


## ORIGINAL ARTICLE

# Different incidence of interstitial lung disease according to different kinds of EGFR-tyrosine kinase inhibitors administered immediately before and/or after anti-PD-1 antibodies in lung cancer

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## Keywords

Afatinib; EGFR-TKI; ILD; nivolumab; osimertinib.

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Received: 28 January 2019;

Accepted: 19 February 2019.

doi: 10.1111/1759-7714.13039

Thoracic Cancer **10** (2019) 975–979

## Abstract

**Background:** The aim of our study was to retrospectively assess the incidence of interstitial lung disease (ILD) related to EGFR-tyrosine kinase inhibitor (TKI) treatment immediately before and/or after the administration of a PD-1 antibody.

**Methods:** We analyzed the data of 26 patients who underwent treatment with EGFR-TKIs immediately before and/or after the administration of an anti-PD-1 antibody.

**Results:** Four out of the 26 patients developed ILD during EGFR-TKI treatment: three patients during the administration of osimertinib immediately after, and one during afatinib immediately before treatment with an anti-PD-1 antibody. Three of 12 patients who underwent EGFR-TKI therapy immediately after anti-PD-1 antibody treatment experienced osimertinib-induced ILD. ILD was not observed in the five patients administered an anti-PD-1 antibody followed by first or second-generation EGFR-TKIs.

**Conclusion:** ILD was observed in the treatment sequence of an anti-PD-1 antibody followed by osimertinib, but not with first or second-generation EGFR-TKIs.

## Introduction

EGFR-tyrosine kinase inhibitors (TKIs) have contributed significantly to improving the prognosis of patients with advanced non-small cell lung cancer (NSCLC) harboring *EGFR* mutations. However, drug-induced interstitial lung disease (ILD) has been recognized as a serious potential side effect. Recently, Ahn *et al.* reported that the combination of osimertinib, a third-generation EGFR-TKI, and durvalumab, an anti-PD-L1 immune checkpoint inhibitor (ICI), is not appropriate for patients with advanced *EGFR* mutation-positive NSCLC, because of the increased incidence of ILD.<sup>1</sup> Although 34 patients were treated with this combination therapy in their study, ILD was observed in 38% of all patients and 60% of Japanese patients.<sup>1</sup> Moreover, recent reports also have described an increased incidence of ILD in patients administered osimertinib immediately after nivolumab, an anti-PD-1 antibody.<sup>2–4</sup> It

remains unknown whether the use of gefitinib or erlotinib, which are first-generation EGFR-TKIs (1st TKIs), or afatinib, a second-generation EGFR-TKI (2nd TKI), increases the incidence of ILD in patients who have received anti-PD-1/PD-L1 antibody therapy immediately prior to TKIs. In addition, little is known about the incidence of ILD related to EGFR-TKIs when they are administered immediately before anti-PD-1/PD-L1 antibody therapy. We retrospectively examined the incidence of ILD associated with EGFR-TKI treatment both immediately before and after nivolumab therapy.

## Methods

### Patient selection

We selected patients with cytologically or histologically proven advanced *EGFR* mutation-positive NSCLC (stage

III or IV, or recurrence after surgical resection) aged > 20 years who received EGFR-TKIs immediately before and/or after nivolumab or pembrolizumab treatment. Exclusion criteria were serious situations, such as concomitant serious illness, uncontrolled angina pectoris, heart failure, or uncontrolled diabetes mellitus. The institutional ethics committee of the Saitama Medical University International Medical Center approved this study.

