

Clinical Roundtable Monograph

Clinical Advances in Hematology & Oncology

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Current Management and Treatment of T-cell Lymphoma: A Multidisciplinary Approach

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Abstract

T-cell lymphomas are a type of non-Hodgkin lymphoma that arise from specific immune system cells termed *T lymphocytes*. This relatively rare lymphoma is generally classified as either cutaneous T-cell lymphoma (CTCL) or peripheral T-cell lymphoma (PTCL). While CTCL initially manifests as skin lesions before metastasizing to other organs, PTCL may occur both systemically or cutaneously. The most common forms of PTCL are the nodal subtypes, including PTCL not otherwise specified, angioimmunoblastic T-cell lymphoma, and anaplastic large cell lymphoma (ALCL). Unfortunately, most cases of nodal PTCL are aggressive and respond poorly to available treatments. An increased understanding of the molecular and immunologic characteristics of PTCL has promoted the investigation of several agents for both the frontline and relapsed/refractory setting. One of these, pralatrexate, received US Food and Drug Administration approval in the fall of 2009. This represented a major advancement in the treatment of PTCL, as this is the first and only drug to receive approval for relapsed/refractory PTCL. Together, the rare and aggressive nature of this disease, the increasing number of clinical trials under way to test new treatment strategies, and the many special issues to be considered when managing PTCL patients indicate that patient care providers should be educated on the most current understanding of this disease.

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Target Audience

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

Statement of Need/Program Overview

Data are emerging on novel agents as well as new combination regimens for the treatment of lymphoma. This monograph reviews some of the salient new data recently presented at international meetings of hematologists/oncologists.

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 lymphoma.
- Summarize how different roles impact clinical treatment and management of T-cell lymphoma – including but not limited to, PTCL.
- Explain the latest knowledge and methods for diagnosing and treating patients with T-cell lymphoma in an effort to improve current prognosis statistics.
- Identify future research directions for all therapies in T-cell lymphoma.

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T-cell Lymphoma: Where We Are

Barbara Pro, MD

Overview of the Disease

Peripheral T-cell lymphoma (PTCL) describes a lymphoproliferative disorder of cells that have a postthymic mature T-cell lineage. PTCL accounts for approximately 12–15% of all non-Hodgkin lymphomas (NHLs) in Western countries.¹ Epidemiologic studies suggest that the incidence of PTCL varies geographically, and may reflect differing exposures to certain pathogenic viruses.² For example, an increased incidence of PTCL in Asian countries may be due to a high rate of infection with the human T-cell leukemia virus 1 (HTLV-1) and Epstein Barr virus.³

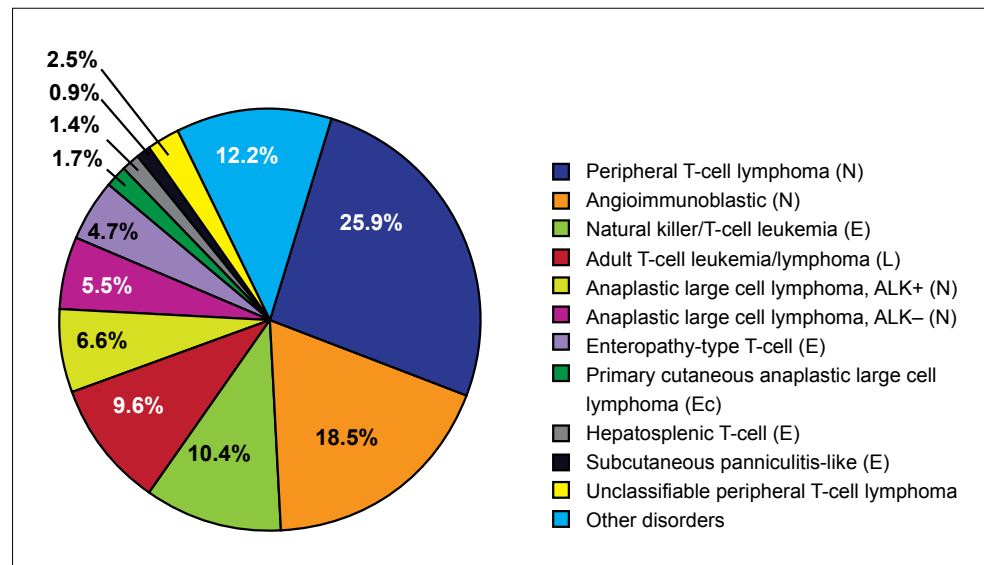
Clinically and biologically, PTCL is a strikingly heterogeneous malignancy (Figure 1). The disease-specific clinical and pathologic characteristics of the various subtypes have allowed each to become increasingly recognized as distinct entities. Correct diagnosis of the particular subtype is essential to ensure optimal patient outcome, as each is managed in different ways. Traditionally, PTCL was classified based on morphologic criteria; however, this system notoriously overlooked many subtypes. Two classification schemes have been developed to identify the unique PTCL subtypes based on clinical and pathological characteristics. The Revised European-American Lymphoma (REAL) classification, first proposed in 1994, incorporates morphologic, histologic, immunologic, and genetic characteristics, as well as the clinical presentation and disease course to define each subtype.⁴

The REAL classification provided the basis for the development of the World Health Organization (WHO) classification, which also includes natural killer T-cell lymphomas (NKTCL) because they arise from a common progenitor cell.⁵ According to the WHO classification system, PTCLs are divided into 3 major groups—predominantly leukemic, nodal, and extranodal. Of these, the most common are the nodal subtypes. Nodal PTCL is further subdivided into PTCL not otherwise specified (PTCL-NOS), angioimmunoblastic T-cell lymphoma (AITL), and anaplastic large cell lymphoma (ALCL).

PTCL-NOS is the most commonly occurring subtype of PTCL in North America and Europe, accounting for 10–30% of all cases.⁶ A recent International T-Cell Lymphoma Project study of 1,153 PTCL and NKTCL cases reported 25.9% were PTCL-NOS, thus making it the top subtype identified.⁷ PTCL-NOS includes cases that do not fit well into one of the other subtype classifications and reflect the fact that our understanding of PTCL is incomplete. Although classified in the nodal group, many patients with PTCL-NOS present with extranodal involvement to the liver, bone, gastrointestinal tract, or skin.⁸ The typical immunophenotype of PTCL-NOS is CD4-positive, CD2-positive, and CD3-positive, and most cells are also CD7-negative; approximately one-third of cells are also CD30-positive.¹ Common symptoms of PTCL-NOS at presentation include

Figure 1. Peripheral T-cell lymphoma subtype distribution.

