstrated when the upper confidence limit of the HR was lower than 1·2. A stratified log-rank test was used to assess a superiority hypothesis. Efficacy analyses were done in the intention-to-treat population, which comprised all randomly assigned patients. Objective response was analysed in patients with measurable lesions at baseline. Safety was analysed in the safety population, which comprised all patients who received at least one dose of treatment. All statistical analyses were performed using SAS, version 9.2 (SAS Institute, Cary, NC, USA).

Initially, two interim analyses of progression-free survival were planned to investigate early study termination for efficacy when 50% (82 events) and 75% (123 events) of the required number of progression-free survival events had been observed. However, following promising results from the AF-001JP study[22] (data cutoff Jan 31, 2014), the protocol was amended to include an interim analysis after 33% (55 events) of the events had occurred. The interim analyses were undertaken by the independent data coordinating centre, and results were assessed by the independent data monitoring committee (IDMC).

This study is registered with the Japan Pharmaceutical Information Center (number JapicCTI-132316).

Role of the funding source

The trial was designed and funded by Chugai Pharmaceutical Co, Ltd. The funder was involved in the study design, data collection, data analysis, data interpretation, and writing of the report for publication. All authors had full access to relevant aggregated study data and the corresponding author had final responsibility for the decision to submit for publication.

Results

Between Nov 18, 2013, and Aug 4, 2015, 207 patients were enrolled and randomly assigned to receive alectinib (n=103) or crizotinib (n=104; figure 1).

The numbers of patients with measurable disease at baseline, as assessed by the IRF, were 83 (81%) of 103 in

the alectinib group and 90 (87%) of 104 in the crizotinib group. Patient characteristics were balanced between the two treatment groups (table 1). The only exception was the proportion of patients with brain metastases at baseline, which was higher in the crizotinib group (29 [28%] of 104) than in the alectinib group (14 [14%] of 103). Only four patients (two [2%] in each treatment group) with ECOG performance status 2 were enrolled.

The study met its primary endpoint of showing superiority of alectinib in IRF-assessed progression-free survival, at the second preplanned interim analysis (Dec 3, 2015); non-inferiority was also shown compared with crizotinib (the upper confidence limit of HR was lower than pre-defined non-inferiority margin 1·2; appendix p 3); the median follow-up was 12·0 months (IQR 6·5–15·7) in the alectinib group and 12·2 months (8·4–17·4) in the crizotinib group. The funder decided to immediately release the trial results on the basis of a recommendation from the IDMC. Median progression-free survival was significantly improved with alectinib (not estimable [NE] [95% CI 20·3–NE]) compared with crizotinib (10·2 months [8·2–12·0]; HR 0·34 [99·7% CI 0·17–0·71]; stratified log-rank test p<0·0001) with 83 progression-free survival events (25 in the alectinib group and 58 in the crizotinib group; figure 2A). Patients receiving alectinib in both the first-line and second-line setting showed consistently improved progression-free survival compared with crizotinib; in the first-line setting median progression-free survival was NE (95% CI 17·5–NE) in the alectinib group versus 10·2 months (8·3–13·9) in the crizotinib group (HR 0·31 [95% CI 0·17–0·57]), and in the second-line setting it was 20·3 months (20·3–NE) versus 8·2 months (6·4–15·7; HR 0·40 [0·19–0·87]; figure 2B). Both in postoperative patients and in patients with stage IIIB or stage IV disease, alectinib showed consistently improved progression-free survival compared with crizotinib (postoperative patients: NE [10·2–NE] in the alectinib group *vs* 11·8 months [8·3–NE] in the crizotinib group; HR 0·55 [95% CI 0·20–1·48]; stage IIIB or IV patients: 20.3 [17·5–NE] in the alectinib group *vs* 8·3 months [6·5–13·9] in the crizotinib group; HR 0·30 [95% CI 0·18–0·52]; figure 2C). In general, the superiority trend in terms of progression-free survival of alectinib over crizotinib was consistent across most predefined patient subgroups (figure 3).

Investigator-assessed progression-free survival and preplanned sensitivity analyses with regards to the definition of progression-free survival showed similar results to the primary analysis (appendix p 6). Multiple stratified Cox regression analysis, adjusting for the potential effect of imbalance in the distribution of prognostic factors between treatment groups—including brain metastases—on IRF-assessed progression-free survival, also showed a similar HR for treatment groups as the primary analysis (HR 0·34 [95% CI 0·21–0·55]; p<0·0001; appendix p 7).

