Original Article

Impact of docetaxel plus ramucirumab therapy on interstitial lung disease in recurrent advanced non-small cell lung cancer patients

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Background: Few studies have examined the safety and efficacy of docetaxel/ramucirumab (DOC/RAM) therapy in advanced non-small cell lung cancer (NSCLC) complicated by interstitial lung disease (ILD). Given the potential of vascular endothelial growth factor inhibitors to prevent drug-induced pneumonia, we aimed to clarify the role of this therapy in NSCLC with ILD.

Methods: This retrospective observational study evaluated the incidence of ILD in stage IV NSCLC patients receiving DOC/RAM therapy at our institution, stratified by ILD status. We also assessed the efficacy of this treatment. The primary objective was to investigate the incidence of ILD, while secondary objectives included evaluating the objective response rate (ORR), progression-free survival (PFS), and overall survival (OS), stratified by ILD status.

Results: Among patients with pre-existing ILD, 7 out of 28 (25%) developed DOC/RAM-induced interstitial pneumonia, while none of the 40 patients without pre-existing ILD developed this condition (P<0.001). Comparing historical controls (DOC only) with the DOC/RAM group, RAM did not significantly alter the incidence of interstitial pneumonia (P=0.33). There were no significant differences in ORR, PFS, or OS between patients with and without ILD. Subgroup analysis of smokers showed a non-significant trend toward worse survival in those with pre-existing ILD (P=0.20).

Conclusions: DOC/RAM therapy significantly increased the incidence of interstitial pneumonia in NSCLC patients with pre-existing ILD but did not significantly affect efficacy outcomes such as ORR, PFS, or OS.

Keywords: Recurrent advanced non-small cell lung cancer (recurrent advanced NSCLC); retrospective analysis; interstitial lung disease (ILD); docetaxel/ramucirumab (DOC/RAM); real-world clinical setting

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Introduction

Lung cancer is the leading cause of cancer-related death worldwide (1). Although its treatment has made great strides, especially with the introduction of immune checkpoint inhibitor (ICI) therapy, recurrence remains a significant challenge and requires the use of anticancer agents after second-line therapy. Prior to the introduction of ICI therapy, docetaxel (DOC) was the cornerstone of second-line therapy for non-small cell lung cancer (NSCLC) patients who had received platinum-based combination therapy (2,3). DOC remains an important component of second-line therapy after both ICI and platinum-based combination therapy. In the area of angiogenesis inhibition, agents such as bevacizumab and ramucirumab (RAM) have emerged as important tools, exerting their anticancer effects by inhibiting tumor angiogenesis. RAM is a human IgG1 monoclonal antibody that targets vascular endothelial growth factor receptor-2 (VEGFR-2) (4) and has shown promising results in combination with DOC in stage IV NSCLC patients treated with platinum-based combination therapies, with superior overall survival (OS) compared with DOC alone (5).

Drug-induced interstitial lung disease (ILD) is an increasingly common cause of morbidity and mortality (6). ILD induced by drug therapy for NSCLC is a particularly common and noteworthy concern in the Japanese population (7,8). The pathogenesis of drug-induced lung injury is complex and multifactorial, involving direct cytotoxic effects on pulmonary tissue, increased vascular permeability leading to interstitial edema, and an alveolar proteinosis-like condition (9-11). VEGF inhibitors such as RAM have been shown to suppress increased vascular permeability, protect alveolar epithelial integrity, and mitigate direct cellular injury in the lungs (12,13). The concomitant administration of cytotoxic anticancer drugs and a VEGF inhibitor in lung cancer patients complicated by interstitial pneumonia has been associated with a potential reduction in the frequency of exacerbations of interstitial pneumonia, as demonstrated in a retrospective observational study by Hamada *et al.* (14). In a systematic review of ILD incidence in NSCLC patients in randomized trials, it was reported that VEGF/VEGFR inhibitors significantly reduced the incidence of ILD of all grades with epidermal growth factor receptor tyrosine kinase inhibitors, while no significant reduction in ILD incidence was observed with ICI inhibitors (15).

Pre-existing interstitial pneumonia is a recognized risk factor for drug-induced lung disease during anticancer treatment (16,17). Given RAM's role as a VEGFR inhibitor, it is possible that, when combined with DOC, there is a reason to consider its potential to reduce ILD exacerbations. The REVEL study (5) found no significant difference in the incidence of ILD between the RAM and placebo groups. This suggests that adding RAM to DOC therapy may not substantially affect the incidence of ILD compared to DOC alone. However, since this trial excluded patients with pre-existing interstitial pneumonia, the impact of adding RAM in patients with ILD remains unknown. Few studies have examined the safety and efficacy of DOC/RAM therapy in NSCLC complicated by ILD. Therefore, we designed a retrospective observational study of patients who received DOC/RAM therapy as second- or later-line therapy at our institution to evaluate the incidence of ILD in stage IV NSCLC patients stratified by ILD status, as well as to assess the efficacy of this treatment modality. We present this article in accordance with the STROBE reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-460/rc).

