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Recent Advances in the Treatment of T-Cell Lymphoma

A Review of Selected Presentations From
the 52nd American Society of Hematology
Annual Meeting and Exposition
December 4–7, 2010
Orlando, Florida

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Target Audience

This activity has been designed to meet the educational needs of hematologists, oncologists, and other healthcare professionals involved in the management of patients with T-cell lymphomas.

Statement of Need/Program Overview

T-cell lymphomas can be clinically aggressive, and although they are relatively rare compared with B-cell lymphomas, they are just as diverse. T-cell lymphomas include entities such as mycosis fungoides and Sezary syndrome. To date, there are no curative treatments for stage II–IV mycosis fungoides/Sezary syndrome. Several treatments for relapsed or refractory cutaneous T-cell lymphomas and peripheral T-cell lymphomas have been examined in clinical trials. However, presently, available options for the treatment of relapsed/refractory peripheral T-cell lymphomas remain limited. This suggests that better treatment strategies are warranted for patients with aggressive T-cell lymphomas.

Educational Objectives

After completing this activity, the participant should be better able to:

1. Describe the importance of new study findings in the form of selected abstracts/poster summaries from the American Society of Hematology Annual Meeting in the natural history of T-cell lymphoma
2. Assess the results of these new study findings including current clinical trials evaluating therapy in the treatment of T-cell lymphoma
3. Describe how to integrate into clinical practice the latest knowledge and methods for treating patients with T-cell lymphoma
4. Identify future research directions for all therapies in T-cell lymphoma

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Recent Advances in the Treatment of T-Cell Lymphoma

A Review of Selected Abstracts from the 52nd American Society of Hematology Annual Meeting and Exposition
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114 Final Results from a Pivotal, Multicenter, International, Open-Label, Phase 2 Study of Romidepsin in Progressive or Relapsed Peripheral T-Cell Lymphoma (PTCL) Following Prior Systemic Therapy[1]

B Coiffier, B Pro, HM Prince, FM Foss, L Sokol, M Greenwood, D Caballero, P Borchmann, F Morschhauser, M Wilhelm, L Pinter-Brown, S Padmanabhan, A Shustov, J Nichols, S Carroll, J Balser, SM Horwitz

Several agents currently used in the treatment of relapsed or refractory cutaneous T-cell lymphoma (CTCL) have been investigated for their potential efficacy in peripheral T-cell lymphoma (PTCL). One example is romidepsin, a histone deacetylase (HDAC) inhibitor currently approved for the treatment of relapsed or refractory CTCL. In CTCL, romidepsin has been shown to result in a 34% rate of overall response (OR) and a median duration of response of up to 15 months in patients with relapsed or refractory disease.[2,3] A preliminary phase II clinical trial has recently been published, which investigated single-agent romidepsin in patients with relapsed or refractory PTCL.[4] In that study, an OR rate of 38% was achieved with a median duration of response of 8.9 months (range, 2–74 months). Notably, responses were observed across various PTCL subtypes, including PTCL not otherwise specified (NOS), angioimmunoblastic T-cell lymphoma (AITL), and anaplastic lymphoma kinase (ALK)-negative anaplastic large cell lymphoma (ALCL). In this abstract, Coiffier and colleagues further evaluated romidepsin in a larger cohort of PTCL patients.[1]

Patients (N=131) with histologically confirmed PTCL were allowed in this prospective, multicenter, international, single-arm, open-label phase II study. Although a number of PTCL subtypes were allowed, most patients had PTCL-NOS (53%), AITL (21%), or ALK-negative ALCL (16%). Approximately three-quarters of patients (76%) had an International Prognostic Index (IPI) score of 2 or higher, and most patients (86%) had an Eastern Cooperative Oncology Group (ECOG) performance score of 0 or 1. A median of 1.3 years (range, 0.2–17.0 years) had passed since the patients' first diagnosis; 70% of patients were diagnosed with stage III/IV disease. All patients (median age, 61 years) were refractory to any systemic therapy, which included chemotherapy (99%), monoclonal antibody therapy (15%), or another type

Table 1. Efficacy Evaluations by Independent Review Committee

Efficacy Assessments	Radiology, n (%)	Clinical, n (%)
CR + CRu	19 (15%)	17 (13%)
PR	15 (12%)	17 (13%)
SD	36 (28%)	32 (25%)
ORR	34 (26%)	34 (26%)
Median duration of response		
CR + CRu	–	Not reached (range, 1–801+ days)
ORR	–	12 mos (range, 1–801+ days
Median time to response	–	3.6 mos (range, 55–169 days)

CR=complete response; CRu=unconfirmed complete response; ORR=overall response rate; PR=partial response; SD=stable disease.

Data from Coiffier B et al. *Blood* (ASH Annual Meeting Abstracts). 2010;116:Abstract 114.[1]

of immunotherapy (11%), such as denileukin diftitox or interferon. A total of 38% of patients were refractory to their most recent treatment. Intravenous romidepsin (14 mg/m^2) was administered on days 1, 8, and 15 every 28 days for up to 6 cycles. Patients without disease progression had the option to continue romidepsin treatment.

Romidepsin was associated with a 26% objective response rate by central review, with 13% of patients achieving a complete response (CR) or unconfirmed CR (CRu; the primary study endpoint) and 13% of patients achieving a partial response (PR). Another 25% of treated patients experienced stable disease. These responses were considered to be durable, with a median duration of response of 12 months (range, <1 to 26.0+ months) for objective responses and a median duration of response that was not reached (range, <1 to 26.3+ months) for CR and CRu (Table 1). Responses were quickly attained, with a median time to objective response of 2 months (range, 2–6 months) and a median time to CR or CRu of 4 months (range, 2–9 months). The median time to disease progression was 6 months (range, <1 to 28+ months).

Responses were only observed in patients with PTCL-NOS, AITL, and ALK-negative ALCL, but no other PTCL subtypes. However, responses were well maintained across several other patient subgroups, including sex (male vs female), age (<65 years vs ≥65 years), baseline IPI score (<2 vs ≥2), number of prior systemic therapies administered (<3 vs ≥3), and prior use of stem cell transplant, pralatrexate, monoclonal antibody, or immunotherapy (yes vs no).

