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The incidence of ALK inhibitor-related pneumonitis in advanced non-small-cell lung cancer patients: A systematic review and meta-analysis☆

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ABSTRACT

Introduction: We evaluated the incidence of pneumonitis in clinical trials of anaplastic lymphoma kinase (ALK) inhibitors in patients with advanced non-small cell lung cancer (NSCLC) and compared the incidence among different cohorts, in order to identify possible predisposing factors for ALK inhibitor-related pneumonitis.

Methods: MEDLINE and EMBASE search up to 1/30/18 using the keywords, "alectinib", "ceritinib", "crizotinib", "brigatinib", and "lung cancer", resulting in a total of 20 eligible cohorts with 2261 patients treated with ALK inhibitor monotherapy for advanced NSCLC. The pooled incidences of all-grade, high-grade, and grade 5 pneumonitis were calculated. Subgroup analyses were conducted with meta-regression using study-level covariates.

Results: The overall pooled incidence of pneumonitis was 2.14% (95% CI: 1.37–3.34) for all grade, 1.33% (95% CI: 0.80–2.21) for high grade, and 0.22% (95% CI: 0.09-0.52) for grade 5 pneumonitis. The incidence was significantly higher in studies from Japan compared to studies of non-Japan origin, for all-grade (6.25% vs 1.14%, $p < 0.001$) and high-grade pneumonitis (3.31% vs 0.39%, $p < 0.001$). Multivariate meta-regression demonstrated the cohorts from Japanese studies had significantly higher odds of pneumonitis for all-grade (odds ratio [OR]: 4.329 [95% CI: 1.918, 9.770], $p < 0.001$) compared to those of non-Japan origin, after adjusting for types of ALK inhibitors.

Conclusions: The overall incidence of ALK inhibitor pneumonitis was 2.14% in patients with advanced NSCLS. The patients from Japanese cohorts had a higher incidence of ALK-inhibitor pneumonitis, which indicates the need for increased awareness and caution for pneumonitis in Japanese patients treated with ALK inhibitors.

1. Introduction

Precision medicine approaches based on genomic abnormalities have brought a paradigm shift in the treatment for patients with advanced non-small cell lung cancer (NSCLC) in the past decades. [1] Anaplastic lymphoma kinase (ALK) inhibitors for oncogenic ALK gene rearranged NSCLC, noted in 3.6–4.4% of patients with NSCLC [2,3], is one of the leading examples of precision oncology for lung cancer. In 2011, crizotinib received accelerated approval for the ALK-positive locally advanced or metastatic NSCLC by U.S. Food and Drug Administration (FDA). [4] After 2014, newer ALK inhibitors, including alectinib, [5] ceritinib, [6] and brigatinib [7] have also received FDA approvals for patients with metastatic non-small cell lung cancer (NSCLC) who have progressed on crizotinib. Alectinib and ceritinib have also been approved as the first-line therapy for ALK-rearranged NSCLC patients. Most recently, another ALK-directed agent, lorlatinib, has been approved for NSCLC patients as the 2nd or 3rd line therapy in November 2018 [8].

Pneumonitis as one of the major adverse events in tyrosine kinase inhibitors for lung cancer, well studied in patients treated with EGFR inhibitors, [9] however, not extensively studied for ALK inhibitors especially in the setting of newly approved ALK inhibitors. The first report of the histologically documented crizotinib-associated pneumonitis was described in one Japanese patient treated with crizotinib for

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metastatic NSCLS. [10] Sporadic case reports [11,12] and the results of the clinical trials especially in the setting of brigatinib, [13] indicate that ALK-inhibitor related pneumonitis can be a clinically significant problem in some patients.

In the present study, we performed a systematic review and meta-analyses of the incidence of pneumonitis in clinical trials of ALK inhibitors in patients with advanced NSCLC and compared the incidence among different cohorts with different clinical characteristics and countries of study origin, in order to identify possible predisposing factors for ALK inhibitor-related pneumonitis.

