5 Minute JournalClub

Key ASH Presentations

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CME Information

LEARNING OBJECTIVES

- Counsel patients with PTCL who have previously received ICE-based therapy about the benefits and risks of further treatment with pralatrexate.
- Describe the mechanism of action of romidepsin, and recall the efficacy and safety of this agent for patients with relapsed or refractory PTCL.
- Describe the efficacy and safety of brentuximab vedotin (SGN-35) in patients with relapsed or refractory sALCL.
- Assess the safety and efficacy of denileukin diftitox re-treatment for patients with relapsed CD25-positive CTCL.
- Identify the optimal dose and schedule of pralatrexate for the treatment of relapsed or refractory CTCL.

CREDIT DESIGNATION STATEMENT

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CME Information (Continued)

FACULTY DISCLOSURES
The following faculty (and their spouses/partners) reported real or apparent conflicts of interest, which have been resolved through a conflict of interest resolution process:

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Final Results from a Pivotal, Multicenter, International, Open-Label, Phase 2 Study of Romidepsin in Progressive or Relapsed Peripheral T-Cell Lymphoma Following Prior Systemic Therapy[1]

Pralatrexate is Effective in Patients with Relapsed or Refractory Peripheral T-Cell Lymphoma (PTCL) with Prior Ifosfamide, Carboplatin, and Etoposide (ICE)-Based Regimens (slide 9)[2]

[1]Coiffier B et al.
Proc ASH 2010;Abstract 114.

[2]Goy A et al.
Proc ASH 2010;Abstract 1753.

Final Results from a Pivotal, Multicenter, International, Open-Label, Phase 2 Study of Romidepsin in Progressive or Relapsed Peripheral T-Cell Lymphoma Following Prior Systemic Therapy

Coiffier B et al.

Proc ASH 2010;Abstract 114.

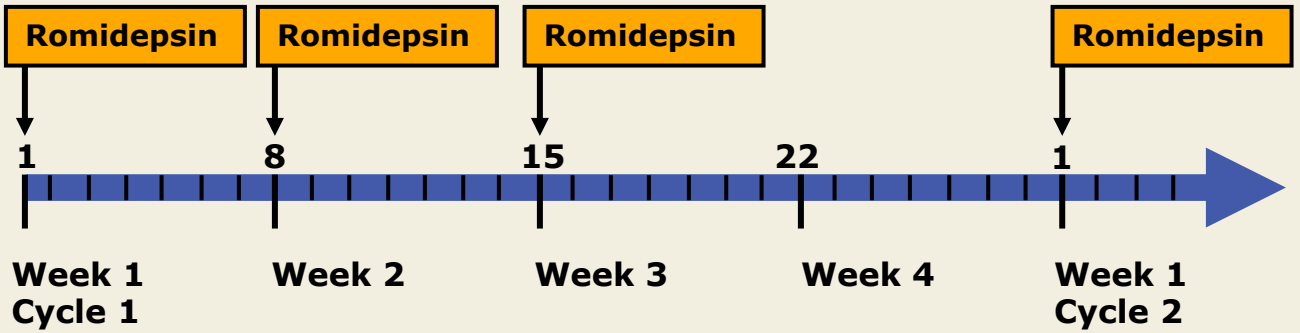
Background

- Peripheral T-cell lymphoma (PTCL) is a rare heterogeneous group of non-Hodgkin's lymphoma.
  - Aggressive clinical behavior
  - Poor response to chemotherapy
  - High relapse rate
  - Poor long-term survival
- Romidepsin is a histone deacetylase (HDAC) inhibitor, currently approved for patients with cutaneous T-cell lymphoma (CTCL) who have received at least one prior systemic therapy.

Coiffier B et al. *Proc ASH* 2010;Abstract 114.