Two-thirds (66%) of patients experienced a grade 3 or lower adverse event, which included thrombocytopenia, neutropenia, infection, and anemia. Other adverse events (all grades) reported in 30% or more of patients were nausea, infection, fatigue, vomiting, thrombocytopenia, diarrhea, pyrexia, and neutropenia. A specific cardiac toxicity analysis was performed, but no significant changes in either the mean QTcF or QTcB intervals were noted during cycles 1–4. Electrocardiogram abnormalities were reported in 8 patients, and 2 patients had a grade 3 or higher cardiac abnormality. A total of 8 patients died within 30 days of their last romidepsin treatment; 3 of these deaths were due to disease progression and 5 were due to infection. One patient's death, resulting from sepsis leading to multiorgan failure, was determined to be possibly related to treatment.

After a median follow-up of 8.2 months, 9 of the 17 patients who had achieved a CR or CRu continued to receive romidepsin therapy. Of the remaining 8 patients, 5 discontinued treatment (4 cases due to physician or patient decision and 1 patient due to proceeding to transplant) and 3 experienced disease progression.

961 Complete Remissions with Brentuximab Vedotin (SGN-35) in Patients with Relapsed or Refractory Systemic Anaplastic Large Cell Lymphoma[5]

AR Shustov, R Advani, P Brice, NL Bartlett, JD Rosenblatt, T Illidge, J Matous, R Ramchandren, MA Fanale, JM Connors, Y Yang, EL Sievers, DA Kennedy, B Pro

The novel investigational agent brentuximab vedotin (SGN-35) is currently under investigation in CD30-positive PTCL. This antibody-drug conjugate is composed of the potent antimitotic agent monomethylauristatin E (MMAE) covalently coupled to the anti-CD30 monoclonal antibody cAC10 via a valine-citrulline peptide linker. Recently, it was shown that the mechanism explaining the potent activity of brentuximab vedotin is based upon specific binding of the agent to CD30-positive cells, followed by receptor-mediated internalization and cellular uptake, lysosomal degradation and release of MMAE, and retention of the MMAE component.[6] The half-life of cellular retention of MMAE is 15–20 hours. Preclinical studies with brentuximab vedotin revealed it had high potency (half maximal inhibitory concentration [IC_{50}] <10 ng/mL) in CD30-positive cell lines, and activity in a mouse xenograft model of ALCL.[7] In a phase I, open-label, multicenter, dose-escalation study, which included relapsed or refractory patients with CD30-positive lymphomas (primarily Hodgkin lymphoma and ALCL), several durable objective responses to brentuximab vedotin treatment were noted.[8] Further, that study established the maximum tolerated dose of brentuximab vedotin as 1.8 mg/kg every 3 weeks. Here, Shustov and colleagues evaluated the safety and efficacy of brentuximab vedotin specifically in patients with relapsed or refractory systemic ALCL.[5]

This was a single-arm, multicenter, phase II clinical trial that enrolled 58 patients with relapsed or refractory systemic ALCL. Of these, data from the first 30 patients treated on-study were available. This cohort included 47% male patients with a median age of 55 years (range, 14–71 years). Most patients (70%) had ALK-negative ALCL, and 13% of patients exhibited bone marrow involvement at baseline. Nearly two-thirds of patients (63%) had primary refractory disease, whereas half (53%) had not responded to their most recent prior therapy. Patients had a median of 2 (range, 1–6) chemotherapy regimens administered prior to the study. One-quarter (27%) of patients had failed previous autologous stem cell transplantation. Patients were given up to 16 cycles of brentuximab vedotin (1.8 mg/kg every 3 weeks as an outpatient infusion over 30 min).

Single-agent brentuximab vedotin was found to have a high activity in ALCL, as demonstrated by a high rate of objective response (87%; n=26) achieved in this

study by investigator assessment. Of these, 57% were a CR and 30% were a PR. The remaining 4 patients either had stable disease (n=3) or were not evaluable for response (n=1). The median time to objective response was 6 weeks (range, 5–12 weeks), with a duration of response ranging from 4–36 weeks (responses continued in 18 patients at the time of this abstract). Response rates were similar regardless of whether the patient had ALK-positive or ALK-negative disease. Notably, nearly all patients (97%) demonstrated a reduction in tumor burden following treatment. Similarly, 90% of those patients with B symptoms at baseline experienced resolution of symptoms. One-third (33%) of those patients who achieved a CR were able to continue on to either autologous or allogeneic stem cell transplant.

Overall, brentuximab vedotin treatment was considered to be well tolerated and the toxicities that occurred during treatment were considered to be manageable. Several grade 3/4 adverse events, which were considered to be related to brentuximab vedotin treatment, were reported in patients. These included neutropenia (17%), peripheral sensory neuropathy (13%), diarrhea (7%), and anemia (7%). The most commonly observed adverse events of any grade included nausea (47%), diarrhea (40%), peripheral sensory neuropathy (40%), pyrexia (33%), dyspnea (30%), fatigue (27%), insomnia (23%), and neutropenia (23%).

Table 2. Efficacy Analysis of Patients With CTCL

	All Evaluable Patients (N=38)				
Stage	**Total**	**CR**	**PR**	**SD**	**PD**
IA	1			1	
IB	2			2	
IIB	11		2	7	2
IIIA	1		1		
IIIB	4		1	2	1
IVA	15	2	8	4	1
IVB	4		1	3	
All	38	2	13	19	4

CTCL=cutaneous T-cell lymphoma; CR=complete response; PD=progressive disease; PR=partial response; SD=stable disease.

