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A phase II study of pembrolizumab and paclitaxel in patients with relapsed or refractory small-cell lung cancer

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ABSTRACT

Objective: Patients with etoposide/platinum-refractory extensive disease (ED) small-cell lung cancer (SCLC) have a dismal prognosis. We aimed to evaluate the efficacy and safety of pembrolizumab and paclitaxel combination therapy in these patients.

Methods: In this multi-center, phase II study, ED-SCLC patients who showed progression after etoposide/platinum chemotherapy received paclitaxel 175 mg/m^2 every 3 weeks for up to six cycles. Pembrolizumab 200 mg was added from the second cycle and continued until disease progression or unacceptable toxicity. The primary endpoint was the objective response rate (ORR) and the secondary endpoints were progression-free survival (PFS), overall survival (OS), safety, and biomarker analyses including programmed death-ligand 1 (PD-L1) expression, next-generation sequencing, and flow cytometric analysis of peripheral blood cells.

Results: Of the 26 patients enrolled, the confirmed ORR was 23.1% (95%CI: 6.9%–39.3%); complete response: 3.9%, confirmed partial response [PR]: 19.2%, stable disease: 57.7%, progressive disease: 7.7%, and not evaluable: 11.5%. Including 4 cases of unconfirmed PRs, 38.5% of patients were responding and the disease control rate was 80.7%. The median PFS and OS were 5.0 months (95% CI: 2.7–6.7) and 9.1 months (95% CI: 6.5–15.0), respectively. The grade 3 or 4 adverse events observed included febrile neutropenia (7.7%), neutropenia (7.7%), asthenia (7.7%), hyponatremia (7.7%), and type I diabetes (7.7%). Targeted gene sequencing identified no specific genetic alterations correlated with the treatment, except for the*MET* copy number gain (PFS 10.5 *versus* 3.4 months, $p = 0.019$).

Conclusions: Pembrolizumab and paclitaxel combination therapy showed a moderate activity with acceptable toxicity in patients with refractory ED-SCLC.

1. Introduction

Small-cell lung cancer (SCLC) is an aggressive tumor characterized by a high growth fraction and an early development of metastases [1–3]. Despite a good response to initial chemotherapy or radiotherapy, approximately 70% of limited-stage and nearly all ED- SCLC patients become refractory to subsequent treatments. Patients progressing after first-line chemotherapy have a poor prognosis, with the median overall survival (OS) being less than 6 months [4].

Single regimens of paclitaxel have shown modest efficacy in refractory SCLC. The results from previous phase II trials with paclitaxel reported an objective response rate (ORR) of up to 29% and median OS of 4 months [5–7]. The efficacy of paclitaxel as a monotherapy in refractory SCLC was marginal. Thus, a combination treatment of paclitaxel with other agents might be necessary to improve the clinical benefit in this patient population. Recently, immunotherapy using immune checkpoint inhibitors has shown promising activity in several solid tumors, including SCLC [8,9]. Pembrolizumab is a highly selective monoclonal antibody (mAb) that blocks the interaction between programmed death-1 (PD-1) and programmed death-ligand 1 (PD-L1),

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thereby activating the function of effector T cells against tumor cells. Results from the KEYNOTE-028 study have shown the antitumor activity of pembrolizumab in PD-L1–positive ED-SCLC with an ORR of 33% and median OS of 9.7 months [8].

There have been data that cytotoxic chemotherapeutic agents modulate PD-L1 expression on the tumor cell surface. For example, doxorubicin downregulates PD-L1 expression on the cell surface both in vitro and in vivo in breast cancer cells while paclitaxel and etoposide upregulate it [10,11]. Given the predictive role of PD-L1 expression on tumor cells, these preliminary studies suggest that prior treatment with paclitaxel may induce PD-L1 expression on tumor cells, which in turn would improve the antitumor effect of PD-1/PD-L1 therapy.

