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ORIGINAL ARTICLE

Generalization and representativeness of phase III immune checkpoint blockade trials in non-small cell lung cancer

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Abstract

Background: Strict eligibility criteria for patient enrollment in phase III trials raise questions regarding generalization to ineligible patients. We evaluated whether pivotal phase III trials of immune checkpoint blockades (ICBs) represent the overall population of non-small cell lung cancer (NSCLC) patients.

Methods: We reviewed the inclusion and exclusion criteria of three phase III trials (CheckMate057, CheckMate017, and KEYNOTE-010). Stage IIIB or IV NSCLC patients diagnosed from 2011 to 2013 at Seoul National University Hospital (cohort 1) were reviewed. We also analyzed the criteria in 53 patients with NSCLC who were treated with nivolumab or pembrolizumab as routine practice (cohort 2).

Results: Among the 715 patients in cohort 1, 499 (69.9%) were ineligible for the three trials. Reasons for ineligibility included: no prior platinum doublet treatment (23.6%), lack of tissue availability (22.7%), Eastern Cooperative Oncology Group performance status > 1 (14.1%), steroid use (18.2%), active cerebral nervous system metastasis (8.3%), hepatitis B/hepatitis C/human immunodeficiency virus (8.0%), and no measurable lesion (7.3%). *EGFR* mutations were more common in the ineligible group. In cohort 2, 67.9% of patients were classified as ineligible. Treatment outcomes of ICB in cohort 2 appeared inferior to those in the three pivotal trials, with a response rate of 11.3% and median progression-free survival of 1.67 months.

Conclusion: Only 30% of NSCLC patients were eligible for ICB phase III trials. The actual efficacy in the 70% of ineligible patients is unknown. These findings suggest a huge gap between practice-changing phase III trials and the overall population of NSCLC patients.

Introduction

Because immune checkpoint blockade drugs (ICBs) produced durable clinical response and survival gain in several phase III studies,[1–3] they are currently the standard of care for patients with non-small cell lung cancer (NSCLC) who fail to respond to platinum-based chemotherapy.[4] The number of phase III studies of ICBs is rapidly increasing, resulting in substantially more United States (US) Food and Drug Administration (FDA) approved immune-based molecular agents.[5]

The aim of phase III trials is to evaluate the benefits of experimental treatment compared with standard treatment. Therefore, eligibility criteria for phase III trials should be sufficiently strict to control bias but broad enough so that the results are generalizable to the patient population they are intended for.[6] However, eligibility criteria of ICB phase III trials are frequently extensive and strict; they exclude elements such as poor performance status (PS), active central nervous system (CNS) metastasis (a common situation in NSCLC), and autoimmune disease or viral infection. Not all of the components of these rigorous eligibility criteria are supported by a biological hypothesis and clinical rationale; most are simply duplicated from the protocols of prior studies.[7] Unnecessary eligibility criteria restrict the

diversity of patients that are enrolled in these studies. Moreover, patients with characteristics beyond the eligibility criteria can receive the study drug without any regulation after FDA approval. Phase III trials should reflect the total affected patient population so that the findings can be applied to the general population to which the drug will be prescribed[6] strict criteria for these trials raise questions regarding their generalization to the actual patient population.

Hence, the aim of this study was to evaluate whether pivotal phase III trials for ICBs represent the total population of NSCLC patients. We measured the proportion of potentially eligible patients and compared the outcomes using ICBs between eligible and ineligible patients.

Methods

Patient selection

This retrospective study analyzed two patient cohorts: overall NSCLC patients (cohort 1) and NSCLC patients who received ICBs as routine practice (cohort 2). For cohort 1, we analyzed patients diagnosed with NSCLC at Seoul National University Hospital (SNUH) from January 2011 to December 2013. Our inclusion criteria were (i) cytological or pathological diagnosis of stage IIIB or IV NSCLC, (ii) treatment with palliative chemotherapy ± concurrent radiation therapy, (iii) failure of first-line chemotherapy, and (iv) aged > 19 years at the time of diagnosis. Patients who received only supportive care without chemotherapy, or whose records lacked sufficient information to evaluate the eligibility criteria of three major trials (CheckMate057 [NCT01673867], CheckMate017 [NCT01642004], and KEYNOTE-010 [NCT01905657]) were excluded.[1–3] Cohort 1 included 715 NSCLC patients (Fig 1). Cohort 2 included patients with a diagnosis of NSCLC who had received either nivolumab (BMS936558) or pembrolizumab (MK-3475) PD-1 inhibitors as routine practice. Patients whose records contained insufficient information to evaluate the same eligibility criteria as cohort 1 were excluded. We collected the following demographic and clinical characteristics for both cohorts: age, gender, stage at the time of diagnosis, reason for palliative therapy, smoking status, histological type, *EGFR* mutation, and *EML4-ALK* fusion. Responses to ICB treatment in cohort 2 were assessed by immune-related Response Evaluation Criteria in Solid Tumors version 1.1.