Parentheses indicate anatomic presentation: N=nodal; E=extranodal; L=leukemic or disseminated; Ec=extranodal-cutaneous.



generalized lymphadenopathy and B symptoms (fever, weight loss, night sweats). Unfortunately, the majority of PTCL-NOS patients present with advanced and aggressive disease. Thus, the typical prognosis of this subtype is poor, with a 5-year overall survival (OS) of 30% using standard chemotherapy regimens.¹ Interestingly, a retrospective study presented evidence suggesting PTCL-NOS patients could further be subdivided into risk categories.⁹ Patients with no risk factors had significantly improved 5-year and 10-year rates of OS compared with patients having 3 or 4 risk factors (5-year OS, 62.3% vs 18.3%; 10-year OS, 54.9% vs 12.6%; $P \leq .0001$ for both comparisons). Those risk factors found to independently predict poor OS in multivariate analysis included age (>60 years), elevated lactic dehydrogenase (LDH) levels (\geq normal levels), performance status (≥ 2), and bone marrow involvement.

The next most common subtype of nodal PTCL is AILT. In the International T-Cell Lymphoma Project study, 18.5% of cases were found to be AILT.⁷ Immunophenotypically, AILT cells are typically CD3-positive and CD4 positive.¹ Because these immunotypes are also associated with PTCL-NOS, it is often necessary to use clinical features to further distinguish the subtypes. Clinical features indicative of AILT include prominent vascularization by arborizing venules and irregular expansion of CD21-positive follicular dendritic cell networks. The majority of patients with AILT are elderly, and nearly all exhibit Epstein Barr virus-infected cells. Typical symptoms of AILT at presentation are generalized lymphadenopathy, skin rash, hepatosplenomegaly, hypergammaglobulinemia, and B symptoms.⁸ Like PTCL-NOS, the prognosis associated with AILT is poor; the 5-year rate of OS is 32%, and the 5-year rate of progression-free survival (PFS) is only 13%.^{6,7}

The least commonly occurring nodal PTCL subtype is ALCL. Most ALCL cases are immunophenotypically identified as CD2-positive and CD4-positive, with variable CD3 expression.¹ Unlike other PTCL subtypes, which generally are not associated with any significantly recurrent genetic lesion, some cases of ALCL exhibit a chromosomal translocation [t(2;5)] involving the anaplastic lymphoma kinase (ALK) gene. This translocation results in the expression of an ALK-containing fusion protein, which can be detected by immunohistochemistry. The WHO classification breaks down ALCL into primary cutaneous ALCL and primary systemic ALCL, which is further subdivided into ALK-positive and ALK-negative disease. ALK-positive ALCL is most common in children and young adults, while ALK-negative ALCL occurs predominantly in older patients.⁸ As shown in the International T-Cell Lymphoma Project study, ALK-positive and -negative ALCL occur at similar rates (6.6% and 5.5%, respectively).⁷ As a whole, ALCL has a considerably superior survival compared with other PTCLs. However, ALK-positive ALCL

patients experience an improved prognosis compared with ALK-negative ALCL patients, achieving a significantly superior rate of 5-year failure-free survival (FFS, 60% vs 36%; $P = .015$) and 5-year OS (70% vs 49%; $P = .016$).¹⁰ In contrast, primary cutaneous ALCL has a notably indolent course. The majority of patients (64% of ALK-positive and 58% of ALK-negative ALCL) present with advanced stage III or IV disease, experiencing extranodal involvement and systemic symptoms.¹¹

Standard Therapy

PTCL is notoriously unresponsive to standard chemotherapy regimens, and thus patients generally have a poor prognosis and shorter survival times.⁸ In the Group d'Etudes des Lymphomas de l'Adulte (GELA) study, which compared patients with PTCL (all subgroups included) to patients with similar characteristics who had B-cell lymphoma, those with PTCL had worse outcomes on all measured endpoints.¹² This retrospective study ($n = 1,883$) reported significantly improved rates of complete remission (CR) in patients with B-cell lymphoma compared with PTCL (63% vs 54%, $P = .004$), as well as 5-year OS (53% versus 41%, $P = .0004$) and 5-year event-free survival (EFS) rates (42% vs 33%, $P < .0001$). Interestingly, this same study showed that patients with ALCL had a superior OS rate (64%) compared with all other PTCLs (35%) and with diffuse large B-cell lymphoma (DLBCL; 53%). Similar results showing PTCL has a poorer prognosis than DLBCL, and that both diseases have a worse prognosis compared with ALCL, were also demonstrated in the NHL Classification Project.¹³

Due to its rare occurrence, patients with PTCL have historically been included with aggressive B-cell lymphoma patients in prospective randomized trials. Because these PTCL patient subgroups have a limited sample size, it has been difficult to assess the true impact of a new therapeutic regimen in this malignancy. Conventional chemotherapy has traditionally been used to treat the disease, with only very little success. To date, no prospective randomized phase III clinical trials have directly compared chemotherapy regimens in a PTCL-exclusive patient population. Therefore, no standard treatment has been established for this disease; instead, the National Comprehensive Cancer Network (NCCN) guidelines recommend that clinical trials are the preferred treatment option for PTCL patients.⁸

One of the most commonly used chemotherapy regimens for first-line PTCL treatment is traditional cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP). However, only patients with ALK-positive ALCL respond well to CHOP therapy. The International PTCL clinical and pathologic review project demonstrated that anthracycline-based chemotherapy was associated with a poor outcome across all PTCL patients ($n = 1,153$), except for those with ALK-positive ALCL.⁷ This retrospective study also showed that anthracycline administration had no benefit

on OS in PTCL-NOS or AILT. The presence of risk factors significantly impact response to CHOP, as shown in a British Columbia Cancer Agency retrospective analysis of PTCL patients.⁶ Using the International Prognostic Index (IPI) prognostic score, patients (n=199) were separated into low risk (IPI 0 or 1) or poor risk (IPI \geq 2) groups. For patients with PTCL-NOS, the 5-year OS was significantly improved among patients with low risk versus poor risk disease (64% vs 20%; $P < .00001$). A similar significant trend in 5-year OS was also noted among ALCL patients (65% vs 15–20%; $P = .006$). Within the ALCL subtype, the majority of patients with ALK-positive disease were considered to be low risk; these patients achieved a markedly improved 5-year OS compared with the remaining ALCL patients, who were mainly ALK-negative (75% vs 25%; $P = .05$).

