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The impact of high PD-L1 expression on the surrogate endpoints and clinical outcomes of anti-PD-1/PD-L1 antibodies in non-small cell lung cancer

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ABSTRACT

Background: Recent reports have indicated that the objective response rate (ORR) and progression-free survival (PFS) cannot serve as surrogates for predicting overall survival (OS) in immune checkpoint inhibitor (ICI) trials. We performed a trial-based correlative analysis to evaluate conventional endpoints as surrogates for predicting OS in ICI-treated non-small cell lung cancer (NSCLC) patients.

Methods: A systematic electronic literature search for randomized clinical trials using ICI monotherapies for NSCLC revealed 7 trials. The correlative analysis to clarify the correlations among clinical outcomes used a weighted Spearman rank correlation coefficient (wS), weighted Pearson correlation coefficient (wP), and weighted linear regression model (wL) in all patients and patients with high PD-L1 expression.

Results: The correlative analysis of the total population revealed that the odds ratio of the ORR (OR-ORR) and the hazard ratio of OS (HR-OS) were strongly correlated with the hazard ratio of PFS (HR-PFS) (R for wP and wS, R^2 for wL; −0.869, −0.968, 0.756 between OR-ORR and HR-PFS; 0.923, 0.959, 0.851 between HR-PFS and HR-OS). The strongest correlation was observed between one-year overall survival (1y-OS) and the HR-OS (R for wP and wS, R^2 for wL; 0.985, 1.000, R^2: 0.968). In those with high PD-L1 expression, the ORR and PFS were strongly associated with OS (R^2: 0.842 between ORR and OS; 0.771 between PFS and OS).

Conclusions: The OR-ORR and HR-PFS could serve as surrogate endpoints for predicting the HR-OS in randomized trials using ICIs for NSCLC, while the ORR and PFS could be useful endpoints for predicting OS in trials with patient selection based on high PD-L1 expression.

1. Introduction

Immune checkpoint inhibitors (ICIs), including anti-programmed cell death 1 (PD-1) or anti-programmed death ligand 1 (PD-L1) monoclonal antibodies, have demonstrated survival benefits compared with standard therapies in various advanced cancers. Notably, non-small cell lung cancer (NSCLC) has become a main target of immunotherapy using ICIs. In previously treated NSCLC patients, nivolumab, pembrolizumab and atezolizumab have demonstrated superiority to docetaxel in terms of overall survival (OS) [1–3]. However, conventional evaluations using the Response Evaluation Criteria in Solid Tumors (RECIST) may not show the full benefits of ICIs in terms of the objective response rate (ORR) or progression-free survival (PFS). In fact, the ORR of ICI monotherapies for previously treated NSCLC patients was approximately 15–20%, and there was no improvement in PFS. Historically, while OS has been considered the most meaningful endpoint in oncology trials, the use of OS in clinical trials has several issues. Phase III trials using OS as the primary endpoint require large amounts of time, extensive research funding and large sample sizes. Therefore, it is important to elucidate appropriate surrogate endpoints that can be assessed over shorter periods with the aim of utilizing such endpoints in early-phase clinical trials to keep up with the rapid improvements in cancer therapy.

PD-L1 protein expression on tumor cells has been considered an

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effective biomarker for predicting the objective responses to anti-PD-1/PD-L1 immune inhibitors [4,5]. PD-L1 expression on tumor cells is upregulated when stimulated by interferon γ secreted from infiltrating lymphocytes [6]. PD-L1 expression on tumor cells may reflect the immunological reaction and could be a potential biomarker for predicting the efficacy of immunotherapy. The usefulness of PD-L1 expression on tumor cells as a biomarker in clinical trials was thoroughly investigated in the development of pembrolizumab for NSCLC. PD-L1 expression was evaluated in the large phase 1 trial named KEYNOTE001 [7]. In this study, PD-L1 expression on at least 50% of tumor cells was selected as an adequate cutoff based on a receiver operating characteristic (ROC) curve analysis to predict the objective response to pembrolizumab. This cutoff was validated in further randomized trials, i.e., KEYNOTE010 and KEYNOTE024. KEYNOTE010 was a randomized phase III trial performed to investigate the efficacy and safety of pembrolizumab for previously treated advanced NSCLC patients with PD-L1 expression [8]. The primary endpoints of this study were OS and PFS both in the total population (PD-L1 expression ≥1%) and in patients with high PD-L1 expression (PD-L1 expression ≥50%). The OS in the total population was significantly longer in the pembrolizumab arm than in the docetaxel arm. On the other hand, the ORR and PFS did not show a significant difference in either arm. In patients with high PD-L1 expression, the HR-OS was significantly better in the pembrolizumab arm. Likewise, in this selected population, the ORR and PFS were significantly better in the pembrolizumab arm. KEYNOTE024 was the first randomized phase III trial to investigate the efficacy and safety of pembrolizumab compared with standard chemotherapy in chemotherapy-naive advanced NSCLC patients with high PD-L1 expression [9]. This trial demonstrated that the superiority of pembrolizumab in benefits to not only OS but also the ORR and PFS. These trials showed that high PD-L1 expression was an adequate biomarker for selecting immunotherapy-sensitive NSCLC patients. In designing clinical trials of novel agents for the development of NSCLC therapy, it has been shown that patient selection methods based on molecular biomarkers, such as epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase, are very useful. Likewise, strategies using high tumor cell PD-L1 expression will be useful in trials of ICIs for treating NSCLC. However, it has not yet been determined whether differences in populations based on biomarkers influence appropriate surrogate endpoints.

