OXFORD

Atezolizumab for Pretreated Non-Small Cell Lung Cancer with Idiopathic Interstitial Pneumonia: Final Analysis of Phase II AMBITIOUS Study

Satoshi Ikeda[*,1,] (iD)**, Terufumi Kato**[2]**, Hirotsugu Kenmotsu**[3]**, Takashi Ogura**[1]**, Yuki Sato**[4]**, Aoi Hino**[5]**,
Toshiyuki Harada**[6]**, Kaoru Kubota**[7]**, Takaaki Tokito**[8]**, Isamu Okamoto**[9]**, Naoki Furuya**[10]**,
Toshihide Yokoyama**[11]**, Shinobu Hosokawa**[12]**, Tae Iwasawa**[13]**, Rika Kasajima**[14]**, Yohei Miyagi**[14]**,
Toshihiro Misumi**[15]**, Hiroaki Okamoto**[16]

[1]Department of Respiratory Medicine, Kanagawa Cardiovascular and Respiratory Center, Yokohama, Kanagawa, Japan
[2]Department of Thoracic Oncology, Kanagawa Cancer Center, Yokohama, Kanagawa, Japan
[3]Division of Thoracic Oncology, Shizuoka Cancer Center, Shizuoka, Japan
[4]Department of Respiratory Medicine, Kobe City Medical Center General Hospital, Kobe, Hyogo, Japan
[5]Department of Respirology, Chiba University Graduate School of Medicine, Chuo-ku, Chiba, Chiba, Japan
[6]Department of Respiratory Medicine, Japan Community Healthcare Organization Hokkaido Hospital, Sapporo, Hokkaido, Japan
[7]Department of Pulmonary Medicine and Oncology, Graduate School of Medicine, Nippon Medical School, Bunkyo-ku, Tokyo, Japan
[8]Division of Respirology, Neurology, and Rheumatology, Department of Internal Medicine, Kurume University School of Medicine, Kurume, Fukuoka, Japan
[9]Research Institute for Diseases of the Chest, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Fukuoka, Japan
[10]Department of Internal Medicine, Division of Respiratory Medicine St. Marianna University School of Medicine, Kawasaki, Kanagawa, Japan
[11]Department of Respiratory Medicine, Kurashiki Central Hospital, Kurashiki, Okayama, Japan
[12]Department of Respiratory Medicine, Japanese Red Cross Okayama Hospital, Kita-ku, Okayama, Okayama, Japan
[13]Department of Radiology, Kanagawa Cardiovascular and Respiratory Center, Yokohama, Kanagawa, Japan
[14]Molecular Pathology and Genetics Division, Kanagawa Cancer Center Research Institute, Asahi-ku, Yokohama, Kanagawa, Japan
[15]Department of Biostatistics, Yokohama City University School of Medicine, Yokohama, Kanagawa, Japan
[16]Department of Respiratory Medicine and Medical Oncology, Yokohama Municipal Citizen's Hospital, Kanagawa-ku, Yokohama, Kanagawa, Japan
*Corresponding author: Satoshi Ikeda, MD, PhD, Department of Respiratory Medicine, Kanagawa Cardiovascular and Respiratory Center, 6-16-1 Tomioka-Higashi, Kanazawa-ku, Yokohama 236-0051, Japan. Tel: +81 45 701 9581; Email: isatoshi0112@gmail.com
‡Principal Investigator: Terufumi Kato

Abstract

Background: Interstitial pneumonia (IP) is a poor prognostic comorbidity in patients with non-small cell lung cancer (NSCLC) and is also a risk factor for pneumonitis. The TORG1936/AMBITIOUS trial, the first known phase II study of atezolizumab in patients with NSCLC with comorbid IP, was terminated early because of the high incidence of severe pneumonitis.

Methods: This study included patients with idiopathic chronic fibrotic IP, with a predicted forced vital capacity (%FVC) of >70%, with or without honeycomb lung, who had previously been treated for NSCLC. The patients received atezolizumab every 3 weeks. The primary endpoint was the 1-year survival rate.

Results: A total of 17 patients were registered; the median %FVC was 85.4%, and 41.2% had honeycomb lungs. The 1-year survival rate was 53.3% (95% CI, 25.9-74.6). The median overall and progression-free survival times were 15.3 months (95% CI, 3.1-not reached) and 3.2 months (95% CI, 1.2-7.4), respectively. The incidence of pneumonitis was 29.4% for all grades, and 23.5% for grade ≥3. Tumor mutational burden and any of the detected somatic mutations were not associated with efficacy or risk of pneumonitis.

Conclusion: Atezolizumab may be one of the treatment options for patients with NSCLC with comorbid IP, despite the high risk of developing pneumonitis. This clinical trial was retrospectively registered in the Japan Registry of Clinical Trials on August 26, 2019, (registry number: jRCTs031190084, https://jrct.niph.go.jp/en-latest-detail/jRCTs031190084).

Key words: atezolizumab; non-small cell lung cancer; interstitial pneumonia; pneumonitis; immune checkpoint inhibitor.