Highlight box

Key findings

- Among patients with pre-existing interstitial lung disease (ILD), docetaxel/ramucirumab (DOC/RAM) therapy for recurrent advanced non-small cell lung cancer (NSCLC) was associated with a higher risk of ILD exacerbation, with a significant portion developing DOC/RAM-induced interstitial pneumonia.
- No cases of DOC/RAM-induced interstitial pneumonia were observed in patients without pre-existing ILD.
- The highest incidence of interstitial pneumonia was seen in patients with a history of drug-induced interstitial pneumonia.

What is known and what is new?

- Vascular endothelial growth factor receptor inhibitors like RAM can help suppress drug-induced pneumonia.
- This study adds that while DOC/RAM therapy is effective for NSCLC patients, it increases the risk of ILD exacerbation.
- The risk is particularly high in patients with a history of drug-induced interstitial pneumonia.

What is the implication, and what should change now?

- These findings suggest the need for careful monitoring of NSCLC patients with ILD undergoing DOC/RAM therapy.
- It is crucial to assess the history of drug-induced interstitial pneumonia before starting treatment.
- Consideration of alternative treatments or closer monitoring to manage the higher risk of ILD exacerbation is recommended.

Methods

Study design and patients

We retrospectively analyzed consecutive patients with recurrent advanced NSCLC who received intravenous DOC 60 mg/m^2 plus intravenous RAM 10 mg/kg every 3–4 weeks, after platinum-doublet chemotherapy, at Fukuoka University Hospital between August 2016 and February 2024. The primary objective of this study was to investigate the incidence of ILD in stage IV NSCLC patients stratified by ILD status. The secondary objectives were to evaluate the objective response rate (ORR), progression-free survival (PFS), and OS stratified by ILD status. Patient data, including age, sex, performance status (PS), smoking history, histological tumor type, tumor stage, results of programmed cell death ligand 1 (PD-L1) (22C3) assays, presence of driver mutations, and history of ICI administration, were retrieved from medical records. The clinical stages of all patients were classified according to the eighth edition of the Tumor, Node, and Metastasis Classification of Malignant Tumors (18). This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and received approval from Fukuoka University Medical Ethics Review Board (No. H23-12-005). Because this was a retrospective study, the requirement for informed consent was waived, and the opt-out option was facilitated through the official website [available at: https://fukuoka.bvits.com/rinri/publish.aspx (last accessed on April 20, 2024)].

Study assessment

In this study, it was difficult to strictly determine whether the onset of ILD was spontaneous, an exacerbation of pre-existing ILD, or caused by the drug itself. Therefore, ILD that occurred after DOC/RAM administration was counted as DOC/RAM-induced interstitial pneumonia. The reported incidence of DOC-induced interstitial pneumonia in NSCLC patients ranges from 2.9% to 5.3% (19-21). Retrospective analyses indicate a higher incidence in patients with pre-existing ILD, ranging from 14.3% to 25.9% (22-24). In our study, we examined the incidence of DOC/RAM-induced interstitial pneumonia, stratified by ILD status. The incidence of ILD in patients with and without pre-existing ILD was compared to historical control data for DOC-induced ILD. Additionally, to determine whether RAM affects the incidence of ILD, we compared the incidence of ILD in the DOC/RAM group to the historical incidence of ILD in the DOC group.

Lung cancer response was assessed using the new guidelines for solid cancer response assessment (RECIST guidelines: revised version 1.1) (25). Each physician evaluated adverse events according to the Common Terminology Criteria for Adverse Events version 5.0 (26). OS was determined as the time between the initiation of DOC/RAM therapy and the date of death. PFS was defined as the date of the commencement of DOC/RAM therapy to the date of disease progression or death from any cause. The cut-off date for data collection was April 20, 2024.

In this study, pre-existing ILD was defined as interstitial pneumonia diagnosed based on clinical features and high-resolution computed tomography (HRCT) revealing interstitial shadows before DOC/RAM therapy. Causative diseases, such as collagen diseases, were investigated when possible, and cases without a known cause were managed as idiopathic interstitial pneumonia. The classification included collagenous interstitial pneumonia, drug-induced interstitial pneumonia from prior treatment, and radiation pneumonitis, while excluding infections, pneumoconiosis, and sarcoidosis.

All patients underwent HRCT before starting DOC/RAM therapy, with ILD presence evaluated by both a pulmonologist and a radiologist. Detailed interviews were conducted regarding new medications, environmental changes, and dust exposure. The presence of ILD was confirmed at the time of NSCLC diagnosis, and the presence of pneumoconiosis and typical sarcoidosis findings were monitored for imaging changes before DOC/RAM therapy. A thorough physical examination was performed to identify the presence of fine crackles on auscultation and other signs suggestive of other potential causes of ILD that may suggest collagen disease, and comprehensive diagnostics including blood tests [blood count, leukocyte fraction, C-reactive protein (CRP), Krebs von den Lungen-6 (KL-6), surfactant protein D (SP-D), B-type natriuretic peptide (BNP), and blood gas analysis], echocardiograms, and infection differentiation tests (sputum examination, urinary antigen, β-D-glucan, cytomegalovirus antigenemia) were performed. Bronchoalveolar lavage (BAL) was conducted via bronchoscopy when possible.