2. Methods

2.1. Search methods and study selection

This systematic review and meta-analysis were conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. [14] A systematic computerized search of the literature in MEDLINE (PUBMED) and EMBASE database was performed to find published reports of the clinical trials of ALK inhibitors, crizotinib, alectinib, ceritinib, and brigatinib, for advanced NSCLC. These four ALK inhibitor agents were chosen for the purpose of the study because they have been approved by FDA for treatment of ALK-rearranged NSCLC at the time of the study. The search term combined synonyms of keywords, i.e. “alectinib”, “ceritinib”, “crizotinib”, “brigatinib", and “lung cancer” as follows: (alectinib OR ceritinib OR crizotinib OR brigatinib) AND ("lung cancer" OR "non-small cell lung cancer" OR NSCLC). The database was searched for literature published on or before 1/30/18. Conference abstracts with no published full-text were not eligible for our study, as in the prior published studies [9,15]. Abstracts were excluded because of the difficulty of obtaining the detailed information about the number of patients with all-grade, high-grade, and grade 5 pneumonitis, and the possibility of the overlap with the full-text articles that are subsequently published. Additionally, some abstracts may present “trial-in-progress” data which may change in the final publication.

2.2. Data extraction

The number of patients who were treated with ALK inhibitor and were assessed for toxicity, the number of patients who developed pneumonitis of all grades and of grade 3 or above (high-grade), and the number of patients with pneumonitis-related death (grade 5) were extracted from the eligible trial reports. The cases listed as pneumonitis, interstitial lung disease (ILD), and interstitial lung disease-like events were regarded as the event of pneumonitis to accommodate the different terminology used among trials from different regions across the world. [9,16] Other conditions indicated separately as “respiratory events” or “pneumonia” without a specific diagnosis were not included as pneumonitis [9].

Types of specific ALK inhibitor (alectinib, ceritinib, crizotinib, or brigatinib) were recorded. Treatment lines of ALK inhibitor for the cohorts were reviewed and recorded as 1) first-line ALK inhibitor treatment without any prior systemic therapy (first-line group), 2) ALK inhibitor treatment after prior chemotherapy without prior ALK inhibitor (prior chemotherapy group), 3) ALK inhibitor retreatment after previous ALK inhibitor treatment (ALK inhibitor retreatment group), and 4) cohorts with a mixture of patients with two or more treatment lines described in 1, 2, and 3 (mixed treatment group). The present study focused on patients treated with ALK inhibitor monotherapy (single-agent ALK inhibitor therapy), therefore, the patient cohorts treated with combination or sequential therapy with ALK inhibitor and other agents were not included. Countries of the trial sites and the phase of the trials were also recorded for each trial.

The data extraction was independently conducted by two reviewers (C.H.S., K.W.K.), which were then independently reviewed by an additional two reviewers (M.N. and H.H.) in accordance with the PRISMA guidelines.

2.3. Statistical methods

The pooled incidences of all-grade, high-grade, and grade 5 pneumonitis were calculated with the binomial-normal model. [17,18] Because this study focused on the estimation of rare events, we obtained the pooled incidence using mixed-effects logistic regression model for dichotomous data, i.e. binomial-normal model, instead of inverse-variance weighting model which needs normality assumption [9,19,20]. Heterogeneity was assessed using the Higgins inconsistency index (I^2) test and $I^2 > 50\%$ indicates substantial heterogeneity. [21]

The pooled incidences of pneumonitis were also calculated for each subgroup classified according to the types of ALK inhibitors, treatment lines, countries of the trial sites, and trial phases. Univariate meta-regression analyses were conducted to assess the association between each of study level covariates and the incidence of ALK-inhibitor pneumonitis. The multivariate meta-regression analysis was conducted adjusting for candidate covariates that demonstrated significant effects at $p < 0.20$ in the univariate meta-regression analyses, as well as for covariates that were regarded as clinically significant. [9] To test if study-level covariates as moderators have statistical effects in meta-regression, a Wald-type chi-square test was used with multiplicity adjustment and the regression coefficient was obtained to estimate the intervention effect on each subgroup from a reference group, as described previously [9].

All statistical analyses were conducted using the “metafor” package in R version 3.4.1 (R foundation for Statistical Computing, Vienna, Austria). [22] In meta-regression, we utilized the Knapp and Hartung adjustment, which typically used in mixed effects meta-regression model, to control the Type 1 error rate of 0.05 for each analysis and reported multiplicity-adjusted p values and 95% confidence intervals [23,24].

