Continuation of Pembrolizumab with Additional Chemotherapy after Progression with PD-1/PD-L1 Inhibitor Monotherapy in Patients with Advanced NSCLC: A Randomized, Placebo-Controlled Phase II Study

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ABSTRACT

Purpose: Although programmed cell death 1 (PD-1) or programmed cell death ligand 1 (PD-L1) inhibitors have shown survival benefits in patients with non–small cell lung cancer (NSCLC), most patients progress. This study evaluated whether continuing pembrolizumab with additional chemotherapy after failure of prior PD-1/PD-L1 inhibitor extends survival.

Patients and Methods: This placebo-controlled, double-blind, randomized phase II study enrolled patients with NSCLC who received one or two cytotoxic chemotherapy, including at least one platinum-doublet regimen, and progressed on second- or third-line PD-1/PD-L1 inhibitor monotherapy as the last systemic therapy. Patients were randomized (1:1) to pembrolizumab or placebo plus chemotherapy, stratified by histology and clinical outcomes to prior PD-1/PD-L1 inhibitor. The primary endpoint was progression-free survival (PFS).

Results: A total of 98 patients were randomized to the pembrolizumab-chemotherapy ($N = 47$) and placebo-chemotherapy arm ($N = 51$). At the median follow-up duration of 10.5 months, there was no statistical difference in PFS [median 4.1 months vs. 5.9 months; HR = 1.06; 95% confidence interval (CI), 0.69–1.62; $P = 0.78$) and overall survival (median 11.5 months vs. 12.0 months; HR = 1.09; 95% CI, 0.66–1.83; $P = 0.73$) between the pembrolizumab-chemotherapy and placebo-chemotherapy arms. In a subgroup with PD-L1 expression in ≥50% of tumor cells and favorable clinical outcomes to prior PD-1/PD-L1 inhibitor (partial response or 6 months or longer of stable disease), the pembrolizumab-chemotherapy arm showed a higher 24-month survival rate than the placebo-chemotherapy arm (74% vs. 38%; HR = 0.52; 95% CI, 0.13–2.1; $P = 0.34$).

Conclusions: This study did not show a survival benefit with the continuation of pembrolizumab with chemotherapy in patients whose NSCLC progressed on second- or third-line PD-1/PD-L1 inhibitors.

See related commentary by Tseng and Gainor, p. 2206

Introduction

Anti–programmed cell death 1 (PD-1) or programmed cell death ligand 1 (PD-L1) agents increase overall survival (OS) compared with second-line chemotherapy in patients who have been pretreated with platinum-doublet chemotherapy for non–small cell lung cancer (NSCLC) harboring no EGFR or ALK mutations (1–4). Therefore, current clinical guidelines recommend monotherapy with nivolumab, atezolizumab, or pembrolizumab as a subsequent therapy for patients who had prior treatment with platinum-doublet chemotherapy (5, 6).

However, the proportion of patients who achieve objective response with single PD-1/PD-L1 agents is minimal, ranging from 9% to 14% in patients with NSCLC (1–4). In addition, most patients experience disease progression and require subsequent chemotherapy. Among several biological mechanisms suggested as the reasons for the primary or acquired resistance to PD-1/PD-L1 inhibitors, inadequate T-cell infiltration around tumor cells or T-cell exhaustion related with disrupted antigen presentation or immunosuppressive microenvironment are regarded as important resistance mechanisms (7).

Many retrospective trials, including our previous one, have shown unexpectedly high objective response rates with subsequent chemotherapy administered after a single PD-1/PD-L1 agent in patients with various tumor types, including NSCLC (8–11). The underlying biological mechanism for the high objective response rates for subsequent chemotherapy after immunotherapy has not been fully investigated. However, it is assumed that the activated immune cells in association with long half-life (26–27 days) of PD-1/PD-L1 inhibitors work for a long time in patients even after discontinuation of anti-PD-1/PD-L1 therapy (12, 13), and could exert synergistic effects when chemotherapy is subsequently administered. This hypothesis of synergism between prior PD-1/PD-L1 inhibitor therapy and subsequent chemotherapy is supported by laboratory studies, which showed immunologic cell death and favorable immune modulation induced by chemotherapy (14). In addition, the synergism has been well supported by many clinical studies, where concurrent chemotherapy with a PD-1/PD-L1 inhibitor is superior to chemotherapy alone in patients with NSCLC (15–17).

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Note: Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

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Translational Relevance

This is the first prospective study to investigate whether the continuation of PD-1/PD-L1 inhibitors with additional chemotherapy improves clinical outcomes compared with chemotherapy alone in patients with non–small cell lung cancer (NSCLC), after disease progression on a single PD-1/PD-L1 inhibitor agent. Continuation of pembrolizumab with additional chemotherapy after progression with PD-1/PD-L1 inhibitor did not improve clinical outcomes. However, in the subgroups [PD-L1 tumor proportion score (TPS) ≥50% and favorable outcome with prior PD-1/PD-L1 inhibitor], slightly longer survival was related with continuation of pembrolizumab. Further study could be investigated with new chemotherapeutic or biological agents in some favorable subgroups.

