ORIGINAL ARTICLE

Pneumonitis During Durvalumab Consolidation Therapy Affects Survival in Stage III NSCLC

Yuhei Kinehara, MD, PhD,[a] Takayuki Shiroyama, MD, PhD,[b,*] Akihiro Tamiya, MD,[c] Motohiro Tamiya, MD,[d] Seigo Minami, MD, PhD,[e] Masaki Kanazu, MD,[f] Osamu Morimura, MD, PhD,[g] Toshie Niki, MD, PhD,[h] Satoshi Tetsumoto, MD, PhD,[i] Yoshihiko Taniguchi, MD,[c] Tomoki Kuge, MD,[b,f] Kazumi Nishino, MD, PhD,[d] Izumi Nagatomo, MD, PhD,[b] Atsushi Kumanogoh, MD, PhD,[b,j,k,l,m,n] Isao Tachibana, MD, PhD[a]

[a]*Department of Respiratory Medicine and Clinical Immunology, Nippon Life Hospital, Osaka, Japan*
[b]*Department of Respiratory Medicine and Clinical Immunology, Osaka University Graduate School of Medicine, Osaka, Japan*
[c]*Department of Internal Medicine, National Hospital Organization Kinki-Chuo Chest Medical Center, Osaka, Japan*
[d]*Department of Thoracic Oncology, Osaka International Cancer Institute, Osaka, Japan*
[e]*Department of Respiratory Medicine, Osaka Police Hospital, Osaka, Japan*
[f]*Department of Thoracic Oncology, National Hospital Organization Osaka Toneyama Medical Center, Osaka, Japan*
[g]*Department of Respiratory Medicine, Toyonaka Municipal Hospital, Osaka, Japan*
[h]*Department of Respiratory Medicine, Nishinomiya Municipal Central Hospital, Hyogo, Japan*
[i]*Department of Respiratory Medicine and Clinical Immunology, Suita Municipal Hospital, Osaka, Japan*
[j]*Department of Immunopathology, WPI, Immunology Frontier Research Center (iFReC), Osaka University, Osaka, Japan*
[k]*Integrated Frontier Research for Medical Science Division, Institute for Open and Transdisciplinary Research Initiatives (OTRI), Osaka University, Osaka, Japan*
[l]*Center for Infectious Diseases for Education and Research (CiDER), Osaka University, Suita, Osaka, Japan*
[m]*Japan Agency for Medical Research and Development—Core Research for Evolutional Science and Technology (AMED-CREST), Osaka University, Osaka, Japan*
[n]*Center for Advanced Modalities and DDS (CAMaD), Osaka University, Osaka, Japan*

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*Corresponding author.

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Address for correspondence: Takayuki Shiroyama, MD, PhD, Department of Respiratory Medicine and Clinical Immunology, Osaka University Graduate School of Medicine, 2-2 Yamadaoka, Suita City, Osaka 565-0871, Japan. E-mail: shiroyamat@imed3.med.osaka-u.ac.jp

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ABSTRACT

Introduction: Durvalumab consolidation therapy is the standard of care after concurrent chemoradiotherapy (CRT) for stage III NSCLC. Immune-related pneumonitis during durvalumab treatment is potentially fatal; however, information is lacking regarding the impact of pneumonitis on patient survival. This study investigates the effect of pulmonary and nonpulmonary immune-related adverse events (irAEs) on the efficacy of durvalumab treatment in patients with stage III NSCLC.

Methods: We retrospectively assessed 158 patients who received durvalumab after CRT at nine Japanese institutions between July 2018 and March 2020. Survival outcomes were compared between patients who developed pneumonitis with those who developed irAEs other than pneumonitis. Patients who survived for less than 3 months were excluded to reduce immortal time bias.

Results: Among 158 evaluated patients, 76 (48%) experienced grade less than or equal to one irAEs, whereas 82 (52%) experienced grade greater than or equal to two irAEs. Among the patients with grade greater than or equal to two irAEs, those with grade greater than or equal to two pneumonitis (n = 55) were compared with those with grade greater than or equal to two irAEs other than pneumonitis (n = 27). Patients with grade greater than or equal to two pneumonitis exhibited a significantly worse overall survival than those with grade greater than or equal to two irAEs that excluded pneumonitis. Multivariate analysis revealed that grade greater than or equal to two pneumonitis (hazard ratio = 3.71; 95% confidence interval, 1.85–7.45; $p < 0.001$) and squamous histology (hazard ratio = 2.64; 95% confidence interval, 1.29–5.42; $p = 0.008$) were independently associated with worse overall survival.

