

# Efficacy and safety of second-line chemotherapy for patients with advanced non-small cell lung cancer complicated by interstitial lung disease

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## Abstract

**Background:** Treatment of non-small cell lung cancer (NSCLC) patients with interstitial lung disease (ILD) is limited because of the risk of its acute exacerbation (AE). Furthermore, the efficacy and safety of second-line chemotherapy for these patients is unclear.

**Methods:** To investigate the efficacy and safety of second-line chemotherapy for NSCLC patients with ILD, we retrospectively reviewed patients who were treated at our institute between April 2010 and December 2018.

**Results:** Thirty-five patients received two or more regimens. Thirty-four patients were male and the median age at the initiation of second-line chemotherapy was 70 years. Almost all patients had a smoking history. Fourteen patients had adenocarcinoma and 15 had squamous cell carcinoma histology. Stages III and IV were observed in 20 and 11 patients, respectively. With respect to the type of ILD, 12 patients had usual interstitial pneumonia (UIP). The overall response rate and disease control rate were 11.4 and 68.6%, respectively. The median progression-free and median overall survival were 4.1 and 6.4 months, respectively. The AE of ILD was observed in eight patients, five of whom died. UIP and low percentage vital capacity were detected as significant risk factors for the AE of ILD.

**Conclusion:** Second-line chemotherapy among patients with NSCLC complicated by ILD showed a certain effectiveness, but some patients experienced the AE of ILD, which may lead to death. The risk of the AE of ILD must be considered especially for patients with UIP and low percentage VC.

## KEYWORDS

acute exacerbation, chemotherapy, interstitial lung disease, non-small cell lung cancer, usual interstitial pneumonia pattern

## INTRODUCTION

Lung cancer (LC) is a leading cause of cancer death worldwide, and its mortality rate is still increasing. Non-small cell lung cancer (NSCLC) is the most common type of LC, accounting for approximately 80%. Chemotherapy for patients with NSCLC has been shown to provide a survival benefit in clinical trials, but patients complicated by interstitial lung disease (ILD) are excluded from most clinical trials. A few prospective trials have evaluated the efficacy and safety of first-line chemotherapy for NSCLC complicated by ILD.<sup>1-5</sup>

Interstitial lung disease is a slowly progressive pulmonary disease that is known to be a risk factor for the development of LC. It is reported that approximately 10.9% of cases of ILD were complicated by LC.<sup>6</sup> Another study reported that 5.8% of patients with LC who received surgery were complicated by ILD.<sup>7</sup> Although the efficacy of chemotherapy for LC patients with ILD is considered to be equivalent to that of patients without ILD,<sup>1-5,8-17</sup> some patients experience an acute exacerbation (AE) of ILD due to chemotherapy. The incidence rate of the AE of ILD due to chemotherapy is reported to be approximately

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0%–26.7%, with the fatality rate ranging from 0% to 13.3%.<sup>1–5,8–17</sup>

After the progression of NSCLC in patients who receive first-line chemotherapy, we usually provide second-line chemotherapy. Cytotoxic agents, including docetaxel, pemetrexed, tegafur-gimeracil-oteracil (S-1), and ramucirumab plus docetaxel are recommended as second-line chemotherapy, but patients with ILD have been excluded from clinical trials.<sup>18–21</sup> To our knowledge, no prospective studies have evaluated second-line cytotoxic chemotherapy for NSCLC in patients with ILD and only a few retrospective studies have been reported.<sup>22,23</sup> Therefore, it remains unclear whether second-line cytotoxic chemotherapy really provides a benefit exceeding the risk to these patients. We therefore conducted a retrospective study to investigate the efficacy and safety of second-line chemotherapy for NSCLC complicated by ILD.

## METHODS

### Patients and study design

Patients who were diagnosed with NSCLC in the Department of Respiratory Medicine and Rheumatology at Tokushima University Hospital from April 2010 to December 2018, were retrospectively analyzed. We found 103 consecutive NSCLC patients complicated with ILD and 65 (63.1%) patients who underwent chemotherapy. Thirty-five (53.8%) of the 65 NSCLC patients with ILD received two or more regimens (Figure 1). We reviewed their clinical features, chemotherapy regimens, and the efficacy and safety of treatment, and then evaluated the various pretreatment clinical features as potential risk factors for the AE of ILD.