The aim of this study was to clarify appropriate surrogate endpoints for designing early-phase clinical trials of ICIs conducted over relatively short periods. We conducted a trial-based correlative analysis to evaluate surrogates for conventional endpoints in predicting the survival benefits of ICIs in NSCLC patients. In addition, surrogate endpoints in trials that selected patients based on high PD-L1 expression were examined.

2. Methods

2.1. Selection of clinical trials

We searched for phase II and III randomized controlled trials that compared anti-PD-1 or anti-PD-L1 antibody monotherapy and standard chemotherapy. This analysis included trials published in English available on PubMed and Embase® (MEDLINE and EMBASE). We also searched the international conference of lung cancer abstracts presented in annual meetings of the American Society of Clinical Oncology (ASCO), European Society of Medical Oncology (ESMO) and World Conference on Lung Cancer (WCLC). Two authors, KI and TS, checked all candidate trials according to the selection criteria. The search formula used to select trials is described in Supplemental data. We hypothesized that PD-L1 expression had an influence on the efficacy of potential surrogate clinical outcomes; therefore, a correlative analysis regarding the odds ratio (OR) and hazard ratio (HR) was also conducted for subgroups based on PD-L1 expression in each trial. Studies not on NSCLC, without an interest in survival benefits, not on advanced-stage patients, not on anti-PD-1/PD-L1 antibodies, or not examining monotherapies were excluded.

2.2. Clinical endpoints

We assessed the endpoints that are generally available for randomized trials: the ORR, PFS, and OS. The definition of each endpoint followed the definition in each trial. The hazard ratio of overall survival (HR-OS), the hazard ratio of progression-free survival (HR-PFS) and the odds ratio of the objective response rate (OR-ORR) were also included in this analysis. If the OR was not described in the published report, we calculated it using the RR data in the published report, as follows: [(the number of partial response (PR) or complete response (CR) in the study arm) times (the number of stable disease (SD) or Progressive disease (PD) in the control arm)] divided by [(the number of SD or PD in the study arm) times (the number of PR or CR in the control arm)]. Additionally, the one-year survival rate (1y-SR), which was defined as the proportion of survivors at one year, was included in this analysis.

2.3. Analysis of total population and subgroup based on high PD-L1 expression

The total population was defined as all patients who were enrolled in each trial. The high PD-L1 expression subgroup was defined as the group with the highest PD-L1 expression from each trial. The assay for evaluating PD-L1 expression was different for each ICI trial. The pembrolizumab trials distinguished the subpopulation using PD-L1 expression on at least 50% of tumor cells, as evaluated by anti-PD-L1 antibody 22C3. The nivolumab trials distinguished the subpopulation using PD-L1 expression on at least 10% of tumor cells, as evaluated by anti-PD-L1 antibody 22-8. In the atezolizumab trials, the definition of PD-L1 expression was different from the others; PD-L1 staining was evaluated on tumor cells (TCs) as well as on tumor-infiltrating immune cells (ICs), and the subpopulation of patients with high PD-L1 expression was defined using TC3 and IC3. Herbst et al. have previously described the details of this method [5].

2.4. Statistical analysis

The coefficient of determination was calculated for each index using a weighted Spearman rank correlation coefficient (wS), weighted Pearson correlation coefficient (wP), and weighted linear regression model (wL). A P-value of less than 0.05 was defined as statistically significant in all analyses. A forest plot was created using RevMan ver. 5.0 to evaluate each endpoint in the total population and in the subpopulation with high PD-L1 expression. All statistical calculations were performed using SPSS ver. 23.0 and SAS ver.9.4.

