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ORIGINAL REPORT

Three-Year Follow-Up of an Alectinib Phase I/II Study in *ALK*-Positive Non–Small-Cell Lung Cancer: AF-001JP

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ABSTRACT

Purpose

Alectinib is an anaplastic lymphoma kinase (ALK) –specific kinase inhibitor that seems to be effective against non–small-cell lung cancer (NSCLC) with a variety of *ALK* mutations. The primary analysis of AF-001JP reported a promising overall response rate. To assess progression-free survival (PFS) and overall survival (OS), patients from the phase II part of AF-001JP were followed up for approximately 3 years.

Patients and Methods

Oral alectinib 300 mg was administered twice per day to patients with ALK inhibitor–naïve, *ALK*-positive NSCLC who had progressed after one or more regimens of previous chemotherapy. In this long-term follow-up, efficacy (PFS, OS), correlation between tumor shrinkage and PFS, safety of alectinib, and relief of cancer symptoms were evaluated.

Results

At the updated data cutoff (September 10, 2015; first patient in August 30, 2011, last patient in April 18, 2012), 25 of 46 phase II patients were still receiving alectinib. Disease progression was confirmed in 18 patients (39%); median PFS was not reached (3-year PFS rate, 62%; 95% CI, 45 to 75). Fourteen patients had brain metastases at baseline; of these, 6 remained in the study without CNS and systemic progression. Tumor shrinkage and PFS showed no correlation. The 3-year OS rate was 78% (13 events). The most common treatment-related adverse event (all grades) was increased blood bilirubin (36.2%). Most cancer symptoms were relieved early, and medication for symptoms was dramatically decreased during alectinib therapy.

Conclusion

Alectinib was effective in this 3-year follow-up with a favorable safety profile over a long administration period in *ALK*-positive NSCLC without previous ALK inhibitor treatment.

INTRODUCTION

A fusion gene comprising the echinoderm microtubule-associated protein-like 4 (*EML4*) gene and the anaplastic lymphoma kinase (*ALK*) gene has been identified as an oncogenic driver mutation in non–small-cell lung cancer (NSCLC).[1] *ALK*-positive disease is a distinct subset of NSCLC, occurring in approximately 5% of patients with advanced adenocarcinoma.[2] As *ALK*-positive tumors are dependent on signaling from the EML4-ALK fusion protein to survive, this was a rational target for the development of new treatments.

The ALK inhibitor crizotinib is approved for the treatment of patients with *ALK*-positive NSCLC in the United States, the European Union, Japan, and other countries.[3-5] In patients who have not been previously treated with an ALK inhibitor (ALKi naïve), studies of crizotinib have reported an objective response rate (ORR) of up to 74% and median progression-free survival (PFS) of up to 10.9 months (global PROFILE 1014 study).[6] However, patients receiving crizotinib often experience disease progression within a year, partly due to secondary resistance mutations occurring. In addition, because of poor penetration of crizotinib across the blood–brain barrier, progression to the CNS is a common problem in patients with *ALK*-positive NSCLC treated with crizotinib. Therefore, alternative ALK inhibitors, which have both CNS efficacy

ASSOCIATED CONTENT

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Appendix
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and a broader range of efficacy against secondary *ALK* mutations, are needed.

Alectinib is a highly selective oral ALK inhibitor and has shown efficacy both systemically and in the CNS in multiple studies.[7-10] Recent data also suggest that alectinib may be active against *ALK* mutations that are resistant to crizotinib treatment, providing a broader range of efficacy.[11] The Japanese AF-001JP study of patients with *ALK*-positive NSCLC who had not previously received an ALK inhibitor (n = 46 in the phase II part) demonstrated an ORR of 93.5% (95% CI, 82 to 99), including two complete responses and 41 partial responses.[12] This met the primary end point statistics of an ORR threshold of 45%. At the time of the primary analysis, no progression of CNS lesions in any of the patients in the phase II part was noted.

Here, we detail the long-term efficacy and safety of alectinib in the Japanese AF-001JP study to evaluate whether the impressive primary analysis results are sustained during long-term treatment.

PATIENTS AND METHODS

Detailed methods have been published previously.[12,13] Briefly, in this multicenter, Japanese, single-arm, open-label phase I/II study, patients with *ALK*-positive stage IIIB/IV or relapsed NSCLC who had not previously received an ALK inhibitor (with one or more prior regimens of chemotherapy) and who had Eastern Cooperative Oncology Group performance status 0 or 1 were enrolled between September 10, 2010 and April 18, 2012. Patients received 20 to 300 mg of alectinib in the phase I dose-escalation part of the study. Dose escalation was stopped at 300 mg for the phase I part because of reaching the historical maximum intake level in Japan of an excipient of alectinib. Therefore, the approved dose in Japan is 300 mg twice per day. Patients in the phase II part received 300 mg of alectinib administered orally twice per day until disease progression (or no clinical benefit, in the latest version of the protocol), unacceptable toxicity, death, or withdrawal of patient consent. Patients treated with stereotactic radiotherapy could continue receiving alectinib, but alectinib could not be administered on the same day as radiotherapy. Tumors were assessed every cycle (21 days or 42 days after cycle 26 in the latest version of the protocol) until cycle four, then every two cycles thereafter, according to the Response Evaluation Criteria in Solid Tumors version 1.1. Adverse events (AEs) were assessed using National Cancer Institute Common Terminology Criteria for AEs version 4. Status of use of drugs for cancer symptoms was confirmed every cycle (21 days or 42 days after cycle 26 in the latest version of the protocol).

The end points of the phase I part were dose-limiting toxicities, maximum tolerated dose, safety, pharmacokinetics, and antitumor activity. The primary end point of the phase II part was ORR by independent review committee; secondary end points included disease control rate, PFS, overall survival (OS), pharmacokinetics, and safety. Exploratory end points in this follow-up analysis included evaluation of correlation between tumor shrinkage and PFS and medication to relieve cancer symptoms.

