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ORIGINAL REPORT

Final Results From a Multicenter, International, Pivotal Study of Romidepsin in Refractory Cutaneous T-Cell Lymphoma

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A B S T R A C T

Purpose
The primary objective of this study was to confirm the efficacy of romidepsin in patients with treatment refractory cutaneous T-cell lymphoma (CTCL).

Patients and Methods
This international, pivotal, single-arm, open-label, phase II study was conducted in patients with stage IB to IVA CTCL who had received one or more prior systemic therapies. Patients received romidepsin as an intravenous infusion at a dose of 14 mg/m^2 on days 1, 8, and 15 every 28 days. Response was determined by a composite assessment of total tumor burden including cutaneous disease, lymph node involvement, and blood (Sézary cells).

Results
Ninety-six patients were enrolled and received one or more doses of romidepsin. Most patients (71%) had advanced stage disease (≥ IIB). The response rate was 34% (primary end point), including six patients with complete response (CR). Twenty-six of 68 patients (38%) with advanced disease achieved a response, including five CRs. The median time to response was 2 months, and the median duration of response was 15 months. A clinically meaningful improvement in pruritus was observed in 28 (43%) of 65 patients, including patients who did not achieve an objective response. Median duration of reduction in pruritus was 6 months. Drug-related adverse events were generally mild and consisted mainly of GI disturbances and asthenic conditions. Nonspecific, reversible ECG changes were noted in some patients.

Conclusion
Romidepsin has significant and sustainable single-agent activity (including improvement in pruritus) and an acceptable safety profile, making it an important therapeutic option for treatment refractory CTCL.

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INTRODUCTION

Primary cutaneous T-cell lymphomas (CTCLs) are rare forms of non-Hodgkin's lymphoma that present in the skin. The most common type of CTCL is mycosis fungoides (MF). Skin manifestations of MF include patches, plaques, tumors, and erythroderma. Disease progression in MF may lead to involvement of blood, lymph nodes, and viscera. Sézary syndrome (SS) is a leukemic variant of CTCL with diffuse skin involvement (erythroderma).

Accurate staging of CTCL is important because therapeutic strategies are primarily based on the clinical stage of the disease.[1-3] Studies have shown that the most significant prognostic factors include type and extent of skin involvement and extracutaneous disease.[4]

Early stage disease (IA to IIA) with limited skin involvement is generally treated with skin-directed therapies.[3,5] Treatment of advanced stage disease (≥ IIB) includes systemic therapy with alpha interferon, bexarotene, photopheresis, denileukin diftitox, vorinostat, cytotoxic chemotherapy, or combined modality therapies.

Romidepsin is a novel agent in the new class of antineoplastic agents known as histone deacetylase (HDAC) inhibitors. HDAC inhibitors have been shown to increase acetylation of histones and other proteins, which is associated with antitumor activity such as chromatin remodeling, tumor suppressor gene transcription, growth inhibition, and apoptosis.[6-10] Romidepsin inhibits class I and II HDACs, and preclinical studies suggest that romidepsin is among the most

potent inhibitors of HDACs, demonstrating activity at nanomolar concentrations.[7]

Romidepsin activity in T-cell lymphomas was observed in phase I and II trials conducted by the National Cancer Institute (NCI) in patients with both MF and SS.[11-15] The primary objective of the study reported here was to confirm this activity in patients with pretreated CTCL and to support the US Food and Drug Administration (FDA) approval of romidepsin in this patient population. Secondary objectives were to evaluate the duration of objective response (DOR), time to progression (TTP), and time to response (TTR) and to assess improvement in pruritus, a significant symptom of CTCL. The safety profile of romidepsin was also assessed.