Evaluation of trial eligibility and ineligibility

To evaluate whether a patient would have met the eligibility criteria, we used data from the time of failure of first-line treatment because the aforementioned trials were all

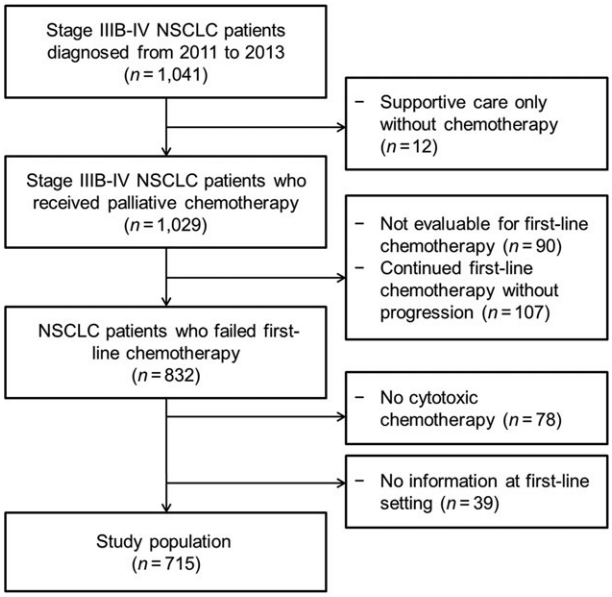

Figure 1 Flow chart of patients in cohort 1. NSCLC, non-small cell lung cancer.

intended to evaluate the efficacy of ICBs in the second-line setting. We first identified inclusion and exclusion criteria from the three trials (Table S1), and then used the criteria to create three categories of eligibility: A, B, and C. According to the first eligibility criteria (A), an ineligible patient was defined as a person who failed to fulfill any of the nine criteria. There were three inclusion criteria: failure of double-platinum chemotherapy, measurable lesion, and Eastern Cooperative Oncology Group (ECOG) PS 0 or 1; and six exclusion criteria: active CNS disease, leptomeningeal seeding (LMS), prior use of docetaxel, autoimmune disease, steroid use above a certain dose mentioned in the trial, and experience with an investigational agent. The second eligibility criteria (B) added one element to the criteria included in the A group: tissue availability. Finally, the third (C) determined eligibility based on five additional exclusion criteria: interstitial lung disease; malignant neoplasm; evidence of viral infection, such as hepatitis B or C virus (HBV/HCV) or human immunodeficiency virus (HIV); radiation therapy to the thorax within the prior six months; and major surgery within three months. Patients with *EGFR*-mutated NSCLC were evaluated for prior double platinum failure criterion when they experienced failure to both EGFR-tyrosine kinase inhibitors and sequential chemotherapy. They were considered eligible if they showed progression against platinum doublet chemotherapy after *EGFR*-targeted treatment failure.

We evaluated ineligible patients in cohort 1 for each of the three categories of criteria. For cohort 2, the same criteria were applied to the patients receiving ICB at the time of the first dose. Additionally, we investigated whether a

PD-L1 assay was performed. In such patients, PD-L1 expression was determined by immunohistochemistry (IHC) using rabbit anti-PD-L1 (E1L3N) XP mAb (Cell Signaling Technology, Danvers, MA, USA) with the Ventana Benchmark XT system (Ventana Medical Systems, Tucson, AZ, USA) at the Department of Pathology at SNUH. Membrane staining for PD-L1 in > 1% of tumor cells was regarded as positive for PD-L1.

Statistical analysis

For cohorts 1 and 2, descriptive data of the patients who were ineligible according to three separate criteria were presented as counts and percentages. For each cohort, demographic and clinical characteristics were compared between eligible and ineligible patients using a Student's *t* test for continuous variables and chi-square test for categorical variables. Survival outcomes were analyzed using Kaplan–Meier estimation. For cohort 1, overall survival (OS) was defined as the duration from the date of palliative diagnosis (stage IIIB or IV) to the date of death or last follow-up if censored. For cohort 2, OS was defined as the duration from the date of the first dose of ICB to death or the last follow-up date. Progression-free survival (PFS) was defined as the duration from the date of the first dose of ICB to the date of progression or last follow-up if censored. A log-rank test was performed to compare OS or PFS according to each eligibility criterion. To identify the difference in survival by *EGFR* mutation status in cohort 1, subgroup analyses were performed by stratification. In addition, for cohort 1, factors associated with OS were analyzed using univariate and multivariate Cox regression analyses. Statistical significance was defined as $P < 0.05$. All statistical tests were two-sided and were conducted using STATA version 12 (StataCorp LP, College Station, TX, USA).