On the basis of this rationale, we hypothesis that paclitaxel, rather than topotecan, might have anti-tumor effect of SCLC as well as role of PD-L1 inducer. We designed a phase II study in which paclitaxel was given alone during the first cycle to induce PD-L1 expression prior to pembrolizumab treatment. We assumed that the addition of the induction phase with paclitaxel might improve the therapeutic effect of pembrolizumab in refractory SCLC patients. Therefore, we evaluated the effect of the pembrolizumab and paclitaxel combination treatment in refractory ED-SCLC patients who failed to respond to etoposide/platinum chemotherapy.

2. Materials and methods

2.1. Patient eligibility

The subjects eligible for this study were those who met the following criteria: 1) histologically or cytologically confirmed ED-SCLC; 2) disease progression at any time after first-line treatment with etoposide plus cisplatin or carboplatin regardless of their initial best response; 3) Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1; 4) one or more measurable lesion according to the Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1 [12] and 5) adequate organ function. Patients with brain metastases were eligible if they were asymptomatic or neurologically stable without steroid therapy after surgery or radiotherapy.

Patients who met the following criteria were also excluded: a diagnosis of immunodeficiency or receipt of systemic steroid treatment or any other form of immunosuppressive treatment; and history of a malignancy other than adequately treated and completely excised cervical cancer in situ, ductal carcinoma in situ, or basal cell or squamous cell carcinoma of the skin.

2.2. Study design and endpoints

This study was a phase II, multi-center, open-label, single-arm study of pembrolizumab in combination with paclitaxel in subjects with ED-SCLC who had not responded to or had progressed on the first-line etoposide/platinum therapy. The primary endpoint of this study was to evaluate the ORR of the pembrolizumab and paclitaxel combination treatment. The secondary endpoints were to evaluate OS, progression-free survival (PFS), safety, analysis of biomarkers including PD-L1 expression, next-generation sequencing (NGS), and flow cytometric analysis of peripheral blood immune cells.

2.3. Treatment plan

The study treatment period consisted of three phases: PD-L1 induction phase, post-induction phase, and maintenance phase. During the PD-L1 induction phase, the patients received paclitaxel at a dose of 175 mg/m^2 administered intravenously over 3 h on day 1 of each 3-week cycle (Q3W). Thereafter, in the post-induction treatment phase, pembrolizumab and paclitaxel at a dose of 200 mg and 175 mg/m^2, respectively, were administered on day 1 of each 3-week cycle (Q3W) for up to five cycles. Because of cumulative toxicity of peripheral neuropathy, paclitaxel was given maximum 6 cycles. After 6 cycles of paclitaxel, maintenance pembrolizumab monotherapy was given. During the maintenance phase, pembrolizumab monotherapy was administered until disease progression or unacceptable toxicity.

2.4. Assessments

The tumor response was evaluated according to the RECIST version 1.1 [12]. Radiologic imaging including chest computed tomography (CT) and brain magnetic resonance imaging was performed at baseline to assess the clinical response and repeated at least every two cycles until six cycles. Thereafter, CT was performed every 3 cycles. After the initial evidence of radiologic progression, patients who were clinically stable could remain on the study treatment until progression was reconfirmed at least 4 weeks later. Adverse events were graded based on the National Cancer Institute Common Toxicity Criteria, version 4.0.

2.5. PD-L1 immunohistochemistry

Representative, formalin-fixed, paraffin-embedded tissue blocks from each case were submitted for immunohistochemistry (IHC) using anti-PD-L1 antibody DAKO22C3 pharmDx assay (Dako, Carpinteria, CA, USA) [13]. The percentage of tumor cells showing different staining intensities was determined by a board-certified pathologist. PD-L1 IHC was evaluated based on the intensity and proportion of membranous staining, without cytoplasmic staining, in tumor cells. PD-L1 staining intensity was scored in four categories: no staining (0), weak (1+), moderate (2+), and strong (3+) staining. Tumor cells were considered positive for PD-L1 if the expression in ≥1% tumor cells was at an intensity of ≥1 + . This was same criteria with tumor proportion score [13].