3. Results

3.1. Selected studies and clinical outcomes

A search of the literature according the selection criteria yielded a total of seven trials (Fig. 1): three trials of nivolumab, two trials of pembrolizumab, and two trials of atezolizumab (Table 1). A total of 3752 patients were included in these studies, and 1381 (36.8%) of them were included in the high PD-L1 expression subgroup. The measurable outcomes in the total population and the high PD-L1 expression subgroup of each trial are presented in Tables 1 and 2, respectively. The KEYNOTE-010, KEYNOTE-024, POPLAR, and OAK studies did not report OR-ORR data. Therefore, the OR-ORR of these trials was calculated by the authors using the formula described in the Methods section.

3.2. Correlations among clinical outcomes in the total population

For the analysis of the total population, we analyzed the six trials

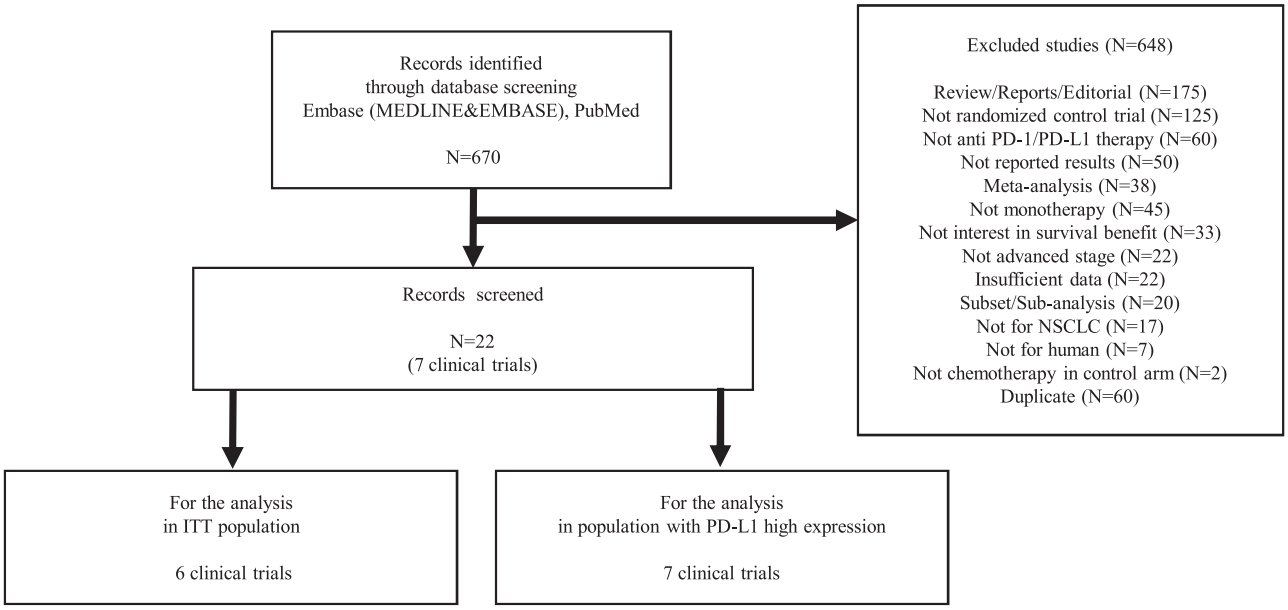

Fig. 1. Flow diagram of selection in accordance with the inclusion and exclusion criteria.

shown in Table 1. The KEYNOTE-024 trial was excluded from this analysis because this trial included only patients with high PD-L1 expression. In this analysis, the ORR and PFS could not serve as surrogates for PFS and OS, respectively, with correlation coefficients less than 0.6. These results were consistent regardless of the statistical method used for the correlative analysis (Table 3). However, the OR-ORR and HR-PFS were strongly correlated with the HR-PFS and HR-OS, with correlation coefficients greater than 0.85 in absolute value, as determined by the wP (wPs between OR-ORR and HR-PFS, HR-PFS and HR-OS; -0.869 and 0.923, respectively). We confirmed similar results by wL and wS (R^2 between OR-ORR and HR-PFS, HR-PFS and HR-OS; 0.756 and 0.851, respectively: R by wS between OR-ORR and HR-PFS, HR-PFS and HR-OS; -0.968 and 0.959, respectively) (Table 3). The correlative coefficients between OS and one-year overall survival (1y-OS) were the highest, with coefficients greater than 0.95 and completely linear correlations (Fig. 2A).

3.3. Correlations among clinical outcomes in patients selected based on PD-L1 expression

Next, we analyzed the outcomes in a subpopulation with high PD-L1 expression. The seven trials included in this analysis are listed in Table 2. The wPs between the ORR and PFS and the PFS and OS were 0.899 and 0.878, respectively (Table 3).

