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ORIGINAL REPORT

# Phase II Multi-Institutional Trial of the Histone Deacetylase Inhibitor Romidepsin As Monotherapy for Patients With Cutaneous T-Cell Lymphoma

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## ABSTRACT

### Purpose
Romidepsin (depsipeptide or FK228) is a member of a new class of antineoplastic agents active in T-cell lymphoma, the histone deacetylase inhibitors. On the basis of observed responses in a phase I trial, a phase II trial of romidepsin in patients with T-cell lymphoma was initiated.

### Patients and Methods
The initial cohort was limited to patients with cutaneous T-cell lymphoma (CTCL), or subtypes mycosis fungoides or Sézary syndrome, who had received no more than two prior cytotoxic regimens. There were no limits on other types of therapy. Subsequently, the protocol was expanded to enroll patients who had received more than two prior cytotoxic regimens.

### Results
Twenty-seven patients were enrolled onto the first cohort, and a total of 71 patients are included in this analysis. These patients had undergone a median of four prior treatments, and 62 patients (87%) had advanced-stage disease (stage IIB, n = 15; stage III, n= 6; or stage IV, n = 41). Toxicities included nausea, vomiting, fatigue, and transient thrombocytopenia and granulocytopenia. Pharmacokinetics were evaluated with the first administration of romidepsin. Complete responses were observed in four patients, and partial responses were observed in 20 patients for an overall response rate of 34% (95% CI, 23% to 46%). The median duration of response was 13.7 months.

### Conclusion
The histone deacetylase inhibitor romidepsin has single-agent clinical activity with significant and durable responses in patients with CTCL.

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## INTRODUCTION

Histone deacetylase inhibitors (HDIs) cause growth arrest, cellular differentiation, and apoptosis.[1-4] Their antitumor effects have been hypothesized to occur through modulation of gene expression; however, acetylation of nonhistone proteins may be more important.[5,6] Romidepsin (FK228, FR901228, depsipeptide), (1S,4S,7Z,10S,16E,21R)-7-ethylidene-4,21-bis(1-methyletheyl)-2-oxa-12,13-dithia-5,8,20,23-tetraazabicyclo[8.7.6]tricos-16-ene-3,6,9,19,22-pentone, is a potent HDI isolated from *Chromobacterium violaceum* (Appendix Fig A1, online only).[7,8] Dramatic responses observed in patients with T-cell lymphoma[9-11] prompted a phase II trial to assess the response rate and toxicity profile. The activity of romidepsin in cutaneous T-cell lymphoma (CTCL) seems to be a class effect, with other HDIs also found to demonstrate activity.[12,13]

Between 2,000 and 3,000 new cases of CTCL occur in the United States each year, with mycosis fungoides (MF) and the Sézary syndrome (SS) being the predominant subtypes.[14] MF is categorized as limited stage (IA, IB, and IIA), characterized as plaques or patches limited to skin, and advanced stage (IIB to IVB), characterized by cutaneous tumors and involvement of the blood, lymph nodes, bone marrow, or visceral organs.[15] SS is characterized by generalized erythroderma and abnormal lymphoid cells in the blood.[16] Limited-stage disease may effectively be treated with skin-directed therapies including topical nitrogen mustard or psoralen plus ultraviolet A therapy.[17] However, in patients with advanced disease, control is often short lived, and the disease is relentlessly progressive. Although

response rates to cytotoxic chemotherapy range from 60% to 80% in patients with advanced disease, the median duration of response is usually measured in months.[18] Agents with novel mechanisms of action have been pursued, including retinoids, interferon, monoclonal antibodies, and denileukin diftitox; none has been found to be curative.

This trial was initiated to evaluate the efficacy of romidepsin in patients with T-cell lymphoma. Secondary goals included evaluation of long-term safety of romidepsin. This report is limited to patients with MF or SS; patients with peripheral T-cell lymphoma (PTCL) will be reported separately.