As an alternative to CHOP, the NCCN guidelines also include cyclophosphamide, vincristine, doxorubicin, and dexamethasone (hyperCVAD) alternating with high-dose methotrexate and cytarabine for first-line PTCL therapy.⁸ Unfortunately, neither hyperCVAD nor other chemotherapeutic regimens more intensive than CHOP have been found to significantly improve PTCL patient outcome.¹⁴

It has been postulated that one of the reasons PTCL responds so poorly to chemotherapy, especially anthracycline-based regimens, is due to the elevated expression of P-glycoprotein (P-gp).¹⁵ A member of the multi-drug resistant 1 (MDR1) family of cell membrane-associated transporters, P-gp has been shown to preferentially efflux anthracyclines.¹⁶ Because of this, the response to CHOP and other anthracycline-based chemotherapy regimens may not ever be improved, regardless of manipulation, and thus may not be an appropriate treatment for PTCL.

Role of Stem Cell Transplantation

Given the poor response elicited by conventional chemotherapy, stem cell transplantation has been explored as a treatment for PTCL. In particular, high-dose therapy followed by autologous stem cell transplant (HDT/ASCT) has been evaluated as first-line consolidation therapy. Most of the retrospective studies of HDT/ASCT are heterogeneous in terms of the use of lymphoma classification system, combination of distinct PTCL subtypes, treatment in either the first-line or the relapsed/refractory setting, and patient characteristics, therefore making comparisons across studies difficult.¹⁷⁻¹⁹ Another major reason for inter-study variability is the differing inclusion of the ALCL subtype, which is well established to be more responsive to treatment. The rate of OS varies greatly among these studies, ranging from 35% at 2 years to 70% at 5 years.

ASCT has also been investigated in prospective PTCL trials as first-line consolidation therapy. Importantly, these studies have excluded patients with ALK-positive ALCL. In one prospective phase II study, conducted by the Gel-Tamo Study Group, ASCT was administered to 19 patients who

had achieved a CR or partial response (PR) to induction therapy with MegaCHOP (CHOP using high-dose cyclophosphamide).²⁰ At a 2-year post-transplant follow-up, the OS was 84%, the PFS was 56%, and the disease-free survival (DFS) was 63%, indicating this was an active treatment for these patients. In a second phase II study, conducted by the Nordic Lymphoma Group (NLG), induction therapy with CHOEP followed by ASCT (following a response to induction therapy) produced a CR at 1 year post-transplant in 30 of 39 patients.²¹ Most recently, Reimer and colleagues reported the final results of the largest multicenter prospective study of HDT and total body irradiation (TBI) followed by ASCT in newly diagnosed PTCL.²² Out of the 83 patients enrolled, 55 patients achieved either a CR or PR in response to 4-6 cycles of CHOP induction therapy and were able to go on to ASCT. After a median follow-up of 33 months, the estimated 3-year rate of OS and DFS for patients in CR was 48% and 53%, respectively. The estimated 3-year rate of PFS was 36%. There was no evidence of a clear plateau in the OS and PFS curves at the median follow-up, suggesting a longer follow-up is necessary. Overall, compared with patients who did not undergo ASCT, patients that did undergo the procedure experienced a significantly superior 3-year OS (11% vs 71%; $P < .001$). Notably, one-third of the patients (33%) were unable to complete the full study protocol, and 29% developed progressive disease.

Taken together, the retrospective and prospective studies of ASCT in the first-line treatment setting of PTCL show any associated benefit to be inconclusive. According to the NCCN guidelines, in the absence of randomized trials directly comparing conventional chemotherapy regimens with HDT/ASCT, ASCT is only an appropriate treatment for patients who experience a good response to induction therapy.⁸ Currently, studies are ongoing to clearly demonstrate or negate ASCT as a potential alternative or superior treatment for PTCL. Importantly, many of these trials are addressing the potential benefit of ASCT in the distinct PTCL subtypes, in order to determine if one subtype responds preferentially to ASCT compared with another.

Pralatrexate—Newly Approved for PTCL

Because of the characteristically poor response most PTCL subtypes have in response to conventional chemotherapy, several new agents have been evaluated. This is especially true for patients with relapsed/refractory PTCL, who have even fewer treatment options to select from.

One of the newest of the approved alternative agents for PTCL is pralatrexate.²³ Pralatrexate is a novel antifolate agent that has been shown to have a high affinity for the reduced folate carrier type 1 (RFC-1), allowing it to selectively accumulate in tumor cells.²⁴ Preclinical studies suggested that pralatrexate was active in lymphoma cell lines, with activity that was superior to traditional antifolate agents, leading to the initiation of a clinical trial program.

Subsequent phase I clinical studies demonstrated that pralatrexate was safe as well as active in PTCL patients.²⁵ The major dose-limiting toxicity of pralatrexate was found to be mucositis, which was mitigated with pretreatment of folic acid and vitamin B₁₂.²⁶ Another trial reported pralatrexate was highly active in relapsed/refractory PTCL, and established a maximum tolerated dose of 30 mg/m² for 6 weeks every 7 weeks.²⁷ This same trial found an OR rate of 54% among PTCL patients.

Based on this promising phase I data, a phase II clinical trial was initiated. Pralatrexate in Patients with Relapsed or Refractory Peripheral T-Cell Lymphoma (PROPEL) was a pivotal phase II international, multicenter, open-label, single-arm study that enrolled patients (n=115) with relapsed or refractory PTCL (53% PTCL-NOS).²⁸ This was a heavily pretreated population, with patients having failed a median of 3 prior therapies (70% CHOP; 16% ASCT). Other eligibility criteria included histologically confirmed PTCL and a good performance status. Each treatment cycle, patients received intravenous pralatrexate (30 mg/m²) once weekly for 6 weeks followed by 1 week of treatment rest. Treatment was supplemented with intramuscular vitamin B₁₂ (1 mg every 8-10 weeks) and oral folic acid (1.25 mg daily). By central review, 27% of patients achieved the primary study endpoint of an objective response (39% by investigator assessment). A total of 10% of patients achieved a CR, and 17% had a PR. The disease control rate was 49%, with many patients achieving stable disease. Some patients experienced a duration of response of >1 year, although a median duration of response was not yet met. Over two-thirds (69%) of responding patients achieved this response after the first treatment cycle. Mucosal inflammation (21%) and thrombocytopenia (33%) were the most common grade 3/4 adverse events. The activity single-agent pralatrexate exhibited in the PROPEL study prompted the US Food and Drug Administration (FDA) to approve pralatrexate for the treatment of relapsed/refractory PTCL in September 2009. Pralatrexate is the first agent the FDA has specifically approved for the treatment of PTCL. Because of its activity as a single-agent, pralatrexate is now being explored in combination with other agents to increase their response rate in patients with this difficult to treat disease.

