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Clinically significant responses achieved with romidepsin across disease compartments in patients with cutaneous T-cell lymphoma

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Abstract

Cutaneous T-cell lymphoma (CTCL) is a rare heterogeneous group of non-Hodgkin lymphomas that arises in the skin but can progress to systemic disease (lymph nodes, blood, viscera). Historically, in clinical trials of CTCL there has been little consistency in how responses were defined in each disease "compartment"; some studies only assessed responses in the skin. The histone deacetylase inhibitor romidepsin is approved by the US Food and Drug Administration for the treatment of CTCL in patients who have received at least one prior systemic therapy. Phase II studies that led to approval used rigorous composite end points that incorporated disease assessments in all compartments. The objective of this analysis was to thoroughly examine the activity of romidepsin within each disease compartment in patients with CTCL. Romidepsin was shown to have clinical activity across disease compartments and is suitable for use in patients with CTCL having skin involvement only, erythroderma, lymphadenopathy and/or blood involvement.

Keywords: Lymphoma and Hodgkin disease, pharmacotherapeutics, prognostication

Introduction

Cutaneous T-cell lymphoma (CTCL) is a primarily indolent, heterogeneous group of non-Hodgkin lymphomas (NHLs) associated with a poor prognosis in late-stage disease (≥ IIB) [1,2]. The two most common subtypes of CTCL are mycosis fungoides (MF) and Sézary syndrome (SS), which constitute the majority of diagnoses [2–4], and CTCL is sometimes used interchangeably with MF/SS [5,6]. As a whole, CTCL is quite rare, constituting ~4% of NHL diagnoses in the United States [3], with an age-adjusted annual incidence (Surveillance, Epidemiology, and End Results 2005–2009) of 10.2 per million persons [4]. CTCL arises in the skin but can progress to systemic disease (lymph nodes, blood, viscera), resulting in significantly reduced survival [2,6–8]. Staging of CTCL is based on disease involvement in these compartments [6], and a multivariate analysis showed that lymph node and blood involvement were independent prognostic factors for poor survival [7]. Even in patients with early-stage disease, pruritus is a common symptom of CTCL that can be debilitating and significantly impact patient quality of life [9–13].

Despite the knowledge that CTCL can progress to extracutaneous disease involvement, historically there had been little consistency in clinical trial response definitions in each disease "compartment" for patients with CTCL [14], even for systemic agents approved by the US Food and Drug Administration (FDA) for the treatment of CTCL (bexarotene [15,16], denileukin diftitox [17,18], romidepsin [19,20] and vorinostat [21,22]; exact indications vary). In 2007, the International Society for Cutaneous Lymphomas (ISCL) and European Organisation for Research and Treatment of Cancer (EORTC) published an update for patients with MF/SS that adjusted the tumor/node/metastasis classification used and incorporated a blood classification into staging [6]. Then in 2011, the ISCL, United States Cutaneous Lymphoma Consortium (USCLC) and the Cutaneous Lymphoma Task force of the EORTC developed consensus guidelines for response definitions in the skin, lymph nodes, blood and viscera – as well as a composite global response score that includes all of these compartments – in patients with MF/SS [14].

Romidepsin is a structurally unique, potent, bicyclic, class I selective histone deacetylase inhibitor [23–25] approved by

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the FDA in 2009 for the treatment of CTCL in patients who have received at least one prior systemic therapy and in 2011 for the treatment of peripheral T-cell lymphoma in patients who have received at least one prior therapy [19]. Approval in CTCL was based on results from two phase II studies of romidepsin for the treatment of CTCL in patients who had received at least one prior systemic therapy that demonstrated durable responses (composite objective response rate [ORR] of 34% with median duration of response [DOR] of 13.7–15 months) [20,26]. Although these studies were initiated before the development of the updated staging system and consensus guidelines on response definitions, they both incorporated disease assessment in all compartments, and used a composite response rate as the primary end point [20,26]. The pivotal trial also incorporated an assessment of pruritus reduction as an additional measure of clinical benefit [20,27].

The objective of this analysis of the pivotal study of romidepsin for the treatment of CTCL was to examine disease compartment data in greater detail. Baseline characteristics, responses, adverse events and pruritus in patients with disease in skin (erythrodermic vs. non-erythrodermic), lymph nodes and/or blood, as well as compartment-specific responses, were examined.