PATIENTS AND METHODS

Study Design and Eligibility Criteria

This prospective, single-arm, open-label, phase II study was conducted at 33 centers in eight countries. Patients with stage IB to IVA CTCL (at study entry) confirmed by centrally reviewed biopsy, including patients with MF and SS, were eligible. Staging was based on original American Joint Committee on Cancer (AJCC)[16] criteria according to the Tumor-Node-Metastasis-Blood (TNMB) categories and the overall staging system described at the NCI workshop.[17] Patients with CTCL who were age $\geq$ 18 years, had experienced one or more systemic therapy failures, and had adequate organ function (hemoglobin $\geq$ 9.0 g/dL, absolute neutrophil count $> 1.5 \times 10^9$/L, platelets $\geq 100 \times 10^9$/L, total bilirubin $\leq$ 1.25$\times$ upper limit of normal (ULN), AST and ALT $\leq$ 2.0$\times$ ULN, and serum creatinine $\leq$ 2.0$\times$ ULN) were eligible. Study entry required Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and no known significant cardiac abnormalities (eg, congenital long QT syndrome, QTc $>$ 480 milliseconds, cardiac arrhythmia requiring antiarrhythmic medication, myocardial infarction within the previous 12 months, history of coronary artery disease, symptomatic congestive heart failure, ventricular tachycardia, ventricular fibrillation, Torsades de pointes, or cardiac arrest). Patients receiving QTc-prolonging or CYP3A4-inhibiting drugs, and those requiring concomitant steroids (topical or systemic) or antihistamines were excluded.

The protocol, informed consent form, and other relevant study documentation were approved by the appropriate institutional review board or independent ethics committee before any patients were enrolled. All patients provided written informed consent to participate in the study before any study-specific procedure was performed.

Patients received romidepsin 14 mg/m^2 as a 4-hour intravenous infusion on days 1, 8, and 15 of each 28-day cycle for up to six cycles, with optional extension of treatment for patients with stable disease or response. This dose and schedule were based on findings of the phase II NCI study of romidepsin in patients with CTCL.[15] Disease assessment was conducted at screening, baseline, the first day of all subsequent cycles, and 30 days after the last cycle.

Efficacy Assessment and Response Criteria

Current standard criteria for the assessment of response in solid tumors[18] and in lymphomas[19] do not adequately account for assessment of disease in the skin or blood. To assess the efficacy of romidepsin in CTCL, a composite end point was used, which included the severity-weighted assessment tool (SWAT)[20,21] and erythroderma[22,23] scores, with added criteria for the assessment of nodal disease and blood involvement.

A complete response (CR) was defined as complete resolution of skin disease, no evidence of abnormal lymph nodes, and the absence of circulating Sézary cells. A partial response (PR) was defined as a $\geq$ 50% improvement in the sum of the three assessments (change in skin, change in lymph node, and change in peripheral blood) but with a $\geq$ 30% improvement in the change in skin, no worsening in lymph nodes or Sézary cells, and no evidence of new tumors. CR/PR documentation required confirmation of response after 4 weeks.

Patients with evidence of a new cutaneous or noncutaneous tumor or $>$ 25% worsening from baseline in the sum of the three assessments (with a $\geq$ 15% worsening in skin) were considered to have progressive disease (PD). Patients who did not have enough improvement in the sum of the three assessments to qualify as PR or PD and had no evidence of new tumors were considered to have stable disease.

Skin involvement was based on the SWAT score,[20,21] which was calculated by determining the percentage of body surface area affected by patches, plaques, and tumors within 12 body regions. The percentage of body surface area for each lesion type was multiplied by a number: patch = 1, plaque = 2, and tumor = 3. The three weighted subtotals were added to determine the total score. Patients with erythroderma had five areas assessed using a 5-point scale from 0 (no erythroderma) to 4 (severe [ie, diffuse] erythema). Standard photographic documentation of skin lesions was performed at baseline and on day 1 of each cycle.

Response Evaluation Criteria in Solid Tumors (RECIST) methodology was used to assess abnormal lymph nodes.[18] Lymph nodes were usually measured by computed tomography or magnetic resonance imaging, although clinical measurement was allowed if appropriate. A consistent assessment method was used for each abnormal node.

The presence of circulating malignant T-cells (Sézary cells originally defined by CD4$^+$/CD7$^-$/CD26$^-$ and subsequently by CD4$^+$/CD7$^-$ and/or CD4$^+$/CD26$^-$ immunophenotype) in the peripheral blood was assessed by flow cytometry in most cases. Morphology was used occasionally.

The DOR was defined as the time from the first date of objective response to the first date of PD. The TTR was defined as the time from the first date of study drug to the first date of response. The TTP was defined as the time from the first date of study drug to the first date of PD.

Pruritus was reported monthly by the patients using a 100-mm visual analog scale (VAS).[22,23] Patients were considered to have significant pruritus if their baseline VAS score was $\geq$ 30 mm. Clinically meaningful reduction in pruritus was defined as a decrease in VAS score of $\geq$ 30 mm or a score of 0 for at least two consecutive cycles.

