Clinical Efficacy of Romidepsin in Tumor Stage and Folliculotropic Mycosis Fungoides

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Abstract

Patients with cutaneous T-cell lymphoma (CTCL) who have cutaneous tumors or folliculotropic disease involvement typically have a poor prognosis. Analysis of the pivotal phase II trial of romidepsin for relapsed or refractory CTCL showed that single-agent romidepsin induced a clinical response or stable disease in most patients with cutaneous tumors and/or folliculotropic disease involvement, supporting its use in these patient populations.

Background: Tumor stage and folliculotropic mycosis fungoides are uncommon subtypes of cutaneous T-cell lymphoma (CTCL) with an aggressive disease course. Romidepsin is a histone deacetylase inhibitor approved by the US Food and Drug Administration for patients with CTCL who have received ≥ 1 previous systemic therapy. In the present study, we examined the efficacy and safety of romidepsin in patients from the pivotal, single-arm, open-label, phase II study of relapsed or refractory CTCL with cutaneous tumors and/or folliculotropic disease involvement. **Materials and Methods:** Patients with CTCL who had received ≥ 1 previous systemic therapy received romidepsin at 14 mg/m^2 on days 1, 8, and 15 of 28-day cycles. Responses were determined by a composite endpoint (assessments of the skin, blood, and lymph nodes). Patients with cutaneous tumors and/or folliculotropic disease involvement were identified by review of diagnosis and histology reports. **Results:** The objective response rate to romidepsin was 45% in patients with cutaneous tumors (n = 20) and 60% in patients with folliculotropic disease involvement (n = 10). **Conclusion:** Romidepsin is active in subtypes of CTCL with less favorable outcomes, such as tumor stage and folliculotropic mycosis fungoides.

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Introduction

Cutaneous T-cell lymphomas (CTCLs) are a heterogeneous group of non-Hodgkin lymphomas that are primarily indolent but can be aggressive and are associated with a poor prognosis in late-stage disease.[1-3] CTCL is relatively rare, comprising ≈4% of diagnosed cases of non-Hodgkin lymphoma in the United States.[4] Although CTCL arises in the skin, it can progress to systemic disease (lymph nodes, blood, viscera), resulting in significantly reduced survival.[2,3,5] The most common forms of CTCL are mycosis fungoides (MF) and Sézary syndrome (SS).[1] The term CTCL is sometimes used interchangeably with MF/SS, but CTCL encompasses various non-MF/SS subtypes.[1,6,7] Many patients with CTCL experience pruritus, visible manifestations of disease in the skin, and infections, all of which can lead to significant psychological burden, in addition to the physical burden of the disease.[8,9] CTCL is staged according to the disease involvement in the skin, lymph nodes, visceral organs, and blood.[10] In early-stage disease, skin involvement includes patches, plaques, and/or papules. Cutaneous tumors represent a distinct classification and correspond to a higher stage of disease (TNMB skin classification T3, clinical stage IIB) in the World Health Organization/European Organization for Research and Treatment of Cancer staging system.[10] The presence of cutaneous tumors is also known to be an independent negative prognostic factor for disease progression and survival and can be accompanied by histologic large cell transformation.[2,11]

Folliculotropic mycosis fungoides (FMF) is characterized by infiltration of the hair follicle by neoplastic T lymphocytes.[12,13] FMF is associated with an aggressive disease course, a poor response to treatment, an increased risk of disease progression, and inferior overall survival.[2,12] Patients with early-stage FMF typically

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respond less well to modalities such as ultraviolet light and topical therapies, which tend to be efficacious for early-patch and plaque-stage disease. In many cases, patients with FMF respond similarly to those with tumor-stage disease.[12,14] Similar to other patients with MF, those with FMF often have moderate to severe pruritus,[14] which can significantly affect patients' quality of life.[15]

The epigenetic modifier romidepsin is a structurally unique, potent, bicyclic, class I selective histone deacetylase inhibitor[16-18] approved by the US Food and Drug Administration for the treatment of peripheral T-cell lymphoma (PTCL) in patients who have received $\geq$ 1 previous therapy and for the treatment of CTCL in patients who have received $\geq$ 1 previous systemic therapy.[19] Approval for CTCL was based primarily on the results from a pivotal phase II study of romidepsin administered at a dose of 14 mg/m^2 on days 1, 8, and 15 of 28-day cycles to patients with relapsed or refractory CTCL (N = 96). The objective response rate (ORR) was 34%, including 6% with a complete response, and the median duration of response (DOR) was 15 months.[20] Clinically meaningful reductions in pruritus were noted in both objective responders and clinical nonresponders.[21]

