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A SPECIAL MEETING REVIEW EDITION

Highlights in T-Cell Lymphoma From the 2013 American Society of Hematology Annual Meeting and Exposition

A Review of Selected Presentations From the 2013 American Society of Hematology Annual Meeting and Exposition • December 7-10, 2013 • New Orleans, Louisiana

Special Reporting on:

- A Phase II Study of Cyclophosphamide, Etoposide, Vincristine and Prednisone (CEOP) Alternating With Pralatrexate (P) as Front Line Therapy For Patients With Peripheral T-Cell Lymphoma (PTCL): Preliminary Results From the T-Cell Consortium Trial
- Analysis of Peripheral T-Cell Lymphoma (PTCL) Subtype by Race and Geography Using the Comprehensive Oncology Measures for Peripheral T-Cell Lymphoma Treatment (COMPLETE) Dataset
- The Combination of Hypomethylating Agents and Histone Deacetylase Inhibitors (HDACi) Are Synergistically Cytotoxic and Reverse the Malignant Phenotype in Preclinical Models of T-Cell Lymphoma
- Phase II Trial of Brentuximab Vedotin For CD30+ Cutaneous T-Cell Lymphomas and Lymphoproliferative Disorders
- Preliminary Results of a Phase II Study of Single Agent Bay 80-6946, a Novel PI3K Inhibitor, in Patients With Relapsed/Refractory, Indolent or Aggressive Lymphoma
- Romidepsin Is Effective and Well-Tolerated in Patients ≥60 Years Old With Relapsed or Refractory Peripheral T-Cell Lymphoma (PTCL): Analysis From Phase 2 Trials

PLUS Meeting Abstract Summaries

With Expert Commentary by:

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When PTCL Returns…

BE READ

WITH FOLO

(pralatrexate

Important Safety Information

Warnings and Precautions

- FOLOTYN may suppress bone marrow function, manifested by thrombocytopenia, neutropenia, and anemia. Monitor blood counts and omit and/or reduce dose for hematologic toxicities.
- Mucositis may occur. Monitor at least weekly. If ≥Grade 2 mucositis is observed, omit and/or reduce dose. Patients should be instructed to take folic acid and receive vitamin B_{12} to potentially reduce treatment-related hematological toxicity and mucositis.
- Dermatologic reactions, including fatal reactions, have occurred and may be progressive and increase in severity with further treatment. Patients with dermatologic reactions should be monitored closely, and omit, and/or reduce dose or discontinue FOLOTYN.
- Tumor lysis syndrome may occur. Monitor patients and treat promptly.
- FOLOTYN can cause hepatic toxicity and liver function test abnormalities. Monitor liver function tests and if abnormalities are ≥Grade 3, omit until recovery then reduce dose or discontinue FOLOTYN as required.
- Patients with moderate to severe renal function impairment may be at greater risk for increased exposure and toxicity. Monitor patients for renal function and systemic toxicity and adjust dosing accordingly. Avoid FOLOTYN use in patients with end stage renal disease including those undergoing dialysis unless the potential benefit justifies the potential risk.
- FOLOTYN can cause fetal harm. Women should avoid becoming pregnant while being treated with FOLOTYN and pregnant women should be informed of the potential harm to the fetus.

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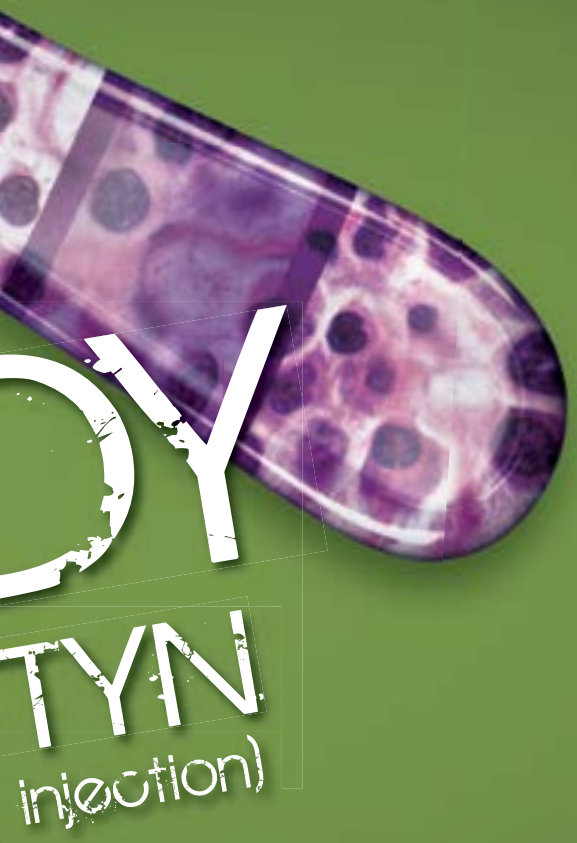
Please see accompanying brief

FOLOTYN is indicated for the treatment of patients with relapsed or refractory peripheral T-cell lymphoma. The indication for FOLOTYN is based on overall response rate. Clinical benefit such as improvement in progression-free survival or overall survival has not been demonstrated.



Demonstrated response in relapsed or refractory PTCL[1]

27% overall response rate (CR+CRu+PR) by independent central review (95% CI, 19-36)*

Of the responders,

66% responded within Cycle 1*

—*Median time to first response was 45 days (range=37-349 days)*

9.4-month median duration of response by central review (range=1-503 days)*

—*12% (95% CI, 7-20) of patients had responses lasting ≥14 weeks (range=98-503 days)*

Demonstrated response in **PROPEL**—the first large, prospective, single-arm, open-label clinical trial in PTCL

*Per independent central review

Reference: 1. FOLOTYN Prescribing Information. Allos Therapeutics, Inc., 2012.

Adverse Reactions

- The most common adverse reactions were mucositis (70%), thrombocytopenia (41%), nausea (40%), and fatigue (36%). The most common serious adverse events were pyrexia, mucositis, sepsis, febrile neutropenia, dehydration, dyspnea, and thrombocytopenia.

Drug Interactions

- Co-administration with probenecid or other drugs that may affect relevant transporter systems (eg, NSAIDs), requires close monitoring for signs of systemic toxicity.

Use in Specific Patient Populations

- Nursing mothers should be advised to discontinue nursing or the drug, taking into consideration the importance of the drug to the mother.
- Approximately one third of the administered dose of FOLOTYN is cleared by the kidneys. FOLOTYN has not been studied in patients with renal impairment.

Please see FOLOTYN Full Prescribing Information.

FOLOTYN® (pralatrexate injection)

summary of Prescribing Information.

www.FOLOTYN.com

Brief summary of Full Prescribing Information for FOLOTYN® (pralatrexate injection)—Please consult Full Prescribing Information.

INDICATIONS AND USAGE

FOLOTYN is indicated for the treatment of patients with relapsed or refractory peripheral T-cell lymphoma (PTCL). This indication is based on overall response rate. Clinical benefit such as improvement in progression-free survival or overall survival has not been demonstrated.

WARNINGS AND PRECAUTIONS

Bone Marrow Suppression

FOLOTYN can cause bone marrow suppression, manifested by thrombocytopenia, neutropenia, and/or anemia. Monitor complete blood counts and omit and/or reduce the dose based on ANC and platelet count prior to each dose as outlined in Table 2. Administer vitamin B_{12} and instruct patients to take folic acid to reduce the risk of treatment-related hematological toxicity.

Mucositis

FOLOTYN can cause mucositis. Monitor for mucositis weekly and if ≥ Grade 2 mucositis is observed, omit and/or reduce the dose as outlined in Table 1. Administer vitamin B_{12} and instruct patients to take folic acid to reduce the risk of mucositis.

Dermatologic Reactions

FOLOTYN can cause severe dermatologic reactions, which may result in death. These dermatologic reactions have been reported in clinical studies (14/663 patients [2.1%]) and post marketing experience, and have included skin exfoliation, ulceration, and toxic epidermal necrolysis (TEN). They may be progressive and increase in severity with further treatment, and may involve skin and subcutaneous sites of known lymphoma. Monitor patients with dermatologic reactions closely, and if severe, withhold or discontinue FOLOTYN.

Tumor Lysis Syndrome

FOLOTYN can cause tumor lysis syndrome (TLS). Monitor patients who are at increased risk of TLS and treat promptly.

Hepatic Toxicity

FOLOTYN can cause hepatic toxicity and liver function test abnormalities. Persistent liver function test abnormalities may be indicators of hepatic toxicity and require dose modification or discontinuation. Monitor liver function tests. Omit dose until recovery, adjust or discontinue therapy based on the severity of the hepatic toxicity.

Risk of Increased Toxicity in the Presence of Impaired Renal Function

Patients with moderate to severe renal function impairment may be at greater risk for increased exposure and toxicity. Monitor patients for renal function and systemic toxicity and adjust dosing accordingly. Serious adverse drug reactions including toxic epidermal necrolysis and mucositis were reported in patients with end stage renal disease (ESRD) undergoing dialysis who were administered FOLOTYN therapy. Avoid FOLOTYN use in patients with ESRD including those undergoing dialysis unless the potential benefit justifies the potential risk.

Embryo-Fetal Toxicity

FOLOTYN can cause fetal harm when administered to a pregnant woman. FOLOTYN was embryotoxic and fetotoxic in rats and rabbits. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

ADVERSE REACTIONS

The following serious adverse reactions are described below and elsewhere in the labeling: Bone Marrow Suppression, Mucositis, Dermatologic Reactions, Tumor Lysis Syndrome, Hepatic Toxicity.

The most common adverse reactions observed in patients with peripheral t-cell lymphoma (PTCL) treated with FOLOTYN were mucositis, thrombocytopenia, nausea, and fatigue.

Clinical Trials Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

The safety of FOLOTYN was evaluated in 111 PTCL patients in a single-arm clinical study in which patients received a starting dose of 30 mg/m^2 once weekly for 6 weeks in 7-week cycles. The median duration of treatment was 70 days (range 1-540 days).

Most Frequent Adverse Reactions

Table 4 summarizes the most frequent adverse reactions, regardless of causality, using the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI CTCAE, version 3.0).

Table 4 Adverse Reactions Occurring in PTCL Patients (Incidence ≥10% of patients)

	N=111					
	Total		Grade 3		Grade 4	
Preferred Term	**N**	**%**	**N**	**%**	**N**	**%**
Any Adverse Event	111	100	48	43	34	31
Mucositis[a]	78	70	19	17	4	4
Thrombocytopenia[b]	45	41	15	14	21	19[b]
Nausea	44	40	4	4	0	0
Fatigue	40	36	5	5	2	2
Anemia	38	34	17	15	2	2
Constipation	37	33	0	0	0	0
Pyrexia	36	32	1	1	1	1
Edema	33	30	1	1	0	0
Cough	31	28	1	1	0	0
Epistaxis	29	26	0	0	0	0
Vomiting	28	25	2	2	0	0
Neutropenia	27	24	14	13	8	7
Diarrhea	23	21	2	2	0	0
Dyspnea	21	19	8	7	0	0
Anorexia	17	15	3	3	0	0
Hypokalemia	17	15	4	4	1	1
Rash	17	15	0	0	0	0
Pruritus	16	14	2	2	0	0
Pharyngolaryngeal pain	15	14	1	1	0	0
Liver function test abnormal[c]	14	13	6	5	0	0
Abdominal pain	13	12	4	4	0	0
Pain in extremity	13	12	0	0	0	0
Back pain	12	11	3	3	0	0
Leukopenia	12	11	3	3	4	4
Night sweats	12	11	0	0	0	0
Asthenia	11	10	1	1	0	0
Tachycardia	11	10	0	0	0	0
Upper respiratory tract infection	11	10	1	1	0	0

[a] Stomatitis or mucosal inflammation of the gastrointestinal and genitourinary tracts
[b] Five patients with platelets <10,000/mcL
[c] Alanine aminotransferase, aspartate aminotransferase, and transaminases increased

Serious Adverse Events

Forty-four percent of patients (n=49) experienced a serious adverse event while on study or within 30 days after their last dose of FOLOTYN. The most common serious adverse events (>3%), regardless of causality, were pyrexia, mucositis, sepsis, febrile neutropenia, dehydration, dyspnea, and thrombocytopenia. One death from cardiopulmonary arrest in a patient with mucositis and febrile neutropenia was reported in this trial. Deaths from mucositis, febrile neutropenia, sepsis, and pancytopenia occurred in 1.2% of patients treated on all FOLOTYN trials at doses ranging from 30 to 325 mg/m^2.

Discontinuations

Twenty-three percent of patients (n=25) discontinued treatment with FOLOTYN due to adverse reactions. The adverse reactions reported most frequently as the reason for discontinuation of treatment were mucositis (6%, n=7) and thrombocytopenia (5%, n=5).

Dose Modifications

The target dose of FOLOTYN was 30 mg/m^2 once weekly for 6 weeks in 7-week cycles. The majority of patients (69%, n=77) remained at the target dose for the duration of treatment. Overall, 85% of scheduled doses were administered.

Post Marketing Experience

Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Dermatologic Reactions

Toxic epidermal necrolysis, sometimes fatal, has been reported during post-marketing use of FOLOTYN. Fatal cases have been reported following the first dose of FOLOTYN, including when a reduced dose is given, and have been reported in patients with end-stage renal disease undergoing dialysis.

DRUG INTERACTIONS

No formal clinical assessments of pharmacokinetic drug-drug interactions between FOLOTYN and other drugs have been conducted. The effect of co-administration of the uricosuric drug probenecid (an inhibitor of multiple transporter systems including the multidrug resistance-associated protein 2 (MRP2) efflux transporter) on pralatrexate pharmacokinetics was investigated in a Phase 1 clinical study. Co-administration of increasing doses of probenecid resulted in delayed clearance of pralatrexate and a commensurate increase in exposure.

When administering FOLOTYN to patients receiving probenecid or other drugs that may affect relevant transporter systems (eg, NSAIDs), monitor patients closely for signs of systemic toxicity due to increased drug exposure.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category D

Embryo-Fetal Toxicity (see Warnings and Precautions)

FOLOTYN can cause fetal harm when administered to a pregnant woman. Pralatrexate was embryotoxic and fetotoxic in rats at IV doses of 0.06 mg/kg/day (0.36 mg/m^2/day or about 1.2% of the clinical dose on a mg/m^2 basis) given on gestation days 7 through 20. Treatment with pralatrexate caused a dose-dependent decrease in fetal viability manifested as an increase in late, early, and total resorptions. There was also a dose-dependent increase in post-implantation loss. In rabbits, IV doses of 0.03 mg/kg/day (0.36 mg/m^2/day) or greater given on gestation days 8 through 21 also caused abortion and fetal lethality. This toxicity manifested as early and total resorptions, post-implantation loss, and a decrease in the total number of live fetuses. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Nursing Mothers

It is not known whether pralatrexate is excreted in human milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from this drug, a decision should be made whether to discontinue nursing or to discontinue FOLOTYN, taking into account the importance of FOLOTYN to the mother.