All patients enrolled in this study were histologically or cytologically diagnosed with NSCLC. The histological types of NSCLC were defined according to the WHO classification, and the staging of NSCLC was based on the international TNM criteria for cancer staging. The performance status (PS) was assessed according to the Eastern Cooperative Oncology Group (ECOG) classification. A diagnosis of ILD was determined in accordance with the American Thoracic Society/European Respiratory Society criteria.<sup>24</sup> In the absence of histological evidence, the diagnosis of ILD patterns was based on evidence from chest computed

tomography (CT) and clinical features. Patients with usual interstitial pneumonia (UIP), nonspecific interstitial pneumonia (NSIP), desquamative interstitial pneumonia, pleuroparenchymal fibroelastosis patterns detected in a histological analysis or on chest CT were classified into the ILD group.

This study was performed in accordance with the Declaration of Helsinki, and the study protocol was approved by the Institutional Review Board of Tokushima University Hospital.

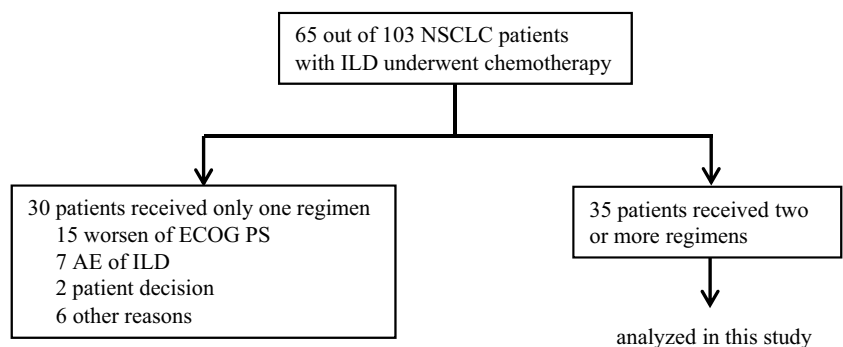
### Assessments of efficacy and AEs of ILD

Computed tomography was performed for tumor assessment and the responses were evaluated in accordance with the Response Evaluation Criteria in Solid Tumors, version 1.1. The overall response rate (ORR) was defined as the proportion of patients with a best overall response of complete response (CR) or partial response (PR). The disease control rate (DCR) was defined as the proportion of patients who have achieved CR, PR, or stable disease. Progression-free survival (PFS) was defined as the time from the start of the second-line treatment to tumor progression or death, and overall survival (OS) was calculated from the start of the second-line treatment until death or the last follow-up examination.

An AE of ILD was defined as follows: the exacerbation of dyspnea within 1 month; newly-developed diffuse pulmonary opacities on chest CT and/or chest radiography; decreased arterial oxygen tension of more than 10 Torr under similar conditions; the absence of heart failure or lung infection; and the development of an AE of ILD within 6 months after the last chemotherapy treatment, thereby avoiding underestimation of the frequency of treatment-related AEs. AEs of ILD were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 5.0.

### Statistical analysis

All comparisons between populations were performed using Fisher's exact test, or Student's *t*-test, as



**FIGURE 1** Overview of chemotherapy among NSCLC patients with ILD. AE, acute exacerbation; ECOG PS, Eastern Cooperative Oncology Group performance status; ILD, interstitial lung disease; NSCLC, non-small cell lung cancer.

**TABLE 1** Patient characteristics

	<i>N</i> = 35
Gender (%)	
Male	34 (97.1)
Female	1 (2.9)
Age	
Median (range)	70 (59–83)
ECOG PS (%)	
0	7 (20.0)
1	27 (77.1)
2	1 (2.9)
Smoking status (%)	
Never	1 (2.9)
Ex/current	34 (97.1)
Median BI (range)	1360 (0–2280)
Histology (%)	
Adenocarcinoma	14 (40.0)
Squamous cell carcinoma	15 (42.9)
Adenosquamous cell carcinoma	1 (2.9)
NOS	5 (14.3)
Stage (%)	
II	4 (11.4)
III	20 (57.1)
IV	11 (31.4)
ILD pattern (%)	
UIP	12 (34.3)
NSIP	17 (48.6)
DIP	1 (2.9)
PPFE	5 (14.3)
First-line chemotherapy regimens (%)	
Platinum+S-1	20 (57.1)
CBDCA+PTX/nab-PTX	12 (34.3)
Others	3 (8.6)