Despite the poor prognosis for patients with cutaneous tumors and those with folliculotropic involvement, relatively few studies have analyzed the clinical benefit of approved systemic therapies. We present an analysis of the efficacy and safety of single-agent romidepsin in patients with cutaneous tumors and/or folliculotropic disease from the pivotal phase II trial.

Materials and Methods

Study Design

The details for the phase II, open-label, single-arm, international study (GPI-04-0001; ClinicalTrials.gov identifier, NCT00106431) have been previously reported in detail.[20] In brief, adult patients with stage IB-IVA CTCL, including those with MF and SS, who had received $\geq$ 1 previous systemic therapy were required to have adequate organ function, Eastern Cooperative Oncology Group performance status of 0 to 1, and no known significant cardiac abnormalities. The study was conducted in accordance with the Guidelines of the World Medical Association Declaration of Helsinki. The appropriately constituted institutional review board and/or independent ethics committee of the participating institutions reviewed and approved the study documentation. All the patients provided written informed consent. Patients with cutaneous tumors and/or folliculotropic involvement (diagnosed as FMF or CTCL with a folliculotropic component) were identified by a review of the diagnosis and histology reports. Romidepsin was administered at 14 mg/m^2 as a 4-hour intravenous infusion on days 1, 8, and 15 of 28-day cycles for $\leq$ 6 cycles. Patients with stable disease (SD) or response could continue treatment beyond 6 cycles at the discretion of the patient and investigator. Concomitant antipruritic medications (eg, steroids, antihistamines) were not allowed to isolate the benefits of romidepsin treatment on pruritus. The response to treatment was assessed at patient screening, at baseline, on day 1 of each treatment cycle, and 30 days after the last cycle.

Efficacy and Safety Assessments

The primary endpoint was the ORR, which was determined by a rigorous composite assessment of response in the skin, lymph nodes, and blood. Key secondary endpoints included the DOR, time to response (TTR), and time to progression. The reduction in pruritus was measured using a patient-assessed 100-mm visual analog scale (VAS; no itching [VAS = 0] to unbearable itching [VAS = 100]). Patients with a baseline VAS score of 30 to 69 and 70 to 100 were considered to have moderate and severe pruritus, respectively. Treatment-emergent adverse events (AEs) were assessed at the weekly treatment visits (days 1, 8, and 15 of each cycle) using the National Cancer Institute Common Terminology Criteria for Adverse Events grading system (version 3) and tabulated using the Medical Dictionary for Regulatory Activities system organ class.

Statistical Analysis

All patients who had received $\geq$ 1 dose of romidepsin were included in the efficacy and safety analyses. Changes from baseline over time in the VAS pruritus scores and TTR were assessed using descriptive statistics. Time-to-event data were summarized using the Kaplan-Meier method.

Results

Patient Baseline Demographics and Characteristics

Of 96 patients with CTCL, 20 had cutaneous tumors and 10 had folliculotropic involvement (Table 1). Two patients had both cutaneous tumors and folliculotropic involvement and were included in both groups for the present analysis. Patients with folliculotropic involvement were variably described in the histology reports as having FMF/CTCL (n = 3), follicular involvement (n = 4), folliculotropic element (n = 1), secondary follicular inflammatory changes (n = 1), or involvement of the hair follicles (n = 1). The median age of the patients with cutaneous tumors and/or folliculotropic involvement was comparable to that of the overall study population, and most patients in both subpopulations were male. Patients with cutaneous tumors and/or folliculotropic involvement had undergone a similar number of previous skin-directed therapies but a greater median number of previous systemic therapies than that of the overall study population (Table 1). One patient in the overall study had large cell transformation (55-year-old woman, stage IIB at diagnosis) with cutaneous tumors and had previously received 4 topical and 4 systemic therapies.

