A randomized phase II study of S-1 plus oral leucovorin versus S-1 monotherapy in patients with gemcitabine-refractory advanced pancreatic cancer[†]

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Background: We evaluated the efficacy and toxicity of adding oral leucovorin (LV) to S-1 when compared with S-1 monotherapy in patients with gemcitabine-refractory pancreatic cancer (PC).

Patients and methods: Gemcitabine-refractory PC patients were randomly assigned in a 1:1 ratio to receive S-1 at 40, 50, or 60 mg according to body surface area plus LV 25 mg, both given orally twice daily for 1 week, repeated every 2 weeks (SL group), or S-1 monotherapy at the same dose as the SL group for 4 weeks, repeated every 6 weeks (S-1 group). The primary end point was progression-free survival (PFS).

Results: Among 142 patients enrolled, 140 were eligible for efficacy assessment (SL: $n = 69$ and S-1: $n = 71$). PFS was significantly longer in the SL group than in the S-1 group [median PFS, 3.8 versus 2.7 months; hazard ratio (HR), 0.56; 95% confidence interval (CI), 0.37–0.85; $P = 0.003$]). The disease control rate was significantly higher in the SL group than in the S-1 group (91% versus 72%; $P = 0.004$). Overall survival (OS) was similar in both groups (median OS, 6.3 versus 6.1 months; HR, 0.82; 95% CI, 0.54–1.22; $P = 0.463$). After adjusting for patient background factors in a multivariate analysis, OS tended to be better in the SL group (HR, 0.71; 95% CI, 0.47–1.07; $P = 0.099$). Both treatments were well tolerated, although gastrointestinal toxicities were slightly more severe in the SL group.

Conclusion: The addition of LV to S-1 significantly improved PFS in patients with gemcitabine-refractory advanced PC, and a phase III trial has been initiated in a similar setting.

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Key words: phase II study, S-1, leucovorin, gemcitabine-refractory pancreatic cancer, pancreatic resection, albumin

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introduction

Pancreatic cancer (PC), known for its poor prognosis, is the eighth leading cause of cancer-related mortality in the world [1]. Although FOLFIRINOX has become a standard regimen for advanced PC, its use is limited to patients in good medical condition because of its severe toxicity [2]. Gemcitabine plus nab-paclitaxel is another treatment option for patients in fair

condition [3]. Some patients still receive gemcitabine monotherapy as first-line treatment.

Even with intensive chemotherapy regimens such as FOLFIRINOX and gemcitabine plus nab-paclitaxel, the median progression-free survival (PFS) is ∼6 months. Furthermore, a considerable number of patients cannot tolerate intensive chemotherapy after first-line chemotherapy. Although a combination of oxaliplatin, leucovorin (LV), and fluorouracil (OFF) prolonged survival when compared with fluorouracil plus LV (FF) after gemcitabine failure (CONKO-003 trial) [4], there are various unmet needs that should be addressed in a second-line setting for advanced PC.

In Japan, S-1 (Taiho Pharmaceutical, Co., Ltd, Tokyo, Japan), an oral fluoropyrimidine that inhibits dihydropyrimidine dehydrogenase, has been demonstrated to be non-inferior to gemcitabine as first-line chemotherapy for advanced PC [5]. In gemcitabine-refractory patients, a previous phase II study reported that S-1 was moderately effective, with a response rate (RR) of 15%, a median PFS of 2.0 months, and a median overall survival (OS) of 4.5 months [6]. Furthermore, although oxaliplatin and irinotecan can be key drugs, neither S-1 plus oxaliplatin nor S-1 plus irinotecan provided a survival benefit over S-1 monotherapy in patients with gemcitabine-refractory PC [7, 8]. Because S-1 monotherapy is less toxic than these doublet regimens, it is widely used in gemcitabine-refractory patients as the practical standard care in Japan.