Safety Assessments

Vital sign measurements, ECOG performance status, ECG (digital in triplicate with central read), clinical laboratory assessments, and adverse event recording were performed at weekly study visits. Patients who discontinued the study for reasons other than PD were to continue follow-up every 2 months for disease status.

Statistical Methods

All patients who received one or more doses of romidepsin were included in the efficacy and safety analyses. Response (CR or PR) was determined by investigators using a composite assessment. A two-sided 95% CI was constructed about the objective response rate (ORR) using exact methods based on binomial distribution. Changes from baseline over time in pruritus VAS score and TTR were assessed using descriptive statistics. DOR and TTP were analyzed by Kaplan-Meier product limit estimates.

RESULTS

Patient Characteristics

Between February 2005 and July 2007, 96 patients with CTCL received one or more doses of romidepsin, and all were included in the analyses. Thirty-five patients (36%) completed six cycles of treatment, with 10 of these patients continuing treatment beyond six cycles, including four with confirmed PR who were still receiving romidepsin at the time of this analysis. Sixty-one (64%) of 96 patients discontinued treatment during cycles 1 to 6, most commonly because of disease progression (21 patients [22%]), withdrawal of consent (21 patients [22%]), and adverse events (17 patients [18%]).

Patient demographics and baseline characteristics are presented in Table 1. Most patients (71%) had advanced disease (stage $\geq$ IIB), and the median number of prior systemic therapies was three. Thirty-seven patients (39%) had blood involvement

Table 1. Patient Demographics and Baseline Characteristics

Characteristic	All Patients (N = 96) No.	%
Sex		
Male	59	61
Female	37	39
Age, years		
Mean	57	
SD	12	
White race/ethnicity	90	94
ECOG performance score		
0	49	51
1	47	49
Duration CTCL, years		
Median	3	
Range	< 1-26	
Disease stage*		
IB	15	16
IIA	13	14
IIB	21	22
III	23	24
IVA	24	25
Patients with blood involvement†	37	39
Pruritus‡		
Moderate	29	30
Severe	36	38
Prior therapy		
Any		
Median	4	
Range	1-11	
Systemic		
Median	3	
Range	1-8	
Chemotherapy§	74	77
Immunotherapy¶	36	38
Bexarotene	32	33
Photopheresis	18	19
Denileukin diftitox	14	15
Steroids	12	13
Skin-directed		
Median	2	
Range	1-5	
Phototherapy	51	53
Radiotherapy	36	38
Steroids	35	36
Other skin directed therapy	18	19

Abbreviations: SD, standard deviation; ECOG, Eastern Cooperative Oncology Group; CTCL, cutaneous T-cell lymphoma.
*Stage based on a report from the American Joint Committee on Cancer.
†Includes patients with > 5% of lymphocytes as Sézary cells at baseline; this designation is independent of stage.
‡Moderate pruritus, 100-mm visual analog scale (VAS) score ≥ 30-69; severe pruritus, VAS score ≥ 70.
§Cyclophosphamide, doxorubicin, vincristine, prednisone; cyclophosphamide, vincristine, prednisone; or methotrexate.
¶Includes alpha interferon, actimmune, sargramostin, peg-intron, and CpG trial (an experimental combination), with interleukin-1 [IL-1] beta.

(> 5% of peripheral blood lymphocytes as Sézary cells at baseline, by AJCC/NCI criteria). Thirteen patients had a higher blood tumor burden (Sézary cells at > 1,000/μL and/or Sézary cells > 20% of lymphocytes).

Efficacy

The ORR was 34%, including six CRs (Table 2). Response to romidepsin was observed in all stages of disease, including the advanced disease group: 26 (38%) of 68 patients with advanced stage disease (≥ IIB) responded, including five CRs. Among the 44 patients who received two or more systemic therapies before study entry, the ORR was 30%; of the 37 patients who had received prior therapy with either bexarotene or denileukin diftitox, the ORR was 35%. The ORR was 34% in the 74 patients who received prior chemotherapy.

