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# Highlights in T-Cell Lymphoma From the 2011 American Society of Hematology Annual Meeting and Exposition

A Review of Selected Presentations From
the 53rd Annual Meeting and Exposition
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# Table of Contents

## Target Audience

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

## Statement of Need/Program Overview

Advances in the treatment of patients with lymphomas have improved response rates and survival outcomes dramatically. In order to maintain and further these advancements, it is essential that cutting-edge medical developments be communicated as effectively and efficiently as possible in order to optimize patient care. A perfect vehicle for meeting this educational need is the use of an educational abstracts/posters supplement focused on the significant presentations and clinical trial data presented at the American Society of Hematology (ASH) 2011 Annual Meeting, which is the premier event in the hematology/oncology community. This supplement will enable medical professionals to quickly and accurately synthesize the plethora of new information presented at the ASH 2011 Annual Meeting, and apply it appropriately to positively impact patient management strategies, prolong survival, and perhaps achieve the truly elusive goal of curing patients with hematologic malignancies.

## Educational Objectives

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

- Describe the importance of new study findings in the form of selected abstracts/poster summaries in the natural history of T-cell lymphomas presented at the ASH 2011 Annual Meeting
- Assess the results of these new study findings, including current clinical trials evaluating therapy in the treatment of T-cell lymphomas
- Integrate into clinical practice the latest knowledge and methods for treating patients with these lymphomas in an effort to improve current prognosis statistics
- Identify future research directions for all therapies in T-cell lymphomas

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# Highlights in T-Cell Lymphoma From the 2011 American Society of Hematology Annual Meeting and Exposition

## 591 Analysis of Patients with Common Peripheral T-Cell Lymphoma Subtypes From a Phase 2 Study of Romidepsin in Relapsed or Refractory Peripheral T-Cell Lymphoma[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, AR Shustov, J Nichols, S Carroll, J Balser, SM Horwitz

Romidepsin is a histone deacetylase (HDAC) inhibitor that is approved by the US Food and Drug Administration (FDA) for the treatment of patients with cutaneous T-cell lymphoma (CTCL) or peripheral T-cell lymphoma (PTCL) who have received at least 1 prior therapy.[2] In this phase II, single-arm, open-label registration study, Coiffier and colleagues evaluated the activity of romidepsin in patients with progressive or relapsed PTCL, in a subanalysis of a study reported last year.[3] The previous phase II study found durable clinical benefit and tolerability of romidepsin in patients with recurrent or refractory PTCL.

A total of 131 patients were enrolled, and 130 patients had histologically confirmed PTCL by central review. Among these patients, 69 were diagnosed with PTCL not otherwise specified (PTCL-NOS), 27 were diagnosed with angioimmunoblastic T-cell lymphoma (AITL), and 21 were diagnosed with anaplastic lymphoma kinase (ALK)-negative anaplastic large cell lymphoma (ALCL). The patients with the different subtypes were similar in prognostic index, duration of disease, and number of prior systemic therapies. The patients had received a median of 2 prior systemic therapies (range, 1–8). The patients received romidepsin 14 mg/m$^2$ as a 4-hour infusion once a week on days 1, 8, and 15, every 28 days, for up to 6 cycles. Romidepsin was continued for patients achieving stable disease. Assessment of overall disease control was based on both the overall response rate (ORR) and achievement of stable disease for at least 90 days. Efficacy was assessed by an independent committee based on review of radiographic images and overall clinical assessment.

The primary endpoint was the rate of complete response (CR) and unconfirmed complete response (CRu), which was similar across the PTCL subtypes (19% overall). CR/CRu was achieved by 10 (14%) PTCL-NOS patients, 5 (19%) AITL patients, and 4 (19%) ALK-1–negative ALCL patients (Table 1). The ORR was similar across the subtypes, at 33% (n=28). The ORR was 20 (29%) for PTCL-NOS patients, 8 (30%) for AITL patients, and 5 (24%) for ALK-1–negative ALCL patients. Stable disease for more than 3 months was achieved by 25% of the patients enrolled, and the median duration of response was 17 months for PTCL-NOS patients and 12 months for ALK-negative ALCL patients. It was not yet evaluable for AITL patients, whose duration of response was still ongoing at 34 months.

The authors noted that a high response rate was achieved by patients who were refractory to prior chemotherapy. The longest duration of response was ongoing at 34 months. The median duration of objective response was 17 months (range, <1–17) for patients with PTCL-NOS and 12 months (range, 4–16+) for patients with ALK-1–negative ALCL. Patients with AITL had a higher rate of progression-free survival (PFS) and a longer duration of response.

Adverse events (AEs) did not differ between the different PTCL subtypes evaluated (Table 2). The primary toxicity was hematologic, with grade 3/4 thrombocytopenia reported in 29 (25%) patients, neutropenia in 21 (18%), infections with or without neutropenia in 18 (15%), anemia in 10 (9%), fatigue in 8 (7%), and leukopenia in 6 (5%). The rates of infection were higher in those patients who had disease with bone marrow involvement or who had received prior monoclonal antibody therapy.

The authors concluded that patients treated with romidepsin at the time of relapse achieved durable responses. The 3 subtypes of PTCL had similar rates of CR/CRu, with 66% of patients achieving CR/CRu, although they had not shown any response to prior chemotherapy. Nearly half (46%) of the patients achieved disease control, defined as CR, partial response (PR), or long, stable disease. The median duration of response was 17 months, with some patients still responding more than 3 years after the initiation of treatment. The toxicity was primarily hematologic and did not differ among the subtypes. The authors suggest that the data support the use of single-agent romidepsin to treat relapsed or refractory PTCL-NOS, AITL, and ALK-1–negative ALCL. The authors also suggest that the data support development of romidepsin-based treatment regimens and frontline therapies for these PTCL subtypes.

**Table 1.** Romidepsin in Common PTCL Subtypes[1]

| | PTCL-NOS (n=69) | AITL (n=27) | ALK-1–negative ALCL (n=21) | Total (n=117) |
|---|---|---|---|---|
| **Response Rates, n (%)** | | | | |
| CR/CRu | 10 (14) | 5 (19) | 4 (19) | 19 (16) |
| ORR (CR/CRu + PR) | 20 (29) | 8 (30) | 5 (24) | 33 (28) |
| ORR + SD* | 34 (49) | 12 (44) | 8 (38) | 54 (46) |
| **Duration of Objective Response in Months, Median (Range)†** | | | | |
| Patients who achieved CR/CRu | 17 (<1–17) | NE (2–34+) | NE (4–16+) | 17 (<1–34+) |
| All responders (CR/CRu + PR) | 17 (<1–17) | NE (<1–34+) | 12 (4–16+) | 17 (<1–34+) |

*Only patients with stable disease >90 days were considered.
†Median patient follow-up was 10.9 months.
AITL=angioimmunoblastic T-cell lymphoma; ALCL=anaplastic large cell lymphoma; ALK=anaplastic lymphoma kinase; CR=complete response; CRu=unconfirmed complete response; NE=not evaluable; ORR=overall response rate; PR=partial response; PTCL=peripheral T-cell lymphoma; PTCL-NOS=peripheral T-cell lymphoma not otherwise specified; SD=stable disease.
Data from Coiffier B et al. *Blood* (ASH Annual Meeting Abstracts). 2011;118(21): Abstract 591.[1]

**Table 2.** Adverse Events Associated With Romidepsin in PTCL*[1]

| | PTCL-NOS n (%) | AITL n (%) | ALK-1–negative ALCL n (%) | Total n (%) |
|---|---|---|---|---|
| Thrombocytopenia | 15 (22) | 8 (30) | 6 (29) | 29 (25) |
| Neutropenia | 12 (17) | 6 (22) | 3 (14) | 21 (18) |
| Infections (all types pooled) | 9 (13) | 6 (22) | 3 (14) | 18 (15) |
| Anemia | 4 (6) | 4 (15) | 2 (10) | 10 (9) |
| Fatigue | 6 (9) | 1 (4) | 1 (5) | 8 (7) |
| Leukopenia | 4 (6) | 2 (7) | 0 | 6 (5) |

*Most common (≥5% overall) grade ≥3 adverse events.
AITL=angioimmunoblastic T-cell lymphoma; ALCL=anaplastic large cell lymphoma; ALK=anaplastic lymphoma kinase; PTCL=peripheral T-cell lymphoma; PTCL-NOS=peripheral T-cell lymphoma not otherwise specified.
Data from Coiffier B et al. *Blood* (ASH Annual Meeting Abstracts). 2011;118(21): Abstract 591.[1]

## **266** Phase II Trial of Lenalidomide-Rituximab +/- Dexamethasone in Relapsed or Refractory Indolent B-Cell or Mantle Cell Lymphomas Resistant to Rituximab[4]

T Ahmadi, EA Chong, A Gordon, N Aqui, YY Xu, J Svoboda, SD Nasta, SJ Schuster

Lenalidomide is an immunomodulatory drug that may enhance both antibody-dependent cell-mediated cytotoxicity and the development of specific anti-tumor immune responses. This phase II, single-center, open-label trial tested the efficacy of lenalidomide combined with rituximab in patients with indolent B-cell or mantle cell lymphomas that were previously resistant to rituximab. Since a significant number of patients do not respond to rituximab, and since most patients who are treated repeatedly over time develop resistance to rituximab, Ahmadi and colleagues hypothesized that lenalidomide could overcome the resistance to rituximab. Lenalidomide has been described as increasing the count and function of

natural killer cells,[5] and preclinical data suggested a synergy between lenalidomide and rituximab.[6]

The trial had 2 parts. In the first part, patients were treated with lenalidomide 10 mg daily for 28 days continuously for 2 cycles and with or without dexamethasone 8 mg once weekly. After 2 months, the patients were assessed for interim response, which concluded the first part of the trial. The 3 objectives of the first part were to assess immunomodulatory responses before exposing patients to rituximab, to assess the interim response to lenalidomide so the responses could be compared after rituximab was introduced, and to attain biologic samples. The trial compared the biologic samples from the beginning of the trial, the end of part one, and the conclusion of the trial.

The second part of the trial began after assessment of interim responses in all patients, even those with progressive disease. The patients were treated with 4 weekly doses of rituximab 375 mg/m$^2$, and then their final response was assessed 3 months later. After the final response assessment, the patients all continued lenalidomide with or without dexamethasone, staying in this phase until their disease progressed or they withdrew from the trial.

A total of 45 patients enrolled, with 27 in the cohort receiving dexamethasone and 18 in the cohort not receiving dexamethasone. The median age was 58 years (range, 35–85 years). All the enrolled patients had rituximab-resistant disease, which was defined as refractory disease that relapsed within 6 months of a prior rituximab-containing regimen. Their diagnoses included follicular lymphoma (n=28), mantle cell lymphoma (n=11), small lymphocytic lymphoma (n=4), and marginal zone lymphoma (n=2). The median number of prior therapies was 3 (range, 1–7), and 90% of patients had elevated lactate dehydrogenase (LDH) levels at the time of enrollment. A total of 40 patients received the full dose of rituximab and had their final response assessed 3 months later.

The primary objective was ORR at the final response assessment. The ORR did not differ significantly between patients receiving dexamethasone and those not receiving dexamethasone. Among the 40 patients who completed both parts of the trial and were assessed after 3 months, the ORR was 37% (6 CR and 7 PR) after the first 2 months of lenalidomide and 63% (12 CR and 9 PR) after rituximab was added in the second part of the trial. Notably, a total of 48% of the patients achieved CR when rituximab was added. All the patients with mantle cell lymphoma who responded in the trial achieved a CR.

The overall survival (OS) rate for all patients, after a median follow-up of 11.8 months, was 82%. The PFS rate was 73% (95% confidence interval [CI], 53–86%), which was calculated from the final response assessment with a median follow-up of 11.8 months.

The regimen was well-tolerated, with the predominant toxicity being neutropenia. No cases of febrile neutropenia occurred. One death occurred during the trial that was considered possibly related to the drug. Two patients, both with small lymphocytic lymphoma, had grade 3 tumor flare. Also, 2 patients had a grade 3 rash, which improved in the first 2 months.

Ahmadi and colleagues concluded that lenalidomide with or without dexamethasone followed by a single 4-week course of rituximab achieved high response rates and durable responses in patients with rituximab-resistant low-grade lymphoma. The responses improved after the addition of rituximab, although the authors stated that, for at least some patients, the results may be due to a continued benefit from lenalidomide. Lenalidomide may cause immunomodulatory changes that enhance antibody-dependent cell-mediated cytotoxicity, which restores the efficacy of rituximab and allows patients to benefit from this protocol.

## **2673** Early Results of a Phase Ib/II Dose-Escalation Trial of Romidepsin in Association with CHOP in Patients with Peripheral T-Cell Lymphomas (PTCL)[7]

J Dupuis, R-O Casasnovas, F Morschhauser, H Ghesquieres, C Thieblemont, V Ribrag, H Tilly, B Coiffier

Previous evaluations of romidepsin in recurrent or refractory PTCL have found ORRs of 30–38%.[3,8] This study aimed to evaluate the safety, tolerability, and efficacy of escalating doses of romidepsin with cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) in patients with previously untreated PTCL. The study plan calls for participating patients with biopsy-proven PTCL to receive 8 cycles of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) with cyclophosphamide 750 mg/m$^2$, doxorubicin 50 mg/m$^2$, and vincristine 1.4 mg/m$^2$ on day 1; and prednisone 40 mg/m$^2$ on days 1–5. The starting dose of romidepsin was 10 mg/m$^2$ on days 1 and 8.

Dupuis and colleagues reported on 6 patients (3 men, 3 women, ages 47–67 years) enrolled so far. Their diagnoses were PTCL-NOS (n=3), AITL (n=1), primary cutaneous CD4+ small-medium T-cell lymphoma (n=1), and enteropathy-associated T-cell lymphoma (n=1). The Eastern Cooperative Oncology Group (ECOG) performance status scores were good (0–1) in all patients.