Conclusions: After minimizing immortal time bias, pneumonitis grade two or greater and squamous histology were poor prognostic factors in patients who received consolidation durvalumab after CRT.

Keywords: Immune-related adverse event; Chemoradiotherapy; Durvalumab; Pneumonitis; Stage III

Introduction

Immune checkpoint inhibitors have dramatically improved the prognosis of many patients with cancer. Therefore, immune-related adverse events (irAEs) are of great interest in clinical practice, because they can lead to treatment discontinuation and even fatal outcomes. Pneumonitis is the most common fatal irAE in patients receiving programmed cell death protein 1 (PD-1) and programmed death ligand-1 (PD-L1) inhibitors (such as durvalumab), and it accounts for 35% of all fatalities from irAEs.[1]

Durvalumab maintenance therapy is the standard of care after definitive concurrent chemoradiotherapy (CRT) for stage III NSCLC. In the PACIFIC study,[2] pneumonitis of any grade occurred in 33.9% of patients treated with durvalumab and was the most frequent adverse event that led to treatment discontinuation. Therefore, pneumonitis is an adverse event of special concern in patients with locally advanced NSCLC.

Previous studies have confirmed that irAEs are associated with improved survival outcomes in patients with advanced or recurrent NSCLC.[3–5] Immune-related pneumonitis, however, is reportedly associated with a worse survival outcome in patients with advanced NSCLC.[6–9] Nevertheless, in locally advanced NSCLC, data on the association between development of pneumonitis and the efficacy of durvalumab treatment are currently lacking. Therefore, the present study aimed to investigate the impact of pulmonary and nonpulmonary irAEs on the efficacy of durvalumab treatment in patients with stage III NSCLC.

Materials and Methods

Study Population

This multicenter retrospective study was approved by the ethics review board of each participating institution. The study was conducted in accordance with the Declaration of Helsinki and its subsequent amendments. We evaluated patients with unresectable stage III NSCLC who were treated with at least one dose of durvalumab after concurrent CRT. Patients were enrolled from nine institutes in Japan between July 2018 and March 2020. Those with active steroid treatment or poor Eastern Cooperative Oncology Group performance status (ECOG PS) (≥2) were excluded from the study. Furthermore, patients who survived for less than 3 months were excluded to reduce immortal time bias. The indication for durvalumab therapy after CRT was determined by the absence of grade greater than or equal to two radiation pneumonitis. Durvalumab was administered every 2 weeks for up to 12 months at a dose of 10 mg/kg or until disease progression or intolerance occurred. Pneumonitis was diagnosed by multiple pulmonologists and radiologists, primarily based on the clinical course, laboratory data, and computed tomography findings. Patients presenting with apparent pulmonary infection, heart failure, tumor progression, or a substantial likelihood of one of these conditions were excluded. Nevertheless, patients in which radiation pneumonitis was