Data from Duvic M et al. *Blood* (ASH Annual Meeting Abstracts). 2010;116:Abstract 962.[9]

962 Results of a Phase 1/2 Study for KW-0761, a Monoclonal Antibody Directed Against CC Chemokine Receptor Type 4 (CCR4), In CTCL Patients[9]

M Duvic, L Pinter-Brown, FM Foss, L Sokol, J Jorgensen, GL Spitalny, YH Kim

Another molecular target with potential for exploitation in T-cell lymphomas is the CC chemokine receptor type 4 (CCR4). CCR4 has previously been shown to be overexpressed in several tumor types, including PTCL and CTCL.[10,11] Mogamulizumab (KW-0761) is a humanized defucosylated anti-CCR4 antibody, which has been developed and examined in both the preclinical and early clinical settings.[12,13] The results of a pilot phase I dose-escalation study in 16 patients with relapsed CCR4-positive PTCL or adult T-cell leukemia-lymphoma were recently published, showing that 5 patients (31%) achieved an objective response, of which 2 were CR.[14] Further, the phase I clinical trial found KW-0761 to be well tolerated; grade 3/4 adverse events reported included lymphopenia, neutropenia, leucopenia, herpes zoster, skin rash, febrile neutropenia, and acute infusion reaction/cytotoxin release syndrome. Dose escalation did not increase the frequency or severity of adverse events, and, therefore, the maximum tolerated dose in this study was not reached. On the basis of these results, the investigators recommended a dose of 1.0 mg/kg KW-0761 for further phase II investigations. However, it has been noted that this dose is much lower than those of other antibodies used for lymphoma treatment, and there is a possibility that a higher dosage may result in greater efficacy with tolerable toxicity.[15] In this abstract, Duvic and colleagues reported on the results of a phase I//II study, which evaluated KW-0761 in previously treated PTCL or CTCL.[9]

This was a multicenter, open-label, dose-escalation, phase I/II clinical trial comprising a dose-escalation phase (phase I) and a preliminary assessment of the safety and efficacy of KW-0761 (phase II). A total of 42 patients (median age, 67 years) with previously treated PTCL or CTCL were enrolled. All patients had received at least 1 prior systemic therapy, and the median number of prior therapies was 5 (range, 1–17). Slightly more men (57%) than women (43%) were enrolled. During the phase I portion, patients were given KW-0761 in a standard 3+3 study design, at doses of 0.1, 0.3, and 1 mg/kg. Intravenous KW-0761 was administered once weekly for the first 4 weeks, followed by a 2-week observation period. Patients with a response or stable disease were then permitted to continue KW-0761 treatment every other week until either disease progression or study withdrawal. Responses in PTCL were assessed by the International Working Group criteria, and responses in CTCL were measured by a composite overall global response score measuring response in skin, lymph nodes, viscera, and blood (for patients with Sézary syndrome).

At least 4 KW-0761 doses were administered to a total of 40 patients, at doses of 0.1 mg/kg (n=3), 0.3 mg/kg (n=3), and 1 mg/kg (n=34). During the dose-escalation portion, no dose-limiting toxicities or drug-related serious adverse events were reported. The most frequent adverse events observed included chills, headache, nausea, pyrexia, infusion-related reactions, and back pain. Most of the adverse events experienced by patients were mild or moderate in severity, and none (including infection) appeared to be related to the dose of KW-0761. The only significant hematologic toxicity reported was lymphopenia. A total of 6 patients developed a new skin eruption, which was determined to not be consistent with the underlying disease. One example of this was a patient who experienced a grade 3 hypersensitivity rash with eosinophils. Again, a maximum-tolerated dose was not established in this study.

Efficacy of KW-0761 treatment was evaluable in 38 patients; all of whom were diagnosed with CTCL (23 with mycosis fungoides and 15 with Sézary syndrome). Of these 38 patients, 15 (39%) achieved an objective response, 2 of which were a CR and 13 of which were a PR. An additional 19 patients experienced stable disease. Only 4 patients demonstrated progressive disease. Responses occurred across disease stages IIB–V (Table 2).

Table 3. Efficacy Assessments

Efficacy Assessments	Investigator Assessment (n=20)	Central Review Assessment (n=20)
ORR	8 (40%)	8 (40%)
CR	5 (25%)	3 (15%)
PR	3 (15%)	5 (25%)
SD	5 (25%)	2 (10%)
PD	6 (30%)	4 (20%)
Not evaluable	1 (5%)	6 (30%)*
Median duration of response	16.2 months	13.1 months
Median PFS†	4.8 months	14.4 months
Median OS	12 months	

*Two patients were not evaluable, and 4 missing as off-treatment in cycle 1.

†Per a Kaplan-Meier estimate.

CR=complete response; ORR=overall response rate; OS=overall survival; PD=progressive disease; PFS=progression-free survival; PR=partial response; SD=stable disease.

Data from Goy A et al. *Blood* (ASH Annual Meeting Abstracts). 2010;116:Abstract 1753.[16]

1753 Pralatrexate is Effective in Patients with Relapsed or Refractory Peripheral T-Cell Lymphoma (PTCL) with Prior Ifosfamide, Carboplatin, and Etoposide (ICE)-Based Regimens[16]

A Goy, B Pro, KJ Savage, NL Bartlett, MJ Lechowicz, ED Jacobsen, F Young, M Crump, H Borghaei, B Link, SM Fruchtman, OA O'Connor

The ifosfamide/carboplatin/etoposide (ICE) backbone regimen is often used as combination chemotherapy for the treatment of relapsed or refractory peripheral T-cell lymphomas (PTCL). Despite a lack of supporting clinical data, ICE is included as a suggested regimen in this setting in the current guidelines from the National Comprehensive Cancer Network (NCCN).[17] This suggestion is primarily based on a report of efficacy associated with ICE in 222 patients with relapsed or refractory aggressive non-Hodgkin lymphoma, only some of whom had PTCL (13%).[18] Although increases in the response to ICE may be achieved with the addition of rituximab (rituximab/ICE, RICE) or dexamethasone (dexamethasone/ICE, DICE), only a minimal benefit is achieved, and few patients are able to progress to a stem cell transplant.[19] Thus, there is a need for more effective second-line therapy for relapsed and refractory PTCL.