Among the first 3 patients, who were treated at the initial romidepsin dose of 10 mg/m$^2$, 1 had a dose-limiting toxicity of grade 3 malaise after cycle 2. Three more patients were treated at this dose level, and 2 other dose-limiting toxicities were observed. One patient experienced a dose-limiting toxicity from grade 3 general

status deterioration and also grade 3 hematologic toxicity lasting more than 7 days. The other dose-limiting toxicity was grade 4 hematologic toxicity lasting more than 3 days.

Of the 269 AEs observed during the 34 analyzable cycles, the most frequent AEs were neutropenia (n=22; grade 3 or 4, n=12), thrombocytopenia (n=28; grade 3 or 4, n=5), digestive complaints (n=18; none grade >2), and asymptomatic increase of liver enzymes (n=7; 1 grade 3). The patients' QT intervals had a mean increase of 19 ms (range, -43 to +79) between preromidepsin and postromidepsin electrocardiographs (ECGs), although no clinically relevant cardiac events were reported. Two patients finished the 8 planned cycles, and both were in CR when the study was presented. Three patients were under treatment with no evidence of progression. One patient progressed after completing 5 cycles.

The authors concluded that romidepsin can be combined with CHOP without unexpected toxicities. Because the romidepsin dose of 10 mg/m$^2$ on days 1 and 8 was associated with excessive hematologic toxicity, the study is ongoing with a lower dose of 8 mg/m$^2$ on days 1 and 8.

## **2680** Exposure-QTc Response Analysis of Class 1 Selective Histone Deacetylase Inhibitor Romidepsin[9]

CJ Godfrey, CH Cabell, B Balser, J Wolfson, J Nichols, HA Burris

Romidepsin is in a class of HDAC inhibitors with potential cardiac effects. Previously, detailed ECG analyses from 110 patients across 3 clinical studies found clinically insignificant, transient ECG changes.[10] The changes were not associated with functional cardiovascular changes. Here, Godfrey and colleagues sought to further evaluate the potential of romidepsin to prolong QT and to assess possible relationships between the plasma concentration of romidepsin and the heart rate–corrected QT interval duration (QTc).

The authors examined ECG data from 26 patients who were treated with intravenous (IV) romidepsin at 14 mg/m$^2$ infused over 4 hours, which is the approved dosing regimen. Among those patients, 14 also received romidepsin at 8–12 mg/m$^2$ over a 1-hour IV infusion, with 3 receiving 8 mg/m$^2$, 6 receiving 10 mg/m$^2$, and 5 receiving 12 mg/m$^2$. Those who received 12 mg/m$^2$ had a median maximum plasma concentration that was up to 2.5-fold higher than that observed with the approved dosing regimen.

When Godfrey and associates examined the time course of mean QT Fridericia correction (QTcF), the time course of QT individual correction (QTcI), the change in QTcF, and the median romidepsin plasma concentrations, no marked trends were evident, and there was no consistent pattern of pharmacokinetic counterclockwise hysteresis across or within patients. Romidepsin concentration did not affect QTc in a statistically significant manner, although there were slight decreases in QTcF from the postantiemetic baseline after romidepsin was administered, and QTcF had a mean increase relative to the preantiemetic baseline (Figure 1). Data from the 14 mg/m$^2$ 4-hour infusions indicated no mean changes in QTcF from the postantiemetic, preromidepsin baseline values for all the assessments. At the 6-hour time point, the mean change in QTcF was -0.11 ms, and the change from the postantiemetic, preromidepsin baseline value had a maximum upper-bound of the 90% CI of 5.59 ms. In the 24 hours after infusion began, no patients developed a QTcF above 450 ms. The researchers did not observe any trends for the lower doses of 8 mg/m$^2$, 10 mg/m$^2$, and 12 mg/m$^2$ infused over 1 hour.

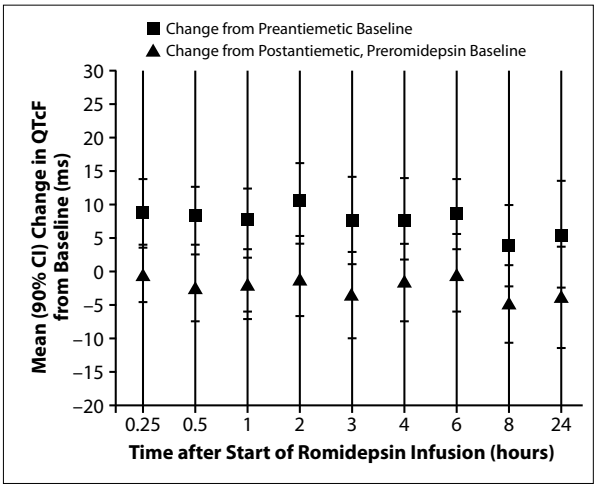


**Figure 1.** Change in QTcF from baseline after dosing of romidepsin 14 mg/m$^2$ intravenous administered throughout 4 hours. CI=confidence interval; QTcF=QT Fridericia correction. Reprinted from Godfrey CJ et al. *Blood* (ASH Annual Meeting Abstracts). 2011;118(21): Abstract 2680.[9]

Godfrey and colleagues concluded that they identified no concentration-dependent effects of romidepsin on the duration of the QTc interval. This study included romidepsin exposures up to 2.5-fold above the approved and clinically used dose of 14 mg/m$^2$ infused over 4 hours.

## **2688** Modified SMILE in the Treatment of Natural Killer T-Cell Lymphoma, Nasal and Nasal Type: A Single Center US Experience[11]

MA Lunning, E Pamer, L Wintman, V Bhatt, J Yahalom, AJ Moskowitz, JD Goldberg, DJ Straus, P Hamlin, AD Zelenetz, SM Horwitz

Extranodal natural killer (NK)/T-cell lymphoma (ENKL), a rare subtype of PTCL, has historically shown poor respon-

siveness to chemotherapy and poor OS for patients with advanced disease. Significant response rates have recently been obtained with L-asparaginase alone or combined with other cytotoxic chemotherapy. The novel regimen of dexamethasone, methotrexate, ifosfamide, L-asparaginase, and etoposide (SMILE) has shown particular activity in ENKL.[12] Lunning and colleagues explored a modification of SMILE (mSMILE) that substituted a single dose of pegylated-L-asparaginase for 6 doses of L-asparaginase per cycle and shortened the cycle length to 3 weeks by using growth factors.

Eight patients with newly diagnosed ENKL were treated with 2 cycles of mSMILE followed by field radiation therapy to 45 cGy (n=5), or with 3 cycles of mSMILE in locally advanced (n=1) and disseminated disease (n=2) along with radiotherapy to prior bulky sites. These treatments were followed by autologous (n=1) or allogeneic (n=2) stem cell transplantation (SCT). All of the patients responded to mSMILE after 1 or 2 cycles, with 88% (7 of 8) achieving CR and 12% (1 of 8) achieving PR.

Significant hematologic toxicity occurred with this regimen. Observed grade 3/4 AEs included neutropenia (n=6), anemia (n=2), thrombocytopenia (n=2), and nausea and vomiting (n=3). Other AEs included upper respiratory infection (n=2), syncope (n=1), and febrile neutropenia (n=1). Increased liver function tests occurred in all patients during treatment, with 1 patient having a grade 3 or 4 increase. These increases were all resolved prior to the next cycle and did not affect dosing or drug administration.

After a median follow-up of 5.5 months (range, 4–23), 7 of the patients were alive, with 5 in remission post-therapy for a median of 14 months (range, 4–23) and 2 patients (1 CR; 1 PR) undergoing radiotherapy after responding to mSMILE. One patient with disseminated disease died in remission of tacrolimus-induced thrombotic thrombocytopenic purpura on day 83 after allogeneic SCT.

Lunning and coworkers concluded that the activity shown by the mSMILE regimen suggests that it is a more active regimen than those previously used, such as CHOP. The CR rate of 88% suggests that this regimen has the potential to improve outcomes in ENKL patients. The authors state that a larger study is needed to validate their observations.

## **443** Brentuximab Vedotin (SGN-35) in Patients with Relapsed or Refractory Systemic Anaplastic Large Cell Lymphoma: A Phase 2 Study Update[13]

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

Uniform expression of CD30 characterizes systemic anaplastic large cell lymphoma (sALCL), which is a T-cell non-Hodgkin lymphoma (NHL) that accounts for 2–5% of all cases of NHL. After frontline treatment, the disease recurs in 40–65% of patients, and few effective treatment options exist. Brentuximab vedotin (SGN-35) is an antibody-drug conjugate consisting of an anti-CD30 antibody with the potent antimicrotubule agent monomethyl auristatin E (MMAE) conjugated to the antibody by a protease-cleavable linker. In this abstract, Advani and colleagues updated the results of their multicenter, open-label phase II trial that is determining the efficacy and safety of brentuximab vedotin in sALCL.

The trial enrolled 58 patients. The median age was 52 years (range, 14–76 years), and the median number of prior therapies was 2 (range, 1–6). Most patients had a performance status of 0–1. The disease was ALK-negative in 72% of patients. Sixty-two percent were refractory to frontline therapy, 50% were refractory to their most recent therapy, and 22% did not respond to any therapy. The patients were treated with brentuximab vedotin 1.8 mg/kg every 3 weeks by IV infusion over 30 minutes for a maximum of 16 cycles.

The ORR was 86%, with a median duration of 13.2 months (range, 0.1–19.1+). A total of 59% of patients achieved a CR, which had a median duration of 17.1 months (range, 0.7–19.1+). Patients who benefited from the treatment included those with primary refractory disease, those with ALK-negative disease, or those who had not responded to any prior therapy. Notably, of the 13 patients who had not responded to any prior therapy, objective response was achieved by 10 (77%) and CR by 4 (31%). Patients with 1 prior therapy or bone marrow involvement had lower response rates than other patients. The level of antitumor activity achieved was similar across subgroups of patients, regardless of baseline disease characteristics, tumor burden, or prior treatment history.

The median PFS was 14.6 months with brentuximab vedotin, which was significantly longer than the median PFS achieved with the most recent prior therapy (20.0 months vs 5.9 months; $P<.001$). The OS rate at 1 year was approximately 17%, with a median follow-up of approximately 14.7 months. A subanalysis of patients who achieved a CR found that the 20 patients who did not go on to receive an SCT had a median PFS of 18 months. A total of 14 patients in CR did receive an SCT. Those receiving an allogeneic transplant had a median PFS of 16.9 months, whereas those receiving autologous transplant had not reached a median PFS at the time the study was presented.

Most AEs were grade 1 or 2, and the most common were peripheral sensory neuropathy (41%), nausea (40%), fatigue (38%), pyrexia (34%), diarrhea (29%), rash (24%), constipation (22%), and neutropenia (21%). Ten patients (17%) experienced grade 3 peripheral neuropathy, and there were no grade 4 events. At least 1 peripheral neuropathy event occurred in 57% of the patients. The peripheral

neuropathy events had a median time to onset of 15 weeks, and they were managed by delaying or reducing doses to 1.2 mg daily. The peripheral neuropathy was resolved or improved in about 80% of patients, with the median time to resolution being 13.4 weeks for any grade, 6 weeks for grade 2, and 6–8 weeks for grade 3.

Advani and colleagues concluded that durable CRs were achieved with brentuximab vedotin in relapsed or refractory ALCL patients. The CRs appear durable after treatment was completed. The toxicity, including the peripheral neuropathy, was manageable. These results have led to an ongoing frontline phase I trial[14] and to plans for a randomized phase III trial that will include ALCL and other CD30-positive mature T-cell lymphomas.

## **331** High-Dose Chemotherapy and Autologous Stem Cell Transplantation in Previously Untreated Peripheral T-Cell Lymphoma - Final Analysis of a Large Prospective Multicenter Study (NLG-T-01)[15]

F d'Amore, T Relander, GF Lauritzsen, E Jantunen, H Hagberg, H Anderson, H Holte Jr, A Österborg, M Merup, P de Nully Brown, O Kuittinen, M Erlanson, B Østenstad, U-M Fagerli, O Gadeberg, C Sundström, J Delabie, E Ralfkiaer, M Vornanen, H Toldbod

D'Amore and colleagues presented the final report of the prospective, phase II, PTCL-restricted NLG-T-01 study, which was conducted by the Nordic Lymphoma Group. This report, based on a median follow-up of 5 years, evaluated the efficacy of a dose-dense approach that was consolidated by upfront high-dose chemotherapy and supported by autologous stem-cell transplantation (HDT/ASCT). The induction regimen was 6 cycles of biweekly cyclophosphamide, doxorubicin, etoposide, vincristine, and prednisone (CHOEP), although the etoposide was omitted for patients older than 60 years. Patients in partial or complete remission were given high-dose chemotherapy with carmustine, etoposide, cytarabine, and melphalan or cyclophosphamide (BEAM/BEAC) that was followed by HDT/ASCT.

The study enrolled 166 patients with previously untreated PTCL, and excluded those with ALK-positive ALCL. The histopathology was confirmed for 160 patients, and the subtypes of PTCL included were PTCL-NOS (n=62; 39%), ALK-negative ALCL (n=31; 19%), AITL (n=3; 19%), enteropathy-associated T-cell lymphoma (n=21; 13%), panniculitis-like lymphoma (n=6; 4%), T/NK nasal-type lymphoma (n=5; 3%), and hepatosplenic lymphoma (n=5; 3%). The median age was 57 years (range, 22–67 years), the male to female ratio was 2.0, and 71% had a good performance score of 0–1 based on the World Health Organization (WHO) criteria at inclusion. However, most patients had advanced stage disease (81%), B symptoms (59%), and elevated serum LDH (62%). The distribution of International Prognostic Index (IPI) risk factors was 45 patients with 1 risk factor (28%), 52 with 2 risk factors (32%), 30 with 3 risk factors (19%), and 33 with 4 or 5 risk factors (21%).

A total of 114 patients (71%) underwent HDT/ASCT, and 90 were in complete remission 3 months after transplant. A total of 26% of the patients experienced early failures. The treatment had a low rate of related mortality (4%). A total of 83 patients were alive at the median follow-up of 60 months. The deceased patients (n=77) had a median follow-up of 9 months. For the entire cohort, the consolidated 5-year rate of OS was 51%, and the PFS was 44%. The ALK-negative ALCL patients had the best results, with 5-year OS of 70% and 5-year PFS of 61%.