	Alectinib (n=103)	Crizotinib (n=104)
Age (years)	61·0 (27–85)	59·5 (25–84)
Sex		
Male	41 (40%)	41 (39%)
Female	62 (60%)	63 (61%)
ECOG performance status		
0	54 (52%)	48 (46%)
1	47 (46%)	54 (52%)
2	2 (2%)	2 (2%)
Cellular classification		
Squamous cell carcinoma	2 (2%)	0
Adenocarcinoma	100 (97%)	103 (99%)
Other	1 (1%)	1 (1%)
Disease stage		
IIIB	3 (3%)	3 (3%)
IV	76 (74%)	75 (72%)
Postoperative recurrence	24 (23%)	26 (25%)
Treatment line		
First	66 (64%)	67 (64%)
Second	37 (36%)	37 (36%)
Measurable disease at baseline (IRF)		
Yes	83 (81%)	90 (87%)
No	20 (19%)	14 (13%)
Brain metastases at baseline (IRF)		
Yes	14 (14%)	29 (28%)
No	89 (86%)	75 (72%)
Brain metastases at baseline (investigator)		
Yes	16 (16%)	31 (30%)
No	87 (84%)	73 (70%)
Smoking status		
Never smoked	56 (54%)	61 (59%)
Current smoker	2 (2%)	3 (3%)
Past smoker	45 (44%)	40 (38%)
ALK test method		
Immunohistochemistry and FISH	96 (93%)	94 (90%)
RT-PCR	7 (7%)	10 (10%)

Data are median (range) and n (%). ECOG=Eastern Cooperative Oncology Group. IRF=independent review facility. ALK=anaplastic lymphoma kinase. FISH=fluorescence in-situ hybridisation.

Table 1: **Baseline patient characteristics**

Overall survival data in both groups are still immature with only nine events reported (two [2%] of 104 in the crizotinib group and seven [7%] of 103 in the alectinib group).

The proportion of patients with at least one measurable lesion, who achieved an objective response as assessed by the IRF, was greater with alectinib (76 of 83 [92%, 95% CI 85·6–97·5]) than with crizotinib (71 of 90 [79%, 70·5–87·3]; table 2; appendix p 5). Time to response with alectinib and crizotinib was short, and most patients had responded within 1 month. Objective response assessed by the investigators also favoured alectinib, at 85% (95% CI 78·6–92·3; 88 of 103) compared with 70% (61·4–79·0; 73 of