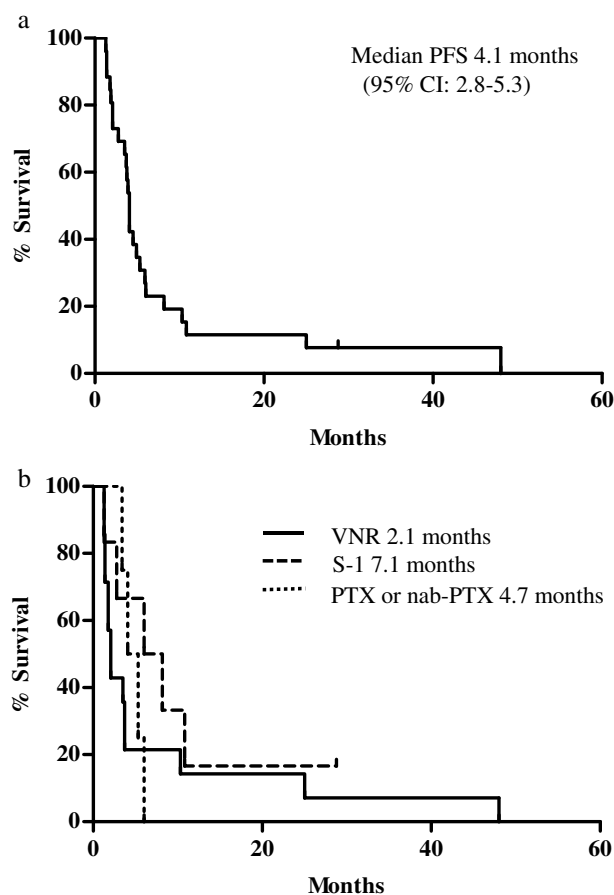
Abbreviations: BI, Brinkman index; CBDCA, carboplatin; DIP, desquamative interstitial pneumonia; ECOG PS, Eastern Cooperative Oncology Group performance status; HRCT, high resolution computed tomography; ILD, interstitial lung disease; nab-PTX, nanoparticle albumin-bound-paclitaxel; NOS, not otherwise specified; NSIP, nonspecific interstitial pneumonia; PPFE, pleuroparenchymal fibroelastosis; PTX, paclitaxel; S-1, tegafur-gimeracil-oteracil; UIP, usual interstitial pneumonia.

appropriate. Survival was estimated using the Kaplan–Meier method. Results were reported as the mean  $\pm$  standard error of the mean. Two-sided comparisons of laboratory data between patients with and without an AE of ILD were performed using Student's *t*-test. *p*-values of  $<0.05$  were considered statistically significant. 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).

**TABLE 2** Distribution of second-line chemotherapy regimens and the efficacy

Regimen	<i>N</i>	ORR (%)	DCR (%)
VNR	15	3/15 (20.0)	10/15 (66.7)
S-1	8	0/8 (0)	5/8 (62.5)
PTX	4	0/4 (0)	3/4 (75.0)
Nab-PTX	3	1/3 (33.3)	1/3 (33.3)
Others	5	0/5 (16.7)	5/5 (100)
Total	35	4/35 (11.4)	24/35 (68.6)

Abbreviations: CR, complete response; DCR, disease control rate (CR + PR + SD); nab-PTX, nanoparticle albumin-bound-paclitaxel; ORR, objective response rate (CR + PR); PR, partial response; PTX, paclitaxel; S-1, tegafur-gimeracil-oteracil; SD, stable disease; VNR, vinorelbine.



**FIGURE 2** PFS after second-line chemotherapy for all patients (a) and for each regimen (b). nab-PTX, nanoparticle albumin-bound-paclitaxel; PFS, progression-free survival; PTX, paclitaxel; S-1, tegafur-gimeracil-oteracil; VNR, vinorelbine.