Overall prognosis was discriminated by IPI for the low/low-intermediate versus intermediate-high/high groups regarding 5-year OS ($P$=.047) and 5-year PFS ($P$=.029). When IPI was applied separately to each of the 4 major subtypes, IPI was predictive for OS in AITL ($P$=.02) and for PFS in both AITL ($P$=.02) and PTCL-NOS ($P$=.03). Both OS and PFS were significantly impacted by female sex, which was associated with a better outcome; age (when analyzed as a continuous variable; performance score of 2 or higher), which correlated with poor outcomes; and cytotoxic phenotype, which correlated with poor outcomes in AITL.

D'Amore and colleagues concluded that this regimen of dose-dense induction followed by HDT/ASCT is well tolerated, leading to long-term PFS in 44% of patients with systemic PTCL. Because the study population had a high median age and adverse risk profile, these results are encouraging. The authors suggest consideration of dose-dense induction and HDT/ASCT in PTCL patients who are eligible for SCT.

## **1646** A Phase I/II Trial of Combination Gemcitabine and Bortezomib (VELCADE®) for Relapsed/Refractory T-Cell Non-Hodgkin Lymphoma (NHL) and Aggressive B-Cell NHL[16]

AM Evens, ST Rosen, LI Gordon, I Helenowski, J Kline, A Larsen, JN Winter, SM Smith, KM Van Besien

Bortezomib is a proteasome inhibitor with the capacity to reverse the downstream consequences of the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), which is deregulated in B-NHL and T-NHL subtypes. Gemcitabine has single-agent activity in relapsed or refractory NHL.[17] A combination regimen of bortezomib and

gemcitabine was investigated by Evens and colleagues based on these data and the unmet clinical needs of patients with relapsed or refractory aggressive NHL who were ineligible for SCT or relapsed after SCT. This novel combination was investigated in a 2-center, phase I/II clinical trial.

The enrolled patients (n=32) included 16 with T-NHL, with 12 having PTCL-NOS and one each having AITL, NK/T-NHL, transformed large cell lymphoma (from pre-existing CTCL), and hepatosplenic lymphoma. All of the 16 patients with B-NHL had relapsed or refractory diffuse large B-cell lymphoma (DLBCL). The median age of the patients was 61 years (range, 37–85), and men and women were equally represented (n=16 for each). The patients had a median ECOG performance status of 1 (range, 0–2) and had received a median of 2.5 prior therapies (range, 1–5). Prior autologous SCT had failed in 35% of the patients.

Initially, patients were treated with a classic 3+3 design, with dose escalation of bortezomib (1.3 mg/m$^2$ to 1.6 mg/m$^2$ given on days 1 and 8) and static gemcitabine dosing (800 mg/m$^2$ on days 1 and 8) that was given in 21-day cycles. However, 67% of the first 18 patients treated experienced grade 3 or 4 neutropenia with or without grade 3 or 4 thrombocytopenia, primarily on day 8 of the treatment cycles. Repeated treatment delays were caused by these recurrent day 8 cytopenias, so these 18 patients had a median of 1.0 cycles delivered and, thus, a low (59%) median normalized dose-intensity.

This intolerability led to an amended treatment schedule wherein gemcitabine 800 mg/m$^2$ and bortezomib 1.6 mg/m$^2$ were both administered on days 1 and 15 of a 28-day schedule for the remaining 22 patients. This modified schedule markedly reduced treatment-related toxicity, with only 1 grade 3 anemia event and 1 grade 3 thrombocytopenia event.

All 32 patients enrolled had an ORR of 16% (CR 13%), with an ORR of 6% for all B-NHL patients (no CR) and 25% for all T-NHL patients (19% CR). The modified treatment schedule had an ORR of 0% for B-NHL patients and 50% for T-NHL patients (3 of 6). These 3 T-NHL patients on the modified schedule remained in remission at 29+, 26+, and 19+ months. Regardless, the data monitoring committee recommended premature study closure.

In conclusion, the dosing schedule of combined bortezomib and gemcitabine on days 1 and 8 of 21-day cycles was not tolerated. The authors do not recommend it for further study. The improved tolerance of the modified dosing schedule of combined bortezomib and gemcitabine on days 1 and 15 of a 28-day cycle allowed consistent treatment delivery. However, the clinical efficacy of this combination was low with either schedule. Notably, a few patients in the T-NHL subgroup showed potential activity and durable responses with the modified treatment schedule.

## **95** Phase 2 Trial of Alisertib (MLN8237), An Investigational, Potent Inhibitor of Aurora A Kinase (AAK), in Patients (pts) with Aggressive B- and T-Cell Non-Hodgkin Lymphoma (NHL)[18]

J Friedberg, D Mahadevan, JA Jung, DO Persky, IS Lossos, H Danaee, X Zhou, EJ Leonard, SH Bernstein

Aurora kinases, which are localized to centrosomes and proximal mitotic spindles, regulate multiple phases of the mitotic signaling cascade. Aurora A kinase (AAK) expression is increased in aggressive lymphomas, particularly in high-risk DLBCL and Burkitt lymphoma, as well as T-cell lymphomas. Alisertib inhibits AAK and results in mitotic defects that cause cell death through both apoptosis and senescence. The phase I trials of this orally available inhibitor mainly focused on leukemias.

Friedberg and colleagues presented their phase II, multicenter study of alisertib 50 mg administered orally twice daily for 7 days on 21-day cycles. They sought to treat relapsed, refractory, aggressive B-cell NHL or noncutaneous-type T-cell lymphomas. A total of 48 patients were enrolled, with 41 being evaluable. The histologies included were DLBCL (n=21, 41%), mantle cell lymphoma (n=13, 27%), PTCL (n=8, 17%), transformed follicular lymphoma (n=5, 10%), and Burkitt lymphoma (n=1, 2%). To be eligible, the patients had to have normal liver function, adequate neutrophil and platelet counts, and no prior allogeneic transplant. The median age of the enrolled patients was 68 years (range, 32–85), and the median number of prior regimens was 3 (range, 1–11), with 11 patients having received prior autologous SCT.

The major AEs observed with alisertib were cytopenias, with 30 patients having grade 3 or 4 neutropenia (63%), including 7 cases of febrile neutropenia, and 15 having grade 3 or 4 thrombocytopenia (31%). Other grade 3 or 4 AEs included stomatitis (15%) and fatigue (6%). Half of the patients (n=24) required dose reductions to alisertib 40 mg twice daily, with the majority of dose reductions occurring in the second cycle. The dose was further reduced to 30 mg twice daily for 6 patients. Pharmacokinetic analysis revealed that patients who had a dose reduction for AEs had a trend toward higher steady state trough concentrations of alisertib than those who did not require a dose reduction. A total of 11 patients discontinued the study.

All 4 deaths reported in this study occurred during the first cycle; 2 of these patients had rapidly progressive DLBCL. One patient died of treatment-related sepsis on day 14, and a T-cell lymphoma patient died of an unknown cause (n=1). Additionally, 1 case of myelodysplasia was reported during follow-up.

This highly relapsed patient population had an ORR of 32% (95% CI, 0.181–0.481), which included 12% CR. Only 29% of patients had progressive disease. Pharmacogenomic analysis of patient responses did not reveal any correlation to AAK protein expression or AAK gene amplification, as analyzed by fluorescence in situ hybridization (FISH) and by protein immunohistochemistry. Responses were not evaluable for 7 patients.

Among T-cell NHL patients, 4 of 7 patients (57%) responded. One patient achieved stable disease and went on to an autologous transplant. The remaining 3 T-cell lymphoma patients remained on therapy, some for more than a year. One patient with enteropathy-associated T-cell lymphoma had a CR as evaluated by CT and PET, although the disease had relapsed and become widespread, and included several FDG-avid pulmonary and liver nodules.

Among B-cell NHL patients, the ORR was 20% for DLBCL patients, and 23% for mantle cell lymphoma patients. The one patient with Burkitt's lymphoma responded, and the patients with transformed follicular lymphoma also had responses.

Friedberg and colleagues concluded that alisertib is generally well-tolerated and generates responses in heavily pretreated patients with aggressive B- and T-cell NHL, including patients with prior autologous SCT. Treatment was continued for more than a year in 7 patients, and some patients will continue well beyond that. The overall response was favorable in the patients with T-cell lymphoma.

Several further studies of alisertib are planned. Based on preclinical evidence of synergy between alisertib and vincristine,[19] that combination will be further explored. A phase II single-agent study in relapsed, refractory T-cell lymphoma was recently opened. A phase I study of B-cell lymphoma with alisertib plus rituximab plus vincristine is accruing, and a phase II study of aggressive B-cell lymphomas will follow. Other trials may be developed through the National Cancer Institute's cooperative research groups.

## **882** Final Results of Phase II Trial of Pegylated Liposomal Doxorubicin (PLD) Followed by Bexarotene (Bex) in Advanced Cutaneous T-Cell Lymphoma (CTCL)[20]

DJ Straus, M Duvic, SM Horwitz, KB Hymes, A Goy, FJ Hernandez-Ilizaliturri, T Feldman, B Wegner, P Myskowski

Straus and colleagues reported final results of their multi-institutional phase II trial for patients with advanced stage or refractory CTCL. This trial sought to clarify the true ORR for pegylated liposomal doxorubicin (PLD) and to assess if the duration of remissions could be improved by following PLD with bexarotene. Currently, PLD, which concentrates highly in the skin, has approval to treat Kaposi sarcoma. Previous research on PLD in CTCL without strictly defined response criteria found ORR rates, defined as the sum of CR and PR rates, ranging from 56–88%, whereas CR rates from 20–44% have been reported.[21,22] Bexarotene, a synthetic retinoid, has an ORR of approximately 50% in relapsed or refractory CTCL.[23,24]

A total of 37 patients with CTCL enrolled and completed 32 weeks of treatment. The treatment regimen consisted of PLD 20 mg/m$^2$ every 2 weeks for 8 doses (throughout a total of 16 weeks), followed by 16 weeks of bexarotene 300 mg/m$^2$ orally. The enrolled patients included 21 at stage IV (including 7 with Sézary syndrome), 10 at stage IIB, and 6 refractory patients at earlier stages. The patients had a median age of 57 years (range, 27–81), with 20 men and 17 women enrolled. All of the patients had been treated topically prior to the study, with or without irradiation. A total of 14 of the patients had not been treated with prior systemic therapies. Among the 23 patients who had received systemic therapies, the median amount was 2 (range, 1–11).

The ORR was 41% (n=14) for the 34 patients who were assessed, with 12 patients achieving PR and 2 achieving clinical CR. The 3 patients who were not assessed included 2 who withdrew consent and 1 who died of disease progression 5 days after the first cycle was initiated. The median follow-up for surviving patients was 7.54 months (range, 0.7–41.9). All of the maximum responses were observed after 16 weeks of PLD treatment, which was administered prior to the bexarotene treatment.

The median PFS was 4.82 months. At the time of the study presentation, 18 patients had died of disease progression and 1 patient, who had a pretreatment left ventricular ejection fraction of 60%, died of congestive heart failure that occurred 3 months after the last study intervention.

Grade 3 or 4 AEs occurred in 9 patients, and these events included tumor pain in 4 patients, grade 3 hand-foot syndrome in 2 patients, cellulitis infections in 2 patients (1 with a normal absolute neutrophil count and 1 with an unknown absolute neutrophil count), and neutropenia in 1 patient.

Straus and colleagues concluded that the ORR with PLD treatment is among the highest reported for single agents for CTCL, although it was lower than previous reports. A high proportion of this study population had advanced disease, which was reflected in the initial stage and their poor survival. The authors also found that sequential bexarotene did not increase either the rate or duration of response.

## **1638** Phase II Multicenter Trial of Lenalidomide: Clinical and Immunomodulatory Effects in Patients with CTCL[25]

C Querfeld, ST Rosen, J Guitart, M Duvic, YH Kim, C Goolsby, T Kuzel

Querfeld and colleagues conducted a multicenter phase II trial in relapsed CTCL patients, and investigated the immunomodulatory effects of lenalidomide in a subset of the patients. The mechanism of action of lenalidomide is currently unknown, but it appears to be mediated by the immune system, as the functions of T cells and NK cells are stimulated and the production and cytotoxic activity of Th1 cytokines are induced.

This trial enrolled 35 patients who had been heavily pretreated, with a median of 7 prior treatments (range, 1–14). The clinical stages of disease were IB in 7 patients (24%), IIA in 2 patients (7%), IIB in 4 patients (14%), III in 6 patients (21%), IVA in 8 patients (28%), and IVB in 1 patient (4%). The first 18 patients were treated with lenalidomide 25 mg daily for 21 days followed by 7 rest days in 28-day cycles. Unacceptable cutaneous flare reactions led to a study amendment, and so the subsequent patients were treated with a starting dose of 10 mg that was titrated up to 25 mg as tolerated.

The ORR was 32% (n=9), with all the responding patients achieving PR with the 25 mg daily dose. The median duration of response was 5 months (range, 1–12+). The patients had a median time to first response of 3 months (range, 1–5). A total of 17 patients (61%) reached stable disease, and 2 (7%) had progressive disease.

The grade 3 AEs experienced by the enrolled patients were fatigue (22%), infection (9%), leukopenia (3%), and neutropenia (3%). No grade 4 toxicities occurred. Grade 1 or 2 tumor flare occurred in 8 patients (25%) after initiation of lenalidomide treatment, although patients had fewer flares as their doses escalated.

Screening for immunomodulatory changes revealed that 4 of the 6 patients screened had decreased CD4+ T cells (range, 24–68%) and decreased CD4+, CD25+ T regulatory cells (range, 18–87%). Among these 4 patients, 2 had a clinical response of PR, whereas 2 remained stable during therapy. The other 2 patients who were screened had increased CD4+ T-cells (by 2% and 43%) and increased CD4+, CD25+ T-regulatory cells (by 50% and 73%).