Recently, the folate analog pralatrexate became the first agent approved by the Food and Drug Administration (FDA) for the treatment of relapsed and refractory PTCL, based on data from the pivotal PROPEL (Pralatrexate in Patients with Relapsed or Refractory Peripheral T-Cell Lymphoma) study.[20] In this study, pralatrexate was demonstrated to induce durable responses in patients with relapsed or refractory PTCL, regardless of histologic subtype, amount of prior therapy, and prior stem cell transplant. In this current study, Goy and colleagues reported the results of an exploratory analysis of the PROPEL study, in which the efficacy of pralatrexate was limited in examination to patients who had previously failed an ICE-based treatment.[16]

Of the 115 total PTCL patients enrolled in the PROPEL study, 109 were considered evaluable. Of these, 20 patients (median age, 45 years) had previously received an ICE-based regimen and had progressed at some point prior to study enrollment. Nearly half (n=9) of these patients had received the ICE-based regimen as their most recent line of chemotherapy prior to initiating pralatrexate treatment. The overall response rate to the prior ICE-based treatment was 25%, including 3 (15%) CRs and 2 (10%) PRs. However, the duration of response to ICE was very short (median duration of response, <1 month). In PROPEL, patients were treated with

intravenous pralatrexate (30 mg/m^2 each week) for 6 weeks of a 7-week cycle.

This subset of ICE-treated PTCL patients achieved a 40% (n=8) OR rate both by central review and investigator assessment, suggesting that pralatrexate was highly active in these patients. Of these, 15% (n=3) were defined as a CR, and 25% (n=5) were defined as having a PR by central review assessment (25% and 15%, respectively, by investigator assessment). The remaining patients either maintained stable disease (10%; n=2) or experienced progressive disease (20%; n=4) when assessed by central review. A total of 6 patients (30%) were considered either not evaluable or missing as off-treatment in cycle 1 by central review assessment. Importantly, the responses achieved by these patients were found to be durable (median duration of response 13.1 months or 16.2 months by central review or investigator assessment, respectively) and markedly longer than had previously been achieved with ICE-based treatment. The estimated median progression-free survival (PFS) was 14.4 months by central review assessment (4.8 months by investigator assessment), and the median overall survival (OS) was 12 months (Table 3).

Specific responses in select patients were found to be particularly intriguing, and were reported by the investigators. For example, 2 of the responding patients had not responded at all to their prior ICE-based regimen, but did respond to pralatrexate (1 CR, 1 PR). Also, 2 patients who achieved a CR with pralatrexate successfully proceeded to stem cell transplant, with a censored duration of response at 1.3 and 4.9 months. After follow-up, these patients remained in CR at the time of this report, with a disease-free period (including on-study treatment and stem cell transplant periods) of 10.9 and 30.8 months. The response rate achieved in the ICE-treated patient subset was somewhat higher than that achieved in the overall PROPEL study population (29%).

In this exploratory analysis, the most frequently reported grade 3 adverse events included anemia (n=8) and mucositis (n=5), and the most common grade 4 adverse event was thrombocytopenia (n=6). A total of 5 patients discontinued pralatrexate therapy due to toxicities. However, despite these adverse events, pralatrexate was still considered to have a favorable toxicity profile compared with ICE-based chemotherapy, which often requires hospitalization during administration.[21] The grade 3/4 adverse events noted in this exploratory patient population were similar to those reported in the overall PROPEL study population (32% thrombocytopenia, 22% mucositis, 22% neutropenia, 18% anemia).

2800 Identification of an Active, Well-Tolerated Dose of Pralatrexate in Patients with Relapsed or Refractory Cutaneous T-cell Lymphoma (CTCL): Final Results of a Multicenter Dose-Finding Study[22]

SM Horwitz, YH Kim, FM Foss, JM Zain, P Myskowski, MJ Lechowicz, DC Fisher, A Shustov, NL Bartlett, ML Delioukina, T Koutsoukos, SM Fruchtman, OA O'Connor, M Duvic

Based on the success seen in the PROPEL study and subsequent approval of pralatrexate for PTCL, this antifolate has also been investigated for its efficacy and safety in CTCL. An early study with pralatrexate suggested that this agent may also be active in patients with CTCL,[23] although it has yet to be optimized for this specific lymphoma. Unlike PTCL, which is a characteristically aggressive lymphoma, CTCL is often more indolent in nature, necessitating continuous and maintenance treatment. Thus, treatments designed for CTCL should have the potential to be administered over a long time period. Here, Horwitz and colleagues presented the final results of the PDX-010 study, designed to identify an optimal pralatrexate dose with clinical activity but minimal toxicity in patients with relapsed or refractory CTCL.[22]

PDX-010 was a phase I, multicenter, open-label, dose-finding study of pralatrexate in 54 patients with relapsed or refractory CTCL. The CTCL histologies included in this study were mycosis fungoides, Sézary syndrome, and primary cutaneous ALCL. All patients had progressed after a minimum of 1 prior systemic treatment. In this study, intravenous pralatrexate was initiated at a dose of 30 mg/m^2 each week for 3 weeks of a 4-week cycle, based on data supporting the safety and efficacy of this dose in patients with aggressive lymphoma.[20,29] In PDX-010, a dose de-escalation strategy was used to identify the minimally active dose. If toxicity was observed, subsequent patient cohorts were treated with either reduced pralatrexate doses (20, 15, or 10 mg/m^2 weekly) and/or alternative schedules (3 weeks of a 4-week schedule or 2 weeks of a 3-week schedule). As was established in the PROPEL study, all patients received vitamin B_{12} (1 mg every 8–10 weeks) and folic acid (1 mg daily) to mitigate pralatrexate-related toxicity.[20]

In the dose-finding portion of this study, patients (N=31) were sequentially enrolled into 6 cohorts, and subsequently treated as described above. Based on this phase, the optimal dose and schedule of pralatrexate in relapsed or refractory CTCL was determined to be 15 mg/m^2 weekly for 3 weeks of a 4-week cycle. This dose was associated with a 50% OR rate among the initial 6 patients treated with this schedule. Overall, patients treated with pralatrexate at a dose intensity of 15 mg/m^2

Table 4. Grade 1/2 Adverse Events Occurring in More Than 10% of Patients

Adverse Event	Percent of Patients
Fatigue	34%
Mucositis*	28%
Nausea	24%
Edema	24%
Epistaxis	21%
Pyrexia	17%
Constipation	14%
Vomiting	14%
Anemia	14%

*Mucositis was the only grade 3 adverse event reported in more than 10% of patients (17%).