2.6. Targeted gene sequencing and flow cytometric analysis

Targeted gene sequencing (TGS) was performed with the ultra-deep sequencing method using Illumina HiSeq2500 (Theragen Etex Bioinstitute, Suwon, Korea). A TGS panel was designed to capture the target region covering 90 cancer-related genes, the details of which are summarized in Supplementary Material (available at *lung Cancer* online). A total of 14 patients were available for TGS.

Freshly collected whole blood was labeled with the following fluorescence-conjugated mAbs for 15 min at room temperature (RT): BD Multitest CD3 FITC/CD8 PE/CD45 PerCP/CD4 APC and BD Multitest CD3 FITC/CD16 + CD56 PE/CD45 PerCP/CD19 APC (both BD Biosciences, San Jose, CA, USA). To remove red blood cells (RBCs), FACS lysis solution (BD Biosciences, San Jose, CA, USA) was added to whole blood and incubated for 15 min at RT. Data acquisition and analysis were performed using a FACS Calibur flow cytometer and CellQuest software (BD Biosciences, San Jose, CA, USA).

2.7. Statistical analysis

The sample size was calculated with the assumption of the null hypothesis $P_0 = 0.25$ and alternative hypothesis $P_1 = 0.50$ [5–7]. With a desired power level of 0.80 and α-error of 0.05, the number of patients was determined to be 23. Considering a 10% drop-out rate, a total of 26 patients were planned to be enrolled. The Kaplan-Meier method was used to analyze PFS and OS. All statistical tests were two-sided with significance defined as $P < 0.05$. All analyses were performed using SPSS for Windows Version 23.0 (IBM, Chicago, IL, USA). The study protocol was reviewed and approved by the institutional review boards of each hospital.

2.8. Ethics

The study protocol was reviewed and approved by the institutional

Table 1
Baseline Characteristics (n = 26).

Characteristics	No. of patients (%)
Age, median, years (range)	68.5 (54–78)
Gender	
Male	23 (88.5)
Female	3 (11.5)
ECOG performance status	
0	3 (11.5)
1	23 (88.5)
Previous chemotherapy	
Etoposide/platinum combination	26 (100.0)
Previous radiotherapy	
Yes	13 (50.0)
No	13 (50.0)
Site of radiotherapy	
Brain only	5 (19.2)
Thorax only	3 (11.5)
Both brain and thorax	3 (11.5)
Others	2 (7.7)
PD-L1 immunohistochemistry	
Positive	4 (15.4)
Negative	22 (84.6)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; PD-L1, programmed death-ligand 1.

review boards of each hospital. The study was conducted in accordance with the Declaration of Helsinki and International Conference on Harmonization Guidelines for Good Clinical Practice. Written informed consent was obtained from all the patients before participation. The trial is registered with ClinicalTrials.gov (NCT02551432)

3. Results

3.1. Patient characteristics

From April 2016 to March 2018, a total of 26 patients with etoposide/platinum-refractory ED-SCLC were enrolled. Patients' baseline characteristics are shown in Table 1. The median age of the study population was 68.5 years (range, 54–78 years). All patients received etoposide/platinum-based first-line chemotherapy and a half of these patients also received the prior radiotherapy to the brain as a prophylactic or palliative (30.8%) and/or thorax (23.1%).

3.2. Treatment response

The efficacy and toxicity analyses were performed for all patients who had received at least one cycle of the paclitaxel. The best responses are shown in Table 2. Of the 26 patients enrolled, 23 patients were evaluable for treatment response. The results show a confirmed ORR of 23.1% (6/26, 95%CI: 6.9%–39.3%) among all patients with refractory ED-SCLC treated with the combination of pembrolizumab and paclitaxel, with CR in one patient (3.9%) and PR in five patients (19.2%). PD and SD were observed in 2 (7.7%) and 15 (57.7%) patients,

Table 2
Best Overall Response.