3. Results

3.1. Eligible studies and characteristics

The search has identified 71 articles. After screening and eligibility assessments, a total of 18 eligible clinical trials were identified and included in this study (Fig. 1). [13,25–41] Two of these clinical trials had two arms treated with different ALK inhibitors within each trial [30,35], resulting in 20 eligible cohorts with a total of 2261 patients treated with ALK inhibitor monotherapy for advanced NSCLC for analyses in the present study.

Table 1 lists the characteristics of the eligible trial cohorts, published between 2012 and 2017, with the their characteristics and the number of pneumonitis cases. Among the 20 cohorts, 7 cohorts were treated with alectinib, [28–31,34,35,37,41] 6 were treated with ceritinib, [26,27,32,33,36,40] 5 were treated with crizotinib, [25,30,35,38,39] and 1 was treated with brigatinib. [13] In terms of treatment line, 4 cohorts were categorized as first-line group [35,39,40], 1 was categorized as prior chemotherapy group [38], 6 were categorized as ALK inhibitor retreatment group [13,27,28,34,36,37], and 9 were categorized as mixed treatment [25,26,29–33,41]. Six cohorts were from Japan only [29,29,30,31,33,41].

Not all studies provided the number of patients with pneumonitis in all three grade categories (all grade, high grade, and grade 5). Therefore, for each grade group of pneumonitis, the studies reporting the number of pneumonitis in the groups were including the analyses, generating different numbers of studies for three groups.

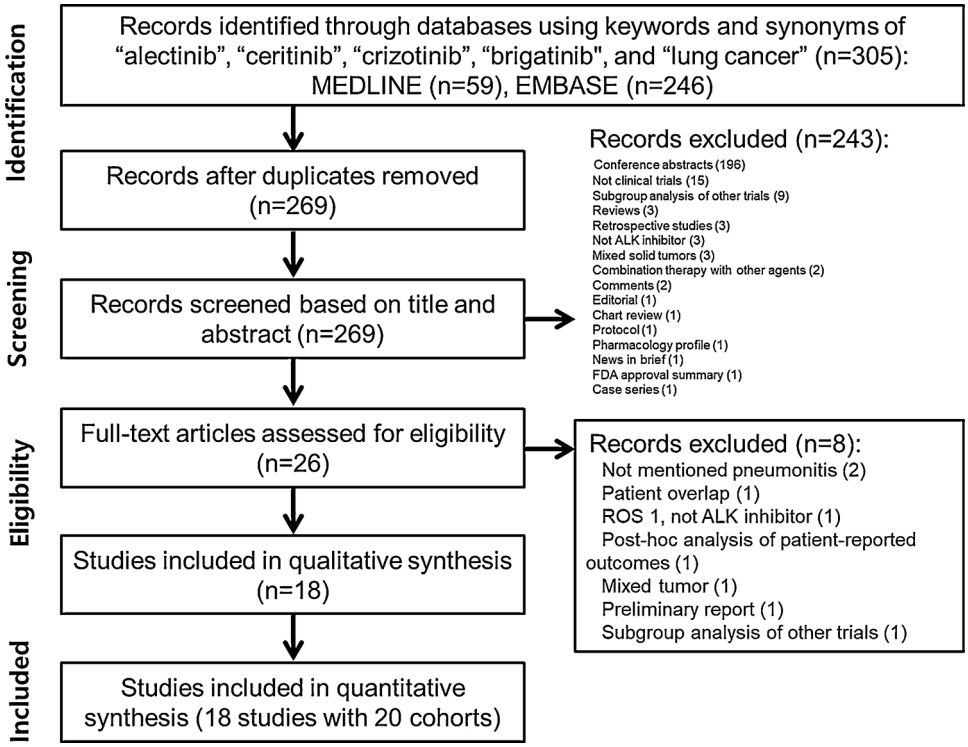

Fig. 1. Flow diagram of study inclusion.