However, based on our previous study, although the objective response rate for subsequent chemotherapy after PD-1/PD-L1 inhibitor was significantly higher than that for last the chemotherapy administered before PD-1/PD-L1 inhibitor therapy, the progression-free survival (PFS) did not increase comparatively (9). We suspected that the failed prolongation of PFS for the subsequent chemotherapy was attributed to the insufficient maintenance of the antitumor effect of prior PD-1/PD-L1 inhibitors, since immunotherapy was no longer administered. Compatible with our hypothesis, one retrospective study suggested the clinical relevance of continuation of PD-1/PD-L1 inhibitors, and it was reported that some patients with NSCLC who had acquired resistance to PD-1/PD-L1 inhibitors achieved long-term survival with the continuation of pembrolizumab, with or without addition of local therapy for progressing tumor sites (18). In addition, the continuation of pembrolizumab with additional ipilimumab, anti–CTLA-4 inhibitor, have recently shown promising clinical outcomes in patients with advanced melanoma who had progressed on prior PD-1/PD-L1 inhibitors (19).

We hypothesized that the continuation of treatment with the PD-1 inhibitor, pembrolizumab, combined with additional chemotherapy could overcome the primary or acquired resistance, using a synergistic effect between the two treatment modalities. Based on this hypothesis, we investigated whether the continuation of pembrolizumab combined with additional chemotherapy would improve clinical outcomes compared with chemotherapy alone after disease progression to prior PD-1/PD-L1 inhibitor monotherapy.

Patients and Methods

Participants

Patients diagnosed with histologically confirmed advanced NSCLC with EGFR and ALK wild-type were eligible. Other major inclusion criteria included patients who previously received anti PD-1/PD-L1 inhibitor monotherapy as the last systemic therapy for NSCLC within 6 weeks before enrollment; previously received one or two cytotoxic chemotherapy regimens, including at least one platinum-doublet regimen, before receiving PD-1/PD-L1 inhibitor monotherapy for advanced NSCLC; had at least one measurable lesion based on RECIST 1.1; had an Eastern Cooperative Oncology Group (ECOG) performance score of 0 or 1. Patients with previously treated and radiologically stable brain metastasis could be enrolled. Detailed guidance regarding study participation is included in the protocol available as a supplementary material. All patients provided written informed consent, and this study was performed under the supervision of an institutional review board (IRB; IRB no. 2018–07–044). This study was conducted in accordance with the Declaration of Helsinki (Clinical Trial Gov. No. 03656094).

Study design, randomization, and treatment schedule

This study was conducted at the Samsung Medical Center, Seoul, Korea. Patients were randomized in a 1:1 fashion into pembrolizumab plus chemotherapy or placebo plus chemotherapy arm based on two stratification factors. The first factor was clinical outcome to previous PD-1/PD-L1 inhibitors (favorable clinical outcome: partial response as the best response or 6 months or longer of stable disease vs. poor clinical outcome: progressive disease as the best response or less than 6 months of stable disease) and the second factor was histology (adenocarcinoma vs. nonadenocarcinoma). Randomization was conducted using the dynamic allocation online system at the Samsung Medical Center academic clinical research organization (A-CRO).

For the partner chemotherapy regimen combined with pembrolizumab or placebo, one regimen was chosen based on the investigator's decision from the following: gemcitabine [1250 mg/m^2, day 1 (D1) and day 8 (D8) every 3 weeks], pemetrexed (500 mg/m^2, D1 every 3 weeks), docetaxel (60 mg/m^2, D1 every 3 weeks), and vinorelbine (30 mg/m^2, D1, and D8 every 3 weeks). Pemetrexed was not allowed to patients with nonadenocarcinoma. Pembrolizumab (200 mg) or placebo plus chemotherapy was administered every 3 weeks starting on the same day until disease progression or unacceptable toxicity. The continuation of treatment beyond progression is not allowed.

Response evaluation was performed with chest CT with or without abdominal CT every 6 weeks until 18 weeks after enrolment and every 9 weeks thereafter during the study period.

Unblinding during the study treatment period was conducted based on the predefined procedure only when serious or unexpected adverse events were suspected to be causally related to the study drugs. The code breaking document was filled and signed by the principal investigator and sent to the A-CRO for the unblinding process.

Study endpoints

The primary objective of this study was PFS, and the secondary objectives were objective response rate [ORR; complete response (CR) and partial response (PR) according to the RECIST criteria 1.1), OS, and safety. The safety objectives were evaluated according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.

As an explorative analysis, the relationship between the survival outcomes of treatment arms and various clinical characteristics, including PD-L1 expression, was analyzed. PD-L1 expression was evaluated with IHC using 22C3 antibody on tissues acquired before prior PD-1/PD-L1 inhibitor therapy and was assessed using the tumor proportion score (TPS), the proportion of PD-L1–positive tumor cells out of 100 tumor cells.