Efficacy

Patients with cutaneous tumors and/or folliculotropic involvement experienced a rapid response to romidepsin (median TTR, 1.9 and 2.1 months) with an ORR of 45% (9 of 20) and 60% (6 of 10), respectively (Table 2). No significant differences were observed in the ORR between the patients with and those without cutaneous tumors (P = .443) or between the patients with and those without folliculotropic involvement (P = .075). Most patients with cutaneous tumors and/or folliculotropic involvement were able to achieve SD or better (both 90%). One patient with cutaneous tumors and large cell transformation had a best response of progressive disease (PD). The DOR was not significantly different statistically for the patients with and without cutaneous tumors (P = .748) or for patients with and without folliculotropic involvement (P = .060). The longest DOR for the patients with folliculotropic involvement ($\geq$ 5.0 months) was in a patient who remained in

Table 1 Patient Demographics and Characteristics

Variable	Overall (n = 96)	Cutaneous Tumors (n = 20)[a]	Folliculotropic Involvement (n = 10)[a]
Male sex	59 (61)	14 (70)	7 (70)
Age (y)			
Median	57	56	54
Range	21-89	21-77	36-83
Previous skin-directed therapies			
Median	2	2	2
Range	0-6	1-5	1-5
Previous systemic therapies			
Median	2	3	3.5
Range	1-8	1-7	1-7
Stage at diagnosis			
IB	15 (16)	1 (5)[b]	1 (10)
IIA	13 (14)	0 (0)	2 (20)
IIB	21 (22)	9 (45)	1 (10)
III	23 (24)	4 (20)	2 (20)
IVA	24 (25)	6 (30)	4 (40)
Pruritus at baseline[c]			
Moderate to severe[d]	65 (69)	13 (68)	6 (67)
Severe[e]	36 (38)	10 (53)	4 (44)

Data presented as n (%), unless otherwise noted.
[a]Two patients had both cutaneous tumors and folliculotropic involvement and were included in both groups.
[b]The patient was recorded as having cutaneous tumors and stage 1B disease at baseline.
[c]Measured using 100-mm visual analog scale from no itching (score, 0) to unbearable itching (score, 100); 2 patients overall and 1 patient with both cutaneous tumors and folliculotropic involvement did not have a baseline pruritus assessment.
[d]Visual analog scale score, 30 to 100 mm.
[e]Visual analog scale score, 70 to 100 mm.

complete response after completion of the planned 6 cycles of treatment but chose to withdraw from the study (Figure 1). Patients with cutaneous tumors and/or folliculotropic involvement experienced marked reductions in pruritus from baseline (Table 2). In the overall study population, 7 patients (2 with cutaneous tumors and 1 with folliculotropic involvement) had severe pruritus at baseline that was completely resolved after treatment with romidepsin (VAS score, 0 for $\geq$ 2 consecutive cycles). Patients with severe or moderate-to-severe pruritus at baseline reported improvements similar to that of the overall population. Increased pruritus was reported in only 1 patient with cutaneous tumors and 1 patient with folliculotropic involvement.

Safety

Treatment-emergent AEs in patients with cutaneous tumors and/or folliculotropic involvement were generally comparable to those of the overall study population (Figure 2). Patients with folliculotropic involvement had a lower incidence of total AEs (all grades and grades $\geq$ 3). Nausea was the most common AE (56%; all drug-related) and was lowest in patients with folliculotropic involvement (40% vs. 55% of patients with cutaneous tumors). Although grade $\geq$ 3 gastrointestinal AEs (vomiting, diarrhea, nausea) were reported in the overall treatment population, no grade $\geq$ 3 gastrointestinal AEs were reported in patients with cutaneous tumors and/or folliculotropic involvement. Common (> 10%) hematologic AEs (thrombocytopenia, anemia) were more frequently reported in patients with cutaneous tumors. In contrast, patients with folliculotropic involvement had the lowest incidence. Overall, the analysis of AEs (both treatment-emergent and drug-related) in patients with cutaneous tumors and/or folliculotropic involvement showed no new safety signal. The patients in these 2 subgroups had AE profiles that were generally comparable to those of the overall study population.