> **Lessons Learned**
> - This was the world's first phase II study of atezolizumab in non–small cell lung cancer with interstitial pneumonia.
> - This study was terminated because 24% of patients developed pneumonitis grade ≥3.
> - Although the planned enrollment of 38 patients could not be completed and only 17 patients were enrolled, the primary endpoint of the 1-year survival rate was high at 53.3% (95% CI, 25.9-74.6).
> - Honeycomb lung on high-resolution computed tomography might be a candidate risk factor for pneumonitis.

Discussion

This was the first phase II study conducted to evaluate the efficacy and safety of atezolizumab in patients with NSCLC and comorbid IP. Although the planned enrollment of 38 patients could not be completed and only 17 patients were enrolled, the primary endpoint of the 1-year survival rate was 53.3% (95% CI, 25.9-74.6), and the lower limit of the 95% CI exceeded the threshold of 15% (Table 1, Fig. 1). It is noteworthy that although IP is a distinctly poor prognostic comorbidity in patients with NSCLC and pneumonitis of grade ≥3 developed frequently in this study, the efficacy and survival benefits of atezolizumab were comparable between patients with comorbid IP in this study and those without IP treated in previous prospective trials. Evidence on the efficacy of cytotoxic agents as second-line or later therapy in patients with comorbid IP is limited, and long-term survival can hardly be expected. Therefore, for patients with NSCLC with comorbid IP who have a poor prognosis and few treatment options, immune checkpoint inhibitor (ICI) continues to hold promise as the only existing treatment option that can provide long-term survival.

However, even if the balance between safety and efficacy of atezolizumab is considered, the 23.5% rate of developing grade ≥3 severe pneumonitis may be too risky. The logistic regression analysis suggested that honeycomb lung on chest computed tomography (CT) may be a risk factor for the development of pneumonitis. This result, however, was not significant, and the risk factor analysis was done post hoc on only a small number of cases, so no definitive conclusion can be drawn from these results alone. For appropriate patient selection, large observational and retrospective studies that include data, such as CT and pulmonary function
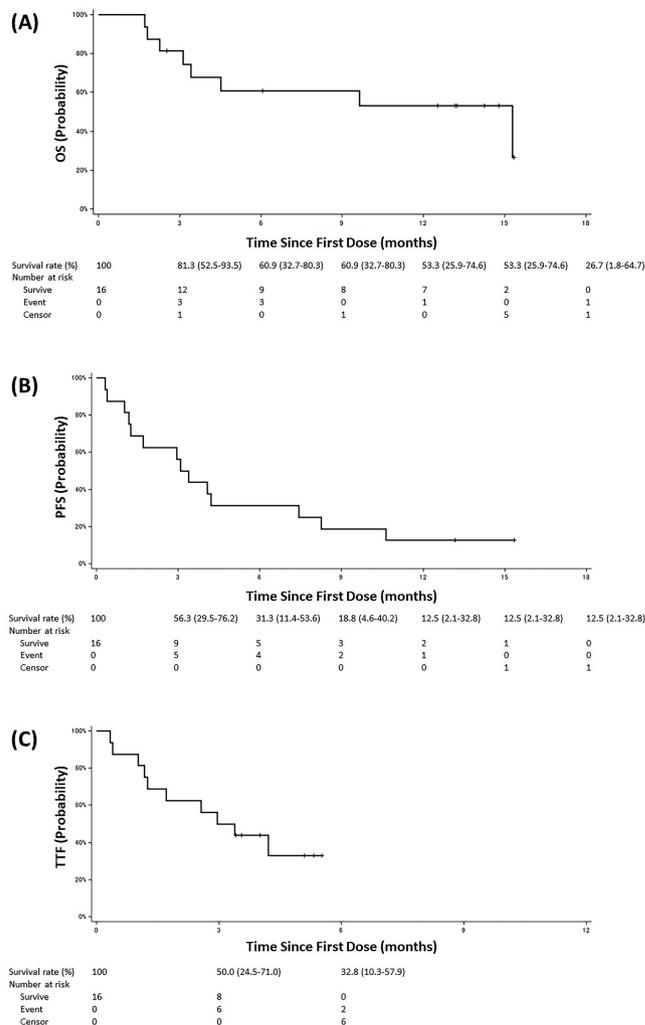

Figure 1. Kaplan-Meier curves: (**A**) overall survival, (**B**) progression-free survival, and (**C**) time to treatment failure. The vertical lines indicate censored events.

tests, are needed to identify the risk factors for ICI-induced pneumonitis.

As biomarkers of efficacy, our post hoc analysis results showed a tendency for longer overall survival and progression-free survival in patients with PD-L1 ≥50% than in those with PD-L1 <50%. In practice, the decision to administer atezolizumab would need careful consideration of the risks (especially pneumonitis) and benefits, with reference to PD-L1 expression.

Table 1. Efficacy endpoints.