Pediatric Use

Pediatric patients were not included in clinical studies with FOLOTYN. The safety and effectiveness of FOLOTYN in pediatric patients have not been established.

Geriatric Use

In the PTCL efficacy study, 36% of patients (n=40) were 65 years of age and over. No overall differences in efficacy and safety were observed in patients based on age (<65 years compared with ≥65 years).

Due to the contribution of renal excretion to overall clearance of pralatrexate (approximately 34%), age related decline in renal function may lead to a reduction in clearance and a commensurate increase in plasma exposure. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. Since elderly patients may be at higher risk, monitor more closely. Omit dose and subsequently adjust or discontinue therapy for exposure related toxicity.

Hepatic Impairment

The safety, efficacy and pharmacokinetics of FOLOTYN have not been evaluated in patients with hepatic impairment. Patients with the following laboratory values were excluded from the pralatrexate lymphoma clinical trials: total bilirubin > 1.5 mg/dL; aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 2.5 × upper limit of normal (ULN); and AST or ALT > 5 × ULN if documented hepatic involvement with lymphoma. Treatment with FOLOTYN can cause hepatic toxicity and liver function test abnormalities (*see Dosage and Administration and Warnings and Precautions*).

Renal Impairment

The safety, efficacy and pharmacokinetics of FOLOTYN have not been evaluated in patients with renal impairment. The risk for toxicity may be greater when administering FOLOTYN to patients with moderate-to-severe impairment due to the contribution of renal excretion (approximately 34%) to the overall clearance of pralatrexate. Serious adverse drug reactions, including TEN and mucositis have been reported in patients with ESRD undergoing dialysis. Monitor patients for renal function and for systemic toxicity due to increased drug exposure and adjust dosing accordingly. Avoid the use of FOLOTYN in patients with ESRD undergoing dialysis unless the potential benefit justifies the potential risk.

OVERDOSAGE

No specific information is available on the treatment of overdosage of FOLOTYN. If an overdose occurs, general supportive measures should be instituted as deemed necessary by the treating physician. Based on FOLOTYN's mechanism of action, consider the prompt administration of leucovorin.

PATIENT COUNSELING INFORMATION

See FDA-approved Patient Package Insert.

Patients should be instructed to read the Patient Package Insert carefully.

DOSAGE AND ADMINISTRATION

Pretreatment Vitamin Supplementation

Folic Acid: Patients should take folic acid 1.0-1.25 mg orally once daily beginning 10 days before the first dose of FOLOTYN. Continue folic acid during the full course of therapy and for 30 days after the last dose of FOLOTYN.

Vitamin B_{12}: Administer vitamin B_{12} 1 mg intramuscularly within 10 weeks prior to the first dose of FOLOTYN and every 8-10 weeks thereafter. Subsequent vitamin B_{12} injections may be given the same day as treatment with FOLOTYN.

Dosing and Administration

The recommended dose of FOLOTYN is 30 mg/m^2 administered as an intravenous (IV) push over 3-5 minutes via the side port of a free-flowing 0.9% Sodium Chloride Injection, USP IV line once weekly for 6 weeks in 7-week cycles until progressive disease or unacceptable toxicity.

FOLOTYN is a clear, yellow solution. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use any vials exhibiting particulate matter or discoloration.

Monitoring and Dose Modifications

Management of severe or intolerable adverse reactions may require dose omission, reduction, interruption, or discontinuation of FOLOTYN therapy.

Monitoring

Monitor complete blood cell counts and severity of mucositis at baseline and weekly. Perform serum chemistry tests, including renal and hepatic function, prior to the start of the first and fourth dose of each cycle.

Dose Modification Recommendations

Prior to administering any dose of FOLOTYN:

- Mucositis should be ≤Grade 1.
- Platelet count should be ≥100,000/mcL for first dose and ≥50,000/mcL for all subsequent doses.
- Absolute neutrophil count (ANC) should be ≥1,000/mcL.

Doses may be omitted or reduced based on patient tolerance. Omitted doses will not be made up at the end of the cycle; once a dose reduction occurs for toxicity, do not re-escalate. For dose modifications and omissions, use the guidelines in Tables 1, 2, and 3.

Table 1 FOLOTYN Dose Modifications for Mucositis

Mucositis Grade[a] on Day of Treatment	Action	Dose upon Recovery to ≤Grade 1
Grade 2	Omit dose	Continue prior dose
Grade 2 recurrence	Omit dose	20 mg/m^2
Grade 3	Omit dose	20 mg/m^2
Grade 4	Stop therapy	

[a] Per National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI CTCAE, Version 3.0)

Table 2 FOLOTYN Dose Modifications for Hematologic Toxicities

Blood Count on Day of Treatment	Duration of Toxicity	Action	Dose upon Restart
Platelet <50,000/mcL	1 week	Omit dose	Continue prior dose
	2 weeks	Omit dose	20 mg/m^2
	3 weeks	Stop therapy	
ANC 500-1,000/mcL and no fever	1 week	Omit dose	Continue prior dose
ANC 500-1,000/mcL with fever or ANC <500/mcL	1 week	Omit dose, give G-CSF or GM-CSF support	Continue prior dose with G-CSF or GM-CSF support
	2 weeks or recurrence	Omit dose, give G-CSF or GM-CSF support	20 mg/m^2 with G-CSF or GM-CSF support
	3 weeks or 2nd recurrence	Stop therapy	

G-CSF=granulocyte colony-stimulating factor; GM-CSF=granulocyte macrophage colony-stimulating factor

Table 3 FOLOTYN Dose Modifications for All Other Treatment-related Toxicities

Toxicity Grade[a] on Day of Treatment	Action	Dose upon Recovery to ≤Grade 2
Grade 3	Omit dose	20 mg/m^2
Grade 4	Stop therapy	

[a] Per National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI CTCAE, Version 3.0)

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Table of Contents

A Phase II Study of Cyclophosphamide, Etoposide, Vincristine and Prednisone (CEOP) Alternating With Pralatrexate (P) as Front Line Therapy For Patients With Peripheral T-Cell Lymphoma (PTCL): Preliminary Results From the T-Cell Consortium Trial

Delineating optimal therapy for patients with peripheral T-cell lymphoma (PTCL) remains a challenge. Most PTCL subtypes, with the exception of anaplastic large cell lymphoma (ALCL), are associated with low response rates and short duration of response with conventional anthracycline-containing chemotherapy regimens, including cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP).[1] Some studies suggest that incorporating etoposide into the CHOP regimen may improve 3-year event-free survival and overall survival.[2] In addition, alternatives to conventional CHOP, such as the folate inhibitor pralatrexate, have demonstrated improvements in overall response rate (ORR) in relapsed or refractory PTCL.[3]

The present study of patients with PTCL assessed the safety and efficacy of replacing the anthracycline with etoposide in CHOP, and alternating treatment with pralatrexate.[4] Dr Ranjana Advani presented preliminary results from this phase 2 trial from the T-Cell Consortium. The study enrolled adult patients with stage 2 to stage 4 PTCL. Subtypes included PTCL not otherwise specified (PTCL-NOS), angioimmunoblastic T-cell lymphoma, and ALCL (patients who were positive for anaplastic lymphoma kinase [*ALK*] were enrolled only if their International Prognostic Index [IPI] was at least 3). Patients had not received prior treatment, and they had adequate end organ function. Treatment cycle A (COEP) consisted of cyclophospha-

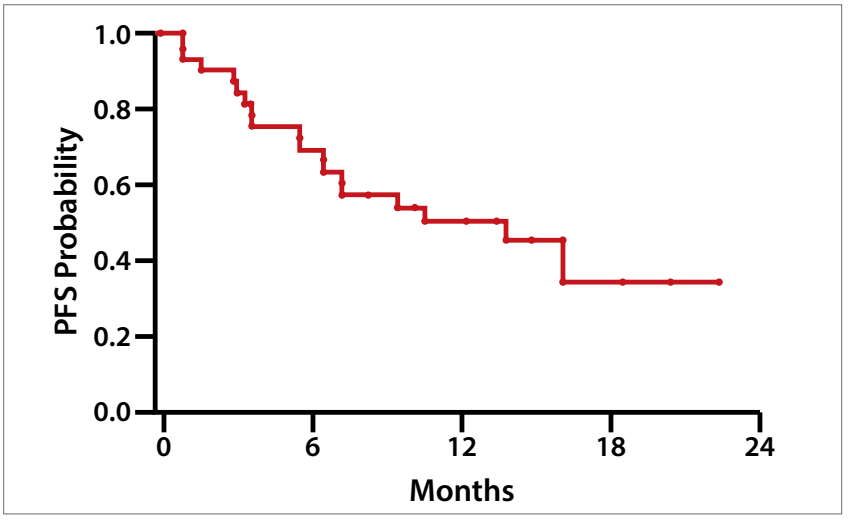

Figure 1. PFS in a phase 2 trial of cyclophosphamide, etoposide, vincristine, and prednisone alternating with pralatrexate as frontline therapy in peripheral T-cell lymphoma. PFS, progression-free survival. Adapted from Advani R et al. ASH abstract 3044. *Blood*. 2013;122(21 suppl).[4]

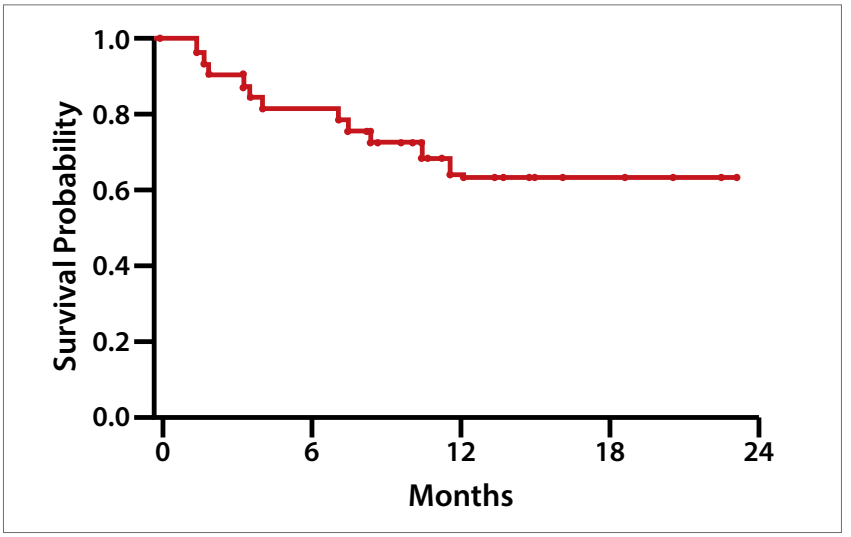

Figure 2. Overall survival in a phase 2 trial of cyclophosphamide, etoposide, vincristine, and prednisone alternating with pralatrexate as frontline therapy in peripheral T-cell lymphoma. Adapted from Advani R et al. ASH abstract 3044. *Blood*. 2013;122(21 suppl).[4]

mide (750 mg/m^2 intravenous [IV] on day 1), etoposide (100 mg/m^2 IV on days 1-3), vincristine (2 g IV on day 1), and prednisone (100 mg/day × 5). This regimen was alternated with cycle B, which consisted of pralatrexate (30 mg/m^2 IV on days 15, 22, and 29) plus vitamin B_{12} and folate supplementation; growth factor support was also used. Patients were assessed for response after cycles 2B, 4B, and 6B. Patients who achieved remission were eligible for autologous stem cell transplantation (ASCT) after cycle 4B. The primary endpoint of the study was an improvement in complete response (CR) from 40% to 63%. Additional endpoints included event-free survival, overall survival, and toxicity.

There were 33 evaluable patients in the study (median age, 62 years; 24 were male). Patients received a median of 4 cycles of treatment (range, 1-6), with a median follow-up of 13 months. The most common grade 3 adverse events (AEs) were anemia (n=8), mucositis (n=6), and decreased white blood cell count (n=6). The most common grade 4 AEs were decreased neutrophil count (n=6), sepsis (n=5), and respiratory failure (n=4). There were 11 deaths during the study, from progressive disease (n=5), sepsis (n=3), renal failure (n=1), cardiac failure (n=1), and subdural trauma (n=1).

ORR was 70% (n=23 patients): 17 patients achieved a CR (52%), 6 patients achieved a partial response (18%), 8 patients had progressive disease (24%), and 2 patients had stable disease (6%). The estimated 1-year progression-free survival (PFS) and 2-year PFS were 50% and 34%, respectively (Figure 1), and the estimated rate of 1-year and 2-year overall survival was 64% (Figure 2). There were 15 patients (45%) who went on to ASCT. When patients were stratified according to risk factors, a better PFS was associated with younger age (<60 years), a low IPI score, a CR, and consolidation with ASCT. A better overall survival was associated with lack of B symptoms, a low IPI score, a CR, and consolidation with ASCT. Although the prespecified primary endpoint goal was not met, the investigators noted that the CR was high enough to warrant further investigation. In addition, longer follow-up is needed to evaluate event-free survival and overall survival.

ABSTRACT SUMMARY A Single Center Experience With Pralatrexate Alone or in Combination With Bexarotene: Long Term Responses on Advanced Stage Relapsed/Refractory Cutaneous T-Cell Lymphoma

In older patients with advanced-stage relapsed or refractory CTCL, pralatrexate alone or in combination with bexarotene was well tolerated and had long-term durable responses in phase 1/2 dose-finding trials, such as PDX-010 (ASH 2010, Abstract 2800) and PDX-018 (ClinicalTrials.gov Identifier: NCT01134341). Intravenous pralatrexate (15 mg/m^2 weekly for 3 of 4 weeks in the cycle) was administered alone or with oral bexarotene (150 mg/m^2). Patients received levothyroxine, atorvastatin, bimonthly vitamin B_{12}, and daily folic acid supplementation. This in-print only abstract provided an analysis of the 26 patients from the MD Anderson Cancer Center who were enrolled in these 2 trials (Abstract 5113). The ORR for patients in both trials was 42%. The ORR was higher for patients in the pralatrexate plus bexarotene treatment group compared with patients in the trial of pralatrexate alone (50% [7/14 patients] vs 30% [4/12 patients]). Three patients receiving pralatrexate alone and 7 patients receiving pralatrexate plus bexarotene received more than 9 cycles of treatment. For these 10 patients, the median age was 71 years (range, 41-82 years), and 6 patients were male. They had received a median of 4 prior therapies (range, 2-5). The patients were treated with a median of 13 cycles (range, 9-23 cycles), with a median time to response of 15.75 weeks (range, 4-24 weeks). At the time of the report, the median duration of response was 26.75 weeks (range, 8.5-49.5 weeks); however, treatment was ongoing in 4 responding patients. Among the 10 long-term responders, in 3 patients the frequency of therapy was reduced to 10 mg/m^2 every other week. Adverse events included stomatitis, neutropenia, headaches, dizziness, nausea, and fatigue.