Data from Horwitz SM et al. *Blood* (ASH Annual Meeting Abstracts). 2010;116:Abstract 2800.[22]

or higher weekly for 3 weeks of a 4-week cycle achieved a 61% (11/18) OR, compared to only 8% (1/13) in patients treated at lower dose intensities.

Using the optimal dose identified, 23 additional patients were treated in the second phase of this study, which was focused on determining the safety and efficacy of this dose in relapsed or refractory CTCL. In this analysis, the efficacy and safety data for all patients treated at the optimal identified dose (n=6 in phase I and n=23 in phase II of PDX-010) were included together. Among these 29 patients, the median number of pralatrexate cycles administered was 4 (range, 1–23), and the median number of prior systemic therapies was 4.5 (range, 1–11). In the event of failure to achieve a CR and in the absence of toxicity, the dose of pralatrexate could be escalated at the investigator's discretion. The OR observed at the optimal dose was 43%. Among the entire PDX-010 study population that was treated with pralatrexate at a dose intensity of 15 mg/m^2 or higher weekly for 3 weeks of a 4-week cycle (n=40), the OR rate was 50%.

The optimal pralatrexate dose was associated with a well-tolerated safety profile. The only grade 3 nonhematologic adverse event reported in more than 10% of patients was mucositis (17%). Other nonhematologic adverse events seen in more than 10% of patients were limited to grade 1/2 fatigue, mucositis, nausea, edema, epistaxis, pyrexia, constipation, and vomiting (Table 4). Severe hematologic toxicities included grade 4 leucopenia (3%), grade 3 thrombocytopenia (3%), grade 3 neutropenia (3%), and grade 3 anemia (3%). Grade 1/2 anemia (14%), thrombocytopenia (7%), and leucopenia (3%) were also reported. Based on the lack of significant hematologic and nonhematologic toxicities observed at the optimal dose, combined with promising clinical activity, it is possible that a low-dose long-term pralatrexate schedule could become an alternative therapy for patients with relapsed or refractory CTCL.

1762 Pralatrexate Is an Effective Treatment for Heavily Pretreated Patients with Relapsed/Refractory Transformed Mycosis Fungoides (tMF)[24]

FM Foss, SM Horwitz, L Pinter-Brown, A Goy, B Pro, B Coiffier, L Popplewell, KJ Savage, A Shustov, JM Zain, T Koutsoukos, SM Fruchtman, OA O'Connor

Although most cases of CTCL are indolent, some patients undergo large cell transformation, a process in which the typical small and medium-sized lymphocytes, normally characteristic of mycosis fungoides, are replaced by large cells (similar in appearance to those observed in ALCL and ≥4 times the size of the small lymphocyte). By definition, these large cells comprise more than 25% of the total lymphoid infiltrate, and represent an evolution from the original malignant clone.[25-27] Transformed mycosis fungoides is relatively rare, occurring in 8–55% of cases.[28] Unlike the more indolent mycosis fungoides, transformed mycosis fungoides is aggressive and associated with an extremely poor prognosis. From the time of diagnosis of large-cell transformation, the median OS is only 2.2 years.[29] There is no current standard therapy for the treatment of transformed mycosis fungoides; instead, patients are generally given systemic single-agent or combination chemotherapy regimens. According to the NCCN guidelines, preferred systemic agents for transformed mycosis fungoides include liposomal doxorubicin, gemcitabine, denileukin diftitox, and romidepsin, among others.[17]

Because transformed mycosis fungoides is associated with such a poor prognosis and aggressive nature, similar to PTCL, patients with this form of CTCL were also included in the PROPEL study.[20] In this abstract, Foss and colleagues reported an analysis of the subset of patients with relapsed or refractory transformed mycosis fungoides from the PROPEL study.[24]

Of the 115 total PTCL patients enrolled in the PROPEL study, 109 were considered evaluable. Of these, 12 patients (median age, 56.5 years) had histologically confirmed relapsed or refractory transformed mycosis fungoides. These individuals were heavily pretreated, with a median of 6.5 prior therapies (range, 1–12), and 5 patients had received 5 or more prior systemic therapies. The most common prior treatment was cyclophosphamide/doxorubicin/vincristine/prednisone (CHOP) or a CHOP-based

regimen (67%), although 17% of patients also received other combination chemotherapy regimens. However, of the 12 patients, only 1 had achieved a response to the most recent chemotherapy given prior to enrollment on the PROPEL study. In PROPEL, patients were treated with intravenous pralatrexate (30 mg/m^2 each week) for 6 weeks of a 7-week cycle.

A median of 10 doses of pralatrexate was administered to this patient subset, and patients remained on therapy for a median of 89 days. Following pralatrexate treatment, the OR rate achieved by patients with relapsed or refractory transformed mycosis fungoides was 25% by central review and 58% by investigator assessment. The large difference between the 2 types of assessment was attributed to a difficulty associated with photodocumentation of response assessment of cutaneous lesions. By investigator assessment, the duration of this response was 4.4 months. The median PFS and median OS achieved was 5.3 months and 13 months, respectively.

In this patient subset, pralatrexate was well tolerated, and no patients discontinued treatment due to toxicity. Two patients experienced a grade 4 adverse event, including fatigue (n=1) and thrombocytopenia (n=1). Mucosal inflammation was reported in 7 patients (58%), of which 1 was described as grade 3 in severity.