Study Schema

Eligibility (n = 131)
Confirmed PTCL
Failed at least one prior systemic therapy
Measurable disease
Primary endpoint: Complete response by Independent Review Committee



Romidepsin 14 mg/m^2 IV over 4 hours
Days 1, 8 and 15 of a 28-day cycle x 6 cycles
Responding patients could continue to receive treatment beyond 6 cycles at discretion of patient and investigator

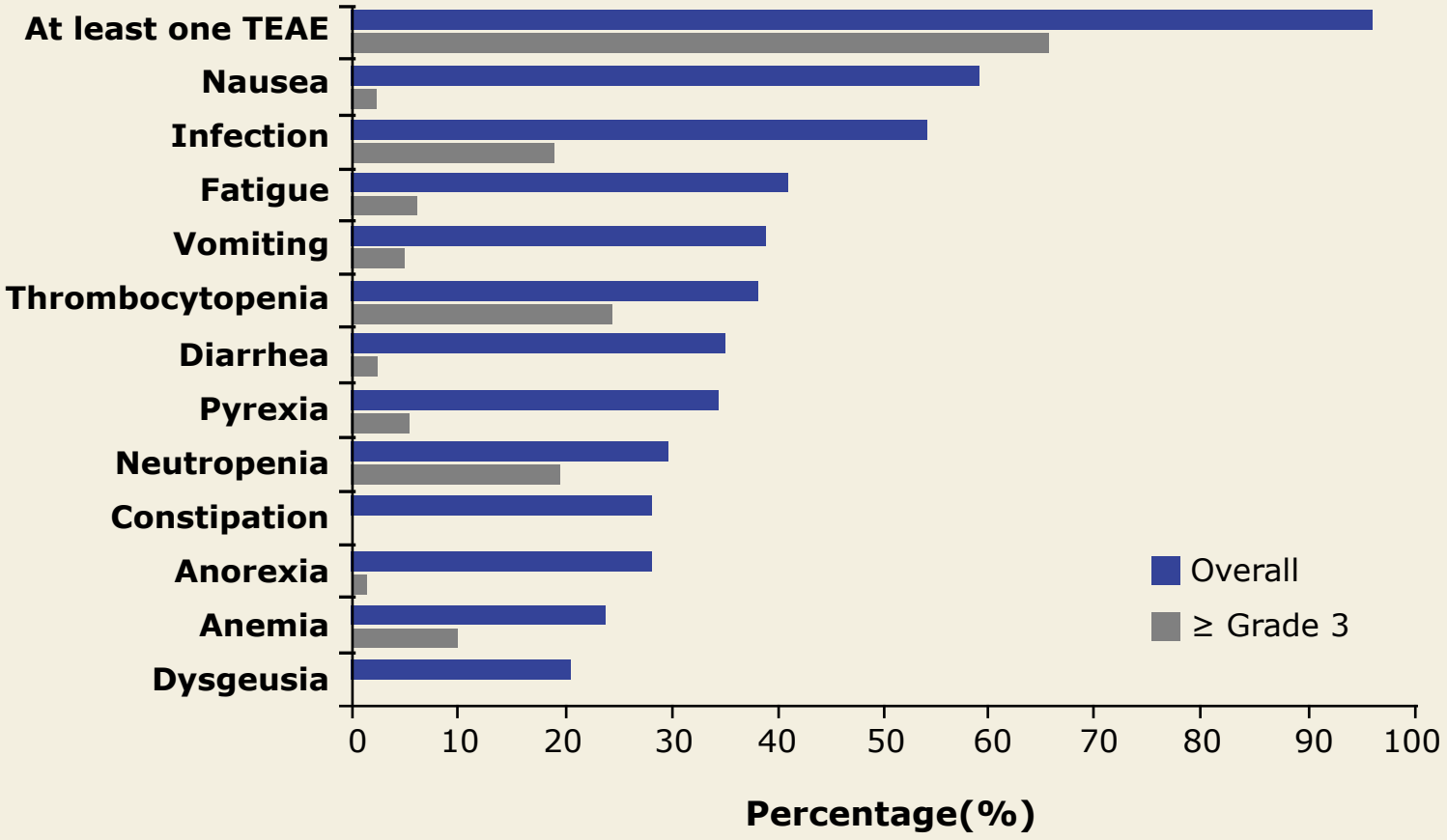
Coiffier B et al. *Proc ASH* 2010;Abstract 114.

Efficacy Outcomes

Efficacy Outcomes (n = 130)	Independent Review Committee (IRC) Assessment	Investigator's Assessment
Objective response rate (ORR)	26%	29%
Duration of objective response (median)	12 months	12 months
Time to objective response	2 months	2 months
Complete response (CR/CRu) CR CRu	13% 8% 5%	16% 14% 2%
Duration of complete response (median)	Not reached	14 months
Partial response	13%	13%

Coiffier B et al. *Proc ASH* 2010;Abstract 114.