	(N = 16)
One-year survival rate, % (95% CI)	53.3 (25.9-74.6)
Median overall survival, months (95% CI)	15.3 (3.1-not reached)
Median progression-free survival, months (95% CI)	3.2 (1.2-7.4)
Median time to treatment failure, months (95% CI)	3.2 (1.2-not reached)
Objective response	
Partial response, n (%)	1 (6.3)
Stable disease, n (%)	9 (56.3)
Progressive disease, n (%)	6 (37.5)
Objective response rate, % (95% CI)	6.3 (0.2-30.2)
Disease control rate, % (95% CI)	62.5 (35.4-84.8)

Author disclosures and references available online.

TRIAL INFORMATION	
Disease	Unresectable stage 3/4 or recurrent non–small cell lung cancer with comorbid chronic fibrotic interstitial pneumonia
Stage of disease/ treatment	Unresectable stage 3/4 or recurrent
Prior therapy	Received prior chemotherapy including platinum doublet
Type of study	Single arm, phase II study
Primary endpoint	One-year survival rate
Secondary endpoints	Incidence of pneumonitis (defined as the appearance of new interstitial shadows after atezolizumab administration that were judged by the investigator not to be infection, heart failure, or exacerbation of carcinomatous lymphangitis) within 1 year after treatment initiation, overall survival (OS), progression-free survival (PFS), objective response rate (ORR), time to treatment failure (TTF), mortality rate from pneumonitis during the observation period, and safety.
Investigator's analysis	Active but too toxic as administered in this study

Additional Details of Endpoints or Study Design

Exploratory Endpoints

Analysis of tumor mutational burden (TMB), somatic variations in 409 cancer-related genes, and microsatellite instability (MSI), exploratory study of efficacy by TMB, detected somatic mutations, and MSI

Inclusion Criteria

(1) Histologically or cytologically proven non–small cell lung cancer
(2) Unresectable stage 3/4 or recurrent
(3) Received prior chemotherapy including platinum doublet
(4) Chronic fibrotic interstitial pneumonia (the following 4 items must be met):
  - HRCT revealed reticular shadow with basal and peripheral predominance suggestive of UIP patterns, or peri-bronchovascular shadow suggestive of NSIP pattern
  - Without known etiology (eg, infection, pneumoconiosis, collagen vascular disease)
  - % Forced vital capacity >70%
  - % Diffusing capacity for carbon monoxide >35%
(5) Age ≥20 years
(6) ECOG Performance Status 0-1
(7) With measurable or evaluable lesions according to RECIST Version 1.1
(8) Vital organ functions are preserved
(9) Received sufficient explanations about the name and severity of the illness
(10) Written informed consent

Exclusion Criteria

(1) History of acute exacerbation of IPF
(2) Treatment history with immune-checkpoint inhibitor
(3) Systemic treatment with steroids at a daily dose >10 mg of prednisolone equivalent or immunosuppressants
(4) Active autoimmune disease or history of autoimmune disease requiring treatment
(5) Symptomatic brain metastasis or spinal cord metastases
(6) Active viral hepatitis

(7) Active infection
(8) Synchronous or metachronous active double malignancies
(9) Pregnant or breastfeeding
(10) Disapprove of contraception during the protocol treatment period
(11) Treatment history with thoracic radiotherapy
(12) History of serious drug allergies
(13) Other conditions not suitable for the study

Criteria for Discontinuation of Study Treatment

(1) Disease progression
(2) Occurrence of acute exacerbation of preexisting interstitial pneumonia
(3) Occurrence of unacceptable immune-related adverse events with CTCAE grade ≥3
  - pneumonitis
  - hepatotoxicity
  - hepatitis
  - nervous system disorder
  - renal disorder
  - eye disorder
  - myocarditis
(4) Occurrence of unacceptable immune-related adverse events with CTCAE grade ≥2
  - colitis/diarrhea
  - pancreatitis
  - pan-hypopituitarism
  - skin disorder
(5) Occurrence of unacceptable immune-related adverse events with CTCAE grade ≥1
  - encephalitis, meningitis
  - Guillain–Barre syndrome
  - myasthenia gravis

Sample Size

In this study, we set the threshold for the primary endpoint of the 1-year survival rate at 15%. Assuming a clinically meaningful 25% increase and a set expected value of 40%, 36 patients were required in this study according to the exact binomial test (2-sided $\alpha = 0.05$, $1 - \beta = 0.9$). Considering patient ineligibility, a sample size of 38 was set.

DRUG INFORMATION

Generic/working name	Atezolizumab
Company name	Chugai Pharmaceutical Co., Ltd. Roche Holding AG
Drug type	Anti-PD-L1 monoclonal antibody
Drug class	Antineoplastic agent
Dose	1200 mg
Unit	mg
Route	i.v.
Schedule of administration	every 3 weeks

PATIENT CHARACTERISTICS

Number of patients, male	16
Number of patients, female	1
Stage (IIIA/IIIB/IIIC/IVA/IVB/recurrent)	2/4/2/3/3/3
Age: median [interquartile ranges]	70.0 [66.0, 73.0] years
Number of prior systemic therapies: median [interquartile ranges]	1 [1, 2]
Performance status: ECOG	1-13 2-0 3-0 4-0
Cancer types or histologic subtypes	Adenocarcinoma, 9 Squamous cell carcinoma, 7 Non–small cell lung cancer, not otherwise specified

Study Details

Registration began on September 2, 2019. At the time of enrollment of 15 patients, 3 patients (20%) developed grade 3 pneumonitis, so the new patient enrollment was interrupted on January 31, 2020. Two patients from whom consent had already been obtained were reintroduced, and a total of 17 patients were eventually registered (the last patient enrollment was on February 10, 2020). Subsequently, one patient with pneumonitis worsened from grade 3 to 5, and one new patient developed grade 3 pneumonitis. Therefore, the present study was terminated following the recommendation of the efficacy and safety evaluation committee.

