Final Results from a Multicenter, International, Pivotal Study of Romidepsin in Refractory Cutaneous T-Cell Lymphoma

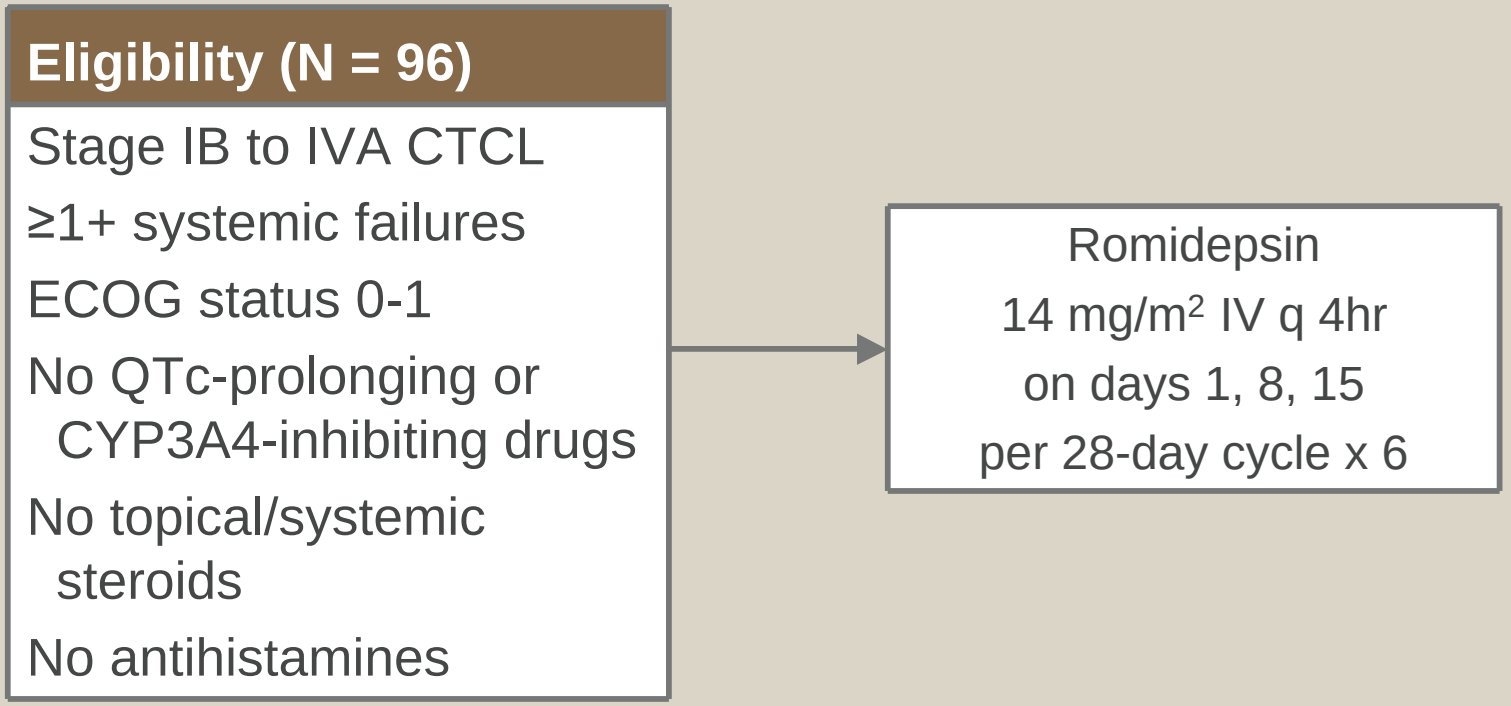
Whittaker SJ et al.
J Clin Oncol 2010;28(29):4485-91.

Introduction

- Primary cutaneous T-cell lymphoma (CTCL) is a rare class of non-Hodgkin's lymphoma that originates in the skin.
- Single-agent romidepsin induces apoptotic events in cancer cells by inhibiting histone deactylase (HDAC) enzymes.
- A Phase II trial of romidepsin monotherapy has shown clinical benefit in patients (pts) with CTCL (*JCO* 2009;27:5410).
- Current study objective:
  - Confirm the safety and efficacy of romidepsin in pts with pretreated CTCL in support of the US Food and Drug Administration approval of this agent in this patient population.

Whittaker SJ et al. *J Clin Oncol* 2010;28(29):4485-91.