## PATIENTS AND METHODS

### *Patient Eligibility*

Patients with relapsed, refractory, or advanced CTCL, either as MF or SS, were eligible. The first cohort included patients who had received no more than two systemic cytotoxic chemotherapy regimens. Topical therapies, such as psoralen plus ultraviolet A therapy or topical chemotherapy; systemic therapies, such as corticosteroids, retinoids, interferon, or denileukin diftitox; and nonradiolabeled antibodies, such as alemtuzumab, were not considered cytotoxic chemotherapy; prior therapy with any number of these therapies was allowed. Patients with stage IA, IB, or IIA disease[15] were only eligible if they were refractory to, intolerant of, or had reached a 6-month or longer response plateau on at least two prior CTCL therapies. The observed activity led us to open the trial at additional sites and to include patients who had previously received more than two cytotoxic therapies. In addition, after completion of the first cohort, a replicate cohort with the same inclusion criteria was undertaken. The protocol, informed consent, and subsequent amendments were approved by the institutional review boards of all participating institutions. Histologic diagnosis was confirmed by the respective treating institution. All patients signed informed consent. Standard phase II inclusion and exclusion criteria were used (detailed in Appendix Table A1, online only). Patients maintained on a stable dose of corticosteroids at protocol entry were allowed, with tapering to follow initiation of therapy. Effective birth control was required.

### *Trial Design and Treatment Plan*

Romidepsin (NSC 630176) was provided by the Cancer Therapy Evaluation Program of the National Cancer Institute (NCI). Romidepsin was administered as a 4-hour infusion at 18 mg/m$^2$ on days 1 and 5 of a 21-day cycle for the first three patients, which was the schedule originally studied at the NCI.[9] Subsequently, by amendment, patients were treated on the more tolerable schedule of 14 mg/m$^2$ on days 1, 8, and 15 of a 28-day cycle (Appendix Fig A2, online only).[10] Doses were held for absolute neutrophil count less than $0.5 \times 10^9$ cells/L, platelet count less than $50 \times 10^9$/L, or grade 3 or worse nonhematologic toxicity. Doses were reduced from 14.0 to 10.5 mg/m$^2$ (dose level –1) or from 10.5 to 8.0 mg/m$^2$ (dose level –2) for absolute neutrophil count between 0.5 and $1.0 \times 10^9$ cells/L or platelet count between 50 and $75 \times 10^9$/L on days 8 or 15. Dose escalation to 17.5 mg/m$^2$ (dose level +1) was allowed in the absence of toxicity. Radiotherapy of nonresponding lesions was allowed for patients with evidence of overall response. Irradiated lesions were not included in response assessment after radiation. Patients who received radiation while on protocol were not categorized as complete responders. The NCI Common Toxicity Criteria, version 2.0, were used.

### *Supportive Care*

Patients with CTCL are at risk for hypomagnesemia.[19] Because hypomagnesemia and hypokalemia are associated with T-wave and ST segment abnormalities and QT interval prolongation, findings also associated with HDI therapy, the protocol was amended to mandate supplementation of electrolytes to achieve serum magnesium and potassium levels of greater than 0.85 mmol/L and 4.0 mmol/L, respectively, before romidepsin administration.[20] The protocol was also amended to exclude medications known to either

**Table 1.** Patient Demographics and Clinical Characteristics

| Characteristic | Cohort 1 (n = 27) No. of Patients | Cohort 1 (n = 27) % | All Patients (N = 71) No. of Patients | All Patients (N = 71) % |
|---|---|---|---|---|
| Sex | | | | |
| Male | 20 | | 48 | |
| Female | 7 | | 23 | |
| Age, years | | | | |
| Median | 57 | | 57 | |
| Range | 31-77 | | 28-84 | |
| < 50 | 5 | | 20 | |
| ≥ 50 | 22 | | 51 | |
| Disease stage at time of enrollment | | | | |
| IA | 0 | | 1 | |
| IB | 2 | | 6 | |
| IIA | 0 | | 2 | |
| IIB | 5 | | 15 | |
| IIIA | 2 | | 3 | |
| IIIB | 0 | | 3 | |
| IVA | 14 | | 28 | |
| IVB | 4 | | 13 | |
| ECOG performance status | | | | |
| 0 | 5 | | 16 | |
| 1 | 16 | | 45 | |
| 2 | 6 | | 10 | |
| Elevated LDH | 10 | | 30 | |
| Low albumin | 8 | | 43 | |
| No. of prior therapies* | | | | |
| Median | 3 | | 4 | |
| Range | 1-11 | | 0-14 | |
| Previous topical therapies | 17 | 63 | 43 | 61 |
| PUVA | 16 | 59 | 39 | 55 |
| Topical NM | 7 | 26 | 16 | 23 |
| Topical bexarotene | 3 | 11 | 4 | 6 |
| Topical steroids | 4 | 15 | 11 | 15 |
| Previous radiation therapy† | 15 | 56 | 40 | 56 |
| Localized radiotherapy | 12 | 44 | 32 | 45 |
| TSEB | 6 | 22 | 13 | 18 |
| Previous extracorporeal photopheresis | 4 | 15 | 16 | 23 |
| Previous biologic therapies | 22 | 81 | 48 | 68 |
| IFN | 9 | 33 | 23 | 32 |
| Denileukin diftitox | 6 | 22 | 14 | 20 |
| Alemtuzumab | 1 | 4 | 4 | 6 |
| Anti-Tac antibody | 1 | 4 | 5 | 7 |
| Oral corticosteroids | 6 | 22 | 18 | 25 |
| Retinoid: oral bexarotene | 12 | 44 | 32 | 45 |
| Retinoid: other‡ | 5 | 19 | 10 | 14 |
| Previous systemic chemotherapy regimens§ | 13 | 48 | 46 | 65 |
| 0 | 14 | 52 | 25 | 35 |
| 1 | 11 | 41 | 20 | 28 |
| 2 | 2 | 7 | 14 | 20 |
| > 2 | 0 | 0 | 12 | 17 |