3.2. Incidence of ALK inhibitor pneumonitis

We evaluated the incidence of pneumonitis in a total of 20 cohorts, for all-grade, high-grade, and grade 5 pneumonitis. The overall pooled incidence of pneumonitis was 2.14% (95% CI: 1.37–3.34) for all grade, 1.33% (95% CI: 0.80–2.21) for high grade, and 0.22% (95% CI: 0.09-0.52) for grade 5 pneumonitis (Table 2). Heterogeneity was observed for all-grade pneumonitis (I^2 = 54.81%), whereas no heterogeneity was noted for high-grade (I^2 = 34.42%) and grade 5 (I^2 = 0.0%). Table 2 also lists the incidence of ALK inhibitor pneumonitis in the subgroups classified according to ALK inhibitors, treatment lines, countries, and trial phase, which were further analyzed in meta-regression. The incidence was significantly higher in studies from Japan compared to studies of non-Japan origin, for all-grade (6.25% vs 1.14%, $p < 0.001$) and high-grade pneumonitis (3.31% vs 0.39%, $p < 0.001$).

In univariate meta-regression analyses, the cohorts from Japan had significantly higher odds for all-grade pneumonitis (odds ratio [OR]: 3.633 [95% CI: 1.538, 8.583], $p = 0.006$) compared to those of non-Japan origin (Table 3). No significant differences were observed for the incidence of pneumonitis among different ALK inhibitors, among different trial phases, or among different treatment line groups. Due to the rare case of grade 5 pneumonitis reported in the studies (Table 1), it was not possible to estimate the odds ratio of grade 5 pneumonitis in the statistical model.

In multivariate meta-regression analyses, the cohorts from Japanese studies had significantly higher odds of pneumonitis for all-grade (odds ratio [OR]: 4.329 [95% CI: 1.918, 9.770], $p < 0.001$) compared to those of non-Japan origin, after adjusting for types of ALK inhibitors (Table 4).

4. Discussion

In the present meta-analyses, the overall incidence of pneumonitis was 2.14% in advanced NSCLC patients treated with ALK inhibitor monotherapy in clinical trials. The cohorts from Japan had a higher incidence of ALK-inhibitor pneumonitis both for all-grade and for high-grade, when compared to the cohorts from countries other than Japan, which remained significant after adjusting for types of ALK inhibitors. The study demonstrated the incidence of ALK inhibitor pneumonitis, and provided an evidence for a higher incidence of ALK inhibitor pneumonitis in Japanese population based on the datasets from clinical trials.Due to a low incidence of pneumonitis and a low prevalence of ALK-rearrangement in advanced NSCLC patients accounting for about 5% of NSCLC patients, the exact incidence of ALK-inhibitor related pneumonitis based on a large dataset has not been previously described. The present study defined the incidence of ALK inhibitor pneumonitis among ALK-rearranged advanced NSCLC patients from the dataset of 18 clinical trials, which was 2.14% for all-grade, 1.33% for high-grade, and 0.22% for grade 5 pneumonitis. The incidence of all-grade pneumonitis is consistent with the prior report by Pellegrino et al, which reported 2.1% overall incidence; however, the details of the incidence in high-grade and grade 5 pneumonitis, and the detailed comparisons among different subgroups have not been reported [42]. The incidence of all-grade and high-grade pneumonitis is higher compared to the results of the previous meta-analysis of EGFR-TKI pneumonitis, where the overall incidence of EGFR-TKI pneumonitis was 1.12% for all grade, and 0.61% for high-grade [9]. However, the incidence of grade 5 pneumonitis is similarly very low for ALK pneumonitis (0.22%) and for EGFR pneumonitis (0.20%) from these meta-analyses studies.

In terms of the risk factors associated with ALK- inhibitor pneumonitis, the cohorts from Japanese studies had a significantly higher incidence compared to the cohorts of studies of non-Japan origin for all-grade (6.25% vs. 1.14%) and for high-grade pneumonitis (3.31%, and 0.39%, respectively), with the OR of 3.633 for all-grade and 4.329 for high-grade pneumonitis. Japanese studies remained as a significant factor for increased risk of pneumonitis in multivariate meta-regression analyses (OR: 4.329), after adjusting for types of ALK inhibitors. The results of the present study provided the robust data to support that the Japanese patients are more susceptible to develop ALK inhibitor pneumonitis, with 4 times higher odds compared to others. The results also emphasized a much lower incidence of pneumonitis (1.1% for all-grade pneumonitis) in the cohorts of non-Japan origin. Our results are

Table 1
Characteristics of the eligible trial cohorts.

