Brief Report: Risk of Recurrent Interstitial Lung Disease From Osimertinib Versus Erlotinib Rechallenge After Symptomatic Osimertinib-Induced Interstitial Lung Disease

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ABSTRACT

Introduction: Interstitial lung disease (ILD) is the most frequent cause of drug-related mortality from EGFR tyrosine kinase inhibitors (TKIs). Yet, for patients with symptomatic osimertinib-induced ILD, the risk of recurrent ILD associated with EGFR TKI rechallenge, either with osimertinib or another TKI, such as erlotinib, is unclear.

Methods: Retrospective study of 913 patients who received osimertinib treatment for *EGFR* mutation-positive NSCLC. Clinical characteristics, ILD treatment history, and subsequent anticancer therapy of patients with symptomatic osimertinib-induced ILD were collated. The primary end point was to compare the incidence of recurrent ILD with osimertinib versus erlotinib rechallenge.

Results: Of 913 patients, 35 (3.8%) had symptomatic osimertinib-induced ILD, of which 12 (34%), 15 (43%), and eight (23%) had grade 2, 3 to 4, and 5 ILD, respectively. On ILD recovery, 17 patients had EGFR TKI rechallenge with eight received osimertinib and nine received erlotinib. The risk of recurrent ILD was higher with osimertinib rechallenge than erlotinib ($p = 0.0498$). Of eight, five (63%) developed recurrent ILD on osimertinib rechallenge, including three patients with fatal outcomes. In contrast, only one of nine patients (11%) treated with erlotinib had recurrent ILD. Median time to second ILD occurrence was 4.7 (range 0.7–12) weeks. Median time-to-treatment failure of patients with erlotinib rechallenge was 13.2 months (95% confidence interval: 8.6–15.0).

Conclusions: The risk of recurrent ILD was considerably higher with osimertinib rechallenge than erlotinib. Osimertinib rechallenge should be avoided, whereas erlotinib may be considered in patients with symptomatic osimertinib-induced ILD.

Keywords: Epidermal growth factor receptor; Interstitial lung disease; Osimertinib; Erlotinib; Rechallenge

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Introduction

Osimertinib is the standard first-line treatment for patients with metastatic *EGFR* mutation-positive NSCLC, given its superiority compared with first-generation EGFR tyrosine kinase inhibitors (TKIs) in terms of progression-free survival and overall survival.[1] Interstitial lung disease (ILD) is rare but the most frequent cause of drug-induced mortality from EGFR TKI.[2] The incidence of osimertinib-induced ILD is approximately 4%.[1,3] The best strategy for patients who develop this complication is unclear. Permanent drug discontinuation is recommended for patients who develop osimertinib-induced ILD, but patients would lose the most effective treatment option.[1,3,4] Two retrospective studies from Japan suggested that osimertinib rechallenge might be safe in patients who had mild ILD,[5,6] but there is limited evidence on the safety of such approach in patients with symptomatic disease. Because all EGFR TKIs are potentially associated with ILD, there is also concern on the safety of switching to another EGFR TKI. Here, we performed a retrospective study to compare the risk of recurrent ILD between osimertinib rechallenge versus in-class switch to first-generation EGFR TKI in patients with history of symptomatic osimertinib-induced ILD.

Materials and Methods

Case records of all patients who received osimertinib for *EGFR* mutation-positive NSCLC at the Prince of Wales Hospital, Hong Kong, between November 1, 2017, and May 11, 2023, were reviewed. The diagnosis and grading of osimertinib-induced ILD were independently determined by two board-certified medical oncologists (M.L. and K.L.) according to the Common Terminology Criteria for Adverse Events version 5.0. Patients who developed grade 2 or above ILD from osimertinib were included. Exclusion criteria include concomitant coronavirus disease 2019 infection, infectious pneumonia, or radiation-induced pneumonitis as per radiotherapy portal. Clinical characteristics, ILD treatment history, and data on subsequent EGFR TKI treatment (osimertinib versus first-generation EGFR TKI) were collated. The primary end point was to compare the incidence of recurrent symptomatic ILD with osimertinib rechallenge versus that with first-generation EGFR TKI treatment. Secondary end point was time-to-treatment failure of patients on EGFR TKI rechallenge. The study was approved by the Institutional Review Board at the Chinese University of Hong Kong. Continuous variables and categorical variables were compared by *U* test, chi-square test, or Fisher's exact test, as appropriate. A two-sided *p* value less than 0.05 was considered significant.