LV is known to enhance the efficacy of fluorouracil in metastatic colorectal cancer (CRC) [9]. In preclinical studies, combined treatment with LV and S-1 was suggested to enhance therapeutic efficacy [10]. A randomized phase II study suggested that adding to LV to capecitabine might not increase efficacy because of increased intolerable toxicities [11]. Given the time-dependent antitumor effects and toxicities of fluoropyrimidine plus LV, various schedules of S-1 plus LV (SL) were studied in metastatic CRC, and a 2-week schedule (1 week on, 1 week off) was designated as the optimal schedule, maintaining high antitumor efficacy with manageable toxicity [12, 13]. These findings encouraged us to perform a randomized phase II clinical trial comparing SL with S-1 monotherapy in patients with gemcitabine-refractory advanced PC.

methods

study design

This multicenter, open-labeled, randomized phase II study, sponsored by Taiho Pharmaceutical Co., Ltd, Tokyo, Japan, was conducted at 27 centers in compliance with the Declaration of Helsinki and Good Clinical Practice guidelines. An independent data and safety monitoring committee reviewed efficacy and safety data. The study protocol was approved by the institutional review board of each participating center. All patients provided written informed consent before study entry.

patients

Eligible patients were 20–79 years of age and had a histologically or cytologically confirmed diagnosis of adenocarcinoma or adenosquamous carcinoma of the pancreas that was refractory to first-line treatment with gemcitabine. Patients had measurable lesions according to the Response Evaluation Criteria in Solid Tumors (RECIST; version 1.1). Other eligibility criteria were as follows: (i) no prior radiotherapy for PC, (ii) an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1, and (iii) adequate

bone-marrow, hepatic, and renal functions on laboratory tests carried out within 7 days before enrollment. Patients could have no serious comorbidities (supplementary Appendix SA2, available at *Annals of Oncology* online).

Disease progression during first-line gemcitabine-based chemotherapy or recurrence during or within 6 months after the completion of postoperative adjuvant gemcitabine chemotherapy was assessed on computed tomography (CT), magnetic resonance imaging (MRI), or other imaging techniques and was confirmed by an independent review committee (IRC).

randomization

After confirming eligibility, patients were randomly assigned in a 1:1 ratio to receive S-1 plus LV (SL group) or S-1 monotherapy (S-1 group). Random assignment was carried out centrally at an independent data center by the minimization method, using the duration of prior gemcitabine treatment (≤6 versus >6 months) and ECOG PS (0 versus 1) as allocation factors.

treatment

The dose of S-1 was determined according to the body surface area as follows: <1.25 m^2, 40 mg; 1.25 to <1.5 m^2, 50 mg; and ≥1.5 m^2, 60 mg, given twice daily after meals in both treatment groups. In the SL group, LV at a fixed dose of 25 mg was additionally given with each dose of S-1. Patients assigned to the SL group received S-1 plus LV orally for 1 week, followed by a 1-week rest, repeated every 2 weeks. Patients assigned to the S-1 group received the same dose of S-1 orally for 4 consecutive weeks, followed by a 2-week rest, repeated every 6 weeks. The details of dose modification of S-1 are defined in supplementary Appendix SA3, available at *Annals of Oncology* online. Treatment was continued until disease progression, unacceptable toxic effects, or the withdrawal of consent.

assessments

Patients' conditions were assessed every 2 weeks during the protocol treatment. All adverse events were evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0). CT or MRI was carried out every 4 weeks during the first 16 weeks and every 6 weeks thereafter until disease progression. Response was assessed by the attending physicians and confirmed by the IRC according to RECIST version 1.1. If there was any discordance between an investigator and the IRC, the date of disease progression as evaluated by the IRC was used to calculate PFS. Data on patients in whom treatment was discontinued before disease progression was confirmed by the IRC were censored on the last day of tumor assessment (no events).

end points

The primary end point was PFS, defined as the time from randomization to disease progression or death from any cause. Secondary end points were OS, RR, disease control rate (DCR), duration of response, time to treatment failure (TTF), time to progression (TTP), dose intensity, and adverse events (supplementary Appendix SA4, available at *Annals of Oncology* online).

statistical analysis

The hazard ratio (HR) for PFS was expected to be 0.67, corresponding to a median PFS of 3.0 months in the SL group and 2.0 months in the S-1 group. These estimates were based on the results of a previous study [6]. To detect such an improvement in the HR with ≥80% power and a one-sided significance level of 0.10, a total of 110 events of progressive disease confirmed by the IRC in the full analysis set (FAS) were required. Given a 10% loss of events due to discordance in the PFS assessment between the IRC and the investigators and a 5% dropout rate from the FAS for various reasons, the sample size was set at 140 patients. Time-to-event variables, such as PFS, OS, TTF, and TTP, were analyzed with the Kaplan–Meier method, and the HR for these end points was calculated with a Cox proportional-hazards model. Primary

comparisons of PFS between the treatment groups were made with the stratified log-rank test adjusted for allocation factors. The secondary end points of OS, TTF, and TTP were analyzed with the use of log-rank tests. RR and DCR were compared with the use of Fisher's exact test. Interaction tests between treatment effect and patient characteristics were done for PFS and OS.