Response	No. of patients (%)
Best response	
Complete response	1 (3.9)
Partial response	5 (19.2)
Stable disease	15 (57.7)
Progressive disease	2 (7.7)
Not evaluable	3 (11.5)
Unconfirmed partial response	4 (15.4)
Objective response rate	6 (23.1)
Disease control rate	21 (80.7)

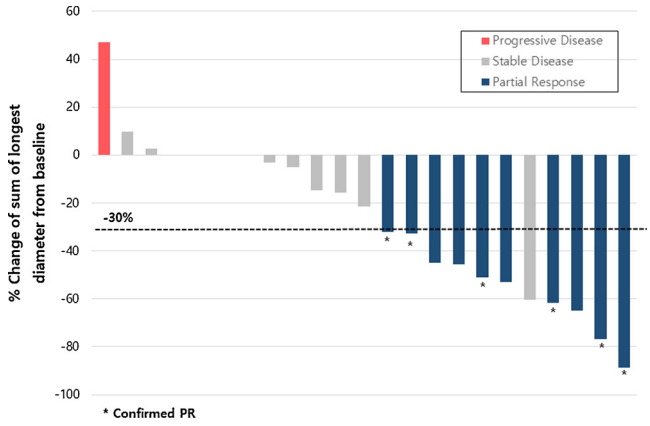

Fig. 1. Waterfall plots of best percentage changes in the sum of the longest tumor diameter.

respectively, resulting in the disease control rate of 80.7%. Furthermore, when four cases of PR unconfirmed were included, a total of 38.5% of patients were unconfirmed PR to the treatment. The tumor shrinkage of target lesions according to RECIST ver. 1.1 is shown by a waterfall plot (Fig. 1). The median duration of response was 9.1 months (range, 3.6–11.6 months).

3.3. Survival and its correlation to molecular biomarkers

The Kaplan-Meier curves of PFS and OS are shown in Fig. 2. The median follow-up was 11.1 months (95% CI: 9.0–16.8), and the median PFS and OS were 5.0 months (95% CI: 2.7–6.7) and 9.1 months (95% CI: 6.5–15.0), respectively.

We also analyzed potential molecular biomarkers such as PD-L1, TGS, and tumor mutation burden (TMB) in predicting the clinical outcome of refractory ED-SCLC patients treated with pembrolizumab and paclitaxel. Twenty-two (85%) patients were PD-L1 negative, and PD-L1 positivity was not found to be significantly associated with PFS (3.9 *versus* 5.0 months, $p = 0.897$, Supplementary Fig. 1). All the coding exons of 87 cancer-related genes and eight additional genes were analyzed for the detection of genetic alterations and gene fusions on 12 individual tumor tissues (Fig. 3, Supplementary Fig. 2). We analyzed all the genes to find their impact on ORR and PFS. Favorable survival outcomes were obtained in SCLC patients harboring *MET* copy number gain (PFS; 3.4 *versus* 10.5 months, $p = 0.019$, Supplementary Fig. 3). Overall, TMB was correlated neither with the tumor response nor with the survival outcome (Supplementary Fig. 4). Natural killer (NK) cell activity in peripheral blood was measured by flow cytometry. Lower NK cell activity after 2 cycles of treatment was significantly associated with tumor response ($p = 0.022$, Supplementary Fig. 5).

3.4. Toxicity

The hematological and non-hematological toxic profiles of all grades are summarized in Table 3. There were no treatment-related deaths reported during the study period. All 26 patients experienced adverse events (AEs) of any grade: there were 12 incidences of AEs of grade ≥ 3. The most frequently reported grade 3–4 AEs occurring in 5% of patients or more were neutropenia (7.7%), febrile neutropenia (7.7%), asthenia (7.7%), and hyponatremia (7.7%).

A total of 13 serious AEs were observed in nine patients. Six and three of the treatment-related serious AEs were attributable to pembrolizumab and paclitaxel, respectively. Five treatment-related AEs including type 1 diabetes, febrile neutropenia and pneumonia led to the discontinuation of the treatment in four patients, three of whom resolved upon treatment. Dose reductions of paclitaxel were required in two patients with neutropenia and febrile neutropenia.