PD-L1 expression, which was measured using the Dako PD-L1 immunohistochemistry 22C3 pharmDx assay (Agilent Technologies, Santa Clara, California, USA), was ≥50% in 7 patients (41.2%), 1-49% in 3 patients (17.6%), <1% in 4 patients (23.5%), and unknown in 3 patients (17.6%). The median %FVC and % diffusing capacity for carbon monoxide were 85.4% and 54.4%, respectively. Regarding the radiological findings of pre-existing IP as judged by the central review committee, 6 patients (35.3%) had UIP patterns, 3 patients (17.6%) had probable UIP patterns, and 8 patients (47.1%) had indeterminate UIP patterns. Seven patients (41.2%) had honeycomb lung on HRCT.

The median number of delivered cycles of atezolizumab as the study treatment was 3 [interquartile range: 2, 5]. Five of 6 patients who were on treatment at the time the trial was terminated agreed to continue receiving atezolizumab as usual clinical treatment outside of this trial, with a median number of additional cycles of 3 [interquartile range: 3, 8].

For translational research on the predictive biomarkers of atezolizumab efficacy, we extracted deoxy-nucleic acids from archival formalin-fixed paraffin-embedded tumor tissues and analyzed tumor mutational burden (TMB) and somatic variations in 409 cancer-related genes using the Oncomine Tumor Mutation Load Assay (Thermo Fisher Scientific, US) and analyzed microsatellite instability (MSI) on a panel of Bethesda markers (BAT25, BAT26, NR21, NR24, and MONO27). In all 17 enrolled patients, consent for the use of archival tumor samples was obtained. However, due to the insufficient amount of residual tumor samples, not all items could be measured in 4 patients, and one patient could be analyzed only for MSI. For TMB, 33.3% (4/12) had ≥10 mutations per megabase (mut/Mb), and 66.7% (8/12) had <10 mut/Mb. *TP53* mutation was detected in 50.0% (6/12), *KRAS* mutation in 25.0% (3/12), and abnormalities of RAS/RAF/MAPK signaling pathway (including *KRAS* mutation) in 33.3% (4/12), and abnormalities of PI3K-AKT signaling pathway in 25.0% (3/12). All cases were classified as microsatellite stable, and no cases were classified as MSI-high or MSI-low.

PRIMARY ASSESSMENT METHOD

Title	Efficacy endpoints
Number of patients screened	17
Number of patients enrolled	17
Number of patients evaluable for toxicity	17
Number of patients evaluated for efficacy	16

Title	Efficacy endpoints
Evaluation method	RECIST 1.1
Response assessment, PR	1 (6.3%)
Response assessment, SD	9 (56.3%)
Response assessment, PD	6 (37.5%)
(Median) duration assessments, OS	15.3 months (95% CI, 3.1-not reached)
(Median) duration assessments, PFS	3.2 months (95% CI, 1.2-7.4)
(Median) duration assessments, TTF	3.2 months (95% CI, 1.2-not reached)
Outcome notes	The 1-year survival rate (the primary endpoint of this study) was 53.3% (95% CI, 25.9-74.6) (Table 1). The ORR and disease control rate were 6.3% (95% CI, 0.2-30.2) and 62.5% (95% CI, 35.4-84.8), respectively.

SECONDARY ASSESSMENT METHOD	
Title	**Adverse events**
Number of patients screened	17
Number of patients enrolled	17
Number of patients evaluable for toxicity	17
Number of patients evaluated for efficacy	16
Outcome notes	The updated results of major adverse events are presented in Table 2. The incidence of pneumonitis within 1 year after treatment initiation, one of the secondary endpoints, was 29.4% (95% CI, 10.3-56.0). According to the CTCAE grading, 23.5% of patients developed treatment-related pneumonitis of grade ≥3 and 5.9% of patients developed treatment-related pneumonitis of with grade 5. All 4 patients who developed grade ≥3 pneumonitis were started on high-dose corticosteroids immediately after diagnosis, with 3 patients on intravenous methylprednisolone pulse therapy and one on oral prednisolone 60 mg/day. The mortality rate from pneumonitis during the observation period was 17.6% (95% CI, 3.8-43.4). Except for pneumonitis, the most common grade ≥3 adverse event was dyspnea (23.5%), followed by lung infection (17.6%) and hypoalbuminemia (11.8%).

ASSESSMENT, ANALYSIS, AND DISCUSSION	
Completion	The study terminated prior to completion.
Investigator's assessment	Active but too toxic as administered in this study.