Ethics

The SNUH institutional review board approved the study protocol (approval number: H-1707-171-873). We conducted the study in accordance with the Principles of the Declaration of Helsinki. Patient consent to participate was waived because of the retrospective design of the study.

Results

Proportion of patients fulfilling eligibility criteria

In cohort 1 (715 NSCLC patients) the proportions of eligible and ineligible patients are shown in Table 1 and Fig 2a. According to eligibility A criteria, 53% of the patients were ineligible. Approximately half of them did not meet one element, 30% did not meet two elements, and one patient did not meet five elements (Fig 2a). Using the additional element, available tissue (eligibility B), 11.4% of the overall patients were added to the ineligible group. Using eligibility C, 69.8% of patients were considered ineligible. The reasons for ineligibility included: no platinum doublet (23.6%), lack of tissue (22.7%), ECOG PS >1 (14.1%), steroid use (18.2%), active CNS metastasis (8.3%), HBV/HCV/HIV (8.0%), and no measurable lesion (7.3%).

The results of applying the three criteria (A, B, C) to cohort 2 patients receiving anti-PD-1 inhibitors are described in Table 1 and Fig 2b. Similar to cohort 1, 66% of 53 patients in cohort 2 did not satisfy eligibility criteria A and B. Based on eligibility C, 67.9% of patients were classified as ineligible because one additional patient with interstitial lung disease was ineligible. Among 35 patients who did not meet eligibility A (or B), half were excluded

Table 1 Proportion of each eligibility criterion of ineligible patients in cohorts 1 and 2

Criteria	Type of ineligibility	Number of ineligible patients: Cohort 1 (*n* = 715) *n*	%	Cohort 2 (*n* = 53) *n*	%
Inclusion criteria					
Failed platinum double chemotherapy	A	169	23.6	9	17.0
Measurable lesion	A	52	7.3	1	1.9
ECOG 0–1	A	101	14.1	14	26.4
Available tissue†	B	162	22.7	6	11.3
Exclusion criteria					
Active CNS metastasis	A	59	8.3	7	13.2
LMS	A	24	3.4	3	5.7
Prior docetaxel use	A	33	4.6	14	26.4
Steroid use	A	130	18.2	6	11.3
Autoimmune disease	A	7	1.0	0	0.0
New investigational agent	A	36	5.0	8	15.1
Interstitial lung disease‡	C	9	1.3	2	3.8
Other malignancy§	C	31	4.3	0	0.0
HBV/HCV/HIV§	C	57	8.0	1	1.9
Thoracic RTx§	C	14	2.0	10	18.9
Major surgery§	C	4	0.6	1	1.9
Summary					
Eligibility A		380	53.1	35	66.0
Eligibility B		461	64.5	35	66.0
Eligibility C		499	69.8	36	67.9

† Included in both CheckMate057 and CheckMake017. ‡ Included in both CheckMate017 and KEYNOTE-010. § Included in KEYNOTE-010. CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; ILD, interstitial lung disease; LMS, leptomeningeal seeding; RTx, radiation therapy.

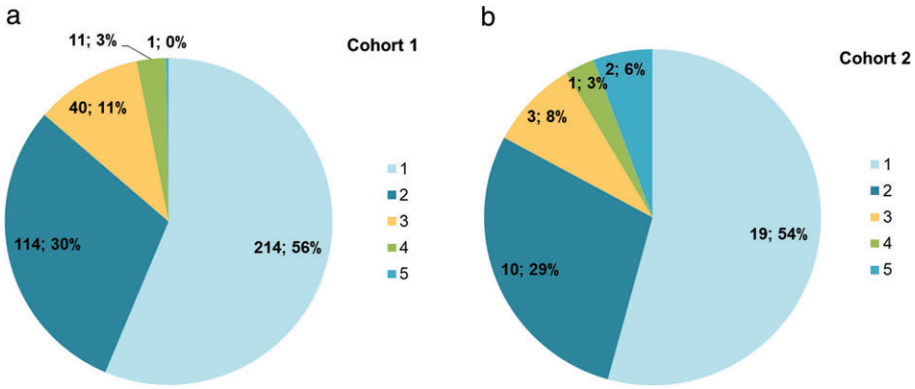

Figure 2 Number of ineligible criteria in patients: (**a**) ineligible for trial in cohort 1. 1, 2, 3, 4, 5; and (**b**) who received anti-PD-1 inhibitor in cohort 2 according to eligibility A. 1, 2, 3, 4, 5.

