

**A SPECIAL MEETING REVIEW EDITION**

**Highlights in Cutaneous T-Cell Lymphoma From the  
60th American Society of Hematology Annual Meeting**

A Review of Selected Presentations From the 60th American Society of  
Hematology Annual Meeting • December 1-4, 2018 • San Diego, California

**Special Reporting on:**

- Efficacy of Mogamulizumab By Prior Systemic Therapy in Patients With Previously Treated Cutaneous T-Cell Lymphoma: Post Hoc Analysis From the Phase 3 MAVORIC Study
- The Novel SYK/JAK Inhibitor Cerdulatinib Demonstrates Good Tolerability and Clinical Response in a Phase 2a Study in Relapsed/Refractory Peripheral T-Cell Lymphoma and Cutaneous T-Cell Lymphoma
- Long-Term Clinical Benefit to Anti-CCR4 Mogamulizumab: Results From the Phase 3 MAVORIC Study in Previously Treated Cutaneous T-Cell Lymphoma
- IPH4102; An Anti-KIR3DL2 Monoclonal Antibody in Refractory Sézary Syndrome: Results From a Multicenter Phase 1 Trial
- Evaluation of Symptom and Side Effect Burden in Cutaneous T-Cell Lymphoma Patients Treated With Mogamulizumab or Vorinostat
- Phase 1/2 Trial of Durvalumab and Lenalidomide in Patients With Cutaneous T-Cell Lymphoma: Preliminary Results of Phase I Results and Correlative Studies
- Superior Clinical Benefit of Brentuximab Vedotin in Mycosis Fungoides Versus Physician's Choice Irrespective of CD30 Level or Large Cell Transformation Status in the Phase 3 ALCANZA Study
- Mechanistic Analysis of Prolonged Negative Impacts of Anti-CCR4 Antibody Mogamulizumab on Regulatory T-Cell Homeostasis After Allogeneic Hematopoietic Stem Cell Transplantation
- Phase 1 Trial of Cobomarsen, an Inhibitor of Mir-155, in Cutaneous T-Cell Lymphoma

**PLUS Meeting Abstract Summaries**

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## *In CTCL subtypes mycosis fungoides (MF) and Sézary syndrome (SS)...*

**POTELIGEO is indicated for the treatment of adult patients with relapsed or refractory MF or SS after at least one prior systemic therapy.**

### **Important Safety Information**

#### **Warnings and Precautions**

**Dermatologic toxicity:** Monitor patients for rash throughout the course of treatment. For patients who experienced dermatologic toxicity in Trial 1, the median time to onset was 15 weeks, with 25% of cases occurring after 31 weeks. Interrupt POTELIGEO for moderate or severe rash (Grades 2 or 3). Permanently discontinue POTELIGEO for life-threatening (Grade 4) rash or for any Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN).

**Infusion reactions:** Most infusion reactions occur during or shortly after the first infusion. Infusion reactions can also occur with subsequent infusions. Monitor patients closely for signs and symptoms of infusion reactions and interrupt the infusion for any grade reaction and treat promptly. Permanently discontinue POTELIGEO for any life-threatening (Grade 4) infusion reaction.

**Infections:** Monitor patients for signs and symptoms of infection and treat promptly.

**Autoimmune complications:** Interrupt or permanently discontinue POTELIGEO as appropriate for suspected immune-mediated adverse reactions. Consider the benefit/risk of POTELIGEO in patients with a history of autoimmune disease.

**Complications of allogeneic HSCT after POTELIGEO:** Increased risks of transplant complications have been reported in patients who received allogeneic HSCT after POTELIGEO. Follow patients closely for early evidence of transplant-related complications.

#### **Adverse Reactions**

**The most common adverse reactions** (reported in  $\geq 10\%$  of patients) with POTELIGEO in the clinical trial were rash, including drug eruption (35%), infusion reaction (33%), fatigue (31%), diarrhea (28%), drug eruption (24%), upper respiratory tract infection (22%), musculoskeletal pain (22%), skin infection (19%), pyrexia (17%), edema (16%), nausea (16%), headache (14%), thrombocytopenia (14%), constipation (13%), anemia (12%), mucositis (12%), cough (11%), and hypertension (10%).

You are encouraged to report suspected adverse reactions to Kyowa Kirin, Inc. at 1-844-768-3544 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

**Please see Brief Summary on adjacent pages.**

**Reference: 1.** POTELIGEO [package insert]. Kyowa Kirin, Inc., Bedminster, NJ USA.

# Make progress. Delay progression.

**Progression-free survival (PFS) more than doubled in a study of MF and SS patients<sup>1</sup>**

**POTELIGEO reduced the risk of disease progression 47% vs vorinostat (median PFS 7.6 months vs 3.1 months, respectively;  $P < 0.001$ )<sup>1</sup>**

More than 5x as many POTELIGEO-treated patients had an overall response (28% vs 5%), with higher response rates than comparator in skin, blood, and lymph nodes.<sup>1</sup>

**Study design:** Phase 3 trial in 372 adult patients with MF or SS stages IB to IV, who had received at least 1 prior systemic therapy, randomized to either POTELIGEO (1 mg/kg administered once weekly for the first 5 infusions and once every 2 weeks thereafter) or active comparator (vorinostat), dosed per prescribing information. Primary endpoint was PFS evaluated by disease progression in any compartment (skin, blood, lymph nodes, or viscera).

Learn more about the 1<sup>st</sup> FDA-approved CCR4-targeted treatment. [www.poteligeohcp.com](http://www.poteligeohcp.com)

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**POTELIGEO<sup>®</sup>**  
(mogamulizumab-kpkc) Injection

*Targeted for Control*

**KYOWA KIRIN**

## Brief Summary of the Prescribing Information for POTEIGEO® (mogamulizumab-kpkc) injection, for intravenous use

### 1 INDICATIONS AND USAGE

POTEIGEO (mogamulizumab-kpkc) is indicated for the treatment of adult patients with relapsed or refractory mycosis fungoides (MF) or Sézary syndrome (SS) after at least one prior systemic therapy.