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T-cell Lymphoma: Where We Are Going

Steven M. Horwitz, MD

Traditionally, many of the agents and regimens that have been used for the treatment of T-cell lymphomas were first evaluated and established to be effective in aggressive B-cell lymphomas. However, despite some of the similarities that exist between the 2 malignancies, morphologic, molecular, and genetic data all demonstrate that these are 2 truly unique diseases. This supports data that show some drugs are active in B-cell lymphoma but are not in T-cell lymphoma, and vice versa. One example of this is the newly approved agent pralatrexate, which showed in early studies to have a much greater degree of activity in T-cell lymphoma compared with B-cell lymphoma (although studies with pralatrexate in the B-cell lymphoma setting are still currently being pursued).¹ Thus, many of the new agents currently under investigation for the treatment of T-cell lymphoma were developed specifically for this disease.

HDAC Inhibitors

Histone deacetylase (HDAC) inhibitors, as a class, are some of the most promising agents for the treatment of T-cell lymphomas. By inhibiting the HDAC enzyme, these agents cause histone hyperacetylation, thereby altering chromatin structure and affecting gene expression.²

Vorinostat was the first HDAC inhibitor approved for T-cell lymphoma, and specifically cutaneous T-cell lymphoma (CTCL). Vorinostat received FDA approval in 2006, and currently is indicated for progressive, persistent, or recurrent CTCL either during or following 2 systemic therapies.³ Another more recently approved HDAC inhibitor, romidepsin, is also FDA-approved for CTCL patients who have received at least 1 prior systemic therapy.⁴ Both vorinostat and romidepsin produce approximately a 30% response rate in CTCL.^{5,6}

Although vorinostat is very active in CTCL, there are very little data regarding its activity in PTCL. Conversely, encouraging results with romidepsin in PTCL were reported in a phase II study led by Piekarz and colleagues.^{6,7} As single-agent therapy in 46 patients with recurrent or refractory PTCL, romidepsin produced an overall response rate of 33%, including 5 CRs and 10 PRs. The overall median duration of response among these patients was 9 months (range, 1.8 months–5.8 years). The activity of romidepsin in these PTCL patients was irrespective of prior therapies, as some patients had undergone a prior stem cell transplant while some had not. These positive results have prompted the initiation of a follow-on phase II prospective trial evaluating romidepsin in approximately 130 PTCL patients.

Although these study results are not known yet, there is hope that romidepsin will show robust activity in a larger population of PTCL patients.

Other HDAC inhibitors are currently in clinical development, including MGCD0103, panobinostat, belinostat, and entinostat. An initial phase II study of belinostat in 20 patients with previously treated PTCL reported an OR rate of 25%, with a median duration of response of 159 days (range, 1–504+ days).⁸ This same study also included 29 patients with previously treated CTCL, in whom a 14% OR rate was reported. Interestingly, CTCL patients had a short time to response, with a median of 16 days (range, 14–35 days). Because of this data in both PTCL and CTCL, a larger confirmatory phase II trial is now planned.

Although mainly studied for their benefit as single-agent therapy, HDAC inhibitors also may be effective in combination regimens.⁹ For example, several investigations are under way to evaluate the combination of HDAC inhibitors with DNA methyltransferase inhibitors and proteasome inhibitors. Other cytotoxic agents may also be effective in combination with HDAC inhibitors, including topoisomerase inhibitors, tubulin-targeting agents, and biologic therapies. Important issues to consider when designing HDAC-inhibitor–based combination regimens include the sequence of therapies given and their optimal doses in combination.

Antibody Therapies

The discovery and introduction of the anti-CD20 monoclonal antibody rituximab changed the paradigm for the treatment of B-cell lymphomas. However, a parallel advancement in the use of antibody treatments for T-cell lymphomas has not yet been made. However, the investigation of several novel biological therapies may change this in the near future (Table 1).

One molecule that has been targeted in the development of T-cell antibody therapy is the cell surface antigen CD30. CD30 is a member of the tumor necrosis receptor superfamily. CD30 is expressed on activated B and T cells, and thus its expression is especially noted on Reed-Sternberg cells in Hodgkin lymphoma, both ALK-positive and -negative ALCL, and occasionally other forms of CTCL and PTCL subtypes. Several antibodies have been developed to target the CD30 protein, including the fully humanized monoclonal antibody MDX-060 and the chimeric mouse-human monoclonal antibody SGN-30.¹⁰

Table 1. Novel Agents: Monoclonal Antibodies for the Treatment of Peripheral T-cell Lymphoma

Monoclonal Antibodies	Target	Notes
MDX-060	CD30	Fully human IgG1κ
SGN-30	CD30	Chimeric murine/human antibody
Brentuximab vedotin (SGN-35)	CD30	SGN-30 fused with antitubulin agent
Zanolimumab	CD4	IgG1κ; targets T-helper cells
Alemtuzumab	CD52	IgG1; CD52 highly expressed on malignant T cells
KW-0761	CCR4	Defucosylated humanized IgG1

Data adapted from Ansell,¹¹ Pro,⁴⁸ Enblad,⁴⁹ and Yamamoto.⁵⁰

Early results with unmodified anti-CD30 antibodies have proved them to have very little toxicity, but almost no activity. For example, a phase I/II clinical trial of MDX-060 in Hodgkin lymphoma and ALCL revealed that no maximum tolerated dose (MTD) was reached.¹¹ However, the phase II portion of this trial, which included several MDX-060 dosages, showed that only 6 of the 72 patients achieved a clinical response. An additional 25 patients experienced stable disease. Recently, another study reported that the newer anti-CD30 antibody MDX-1401 displayed greater *in vitro* and *in vivo* activity than its parental antibody MDX-060.¹²