Querfeld and coauthors found that lenalidomide has activity in patients with relapsed or advanced CTCL that is consistent with the activity of other agents that are currently available. The toxicity profile of lenalidomide is manageable. The cutaneous effects of lenalidomide in modulating the immune system may be associated with decreased T regulatory cells, and the effects are correlated with the number of CD4+ T-cells in the blood. The authors are investigating cytokine expression before and after therapy in skin biopsies from 6 patients. They concluded that investigation of lenalidomide as maintenance therapy or combined with other biologic agents is worthwhile.

## **1642** Phase I Study of mTOR Inhibitor Everolimus Plus CHOP in Patients with Advanced, Aggressive T-Cell Lymphomas[26]

SJ Kim, HJ Kang, JS Kim, H-S Eom, J Huh, YH Ko, D-S Yim, S-Y Lee, C Suh, WS Kim

Although CHOP-based regimens are the primary treatment for advanced stage T-cell lymphomas, the outcomes are unsatisfactory. Kim and coworkers sought to improve the efficacy of the CHOP regimen by incorporating everolimus, an oral inhibitor of the mammalian target of rapamycin (mTOR). Because the mTOR pathway promotes the growth and survival of malignant cells, it is an emerging target in treating lymphoma. Furthermore, animal studies indicate that everolimus may enhance the effects of vincristine and cyclophosphamide.[27,28]

This phase I study evaluated the feasibility and safety of everolimus added to CHOP chemotherapy for patients with newly diagnosed, advanced, aggressive T-cell lymphomas. The patients were treated with everolimus once daily from day 1 to day 15 (at 4 dose levels of 2.5 mg, 5 mg, 7.5 mg, and 10 mg) together with cyclophosphamide 750 mg/m$^2$, doxorubicin 50 mg/m$^2$, vincristine 1.4 mg/m$^2$ on day 1, and prednisolone 100 mg daily on days 1–5. The study planned for 6 cycles of therapy administered every 21 days.

A total of 15 patients were enrolled, which included 8 with PTCL-NOS, 4 with AITL, 1 with ALCL, and 2 with CTCL. Of these patients, 10 were at stage IV (66.7%), and 13 (86.7%) had elevated serum LDH levels. Most of the patients had high or high-intermediate IPI scores (n=9, 60%).

No dose-limiting toxicities occurred at the 2.5-mg dose of everolimus. Among the 6 patients who received the 5-mg dose, 1 patient experienced grade 4 thrombocytopenia. Among the 6 patients who received everolimus at 7.5 mg, 2 patients experienced dose-limiting toxicities, which were grade 4 AEs of thrombocytopenia and febrile neutropenia. These dose-limiting toxicities led the authors to conclude that 5 mg was the maximum tolerated dose of everolimus. None of the 3 doses tested had nonhematologic dose-limiting toxicities. The pharmacokinetic profile did not reveal any differences in the steady state trough concentrations of everolimus administered at daily doses of 2.5 mg, 5 mg, or 7.5 mg when concentrations were measured at the end of cycles 1 and 2.

Among the 15 total patients, 14 responded to the treatment, with 7 achieving CRs and 7 achieving PRs. However, 5 patients experienced relapse or progression during follow-up.

Kim and colleagues concluded that everolimus could be safely combined with CHOP chemotherapy for advanced stage, aggressive T-cell lymphomas. The main toxicities of everolimus were hematologic, which overlapped with the toxicity of the CHOP regimen, but these toxicities were manageable. They found that this constitutes an active regimen for these patients. A phase II study will evaluate the use of everolimus 5 mg once daily with CHOP as a first-line treatment for aggressive T-cell lymphomas.

## **4110** First Interim Safety Analysis of a Phase III Randomized Trial in Newly Diagnosed Systemic Peripheral T-Cell Lymphoma Treated with CHOP Chemotherapy with or without Alemtuzumab and Consolidated by Autologous Hematopoietic Stem Cell Transplant[29]

F d'Amore, MG da Silva, S Leppa, T Relander, A Pezzutto, GF Lauritzsen, E Weidmann, M Van Gelder, M Merup, H Hagberg, UM Fagerli, P de Nully Brown, PB Hansen, JM Mariz, M Jankovska, J Walewski, J Doorduijn, A Van Hoof, I Christiansen, S Jyrkkiö, JC Kluin-Nelemans, M van Marwijk Kooy, R Fijnheer, W Stevens, J Zijlstra, L Böhmer, PJ Lugtenburg, M Grube, V Prochazka, D Salek, R Greil, L Trümper, G Wulf, B Altmann, M Ziepert, M Loeffler, E Jantunen, G Hopfinger, E Van den Neste, H Toldbod

D'Amore and colleagues presented the first planned interim safety analysis of the ACT-1 (Alemtuzumab and CHOP in T-Cell Lymphomas 1) trial, in which patients newly diagnosed with PTCL were treated with alemtuzumab added to 6 courses of biweekly CHOP, followed, in younger patients, by HDT/ASCT. This interim analysis occurred after enrollment of the first 51 randomized patients and is based on the 43 patients who had a complete set of evaluable data.

The dose of alemtuzumab was amended from 360 mg (with 30 mg on days 1 and 2 of each CHOP course) to 120 mg (30 mg on day 1 of CHOP courses 1–4), so the results have 2 data subsets, with 5 patients receiving the higher dose, 17 receiving the lower dose, and 21 belonging to the control arm that did not receive the alemtuzumab antibody. The treatment arms were well-balanced in regard to histologic subtypes, IPI subgroups, and single prognostic factors. No significant treatment delays occurred for either alemtuzumab dose. The median duration of chemotherapy, which had an expected cumulative duration of 70 days for 5 biweekly cycles, was 73 days for patients not receiving alemtuzumab and 81 days for patients receiving alemtuzumab.

Patients receiving alemtuzumab had more frequent grade 3 or 4 leukopenia and anemia than patients in the control arm (71% vs 29% and 47 vs 14%, respectively). However, thrombocytopenia was not significantly different between patients receiving or not receiving alemtuzumab (17% vs 18%), and the 2 groups had similar nonhematologic toxicity unrelated to infectious complications. There were no reports of suspected unexpected serious AEs.

Among patients treated with the higher alemtuzumab dose, there were 2 cases of systemic fungal infections, including 1 with a fatal outcome. The fatal infection was verified as aspergillosis, and it occurred in a patient with pre-existing type II diabetes and chronic obstructive pulmonary disease that was treated with a steroid. These 2 events prompted an amendment to reduce the alemtuzumab dose, which led to a significant decrease in the number of serious AEs for the patients treated with alemtuzumab, from 2.6 preamendment to 0.76 postamendment. The level of serious AEs after the amendment was comparable to that of the control arm, which had levels of 0.67 preamendment and 0.44 postamendment.

Patients treated with alemtuzumab and those in the control arm had similar frequencies of reported fungal infections, but bacterial infections were more common in the control arm (55% vs 46%) and viral infections were more common in the alemtuzumab arm (29% vs 35%). Among the alemtuzumab-treated patients, there were 8 cases of cytomegalovirus reactivation, only 2 of which were clinically symptomatic. These infections regressed when they were specifically treated.

D'Amore and colleagues noted that the reduction in serious AEs that occurred after the dose of alemtuzumab was decreased has been further confirmed by a larger cohort of patients who have been treated at the lower alemtuzumab dose. The larger cohort includes patients in both ACT-1 and ACT-2. ACT-2 is another arm of the study focused on older patients.

## **3493** PI3K Inhibition As a Potential Therapeutic Strategy in Peripheral T-Cell Lymphomas[30]

E Martin-Sanchez, SM Rodriguez-Pinilla, L Lombardia, B Dominguez-Gonzalez, M Sanchez-Beato, D Romero, MB Wozniak, M Mollejo, J Alves, JL Rodriguez-Peralto, J Menarguez, JC Cigudosa, PL Ortiz-Romero, JF Garcia, JR Bischoff, MA Piris

Most types of PTCLs lack animal models and representative cell lines, which makes it difficult to conduct functional and pharmacodynamic studies of these very aggressive malignancies. Cell proliferation and survival requires phosphoinositide 3-kinase (PI3K) signaling, which is frequently altered in human cancer and seems to have a critical role in the development and activation of T-cells.

Martin-Sanchez and colleagues used gene expression profiling and PTCL cell lines to determine the efficacy of inhibiting PI3K in PTCL, to identify pharmacodynamic markers, and to identify those markers that could distinguish responders from nonresponders.

Gene expression profiling from 22 cases of PTCL and 7 reactive lymph nodes found several PI3K/mTOR inhibitors. The *PIK3CD* gene was identified as being significantly correlated to the activation of the CD40, NF-κB, and T-cell receptor pathways. Additionally, *PIK3CD* was strongly overexpressed in 6 PTCL-derived cell lines that were compared with normal T cells from healthy donors.

When 6 PTCL cell lines from different PTCL subgroups were treated with 3 pharmacologic PI3K inhibitors (LY294002, ETP-45658, and GDC-0941), G1 cell cycle arrest occurred in all the cell lines, and apoptosis occurred in some of the cell lines. Additionally, all the treated cell lines had decreased levels of pAKT(S473), whereas only sensitive cell lines had decreases in pGSK3B(S9) and p-p70S6K(T389).

Martin-Sanchez and coworkers found that genetically inhibiting the PI3K delta isoform could induce apoptosis in those PTCL cell lines that are sensitive to PI3K inhibitors, but not in resistant cell lines. The genetic inhibition of the PI3K alpha isoform did not have similar effects.

In conclusion, the PI3K delta isoform is relevant to at least a subset of PTCL. Inhibition of PI3K, particularly the delta isoform, may be an effective approach for therapy for PTCL. The delta isoform of PI3K may also be helpful to identify potential markers to stratify patients and make pharmacodynamic assessments.

## **96** Survival of Peripheral T-Cell Lymphomas (PTCLs) Patients Following Relapse: Spectrum of Disease and Rare Long-Term Survivors[31]

V Mak, JM Connors, R Klasa, LH Sehn, D Villa, T Shenkier, M Chhanabhai, RD Gascoyne, KJ Savage

In this population-based study, Mak and coworkers sought to determine the spectrum of survival in PTCL patients and to understand the factors influencing survival, such as the impact of novel therapies, the expected survival in relapsed PTCL, and whether indolent subgroups exist in PTCL. Several novel therapies are currently under investigation in PTCL, but their impact on outcomes was unknown.

The Centre for Lymphoid Database in British Colombia was searched to identify patients older than 16 years with primary PTCL from 1976–2010 who had relapsed or progressed after primary therapy. Researchers excluded 72 patients who had complications during primary chemotherapy and 27 patients who had not received primary chemotherapy. They identified 204 evaluable patients. The study focused on the 3 most common WHO PTCL subtypes, and included 109 patients with PTCL-NOS (29%); 54 with ALCL (26%; among whom 18 were ALK-positive, 33 were ALK-negative, and 3 had unknown ALK status); and 45 with AITL (22%).

Of the 204 patients, 57 were initially intended for transplant, but only 38 ultimately underwent transplant, with 21 receiving autologous SCT and 17 receiving allogeneic SCT. Clinical features did not differ between autologous and allogeneic SCT recipients. The patients who did not receive a transplant were older and had worse performance status, multiple extranodal sites, more advanced stage, and high IPI score. Palliative treatment was received by 166 patients. Systemic treatment for relapsed PTCL was received by 103 patients (62%), including 93 treated at first relapse. A total of 43 patients (26%) received either no therapy or steroids only. The remaining 20 patients received palliative radiotherapy. The second PFS was defined as the date of first relapse or progression to the date of second relapse or progression, or the start of new therapy or death due to any cause.

The median age was 62 years at diagnosis and 63 years (range, 20–86) at the time of relapse. The patients in the ALK-positive ALCL subgroup were younger. At diagnosis, bone marrow involvement occurred in 27% of the patients, including 52% of the AITL patients. CHOP was the initial therapy for the majority of the patients.

The overall median second PFS was 4.7 months, and the median OS after relapse or progression was 7.1 months. Transplanted patients had a median second OS of 47.2 months. From the date of transplant, the median second PFS was 15.4 months, and the median OS was 23 months. Patients who did not receive a transplant had a median second PFS of 3 months and median OS after relapse or progression of 5.7 months. Overall, the majority of patients had short survivals after relapse or progression.

Age was the only prognostic factor for patients receiving transplants when second PFS was examined by univariate analysis. For the nontransplant group, elevated LDH, performance status, IPI score, and the timing of the relapse were prognostic. Univariate analysis of OS after relapse or progression found that age was not prognostic in the nontransplant group.

Elevated LDH, poor performance status, and multiple extranodal sites were unfavorable for both second PFS and OS after relapse or progression when examined by multivariate analysis. Favorable outcomes were seen in patients who relapsed late and who received transplants. Patients who received chemotherapy at relapse or progression had a median second PFS of 4.1 months and a median OS after relapse or progression of 7 months.

Patients with good performance status who received a transplant had a median second PFS of just under 6 months and OS of more than 1 year. This striking dif-

ference between median PFS and OS suggests that these patients may have a different disease biology and the ability to maintain responsiveness to chemotherapy. Patients with a performance status of 2 or more had a median second PFS of 2.8 months and died shortly after progression.

Long-term survivors were defined as those who survived 2 years or more after relapse or progression. When Mak and colleagues analyzed the clinical features of long-term survivors, they found associations with late relapse, skin-only relapse, performance status of 0 or 1, and low IPI scores. Long-term survival was not associated with chemotherapy at first relapse or progression, which basically excluded those patients who were too frail for any treatment except steroids or radiotherapy. The long-term survivors may have a subtype of disease with an indolent biology. These long-term survivors had a very favorable median PFS of 25.4 months and an OS of 41.4 months, and those who did not undergo high-dose chemotherapy/SCT had a median PFS of 14 months and an OS of 32.3 months.

Mak and associates concluded that patients with relapsed PTCL in the absence of transplant have a poor prognosis. Many of these patients were too ill for any therapy. Patients who were able to receive SCT had far superior outcomes, so efforts should focus on expanding the number of patients who are eligible for this curative therapy. Standard clinical factors correlate with second PFS and OS after relapse or progression, so these factors are relevant for comparing different therapies. The small subset of patients with long-term survival after relapse may have an indolent disease biology.