### 2 DOSAGE AND ADMINISTRATION

#### 2.1 Recommended Dosage

The recommended dose of POTEIGEO is 1 mg/kg administered as an intravenous infusion over at least 60 minutes. Administer on days 1, 8, 15, and 22 of the first 28-day cycle, then on days 1 and 15 of each subsequent 28-day cycle until disease progression or unacceptable toxicity.

Administer POTEIGEO within 2 days of the scheduled dose. If a dose is missed, administer the next dose as soon as possible and resume dosing schedule.

Do not administer POTEIGEO subcutaneously or by rapid intravenous administration.

#### Recommended Premedications

Administer premedication with diphenhydramine and acetaminophen for the first POTEIGEO infusion.

#### 2.2 Dose Modifications for Toxicity

##### Dermatologic Toxicity

- Permanently discontinue POTEIGEO for life-threatening (Grade 4) rash or for any Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) [see *Warnings and Precautions* (5.1)]. If SJS or TEN is suspected, stop POTEIGEO and do not resume unless SJS or TEN has been excluded and the cutaneous reaction has resolved to Grade 1 or less.
- If moderate or severe (Grades 2 or 3) rash occurs, interrupt POTEIGEO and administer at least 2 weeks of topical corticosteroids. If rash improves to Grade 1 or less, POTEIGEO may be resumed [see *Warnings and Precautions* (5.1)].
- If mild (Grade 1) rash occurs, consider topical corticosteroids.

##### Infusion Reactions

- Permanently discontinue POTEIGEO for a life-threatening (Grade 4) infusion reaction [see *Warnings and Precautions* (5.2)].
- Temporarily interrupt the infusion of POTEIGEO for mild to severe (Grades 1 to 3) infusion reactions and treat symptoms. Reduce the infusion rate by at least 50% when restarting the infusion after symptoms resolve. If reaction recurs and is unmanageable, discontinue infusion [see *Warnings and Precautions* (5.2)].
- If an infusion reaction occurs, administer premedication (such as diphenhydramine and acetaminophen) for subsequent POTEIGEO infusions.

### 4 CONTRAINDICATIONS

None.

### 5 WARNINGS AND PRECAUTIONS

#### 5.1 Dermatologic Toxicity

Fatal and life-threatening skin adverse reactions, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have occurred in recipients of POTEIGEO. Rash (drug eruption) is one of the most common adverse reactions associated with POTEIGEO. In Trial 1, 25% (80/319) of patients treated with POTEIGEO had an adverse reaction of drug eruption, with 18% of these cases being severe (Grade 3) and 82% of these cases being Grade 1 or 2. Of 528 patients treated with POTEIGEO in clinical trials, Grade 3 skin adverse reactions were reported in 3.6%, Grade 4 skin adverse reactions in <1%, and SJS in <1%. The onset of drug eruption is variable, and the affected areas and appearance vary. In Trial 1, the median time to onset was 15 weeks, with 25% of cases occurring after 31 weeks. The more common presentations reported included papular or maculopapular rash, lichenoid, spongiotic or granulomatous dermatitis, and morbilliform rash. Other presentations included scaly plaques, pustular eruption, folliculitis, non-specific dermatitis and psoriasiform dermatitis.

Monitor patients for rash throughout the treatment course. Management of dermatologic toxicity includes topical corticosteroids and interruption or permanent cessation of POTEIGEO [see *Dosage and Administration* (2.2)]. Consider skin biopsy to help distinguish drug eruption from disease progression.

Discontinue POTEIGEO permanently for SJS or TEN or for any life-threatening (Grade 4) reaction. For possible SJS or TEN, interrupt POTEIGEO and do not restart unless SJS or TEN is ruled out and the cutaneous reaction has resolved to Grade 1 or less.

#### 5.2 Infusion Reactions

Fatal and life-threatening infusion reactions have been reported in patients treated with POTEIGEO. In Trial 1, infusion reactions occurred in 35% (112/319) of patients treated with POTEIGEO, with 8% of these reactions being severe (Grade 3). Most reactions (approximately 90%) occur during or shortly after the first infusion. Infusion reactions can also occur with subsequent infusions. The most commonly reported signs include chills, nausea, fever, tachycardia, rigors, headache, and vomiting.

Consider premedication (such as diphenhydramine and acetaminophen) for the first infusion of POTEIGEO in all patients. Whether premedication reduces the risk or severity of these reactions is not established. In Trial 1, infusion reactions occurred in 42% of patients without premedication and 32% of patients with premedication. Monitor patients closely for signs and symptoms of infusion reactions and interrupt the infusion for any grade reaction and treat promptly [see *Dosage and Administration* (2.2)].

#### 5.3 Infections

Fatal and life-threatening infections have occurred in patients treated with POTEIGEO, including sepsis, pneumonia, and skin infection. In Trial 1, 18% (34/184) of patients randomized to POTEIGEO had Grade 3 or higher infection or an infection-related serious

adverse reaction. Monitor patients for signs and symptoms of infection and treat promptly.

#### 5.4 Autoimmune Complications

Fatal and life-threatening immune-mediated complications have been reported in recipients of POTEIGEO. Grade 3 or higher immune-mediated or possibly immune-mediated reactions have included myositis, myocarditis, polymyositis, hepatitis, pneumonitis, and a variant of Guillain-Barré syndrome. Use of systemic immunosuppressants for immune-mediated reactions was reported in 1.9% (6/319) of recipients of POTEIGEO in Trial 1, including for a case of Grade 2 polymyalgia rheumatica. New-onset hypothyroidism (Grade 1 or 2) was reported in 1.3% of patients and managed with observation or levothyroxine. Interrupt or permanently discontinue POTEIGEO as appropriate for suspected immune-mediated adverse reactions. Consider the benefit/risk of POTEIGEO in patients with a history of autoimmune disease.