Romidepsin was active in all compartments of disease, including blood, skin, and lymph nodes. Of 37 patients with blood involvement, 12 patients (32%) had a response to romidepsin therapy, including two CRs. Of the 13 patients with a higher blood tumor burden at baseline, four (31%) had an objective response by the composite assessment, and six patients for whom Sézary cell counts for multiple cycles were available had rapid and sustained decrease in Sézary cell

Table 2. Disease Response

Response	All Patients (N = 96) No.	%	95% CI
ORR (CR + PR)	33	34	25 to 45
CR	6	6	2 to 13
PR	27	28	19 to 38
SD	45	47	37 to 57
PD	10	10	5 to 18
Stage IB and IIA (n = 28)			
ORR	7	25	
CR	1	4	
Stage IIB (n = 21)			
ORR	9	43	
CR	2	10	
Stage III (n = 23)			
ORR	9	39	
CR	1	4	
Stage IVA (n = 24)			
ORR	8	33	
CR	2	8	
Stage IIB to IVA (n = 68)			
ORR	26	38	
CR	5	7	
ORR in patients with blood involvement (n = 37)	12	32	
Duration of response (OR; n = 33), months*			
Median	15.0		
Range	0.0+-19.8+		
TTR (OR; n = 33), months			
Median	2.0		
Range	0.9-4.8		
TTR (CR; n = 6), months			
Median	4		
Range	0.9-6.9		
TTP (n = 33), months			
Median	8		
Range	0+-21.7+		

Abbreviations: ORR, objective response rate; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; OR, overall response; TTR, time to response; TTP, time to progression; (+) denotes censored value.
*Patients were censored to their last evaluation with a global tumor assessment if they did not progress.

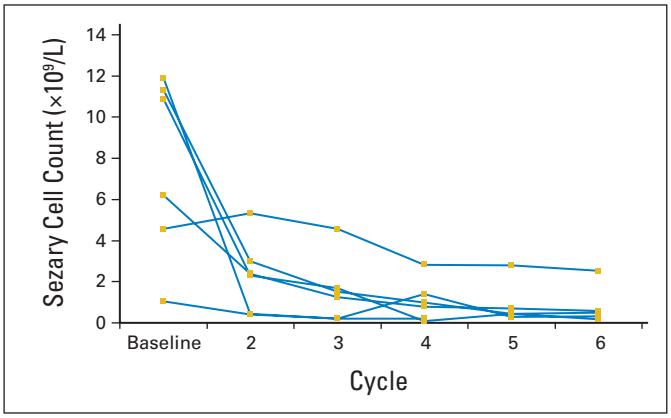

Fig 1. Sézary cell counts for six of the 13 patients with a higher blood tumor burden (Sézary cells at > 1,000/μL and/or Sézary cells > 20% of lymphocytes) at baseline.

counts (Fig 1). There was a ≥ 50% reduction in SWAT and/or erythroderma scores in 38 patients (40%; Figs 2A and 2B). All patients with a global tumor response had a ≥ 50% improvement in skin SWAT score. Representative photographs of skin lesions are provided in Figures 3A, 3B, and 3C. Among the 37 patients with lymphadenopathy, 13 (35%) exhibited a response by RECIST criteria (≥ 30% reduction in the sum of the longest diameters of nodes; Fig 2C). Representative scans are provided in Figure 3D. The median DOR was 15 months. The median time to response was 2 months, while the median time to CR was 4 months (Table 2).

Most (92%) of the 65 patients with moderate to severe pruritus at baseline showed improvement in their pruritus score. Clinically meaningful improvement in pruritus (a VAS decrease of ≥ 30 mm or a score of 0 for two consecutive cycles) was observed in 28 (43%) of 65 patients, including patients who did not achieve an objective disease response. Figure 2D shows changes from baseline in VAS for individual patients. The median duration of pruritus relief was 6 months. Seven patients with a response (three CR, four PR) who had severe pruritus (VAS of 70 to 100 mm) at baseline reported pruritus resolution (VAS of 0 mm) that was sustained for 2 to 8 months.

Safety

The most common drug-related adverse events were GI disturbances and asthenic conditions (Table 3). Most events were mild to moderate in severity. Drug-related adverse events led to discontinuation in 14 patients (15%) and included fatigue (four patients), prolonged QT (two patients), and pyrexia (one patient). The incidence of drug-related serious adverse events was low, with tumor lysis syndrome being the only such event reported in one or more patients. In addition, seven of 17 grade 3 or 4 drug-related serious adverse events occurred in a single patient (Table 3).