Calculation for sample size

Based on our previous study, a median PFS of 4.2 months with a 6-month PFS rate of 28% was observed in patients who received chemotherapy after progression to PD-1/PD-L1 inhibitor monotherapy (9). We expected median PFS of the experimental arm to be 5.6 months with a 6-month PFS rate of 48%, leading to the HR for the experimental arm to be 0.58. We expected an accrual time of 2 years and an additional follow-up period of 6 months. Based on this hypothesis, a total of 81 progression or death events and 92 patients from the sample size were required to satisfy the power of 80% by one-sample log-rank test with one-sided α of 5%. This study was designed

to enroll a total of 98 patients by accounting for up to 5% of attrition due to dropout.

Statistical analysis

The χ^2 test and Student *t* test were used to calculate the statistical difference between categorical and continuous variables, respectively. PFS was calculated as the interval between the first date of study treatment and the date of disease progression or all-cause mortality. OS was calculated as the interval between the first date of study treatment and the date of all-cause mortality. The Kaplan–Meier curve was used to estimate the survival distribution, and the log-rank test was used to calculate the *P* value between patient groups. Objective response (OR) was defined as a CR or PR using RECIST criteria version 1.1.

Subgroup analysis was conducted according to PD-L1 expression (subgroups of PD-L1: TPS ≥50%, 1%–49%, and <1%), treatment outcomes with prior PD-1/L1 inhibitor (favorable clinical outcome and poor clinical outcome), histologic subtypes (adenocarcinoma and nonadenocarcinoma), and types of prior PD-1/PD-L1 inhibitors (pembrolizumab and nivolumab or atezolizumab). All *P* values were two-sided, and a P value < 0.05 was considered statistically significant. All data were analyzed using the Statistical Package for Social Sciences software (version 24.0; IBM Corp.).

Data availability statement

The data generated in this study are available within the article and its supplementary data file.

Results

Study population and clinical characteristics

A total of 100 patients were screened between November 2018 and November 2020. Among them, 98 patients were enrolled in this study and randomized to either the pembrolizumab plus chemotherapy arm ($N = 47$) or placebo plus chemotherapy arm ($N = 51$; **Fig. 1**). The baseline characteristics of the two treatment arms were well balanced (**Table 1**). As the combined chemotherapy regimens, docetaxel ($n = 64$) was most frequently used, followed by gemcitabine ($n = 26$), pemetrexed ($n = 7$), and vinorelbine ($n = 1$) in the total 98 patients.

All patients received the planned study drugs, were included in the analysis for efficacy and safety. The data lock and unblinding of study arms were performed on July 5, 2021, by when 86 events of disease progression or death had occurred.

Comparison of efficacy between treatment arms in the total population

The median follow-up duration for survival was 10.5 months [95% confidence interval (CI), 8.9–12.1]. Median cycle was six cycles (range 1–46) for the pembrolizumab plus chemotherapy arm and six cycles (range 1–27) for the placebo plus chemotherapy arm ($P = 0.36$). Median PFS was 4.1 months (95% CI, 3.4–4.8) for the pembrolizumab plus chemotherapy arm and 5.9 months (95% CI, 3.6–8.2) for the placebo plus chemotherapy arm (HR = 1.06; 95% CI, 0.69–1.62; $P = 0.78$; **Fig. 2A**). Median OS was 11.5 months (95% CI, 7.1–16.0) for the pembrolizumab plus chemotherapy arm and 12.0 months (95% CI, 7.3–16.7) for the placebo plus chemotherapy arm (HR = 1.09; 95% CI, 0.66–1.83; $P = 0.73$; **Fig. 2B**). The ORR was 30% (14/47: two complete response and 12 partial response) in the pembrolizumab plus chemotherapy arm and 33% (17/51: one complete response and 16 partial response) in the placebo plus chemotherapy arm ($P = 0.14$; Supplementary Fig. S1). The confirmed response rate was 28% (13/47: two complete response and 11 partial response) in pembrolizumab plus chemotherapy arm and 29% (15/51: 15 partial response) in the placebo plus chemotherapy arm ($P = 1.0$).

The swimmer plot for the whole study population shows the treatment duration of the study treatment as well as the treatment duration of the prior PD-1/PD-L1 inhibitors (**Fig. 3**). There were 5 and 7 patients in the chemotherapy alone arm and pembrolizumab plus chemotherapy arm, respectively, who were undergoing the study treatment at the time of data-lock. In addition, the plot shows that 4 patients underwent treatment with pembrolizumab plus chemotherapy for over 20 months, while there was no one with such a long treatment duration in the chemotherapy alone arm.

Comparison of efficacy between the treatment arms in various subgroups

The comparison of PFS and OS for the two study arms in various subgroups is summarized in Supplementary Fig. S2. When two treatment arms were compared in three different PD-L1 expression groups (TPS ≥50%, 1%–49%, and <1%), there was no difference in PFS and OS between the two treatment arms. Compared with the placebo-chemotherapy arm, the HR (95% CI) for OS of the pembrolizumab-chemotherapy arm was 2.06 (0.66–6.41), 0.96 (0.34–2.74), and 0.69 (0.33–1.45) for PD-L1 TPS <1%, 1% to 49%, and ≥50%, respectively (Supplementary Fig. S2; Supplementary Fig. S3).