In this follow-up analysis, PFS, OS, correlation between tumor shrinkage and PFS, and relief of cancer symptoms were evaluated using the phase II intent-to-treat population. For the safety analysis, the phase I 300-mg cohort and the phase II part were combined as the safety population (all phase I 300-mg cohort and phase II patients who received at least one dose of study drug).

This study is registered with the Japan Pharmaceutical Information Center, number JapicCTI-101264.[14] Patients gave written informed consent for *ALK* assessment by a central laboratory. If tumors were confirmed to be *ALK* positive, patients signed another informed consent form for enrollment into the trial. The study was approved by the institutional review board at each participating institution and carried out in accordance with the Declaration of Helsinki and Good Clinical Practice in Japan.

RESULTS

Patients

At the updated data cutoff (September 10, 2015; first patient was registered on August 30, 2011, last patient was registered on April 18, 2012), 25 out of the 46 patients in the phase II part were still receiving treatment with alectinib. Baseline characteristics of these 46 patients and the safety population (n = 58) are shown in Table 1. Of note, 32.6% of the phase II patients had brain metastases at baseline.

Efficacy

At the time of data cutoff, disease progression was confirmed in 18 patients (39%). Of the 14 patients who had brain metastases at baseline, six remained in the study without CNS and systemic progression at the time of data cutoff. The nature of disease progression (systemic *v* CNS) by baseline CNS metastases is shown in Appendix Table A1 (online only). In the phase II population,

Table 1. Baseline Characteristics

Characteristic	Phase II ITT Population (n = 46)	Safety Population* (n = 58)
Median age, years (range)	48.0 (26-75)	49.5 (26-75)
Sex, %		
Male	47.8	43.1
Female	52.2	56.9
ECOG performance status		
0	43.5	41.4
1	56.5	58.6
Disease stage		
IIIB	4.3	3.4
IV	67.4	63.8
Postoperative recurrence	28.3	32.8
Smoking status		
Current	2.2	1.7
Former	39.1	37.9
Never	58.7	60.3
No. of prior chemotherapy regimens for metastatic disease		
0	2.2†	1.7†
1	45.7	36.2
2	19.6	31.0
≥ 3	32.6	31.0
Brain metastases‡		
Yes	30.4	29.3
No	69.6	70.7
EGFR mutation		
No	89.1	89.7
Unknown	10.9	10.3

NOTE. Data presented as percentage unless otherwise noted.
Abbreviations: ECOG, Eastern Cooperative Oncology Group; *EGFR*, epidermal growth factor receptor; ITT, intent-to-treat.
*The phase I 300-mg cohort and the phase II part were combined as the safety population.
†Regarded as eligible for inclusion because relapse occurred within 6 months of completion of adjuvant chemotherapy.
‡Forty-six phase II patients were determined by an independent review committee.

median PFS was not reached (95% CI, 33.1 months to not reached) at this time (Fig 1A). When PFS was assessed by subgroups (stratified by brain metastases, disease stage, number of previous chemotherapy regimens, smoking history, or sex; Figs 1B to 1F), median PFS was only reached in patients with brain metastases (n = 14; median PFS, 38 months; 95% CI, 9 months to not reached) and male patients (n = 22; median PFS, 35.3 months; 95% CI, 18 months to not reached). The 3-year PFS rate for all phase II patients was 62% (95% CI, 45 to 75; Fig 1A). The scatter plot of tumor shrinkage and PFS showed no apparent correlation between these outcomes (eg, increased tumor shrinkage did not seem to correlate with longer PFS; Fig 2).

Twenty-one patients stopped trial treatment before the data cutoff. Of these, 17 received further systemic therapies (range, 1 to 5). Of the 17 patients, 12 went on to receive an ALK inhibitor other than alectinib. At the data cutoff, OS was still immature with just 13 events, and the median was not estimable (Appendix Fig A1, online only). The 3-year OS rate was 78% (95% CI, 63 to 88).

Safety

The safety population comprised all patients in the phase I 300-mg cohort and phase II parts who received at least one dose of study drug (n = 58; first patient was registered on May 13, 2011, last patient was registered on April 18, 2012). Fifty-six patients (96.6%) reported treatment-related AEs (Table 2). Treatment-related grade 3 AEs were reported in 16 patients (27.6%). There were no treatment-related grade 4 or 5 AEs. The common treatment-related AEs (all grades) were increased blood bilirubin (36.2%), dysgeusia (34.5%), increased aspartate aminotransferase (32.8%), increased blood creatinine (32.8%), and constipation (31.0%). Serious AEs were reported in 24.1% of the safety population and 21.7% of phase II patients, and grade ≥ 3 AEs were observed in 51.7% and 50%, respectively. Time to onset of AEs (both all-grade and ≥ 3 AEs) are shown in Appendix Fig A2 (online only). Most AEs had the majority of onset incidents within the first 6 months of treatment; however, the onset of all-grade diarrhea continued throughout treatment.