#### 5.5 Complications of Allogeneic Hematopoietic Stem Cell Transplantation (HSCT) after POTEIGEO

Increased risks of transplant complications have been reported in patients who receive allogeneic HSCT after POTEIGEO including severe (Grade 3 or 4) acute graft-versus-host disease (GVHD), steroid-refractory GVHD and transplant-related death. Among recipients of pre-transplantation POTEIGEO, a higher risk of transplant complications has been reported if POTEIGEO is given within a shorter time frame (approximately 50 days) before HSCT. Follow patients closely for early evidence of transplant-related complications.

### 6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in other sections of the labeling:

- Dermatologic Toxicity [see *Warnings and Precautions* (5.1)].
- Infusion Reactions [see *Warnings and Precautions* (5.2)].
- Infections [see *Warnings and Precautions* (5.3)].
- Autoimmune Complications [see *Warnings and Precautions* (5.4)].
- Complications of Allogeneic HSCT after POTEIGEO [see *Warnings and Precautions* (5.5)].

#### 6.1 Clinical Trial Experience

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

**Trial 1:** The data described below reflect exposure to POTEIGEO in a randomized, open-label, actively controlled clinical trial for adult patients with MF or SS who received at least one prior systemic therapy [see *Clinical Studies* (14)]. Of 370 patients treated, 184 (57% with MF, 43% with SS) received POTEIGEO as randomized treatment and 186 (53% with MF, 47% with SS) received vorinostat. In the vorinostat arm, 135 patients (73%) subsequently crossed over to POTEIGEO for a total of 319 patients treated with POTEIGEO. POTEIGEO was administered at 1 mg/kg intravenously over at least 60 minutes on days 1, 8, 15, and 22 of the first 28-day cycle and on days 1 and 15 of subsequent 28-day cycles. Premedication (diphenhydramine, acetaminophen) was optional and administered to 65% of randomized patients for the first infusion. The comparator group received vorinostat 400 mg orally once daily, given continuously in 28-day cycles. Treatment continued until unacceptable toxicity or progressive disease.

The median age was 64 years (range, 25 to 101 years), 58% of patients were male, 70% were white, and 99% had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Patients had a median of 3 prior systemic therapies. The trial required an absolute neutrophil count (ANC)  $\geq 1500/\mu\text{L}$  ( $\geq 1000/\mu\text{L}$  if bone marrow was involved), platelet count  $\geq 100,000/\mu\text{L}$  ( $\geq 75,000/\mu\text{L}$  if bone marrow was involved), creatinine clearance  $> 50 \text{ mL/min}$  or serum creatinine  $\leq 1.5 \text{ mg/dL}$ , and hepatic transaminases  $\leq 2.5$  times upper limit of normal (ULN) ( $\leq 5$  times ULN if lymphomatous liver infiltration). Patients with active autoimmune disease, active infection, autologous HSCT within 90 days, or prior allogeneic HSCT were excluded.

During randomized treatment, the median duration of exposure to POTEIGEO was 5.6 months, with 48% (89/184) of patients with at least 6 months of exposure and 23% (43/184) with at least 12 months of exposure. The median duration of exposure to vorinostat was 2.8 months, with 22% (41/186) of patients with at least 6 months of exposure. Fatal adverse reactions within 90 days of the last dose occurred in 2.2% (7/319) of patients who received POTEIGEO as randomized or crossover treatment.

Serious adverse reactions were reported in 36% (66/184) of patients randomized to POTEIGEO and most often involved infection (16% of patients; 30/184). Serious adverse reactions reported in  $> 2\%$  of patients randomized to POTEIGEO were pneumonia (5%), sepsis (4%), pyrexia (4%), and skin infection (3%); other serious adverse reactions, each reported in 2% of patients, included hepatitis, pneumonitis, rash, infusion related reaction, lower respiratory tract infection, and renal insufficiency. POTEIGEO was discontinued for adverse reactions in 18% of randomized patients, most often due to rash or drug eruption (7.1%).

#### Common Adverse Reactions

The most common adverse reactions (reported in  $\geq 20\%$  of patients randomized to POTEIGEO) were rash (including drug eruption), infusion related reactions, fatigue, diarrhea, upper respiratory tract infection and musculoskeletal pain. Other common adverse reactions (reported in  $\geq 10\%$  of patients randomized to POTEIGEO) included skin infection, pyrexia, nausea, edema, thrombocytopenia, headache, constipation, mucositis, anemia, cough and hypertension. Table 1 summarizes common adverse reactions having a  $\geq 2\%$  higher incidence with POTEIGEO than with vorinostat in Trial 1.

*Other Common Adverse Reactions in  $\geq 10\%$  of POTEIGEO Arm<sup>a, b</sup>*

- **General disorders:** fatigue (31%), edema (16%); **Gastrointestinal disorders:** diarrhea (28%), nausea (16%), constipation (13%); **Blood and lymphatic system disorders:**

thrombocytopenia (14%), anemia (12%); **Nervous system disorders:** headache (14%); **Vascular disorders:** hypertension (10%); **Respiratory disorders:** cough (11%)