Most withdrawals from treatment in both subgroups were because of PD. Seven patients (35%) with cutaneous tumors and 3 (30%) with folliculotropic involvement (1 patient with both) withdrew because of PD. No patients with folliculotropic involvement withdrew from treatment because of an AE. One patient with cutaneous tumors withdrew from treatment because of an AE (fatigue) that was deemed drug-related. One patient with cutaneous tumors died of cardiopulmonary failure, which was assessed by the investigator as possibly related to the study drug. By independent review, the death was assessed as caused by PD with attendant cardiopulmonary insufficiency as the terminal event. No other deaths occurred in either subgroup.

Discussion

Previous studies have shown that romidepsin is effective in treating CTCL in all disease compartments (skin, lymph nodes, and blood), in all disease stages (IB-IVA), and in populations with a poor prognosis (SS) and greater risk of disease progression.[2,20,22]

Table 2 Outcomes With Romidepsin Treatment

Variable	Overall (n = 96)	Cutaneous Tumors (n = 20)[a]	Folliculotropic Involvement (n = 10)[a,b]
Treatment duration (mo)			
Median	3.6	3.6	4.3
Range	< 0.1-21.9	0.5-21.9	0.5-8.0
Best response			
ORR	33 (34)	9 (45)	6 (60)
CR	6 (6)	2 (10)	1 (10)
SD	45 (47)	9 (45)	3 (30)
SD90	28 (29)	3 (15)	2 (20)
Time to response (mo)			
Median	1.9	1.9	2.1
Range	0.9-4.8	1.9-4.7	1.0-4.8
DOR (mo)			
Median	15.0	NR	3.6
Range	<0.1 to 19.8+	1.4 to 18.7+	2.1 to 5.0+
Best change in pruritus VAS score[c]			
Moderate to severe pruritus at baseline[d]	−38 ± 28	−43 ± 27	−53 ± 35
Severe pruritus at baseline[e]	−49 ± 28	−45 ± 29	−60 ± 42
Time to progression (mo)			
Median	8.3	3.8	8.3
Range	<0.1 to 21.7	0.9 to 21.7+	<0.1 to 8.3+

Data presented as n (%) or mean ± standard deviation, unless otherwise noted.
Abbreviations: CR = complete response; DOR = duration of response; NR = not reached; ORR = objective response rate; SD = stable disease; SD90 = stable disease for ≥ 90 days; VAS = visual analog scale.
[a]Two patients had both cutaneous tumors and folliculotropic involvement and were included in both groups.
[b]Response data missing for 1 patient with folliculotropic involvement.
[c]Included patients with baseline and postbaseline VAS data and a lack of confounding pruritus treatments necessary to calculate the change in VAS scores.
[d]VAS score, 30 to 100 mm.
[e]VAS score, 70 to 100 mm.

Additionally, reductions in pruritus were observed in each of these subpopulations, demonstrating that romidepsin is effective at providing clinical benefit beyond the objective response in traditionally challenging CTCL subpopulations.[22]

Patients with cutaneous tumors represent a subpopulation of CTCL with inferior outcomes.[2,3] The presence of cutaneous tumors is an independent prognostic factor for poorer overall survival, disease-dependent survival, and risk of disease progression, with the