Treatment-Emergent Adverse Events (TEAEs)



With permission from Coiffier B et al. *Proc ASH* 2010;Abstract 114.

Author Conclusions

- Significant activity demonstrated with single-agent romidepsin in relapsed/refractory PTCL.
  - ORR = 26% (IRC), 29% (Investigator)
  - Median duration of response = 12 mos (IRC and Investigator)
- Rate of CR/CRu = 13% (IRC), 16% (Investigator)
  - Median duration of response = Not reached (IRC), 14 mos (Investigator)
- Responses reported across all major PTCL subtypes (data not shown).
- Single-agent romidepsin therapy was generally well tolerated with manageable toxicities.

Coiffier B et al. *Proc ASH* 2010;Abstract 114.

Investigator comment on romidepsin in relapsed or refractory peripheral T-cell lymphoma (PTCL)

This is a relatively large Phase II study of romidepsin in relapsed/ refractory PTCL, and it enrolled almost all subtypes. A central review of pathology was conducted, and responses were also centrally assessed. The real highlight of these data is an independently assessed CR rate of 13 percent, which is high, and the duration of response is also quite good. The drug might be approved for PTCL in the relapsed setting. Also, because there does not appear to be any cumulative toxicity, we might be able to use it in a maintenance fashion in the future.

Comparing the data to those with pralatrexate, an approved drug for relapsed/refractory PTCL, the efficacy seems similar though the toxicities are different. The main toxicity of pralatrexate is mucositis, while the toxicities associated with romidepsin are nausea, vomiting and fatigue. I believe no compelling reason exists to prefer one over the other, and like pralatrexate, investigators will try to figure out a way to incorporate romidepsin into earlier lines of therapy.

Interview with Steven M Horwitz, MD, December 29, 2010

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

Goy A et al.

Proc ASH 2010;Abstract 1753.

PROPEL Study Schema

Accrual = 109 (Closed)

Eligibility

Confirmed PTCL
Documented progression after at least one prior therapy

Pralatrexate 30 mg/m^2 IV push over 3-5 minutes
Weekly administration x 6 weeks of 7-week cycles
with concurrent vitamin B12, 1 mg IM q 8-10 wks
and folic acid, 1.0-1.25 mg po qd

Primary Endpoint:
Response rate

Secondary Endpoints:
Duration of response (DOR)
Progression-free survival (PFS)
Overall survival (OS)

Current exploratory analysis objective:
To assess efficacy and safety in a subset of patients in the PROPEL study who received pralatrexate after failure of ICE-based regimens

ClinicalTrials.gov Identifier NCT00364923
Goy A et al. *Proc ASH* 2010;Abstract 1753.

Efficacy of Pralatrexate in Patients Who Received Prior ICE-Based Regimens

Efficacy Outcomes (n = 20)	Independent Central Review	Investigator Assessment
Objective Response	40%	40%
Median DOR	13.1 months	16.2 months
Complete Response	15%	25%
Partial Response	25%	15%
Median PFS	14.4 months	4.8 months
Median OS	12.0 months	

Goy A et al. *Proc ASH* 2010;Abstract 1753.

Efficacy Comparison of Pralatrexate with Prior ICE-Based Regimen Outcomes

Efficacy Outcomes (n = 20)	Patient Responses to Pralatrexate (Independent Central Review)	Patient Responses to Prior ICE-Based Regimens
Objective Response	40%	25%
Complete Response	15%	15%
Partial Response	25%	10%
Median DOR	13.1 months	<1 month

Goy A et al. *Proc ASH* 2010;Abstract 1753.

Select Adverse Events (AEs)

Grade 3 or 4 AEs ≥5%	Incidence
Anemia	45%
Thrombocytopenia	40%
Mucosal inflammation	30%
Fatigue	5%
Cough	5%
Diarrhea	5%

Goy A et al. *Proc ASH* 2010;Abstract 1753.

Author Conclusions

- Pralatrexate was active in patients with PTCL who received prior ICE-based chemotherapy.
  - Objective response rate = 40%, including CRs leading to stem cell transplant in two patients
- Single-agent pralatrexate safety profile and outpatient administration appear to compare favorably with ICE-based regimens, which typically require hospitalization for administration.
- Pralatrexate can reverse the characteristic progressive resistance of PTCL and is an effective second-line treatment for patients with PTCL.