2863 Efficacy of Denileukin Diftitox Retreatment in Patients with Cutaneous T-Cell Lymphoma Who Relapsed After Initial Response[30]

M Duvic, A Martin, EA Olsen, D Fivenson, M Prince

The genetically engineered fusion protein denileukin diftitox, which is composed of a recombinant version of the interleukin-2 protein attached to diphtheria toxin, is currently FDA-approved for the treatment of persistent or recurrent CD25-positive CTCL. The mechanism of action of denileukin diftitox involves targeting the molecule to interleukin-2–expressing cells, and delivering the cytotoxic diphtheria toxin to the cell, thus inhibiting protein synthesis and inducing cell death. Denileukin diftitox was shown to induce higher responses (44% vs 15.9%) and significantly longer median PFS (>2 years vs 124 days; P<.001) compared with placebo in L4389-11, a recent multicenter, randomized, international, phase III clinical trial.[31] In that trial, patients (N=144) were treated with either of 2 doses of denileukin diftitox—9 or 18 µg/kg daily—or placebo. Both doses were demonstrated to be significantly superior versus placebo, although the 18 µg/kg dosage was associated with a higher OR rate compared with the 9 µg/kg dosage (49.1% vs 37.8%). In this current study, Duvic and colleagues report the results of a subset analysis of the L4389-14 study, which evaluated the efficacy of denileukin diftitox specifically in a cohort of patients with CTCL who had previously been treated with denileukin diftitox and were retreated after disease progression.[30]

The L4389-14 study was a multicenter, international, open-label, phase III trial, which aimed to determine the efficacy and safety of denilekin diftitox in patients diagnosed with stage IA–III CD25-positive CTCL. All patients had received 3 or fewer therapies prior to study enrollment and had a relatively good prognosis (life expectancy ≥12 months). This subset analysis was restricted to those patients (n=20) who had previously been treated with denileukin diftitox (either 9 or 18 µg/kg daily) but who had then relapsed. Of these 20 patients (median age, 59.5 years), 4 had achieved a CR, 13 had achieved a PR, 1 had experienced stable disease, and 2 had an unrecorded response to the prior denileukin diftitox treatment. The majority of these patients was male (70%) and white (80%), and most (80%) had early-stage CTCL (≤ stage IIA). These patients were retreated with up to 8 cycles of 18 µg/kg daily denileukin diftitox on days 1–5 of a 21-day cycle. A median of 8 cycles of denileukin diftitox was administered as retreatment. Patients were assessed for the primary study endpoint, which was overall response, at each study visit by measuring the percentage change in tumor burden; responses were confirmed over 3 consecutive denileukin diftitox cycles. Secondary endpoints included PFS, time to treatment failure, and safety.

A total of 40% of patients achieved a second OR to denileukin diftitox retreatment. Most of these (30%) were PRs. Patients with higher-stage disease tended to achieve better OR rates compared to those with lower-stage CTCL at baseline (50% vs 38% for ≥ stage IIB vs ≤ stage IIA). Nine patients exhibited signs of disease progression; all of these patients had stage IIA or better CTCL at baseline. The estimated median time to response was 102 days (intent-to-treat population), and the response was durable (median duration of response, 274 days). Among the intent-to-treat population, the estimated median PFS was 205 days (95% confidence interval [CI], 170–429), and the median time to treatment failure was 189 days (95% CI, 72–429).

Treatment-related adverse events were observed in 85% of patients; 55% of the events were grade 3/4 in severity, and 5% were a serious adverse event (involving pleural effusion). The most common treatment-related adverse events reported included nausea (35%), fatigue (25%), rigors (20%), headache (15%), and pyrexia (10%). This safety profile is relatively similar to that of patients receiving denileukin diftitox for the first time, as was shown in the L4389-11 trial.[31]

3937 The Combination of Histone Deacetylase Inhibitors and Hypomethylating Agents Exhibits Marked Synergy in Preclinical Models of T-Cell Lymphoma[32]

E Marchi, DC Bongero, M Kalac, L Scotto, OA O'Connor

An abstract presented by Marchi and colleagues also investigated the potential role of romidepsin in PTCL.[32] In this study, the investigators used preclinical models of T-cell lymphoma to determine the activity of various HDAC inhibitors and hypomethylating agents in this malignancy. Specifically, 3 agents were evaluated; in addition to romidepsin, another HDAC inhibitor, belinostat, and the hypomethylating agent decitabine were included. The rationale for using HDAC inhibitors in T-cell lymphoma can be traced to the fact that HDAC expression, which normally controls cell transcription and gene expression by regulating the acetylation of histone proteins, is often dysregulated in hematologic malignancies.[33] In addition to romidepsin, vorinostat has also received FDA approval for the treatment of CTCL. Belinostat is also currently under investigation in lymphomas. At the 2010 American Society of Clinical Oncology (ASCO) annual meeting, an ongoing, multicenter, open-label, phase II trial of belinostat in patients with relapsed or refractory PTCL was reported.[34] That study is aiming to investigate the safety and efficacy of single-agent belinostat, with a primary study endpoint of objective response. Inhibition of DNA methylation has also been shown to be a promising potential intervention in T-cell lymphoma.[35] The combination of decitabine with HDAC inhibitors has been shown to be synergistic.[36] Thus, the synergistic potential of romidepsin, belinostat, and decitabine in hematologic malignances was examined in this current study.

Several different lymphoma and leukemia cell lines were used, including the CTCL cell lines H9 and HH, as well as the T-acute lymphoblastic leukemia cell lines P12 and PF-382 (both resistant to gamma-secretase inhibition). Cytotoxicity was assayed by measuring cell viability using luminescence. Drug combination activity was calculated by determining the relative risk ratio, with synergism defined as a relative risk ratio of less than 1. Cell death, or apoptosis, was measured by cell staining followed by flow cytometry. Proteins were quantified using the Bradford protein assay against the whole cell lysate, and qualitatively analyzed by Western blot.