Six patients (6%) died within 30 days of receiving their last dose of romidepsin. One death (cardiopulmonary failure) was considered

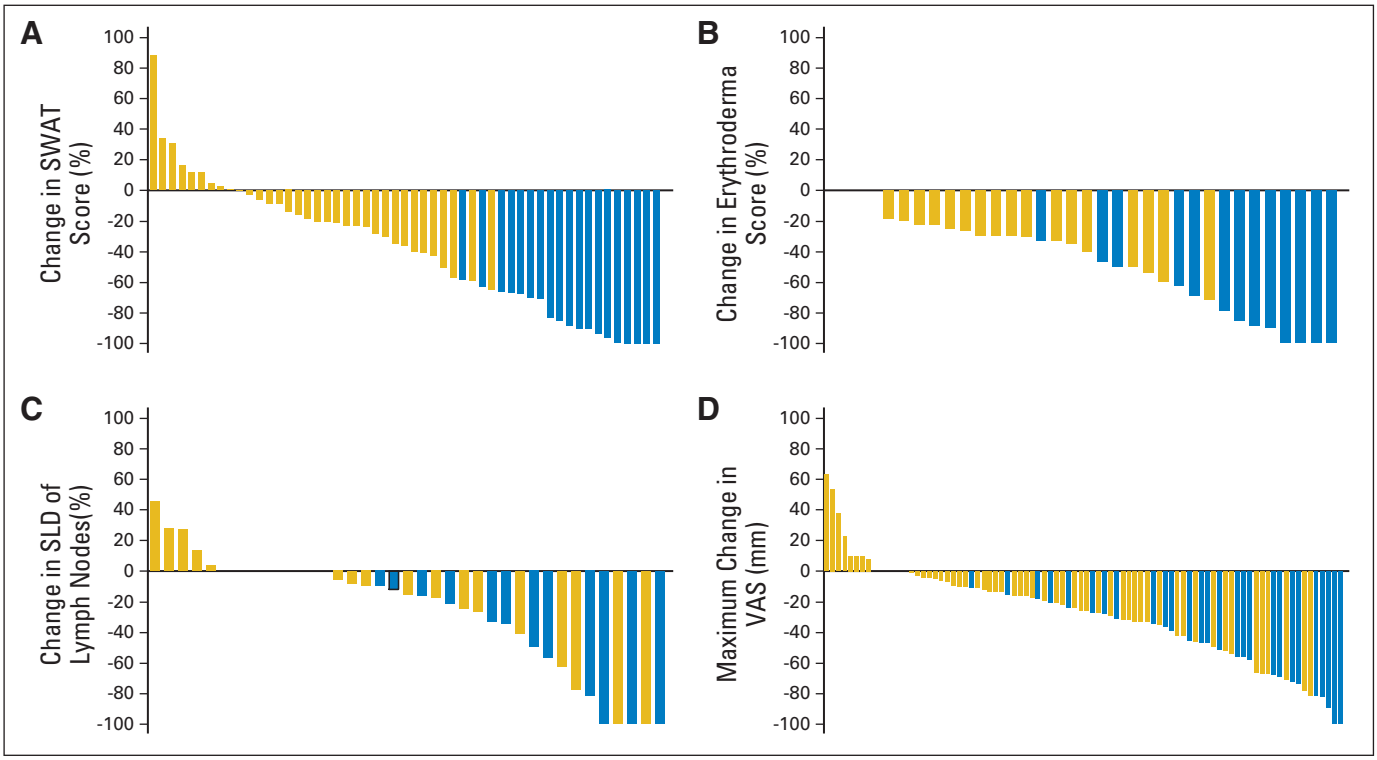

Fig 2. Maximum percent improvements from baseline in (A) severity-weighted assessment tool (SWAT) scores (in 53 patients without erythroderma at baseline), (B) erythroderma scores (in 34 patients with erythroderma at baseline), (C) sum of the longest diameter of lymph nodes (in 37 patients who had lymphadenopathy at baseline, and postbaseline data). Responders (complete response [CR] and partial response [PR]) are depicted by blue bars and nonresponders by gold bars. For SWAT, all patients with a clinical response as assessed by the composite had a ≥ 50% improvement in SWAT score. Lymphadenopathy was defined as one or more peripheral lymph nodes ≥ 15 mm by conventional measurements or one or more central lymph nodes ≥ 10 mm by spiral computed tomography. (D) Maximum improvement from baseline using a 100-mm visual analog scale (VAS) in the 85 patients with a VAS score at study entry (baseline or screening) and who had postbaseline VAS data available. Responders (CR and PR) are depicted by blue bars and nonresponders by gold bars.