Goy A et al. *Proc ASH* 2010;Abstract 1753.

Investigator comment on pralatrexate in relapsed or refractory PTCL previously treated with ICE-based regimens

Pralatrexate is definitely active in this subset of patients, and on face value, it appears that patients who received pralatrexate had a higher response rate and a longer duration of response than they achieved with prior ICE-based regimens. At our institution, the response rate with ICE is much higher and approximately 70 percent, so maybe the PROPEL study was selecting for a group of patients in whom ICE was particularly ineffective. The other issue is that ICE is usually administered for a limited number of cycles because of cumulative toxicity, and pralatrexate in this study was administered until progression. In view of this, I don't believe that comparing the duration of response to the two regimens is fair.

Overall, I believe that the conclusion is a little bit exaggerated that pralatrexate reverses the progressive resistance of patients with T-cell lymphoma to second-line chemotherapy. However, I also believe that these data definitely suggest that pralatrexate is active in patients who are refractory to ICE-based regimens and can be used.

Interview with Steven M Horwitz, MD, December 29, 2010

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

Shustov AR et al.

Proc ASH 2010;Abstract 961.

Background

- Systemic anaplastic large cell lymphoma (sALCL) is a CD30-positive aggressive subtype of peripheral T-cell lymphoma (PTCL).
  - Comprises approximately 2-3% of all cases of non-Hodgkin's lymphoma
- Patients with newly diagnosed high-risk ALK-positive and ALK-negative sALCL have a poor prognosis.
  - Approximately 50% will fail front-line therapy
  - Few salvage therapies exist for relapsed or refractory sALCL
  - Pralatrexate is the only FDA-approved treatment for recurrent PTCL (including sALCL)
- Brentuximab vedotin (SGN-35) is a novel antibody-drug conjugate.
  - Delivers the highly potent antimicrotubule agent monomethyl auristatin E (MMAE) to CD30-positive malignant cells

Shustov AR et al. *Proc ASH* 2010;Abstract 961.

Study Schema

Accrual = 58 (Closed)

Eligibility
Relapsed or refractory sALCL
Measurable disease ≥1.5 cm FDG-avid
ECOG PS 0-1

→ Brentuximab vedotin, 1.8 mg/kg IV q 3-weeks x (up to) 16 cycles

Primary Endpoint:

Overall objective response rate (ORR) by independent review facility (IRF)

Secondary Endpoints:

Complete remission rate
Duration of response
Progression-free survival (PFS)
Overall survival (OS)
Safety and tolerability

Shustov AR et al. *Proc ASH* 2010;Abstract 961; ClinicalTrials.Gov Identifier NCT00866047.