Approximately 5%-10% of patients with advanced non–small cell lung cancer (NSCLC) have comorbid interstitial pneumonia (IP) at the time of diagnosis and are reported to have a poor prognosis.[1] There is no significant difference in the proportion of patients with comorbid IP at diagnosis between Japan and the US. Among idiopathic IPs, the incidence of lung cancer complications varies, with Kreuter et al reporting 15.8% for idiopathic pulmonary fibrosis, 6.3% for nonspecific interstitial pneumonia, and 5.6% for cryptogenic organizing pneumonia.[2] Common risk factors for the development of IPs and lung cancer have been reported to include smoking, environmental, and occupational exposure to toxic substances, bacterial and viral infections, and chronic tissue damage.[3] In addition, microsatellite instability, loss of heterozygosity, p53 mutations, and fragile histidine triad mutations have been reported as common genetic alterations in the pathogenesis of lung cancer and IP.[4,5] Pharmacotherapy for NSCLC can occasionally cause pneumonitis or acute exacerbation of preexisting IP (5%-20%), with a mortality rate of 30%-50%. Because there are only few prospective studies on patients with NSCLC with comorbid IP, there is an urgent need to establish a safe and effective pharmacotherapy, especially for second-line or later lines.

This was the first phase II study conducted to evaluate the efficacy and safety of the anti-programmed cell death-ligand 1 (PD-L1) antibody in patients with NSCLC with comorbid IP. In this study, we distinguish between the terms "IP" for pre-existing interstitial lung disease and "pneumonitis" for new interstitial shadows that appeared after immune check-point inhibitor (ICI) administration. The term "pneumonitis" is usually used to refer to noninfectious causes of lung inflammation, such as those induced by anti-cancer drugs. Meanwhile, interstitial lung disease of unknown cause characterized by fibrosis and inflammation in the lung interstitium, that progresses in a chronic course, is usually described as "idiopathic IP." In addition, when new interstitial shadows appear after ICI administration in patients with preexisting IP, it is difficult to distinguish between "pneumonitis as pure immune-related adverse events" and "acute exacerbation of pre-existing IP triggered by ICI administration." Therefore, in this study, the appearance of new interstitial shadows after atezolizumab administration that was judged by the investigator not to be infection, heart failure, or an exacerbation of carcinomatous lymphangitis, was collectively defined as "(ICI-induced) pneumonitis."

Because of the high incidence of severe pneumonitis, the present study was terminated and the planned enrollment of 38 patients could not be completed; therefore, only 17 patients were enrolled.[6] However, the primary endpoint of 1-year survival rate was 53.3% (95% CI, 25.9-74.6), and the lower limit of the 95% CI exceeded the threshold of 15% (Table 1, Figs.1 and 2). In the OAK study on pretreated

NSCLC without IP, the 1-year survival rate of atezolizumab was 55%, which was comparable with the results shown in this study.[7] Furthermore, this study had comparable survival rates with the OAK study, which reported median overall survival (OS) of 13.8 months (95% CI, 11.8–15.7), median progression-free survival (PFS) of 2.8 months (95% CI, 2.6-3.0), objective response rate of 13.6%, and disease control rate of 48.9%. It is noteworthy that although IP is a distinctly poor prognostic comorbidity in patients with NSCLC,[8] the efficacy and survival benefits of atezolizumab were comparable between the patients with NSCLC with comorbid IP in this study and those without IP in previous prospective trials. However, it should be considered that this study included a small number of patients.

Although no standard treatment has been established for pretreated NSCLC with comorbid IP, S-1 or docetaxel has been considered by retrospective studies to be relatively safe and has been often administered in clinical practice in Japan.[9-11] However, all retrospective studies on cytotoxic agents as second-line or later therapy in patients with NSCLC and comorbid IP have shown a 1-year survival rate of at most 10%.[9,12] These results were inferior to the data from the EAST-LC study on Asian patients with previously treated NSCLC without IP; that study reported a 1-year OS of 50% in both the S-1 and docetaxel groups, with a median OS of 12.8 months in the S-1 group and 12.5 months in the docetaxel group.[13] Evidence on the efficacy of cytotoxic agents as second-line or later therapy in patients with NSCLC and comorbid IP is limited, and long-term survival can hardly be expected. Therefore, for patients with NSCLC with comorbid IP who have a poor prognosis and few treatment options, ICI holds great promise as the only existing treatment option that can provide long-term survival.

However, even if the balance between safety and efficacy of atezolizumab is considered, the 23.5% rate of developing grade ≥3 severe pneumonitis and the associated 17.6% mortality may be too risky (Table 2). Therefore, in order for atezolizumab to become a recommended treatment option for patients with NSCLC and comorbid IP, further investigation is required to clarify the following risk factors for the development of pneumonitis: severity, subtype, and specific radiologic findings of the preexisting IP; serum biomarkers; and the presence of specific genetic alterations. In the present report, to verify the risk factors for pneumonitis, we repeated the post hoc logistic regression analysis and included as new covariates the detected genetic alterations, such as TP53 mutation, which is a possible common etiology of lung cancer and IP.[14] However, no new risk factors for pneumonitis were identified (Table 3). Although the presence of honeycomb lung on HRCT was suggested as a candidate risk factor, the result was not significant and the risk factor analysis was done post hoc on only a small number of cases. Therefore, no definitive conclusion can be drawn from these results alone. For appropriate patient selection, large observational and retrospective studies that include data, such as CT and pulmonary function tests, are needed to identify the risk factors for ICI-induced pneumonitis.