Abbreviations: ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; PUVA, psoralen plus ultraviolet A therapy; NM, nitrogen mustard; TSEB, total skin electron beam; IFN, interferon.

*Other treatments not listed include cyclosporine, tacrolimus, azathioprine, remicade, dendritic cell vaccine, and peldesine.

†Some patients had both localized radiation and TSEB.

‡Other retinoids include isotretinoin, acitretin, and etretinate. Three patients received bexarotene as well as another retinoid.

§Chemotherapies included monotherapy such as chlorambucil, cladribine, fludarabine, gemcitabine, liposomal doxorubicin, methotrexate, or pentostatin and combination therapy such as cyclophosphamide, doxorubicin, vincristine, and prednisone; infusional etoposide, vincristine, and doxorubicin with bolus cyclophosphamide; and cyclophosphamide, vincristine, and prednisone.

**Table 2.** Administered Therapy

| Treatment | Cohort 1 (n = 27) | All Patients (N = 71) |
|---|---|---|
| Total No. of cycles | 293 | 538 |
| Cycles per patient, No. of cycles | | |
| Median | 5 | 4 |
| Range | 1-72 | 1-72 |
| Cycles per patient, No. of patients | | |
| ≤ 2 | 4 | 13 |
| 3-5 | 10 | 31 |
| ≥ 6 | 13 | 27 |
| No. of doses per patient | | |
| Median | 15 | 12 |
| Range | 2-141 | 2-141 |
| No. of doses | | |
| Total | 756 | 1,462 |
| Full dose | 554 | 1,110 |
| Dose escalated | 39 | 102 |
| Reduced, total | 163 | 250 |
| Reduced as a result of toxicity | 22 | 42 |
| Held* | 2 | 8 |
| Dose administered | | |
| Cumulative dose, mg/m$^2$ | | |
| Median | 210 | 168 |
| Range | 28-2,538 | 28-2,538 |
| Cumulative dose, mg | | |
| Median | 386 | 306 |
| Range | 43-5,681 | 43-5,681 |

*According to protocol criteria.

prolong the QTc or interfere with CYP3A4 metabolism. The latter exclusion was added after it was found that romidepsin may be metabolized in part by CYP3A4.[21,22] Antiemetics were administered to prevent nausea.

### Response Evaluation

Response assessment used a rigorous composite approach. Disease in skin or viscera was assessed by Response Evaluation Criteria in Solid Tumors (RECIST) criteria,[23] and lymph node disease was assessed using International Working Group guidelines.[24] Bone marrow involvement, as recommended by International Working Group criteria, was scored as present or absent. Generalized erythroderma was scored as present or absent. Although the presence of circulating tumor cells is considered prognostically significant, the change in quantity of cells during therapy has not been demonstrated to be predictive of response.[25] Thus, flow cytometry of blood was assessed as present or absent. Complete response required clearing of known sites of disease. Partial response required documented response in skin or lymph nodes.

### Pharmacokinetic Analysis

Blood samples were collected with the first dose before drug administration, at the end of infusion (4 hours), and at 6, 11, 13, 15, 18, and 22 hours after start of infusion. Samples were centrifuged for 5 minutes at 1,200 × *g*, and collected plasma was stored at −80°C. Samples were analyzed using a sensitive analytic liquid chromatography-mass spectrometry assay validated for the range of 2 to 1,000 ng/mL.[26] Noncompartmental pharmacokinetic data analysis was performed using WINNonlin v.5 (Scientific Consultant, Apex, NC). The area under the curve (AUC) from time zero to time of final quantifiable sample was calculated using the linear trapezoidal method, whereas AUC extrapolated to infinity ($AUC_{inf}$) was calculated by extrapolation to infinity. Volume of distribution was estimated during the terminal phase, and systemic clearance was calculated as dose divided by $AUC_{inf}$.