Table 1. Patient Characteristics

Characteristics	Patients With Symptomatic ILD (n = 35)
Age, y	
Median (range)	69 (47-90)
Sex	
Male	11 (31)
Female	24 (69)
Race	
Chinese	34 (97)
Whites	1 (3)
Smoker	
Never	29 (83)
Current/former	6 (17)
Stage	
IB (adjuvant)	1 (3)
IV	34 (97)
EGFR mutation	
Exon 19 mutation	19 (54)
Exon 21 L858R mutation	15 (43)
Others	1 (3)
Line of osimertinib treatment	
1	17 (49)
2	14 (40)
3 or above	4 (11)
PS	
0-1	22 (63)
2	13 (37)
Prior ILD (including drug-induced ILD)	0
Prior radiotherapy to chest or thoracic spine	8 (23)
<3 mo	4 (11)
3-6 mo	1 (3)
>6 mo	3 (9)
Prior immune checkpoint inhibitor within 3 mo	2 (6)
CTCAE grade	
2	12 (34)
3-4	15 (43)
5	8 (23)
Subsequent treatment after recovery from ILD	n = 27
Osimertinib rechallenge	8 (30)
Erlotinib	9 (33)
Chemotherapy	2 (7)
Best supportive care	8 (30)

Note: All values are n (%) unless otherwise specified.
CTCAE, Common Terminology Criteria for Adverse Events; ILD, interstitial lung disease; PS, performance status.

Results

Patient Demographics

A total of 913 patients received osimertinib treatment during the study period, of which, 35 (3.8%) developed symptomatic ILD. Clinical characteristics were summarized in Table 1. Number of patients with grade 2, 3 to 4, and 5 ILD was 12 (34%), 15 (43%), and eight (23%), respectively. Median time from initiation of