Biomarkers of efficacy are also important to consider when deciding on the choice of a high-risk treatment. Compared with previous prospective trials on NSCLC without IP, 2 previously reported trials on nivolumab in NSCLC with mild IP showed higher efficacy.[15,16] The relatively high efficacy of ICI in patients with IP has been speculated to be associated with high tumor mutational burden (TMB) and microsatellite instability (MSI), which may also be related to the etiology of IP. However, this study did not demonstrate superior efficacy or survival benefit, compared with the data from previous studies on NSCLC without IP. Moreover, MSI was not observed in any of the cases, and TMB was not associated with efficacy (Table 4). On the other hand, our post hoc analysis results showed a tendency for longer OS and PFS in patients with PD-L1 ≥50% than in those with PD-L1 <50% (Fig. 3). On post hoc analysis, compared with patients with PD-L1 <50%, those with PD-L1 ≥50% had a tendency to have a higher 1-year survival rate (71.4% [95% CI, 38.0-not estimable] vs. 51.4% [95% CI, 11.5-91.4]), longer OS (median not estimable [95% CI, not estimable] vs. median 15.3 months [95% CI, not estimable], log-rank test P = .371) and longer PFS (median 7.4 months [95% CI, 3.7-18.6 months] vs. median 1.7 months [95% CI, 0.5-2.9 months], log-rank test P = .184). In practice, the decision to administer ICI would need careful consideration of the risks (especially pneumonitis) and benefits, with reference to PD-L1 expression.

A limitation of this study was that it was a single-arm phase II trial with a small number of patients and was terminated prematurely. Therefore, definitive conclusions on both safety and efficacy cannot be drawn from the results of this study alone. In the future, accumulation of further knowledge is needed by conducting more studies on a large number of patients that have observational and retrospective designs, rather than prospective studies alone.

Acknowledgments

Funding

Conflict of Interest

Satoshi Ikeda: Chugai, AstraZeneca (RF), Chugai, AstraZeneca, Boehringer Ingelheim, Ono, Taiho, Bristol Myers Squibb, Eli Lilly, Pfizer (H); **Terufumi Kato:** Chugai, Abbvie, Amgen, AstraZeneca, Chugai, Eli Lilly, Merck Biopharma, MSD, Novartis, Pfizer, Regeneron (RF), Chugai, AstraZeneca, Eli Lilly, Merck Biopharma, Daiichi-Sankyo, Eli Lilly, MSD, Novartis, Pfizer, Takeda (H); AstraZeneca, Eli Lilly, Merck Biopharma, Daiichi-Sankyo, Eli Lilly, MSD, Novartis, Pfizer, Takeda (SAB); **Hirotsugu Kenmotsu:** Chugai, AstraZeneca, Novartis, Daiichi-Sankyo (RF), Chugai, AstraZeneca, Novartis, Daiichi-Sankyo, Ono, Boehringer Ingelheim, Eli Lilly, Kyowa Hakko Kirin, Bristol Myers Squibb, MSD, Pfizer, Taiho; **Takashi Ogura:** Shionogi, Boehringer Ingelheim, Eisai (H);

Data Availability

All data generated or analyzed during this study are included in this published article.