*Adverse Reactions in ≥5% but <10% of POTELIGE Arm<sup>a,b</sup>*

- **Infections:** candidiasis (9%), urinary tract infection (9%), folliculitis (8%), pneumonia (6%), otitis (5%), herpesvirus infection (5%); **Investigations:** renal insufficiency (9%), hyperglycemia (9%), hyperuricemia (8%), weight increase (8%), weight decrease (6%), hypomagnesemia (6%); **Psychiatric disorders:** insomnia (9%), depression (7%); **Skin and subcutaneous disorders:** xerosis (8%), alopecia (7%); **Nervous system disorders:** dizziness (8%), peripheral neuropathy (7%); **Metabolism and nutrition disorders:** decreased appetite (8%); **Respiratory disorders:** dyspnea (7%); **General disorders:** chills (7%); **Gastrointestinal disorders:** vomiting (7%), abdominal pain (5%); **Injury, poisoning and procedural complications:** fall (6%); **Musculoskeletal disorders:** muscle spasms (5%); **Cardiovascular disorders:** arrhythmia (5%); **Eye disorders:** conjunctivitis (5%)

*Selected Other Adverse Reactions<sup>a,b</sup>*

- Tumor lysis syndrome (<1%); Myocardial ischemia or infarction (<1%); Cardiac failure (<1%)

<sup>a</sup> Includes grouped terms; <sup>b</sup> From 184 patients randomized to POTELIGE

**Table 1: Common Adverse Reactions (≥10%) with ≥2% Higher Incidence in the POTELIGE Arm**

Adverse Reactions by Body System <sup>a,b</sup>	POTELIGE (n=184)		Vorinostat (n=186)	
	All Grades (%)	≥Grade 3 (%)	All Grades (%)	≥Grade 3 (%)
<b>Skin and subcutaneous tissue disorders</b>				
Rash, Including Drug Eruption	35	5	11	2
Drug Eruption	24	5	<1	0
<b>Procedural complications</b>				
Infusion Related Reaction	33	2	0	0
<b>Infections</b>				
Upper Respiratory Tract Infection	22	0	16	1
Skin Infection	19	3	13	4
<b>Musculoskeletal and connective tissue disorders</b>				
Musculoskeletal Pain	22	<1	17	3
<b>General disorders</b>				
Pyrexia	17	<1	7	0
<b>Gastrointestinal</b>				
Mucositis	12	1	6	0

<sup>a</sup> Adverse reactions include groupings of individual preferred terms.

<sup>b</sup> Includes adverse reactions reported up to 90 days after randomized treatment.

Rash/Drug Eruption includes: dermatitis (allergic, atopic, bullous, contact, exfoliative, infected), drug eruption, palmoplantar keratoderma, rash (generalized, macular, maculopapular, papular, pruritic, pustular), skin reaction, toxic skin eruption

Upper Respiratory Tract Infection includes: laryngitis viral, nasopharyngitis, pharyngitis, rhinitis, sinusitis, upper respiratory tract infection, viral upper respiratory tract infection

Skin Infection includes: cellulitis, dermatitis infected, erysipelas, impetigo, infected skin ulcer, periorbital cellulitis, skin bacterial infection, skin infection, staphylococcal skin infection

Musculoskeletal Pain includes: back pain, bone pain, musculoskeletal chest pain, musculoskeletal pain, myalgia, neck pain, pain in extremity

Mucositis includes: aphthous stomatitis, mouth ulceration, mucosal inflammation, oral discomfort, oral pain, oropharyngeal pain, stomatitis

Table 2 summarizes common treatment-emergent laboratory abnormalities having a ≥2% higher incidence with POTELIGE than with vorinostat.

**Table 2: Common New or Worsening Laboratory Abnormalities (≥10%) with ≥2% Higher Incidence in the POTELIGE Arm**

Laboratory Test <sup>a</sup>	POTELIGE (n=184)		Vorinostat (n=186)	
	All Grades (%)	≥Grade 3 (%)	All Grades (%)	≥Grade 3 (%)
<b>Chemistry</b>				
Albumin Decreased	34	2	27	3
Calcium Decreased	30	3	20	2
Uric Acid Increased	29	29	11	11
Phosphate Decreased	27	5	26	5
Magnesium Decreased	17	<1	8	<1
Glucose Decreased	14	0	8	<1
Calcium Increased	12	<1	8	<1
<b>Hematology</b>				
CD4 Lymphocytes Decreased <sup>b</sup>	63	43	17	8
Lymphocytes Decreased	31	16	12	4
White Blood Cells Decreased	33	2	18	2

<sup>a</sup> Includes laboratory abnormalities, reported up to 90 days after treatment, that are new or worsening in grade or with worsening from baseline unknown.

<sup>b</sup> Out of 99 evaluable recipients of POTELIGE and 36 evaluable recipients of vorinostat.

Other common treatment-emergent laboratory abnormalities in the POTELIGE arm included hyperglycemia (52%; 4% Grade 3-4), anemia (35%; 2% Grade 3-4), thrombocytopenia (29%, none Grade 3-4), aspartate transaminase (AST) increased (25%; 2% Grade 3-4), alanine transaminase (ALT) increased (18%; 1% Grade 3-4), alkaline phosphatase increased (17%; 0% Grade 3-4) and neutropenia (10%; 2% Grade 3-4). Grade 4 treatment-emergent laboratory abnormalities observed in ≥1% of the POTELIGE arm included lymphopenia (5%), leukopenia (1%) and hypophosphatemia (1%).

## 6.2 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of incidence of antibodies to POTELIGE with the incidences of antibodies in other studies or to other products may be misleading.

Among 258 patients treated with POTELIGE in Trial 1, 10 (3.9%) tested positive for treatment-emergent (treatment-induced or treatment-boosted) anti-mogamulizumab-kpcc antibodies by an electrochemiluminescent assay. There were no positive neutralizing antibody responses.

## 6.3 Postmarketing Safety Information

The following adverse reactions have been identified during post-approval use of POTELIGE. 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.