The IC_{50} for each drug alone was calculated for each cell line at 3 time points (24, 48, and 72 hours). For belinostat, the IC_{50} measurements in the H9 (108.1, 35.7, and 29.1 nM) and HH (240.1, 67.6, and 39.01 nM) CTCL cell lines were in the high-to-mid nanomolar range, as were the IC_{50} measurements in the P12 (386.9, 99.9, and 99.8 nM) and PF-382 (267.1, 135, and 118.3 nM) leukemia cell lines. The IC_{50} levels for romidepsin were in the lower nanomolar range for the H9 (5, 2.1, and 2.2 nM) and HH (14, 2.6, and 2.5 nM) CTCL cell lines and the P12 (6.2, 2.4, 2.1 nM) and PF-382 (6.1, 1.7, and 1.5 nM) leukemia cell lines. In contrast, the IC_{50} levels for decitabine were in the micromolar range; only the IC_{50} at 72 and 96 hours were provided for the CTCL cell lines H9 (7.4 and 3.7 μM) and HH (>20 μM).

Synergism between decitabine and either belinostat or romidepsin was demonstrated by a cytotoxicity assay in all 4 cell lines after 72 hours of drug exposure. For example, in the CTCL cell line H9, the relative risk ratios ranged between 0.4 and 0.7 for the combination of 0.5 μM decitabine with 50–100 nM belinostat, and between 0.5 and 0.7 for the combination of 1 μM decitabine with 50–100 nM belinostat. Similarly, the relative risk ratios were between 0.3 and 0.9 for the combination of 0.5 μM decitabine with 0.5–2 nM romidepsin, and between 0.3 and 0.9 for the combination of 1 μM decitabine with 0.5–2 nM romidepsin. For the leukemia cell line PF-382, the relative risk ratios were 0.8 and 0.7 for the combination of 150 nM belinostat with 0.5 μM and 1 μM decitabine, respectively. The relative risk ratios ranged between 0.1 and 0.8 for the combination of 0.5 μM decitabine with 1–2 nM romidepsin and between 0.1 and 0.7 for the combination of 1 μM decitabine with 1–2 nM romidepsin.

Markedly higher rates of apoptosis were also observed with the combination of either belinostat or romidepsin with decitabine compared to either drug alone after 72 hours of treatment (Table 5). In the CTCL cell line H9, 22.9% and 17.9% of cells were apoptotic or dead after 100 nM belinostat or 0.5 μM decitabine treatment alone, but when the drugs were combined, this proportion increased to 51.5% (relative risk ratio, 0.7). Also in the H9 cell line, 22.2% and 17.9% of cells were apoptotic or dead after exposure to 2 nM romidepsin or 0.5 μM decitabine alone, but when the drugs were combined, this was increased to 63.6% (relative risk ratio, 0.5). Similarly, in the CTCL cell line HH, the proportion of apoptotic or dead cells was 42.9% and 46.9% after 100 nM belinostat or 1 μM decitabine treatment alone, but increased to 61.3% when the 2 drugs were combined (relative risk ratio, 0.8). In the HH cell line, 80% and 46.9% of cells were apoptotic or dead after 2 nM romidepsin or 1 μM decitabine alone, but 89.7% were dead after exposure to both drugs together (relative risk ratio, 0.6).

Protein analysis demonstrated changes in several proteins. For example, histone 3 displayed increased levels of acetylation after treatment with romidepsin, which was

Table 5. Rates of Apoptosis in Patients Receiving Belinostat, Decitabine, and Romidepsin

Lymphoma and Leukemia Cell Lines	B	D	B+D	
	% Apoptotic and Dead Cells			RRR
H9	100 nM (22.9%)	500 nM (17.9%)	51.5%	0.7
HH	100 nM (42.9%)	1 uM (46.9%)	61.3%	0.8
P12	150 nM (16%)	1 uM (42.7%)	80.1%	0.4
PF-382	100 nM (8.3%)	1 uM (27.9%)	40.1%	0.8
	R	D	R+D	
H9	2 nM (22.2%)	500 nM (17.9%)	63.6%	0.5
HH	2 nM (80%)	1 uM (46.9%)	89.7%	0.6
P12	2 nM (9.9%)	10 uM (58.7%)	98%	0.03
PF-382	2 nM (54.5%)	500 nM (17.9%)	88.7%	0.2

B=belinostat; D=decitabine; R=romidepsin; RRR=relative risk ratio.

Data from Marchi E et al. *Blood* (ASH Annual Meeting Abstracts). 2010;116:Abstract 3937.[32]

synergistically increased in samples, which were treated with romidepsin combined with decitabine.

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Commentary

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Peripheral T-cell lymphomas (PTCLs) are a heterogeneous group of lymphoproliferative disorders, which account for approximately 12–15% of all non-Hodgkin lymphomas (NHLs) in Western countries. The rarity of the disease, the difficulty in establishing diagnosis, and the extremely aggressive clinical behavior have in the past posed tremendous obstacles in the development of treatment strategies specific for these disorders. Traditionally, many of the chemotherapy regimens known to be effective in aggressive B-cell lymphoma have been used for the treatment of T-cell lymphoma, with disappointing results. To date, no standard treatment has been established for this disease, and enrollment in clinical trials is the preferred option in both the frontline and relapsed setting. Fortunately, over the last several years, there has been a major effort in the development of clinical trials for the investigation of new agents, and an increasing number of treatment options are becoming available for patients with PTCL.

One class of drugs that has emerged as having significant and selective activity in T-cell lymphomas is the histone deacetylase (HDAC) inhibitors, and a number of these agents, with different chemical structures and selectivity, are currently being tested in clinical trials.

Romidepsin, previously known as depsipeptide or FK228, is a potent HDAC inhibitor, which has been recently granted approval by the US Food and Drug Administration (FDA) for the treatment of relapsed or refractory cutaneous T-cell lymphoma (CTCL). Coiffier and associates[1] presented the final results of a pivotal phase II multicenter study of romidepsin in patients with relapsed or refractory PTCL who had failed prior systemic therapy. These patients were treated with the standard 14 mg/m^2 dose given as a 4-hour infusion on days 1, 8, and 15 of an every-28-day cycle. The overall response rate (ORR) was 26% as assessed by central review, with a 13% complete remission (CR) rate. The observed responses were durable, with a median duration of 12 months. Clearly, the next step will be to design studies of combination regimens, with the major challenge of finding the optimal dose and schedule and avoiding possible overlapping toxicity. In this regard, Marchi and colleagues[2] presented interesting preclinical data of the combination of HDAC inhibitors and hypomethylating agents. Synergism and higher rates of apoptosis were reported with the combination of either belinostat or romidepsin with decitabine. It is hoped that these data can be used to plan future phase I/II clinical trials.