Table 1. Baseline Patient Characteristics Classified According to Severity Grade

Characteristics	Overall, N = 158	Grade ≤ 1, n = 76	Grade ≥ 2, n = 82	*p* Value
Age (IQR), y	69 (62-75)	69 (63-75)	69 (62-75)	0.76
Sex, n (%)				0.25
F	42 (27)	17 (22)	25 (30)	
M	116 (73)	59 (78)	57 (70)	
Performance status, n (%)				0.80
0	64 (41)	30 (39)	34 (41)	
1	94 (59)	46 (61)	48 (59)	
Smoking status, n (%)				0.49
Current	64 (40)	34 (45)	30 (37)	
Former	83 (53)	38 (50)	45 (55)	
Never	11 (7)	4 (5)	7 (8)	
Histology, n (%)				0.97
Nonsquamous	85 (54)	41 (54)	44 (54)	
Squamous	73 (46)	35 (46)	38 (46)	
Stage, n (%)				0.82
IIIA	90 (57)	44 (58)	46 (56)	
IIIB/IIIC	68 (43)	32 (42)	36 (44)	
PD-L1 status, n (%)				0.92
<25%	62 (39)	31 (41)	31 (38)	
≥25%	74 (47)	35 (46)	39 (48)	
Unknown	22 (14)	10 (13)	12 (15)	
Driver mutation, n (%)				0.47
Negative	145 (92)	71 (93)	74 (90)	
Positive	13 (8.2)	5 (6.6)	8 (9.8)	
Time to durvalumab, n (%)				0.65
<28 d	119 (75)	56 (74)	63 (77)	
≥28 d	39 (25)	20 (26)	19 (23)	
Irradiation type, n (%)				0.86
ENI	82 (52)	40 (53)	42 (51)	
IFRT	76 (48)	36 (47)	40 (49)	
RT method, n (%)				0.24
3D-CRT	105 (66)	54 (71)	51 (62)	
IMRT[a]	53 (34)	22 (29)	31 (38)	
RT dose, Gy, n (%)				>0.99
<60 Gy	3 (1.9)	1 (1.3)	2 (2.4)	
>66	1 (0.6)	0 (0)	1 (1.2)	
60-66	154 (97)	75 (99)	79 (96)	
NLR at baseline (IQR)	3.45 (2.32-5.48)	3.73 (2.28-5.46)	3.38 (2.43-5.69)	0.90
No. of durvalumab doses (IQR)	19 (7-24)	23 (18-24)	13 (4-19)	<0.001
Time to durvalumab (IQR), d	15 (10-27)	16 (11-28)	14 (9-25)	0.21
V5, %	33.3 (28.0-43.8)	33.0 (28.1-40.1)	34.4 (27.9-46.0)	0.30
V20, %	20.0 (15.5-24.8)	20.0 (16.5-23.7)	20.0 (14.4-25.2)	0.90
MLD, Gy	11.3 (8.5-14.0)	11.3 (9.0-14.0)	11.4 (7.8-14.1)	0.93

[a]Data included five cases of VMAT.
ENI, elective nodal irradiation; F, female; IFRT, involved-field radiotherapy; IMRT, intensity-modulated radiation therapy; IQR, interquartile range; M, male; MLD, mean lung dose; NLR, neutrophil-to-lymphocyte ratio; PD-L1, programmed death-ligand 1.

suspected to coexist with checkpoint inhibitor-related pneumonitis were included. Pneumonitis grade was established according to the Common Terminology Criteria for Adverse Events version 5.0.

Statistical Analysis

Considering the lead time bias due to the time-dependent nature of irAEs, a landmark analysis was conducted to minimize the immortal time bias. Patients who survived for less than 3 months were excluded from the evaluation to minimize immortal time bias. Progression-free survival (PFS) and overall survival (OS) were measured, as from the initiation of durvalumab treatment. Survival curves were analyzed using the Kaplan–Meier method and compared between groups with the log-rank test. Continuous variables were analyzed through the Mann–Whitney *U* test and categorical variables with Fisher's exact test. Univariate and