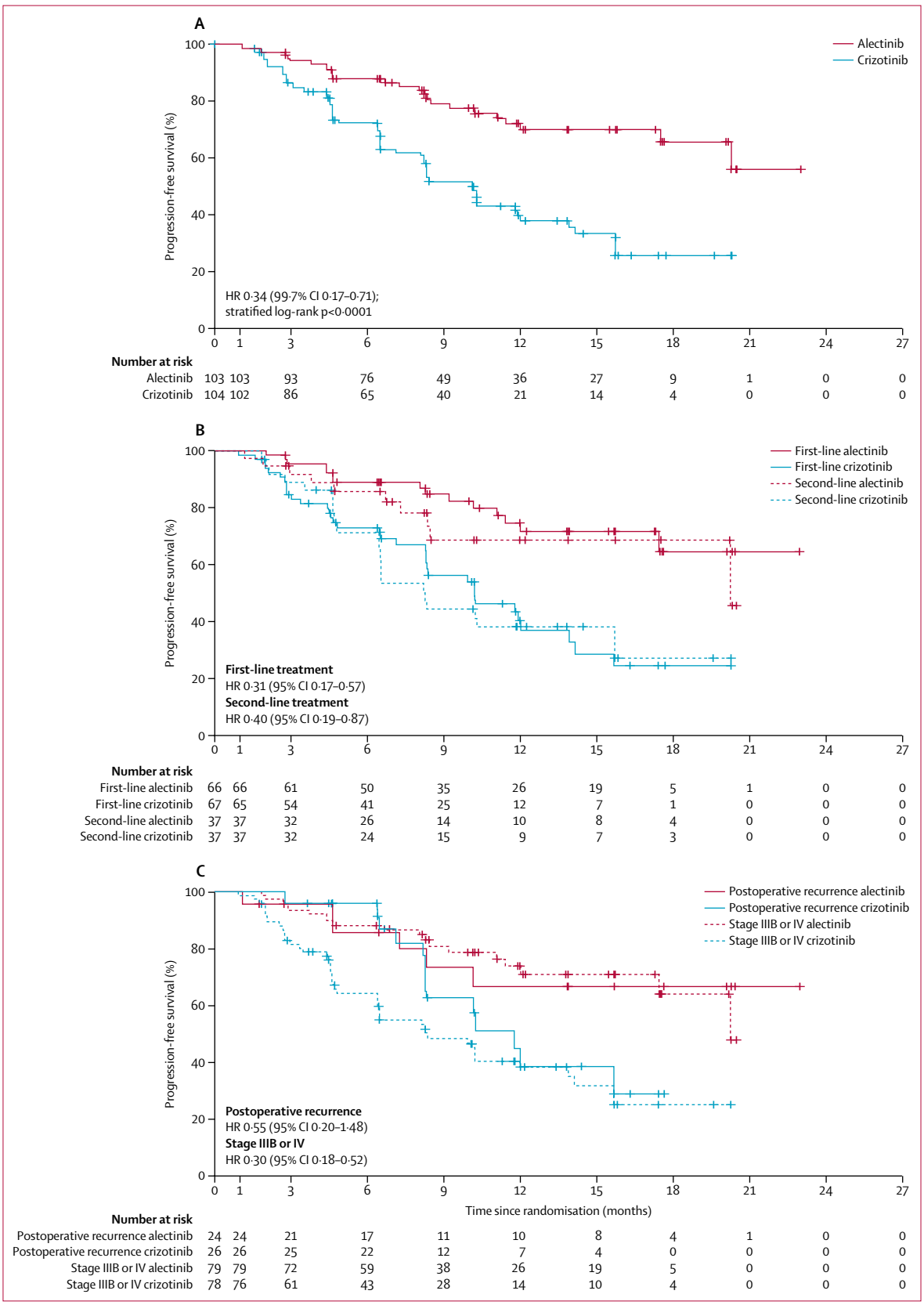

***Figure 2*: Progression-free survival outcomes**
Kaplan-Meier curves of progression-free survival in the intention-to-treat population (A), by line of treatment (B), and by disease stage (C). Hazard ratios were estimated by a stratified Cox analysis.