In the subgroup analysis according to treatment outcomes for prior PD-1/PD-L1 inhibitor monotherapy, the pembrolizumab continuation arm showed slightly improved PFS and OS compared with the chemotherapy alone arm in the subgroup that achieved favorable clinical outcomes with prior PD-1/PD-L1 inhibitor monotherapy. In the subgroup that showed poor clinical outcomes with prior PD-L1/PD-L1 inhibitor monotherapy, the HRs for PFS and OS of the pembrolizumab-chemotherapy arm were 1.64 (0.96–2.80) and 1.36 (0.74–2.48), respectively, compared with the placebo-chemotherapy arm, whereas they were 0.78 (0.37–1.65) and 0.80 (0.30–2.14), respectively, in the subgroup that achieved favorable clinical outcomes with prior PD-1/PD-L1 inhibitor monotherapy (Supplementary Fig. S4).

In the comparative analysis between the two treatment arms in subgroups according to histology (adenocarcinoma and nonadenocarcinoma) and the types of prior PD-1/PD-L1 inhibitors (pembrolizumab and nivolumab or atezolizumab), there were no significant or clinically meaningful tendencies in PFS and OS (Supplementary Fig. S2).

Efficacy in the subgroup with high PD-L1–expressing tumor and favorable clinical outcomes with prior PD-1/PD-L1 inhibitor monotherapy

In the subgroup with high PD-L1–expressing tumor and favorable clinical outcome with prior PD-1/PD-L1 inhibitor monotherapy, slightly longer survival outcomes were associated with the pembrolizumab continuation arm. Although the median PFS (7.5 months vs. 6.4 months; HR = 0.65; 95% CI, 0.24–1.76) and OS (not reached vs. 22.0 months; HR = 0.52; 95% CI, 0.13–2.10) were not significantly different between the pembrolizumab plus chemotherapy and placebo plus chemotherapy arms, the survival curves diverge from 9 months after initiation of treatment, leading to different 18-month PFS rates (40% vs. 12%) and 24-month OS rates (74% vs. 38%) between the two arms (**Fig. 4**).

The swimmer plot for this subgroup shows a longer treatment duration for the pembrolizumab plus chemotherapy arm compared with the chemotherapy alone arm (Supplementary Fig. S5). Among 7 patients with ongoing treatment in pembrolizumab plus chemotherapy arm, 5 patients were included in the subgroup with high

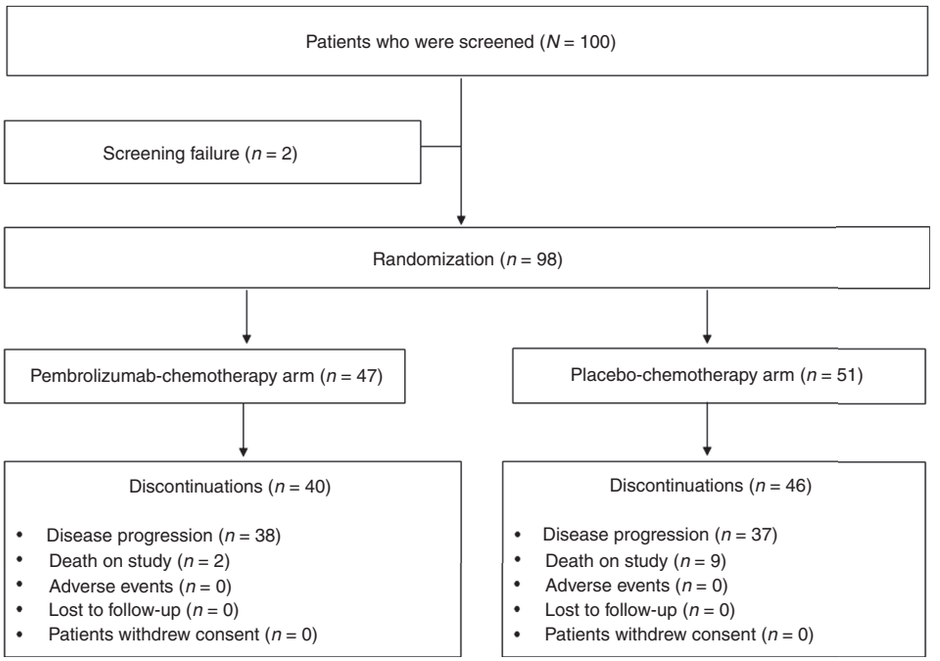

Figure 1.
CONSORT diagram for the whole study population.

PD-L1–expressing tumor and favorable clinical outcomes with prior PD-1/PD-L1 inhibitor monotherapy, while only 1 among 5five patients undergoing chemotherapy alone was included in the subgroup with high PD-L1–expressing tumor and favorable clinical outcomes with prior PD-1/PD-L1 inhibitor monotherapy (**Fig. 2**; Supplementary Fig. S5).

Safety profile

Any cause of adverse events was observed in 81% ($N = 38$) of the pembrolizumab plus chemotherapy arm and 82% ($N = 42$) of the placebo plus chemotherapy arm. In the pembrolizumab plus chemotherapy arm, 35 patients (75%) experienced treatment-related adverse events due to the study drug, the majority of which were grade 1 and 2 adverse events. In the placebo plus chemotherapy arm, 78% ($N = 40$) experienced treatment-related adverse events, and grade 1 or 2 adverse events were the most common (**Table 2**).