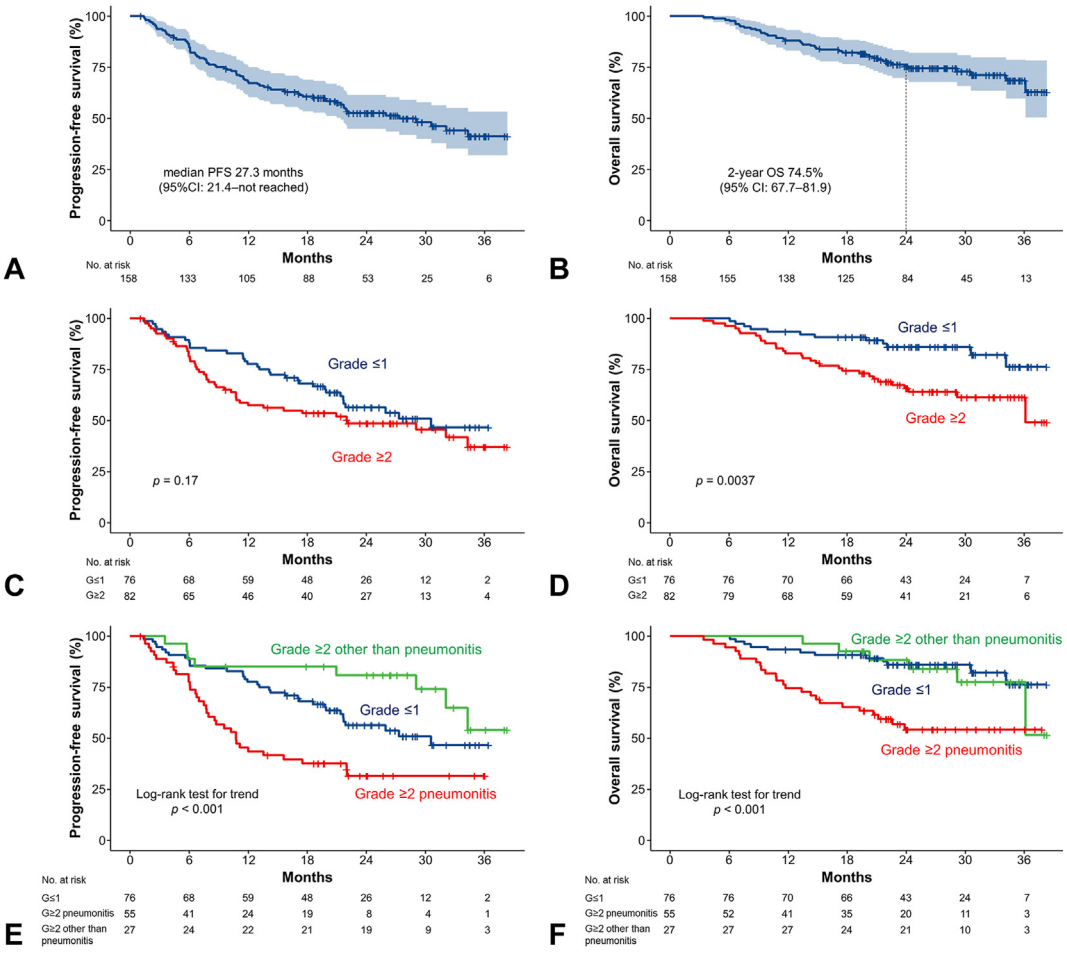

Figure 1. Kaplan-Meier curves of PFS and OS in patients with stage III NSCLC who received durvalumab consolidation therapy. (*A*, *B*) All patients, n = 158. (*C*, *D*) Patients were divided into two groups based on the severity and type of irAEs they experienced: grade less than or equal to one irAEs and grade greater than or equal to two irAEs. (*E*, *F*) Patients were divided into the following three groups: grade less than or equal to one irAEs, grade greater than or equal to two pneumonitis, and grade greater than or equal to two irAEs other than pneumonitis. CI, confidence interval; irAE, immune-related adverse event; OS, overall survival; PFS, progression-free survival.

multivariate analyses were performed using the Cox proportional hazards and logistic regression models. Variables with a *p* value less than 0.1 on univariate analysis and those related to treatment outcome based on previous reports were included in the multivariate Cox model analysis. All statistical analyses were conducted using R software version 4.2.1 (R Core Team, Vienna, Austria). All *p* values were two sided, and a *p* less than 0.05 was considered statistically significant.

Results

In total, 158 patients with unresectable stage III NSCLC who underwent definitive CRT followed by durvalumab therapy were included in the analysis. The baseline demographic and clinicopathologic characteristics of the patients according to the irAE grade are summarized in Table 1. The median patient age was 69 (interquartile range [IQR], 62–75) years. Most patients were men (73%), had an ECOG PS of 1 (59%), were at stage IIIA (57%), and were current or former smokers (93%). The PD-L1 tumor proportion score (TPS) was evaluated in 136 patients, of which 62 (39%) had a TPS less than 25% and 74 (47%) had a TPS greater than or equal to 25%. The expression of PD-L1 was assessed by immunohistochemistry using 22C3 pharmDx testing. The median radiation dose was 60 Gy (IQR: 60–66), and 97% of patients received 60–66 Gy. The median V5, V20, and mean lung doses in the entire cohort were 33.3% (IQR: 28.0–43.8), 20.0% (IQR, 15.5–24.8), and 11.3 Gy (IQR: 8.5–14.0), respectively. The median number of durvalumab doses administered was 19 (IQR: 7–24).

Overall, 76 (48%) patients developed grade one or no irAEs (defined as the low-grade group) and 82 (52%) developed grade greater than or equal to two irAEs (defined as the high-grade group). The number of

durvalumab doses received was lower in the high-grade than in the low-grade group ($p < 0.001$); however, there were no differences in other baseline characteristics between these groups (Table 1). Moreover, there were no significant differences in the V5, V20, or mean lung doses between the two groups.