The ORR and PFS were strongly correlated with OS in the population with high PD-L1 expression (Fig. 2B). All correlation coefficients between PFS and OS in this population were greater than those in the total population. The correlation between the OR-ORR or HR-PFS and the HR-OS was weakened according to all three statistical methods. An analysis of the 1y-SR was not performed because there were no data about the 1y-SR in the subgroup with high PD-L1 expression in three trials.

3.4. Forest plot of OR and HR in the total population and selected subgroup

The forest plot revealed that compared to the total population, the high PD-L1 expression subgroup had superior HRs and ORs. The values of change from the total population to the high PD-L1 expression subgroup were 1.39 to 3.29 in the OR-ORR (Fig. 3A, B), 0.89 to 0.62 in the HR-PFS (Fig. 3C, D), and 0.72 to 0.56 in the HR-OS (Fig. 3E, F). In addition, the 95% confidence interval (CI) for each outcome in the subgroup with high PD-L1 expression showed no overlap with that in the total population (95% CI of total and high PD-L1 expression; OR-ORR, 1.16–1.65 and 2.49–4.36; HR-PFS, 0.83-0.96 and 0.55-0.70; HR−OS, 0.67-0.79 and 0.48-0.64). These results indicate that all outcomes in the subgroup with high PD-L1 expression were significantly better than those in the total population, with larger OR-ORRs and smaller HR-PFS and HR−OS values. The funnel plots were almost symmetrical, as shown in Supplemental Figure.

4. Discussion

This research was performed to investigate appropriate surrogate endpoints for designing early-phase clinical trials of ICIs in NSCLC. The correlative analysis of the total population showed no relationships among the ORR, PFS, and OS, whereas a moderate association of the OR-ORR or HR-PFS with the HR-OS was found. These results suggest the potential utility of the OR-ORR and HR-PFS as surrogate endpoints

Table 1
Randomized controlled trials of immune checkpoint inhibitor for unselected total population.

Total population	N	ORR (%)	ORR-OR [95%CI]	PFS (m)	PFS-HR [95%CI]	OS (m)	OS-HR [95%CI]	1-y OS rate (%)
CM017	135	20	2.6 [1.3–5.5]	3.5	0.62 [0.47–0.81]	9.2	0.59 [0.44–0.79]	42
CM057	292	20	1.7 [1.1–2.6]	2.3	0.92 [0.77–1.11]	12.2	0.73 [0.59–0.89]	51
CM026 (> 5%)	271	26.1	0.70 [0.46–1.06]	4.2	1.15 [0.91–1.45]	14.4	1.02 [0.80–1.30]	56.3
KN010 [2 mg/kg]	344	18.0	2.14*	3.9	0.88 [0.74–1.05]	10.4	0.71 [0.58–0.88]	43.2
KN010 [10 mg/kg]	346	18.5	2.21*	4	0.79 [0.66–0.94]	12.7	0.61 [0.49–0.75]	52.3
POPLAR	144	15	0.99*	2.7	0.94 [0.72–1.23]	12.6	0.73 [0.53–0.99]	52
OAK	425	14	1.02*	2.8	0.95 [0.82–1.10]	13.8	0.73 [0.62–0.87]	55

ND, Not described; NR, Not reached; the odds ratio with asterisk (*) was calculated using the published data.

Table 2
Population with PD-L1 high expression in randomized controlled trials.

Trial (PD-L1 expression)	N	ORR (%)	ORR-OR [95%CI]	PFS (m)	PFS-HR [95%CI]	OS (m)	OS-HR [95%CI]	1-year OS rate (%)
CM017 (> 10%)	36	19	2.4*	3.7	0.58 [0.33–1.02]	11.0	0.50 [0.28–0.89]	ND
CM057 (> 10%)	86	37	4.1 [1.8–10.1]	5.0	0.52 [0.37–0.75]	19.9	0.40 [0.27–0.58]	ND
CM026 (> 50%)	88	ND	ND	5.4	1.07 [0.77–1.49]	15.9	0.90 [0.63–1.29]	ND
KN010 [2 mg/kg] (> 50%)	139	30.2	5.05*	5.0	0.59 [0.44–0.78]	14.9	0.54 [0.38–0.77]	ND
KN010 [10 mg/kg] (> 50%)	151	29.1	4.80*	5.2	0.59 [0.45–0.78]	17.3	0.50 [0.36–0.70]	ND
KN024 (> 50%)	154	45.5	1.96*	10.3	0.50 [0.37–0.68]	30.0	0.63 [0.47–0.86]	70.3
POPLAR (IC3TC3)	47	37.5	4.02*	7.8	0.60 [0.31–1.16]	15.5	0.49 [0.22–1.07]	ND
OAK(IC3TC3)	72	30.6	3.65*	4.2	0.63 [0.43–0.91]	20.5	0.41 [0.27–0.64]	69

ND, Not described; NR, Not reached; the odds ratio with asterisk (*) was calculated using the published data.