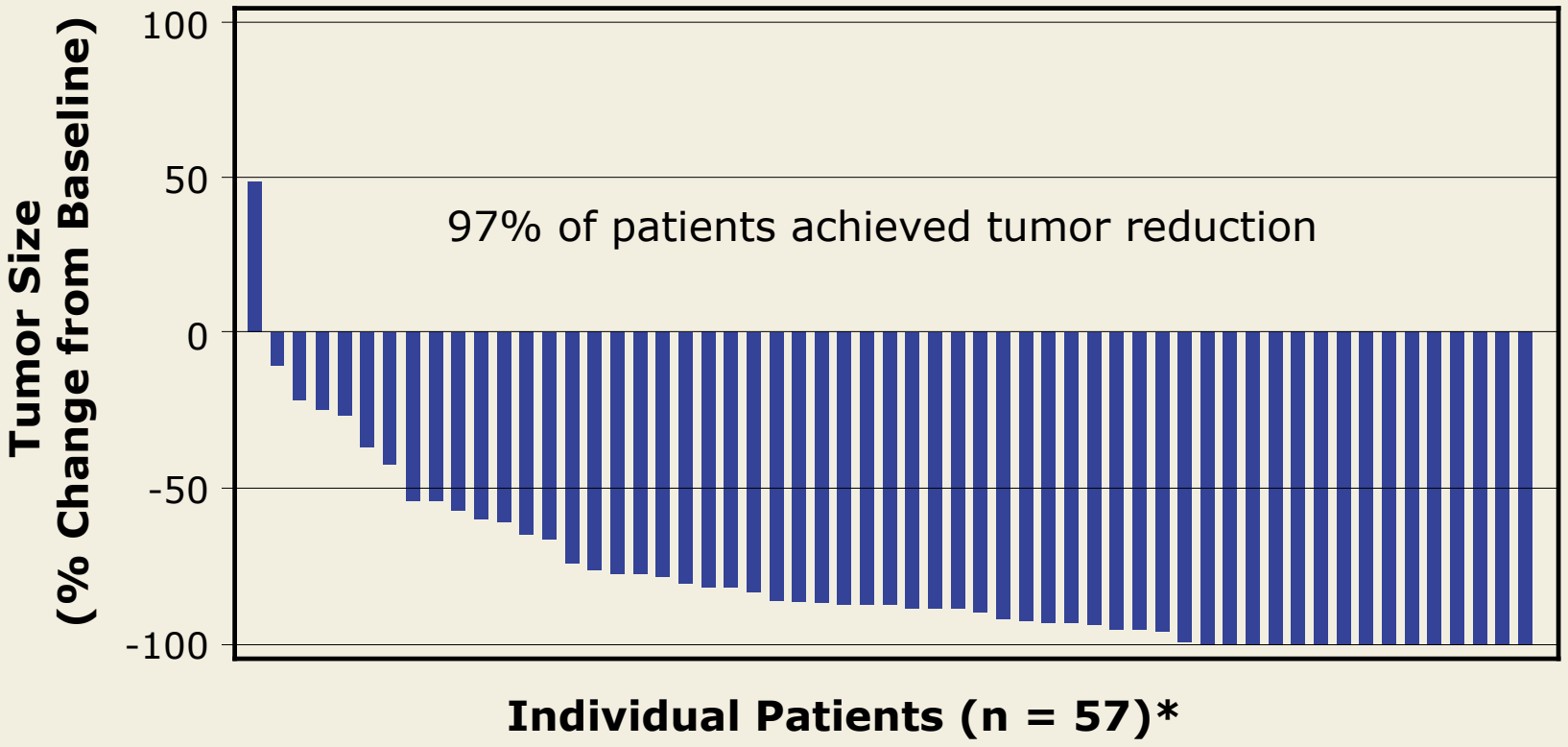
Efficacy Outcomes (n = 58)

Response	IRF	Investigator
Overall response rate Complete remission Partial remission	86% 53% 33%	81% 59% 22%
Stable disease	3%	9%
Progressive disease	5%	3%

Secondary Endpoints	IRF	Investigator
Median duration of OR	Not reached	36 weeks
Median duration of CR	Not reached	Not reached
Median PFS	Not reached	41 weeks
Median OS	Not reached	

Shustov AR et al. *Proc ASH* 2010;Abstract 961.

Maximum Tumor Reduction per IRF



* 57 of 58 patients with post-baseline CT assessments

With permission from Shustov AR et al. *Proc ASH* 2010;Abstract 961.

Select Adverse Events

Treatment-Related Adverse Events (AE)	All Grades*	Grade 3 or 4*
Nausea	38%	Not reported
Peripheral sensory neuropathy	38%	10%†
Fatigue	34%	3%
Pyrexia	33%	Not reported
Diarrhea	29%	Not reported
Rash	21%	Not reported
Neutropenia	21%	21%
Thrombocytopenia	Not reported	14%
Anemia	Not reported	7%†

*All grade AEs occurring in ≥20% of patients and Grade 3/4 AEs occurring in ≥5% of patients

† Grade 3 only

Shustov AR et al. *Proc ASH* 2010;Abstract 961.

Author Conclusions

- Remission was achieved by 86% of highly refractory systemic ALCL patients.
  - Complete remission rate: 53% (by IRF)
  - Patients achieving tumor reduction = 97%
- Complete remissions observed in ≥50% of patients with ALK-negative and ALK-positive disease.
- Brentuximab vedotin treatment is associated with a manageable adverse event profile.
- Brentuximab vedotin is a promising new agent in the management of systemic ALCL.

Shustov AR et al. *Proc ASH* 2010;Abstract 961.

Investigator comment on brentuximab vedotin (SGN-35) in relapsed or refractory systemic anaplastic large cell lymphoma (sALCL)

sALCL is one of the subtypes of peripheral T-cell lymphoma (PTCL) and constitutes about 20 percent of PTCLs. This trial essentially shows that in the relapsed/refractory setting, brentuximab as a single agent has good activity with a high response rate. A total of 58 patients received treatment, which does not appear to be a huge number, but for a subset of PTCL, it is a big number.