Phase II Study Design



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Efficacy Data

Clinical Response Status	Romidepsin n (%)	95% CI
Overall response rate (ORR) (N = 96)	33 (34)	25 - 45
Complete response (CR)	6 (6)	2 - 13
Partial response (PR)	27 (28)	19 - 38
Median duration of response (n = 33)	15.0 mo	—
Median time to response (n = 33)	2.0 mo	—
Median time to progression (n = 33)	8.0 mo	—
Disease Status		
Stable disease	45 (47)	37 - 57
Progressive disease	10 (10)	5 - 18

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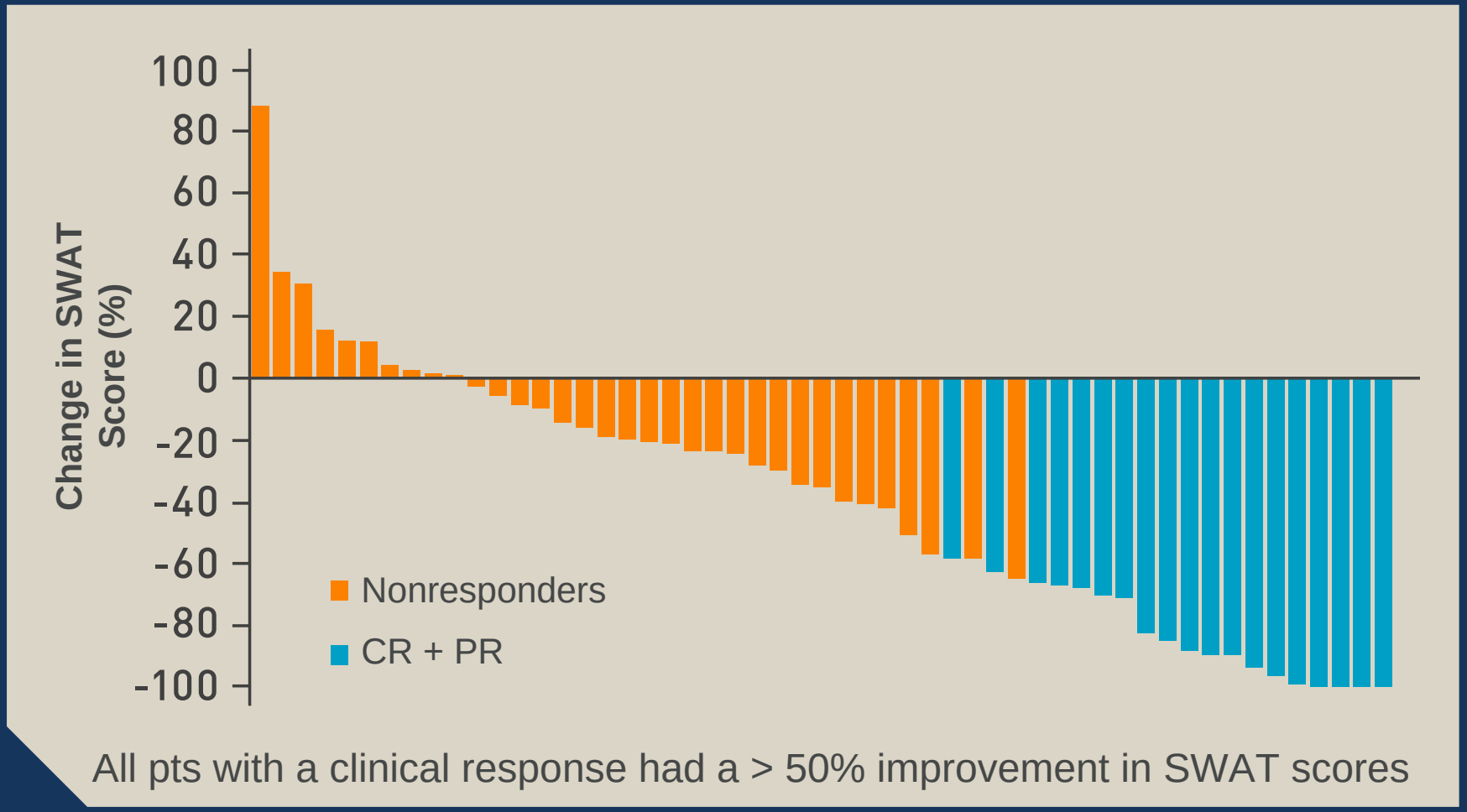
Severity-Weighted Assessment Tool (SWAT)



With permission from Whittaker SJ et al. *J Clin Oncol* 2010;28(29):4485-91.