Table 3
Correlative coefficient among clinical outcome based on statistical methods.

Index		Total population			Subgroup with PD-L1 high expression		
		R in weighted Pearson *p* value	R in weighted Spearman *p* value	R^2 in weighted liner regression *p* value	R in weighted Pearson *p* value	R in weighted Spearman *p* value	R^2 in weighted liner regression *p* value
ORR	PFS	0.545 < 0.0001	0.333 < 0.0001	0.297 0.206	0.899 < 0.0001	0.483 < 0.0001	0.808 0.006
ORR	OS	−0.017 0.4564	−0.141 < 0.0001	< 0.001 0.971	0.917 < 0.0001	0.774 < 0.0001	0.842 0.004
PFS	OS	−0.149 < 0.0001	0.270 < 0.0001	0.022 0.750	0.878 < 0.0001	0.467 < 0.0001	0.771 0.004
OS	1yOSR	0.985 < 0.0001	1.000 < 0.0001	0.968 < 0.001	NE	NE	NE
OR-ORR	HR-PFS	−0.869 < 0.0001	−0.968 < 0.0001	0.756 0.011	0.668 < 0.0001	0.563 < 0.0001	0.446 0.101
OR-ORR	HR-OS	−0.753 < 0.0001	−0.959 < 0.0001	0.568 0.051	−0.500 < 0.0001	−0.209 < 0.0001	0.250 0.253
HR-PFS	HR-OS	0.923 < 0.0001	0.959 < 0.0001	0.851 0.003	0.765 < 0.0001	−0.011 0.2394	0.585 0.027

for OS in randomized trials evaluating the efficacy of ICIs. Meanwhile, the corelative analysis indicated that the ORR and PFS were correlated with OS in patients with high PD-L1 expression. This result indicates that the ORR and PFS are valid surrogate endpoints for prospective trials of ICIs if appropriate patient selection based on high PD-L1 expression is performed.

Traditionally, the standard endpoint in phase III randomized clinical trials of NSCLC is OS because it can be measured without bias and reflects drug efficacy in terms of survival. However, there are several difficulties in planning to use this endpoint, including the need for a large number of participants, a long follow-up period, and large amounts of research funding. The use of surrogate endpoints would allow the rapid assessment of therapeutic efficacy and might reduce the cost of drug development. A meta-analysis of 14 trials of advanced NSCLC showed that the association between the ORR and PFS was strong, whereas neither the ORR nor PFS could predict survival benefits [10]. The ORR and PFS could not predict survival benefit because the OS analysis contains many cofounding factors, such as crossover effects, post-progression survival and subsequent therapies, especially in trials of molecular targeted therapies. Recently, endpoints based on tumor response, such as the ORR or PFS, have been used in considerations of the approval of molecular targeted drugs for rare driver mutations, such as crizotinib for ROS1-rearranged NSCLC. This is because the tumor response was considered the proof of concept in molecular targeted therapeutic strategies, and the contributions of these types of treatments to OS have been proven in patients with a variety of driver mutations [11,12]. However, the ORR or PFS may not be the optimal endpoint for ICIs because the clinical benefit of immunotherapies is prolonged survival. A systematic review of trials using PD-1/PD-L1 inhibitors demonstrated that the ORR and PFS were not correlated with OS [13]. In the era of treating NSCLC with immunotherapies, investigations into surrogate endpoints for predicting the survival benefits of ICIs are urgently needed.

Our correlative analysis of outcomes in the total population showed no relationships among the ORR, PFS, and OS but a strong correlation between OS and 1y-OS, with a coefficient greater than 0.95. These data are consistent with the results of previous reports [13,14]. One meta-analysis of 14 trials of treatments for advanced NSCLC reported findings in terms of milestone endpoints. This meta-analysis showed a moderate association between the 9-month or 12-month survival rate and the HR-OS ($R^2 = 0.67$ and $R^2 = 0.80$, respectively). The limitation of this analysis is that it simultaneously included a variety of treatment modalities, such as chemotherapy, molecular targeted therapy and ICIs. Since the analysis did not include only trials using immunotherapies, the suitability of the milestone endpoints for ICI trials remains unknown. Our results support the use of milestone endpoints, such as the 1y-SR, as optimal surrogate endpoints for evaluating the efficacy of immunotherapies over shorter periods.