## **444** Effects of Anti-CCR4 Antibody (KW-0761) on Regulatory T Cells and Natural Killer Cells in Patients with Cutaneous T-Cell Lymphoma[32]

X Ni, JL Jorgensen, M Goswami, P Challagundla, WK Decker, YH Kim, M Duvic

Malignant T-cells in CTCL and the surface of T-regulatory cells express the CC chemokine receptor 4 (CCR4). Because T-regulatory cells express the transcription factor foxP3 and also suppress effector immune cells that include NK cells, impaired antitumor immunity is associated with increased T-regulatory cells in the tumor microenvironment. The monoclonal antibody KW-0761 binds CCR4 and induces antibody-dependent cell-mediated cytotoxicity against CCR4+ malignant T cells.

Ni and colleagues conducted their phase I/II trial to determine the safety and efficacy of KW-0761 in CTCL patients. Their report focused on the translational component of the trial, which analyzed peripheral blood mononuclear cells (PBMCs) from 20 patients (10 with mycosis fungoides and 10 with Sézary syndrome) by flow cytometry both before and after treatment, quantified foxP3 mRNA and CCR4 mRNA by real-time PCR, and assessed the cytotoxicity of NK cells with the standard 4-hour $^{51}$CR release assay.

At baseline, 15 of the 20 patients (75%) had detectable CD3+, CD4+, CD25+, CD127- T-regulatory cells, with 60–100% of those cells being positive for CCR4 (with an average of 67.2%). After the patients were treated for 4–6 weeks with KW-0761, the percentage of T-regulatory cells decreased from 1.26±1.09% to 0.39±0.49% (Figure 2), and the percentage of T-regulatory cells positive for CCR4 was significantly reduced to 24.6% ($P$<.01). Along with the cells, mRNA levels of foxP3 and CCR4 significantly decreased from baseline (foxP3: from 0.57±0.91 to 0.07±0.08; $P$<.01; CCR4: from 23.40±33.50 to 1.73±2.35; $P$<.05).

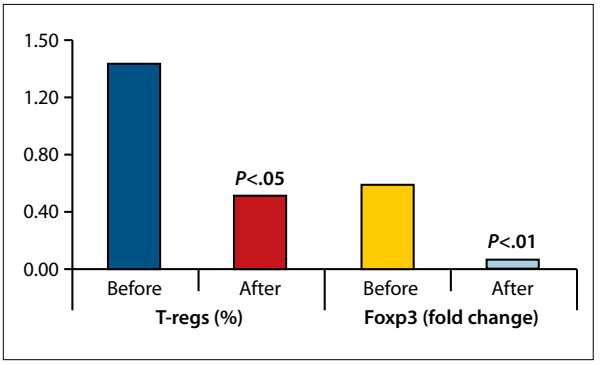


**Figure 2.** Effect of KW-0761 on regulatory T cells in cutaneous T-cell lymphoma. Reprinted from Ni X et al. *Blood* (ASH Annual Meeting Abstracts). 2011;118(21): Abstract 444.[32]

The level of NK cells in 10 of the 14 patients tested (71.4%) increased after 4–16 weeks of treatment from baseline levels (pretreatment: 16.02±15.86% vs post-treatment 22.64±13.93%; $P$=.05). A dose-dependent increase in NK cell cytotoxicity occurred in 5 of the 6 patients studied with the $^{51}$CR release assay.

Among the 10 patients with Sézary syndrome, baseline levels of NK cells, foxP3 mRNA, and CCR4 mRNA were higher compared with the 10 patients with mycosis fungoides. After treatment, paired samples from the Sézary syndrome patients revealed increased NK cells, and reduced T-regulatory cells, foxP3 mRNA, and CCR4 mRNA. Blood improvement occurred in 6 of 7 Sézary syndrome patients, in the form of 3 CRs and 3 PRs.

Ni and colleagues concluded that KW-0761 may reduce T-regulatory cells in most CTCL patients, and may subsequently increase NK numbers and function in some patients. This effect is in addition to the antibody-

dependent cell-mediated cytotoxicity of KW-0761 toward malignant cells. Follow-up studies are needed to confirm the findings.

## 2727 Combination of Epigenetic Agents Synergistically Reverse the Malignant Phenotype in Models of T-Cell Lymphoma[33]

E Marchi, M Kalac, DC Bongero, CM McIntosh, LK Fogli, L Scotto, M Rossi, PL Zinzani, S Pileri, PP Piccaluga, OA O'Connor

Marchi and coworkers used in vitro, in vivo, and molecular techniques to investigate the interactions between the DNA methyltransferase inhibitor decitabine and 4 HDAC inhibitors: romidepsin (depsipeptide), belinostat, vorinostat, and panobinostat. Currently, HDAC inhibitors have approval for treating relapsed or refractory CTCL and PTCL because of their marked single-agent activity in these diseases.

Cytotoxicity assays found synergism when decitabine was combined with each of the 4 HDAC inhibitors studied for 2 CTCL and 2 T-acute lymphoblastic leukemia (T-ALL) cell lines (relative risk reductions from 0.0007–0.9). More apoptosis occurred when CTCL or T-acute lymphoblastic leukemia cell lines were treated with combinations of decitabine and either belinostat or romidepsin than occurred with single drugs or controls.

The CTCL cell line, HH, was subcutaneously injected into female beige mice with severe combined immunodeficiency, ages 6–8 weeks, which were next treated with romidepsin, belinostat, or both. These in vivo experiments found that the combination of romidepsin and belinostat significantly inhibited tumor growth compared with either drug alone. Microarray analysis of gene expression revealed that each single treatment and the combination had differentially expressed genes and modulated pathways. Each of the 2 drugs and the combination of them had largely different effects, with all 3 treatments having only 39 genes modified in common. The combination treatment maintained most of the effects induced by each single-agent treatment, with 174 of 191 genes maintained for romidepsin and 211 of 221 maintained for decitabine. Furthermore, the combination treatment appears to uniquely modulate an additional 944 genes (Figure 3). These unique modulations provide strong support at the molecular level for the hypothesis of synergism.

Marchi and colleagues concluded that combining a DNA methyltransferase inhibitor with an HDAC inhibitor is synergistic in both in vitro and in vivo models of T-cell lymphoma. This combination can synergistically reverse the malignant gene signature at the molecular level. They suggest that the data may provide a basis for future phase I and II clinical trials.

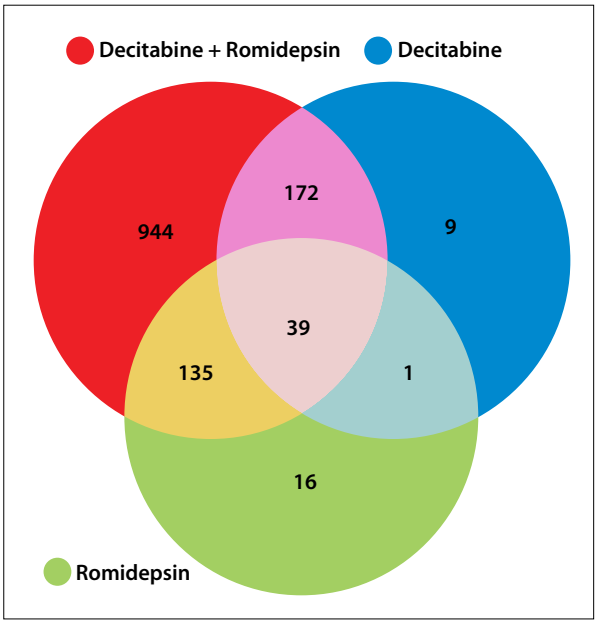


**Figure 3.** Cytotoxicity assays found synergism when decitabine was combined with various histone deacetylase inhibitors. The effects of decitabine and romidepsin are largely different (only 39 genes modified in common by all the treatment groups). Most of the effects induced by the single-agent treatment are maintained in the combination group. Reprinted from Marchi E et al. *Blood* (ASH Annual Meeting Abstracts). 2011;118(21): Abstract 2727.[33]

## Education Session

### *Current Treatments for Peripheral T-Cell Lymphomas*

In an Education Session, Kerry Savage, MD, discussed treatment of PTCL.[34] The standard therapy for PTCLs is CHOP. This standard is based on a large randomized trial conducted by the Southwest Oncology Group (SWOG) that found CHOP to be equally efficacious and less toxic when compared with second- and third-generation CHOP-like regimens.[35] Notably, that SWOG trial was conducted in an era when diagnoses were based on the Working Formulation, and it was not yet routine practice to determine T-cell immunophenotypes. Thus, the influence of these intensive regimens on outcomes is still unknown.

PTCL outcomes are poor compared with DLBCL, even in the prerituximab era, except for subtypes of ALCL. In the heterogeneous ALCL category, 50–60% of cases express ALK, which can be recognized with the ALK-1 antibody, and ALK-positive cases have a more favorable prognosis. Although survival is largely driven by age, the ALK-positive ALCL subtype does have generally favorable survival with anthracycline-based chemotherapy. However, the ALK phenotype is not the only important factor, since cases of ALK-positive ALCL with multiple IPI factors will have a poorer outcome. Biology must be considered along with clinical factors.

When CHOP is used to treat PTCL, the 5-year failure-free survival range is 20–35% across studies. Some have speculated that CHOP does not work well for PTCL because PTCLs have an inherent resistance to anthracycline. However, the International T-cell Lymphoma Project compared patients with PTCL-NOS receiving anthracyclines to those who did not and found no difference in outcome.[36] This analysis raises the questions of whether CHOP is the right combination, and whether a different chemotherapy backbone should be in development, since PTCLs are a very heterogeneous group of diseases.

Although it is easy to say that CHOP does not work, it is much harder to identify anything that works better. Since the diseases are rare, randomized controlled trials are sparse. When CHOP was compared to etoposide, ifosfamide, and cisplatin (VIP) alternated with doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) as a frontline treatment for noncutaneous PTCL, the event-free survival rates were the same for both regimens, with CHOP having a 5-year event-free survival of 35%.[37] The role of etoposide was examined in a German retrospective analysis of 340 patients.[38] Outcomes did not differ when the cycle was shortened from 3 weeks to 2 weeks, when etoposide was added to treatments for elderly patients, or when 8 versus 6 cycles were used. A subgroup analysis of patients who were young and at good risk found no significant difference for CHOP treatment cycles of 3 versus 2 weeks or for CHOP with or without the addition of etoposide. When this study examined dose escalation in young, high-risk patients, the dose-intensive group had a trend toward a worse prognosis.

No randomized controlled trials have examined whether patients with PTCL should receive consolidated autologous SCT in first remission. A 5-year OS of 80% has been reported with the use of autologous SCT for patients in first CR.[39] Also, a retrospective analysis reported by the MD Anderson Cancer Center found better outcomes for patients who underwent transplant at their first CR.[40] In contrast, an analysis by the Groupe d'Etude des Lymphomes de l'Adulte (GELA) focused on patients who achieved a CR and compared those who received chemotherapy with those who received chemotherapy and SCT.[41] No difference was found in event-free survival and OS for these treatment groups, however, not all patients received CHOP.

The Nordic group has completed the largest prospective phase II trial of upfront transplantation.[15] The study included 160 patients, who were up to age 67 years, had newly diagnosed PTCL, and were excluded if they had an ALK-positive phenotype. Dose-dense induction followed by HDT/ASCT led to PFS in 44% of patients, and ALK-negative ALCL patients had a 5-year PFS of 61%. This finding suggests the need to tailor treatments for specific PTCL subtypes, which is difficult to study in practice.

For localized nasal NK/T-cell lymphoma (TCL), early radiotherapy at high doses is key.[42] Recent literature suggests that adding cisplatin as a radiosensitizer may improve outcomes and allow for more aggressive therapy.[43] For advanced-stage nasal NK/TCL, L-asparaginase appears to be a very active agent. A retrospective study of 15 patients found an ORR of 87% with L-asparaginase, with 50% CRs.[44] Subsequent phase II studies include a recent trial of 38 patients, including 20 with stage IV newly diagnosed NK/TCL.[45] The 1-year PFS rate was an encouraging 55%. The regimen has significant toxicity, with 92% of patients experiencing grade 4 neutropenia and two thirds of patients having a grade 3 or 4 infection. Additionally, the Kettering Group recently reported that 88% of patients achieved a CR after 1 or 2 cycles of a modified regimen of SMILE.[11]

Hepatosplenic TCL is a rare PTCL subtype that is seen in immunosuppression, solid organ transplants, or tumor necrosis factor alpha inhibitors in Crohn's disease. A recent literature review evaluated allogeneic SCT in hepatosplenic TCL and found that 7 of 17 patients were alive and in remission, including some with refractory disease.[46] These results are better than would be expected with conventional chemotherapy, so allogeneic SCT should be considered upfront for appropriate patients.

The poor results achieved with CHOP have generated interest in considering other chemotherapies for PTCL. Gemcitabine is an emerging agent that does not depend on the P ligand protein, which is thought to be a mechanism of resistance for PTCLs. In a limited study that included 16 PTCL patients, gemcitabine (800 mg/m$^2$) and bortezomib (1.6 mg/m$^2$ on days 1 and 15 for 28 days) generated an ORR of 16%.[16] Gemcitabine is now being incorporated into the upfront setting in a few phase II studies.

Recently, SWOG completed a phase II study of cisplatin, etoposide, gemcitabine, and Solu-Medrol in patients with PTCL.[47] Most of the patients (79%) were newly diagnosed. At 1 year, the PFS was a somewhat disappointing 38%, a rate similar to that seen with CHOP regimens.

A phase II study of gemcitabine with ifosfamide and oxaliplatin was piloted by an Italian group.[48] This study targeted newly diagnosed patients, and appropriate patients could go on to receive high-dose chemotherapy/SCT. Among the 21 patients whose outcomes were presented at the 2010 American Society of Hematology meeting, the ORR was very high (86%), and the 5-year event-free survival of 49% was promising.

A number of agents have been added to the backbone of CHOP, including alemtuzumab. Alemtuzumab is a humanized monoclonal antibody targeting the CD52 antigen, which is widely expressed on B cells and T cells, along with other immune cells. This wide expression of CD52 has led to problems with immune suppression.