References

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4. Advani R, Ansell S, Lechowicz MJ, et al. A phase II study of cyclophosphamide, etoposide, vincristine and prednisone (CEOP) alternating with pralatrexate (P) as front line therapy for patients with peripheral T-cell lymphoma (PTCL): preliminary results from the T-cell consortium trial [ASH abstract 3044]. *Blood*. 2013;122(21 suppl).

Analysis of Peripheral T-Cell Lymphoma (PTCL) Subtype by Race and Geography Using the Comprehensive Oncology Measures for Peripheral T-Cell Lymphoma Treatment (COMPLETE) Dataset

The Comprehensive Oncology Measures for Peripheral T-Cell Lymphoma Treatment (COMPLETE) registry was designed to gather information on characteristics, treatments, and outcomes of PTCL patients in academic and community practices.[1] The registry includes patients with newly diagnosed PTCL. Enrollment began in February 2010, and the estimated primary completion date is February 2015.

Dr Kenneth Carson and associates performed a univariate analysis on the COMPLETE registry with PTCL to compare disease subtype, stratified by race and geography within the United States.[2] Owing to low numbers, 8 Asian patients (3%) and 8 patients with unknown race (3%) were excluded from the analysis. The remaining patients were black (n=47; 18%) or white (n=206; 77%). Overall, there was a slight independent influence of race and geographic region on the histologic subtype of PTCL. In the univariate analysis of PTCL subtype by race, the biggest differences occurred for angioimmunoblastic T-cell lymphoma (AITL; black, 2%; white, 18%), PTCL-NOS (black, 45%; white, 32%), and "other" (black, 28%; white, 18%; Table 1). In the univariate analysis of PTCL subtype by region, the most profound differences occurred for AITL (Midwest, 15%; Northeast, 13%; South, 4%; West, 30%), PTCL-NOS (Midwest, 31%; Northeast, 28%; South, 55%; West, 30%), and transformed mycosis fungoides (Midwest, 13%; Northeast, 0%; South, 6%; West, 4%). The most prevalent subtype by region was PTCL-NOS in the Midwest (31%) and the South (55%), "other" in the Northeast (30%), and AITL and PTCL-NOS in the West (both 30%). In the Northeast and the West, transformed mycosis fungoides was the least prevalent (0% and 4%, respectively), whereas T-cell/natural killer cell lymphoma was least common in the Midwest and the South (2% and 4%, respectively). The investigators noted that the extent to which these geographic differences were influenced by patient selection bias, regional differences in histology interpretation, or environmental factors cannot be determined from this study. The investigators will perform further analyses when the patient sample size increases.

Table 1. Univariate Analyses of PTCL Subtype by Race

	Total N=253	Black n=47	White n=206	*P* Value
PTCL Subtype				.10
ALCL, *ALK*-	27 (11%)	4 (9%)	23 (11%)	
ALCL, *ALK*+	20 (8%)	3 (6%)	17 (8%)	
AITL	38 (15%)	1 (2%)	37 (18%)	
PTCL-NOS	87 (34%)	21 (45%)	66 (32%)	
T-cell/NK-cell	16 (6%)	2 (4%)	14 (7%)	
Transformed MF	14 (6%)	3 (6%)	11 (5%)	
Other	51 (20%)	13 (28%)	38 (18%)	

AITL, angioimmunoblastic T-cell lymphoma; ALCL, anaplastic large cell lymphoma; ALK, anaplastic lymphoma kinase; MF, mycosis fungoides; NK, natural killer; NOS, not otherwise specified; PTCL, peripheral T-cell lymphoma.

Data from Carson KR et al. ASH abstract 4284. *Blood*. 2013;122(21 suppl).[2]

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2. Carson KR, Foss FM, Pinter-Brown LC, et al. Analysis of peripheral T-cell lymphoma (PTCL) subtype by race and geography using the Comprehensive Oncology Measures for Peripheral T-Cell Lymphoma Treatment (COMPLETE) dataset [ASH abstract 4284]. *Blood*. 2013;122(21 suppl).

The Combination of Hypomethylating Agents and Histone Deacetylase Inhibitors (HDACi) Are Synergistically Cytotoxic and Reverse the Malignant Phenotype in Preclinical Models of T-Cell Lymphoma

T-cell lymphoma is a challenging subset of lymphoma that is often associated with a poor prognosis. Given the difficult nature of this disease, investigators are seeking insights into epigenetic defects with the hope that disease progression can be halted or reversed using inhibitors that alter gene expression patterns. Evidence of epigenetic defects in T-cell lymphomas has been observed in relation to histone deacetylases (HDACs), histone demethylases, and nucleosome remodeling. Both overexpression of HDAC2 and high levels of histone acetylation have been detected in cutaneous T-cell lymphoma (CTCL).[1] Aberrant cysteine methylation of genomic DNA has been reported to occur in the *DNMT3A, TET*, and *IDH2* genes in PTCL and AITL.[2,3] In CTCL, the HDAC inhibitors vorinostat,[4,5] romidepsin,[6,7] panobinostat,[8,9] and belinostat[10] have demonstrated some efficacy; romidepsin[11,12] and belinostat[13] have shown efficacy in PTCL (Table 2). Response rates range from 14% to 38%. Both vorinostat and romidepsin have received approval from the US Food and Drug Administration for the treatment of CTCL in patients with progressive, persistent, or recurrent disease. A pivotal study of belinostat in patients with relapsed and refractory PTCL has just been completed.[14] HDAC inhibitors have different activities against the different isoforms of these particular enzymes.

Little is known about the combination of HDAC inhibitors and DNA methylation inhibitors in lymphomas. Dr Owen O'Connor and colleagues hypothesized that dual targeting of the epigenetic apparatus with HDAC inhibitors and hypomethylating agents might be a meritorious strategy for the treatment of T-cell lymphoma. They analyzed the synergistic interaction of a panel of HDAC inhibitors (panobinostat, belinostat, romidepsin, and vorinostat) and DNA methylation inhibitors (decitabine and 5-azacitidine) in models of T-cell lymphoma.[15] In addition, an analysis of the molecular basis for the synergistic effect of HDAC inhibitors and DNA methylation inhibitors was presented.

In an analysis of the HDAC inhibitors across a panel of 4 cell lines (2 CTCL, 2 T-ALL), romidepsin and belinostat demonstrated the highest levels of cytotoxic activity; the activity was dependent on the HDAC inhibitor concentration. The mean 48-hour IC_{50} was 2.2 nM (range, 1.7-2.7 nM) for romidepsin and 85 nM (range, 36-136 nM) for belinostat. The DNA methylation inhibitor decitabine also demonstrated some activity against the 4 cell lines, but a reduction in cell viability was not observed until after 72 hours of exposure to decitabine (mean IC_{50} of 14.8 µM [range, 0.4 µM to >20 µM]). In contrast to the HDAC inhibitors, there was no increase in the

ABSTRACT SUMMARY Primary T-Prolymphocytic Leukemia (T-PLL) Cells Are Sensitive to BCL-2 and HDAC Inhibitors: Results From High-Throughput Ex Vivo Drug Testing

In systematic high-throughput ex vivo drug sensitivity and resistance assays, primary T-prolymphocytic leukemia cells demonstrated sensitivity to BCL-2 and HDAC inhibitors (Abstract 3828). Primary T-prolymphocytic leukemia cells were derived from 3 patients. The T-cell phenotypes were as follows: patient 1 was positive for expression of CD4, CD8, CD3, and Vβ.14; patient 2 was positive for expression of CD4 and CD3; and patient 3 was positive for expression of CD4, CD3, and Vβ.2. The assay included 306 approved and investigational oncology agents using a 10,000-fold concentration range. All patient samples assayed demonstrated sensitivity to the BCL-2 inhibitors navitoclax and ABT-199. Mutational analysis failed to detect mutations linked to the *BCL-2* family of genes in the primary T-prolymphocytic leukemia cells. Expression levels of the proapoptotic BLC-2 family members BID and BAD were increased, whereas expression levels of BCL-2 and BCL-XL were similar to healthy CD4-positive T cells. In addition, cells from patients 1 and 2 demonstrated sensitivity to the HDAC inhibitors panobinostat and quisinostat. The primary T-prolymphocytic leukemia cells were not sensitive to inhibitors of Akt (MK-2206) or mammalian target of rapamycin (mTOR; temsirolimus and everolimus), even though the Akt1/mTOR pathway is activated in patients with T-prolymphocytic leukemia and both Akt1 and TCL1A were upregulated in the T-prolymphocytic leukemia cells. Approximately half of patients with T-prolymphocytic leukemia have a mutation in *JAK1* and *JAK3* (Bellanger D et al. *Leukemia* [19 September 2013] doi:10.1038/leu.2013.271), but the JAK inhibitors ruxolitinib and momelotinib had no activity against the primary T-prolymphocytic leukemia cells. In addition, the assay found that prednisolone and methylprednisolone had no activity against the T-prolymphocytic leukemia cells.

synergy coefficient as a function of the hypomethylating agent concentration.

The investigators also assessed the cooperative activity of HDAC inhibitors and histone demethylases against a panel of T-cell lymphoma non-Hodgkin lymphoma (NHL) cells. The combination of decitabine plus belinostat or decitabine plus romidepsin, at IC_{10}, IC_{20}, and IC_{50}, exhibited marked synergy as evidenced by a significant reduction in viable T-cell lymphoma cells that was greater than the activity observed with belinostat or romidepsin alone.

To analyze the interaction between decitabine and romidepsin, Dr O'Connor and colleagues performed gene expression profiling and methylation arrays. Supervised hierarchical clustering based on gene expression profiles revealed a significant upregulation of genes involved in cell-cycle arrest and a significant downregulation of genes involved in biosynthetic pathways. Most of the genes modulated by single-agent treatment with either decitabine or romidepsin (114 of 138; 92%) were similarly modulated by the combination treatment. However, there were 9, 15, and 390 different genes that were exclusively affected by decitabine, romidepsin, or the combination of romidepsin and decitabine, respectively. Dr O'Connor postulated that further analysis of these genes will reveal the synergistic mechanism of action of these agents against T-cell lymphomas.

Hierarchical clustering of CTCL samples according to the differential methylation pattern induced by different treatments was also performed. There were 175 genes differentially methylated with decitabine and 79 genes differentially methylated with the combination of romidepsin and decitabine; 78 genes were common between decitabine and combination treatment. Dr O'Connor indicated that these results further suggest a molecular basis for synergism between these agents.

There was a significant inverse relationship (R^2=0.657) with genes found to be differentially expressed in gene expression profiling and methylation analysis. There were 5 common genes that were both differentially expressed and differentially methylated during combination treatment: *GAGE2B, MAEL, TDRD9, PNLDC1,* and *GRIN1*. These genes were validated by polymerase chain reaction, and most of them appeared to be cancer testis antigens. Dr O'Connor noted that it is likely that in lymphomas, these cancer testis antigens are not expressed, so they happen to be the genes that are the most markedly differentially expressed as a function of the 2 different assays.

The investigators then extended their studies into a rodent (severe combined immunodeficiency-beige) xenograft model of CTCL using HH, the most resistant cell line derived from T-cell lymphoma. The mice were treated with decitabine (1.5 mg/kg on days 29, 33, 35, 37, 39, 41, and 43) and/or belinostat (100 mg/kg on days 29-47). The mice treated with the combination of belinostat plus decitabine exhibited statistically significant delays in tumor growth compared with the control mice or mice treated with either agent alone (decitabine alone, *P*=.002; belinostat alone, *P*=.001; Figure 3). Dr O'Connor noted that similar studies using romidepsin are planned.

Dr O'Connor concluded by stating that these studies indicate that the combination of HDAC inhibitors and

Table 2. Response Rates of HDAC Inhibitors in T-Cell Lymphomas

	Vorinostat	Romidepsin	Panobinostat	Belinostat
CTCL	24%[4] 30%[5]	34%[6] 35%[7]	17.3%	14%[10]
PTCL	—	38%[11] 26%[12]	—	32%[10] 26%[13]

CTCL, cutaneous T-cell lymphoma; HDAC, histone deacetylases; PTCL, peripheral T-cell lymphoma.

Data from O'Connor OA et al. ASH abstract 646. *Blood*. 2013;122(21 suppl).[14]

ABSTRACT SUMMARY The Use of GDP (Gemcitabine, Dexamethasone and Cisplatin) in the Primary Therapy of Peripheral T-Cell Lymphomas

PTCL patients generally respond poorly to CHOP. Gemcitabine, dexamethasone, and cisplatin (GDP) have been added to CHOP in select patients in an attempt to improve outcomes. However, there are no guidelines regarding which patients are most likely to benefit from this approach. Lavoie and colleagues searched databases (BC Agency Centre for Lymphoid Cancer and pharmacy databases) to identify newly diagnosed PTCL patients who had received at least 1 cycle of GDP during primary therapy (Abstract 1804). The search identified 35 patients treated with GDP (median age, 58 years; 34% female). IPI scores were 0 to 1 in 6 patients (17%), 2 to 3 in 21 patients (60%), and 4 to 5 in 8 patients (23%). Most patients had PTCL-NOS (57%) or ALCL (29%). The patients received a median of 3 cycles of GDP (range, 1-8). The most common AEs were hematologic (neutropenia requiring granulocyte-colony stimulating factor, 26%; low hemoglobin or platelets, 17%). The other most frequent AEs were tinnitus/hearing loss (11%), neuropathy (11%), infection (8%), and thromboembolism (8%). CHOP plus GDP resulted in an ORR of 82% and was generally well tolerated. The 2-year overall survival was 67%, the 2-year PFS was 37%, and the ORR was 87% (CR, 62%). When patients were stratified according to IPI status, patients with an IPI of 2 to 3 had the longest overall survival, whereas patients with an IPI of 0 to 1 had the shortest overall survival. In a retrospective comparison of matched patients treated with CHOP-GDP vs CHOP alone (n=32 patients per group), both the overall survival (*P*=.02) and the time to progression (*P*=.02) were better in patients treated with CHOP-GDP.