The FAS was based on all eligible patients, and the safety analysis set was defined as the patients who received the study treatment at least once. Data analyses were carried out with the use of SAS, version 9.2. Subset analyses were pre-planned.

results

patients

Between August 2011 and August 2012, a total of 142 patients were enrolled. All randomized patients were confirmed to have gemcitabine-refractory PC by the IRC. A total of 140 patients

were eligible and included in the FAS (supplementary Figure S1, available at *Annals of Oncology* online). Two patients in the SL group were ineligible because they had no target lesions on IRC assessment. There were some imbalances in patient characteristics, such as the serum albumin level, sum of the diameters of target lesions, and prior pancreatic resection (Table 1).

efficacy

At the cut-off date for PFS analysis of 17 December 2012, when 117 events had been reported by the investigators, 97 events were confirmed, and data on 25 patients were censored by the IRC. The median PFS was 3.8 months [95% confidence interval (CI), 3.7–6.0 months] in the SL group and 2.7 months (95% CI, 1.9–3.7 months) in the S-1 group (Figure 1A). SL significantly decreased the risk of disease progression by 44% when compared with S-1 (HR, 0.56; 95% CI, 0.37–0.85; $P = 0.003$). The results for TTP were exactly the same as those for PFS because no death occurred before disease progression. In the pre-specified subgroup analyses of PFS, the effect of SL was better in most categories (supplementary Figure S2A, available at *Annals of Oncology* online). On multivariate analysis adjusting for patient characteristics such as gender, age, number of metastatic organs, pancreatic resection, and albumin levels in addition to stratification factors (ECOG PS, duration of gemcitabine

Table 1. Patient characteristics

	S-1/LV ($n = 69$) n (%)	S-1 ($n = 71$) n (%)	P-value[a]
Gender			
Male	41 (59.4)	38 (53.5)	F: 0.500
Female	28 (40.6)	33 (46.5)	
Age (years)			
Mean	64.2	63.3	t: 0.444
Median	65.0	64.0	
<65	34 (49.3)	38 (53.5)	F: 0.735
≥65	35 (50.7)	33 (46.5)	
BSA (m²)			
Median	1.538	1.547	t: 0.932
Range	1.165–1.861	1.225–1.953	
<1.250	3 (4.3)	2 (2.8)	W: 0.705
1.250 to <1.500	28 (40.6)	28 (39.4)	
1.500–<	38 (55.1)	41 (57.7)	
ECOG PS			
0	45 (65.2)	48 (67.6)	F: 0.858
1	24 (34.8)	23 (32.4)	
Albumin (g/dL)			
<4.0	39 (56.5)	30 (42.3)	F: 0.128
≥4.0	30 (43.5)	41 (57.7)	
Sum of the diameter of target lesions (mm)			
Mean	48.0	42.1	t: 0.181
Median	44.7	35.3	
Pancreatic resection			
No	56 (81.2)	47 (66.2)	F: 0.056
Yes	13 (18.8)	24 (33.8)	
Treatment duration of first-line gemcitabine			
≤6 months	52 (75.4)	54 (76.1)	F: 1.000
>6 months	17 (24.6)	17 (23.9)	
Previous gemcitabine treatment			
Advanced	58 (84.1)	55 (77.5)	F: 0.394
Recurrent (adjuvant chemotherapy)	11 (15.9)	16 (22.5)	

ECOG PS, Eastern Cooperative Oncology Group performance status.
[a]P-values were calculated with Fisher's exact test (F), t-test (t) or Wilcoxon's rank-sum test (W).
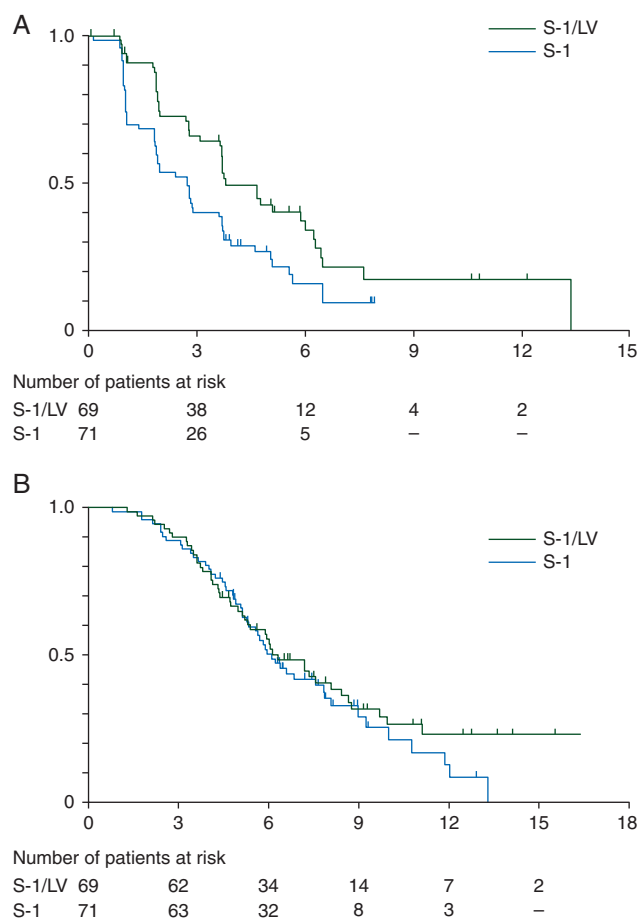