Statistical analysis

The incidence of DOC/RAM-induced interstitial pneumonia was compared among patients with and without a history of ILD, as well as historical controls. Incidence

rates with and without concurrent steroid use during DOC/RAM therapy were also analyzed. Chi-squared tests assessed differences in incidence rates, while logistic regression evaluated the impact of adding RAM on ILD incidence. Patient characteristics and ORR were also compared using Chi-squared tests. PFS and OS were assessed using the Kaplan-Meier method and compared using the log-rank test. All P values were two-sided, with the threshold for statistical significance set at P<0.05. All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria) (27).

Results

Characteristics of the study population

The clinicopathological characteristics of the 68 participants in the study are summarized in *Table 1*. The median age was 66 years, ranging from 39 to 76 years. Most of the patients were male (51, 75%), and all had a PS of 0 or 1. Additionally, 49 patients (72%) were current or former smokers. The predominant pathology was adenocarcinoma, accounting for 69% of cases, and 37 patients (54%) presented with stage IV disease. This was followed by 18 patients (26%) with post-operative recurrence. Driver mutations were identified in 20 patients (29%). Upon evaluating the PD-L1 tumor proportion score (TPS), it was found that 39 patients (57%) had a TPS of ≥1%. Prior to receiving DOC/RAM as a second-line or subsequent therapy, 52 patients (76%) had been treated with ICIs. Of the patients studied, 28 had ILD before starting DOC/RAM therapy, while 40 did not. Patient characteristics that differed significantly between the ILD and non-ILD groups were pathology and driver gene mutations, and significant trends were gender and smoking history. The ILD group included fewer women, fewer non-smokers, higher rates of recurrence after chemoradiotherapy, a larger proportion of non-adenocarcinomas, fewer driver mutations, and a noticeable disparity in patient distribution between the two groups.

Pre-existing ILD characteristics

Before undergoing DOC/RAM therapy, out of the 28 patients with pre-existing ILD, there were 8 cases of interstitial pneumonia, 10 cases of drug-induced pneumonia, and 12 cases of radiation-induced pneumonia. Additionally, one case involved both interstitial pneumonia and drug-induced pneumonia, while another case involved radiation-induced pneumonia along with drug-induced pneumonia. All patients had no symptoms and only imaging findings of interstitial shadows. No cases exhibited a radiographically apparent usual interstitial pneumonia pattern. The interstitial pneumonia was classified as early stage, and both drug-induced and radiation-induced pneumonitis were considered stable. For details on 8 cases of pre-existing interstitial pneumonia, 10 cases of drug-induced pneumonia and 12 cases of radiation pneumonia, please refer to Tables S1-S3.

DOC/RAM-induced interstitial pneumonia

Tables 2,3 show data on interstitial pneumonia induced by DOC/RAM therapy. Within the group of patients with pre-existing ILD, 7 out of 28 (25%) developed DOC/RAM-induced interstitial pneumonia. The severity was graded as follows: grade 1 in one patient, grade 2 in three patients, grade 3 in one patient, and grade 4 in two patients. In contrast, none of the 40 patients without pre-existing ILD developed this condition. The overall incidence rate among all 68 patients was 10% (7 cases). To compare the incidence of DOC/RAM-induced interstitial pneumonia between patients with and without pre-existing ILD, we performed a Chi-squared test, which indicated a statistically significant difference (P<0.001). When comparing the historical control group (DOC only) with the study group (DOC/RAM), another Chi-squared test showed no significant difference in incidence (P=0.38). Logistic regression analysis showed that RAM did not significantly alter the incidence of interstitial pneumonia (P=0.33). These results suggest that RAM does not reduce the incidence of interstitial pneumonia in patients with pre-existing ILD. The difference in incidence with and without concurrent steroid use during DOC/RAM therapy is not significant: 3 out of 8 patients using steroids and 4 out of 20 patients not using steroids developed interstitial pneumonia (P=0.37). This suggests that steroids also do not reduce the incidence.

Breaking down the incidence within the ILD subgroup, of the eight patients with pre-existing interstitial pneumonia, one experienced grade 1 and another grade 4 interstitial pneumonia. Of the 10 patients with drug-induced pneumonia, two had grade 2, one had grade 3, and two had grade 4. Of the 12 patients with radiation pneumonia,

Table 1 Patient characteristics

Factors	Total (n=68)	Pre-ILD		P value
		Yes (n=28)	No (n=40)	
Age (years), median [range]	66 [39–76]	66 [44–75]	66 [39–76]	0.80
Gender				0.09
Male	51	23	28	
Female	17	5	12	
Performance status				0.23
0	33	11	22	
1	35	17	18	
Smoking history				0.05
Yes	49	24	25	
No	19	4	15	
Pathology				0.007
Adenocarcinoma	47	14	33	
Non-adenocarcinoma	21	14	7	
Stage				0.14
III/IV	2/37	2/11	0/26	
Recurrence (post-operation/post-CRT)	18/11	4/11	14/0	
Treatment line				0.62
2nd	33	15	18	
3rd or later	35	13	22	
PD-L1 TPS (%)				0.46
Positive	39	18	21	
Negative or unknown	29	10	19	
Driver gene mutation				0.03
Positive	20	5	15	
Negative or unknown	48	23	25	
ICI treatment history				0.56
Yes	52	20	32	
No	16	8	8	
Median period since last ICI administration (month)	1.8	2.5	1.4	0.23

Pre-ILD, pre-existing interstitial lung disease; CRT, chemoradiotherapy; PD-L1, programmed cell death ligand 1; TPS, tumor proportion score; ICI, immune checkpoint inhibitor.

one developed grade 2 interstitial pneumonia. In terms of treatment history, ICIs were administered to 2 out of the 8 patients with pre-existing interstitial pneumonia, 8 out of the 10 with drug-induced pneumonia, and all 12 patients with radiation pneumonia.