Activity of other single agents in relapsed T-cell lymphomas is in the range of 20 to 30 percent, so the response rates reported here are very promising in this specific subset of T-cell lymphoma. The drug might become available within the next year for relapsed disease, and ultimately people will consider incorporating brentuximab into earlier lines of therapy. Overall, I believe it is positive and optimistic.

Interview with Steven M Horwitz, MD, December 29, 2010

Efficacy of Denileukin Diftitox Retreatment in Patients with Cutaneous T-Cell Lymphoma Who Relapsed After Initial Response[1]

Identification of an Active, Well-Tolerated Dose of Pralatrexate in Patients with Relapsed or Refractory Cutaneous T-Cell Lymphoma (CTCL): Final Results of a Multicenter Dose-Finding Study (slide 8)[2]

[1]**Duvic M et al.**
Proc ASH 2010;Abstract 2863.

[2]**Horwitz SM et al.**
Proc ASH 2010;Abstract 2800.

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

Duvic M et al.

Proc ASH 2010;Abstract 2863.

Study 93-04-14
Methods and Objectives

- Study 93-04-14 was a Phase III, multicenter, open-label study that evaluated the efficacy and safety of denileukin diftitox (DD) administered to patients with cutaneous T-cell lymphoma (CTCL) who had participated in three earlier trials of DD.
  - Patients from Study 93-04-11 randomly assigned to placebo, stable or progressive disease after 8 courses
  - Patients from Study 93-04-11 randomly assigned to DD, stable disease after 8 courses
  - **Patients from Studies 92-04-01, 93-04-10 and 93-04-11 who had relapsed after an initial response to DD**
  - Patients excluded from 93-04-11 due to being CD25 assay-negative
- The current analysis is limited to the DD relapsed and retreated cohort
- **Primary objective**: Overall response rate (ORR)
- **Secondary objectives**: Progression-free survival (PFS), time to treatment failure (TTF) and safety

Duvic M et al. *Proc ASH* 2010;Abstract 2863.

Study 93-04-14 Design: Relapsed-Retreated Subgroup

Eligibility for Relapsed-Retreated Subgroup (N = 20)

- **Initial response to DD during Studies 92-04-01, 93-04-10 and 93-04-11 followed by relapse**
- **Histopathologically confirmed Stage IA-III CTCL**
- **≤3 prior treatment regimens**
- **CD25 assay-positive expression**

→ **DD, IV 18µg/kg/d on days 1-5, q3wks up to 8 courses**

Duvic M et al. *Proc ASH* 2010;Abstract 2863.

Best Tumor Response Among Relapsed-Retreated Patients

Response	All Patients (n = 20)	Disease Stage at Baseline	
		Stage ≤IIA (n = 16)	Stage ≥IIB (n = 4)
ORR CR/CCR PR	40% 10% 30%	37.5% 12.5% 25%	50% 0% 50%
ORR, exact 95% CI	19.1, 63.9	15.2, 64.6	6.8, 93.2
SD	25%	18.8%	50%
PD	35%	43.8%	0%

CR = complete response; CCR = clinical complete response; PR = partial response; SD = stable disease; PD = progressive disease

Duvic M et al. *Proc ASH* 2010;Abstract 2863.

Results Summary
Secondary Endpoints

- **PFS**
  - Median PFS = 205 days (Kaplan-Meier estimate)
  - Progression events were observed in 9/20 patients (45%), all of whom had Stage ≤IIA disease at baseline
- **TTF**
  - Median TTF = 189 days (Kaplan-Meier estimate)
  - Failure events were observed for 12/20 patients (60%)
- **Safety**
  - All 20 patients (100%) experienced ≥1 adverse event (AE) during treatment.
    - One patient (5%) had a treatment-related serious AE (pleural effusion)
  - The most common treatment-related AEs were nausea (35%), fatigue (25%), rigors (20%), headache (15%) and pyrexia (10%).
  - There were no instances of severe capillary leak syndrome or death.

Duvic M et al. *Proc ASH* 2010;Abstract 2863.