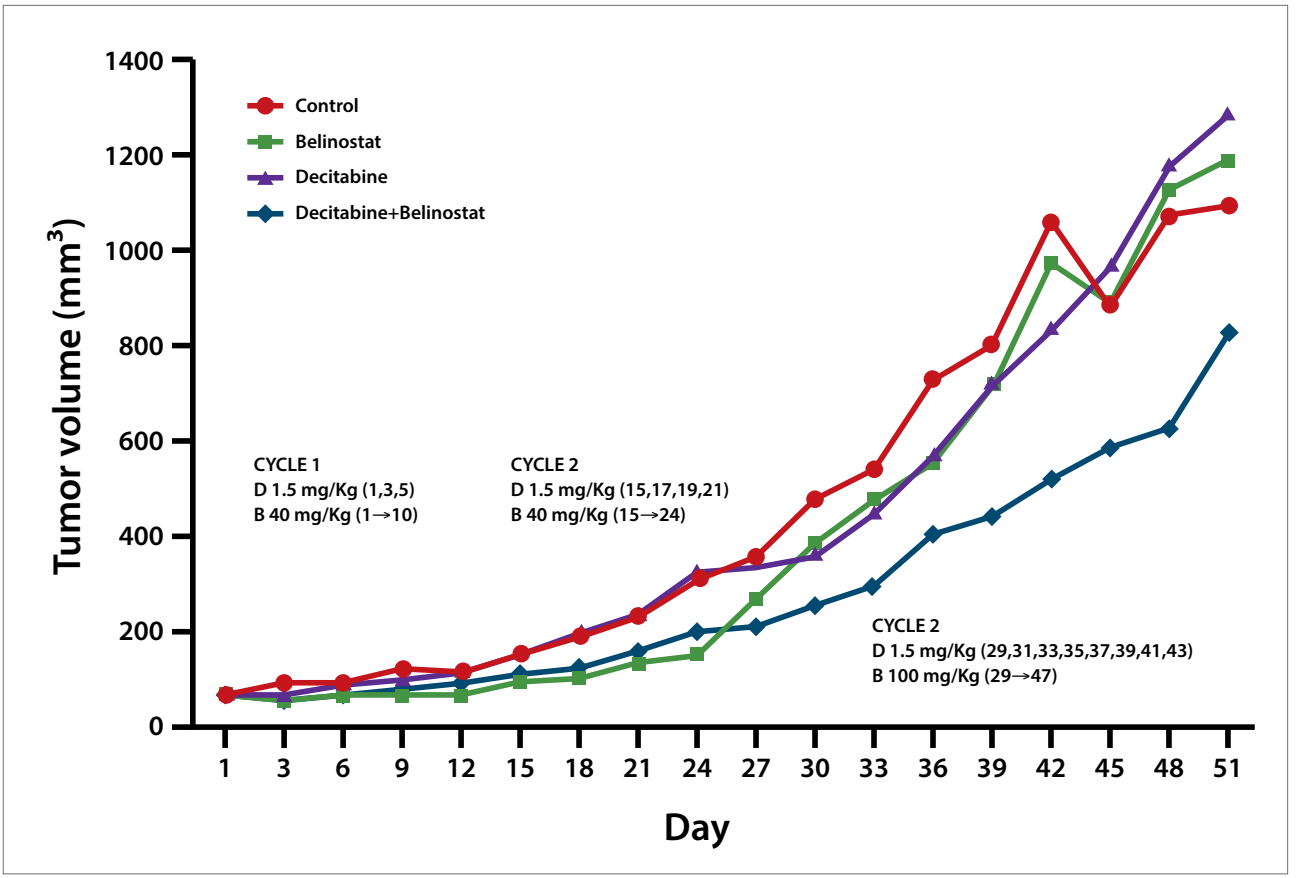

Figure 3. In a SCID-Bg xenograft model of cutaneous T-cell lymphoma using HH, the most resistant cell line derived from T-cell lymphoma, mice treated with the combination of belinostat plus decitabine exhibited statistically significant delays in tumor growth compared with the control mice or mice treated with either agent alone. SCID-Bg, severe combined immunodeficiency-beige. Adapted from O'Connor OA et al. ASH abstract 646. *Blood*. 2013;122(21 suppl).[15]

DNA methylation inhibitors has significant synergistic activity in both in vitro and in vivo models of T-cell lymphoma. Studies aimed at determining the mechanism of action for HDAC inhibitors in combination with DNA methylation inhibitors are ongoing. A phase 1 study of 5-azacytidine and romidepsin is actively accruing and will have extensive correlative analyses.[16]

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Phase II Trial of Brentuximab Vedotin For CD30+ Cutaneous T-Cell Lymphomas and Lymphoproliferative Disorders

Several subtypes of CTCLs are associated with expression of the CD30 antigen. The CD30-positive lymphoproliferative disorders include lymphomatoid papulosis and primary cutaneous ALCL. In addition, mycosis fungoides that presents as patches and plaques can transform into tumors, which may or may not express CD30.

Brentuximab vedotin is approved for systemic ALCL and for relapsed or refractory Hodgkin disease. This antibody-drug conjugate consists of a microtubule-disrupting agent, monomethyl auristatin E (MMAE), which is attached to the anti-CD30 antibody by a protease cleavable linker. Although the anti-CD30 antibody by itself has demonstrated activity against CD30-positive skin lymphoma,[1] it is unknown whether brentuximab vedotin has activity against CD30-positive lymphoproliferative disorders.

To determine the safety and efficacy of brentuximab vedotin for the treatment of primary cutaneous CD30-positive lymphoproliferative disorders, Dr Madeleine Duvic and colleagues conducted a phase 2, open-label trial.[2] Enrolled patients had experienced CD30-positive skin lesions within the past 3 years. Additional eligibility requirements for lymphomatoid papulosis patients included 10 lesions per month or the need for systemic therapy. Requirements for primary cutaneous ALCL patients included recurrent or refractory tumors; regional lymph node involvement was allowed. Patients with CD30-positive mycosis fungoides were required to have stage IB disease or higher, history of at least 1 prior systemic or topical therapy, and an Eastern Cooperative Oncology Group (ECOG) score of 2 or lower.

Brentuximab vedotin was infused at 1.8 mg/kg throughout 30 minutes every 21 days. After 8 cycles, if partial response was achieved, patients received up to 16 total doses. For patients achieving a CR, 2 additional doses were administered. Biopsies were taken from each type of clinical lesion at baseline, during the trial, and at the end of the trial to confirm CR, progressive disease, or new lesions. The investigators also measured serum-soluble CD30 levels at baseline and at the end of the study. T-cell clonality was studied to identify multiple heterogeneous lesions within patients. The definition of response varied according to the type of lesion; for lymphomatoid papulosis, it was a 50% decrease in lesions; for primary cutaneous ALCL, it was a 50% tumor reduction; and for mycosis fungoides, it was a 50% reduction in the modified skin-weighted assessment tool.

Dr Duvic presented the results of the 48 evaluable patients who received at least 2 doses of brentuximab vedotin. The median age of the patients was 59.5 years, 54% were men, and 63% were white. There were 28 patients with mycosis fungoides, 2 patients with primary cutaneous ALCL, 9 patients with lymphomatoid papulosis, 7 patients with lymphomatoid papulosis/mycosis fungoides, and 2 patients with primary cutaneous ALCL/lymphomatoid papulosis/mycosis fungoides. For all patients in the trial, the ORR was 73% (35 of 48 patients). All patients with primary cutaneous ALCL, lymphomatoid papulosis, lymphomatoid papulosis/mycosis fungoides, primary cutaneous ALCL/lymphomatoid papulosis, or ALCL/

ABSTRACT SUMMARY Three-Year Survival Results From an Ongoing Phase 2 Study of Brentuximab Vedotin in Patients With Relapsed or Refractory Systemic Anaplastic Large Cell Lymphoma

This ongoing, phase 2, multicenter, open-label study is evaluating the ORR, CR, duration of response, PFS, overall survival, and safety of brentuximab vedotin for patients with relapsed or refractory systemic ALCL (Abstract 1809). The study enrolled relapsed or refractory patients with CD30-positive systemic ALCL, an ECOG score of 0 to 1, and measurable disease of at least 1.5 cm, who were avid for fluorodeoxyglucose. Data were reported for 58 patients. They received a 30-minute infusion of brentuximab vedotin (1.8 mg/kg) every 21 days for 8 to 16 cycles (median, 7). The most common AEs of all grades were peripheral neuropathy, nausea, fatigue, pyrexia, diarrhea, rash, constipation, and neutropenia. The most common grade 3 AEs were peripheral neuropathy (17%) and neutropenia (12%). Grade 4 AEs included neutropenia (9%) and fatigue (2%). Although the median overall survival had not been reached, 64% of patients were alive at the time of the last follow-up (median observation time, 33.4 months). The estimated overall survival rate at 3 years was 63% (95% CI, 51%-76%). Overall survival was longer in patients who achieved a CR than in patients who did not (not yet reached vs 7.7 months, respectively). Of the 34 patients with a CR, 16 (47%) were still in remission at the last follow-up (10 received stem cell transplant and 6 had no new treatments). The investigators indicated that an early negative positron emission tomography scan appeared to predict long-term survival in relapsed or refractory systemic ALCL patients treated with brentuximab vedotin.

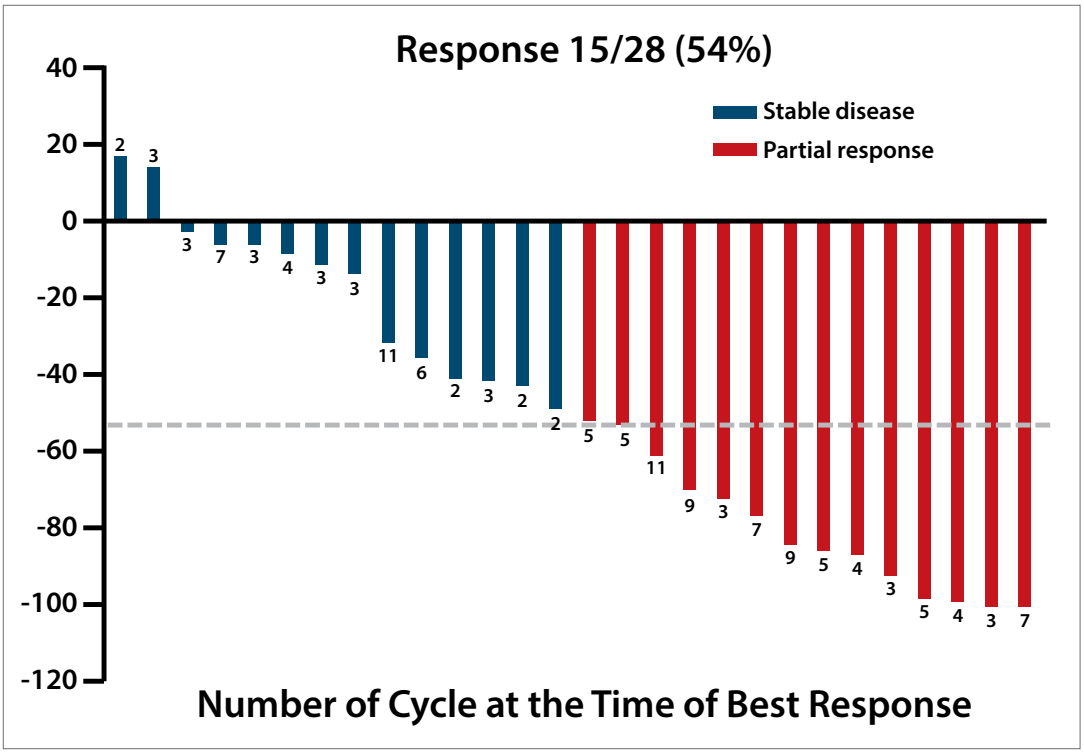

Figure 4. In a phase 2 trial of brentuximab vedotin, 54% of patients with mycosis fungoides had a response. mSWAT, modified severity weighted assessment tool. Adapted from Duvic M et al. ASH abstract 367. *Blood*. 2013;122(21 suppl).[2]

ABSTRACT SUMMARY Final Report of a Phase II Clinical Trial of Lenalidomide Monotherapy for T-Cell Lymphoma

Oral lenalidomide monotherapy demonstrated clinical efficacy in patients with T-cell lymphomas (Abstract 4376). This phase 2, multicenter trial included 40 patients with relapsed/refractory T-cell lymphomas (excluding mycosis fungoides) or untreated T-cell lymphomas, who were not candidates for combination chemotherapy. Oral lenalidomide (25 mg daily) was administered on days 1 to 21 of 28-day cycles until disease progression, death, or unacceptable toxicity. The investigators used standard dose reductions for toxicity. The most common grade 3 AEs were unspecified pain (21%), neutropenia (13%), dyspnea (10%), dehydration (10%), and muscle weakness (10%). Patients with AITL and PTCL-NOS had responses to lenalidomide. The ORR was 26% (10 of 39 patients). Three patients had a CR, 7 patients had a partial response, and 3 patients had stable disease. The median PFS was 4 months (range, <1 to 50+ months), the median overall survival was 12 months (range <1 to 69+ months), and the median duration of response was 13 months (range, 2 to 37+ months). For patients with relapsed/refractory disease (n=29), the median ORR was 24%, the median overall survival was 12 months, the median PFS was 4 months, and the duration of response was 5 months (range, 2 to 37+ months). These results for lenalidomide are comparable to those seen with other available monotherapies for this population. In contrast, the ORR (43%), median overall survival (22 months), and duration of response (21 months; range, 5 to 28+ months) were better in the previously untreated patients who were not eligible for combined chemotherapy (n=8). However, the PFS was shorter in these patients (2 months). The investigators concluded that future studies should focus on identifying those patients who will most likely benefit from lenalidomide therapy because only a few patients achieved a durable response.

mycosis fungoides achieved a CR or a partial response. Only 54% of patients with mycosis fungoides had a response (2 CRs, 13 partial responses, 12 stable disease, and 1 progressive disease; Figure 4). The overall survival was not yet reached, and the PFS was 50% at 1.5 years.

The investigators examined the expression of the CD30 molecule in biopsies from the 28 patients with mycosis fungoides who had a response to treatment. The response rates among the different intensities of CD30 staining were similar (low expression, 50% response; medium expression, 58% response; high expression, 50% response). Dr Duvic reported that there was no correlation between baseline CD30 expression and whether the mycosis fungoides lesions responded to brentuximab vedotin. Levels of soluble CD30 were lowest in the patients with CRs and highest in the patients with partial responses.