Table 4 provides information on seven cases of DOC/RAM-induced interstitial pneumonia. The onset of the condition occurred during cycle 1 for three patients, and

during cycles 2, 4, 5, and 6 for one patient each. Prior to starting DOC/RAM therapy, three patients were treated with steroids. The median duration from ILD diagnosis to the development of DOC/RAM-induced interstitial pneumonia was 7.9 months. The outcomes varied: three cases improved, two remained stable, two deteriorated, and two resulted in fatalities. All cases in which the time between the onset of pre-existing ILD and the initiation of DOC/RAM therapy was less than one month developed DOC/RAM-induced interstitial pneumonia during cycle 1, emphasizing that earlier development corresponds to worse outcomes (2 out of 3 patients died).

Figure 1 displays chest CT images of DOC/RAM-induced interstitial pneumonia. The top row shows the baseline condition or the initial development of drug-induced interstitial pneumonia. The middle row shows the status of the lungs prior to the administration of DOC/RAM, with evidence of drug-induced interstitial pneumonia visible in the pre-dose CT scans for three cases. The bottom-row images illustrate DOC/RAM-induced interstitial pneumonia at its onset.

Table 2 Interstitial pneumonia induced by docetaxel plus ramucirumab therapy

Category	Total (n=68)	Pre-ILD		P value
		Yes (n=28)	No (n=40)	
Grade 1	1	1	0	–
Grade 2	3	3	0	–
Grade 3	1	1	0	–
Grade 4	2	2	0	–
Total	7	7	0	–
Incidence rate (%) [95% CI]	10 [4–20]	25 [11–45]	0 [0–9]	<0.001

Pre-ILD, pre-existing interstitial lung disease; CI, confidence interval.

Treatment administration status and discontinuation reasons

Table 5 presents the treatment administration status for 68 patients. Currently, only two patients remain on DOC/RAM therapy, while 66 have discontinued it. The main reasons for discontinuation were disease progression and adverse events. Within the ILD group, out of 26 patients who stopped treatment, 12 did so due to adverse events. Notably, 7 of these cases were specifically due to DOC/RAM-induced interstitial pneumonia.

Efficacy according to the pre-existing ILD

The tumor response to DOC/RAM therapy was observed in 6 out of 28 patients in the ILD group, resulting in a response rate of 21% [95% confidence interval (CI): 8–41%]. In the non-ILD group, 13 out of 40 patients exhibited tumor response, leading to a response rate of 33% (95% CI: 19–49%). There was no significant difference between the two groups (P=0.41). The median number of DOC/RAM therapy cycles was four and six for the ILD and non-ILD groups, respectively.

Among the 68 patients, 61 PFS events (90%) and 49 OS events (72%) occurred over the median follow-up period of 12.9 months to the time of analysis. *Figure 2* presents the PFS and OS of patients with recurrent advanced NSCLC receiving DOC/RAM, categorized by pre-existing ILD. The median PFS was 4.6 months, and the median OS was 9.7 months in the ILD group. In contrast, the non-ILD group showed a PFS of 6.0 months and an OS of 14.2 months. The differences in PFS (P=0.50) and OS (P=0.44) were not significant between patients with and without ILD, indicating the consistent but limited efficacy of DOC/RAM therapy regardless of ILD status.

Table 3 Interstitial pneumonia induced by docetaxel plus ramucirumab therapy according to pre-ILD type

Pre-ILD type	History of ICI administration (n)	Grade				Incidence rate (%)
		1	2	3	4	
Pre-existing interstitial pneumonia (n=8)	2	1	0	0	1	25
Drug-induced pneumonia (n=10)	8	0	2	1	2	50
Radiation pneumonitis (n=12)	12	0	1	0	0	8

One case involved both interstitial pneumonia and drug-induced pneumonia. Another case involved radiation-induced pneumonia along with drug-induced pneumonia. Pre-ILD, pre-existing interstitial lung disease; ICI, immune checkpoint inhibitor.

Table 4 Details of interstitial pneumonia cases induced by DOC/RAM therapy

Case	Age (years)	Gender	Pre-ILD type	Cycle	Grade at onset	Steroid administration maximum dose	Time from onset of ILD to exacerbation (months)	Steroids at the start of DOC/RAM	Outcome
1	66	Female	Drug-induced pneumonia B1	1	2	PSL 40 mg	0.9	No medication	Improved
2	64	Male	Drug-induced pneumonia B2	2	2	No medication	10.3	No medication	Improved
3	72	Male	Pre-existing interstitial pneumonia A3	5	1 (enlargement of interstitial shadows)	No medication	47.5	No medication	No change
4	66	Male	Radiation pneumonitis C7	6	2	PSL 30 mg	11.4	PSL 2.5 mg	No change
5	69	Male	Drug-induced pneumonia B7	4	3	PSL 60 mg	7.9	PSL 5 mg	Improved
6	44	Male	Drug-induced pneumonia B8	1	4	mPSL 125 mg	0.2	Dex 3 mg	Progressed
7	67	Male	Pre-existing interstitial pneumonia A8 + drug-induced pneumonia B10	1	4	mPSL 125 mg	0.5	No medication	Progressed

See Tables S1-S3 for detailed numbering and additional information. DOC/RAM, docetaxel plus ramucirumab; pre-ILD, pre-existing interstitial lung disease; PSL, prednisolone; mPSL, methylprednisolone; Dex, dexamethasone.