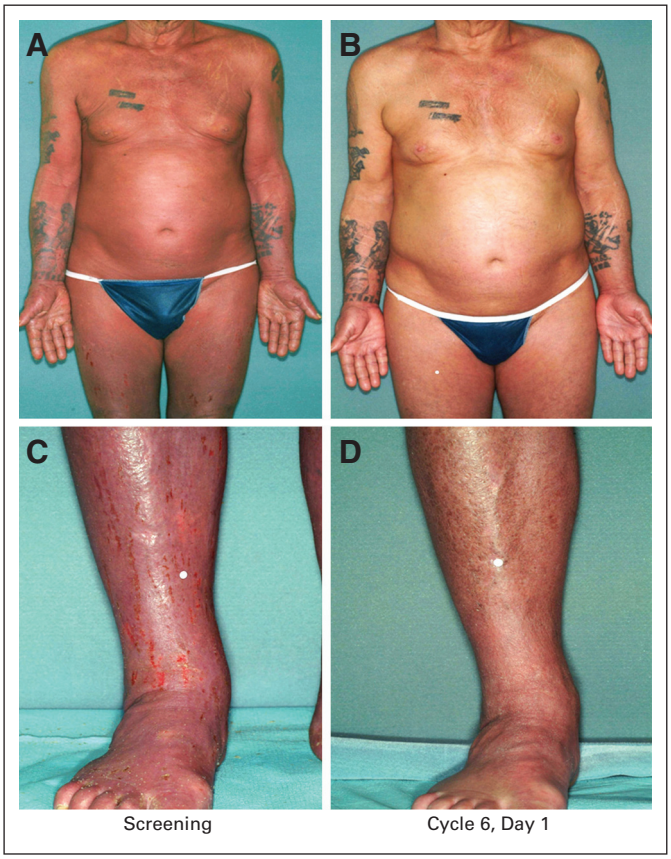

Fig 3. Photographs and computed tomography (CT) scan at baseline and during romidepsin treatment. (A-D) This patient (stage III) had moderate to severe erythroderma at baseline and had previously experienced three chemotherapy regimen failures. Best overall response: complete response (CR); time to response: 2 months; duration of response: ≥ 5 months. (Figure continued on next column.)

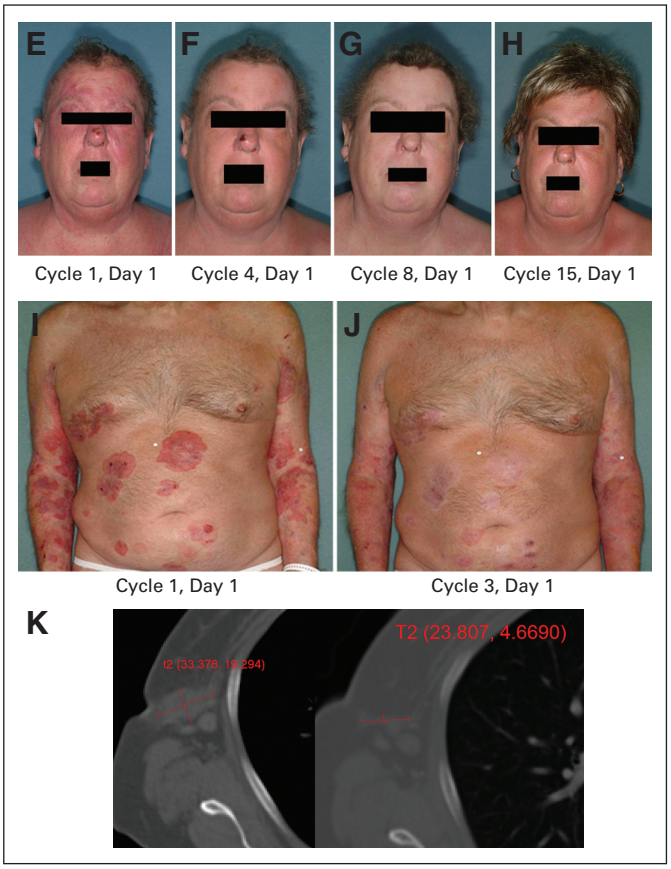

Fig 3. Continued. (E-H) This patient (stage IIB) experienced treatment failure of interferon, methotrexate, and deoxycoformycin; psoralens plus ultraviolet radiation (PUVA); and total skin electron beam therapies. Best response: CR; time to partial response (PR): 3 months; time to CR: 7 months; overall duration of response: 19 months. (I, J) This patient (stage IIB) experienced treatment failure of bexarotene and denileukin diftitox. Best overall response: PR; time to response: 1 month; duration of response: ≥ 20 months. (K) This patient (stage IVA) had erythroderma and 34% circulating Sézary cells at baseline and had received prior PUVA, methotrexate, and bexarotene. Best overall response: PR; time to response: 1 month; duration of response: ≥ 6 months. The spiral CT scan is of a lymph node; measurements of the node are as indicated.