Author Conclusions

- This is the first trial of DD therapy that included patients with relapsed CTCL who were retreated with DD.
- Patients with CD25-positive CTCL who responded and then relapsed during prior DD treatment can attain durable responses after DD retreatment.
- The ORR of 40% is similar to that seen during primary DD treatment, with an estimated median duration of response of 9.8 months (data not shown).
- The ORR of 40% and comparable duration of response suggest that any presence of anti-DD neutralizing antibodies generated during prior DD exposure does not affect retreatment with DD.
- Adverse events were generally mild to moderate in severity and reversible.
- The results of this study establish that DD retreatment is safe and effective in patients with relapsed CD25-positive CTCL.

Duvic M et al. *Proc ASH* 2010;Abstract 2863.

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

Horwitz SM et al.

Proc ASH 2010;Abstract 2800.

PDX-010 Study Objectives

- To determine an effective and well tolerated dose and schedule of pralatrexate for patients with relapsed or refractory CTCL (Stage 1 objective).
- To characterize the safety profile of pralatrexate in CTCL when administered with vitamin B_{12} and folic acid.
- To evaluate safety and efficacy for additional patients at the optimal dose (Stage 2 objective).
- **Eligibility**
  - Confirmed relapsed/refractory CTCL
  - Progression or relapse after ≥ 1 systemic therapy

Horwitz SM et al. *Proc ASH* 2010;Abstract 2800.

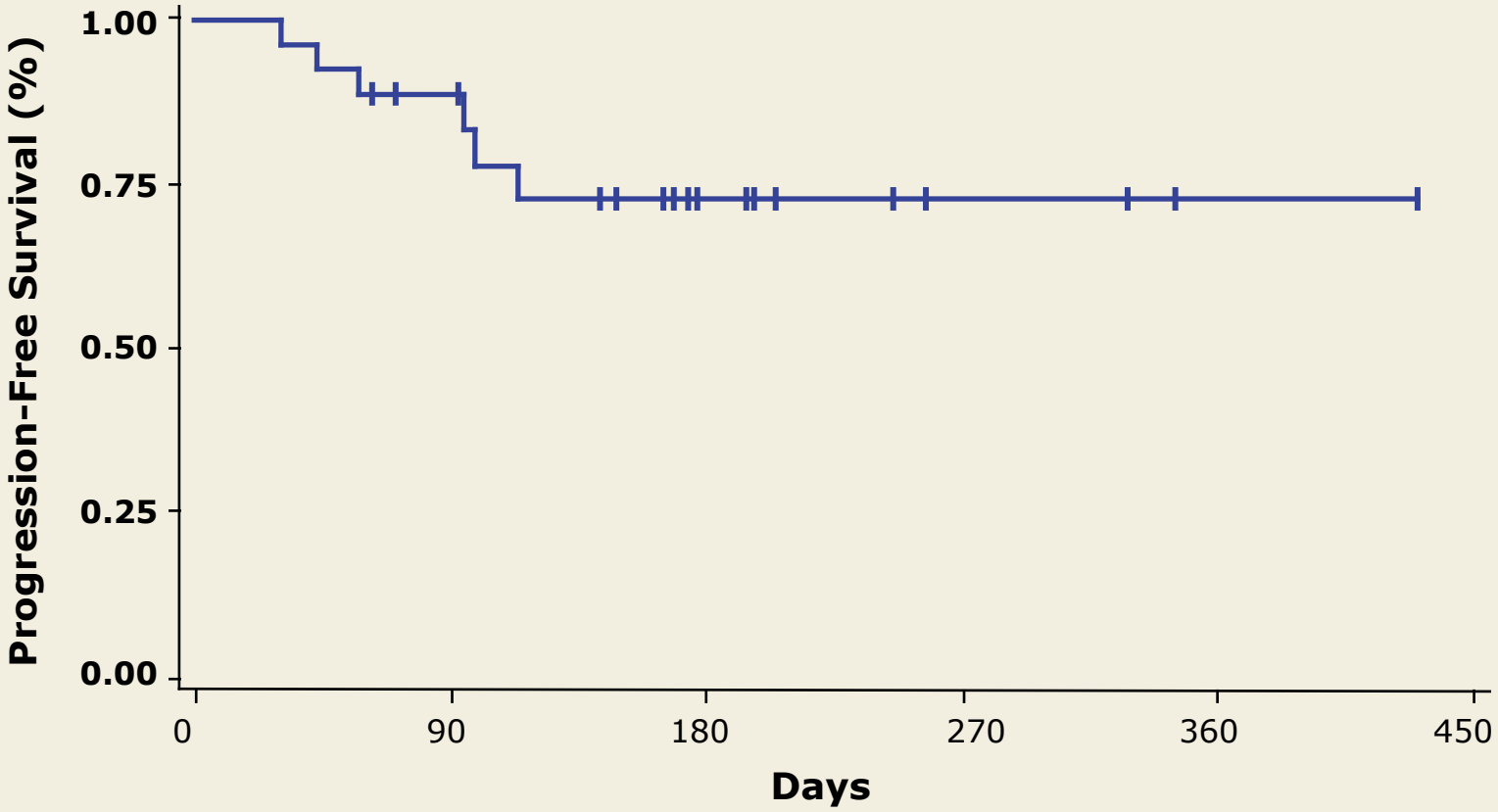
Objective Response Rates and Dose Limiting Toxicities (DLTs) in Stage 1