Patients and methods

Study design

GPI-04-0001 (trial registration: NCT00106431) was a pivotal, single-arm, open-label, phase II, multicenter study of patients with CTCL enrolled at 33 centers in eight countries. The study design and eligibility criteria have been previously described in detail [20]. Briefly, adult patients with stage IB–IVA CTCL (at study entry, by the Mycosis Fungoides Cooperative Group [MFCG]/American Joint Committee on Cancer [AJCC] criteria [28] according to the tumor–node–metastasis–blood [TNMB] categories and staging system described at the National Cancer Institute [NCI] workshop published in 1979 [29]) who had previously experienced ≥ 1 failure of systemic treatment were treated with romidepsin at 14 mg/m^2 intravenously for 4 h on days 1, 8 and 15 of up to six 28-day cycles. Patients with at least stable disease could continue treatment beyond six cycles. The protocol, informed consent form and other study documentation were approved by an institutional review board or independent ethics committee prior to patient enrollment. All patients provided written informed consent before beginning the study.

Efficacy and safety assessments

Efficacy assessments and response criteria have also been previously described in detail [20]. Disease assessments were performed for skin, lymph nodes and blood involvement. The extent of disease in the skin was determined using the Severity-Weighted Assessment Tool (SWAT) [30,31] and erythroderma score [18,32]. Nodal involvement was measured with the Response Evaluation Criteria In Solid Tumors (RECIST) methodology [33], and blood involvement was measured by determining the absolute count and percentage of circulating malignant T cells (Sézary cells) primarily via flow cytometry (CD4+/CD7− and/or CD4+/CD26− immunophenotype).

The primary end point was the ORR (complete [CR] and partial [PR] responses), using a rigorous composite end point based on the sum of the percentage changes in measurements in the skin, lymph nodes and blood (Table I). Reduction in pruritus was not part of the ORR, but was assessed and analyzed as an additional indicator of clinical benefit. DOR was also a key secondary end point. Objective responses as well as pruritus scores based on a visual analog scale (VAS) were assessed within 2 weeks of treatment initiation, on day 1 of each treatment cycle, at the end-of-study visit (30 days after the last romidepsin dose) and every 2 months for patients who went off study without disease progression.

Clinically meaningful reduction in pruritus (CMRP) on this trial was the focus of a previous article [29]. Pruritus was measured using a 100 mm VAS [18,22,32,34,35] from no itching (VAS = 0) to unbearable itching (VAS = 100). Patients with a baseline VAS score ≥ 30 were considered to have clinically significant pruritus; moderate pruritus was defined as a VAS score of 30–69; and severe pruritus was defined as a VAS score ≥ 70 [18,22,32,35]. CMRP was defined as a decrease in VAS score of ≥ 30 for ≥ 2 consecutive cycles for patients with

Table I. Objective primary disease response evaluation criteria.*

Complete response	• Complete resolution of skin patches, plaques and tumors (or erythroderma) • No evidence of abnormal lymph nodes • Absence of circulating Sézary cells • No evidence of new tumors (cutaneous or non-cutaneous) • Requires confirmation by skin biopsy
Partial response	• ≥ 50% improvement in the composite end point (Δ skin† + Δ lymph node‡ + Δ peripheral blood§) with ≥ 30% improvement in skin • No worsening in lymph nodes or circulating Sézary cells • No evidence of new tumors (cutaneous or non-cutaneous)
Stable disease	• Patients who do not have enough improvement or worsening to qualify for PR or PD, respectively
Progressive disease	• > 25% worsening in composite end point (Δ skin† + Δ lymph node‡ + Δ peripheral blood§) with > 15% worsening in skin, or • Evidence of new tumors (cutaneous or non-cutaneous)

CT, computed tomography; MRI, magnetic resonance imaging; PD, progressive disease; PR, partial response.
*Confirmed responses must be repeated at least 1 month after initial assessment.
†Δ skin = percentage change in total score from baseline of weighted body surface area (patients without erythroderma) or erythroderma scale (patients with erythroderma).
‡Δ lymph node = percentage change in size of abnormal lymph nodes (sum of longest diameter) from baseline based on physical examination and/or CT/MRI.
§Δ peripheral blood = percentage change in absolute number of circulating malignant T-cells (Sézary cells) from baseline.

moderate to severe pruritus at baseline; this threshold was prospectively selected based on expert input and previous use in clinical trials of other FDA-approved agents for CTCL [18,22,32,35].

Treatment-emergent adverse events (TEAEs) were assessed on days 1, 8 and 15 of each cycle according to the NCI Common Terminology Criteria for Adverse Events grading system (version 3) and tabulated by Medical Dictionary for Regulatory Activities system organ class.