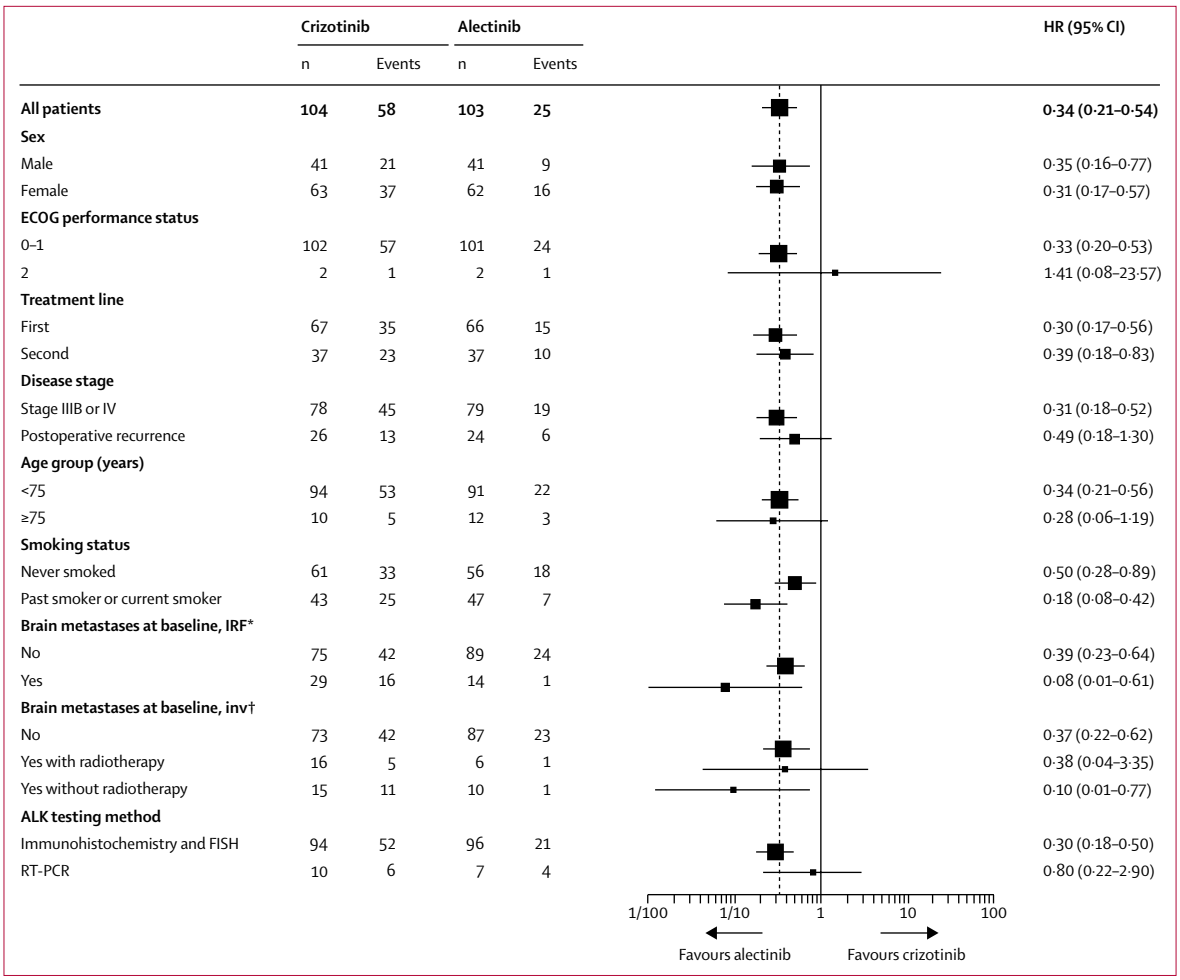

Figure 3: **Forest plot of progression-free survival in patient subgroups**
HRs were estimated by an unstratified Cox model. ALK=anaplastic lymphoma kinase. ECOG=Eastern Cooperative Oncology Group. FISH=fluorescence in-situ hybridisation. HR=hazard ratio. Inv=investigator. IRF=independent review facility. *Assessed by IRF. †Assessed by study investigator.

104) in the crizotinib group (table 2). According to the IRF, duration of response was longer with alectinib than with crizotinib (HR 0·32, 95% CI 0·17–0·60; table 2). The HR for the time to progression of brain metastatic lesion or death for patients with brain metastatic lesions at baseline was 0·16 (0·02–1·28) and HR for the time to onset of brain metastatic lesion or death for patients without brain metastatic lesions at baseline was 0·41 (0·17–1·01).

All patients were included in the safety population. All-grade adverse events occurring at a frequency of more than 20% with crizotinib were nausea (77 [74%] of 104 patients), diarrhoea (76 [73%]), vomiting (60 [58%]), visual disturbances (57 [55%]), dysgeusia (54 [52%]), constipation (46 [44%]), alanine aminotransferase increase (33 [32%]), aspartate aminotransferase increase (32 [31%]), nasopharyngitis (24 [23%]), pyrexia (21 [20%]), and decreased appetite (21 [20%]). Only two all-grade adverse events were reported at a frequency of more than 20% in the alectinib group, namely constipation (36 [35%] of 103 patients) and nasopharyngitis (21 [20%]; table 3). Several adverse events occurred with a 10% or greater difference in the crizotinib group versus the alectinib group, with the greatest difference seen for nausea (77 [74%] of 104 *vs* 11 [11%] of 103), diarrhoea (76 [73%] *vs* nine [9%]), and visual disturbances (57 [55%] *vs* one [1%]; table 3). The total number of patients with at least one grade 3 or 4 adverse event was higher in the crizotinib group (54 [52%] of 104) than in the alectinib group (27 [26%] of 103; appendix p 8). Dose interruptions due to adverse events were more frequent with crizotinib (77 [74%] of 104) than alectinib (30 [29%] of 103), and more patients receiving crizotinib discontinued study drug due to an adverse event (21 [20%]) than those receiving alectinib (nine [9%]). The main reasons for withdrawal included grade 1–3 interstitial lung disease (eight [8%] of 104 for crizotinib *vs* eight [8%] of 103 for alectinib), grade 3–4 abnormal hepatic function (five [5%] *vs* none), and grade 3–4 increased alanine aminotransferase (four [4%] *vs* none). No adverse events with a fatal outcome occurred.

Alectinib plasma trough concentrations were measured on day 57 and day 113 (before the morning dose) following 300 mg twice daily dosing. The mean (SD) trough concentrations were similar, at 479 (SD 240) ng/mL on day 57, and 493 (287) ng/mL on day 113.