Cohort	Pralatrexate Dose (mg/m^2/week); Schedule	n	Patients with DLTs	Overall Response Rates (ORR)
1	30; 3/4 weeks	2	2	100%
2	20; 3/4 weeks	3	2	67%
3	20; 2/3 weeks	7	3	57%
4	15; 3/4 weeks	6	3	50%
5	15; 2/3 weeks	3	2	0%
6	10; 3/4 weeks	10	3	10%

Optimal dose and schedule selected as 15 mg/m^2 administered 3 out of 4 weeks (Cohort 4)

Horwitz SM et al. *Proc ASH* 2010;Abstract 2800.

Progression-Free Survival at Optimal Dose and Schedule: Stage 2



With permission from Horwitz SM et al. *Proc ASH* 2010;Abstract 2800.

Response Rates

	n	Response Rates
Patients on Optimal Dose and Schedule	29	45%
Patients on ≥ Optimal Dose and Schedule	41	51%
Patients on < Optimal Dose and Schedule	13	8%
All Patients	54	41%

Optimal Dose/Schedule: 15 mg/m^2 administered 3 out of 4 weeks

Horwitz SM et al. *Proc ASH* 2010;Abstract 2800.

Treatment-Related Adverse Events at Optimal Dose/Schedule

Adverse Events (AEs)	All Grades	Grade 3/4
Mucosal inflammation	48%	17%
Fatigue	38%	3%
Nausea	31%	0%
Vomiting	14%	0%
Anorexia	10%	0%
Thrombocytopenia	7%	3%

Optimal Dose/Schedule: 15 mg/m^2 administered 3 out of 4 weeks

Horwitz SM et al. *Proc ASH* 2010;Abstract 2800.

Author Conclusions

- Pralatrexate demonstrated high activity in patients with heavily pretreated relapsed/refractory CTCL.
  - ORR (at optimal dose and schedule) = 45%
  - PFS (at optimal dose and schedule) = Not reached
- Toxicity generally acceptable at the optimal dose/schedule.
  - Mucosal inflammation = 48% (primarily Grade 1/2)
  - Absence of Grade 3/4 neutropenia
  - Single event of Grade 3 thrombocytopenia
- Pralatrexate should be evaluated in earlier lines of therapy and also in combination with other therapeutics in CTCL.

Horwitz SM et al. *Proc ASH* 2010;Abstract 2800.

Investigator comments on pralatrexate and denileukin diftitox (DD) in relapsed or refractory CTCL

Our study investigated pralatrexate in a dose de-escalation design in CTCL. As long as there was some activity, we would dose reduce to the next lower level. In the first part of the study, we identified two active doses with reasonable toxicity: 15 mg/m^2 three out four weeks and 20 mg/m^2 two out of three weeks.

Because the toxicities were a little less clinically significant in the 15 mg/m^2 cohort, that was expanded in part 2. Almost no hematologic toxicity was observed with some Grade 2 or 3 mucositis in the expanded cohort. The median duration of response was not reached at the time of the presentation. Pralatrexate, at an easier dose and schedule, appears quite active in CTCL for long-term use.

Interview with Steven M Horwitz, MD, December 29, 2010

The first trials of DD didn't use steroid premedication. Consequently, a number of patients developed infusion reactions. Now when we use DD in practice, we administer steroid premedication. The incidence of infusion-related reactions has gone down significantly. We manage vascular leak with diuresis and IV fluids, if needed.

Interview with Francine Foss, MD, January 13, 2011