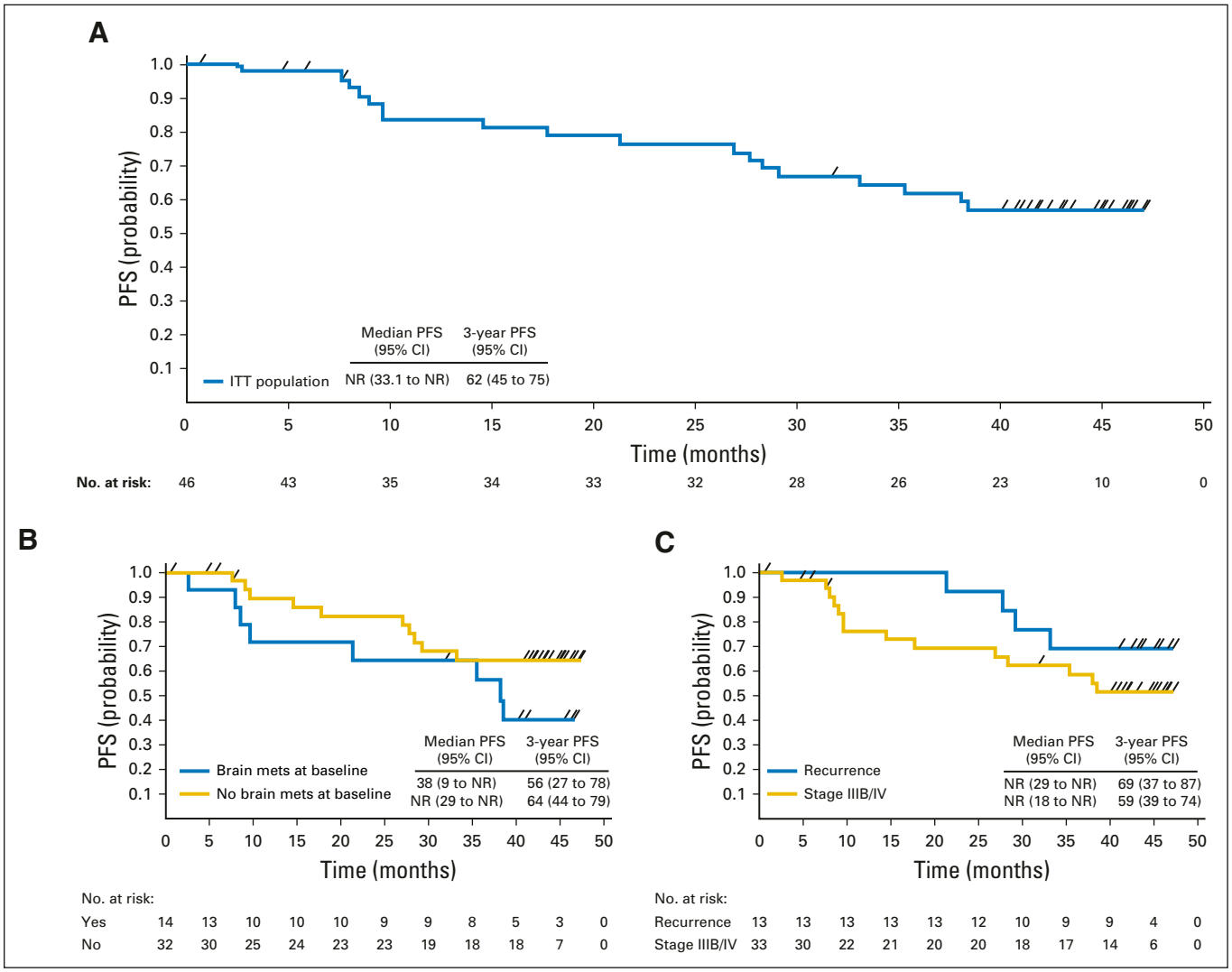

Fig 1. (A) Kaplan-Meier curve of progression-free survival (PFS) in the overall phase II population, and (B-F) PFS by subgroups: (B) brain metastases (mets); (C) disease stage; (D) number of chemotherapy regimens; (E) sex; (F) smoking status. ITT, intent to treat; NR, not reached.