	Alectinib	Crizotinib
Assessed by IRF		
Total	83	90
Objective response	92% (85·6–97·5)	79% (70·5–87·3)
Complete response	2 (2%)	2 (2%)
Partial response	74 (89%)	69 (77%)
Stable disease	4 (5%)	12 (13%)
Time to response (months)	1·0 (1·0–1·1)	1·0 (1·0–1·0)
Duration of response (months)	NE (NE–NE)	11·1 (7·5–13·1)
Assessed by investigators		
Total	103	104
Objective response	85% (78·6–92·3)	70% (61·4–79·0)
Complete response	5 (5%)	2 (2%)
Partial response	83 (81%)	71 (68%)
Stable disease	13 (13%)	19 (18%)
Time to response (months)	1·0 (1·0–1·1)	1·0 (1·0–1·0)
Duration of response (months)	NE (16·7–NE)	11·2 (8·5–13·9)

Data are n, % (95% CI), n (%), or median (95% CI). IRF=independent review facility. NE=not estimable.

Table 2: **Summary of response data**

	All grades		Grade 3 or 4	
	Alectinib (n=103)	Crizotinib (n=104)	Alectinib (n=103)	Crizotinib (n=104)
Gastrointestinal disorders				
Nausea	11 (11%)	77 (74%)	0	2 (2%)
Diarrhoea	9 (9%)	76 (73%)	0	2 (2%)
Constipation	36 (35%)	46 (44%)	1 (1%)	1 (1%)
Vomiting	6 (6%)	60 (58%)	0	2 (2%)
Stomatitis	12 (12%)	10 (10%)	0	0
Oesophagitis	0	11 (11%)	0	2 (2%)
Upper abdominal pain	2 (2%)	7 (7%)	0	0
Infections				
Nasopharyngitis	21 (20%)	24 (23%)	0	0
Upper respiratory tract infection	17 (17%)	15 (14%)	0	0
Bronchitis	6 (6%)	5 (5%)	0	0
Pharyngitis	7 (7%)	3 (3%)	0	0
Cystitis	6 (6%)	3 (3%)	0	0
Changes in laboratory values from baseline				
Aspartate aminotransferase increase	11 (11%)	32 (31%)	1 (1%)	5 (5%)
Alanine aminotransferase increase	9 (9%)	33 (32%)	1 (1%)	13 (13%)
Blood creatine phosphokinase increase	18 (17%)	11 (11%)	5 (5%)	3 (3%)
Neutrophil count decrease	3 (3%)	19 (18%)	2 (2%)	14 (14%)
Blood creatinine increase	11 (11%)	9 (9%)	0	0
Electrocardiogram QT prolonged	3 (3%)	15 (14%)	2 (2%)	7 (7%)
Blood bilirubin increase	12 (12%)	1 (1%)	0	0

(Table 3 continues on next page)

A preplanned exploratory analysis of cumulative incidence with competing events of death, CNS progression, and non-CNS progression indicated that alectinib reduced the risk of progression in both non-CNS and CNS lesions compared with crizotinib (appendix p 4).

Discussion

This is the first trial, to our knowledge, to directly compare two ALK inhibitors in a majority first-line treatment setting, resulting in a favourable progression-free survival for alectinib compared with crizotinib. The results show that alectinib has both systemic efficacy and can lead to intracranial disease control in patients with *ALK*-positive non-small-cell lung cancer and brain metastases. The characteristics of alectinib, including its potent ALK inhibitory activity, high selectivity, activity against *ALK* secondary mutations that are resistant to crizotinib, and CNS penetration,[14,15,23] might contribute to the significant result obtained in this study. This hypothesis was also supported by the result of a cumulative incidence analysis that indicated that alectinib reduced the risk of progression compared with crizotinib in both non-CNS and CNS lesions. In general, the superiority trend in terms of progression-free survival of alectinib over crizotinib was consistent across different patient subgroups. Notably, alectinib showed consistently improved progression-free survival compared with crizotinib in patients who had received one previous line of chemotherapy, and in those who were chemotherapy naive.