Furthermore, we found associations between the OR-ORR and HR-PFS and between the HR-PFS and HR-OS. To the best of our knowledge, this is the first report on the efficacy of the OR-ORR or HR-PFS in predicting the HR-PFS or HR-OS in trials of ICIs for treating advanced NSCLC patients. The HR-PFS could be useful as a surrogate endpoint in future randomized trials using ICIs to predict survival benefits because it can yield results earlier than the HR-OS.

In the high PD−L expression subgroup, associations between the OR-ORR and HR-PFS and between the HR-PFS and HR−OS were not indicated. However, as shown in Fig. 2B, the HR-PFS or HR−OS values among all trials were approximately similar, which could make it difficult to prove correlations among these outcomes in a population of patients with high PD-L1 expression. Although we could not verify the associations between the OR-ORR and HR-PFS and between the HR-PFS and HR−OS, the stable value of these relationships could be interpreted as indicating rather stable benefits compared to chemotherapy.

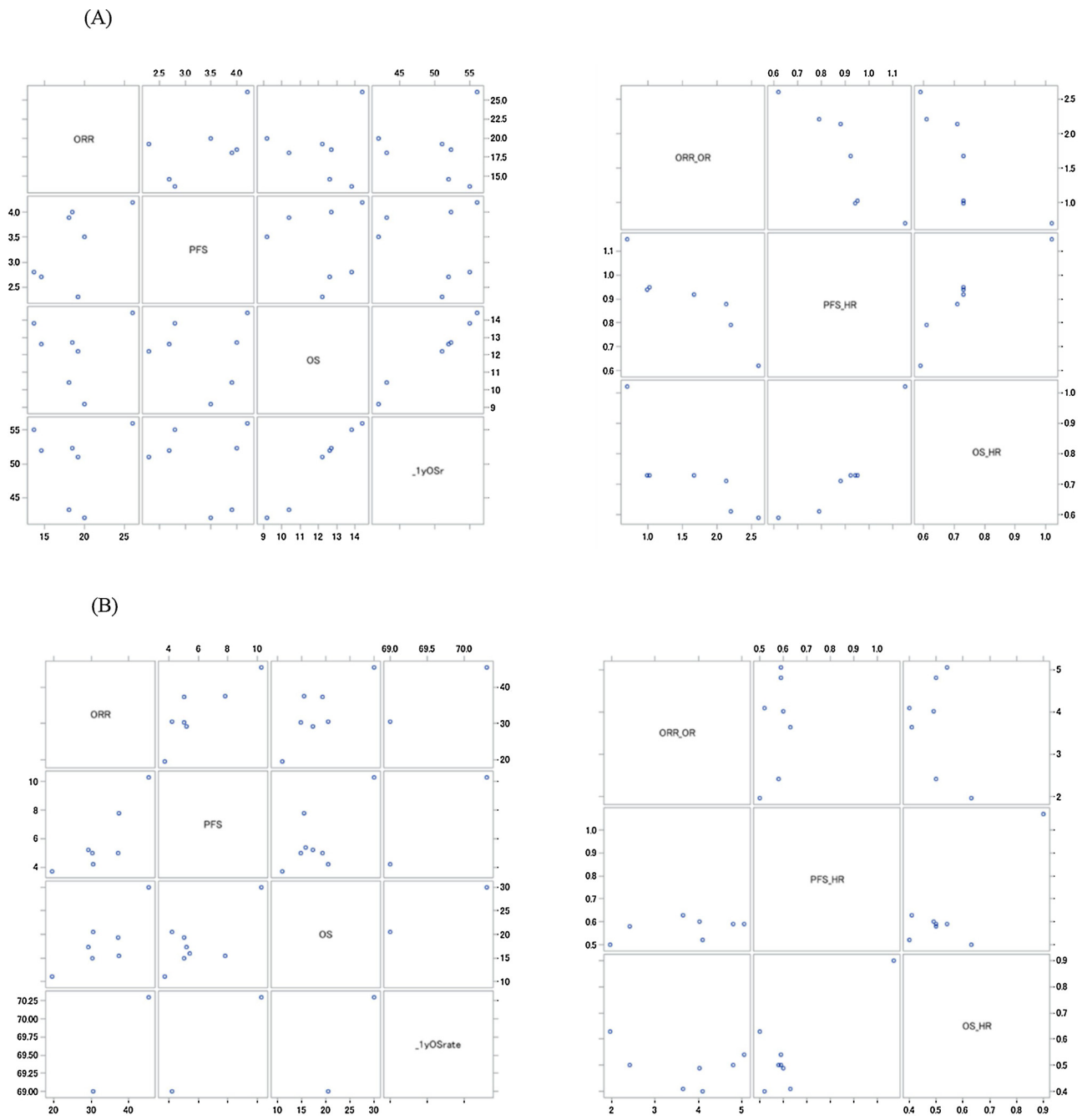

Fig. 2. Scatter plot matrix of clinical outcome (A) Total population (B) Population with high PD-L1 expression.