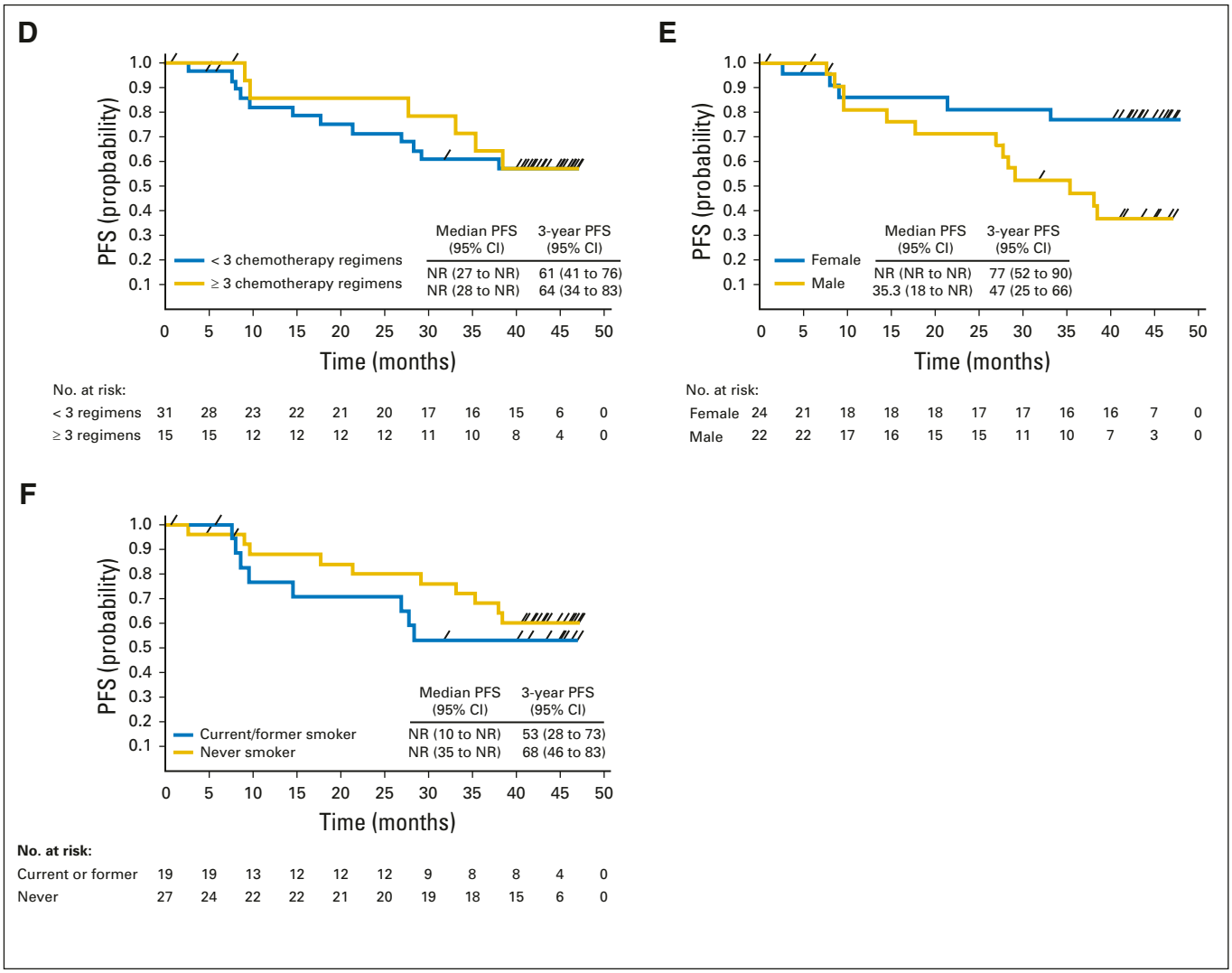

Fig 1. (Continued).

Only one patient required a dose reduction because of rash, which was reported previously.[12] No new AEs requiring a dose reduction were recorded in this extended follow-up. A total of six AEs resulted in discontinuation from the phase II part of the study (grade 3 brain edema, grade 3 esophageal carcinoma, grade 3 tumor hemorrhage, grade 2 sclerosing cholangitis, grade 3 increase in ALT, and grade 1 interstitial lung disease). Two of these were newly recorded in this extended follow-up.

At baseline, 15 of the 46 phase II patients were being treated for cancer pain, cough, or sputum production. Most of the symptoms were relieved early in the treatment course, and the drugs used in the treatment of these symptoms were able to be dramatically decreased over the course of alectinib treatment (Appendix Fig A3, online only).

DISCUSSION

The discovery of the *ALK* rearrangement *EML4-ALK* as an oncogenic driver mutation in NSCLC has led to the development of several ALK inhibitors. Crizotinib was the first ALK inhibitor approved for the treatment of *ALK*-positive NSCLC, after superior benefit over chemotherapy in the first- or second-line setting for *ALK*-rearranged NSCLC, with a median PFS of 10.9 months and 7.7 months, respectively.[6,15] In the ALKi-naïve setting, crizotinib has demonstrated an ORR of 74% in a global patient population.[6] ALKi-naïve patients treated with ceritinib reported an ORR of 63.7%, duration of response of 9.3 months, and median PFS of 11.1 months.[16] In the same setting, alectinib demonstrated an ORR of 93.5% in the primary analysis of the AF-001JP study, suggesting alectinib may be superior to ceritinib in this setting.[12]

We have described here the results from a 3-year long-term follow-up of the AF-001JP study, to determine whether the impressive results reported in the primary analysis could be maintained with extended administration of alectinib. On the basis of this long-term follow-up, alectinib seems to be an effective treatment when administered for an extended time frame, with a 3-year PFS rate of 62%. Efficacy was consistent across the subgroups analyzed, suggesting that alectinib could be suitable for a wide range of patients with *ALK*-positive NSCLC. The results of the

Table 2. Summary of Treatment-Related AEs With ≥ 10% Frequency by Grade in the Safety Population (n = 58)

AE	Total	Grade 1	Grade 2	Grade 3	Grade 4
Blood bilirubin increased	21 (36.2)	3 (5.2)	16 (27.6)	2 (3.4)	0 (0)
Dysgeusia	20 (34.5)	20 (34.5)	0 (0)	0 (0)	0 (0)
AST increased	19 (32.8)	16 (27.6)	3 (5.2)	0 (0)	0 (0)
Blood creatinine increased	19 (32.8)	10 (17.2)	9 (15.5)	0 (0)	0 (0)
Constipation	18 (31.0)	15 (25.9)	3 (5.2)	0 (0)	0 (0)
Rash	17 (29.3)	15 (25.9)	2 (3.4)	0 (0)	0 (0)
ALT increased	15 (25.9)	12 (20.7)	1 (1.7)	2 (3.4)	0 (0)
Neutrophil count decreased	15 (25.9)	1 (1.7)	10 (17.2)	4 (6.9)	0 (0)
Blood creatine phosphokinase increased	12 (20.7)	10 (17.2)	0 (0)	2 (3.4)	0 (0)
White blood cell count decreased	12 (20.7)	3 (5.2)	8 (13.8)	1 (1.7)	0 (0)
Stomatitis	10 (17.2)	9 (15.5)	1 (1.7)	0 (0)	0 (0)
Myalgia	9 (15.5)	9 (15.5)	0 (0)	0 (0)	0 (0)
Nausea	9 (15.5)	9 (15.5)	0 (0)	0 (0)	0 (0)
Blood alkaline phosphatase increased	8 (13.8)	6 (10.3)	2 (3.4)	0 (0)	0 (0)
Diarrhea	7 (12.1)	6 (10.3)	1 (1.7)	0 (0)	0 (0)
Malaise	7 (12.1)	7 (12.1)	0 (0)	0 (0)	0 (0)
Nasopharyngitis	6 (10.3)	3 (5.2)	3 (5.2)	0 (0)	0 (0)

NOTE. Data presented as No. (%). No grade 5 AEs were reported.
Abbreviation: AE, adverse event.

scatter plot of tumor shrinkage correlated with PFS show that alectinib treatment can impart sustained PFS regardless of reduction in tumor volume, suggesting that alectinib may provide benefit by suppressing tumor regrowth.