During the study period, unblinding was required for nine patients. In the pembrolizumab plus chemotherapy arm, 2 patients were unblinded for the evaluation of grade 2 pleural effusion ($N = 1$) and grade 3 pneumonitis ($N = 1$). In the placebo plus chemotherapy arm, 7 patients were unblinded for the evaluation and treatment of grade 2 fever ($N = 1$) and grade 2 pneumonitis ($N = 6$).

Discussion

This is the first prospective study to investigate whether the continuation of PD-1/PD-L1 inhibitors with additional chemotherapy improves clinical outcomes compared with chemotherapy alone in patients with NSCLC, after disease progression on a single PD-1/PD-L1 inhibitor agent. Although this study failed to show improved clinical outcomes with this strategy, the ORR in the study population was 32% (31 out of 98), which is higher than that for second-line docetaxel chemotherapy in previous trials (9%–14%; refs. 1–4). This implies that the effect of prior immunotherapy as a chemosensitizer for subsequent chemotherapy was still working in the population of the current study. However, similar clinical outcomes between two study arms with and without continuation of pembrolizumab suggest that the synergistic antitumor effect between continuing pembrolizumab and additional chemotherapy is insufficient to overcome the resistance to prior PD-1/PD-L1 inhibitors in patients with NSCLC. Our results are supported by a preclinical research which suggested that there is irreversible epigenetically programmed T-cell exhaustion that is hard to be reversed by PD-1 blockade (20).

One reason for the failure of this study might be that a large population with immunologically cold tumors was included in the current study. Approximately 62% ($N = 61$) of the 98 enrolled patients showed poor clinical outcomes with prior PD-1/PD-L1 inhibitors. Accordingly, the pembrolizumab-chemotherapy arm showed slightly lower PFS (HR = 1.64; 95% CI, 0.96–2.80) and OS (HR = 1.36; 95% CI, 0.74–2.48) than the placebo-chemotherapy arm in this subgroup (Supplementary Fig. S2A and S2B). This phenomenon is compatible with the data from a previous retrospective study; the median PFS for chemotherapy administered immediately after disease progression prior to PD-1/PD-L1 inhibitor therapy was longer (6.8 vs. 5.7 months) than that for chemotherapy immediately before PD-1/PD-L1 inhibitor therapy for the subgroup that clinically benefited from PD-1/PD-L1 inhibitor therapy, while it was not (3.0 vs. 3.9 months) for the group that was primary resistant to PD-1/PD-L1 inhibitor therapy (21).

In the same context, our subgroup analysis helped us identify the population that showed longer survival outcomes with the continuation of pembrolizumab therapy. There was a tendency for improved PFS (40% vs. 12% at 18 months) and OS (74% vs. 38% at 24 months) with the continuation of pembrolizumab compared with chemotherapy alone in the subgroup with high PD-L1 expression (PD-L1 TPS ≥ 50) and favorable clinical outcomes with prior PD-1/PD-L1 inhibitor therapy (**Fig. 4**). Similarly, in this subgroup, there were 4 patients with treatment duration longer than 20 months with pembrolizumab plus chemotherapy, while there were none in the chemotherapy alone arm (Supplementary Fig. S4). In addition, the swimmer plot for the whole population (**Fig. 3**) shows there was a tendency for patients with long treatment duration with pembrolizumab plus chemotherapy to be related with long treatment duration with prior PD-1/PD-L1 inhibitor

Table 1. Baseline characteristics.

		Pembrolizumab plus chemotherapy (*N* = 47)	Placebo plus chemotherapy (*N* = 51)	*P* value
Gender	Male	37 (78.7%)	43 (84.3%)	0.60
	Female	10 (21.3%)	8 (15.7%)	
Age	Median (range)	63 (36–82)	64 (38–79)	0.55
	<65	28 (59.6%)	27 (52.9%)	
	≥65	19 (40.4%)	24 (47.1%)	
ECOG performance status	0	2 (4.3%)	1 (2.0%)	0.61
	1	45 (95.7%)	50 (98.0%)	
Smoking	Never smoker	6 (12.8%)	7 (13.7%)	1.0
	Ex-smoker	36 (76.6%)	39 (76.5%)	
	Current smoker	5 (10.6%)	5 (9.8%)	
Histology	Adenocarcinoma	26 (55.3%)	25 (49.0%)	0.55
	Squamous cell carcinoma	20 (42.6%)	25 (49.0%)	
	Pleomorphic carcinoma	1 (2.2%)	1 (2.0%)	
Metastatic organs	Brain	12 (25.5%)	10 (19.6%)	0.63
	Liver	5 (10.6%)	5 (9.8%)	1.0
	Bone	7 (14.9%)	11 (21.6%)	0.44
PD-L1 TPS	<1%	8 (17.0%)	15 (29.4%)	0.61
	1–49%	15 (31.9%)	8 (15.7%)	
	≥50%	24 (51.1%)	28 (54.9%)	
Prior PD-1/PD-L1 inhibitor	Pembrolizumab	29 (61.8%)	30 (58.8%)	0.45
	Nivolumab	9 (19.1%)	6 (11.8%)	
	Atezolizumab	9 (19.1%)	15 (29.4%)	
Clinical outcome with prior PD-1/PD-L1 inhibitor	Poor outcome (PD or SD <6 months)	28 (59.6%)	33 (64.7%)	0.68
	Favorable outcome (PR or SD ≥6 months)	19 (40.4%)	18 (35.3%)	
Number of prior chemotherapy lines before PD-1/PD-L1 inhibitor	1	35 (74.5%)	43 (84.3%)	0.32
	2	12 (25.5%)	8 (15.7%)	
Combined chemotherapy regimen with pembrolizumab or placebo	Gemcitabine	11 (23.4%)	15 (29.4%)	0.11
	Pemetrexed	6 (12.8%)	1 (2.0%)	
	Docetaxel	29 (61.7%)	35 (68.6%)	
	Vinorelbine	1 (2.1%)	0 (0%)	