by the investigator as possibly related to treatment, but an independent review concluded that disease progression was the most likely cause of death. Three of the other five deaths were due to disease progression alone; one was due to disease progression and dyspnea, and one was due to disease progression and acute renal failure.

The mean QTcF change from a baseline before antiemetic medication to 2 hours after romidepsin dose was 4.6 milliseconds (90% CI, 1.8 to 7.4 milliseconds). The mean QTcF change from a baseline after antiemetic administration was 1.3 milliseconds (90% CI, 1.6 to 4.2 milliseconds), indicating the contribution of antiemetic medications to the QTcF change. No patients had QTcF values > 480 milliseconds, and there was no change from baseline of > 60 milliseconds. Prolonged QT interval and corrected prolonged QTc interval were reported as adverse events in three and two patients, respectively. The ECG values returned to baseline within 24 hours and were not associated with functional cardiovascular changes or symptoms.

DISCUSSION

In this single-arm, open-label, pivotal study of 96 patients, romidepsin demonstrated clinical benefit in CTCL with an ORR of 34%, including six CRs. Of patients with advanced stages of disease (≥ IIB), 38% achieved an objective response, including five CRs.

To the best of our knowledge, this is the first CTCL study to evaluate a global tumor (composite) response in all disease sites commonly involved in advanced disease, namely skin, lymph node, and peripheral blood tissue compartments. Previous studies have concentrated on assessment of tumor burden within the skin alone (eg, High-dose spatially-fractionated radiation [GRID], physician's global assessment [PGA], SWAT, erythroderma scores, Composite Assessment of Index Lesion Severity [CAILS]) as the primary site of disease.[22,24,25] This study employed a rigorous composite end point that was based on a summation of the assessment of cutaneous disease using the standard SWAT or erythroderma score as well as RECIST computed tomography measurement for nodal responses and changes in peripheral blood tumor burden (Sézary cells) based on flow cytometry. In addition, although global tumor PRs were required to include a minimum of 30% improvement in the skin score, all patients with a PR had a > 50% improvement in SWAT scores. These findings indicate that all disease sites can show a clinical response to romidepsin and that the ORR represents a meaningful global tumor response.

Table 3. Drug-Related Adverse Events (N = 96)

Event	All Grades		Grade 3		Grade 4	
	No.	%	No.	%	No.	%
Most common (in ≥ 10% of patients)						
Nausea	54	56	2	2	0	
Asthenic conditions*	42	44	6	6	0	
Vomiting	25	26	1	1	0	
Anorexia	19	20	0		0	
Diarrhea	13	14	0		1	1
Headache	13	14	0		0	
Aguesia	12	13	0		0	
Thrombocytopenia	11	11	0		0	
Dysguesia	11	11	0		0	
Anemia	10	10	2	2	0	
Serious with ≥ one incidence of grade 3 or 4†						
Tumor lysis syndrome‡	2	2	1	1	1	1
Oral candidiasis	1	1	1	1	0	
Oropharyngeal candidiasis	1	1	1	1	0	
Anemia	1	1	1	1	0	
Atrioventricular block‡	1	1	1	1	0	
Cardiac failure	1	1	1	1	0	
Cardiopulmonary failure	1	1	1	1	0	
Hyperglycemia	1	1	1	1	0	
Hypoalbuminemia‡	1	1	1	1	0	
Leukocytosis	1	1	1	1	0	
Pleural effusion‡	1	1	1	1	0	
Pyrexia	1	1	1	1	0	
Sepsis	1	1	0		1	1
Dermatitis medicamentosa	1	1	0		1	1
Ventricular tachycardia‡	1	1	0		1	1
Troponin 1 increase‡	1	1	0		1	1
Cardiac tamponade‡	1	1	0		1	1