Interestingly, the ORR and PFS were statistically correlated with OS in patients with high PD-L1 expression, regardless of the statistical method used. This tendency has not yet been shown in NSCLC trials. Previous reports have revealed no correlations between the ORR or PFS and OS in trials of other targeted agents, including EGFR tyrosine kinase inhibitors (EGFR-TKIs) [10,15]. Our analysis indicates that the first tumor response to ICIs could influence OS only in NSCLC patients with high PD-L1 expression.

As mentioned above, biomarkers have been important for selecting responders in recent clinical trials in the field of oncology. When evaluating correlations among the outcomes, various outcomes are expressed as fixed points without considering the range of the CI. To solve this issue, we considered the sample size using weighted statistical methods and created a forest plot based on PD-L1 expression. The forest plot showed widened 95% CIs in the subgroup of patients with high PD-L1 expression. However, this forest plot showed a tendency for larger OR-ORRs and smaller HR-PFS and HR-OS values with ICI treatment in patients with high PD-L1 expression compared to the total population. Therefore, this hybrid of a correlative analysis and a meta-analysis shows that higher PD-L1 expression improves the ORR, PFS, and OS and that these parameters are correlated with each other in patients with high PD-L1 expression.

This research had several limitations. First, the number of studies was too small to effectively evaluate correlations. Comparing the effectiveness of PD-1 antibodies and the PD-L1 antibody is difficult because only two trials have been conducted using the PD-L1 antibody. Thus, further investigations are needed that apply both PD-1 and PD-L1 antibodies. Second, the 1y-SR in the high PD-L1 expression subgroup was unpublished in nearly all the trials; consequently, we could not sufficiently evaluate those correlations. The CheckMate-026 trial