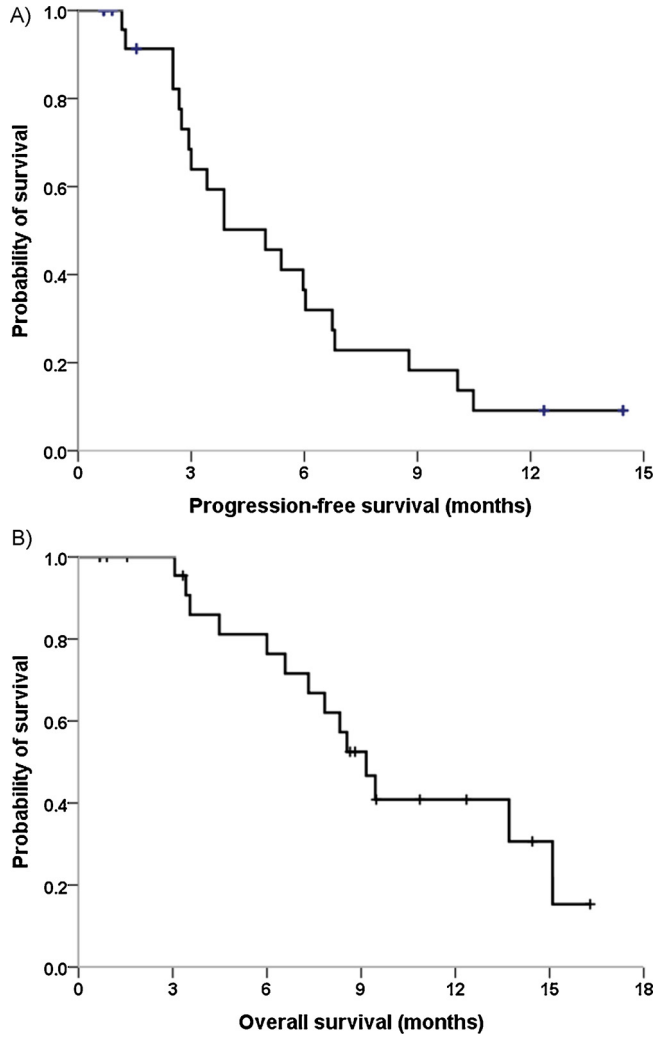

Fig. 2. Kaplan-Meier curve for *(A)* progression-free survival and *(B)* overall survival.

4. Discussion

We evaluated the efficacy and toxicity of pembrolizumab combined with paclitaxel in etoposide/platinum-refractory ED-SCLC patients. The combined treatment of pembrolizumab with paclitaxel demonstrated a moderate anti-tumor activity with a confirmed ORR of 23.1% and median PFS and OS of 5.0 and 9.1 months, respectively. The toxicity was manageable and similar to those reported [8,14] previously for other solid tumor types including SCLC, except for hematological toxicities due to paclitaxel.

Tumors with a high mutation burden have more potential to present tumor-specific neoantigens that stimulate the T-cell mediated immune response. It is known that smoking, the leading cause of SCLC, contributes to the high mutation rate characteristic of SCLC [15,16]. In addition, the increased levels of tumor-infiltrate lymphocytes have been shown to be associated with the prolonged survival in SCLC [17]. Therefore, therapeutic intervention with immunotherapy seems to be a reasonable option for SCLC patients. Thus far, there has been only little evidence supporting this rationale. Although the promising results came from earlier phase II studies using ipilimumab, an anti-CTLA-4 antibody (Ab) in the frontline setting, a confirmatory phase III study failed to show improved survival over that achieved with chemotherapy [18]. The phase I/II CheckMate 032 trial evaluated the efficacy of nivolumab alone or in combination with ipilimumab [19]. The ORR of approximately 20% with nivolumab and ipilimumab was achieved in SCLC patients who had received the prior lines of therapy [19]. Durvalumab plus tremelimumab showed RR of 9.5% in platinum-refractory ED-SCLC [20]. Atezolizumab monotherapy in relapsed SCLC failed to show significant efficacy over chemotherapy (ORR: 2.3% in atezolizumab *vs.* 10.0% in chemotherapy) [21]. Nivolumab showed ORR of 14% with durable response, but failed to show better efficacy over chemotherapy [22].