by one criterion and a third by two criteria (Fig 2b). Because cohort 2 included patients who received anti-PD-1 inhibitors, we investigated PD-L1 testing frequency, and 20 patients (37.7%) were regarded as having positive results, 11 (20.7%) as negative, and 22 (41.5%) did not undergo the test. Overall, 88.7% of patients were ineligible because of eligibility C and PD-L1 criterion. The reasons for ineligibility were distributed differently from those of cohort 1: ECOG PS >1 (26.4%), docetaxel use (26.4%), thoracic radiation (18.9%), no platinum doublet (17.0%), and the use of a new investigation agent (15.1%). Patients without available tissue comprised 11.3% of this group. More patients were designated as having active CNS metastasis ± LMS in cohort 2 than in cohort 1 (13.2% vs. 8.3%).

Baseline characteristics according to eligibility

Table 2 shows the differences in the characteristics of the groups based on eligibility A in cohort 1. The median age was 62 years (range 25–88). The group who were ineligible for the trials included greater numbers of women, patients with recurrent disease, and patients who had never smoked. Stage and histological type did not differ between the two groups. More patients were positive for *EGFR* mutations in the ineligible group than in the eligible group (44.7% vs. 19.7%). This difference was less prominent in cohort 2. Similar trends were observed in comparisons of characteristics between the groups defined by eligibility C (Tables S2 and S3).

Overall survival according to eligibility in cohort 1

In cohort 1, OS appeared longer in the ineligible than in the eligible group, as defined by the three eligibility criteria (Fig S1a–c). However, as *EGFR*-mutated NSCLC patients have different survival outcomes from *EGFR* wild-type patients, we examined OS according to *EGFR* mutation status. When stratified by *EGFR* mutation status, the association between ineligibility for the trials and longer OS was only observed in *EGFR*-positive patients, whereas the two eligibility groups did not differ in OS in the *EGFR*-negative group or in those who did not undergo the *EGFR* test (Fig S2a–c). To determine which component of ineligibility in the *EGFR*-positive group affected OS, we examined the proportion of each component and evaluated its effect on OS by subgroup analysis (Table S4, Fig S3). Platinum doublet failure as a reason for ineligibility accounted for almost half (48.7%) of such patients. Patients who experienced platinum doublet failure had longer OS than those who did not (hazard ratio [HR] 0.51, 95% confidence interval [CI] 0.38–0.68; $P < 0.001$), whereas patients with LMS or poor PS had shorter OS.

In addition, we performed univariate and multivariate Cox regression analyses of patients in cohort 1 to identify factors associated with OS (Table 3). Based on univariate analysis, eligibility (criteria A, B, and C) seemed to be associated with shorter OS. However, after adjusting for age, gender, palliative treatment, smoking status, histological subtypes, and *EGFR*/*ALK* status, the OS rate did not differ between groups eligible or ineligible for the trials, regardless of eligibility criteria. Initially, metastatic disease ($P = 0.009$) and histological subtypes other than adenocarcinoma ($P = 0.022$) were the only prognostic factors for shorter OS, whereas *EGFR* or *ALK* positive groups survived longer than those who did not undergo these tests ($P < 0.001$ for both).

Treatment outcome according to eligibility in cohort 2

The treatment outcomes of patients administered anti-PD-1 inhibitors are presented in Figure 3 and Table S5. The median follow-up duration in these patients was 15 months and did not differ significantly between those who were ineligible or eligible (14.0 vs. 15.5 months, respectively; $P = 0.836$). Among the 53 patients in cohort 2, the best responses included partial response (8), stable

Table 2 Comparison of characteristics between trial-eligible and ineligible patients according to eligibility A in cohorts 1 and 2