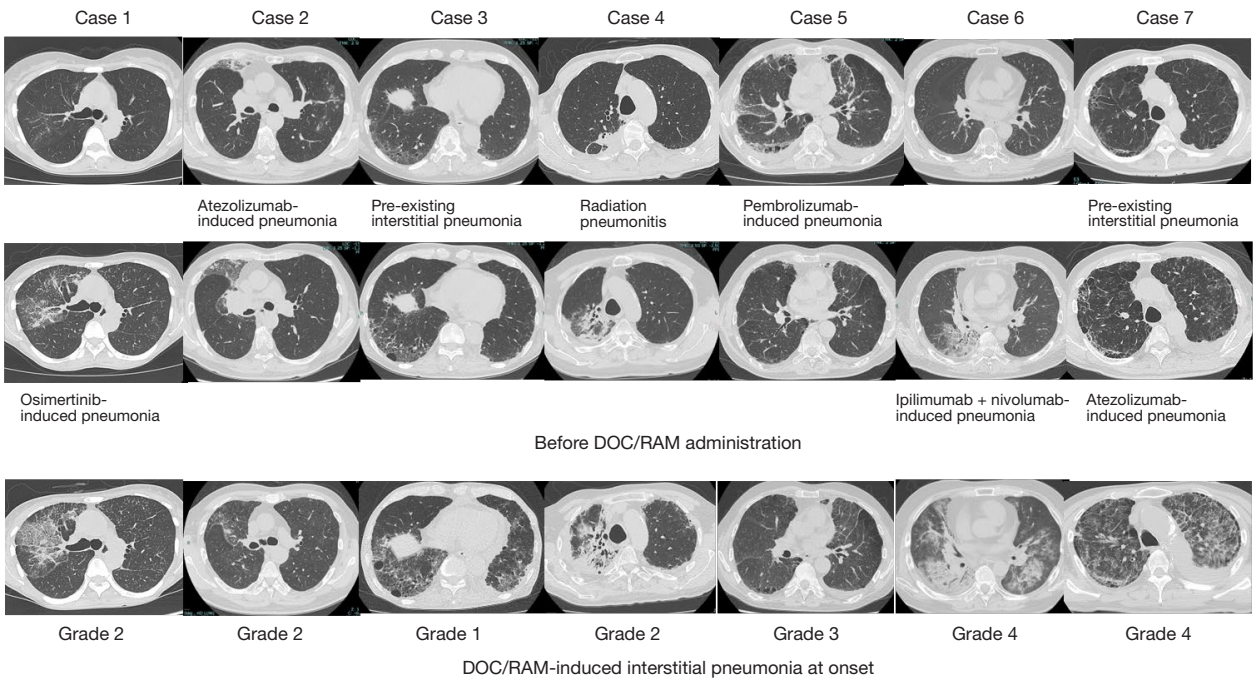

Figure 1 Chest CT images of interstitial pneumonia induced by docetaxel plus ramucirumab therapy. Baseline status: the top-row images either show the baseline lung condition or the onset of drug-induced interstitial pneumonia. Pre-DOC/RAM administration: the middle-row images represent the state of the lungs prior to DOC/RAM treatment, with three cases showing drug-induced interstitial pneumonia on the pre-dose CT scans. Post-DOC/RAM onset: the bottom-row images illustrate DOC/RAM-induced interstitial pneumonia at its onset. DOC/RAM, docetaxel plus ramucirumab; CT, computed tomography.

Table 5 Treatment administration status and reasons for discontinuation of DOC/RAM

DOC/RAM therapy	Pre-ILD	
	Yes (n=28)	No (n=40)
Treatment ongoing	2	0
Treatment discontinuation	26	40
Discontinuation reasons		
Progressive disease	13	28
Adverse events	12 (interstitial pneumonia: 7; severe stomatitis: 1; intestinal perforation: 1; pneumothorax: 1; fatigue: 2)	11 (PS deterioration: 4; anaphylaxis: 1; FN, stomatitis: 1; FN, nausea: 1; dizziness, edema: 1; fatigue, edema: 1; hand-foot syndrome: 1; GI bleeding: 1)
Others	Medical transfer: 1	Lost to follow-up: 1

DOC/RAM, docetaxel plus ramucirumab; pre-ILD, pre-existing interstitial lung disease; PS, performance status; FN, febrile neutropenia; GI, gastrointestinal.