The CNS is a common site of progression in patients with *ALK*-positive NSCLC treated with crizotinib. Therefore, it is important to ensure that ALK inhibitors are developed that can show efficacy in the CNS as well as demonstrating systemic effects. Although crizotinib is a substrate for P-glycoprotein efflux,[3] a key mechanism in removing drugs from the brain,[17] alectinib is not removed by P-glycoprotein. This may be the reason for the high brain-to-plasma ratio of alectinib,[18] which may be why alectinib shows favorable efficacy in the CNS compared with other agents. Alectinib has been shown to be an effective treatment of *ALK*-positive NSCLC, both systemically and within the CNS, supported by data from two multicenter phase II trials in patients who have progressed or are intolerant to crizotinib.[7,8] In the JP28927 study of alectinib with or without previous crizotinib treatment, 13 out of 19 patients with brain metastases at baseline were still receiving treatment without progression after a median follow-up of 141 days,[19] demonstrating the efficacy of alectinib in the CNS. In this extended follow-up of the AF-001JP study, six out of 14 patients (43%) with baseline CNS metastases had not progressed in the CNS or systemically at the data cutoff, suggesting that alectinib would be a suitable first-line ALK inhibitor therapy with demonstrable efficacy in the CNS. This analysis reported that progression due to brain metastases occurred in < 10% of patients, regardless of whether they had brain metastases at baseline. Overall, efficacy outcomes were similar in patients with or without CNS metastases at baseline, suggesting that alectinib would be suitable for *ALK*-positive disease, regardless of CNS involvement.

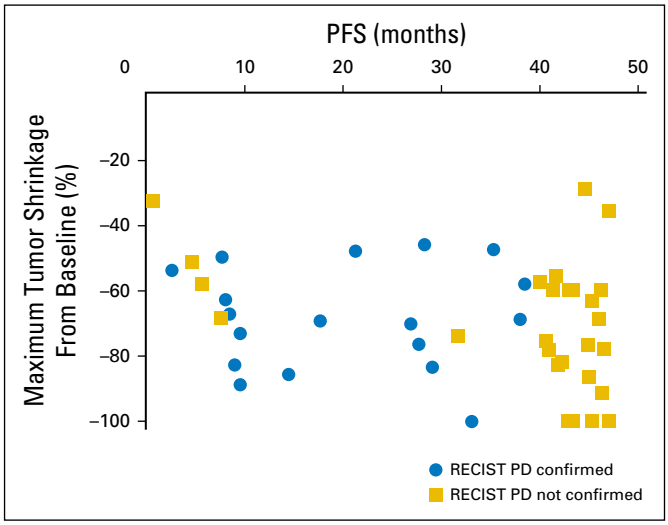

Fig 2. Relationship between tumor shrinkage and progression-free survival (PFS). PD, progressive disease; RECIST, Response Evaluation Criteria in Solid Tumors.

Despite the long administration time, AEs reported were still only mild to moderate in severity, with no treatment-related grade 4 or 5 AEs at this cutoff. Many of the AEs initially occurred in the first 6 months of treatment, with only all-grade diarrhea continuing to develop throughout treatment. Although the treatment duration was extended, few patients discontinued because of AEs, and only one patient needed a dose reduction because of an AE, suggesting that alectinib has a favorable safety profile for long-term treatment. The reduction of systemic AEs is a key component in the age of personalized medicine and targeted therapy. Alectinib is a highly specific ALK inhibitor, and because ALK is only expressed at low levels in normal adult tissue, inhibition of just ALK will have limited impact on normal body system functions.[20] This means there should be fewer off-target AEs seen with alectinib than are seen with more general kinase inhibitors, which could affect several pathways leading to more toxicities. Medications for cancer symptoms were able to be reduced and maintained at a low level during the course of alectinib treatment. This could mean that patients receiving alectinib see improvements in symptoms, and therefore the influence of symptoms on their daily lives is

minimized. The lack of definitive quality-of-life data or patient-reported outcomes is a limitation of this study.

Other limitations of this analysis to consider when reviewing these data include the single-arm, nonrandomized nature of the study, its small enrollment size of only Japanese patients, and insufficient follow-up period for median PFS and OS. A strength of this analysis is the extended follow-up time, the first to our knowledge for an ALK inhibitor in NSCLC.

On the basis of the promising data from the AF-001JP study, a randomized, open-label, phase III trial (JO28928; JapicCTI-132316; J-ALEX) was initiated to compare alectinib with crizotinib in ALKi-naïve Japanese patients with *ALK*-positive NSCLC. Recently, the primary results for J-ALEX were presented and demonstrated that alectinib is superior to crizotinib in terms of PFS in the ALKi-naïve setting.[21] Meanwhile, a global randomized phase III trial, which will evaluate the efficacy of alectinib compared with crizotinib in the same setting, is being performed. After the J-ALEX results, this ongoing study will provide more evidence for the role of alectinib.

In conclusion, because there are few treatment options for *ALK*-positive NSCLC, the confirmation of long-term efficacy of alectinib, a highly selective, CNS-active ALK inhibitor, active against several *ALK* variants, is an important advance in this field. To our knowledge, alectinib is the first ALK inhibitor to report such long-term efficacy and safety data. It will be of great interest to see how these data compare with any future long-term data from other ALK inhibitors.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