Similarly, SGN-30 was also found to be safe in a phase I examination in 24 patients with relapsed or refractory Hodgkin lymphoma and CD30-positive NHL.¹³ Again, no MTD was reached with SGN-30. One patient with cutaneous ALCL achieved a CR, and 6 patients experienced stable disease. Subsequently, 2 open-label phase II studies of SGN-30 were conducted. The first, which included 79 patients with relapsed or refractory Hodgkin lymphoma or systemic ALCL, reported only 2 CRs and 5 PRs among ALCL patients, and no responses among Hodgkin lymphoma patients.¹⁴ In the second, patients with primary cutaneous ALCL, lymphomatoid papulosis, and transformed mycosis fungoides were treated with SGN-30. A more robust 70% OR rate was achieved, with 10 patients reaching a CR and 6 patients reaching a PR. SGN-30 also has a second-generation counterpart, termed *SGN-35*. This antibody-drug conjugate is comprised of the SGN-30 anti-CD30 antibody and the potent antimetabolic drug monomethylauristatin (MMAE).¹⁵ Molecular characterization of SGN-35 has revealed that the anti-CD30 antibody portion of the conjugate acts to target the agent to CD30-positive cells.¹⁶ Once bound to cells, MMAE is taken

in by the cell due to its membrane permeability, where it acts intracellularly as a cytotoxic drug. In a phase I dose escalation study, 17 patients with relapsed or refractory Hodgkin lymphoma or systemic ALCL were treated with weekly doses of SGN-35.¹⁷ Responses were noted as 7 patients achieved a CR. Only 1 grade 3 adverse event (diarrhea) was reported, and no grade 4 events were reported. Based on these promising results, phase II and 1 phase III study of SGN-35 have now been initiated in both Hodgkin lymphomas, ALCL, and other CD30-positive hematologic malignancies.

Antibodies directed against other targets are also in development for T-cell lymphomas. The human monoclonal antibody zanolimumab targets CD4, a coreceptor residing on T cells. Although some patients with PTCL do not express CD4, it is expressed in a reasonable subset of patients. Zanolimumab rapidly inhibits T-cell signaling while it is simultaneously involved in T-cell antibody-dependent cell-mediated cytotoxicity, suggesting it has multiple mechanisms of action.¹⁸ This antibody has been investigated in both mycosis fungoides and Sézary syndrome, where, surprisingly, patients have not experienced an increased frequency of opportunistic infections despite a depletion of CD4-positive cells.¹⁹ Two phase II prospective open-label trials in 47 patients with refractory CTCL (both mycosis fungoides and Sézary syndrome) reported an especially high response rate (34%) among patients with refractory mycosis fungoides.²⁰ Zanolimumab is now also being investigated in the setting of PTCL.²¹ In the preliminary results of an ongoing phase II trial of 15 heavily pretreated refractory PTCL patients, 4 patients achieved an OR; zanolimumab was well-tolerated in this study.²²

The anti-CC chemokine receptor 4 (anti-CCR4) humanized antibody KW-0761 was assessed in a phase I study of 15 patients with either adult T-cell leukemia/lymphoma or PTCL.²³ No MTD was reached, and a 31% OR was reported (2 CR and 3 PR). KW-0761 is defucosylated, which may increase its cytotoxicity.

Alemtuzumab, a monoclonal antibody targeting CD52, is currently approved for B-cell chronic lymphocytic leukemia. Because CD52 expression is high in PTCL and CTCL, alemtuzumab has been investigated in these malignancies.²⁴ A very high response rate of 84% was reported in a single-center study of alemtuzumab in 19 patients with heavily pretreated erythrodermic CTCL and Sézary syndrome; 10 patients received an escalating dose regimen of alemtuzumab intravenously with a final dose of 30 mg 3 times weekly for 4 weeks, followed by a subcutaneous administration for 8 weeks. The remaining 9 patients were treated with only the subcutaneous or intravenous dosing. Most of the adverse events in this study were grade 2.²⁵ The combination of alemtuzumab with CHOP was tested in 24 PTCL patients.²⁶ Although a high CR rate was reported (71%), administration of this combination was accompanied by several adverse events, some severe in nature.

Other Targeted Agents

Aside from the major drug classes already described here, several other targeted therapies have also been evaluated for T-cell lymphomas. Several of these have already proven beneficial in other hematologic and/or solid malignancies.

One example of these is the immunomodulatory agent lenalidomide. This derivative of thalidomide has already received FDA approval for multiple myeloma and myelodysplastic syndromes,²⁷ and is now under investigation for both PTCL and CTCL.^{28,29} In a multicenter, open-label, single-arm, phase II trial, lenalidomide was administered to patients with T-cell lymphomas (excluding mycosis fungoides).³⁰ Patients either had relapsed or refractory disease, or had not previously received systemic therapy but were ineligible for standard chemotherapy regimens due to comorbid illness. In a report of the first 24 cases, a 30% OR rate was achieved; all of these were PRs.³¹ The median PFS was 96 days (range, 8–696 days). Toxicities reported were consistent with the already established safety profile for lenalidomide, and included grade 4 thrombocytopenia (33.3%) and grade 3 neutropenia (20.8%), febrile neutropenia (16.7%), and pain not otherwise specified (16.7%). The final results of this study, including a larger patient population, are awaited.

Bortezomib, currently approved for the treatment of multiple myeloma and previously treated mantle cell lymphoma, is the first clinically-approved proteasome inhibitor.³² A phase II study of single-agent bortezomib in 10 CTCL patients (all mycosis fungoides) and 2 cutaneous presentations of PTCL-NOS patients reported an OR of 67%.³³ Of these, 2 were a CR and 6 were a PR. Bortezomib was well-tolerated in this patient population, with no grade 4 adverse events reported. Based on this preliminary evidence of single-agent activity in T-cell lymphoma, a subsequent report evaluated bortezomib in combination with the HDAC inhibitor suberoylanilide hydroxamic acid (SAHA) in a pre-clinical study using CTCL cell lines.³⁴ This combination proved to be synergistic, providing a rationale for a similar combination to be studied in clinical trials. For example, a phase II clinical trial is currently recruiting patients with relapsed or refractory T-cell lymphomas, with the goal of determining the response rate and safety after treatment with bortezomib combined with vorinostat.³⁵ Separately, another bortezomib-based combination was also evaluated by the GELA group.³⁶ This phase II trial was designed to determine the safety and efficacy of bortezomib in combination with the standard chemotherapy regimen ACVBP (doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisone) for patients with previously untreated PTCL. Bortezomib was combined with ACVBP during 4 bi-monthly induction cycles, as well as with sequential consolidation therapy (high-dose methotrexate, etoposide and ifosfamide, and cytarabine). In 57 patients, a CR or an unconfirmed CR was achieved by 45% after induction and

46% after consolidation. It is not clear that this represents a higher response rate than with ACVBP alone.