The proportion of patients with an ECOG performance status of 2 (four [2%] of 207) was lower than we anticipated on the basis of the PROFILE 1007 study,[9] but only 5% of patients had an ECOG performance status of 2 in the PROFILE 1014 study,[24] so our results were not markedly different to these previous results. ECOG performance status did not work efficiently as a stratification factor; however, this fact does not affect the conclusions of this study. The proportion of patients with brain metastases at baseline was higher in the crizotinib group (29 [28%]) than in the alectinib group (14 [14%]). Although brain metastasis is a known independent prognostic factor,[25] results of the multiple stratified Cox regression analysis for progression-free survival showed that this imbalance of patients with brain metastasis at baseline did not affect the conclusion of the primary efficacy analysis. Brain metastasis was not selected as a stratification factor in the study, because three stratification factors with eight strata were deemed adequate to ensure a sufficient number of patients in each strata with stable statistical analysis. Furthermore, treatment line, ECOG performance status, and clinical stage were considered to have higher priority as stratification factors than brain metastasis, given their potential influence on patient prognosis.

ALK positivity was confirmed in this study by immunohistochemistry and FISH in parallel, or by RT-PCR, as recommended in published guidelines.[21] The

guidelines suggest that immunohistochemistry can be used first to screen out patients with *ALK*-negative disease, so that only those with *ALK* immunohistochemistry-positive disease are retested by FISH. Some studies suggest that concordance between the immunohistochemistry and FISH ALK test is high;[17,26] the results of this study possibly generalise to the population who confirmed *ALK* positivity by only immunohistochemistry. The use of immunohistochemistry as a sole diagnostic test will be assessed in the ongoing multinational ALEX study (NCT02075840), which is comparing the efficacy and safety of alectinib with crizotinib in patients with treatment-naive *ALK*-positive non-small-cell lung cancer.

No new safety signals were identified with alectinib compared with previous studies,[19,20,22] and the safety profile of crizotinib was consistent with that reported previously in Japanese populations.[27] Alectinib showed a favourable adverse event profile compared with crizotinib. Grade 3 or 4 adverse events were more frequent with crizotinib than with alectinib. Additionally, discontinuation rates and dose interruptions due to adverse events were greater in the crizotinib group than in the alectinib group. Several adverse events were reported at a frequency of more than 20% in the crizotinib group (nausea, diarrhoea, vomiting, visual disturbances, dysgeusia, constipation, alanine aminotransferase increase, and aspartate aminotransferase increase) compared with just two adverse events (constipation and nasopharyngitis) in the alectinib group. The frequency of all-grade interstitial lung disease (8% with crizotinib *vs* 8% with alectinib) was higher than previously reported by Solomon and colleagues[8] (1%, with crizotinib treatment) and Seto and colleagues[16] (2%, with alectinib treatment). The reasons for these differences are unclear, but notably, six of eight patients in the alectinib group who had interstitial lung disease were older than 60 years; older age is a known risk factor for interstitial lung disease. Except for one patient in the crizotinib group, these events had resolved by study treatment discontinuation or concomitant treatment by data cutoff, or both.

	All grades		Grade 3 or 4	
	Alectinib (n=103)	Crizotinib (n=104)	Alectinib (n=103)	Crizotinib (n=104)
(Continued from previous page)				
Nervous system disorders				
Dysgeusia	19 (18%)	54 (52%)	0	0
Headache	5 (5%)	8 (8%)	0	0
Dizziness	2 (2%)	7 (7%)	0	0
Eye disorders				
Visual disturbances	1 (1%)	57 (55%)	0	0
Photopsia	0	14 (14%)	0	0
General disorders and administration site conditions				
Pyrexia	10 (10%)	21 (20%)	1 (1%)	0
Malaise	10 (10%)	19 (18%)	0	0
Peripheral oedema	9 (9%)	19 (18%)	0	1 (1%)
Skin and subcutaneous tissue disorders				
Rash	13 (13%)	17 (16%)	0	1 (1%)
Dry skin	8 (8%)	8 (8%)	0	0
Pruritus	4 (4%)	8 (8%)	0	0
Maculopapular rash	6 (6%)	6 (6%)	3 (3%)	1 (1%)
Musculoskeletal and connective tissue disorders				
Myalgia	16 (16%)	3 (3%)	0	0
Back pain	7 (7%)	6 (6%)	0	0
Respiratory, thoracic, and mediastinal disorders				
Interstitial lung disease	8 (8%)	8 (8%)	5 (5%)	3 (3%)
Metabolism and nutrition disorders				
Decreased appetite	1 (1%)	21 (20%)	1 (1%)	1 (1%)
Psychiatric disorders				
Insomnia	3 (3%)	8 (8%)	0	0
Cardiac disorders				
Sinus bradycardia	1 (1%)	6 (6%)	0	0
Blood and lymphatic system disorders				
Anaemia	6 (6%)	1 (1%)	1 (1%)	0
Hepatobiliary disorders				
Hepatic function abnormal	2 (2%)	8 (8%)	0	6 (6%)

Data are number of patients with at least one event (% of total patients).