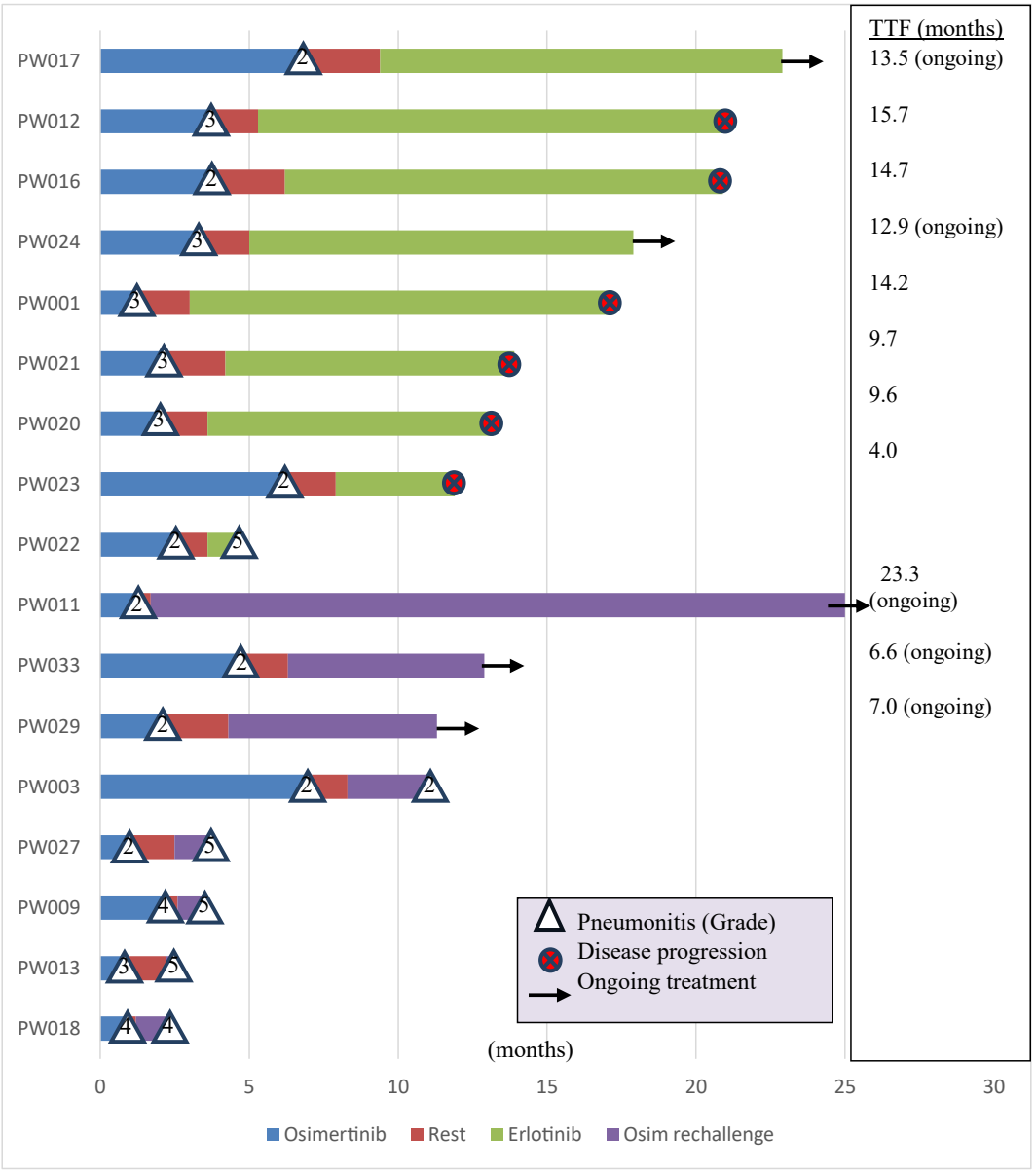

Figure 1. Swimmer plot of patients who received subsequent osimertinib rechallenge or erlotinib treatment. The duration was from the first initiation of osimertinib therapy to drug cessation owing to occurrence of second episode of ILD or disease progression on subsequent EGFR TKI, or data cutoff. ILD, interstitial lung disease; Osim, osimertinib; TKI, tyrosine kinase inhibitor.

osimertinib to diagnosis of ILD was 9.9 weeks (95% confidence interval: 9.1–18.4, range: 1.1–78.3). Osimertinib was withheld for all patients on ILD diagnosis. Furthermore, six of 12 patients (50%) with grade 2 ILD and 14 of 15 patients (93%) with grade 3 to 4 ILD received corticosteroid treatment respectively. Details of clinical characteristics and treatment plan of all 35 patients are reported in Supplementary Table 1.

Incidence of ILD Recurrence With EGFR TKI Rechallenge

There were 27 patients who recovered from ILD, whereas eight patients died. On recovery from ILD, 17 patients (63%) received EGFR TKI rechallenge, of which eight received osimertinib and nine switched to erlotinib (Supplementary Fig. 1). Clinical characteristics were similar between the two cohorts except for prior treatment (Supplementary Table 2). All nine patients in the erlotinib cohort had received first-line osimertinib for advanced disease and no prior exposure to other EGFR TKI. Furthermore, six of eight patients on the osimertinib rechallenge arm received osimertinib as second- or later-line therapy after failing first- or second-generation EGFR TKIs. Among 13 patients who received steroid therapy for TKI-induced ILD and rechallenged TKI, nine were on corticosteroid during the time of TKI