The antimetabolite gemcitabine has been evaluated in several studies for CTCL, and to a lesser extent for PTCL. A phase II clinical trial of 32 patients with advanced and untreated CTCL (mycosis fungoides, Sézary syndrome, and PTCL-NOS with exclusive skin involvement) demonstrated that frontline treatment with single-agent gemcitabine 1,200 mg/m², given intravenously over 30 minutes for a total of 6 cycles on days 1, 8, and 15 of a 28-day schedule, elicited a CR rate of 22% and a PR rate of 53%.³⁷ This was followed by another phase II single-agent gemcitabine study, which reported a 68% OR in 25 CTCL and CD30-positive ALCL patients with advanced and heavily pretreated disease.³⁸ A retrospective study also showed that single-agent gemcitabine was efficacious in advanced stage CTCL, but unlike the 2 previous studies suggested that severe adverse events were associated with treatment.³⁹ Limited trials have tested gemcitabine in PTCL. One combined gemcitabine with cisplatin and methylprednisolone, reporting a 19% CR rate and a 50% PR rate.⁴⁰ Gemcitabine was also combined with pralatrexate in a phase I study of 34 patients with relapsed or refractory lymphoproliferative malignancies.⁴¹ The rationale behind this study was based on preclinical data showing the combination was synergistic in NHL cell lines and xenografts.⁴² Initial dose-limiting toxicities in the phase I trial caused the dosing regimen to be adjusted from a weekly 3/4-week schedule to treatment every 2 weeks. After identifying 2 phase I doses and schedules, the phase II portion of this study is ongoing.⁴³

Denileukin diftitox is a synthetically derived agent comprised of the interleukin-2 protein fused with diphtheria toxin. The inclusion of interleukin-2 allows the drug to be targeted to cells that express interleukin-2 receptors, after which diphtheria toxin can enter the cell to produce specific cytotoxic effects. Denileukin diftitox is currently approved for the treatment of relapsed or refractory CTCL.⁴⁴ A phase II study of single-agent denileukin diftitox in relapsed or refractory PTCL reported an OR rate of 48% in 27 patients; of these, 6 patients experienced a CR.⁴⁵ A preliminary study evaluating denileukin diftitox combined with CHOP revealed the combination to be active in terms of a high CR rate, but also associated with a high degree of toxicity that precluded 40% of patients from completing the planned therapy.⁴⁶

Incorporating Clinical Trials into Patient Management

According to the NCCN guidelines, enrollment in a clinical trial is still the preferred management of patients with PTCL in both the frontline and relapse setting.⁴⁷ Despite recent advancements, these patients typically have a poor prognosis and thus are often excellent candidates for clinical trials. New agents with specific activity in PTCL are being

investigated in clinical trials as single agents and novel combinations primarily in the relapsed setting. Maintenance treatment is another strategy that can be investigated in the clinical trial setting, and may provide an option to help extend the duration of response a patient may experience.

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Optimal Management of Symptoms and Treatment-related Side Effects

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PTCLs are a clinically and biologically heterogeneous group of disorders accounting for 10–15% of all non-Hodgkin lymphomas.¹ The majority of PTCLs are aggressive and fall into the classification of peripheral T-cell lymphomas not otherwise specified, angioimmunoblastic T-cell lymphoma, or anaplastic large cell lymphoma. Combined, these categories make up 60–70% of all T-cell lymphomas.² Traditionally, patients with PTCL have been treated with anthracycline-containing regimens.³ CR rates of 50–70% have been reported; however, for the majority of PTCL subtypes, relapse rate is high, and prognosis is poor with a 5-year overall survival rate of approximately 30%.⁴ Currently, no standard therapy exists for the treatment of PTCL. The National Comprehensive Cancer Network (NCCN) practice guidelines suggest a number of different treatment options, but none, with the exception of pralatrexate, are specific to T-cell lymphoma.⁵ The guidelines also recommend clinical trials at almost every stage of treatment. However, from 1991 to 2007, fewer than 100 PTCL patients were accrued to any single agent trial.⁶ Additionally, there are limited educational resources about PTCL that are available for healthcare providers. As novel therapeutic agents and new treatment strategies become available, there is a growing need to improve education about both PTCL and new agents undergoing investigation.

Treatment-Related Toxicities

The clinical nurse plays a primary role in the treatment, administration, and evaluation of treatment-related toxicities in patients. Nurses and other members of the healthcare team at large cancer research centers who participate in clinical trials gain experience in administering new drugs and observing many of the associated toxicities before these drugs become part of routine clinical practice. In contrast, small oncology practices that do not participate in clinical trials do not receive education about new therapies until they are approved by the FDA. There is a need to educate providers regarding the use of novel agents and toxicities associated in the immediate and long-term setting.

One of the most significant issues affecting PTCL patients is the development of treatment-related toxicities. With emerging evidence that anthracyclines do not affect overall survival in PTCL, and that CHOP-like chemotherapy combinations are not optimal choices in this poor-risk population, a number of agents have been proposed for the management of PTCL.¹ Several of these have demonstrated activity whereas data are still emerging on others.⁷

Pralatrexate is the only approved drug for the treatment of relapsed or refractory PTCL.⁸ Early studies found the major dose-limiting toxicity to be mucositis, of which supplementation with vitamin B₁₂ and folic acid resulted in a significant decrease. The PROPEL study reported several grade 3/4 treatment toxicities that included thrombocytopenia, mucositis, neutropenia, and anemia (Table 1). Although thrombocytopenia was noted, no cases required transfusion. In an effort to minimize mucositis symptoms, patients were administered folic acid and vitamin B₁₂.⁹

HDAC inhibitors are a unique group of drugs that appear to have a class effect in T-cell lymphomas.⁶ Vorinostat, an oral HDAC, is approved for treatment of CTCL and is now being studied in PTCL. Toxicities associated with an oral dose of 400 mg daily include dehydration, diarrhea, and fatigue. Toxicities associated with intravenous formulations include myelosuppression and thrombocytopenia. In both oral and intravenous preparations, toxicities resolve shortly after therapy is discontinued. Healthcare providers should educate patients about these toxicities and provide support care to minimize symptoms.¹⁰