Compartment analysis

Baseline characteristics, composite response rates, CMRP and AEs were examined for patients with only skin involvement, patients with erythroderma, patients with lymphadenopathy (≥ 1 lymph node ≥ 1.5 cm by conventional measurements or ≥ 1.0 cm by spiral computed tomography scan), patients with blood involvement (Sézary cell count $> 5\%$ of lymphocytes) and patients with higher blood tumor burden (Sézary cell counts > 1000 cells/μL and/or Sézary cells $> 20\%$ of lymphocytes) at baseline. In addition, the proportion of patients with responses in each disease compartment was calculated. In skin, lymph nodes and blood, a complete compartment response was defined as no evidence of disease. A partial skin response was defined as a $\geq 50\%$ decrease in SWAT or erythroderma score. A partial lymph node response was defined as a $\geq 30\%$ decrease in the sum of the longest diameter (SLD) of lymph nodes in patients with lymph node involvement at baseline. A partial blood response was defined as a $\geq 50\%$ decrease in circulating Sézary cells in patients with blood involvement or higher blood tumor burden at baseline.

Statistical methods

All patients who received ≥ 1 dose of romidepsin were included in the efficacy and safety analyses. Time to response and DOR data were summarized by Kaplan–Meier methods. *p*-Values were calculated for differences between the following pairs of patient groups: with or without only skin involvement, with or without erythroderma, with or without lymphadenopathy, with or without blood involvement and with or without higher blood tumor burden. Differences in baseline characteristics were assessed by Fisher exact tests, Wilcoxon tests or *t*-tests, differences in response rates were assessed by Fisher exact tests, differences in time to response or DOR were assessed by log-rank tests, differences in AEs were assessed by Fisher exact tests and differences in pruritus reduction were assessed by Wilcoxon tests. Test results were not adjusted for multiple comparisons.

Role of the funding source

Study GPI-04-0001 was conceived and the protocol written by Dr. William McCulloch and colleagues at Gloucester Pharmaceuticals, Inc. (now a wholly owned subsidiary of Celgene Corporation), with the assistance of practicing clinician colleagues, including coauthors Dr. Sean Whittaker and Dr. Youn Kim. The study was funded and run by Gloucester Pharmaceuticals, using a clinical research organization (Inveresk Research Grouop, Inc., which merged with Charles River Laboratories International, Inc., which was then acquired by Kendle International Inc. during the trial). Data interpretation was a collaborative effort by study personnel (Gloucester employees and trial investigators), a number of whom are coauthors. Financial support for medical editorial assistance was provided by Celgene Corporation.

Results

At baseline, 17 of 96 patients were diagnosed with SS, and the majority of patients on trial had advanced disease

Table II. Demographics and baseline characteristics.

	All patients ($n = 96$)	Only skin involvement ($n = 25$)*	Erythroderma ($n = 40$)	Lymphadenopathy ($n = 55$)†	Blood involvement ($n = 37$)‡	Higher blood tumor burden ($n = 13$)§
Male sex, *n* (%)	59 (62)	18 (72)	21 (53)	27 (49)**	22 (60)	4 (31)**
Age in years, mean (SD)	56.9 (12)	58.9 (11)	59.6 (14)	56.5 (13)	57 (13)	58 (17)
ECOG PS, *n* (%)						
0	49 (51)	15 (60)	18 (45)	22 (40)**	21 (57)	5 (39)
1	47 (49)	10 (40)	22 (55)	33 (60)**	16 (43)	8 (62)
Disease stage at study entry¶, *n* (%)						
IB	15 (16)	10 (40)**	1 (3)**	1 (2)**	4 (11)	0**
IIA	13 (14)	4 (16)**	1 (3)**	7 (13)**	4 (11)	0**
IIB	21 (22)	6 (24)**	0**	8 (15)**	8 (22)	0**
III	23 (24)	5 (20)**	21 (53)**	16 (29)**	9 (24)	5 (39)**
IVA	24 (25)	0**	17 (43)**	23 (42)**	12 (32)	8 (62)
Prior no. of systemic therapies, median (range)	2 (1–8)	3 (1–7)	2 (1–6)	2 (1–8)	3 (1–8)	3 (1–6)**
Chemotherapy, *n* (%)	73 (76)	21 (84)	27 (68)	40 (73)	24 (65)	7 (54)
Bexarotene, *n* (%)	32 (33)	8 (32)	14 (35)	17 (31)	17 (46)**	7 (54)
Immunotherapy, *n* (%)	36 (38)	7 (28)	15 (38)	23 (42)	18 (49)	7 (54)
Steroids, *n* (%)	13 (14)	6 (24)	4 (10)	6 (11)	2 (5)	0
Denileukin diftitox, *n* (%)	14 (15)	3 (12)	4 (10)	8 (15)	5 (14)	1 (8)
Photopheresis, *n* (%)	18 (19)	0**	11 (28)	12 (22)	14 (38)**	5 (39)