	Cohort 1 (n = 715)				Cohort 2 (n = 53)			
Characteristic	Total	Trial-eligible (n = 335, 46.8%)	Trial-ineligible (n = 380, 53.2%)	P	Total	Trial-eligible (n = 18, 34.0%)	Trial-ineligible (n = 35, 66.0%)	P
Median age (range)	62 (25–88)	62 (25–85)	63 (29–88)	0.184	62 (33–92)	59.5 (43–76)	62 (33–92)	0.212
Gender								
Male	409 (57.2)	209 (62.4)	200 (52.6)	0.009	38 (71.7)	15 (83.3)	23 (65.7)	0.215
Female	306 (42.8)	126 (37.6)	180 (47.4)		15 (28.3)	3 (16.7)	12 (34.3)	
Stage								
IIIB	23 (3.2)	9 (2.7)	14 (3.7)	0.527	0 (0.0)	0 (0.0)	0 (0.0)	
IV	692 (96.8)	326 (97.3)	366 (96.3)		62 (100.0)	18 (100.0)	35 (100.0)	
Palliative reason								
Initial IIIB or IV	617 (86.3)	299 (89.2)	318 (83.7)	0.031	41 (77.4)	14 (77.8)	27 (77.1)	1.000
Recurred after surgery	98 (13.7)	36 (10.8)	62 (16.3)		12 (22.6)	4 (22.2)	8 (22.9)	
Smoking								
Current or ex-	370 (52.0)	188 (56.6)	182 (47.9)	0.020	22 (41.5)	14 (77.8)	17 (48.6)	**0.041**
Never	342 (48.0)	144 (43.4)	198 (52.1)		31 (58.5)	4 (22.2)	18 (51.4)	
Histology								
ADC	546 (76.4)	243 (72.5)	303 (79.7)	0.077	31 (58.5)	10 (55.6)	21 (60.0)	0.851
SqCC	105 (14.7)	57 (17.0)	48 (12.6)		10 (18.9)	3 (16.7)	7 (20.0)	
Other	64 (8.9)	35 (10.5)	29 (7.6)		12 (22.6)	5 (27.8)	7 (20.0)	
EGFR mutation								
Yes	236 (33.0)	66 (19.7)	170 (44.7)	< 0.001	4 (7.6)	0 (0.0)	4 (11.4)	0.443
No	288 (40.3)	166 (49.5)	122 (32.1)		38 (71.7)	14 (77.8)	24 (68.6)	
Not tested	191 (26.7)	103 (30.8)	88 (23.2)		11 (20.7)	4 (22.2)	7 (20.0)	
ALK translocation								
Yes	100 (14.0)	48 (14.3)	52 (13.7)	0.023	3 (5.7)	2 (11.1)	1 (2.9)	0.537
No	339 (47.4)	175 (52.2)	164 (43.2)		38 (71.7)	12 (66.7)	26 (74.3)	
Not tested	276 (38.6)	112 (33.4)	164 (43.2)		12 (22.6)	4 (22.2)	8 (22.9)	

Data presented as n (%) except age. ADC, adenocarcinoma; ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; SqCC, squamous cell carcinoma.

disease (8), progressive disease (25), and mixed response (3). Nine patients could not be evaluated for the best response, and there were more such patients in the ineligible (n = 8) than the eligible (n = 1) group. Otherwise, the best response between the two groups did not differ.

The mean overall treatment duration was 0.9 months (0.0–-13.2 months), and 40 patients experience disease progression. The median PFS was 1.6 months for all patients and was not significantly different between ineligible and eligible (1.5 vs. 2.5 months, respectively; P = 0.267) groups (Fig 3a).

Among the 26 patients who died during follow-up, 21 were ineligible for the trials and 5 were eligible. The median OS was 6.4 months (2.9–12.3) for all patients, and OS was significantly longer in the eligible than in the ineligible group (12.3 vs. 3.2 months, respectively; P = 0.011) (Fig 3b).

Discussion

Our findings demonstrate that a significant number of NSCLC patients are ineligible for phase III trials of anti-PD-1 inhibitors. These findings are consistent with the results of a previous study indicating that > 55% of melanoma patients were ineligible for an immunotherapy trial.[8] Moreover, similar results were observed in studies examining eligibility for phase III trials of new drugs other than ICBs in other malignancies, such as lung,[9–11] renal,[12,13] breast,[14] and pancreatic cancers.[15] The ineligibility rate observed in our study was significantly higher than that of 4.2% (0–10.6%) reported in a study in a similar setting in Japan before 2000.[16] However, that study was based on trials and eligibility criteria different from our study. Although our eligibility criteria may have been somewhat conservative because categories for PD-L1 or histological subtypes were missing, the high ineligibility rates indicate that a majority of patients with NSCLC are not represented in phase III trials.

Poor performance status, a common cause of worsening treatment outcome and survival, is frequently selected as an exclusion criterion. In our study, poor PS was the fourth leading cause of ineligibility (14.1%) in cohort 1, and the first (26.4%) in cohort 2. Evidence from previous trials of NSCLC

Table 3 Univariate and multivariable Cox regression analysis of overall survival in cohort 1