For the patients with mycosis fungoides, the median time to response was 12 weeks (range, 3-39 weeks), and the duration of response was 32 weeks

(range, 3-93 weeks). Most patients lost their response after stopping treatment. Among patients with lymphomatoid papulosis, ALCL, or lymphomatoid papulosis/mycosis fungoides, the median time to response was only 3 weeks (range, 3-9 weeks), and the duration of response was 26 weeks (range, 6-44 weeks).

During the course of treatment, 12 patients had a dose reduction to 1.2 mg/kg owing to grade 2 peripheral neuropathy (n=9), elevated liver function and fatigue (n=1), and generalized arthralgias (n=2). The most common AE was peripheral neuropathy, which occurred in 31 of the 48 patients (65%). The median time to onset of peripheral neuropathy was 6 weeks for grade 1 and 12 weeks for grade 2. The median duration of peripheral neuropathy was 60 weeks, with resolution in 14 of the 31 patients. Most AEs were mild and included drug rashes, diarrhea, fatigue, alopecia, myalgias, and nausea. The grade 3 AEs that occurred consisted primarily of neutropenia and nausea.

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Preliminary Results of a Phase II Study of Single Agent Bay 80-6946, a Novel PI3K Inhibitor, in Patients With Relapsed/Refractory, Indolent or Aggressive Lymphoma

The phosphatidylinositol 3-kinase (PI3K) family of lipid kinases plays a central role in a number of signaling pathways, including signaling cascades downstream of the B-cell receptors. In addition, many components of the PI3K signaling pathways are altered in a variety of human cancers owing to somatic or germline mutations.[1] Investigations are targeting the PI3K pathway for pharmacologic intervention against a broad spectrum of human cancers. One such inhibitor of the PI3K pathway is copanlisib (BAY 80-6946). Copanlisib is a novel, reversible, class-1 PI3K inhibitor with activity against both PI3K-δ and PI3K-α isoforms; the PI3K-δ isoform is active in B-cell signaling, development, and survival, whereas the PI3K-α isoform is active in insulin signaling and angiogenesis (Table 3).[2] Copanlisib has demonstrated efficacy in a number of preclinical tumor models, including both aggressive and indolent NHL.[3] In addition, copanlisib demonstrated promising activity in a phase 1 dose-escalation study in patients with follicular lymphoma.[4]

Dr Martin Dreyling presented the preliminary results of a phase 2 open-label study of single-agent copanlisib.[5] Patients were eligible for inclusion in the study if they had histologically confirmed indolent or aggressive lym-

Table 3. Activity of PI3K Isoforms

Class I PI3K Isoform	Cellular Expression	Primary Physiologic Role
α	Broad	Insulin signaling and angiogenesis
β	Broad	Platelet function
γ	Leukocytes	Neutrophil and T-cell function
δ	Leukocytes	B-cell signaling, development, and survival

PI3K, phosphatidylinositol 3-kinase.

Data from Okkenhaug K, Vanhaesebroeck B. *Nat Rev Immunol*. 2003;3(4):317-330.[2]

ABSTRACT SUMMARY Phase 1/2 Study of Brentuximab Vedotin in Pediatric Patients With Relapsed or Refractory (R/R) Hodgkin Lymphoma (HL) or Systemic Anaplastic Large-Cell Lymphoma (sALCL): Preliminary Phase 2 Data For Brentuximab Vedotin 1.8 Mg/Kg in the HL Study Arm

Preliminary results indicate that brentuximab vedotin (1.8 mg/kg every 3 weeks) results in mild-to-moderate AEs and an ORR of 47% in pediatric patients with relapsing or refractory Hodgkin lymphoma (HL; Abstract 4387). The primary endpoint of this phase 2 study was the ORR for brentuximab vedotin at the previously determined phase 2 dosage of 1.8 mg/kg every 3 weeks (Locatelli F et al. *Haematologica*. 2013;98[suppl 2]: Abstract P132.) in pediatric patients with relapsed or refractory HL or systemic ALCL. The most common AEs were nausea, pyrexia, and paresthesia; 7 patients had AEs of grade 3 or higher. There were 4 grade 3 serious AEs: hepatotoxicity, febrile neutropenia, pneumonia, and anaphylactic reaction. Treatment was discontinued in 3 patients owing to AEs (grade 3 hepatotoxicity, grade 3 peripheral neuropathy, and grade 5 cardiac arrest). Among the 15 evaluable patients with relapsed or refractory HL, 5 patients achieved a CR (33%), and 2 patients achieved a partial response (13%). The median time to progression was 4.8 months, the median time to response was 2.7 months, the median event-free survival was 2.1 months, and the PFS was 2.8 months. This study is ongoing and will include 15 patients with systemic ALCL (at least 10 in their first relapse) and 15 patients with HL.

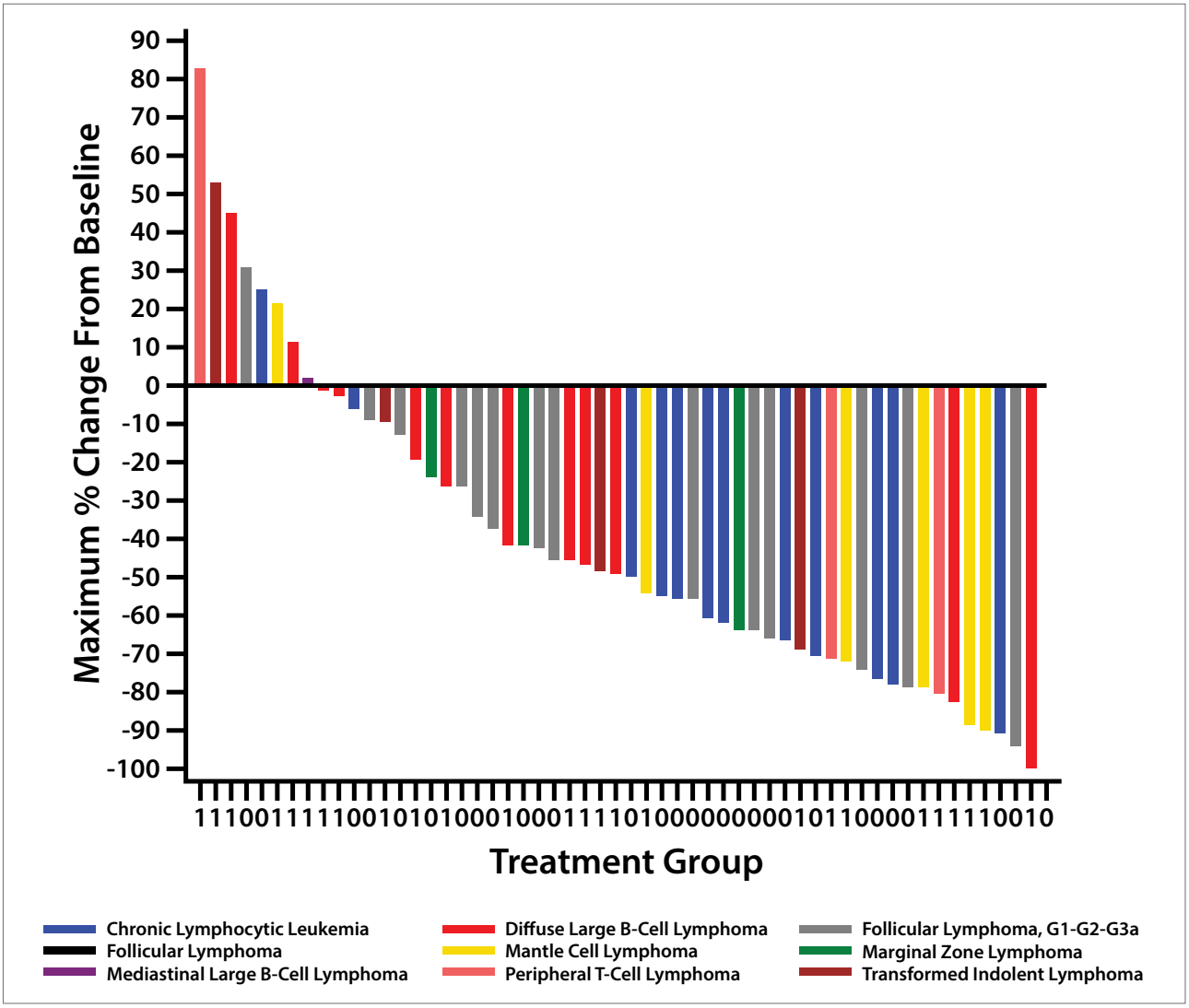

Figure 5. Tumor shrinkage according to histology in a phase 2, open-label study of single-agent copanlisib in patients with histologically confirmed indolent or aggressive lymphoma who were relapsed or refractory after at least 2 prior treatments. Adapted from Dreyling M et al. ASH abstract 87. *Blood*. 2013;122(21 suppl).[5]

phoma and were relapsed or refractory after at least 2 prior treatments. Treatment consisted of a 1-hour intravenous infusion of copanlisib weekly (on days 1, 8, and 15 of a 28-day cycle). The starting dose of copanlisib was 0.8 mg/kg (maximum dose, 65 mg).[4] If necessary, the dose was reduced to 0.6 mg/kg (maximum dose, 48 mg) and 0.4 mg/kg (maximum dose, 32.5 mg). Responses were assessed every 2 cycles. The primary endpoint of the study was ORR up to 16 weeks after the last patient initiated treatment. Additional endpoints included safety, PFS, duration of response, overall survival, and pharmacokinetics. Potential biomarkers were also assessed.

At the time of the presentation, 67 patients were enrolled in the study: 33 with indolent lymphoma and 34 with aggressive lymphoma. The median age of the patients was 67 years, and 52% were female. The histologic subtypes of the indolent lymphomas were follicular lymphoma (48%), chronic lymphocytic leukemia (42%), and marginal zone lymphoma (9%). The aggressive lymphoma subtypes included diffuse large B-cell lymphoma (DLBCL; 44%), mantle cell lymphoma (21%), transformed indolent lymphoma (18%), T-cell lymphoma (12%), mediastinal B-cell lymphoma (3%), and follicular lymphoma (3%). The majority of patients had advanced-stage disease (Ann Arbor stage 1, 2%; stage 2, 11%; stage 3, 26%; and stage 4, 60%). Prior treatments included at least 3 lines of chemotherapy in 80%, prior ASCT in 18%, and prior rituximab in 84%.

As of September 2013, 84% of patients (indolent, 79%; aggressive, 88%) developed an AE that was grade

ABSTRACT SUMMARY The Addition of Sirolimus to the GVHD Prophylaxis Regimen in Reduced Intensity Allogeneic Stem Cell Transplantation for Lymphoma: a Multicenter Randomized Trial

In lymphoma patients undergoing reduced-intensity conditioning stem cell transplant, the addition of sirolimus to prophylaxis for graft-vs-host disease resulted in a significant reduction in the number of patients who developed grade 2 to 4 graft-vs-host disease (Abstract 704). In this phase 3, open-label, multicenter, randomized controlled trial, tacrolimus/sirolimus/methotrexate (with sirolimus starting on day -3 of stem cell transplant) was compared with the control arm of sirolimus-free regimens (tacrolimus/methotrexate) or cyclosporine/mycophenolate mofetil for graft-vs-host disease prophylaxis in patients with any lymphoma (excluding Burkitt lymphoma and MYC-positive DLBCL) receiving reduced-intensity conditioning stem cell transplant. The study enrolled 139 patients; their median age was 57 years (range, 23-70 years). There were 66 patients in the tacrolimus/sirolimus/methotrexate arm and 73 patients in the control arm; only peripheral blood stem cells were used for transplant. The median follow-up was 22 months for survivors. There were 9 fatal toxicities in each group. Grade 3/4 AEs included neutropenia (treatment arm, n=12; control arm, n=17), thrombocytopenia (n=13; n=14), infection (n=8; n=16), and hyperlipidemia (n=2; n=2). The 2-year overall survival and 2-year PFS were similar for the tacrolimus/sirolimus/methotrexate arm (overall survival, 68%; PFS, 59%) and the control arm (overall survival, 66%; PFS, 56%). In patients receiving matched-related and matched-unrelated grafts, the treatment arm had a lower incidence of grade 2 to 4 acute graft-vs-host disease (9%) than the control arm (25%; *P*=.015). There was no significant difference in the incidence of grade 3/4 acute graft-vs-host disease (3% for the treatment arm vs 4% for the control arm) or in the all-grade graft-vs-host disease at 2 years (60% for both arms). The investigators concluded that the addition of sirolimus improved the incidence of grade 2 to 4 acute graft-vs-host disease without increasing toxicity or altering rates of overall survival, PFS, or relapse.

3 or higher. The drug dosage was reduced in 6 patients (9%), and treatment was interrupted in 31 patients (46%). In addition, 29 patients (43%) experienced serious AEs, and there were 6 deaths (9%). As would be expected of a PI3K inhibitor, the metabolic adverse events hyperglycemia and hypertension (all grades) occurred in approximately 57% of patients, but were managed with conventional treatments. Patients also experienced relatively mild gastrointestinal adverse events of diarrhea (grade 1/2, 33%; grade 3/4, 3%) and nausea (grade 1/2, 27%; grade 3/4, 2%). The hematologic toxicities included neutropenia (grade 1/2, 5%; grade 3/4, 24%) and anemia (grade 1/2, 12%; grade 3/4, 11%). Overall, 43 patients discontinued treatment, including 13 patients (19%) who experienced AEs not associated with clinical disease progression.

Preliminary efficacy results were based on a data cutoff of November 2013 and a median number of 3 treatment cycles. Among the majority of patients with indolent lymphoma (adult follicular lymphoma and chronic lymphocytic leukemia), the ORR was 40% to 43% (follicular: 1 CR; 5 partial responses, 9 stable disease, 1 not available; chronic lymphocytic leukemia: 6 partial responses; 6 stable disease; 1 progressive disease; 1 not available). The ORR was 50% for T-cell lymphoma (1 CRu, 1 partial response, 2 progressive disease). Dr Dreyling noted that this cohort is currently being expanded. The ORR was 71% for mantle cell lymphoma (1 CRu, 4 partial responses, 2 progressive disease). The ORR was only 13% for DLBCL (2 CR/CRu, 3 stable disease, 10 progressive disease). Overall, the majority of patients demonstrated tumor shrinkage (Figure 5).