## RESULTS

### Patient characteristics

Thirty-five patients with NSCLC complicated with ILD received two or more regimens of chemotherapy. Thirty-two

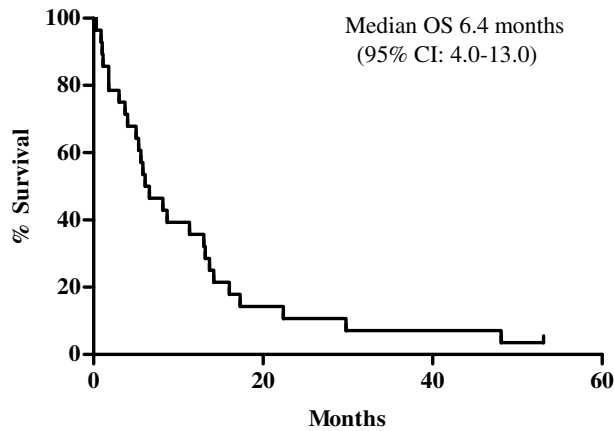


FIGURE 3 OS for all patients. OS, overall survival.

of 35 patients received platinum-doublet chemotherapy as first-line treatment. Twenty of 35 patients received two regimens, 10 patients received three regimens, and five patients received four regimens. No patient received five or more regimens. The characteristics of the patients are shown in Table 1. Almost all patients were male with a smoking history and a good PS. The median age was 70 (range 59–83) years. Histologically, adenocarcinoma and squamous cell carcinoma were observed in 14 (40.0%) and 15 (42.9%) patients, respectively. The disease stage before first-line chemotherapy was stage II in four (11.4%), stage III in 20 patients (57.1%), and stage IV in 11 patients (31.4%). The patients with stage II and III disease were not operable because of their impaired pulmonary function. The UIP pattern and NSIP pattern of ILD were observed in 12 (34.3%) and 17 (48.6%) patients, respectively.

### Efficacy of second-line chemotherapy

The chemotherapeutic agents used for patients with NSCLC complicated with ILD are shown in Table 2. Vinorelbine (VNR) and S-1 were mainly used as second-line regimens. The ORR and the DCR for the second-line chemotherapy of 35 patients were 11.4% and 68.6%, respectively (Table 2). The median PFS (mPFS) was 4.1 months (95% confidence interval [CI]: 2.8–5.3 months) (Figure 2a). The results for each regimen are shown in Figure 2b (VNR, 2.1 months; S-1, 7.1 months; and paclitaxel [PTX] or nanoparticle albumin-bound-paclitaxel [nab-PTX], 4.7 months). The median OS (mOS) was 6.4 months (95% CI: 4.0–13.0 months) (Figure 3). The first-line treatment of 15 patients treated with VNR were platinum and S-1 ( $n = 10$ ), carboplatin (CBDCA) and PTX ( $n = 4$ ), S-1 alone ( $n = 1$ ). Six of eight patients treated with S-1 received CBDCA and PTX or nab-PTX as first-line chemotherapy, and five of seven patients treated with PTX or nab-PTX received platinum and S-1. The ORR for the first-line chemotherapy of patients treated with VNR, S-1, and PTX or nab-PTX were 26.7%, 50.0% and 14.3%, respectively.

TABLE 3 Incidence of AE of ILD by chemotherapy

Regimen	N	AE (%)	Grade 5 AE (%)
VNR	15	5 (33.3)	3 (20)
S-1	8	0 (0)	0 (0)
PTX	4	1 (25)	1 (25)
Nab-PTX	3	2 (66.6)	1 (33.3)
Others	5	0 (0)	0 (0)
Total	35	8 (22.9)	5 (14.3)

Abbreviations: AE, acute exacerbation; nab-PTX, nanoparticle albumin-bound-paclitaxel; PTX, paclitaxel; S-1, tegafur-gimeracil-oteracil; VNR, vinorelbine.

### Development of AEs of ILD and risk factors

Acute exacerbations of ILD were observed in eight (22.9%) patients, five of whom died due to the AE of ILD in the second-line setting. The incidence of the AE of ILD for each regimen is shown in Table 3. Table 4 shows the characteristics and clinical data of patients with and without AEs of ILD. The patients who experienced an AE of ILD were all men with a smoking history and their pattern of ILD was UIP. In the analysis of risk factors for the development of an AE of ILD, the UIP pattern of ILD ( $p = 0.0152$ ) and low percentage VC ( $p = 0.043$ ) were identified as significant risk factors. Other patient characteristics, including sex, age, ECOG PS, smoking status and the volume of KL-6, LDH, and CRP were not detected as significant risk factors.