Abbreviations: PD, progressive disease; SD, stable disease.

monotherapy or high PD-L1 expression, while this tendency could not be found in the chemotherapy alone arm. This implies that there is a small population who benefits from the continuation of pembrolizumab, and selection of the population is necessary in subsequent studies.

As the superior efficacy of PD-1/PD-L1 inhibitor monotherapy was demonstrated compared with first-line platinum-doublet chemotherapy in patients with high PD-L1–expressing NSCLC tumors (22, 23), PD-1/PD-L1 inhibitor monotherapy is more commonly used as first-line therapy rather than as second- or further-lines in patients with high PD-L1–expressing tumors. This change in the optimal timing of PD-1/PD-L1 inhibitor monotherapy in clinical practice makes our current study data, which

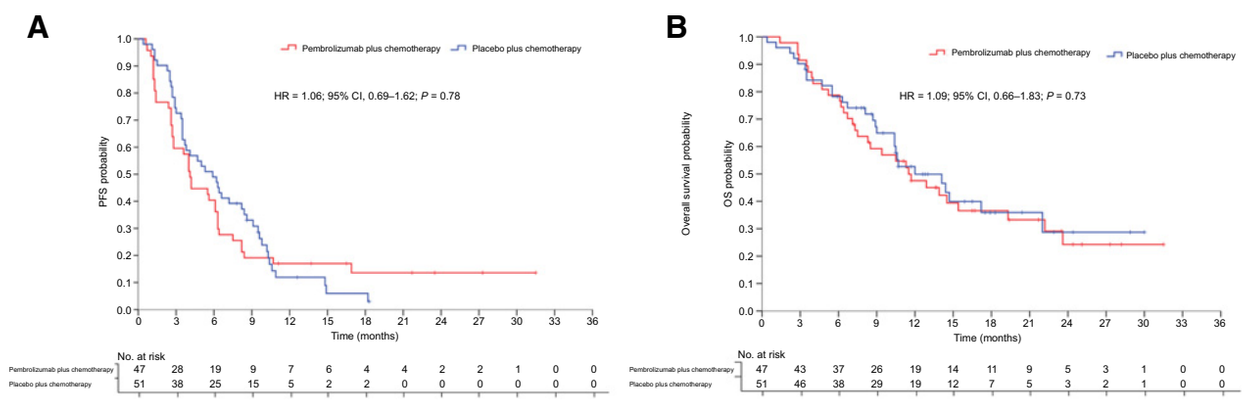

Figure 2.
A, PFS and **B,** OS of the whole study population.