## Results

### Patient demographics

Thirty-one patients with advanced *EGFR* mutation-positive NSCLC were treated with nivolumab at Saitama Medical University International Medical Center from January 2016 to August 2018. Five patients were excluded because they were not administered EGFR-TKIs immediately before or after nivolumab treatment. A total of 26 patients (10 men, 16 women; median age 69 years, range: 44–80) were included in the analysis. Table 1 shows the patient characteristics and the specific sequence of chemotherapeutic agents administered. Eight patients (31%) had a smoking history; 23 had stage IV disease, 1 had stage III; and 2 patients experienced recurrence after surgical resection. Nine (34.6%) patients had an Eastern Cooperative Oncology Group performance status (PS) of 0, six (23.1%) patients a PS of 1, eight (30.7%) patients a PS of 2, and three (11.5%) patients a PS of 3. All tumors had adenocarcinoma (AC) histology. *EGFR* mutation analysis showed that 14 (53.8%) patients had exon 19 deletions, 10 (38.5%) patients had L858R mutations (exon 21), and 2 (7.7%) had other mutations. Only two (7.7%) patients had a history of thoracic radiation therapy, and no patients had pre-existing interstitial lung disease.

### Occurrence of interstitial lung disease

Four patients (15.3%) developed ILD during EGFR-TKI therapy (cases 2, 4, 8, and 15). The detailed characteristics of these patients are presented in Table 2. Three of the four developed ILD during the administration of osimertinib after nivolumab therapy (cases 2, 4, and 15), and the remaining patient during afatinib before nivolumab (case 8). The radiological patterns of ILD were hypersensitive pneumonitis (HP) in one patient and cryptogenic organizing pneumonia (COP) in three patients (Table 2, Fig 1). All patients were treated with steroid therapy after discontinuation of EGFR-TKI therapy, which resulted in ILD resolution in all.

The frequency of ILD occurrence according to the chemotherapy sequence pattern of EGFR-TKI and anti-PD-1 antibody administration was then analyzed. Patients were

categorized into groups as follows: group 1 (cases 2, 4, 13, 19, and 21) were administered EGFR-TKIs after anti-PD-1 antibodies; group 2 (cases 1, 5, 6, 8, 9, 10, 14, 16, 17, 18, 20, 22, 23, and 25) were administered EGFR-TKIs before anti-PD-1 antibodies; and group 3 (cases 3, 7, 11, 12, 15, 24, and 26) were administered EGFR-TKIs both before and after anti-PD-1 antibodies. The five patients in group 1 were administered osimertinib (2), erlotinib (2), and gefitinib (1). The 14 patients in group 2 were administered afatinib (5), erlotinib (4), gefitinib (1), and osimertinib (3). In group 3, three patients were sequentially administered afatinib before nivolumab followed by osimertinib; two were administered erlotinib before nivolumab followed by osimertinib; and two patients were administered osimertinib before nivolumab followed by either erlotinib or afatinib. Twenty-one patients were administered EGFR-TKIs immediately before nivolumab: gefitinib (1), erlotinib (5), afatinib (9), and osimertinib (6). Of these 21 patients, ILD was observed in one patient (4.7%) who was administered afatinib. Twelve patients were treated with the EGFR-TKIs immediately after nivolumab; gefitinib (1), erlotinib (2), afatinib (2), and osimertinib (7). Three (25%) of these patients experienced ILD; osimertinib was administered to all. ILD was not observed in the five patients who were treated with 1st or 2nd TKIs, but ILD was observed in three of the seven patients (42.8%) administered osimertinib.

## Discussion

This is the first study to investigate the incidence of ILD related to a third-generation EGFR-TKI administered immediately before and/or after nivolumab in patients with advanced *EGFR* mutation-positive NSCLC. We found that 1st and 2nd TKIs were not associated with the development of ILD in the treatment sequence of nivolumab followed by EGFR-TKIs, whereas osimertinib, a third-generation TKI, was. Moreover, the administration of an EGFR-TKI immediately before nivolumab therapy was not associated with the development of ILD, even if osimertinib was administered. Although it remains unclear why the synergistic effect differs between nivolumab and EGFR-TKIs of different generations, we believe that 1st or 2nd TKIs should be used preferentially in regimens that prescribe EGFR-TKIs immediately after nivolumab. We also confirmed that the administration of nivolumab is tolerable when immediately following any EGFR-TKI, including osimertinib, without increasing toxicity.