Author (publication year)	Drug	Treatment line	Country	Phase	Total patients	All-grade pneumonitis	High-grade pneumonitis	Grade 5 pneumonitis
Camidge DR, et al. (2012)	Crizotinib	Mixed treatment	Multiple countries including Japan	I	149	at least 4*	3	0
Cho BC, et al. (2017)	Ceritinib	Mixed treatment	Non-Japan study	I	135	0	0	0
Crino L, et al. (2016)	Ceritinib	ALK inhibitor retreatment	Multiple countries including Japan	II	140	2	1	0
Gadgeel SM, et al. (2014)	Alectinib	ALK inhibitor retreatment	Non-Japan study	I /II	47	0	0	0
Hida T, et al. (2016)	Alectinib	Mixed treatment	Japan	I	35	1	0	0
Hida T, et al. (2017)	Alectinib	Mixed treatment	Japan	III	103	8	5	0
Hida T, et al. (2017)	Crizotinib	Mixed treatment	Japan	III	104	8	3	0
Iwama E, et al. (2017)	Alectinib	Mixed treatment	Japan	II	18	not mentioned	not mentioned	0
Kim DW, et al. (2016)	Ceritinib	Mixed treatment	Non-Japan study	I	246	9	8	1
Kim DW, et al. (2017)	Brigatinib	ALK inhibitor retreatment	Multiple countries including Japan	II	219	9	4	0
Nishio M, et al. (2015)	Ceritinib	Mixed treatment	Japan	I	20	not mentioned	not mentioned	0
Ou SH, et al. (2016)	Alectinib	ALK inhibitor retreatment	Non-Japan study	II	138	not mentioned	not mentioned	0
Peters S, et al. (2017)	Crizotinib	First-line	Non-Japan study	III	151	4	3	not mentioned
Peters S, et al. (2017)	Alectinib	First-line	Non-Japan study	III	152	2	0	0
Shaw AT, et al. (2013)	Crizotinib	Prior chemotherapy	Multiple countries including Japan	III	172	2	2	2
Shaw AT, et al. (2016)	Alectinib	ALK inhibitor retreatment	Non-Japan study	II	87	0	0	0
Shaw AT, et al. (2017)	Ceritinib	ALK inhibitor retreatment	Multiple countries including Japan	III	115	1	1	0
Solomon BJ, et al. (2014)	Crizotinib	First-line	Multiple countries including Japan	III	171	3	3	1
Soria JC, et al. (2017)	Ceritinib	First-line	Multiple countries including Japan	III	189	4	1	1
Tamura T, et al. (2017)	Alectinib	Mixed treatment	Japan	I /II	46	1	not mentioned	0

ALK: anaplastic lymphoma kinase.
* For the case with "at least 4" pneumonitis, we used "4" as the number of pneumonitis.

also consistent with a recent study assessing the incidence of pneumonitis associated with crizotinib in 4 PROFILE trial. The study demonstrated that the incidence of pneumonitis was 1.2% (20 of 1644) overall, 1.3% (11 of 838) in whites, and 1.2% (9 of 745) overall in Asians, however, greater at 3.7% (6 of 162) in Japanese patients. [43] In addition, the present study results are similar to the observations in EGFR pneumonitis, where Japanese studies had higher incidence of pneumonitis compared to non-Japanese studies for all-grade pneumonitis (4.77% vs. 0.55%), high grade (2.49% vs. 0.37%), which also remained significant after adjusting for other significant variables [9]. The results of the present study further emphasizes the need for increased caution for the higher risk of pneumonitis related to ALK inhibitor therapy in Japanese patients, which has been less recognized compared to the setting of EGFR inhibitor therapy. The observations also raise an interesting question of a biological basis of increased susceptibility of Japanese population to develop pneumonitis from ALK inhibitors. Genetic polymorphisms of certain genes including MUC5 family, human leukocyte antigen (HLA) alleles, and cytochromes P450 (CYP) family have been indicated as possible markers for interstitial lung disease, allergic lung inflammation, and drug-related lung toxicities [42,44–50], which can be further studied to identify the biologic basis of the findings.