- Infections: Hepatitis B virus reactivation
- Cardiac disorders: Stress cardiomyopathy

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

**Risk Summary:** There are no available data on POTELIGE use in pregnant women to inform a drug-associated risk of major birth defects and miscarriage. In an animal reproduction study, administration of mogamulizumab-kpcc to pregnant cynomolgus monkeys from the start of organogenesis through delivery did not show a potential for adverse developmental outcomes at maternal systemic exposures 27 times the exposure in patients at the recommended dose, based on AUC (see Data). In general, IgG molecules are known to cross the placental barrier and in the monkey reproduction study mogamulizumab-kpcc was detected in fetal plasma. Therefore, POTELIGE has the potential to be transmitted from the mother to the developing fetus. POTELIGE is not recommended during pregnancy or in women of childbearing potential not using contraception. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risks of major birth defects and miscarriage in clinically recognized pregnancies are 2-4% and 15-20%, respectively.

### 8.2 Lactation

**Risk Summary:** There is no information regarding the presence of POTELIGE in human milk, the effects on the breastfed child, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for POTELIGE and any potential adverse effects on the breastfed child from POTELIGE or from the underlying maternal condition.

### 8.3 Females and Males of Reproductive Potential

POTELIGE is not recommended during pregnancy or in women of childbearing potential not using contraception.

**Pregnancy Testing:** For females of reproductive potential, verify pregnancy status prior to initiating POTELIGE.

**Contraception:** Advise females of reproductive potential to use effective contraception during treatment with POTELIGE and for at least 3 months following the last dose of POTELIGE.

### 8.4 Pediatric use

The safety and effectiveness of POTELIGE in pediatric patients have not been established.

### 8.5 Geriatric use

Of 319 patients with MF or SS who received POTELIGE in Trial 1, 162 (51%) were ≥65 years. No overall differences in effectiveness were observed between these patients and younger patients. In patients aged ≥65, Grade 3 or higher adverse reactions were reported in 45% and serious adverse reactions in 36%, whereas in patients aged <65, Grade 3 or higher adverse reactions were reported in 36% and serious adverse reactions in 29%.

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## Efficacy of Mogamulizumab By Prior Systemic Therapy in Patients With Previously Treated Cutaneous T-Cell Lymphoma: Post Hoc Analysis From the Phase 3 MAVORIC Study

Cutaneous T-cell lymphoma (CTCL) consists of a group of rare non-Hodgkin lymphomas that occur primarily in the skin.<sup>1</sup> The 2 most common subtypes are mycosis fungoides and Sézary syndrome. As CTCL progresses, it becomes systemic and is associated with a poor prognosis. Targeted therapies are being developed to provide effective options for the treatment of CTCL. Mogamulizumab is a humanized monoclonal antibody directed against the CC chemokine receptor 4 (CCR4) with a defucosylated Fc region that enhances antibody-dependent cellular cytotoxicity. Mogamulizumab demonstrated efficacy and acceptable tolerability in an early study of patients with peripheral T-cell lymphoma (PTCL) or CTCL.<sup>2</sup>

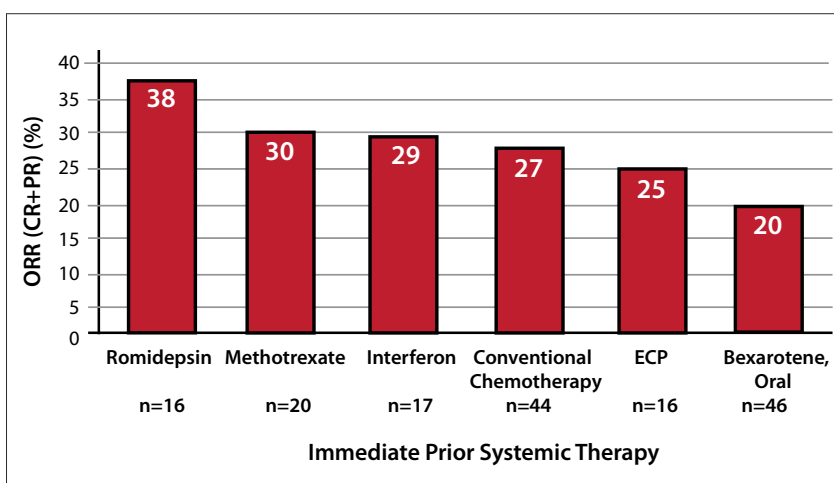
The international, open-label phase 3 MAVORIC trial (Study of KW-0761 Versus Vorinostat in Relapsed/Refractory CTCL) compared mogamulizumab vs vorinostat in patients with previously treated

mycosis fungoides or Sézary syndrome.<sup>3</sup> Eligible patients had an Eastern Cooperative Oncology Group performance score of 1 or lower and adequate renal, hepatic, and hematologic function. Mogamulizumab at 1.0 mg/kg was administered weekly during the first 28-day cycle and on days 1 and 15 of subsequent cycles. Vorinostat at 400 mg was administered daily. Prior to randomization, patients were stratified by CTCL subtype and disease stage. Baseline characteristics, including the number and type of prior systemic therapies, were similar between the 2 arms. Patients in both arms had received a median of 3 prior systemic therapies. The analysis of progression-free survival (PFS), the primary endpoint, was based on results from 372 patients. PFS was 7.7 months with mogamulizumab vs 3.1 months with vorinostat (hazard ratio, 0.53; 95% CI, 0.41-0.69;  $P < .0001$ ). The objective response rate (ORR) was also superior with mogamulizumab,