Table 3: **Adverse events reported in 5% or more of patients in either treatment group**

Since J-ALEX was an open-label study, the primary endpoint was designated as IRF-assessed progression-free survival to avoid potential assessment bias by investigators. The results of IRF-assessed progression-free survival and investigator-assessed progression-free survival were similar; no significant assessment bias was found. Additionally, the safety profile and frequency of adverse events were consistent with those previously reported for alectinib and crizotinib. These findings suggest that the results from J-ALEX are robust and reliable. This study had other limitations that must be considered when interpreting the results. First, because the study results were released early, the estimate of HR might be biased toward overestimation, and should be interpreted with caution. However, based on a report by Freidlin and Korn,[28] the potential bias at the interim analysis with 50% of the required number of events—using a stopping boundary derived by O'Brien and Fleming-type alpha-spending function—was expected to be small. Therefore, the potential bias should not significantly affect the interpretation of the study results. Second, an interim analysis after 33% of required progression-free survival events was added during the course of the study; however, since the study amendment was made at the initial stage (approximately 10 months from first patient randomisation), the study integrity was not jeopardised. Finally, on the basis of combined safety, efficacy, and pharmacokinetics data from the Japanese AF-001JP trial,[16] the approved dose in Japan of 300 mg twice daily for alectinib was selected (the highest dose used based on the available safety information about the additive formulation in Japan at the time the AF-001JP trial was done), and our

J-ALEX study used a dose of 300 mg twice daily for alectinib. However, outside of Japan, doses of 600 mg twice daily are recommended.[14] The ongoing ALEX study is assessing the efficacy and safety of 600 mg alectinib twice daily; whether or not this dose might be associated with a higher frequency of adverse events than the 300 mg twice-daily dose remains unclear.

In conclusion, this phase 3 study demonstrated the superiority of alectinib over crizotinib in progression-free survival with a favourable safety profile in ALK inhibitor-naive patients with *ALK*-positive non-small-cell lung cancer who were chemotherapy naive or had received one previous line of chemotherapy. These results provide the first head-to-head comparison of alectinib and crizotinib and have the potential to change the standard of care for the first-line treatment of patients with *ALK*-positive non-small-cell lung cancer.

Contributors

RA and TTan did literature searches. TTam, KN, TM, NY, TA, and TTan designed the study and were responsible for data analysis. TH, HN, MK, KA, YHK, TSe, YT, MN, HY, FI, KH, SW, KG, MS, TK, TSh, KN, and NY were responsible for data collection. All authors contributed to data interpretation, writing, editing, and final approval of the manuscript.