		Univariate			Multivariable		
Variables	Detail	HR	95% CI	*P*	aHR	95% CI	*P*
Eligibility A	Ineligible (ref: eligible)	0.77	0.66–0.90	0.001	0.99	0.84–1.17	0.918
Eligibility B	Ineligible (ref: eligible)	0.82	0.69–0.96	0.012	—	—	—
Eligibility C	Ineligible (ref: eligible)	0.83	0.69–0.98	0.026	—	—	—
Age	≥ 60 (ref: < 60)	1.46	1.24–1.71	< 0.001	1.18	0.99–1.39	0.063
Gender	Male (ref: female)	1.68	1.43–1.97	< 0.001	1.18	0.94–1.47	0.158
Palliative Reason	Initial IIIB or IV (ref: recurred)	1.37	1.08–1.73	0.008	1.38	1.09–1.75	0.009
Smoking	Smoker (ref: never-smoker)	1.67	1.42–1.96	< 0.001	1.09	0.88–1.37	0.425
Histology	SqCC (ref: ADC)	2.37	1.91–2.96	< 0.001	1.29	0.98–1.70	0.066
	Other (ref: ADC)	2.15	1.65–2.82	< 0.001	1.39	1.05–1.85	0.022
EGFR status	Positive (ref: not tested)	0.49	0.40–0.60	< 0.001	0.53	0.41–0.68	< 0.001
	Negative (ref: not tested)	0.79	0.65–0.95	0.014	0.92	0.75–1.15	0.482
ALK status	Positive (ref: not tested)	0.44	0.34–0.57	< 0.001	0.44	0.33–0.59	< 0.001
	Negative (ref: not tested)	0.81	0.68–0.95	0.012	0.93	0.77–1.12	0.427

ADC, adenocarcinoma; aHR, adjusted hazard ratio; ALK, anaplastic lymphoma kinase; CI, confidence interval; EGFR, epidermal growth factor receptor; HR, hazard ratio; SqCC, squamous cell carcinoma.

demonstrates that PS ≥ 2 was an obstacle to trial eligibility for 39% of patients in the non-tyrosine kinase inhibitor trial,[10] 18–65% in the tyrosine kinase inhibitor trial,[11] and 32% in a large retrospective study screening for clinical trial participation.[9] These results are comparable to 30% of melanoma patients with a PS ≥ 2[8] and 37.2% of patients with renal cell carcinoma with Karnofsky performance status < 80%.[12] However, because ICBs cause fewer adverse effects than cytotoxic chemotherapy in terms of toxicity, consideration should be given to using ICBs despite a poor PS.

Central nervous system metastasis, including cerebral metastasis and LMS, frequently accompanies lung cancer and is a common exclusion category of clinical trials. In 2011, a study reported that among 413 trials from ClinicalTrials.gov, nearly one-fifth excluded patients with LMS, and 14% excluded those with any history of CNS involvement.[17] These findings were more evident in sponsor-initiated than in investigator-initiated trials. Similarly, in our study, the proportion of ineligible patients with LMS was from 3.4% to 5.7%, and a substantial proportion (8.3–11.3%) of patients had active CNS metastases. A concurrent subtrial considering CNS pharmacokinetics might be a remedy for this issue.[17] On the other hand, biological and clinical validity of local treatment for CNS metastases might be questioned for ICB trials. For example, in a study of the efficacy of pembrolizumab in patients with NSCLC with CNS metastases, local treatment did not significantly affect outcome.[18] A third (n = 6) of 18 patients with NSCLC showed brain metastases response and an acceptable safety profile.