### Statistical Methods

The trial began as a single-institution analysis of romidepsin in patients with CTCL or PTCL after no more than two prior cytotoxic therapies evaluated in separate cohorts. The Simon two-stage design[27] for the first cohort required a response in one of nine patients to accrue the full cohort of 24 patients to target a response rate of 25% and rule out a 5% response rate, with 10% probabilities of accepting a poor agent and of rejecting a good agent. Duration of response and time to progression were determined using the Kaplan-Meier method.

## RESULTS

### Patient Characteristics

Seventy-one patients with MF or SS were enrolled onto the phase II trial of romidepsin for patients with T-cell lymphoma as of the cutoff date for this analysis. Twenty-seven patients were enrolled onto the original cohort for patients who had not received more than two systemic cytotoxic chemotherapeutic regimens. Subsequently, by amendment, an additional 44 patients with CTCL were enrolled, 12 of whom had previously received more than two systemic cytotoxic chemotherapeutic regimens. Patient characteristics are listed in Table 1. At enrollment, 25 patients in cohort 1 (93%) and 62 (87%) of the 71 patients overall had advanced disease (stages IIB to IVB). Furthermore, 30 patients had elevated LDH, 43 patients had low albumin, and 51 patients were greater than 50 years old, which are all features associated with poor outcome.[28,29] These three prognostic factors were entirely absent in only three patients. All patients tested negative

**Table 3.** Pharmacokinetics of Romidepsin

| Parameter | 14 mg/m$^2$ | | | 18 mg/m$^2$ | | |
|---|---|---|---|---|---|---|
| | No. of Patients* | Geometric Mean | 95% CI | No. of Patients | Geometric Mean | 95% CI |
| Half-life, hours | 42 | 2.95† | 2.49 to 3.49 | 3 | 2.56 | 1.62 to 4.05 |
| $C_{max}$, ng/mL‡ | 61 | 361.52 | 313.49 to 416.92 | 3 | 722.18 | 366.93 to 1,421.38 |
| $AUC_{last}$, h · ng/mL | 61 | 1,214.23 | 1,044.16 to 1,412.01 | 3 | 2,571.05 | 1,258.64 to 5,251.92 |
| $AUC_{inf}$, h · ng/mL | 42 | 1,456.54 | 1,250.74 to 1,696.21 | 3 | 2,582.65 | 1,263.23 to 5,280.17 |
| $V_{z\ obs}$, L/m$^2$ | 42 | 40.89 | 33.40 to 50.06 | 3 | 25.75 | 13.16 to 50.36 |
| $Cl_{obs}$, L/h/m$^2$§ | 42 | 9.61 | 8.25 to 11.19 | 3 | 6.97 | 3.40 to 14.27 |

Abbreviations: $C_{max}$, maximum plasma concentration; $AUC_{last}$, area under the curve from time zero to time of final quantifiable sample; $AUC_{inf}$, area under the curve extrapolated to infinity; $V_{z\ obs}$, volume of distribution during the terminal phase; $Cl_{obs}$, observed clearance.
*Pharmacokinetic analysis was not possible in seven patients, and a full analysis was not possible in 19 patients.
†The median half-life was 2.64 hours (range, 1.0 to 10.9 hours).
‡$C_{max}$ is reported as observed value.
§Clearance is expressed as L/hour/m$^2$ because of the body-surface area dosing used.

  

for human T-lymphotropic virus. Patients had received a median of four prior regimens (Table 1). Prior therapies included topical treatments (61%), biologic agents (68%), cytotoxic chemotherapy (65%), and radiation therapy (56%).

Patients received a median of four cycles (range, one to 72 cycles) and 12 doses (range, two to 141 doses; Table 2). Among the 1,462 doses administered over 538 cycles, 1,110 (76%) were full doses, 102 (7%) were escalated doses, and 250 (17%) were reduced doses. Eight doses were held; three doses in three patients were held as a result of thrombocytopenia ($< 50 \times 10^9$/L), two were held for persistent grade 3 nausea, and three were held as a result of persistent grade 3 fatigue. Protocol-mandated dose reductions were required for 42 doses in 20 patients for the following reasons: 33 dose reductions were a result of thrombocytopenia ($> 50$ but $< 75 \times 10^9$/L), four were a result of granulocytopenia ($> 0.5$ but $< 1 \times 10^9$ cells/L), three were a result of persistent nausea, and two were a result of fatigue. The remainder of the doses less than 14 mg/m$^2$ (n = 208) were administered as permanent dose reductions in patients who previously had a dose held or had one or more protocol-mandated dose reductions.