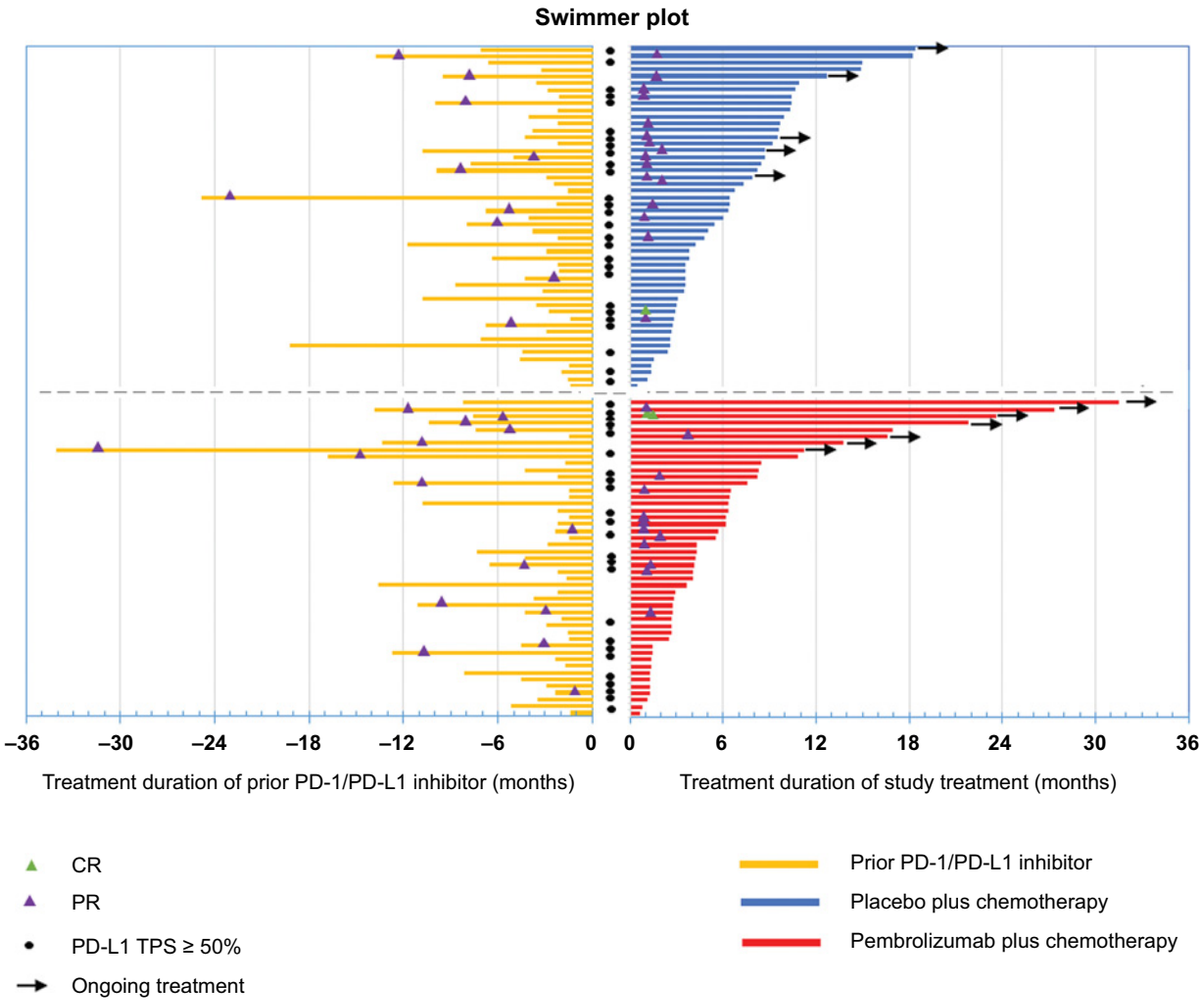

Figure 3.
Swimmer plot for the whole study population.

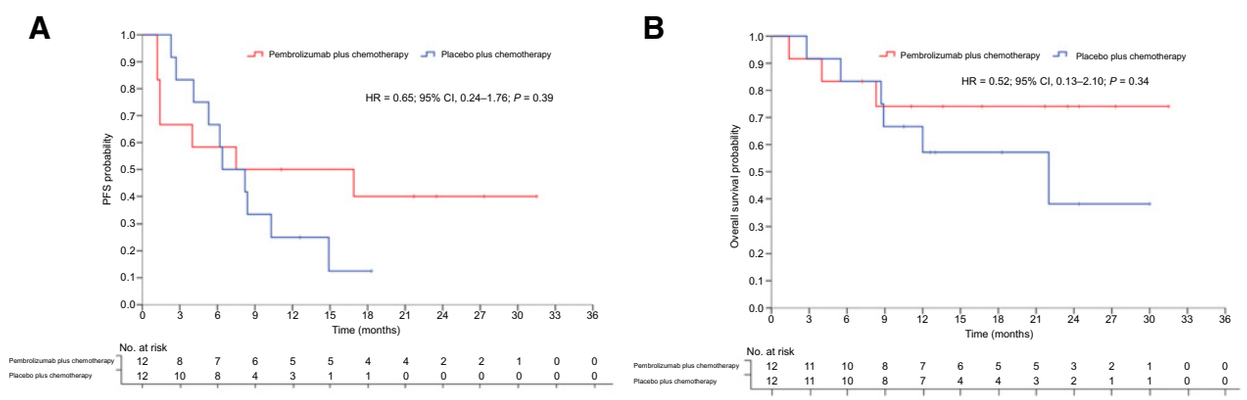

Figure 4.
A, PFS and **B,** OS in a subgroup with a high PD-L1–expressing tumor (TPS ≥ 50%) and favorable clinical outcome with prior PD-1/PD-L1 inhibitor.

Table 2. Adverse events.