SD, standard deviation; ECOG PS, Eastern Cooperative Oncology Group performance status.
*Patients without definitive lymphadenopathy and blood involvement.
†Patients with ≥ 1 lymph node ≥ 1.5 cm by conventional measurements or ≥ 1.0 cm by spiral computed tomography scan.
‡Sézary cells $> 5\%$ of lymphocytes.
§Sézary cell counts > 1000 cells/μL and/or Sézary cells $> 20\%$ of lymphocytes.
¶American Joint Committee on Cancer staging system used at the time of this study was not impacted by blood involvement.
**Indicates significantly different ($p \leq 0.05$) distribution from the alternative category: patients with or without only skin involvement, erythroderma, lymphadenopathy, blood involvement or higher blood tumor burden.

Table III. Composite responses.

	All patients ($n = 96$)	Only skin involvement ($n = 25$)*	Erythroderma ($n = 40$)	Lymphadenopathy ($n = 55$)†	Blood involvement ($n = 37$)‡	Higher blood tumor burden ($n = 13$)§
ORR, *n* (%)	33 (34)	10 (40)	14 (35)	15 (27)	12 (32)	4 (31)
CR, *n* (%)	6 (6)	2 (8)	2 (5)	2 (4)	2 (5)	0
PR, *n* (%)	27 (28)	8 (32)	12 (30)	13 (24)	10 (27)	4 (31)
Time to response in months, median (range)	1.9 (0.9–4.8)	2.1 (0.9–3.0)	1.9 (1.0–4.8)	1.9 (1.0–4.8)	1.9 (1.0–4.8)	1.2 (1.0–4.8)
Duration of response in months, median (range)	15.0 (< 0.1+–19.8+)	15.0 (1.9+–18.7+)	15.0 (< 0.1+–15.0)	NE (< 0.1+–9.2+)	NE (1.6+–19.8+)	NE (3.6+–8.6+)

ORR, objective response rate; CR, complete response; PR, partial response; NE, not evaluable (rate of response ending did not reach 50%).
*Patients without definitive lymphadenopathy and blood involvement.
†Patients with ≥ 1 lymph node ≥ 1.5 cm by conventional measurements or ≥ 1.0 cm by spiral computed tomography scan.
‡Sézary cells > 5% of lymphocytes.
§Sézary cell counts > 1000 cells/μL and/or Sézary cells > 20% of lymphocytes.

(71% ≥ stage IIB) and were heavily pretreated (median of 2 [range 1–8] prior systemic therapies; Table II). Patients with lymphadenopathy were more frequently female with an Eastern Cooperative Oncology Group (ECOG) performance status of 1 than those without lymphadenopathy ($p = 0.006$, $p = 0.014$, respectively). Patients with higher blood tumor burden were also more frequently female and had received more prior systemic therapies than those without higher blood tumor burden ($p = 0.029$, $p = 0.044$, respectively). The types of prior therapies received were similar across the patient subgroups; the only significant differences reported were higher rates of bexarotene and photopheresis for patients with blood involvement versus without blood involvement ($p = 0.047$, $p < 0.001$, respectively), and a lower rate of photopheresis (0%) for patients with only skin involvement versus involvement beyond the skin ($p = 0.003$).

The composite ORR was 34% (33/96), including 6% with CR (Table III). There were no significant differences in composite ORR, time to response or DOR among the patient subgroups examined. Compartment-specific responses in the skin (41% [23/56] for non-erythroderma and 38% [15/40] for erythroderma) and blood (57% [21/37] for blood involvement and 54% [7/13] for higher blood tumor burden) were numerically higher than the composite response rate; in contrast, only 33% (18/55) of patients with baseline lymphadenopathy had a response in their nodal disease (Table IV). Median time to response was 1.9 months in the skin and lymph nodes and ranged from 1.1 months in all patients with blood involvement to 3 months in patients with higher blood tumor burden. Median compartment-specific DORs were generally numerically shorter than the composite median DOR; only the skin response in patients without erythroderma achieved a duration at or above the median composite DOR of 15.0 months (Table IV).

Overall, the most common drug-related TEAEs were nausea, asthenic conditions and vomiting (Table V). Patients with blood involvement or higher blood tumor burden had significantly more frequent diarrhea not otherwise specified (NOS) than patients without blood involvement or higher blood tumor burden ($p = 0.004$, $p = 0.002$, respectively); and patients with blood involvement also had significantly more frequent dysgeusia ($p = 0.003$). There were no other significant differences in common drug-related TEAEs across the patient subgroups examined.