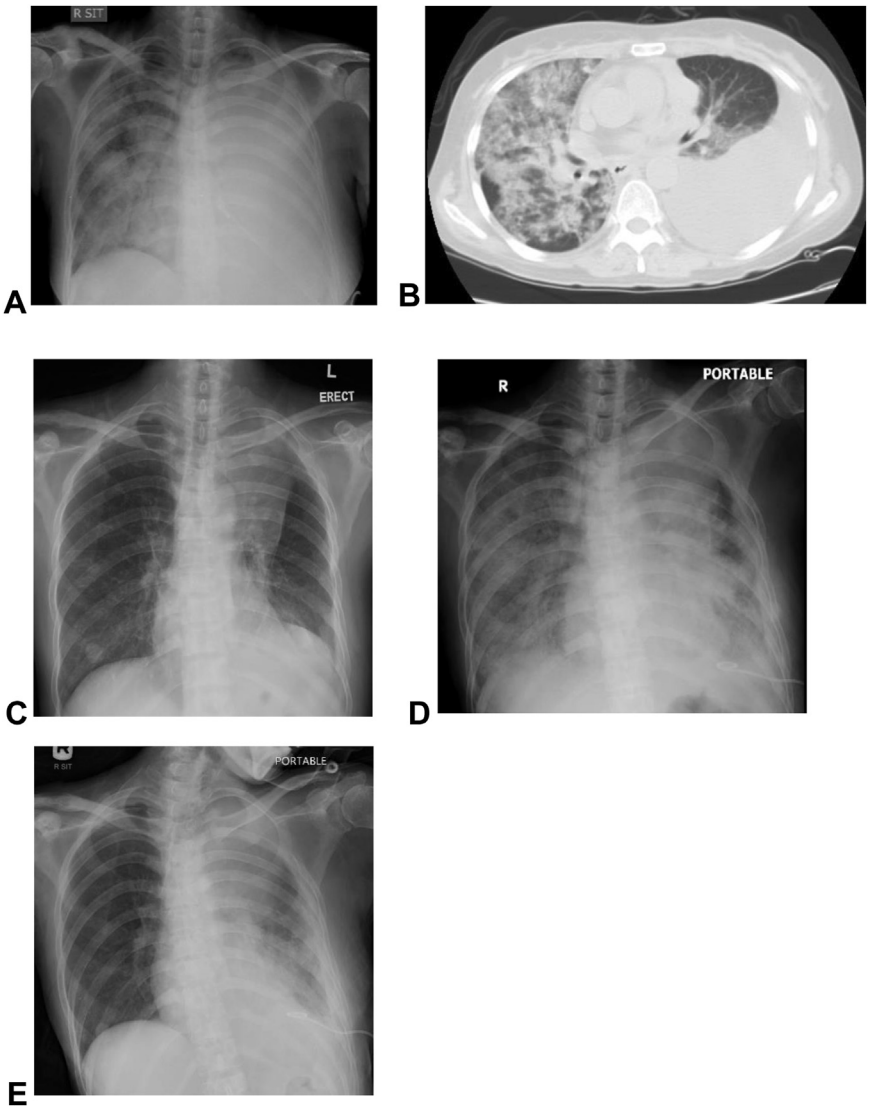

Figure 2. Images of representative patient (PW018) who develop recurrent ILD after osimertinib rechallenge. (a, b) 1st Episode of Pneumonitis (Grade 4); onset 4.4 weeks after initiation of osimertinib. (c) Resolution of Pneumonitis; 1 week after steroid, antibiotic and drainage of malignant pleural effusion. Osimertinib (40mg) rechallenge in view of extensive brain metastases and rapidly recurring left pleural effusion. (d) Recurrence of Pneumonitis (Grade 4); onset 4.9 weeks after osimertinib rechallenge. (e) Resolution of Pneumonitis after corticosteroid and antibiotic. Patient transited to best supportive care in view of poor performance status.

rechallenge. Corticosteroid was administered with TKI for a range of 2 to 56 days but not throughout the entire TKI rechallenge period (Supplementary Table 1).

Until data cutoff on November 15, 2023, all patients had received at least 6 months of EGFR TKI rechallenge for safety analysis. Furthermore, five of eight patients (63%) in the osimertinib rechallenge arm had recurrent ILD, with three fatal events (38%) (Figure 1 and 2). Median time from initiation of osimertinib rechallenge to ILD recurrence was 4.9 weeks (0.7, 3.7, 4.9, 5.4, and 12.0 wk, respectively) (Figure 1). In contrast, only one of nine patients (11%) on erlotinib developed recurrent ILD (Figure 3). This was a grade 5 event after erlotinib treatment for 4.6 weeks. Her initial episode of ILD was grade 2 in severity. ILD recurrence was significantly more frequent with osimertinib rechallenge than with erlotinib treatment ($p = 0.0498$) (Table 2). In particular, in patients who initially had grade 3 to 4 ILD, ILD recurred in all three patients with osimertinib rechallenge but zero of five patients with erlotinib treatment ($p = 0.018$) (Supplementary Table 3).

Treatment Efficacy of Subsequent EGFR TKI Treatment

Three patients (#11, #29, and #33), all of whom initially had grade 2 ILD, were on osimertinib