The expression of CD52 in PTCLs is heterogeneous, with only 35–40% of cases appearing to be CD52+ when examined by immunohistochemistry.[49,50] In ALCL, CD52 expression is largely negative. More recent analysis by flow cytometry has shown a higher frequency of CD52, at least in PTCL-NOS,[51] but different antibodies were used, the detection analysis was different, and its correlation with efficacy was unknown.

The combination of CHOP with alemtuzumab has been investigated with a variety of schedules and doses in 3 published phase II studies.[52-54] The most intensive regimen involved 90 mg alemtuzumab per cycle.[54] The ORR was high (90%), but survival endpoints were disappointing, with a median OS of 27 months and event-free survival of 10 months. At 2 years, OS was 55% and event-free survival was 27%. The Italian study had the best results, with a projected event-free survival of 48%, which was based on limited follow-up of 16 months.[53] However, the study closed early due to 2 treatment-related deaths. The combination of alemtuzumab with CHOP has significant toxicity, with febrile neutropenia experienced by 40% of enrolled patients (8 of 20), including 15% of enrolled patients (3 of 20) developing proliferative disorders.[54] These toxicities speak to the profound immunosuppression that can occur with alemtuzumab. The ACT-1 and ACT-2 trials in Europe are currently examining the role of alemtuzumab in both young and elderly patients. An interim safety analysis based on ACT-1 described the decision to decrease the dose of alemtuzumab from 360 mg per cycle to 120 mg per cycle because of 2 fatal fungal infections.[29]

The combination of CHOP plus denileukin diftitox was recently tested in a phase II study with 49 patients in the intent-to-treat group, and 51% of patients achieved a CR.[55] The PFS was 46%. These findings have resulted in a phase III study being planned.

Bevacizumab, a monoclonal antibody that targets vascular endothelial growth factor A, which is strongly expressed in PTCL, was combined with CHOP in a phase II study from ECOG.[56] The study has been suspended because of the high degree of cardiac involvement. Combinations like this are likely to be limited in PTCL.

Bortezomib has also been added to CHOP[57] or to the CHOP-like regimen doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisone.[58] The outcomes, however, have not been better than with CHOP alone.

Although 3 drugs have been approved for relapsed or refractory PTCL over the last 2 years, a recent study found a poor prognosis for survival after relapse.[31] Pralatrexate was recently approved after the PROPEL (Pralatrexate in Patients with Relapsed or Refractory Peripheral T-cell Lymphoma) phase II study.[59] A total of 111 relapsed or refractory PTCL patients, including some who had received a prior transplant, were treated with pralatrexate and achieved an ORR of 29% and a CR of 11%. The median duration of response was 10 months. These results have led to current studies of pralatrexate in the upfront setting. One study is comparing pralatrexate maintenance after CHOP therapy with observation, and a phase I study is alternating pralatrexate with high-dose chemotherapy in SCT in appropriate patients.

HDAC inhibitors are epigenetic therapies that produce acetylation, and they are being evaluated in a number of hematologic malignancies. Romidepsin is the most well-developed HDAC inhibitor in PTCLs, as 2 phase II studies have now been completed in refractory PTCLs.[3,8] The response rate was very durable across these studies, with median duration of response ranging from 9–12 months. Toxicity was largely hematologic, with the addition of nausea and vomiting. An update of the trial results found that almost half of patients (46%) achieved disease control, and the median duration of response was 17 months, with some patients still responding after 3 years.[1] The higher rate of PFS and longer duration of response in AICL patients suggests the need to tailor treatments to particular PTCL subtypes. These results have led to the evaluation of romidepsin in the upfront setting, with a phase Ib trial recently reporting that combining romidepsin with CHOP does not result in unexpected toxicities.[7]

Brentuximab vedotin (SGN-37) is a conjugate of MMAE, an antitubulin agent, to a CD30-specific monoclonal antibody. ALCL, by definition, has a strong uniform expression of CD30. The recent update of a phase II trial of brentuximab vedotin for relapsed or refractory ALCL found that 59% of patients achieved a CR, the median duration of the CR was 17.1 months, and the toxicity was manageable.[13] These results have led to brentuximab being moved to the earlier setting, with CHOP as the primary therapy in sALCL.

Several other drugs are under evaluation for PTCLs. Alisertib is a selectively available oral kinase inhibitor. A recently reported phase II trial found that 57% of T-cell NHL patients responded to alisertib.[18] A recently completed phase II trial of bendamustine found that 47% of evaluable patients had a response, including 29% CRs, whose median duration was about 5 months.[60] Two phase II studies of lenalidomide reported ORRs of approximately 30%.[4,25]

In summary, a number of new therapies are being seen in both the upfront and the relapsed settings. The rarity of the PTCLs indicates the need for collaborations in clinical trials and between institutions. The future will include tailored treatments for individual subtypes, which is challenging. The role of upfront transplant and its benefit to individual subtypes must be defined. The multitude of agents available points to the need to determine markers of response so that the right patients can be matched to the right therapies.

## References


1. Coiffier B, Pro B, Prince HM, et al. Analysis of patients with common peripheral T-cell lymphoma subtypes from a phase 2 study of romidepsin in relapsed or refractory peripheral T-cell lymphoma. *Blood* (ASH Annual Meeting Abstracts). 2011;118(suppl 21): Abstract 591.
2. Istodax Prescribing Information. Cambridge, MA: Gloucester Pharmaceuticals, Inc.; 2009.
3. Coiffier B, Pro B, Prince HM, et al. 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. *Blood* (ASH Annual Meeting Abstracts). 2010;116(suppl 21): Abstract 114.
4. Ahmadi T, Chong EA, Gordon A, et al. Phase II trial of lenalidomide-rituximab +/- dexamethasone in relapsed or refractory indolent B-cell or mantle cell lymphomas resistant to rituximab. *Blood* (ASH Annual Meeting Abstracts). 2011;118(suppl 21): Abstract 266.
5. Wu L, Adams M, Carter T, et al. Lenalidomide enhances natural killer cell and monocyte-mediated antibody-dependent cellular cytotoxicity of rituximab-treated CD20+ tumor cells. *Clin Cancer Res.* 2008;14:4650-4657.
6. Zhang L, Qian Z, Cai Z, et al. Synergistic antitumor effects of lenalidomide and rituximab on mantle cell lymphoma in vitro and in vivo. *Am J Hematol.* 2009;84:553-559.
7. Dupuis J, Casasnovas R-O, Morschhauser F, et al. Early results of a phase Ib/II dose-escalation trial of romidepsin in association with CHOP in patients with peripheral T-cell lymphomas (PTCL). *Blood* (ASH Annual Meeting Abstracts). 2011;118(suppl 21): Abstract 2673.
8. Piekarz RL, Frye R, Prince HM, et al. Phase 2 trial of romidepsin in patients with peripheral T-cell lymphoma. *Blood.* 2011;117:5827-5834.
9. Godfrey CJ, Cabell CH, Balser B, Wolfson J, Nichols J, Burris HA, III. Exposure-QTc response analysis of class 1 selective histone deacetylase inhibitor romidepsin. *Blood* (ASH Annual Meeting Abstracts). 2011;118(suppl 21): Abstract 2680.
10. Cabell C, Bates S, Piekarz R, et al. Systematic assessment of potential cardiac effects of the novel histone deacetylase (HDAC) inhibitor romidepsin. *Blood* (ASH Annual Meeting Abstracts). 2009;114(22): Abstract 3709.
11. Lunning MA, Pamer E, Wintman L, et al. Modified SMILE in the treatment of natural killer T-cell lymphoma, nasal and nasal type: a single center US experience. *Blood* (ASH Annual Meeting Abstracts). 2011;118(suppl 21): Abstract 2688.
12. Yamaguchi M, Suzuki R, Kwong YL, et al. Phase I study of dexamethasone, methotrexate, ifosfamide, L-asparaginase, and etoposide (SMILE) chemotherapy for advanced-stage, relapsed or refractory extranodal natural killer (NK)/T-cell lymphoma and leukemia. *Cancer Sci.* 2008;99:1016-1020.
13. Advani RH, Shustov AR, Brice P, et al. Brentuximab vedotin (SGN-35) in patients with relapsed or refractory systemic anaplastic large cell lymphoma: a phase 2 study update. *Blood* (ASH Annual Meeting Abstracts). 2011;118(suppl 21): Abstract 443.
14. Fanale MA, Forero-Torres A, Rosenblatt JD, et al. A Phase I weekly dosing study of brentuximab vedotin in patients with relapsed/refractory CD30-positive hematologic malignancies. *Clin Cancer Res.* 2012;18:248-255.
15. d'Amore F, Relander T, Lauritzsen GF, et al. High-dose chemotherapy and autologuos stem cell transplantation in previously untreated peripheral T-cell lymphoma - final analysis of a large prospective multicenter study (NLG-T-01). *Blood* (ASH Annual Meeting Abstracts). 2011;118(suppl 21): Abstract 331.
16. Evens AM, Rosen ST, Gordon LI, et al. A phase I/II trial of combination gemcitabine and bortezomib (VELCADE(R)) for relapsed/refractory T-cell non-Hodgkin lymphoma (NHL) and aggressive B-cell NHL. *Blood* (ASH Annual Meeting Abstracts). 2011;118(suppl 21): Abstract 1646.
17. Venkatesh H, Di Bella N, Flynn TP, Vellek MJ, Boehm KA, Asmar L. Results of a phase II multicenter trial of single-agent gemcitabine in patients with relapsed or chemotherapy-refractory Hodgkin's lymphoma. *Clin Lymphoma.* 2004;5:110-115.
18. Friedberg J, Mahadevan D, Jung J, et al. Phase 2 trial of alisertib (MLN8237), an investigational, potent inhibitor of aurora A kinase (AAK), in patients (pts) with aggressive B- and T-cell non-Hodgkin lymphoma (NHL). *Blood* (ASH Annual Meeting Abstracts). 2011;118(suppl 21): Abstract 95.
19. Mahadevan D, Cooke L, Liu X, et al. Addition of rituximab to MLN8237 an aurora A kinase inhibitor plus vincristine or docetaxel has synergistic anti-tumor activity in a mouse model of aggressive B-cell non-Hodgkin's lymphoma. *Blood* (ASH Annual Meeting Abstracts). 2010;116(suppl 21): Abstract 3933.
20. Straus DJ, Duvic M, Horwitz SM, et al. Final results of phase II trial of pegylated liposomal doxorubicin (PLD) followed by bexarotene (Bex) in advanced cutaneous T-cell lymphoma (CTCL). *Blood* (ASH Annual Meeting Abstracts). 2011;118(suppl 21): Abstract 882.
21. Wollina U, Dummer R, Brockmeyer NH, et al. Multicenter study of pegylated liposomal doxorubicin in patients with cutaneous T-cell lymphoma. *Cancer.* 2003;98:993-1001.
22. Quereux G, Marques S, Nguyen JM, et al. Prospective multicenter study of pegylated liposomal doxorubicin treatment in patients with advanced or refractory mycosis fungoides or Sezary syndrome. *Arch Dermatol.* 2008;144:727-733.
23. Duvic M, Hymes K, Heald P, et al. Bexarotene is effective and safe for treatment of refractory advanced-stage cutaneous T-cell lymphoma: multinational phase II-III trial results. *J Clin Oncol.* 2001;19:2456-2471.
24. Duvic M, Martin AG, Kim Y, et al. Phase 2 and 3 clinical trial of oral bexarotene (Targretin capsules) for the treatment of refractory or persistent early-stage cutaneous T-cell lymphoma. *Arch Dermatol.* 2001;137:581-593.
25. Querfeld C, Rosen ST, Guitart J, et al. Phase II multicenter trial of lenalidomide: clinical and immunomodulatory effects in patients with CTCL. *Blood* (ASH Annual Meeting Abstracts). 2011;118(suppl 21): Abstract 1638.
26. Kim SJ, Kang HJ, Kim JS, et al. Phase I study of mTOR inhibitor everolimus plus CHOP in patients with advanced, aggressive T-cell lymphomas. *Blood* (ASH Annual Meeting Abstracts). 2011;118(suppl 21): Abstract 1642.
27. Saunders P, Cisterne A, Weiss J, Bradstock KF, Bendall LJ. The mammalian target of rapamycin inhibitor RAD001 (everolimus) synergizes with chemotherapeutic agents, ionizing radiation and proteasome inhibitors in pre-B acute lymphocytic leukemia. *Haematologica.* 2011;96:69-77.
28. Crazzolara R, Cisterne A, Thien M, et al. Potentiating effects of RAD001 (Everolimus) on vincristine therapy in childhood acute lymphoblastic leukemia. *Blood.* 2009;113:3297-3306.
29. d'Amore F, da Silva MG, Leppa S, et al. First interim safety analysis of a phase III randomized trial in newly diagnosed systemic peripheral T-cell lymphoma treated with CHOP chemotherapy with or without alemtuzumab and consolidated by autologous hematopoietic stem cell transplant. *Blood* (ASH Annual Meeting Abstracts). 2011;118(suppl 21): Abstract 4110.
30. Martin-Sanchez E, Rodriguez-Pinilla SM, Lombardia L, et al. PI3K inhibition as a potential therapeutic strategy in peripheral T-cell lymphomas. *Blood* (ASH Annual Meeting Abstracts). 2011;118(suppl 21): Abstract 3493.
31. Mak V, Connors JM, Klasa R, et al. Survival of peripheral T-cell lymphomas (PTCLs) patients following relapse: spectrum of disease and rare long-term survivors. *Blood* (ASH Annual Meeting Abstracts). 2011;118(suppl 21): Abstract 96.
32. Ni X, Jorgensen JL, Goswami M, et al. Effects of anti-CCR4 antibody (KW-0761) on regulatory T cells and natural killer cells in patients with cutaneous T-cell lymphoma. *Blood* (ASH Annual Meeting Abstracts). 2011;118(suppl 21): Abstract 444.
33. Marchi E, Kalac M, Bongero DC, et al. Combination of epigenetic agents synergistically reverse the malignant phenotype in models of T-cell lymphoma. *Blood* (ASH Annual Meeting Abstracts). 2011;118(suppl 21): Abstract 2727.
34. Savage KJ. Therapies for peripheral T-cell lymphomas. *ASH Education Program Book.* 2011:515-524.
35. Fisher RI, Gaynor ER, Dahlberg S, et al. Comparison of a standard regimen (CHOP) with three intensive chemotherapy regimens for advanced non-Hodgkin's lymphoma. *N Engl J Med.* 1993;328:1002-1006.
36. Vose J, Armitage J, Weisenburger D, International TCLP. International peripheral T-cell and natural killer/T-cell lymphoma study: pathology findings and clinical outcomes. *J Clin Oncol.* 2008;26:4124-4130.
37. Simon A, Peoch M, Casassus P, et al. Upfront VIP-reinforced-ABVD (VIP-rABVD) is not superior to CHOP/21 in newly diagnosed peripheral T cell lymphoma. Results of the randomized phase III trial GOELAMS-LTP95. *Br J Haematol.* 2010;151:159-166.
38. Schmitz N, Trumper L, Ziepert M, et al. Treatment and prognosis of mature T-cell and NK-cell lymphoma: an analysis of patients with T-cell lymphoma treated in studies of the German High-Grade Non-Hodgkin Lymphoma Study Group. *Blood.* 2010;116:3418-3425.
39. Rodriguez J, Caballero MD, Gutierrez A, et al. High-dose chemotherapy and autologous stem cell transplantation in peripheral T-cell lymphoma: the GEL-TAMO experience. *Ann Oncol.* 2003;14:1768-1775.
40. Beitinjaneh A, Saliba RM, Okoroji G-J, et al. Autologous and allogeneic stem cell transplantation for T-cell lymphoma: the M.D. Anderson Cancer Center experience. *Blood* (ASH Annual Meeting Abstracts). 2011;118(suppl 21): Abstract 4118.
41. Mounier N, Gisselbrecht C, Briere J, et al. All aggressive lymphoma subtypes do not share similar outcome after front-line autotransplantation: a matched-control analysis by the Groupe d'Etude des Lymphomes de l'Adulte (GELA). *Ann Oncol.* 2004;15:1790-1797.
42. Li YX, Yao B, Jin J, et al. Radiotherapy as primary treatment for stage IE and IIE nasal natural killer/T-cell lymphoma. *J Clin Oncol.* 2006;24:181-189.
43. Kim SJ, Kim K, Kim BS, et al. Phase II trial of concurrent radiation and weekly cisplatin followed by VIPD chemotherapy in newly diagnosed, stage IE to IIE, nasal, extranodal NK/T-Cell Lymphoma: Consortium for Improving Survival of Lymphoma study. *J Clin Oncol.* 2009;27:6027-6032.
44. Jaccard A, Petit B, Girault S, et al. L-asparaginase-based treatment of 15 western patients with extranodal NK/T-cell lymphoma and leukemia and a review of the literature. *Ann Oncol.* 2009;20:110-116.
45. Yamaguchi M, Kwong YL, Kim WS, et al. Phase II study of SMILE chemotherapy for newly diagnosed stage IV, relapsed, or refractory extranodal natural killer (NK)/T-cell lymphoma, nasal type: the NK-Cell Tumor Study Group study. *J Clin Oncol.* 2011;29:4410-4416.