The majority of patients (65 of 96) had at least moderately severe pruritus at baseline, over half of which were characterized as severe (36/65; Table VI). Of these patients, 28 (43%) experienced CMRP, including 19 (53%) with severe pruritus at baseline. Unsurprisingly, patients with erythroderma had significantly higher baseline VAS scores than those without erythroderma (mean 78.6 vs. 59.9, $p < 0.001$). Patients with at least moderately severe pruritus at baseline without lymphadenopathy achieved significantly greater improvement in VAS score (−45.2 vs. −33.9, $p = 0.025$) and rate of CMRP (65.4% vs. 28.2%, $p = 0.005$) than those with lymphadenopathy. Presence of erythroderma, blood involvement or higher blood tumor burden did not significantly impact improvement in VAS score or rate of CMRP.

Table IV. Responses by compartment.

	Skin response		Lymph node response in patients with baseline lymphadenopathy ($n = 55$)*	Blood response	
	Patients without erythroderma ($n = 56$)	Patients with baseline erythroderma ($n = 40$)		Patients with blood involvement ($n = 37$)†	Patients with higher blood tumor burden ($n = 13$)‡
ORR, *n* (%)	23 (41)	15 (38)	18 (33)	21 (57)	7 (54)
CR, *n* (%)	4 (7)	4 (10)	4 (7)	3 (8)	1 (8)
PR, *n* (%)	19 (34)	11 (28)	14 (25)	18 (49)	6 (46)
Time to response in months, median (range)	1.9 (0.9–6.5)	1.9 (1.0–6.2)	1.9 (1.0–5.6)	1.1 (0.9–7.6)	3 (1.0–7.6)
Duration of response in months, median (range)	NE (< 0.1+–18.7+)	8.1 (< 0.1+–11.5)	2.6 (< 0.1+–4.3)	3.8 (< 0.1+–13.2)	NE (< 0.1+–5.8+)

ORR, objective response rate; CR, complete response; PR, partial response; NE, not evaluable.
*Patients with ≥ 1 lymph node ≥ 1.5 cm by conventional measurements or ≥ 1.0 cm by spiral computed tomography scan.
†Sézary cells > 5% of lymphocytes.
‡Sézary cell counts > 1000 cells/μL and/or Sézary cells > 20% of lymphocytes.

Table V. Most common (>10%) drug-related (possibly, probably or definitely related) treatment-emergent adverse events.

	All patients ($n=96$)	Only skin involvement ($n=25$)*	Erythroderma ($n=40$)	Lymphadenopathy ($n=55$)†	Blood involvement ($n=37$)‡	Higher blood tumor burden (n = 13)§
Nausea	54 (56)	14 (56)	19 (48)	31 (56)	22 (60)	6 (46)
Asthenic conditions¶	43 (45)	12 (48)	14 (35)	24 (44)	16 (43)	6 (46)
Vomiting NOS	27 (28)	7 (28)	8 (20)	15 (27)	11 (30)	4 (31)
Anorexia	19 (20)	6 (24)	4 (10)	9 (16)	8 (22)	2 (15)
Thrombocytopenia††	14 (15)	5 (20)	4 (10)	7 (13)	4 (11)	1 (8)
Diarrhea NOS	13 (14)	2 (8)	6 (15)	6 (11)	10 (27)**	6 (46)**
Headache	13 (14)	3 (12)	3 (8)	8 (15)	5 (14)	2 (15)
Ageusia	12 (13)	2 (8)	3 (8)	9 (16)	5 (14)	1 (8)
Dysgeusia	11 (12)	2 (8)	3 (8)	4 (7)	9 (24)**	3 (23)
Anemia‡‡	10 (10)	1 (4)	5 (13)	8 (15)	4 (11)	1 (8)

NOS, not otherwise specified; MedDRA, medical dictionary for regulatory activities.
*Patients without definitive lymphadenopathy and blood involvement.
†Patients with ≥ 1 lymph node ≥ 1.5 cm by conventional measurements or ≥ 1.0 cm by spiral computed tomography scan.
‡Sézary cells > 5% of lymphocytes.
§Sézary cell counts > 1000 cells/μL and/or Sézary cells > 20% of lymphocytes.
¶Includes the MedDRA preferred terms asthenia, fatigue, lethargy and malaise.
**Indicates significantly different ($p \leq 0.05$) distribution from the alternative category: patients with or without only skin involvement, erythroderma, lymphadenopathy, blood involvement or higher blood tumor burden.
††Includes the MedDRA preferred terms thrombocytopenia and platelet count decreased.
‡‡Includes the MedDRA preferred terms anemia NOS, hemoglobin decreased and red blood cell count decreased.