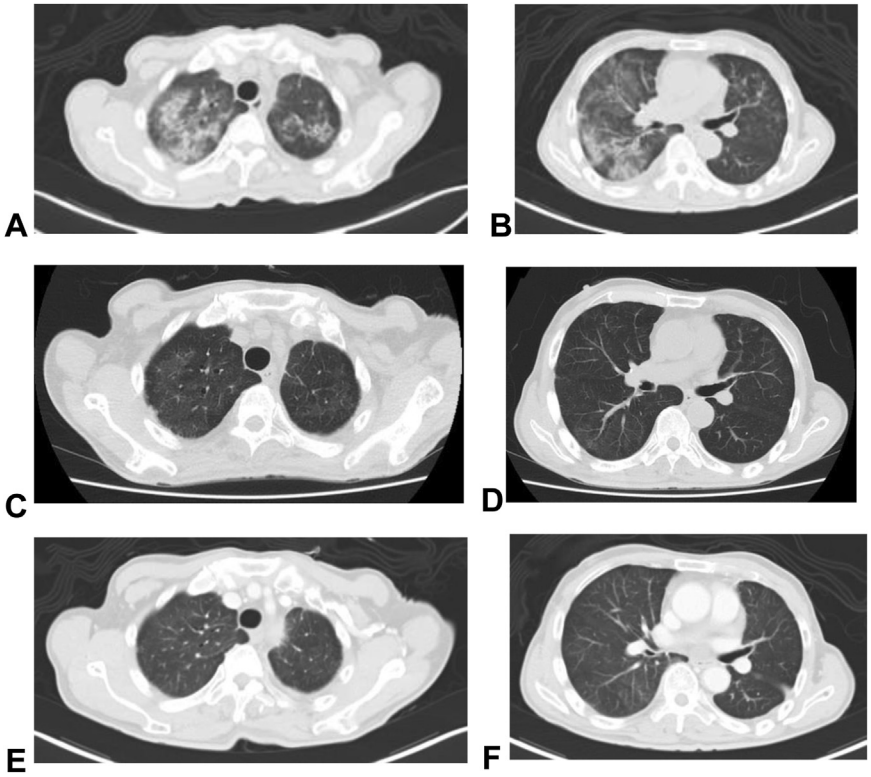

Figure 3. Images of representative patient (PW016) who tolerated Erlotinib after Osimertinib induced ILD. (a, b) 1st Episode of Pneumonitis (Grade 2): onset 3.8 months after initiation of osimertinib. (c, d) Resolution of Pneumonitis after corticosteroid treatment: 4 weeks after onset of pneumonitis. Erlotinib started another 3 weeks later. (e, f) No recurrence of Pneumonitis on 14.7 months of Erlotinib. Patient subsequently stopped Erlotinib due to disease progression.

rechallenge with ongoing response and no ILD recurrence after 23.3, 7.0, and 6.6 months of follow-up, respectively. Duration of response of the eight patients who switched to erlotinib is summarized in Figure 1. The median time-to-treatment failure on erlotinib rechallenge was 13.2 months (95% confidence interval: 8.6–15.0).

Discussion

This retrospective analysis confirmed that osimertinib rechallenge to be associated with a significantly higher risk of ILD recurrence (63%) compared with erlotinib (11%) in patients who experienced symptomatic osimertinib-induced ILD. The mortality rate of recurrent ILD with osimertinib rechallenge was high, thus should be avoided in this population.

Two retrospective studies have investigated the safety of osimertinib rechallenge in patients with osimertinib-induced ILD. Kodama et al.[5] reported no ILD recurrence with osimertinib rechallenge in four patients with grade 1 ILD and one of four patients with grade 2 ILD had recurrence. Another retrospective study investigated 33 patients who had osimertinib-induced ILD but either continued or rechallenged osimertinib. Most patients (26 of 33) had grade 1 disease, and recurrence rate was 15% (five of 33).[6] Authors of both studies suggested that osimertinib rechallenge may be feasible for patients with mild ILD. Nevertheless, the diagnoses of mild ILD in these studies were unclear because two-thirds of grade 1 ILD could be transient asymptomatic pulmonary opacities,[7] a benign radiological finding that does not require osimertinib cessation.[8] In contrast, our study included only symptomatic cases, which more likely represented genuine ILD. Our findings suggest that ILD recurrence risk may be associated with the severity of the initial episode of ILD. A post-marketing analysis conducted in Japan reported a 37% recurrence rate with osimertinib readministration in eight patients with grade 3 or 4 ILD.[9] Taken together, the high ILD recurrence and mortality should be sufficient to warn clinicians against osimertinib rechallenge in patients with symptomatic osimertinib-induced ILD.