Denileukin diftitox is a recombinant DNA fusion protein that is being studied for the treatment of PTCL. In a small study of 27 patients, toxicities were generally mild and transient, with the most significant grade 3 toxicity being pulmonary embolism.¹ There were no grade 4 hematologic events. A link has been reported between Denileukin diftitox and loss of visual acuity, but incidence rate and etiology of this adverse effect remain unclear.¹¹

Gemcitabine, a pyrimidine antimetabolite, is also being studied as both a single agent and in combination. A small study found neutropenia to be the only grade 3–4 toxicity reported.¹² Because of its low toxicity profile, gemcitabine is now being studied in combination with other therapies.¹

Lenalidomide, an immunomodulatory agent, is being investigated in both PTCL and CTCL. In 1 small, multicenter, open-label, single-arm phase II trial in T-cell patients with relapsed or refractory disease, toxicities included grade 4 thrombocytopenia (33.3%), grade 3 neutropenia (20.8%), febrile neutropenia (16.7%), and pain not otherwise specified (16.7%).¹³

Finally, alemtuzumab, a humanized monoclonal antibody that selectively binds to the CD52 antigen, which is expressed on most normal and malignant T- and B-cell lymphomas, is being studied. Unfortunately, CD52 is also expressed on monocytes, macrophages, NK cells, and some

Table 1. PROPEL: Adverse Events (Grade 3/4)

Adverse Event	N (%)
General Events	
Mucositis	24 (22)
Fatigue	8 (7)
Pyrexia	2 (2)
Edema	1 (1)
Blood and Lymphatic Disorders	
Thrombocytopenia	36 (33)
Anemia	20 (18)
Neutropenia	24 (22)
Leukopenia	8 (8)
Gastrointestinal Events	
Nausea	4 (4)
Vomiting	2 (2)
Respiratory, Thoracic, and Mediastinal Events	
Dyspnea	8 (7)
Other Conditions	
Hypokalemia	5 (5)
Anorexia	3 (3)
Abnormal liver function test	6 (5)

Data from O'Connor⁶ and Pinter-Brown.¹⁴
 PROPEL= Pralatrexate in Patients With Relapsed or Refractory
 Peripheral T-cell Lymphoma

dendritic cells; as a result, profound immunosuppression and opportunistic infections have occurred, resulting in early closure of several phase II studies.¹

Symptoms and Patient Care Management in the Clinic

Treatment of PTCL requires aggressive therapy. Patients enrolled in clinical trials can expect long and intensive treatments that may require relocating to the trial site. Treatment regimens are often complex and require frequent visits to the clinic for blood work and evaluation. Patients who relocate for treatment often experience a loss of emotional support systems. The healthcare team should identify the patients' support systems; additionally, patients should be evaluated for signs of situational depression. Referral to psychiatry early on may be beneficial. Because of the relative rarity of the disease, there is a growing need for access to PTCL educational materials for healthcare providers. In particular, healthcare providers should be educated on the differences between T-cell and B-cell lymphomas. The aggressive nature of PTCLs highlights the need to assess patients closely during treatment. Disease progression on therapy is not uncommon. Clinicians and other patient care providers, especially

non-oncologist physicians, should regularly follow-up with their patients. Patients should be asked about the presence of new or enlarging lymph nodes or new symptoms that may be indicative of disease progression. Many patients with PTCL are frail and have numerous systemic symptoms while receiving treatment. In some cases, this frailty may be due to the current treatment regimen; in many cases, the symptoms are the result of cumulative toxicities of multiple treatments for progressive relapsed/refractory disease. For example, thrombocytopenia is a common symptom experienced by PTCL patients. While thrombocytopenia may not be serious enough to require transfusion, it is concerning enough that the physician needs to consider whether the patient should be dose-reduced or removed from a particular trial or therapy. For cases in which these symptoms are interfering with the patient's quality of life, it is often necessary to adjust or stop the therapy. However, when symptoms are related to the disease, the physician needs to decide if continuing treatment despite toxicities is prudent. In order to determine if symptoms are treatment-related or disease-related, it may be necessary to temporarily withhold the drug and/or drugs being administered to see if the symptoms improve. Overall, patients diagnosed with PTCL must be followed closely, and patients receiving treatment should be seen and evaluated frequently for treatment-related toxicities or signs of early relapse. Understanding the common side effects of new agents will benefit healthcare providers in the evaluation of these toxicities and improve patient care.

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WHO Classification of Mature T/NK-Cell Neoplasms

- T-cell prolymphocytic leukemia
- T-cell large granular lymphocytic leukemia
- Chronic lymphoproliferative NK cells
- Aggressive NK-cell leukemia
- Adult T-cell lymphoma/leukemia
- Systemic EBV-positive T-cell lymphoma
- Extranodal NK/T-cell lymphoma, nasal type
- Enteropathy-type intestinal T-cell lymphoma
- Hepatosplenic T-cell lymphoma
- Mycosis fungoides
- Sezary syndrome
- Primary cutaneous CD30+ lymphoproliferative
- Primary cutaneous anaplastic large cell
- Lymphomatoid papulosis
- Borderline lesions
- Subcutaneous panniculitis-like T-cell
- Primary cutaneous gamma-delta T-cell
- Hydroa vacciniforme lymphoma
- Primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell
- Primary cutaneous small/medium CD4+ T-cell lymphoma (provisional)
- Angioimmunoblastic T-cell lymphoma (AITL)
- Anaplastic large cell lymphoma, ALK-positive
- Anaplastic large cell lymphoma, ALK-negative
- Peripheral T-cell lymphoma, NOS

Autologous Stem Cell Transplantation as First-line Therapy in PTCL: Results of a Prospective Multicenter Study

- N=83
- CHOP x 4-6
- IF CR/PR
 - mobilized with DexaBEAM or ESHAP
- TBI + CY-ASCT
- Median F/U: 33 months

PTCL	39%
AITL	33%
ALCL	16%
Med age	46.5 (30-65)
AA-IPI	L-LI 49%
	HI-H 51%
CR/CHOP	39%
PR/CHOP	40%
ASCT	66%
POD	29% (22% CHOP)