Recently, IMpower 133 phase III trial demonstrated that the addition of atezolizumab to chemotherapy in the first-line treatment of ED-SCLC resulted in significantly longer OS and PFS [23]. OS for the atezolizumab plus chemotherapy group was 12.3 months while OS for the placebo plus chemotherapy was 10.3 months. Median PFS was also improved among those receiving atezolizumab (5.2 versus 4.3 months). Atezolizumab in combination with carboplatin and etoposide recently become standard first line treatment for ED-SCLC. The improved clinical benefit of the chemo-immunotherapy was also shown in a recent studies of non-small cell lung cancer (NSCLC) in which pembrolizumab with platinum-based cytotoxic chemotherapy resulted in significantly longer OS and PFS than those associated with chemotherapy alone. First line combination chemotherapy with immune checkpoint inhibitor also becomes standard treatment for NSCLC based on the KEYNOTE189 study [24], KEYNOTE407 study [25], and IMpower150 study [26]. Combination with cytotoxic chemotherapy is proven good combination strategy for partner to immune checkpoint inhibitors.

In the current study, the efficacy of pembrolizumab, another anti-PD-1 Ab, was evaluated in etoposide/platinum-refractory ED-SCLC patients. The efficacy of pembrolizumab combined with paclitaxel in this trial was comparable with that in advanced SCLC in the KEYNOTE-158 study [27] and PD-L1–positive ED-SCLC in the KEYNOTE-028 study [8] (ORR, 23.1% in this study versus 18.7% in KN-158 versus 33.3% in KN-028; median PFS, 5.0 versus 2.0 versus 1.9 months; median OS, 9.1 versus 8.7 versus 9.7 months). Both KEYNOTE-158 study [24] and KEYNOTE-028 study [8] evaluated the efficacy of pembrolizumab monotherapy. Given that the KEYNOTE-028 study included SCLC patients only positive for PD-L1 expression, our result obtained with mostly PD-L1–negative SCLC patients is remarkable, especially when four cases in which PR was unconfirmed are included. In the KN-158 study, RR of pembrolizumab in PD-L1 negative SCLC was only 6% [27]. Thus, this supports the assertion that chemo-immunotherapy using pembrolizumab might be a valuable addition for the treatment of this progressive type of SCLC.

Variable expression of PD-L1 was reported in SCLC, ranging from a few percentage points up to over 70% [28,29]. This reflects the heterogenic property of SCLC. However, there have been technical issues inherent in immunohistochemistry detection systems for PD-L1 and different cut-off points are also problematic. The prevalence of PD-L1 expression in this study (15%) was relatively low compared to those in previous studies [8,24]. It is known that there are two types of mechanisms regulating the biological level of PD-L1. PD-L1 is induced either by inflammation-driven interferon (IFN) γ or constitutive oncogene expression [30,31]. IFNγ-dependent PD-L1 expression occurring at sites of immunologic attacks is dynamic and often associated with an immune filtrate. On the contrary, constitutive PD-L1 expression on tumor cells is mediated by dysregulated signaling pathways such as PTEN, AKT, RAS, JAK/STAT, or EGFR depending on the tumor types. However, little is known about the molecular mechanism of PD-L1 expression in SCLC.

Recent studies have shown that PD-L1 overexpression is a positive predictor for anti-PD1 and PD-L1 directed therapy across multiple tumors [32,33]. NSCLC and melanoma patients with high levels of PD-L1 showed a marked response to PD-1/PD-L1-directed therapies. However, PD-L1–negative patients still showed durable responses although the response in that subset of patients was rare. For this reason, the clinical benefit of the PD-L1 biomarker remains to be elucidated in large trials.