The median follow-up period was 27.3 months (Kaplan–Meier estimate). In the overall cohort, the median PFS was 27.3 months (95% confidence interval [CI]: 21.4–not reached); the median OS was not reached; and the 2-year OS rate was 74.5% (95% CI: 67.7–81.9) (Fig. 1*A* and *B*). The high-grade group exhibited a shorter PFS than the low-grade group (22.1 mo versus 30.6 mo, $p = 0.17$) (Fig. 1*C*). The high-grade group also had a significantly worse OS than the low-grade group (36.1 mo versus not reached, $p = 0.0037$) (Fig. 1*D*). To evaluate the impact of pneumonitis on survival benefit, the high-grade irAE group was split in two according to the presence or absence of pneumonitis, and there was a statistically significant difference among the resultant three groups in terms of both PFS and OS (log-rank test for trend, $p < 0.001$) (Fig. 1*E* and *F*). The patients who developed grade greater than or equal to two pneumonitis had a significantly worse OS than those who developed grade greater than or equal to two irAEs other than pneumonitis. Multivariate analysis of tumor proportion score, histology, and irAE type revealed that squamous histology (hazard ratio [HR] = 2.64; 95% CI: 1.29–5.42; $p = 0.008$) and grade greater than or equal to two pneumonitis (HR = 3.71; 95% CI: 1.85–7.45; $p < 0.001$) were independently associated with OS (Supplementary Table 1).

A total of 27 patients (17%) developed grade greater than or equal to two irAEs other than pneumonitis. Among them, nine required corticosteroid therapy, mainly due to the presence of hepatitis, skin rash, colitis, or arthritis. Grade greater than or equal to two pneumonitis was observed in 35% (55 of 158) of the patients. Of the 52 patients who required corticosteroid therapy, 23 (41%) underwent rechallenge with durvalumab, leading to a relapse of pneumonitis in five (21%) patients. The permanent discontinuation rates in patients who experienced grade greater than or equal to two irAEs other than pneumonitis and those who experienced grade greater than or equal to two pneumonitis were 29.6% (eight of 27) and 50.1% (28 of 55), respectively. A higher severity grade of pneumonitis was significantly associated with decreased OS and PFS (log-rank test for trend, $p < 0.001$) (Supplementary Fig. 1*A* and *B*), and median OS in patients who developed grade greater than or equal to three pneumonitis was as short as 11.5 months (Supplementary Fig. 1*B*). This result was in contrast to the OS of patients who developed grade greater than or equal to three irAEs other than pneumonitis (Supplementary Fig. 1*C*). Although not statistically significant, grade greater than or equal to three pneumonitis was more common in patients with squamous cell carcinoma than in those with nonsquamous cell carcinoma (11.0% versus 5.8%, $p = 0.26$).

Discussion

We established that patients with grade greater than or equal to two irAEs had a significantly worse OS than those with grade one or no irAEs. Moreover, this result could be attributed to the poor prognosis of patients with grade greater than or equal to two pneumonitis. Grade greater than or equal to two pneumonitis was negatively associated with survival outcomes compared with grade greater than or equal to two irAEs other than pneumonitis. Multivariate analysis revealed that grade greater than or equal to two pneumonitis and squamous histology were independent factors associated with worse OS. Our results suggest that a higher grade of pneumonitis and squamous histology are detrimental to the efficacy of consolidation therapy with durvalumab.

Pneumonitis is a common irAE that is of high concern to clinical practitioners because of its potentially fatal prognosis.[1] Previous studies have indeed confirmed that severe immune-related pneumonitis is associated with a poor prognosis among patients with advanced-stage lung cancer.[6–9] Several retrospective studies of patients with stage III NSCLC who received durvalumab, however, revealed that grade greater than or equal to two pneumonitis after durvalumab was not a prognostic factor for PFS.[10,11] Nevertheless, definitive conclusions could not be drawn from these studies due to the short follow-up periods and small sample sizes involved. Our study differed from the aforementioned ones in that it evaluated the relationship between grade greater than or equal to two pneumonitis and its negative impact on OS from durvalumab therapy, and we included a larger sample size and longer follow-up period. Moreover, a recent systematic review and meta-analysis[12] reported that the occurrence of irAEs contributed to OS improvement (pooled HR = 0.54; 95% CI: 0.45–0.65). Nevertheless, benefits varied widely depending on the irAE type present. A significant OS benefit was observed in patients who experienced endocrine or dermatologic irAEs (pooled HR = 0.52 and 0.45, respectively). Conversely, no OS benefit was observed in patients who experienced pulmonary irAEs (pooled HR = 1.22). Our findings align with these results, and the OS of patients who developed grade greater than or equal to two irAEs varied significantly depending on the presence or absence of pneumonitis.