46. Konuma T, Ooi J, Takahashi S, et al. Allogeneic stem cell transplantation for hepatosplenic gammadelta T-cell lymphoma. *Leuk Lymphoma.* 2007;48:630-632.
47. Mahadevan D, Unger J, Persky D, et al. Phase II trial of cisplatin plus etoposide plus gemcitabine plus solumedrol (PEGS) in peripheral T-cell non-Hodgkin lymphoma (SWOG S0350). *Ann Oncol.* 2011;22(suppl 4): Abstract 111.
48. Corazzelli G, Frigeri F, Marcacci G, et al. Gemcitabine, ifosfamide, oxaliplatin (GIFOX) as first-line treatment in high-risk peripheral T-cell/NK lymphomas: a phase II trial. *Blood* (ASH Annual Meeting Abstracts). 2010;116(suppl 21): Abstract 2829.
49. Piccaluga PP, Agostinelli C, Righi S, Zinzani PL, Pileri SA. Expression of CD52 in peripheral T-cell lymphoma. *Haematologica.* 2007;92:566-567.
50. Rodig SJ, Abramson JS, Pinkus GS, et al. Heterogeneous CD52 expression among hematologic neoplasms: implications for the use of alemtuzumab (CAMPATH-1H). *Clin Cancer Res.* 2006;12:7174-7179.
51. Jiang L, Yuan CM, Hubacheck J, et al. Variable CD52 expression in mature T cell and NK cell malignancies: implications for alemtuzumab therapy. *Br J Haematol.* 2009;145:173-179.
52. Kim JG, Sohn SK, Chae YS, et al. Alemtuzumab plus CHOP as front-line chemotherapy for patients with peripheral T-cell lymphomas: a phase II study. *Cancer Chemother Pharmacol.* 2007;60:129-134.
53. Gallamini A, Zaja F, Patti C, et al. Alemtuzumab (Campath-1H) and CHOP chemotherapy as first-line treatment of peripheral T-cell lymphoma: results of a GITIL (Gruppo Italiano Terapie Innovative nei Linfomi) prospective multicenter trial. *Blood.* 2007;110:2316-2323.
54. Kluin-Nelemans HC, van Marwijk Kooy M, Lugtenburg PJ, et al. Intensified alemtuzumab-CHOP therapy for peripheral T-cell lymphoma. *Ann Oncol.* 2011;22:1595-1600.
55. Foss FM, Sjak-Shie NN, Goy A, Advani R, Jacobsen ED. Phase II study of denileukin diftitox with CHOP chemotherapy in newly-diagnosed PTCL: CONCEPT trial. *J Clin Oncol* (ASCO Annual Meeting Abstracts). 2010;28(suppl 15): Abstract 8045.
56. Advani RH, Hong F, Ganjoo KN, et al. Cardiac toxicity associated with the anti-VEGF monoclonal antibody bevacizumab (Avastin) in combination with CHOP (A-CHOP) chemotherapy for peripheral T cell lymphoma (PTCL): the ECOG 2404 trial. *Blood* (ASH Annual Meeting Abstracts). 2009;114(suppl 22): Abstract 1671.
57. Lee J, Suh C, Kang HJ, et al. Phase I study of proteasome inhibitor bortezomib plus CHOP in patients with advanced, aggressive T-cell or NK/T-cell lymphoma. *Ann Oncol.* 2008;19:2079-2083.
58. Delmer A, Fitoussi O, Gaulard P, et al. A phase II study of bortezomib in combination with intensified CHOP-like regimen (ACVBP) in patients with previously untreated T-cell lymphoma: results of the GELA LNH05-1T trial. *J Clin Oncol* (ASCO Annual Meeting Abstracts). 2009;27(suppl 15): Abstract 8554.
59. O'Connor OA, Pro B, Pinter-Brown L, et al. Pralatrexate in patients with relapsed or refractory peripheral T-cell lymphoma: results from the pivotal PROPEL study. *J Clin Oncol.* 2011;29:1182-1189.
60. Damaj G, Gressin R, Bouabdallah K, et al. Preliminary results from an open label multi-center, phase II study of bendamustine in relapsed or refractory T-cell lymphoma from the French GOELAMS group: the Bently trial. *Ann Oncol.* 2011;22(suppl 4): Abstract 126.

# Commentary

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The number of studies dedicated to T-cell lymphomas is increasing, as evidenced by presentations at the 2011 meeting of the American Society of Hematology (ASH). There have been several large, well-designed studies in these rare diseases, which is a very positive development. Most of the larger studies presented at the 2011 ASH meeting provided updates or confirmation of previously presented studies. There were also some early reports describing new, interesting approaches.

## Patient Outcomes in T-Cell Lymphoma

The Vancouver Group, from the British Columbia Cancer Agency, provided an analysis of survival in peripheral T-cell lymphoma (PTCL) from a large database that tracks the management of patients across the province.[1] There are few large studies in relapsed/refractory T-cell lymphoma—or even upfront T-cell lymphoma—and this trial provides some of the better surrogate data we have, outside of a prospective study. We have been questioning how patients fare in the relapse setting. Studies of new drugs, such as pralatrexate and romidepsin, have shown response rates and progression-free survival.[2,3] However, we did not have data regarding comparative patient outcomes. This review provided a nice baseline that allows us to know what to expect in the relapse setting. Not surprisingly, the analysis found that patient outcomes in T-cell lymphoma are relatively poor, with most patients having a short survival and treatment responses that are not very durable.

## Updates of Approved Agents

Coiffier presented updated results of the pivotal romidepsin study.[3] The new analysis provided longer follow-up data, specifically for patients with the most common subtypes of PTCL: PTCL not otherwise specified (PTCL-NOS), angioimmunoblastic T-cell lymphoma, and anaplastic large cell lymphoma.[4] These new data were fairly reflective of the overall study results. In the large romidepsin phase II study, patients with more rare subtypes had a lower rate of response.[3] However, these more rare subtypes were very under-represented; some included only 1 or 2 patients. Among the patients with the most common subtypes seen in practice, response rates were somewhat higher than for the overall series: approximately 28% of these patients had an overall response, with 16% achieving a complete response. The duration of response in the most common subtypes was 17 months. This analysis provides confirmation of what was already known about romidepsin. It can achieve disease control in a significant minority of patients.

Advani presented updated long-term data for brentuximab vedotin in patients with relapsed or refractory anaplastic large cell lymphoma.[5] Results of this study were previously presented at the 2010 ASH meeting.[6] Brentuximab vedotin has a high response rate in this one subset of T-cell lymphomas, anaplastic large cell lymphoma, which is uniformly CD30 positive. In the relapse setting, the overall response rate was 86%, with 59% complete responses.

Interestingly, some of the patients who achieved a complete response also had good durability. Some of these patients went on to transplant, but some were just observed. Among patients who achieved a complete response, the median duration of response was 17 months, with some responses still ongoing at the last follow-up analysis.

Questions have arisen, based on the activity of brentuximab vedotin, regarding whether patients in the relapse setting should be consolidated with transplant. Some have interpreted the durability of some of the responses seen in this study to mean that transplant is not needed. In my view, this study was not designed to answer this question. It is outstanding that some patients achieved very long responses, but whether or not patients went on to undergo transplant was not specified by the study. I believe that until specific data addressing this question are available, consolidation with transplant should still be considered a potentially curative option for patients who respond to second-line therapy, and we do not yet have data to show that brentuximab vedotin alone is curative therapy for some of these patients.

D'Amore presented final data from the largest prospective study of upfront transplant for patients with PTCL: the Nordic study, NLG-T-01.[7] Previously, the largest prospective study of upfront transplant was published by a German group led by Reimer.[8] That study used a CHOP induction, followed by autologous stem cell transplant. Long-term progression-free survival was approximately 36%, which suggests that responders may experience increased progression-free overall survival, but does not show a clear benefit. The Nordic study differed from the Reimer study in that it provided more robust therapy upfront: rather than standard CHOP every 3 weeks, the regimen was CHOP plus etoposide every 2 weeks.

In the Nordic study, overall survival was 51% and progression-free survival was 44%.[7] These outcomes are somewhat better than those in the German study, which could be explained partly by the slightly higher response rate in the patients receiving CHOP plus etoposide, and the higher number of patients who underwent consolidated transplant. The other interesting finding from this study, as compared with the German study, was a difference in outcome among patients with the more common subtypes. Patients with PTCL-NOS and angioimmunoblastic T-cell lymphoma had progression-free survival and overall survival rates that were fairly similar to those in the German study. However, in this study, the group of patients with anaplastic large cell lymphomas (restricted to ALK-negative) did significantly better. These patients already tend to do somewhat better with standard therapy, but it also looks like they achieve the most significant benefit with a high-dose therapy consolidation approach. Interestingly, a retrospective analysis of a German study comparing CHOP and CHOP plus etoposide suggested that etoposide might be an important drug in this population.[9]

The Nordic study is the largest prospective trial of upfront transplant in PTCL (N=160), and results suggest that the regimen used, CHOP plus etoposide every 2 weeks, is a reasonable approach. This study was not randomized, and, overall, the data are not conclusive regarding whether a high-dose therapy consolidation approach is better than standard therapy, such as CHOP. In addition, there is always concern in transplant studies that some of the results might be better than in a typical population due to selection bias, with patients selected for these trials being more fit than the average patient. At least in this study, however, results suggest that patients with anaplastic large cell lymphoma may be the subset that is benefiting the most from upfront transplant. Interestingly, the German study[8] included a relatively low number of patients with anaplastic large cell lymphomas, and outcome data have not been stratified according to patient subset.

## Novel Agents and Approaches

Friedberg presented results from a small, prospective study on a new drug called alisertib (MLN8237), which is an aurora kinase A inhibitor.[10] This study was performed by the Southwest Oncology Group in patients with B-cell lymphoma and T-cell lymphoma. Overall, the drug appears to have some activity. In the 7 patients with T-cell lymphoma, 4 responded. Friedberg highlighted a couple of cases in which the responses appeared to be fairly durable. The Southwest Oncology Group is gathering follow-up data for a larger phase II study looking at alisertib in patients with T-cell lymphoma. If it shows equally high activity as in the data presented by Friedberg, alisertib may be one of the more promising new agents to study, either as a single agent in the relapse setting or perhaps as part of a combination upfront regimen.