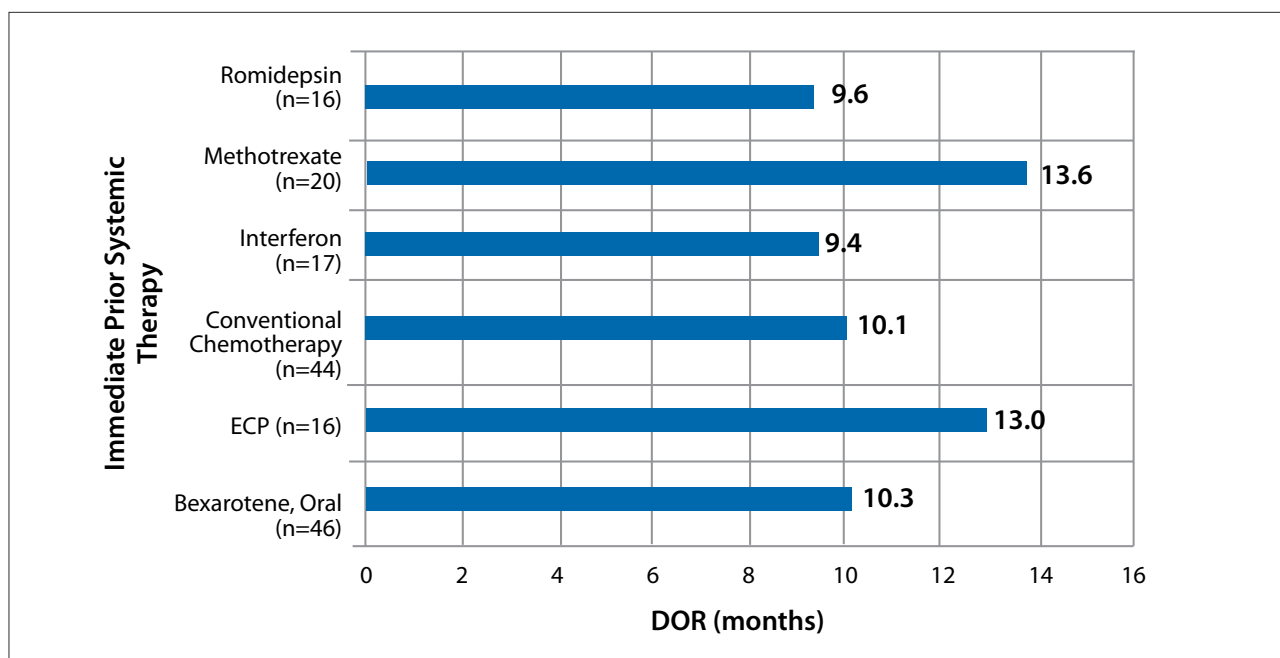
at 28% vs 5% ( $P < .0001$ ). Among the 133 patients who crossed over from vorinostat to mogamulizumab owing to disease progression or intolerance, the ORR was 31%.

A post hoc analysis evaluated the effect of prior therapy on clinical response among the 186 patients randomly assigned to mogamulizumab in the MAVORIC trial.<sup>4</sup> The confirmed ORRs were 25% in those treated with 1 prior therapy, 35% in those treated with 3, and 30% in those treated with more than 6. The most common systemic therapies received immediately prior to study enrollment were oral bexarotene (25%), chemotherapy (24%), methotrexate (11%), interferon- $\alpha$  (9%), extracorporeal photopheresis (9%), and romidepsin (9%). The ORRs based on prior systemic therapy ranged from 38% in patients treated with romidepsin to 20% in those treated with bexarotene (Figure 1). Romidepsin and vorinostat are both inhibitors of histone deacetylase (HDAC). The ORRs in these patients suggest that prior treatment with an HDAC inhibitor does not adversely affect response to mogamulizumab.

In the MAVORIC trial, the median duration of response was 14 months. Based on the patients' prior systemic therapy, the median duration of response to mogamulizumab ranged from 9.4 months in those who had received interferon- $\alpha$  to 13.6 months in those who had received methotrexate (Figure 2). In the mogamulizumab arm, 150 patients had received prior treatment that was immunostimulatory (n=32), immune neutral (n=55), or immune inhibitory (n=63). In these patients, the median time from immediate prior therapy to study entry was 44 days (range, 0-1094). Based on a logistic regression model and using the



**Figure 1.** Overall response rate according to immediate prior therapy in patients treated with mogamulizumab in the phase 3 MAVORIC trial. CR, complete response; ECP, extracorporeal photopheresis; MAVORIC, Study of KW-0761 Versus Vorinostat in Relapsed/Refractory CTCL; ORR, overall response rate; PR, partial response. Adapted from Zinzani PL et al. ASH abstract 1619. *Blood*. 2018;132(suppl 1).<sup>4</sup>



**Figure 2.** The median duration of response to mogamulizumab according to immediate prior therapy among patients in the phase 3 MAVORIC trial. DOR, duration of response; ECP, extracorporeal photopheresis; MAVORIC, Study of KW-0761 Versus Vorinostat in Relapsed/Refractory CTCL. Adapted from Zinzani PL et al. ASH abstract 1619. *Blood*. 2018;132(suppl 1).<sup>4</sup>

immune-neutral cohort as a comparator, ORR did not vary according to prior treatment with immunostimulatory or inhibitory agents. The authors concluded that the clinical response to mogamulizumab treatment in the MAVORIC trial was not influenced by the number or class of prior systemic therapies.