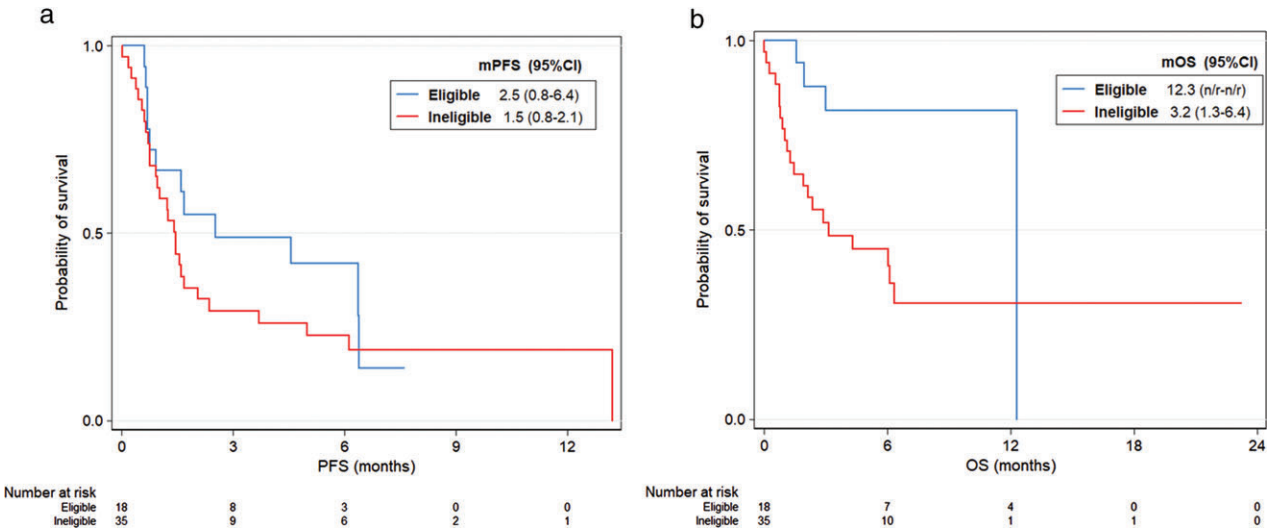

Figure 3 (**a**) Progression-free survival (PFS) Eligible 2.5 (0.8–6.4), Ineligible 1.5 (0.8–2.1) and (**b**) overall survival (OS) by eligibility A of patients included in cohort 2. Eligible 12.3 (n/r-n/r), Ineligible 3.2 (1.3–6.4). CI, confidence interval; mOS, median OS; mPFS, median PFS.

Tissue requirement is a significant hurdle for patient enrollment in ICB trials. In our study, approximately 20% of cohort 1 and 10% of cohort 2 were ineligible because they did not meet the tissue criteria. The reason for this requirement is usually to assess a biomarker. However, if identified as a predictor of response, the biomarker obtained from the population except those unable to participate might be cautiously applied to actual patients. Additionally, barriers to obtain adequate tissue include no feasible location for biopsy, patient refusal, and poor cooperation because of poor PS. Even if the quality of the specimen is inadequate, re-biopsy may be a burden; therefore the patient cannot be enrolled in the trial.

Viral infection, such as HBV, HCV, or HIV, accounted for 8% of patient ineligibility in cohort 1. In Korea, a national endemic of HBV (2% of seropositivity in the general population), meaningful numbers of HBV-infected patients with cancers other than hepatocellular carcinoma, might be potential candidates for an ICB trial.[19] Although the nivolumab trial for hepatocellular carcinoma (CheckMate040) allowed patients with well-controlled HBV infection with an antiviral agent to participate and showed efficacy and safety in these patients, the influence of ICB on HBV reactivation in HBV-infected patients remains unstudied.[20] Similarly, HIV patients are generally excluded from clinical trials because of concerns about drug interaction and immunosuppression.[21] However, it is more reasonable to judge a patient with HIV by CD4+ T-cell counts or the presence of opportunistic infection than by HIV infection alone.[22]

Because immune-related toxicity is a major issue of ICBs, pre-existing autoimmune disease is a typical exclusion criterion. Only 1% of patients in our study presented with an autoimmune disease, but many patients were excluded because of the use of immunosuppressant drugs, such as steroids. Steroid-induced immunosuppression generally arouses concern about compromising anti-tumor immunity and causing tumor growth.[23] However, the limited amount of data available supports a negative effect of steroids on the efficacy of ICB in clinical settings. According to a study of 52 melanoma patients with pre-existing autoimmune disease or immune-related adverse events after ipilimumab administration, anti-PD-1 treatment induced relatively manageable side effects and produced durable responses.[24] Although this study was retrospective and NSCLC patients with an autoimmune disorder should be closely monitored, this finding suggests that approximately 20% of patients who have an autoimmune disorder or are being treated with steroids might be acceptable for participation in ICB trials.

Similar to the results of other studies, our study population who received anti-PD-1 inhibitors (cohort 2) achieved treatment outcomes inferior to those enrolled in the registered trials.[8,12] Although we could not directly compare our results to those trials because individual level patient data was lacking, the median PFS rates in KEYNOTE-010, CheckMate057, and CheckMate017 were 3.9, 2.3, and 3.5 months, respectively, all longer than 1.6 months for the total of cohort 2.[1–3] In addition, these PFS times were longer than the 2.5 months of the eligible group, and 1.5 months of the ineligible group in our study. This discrepancy between real-life and phase III trial data of NSCLC was also consistent with findings from real-world studies of nivolumab in several countries.[25–27] The survival outcomes from studies vary, and might be influenced by the proportion of the ineligible population in the study. In a Japanese study, the median PFS was 58 days, shorter than in CheckMate057 and CheckMate017.[26] Similarly, Dudnik *et al.* reported median OS of 5.9 months among 260 NSCLC patients who received nivolumab as routine practice, significantly shorter than the results of the trials.[25] In most real-world studies, ECOG PS ≥ 2 is associated with poor prognosis. Because of these findings, we suggest that applying the results from the trials to the overall population of NSCLC patients might be hazardous.