Reimer, P. et al. JCO epub Nov2008

PROPEL: Phase II Trial of Pralatrexate for Relapsed/Refractory PTCL

Disease

- Relapsed/refractory PTCL any histology
- Progressive disease after ≥1 previous treatment

Study Objectives

- Primary: Overall response by IWC criteria
- Secondary: DOR, PFS, OS

Schedule

- 7-week treatment cycles
- Pralatrexate 30 mg/m² intravenously weekly for 6 weeks
- Vitamin B12 and folic acid

O'Connor et al., ASH 2008, Abstract # 261

PROPEL: Adverse Events (Grade 3/4)

Adverse Event	N (%)
General Events	
Mucositis	34 (22)
Fatigue	8 (7)
Pyrexia	2 (2)
Edema	1 (1)
Blood and Lymphatic Disorders	
Thrombocytopenia	36 (33)
Anemia	20 (18)
Neutropenia	24 (22)
Leukopenia	8 (8)
GI Events	
Nausea	4 (4)
Vomiting	2 (2)
Respiratory, Thoracic, and Mediastinal Events	
Dyspnea	8 (7)
Other Conditions	
Hypokalemia	5 (5)
Anorexia	3 (3)
Abnormal liver function test	8 (8)

- 26 pts (23%) discontinued treatment because of AEs, most frequently
 - Mucositis (6%)
 - Thrombocytopenia (5%)
- 8 pts (7%) died on treatment or within 30 days after last dose
 - 7 due to PD
 - 1 due to cardiopulmonary arrest 3 weeks after last dose
 - Hospitalized for grade 3 mucosal inflammation and febrile neutropenia 2 weeks before death (never resolved)

O'Connor, ASCO, 2009 (abstr 8561); Pines-Brown, ASH, 2009 (abstr 1875).

Romidepsin

- FK228, depsipeptide, romidepsin, istodax
- A pan histone deacetylase (HDAC) inhibitor
- FDA approved for the treatment of cutaneous T-cell lymphoma (CTCL) in patients who have received ≥1 prior systemic therapy
- Evaluations in patients with peripheral T-cell lymphoma (PTCL) ongoing
- 317 patients with CTCL or PTCL treated with romidepsin at a standard dose and schedule in clinical trials
 - safety data available for all patients
 - response data available for 214 patients

Other Drugs for Peripheral T-cell Lymphoma

- Clofarabine
- Lenalidomide
- Anti-CD 4
- Everolimus
- SGN-35
- Belinostat
- Syk inhibitors
- Nelarabine
- Enzastaurin
- Arsenic trioxide
- Anti-CD 2
- Chemokine receptors
- Fodoline
- Pilidepsin
- Others...
- CD 52-alemtuzumab
- Denileukin Diftitox
- Bortezomib
- Pentostatin

Phase II Study: Belinostat in Recurrent/Refractory CTCL or PTCL

• CTCL or PTCL
 • Failed ≥1 prior systemic therapy (N=53; 48 evaluable: 29 CTCL, 19 PTCL)

Belinostat 1000 mg/m² IV
 Days 1-5 q21d x 2

CR, PR, or SD

Belinostat up to 6 more cycles* or until PD

- CTCL and PTCL arms analyzed separately
- Results (in PTCL)
 - 2 CR, 4 PR, 4 SD in 19 evaluable pts (32% ORR)
 - Both CR in PTCL-NOS pts
 - PFS 40 days; DOR 268+ days (99–847+)
 - Nausea and vomiting were most common AEs

*SD or PR additional cycles
 Pohlman, ASH. 2009 (abstr 520); Advani, ASH. 2007 (abstr 3453).

Phase II Study: Zanolimumab in Relapsed/Refractory Noncutaneous T-cell Lymphoma

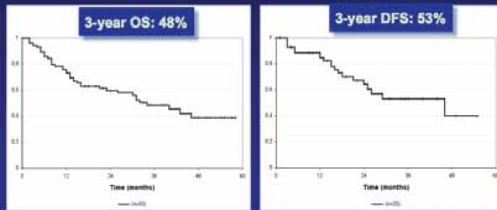
• Biopsy-confirmed CD4+ PTCL (noncutaneous)
 • Refractory/recurrent disease (N=21)

Zanolimumab 960 mg IV qw x 12

- PTCL subtypes (N)
 - PTCL-NOS (7)
 - AITL (9)
 - ALCL (4)
 - EATCL (1)
- Primary endpoint: objective tumor response
- Results
 - ORR: 23.8%
 - 2 CR; 3 PR
 - Zanolimumab + CHOP planned for nodal TCL

d'Amore, ASH. 2007 (abstr 3409).

Autologous Stem Cell Transplantation as First-line Therapy in PTCL: Survival



- Outcome**
- 39% could not be transplanted due to PD
 - 27% progressed after transplant

Reimer, P. et al. JCO epub Nov2008

Autologous SCT in PTCL

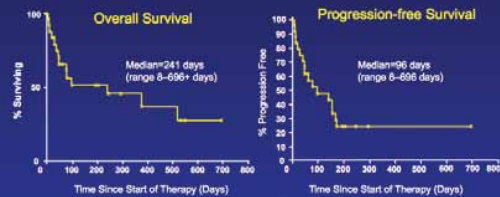
- Debated as a first-line strategy
- Primary refractoriness is still an unsolved problem in a substantial number of pts (25–35%) on prospective trials
- A subset of pts seem to benefit from ASCT
 - Efforts under way to further identify and characterize

Romidepsin: Efficacy Results

	CTCL		PTCL	
	GPI (N=96)	NCI (N=71)	GPI (N=103)*	NCI (N=47)
ORR (CR + PR), n (%)	33 (34%)	25 (35%)	NA	18 (38%)
CR	6 (6%)	4 (6%)	NA	7 (15%)
PR	27 (27%)	21 (29%)	NA	11 (23%)
Median (range) duration of response, months	15 months (1–20)	11 months (1–66)	NA	10 months (2–70)

CTCL=cutaneous T-cell lymphoma; CR=complete response; GPI=Gloucester Pharmaceuticals registration trial; NA=not available; NCI=National Cancer Institute trial; ORR=overall response rate; PR=partial response; PTCL=peripheral T-cell lymphoma.
 *Patients accrued to August 2009.
 Horwitz et al, T-cell Forum, 2010

Lenalidomide in Relapsed/Refractory TCL



Dueck, ASCO. 2009 (abstr 8524).

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