Select Grade 3/4 Adverse Events

Adverse Event N = 96	Romidepsin n (%)
Nausea	2 (2)
Asthenic conditions*	6 (6)
Vomiting	1 (1)
Diarrhea	1 (1)
Anemia	2 (2)
Tumor lysis syndrome	2 (2)

* Includes asthenia, fatigue, lethargy and malaise

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Conclusions

- Single-agent romidepsin is effective for the treatment of previously treated CTCL, including advanced disease (≥Stage IIB):
  - ORR: 34% and 38%, respectively
  - CR: 6% and 7%, respectively
- Assessment of the disease sites indicate that romidepsin has clinical benefit (RECIST and flow cytometry data are not shown).
- The results of this Phase II trial are consistent with the Phase II NCI-sponsored trial.
  - Subsequently, both of these studies have led to the FDA approval in the US on November 2009 for the use of romidepsin in patients with CTCL.

Whittaker SJ et al. *J Clin Oncol* 2010;28(29):4485-91.

Faculty Comments

DR FOSS: Romidepsin has now been approved for CTCL and may also be approved soon for PTCL. The most common adverse events include fatigue and thrombocytopenia, shown as transient with a quick recovery. No direct or long-term effects on bone marrow stem cells are apparent.

DR VOSE: Romidepsin is a potent HDAC inhibitor and has been studied in CTCL and PTCL. It resulted in an ORR of approximately 35 percent. The potential for QTc prolongation has been observed with all HDAC inhibitors, but at this time no serious cause for concern about this issue is apparent. The investigators also evaluated hematological toxicities and found a quick reversibility of and recovery from thrombocytopenia.

Pralatrexate is Active in Cutaneous T-Cell Lymphoma (CTCL): Results of a Multicenter, Dose-Finding Trial

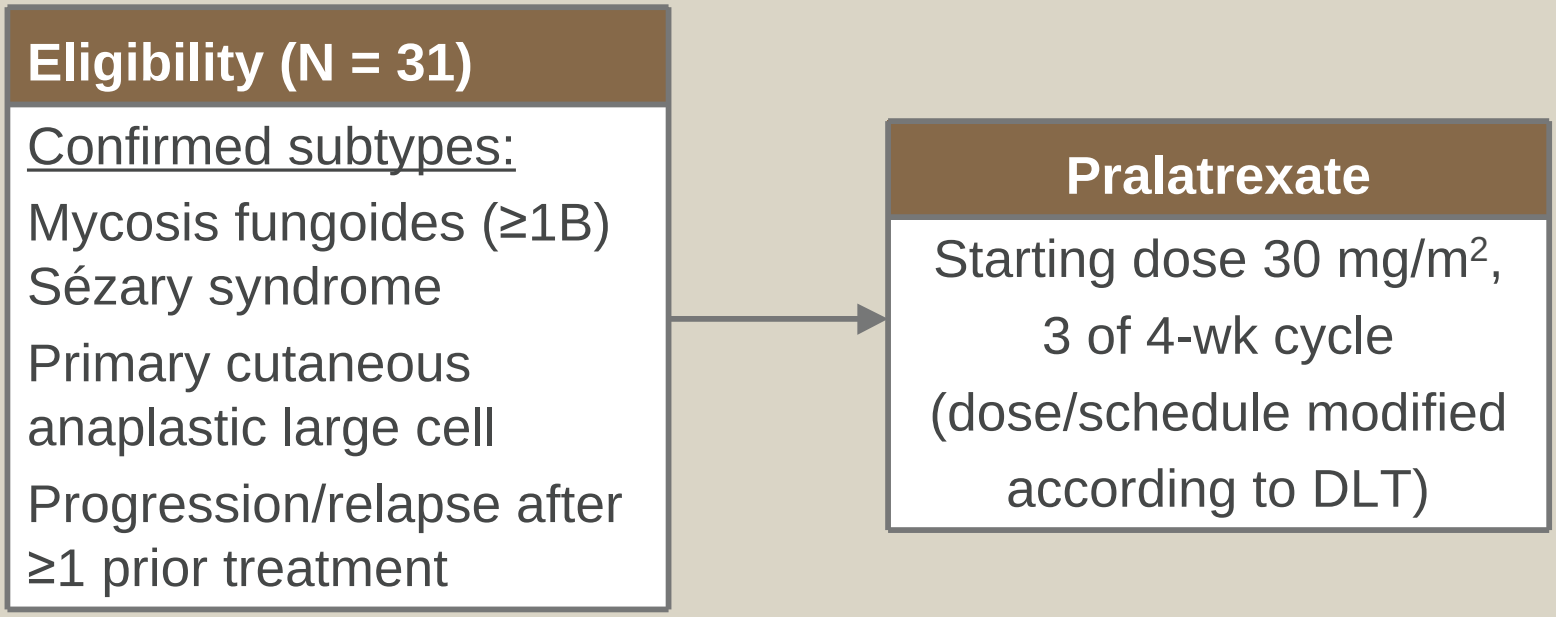
Horwitz SM et al.
Proc ASH 2009;Abstract 919.