Discussion

In this subanalysis of the pivotal phase II trial of romidepsin for the treatment of patients with CTCL who had received ≥ 1 prior systemic therapy, romidepsin was shown to have clinical activity in the skin, lymph nodes and blood (no patient with visceral involvement was enrolled on trial). Overall, patients in this trial were heavily pretreated with mostly advanced disease. Patients with higher blood tumor burden had received significantly more prior systemic therapies than other patients, and patients with blood involvement more often had received bexarotene or photopheresis (no patient with only skin involvement had received photopheresis). As expected, patients with erythroderma at baseline reported significantly higher pruritus at baseline than patients without erythroderma. Surprisingly, increased pruritus at baseline reported in patients with higher blood tumor burden did not reach significance compared with patients without higher blood tumor burden. Composite response rates, time to response and DOR were not significantly different across the patient subgroups, indicating that romidepsin is an effective therapy for patients with CTCL regardless of the compartments in which disease had manifested. When examining responses within each compartment, 40% of patients had a response in the skin (similar response rates were seen in patients with or without erythroderma), 33% of patients with lymphadenopathy had a response in the lymph nodes and more than half of patients with blood involvement or higher blood tumor burden had a response in the blood. Time to response within each compartment was similar to that seen for the composite response; however, the DOR within each compartment may have been shorter compared with the DOR for the composite response, indicating that disease

Table VI. Pruritus at baseline and changes in pruritus visual analog scale.

	All patients ($n=96$)	Only skin involvement ($n=25$)*	Erythroderma ($n=40$)	Lymphadenopathy ($n=55$)†	Blood involvement ($n=37$)‡	Higher blood tumor burden ($n=13$)§
Patients with at least moderately severe pruritus at baseline¶						
n	65	18	30	39	24	9
Baseline VAS, mean (SD)	68.5 (21.0)	67.9 (22.2)	78.6 (18.0)**	69.9 (20.4)	67.7 (18.7)	75.1 (19.0)
Best change in VAS, mean (SD)	−38.4 (27.8)	−43.1 (23.8)	−40.0 (32.8)	−33.9 (30.8)**	−36.3 (27.1)	−37.9 (30.8)
CMRP	28 (43.1)	10 (55.6)	12 (40.0)	11 (28.2)**	10 (41.7)	3 (33.3)
Patients with severe pruritus at baseline††						
n	36	11	22	22	12	7
Baseline VAS, mean (SD)	84.5 (10.7)	82.9 (9.4)	87.5 (10.2)**	84.7 (11.5)	83.7 (9.7)	83.7 (9.1)
Best change in VAS, mean (SD)	−48.9 (27.9)	−52.8 (22.0)	−47.9 (33.4)	−45.9 (31.7)	−48.6 (26.4)	−44.9 (31.8)
CMRP	19 (52.8)	8 (72.7)	11 (50.0)	9 (40.9)	5 (41.7)	3 (42.9)

VAS, visual analog scale; SD, standard deviation; CMRP, clinically meaningful reduction in pruritus (defined as a decrease in VAS score of ≥ 30 for ≥ 2 consecutive cycles for patients with moderate-to-severe pruritus at baseline).
*Patients without definitive lymphadenopathy and blood involvement.
†Patients with ≥ 1 lymph node ≥ 1.5 cm by conventional measurements or ≥ 1.0 cm by spiral computed tomography scan.
‡Sézary cells > 5% of lymphocytes.
§Sézary cell counts > 1000 cells/μL and/or Sézary cells > 20% of lymphocytes.
¶Baseline score of ≥ 30 mm.
**Indicates significantly different ($p \leq 0.05$) distribution from the alternative category: patients with or without only skin involvement, erythroderma, lymphadenopathy, blood involvement or higher blood tumor burden.
††Baseline score of ≥ 70mm.

Table VII. Consensus guidelines from the ISCL, USCLC and Cutaneous Lymphoma Task Force of the EORTC [14].