*Includes asthenia, fatigue, lethargy, and malaise.
†The following grade 1 or 2 serious adverse events occurred in one patient each: malaise, hypotension, syncope, electrocardiogram ST segment depression, bradyarrhythmias, decreased urine output, and pharyngitis.
‡These events all occurred in one patient who was assessed to have stage IIB disease at study entry. Prior therapy included interferon alpha, denileukin diftitox, bexarotene, gemcitabine, total body surface electron beam radiotherapy, photopheresis, psoralen and ultraviolet A radiation, and nitrogen mustard skin-directed therapy. The patient's medical history was notable for hypertension, gastroesophageal reflux disease, depression, hysterectomy, severe restrictive lung disease, hyperlipidemia, osteopenia milia, anterior myocardial infarction (> 1 year before study entry), peripheral neuropathy, rash, and cough. Seven days before study entry, the patient developed a thrombosis in the inferior vena cava, and heparin treatment was started. Study drug was discontinued as a result of cardiac tamponade.

Currently, there is no single standard of care for patients with advanced stages of CTCL.[1] Responses to multiple therapies, including both single and combination chemotherapy regimens, are variable and usually short-lived.[3] In this study, durable responses to romidepsin were observed in all stages of disease, including late-stage (≥ IIB) patients. Furthermore, these patients had refractory disease, with a median of three prior systemic therapies, and > 75% of patients had received prior chemotherapy. Patients with blood involvement (SS) represent a major therapeutic challenge. Of 37 patients with blood involvement, 12 (32%) achieved an overall clinical response, with two CRs. Thirteen of these 37 patients had a higher blood tumor burden, and four achieved a global response. Specifically, romidepsin treatment resulted in a rapid, dramatic, and durable reduction in Sézary cell counts in these patients.

Pruritus, which can be particularly severe in SS, is a significant symptom of CTCL that impairs patients' quality of life.[24,26] After romidepsin administration, most patients (92%) had improvement in pruritus. A clinically meaningful reduction in pruritus (VAS decrease of ≥ 30 mm) was observed in 43% of patients with moderate to severe symptoms at baseline. The median duration of pruritus improvement was 6 months. These results occurred despite the exclusion of steroid (topical or systemic) and antihistamine use in this study. In addition, relief from pruritus was also evident in patients who did not meet objective response criteria, emphasizing that most patients in this study realized a clinical benefit from romidepsin therapy.

While the median TTR was 2 months, the median time to CR was longer (4 months), indicating that CR can occur during continued treatment after a period of sustained PR. Durable clinical response in CTCL is difficult to achieve with currently available therapies. The 15-month median DOR in this study indicates that romidepsin provides a meaningful clinical benefit. The TTR, DOR, and TTP results from this study compare favorably with approved CTCL therapies, although direct comparisons with other clinical trials are difficult because of differences in response criteria.[22,25,27]

Most of the adverse events associated with romidepsin therapy were mild (grade 1 or 2). Common categories of adverse events were consistent with those previously reported with romidepsin[15] and primarily included nausea and asthenia. Minimal hematologic toxicity was observed, and GI symptoms such as diarrhea were rare (17% grade 1 or 2 and 1% grade 4). Patients treated with romidepsin show a small, clinically insignificant change in the QTc that appears to be partially attributed to antiemetics. Initially, the HDAC inhibitors were suspected of having a clinically significant effect on QTc prolongation, but as the data accumulate, that suspicion appears unfounded.[28] However, electrolyte levels (potassium and magnesium) should be normalized before romidepsin infusion. The safety findings in this study suggest that the toxicities associated with romidepsin are tolerable and manageable.

These results indicate that romidepsin is an effective single-agent therapy in patients with CTCL who have received one or more prior systemic therapies. Clinically meaningful, durable responses including CRs were observed across all clinical stages, including patients with advanced disease and those with blood and/or lymph node involvement. The safety profile suggests that romidepsin has a favorable risk-benefit ratio. These results are consistent with the findings of the phase II NCI-sponsored study in a similar population using the same dose and schedule of romidepsin, where the ORR was 34%, including four CRs.[15] A favorable review of these two studies (the pivotal study presented here and the NCI-sponsored study) led to approval by the United States in November 2009 for the use of romidepsin in patients with CTCL.

Despite this new therapy, CTCL remains a chronic illness that, in advanced stages, requires fairly constant therapy. By combining romidepsin with other drugs, regimens that result in even more significant and durable responses may be identified.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked

with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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