First-dose pharmacokinetics were evaluable in a total of 64 patients, three of whom received romidepsin 18 mg/m$^2$ and 61 of whom received romidepsin 14 mg/m$^2$. Full pharmacokinetic parameters are listed in Table 3. $AUC_{inf}$ variation is plotted in Appendix Figure A3 (online only). The pharmacokinetic data were incorporated into a larger population pharmacokinetic analysis.[30]

### Toxicities

Toxicities that were commonly observed were similar to toxicities observed in the phase I trials of romidepsin and reported for other HDIs.[31] Cycle 1 toxicities are listed in Table 4. Common nonhematologic adverse effects (any grade) included fatigue (41%), nausea (52%), vomiting (20%), and anorexia (21%). Hematologic abnormalities included leukopenia (31%), granulocytopenia (37%), lymphopenia (21%), thrombocytopenia (39%), and anemia (37%). Transient elevations of liver function tests, AST or ALT, were observed in 13 patients; two additional patients had isolated grade 1 hyperbilirubinemia. Hyperuricemia was noted in 11 patients (eight patients with grade 1 and three patients with grade 3), and hypophosphatemia was noted in six different patients. As previously described, ECG changes were noted consisting of asymptomatic T-wave flattening (71%) or ST segment depression (9%). Toxicities in later cycles mirrored those observed in the first cycle. Infections occurred in 38 patients (54%) over 58 cycles (11%), including bacterial infections of the skin and upper respiratory, pulmonary, GI, and urinary tracts; bacteremia; and sepsis, and were not related to neutropenia. Neutropenia was noted in only 25 of the 538 cycles, and only one episode of neutropenic fever was noted in a patient while on protocol, occurring with progression of his bone marrow disease. Supportive care included prophylactic antiemetics for all patients and intravenous hydration in the occasional patient with marked nausea, fever, or hypotension.

Three deaths occurred among patients with CTCL while on study, and three deaths occurred within 30 days of removal from study. Deaths on study included a 70-year-old man with hypertension and severe valvular heart disease who had a partial response to romidepsin. After nine cycles of therapy, he developed atrial fibrillation and was placed on warfarin and digoxin. Romidepsin was restarted, and he was found without pulse 1 day after receiving the second dose of the subsequent cycle. Autopsy revealed hypertrophic cardiac disease with significant valvular pathology but no evidence of acute infarction or myocyte injury. Two patients died from sepsis 10 and 12 days after administration of romidepsin, one patient with *Escherichia coli* and another with methicillin-resistant *Staphylococcus aureus*. Each of the three patients who died within 30 days of study removal had been removed as a result of progression of disease and died after receiving cytotoxic chemotherapy.

**Table 4.** Drug-Related Cycle 1 Toxicities

| Toxicity | % of Patients | | | |
|---|---|---|---|---|
| | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
| Hematologic | | | | |
| Leukopenia | 4 | 14 | 11 | 1 |
| Granulocytopenia | 8 | 14 | 10 | 4 |
| Lymphopenia | | | 21 | |
| Thrombocytopenia | 27 | 7 | 6 | |
| Anemia | 20 | 11 | 6 | |
| Constitutional/GI | | | | |
| Fatigue | 27 | 7 | 6 | 1 |
| Headache | 4 | 3 | | |
| Nausea | 34 | 15 | 3 | |
| Vomiting | 11 | 7 | 1 | |
| Anorexia | 13 | 7 | 1 | |
| Dysgeusia | 18 | 1 | | |
| Constipation | 3 | 4 | | |
| Diarrhea | 7 | 1 | | |
| ECG | | | | |
| T-wave or ST changes | 71 | 9 | | |
| QTc prolongation | 9 | | | |
| Cardiac | | | | |
| Hypotension | | 3 | | |
| Supraventricular arrhythmia | 1 | | 1 | |
| Ventricular arrhythmia | 3 | | | |
| Laboratory | | | | |
| Hypoalbuminemia | 14 | 6 | | |
| Hyperbilirubinemia | 3 | | | |
| AST | 8 | 1 | 3 | |
| ALT | 4 | 1 | 3 | |
| Hyperglycemia | 11 | 7 | | |
| Hypermagnesemia | 7 | | | |
| Hyperuricemia | 11 | | | 4 |
| Hypocalcemia | 10 | 31 | 1 | |
| Hypoglycemia | 4 | 1 | | |
| Hypokalemia | 8 | | 1 | |
| Hypomagnesemia | 15 | | | |
| Hyponatremia | 8 | | | |
| Hypophosphatemia | 1 | 3 | 4 | |

NOTE. Drug related was defined as possibly, probably, or definitely related to the drug.