There are huge unmet need in refractory SCLC [34]. While several clinical trials of cytotoxic chemotherapies have been investigated in the

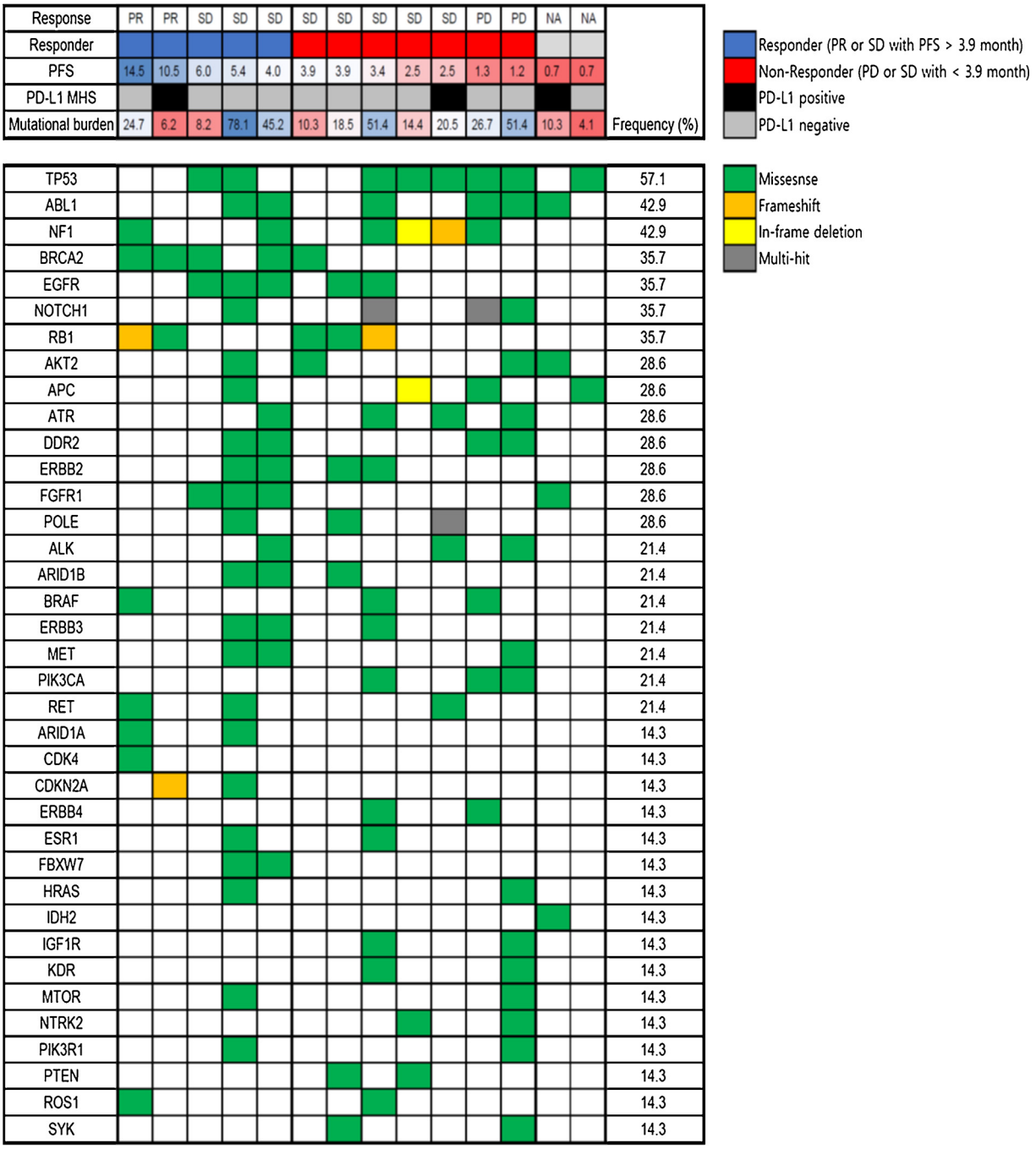

Fig. 3. OncoPlot Summary of somatic mutations among 90 genes for tumors from each case. Distribution of individual patient-specific mutations is represented. Treatment outcomes and PD-L1 positivity are incorporated.