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REFERENCES

1. Soda M, Choi YL, Enomoto M, et al: Identification of the transforming *EML4-ALK* fusion gene in non-small-cell lung cancer. Nature 448:561-566, 2007
2. Gridelli C, Peters S, Sgambato A, et al: ALK inhibitors in the treatment of advanced NSCLC. Cancer Treat Rev 40:300-306, 2014
3. European Medicine Agency: Xalkori product information. http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002489/human_med_001592.jsp&mid=WC0b01ac058001d124
4. Kazandjian D, Blumenthal GM, Chen HY, et al: FDA approval summary: Crizotinib for the treatment of metastatic non-small cell lung cancer with anaplastic lymphoma kinase rearrangements. Oncologist 19:e5-e11, 2014
5. Pharmaceuticals and Medical Devices Agency: Report on the Deliberation Results (Crizotinib), 2012. https://www.pmda.go.jp/files/000153949.pdf
6. Solomon BJ, Mok T, Kim DW, et al: First-line crizotinib versus chemotherapy in *ALK*-positive lung cancer. N Engl J Med 371:2167-2177, 2014
7. Ou SH, Ahn JS, De Petris L, et al: Alectinib in crizotinib-refractory *ALK*-rearranged non-small-cell lung cancer: A phase II global study. J Clin Oncol 34:661-668, 2016
8. Shaw AT, Gandhi L, Gadgeel S, et al: Alectinib in *ALK*-positive, crizotinib-resistant, non-small-cell lung cancer: A single-group, multicentre, phase 2 trial. Lancet Oncol 17:234-242, 2016
9. Barlesi F, Dingemans AMC, Ou I, et al: Updated efficacy and safety results from a global phase 2, open-label, single-arm study (NP28673) of alectinib in crizotinib-refractory ALK+ non-small-cell lung cancer (NSCLC). Eur J Cancer 51, 2015 (suppl 3; abstr P3101)
10. Gadgeel SM, Shaw AT, Govindan R, et al: Pooled analysis of CNS response to alectinib in two studies of pretreated patients with *ALK*-positive non-small-cell lung cancer. J Clin Oncol 34:4079-4085, 2016
11. Puig O, Yang J, Ou S, et al: Pooled mutation analysis for the NP28673 and NP28761 studies of alectinib in *ALK*+ non-small-cell lung cancer (NSCLC). J Clin Oncol 34, 2016 (suppl; abstr 9061)
12. Seto T, Kiura K, Nishio M, et al: CH5424802 (RO5424802) for patients with *ALK*-rearranged advanced non-small-cell lung cancer (AF-001JP study): A single-arm, open-label, phase 1-2 study. Lancet Oncol 14:590-598, 2013
13. Takeuchi K, Togashi Y, Kamihara Y, et al: Prospective and clinical validation of ALK immunohistochemistry: Results from the phase I/II study of alectinib for ALK-positive lung cancer (AF-001JP study). Ann Oncol 27:185-192, 2016
14. iyakuSearch: JAPIC Clinical Trials Information. http://www.clinicaltrials.jp/user/cteList_e.jsp#
15. Shaw AT, Kim DW, Nakagawa K, et al: Crizotinib versus chemotherapy in advanced *ALK*-positive lung cancer. N Engl J Med 368:2385-2394, 2013
16. Felip E, Orlov S, Park K, et al: ASCEND 3: A single arm, open-label, multicentre phase II study of ceritinib in ALKi-naïve adult patients with ALK-rearranged (ALK+) non-small-cell lung cancer. J Clin Oncol 33, 2015 (suppl; abstr 8060)
17. Misra A, Ganesh S, Shahiwala A, et al: Drug delivery to the central nervous system: A review. J Pharm Pharm Sci 6:252-273, 2003
18. Kodama T, Hasegawa M, Takanashi K, et al: Antitumor activity of the selective ALK inhibitor alectinib in models of intracranial metastases. Cancer Chemother Pharmacol 74:1023-1028, 2014
19. Seto T, Hida T, Nakagawa K, et al: Anti-tumor activity of alectinib in crizotinib pre-treated *ALK*-rearranged NSCLC in JP28927 study. Ann Oncol 25:427, 2014 (suppl 4)
20. Morris SW, Kirstein MN, Valentine MB, et al: Fusion of a kinase gene, *ALK*, to a nucleolar protein gene, *NPM*, in non-Hodgkin's lymphoma. Science 263:1281-1284, 1994
21. Nokihara H, Hida T, Kondo M, et al: Alectinib versus crizotinib in ALK-inhibitor naïve *ALK*-positive non-small cell lung cancer: Primary results from the J-ALEX study. J Clin Oncol 34, 2016 (suppl; abstr 9008)

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Appendix

Table A1. Disease Progression Patients With or Without Brain Metastases at Baseline

N	Patients with brain metastases at baseline (n = 14)	Patients without brain metastases at baseline (n = 32)
CNS progression	1	2
Systemic progression	7*	8

*One patient experienced progression of a CNS lesion

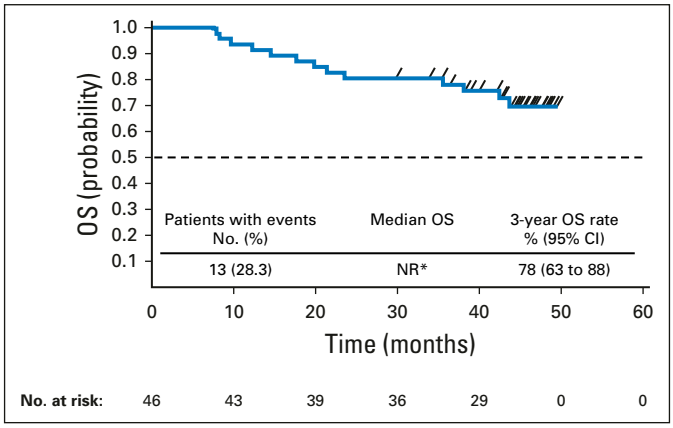

Fig A1. Kaplan-Meier curve of overall survival (OS) in the overall phase II population. (*)Median NR. NR, not reached.