### Responses

In the initial cohort of 27 patients who received no more than two prior cytotoxic regimens, three patients achieved a complete response and eight patients achieved a partial response, for an overall response rate of 41% (95% CI, 22% to 61%), thus exceeding the fraction required to declare the regimen of further interest based on the two-stage design. Detailed response data are listed in Tables 5 and 6 and Appendix Tables A2 and A3 (online only). The overall response rate for the group of 71 patients was 34% (95% CI, 23% to 46%).

**Table 5.** Responses

| Best Response | Cohort 1 (n = 27) Response No. | Cohort 1 (n = 27) Response % | Cohort 1 (n = 27) Response Duration (months) | All Patients (N = 71) Response No. | All Patients (N = 71) Response % | All Patients (N = 71) Response Duration (months) |
|---|---|---|---|---|---|---|
| CR | 3 | 11 | 6, 14*, 63† | 4 | 7 | 6, 14*, 26‡, 63† |
| PR | 8 | 30 | 2§, 2, 5, 10, 14, 20§, 32, 76‡ | 20 | 26 | 1, 1, 2, 2, 2, 2§, 3, 4‡, 5, 5, 6‖, 7§, 10, 11‡, 14, 14, 15, 20§, 32, 76‡ |
| SD | 10 | 37 | 3, 3, 4, 4, 4, 6, 6, 7, 7, 8 | 26 | 38 | 3, 3, 3, 3, 3, 4, 4, 4, 4, 4, 4, 4, 4, 4‖, 5, 6, 6, 6, 6, 6, 7, 7, 8, 8, 10, 11 |
| PD | 3 | 11 | | 15 | 17 | |
| NE | 3 | 11 | | 6 | 12 | |

Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluable.
*After 14 months in CR, this patient developed several small plaques but did not require additional therapy for over 43 months.
†Patient completed therapy 58 months prior to cut off date for this report.
‡Patients with continued responses to therapy at time of this report.
§Patient self-withdrew from study.
‖Death on study.

Representative responses are shown in Figure 1 and Appendix Figure A4 (online only).

Complete responses were observed in four patients (6%); response was documented in all sites of disease. The complete responders included one patient with MF and three patients with SS who had complete clearing of generalized erythroderma, including follow-up skin biopsies without evidence of disease. Involved sites, including lymph nodes and bone marrow, also had response documented in those sites. Two patients remain without evidence of disease at 26 and 63 months. One patient developed progression of disease in his skin after 8 months and was taken off protocol. One patient developed small thin patches of disease after 14 months in complete response. Romidepsin was discontinued, and no further therapy was needed for another 43 months.

Partial responses were observed in 20 patients (28%). Seven patients had skin-only disease, and response was documented by measurement of skin lesions using RECIST criteria. Twelve patients had response documented in skin as well as in their other sites of disease, with documentation of response in lymphadenopathy in seven patients, visceral lesions in three patients, and complete clearing of blood as determined by flow cytometry in seven patients. One patient with minor response of skin disease had primary response determined by lymph node response. Three patients continuing in partial response are being observed on protocol after 11, 13, and 82 months. Of the other 17 patients, 10 developed progression of disease, three self-withdrew from protocol, three came off study after experiencing an adverse event of fatigue, infection, or hypotension, and one died on study (discussed earlier).

Stable disease was noted in 26 patients. Sixteen of these patients developed progression of disease; seven patients withdrew from study, mainly to seek alternative therapy; two patients withdrew as a result of adverse events of infection and fatigue, and one patient died on study from sepsis with methicillin-resistant *S aureus* (discussed earlier). Progression of disease without evidence of response was noted in 15 patients. Six patients were nonevaluable; reasons included intercurrent medical illness of pituitary macroadenoma with associated endocrinopathy, the discovery of an intracardiac mass later shown to be the patient's lymphoma,[32] one death on study as a result of infection (discussed earlier), one patient on study for 2 months who moved and was lost to follow-up, and one patient who refused further therapy after one cycle. The sixth patient, who was taken off protocol as a result of worsening of generalized erythroderma, completely cleared after antibiotic therapy. Two patients, one with partial response and one with stable disease, withdrew from study after reviewing informed consent revised to include discussion of sudden death reported in patients treated with romidepsin.[20] Among the patients with a major response (complete or partial), the median time to response was 2 months (range, 1 to 6 months), and the median duration of overall response was 13.7 months (Appendix Fig A5, online only). The median time to progression was 15.1 months for patients with a major response (complete or partial), 5.9 months for patients with stable disease, and 1.9 months for patients who had disease progression as best response or who were nonevaluable.