In the present study, the development of ILD was observed in patients who underwent osimertinib immediately after nivolumab therapy, consistent with previous reports.<sup>2–4</sup> Kotake *et al.* also reported that ILD was observed in four out of 19 (21%) patients administered osimertinib and three of

**Table 1** Patient demographics

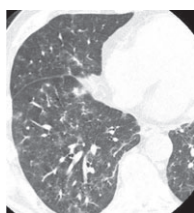
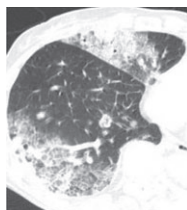
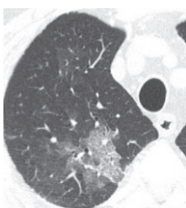
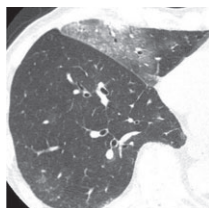
No. of pts	Age	Gender	Smoking history	EGFR mutation	PS	Staging	Radiation prior to ICI	Treatment line of ICI	EGFR-TKI sequence just before or after ICI			ILD
									Drug before ICI	ICI	Drug after ICI	
Case 1	53	F	No	L858R	0	IV	No	6	Afatinib	Nivolumab	Pemetrexed	No
Case 2	57	M	Yes	Del 19	1	IV	No	6	Pemetrexed	Nivolumab	Osimertinib	Yes
Case 3	57	F	No	Del 19	2	IV	No	3	Afatinib	Nivolumab	Osimertinib	No
Case 4	76	M	Yes	Del 19	1	IV	No	6	Docetaxel	Nivolumab	Osimertinib	Yes
Case 5	64	F	No	Del 19	0	IV	No	4	Gefitinib	Nivolumab	none	No
Case 6	69	F	No	Del 19	2	IV	No	4	Afatinib	Nivolumab	none	No
Case 7	75	M	Yes	Del 19	2	IV	No	6	Afatinib	Nivolumab	Osimertinib	No
Case 8	79	F	No	L858R	1	IV	No	6	Afatinib	Nivolumab	none	Yes
Case 9	70	F	Yes	L858R	2	IV	No	3	Afatinib	Nivolumab	none	No
Case 10	62	F	No	Del 19	0	IV	No	3	Afatinib	Nivolumab	DTX/RAM	No
Case 11	51	M	No	Del 19	3	IV	No	3	Erlotinib	Nivolumab	Osimertinib	No
Case 12	71	F	No	L858R	0	IV	No	5	Osimeertinib	Nivolumab	Erlotinib+Bev	No
Case 13	80	M	No	L858R	0	IV	No	2	Pemetrexed	Nivolumab	Gefitinib	No
Case 14	75	F	No	Del 19	0	IV	No	5	Osimeertinib	Nivolumab	none	No
Case 15	73	M	No	L858R	3	Rec	No	3	Erlotinib	Nivolumab	Osimeertinib	Yes
Case 16	44	M	No	Del 19	1	IV	Yes	7	Osimeertinib	Nivolumab	Pemetrexed	No
Case 17	59	M	Yes	L858R	1	III	No	3	Afatinib	Nivolumab	none	No
Case 18	73	F	No	L858R	0	IV	No	5	Osimeertinib	Nivolumab	DTX/RAM	No
Case 19	48	F	Yes	Del 19	3	IV	Yes	7	Pemetrexed	Nivolumab	Afatinib	No
Case 20	77	M	Yes	Del 19	2	IV	No	4	Erlotinib	Nivolumab	DTX/RAM	No
Case 21	70	M	Yes	Del 19	2	IV	No	5	Pemetrexed	Nivolumab	Erlotinib+Bev	No
Case 22	69	F	No	Del 19	0	IV	No	4	Erlotinib+Bev	Nivolumab	none	No
Case 23	67	F	No	L858R	1	IV	No	4	Osimeertinib	Nivolumab	none	No
Case 24	66	F	No	L858R	2	IV	No	5	Osimeertinib	Pembrolizumab	Afatinib	No
Case 25	79	F	No	Del 19	2	Rec	No	8	Erlotinib+Bev	Pembrolizumab	None	No
Case 26	70	F	No	L858R	0	IV	No	4	Afatinib	Nivolumab	Osimeertinib	No