### DISCUSSION

For advanced or metastatic NSCLC patients without ILD, the standard treatment is systemic therapy, including cytotoxic chemotherapeutic agents, molecular targeted agents and immune checkpoint inhibitors; these have been well established in clinical trials. After disease progression on first-line therapy, second-line systemic therapy is recommended in various guidelines. However, for patients with ILD, there is no consensus on the efficacy or safety of systemic therapy because this population is excluded from most clinical trials due to the risk of the AE of ILD. Furthermore, there is only limited information on the efficacy and safety of second-line cytotoxic chemotherapy for this population.<sup>22,23</sup>

Some retrospective and prospective studies have reported the efficacy and safety of first-line chemotherapy for NSCLC patients with ILD.<sup>1–5,8–17</sup> Some phase II studies have shown the efficacy and safety of first-line chemotherapy using regimens such as weekly PTX, nab-PTX, and S-1 combined with carboplatin.<sup>1–5</sup> After the failure of first-line chemotherapy, it was shown that 32.1%–48.9% of NSCLC patients with ILD received treatment with two or more regimens,<sup>10,25</sup> which was similar to our study, while 39.2%–56% of NSCLC patients without ILD were reported to have received two or more regimens.<sup>26,27</sup> The rate of patients with ILD receiving two or more regimens tended to

**TABLE 4** Comparison of characteristics and clinical data between patients with or without AE of ILD

Variables	Patients without AE (N = 27)	Patients with AE (N = 8)	p-value
Gender (%)			0.96
Male	26 (96.3)	8 (100.0)	
Female	1 (3.7)	0 (0)	
Age			0.687
Mean ± SEM	69.6 ± 1.1	70.5 ± 2.1	
ECOG PS			0.806
0	5 (18.5)	2 (25.0)	
1	21 (77.8)	6 (75.0)	
2	1 (3.7)	0 (0)	
Smoking status (%)			
Never	1 (3.7)	0 (0)	
Ex/current	26 (96.3)	8 (100.0)	
BI mean ± SEM	1296.0 ± 96.6	1516.0 ± 193.2	0.292
Pattern of ILD (%)			0.015
UIP	14 (51.9)	8 (100.0)	
Non-UIP	13 (48.1)	0 (0)	
KL-6 (U/ml) Mean ± SEM	989.9 ± 145.1	1266.0 ± 536.1	0.632
LDH (IU/l) Mean ± SEM	251.0 ± 45.6	238.8 ± 15.1	0.887
CRP (mg/dl) Mean ± SEM	1.7 ± 0.5	2.5 ± 1.2	0.514
Percentage VC (%) Mean ± SEM	102.4 ± 2.9	89.4 ± 5.9	0.043

Abbreviations: AE, acute exacerbation; BI, Brinkman index; ECOG PS, Eastern Cooperative Oncology Group performance status; ILD, interstitial lung disease; SEM, standard error of the mean; UIP, usual interstitial pneumonia; VC, vital capacity.

be lower than that in patients without ILD, because of the worsening of their ECOG PS, or the AE of ILD after first-line chemotherapy (as shown in Figure 1), and the limitation regarding the safe use of the regimen in second-line chemotherapy.

With regard to the frequency of the AE of ILD in the first-line setting, previous studies reported that AEs of ILD occurred in 0%–26.7% of patients, and that the fatality rate was 0%–13.3%.<sup>1–5,8–17,23</sup> In the second-line setting, the rate of the AE of ILD and the fatality rate were reported to be 12.8%–14.3% and 2.4%–8.6%, respectively.<sup>10,22</sup> In our study, the rate of the AE of ILD and the fatality rate were 22.9 and 14.3%, respectively. Based on these data, second-line chemotherapy may be associated with a greater risk of the development of AEs of ILD in comparison to first-line chemotherapy. Previous studies have identified the UIP pattern as a risk factor for the AE of ILD in first-line chemotherapy.<sup>6,28</sup> There are no reports of risk factor for the AE of ILD in the second-line setting. In our study, all patients who experienced an AE of ILD had the UIP pattern, and a low percentage VC was also detected as a significant risk factor for the development of AEs of ILD. Our data suggest that in second-line chemotherapy, the UIP pattern and low percentage VC should be considered as risk factors for an AE in patients with ILD and that the indication of chemotherapy for such patients should be carefully determined.