**Table 6.** Responses Divided by Stage

| Stage | No. of Patients: Cohort 1 (n = 27) Total | CR | PR | SD | PD | NE | All Patients (N = 71) Total | CR | PR | SD | PD | NE |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| IA | | | | | | | 1 | | 1 | | | |
| IB | 2 | | 1 | | | 1 | 6 | | 4 | 1 | | 1 |
| IIA | | | | | | | 2 | | 1 | 1 | | |
| IIB | 5 | | 3 | 1 | 1 | | 15 | 1 | 6 | 6 | 1 | 1 |
| IIIA | 2 | | 1 | | 1 | | 3 | | 1 | 1 | 1 | |
| IIIB | | | | | | | 3 | | 1 | | 1 | 1 |
| IVA | 14 | 2 | 2 | 7 | 1 | 2 | 28 | 2 | 3 | 13 | 7 | 3 |
| IVB | 4 | 1 | 1 | 2 | | | 13 | 1 | 3 | 4 | 5 | |
| Total | 27 | 3 | 8 | 10 | 3 | 3 | 71 | 4 | 20 | 26 | 15 | 6 |

Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluable.

## DISCUSSION

This phase II trial was initiated after responses were observed in patients with CTCL and PTCL treated on a phase I trial of romidepsin.[11] Although patients with CTCL may have multiple therapeutic options, responses to those agents are seldom durable. Our patients had prior regimens that included topical therapies, radiation, biologic agents, and systemic chemotherapy. The overall response rate was 34%, with a median duration of response of 13.7 months. Among 62 patients

  