Figure 1 Kaplan-Meier Plot of Duration of Response

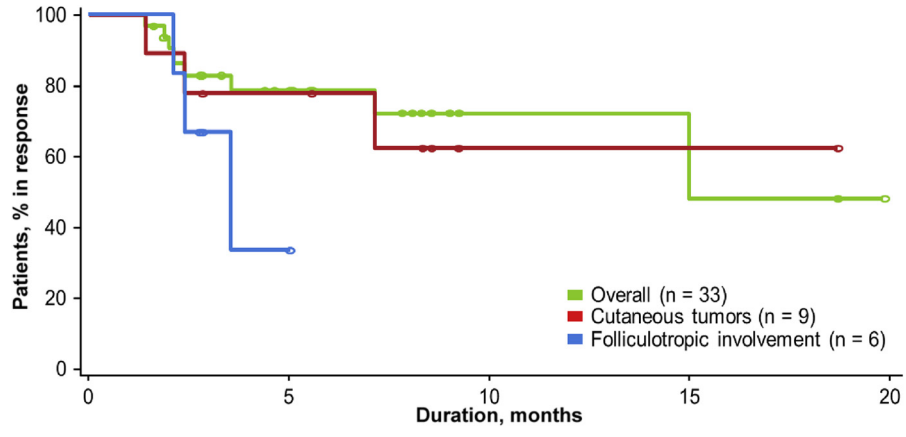
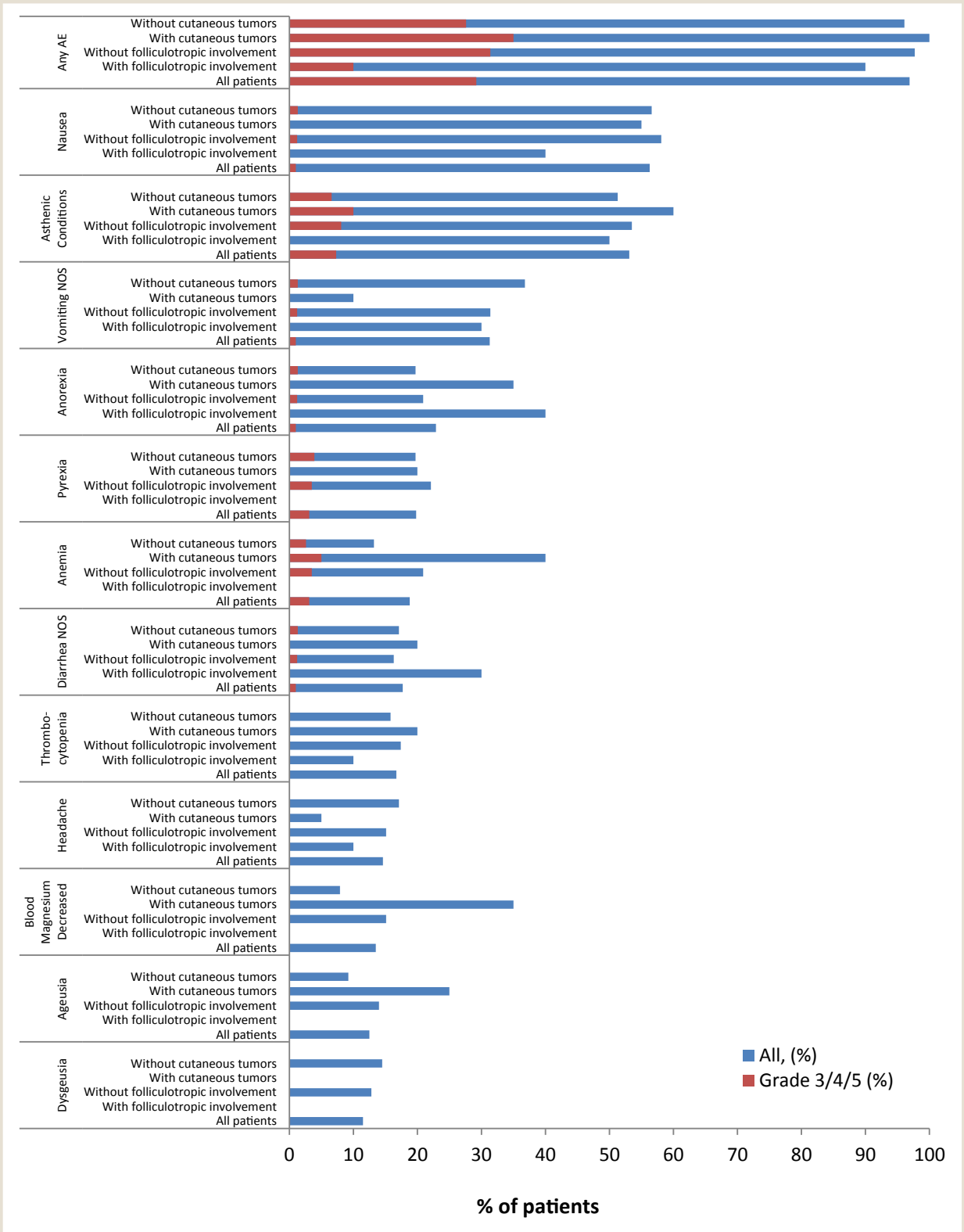


Figure 2 Common (> 10%) Treatment-Emergent Adverse Events (AEs)



NOS, not otherwise specified.

prognostic significance of the risk of disease progression dependent on the tumor distribution (eg, solitary, localized, regional, generalized).[2] Patients with cutaneous tumors have a median survival of 4.1 years compared with 17.7 to 38.3 years for lower stages of skin involvement and 24.4 years for MF/SS overall (all stages).[2,3] The results of the present study demonstrate that romidepsin is effective in this population, with a 45% ORR and median DOR not reached.