Declaration of interests

RA and TA report personal fees from Chugai Pharmaceutical. KG reports grants and personal fees from Chugai Pharmaceutical, AstraZeneca, Taiho Pharmaceutical, Nippon Boehringer Ingelheim, Ono Pharmaceutical, Pfizer, Kyowa Hakko Kirin, Eli Lilly Japan, Novartis Pharma, Daiichi-Sankyo, Quintiles, GlaxoSmithKline, OxOnc, Sumitomo Dainippon Pharma, Takeda Pharmaceutical, Astellas Pharma, Eisai, Amgen, Yakult Honsha, and Bristol-Myers Squibb. TH reports grants and personal fees from Chugai Pharmaceutical, Ono Pharmaceutical, Eli Lilly, Novartis, Taiho Pharmaceutical, AstraZeneca, Nippon Boehringer Ingelheim, Pfizer, Bristol-Meyers Squibb, Clovis Oncology, Eisai, Takeda Bio, Sumitomo Dainippon Pharma, AbbVie, Merck Serono, Kyowa Hakko Kirin, Daiichi-Sankyo, and Astellas Pharma. KH reports grants and personal fees from Chugai Pharmaceutical, AstraZeneca, Eli Lilly Japan, Daiichi-Sankyo, Nippon Boehringer Ingelheim, Nihon Kayaku, Taiho Pharmaceutical, Sanofi-Aventis, and MSD. FI reports grants and personal fees from Chugai Pharmaceutical, AstraZeneca, Pfizer, Nippon Boehringer Ingelheim, Taiho Pharmaceutical, Ono Pharmaceutical, Eli Lilly, and MSD. MK reports grants and personal fees from Chugai Pharmaceutical, Pfizer, Novartis, AstraZeneca, Nippon Boehringer Ingelheim, Taiho Pharmaceutical, and Kirin-Kyoma. TK reports personal fees from Chugai Pharmaceutical, Pfizer, AstraZeneca, Eli Lilly Japan, Taiho Pharmaceutical, Kyowa Hakko Kirin, Sanofi, and Ono Pharmaceutical. TM reports grants and personal fees from Chugai Pharmaceutical, Pfizer, Roche, AstraZeneca, Nippon Boehringer Ingelheim, Taiho Pharmaceutical, Eli Lilly, and Ono Pharmaceutical, MSD, Bristol Myers Squibb, and Novartis. KN reports grants and personal fees from Pfizer Japan, Chugai Pharmaceutical, Eli Lilly Japan, Astellas Pharma, Daiichi-Sankyo, Nippon Boehringer Ingelheim, AstraZeneca, Ono Pharmaceutical, Taiho Pharmaceutical, MSD, Oncotherapy Science, Eisai, EPS Associates, Quintiles, Japan Clinical Research Operations, and Takeda Pharmaceutical Company. MN reports research funding from Novartis, Ono Pharmaceutical, Chugai Pharmaceutical, Bristol-Myers Squibb, Taiho Pharmaceutical, Eli Lilly, Pfizer, Astellas Pharma, and AstraZeneca, and honoraria from Pfizer, Bristol-Myers Squibb, Ono Pharmaceutical, Chugai Pharmaceutical, Eli Lilly, Taiho Pharmaceutical, and AstraZeneca. HN reports research funding from Merck Serono, Pfizer, Eisai, Novartis, Daiichi-Sankyo, GlaxoSmithKline, Yakult Honsha, Quintiles, and Astellas Pharma; personal fees and research funding from Taiho Pharmaceutical, Chugai Pharma, Eli Lilly, AstraZeneca, Nippon Boehringer Ingelheim, and Ono Pharmaceutical; personal fees from Sanofi. MS reports grants and personal fees from Chugai Pharmaceutical, Taiho Pharmaceutical, Eli Lilly Japan, Pfizer Japan, AstraZeneca, Bristol-Myers Squibb, Ono Pharmaceutical, Nippon Boehringer Ingelheim, and Astellas Pharma. TSe reports grants from Astellas Pharma, Bayer Yakuhin, Merck Serono, MSD, Verastem, and Yakult Honsha; grants and personal fees from AstraZeneca, Chugai Pharmaceutical, Eisai, Eli Lilly Japan, Nippon Boehringer Ingelheim, Novartis Pharma, Pfizer Japan, Sanofi, and Taiho Pharmaceutical; and personal fees from Daiichi-Sankyo, Fuji Pharma Company, Hisamitsu Pharmaceutical, Kyowa Hakko Kirin, Mochida Pharmaceutical Company, Nippon Kayaku Company, Ono Pharmaceutical, Roche Diagnostics, Showa Yakuhin Kako Company, Sumitomo Dainippon Pharma, and Takeda Pharmaceutical Company. TSh reports grants from Chugai Pharmaceutical, and personal fees from Pfizer and Chugai Pharmaceutical. YT reports grants and personal fees from Chugai Pharmaceutical, Bristol-Myers Squibb, Kyowa Hakko Kirin, and Merck Serono; grants from Eli Lilly Japan and Mochida Pharmaceutical; and personal fees from AstraZeneca, Japan. TTam reports personal fees for lectures from Chugai Pharmaceutical, Novartis, Taiho Pharmaceutical, Eli Lilly, Ono Pharmaceutical, Eisai, Yakult Honsha, Nippon Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi-Sankyo, and Astellas Pharma. TTan reports personal fees from Chugai Pharmaceutical. NY reports grants and personal fees from Chugai Pharmaceutical, and personal fees from Pfizer. HY reports honoraria from Chugai Pharmaceutical, Pfizer, Eli Lilly Japan, AstraZeneca, Taiho Pharmaceutical, Nippon Boehringer Ingelheim, Nippon Kayaku, Sanofi, and Sumitomo Dainippon Pharma. KA, YHK, and SW declare no competing interests.

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