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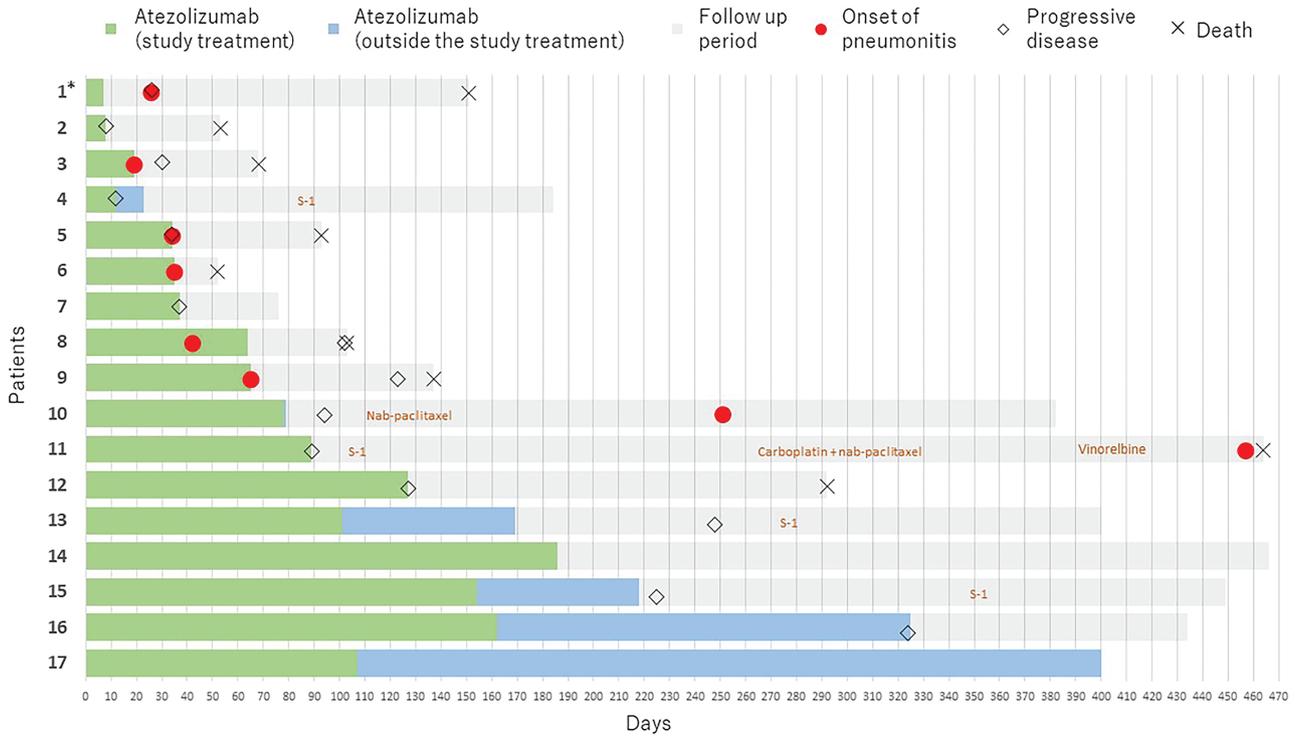
Figure 2. Swimmer's plot. *, In this patient where the exclusion criteria were violated due to a history of thoracic radiotherapy, an adverse event determined by the central judgment to be "radiation recall pneumonitis" with a CTCAE grade 1 occurred.
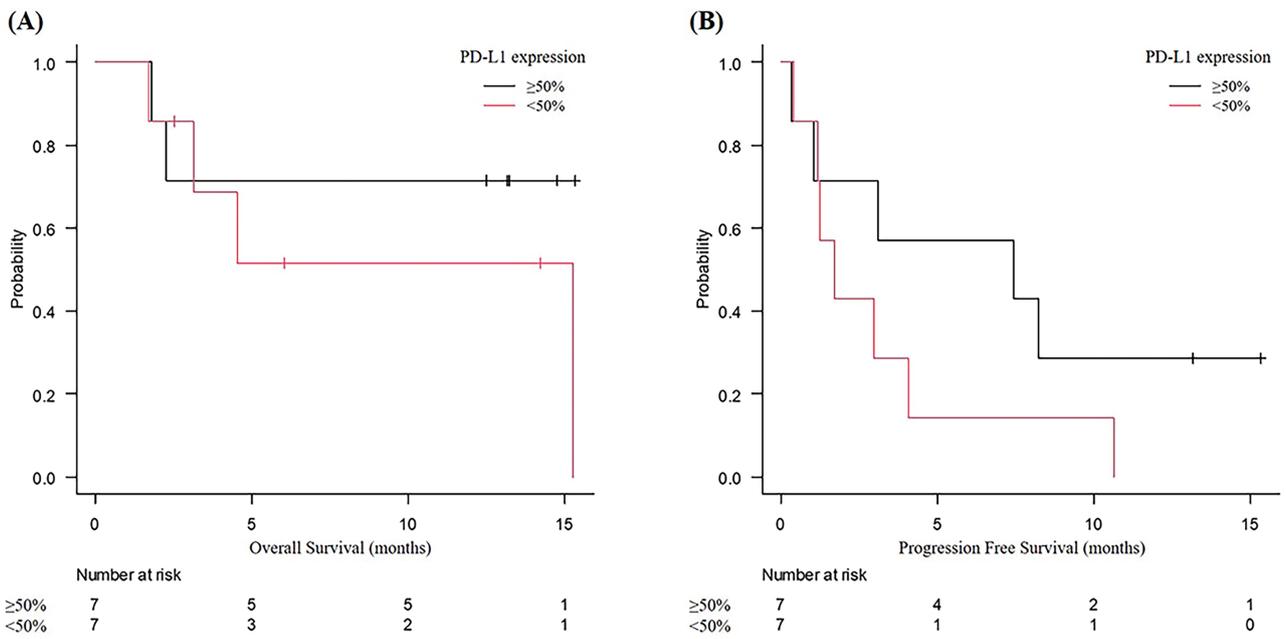
Figure 3. Kaplan-Meier curves by PD-L1 expression. Kaplan-Meier curves of (**A**) overall survival and (**B**) progression-free survival. Vertical lines show censored events. PD-L1 expression was assessed by the immunohistochemistry using 22C3 pharmDx assay (Agilent Technologies, Santa Clara, CA). Abbreviation: PD-L1, programmed cell-death ligand 1.