Pralatrexate, a novel antifolate, is the first drug to be approved by the FDA for the treatment of relapsed or refractory PTCL. Results of the pivotal multicenter study PROPEL (Pralatrexate in patients with Relapsed Or refractory Peripheral T-cell lymphoma) showed an ORR of 29%, with a median duration of response of approximately 10 months. Patients were heavily pretreated and had failed a median of 3 prior regimens. A subset analysis presented by Goy and colleagues[3] confirmed significant single-agent activity (40% ORR) and durable remissions (median duration 13.1 months) in patients who had failed the commonly used salvage regimen of ifosfamide, carboplatin, and etoposide (ICE). An early study with pralatrexate suggested that the agent is active in patients with CTCL. Horwitz and colleagues[4] reported the final results of a phase I, multicenter, dose-finding study of pralatrexate in patients with relapsed/refractory CTCL. Different doses (30, 20, 15, or 10 mg/m^2 weekly) and schedules (3 weeks of a 4-week schedule or 2 weeks of a 3-week schedule) were investigated. The optimal dose was determined to be 15 mg/m^2 for 3 weeks of a 4-week schedule, lower than the one used in the PROPEL study, indicating a different toxicity profile of pralatrexate in this patient population.

Preclinical evidence supports the use of pralatrexate in combination with other novel agents, including HDAC inhibitors, and efforts are under way to develop phase I/II clinical studies.

Following the successful discovery and introduction of the anti-CD20 monoclonal antibody rituximab for the treatment of B-cell lymphomas, a number of monoclonal antibodies for potential use in PTCL have been the focus of several clinical studies. However, a major challenge in the development of effective immunotherapy in PTCL is the fact that potential targets are not uniformly expressed in different histologic subtypes.

One attractive target that has been the focus of much research in the past few years is CD30, a member of the tumor necrosis receptor superfamily. CD30 is expressed in anaplastic large cell lymphoma (ALCL) and in approximately 30% of unspecified PTCL. Early studies with unmodified anti-CD30 antibodies showed a favorable toxicity profile, but minimal activity. Forero-Torres and colleagues[5] reported on 39 patients with refractory or relapsed ALCL treated in a multicenter phase II trial with SGN-30, a CD30-specific chimeric antibody. Two

patients achieved a CR and 6 achieved a partial remission, for an ORR of 21%.

One major advancement in the development of more effective antibody therapy is the development of novel antibody-drug conjugates (ADCs), which offer the potential of targeted drug delivery.

Brentuximab vedotin (SGN-35) is an ADC consisting of the chimeric antibody SGN-30 chemically conjugated to the potent antitubulin agent monomethyl auristatin E (MMAE). After binding CD30, the ADC is internalized with subsequent release of MMAE leading to cell cycle arrest and apoptosis. In the initial phase I dose-escalation study in patients with relapsed CD30+ lymphomas, brentuximab vedotin was administered every 3 weeks at dose levels of 0.1 mg/kg to 3.6 mg/kg. The maximum tolerated dose (MTD) for administration every 3 weeks was 1.8 mg/kg. Treatment was generally well tolerated, with the most common treatment-related adverse events being fatigue, neutropenia, peripheral neuropathy, nausea, diarrhea, and pyrexia. Objective responses were noted in 17 patients, including 11 CRs.[6] Based on these results, a phase II single-arm study for patients with systemic ALCL who had failed prior systemic chemotherapy was initiated, and the preliminary analysis was presented by Shustov and associates.[7] Despite the unfavorable patient characteristics (most patients had ALK-negative status and 63% had primary refractory disease), an impressive 87% response rate was observed, including a CR rate of 57%. The toxicity profile was similar to the previous experience with this agent. Clearly, in order to improve the outcome of patients affected with ALCL, there is a need for the use of brentuximab vedotin earlier in the course of disease, either concurrently or sequentially, as part of first-line therapy. A phase I/II clinical trial in combination with the standard cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP) regimen has been recently initiated for patients with newly diagnosed ALCL, and further studies are planned for other CD30+ lymphoproliferative disorders.

Another molecule that has been targeted in the development of T-cell antibody therapy is the CC chemokine receptor 4 (CCR4). The anti-CCR4 humanized antibody KW-0761 was assessed in a phase I study in patients with either adult T-cell leukemia/lymphoma or PTCL. No MTD was reached, and a 31% ORR was reported, including 2 CRs.[8] Duvic and colleagues[9] reported the preliminary analysis of a phase I/II study of KW-0761 in patients with recurrent PTCL or CTCL. Similarly to the earlier phase I study, a MTD was not reached. In 38 evaluable CTCL patients, the ORR was 39% and included 2 CRs.

Denileukin diftitox represents yet another example of targeted therapy in T-cell lymphoma. The interleukin-2 ligand allows the drug to be targeted to cells that express interleukin-2 receptors, which in turn leads to internalization and release of the diphtheria toxin. Denileukin diftitox has been approved by the FDA for the treatment of refractory/recurrent CD25+ CTCL. The objective of the study presented by Duvic and coauthors[10] was to analyze the efficacy of re-treatment with denileukin diftitox in patients with CTCL. They reported an ORR of 40%, although most of the responses were partial remissions, indicating that this agent is an alternative option in patients with recurrent disease.

In summary, the review of the selected abstracts that were presented at the 2010 meeting of the American Society of Hematology highlights the progress in the treatment of T-cell lymphomas. The challenge for the future is how best to incorporate these new agents into novel treatment strategies and, more importantly, how to integrate them into the initial treatment approach of patients with PTCL.

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