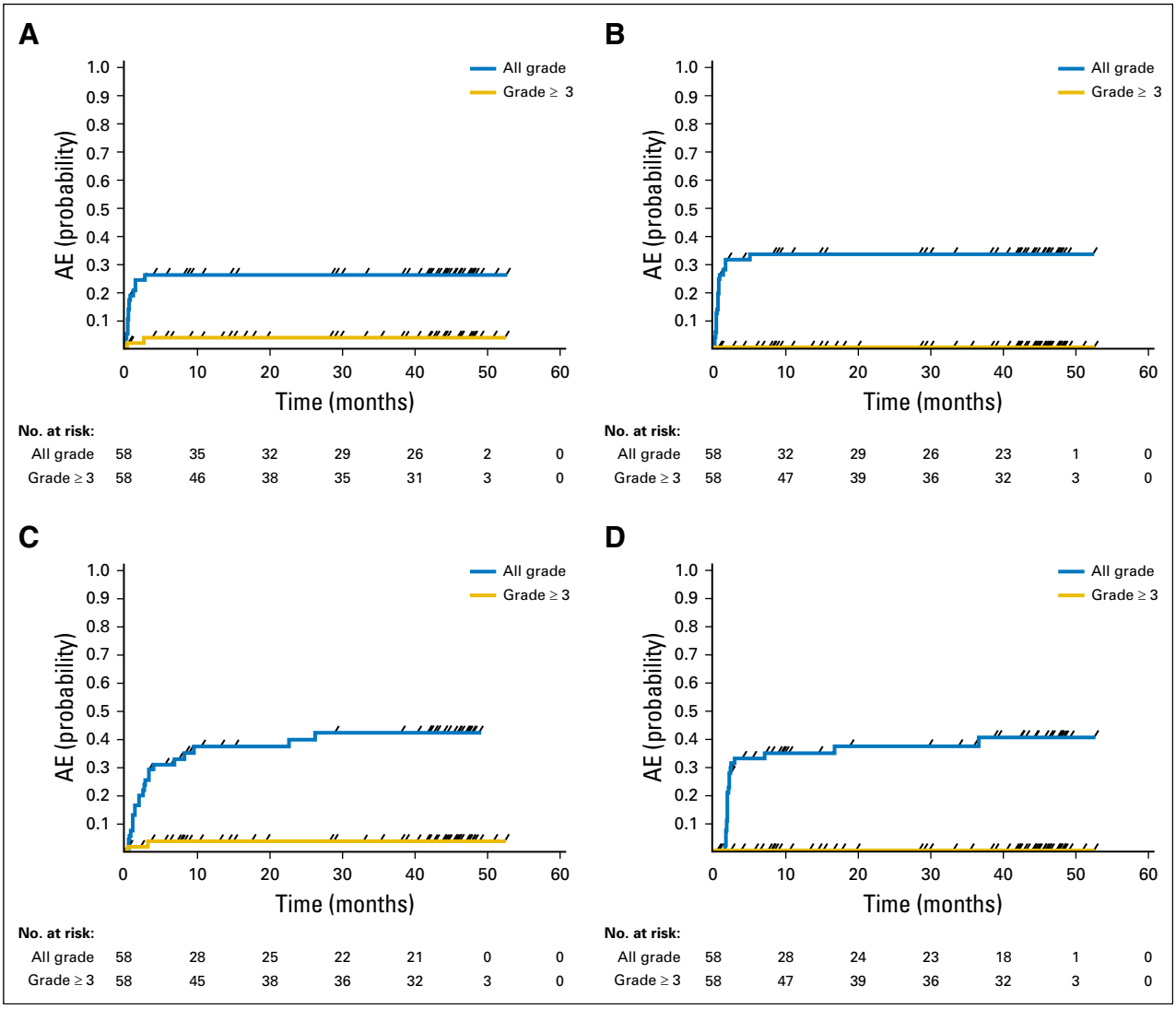

Fig A2. Time to first onset of all-grade and grade ≥ 3 adverse events (AEs). (A) ALT increased, (B) AST increased, (C) blood bilirubin increased, (D) constipation, (E) diarrhea, (F) dysgeusia, (G) neutrophil count decreased, (H) white blood cell count decreased.