	Pembrolizumab plus chemotherapy (*N* = 47)			Placebo plus chemotherapy (*N* = 51)		
	G1	G2	≥G3	G1	G2	≥G3
Hypothyroidism	5 (11%)	1 (2%)	0	0	0	0
Skin rash	8 (17%)	3 (6%)	0	8 (16%)	1 (2%)	0
Pneumonitis	0	3 (6%)	2 (4%)	0	6 (12%)	4 (8%)
Diarrhea	6 (13%)	1 (2%)	1 (2%)	3 (6%)	2 (4%)	1 (2%)
Stomatitis	3 (6%)	2 (4%)	0	5 (10%)	0	0
Fatigue	11 (23%)	2 (4%)	0	11 (22%)	5 (10%)	0
Anorexia	10 (21%)	2 (4%)	0	15 (29%)	4 (8%)	0
Anemia	4 (9%)	0	0	1 (2%)	2 (4%)	0
Neutropenia	0	1 (2%)	1 (2%)	2 (4%)	0	0
Febrile neutropenia	0	1 (2%)	0	0	0	0
Nausea	4 (9%)	1 (2%)	0	7 (14%)	2 (4%)	0
Vomiting	2 (4%)	0	0	0	1 (2%)	0
Alopecia	12 (25%)	0	0	11 (22%)	0	0
Sensory neuropathy	5 (11%)	1 (2%)	0	2 (4%)	1 (2%)	0
Constipation	3 (6%)	0	0	0	0	0
Pleural effusion	1 (2%)	4 (9%)	0	0	2 (4%)	0

included patients who received second- or third-line PD-1/PD-L1 inhibitors, hard to be directly applied into the current clinical practice, and needs subsequent studies. When clinical relevance of the continuation of pembrolizumab is further investigated after failure of the first-line PD-1/PD-L1 inhibitor, the partner chemotherapy would be the platinum-doublet–based regimens in the studies. It would be also different from the design of our current study which used only nonplatinum chemotherapy regimens as the partner for pembrolizumab. The study using platinum-doublet chemotherapy is more likely to show the positive clinical outcomes than ours, based on one laboratory study which showed that a moderate dose of cisplatin strongly induced antigen presentation and T-cell activity in tumor cells (24). This issue is currently investigated in one clinical trial. The INSIGNA study enrolled treatment-naive patients with advanced NSCLC and randomized them into three arms: first-line pembrolizumab monotherapy followed by subsequent pemetrexed plus carboplatin without (arm A) and with (arm B) continuation of pembrolizumab at disease progression prior to pembrolizumab monotherapy, and first-line pembrolizumab, pemetrexed, and carboplatin (arm C; ref. 25). Although the aim of this study was to compare the experimental arms (arm A or B) with the control arm C, the explorative comparison of the efficacy between arm A and B could, in part, explain whether platinum-based chemotherapy exerts a stronger synergistic antitumor effect with PD-1/PD-L1 inhibitors than non–platinum-based chemotherapy does at disease progression to a prior single PD-1/PD-L1 inhibitor agent.

The rationale for the continuation of PD-1/PD-L1 inhibitor combined with additional chemotherapy after disease progression on prior PD-1/PD-L1 inhibitor therapy is supported by unavoidable incidence of pseudoprogression to PD-1/PD-L1 inhibitor therapy (26). Pseudoprogression is a unique response pattern during immunotherapy, which indicates that the tumor initially increases with PD-1/PD-L1 inhibitor therapy followed by a spontaneous decrease in tumor size without any change in treatment. However, the differentiation of pseudoprogression from true progression is difficult, and pseudoprogression is sometimes mistaken for true progression, and the treatment for the patient is accordingly changed. Therefore, the continuation of PD-1/PD-L1 inhibitor with the addition of chemotherapy could be a good treatment strategy to avoid this mistake. However, in a retrospective study with 542 patients with NSCLC, only 14 (3%) showed pseudoprogression with nivolumab therapy, implying that the incidence of pseudoprogression is minimal in a real-world setting and has been overestimated in the previous literature (27). Therefore, our study, combined with the data showing a low incidence of pseudoprogression, suggests that the continuation of PD-1/PD-L1 inhibitor is weakly supported by the concern of pseudoprogression.

The efficacy of PD-1/PD-L1 inhibitor is known to be inferior in patients with EGFR or ALK-mutant NSCLC (28). Therefore, the current study excluded NSCLC harboring these mutations. However, the efficacy of PD-1/PD-L1 inhibitors in patients with other driver mutations has been reported with variable or conflicting results, while immunotherapy seems to be less effective for STK11, PIK3CA, or RET mutant NSCLC (28, 29). Our study did not analyze these mutations with comprehensive methods such as next-generation sequencing, and has a limitation in failing to rule out the confounding effect of the driver mutation on the efficacy of PD-1/PD-L1 inhibitors.

In summary, our study showed no improvement in clinical outcomes with the continuation of pembrolizumab at the time of disease progression after prior to second- or third-line PD-1/PD-L1 inhibitor therapy. Therefore, we do not recommend continuing pembrolizumab or other PD-1/PD-L1 inhibitors in unselected NSCLC populations, although this strategy could be further investigated with new chemotherapeutic or biological agents (VEGF inhibitor or PARP inhibitor) or in some favorable subgroups (30).

Authors' Disclosures

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Authors' Contributions

H.A. Jung: Data curation, software, formal analysis, validation, investigation, visualization, writing–original draft, writing–review and editing. **S. Park:** Data curation, validation, investigation. **Y.-L. Choi:** Formal analysis, validation, investigation. **S.-H. Lee:** Data curation, validation, investigation. **J.S. Ahn:** Data curation, validation, investigation. **M.-J. Ahn:** Data curation, validation, investigation. **J.-M. Sun:** Conceptualization, data curation, formal analysis, validation, investigation, visualization, writing–original draft, writing–review and editing.

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