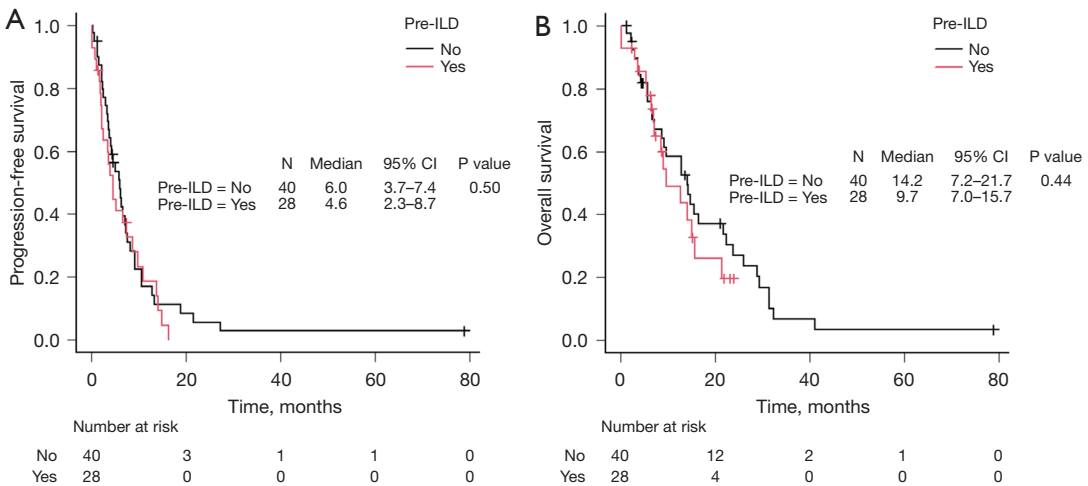

Figure 2 Progression-free survival (A) and overall survival (B) in patients with recurrent advanced non-small cell lung cancer who were treated with docetaxel plus ramucirumab therapy according to the presence of pre-ILD. Pre-ILD, pre-existing interstitial lung disease; N, number; CI, confidence interval.

Subgroup analysis

Given the potential confounding effect of ILD status among smokers, subgroup analyses were conducted to understand its impact. The incidence of ILD was 0% in patients without ILD (0/25 cases) and 25% in patients with ILD (6/24 cases), with a statistically significant P value of <0.01. The ORR was 40% (10/25) and 25% (6/24) in patients without ILD and with ILD, respectively (P=0.36). PFS was 6.0 and 4.6 months in patients without and with ILD, respectively (P=0.31). OS was 14.8 and 9.7 months in patients without and with ILD, respectively (P=0.20). In smokers, pre-existing ILD affects ILD incidence but didn't significantly impact ORR, PFS, or OS. The P value for OS in this subgroup analysis was 0.20, suggesting a non-significant trend toward worse survival (Figure S1).

Subsequent therapies

Table 6 outlines subsequent therapies, all of which consisted of either ICI or monotherapy with cytotoxic anticancer drugs. There was one case of local recurrence during DOC/RAM therapy, which was continued after radiation therapy. Half of the recurrences in the ILD group were managed

Table 6 Subsequent therapy

Progression and therapy	Pre-ILD		Total (n=68)
	Yes (n=28)	No (n=40)	
Progressive disease			
No	4	4	8
Yes	24	36	60
Subsequent therapy regimen			
DOC/RAM[†]	0	1	1
S-1	8	11	19
Pemetrexed	0	5	5
Atezolizumab	3	3	6
Pembrolizumab	1	1	2
Brigatinib	0	1	1
Investigational drug	0	1	1
Best supportive care	12	13	25

[†], DOC/RAM therapy was continued beyond disease progression after radiotherapy for local recurrence. Pre-ILD, pre-existing interstitial lung disease; DOC/RAM, docetaxel plus ramucirumab.

with best supportive care, representing a higher proportion compared with the non-ILD group.

Discussion

This retrospective study investigated the incidence and severity of DOC/RAM-induced interstitial pneumonia in patients with recurrent NSCLC, stratified by the presence or absence of pre-existing ILD. Among the 40 patients without pre-existing ILD, no cases of drug-induced interstitial pneumonia were identified. Conversely, among the 28 patients with pre-existing ILD, 7 (25%) developed DOC/RAM-induced interstitial pneumonia, with severity ranging from grade 1 to 4. Notably, the incidence of DOC/RAM-induced interstitial pneumonia was 25% (2/8) in patients with pre-existing ILD, 50% (5/10) in those with a history of drug-induced interstitial pneumonia, and 8% (1/12) in patients with radiation pneumonitis. These findings highlight the increased risk of developing severe DOC/RAM-induced interstitial pneumonia (grade 3 or higher), particularly in patients with a history of drug-induced interstitial pneumonia.

The occurrence rate of drug-induced interstitial pneumonia resulting from anticancer drug therapy including DOC during the second-line treatment of NSCLC complicated by ILD was reported as 29.2% by Igawa *et al.* (28), aligning closely with the findings of our study.