Bev, bevacizumab; Del 19, exon 19 deletion; DTX, docetaxel; F, female; ICI, immune checkpoint inhibitor; ILD, interstitial lung disease; L858R, exon 21 L858R; M, male; No. of pts., number of patients; PS, performance status; RAM, ramucirumab; Rec, recurrence after operation; TKI, tyrosine kinase inhibitor.

**Table 2** ILD patient characteristics

Factors	Case 2	Case 4	Case 8	Case 15
Age (years)/Gender	57/Male	76/Male	79/Female	73/Male
Interval between the final Niv and initiation of EGFR-TKIs/interval between final EGFR-TKIs and the initiation of Niv	20 days	5 months	2 days	15 days
CTCAE grade of ILD	3	2	2	2
ILD-induced EGFR-TKI	Osimertinib	Osimertinib	Afatinib	Osimertinib
Interval from final EGFR-TKI to onset of ILD	1 month	4 months	1 month	1 month
Radiological pattern of ILD	HP pattern	COP pattern	COP pattern	COP pattern
Treatment for ILD	Corticosteroid	Corticosteroid	Corticosteroid	Corticosteroid
Outcome of ILD	Recovery	Recovery	Recovery	Recovery

COP, cryptogenic organizing pneumonia; CTCAE, Common Terminology Criteria for Adverse Events; HP, hypersensitive pneumonitis; ILD, interstitial lung disease; Niv, nivolumab; TKI, tyrosine kinase inhibitor.

**Case 2****Case 8****Case 4****Case 15**

**Figure 1** Radiological patterns of interstitial lung disease show hypersensitive pneumonitis in one patient (case 2) and cryptogenic organizing pneumonia in three patients (cases 4, 8, and 15).

these four patients were treated with osimertinib immediately after nivolumab.<sup>2</sup> Although the detailed mechanism remains unknown, prior nivolumab treatment may increase the risk of osimertinib-induced ILD. In a previous study, osimertinib-induced ILD was observed in 7.3% of Japanese patients,<sup>5</sup> differing from the 42.8% incidence in our study. A recent trial indicated that nivolumab as an anti-PD-1 antibody continues to bind to the PD-1 on T cells for approximately two months.<sup>6</sup> The synergistic effect of osimertinib and nivolumab may contribute to the high incidence of ILD. Recently, Kato *et al.* reported that nivolumab-induced ILD was observed in 7.2% of patients, with radiological imaging showing a pattern of organized pneumonia or nonspecific interstitial pneumonia without traction bronchiectasis.<sup>7</sup> The radiological findings of ILD in our study also revealed a pattern of organized pneumonia. However, our results suggest that the sequential administration of nivolumab followed by 1st or 2nd TKIs

within a short interval was not linked to the development of ILD. We speculate that the mechanism of ILD development is different between 1st/2nd TKIs and osimertinib, and the activation of T-cell effects by ICIs may upregulate this effect synergistically to cause ILD with osimertinib but not 1st or 2nd TKIs.

In conclusion, the administration of 1st or 2nd TKIs immediately after nivolumab did not increase the risk of the development of ILD, but ILD did occur when nivolumab was followed by osimertinib. Sequential therapy of any EGFR-TKI immediately before nivolumab is acceptable without causing ILD. However, our analysis was retrospective with a limited sample size, which may bias the results of our study. Further investigation with a large-scale prospective study is needed to confirm our results.

## Disclosure

OY, AM, KK, and HK received research grants and speaker honorarium from Boehringer Ingelheim Company.

HK received research grants and speaker honorarium from AstraZeneca Company.

All remaining authors report no conflict of interest.

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