Dr Dreyling concluded that copanlisib demonstrated acceptable toxicities and encouraging results for relapsed and refractory lymphoma. There was significant activity in follicular lymphoma, chronic lymphocytic leukemia, mantle cell lymphoma, PTCL, and DLBCL. In addition, CRs occurred in patients with follicular lymphoma, mantle cell lymphoma, PTCL, and DLBCL. Further studies of copanlisib are in progress for indolent and aggressive NHL.[6]

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Romidepsin Is Effective and Well-Tolerated in Patients ≥60 Years Old With Relapsed or Refractory Peripheral T-Cell Lymphoma (PTCL): Analysis From Phase 2 Trials

Guidelines recommend the use of the class 1 HDAC inhibitor romidepsin for second-line treatment of PTCL,[1] but more information is needed regarding the use of this agent in older patients. Dr Andrei Shustov presented data from a subanalysis of older patients (≥60 years) from 2 studies[2]: the pivotal phase 2 trial that led to the drug's approval[3] and a supportive phase 2 trial from the National Cancer Institute.[4] Both studies enrolled patients with relapsed or refractory PTCL who had failed at least 1 prior systemic therapy. Patients received a 4-hour infusion of romidepsin (14 mg/m^2) on days 1, 8, and 15 of 28-day cycles. Approximately half of the patients in each trial were older than 60 years; the average age was 59 to 61 years in the overall population and 67 to 68 years in the older population. All patients were heavily pretreated, with a median of 2 (pivotal trial) or 3 (supportive trial) prior therapies. In the pivotal trial, 10% to 16% of patients received prior ASCT, and in the supportive trial, 35% to 40% received prior ASCT.

The subanalysis found similar response rates between the overall patient population and the older patients within each trial. In the pivotal trial, the ORR was 25% (same for both groups), and the CR/CR unconfirmed (CRu) rate was 15% overall vs 14% in the older group. The partial response was 11% (same for both groups). The rate of stable disease was 25% overall vs 31% for the older group, and the median duration of response was 28 months (same for both groups). In the supportive trial, the ORR was 38% overall vs 32% in the older group. The CR/Cru rate was 18% vs 14%, the partial response rate was 20% vs 18%,

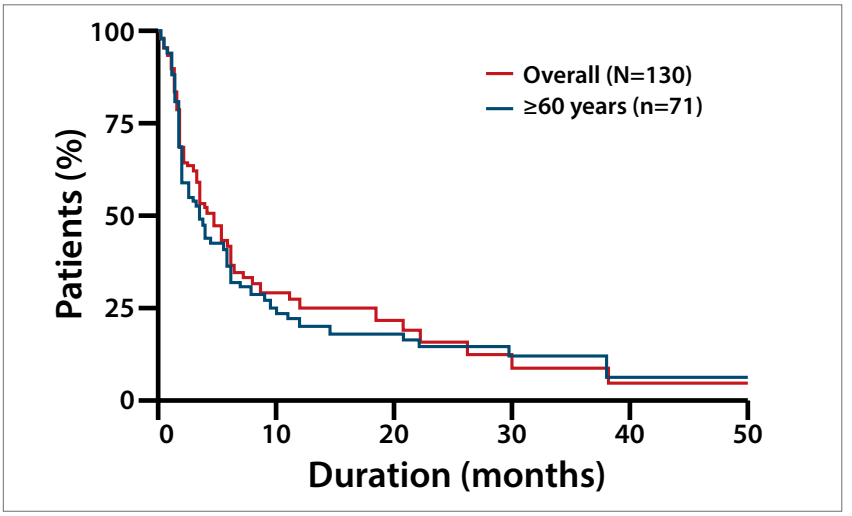

Figure 6. In a pivotal trial of romidepsin in patients with relapsed or refractory peripheral T-cell lymphoma, progression-free survival was similar in older and younger patients. Adapted from Shustov AR et al. ASH abstract 4385. *Blood*. 2013;122(21 suppl).[2]

ABSTRACT SUMMARY A Phase I/II Combination of RAD001 (Everolimus) and Lenalidomide for Relapsed Lymphoid Malignancy: Phase I Results

Everolimus plus lenalidomide demonstrated tolerable safety profiles and promising clinical efficacy in patients with heavily pretreated relapsed or refractory HL and NHL (Abstract 4350). This phase 1 study enrolled 25 adult patients (median age, 60.5 years; 71% male) with relapsed or refractory HL and NHL. The patients had measurable disease and an ECOG performance status of 2 or lower. The patients had HL (n=4); DLBCL (n=14); follicular lymphoma, grade 1 or 2 (n=3); follicular lymphoma, grade 3 (n=2); lymphoplasmacytic lymphoma (n=3); mantle cell lymphoma (n=1); or mycosis fungoides (n=1). In 10 patients, the subtype was other or unknown. Most of the patients had stage IV disease (70%). Most patients were heavily pretreated; 50% had received at least 3 prior therapies, and 40% had undergone stem cell transplant. As a starting dose, patients received 5 mg/day of everolimus and 10 mg of lenalidomide on days 1 to 21; each treatment cycle was 28 days. Dose-limiting toxicity was defined as grade 4 neutropenia lasting at least 7 days, grade 4 thrombocytopenia lasting at least 7 days, grade 4 infection, and nonhematologic toxicity of at least grade 3. The investigators determined that the maximum-tolerated dose was 5 mg/day of everolimus for 28 days and 10 mg/day of lenalidomide for 21 days. The most common toxicities (grade ≥3) were neutropenia (43%), infection (32%), thrombocytopenia (30%), fatigue (17%), and anemia (10%). Responses were observed for 4 of 23 patients; 10 of these patients had stable disease. At the time of the report, 15 of 38 patients were receiving therapy, and 22 of 38 patients had not progressed. The phase 2 trial is under way.

Table 4. Grade ≥3 Adverse Events According to Age in Trials of Romidepsin

	Pivotal Trial[3]		Supportive Trial[4†]	
Adverse Event,* n (%)	**Overall (N=131)**	**≥60 years (n=72)**	**Overall (N=47)**	**≥60 years (n=23)**
Thrombocytopenia	32 (24)	15 (21)	14 (30)	7 (30)
Neutropenia	26 (20)	13 (18)	21 (45)	12 (52)
Infections (all types pooled)	25 (19)	15 (21)	10 (21)	4 (17)
Anemia	14 (11)	5 (7)	9 (19)	4 (17)
Asthenia/fatigue	11 (8)	8 (11)	6 (13)	3 (13)
Leukopenia	8 (6)	4 (6)	21 (45)	11 (48)
Vomiting	6 (5)	2 (3)	4 (9)	1 (4)
Pyrexia	7 (5)	6 (8)	5 (11)	2 (9)
Thrombocytopenia	32 (24)	15 (21)	14 (30)	7 (30)

*Reported in ≥5% of patients in the pivotal trial.

†All abnormalities were reported as adverse events regardless of clinical significance.

Data from Shustov AR et al. ASH abstract 4385. *Blood*. 2013;122(21 suppl).[2]

and the stable disease rate was 11% vs 9%. The median duration of response was 9 months overall vs 5 months in the older group. In the pivotal trial, there were 10 patients who achieved CR/CRu and were at least 60 years old; in 6 of these patients, the duration of response was at least 12 months. In the supportive trial, 3 patients achieved a CR/CRu and were at least 60 years old; 1 patient had a duration of response of at least 12 months, 1 had no evidence of disease after relapse and resumption of the protocol, and 1 patient died. Both the median PFS (4 months overall vs 4.6 months in the older group; Figure 6) and the median overall survival (11.3 months overall vs 11.8 months in the older group) were comparable. In addition, the AEs, dose reductions, and treatment cycles were also similar between the overall and older populations within each trial (Table 4).

The investigators concluded that safety and efficacy were similar for the overall and older populations within each trial. They suggested that romidepsin is a suitable option for salvage therapy in patients older than 60 years with relapsed or refractory PTCL.

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Commentary

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A primary issue in systemic T-cell lymphomas is inadequate response to initial therapy, in terms of both quality of response and duration of response. Studies presented at the 2013 American Society of Hematology (ASH) meeting provided new data on modifying initial therapy by adding new drugs or using novel regimens. Dr Michelle Fanale presented updated results of a phase 1/2 study that added brentuximab vedotin to combination chemotherapy in patients with newly diagnosed CD30-positive mature T-cell and natural killer [NK]-cell lymphomas.[1] This study was based on trial data showing activity of brentuximab vedotin in relapsed or refractory anaplastic large cell lymphoma (ALCL)[2] and other T-cell lymphomas with CD30 expression,[3] which led to the agent's approval for systemic ALCL. A study was initiated combining brentuximab vedotin with cyclophosphamide, doxorubicin, and prednisone (CHP); vincristine was omitted from the usual cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) regimen because of concerns about overlapping toxicity.[4] That study showed an overall response rate of 100%, and many patients achieved a complete response. There was activity in ALCL patients with high CD30 expression as well as in patients with other CD30-positive T-cell lymphomas. Brentuximab vedotin at a full dose of 1.8 mg/kg was added to chemotherapy without any clearly increased toxicity. This important study has set the groundwork for an ongoing phase 3 randomized trial comparing brentuximab vedotin plus CHP vs CHOP.[5] It is one of the first randomized trials examining an approach that could potentially challenge CHOP and CHOP-like regimens as the standard initial therapy for T-cell lymphomas.

Another study with a similar goal was presented by Dr Ranjana Advani.[6] This phase 2 trial incorporated pralatrexate into upfront chemotherapy for patients with newly diagnosed peripheral T-cell lymphoma. Previous studies in the relapsed setting that combined pralatrexate with chemotherapy, particularly gemcitabine, have shown excess hematologic toxicity.[7] The study by Advani and colleagues examined interdigitating pralatrexate as part of an initial chemotherapy regimen. Chemotherapy consisted of cyclophosphamide, etoposide, vincristine, and prednisone (CEOP), which is a CHOP-like regimen that substitutes etoposide for doxorubicin. A cycle of CEOP was alternated with a 3-week cycle of pralatrexate at 30 mg/m^2 per dose. Pralatrexate is known to have activity in the second-line setting,[8] and it was hoped that the addition of pralatrexate to frontline treatment would increase the overall response rate. As established in previous stud-

ABSTRACT SUMMARY Gemcitabine, Dexamethasone, and Cisplatin (GDP) as Secondary Chemotherapy in Relapsed/Refractory Peripheral T-Cell Lymphoma

GDP demonstrated efficacy in relapsed or refractory PTCL patients as a bridge to transplant and as palliative care (Abstract 4345). Between 2002 and 2012, 51 patients with relapsed (n=31) or refractory (n=20) PTCL (excluding cutaneous ALCL) who received GDP were identified from the BC Cancer Agency Lymphoid Cancer database, the provincial cancer pharmacy database, and the Leukemia/Bone Marrow Transplant Program of the BC Cancer Agency database. The most prevalent disease subtypes were PTCL-NOS (33%), ALCL (27%), and AITL (25%). Most patients received CHOP as first-line treatment (76%). At the time of relapse or progression, patients had a median age of 56 years, 88% were stage III/IV, and 57% had an IPI of 3 to 5. Twenty patients (39%) received 1 to 2 cycles, 23 patients (45%) received 3 to 4 cycles, and 8 patients (16%) received 5 to 6 cycles of GDP. At a median follow-up of 10.4 months, the ORR was 80%: 47% (n=24) achieved a CR, 33% (n=17) achieved a partial response, and 20% (n=10) developed progressive disease. The 2-year PFS was 25%, with a median PFS of 5.2 months. The 2-year overall survival was 43%, with a median overall survival of 11.4 months. Among the 26 patients who then underwent transplant (autologous, n=15; allogeneic, n=11), 73% (n=19) achieved CR, 23% (n=6) achieved partial response, and 4% (n=1) developed progressive disease. The patients who underwent transplant ultimately achieved improved 2-year PFS (34%, median PFS of 11.6 months) and 2-year overall survival (54%, median overall survival of 66.3 months) compared with patients who did not undergo transplant (PFS, 16%; median PFS, 4.4 months; overall survival, 32%; median overall survival, 6.8 months). Among the palliative patients (n=15), the 2-year PFS was 13% and 2-year overall survival was 27%.

ies, the baseline complete response rate to CHOP is approximately 40%.[9] The aim of this study was to improve the complete response rate to 63%. Among the 34 patients in the study, 45% achieved a complete response. The 1-year overall survival was 70%, but the 1-year event-free survival was only 48%. The regimen was reasonably well tolerated, but not clearly better than CHOP.

A study from the British Columbia Cancer Agency examined a novel upfront regimen of gemcitabine, dexamethasone, and cisplatin in 34 patients with untreated T-cell lymphoma.[10] In the frontline setting, the overall response was 82%, with 62% complete responses. For patients with T-cell lymphoma, these results, particularly the CR rate, appear higher than typically seen with CHOP, although they did not seem to translate into better time to progression, with PFS rates of 50% at 1 year and 36% at 2 years. The gemcitabine, dexamethasone, and cisplatin regimen appears to be active but perhaps not durable, like many other regimens in T-cell lymphoma. The high response rate is an interesting finding especially in light of an earlier trial from the Southwest Oncology Group with a similar chemotherapy regimen consisting of cisplatin, etoposide, gemcitabine, and methylprednisolone.[11] In that study, the overall response rate for peripheral T-cell lymphoma was only 39%. It is difficult to reconcile the difference in overall response between these 2 studies.

The group from the British Columbia Cancer Agency also studied the gemcitabine, dexamethasone, and cisplatin regimen in 51 patients with relapsed or refractory peripheral T-cell lymphoma.[12] The ORR was 80% at a median follow-up of 10.4 months. A complete response was reported in 47% and a partial response in 33%. Progressive disease occurred in 20%. Median PFS was 5.2 months, with a 2-year PFS of 25%. At 2 years, the overall survival was 43%, and the median overall survival was 11.4 months.