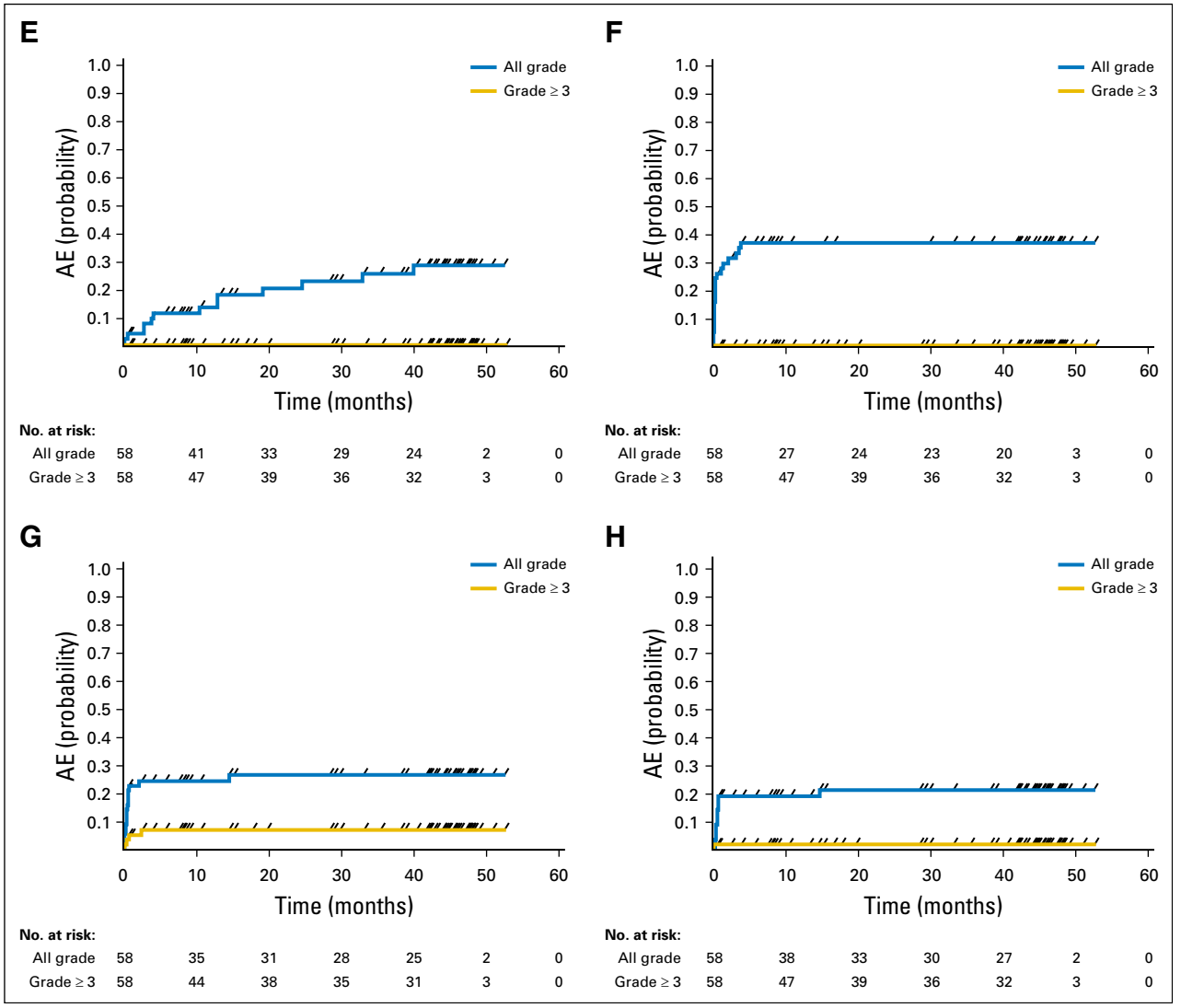

Fig A2. (Continued).

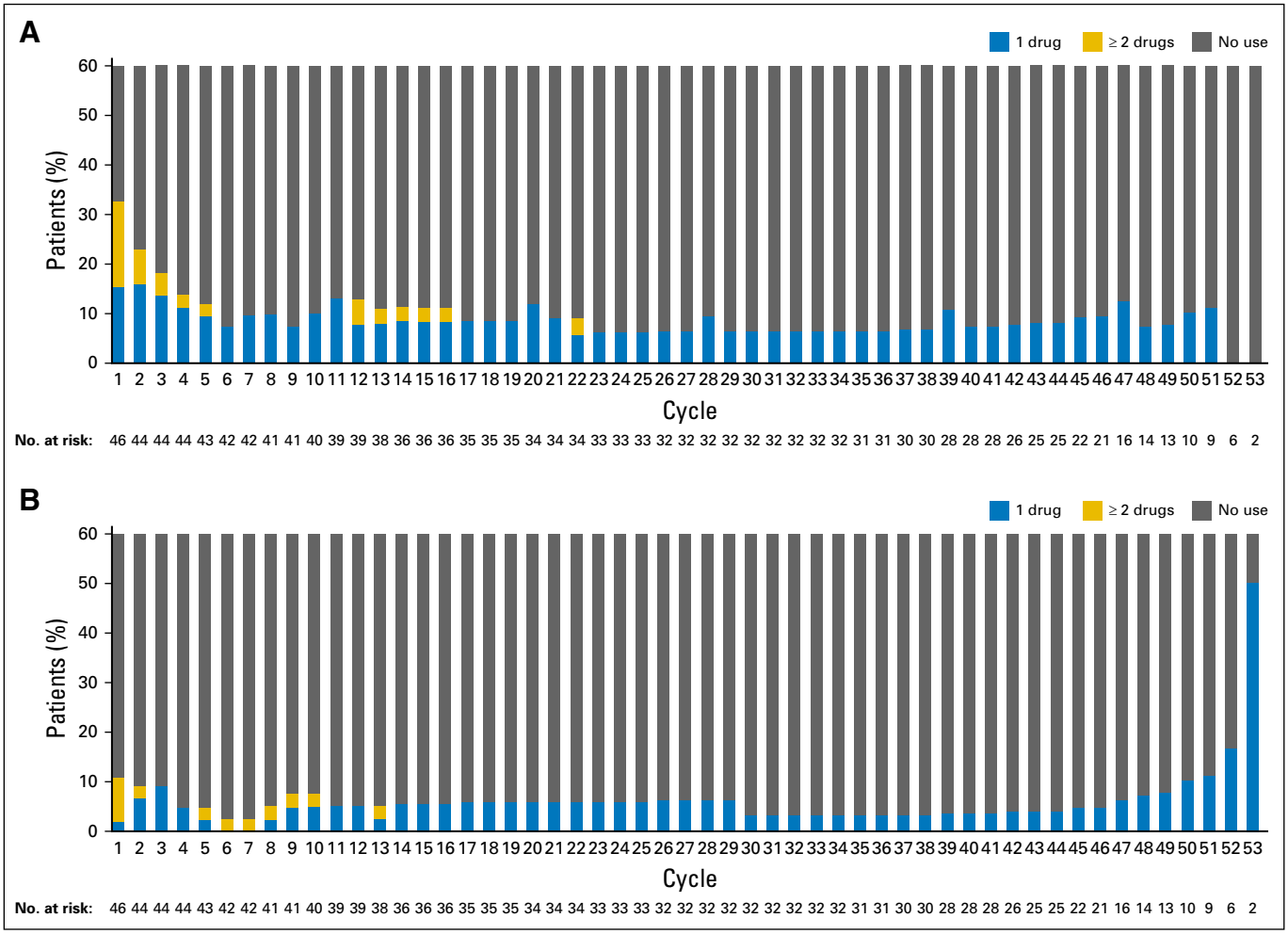

Fig A3. Use of medication for symptomatic relief of (A) cancer-related pain, and (B) cough and/or sputum production.