Data on the use of anti-CCR4 antibody KW-0761 in cutaneous T-cell lymphoma were presented by Ni.[11] There have been clinical studies of this drug in PTCL and cutaneous T-cell lymphoma,[12] most specifically mycosis fungoides and Sézary syndrome, and in adult T-cell leukemia lymphoma.[13,14] This drug appears to have reasonable activity in these populations. These subsets of T-cell lymphoma frequently express CCR4, so that target makes sense. In the United States, KW-0761 will likely be examined in prospective and/or randomized studies in patients with mycosis fungoides and HTLV-1–associated T-cell lymphomas. It is not yet known how broadly other T-cell lymphomas express CCR4. Ongoing studies in Japan are examining KW-0761 in other T-cell lymphomas.[15]

Our group presented preliminary data regarding the regimen dexamethasone, methotrexate, ifosfamide, L-asparaginase, and etoposide (SMILE), which was developed in Japan, and piloted there, for patients specifically

with natural killer–T-cell lymphoma, nasal type.[16] In these patients, it appears that asparaginase has particularly good single-agent activity. In a Japanese trial, the SMILE regimen showed high response rates in the relapse setting, and even higher response rates in the upfront setting.[17] In our study, we slightly modified the regimen, adding pegylated asparaginase. Among the first 8 patients treated with this approach, 7 had complete responses, an encouraging result in a disease often thought of as somewhat chemorefractory. The SMILE regimen was administered prior to radiation in these patients. Although these data must be confirmed in a large study, it appears that this is another subset of T-cell lymphoma—NK T-cell lymphoma, nasal type—that may require its own unique treatment strategy.

Other preliminary studies are examining novel combinations of agents. Evens presented some phase I/II data regarding the combination of gemcitabine with bortezomib in patients with relapsed/refractory T-cell and B-cell lymphoma.[18] It was hoped that this gemcitabine-based regimen could supplant CHOP as the preferred initial approach. Although early attempts are not promising, gemcitabine and bortezomib appear to be active in these patients. The Groupe d'Etude des Lymphomes de l'Adulte (GELA) recently initiated a phase I study evaluating the combination of romidepsin with CHOP as an upfront regimen in T-cell lymphoma.[19] They presented some very early phase I data, looking at feasibility and toxicity. Preliminarily, it appears that romidepsin can be combined with CHOP without unexpected toxicity, but any data regarding activity are yet to be available.

## Conclusion

The level of activity devoted to studying T-cell lymphomas is incredibly encouraging, and we are now seeing the fruits of that effort as novel drugs are making their way to the clinic where they can help the greatest number of patients. However, hard work remains. The favored regulatory pathway is to combine a novel agent with a standard such as CHOP, and those studies are under way. But as we have seen with adding other drugs to CHOP, and even consolidation with high-dose therapy and autologous transplantation, this often results in, at best, incremental benefit. With a few exceptions, it may well be that we need wholesale new regimens. As we find more potential drugs, the need to cooperate at many levels and intelligently design clinical trials becomes even more important to identify the most active combinations to move into the upfront setting.

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## References

1. Mak V, Connors JM, Klasa R, et al. Survival of peripheral T-cell lymphomas (PTCLs) patients following relapse: spectrum of disease and rare long-term survivors. *Blood* (ASH Annual Meeting Abstracts). 2011;118(suppl 21): Abstract 96.
2. O'Connor O, Pro B, Pinter-Brown L, et al. PROPEL: results of the pivotal, multicenter, phase II study of pralatrexate in patients with relapsed or refractory peripheral T-cell lymphoma (PTCL). *J Clin Oncol*. 2009;27(suppl 15):8561.
3. Coiffier BC, Horwitz S, Whittaker S, et al. Romidepsin experience in 317 patients with T-cell lymphomas. *Haematologica*. 2010;95(suppl 2):238: Abstract 0572.
4. Coiffier B, Pro B, Prince HM, et al. Analysis of patients with common peripheral T-cell lymphoma subtypes from a phase 2 study of romidepsin in relapsed or refractory peripheral T-cell lymphoma. *Blood* (ASH Annual Meeting Abstracts). 2011;118(suppl 21): Abstract 591.
5. Advani RH, Shustov AR, Brice P, et al. Brentuximab vedotin (SGN-35) in patients with relapsed or refractory systemic anaplastic large cell lymphoma: a phase 2 study update. *Blood* (ASH Annual Meeting Abstracts). 2011;118(suppl 21): Abstract 443.
6. Shustov AR, Advani R, Brice P, et al. Complete remissions with brentuximab vedotin (SGN-35) in patients with relapsed or refractory systemic anaplastic large cell lymphoma. *Blood* (ASH Annual Meeting Abstracts). 2010;116(suppl 21): Abstract 961.
7. D'Amore F, Relander T, Lauritzsen GF, et al. High-dose chemotherapy and autologuos stem cell transplantation in previously untreated peripheral T-cell lymphoma - final analysis of a large prospective multicenter study (NLG-T-01). *Blood* (ASH Annual Meeting Abstracts). 2011;118(suppl 21): Abstract 331.
8. Reimer P, Rüdiger T, Geissinger E, et al. Autologous stem-cell transplantation as first-line therapy in peripheral T-cell lymphomas: results of a prospective multicenter study. *J Clin Oncol*. 2009;27:106-113.
9. Schmitz N, Trümper L, Ziepert M, et al. Treatment and prognosis of mature T-cell and NK-cell lymphoma: an analysis of patients with T-cell lymphoma treated in studies of the German High-Grade Non-Hodgkin Lymphoma Study Group. *Blood*. 2010;116:3418-3425.
10. Friedberg J, Mahadevan D, Jung J, et al. Phase 2 trial of alisertib (MLN8237), an investigational, potent inhibitor of aurora A kinase (AAK), in patients (pts) with aggressive B- and T-cell non-Hodgkin lymphoma (NHL). *Blood* (ASH Annual Meeting Abstracts). 2011;118(suppl 21): Abstract 95.
11. Ni X, Jorgensen JL, Goswami M, et al. Effects of anti-CCR4 antibody (KW-0761) on regulatory T cells and natural killer cells in patients with cutaneous T-cell lymphoma. *Blood* (ASH Annual Meeting Abstracts). 2011;118(suppl 21): Abstract 444.
12. Duvic M, Jorgensen J, Ni X, et al. KW-0761, a monoclonal antibody directed against CC chemokine receptor type 4 (CCR4), in PTCL and CTCL patients: antigen expression may correspond to higher likelihood of clinical response. Presented at: First World Congress of Cutaneous Lymphomas; September 22-25, 2010; Chicago, IL. Abstract 77.
13. Ishii T, Ishida T, Utsunomiya A, et al. Defucosylated humanized anti-CCR4 monoclonal antibody KW-0761 as a novel immunotherapeutic agent for adult T-cell leukemia/lymphoma. *Clin Cancer Res*. 2010;16:1520-1531.
14. Ishida T, Joh T, Uike N, et al. Defucosylated anti-CCR4 monoclonal antibody (KW-0761) for relapsed adult T-cell leukemia-lymphoma: a multicenter phase II study. *J Clin Oncol*. 2012 Feb 6. [Epub ahead of print]
15. Yamamoto K, Utsunomiya A, Tobinai K, et al. Phase I study of KW-0761, a defucosylated humanized anti-CCR4 antibody, in relapsed patients with adult T-cell leukemia-lymphoma and peripheral T-cell lymphoma. *J Clin Oncol*. 2010;28:1591-1598.
16. Lunning MA, Pamer E, Wintman L, et al. Modified SMILE in the treatment of natural killer T-cell lymphoma, nasal and nasal type: a single center US experience. *Blood* (ASH Annual Meeting Abstracts). 2011;118(suppl 21): Abstract 2688.
17. Yamaguchi M, Suzuki R, Kwong YL, et al. Phase I study of dexamethasone, methotrexate, ifosfamide, L-asparaginase, and etoposide (SMILE) chemotherapy for advanced-stage, relapsed or refractory extranodal natural killer (NK)/T-cell lymphoma and leukemia. *Cancer Sci*. 2008;99:1016-1020.
18. Evens AM, Rosen ST, Gordon LI, et al. A phase I/II trial of combination gemcitabine and bortezomib (VELCADE(R)) for relapsed/refractory T-cell non-Hodgkin lymphoma (NHL) and aggressive B-cell NHL. *Blood* (ASH Annual Meeting Abstracts). 2011;118(suppl 21): Abstract 1646.
19. Dupuis J, Casasnovas R-O, Morschhauser F, et al. Early results of a phase Ib/II dose-escalation trial of romidepsin in association with CHOP in patients with peripheral T-cell lymphomas (PTCL). *Blood* (ASH Annual Meeting Abstracts). 2011;118(suppl 21): Abstract 2673.

# Highlights in T-Cell Lymphoma From the 2011 American Society of Hematology Annual Meeting and Exposition

**CME Post-Test:** *Circle the correct answer for each question below.*

1. In an analysis presented by Coiffier of patients with common peripheral T-cell lymphoma subtypes from a phase II study of romidepsin in relapsed or refractory peripheral T-cell lymphoma, the overall response rate was similar across the subtypes, at ____.

   a. 22%
   b. 33%
   c. 44%
   d. 55%

2. Which of the following agents is an immunomodulatory drug that may enhance both antibody-dependent cell-mediated cytotoxicity and the development of specific anti-tumor immune responses?

   a. Bortezomib
   b. Lenalidomide
   c. Rituximab
   d. Romidepsin

3. In a phase II study update presented by Advani, brentuximab vedotin was associated with an overall response rate of ____ in patients with relapsed or refractory systemic anaplastic large cell lymphoma.

   a. 58%
   b. 64%
   c. 71%
   d. 86%

4. The novel regimen of dexamethasone, methotrexate, ifosfamide, L-asparaginase, and etoposide (SMILE) has shown particular activity in _____.

   a. Anaplastic large cell lymphoma
   b. Angioimmunoblastic T-cell lymphoma
   c. Extranodal natural killer/T-cell lymphoma
   d. Hepatosplenic T-cell lymphoma

5. Which of the following agents is in a class of histone deacetylase inhibitors with potential cardiac effects?

   a. Bortezomib
   b. Lenalidomide
   c. Rituximab
   d. Romidepsin

6. In a study by Kim of everolimus added to CHOP chemotherapy for patients with newly diagnosed, advanced, aggressive T-cell lymphomas, what was the maximum tolerated dose of everolimus?

   a. 2.5 mg
   b. 5 mg
   c. 7.5 mg
   d. 8 mg

7. In the final report of a phase II study presented by D'Amore, dose-dense induction followed by high-dose chemotherapy/autologous stem-cell transplantation led to a long-term progression-free survival of ____ in patients with systemic PTCL.

   a. 25%
   b. 32%
   c. 44%
   d. 57%

8. Which of the following agents is a proteasome inhibitor with the capacity to reverse the downstream consequences of the nuclear factor kappa-light-chain-enhancer of activated B cells?

   a. Bortezomib
   b. Lenalidomide
   c. Rituximab
   d. Romidepsin

9. In a phase II study presented by Friedberg, alisertib had an overall response rate of ____ in a highly relapsed B- and T-cell non-Hodgkin lymphoma patient population.

   a. 25%
   b. 32%
   c. 44%
   d. 57%

10. In a population-based study by Mak and colleagues of peripheral T-cell lymphoma patients after relapse, the overall median second progression-free survival was ____.

    a. 4.7 months
    b. 5.8 months
    c. 7.4 months
    d. 8.5 months

Project ID: 8733

## Evaluation Form: Highlights in T-Cell Lymphoma From the 2011 American Society of Hematology Annual Meeting

PIM is committed to excellence in continuing education, and your opinions are critical to us in this effort. To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please take a few minutes to complete this evaluation form. You must complete this evaluation form to receive acknowledgment for completing this activity.

**Please rate your level of agreement by circling the appropriate rating:**
1 = Strongly Disagree 2 = Disagree 3 = Neutral 4 = Agree 5 = Strongly Agree

**Learning Objectives**
After participating in this activity, I am now better able to:

| | |
|---|---|
| 1. Describe the importance of new study findings in the form of selected abstracts/poster summaries in the natural history of T-cell lymphomas presented at the ASH 2011 Annual Meeting | 1 2 3 4 5 |
| 2. Assess the results of these new study findings, including current clinical trials evaluating therapy in the treatment of T-cell lymphomas | 1 2 3 4 5 |
| 3. Integrate into clinical practice the latest knowledge and methods for treating patients with these lymphomas in an effort to improve current prognosis statistics | 1 2 3 4 5 |
| 4. Identify future research directions for all therapies in T-cell lymphomas | 1 2 3 4 5 |

**Based upon your participation in this activity, choose the statement(s) that apply:**
❒ I gained new strategies/skills/information that I can apply to my area of practice.
❒ I plan to implement new strategies/skills/information into my practice.
❒ I need more information before I can implement new strategies/skills/information into my practice behavior.
❒ This activity will not change my practice, as my current practice is consistent with the information presented.
❒ This activity will not change my practice, as I do not agree with the information presented.

**What strategies/changes do you plan to implement into your practice?** _____

**How confident are you that you will be able to make this change?**
❒ Very confident ❒ Somewhat confident ❒ Unsure ❒ Not very confident

**What barriers do you see to making a change in your practice?** _____

**Please rate your level of agreement by circling the appropriate rating:**
1 = Strongly Disagree 2 = Disagree 3 = Neutral 4 = Agree 5 = Strongly Agree

**The content presented:**

| | |
|---|---|
| Enhanced my current knowledge base | 1 2 3 4 5 |
| Addressed my most pressing questions | 1 2 3 4 5 |
| Promoted improvements or quality in health care | 1 2 3 4 5 |
| Was scientifically rigorous and evidence-based | 1 2 3 4 5 |
| Avoided commercial bias or influence | 1 2 3 4 5 |
| Provided appropriate and effective opportunities for active learning (e.g., case studies, discussion, Q &A, etc) | 1 2 3 4 5 |
| My opportunity for learning assessment was appropriate to the activity | 1 2 3 4 5 |

**Handout materials were useful:** ❒ Yes ❒ No ❒ No handouts for this activity

**Would you be willing to participate in a post-activity follow-up survey?** ❒ Yes ❒ No

**Please list any clinical issues/problems within your scope of practice you would like to see addressed in future educational activities:** _____

If you wish to receive acknowledgment for completing this activity, please complete the post-test by selecting the best answer to each question, complete this evaluation verification of participation, and fax to: (303) 790-4876. You may also complete the post-test online at www.cmeuniversity.com. On the navigation menu, click on "Find Post-tests by Course" and search by **project ID 8733**. Upon successfully registering/logging in, completing the post-test and evaluation, your certificate will be made available immediately.

### Post-test Answer Key

| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
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