Cutaneous toxicity has been reported in patients with T-cell lymphoma and significant skin involvement and can lead to infection, treatment discontinuation, and death. A phase II study of panobinostat was terminated because of severe infections associated with skin tumor shrinkage in patients with adult T-cell leukemia/lymphoma.[23,24] Additionally, severe skin erosions leading to treatment discontinuation and fatal septic shock have been reported in patients with adult T-cell leukemia/lymphoma treated with pralatrexate and cytotoxic chemotherapy.[25,26] In a retrospective study of pralatrexate in 22 patients with CTCL or PTCL, 14 of 18 patients with CTCL (78%) who had received pralatrexate developed cutaneous toxicity, resulting in infection and treatment discontinuation in some patients. One patient with PTCL developed cutaneous toxicity that resulted in death.[27] In the present study, no patients with cutaneous tumors who were treated with romidepsin experienced cutaneous toxicity. Only 1 patient withdrew from treatment because of an AE (fatigue), and most withdrawals from treatment were because of PD.

The development of cutaneous toxicity in patients with T-cell lymphoma and significant skin involvement during treatment response is believed to be caused by the rapid lysis of tumor cells in the skin and has been suggested to be akin to the conventional tumor lysis syndrome typically observed during treatment with chemotherapy.[25,26] With chemotherapy agents, toxicity often occurs after administration of the first dose.[25-27] However, treatment with romidepsin in the present study resulted in a median TTR of 1.9 months in patients with cutaneous tumors without cutaneous toxicity.

Skin-directed therapies used in treating early-stage MF are often inadequate for patients with FMF, necessitating treatment with systemic agents or radiation.[6,14,28] No standardized treatment paradigm is available for patients with CTCL, and relatively few data are available regarding systemic treatments specifically focused on FMF.[6,14] Previous retrospective studies of patients with FMF have reported on treatment outcomes for small numbers of individual patients.[12-14,28,29] In the present study, most patients with folliculotropic involvement responded to romidepsin, and 90% achieved SD or better. Although the median DOR for those with a treatment response was 3.6 months, a measure of the potential durability is difficult owing to the small patient numbers and because the patient with the longest response discontinued treatment while in response at the end of the planned 6 cycles.

In the overall population of the pivotal phase II study, which was the basis of the present analysis, 60 of 65 patients (92%) who reported moderate to severe pruritus at baseline achieved a reduction in itch.[20,21] In the present retrospective analysis of the pivotal study, patients with cutaneous tumors and/or folliculotropic involvement achieved reductions in pruritus similar to those of the overall treatment population. Similar reductions in pruritus were reported with the oral histone deacetylase inhibitor vorinostat in patients with relapsed or refractory CTCL; however, concomitant antipruritic treatments were allowed.[30] A reduction in pruritus has been a significant patient-related endpoint in the treatment of CTCL, because intractable pruritus is frequently the most difficult aspect of the disease to control.

Conclusion

Patients with cutaneous tumors and/or folliculotropic involvement represent 2 CTCL subpopulations associated with poorer outcomes and a greater risk of disease progression. In both cases, systemic therapies are often used after disease progression with skin-directed therapies. Agents with favorable efficacy and safety profiles, such as romidepsin, provide additional therapeutic options for patients with these difficult and disabling subsets of CTCL.

Clinical Practice Points

- Cutaneous tumors and/or folliculotropic involvement are negative prognostic factors for patients with CTCL.
- The histone deacetylase inhibitor romidepsin induced a clinical response or stable disease in most patients with cutaneous tumors and/or folliculotropic disease involvement.
- Patients with cutaneous tumors and/or folliculotropic involvement treated with romidepsin experienced marked reductions in pruritus.
- Although treatment-associated cutaneous toxicity is a potential concern for patients with T-cell lymphoma and significant skin involvement, no cutaneous toxicity in patients with cutaneous tumors treated with romidepsin was reported.
- Data support the use of romidepsin in patients with cutaneous tumors and/or folliculotropic disease involvement.

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Disclosure

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