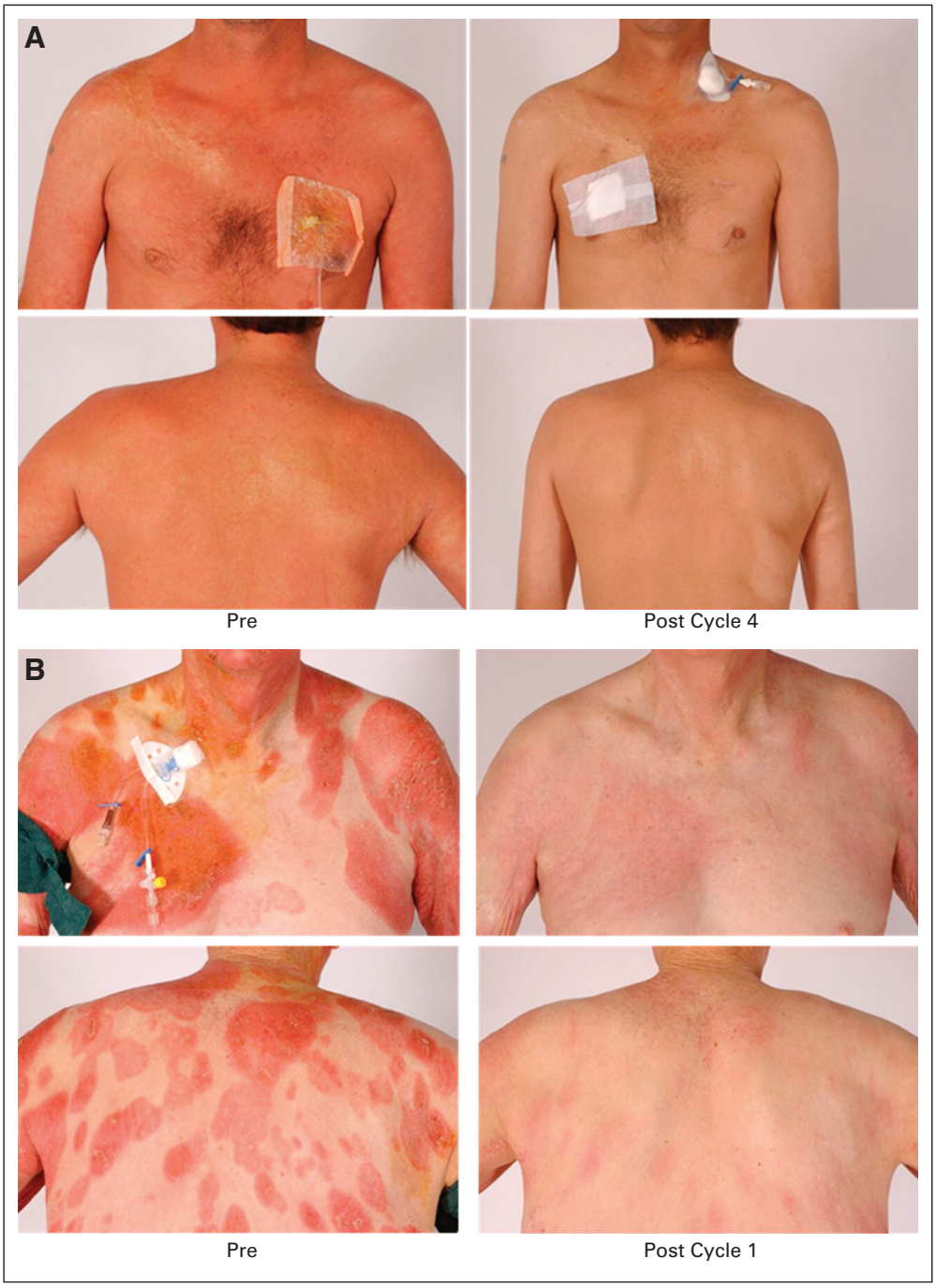


**Fig 1.** (A) This patient with Sézary syndrome had progression of disease after denileukin diftitox and alemtuzumab. He remains in complete response after 63 months. (B) This patient with mycosis fungoides had progression of disease after psoralen with ultraviolet A therapy, etretinate, interferon alfa, and methotrexate. The patient demonstrated a good response that lasted 8 months.

with stage IV disease, 18 (29%) had a complete or partial response. Although it is generally recognized that patients with SS are more refractory to available therapies, three patients with SS achieved a complete response to romidepsin, with one patient continuing in complete remission at 63 months, more than 55 months after romidepsin discontinuation.

Overall, romidepsin was well tolerated. The toxicities observed were similar to those previously reported, including fatigue, nausea, and vomiting.[9,10] Laboratory abnormalities noted included transient granulocytopenia and thrombocytopenia, with values returning to baseline by the next cycle. These toxicities seem to be a class effect among the HDIs.[31] Infectious complications are common in patients with CTCL, who have impaired cellular immunity,[33] and are a significant cause of morbidity and mortality.[34] In addition to compromised integument, the presence of CTCL in the skin contributes to colonization with *S aureus*, which in turn stimulates the growth of lymphoma in the skin.[35]

Because asymptomatic T-wave flattening and ST segment depression were observed in phase I testing,[9,10] cardiac evaluation was incorporated into the study. Analysis of these results in the first 42 patients with CTCL or PTCL treated at the National Institutes of Health Clinical Center (25 of whom are included in this cohort of 71

patients) has been reported.[20] This testing revealed no evidence of acute or cumulative cardiac damage based on serial troponin I values, multiple-gated acquisition scans, or echocardiograms.[20] When ECGs were evaluated for QT interval changes, a median increase of 14 milliseconds was observed, and 0.2% of the 2,051 ECGs evaluated had a QTcB (Bazett's correction) interval of more than 500 milliseconds.[20] Although these studies were evidence of the safety of romidepsin administration, it should be noted that one patient among the 71 died unexpectedly, as discussed in the Results and the Appendix (online only). This patient had severe valvular heart disease, and the protocol was amended to exclude patients at risk for sudden death and to avoid concomitant use of medications that prolong the QT interval or inhibit CYP3A4. A summary of events noted in the patients reported here is found in the Appendix. A detailed review of the cardiac monitoring is in preparation.

The observed responses and duration of response to romidepsin in CTCL are noteworthy and compare favorably to those seen after chemotherapy, bexarotene, or denileukin diftitox. The activity of romidepsin in CTCL has proven to be a class effect, with other HDIs demonstrating activity in this disease.[11-13] With differing structures, potencies, enzyme affinities, and schedules of administration, it is expected that differences in outcome or adverse effects with the HDIs will emerge. The biologic basis of the responsiveness of T-cell lymphoma to HDI therapy remains to be elucidated. It has been postulated that malignancies with an alteration in histone deacetylase or histone acetyltransferase activity may be susceptible to HDIs; however, no such alteration has been described in T-cell lymphomas. Approaches to increase efficacy include combination with agents that have activity in CTCL, particularly denileukin diftitox, retinoids, and cytotoxic agents, that may be potentiated by an HDI.[36]

## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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