Response in skin (based on modified SWAT score)	
CR	• 100% clearance of skin lesions*
PR	• 50–99% clearance of skin disease from baseline and no new tumors in patients without tumors at baseline
SD	• $<$ 25% increase to $<$ 50% clearance in skin disease from baseline and no new tumors in patients without tumors at baseline
PD	• $\geq$ 25% increase in skin disease from baseline or • New tumors in patients without tumors at baseline or • Loss of response in those with CR or PR, increase of skin score of $>$ sum of nadir + 50% baseline score
Relapse	• Any disease recurrence in those with CR
Response in lymph nodes (peripheral and central)	
CR	• All lymph nodes $\leq$ 1.5 cm in greatest transverse diameter (major axis) by method used at baseline or biopsy negative for lymphoma • Lymph nodes that were clinically abnormal with histopathology Dutch grade 3/4 or NCI LN_4 with major axis $\leq$ 1.5 cm or minor axis $>$ 1.0 cm at baseline must now have minor axis $\leq$ 1.0 cm or biopsy negative for lymphoma
PR	• Cumulative reduction of $\geq$ 50% of the sum of the SPD of each abnormal lymph node at baseline and no new lymph node with major axis $>$ 1.5 cm or minor axis $>$ 1.0 cm if the major axis is 1.0–1.5 cm
SD	• Fails to attain the criteria for CR, PR and PD
PD	• $\geq$ 50% increase in SPD from baseline or • Any new node with major axis $>$ 1.5 cm of minor axis $>$ 1.0 cm or major axis 1.0–1.5 cm if proven to be clinically abnormal with histopathology Dutch grade 3/4 or NCI LN_4 or • Loss of response: $>$ 50% increase from nadir in SPD or lymph nodes in those with PR
Relapse	• Any new lymph node with major axis $>$ 1.5 cm in those with CR proven to be N_3 (clinically abnormal with histopathology Dutch grade 3/4 or NCI LN_4)
Response in blood (based on absolute numbers of Sézary cells per μL)	
CR	• $\leq$ 5% of peripheral blood lymphocytes are Sézary cells†
PR	• $>$ 50% decrease in quantitative measurements of blood tumor burden from baseline in those with high tumor burden at baseline‡
SD	• Fails to attain criteria for CR, PR or PD
PD	• $\leq$ 5% of peripheral blood lymphocytes are Sézary cells at baseline to high tumor burden‡ or • $>$ 50% increase from baseline and $\geq$ 5000 Sézary cells/μL or • Loss of response: in those with PR, $>$ 50% increase from nadir and $\geq$ 5000 Sézary cells/μL
Relapse	• Increase of Sézary cells to $>$ 5% of peripheral blood lymphocytes in those with CR
Response in viscera	
CR	• Liver, spleen or any other organ involved at baseline not enlarged on physical exam and considered normal by imaging (no liver or spleen nodules, any post-treatment mass biopsy-negative for lymphoma)
PR	•$\geq$ 50% regression in SPD in splenic nodules, liver nodules or measurable disease in any organs abnormal at baseline • No increase in size of liver or spleen and no new sites of involvement
SD	• Fails to attain the criteria for CR, PR or PD
PD	• $>$ 50% increase in SPD of any organs involved at baseline, or • New organ involvement, or • Loss of response: $>$ 50% increase from nadir in SPD of any previous organ involvement in those with PR
Relapse	• New organ involvement in those with CR
Global response score (based on above compartment scores)	
CR	• Skin: CR; lymph nodes/blood/viscera: all CR/NI
PR	• Skin: CR or PR; lymph nodes/blood/viscera: none with PD, if PR in skin $\geq$ 1 involved at baseline with PR or CR
SD	• Skin: PR; lymph nodes/blood/viscera: none with PD, SD for all involved at baseline
PD	• PD in any compartment (skin/lymph nodes/blood/viscera) or SD in skin
Relapse	• Relapse in any category

ISCL, International Society for Cutaneous Lymphoma; USCLC, United States Cutaneous Lymphoma Consortium; EORTC, European Organisation of Research and Treatment of Cancer; SWAT, Severity-Weighted Assessment Tool; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NCI, National Cancer Institute; SPD, sum of the major axis $\times$ minor axis; NI, not involved.

*Skin biopsy is unnecessary for normal appearing skin, but should be performed in representative area if there is any question of residual disease (persistent erythema or pigmentary change) where otherwise a complete response would exist. If histologic features are suspicious or suggestive of mycosis fungoides or Sézary syndrome response should be considered PR.

†If bone marrow biopsy at baseline unequivocally indicated lymphamatous involvement, a repeat bone marrow biopsy must show no residual disease or the response should be considered PR.

‡$\geq$ 1000 Sézary cells/μL with positive clone matching that of the skin; one of the following can be substituted for Sézary cells: CD4/CD8$\geq$10, CD4+CD7− cells $\geq$ 40% or CD4 + CD26− cells $\geq$ 30%.

may begin to manifest in certain compartments before others during relapse. Further assessment of this is difficult because median DOR was not evaluable in several patient subgroups.