The effect of eligibility for trials on the OS of patients in cohort 1 differed depending on *EGFR* mutation status. Similar to results of studies of melanoma and RCC,[8,12,13] we first hypothesized that patients ineligible for trials would have shorter OS than eligible patients. However, this inverse association was only observed in the population positive for *EGFR* mutations. Examination of the details of eligibility criteria in the *EGFR*-positive group suggested that the large number of patients with platinum doublet failure might have produced the longer OS we observed. Based on this finding, we speculate that *EGFR*-mutated NSCLC patients administered EGFR-tyrosine kinase inhibitors for a longer period and who could not tolerate platinum doublet as salvage chemotherapy might affect the longer OS of ineligible patients with *EGFR*-mutated NSCLC.

Our findings have several clinical implications**.** First, minimizing unnecessary categories of eligibility criteria can enhance both patient participation and generalizability. The objective of eligibility criteria is to ensure that the study population has similar factors that may influence the outcomes from the intervention and protect safety by excluding the population who may be at more risk or are not expected to benefit.[28] Using scientific reasoning to distinguish between a true high-risk and a no-risk population is very important. For example, patients with four features – HIV, brain metastases, minimum age, and organ dysfunction – are commonly excluded from clinical cancer trials. However, when a study drug obtains FDA approval based on the results of sponsor-initiated trials, these patient populations also receive the drug. Inclusion of these

patients should be cautiously considered and should eventually be required to confirm the efficacy and safety of the drug. We suggest that further separate, pragmatic clinical trials are warranted on a scientific and neutral basis for these patients, as recommended by a consensus workshop of the American Society of Clinical Oncology, the Friends of Cancer Research, and the US FDA.[6,29–32] Designing a trial that simultaneously enrolls both patients with restricted eligibility criteria and those defined by expanded eligibility criteria could be an alternative option.[28] Second, physicians should be cautious of interpretation and application of trial results to actual patients who are not well represented by the included study population. Our study findings provide frequencies of overall clinical outcomes and can guide discussions of treatment options, risks, and benefits.

To the best of our knowledge, our study is the first to investigate the potential eligibility of all NSCLC patients for ICB trials including higher frequencies of patients than in a previously reported study.[11] Moreover, compared to a similar study of renal cell carcinoma, we have attempted to minimize the underestimation of ineligibility by clarifying the many specific details of exclusion criteria.[13] Regardless of these strengths, our study has several caveats. First, this study was performed in single center, thus replication in other settings is needed to verify our findings. Further research is warranted using registry-based databases. Second, this retrospective study analyzed patients diagnosed between 2011 and 2013, when anti-PD-1 inhibitors were neither approved nor widely available in Korea. This temporal gap might not reflect the practice pattern at that time. Third, we evaluated all histological types including those of squamous and non-squamous origin in order to assess the common criteria of two trials for different histological types. This limitation may underestimate the results of our study.

In conclusion, our study shows that only limited numbers of all NSCLC patients are eligible for clinical trials of immunotherapy, and the effectiveness of anti-PD-1 inhibitors among these ineligible patients may be inferior to the efficacy demonstrated in strictly restricted trials. These findings suggest a huge gap between practice changing phase III trials and actual NSCLC patients.

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Disclosure

No authors report any conflict of interest.

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Supporting Information

Additional Supporting Informationmay be found in the online version of this article at the publisher's website:

Table S1 Inclusion/exclusion criteria of three trials of anti-PD-1 inhibitor in non-small cell lung cancer (NSCLC)
Table S2 Comparison of characteristics between trial-eligible and ineligible patients according to eligibility C (cohort 1)
Table S3 Comparison of characteristics between trial-eligible and ineligible patients in those who were given programmed death-1 (PD-1) inhibitors according to eligibility C (cohort 2)
Table S4 Proportion of each inclusion/exclusion criteria among ineligible *EGFR*-positive patients (n = 236)
Table S5 Comparison of clinical outcomes by trial eligibility among patients administered PD-1 inhibitors (cohort 2)

Figure S1 Overall survival by eligibility criteria (**a**) A, (**b**) B, and (**c**) C. CI, confidence interval; mOS, median overall survival.

Figure S2 Overall survival by eligibility A stratified by *EGFR* mutation status: (a) *EGFR* mutation-positive, (b) *EGFR* mutation-negative, and (c) patients not evaluated for *EGFR* mutation in cohort 1. CI, confidence interval; mOS, median overall survival.

Figure S3 Subgroup analysis of mortality risk by each inclusion and exclusion criterion and overall eligibility criteria A, B, and C. CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; LMS, leptomeningeal seeding; PS, performance status.