In the present study, the durvalumab discontinuation rate was higher in patients who developed grade greater

than or equal to two pneumonitis than in those who developed grade greater than or equal to two irAEs other than pneumonitis. It has been suggested that the discontinuation of durvalumab consolidation therapy due to adverse events may have significant negative effects on OS.[13,14] Therefore, the high rate of durvalumab discontinuation due to grade greater than or equal to two pneumonitis may have contributed to the worse survival outcomes in our study population. Furthermore, a potential reason for the unfavorable prognosis linked with squamous histology may be the higher frequency of grade greater than or equal to three pneumonitis observed in patients with squamous cell carcinoma compared with that in patients with nonsquamous cell carcinoma.

Our PFS and OS times were longer than those in the PACIFIC study[2] (median PFS 27.3 mo versus 16.8 mo and 2-y OS rate 74.5% versus 66.3%). Nevertheless, our data were comparable with those of two recent investigations; in the PACIFIC-R[15] and PACIFIC-KR[16] studies, in which the median PFS was 21.7 months and 25.9 months and the 2-year OS rate was 71.2% and 71.0%, respectively. Our cumulative incidence of grade greater than or equal to two pneumonitis was 34.8%, which is higher than the 19.8% recorded in the PACIFIC study.[2] Nevertheless, previous real-world data[11,17–22] have reported that the incidence of grade greater than or equal to two pneumonitis ranges from 22.9% to 46.7%, which is comparable with our findings. These data should be interpreted with caution, because the incidence rates may account for radiation-induced pneumonitis and purely checkpoint inhibitor-related pneumonitis.

Our study had some limitations. First, it was a retrospective study with a relatively small number of patients. Second, patients diagnosed with having pneumonitis may have included those with radiation-induced pneumonitis and checkpoint inhibitor-related pneumonitis. Because it is extremely challenging to completely differentiate between these pulmonary adverse events in clinical practice, we defined pneumonitis conservatively to include both immune-related and radiation-induced pneumonitis, suspected to coexist with checkpoint inhibitor-related pneumonitis. Of note, distinctly different clinical signs existed between our patients with grade greater than or equal to two pneumonitis and those with grade greater than or equal to two irAEs other than pneumonitis. Third, the presence of 13 patients harboring driver mutations in the present study (12 with EGFR mutations and one with ALK rearrangements) might have potentially influenced the main results. Nevertheless, supplementary analyses revealed the absence of clinically significant associations between mutation status and both therapeutic efficacy and safety outcomes. Finally, we did not evaluate pulmonary comorbidities and baseline pulmonary function that might have interfered with the course and severity of checkpoint inhibitor-related pneumonitis. Considering these limitations, our study should be regarded as a framework for designing future studies.

In conclusion, we found that the development of grade greater than or equal to two pneumonitis and squamous histology were negatively associated with survival outcomes in patients with stage III NSCLC who were treated with durvalumab after concurrent CRT. Minimizing the occurrence of severe pneumonitis during durvalumab treatment may yield survival benefits. Further studies are warranted to identify the risk factors predisposing patients to high-grade pneumonitis and factors contributing to poor survival outcomes.

CRediT Authorship Contribution Statement

Yuhei Kinehara, Takayuki Shiroyama: Conceptualization, Methodology, Data curation, Formal analysis, Investigation, Methodology, Resources, Writing—original draft, Writing—review and editing.

Akihiro Tamiya, Motohiro Tamiya, Seigo Minami, Masaki Kanazu, Osamu Morimura, Toshie Niki, Satoshi Tetsumoto, Yoshihiko Taniguchi, Tomoki Kuge: Data curation, Investigation, Resources, Writing—review and editing.

Kazumi Nishino, Izumi Nagatomo, Atsushi Kumanogoh, Isao Tachibana: Writing—review and editing.

Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *JTO Clinical and Research Reports* at www.jtocrr.org and at https://doi.org/10.1016/j.jtocrr.2023.100586.

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