The incidence of drug-induced interstitial pneumonia due to anticancer drug therapy, including DOC in patients with a history of ICI-induced ILD was reported to be 50% (29). In our study, 8 out of 10 cases of drug-induced interstitial pneumonia were due to ICIs, and 4 out of these 8 cases developed DOC/RAM-induced interstitial pneumonia, which was consistent with the aforementioned report. Specifically, the incidence of drug-induced interstitial pneumonia was noted as 1 out of 4 for DOC and 2 out of 4 for DOC/RAM. Another report highlighted three cases of interstitial pneumonia attributed to DOC/RAM following the onset of immune-related ILD due to nivolumab (30). These findings emphasize the importance of close monitoring of drug-induced interstitial pneumonia in patients receiving DOC/RAM therapy, especially those with a history of ICI-induced ILD. While a prior study indicated the incidence of ICI-related ILDs in patients with a history of radiation pneumonitis as 26.5% (31), all patients with a history of ICI treatment in our study developed radiation pneumonitis. Notably, only one case of DOC/RAM-induced interstitial pneumonia was documented among patients with radiation pneumonitis in our study.

There are significant differences in patient backgrounds depending on ILD status in our study. It has been reported that smoking is an important risk factor for drug-induced ILD, with a higher prevalence in males, potentially explaining the higher frequency of reports among men (32). Controlling for smoking history was crucial as it could isolate the direct impact of ILD on OS. The subgroup analysis, which indicated a trend (P=0.20) towards ILD status affecting OS, underscored the need for further investigation. Although the trend was not statistically significant, it suggested that ILD could potentially influence OS rates among smokers.

It is unlikely that the onset of ILD in our study was a delayed effect of prior ICI treatment, because the proportion of patients with a history of ICI treatment was similar between the ILD (71%, 20/28) and non-ILD groups (80%, 32/40). Moreover, when comparing the time elapsed between the last dose of ICI and the administration of DOC/RAM, the median was 2.5 and 1.4 months, respectively. These findings suggest that ICI involvement may not be an important factor, especially considering

that ICIs typically occupy approximately 70% of the PD-1 receptor for more than 2 months (33). To address the possibility of ICI-induced ILD, as mentioned by Brahmer *et al.*, it is important to note that no cases of ILD were observed in patients with prior ICI treatment without a history of ILD.

In our study, two patients died among the three patients in whom the time between the onset of pre-existing ILD and the start of DOC/RAM therapy was within one month. The shorter this time interval, the higher the risk of developing early ILD. Additionally, an earlier onset of ILD was associated with an increased risk of death. Clinicians should closely monitor patients who have recently developed ILD and carefully consider whether to offer DOC/RAM therapy. The time between ILD onset and the initiation of DOC/RAM therapy is an important factor, and our findings can serve as valuable reference data for future studies.

One strength of our study is the use of real-world data, which included cases with pulmonary interstitial shadows (excluding those attributed to infection, pneumoconiosis, or sarcoidosis) in the ILD group and those without evident pulmonary interstitial shadows in the non-ILD group. This rigorous case selection process may have contributed to a more accurate assessment of the incidence of DOC/RAM-induced interstitial pneumonia.

There are several limitations to our study, and it should be acknowledged that it was constrained by the small sample size, the retrospective analysis, and the lack of a standard definition for ILD. Additionally, the absence of a direct comparison between DOC alone and DOC/RAM limits our ability to precisely evaluate the incremental benefit of adding RAM. Furthermore, we were unable to evaluate pulmonary function tests (PFTs), which could serve as diagnostic and prognostic indicators of ILD severity. Nevertheless, the real-world clinical practice setting, and the comprehensive dataset used in this study ensure the relevance and applicability of our findings to clinical decision-making. In future research on drug-induced interstitial pneumonia in advanced NSCLC patients receiving DOC/RAM therapy, focus areas should include elucidating risk factors, optimizing treatment strategies, exploring biomarkers, implementing long-term monitoring protocols, and conducting comparative studies. Incorporating PFTs as prognostic indicators for ILD is recommended. A prospective study with a standardized patient population is essential to further clarify findings and increase their applicability.

Conclusions

Our study demonstrated that patients with recurrent advanced NSCLC and pre-existing ILD, particularly those with a history of drug-induced interstitial pneumonia, have a higher risk of developing DOC/RAM-induced interstitial pneumonia. These findings underscore the importance of close monitoring and careful patient selection when considering DOC/RAM therapy in this population. While combination therapy with DOC and RAM holds promise for treating advanced NSCLC, it is crucial to meticulously select and monitor patients, especially those with pre-existing ILD.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-460/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-460/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and received approval from Fukuoka University Medical Ethics Review Board (No. H23-12-005). Because this was a retrospective study, the requirement for informed consent was waived.

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Supplementary

Table S1 Pre-existing interstitial pneumonia

Case	Age (years)	Gender	Pre-existing interstitial pneumonia	Grade at onset	Steroid administration maximum dose	Immunosuppressants when DOC/RAM administered
A1	65	Male	Idiopathic interstitial pneumonia	1	No medication	No medication
A2	47	Male	Collagen lung (polymyositis)	1	PSL 3 mg	PSL 3 mg + CYA + ABT
A3	72	Male	Idiopathic interstitial pneumonia	1	No medication	No medication
A4	55	Female	Collagen lung (scleroderma)	2	PSL 40 mg	mPSL 4 mg + AZA 25 mg
A5	45	Male	Collagen lung (Sjogren's syndrome suspected)	2	PSL 30 mg	PSL 20 mg
A6	65	Male	Interstitial lung abnormality	1	No medication	No medication
A7	70	Female	Interstitial lung abnormality	1	No medication	No medication
A8 (B10)[†]	67	Male	Interstitial pneumonia	1	No medication	No medication

"A" represents cases of pre-existing interstitial pneumonia, with each case in this category numbered sequentially. [†], drug-induced pneumonia in pre-existing interstitial pneumonia. DOC/RAM, docetaxel plus ramucirumab; PSL, prednisolone; CYA, cyclosporine; ABT, abatacept; mPSL, methylprednisolone; AZA, azathioprine.