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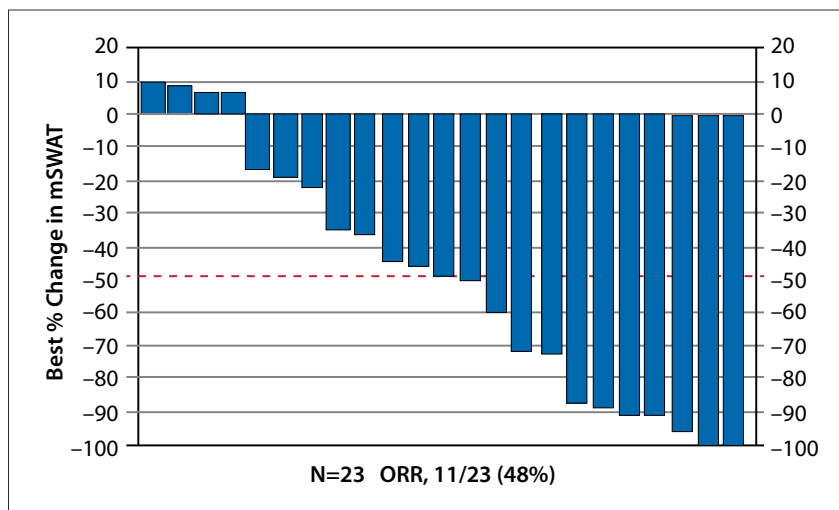
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## The Novel SYK/JAK Inhibitor Cerdulatinib Demonstrates Good Tolerability and Clinical Response in a Phase 2a Study in Relapsed/Refractory Peripheral T-Cell Lymphoma and Cutaneous T-Cell Lymphoma

Preclinical data suggest that spleen tyrosine kinase (SYK) is an oncogenic driver in some T-cell lymphomas. Patients with primary PTCL frequently express SYK, either in its native form or as a fusion protein with inducible T-cell kinase (ITK), and activating mutations in

the JAK/STAT pathway are also common.<sup>1,2</sup> Cerdulatinib is an orally available, adenosine triphosphate (ATP)-competitive inhibitor of SYK, JAK1, JAK3, and Tyk2, with IC<sub>50</sub> values of 32 nM for SYK and 0.5 nM to 12 nM for the JAKs.<sup>3</sup> After phase 1 dose-escalation studies<sup>4,5</sup> and pharmacoki-

netic/pharmacodynamic modeling, a dose of 30 mg twice daily was chosen for cerdulatinib in phase 2 studies. In a phase 2a study, cerdulatinib was associated with ORRs of 61% in CLL and of 46% in follicular lymphoma, and inhibition of SYK/JAK signaling and markers of inflammation correlated



**Figure 3.** The overall response rate as determined by mSWAT among patients treated with cerdulatinib in a phase 2a study. mSWAT modified Severity Weighted Assessment Tool; ORR, overall response rate. Adapted from Horwitz SM et al. ASH abstract 1001. *Blood*. 2018;132(suppl 1).<sup>7</sup>

#### ABSTRACT SUMMARY Epiproteomic Landscape and Histone Code of Cutaneous T-Cell Lymphoma/Sézary Syndrome

Mass spectrometry was used to investigate the role of histone posttranslational modifications in patients with Sézary syndrome (Abstract 780). Histones were isolated from CD4-positive cells obtained from patients with Sézary syndrome, from healthy donors, and from Sézary syndrome cell lines. Based on Pearson correlation and principal component analysis, a distinct pattern of posttranslational modifications was identified in both Sézary syndrome patient samples and CTCL cell lines. Unsupervised hierarchical clustering identified Sézary syndrome-specific posttranslational modifications and accurately classified CTCL cell lines, samples from Sézary syndrome patients, and samples from healthy donors. Two classes of Sézary syndrome patients were identified based on the novel epigenetic profiles. Histone alterations, such as H4K20me, were orthogonally validated by means of Western blotting and time-of-flight mass cytometry. The study also identified histone posttranslational modifications associated with a durable response to treatment with an HDAC inhibitor.

with the degree of tumor reduction.<sup>6</sup> Two grade 3 dose-limiting toxicities occurred.

Cerdulatinib at 30 mg twice daily was evaluated in an open-label, multicenter phase 2a study of patients with relapsed or refractory B-cell or T-cell malignancies.<sup>7</sup> The study included 45 patients with PTCL and 29 with CTCL. In the PTCL cohort,

patients had a median age of 65 years (range, 21-84), and 64% were male. Patients had received a median of 3 prior therapies (range, 1-12), and half were refractory to their most recent therapy. Twenty-seven percent of PTCL patients had undergone prior stem cell transplant. In the CTCL cohort, patients were a median age of 62 years (range, 24-79 years), and

66% were male. The median number of prior therapies was 4 (range, 1-13), and 55% of patients were refractory to their most recent therapy. Three percent of CTCL patients had undergone prior stem cell transplant.

In the evaluable CTCL cohort, 21 patients had mycosis fungoides and 6 had Sézary syndrome. The ORRs for these patients were 29% (6/21) and 17% (1/6), respectively. As determined by the modified Severity Weighted Assessment Tool (mSWAT) in 23 patients, the ORR was 48% (Figure 3). Pruritus scores also improved with treatment.

Among the 41 evaluable PTCL patients, the ORR was 34%, including a complete response (CR) rate of 27%. Among 27 evaluable CTCL patients, the ORR was 26%, including a CR rate of 7%. Eight responding PTCL patients remained on the study drug for at least 3 months. In 5 patients, the duration of response was 6 months or longer. The most common subtypes in the evaluable PTCL cohort were angioblastic T-cell lymphoma/follicular helper T cells and PTCL not otherwise specified. The ORRs in these subtypes were 57% (8/14) and 15% (2/13), respectively. Among 3 patients with adult T-cell leukemia/lymphoma (ATLL), responses included 1 CR and 1 partial response (PR).

Among the entire cohort of 74 patients, the most common treatment-emergent adverse events (AEs) of grade 3 or higher were lipase increase (23%), amylase increase (18%), and sepsis/bacteremia (8%).