No significant differences were observed for the incidence of pneumonitis among different ALK inhibitors or among different trial phases in the univariate analyses. In the multivariable analyses, types of ALK inhibitors remained as a significant factor along with the Japan-origin cohort, and brigatinib had significantly higher odds for all grade pneumonitis (OR: 4.827, $p = 0.007$) compared to alectinib; however, only one publication of a phase 2 study was available to be included in this study to estimate the effect of brigatinib therapy, [13] therefore, it may need careful interpretations. Brigatinib is a newly emerging agent in the treatment of ALK-rearranged NSCLC, and the data are currently accumulating. According to a very recent trial comparing brigatinib and crizotinib in ALK-positive NSCLC published on 9/25/2018 after the data collection of the present meta-analyses, all-grade pneumonitis occurred in 3.7% (5/136) of patients in the brigatinib group and 2.2% (3/137) of patients in the crizotinib group. [51] High-grade pneumonitis occurred in 2.9% (4 of 136) and 0.7% (1 of 137), respectively. Early onset pneumonitis, defined as occurring within 14 days after the initiation of treatment, was observed in 2.9% (4/136) of patients in the brigatinib group only. One retrospective study using brigatinib in patients with alectinib-refractory ALK-positive NSCLC, the incidence of pneumonitis was 9.1% (2 of 22) for all-grade and 4.5% (1 of 22) for high-grade pneumonitis. Further studies are needed to determine the impact of brigatinib on the risk of increasing the incidence of pneumonitis, and to investigate the characteristics and mechanisms of early onset pneumonitis that is somewhat unique to the agent.

Several limitations are noted in the present study, including a relatively small number of eligible cohorts (n = 20). However, we included all available published studies at the time of data collection, to demonstrate the incidence of this under-studied entity of ALK pneumonitis. Lines of treatment were variable, and 7 out of 20 cohorts had "mixed" treatment lines with patients at the different lines of treatment within each cohort. Only the cohort-level data were available for the present meta-analyses, and the patient-level data were not available, which limit the further evaluation of risk factors associated with pneumonitis. Newer trial reports that were published after the data collection were not included, which is inevitable for this rapidly-evolving field. In addition, heterogeneity was observed in the overall incidence of all-grade pneumonitis including all types of ALK inhibitors, treatment line, country, and phase; however, in subgroup analyses, heterogeneity was decreased in most of the testing. Inherent heterogeneity might be explained by grade 1 or 2 pneumonitis which are subject to variable thresholds for toxicity reporting across the study sites and investigators.

In conclusion, the overall incidence of ALK inhibitor pneumonitis

Table 2
Results of multiple subgroup analyses for the incidence of ALK inhibitor-related pneumonitis.

Group/Subgroup		All-grade pneumonitis			High-grade pneumonitis			Grade 5 pneumonitis		
		No. of studies	No. of patients	Incidence (%) (95% CI)	No. of studies	No. of patients	Incidence (%) (95% CI)	No. of studies	No. of patients	Incidence (%) (95% CI)
Overall group		17[#]	2261	2.14 (1.37-3.34)[*]	16[#]	2215	1.33 (0.80-2.21)	19[#]	2286	0.22 (0.09-0.52)
ALK inhibitors	Alectinib	6	470	1.62 (0.48-5.29)[*]	5	424	0.08 (0.00-28.58)[*]	8	626	0.00 (NA)
	Ceritinib	5	825	1.62 (0.72-3.59)	5	825	0.88 (0.27-2.78)	6	845	0.24 (0.06-0.94)
	Crizotinib	5	747	2.68 (1.45-4.90)	5	747	1.87 (1.11-3.14)	4	596	0.50 (0.16-1.55)
	Brigatinib	1	219	4.11 (NA)	1	219	1.83 (NA)	1	219	0.00 (NA)
Treatment line	First-line	4	663	1.96 (1.14-3.35)	4	663	1.05 (0.46-2.42)	3	512	0.39 (0.10-1.55)
	ALK-first line with prior chemotherapy	1	172	1.16 (NA)	1	172	1.16 (NA)	1	172	1.16 (NA)
	ALK ≥ 2	5	608	1.24 (0.35-4.27)	5	608	0.99 (0.44-2.18)	6	746	0.00 (NA)
	Mixed	7	818	3.29 (1.70-6.30)*	6	772	2.32 (1.25-4.28)	9	856	0.12 (0.02-0.82)
Country	Non-Japan study	6	818	1.14 (0.33-3.92)*	6	818	0.39 (0.03-5.19)*	6	805	0.12 (0.02-0.88)
	Japan study	4	288	6.25 (3.97-9.70)	3	242	3.31 (1.66-6.47)	6	326	0.00 (NA)
	Multiple countries including Japan	7	1155	2.15 (1.39-3.32)	7	1155	1.30 (0.78-2.14)	7	1155	0.35 (0.13-0.92)
Phase	I	4	565	2.19 (0.94-5.02)	4	565	1.45 (0.40-5.16)	5	585	0.17 (0.02-1.20)
	II[†]	5	539	1.57 (0.49-4.90)	4	493	1.01 (0.42-2.41)	7	695	0.00 (NA)
	III	8	1157	2.49 (1.38-4.45)*	8	1157	1.46 (0.80-2.66)	7	1006	0.40 (0.15-1.05)