Figure 1. Kaplan–Meier curves of (A) progression-free survival (assessed by independent review committee) and (B) overall survival.

Table 2. Treatment-related adverse events (safety analysis population)

	S-1/LV (n = 71)		S-1 (n = 71)		P-value[a]
	Any grade	Grade 3–4	Any grade	Grade 3–4	(any grade)
Hematological analysis					
Anemia	20 (28.2%)	7 (9.9%)	22 (31.0%)	8 (11.3%)	0.854
Lymphocyte count decreased	15 (21.1%)	9 (12.7%)	13 (18.3%)	8 (11.3%)	0.833
Neutrophil count decreased	17 (23.9%)	6 (8.5%)	16 (22.5%)	4 (5.6%)	1.000
Platelet count decreased	16 (22.5%)	2 (2.8%)	17 (23.9%)	0	1.000
Weight decreased	12 (16.9%)	3 (4.2%)	10 (14.1%)	0	0.817
White blood cell count decreased	16 (22.5%)	5 (7.0%)	18 (25.4%)	3 (4.2%)	0.844
Hypoalbuminemia	8 (11.3%)	0	11 (15.5%)	3 (4.2%)	0.623
Non-hematological analysis					
Lacrimation increased	12 (16.9%)	0	16 (22.5%)	0	0.527
Diarrhea	37 (52.1%)	4 (5.6%)	36 (50.7%)	3 (4.2%)	1.000
Nausea	35 (49.3%)	1 (1.4%)	20 (28.2%)	2 (2.8%)	0.016
Stomatitis	43 (60.6%)	2 (2.8%)	21 (29.6%)	0	0.0004
Vomiting	20 (28.2%)	0	13 (18.3%)	2 (2.8%)	0.233
Fatigue	23 (32.4%)	5 (7.0%)	18 (25.4%)	0	0.459
Malaise	18 (25.4%)	0	15 (21.1%)	0	0.691
Pyrexia	8 (11.3%)	0	4 (5.6%)	0	0.366
Decreased appetite	47 (66.2%)	10 (14.1%)	34 (47.9%)	3 (4.2%)	0.042
Dysgeusia	16 (22.5%)	0	10 (14.1%)	0	0.563
Palmar-plantar erythrodysesthesia syndrome	17 (23.9%)	0	17 (23.9%)	0	1.000
Maculopapular rash	14 (19.7%)	0	4 (5.6%)	0	0.021
Skin hyperpigmentation	46 (64.8%)	0	31 (43.7%)	0	0.018

[a]P-values were calculated with Fisher's exact test for the difference in the incidence of adverse events of any grade.

treatment), the HR was 0.50 in favor of SL (95% CI, 0.33–0.77; $P = 0.001$).

The median OS was 6.3 months (95% CI, 5.3–8.4 months) in the SL group and 6.1 months (95% CI, 5.3–7.8 months) in the S-1 group (HR, 0.82; 95% CI, 0.54–1.22; $P = 0.463$) (Figure 1B). In the pre-specified subgroup analyses of OS, the effect of SL was better in most categories (supplementary Figure S2B, available at *Annals of Oncology* online). However, some interactions between treatment effect and patient backgrounds, such as prior pancreatic resection and albumin level, were suggested. The HR on multivariate analysis adjusting for patient characteristics was 0.71 in favor of SL (95% CI, 0.47–1.07, $P = 0.099$) (supplementary Table S1, available at *Annals of Oncology* online).