In the second-line setting, cytotoxic agents, including docetaxel, pemetrexed, S-1, or (nab-) paclitaxel are

administered for patients without ILD. Associations between these agents and the AE of ILD have been reported in several studies: docetaxel caused more AEs than other agents, while paclitaxel caused no aggravation.<sup>28,29</sup> In our cohort, vinorelbine and (nab-) PTX caused the AE of ILD in five and three cases, respectively, while no aggravation was observed in patients treated with S-1. In addition to these cytotoxic agents, immune checkpoint inhibitors (ICIs) have recently shown dramatic efficacy in the treatment of NSCLC and have been used as a single agent or in combination with chemotherapy. Some retrospective and prospective studies have shown the efficacy and safety of ICIs in the treatment of patients with ILD.<sup>30–32</sup> We are of the opinion that ICIs should be used for patients with mild ILD as late-line treatment because of the risk of AE-ILD. Therefore, no patients in our cohort were treated with ICIs as second-line therapy.

The efficacy of chemotherapy among patients with LC complicated by ILD, was reported to be equivalent to that of patients without ILD.<sup>8,9</sup> In the second-line setting in NSCLC patients without ILD, the ORR, mPFS, and mOS of patients treated with cytotoxic agents was reported to be approximately 9%, 3, and 8 months, respectively.<sup>19</sup> In contrast, when NSCLC patients with ILD were treated with docetaxel as second-line chemotherapy, the ORR, mPFS, and mOS were reported to be 8.6%, 1.6, and 5.1 months, respectively.<sup>22</sup> In our study, the ORR, mPFS, and mOS were 11.4%, 4.1 and 6.4 months, respectively, which seems to be better than the previous retrospective study. The difference

in the chemotherapy regimens used, may be one of the causes in the difference of the efficacy. In addition, patients with stage II and III disease accounted for approximately 68% of the patients in our study, and this may be a reason for the difference. However, our data suggested that the efficacy of second-line chemotherapy among patients in NSCLC with ILD is comparable to that among patients without ILD.

The present study was associated with some limitations, including the relatively small number of patients and the single center setting. Although eight patients who were treated with S-1 seemed to have better PFS, six of these patients received CBDCA and PTX or nab-PTX as first-line chemotherapy and the ORR was 50.0% (4/8 patients). The better PFS of S-1 treatment may have been influenced by the regimen and efficacy of the first-line chemotherapy or a selection bias may have been present. Furthermore, the analysis was conducted retrospectively. Although the GAP (gender, age, and lung physiology) model has been reported to be a good predictive in the prognosis of ILD,<sup>33</sup> many patients lacked data of diffusing lung capacity for carbon monoxide and we were unable to assess the GAP score. Therefore, a large-scale prospective study is required to evaluate the efficacy and safety of second-line chemotherapy for patients with LC complicated by ILD.

In conclusion, our retrospective data suggest that chemotherapy for patients with NSCLC complicated by ILD is effective in the second-line setting; however, we have to consider the risk of the AE of ILD, especially in patients with the UIP pattern and low percentage VC.



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## CONFLICT OF INTEREST

KO holds stocks of Otsuka holdings Co., Ltd. which includes Taiho Pharmaceutical Co., Ltd., outside the submitted work. HN has received research grant funding from Nippon Pfizer Japan Inc., and speaker fees as honoraria from Taiho Pharmaceutical Co., Ltd., Nippon Pfizer Japan Inc., outside the submitted work. YN has received research grant funding from Taiho Pharmaceutical Co., Ltd., Kyowa Kirin Co., Ltd., and speaker fees as honoraria from Taiho Pharmaceutical Co., Ltd., Nippon Pfizer Japan Inc., outside the submitted work.

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