Introduction

- CTCL is an indolent, clinically heterogeneous group of non-Hodgkin's lymphomas that develop in the skin.
- The most common subtypes are mycosis fungoides and Sézary syndrome and are most often managed with maintenance treatment.
- Pralatrexate is an antifolate recently approved for PTCL and acts by selectively entering cancer cells that express the reduced folate carrier type-1 protein.
- Current study objectives:
  - Assess the effective, well-tolerated dose and schedule of pralatrexate in patients with relapsed or refractory CTCL.
  - Evaluate the safety and efficacy of pralatrexate at the optimal dose for additional patients with relapsed or refractory CTCL.

Horwitz SM et al. *Proc ASH* 2009;Abstract 919.

PDX-010: Study Design



- Protocol-defined dose-limiting toxicities (DLT) leading to dose reduction: ≥Grade 3 neutropenia, ≥Grade 2 thrombocytopenia (or any grade with clinically significant bleeding), febrile neutropenia, ≥Grade 2 stomatitis, any toxicity leading to dose reduction or omission in cycle 1
- All patients received vitamin B_{12} 1 mg IM q 8-10 wk and folic acid 1 mg po qd.

Horwitz SM et al. *Proc ASH* 2009;Abstract 919.

Dose-Limiting Toxicities by Dose Cohort

Cohort	Pralatrexate (mg/m^2), Schedule (wk/wk cycle)	N	DLTs N (toxicity/grade)
1	30 mg/m^2, 3/4 weeks	2	2 (Anorexia/2, Weakness/3)
2	20 mg/m^2, 3/4 weeks	3	2 (Stomatitis/2)
3	20 mg/m^2, 2/3 weeks	7	3 (Stomatitis/2-3, LFT/3)
4	15 mg/m^2, 3/4 weeks	6	3 (Stomatitis/2, Fatigue/2)
5	15 mg/m^2, 2/3 weeks	3	2 (Stomatitis/2, Dehydration/2)
6	10 mg/m^2, 3/4 weeks	10	3 (Thrombocytopenia + Neutropenia/3, Skin Lesion/3, Zoster/3)

Horwitz SM et al. *Proc ASH* 2009;Abstract 919.

Response Status

Cohort	Response Rate	Response Type	
#	N (%)	Partial Response	Complete Response
1	2 (100)	2	0
2	2 (67)	2	0
3	4 (57)	3	1
4	3 (50)	3	0
5	0	0	0
6	1 (10)	0	1

Overall response rate: 61% for doses ≥15 mg/m^2 weekly for 3/4 wk

Horwitz SM et al. *Proc ASH* 2009;Abstract 919.

Select Adverse Events

Adverse Event (All Grades)	All Cohorts (n = 31)	Pralatrexate 15 mg/m^2 qwk 3/4 wk (n = 6)
Stomatitis	18 (58%)	4 (67%)
Nausea	16 (52%)	4 (67%)
Fatigue	15 (48%)	4 (67%)
Pyrexia	9 (29%)	3 (50%)
Vomiting	8 (26%)	3 (50%)
Neutropenia	1 (3%)	0
Thrombocytopenia	1 (3%)	0

Horwitz SM et al. *Proc ASH* 2009;Abstract 919.

Conclusions

- Pralatrexate shows impressive clinical activity in patients with relapsed or refractory CTCL at a lower dose intensity than in studies for PTCL.
- The optimal tolerable starting dose and schedule for pralatrexate in patients with CTCL is 15 mg/m^2 qwk for 3/4 wk:
  - Overall response rate: 61% for doses ≥15 mg/m^2
  - Dose escalation was allowed in patients with stable disease or who showed a progressive response.
  - Expansion cohort is enrolling 20 additional patients at this dose and schedule (NCT00554827).

Horwitz SM et al. *Proc ASH* 2009;Abstract 919; www.clinicaltrials.gov.

Faculty Comments

DR VOSE: Pralatrexate is a folate inhibitor that has been mostly studied in PTCL. This study examined the activity of pralatrexate in refractory CTCL and showed activity without unexpected toxicity. This is a potential agent in CTCL also and is continuing to be studied in combinations as well.

DR FOSS: This was a dose and schedule determination study of pralatrexate in patients with refractory CTCL. The study demonstrates good activity in these patients, with an overall response rate of 61 percent for doses greater than or equal to 15 mg/m^2 for three of four weeks. The toxicity profile is similar to what has been seen in patients with PTCL. The dose and schedule moving forward in Phase II is 15 mg/m^2 weekly for three out of four weeks.