The RR was 27.5% (95% CI, 17.5%–39.6%) in the SL group and 19.7% (95% CI, 11.2%–30.9%) in the S-1 group ($P = 0.322$) (supplementary Table S2, available at *Annals of Oncology* online). The DCR was 91.3% (95% CI, 82.0%–96.7%) in the SL group and 71.8% (95% CI, 59.9%–81.9%) in the S-1 group ($P = 0.004$). The median duration of response was 96.5 days in the SL group and 73.0 days in the S-1 group.

At the cut-off date for PFS analysis, the protocol treatment was being continued in 19 patients (27.5%) in the SL group and 16 patients (22.5%) in the S-1 group. The median TTF was 3.7 months (95% CI, 2.6–3.8 months) in the SL group and 2.4 months (95% CI, 1.8–2.9 months) in the S-1 group. The main reason for treatment discontinuation was disease progression (supplementary Figure S1, available at *Annals of Oncology* online).

Post-protocol treatment was given to 27 patients (39.1%) in the SL group and 30 patients (42.3%) in the S-1 group (supplementary Figure S1, available at *Annals of Oncology* online).

The main post-protocol treatments (≥10 patients) were S-1 monotherapy in the SL group and gemcitabine plus S-1 in the S-1 group.

safety

The treatment-related grade 3 or 4 adverse events with ≥5% incidences were anemia (9.9% in the SL group versus 11.3% in the S-1 group), lymphopenia (12.7% versus 11.3%), neutropenia (8.5% versus 5.6%), leukopenia (7.0% versus 4.2%), hyponatremia (5.6% versus 2.8%), diarrhea (5.6% versus 4.2%), fatigue (7.0% versus 0.0%), and decreased appetite (14.1% versus 4.2%) (Table 2). Serious adverse events related to the protocol treatment occurred in 11 patients (15.5%) in the SL group and 8 patients (11.3%) in the S-1 group. Two patients in the SL group died from treatment-related sepsis.

The median relative dose intensity (RDI) of S-1 was 91.0% (range, 28.6%–100%) in the SL group and 92.3% (range, 14.3%–103.7%) in the S-1 group. The main reasons for dose reduction of S-1 and treatment interruption were gastrointestinal toxicities in both groups.

discussion

The significantly better PFS and DCR in the SL group than in the S-1 group suggest that the antitumor activity of S-1 is enhanced by LV in advanced PC. Several clinical studies have shown that adding LV to S-1 enhances antitumor efficacy [12–14]. These results together with the present study provide robust evidence for the enhancement of S-1 activity by LV.

Several regimens of second-line chemotherapy, including OFF and FF plus MM-398, have obtained a median OS of ~6 months [4, 15]. A recent comprehensive analysis of second-line chemotherapy for advanced PC reported that the median OS was 6.0 months in patients who received chemotherapy when compared with only 2.8 months in those who received best supportive care ($P = 0.013$) [16]. In the GEST study, more than 70% of the patients in the gemcitabine monotherapy group received S-1 monotherapy or S-1-based regimens as second-line chemotherapy [5], and the median OS after gemcitabine failure was ~6.0 months. Development of S-1-based regimens seemed especially attractive in this setting, and we therefore directly estimated the benefits of LV added to S-1 when compared with S-1 monotherapy.

Because PC is not a chemotherapy-sensitive tumor, especially in patients receiving second-line treatment, disease control is considered clinically relevant at present. The main objective of this randomized phase II trial was to estimate the increment in effectiveness obtained by adding LV to S-1, and thereby facilitate planning of a subsequent phase III trial with the primary end point of OS. We designated PFS as the primary end point of our trial, and OS, RR, and DCR were secondary end points. As expected, PFS and DCR were significantly better in the SL group than in the S-1 group.

No difference in OS was observed between the two treatment groups, and several reasons may account for this. First, subsequent treatment might have biased the comparison of OS. The regimens used for subsequent treatment differed substantially between the groups, although the proportions of patients who received subsequent chemotherapy were similar. Secondly, there were non-negligible differences in patient backgrounds such as prior pancreatic resection and the serum albumin level between the treatment groups (Table 1) due to small sample size; and there were some interactions between the patients' background characteristics and the response to treatment in terms of both PFS and OS (supplementary Figure S2A and B, available at *Annals of Oncology* online). In particular, both prior pancreatic resection and the serum albumin level were prognostic factors for OS (supplementary Figure S3A and B, available at *Annals of Oncology* online). In fact, multivariate analysis of OS adjusting not only for stratification factors, but also for patient background characteristics resulted in a lower HR (0.71; 95% CI, 0.47–1.07; $P = 0.099$) than that of the primary analysis (0.82; 95% CI, 0.54–1.22; $P = 0.463$). It is speculated that the efficacy of SL, especially in terms of OS, might be underestimated because of some bias related to background characteristics and subsequent treatment. Pancreatic resection and the albumin level should thus be considered as eligibility criteria, stratification factors, or both in future phase III trials.