Dr Madeleine Duvic presented results from a phase 2 study of brentuximab vedotin in patients with CD30-positive cutaneous T-cell lymphomas and lymphoproliferative disorders.[13] Patients in this study had conditions such as primary cutaneous ALCL, an indolent form that presents in the skin; lymphomatoid papulosis, a spontaneously regressing CD30-expressing lymphoproliferative process that occurs in the skin; and mycosis fungoides, which occasionally expresses CD30. Overall, 48 patients were accrued. More than half had mycosis fungoides, and these patients had an overall response rate of 50%. In the more uniformly high CD30-expressing cutaneous lymphomas—primary cutaneous ALCL and lymphomatoid papulosis—the response rate was 100%, although the number of patients with these conditions was smaller. The durations of response were reasonable, at approximately 13.5 weeks in mycosis fungoides, approximately 18 weeks in primary cutaneous ALCL, and approximately 23 weeks in lymphomatoid papulosis. It appears that in lymphomas with any degree of CD30 expression, brentuximab vedotin has activity. An ongoing international study is randomizing patients with mycosis fungoides or primary cutaneous ALCL to treatment with brentuximab vedotin or standard therapy to definitely address the role of brentuximab vedotin in these populations.[14]

Dr Ethan Toumishey presented updated data from a phase 2 study of lenalidomide in several different subtypes of T-cell lymphoma.[15] Published data showed a 30% response rate in 23 patients.[16] This updated analysis included 40 patients who received oral lenalidomide at a standard dosage of 25 mg daily, on days 1 to 21, on a 28-day cycle. The overall response rate was 26%, with 8% complete responses. The median progression-free survival was 4 months, and the median duration of response was 13 months. These outcomes appear similar to those achieved with other approved drugs in T-cell lymphoma, such as pralatrexate and romidepsin.[17,18] However, in contrast to other studies of new agents in T-cell lymphoma, this study also accrued 8 patients (20% of the total) who were untreated and considered ineligible for chemotherapy. In these patients,

ABSTRACT SUMMARY A Pilot Study of Sorafenib in Refractory or Relapsed T-Cell Lymphoma Patients

Sorafenib demonstrated clinical activity in a pilot study of patients with relapsed or refractory T-cell lymphoma (Abstract 4356). The study included relapsed or refractory patients with PTCL (100% female, median age of 50 years) and 9 patients with CTCL (66% female, median age of 69 years). Sorafenib (400 mg) was given twice daily, with dose reductions for toxicity if necessary. All 3 of the PTCL patients achieved a CR; 1 patient with AITL had CR in the lymph nodes but partial response in the marrow. The PFS for the PTCL patients was 3.7 months, and all patients were alive at the time of the report. Among the 9 patients with CTCL, 1 (11%) achieved a CR. Of the remaining patients, 2 (22%) had a mixed response, 2 (22%) had stable disease, 3 (33%) had no response, and 1 (11%) had disease progression. The PFS for the CTCL patients was 2.8 months. Two patients died: 1 from disease progression and 1 from sepsis. The most common AEs (all grade) were fatigue (89%), mucositis/stomatitis (89%), rash (78%), rash with desquamation (44%), systemic infection (44%), and hypertension (33%). The most common grade 3/4 AEs were rash (22%), fatigue (22%), rash with desquamation (11%), systemic infection (11%) and hypertension (11%). Skin toxicity was the principle reason for discontinuing treatment. Lower doses of sorafenib may be necessary to reduce skin toxicity.

the overall response rate was 43%, with a median duration of response of 21 months.

A small pilot study from Yale examined the activity of sorafenib in relapsed or refractory T-cell lymphoma patients.[19] The study enrolled only 12 patients, most of whom had CTCL. Four patients, or 33%, had a complete response, including patients with CTCL and PTCL. There was a high rate of skin toxicity, and 5 patients had to discontinue the drug or have the dosage modified.

Dr Barbara Pro presented a long-term update to the survival results from the initial phase 2 study of brentuximab vedotin in relapsed or refractory ALCL that led to the drug's approval.[2,20] After a median observation time of almost 3 years, the median overall survival had not been reached, and the estimated 3-year survival was 63%. An interesting finding of this study concerns patients who had unmaintained remissions. One common strategy for treating patients with relapsed T-cell lymphoma is that patients who respond to therapy are consolidated with stem cell transplant, either allogeneic or autologous. The high rates of complete response in patients with brentuximab vedotin raised the question of whether it is still necessary to consolidate those remissions, or if some patients might stay in long-term unmaintained remission. In the initial study of 58 patients, 34 achieved a complete response.[2] At the time of this longer-term update, 16 of 34 patients (47%) remained in remission. Fourteen of the patients who achieved a complete response underwent consolidation with stem cell transplantation, but 6 of 20 patients who did not undergo consolidation remained in long-term remission after achieving a complete response without any additional therapy following brentuximab vedotin. At 3-year follow-up, the chance of achieving a long-term unmaintained remission with brentuximab vedotin appeared to be approximately 10%. Brentuximab vedotin clearly has potent activity in ALCL, but whether it is necessary to consolidate a patient postremission on brentuximab vedotin is currently unknown. Only these data are available to help guide decisions, as the majority of patients with long-term remissions had received consolidation with stem cell transplantation.

Dr Andrei Shustov presented data on the use of romidepsin in older patients (≥60 years) with relapsed or refractory peripheral T-cell lymphoma.[21] The data were based on an analysis of older patients in 2 phase 2 trials: a pivotal study by Coiffier and colleagues,[22] which led to the agent's approval, and a similar study from the National Cancer Institute (NCI).[18] It is particularly challenging to treat older patients with relapsed or refractory T-cell lymphoma, in whom the disease can be complicated and chemotherapy can cause increased side effects. There were 72 older patients in the pivotal study and 23 older patients in the NCI study. This analysis showed no difference in outcome between older and younger patients; overall response was 25%, and median duration of response was 48 months. Toxicities were similar between the older and younger patients. This analysis reinforces the idea that romidepsin can be given in a relatively safe, continuous fashion without cumulative toxicity, even in older and/or frail patients.

A trial presented by Dr Martin Dreyling examined the novel agent Bay 80-6949, a phosphatidylinositol 3-kinase (PI3K) inhibitor of both the δ and α isoforms.[23] Activity of PI3K

ABSTRACT SUMMARY Brentuximab Vedotin Administered Before, During, and After Multi-Agent Chemotherapy in Patients (pts) With Newly-Diagnosed CD30+ Mature T- and NK-Cell Lymphomas

Combination treatment with brentuximab vedotin and CHOP without vincristine resulted in an ORR of 100% in treatment-naive patients with mature T-cell lymphomas (Abstract 4386). This phase 1, open-label, multicenter study enrolled 39 treatment-naive patients (ECOG ≤2) to assess the safety and antitumor activity of brentuximab vedotin administered before, during, or after multiagent chemotherapy for the frontline treatment of mature T-cell lymphomas. The disease subtypes included systemic ALCL (n=32; ALK-positive, n=6; ALK-negative, n=26), PTCL-NOS (n=2), AITL (n=2), adult T-cell leukemia/lymphoma (n=2), and enteropathy-associated T-cell lymphoma (n=1). There were 13 patients who received the sequential treatment: 1.8 mg/kg of brentuximab vedotin every 3 weeks for 2 cycles and CHOP every 3 weeks for 6 cycles. Responders received an additional 1.8 mg/kg of brentuximab vedotin every 3 weeks for 8 cycles. For this regimen, the most common grade 3 AEs were febrile neutropenia (15%; n=2) and neutropenia (15%; n=2). After 8 cycles, the ORR was 85% (62% CR), and 2 patients had progressive disease (15%). After a median of 23.8 months, the estimated 1-year PFS was 77%, and the estimated 1-year overall survival was 85%. There were 26 patients who received the combination treatment: brentuximab vedotin plus CHOP without vincristine every 3 weeks for 6 cycles; responders received an additional 10 cycles of 1.8 mg/kg brentuximab vedotin every 3 weeks. This combination regimen did not exceed the dose-limiting toxicity. Although 73% of patients (n=19) experienced treatment-emergent peripheral neuropathy, only 2 patients (11%) experienced grade 3 peripheral neuropathy. The most common serious AEs were febrile neutropenia (31%), pyrexia (8%), and cardiac failure (8%). The ORR was 100% (CR, 84% for systemic ALCL; CR, 100% for other diagnoses). After a median of 21.4 months, the estimated 1-year PFS was 71% (95% CI, 49%-85%), and the estimated 1-year overall survival was 88% (95% CI, 68%-96%).

inhibitors in T-cell lymphoma has previously been reported. Preliminary results of a phase 1 trial showed that IPI-145, which is a gamma and delta inhibitor, had activity in T-cell lymphoma.[24] The study presented by Dr Dreyling enrolled patients with all types of lymphoma; most patients had B-cell lymphoma, but 4 patients had peripheral T-cell lymphoma not otherwise specified (PTCL-NOS). Among these 4 PTCL-NOS patients, 2 responded, with 1 complete response unconfirmed and 1 partial response. This finding suggests that this class of drug probably has activity in T-cell lymphomas.

Dr Ian Flinn presented results from a phase 1 study examining IPI-145 in chronic lymphocytic leukemia, which included patients with T-cell lymphoma.[25] Preliminary results were presented at the 2013 meeting of the American Society of Clinical Oncology.[26] At the data cutoff point, 26 patients with T-cell lymphoma had been treated. The overall response rate was 39%, which included rates of 29% in cutaneous T-cell lymphoma and 50% in patients with PTCL. T-cell lymphoma patients have been included in several studies of PI3 kinase inhibitors, and it appears that these agents have activity in this population.

Acknowledgment

Dr Horwitz has performed research for Celgene, Millennium, Spectrum, Infinity, and Seattle Genetics. He is a consultant for Celgene, Spectrum, and Seattle Genetics.

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Brief summary of Full Prescribing Information for FOLOTYN® (pralatrexate injection)—Please consult Full Prescribing Information.

INDICATIONS AND USAGE

FOLOTYN is indicated for the treatment of patients with relapsed or refractory peripheral T-cell lymphoma (PTCL). This indication is based on overall response rate. Clinical benefit such as improvement in progression-free survival or overall survival has not been demonstrated.

WARNINGS AND PRECAUTIONS

Bone Marrow Suppression

FOLOTYN can cause bone marrow suppression, manifested by thrombocytopenia, neutropenia, and/or anemia. Monitor complete blood counts and omit and/or reduce the dose based on ANC and platelet count prior to each dose as outlined in Table 2. Administer vitamin B_{12} and instruct patients to take folic acid to reduce the risk of treatment-related hematological toxicity.

Mucositis

FOLOTYN can cause mucositis. Monitor for mucositis weekly and if ≥ Grade 2 mucositis is observed, omit and/or reduce the dose as outlined in Table 1. Administer vitamin B_{12} and instruct patients to take folic acid to reduce the risk of mucositis.

Dermatologic Reactions

FOLOTYN can cause severe dermatologic reactions, which may result in death. These dermatologic reactions have been reported in clinical studies (14/663 patients [2.1%]) and post marketing experience, and have included skin exfoliation, ulceration, and toxic epidermal necrolysis (TEN). They may be progressive and increase in severity with further treatment, and may involve skin and subcutaneous sites of known lymphoma. Monitor patients with dermatologic reactions closely, and if severe, withhold or discontinue FOLOTYN.

Tumor Lysis Syndrome

FOLOTYN can cause tumor lysis syndrome (TLS). Monitor patients who are at increased risk of TLS and treat promptly.

Hepatic Toxicity

FOLOTYN can cause hepatic toxicity and liver function test abnormalities. Persistent liver function test abnormalities may be indicators of hepatic toxicity and require dose modification or discontinuation. Monitor liver function tests. Omit dose until recovery, adjust or discontinue therapy based on the severity of the hepatic toxicity.

Risk of Increased Toxicity in the Presence of Impaired Renal Function

Patients with moderate to severe renal function impairment may be at greater risk for increased exposure and toxicity. Monitor patients for renal function and systemic toxicity and adjust dosing accordingly. Serious adverse drug reactions including toxic epidermal necrolysis and mucositis were reported in patients with end stage renal disease (ESRD) undergoing dialysis who were administered FOLOTYN therapy. Avoid FOLOTYN use in patients with ESRD including those undergoing dialysis unless the potential benefit justifies the potential risk.

Embryo-Fetal Toxicity

FOLOTYN can cause fetal harm when administered to a pregnant woman. FOLOTYN was embryotoxic and fetotoxic in rats and rabbits. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

ADVERSE REACTIONS

The following serious adverse reactions are described below and elsewhere in the labeling: Bone Marrow Suppression, Mucositis, Dermatologic Reactions, Tumor Lysis Syndrome, Hepatic Toxicity.

The most common adverse reactions observed in patients with peripheral t-cell lymphoma (PTCL) treated with FOLOTYN were mucositis, thrombocytopenia, nausea, and fatigue.

Clinical Trials Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

The safety of FOLOTYN was evaluated in 111 PTCL patients in a single-arm clinical study in which patients received a starting dose of 30 mg/m^2 once weekly for 6 weeks in 7-week cycles. The median duration of treatment was 70 days (range 1-540 days).

Most Frequent Adverse Reactions

Table 4 summarizes the most frequent adverse reactions, regardless of causality, using the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI CTCAE, version 3.0).

Table 4 Adverse Reactions Occurring in PTCL Patients (Incidence ≥10% of patients)

	N=111					
	Total		Grade 3		Grade 4	
Preferred Term	**N**	**%**	**N**	**%**	**N**	**%**
Any Adverse Event	111	100	48	43	34	31
Mucositis[a]	78	70	19	17	4	4
Thrombocytopenia[a]	45	41	15	14	21	19[b]
Nausea	44	40	4	4	0	0
Fatigue	40	36	5	5	2	2
Anemia	38	34	17	15	2	2
Constipation	37	33	0	0	0	0
Pyrexia	36	32	1	1	1	1
Edema	33	30	1	1	0	0
Cough	31	28	1	1	0	0
Epistaxis	29	26	0	0	0	0
Vomiting	28	25	2	2	0	0
Neutropenia	27	24	14	13	8	7
Diarrhea	23	21	2	2	0	0
Dyspnea	21	19	8	7	0	0
Anorexia	17	15	3	3	0	0
Hypokalemia	17	15	4	4	1	1
Rash	17	15	0	0	0	0
Pruritus	16	14	2	2	0	0
Pharyngolaryngeal pain	15	14	1	1	0	0
Liver function test abnormal[c]	14	13	6	5	0	0
Abdominal pain	13	12	4	4	0	0
Pain in extremity	13	12	0	0	0	0
Back pain	12	11	3	3	0	0
Leukopenia	12	11	3	3	4	4
Night sweats	12	11	0	0	0	0
Asthenia	11	10	1	1	0	0
Tachycardia	11	10	0	0	0	0
Upper respiratory tract infection	11	10	1	1	0	0

[a] Stomatitis or mucosal inflammation of the gastrointestinal and genitourinary tracts
[b] Five patients with platelets <10,000/mcL
[c] Alanine aminotransferase, aspartate aminotransferase, and transaminases increased

Serious Adverse Events

Forty-four percent of patients (n=49) experienced a serious adverse event while on study or within 30 days after their last dose of FOLOTYN. The most common serious adverse events (>3%), regardless of causality, were pyrexia, mucositis, sepsis, febrile neutropenia, dehydration, dyspnea, and thrombocytopenia. One death from cardiopulmonary arrest in a patient with mucositis and febrile neutropenia was reported in this trial. Deaths from mucositis, febrile neutropenia, sepsis, and pancytopenia occurred in 1.2% of patients treated on all FOLOTYN trials at doses ranging from 30 to 325 mg/m^2.

Discontinuations

Twenty-three percent of patients (n=25) discontinued treatment with FOLOTYN due to adverse reactions. The adverse reactions reported most frequently as the reason for discontinuation of treatment were mucositis (6%, n=7) and thrombocytopenia (5%, n=5).