treatment of second line SCLC, none showed a significant clinical activity to be able to exceed topotecan as second-line chemotherapy [31]. Topotecan alone has been shown to increase survival compared with best supportive care (26 weeks *vs.* 14 weeks) [35]. Topotecan was the first approved therapy for second-line treatment for relapsed SCLC, however, RR of topotecan was only 7% [35]. Another agents such as amrubicin [36,37], irinotecan [38], paclitaxel [5–7], gemcitabine [39], pemetrexed [40,41] were evaluated in small numbered phase II trials. These agents showed RR of 0%–47% and OS of 3.3–6.2 months. Even though this is not a direct comparison, the result of our trial was comparable or better than those of other cytotoxic agents.

This study has several limitations. First, this was a single-arm phase II study in second-line treatment. As this is not randomized trial, direct comparison with conventional second-line treatment was not possible. Therefore, the advantages of clinical benefit and toxicity over those of conventional regimens should be interpreted with caution. Second, this study has small sample size with low statistical power. Third, the small number of patients is another limitation for drawing any conclusion based on the biomarker analysis. There were only four patients with PD-L1 positivity in this study population, which were too few on which to base a conclusion about the role of PD-L1 as a predictive biomarker. The other limitation is a lack of data on PD-L1 status of post-treatment specimens. PD-L1 status after treatment needs to be explored since it might provide insight on the clinical course of future immunotherapy. Fourth, given the confirmed ORR of 23.1%, this trial did not meet the primary endpoint of ORR of 50%. Fifth, we did not obtain the data for

Table 3
Summary of Adverse Events.

Adverse Event	All Grades (%)	Grade 3 or 4 (%)
Anemia	6 (23.1)	1 (3.9)
Neutropenia	3 (11.5)	2 (7.7)
Febrile neutropenia	2 (7.7)	2 (7.7)
Asthenia	3 (11.5)	2 (7.7)
Myalgia	9 (34.6)	1 (3.9)
Anorexia	5 (19.2)	0 (0.0)
Nausea	4 (15.4)	0 (0.0)
Vomiting	2 (7.7)	0 (0.0)
Stomatitis	1 (3.9)	0 (0.0)
Diarrhea	6 (23.1)	0 (0.0)
Constipation	4 (15.4)	0 (0.0)
Dizziness	4 (15.4)	0 (0.0)
Headache	2 (7.7)	0 (0.0)
Pruritus	5 (19.2)	0 (0.0)
Rash	2 (7.7)	0 (0.0)
Peripheral motor neuropathy	3 (11.5)	0 (0.0)
Peripheral sensory neuropathy	15 (57.7)	0 (0.0)
Pneumonia	5 (19.2)	1 (3.9)
Hypothyroidism	1 (3.9)	0 (0.0)
Hyponatremia	2 (7.7)	2 (7.7)
Type I diabetes mellitus	2 (7.7)	1 (3.9)

time between enrollment and completion of platinum-etoposide treatment. We could not distinguish the refractory disease without initial response and resistant relapse with enough relapse-free interval.

In conclusion, combination therapy with pembrolizumab and paclitaxel showed a favorable tumor response, prolonged survival, and manageable safety profile in ED-SCLC patients who failed to respond to the first-line treatment. Further evaluation in phase III studies is warranted to confirm the clinical benefit of pembrolizumab and paclitaxel.

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Authors' contribution

BK designed the study, acquired data, analyzed data, interpreted the results, drafted the manuscript, and critically reviewed or revised the manuscript; Y-JK and C-YO acquired data, analyzed data, interpreted the results, drafted the manuscript, and critically reviewed or revised the manuscript; SS analyzed data, interpreted the results, and critically reviewed or revised the manuscript; MK, SHK, KHK, J-SK, TMK, DWK, JSL, and DSH acquired data, interpreted the results, and critically reviewed or revised the manuscript; All authors read and approved the final version of this manuscript.

Declaration of Competing Interest

Dr. Keam had uncompensated consulting/advisory role for MSD without payment. There are no other conflicts of interest to disclose. Other authors have nothing to disclose

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Appendix A. Supplementary data

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