Treatments were well tolerated, and high RDI (>90%) was maintained in both treatment arms. However, gastrointestinal toxicities were slightly more severe in the SL group. PC is generally associated with malnutrition and sometimes cachexia, especially later in the clinical course of the disease. Cachexia induces sarcopenia, which increases adverse effects of chemotherapy [17]. Serum albumin levels have been reported to be an index of sarcopenia [18]. In fact, the incidences of some adverse effects (e.g. anemia, diarrhea, nausea, and malaise) in our study were higher in patients with low albumin levels than in those with normal albumin levels, especially in the SL group (supplementary Table S3, available at *Annals of Oncology* online). Patient selection for second-line chemotherapy for advanced PC is considered very important, especially when a toxic regimen is used.

As for second-line treatment after gemcitabine-based chemotherapy, the use of FOLFIRINOX seems to be limited by its severe toxicity. Regimens with relatively mild chemotherapy and a low risk of severe toxicity (e.g. OFF) are most likely suitable for the second-line chemotherapy of PC. In this respect, SL is considered a promising option for second-line treatment after gemcitabine-based regimens in patients with advanced PC.

Our study had several limitations. First, since it was not placebo-controlled, a bias in PFS evaluation cannot be ruled out. To minimize this bias, disease progression in the treatment arms was confirmed by an IRC under blinded conditions. Secondly, the sample size was small, as discussed above. Thirdly, the primary end point was not OS but PFS. Initially, PFS was not expected to be largely affected by patient background characteristics, and post-progression survival was likely to be short in this setting. Therefore, we thought that PFS would be more suitable than OS to evaluate the benefit of adding LV. However, imbalances in the patients' backgrounds appeared to affect both PFS and OS. Furthermore, differences in subsequent chemotherapy influenced post-progression survival. Although the discrepancy between PFS and OS makes it rather difficult to interpret our results, multivariate analysis of OS suggests a survival benefit of SL.

In conclusion, LV was shown to have an additive effect with S-1 on PFS and DCR and was associated with tolerable toxicity as second-line chemotherapy for patients with gemcitabine-refractory advanced PC. A phase III study to evaluate the survival benefits of SL when compared with S-1 is ongoing in Japan and Korea (JapicCTI-132172).

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Epstein–Barr virus reactivation in extranodal natural killer/T-cell lymphoma patients: a previously unrecognized serious adverse event in a pilot study with romidepsin

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Background: Romidepsin, a histone deacetylase (HDAC) inhibitor, has been approved for the treatment of relapsed and refractory peripheral T-cell lymphoma. However, the efficacy and safety of romidepsin has never been studied in patients with relapsed or refractory extranodal natural killer (NK)/T-cell lymphoma (ENKTL).

Patients and methods: We conducted an open-label, prospective pilot study to evaluate the efficacy and feasibility of romidepsin in the treatment of patients with ENKTL. The treatment was intravenous infusion of romidepsin (14 mg/m^2) for 4 h on days 1, 8, and 15 of a 28-day cycle, and was repeated until disease progression or the occurrence of unacceptable toxicity.

Results: A total of five patients enrolled on to this pilot study. However, three patients developed fever and elevated liver enzyme and bilirubin levels immediately after their first administration of romidepsin. We suspected that these events were associated with Epstein–Barr virus (EBV) reactivation because of the rapidly elevated EBV DNA titers in blood from these patients.

An *in vitro* study with the ENKTL cell line SNK-6 cells also showed that HDAC inhibitors including romidepsin increased the copy number of EBV DNA in a dose-dependent manner. These findings suggested that romidepsin-induced histone acetylation reversed the repressed state of the genes required for EBV reactivation and that romidepsin treatment may have caused EBV reactivation in EBV-infected tumor cells in ENKTL patients. Therefore, we discontinued the enrollment of patients into this pilot study.

Conclusions: Our study suggests that the use of romidepsin may cause severe EBV reactivation in patients with ENKTL.

Key words: extranodal NK/T-cell lymphoma, romidepsin, EBV reactivation

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