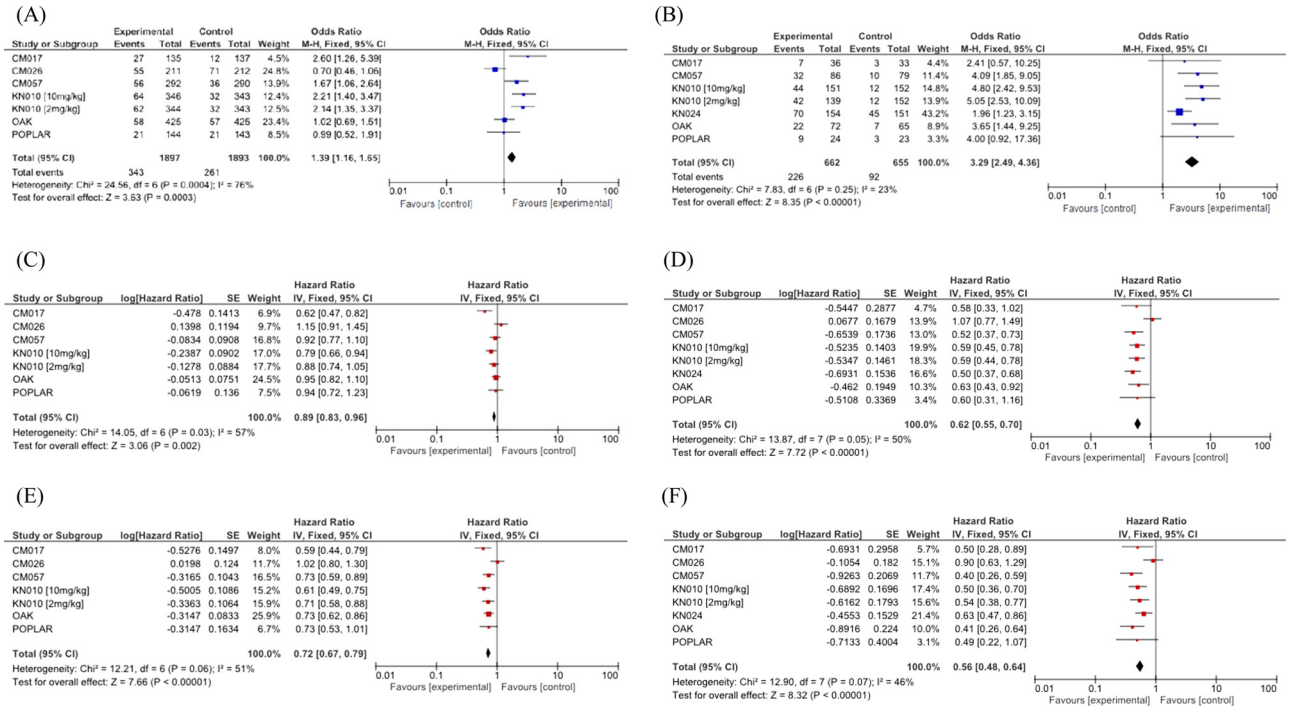

Fig. 3. Forest plot of total population and population with high PD-L1 expression.
(A) Odds ratio of ORR in total population.
(B) Odds ratio of ORR in population with PD-L1 high expression.
(C) Hazard ratio of PFS in total population.
(D) Hazard ratio of PFS in population with PD-L1 high expression.
(E) Hazard ratio of OS in total population.
(F) Hazard ratio of OS in population with PD-L1 high expression.

published few data on the high PD-L1 expression subgroup. We hypothesized that this may have been due to bias, and thus, we analyzed the funnel plot even for the subgroup with high PD-L1 expression. Consequently, the funnel plot shown in supplemental Figure is almost symmetrical. Third, we proposed that the response rate is useful as a surrogate endpoint; however, evaluating the tumor response in the trial using the immune checkpoint inhibitors was difficult. Immunotherapy-specific phenomes, including pseudoprogression and hyperprogressive disease, were reported. The retrospective study suggested that 4.7% and 13.8% of patients experienced pseudoprogression and hyperprogressive disease, respectively [16]. Prospective or observational studies are needed to confirm this result. However, these phenomena may affect the response rate. If the response rate is used as the primary endpoint in future prospective trials, a response confirmation method must be devised. Finally, this analysis was a post hoc study for new surrogate parameters. Thus, the dataset in this analysis included heterogeneity in the primary/secondary endpoints, the line of therapy, patient demographics, the PD-L1 analysis and the follow-up periods. The background differences across trials are described in Supplemental Table 1. Additionally, the PD-L1 antibody and cut-off point for determining the high-expresser differed for each agent (Supplemental Table 1). Therefore, the high PD-L1 expression populations might be nonhomogeneous among the trials. The BLUEPRINT study was a validation study to evaluate the comparability of the PD-L1 staining for four PD-L1 antibodies (22C3, 28-8, SP142 and SP263). This study showed that the PD-L1 assays were closely aligned except that of the SP142 antibody. This result may have been due to the analysis method used for the SP142 antibody. The PD-L1 analysis using the SP142 antibody evaluated PD-L1 expression on tumor cells as well as on immune cells. In contrast, the high PD-L1 expression results were comparable for all antibodies in the BLUEPRINT study [17,18]. All studies using PD-1/PD-L1 antibodies have demonstrated reproducible effectiveness in high PD-L1 expression populations. Further trials are needed to investigate the PD-L1 expression's predictive value, but the usefulness of the high PD-L1 expression has already been established in clinical practice and has been used as the standard method of selecting the appropriate therapy for advanced NSCLC. Thus, our results will provide useful information for conducting new trials on high PD-L1 expression in NSCLC.

5. Conclusion

The present study demonstrates that the OR-ORR and HR-PFS are strongly correlated with the HR-OS in trials using ICIs. The OR-ORR and HR-PFS could serve as new surrogate endpoints for predicting survival benefits in randomized trials using ICIs to treat NSCLC. In addition, we confirmed the efficacy of milestone endpoints for ICI trials. In single-arm early-phase ICI studies selecting patients based on high PD-L1 expression, the ORR and PFS are useful as endpoints for predicting survival. These surrogate endpoints may be considered in accordance with the design of the trials, such as the type of agent or population based on biomarkers in ICI therapy, but it is also necessary to validate with further investigations.

Conflicts of interest

KI has received lecture fees from Ono Pharmaceutical, MSD, Chugai Pharmaceutical, and Eli Lilly and has received research funds from Ono Pharmaceutical and MSD. SM has received lecture fees from Ono Pharmaceutical, Bristol-Myers Squibb, MSD, Chugai Pharmaceutical, and Eli Lilly. HA has received lecture fees from Ono Pharmaceutical, MSD, Chugai Pharmaceutical, and Eli Lilly and has received research funds from MSD. SM has received lecture fees from Ono Pharmaceutical, MSD, Chugai Pharmaceutical, and Eli lily. NY has received lecture fees from Ono Pharmaceutical, MSD, Chugai

Pharmaceutical, and Eli Lilly and has received research funds from MSD, Chugai Pharmaceutical, and Eli Lilly. The remaining authors declare no relevant conflicts of interest in this study.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.lungcan.2018.12.023.

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