Table S2 Drug-induced pneumonia

Case	Age (years)	Gender	Suspected drug	Grade at onset	Steroid administration maximum dose	Steroid when DOC/RAM administered
B1	66	Female	Osimertinib	1	No medication	No medication
B2	64	Male	Atezolizumab	1	No medication	No medication
B3	64	Male	Pembrolizumab	1	PSL 40 mg	PSL 20 mg
B4	69	Male	Atezolizumab	1	No medication	No medication
B5	75	Male	Osimertinib Atezolizumab	1	No medication	No medication
B6 (C9)[†]	62	Male	Ipilimumab + nivolumab	1	mPSL 125 mg	PSL 10 mg
B7	69	Male	Pembrolizumab	3	PSL 60 mg	PSL 5 mg
B8	44	Male	Ipilimumab + nivolumab	1	Dex 3 mg	Dex 3 mg
B9	74	Male	Osimertinib	2	Dex 6 mg	No medication
B10 (A8)[‡]	67	Male	Atezolizumab	1	No medication	No medication

"B" represents cases of drug-induced pneumonia, with each case in this category numbered sequentially. [†], drug-induced pneumonia in pre-existing interstitial pneumonia; [‡], drug-induced pneumonia in radiation pneumonitis. DOC/RAM, docetaxel plus ramucirumab; PSL, prednisolone; mPSL, methylprednisolone; Dex, dexamethasone.

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Table S3 Radiation pneumonitis

Case	Age (years)	Gender	Grade at onset	Steroid administration maximum dose	Steroid when DOC/RAM administered
C1	64	Male	1	No medication	No medication
C2	64	Male	1	No medication	No medication
C3	71	Male	1	No medication	No medication
C4	75	Female	1	No medication	No medication
C5	72	Male	1	No medication	No medication
C6	55	Male	1	No medication	No medication
C7	66	Male	1	PSL 30 mg	PSL 2.5 mg
C8	58	Male	2	PSL 30 mg	No medication
C9 (B7)[†]	62	Male	2	mPSL 125 mg	PSL 10 mg
C10	72	Male	2	PSL 40 mg	No medication
C11	48	Male	1	No medication	No medication
C12	72	Male	1	No medication	No medication

"C" represents cases of radiation pneumonitis, with each case in this category numbered sequentially. [†], drug-induced pneumonia due to ipilimumab + nivolumab after radiation pneumonitis. DOC/RAM, docetaxel plus ramucirumab; PSL, prednisolone; mPSL, methylprednisolone.

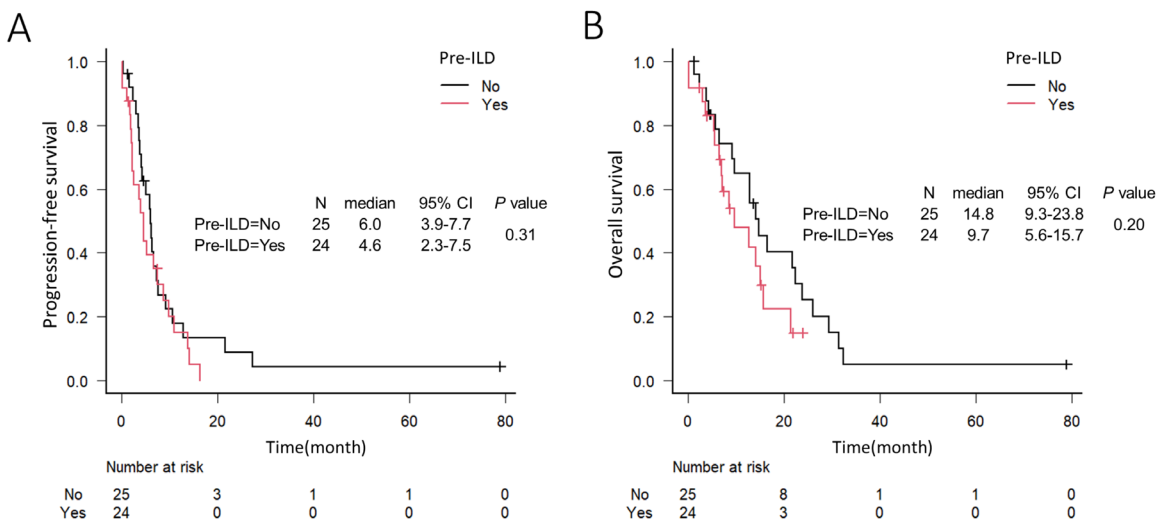

Figure S1 Progression-free survival (A) and overall survival (B) in patients with recurrent advanced non-small cell lung cancer treated with docetaxel plus ramucirumab therapy, categorized by the presence of pre-ILD in the subgroup of smokers. Pre-ILD, pre-existing interstitial lung disease; N, number; CI, confidence interval.

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