To our understanding, the risk of recurrent ILD with erlotinib treatment after osimertinib-induced ILD has not been reported. Although erlotinib may be inferior to osimertinib as a first-line therapy,[1] it represents a safer option with reasonable efficacy as salvage therapy. A

Table 2. Clinical Characteristics Between Patients With or Without Recurrent ILD

Characteristics	ILD Recurrence (n = 6)	No ILD Recurrence (n = 11)	*p* Value
Age, y			
Median (range)	69 (47-90)	66 (50-85)	0.73
Sex			0.42
Female	5 (83)	8 (73)	
Male	1 (17)	3 (27)	
Smoking			0.24
Nonsmoker	6 (100)	8 (73)	
Current or former	0	3 (27)	
EGFR mutation			0.38
Exon 19 deletion	3 (50)	6 (54)	
Exon 21 L858R	3 (50)	5 (46)	
PS			0.09
0-1	3 (50)	10 (91)	
2	3 (50)	1 (9)	
Line of osimertinib before first episode of ILD			0.07
1	2 (33)	9 (82)	
>1	4 (67)	2[a] (18)	
Prior radiotherapy to chest or thoracic spine			0.11
Yes	2 (33)	0	
No	4 (67)	11 (100)	
Grade of previous episode of ILD			0.38
2	3 (50)	6 (55)	
3-4	3 (50)	5 (45)	
Rechallenge agent			**0.0498**
Osimertinib	5 (83)	3 (27)	
Erlotinib	1 (17)	8 (73)	

Note: All values are n (%) unless otherwise specified.
[a]Remark: one patient received osimertinib as fifth-line treatment for lung cancer.
ILD, interstitial lung disease; PS, performance status.

Japanese real-world study revealed that more than 60% of patients did not receive further EGFR TKI after development of osimertinib-induced ILD in the first-line setting, indicating that physicians may avoid EGFR TKI rechallenge for fear of ILD recurrence.[10] Avoidance of further EGFR TKI and opting for chemotherapy may potentially compromise the survival outcomes.[11]

The pathogenesis of EGFR TKI-induced ILD is unknown.[12] Possible mechanisms include cell-mediated autoimmune disease or T cell-mediated delayed hypersensitivity.[13] Osimertinib is a pyrimidine-based irreversible EGFR inhibitor, whereas erlotinib is a quinazoline-based reversible EGFR inhibitor. The different molecular structures of the two drugs may have affected the ILD risk. ILD occurs in one-third of patients who received osimertinib in combination with or sequentially after programmed death-ligand 1 blockade therapy[14]; in contrary, no increase in ILD risk was observed with the combination of programmed death-ligand 1 blockade with erlotinib or gefitinib.[15] This evidence supports our study findings that ILD risk may be a drug-specific rather than a class-specific phenomenon.

Limitation of this retrospective study includes limited number of patients with ILD. Nevertheless, our baseline population of close to 1000 patients with osimertinib exposure is a real-life reflection of common oncology clinical practice. The 3.8% incidence of ILD was similar to prior reports.[1,3] Our retrospective analysis was also limited by the heterogeneous diagnostic criteria and management of TKI-related ILD. Not all patients received corticosteroid protection at the time of TKI rechallenge, although the optimal schedule and benefit of corticosteroid in this context remain unclear.

In conclusion, osimertinib rechallenge confers a high risk of ILD recurrence in patients with prior symptomatic osimertinib-induced ILD. The mortality rate is significantly high, thus osimertinib rechallenge should be avoided, whereas erlotinib rechallenge is safer and associated with reasonable treatment efficacy.

CRediT Authorship Contribution Statement

Molly S. C. Li: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Validation, Visualization, Writing—original draft.

Kirsty W. C. Lee: Data curation, Formal analysis, Investigation, Project administration, Supervision, Validation, Writing—review and editing.

Kevin K. S. Mok: Formal analysis, Investigation, Project administration, Writing—review and editing.

Herbert H. F. Loong: Investigation, Writing—review and editing.

K. C. Lam: Investigation, Writing—review and editing.

Florence S. T. Mok: Investigation, Writing—review and editing.

Landon L. Chan: Formal analysis, Investigation, Writing—review and editing.

Y. M. Lau: Investigation, Writing—review and editing.

K. P. Chan: Investigation, Writing—review and editing.

Joyce T. Y. Ng: Investigation, Writing—review and editing.

Wesley K. Y. Wong: Investigation, Writing—review and editing.

Benjamin H. W. Lam: Investigation, Writing—review and editing.

Allen C. C. Chen: Investigation, Writing—review and editing.

Matthew M. P. Lee: Investigation, Writing—review and editing.

Olivia H. Chen: Investigation, Writing—review and editing.

Tony S. K. Mok: Resources, Supervision, Writing—review and editing.

Disclosure

The authors declare no conflict of interest.

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.2024.100648.

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