Dose Modifications

The target dose of FOLOTYN was 30 mg/m^2 once weekly for 6 weeks in 7-week cycles. The majority of patients (69%, n=77) remained at the target dose for the duration of treatment. Overall, 85% of scheduled doses were administered.

Post Marketing Experience

Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Dermatologic Reactions

Toxic epidermal necrolysis, sometimes fatal, has been reported during post-marketing use of FOLOTYN. Fatal cases have been reported following the first dose of FOLOTYN, including when a reduced dose is given, and have been reported in patients with end-stage renal disease undergoing dialysis.

DRUG INTERACTIONS

No formal clinical assessments of pharmacokinetic drug-drug interactions between FOLOTYN and other drugs have been conducted. The effect of co-administration of the uricosuric drug probenecid (an inhibitor of multiple transporter systems including the multidrug resistance-associated protein 2 (MRP2) efflux transporter) on pralatrexate pharmacokinetics was investigated in a Phase 1 clinical study. Co-administration of increasing doses of probenecid resulted in delayed clearance of pralatrexate and a commensurate increase in exposure.

When administering FOLOTYN to patients receiving probenecid or other drugs that may affect relevant transporter systems (eg, NSAIDs), monitor patients closely for signs of systemic toxicity due to increased drug exposure.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category D

Embryo-Fetal Toxicity (see Warnings and Precautions)

FOLOTYN can cause fetal harm when administered to a pregnant woman. Pralatrexate was embryotoxic and fetotoxic in rats at IV doses of 0.06 mg/kg/day (0.36 mg/m^2/day or about 1.2% of the clinical dose on a mg/m^2 basis) given on gestation days 7 through 20. Treatment with pralatrexate caused a dose-dependent decrease in fetal viability manifested as an increase in late, early, and total resorptions. There was also a dose-dependent increase in post-implantation loss. In rabbits, IV doses of 0.03 mg/kg/day (0.36 mg/m^2/day) or greater given on gestation days 8 through 21 also caused abortion and fetal lethality. This toxicity manifested as early and total resorptions, post-implantation loss, and a decrease in the total number of live fetuses. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Nursing Mothers

It is not known whether pralatrexate is excreted in human milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from this drug, a decision should be made whether to discontinue nursing or to discontinue FOLOTYN, taking into account the importance of FOLOTYN to the mother.

Pediatric Use

Pediatric patients were not included in clinical studies with FOLOTYN. The safety and effectiveness of FOLOTYN in pediatric patients have not been established.

Geriatric Use

In the PTCL efficacy study, 36% of patients (n=40) were 65 years of age and over. No overall differences in efficacy and safety were observed in patients based on age (<65 years compared with ≥65 years).

Due to the contribution of renal excretion to overall clearance of pralatrexate (approximately 34%), age related decline in renal function may lead to a reduction in clearance and a commensurate increase in plasma exposure. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. Since elderly patients may be at higher risk, monitor more closely. Omit dose and subsequently adjust or discontinue therapy for exposure related toxicity.

Hepatic Impairment

The safety, efficacy and pharmacokinetics of FOLOTYN have not been evaluated in patients with hepatic impairment. Patients with the following laboratory values were excluded from the pralatrexate lymphoma clinical trials: total bilirubin > 1.5 mg/dL; aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 2.5 × upper limit of normal (ULN); and AST or ALT > 5 × ULN if documented hepatic involvement with lymphoma. Treatment with FOLOTYN can cause hepatic toxicity and liver function test abnormalities (*see Dosage and Administration and Warnings and Precautions*).

Renal Impairment

The safety, efficacy and pharmacokinetics of FOLOTYN have not been evaluated in patients with renal impairment. The risk for toxicity may be greater when administering FOLOTYN to patients with moderate-to-severe impairment due to the contribution of renal excretion (approximately 34%) to the overall clearance of pralatrexate. Serious adverse drug reactions, including TEN and mucositis have been reported in patients with ESRD undergoing dialysis. Monitor patients for renal function and for systemic toxicity due to increased drug exposure and adjust dosing accordingly. Avoid the use of FOLOTYN in patients with ESRD undergoing dialysis unless the potential benefit justifies the potential risk.

OVERDOSAGE

No specific information is available on the treatment of overdosage of FOLOTYN. If an overdose occurs, general supportive measures should be instituted as deemed necessary by the treating physician. Based on FOLOTYN's mechanism of action, consider the prompt administration of leucovorin.

PATIENT COUNSELING INFORMATION

See FDA-approved Patient Package Insert.

Patients should be instructed to read the Patient Package Insert carefully.

DOSAGE AND ADMINISTRATION

Pretreatment Vitamin Supplementation

Folic Acid: Patients should take folic acid 1.0-1.25 mg orally once daily beginning 10 days before the first dose of FOLOTYN. Continue folic acid during the full course of therapy and for 30 days after the last dose of FOLOTYN.

Vitamin B_{12}: Administer vitamin B_{12} 1 mg intramuscularly within 10 weeks prior to the first dose of FOLOTYN and every 8-10 weeks thereafter. Subsequent vitamin B_{12} injections may be given the same day as treatment with FOLOTYN.

Dosing and Administration

The recommended dose of FOLOTYN is 30 mg/m^2 administered as an intravenous (IV) push over 3-5 minutes via the side port of a free-flowing 0.9% Sodium Chloride Injection, USP IV line once weekly for 6 weeks in 7-week cycles until progressive disease or unacceptable toxicity.

FOLOTYN is a clear, yellow solution. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use any vials exhibiting particulate matter or discoloration.

Monitoring and Dose Modifications

Management of severe or intolerable adverse reactions may require dose omission, reduction, interruption, or discontinuation of FOLOTYN therapy.

Monitoring

Monitor complete blood cell counts and severity of mucositis at baseline and weekly. Perform serum chemistry tests, including renal and hepatic function, prior to the start of the first and fourth dose of each cycle.

Dose Modification Recommendations

Prior to administering any dose of FOLOTYN:

- Mucositis should be ≤Grade 1.
- Platelet count should be ≥100,000/mcL for first dose and ≥50,000/mcL for all subsequent doses.
- Absolute neutrophil count (ANC) should be ≥1,000/mcL.

Doses may be omitted or reduced based on patient tolerance. Omitted doses will not be made up at the end of the cycle; once a dose reduction occurs for toxicity, do not re-escalate. For dose modifications and omissions, use the guidelines in Tables 1, 2, and 3.

Table 1 FOLOTYN Dose Modifications for Mucositis

Mucositis Grade[a] on Day of Treatment	Action	Dose upon Recovery to ≤Grade 1
Grade 2	Omit dose	Continue prior dose
Grade 2 recurrence	Omit dose	20 mg/m^2
Grade 3	Omit dose	20 mg/m^2
Grade 4	Stop therapy	

[a] Per National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI CTCAE, Version 3.0)

Table 2 FOLOTYN Dose Modifications for Hematologic Toxicities

Blood Count on Day of Treatment	Duration of Toxicity	Action	Dose upon Restart
Platelet <50,000/mcL	1 week	Omit dose	Continue prior dose
	2 weeks	Omit dose	20 mg/m^2
	3 weeks	Stop therapy	
ANC 500-1,000/mcL and no fever	1 week	Omit dose	Continue prior dose
ANC 500-1,000/mcL with fever or ANC <500/mcL	1 week	Omit dose, give G-CSF or GM-CSF support	Continue prior dose with G-CSF or GM-CSF support
	2 weeks or recurrence	Omit dose, give G-CSF or GM-CSF support	20 mg/m^2 with G-CSF or GM-CSF support
	3 weeks or 2nd recurrence	Stop therapy	

G-CSF=granulocyte colony-stimulating factor; GM-CSF=granulocyte macrophage colony-stimulating factor

Table 3 FOLOTYN Dose Modifications for All Other Treatment-related Toxicities

Toxicity Grade[a] on Day of Treatment	Action	Dose upon Recovery to ≤Grade 2
Grade 3	Omit dose	20 mg/m^2
Grade 4	Stop therapy	

[a] Per National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI CTCAE, Version 3.0)

Manufactured for:
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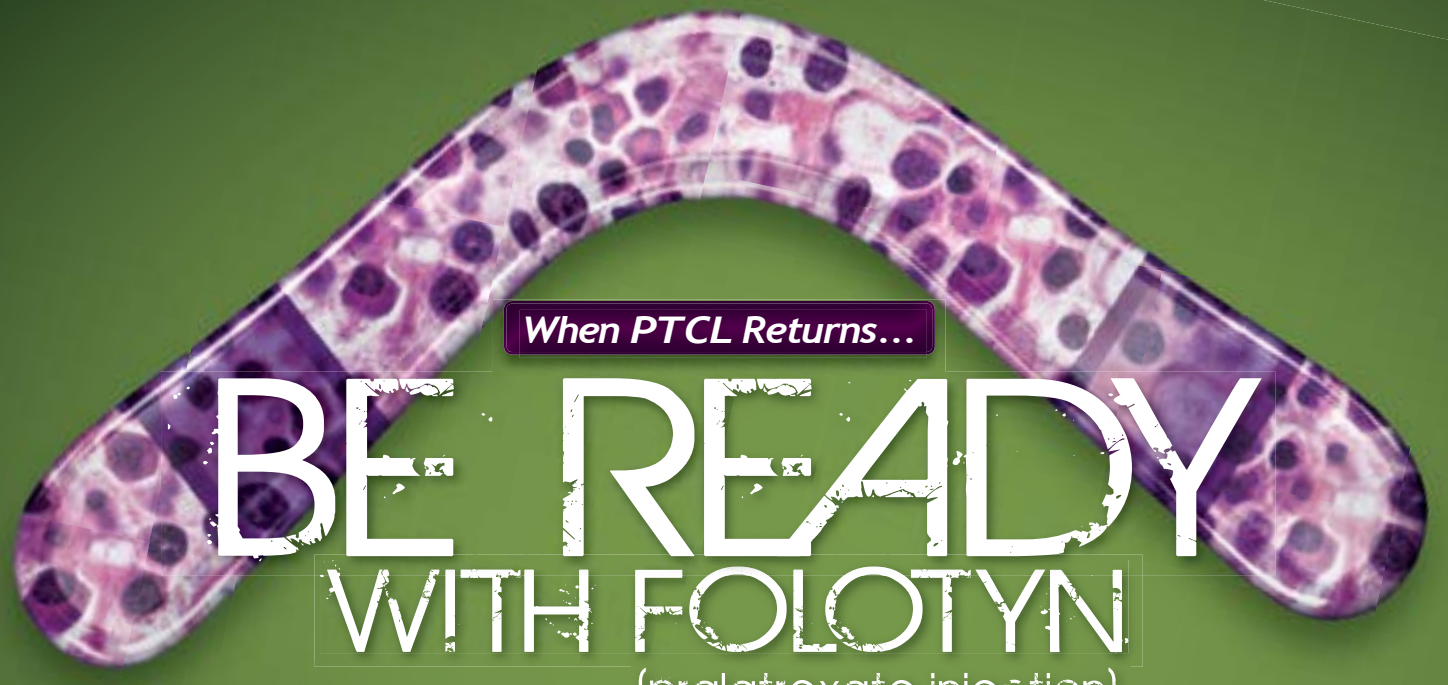
1-888-ALLOS88 (1-888-255-6788)

U.S. Patent: 6,028,071 and 7,622,470
Rev.7: May 2012

FOLOTYN is indicated for the treatment of patients with relapsed or refractory peripheral T-cell lymphoma. The indication for FOLOTYN is based on overall response rate. Clinical benefit such as improvement in progression-free survival or overall survival has not been demonstrated.



When PTCL Returns…

BE READY WITH FOLOTYN

(pralatrexate injection)

Demonstrated response in relapsed or refractory PTCL[1]

27% overall response rate (CR+CRu+PR) by independent central review (95% CI, 19-36)*

Of the responders, 66% responded within Cycle 1*

— *Median time to first response was 45 days (range=37-349 days)*

9.4-month median duration of response by central review (range=1-503 days)*

—*12% (95% CI, 7-20) of patients had responses lasting ≥14 weeks (range=98-503 days)*

Demonstrated response in PROPEL—the first large, prospective, single-arm, open-label clinical trial in PTCL

*Per independent central review

Important Safety Information

Warnings and Precautions

- FOLOTYN may suppress bone marrow function, manifested by thrombocytopenia, neutropenia, and anemia. Monitor blood counts and omit and/or reduce dose for hematologic toxicities.
- Mucositis may occur. Monitor at least weekly. If ≥Grade 2 mucositis is observed, omit and/or reduce dose. Patients should be instructed to take folic acid and receive vitamin B_{12} to potentially reduce treatment-related hematological toxicity and mucositis.
- Dermatologic reactions, including fatal reactions, have occurred and may be progressive and increase in severity with further treatment. Patients with dermatologic reactions should be monitored closely, and omit, and/or reduce dose or discontinue FOLOTYN.
- Tumor lysis syndrome may occur. Monitor patients and treat promptly.
- FOLOTYN can cause hepatic toxicity and liver function test abnormalities. Monitor liver function tests and if abnormalities are ≥Grade 3, omit until recovery then reduce dose or discontinue FOLOTYN as required.
- Patients with moderate to severe renal function impairment may be at greater risk for increased exposure and toxicity. Monitor patients for renal function and systemic toxicity and adjust dosing accordingly. Avoid FOLOTYN use in patients with end stage renal disease including those undergoing dialysis unless the potential benefit justifies the potential risk.
- FOLOTYN can cause fetal harm. Women should avoid becoming pregnant while being treated with FOLOTYN and pregnant women should be informed of the potential harm to the fetus.

Adverse Reactions

- The most common adverse reactions were mucositis (70%), thrombocytopenia (41%), nausea (40%), and fatigue (36%). The most common serious adverse events were pyrexia, mucositis, sepsis, febrile neutropenia, dehydration, dyspnea, and thrombocytopenia.

Drug Interactions

- Co-administration with probenecid or other drugs that may affect relevant transporter systems (eg, NSAIDs), requires close monitoring for signs of systemic toxicity.

Use in Specific Patient Populations

- Nursing mothers should be advised to discontinue nursing or the drug, taking into consideration the importance of the drug to the mother.
- Approximately one third of the administered dose of FOLOTYN is cleared by the kidneys. FOLOTYN has not been studied in patients with renal impairment.

Please see FOLOTYN Full Prescribing Information.

Reference: 1. FOLOTYN Prescribing Information. Allos Therapeutics, Inc., 2012.

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Please see accompanying brief summary of Prescribing Information.

FOLOTYN® (pralatrexate injection)

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