ALK: anaplastic lymphoma kinase, CI: Confidence interval, NA: Not available.

* $I^2 > 50\%$ indicating substantial heterogeneity.

[#] Not all studies provided the number of patients with pneumonitis in all three grade categories (all grade, high grade, and grade 5). Therefore, for each grade group of pneumonitis, the studies reporting the number of pneumonitis in the groups were including the analyses, generating different numbers of studies for three groups.

[†] Two phase I/II studies were included as phase II.

Table 3
Results of univariate meta-regression analyses for the incidence of ALK inhibitor-related pneumonitis.

Subgroup		All-grade pneumonitis		High-grade pneumonitis	
		OR (95% CI)	*P* value	OR (95% CI)	*P* value
Drug	Alectinib	REF		REF	
	Ceritinib	0.746 (0.227, 2.455)	0.605	1.085 (0.246, 4.779)	0.907
	Crizotinib	1.288 (0.405, 4.093)	0.644	1.861 (0.416, 8.331)	0.384
	Brigatinib	1.960 (0.359, 10.70)	0.407	1.814 (0.229, 14.355)	0.542
Treatment line	First-line	REF		REF	
	ALK-first line with prior chemotherapy	0.584 (0.080, 4.222)	0.568	1.102 (0.188, 6.434)	0.906
	ALK ≥ 2	0.853 (0.267, 2.722)	0.772	0.932 (0.272, 3.190)	0.903
	Mixed	1.944 (0.743, 5.081)	0.159	2.361 (0.887, 6.287)	0.080
Country	Non-Japan study	REF		REF	
	Japan study	3.633 (1.538, 8.583)	0.006	2.664 (0.805, 8.818)	0.100
	Multiple countries including Japan	1.223 (0.554, 2.696)	0.593	1.049 (0.374, 2.942)	0.921
Phase	I	REF		REF	
	II	0.787 (0.201, 3.078)	0.712	0.530 (0.126, 2.227)	0.358
	III	1.258 (0.403, 3.930)	0.671	0.909 (0.300, 2.756)	0.856

OR: odds ratio, ALK: anaplastic lymphoma kinase, REF: reference group.
[†]Two phase I/II studies were included as phase II.

Table 4
Results of multivariate meta-regression analyses for the incidence of ALK inhibitor-related pneumonitis.

Subgroup		All-grade pneumonitis		High-grade pneumonitis	
		OR (95% CI)	*P* value	OR (95% CI)	*P* value
Drug	Alectinib	REF		REF	
	Ceritinib	1.959 (0.773, 4.962)	0.156	2.282 (0.584, 8.903)	0.235
	Crizotinib	1.958 (0.895, 4.283)	0.092	2.730 (0.740, 10.069)	0.131
	Brigatinib	4.827 (1.553, 14.999)	0.007	3.976 (0.646, 24.466)	0.137
Country	Non-Japan study	REF		REF	
	Japan study	4.329 (1.918, 9.770)	< 0.001	3.130 (0.888, 11.034)	0.076
	Multiple countries including Japan	0.770 (0.368, 1.611)	0.489	0.712 (0.264, 1.917)	0.502

OR: odds ratio, ALK: anaplastic lymphoma kinase, REF: reference group.

was 2.14% in patients with advanced NSCLC. The patients from Japanese cohorts had a higher incidence of ALK-inhibitor pneumonitis, which indicates the need for increased awareness and caution for pneumonitis in Japanese patients treated with ALK inhibitors. The results of the study also call for further investigations of the mechanisms and risk factors of ALK inhibitor-related pneumonitis.

Conflict of interest

Suh, Pyo: Nothing to disclose

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None

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