The profile of drug-related TEAEs was similar in all patient subgroups examined. The only significant differences detected were higher rates of diarrhea NOS and dysgeusia in patients with blood involvement, with higher rates of diarrhea NOS also seen in patients with higher blood tumor burden. This increased rate of diarrhea could be a result of tumor cell lysis in the blood, although this is speculative. Another speculation is that those with higher blood tumor burden could have had more microscopic disease involvement in the gut. In the pruritus assessment, lymphadenopathy, but not erythroderma, blood involvement or higher blood tumor burden significantly decreased the best change in VAS and rate of achievement of CMRP. Achievement of CMRP was also previously reported in 43% (28/65) of patients with moderate-to-severe pruritus at baseline, including both objective responders ($n = 26$) and non-responders ($n = 11$) to romidepsin, and achievement of CMRP was not directly related to the level of disease improvement in the skin, together suggesting that patients without an objective response may still experience benefit in terms of symptom relief [27].

The 2011 consensus guidelines from the ISCL, USCLC and Cutaneous Lymphoma Task Force of the EORTC suggest using a composite assessment that incorporates responses in the skin, lymph nodes, blood and viscera (Table VII) [14]. However, in the guidelines, responses are defined and categorized within each disease compartment (CR, PR, etc. within that compartment), and the composite assessment is based on which compartments achieved which response. Alternatively, in the romidepsin study discussed herein, the composite assessment summed the percentage changes in each compartment to calculate the composite response (Table I). Notably, both composite assessments recognize the primacy of response in the skin, but the consensus guidelines are more rigorous, as achievement of a composite PR requires $\geq 50\%$ improvement in the skin [14] versus a $\geq 30\%$ improvement in the skin in the romidepsin study. For compartment-specific responses, the consensus guidelines require $\geq 50\%$ improvement to achieve a PR within each compartment [14]. Again, this is more rigorous than the romidepsin study in which a PR in the lymph node compartment was defined as a $\geq 30\%$ improvement.

In the pivotal study of vorinostat for the treatment of CTCL, only responses in the skin were assessed [35]. The pivotal study of bexarotene for the treatment of CTCL applied the Physician's Global Assessment of Clinical Condition (PGA; subjective 0–6 scale, including cutaneous lesions/tumors, lymph nodes and other disease manifestations) and the Composite Assessment of Index Lesion Severity (CAILS) with the addition of disease detection or progression in the lymph nodes and/or viscera [16]. Patients were classified as responders to bexarotene if response criteria for PGA or CAILS were satisfied; however, details of non-cutaneous disease assessments were limited, and measurement of disease presence in blood was not mentioned [16]. In the pivotal study of denileukin diftitox for the treatment of CTCL, a composite assessment was used to determine response that included the SWAT or summation of the bidimensional measurements in skin lesions and lymph nodes, and measurement of circulating tumor cells in the blood via flow cytometry [18]. Thus, although response rates for each of these approved drugs have been reported, the parameters for determining response varied widely, making it difficult to accurately compare response rates among systemic agents tested prior to development of the 2011 consensus guidelines.

The 2011 consensus guidelines also stressed the need to include quality-of-life assessments in trials, including those specific to pruritus [14]. In agreement with the pruritus assessments in the romidepsin study discussed herein, the VAS continues to be used to quantify the severity of pruritus, and the guidelines also recommend elimination or stabilization of confounding pruritus treatments (e.g. antihistamines) when making comparative pruritus measurements [14]. The guidelines also highlight the need to determine what constitutes significant pruritus at baseline and what change in VAS should be considered significant improvement, but they do not make recommendations on how to define these parameters. The pivotal romidepsin study, as well as studies of vorinostat, denileukin diftitox and extracorporeal photochemotherapy for patients with CTCL have used a 100 mm VAS scale with a threshold of 30 mm as the definition of a clinically significantly reduction in pruritus [18,22,32,35]. However, published data on pruritus reduction with systemic agents other than romidepsin are limited. Development of consensus guidelines on measurement of pruritus in patients with CTCL is key to providing therapies that alleviate this debilitating illness.

In the pivotal study of romidepsin for the treatment of CTCL, romidepsin demonstrated clinical activity across disease compartments and is suitable for use in patients with erythroderma, lymphadenopathy and/or blood involvement. Utilization of the 2011 consensus guidelines in future clinical trials will allow for better understanding of the kinetics of disease in each compartment and what initiates and drives patient response or relapse.

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