Table 2. Updated results of major adverse events.

|	CTCAE grade					All grade		Grade ≥3	
	1	2	3	4	5	Total	%	Total	%
Pneumonitis	0	1	3	0	1	5	29.4	4	23.5
Dyspnea	2	0	4	0	0	6	35.3	4	23.5
Lung infection	0	0	3	0	0	3	17.6	3	17.6
Hypoalbuminemia	11	3	2	0	0	16	94.1	2	11.8
Hyponatremia	10	1	0	1	0	12	70.6	1	5.9
Generalized fatigue	3	3	1	0	0	7	41.2	1	5.9
Anemia	6	6	0	0	0	12	70.6	0	0.0
Increased AST	10	1	0	0	0	11	64.7	0	0.0
Increased ALT	8	2	0	0	0	10	58.8	0	0.0
Cough	5	3	0	0	0	8	47.1	0	0.0
Appetite loss	5	2	0	0	0	7	41.2	0	0.0
Increased ALP	5	2	0	0	0	7	41.2	0	0.0
Fever	4	2	0	0	0	6	35.3	0	0.0
Hyperglycemia	5	1	0	0	0	6	35.3	0	0.0
Increased creatinine	5	0	0	0	0	5	29.4	0	0.0
Increased serum amylase	4	1	0	0	0	5	29.4	0	0.0
Hypereosinophilia	4	0	0	0	0	4	23.5	0	0.0
Hyperkalemia	4	0	0	0	0	4	23.5	0	0.0
Increased CPK	2	1	0	0	0	3	17.6	0	0.0
Proteinuria	2	1	0	0	0	3	17.6	0	0.0
Hypothyroidism	3	0	0	0	0	3	17.6	0	0.0
Nausea	3	0	0	0	0	3	17.6	0	0.0
Diarrhea	1	1	0	0	0	2	11.8	0	0.0
Thrombocytopenia	2	0	0	0	0	2	11.8	0	0.0
Hypokalemia	2	0	0	0	0	2	11.8	0	0.0
Palpitations	2	0	0	0	0	2	11.8	0	0.0
Vomiting	2	0	0	0	0	2	11.8	0	0.0
Constipation	2	0	0	0	0	2	11.8	0	0.0
Abdominal pain	2	0	0	0	0	2	11.8	0	0.0
Peripheral sensory neuropathy	2	0	0	0	0	2	11.8	0	0.0

Abbreviations: AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; CPK, creatine phosphokinase.

Table 3. Risk factors for pneumonitis.

	Odds ratio	95% CI		*P*-value
		(Lower limit)	(Upper limit)	
Age ≥ 70 years old	0.476	0.0568	3.99	.494
Body mass Index ≥25	0.350	0.0295	4.15	.406
SpO$_2$	0.642	0.346	1.20	.114
% Forced vital capacity	1.04	0.957	1.13	.384
% Diffusing capacity for carbon monoxide	0.967	0.886	1.05	.425
Indeterminate for usual interstitial pneumonia pattern[1]	0.667	0.0803	5.54	.707
Honeycomb lung on high-resolution computed tomography [2]	12.0	0.936	154	.056
TP53 mutation [3]	4.50	0.491	41.2	.183

A univariate logistic regression analysis was performed to verify the risk of pneumonitis.
[1] Regarding the radiological findings of pre-existing interstitial pneumonia as judged by the central review committee, 8 patients had indeterminate for usual interstitial pneumonia pattern.
[2] Seven patients had honeycomb lung on high-resolution computed tomography.
[3] *TP53* mutations were detected in 6 patients and 11 were negative or unmeasured.

Table 4. Predictive biomarkers for the efficacy of atezolizumab.

	Overall survival			Progression free survival		
	Hazard ratio	95%CI	*P*-value	Hazard ratio	95%CI	*P*-value
Tumor mutation burden≥ 10 mutations per megabase	0.407	0.0414—4.01	.441	0.687	0.168-2.81	.602
TP53 mutation	1.537	0.212—11.14	.671	1.64	0.422-6.38	.475
KRAS mutation	Not applicable	Not applicable	.998	0.215	0.0251-1.84	.160
Abnormality of RAS/RAF/MAPK signaling pathway	Not applicable	Not applicable	.997	0.407	0.0812-2.04	.274
Abnormality of PI3K-AKT signaling pathway	3.11	0.434-22.3	.259	1.76	0.390-7.98	.461

A univariate cox regression analysis was performed to verify whether tumor mutation burden, detected genetic mutations and pathway abnormalities could be predictive biomarkers of efficacy. Hazard ratios were calculated using patients with tumor mutation burden < 10 mutations per megabase and patients with no or unknown genetic mutations or pathway abnormalities as the control group, respectively. For tumor mutation burden, 4 patients had ≥10 mutations per megabase. TP53 mutation was detected in 6 patients, KRAS mutation in 3 patients, abnormalities of RAS/RAF/MAPK signaling pathway (including KRAS mutation) in 4 patients, and abnormalities of PI3K-AKT signaling pathway in 3 patients.