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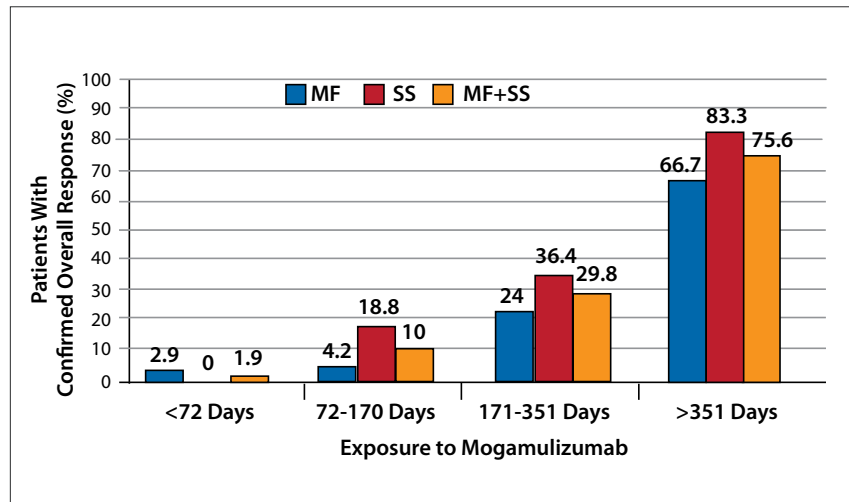
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## Long-Term Clinical Benefit to Anti-CCR4 Mogamulizumab: Results From the Phase 3 MAVORIC Study in Previously Treated Cutaneous T-Cell Lymphoma

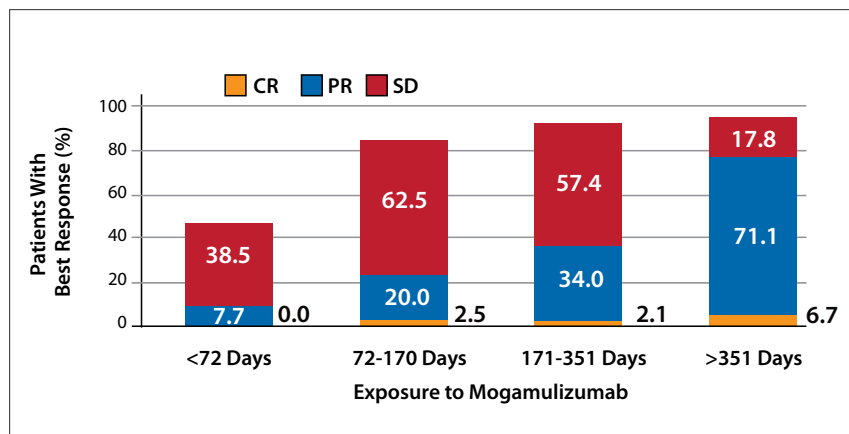
A post hoc analysis assessed the safety and efficacy of mogamulizumab in the MAVORIC trial based on patients' prior treatment exposure.<sup>1,2</sup> The analysis included 184 patients randomly assigned to mogamulizumab. Patients had a mean time of exposure to mogamulizumab of 275.2 days (standard deviation, 292.2 days) and a median exposure of 170.0 days (range, 1-1617 days). The duration of exposure was less than 72 days in 28%, between 72 and 170 days in 22%, between 171 and 351 days in 26%, and longer than 351 days in 24%. Based on quartile assessment, long-term exposure was defined as longer than 351 days.

The rates of confirmed response increased with exposure to mogamulizumab. In the cohort of patients with less than 72 days of exposure, the ORR was 2.9% among mycosis fungoides patients, 0% among Sézary syndrome patients, and 1.9% overall. Among patients with more than 351 days of exposure, the ORR was 66.7% among mycosis fungoides patients, 83.3% among Sézary syndrome patients, and 75.6% overall (Figure 4). The clinical benefit rate, including CRs, PRs, and stable disease, was 46.2% in patients with the shortest exposure to mogamulizumab vs 95.6% in patients with the longest exposure (Figure 5). Among the patients who had a best response of stable disease, 43.8% had received at least 171 days of treatment.

Rates of treatment-emergent AEs in the 4 cohorts were 26.6%, 18.5%,



**Figure 4.** Overall response rates among patients treated with mogamulizumab in the phase 3 MAVORIC trial. MAVORIC, Study of KW-0761 Versus Vorinostat in Relapsed/Refractory CTCL; MF, mycosis fungoides; SS, Sézary syndrome. Adapted from Bagot M et al. ASH abstract 2901. *Blood.* 2018;132(suppl 1).<sup>1</sup>



**Figure 5.** Clinical benefit rate according to duration of exposure to mogamulizumab in the phase 3 MAVORIC trial. CR, complete response; MAVORIC, Study of KW-0761 Versus Vorinostat in Relapsed/Refractory CTCL; PR, partial response; SD, stable disease. Adapted from Bagot M et al. ASH abstract 2901. *Blood.* 2018;132(suppl 1).<sup>1</sup>

23.4%, and 21.7% from the shortest to longest exposure. The rates of serious AEs were 6.5%, 3.3%, 6.0%, and 4.3%. Among patients with the longest exposure to mogamulizumab, the most common treatment-related AEs were drug eruption (20.0%), thrombocytopenia (11.1%), stomatitis (8.9%), and anemia (8.9%). Most grade 3 AEs occurred during the first 2 exposure quartiles (ie, prior to 171 days of exposure). The median time to onset of an AE of grade 3 or higher was 109 days. Drug eruption was defined as a skin rash that the investigator considered to be pos-

sibly, probably, or definitely related to the study drug. In patients receiving mogamulizumab, skin rashes of grade 2 or higher were biopsied if necessary to distinguish between a drug eruption and a new area of lymphoma. In the mogamulizumab arm, 45 patients experienced drug eruptions, which included 9 grade 3 events and 36 grade 1/2 events. The median time to a drug eruption event was 107 days. Twenty-five patients in the mogamulizumab arm experienced thrombocytopenia, and all cases were grade 1/2. The median time to onset of thrombocytopenia was 43 days.

Patients with autoimmune diseases were excluded from the MAVORIC study. However, a safety physician identified 3 patients with a possible autoimmune disease and 2 with a definite autoimmune disease.

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## IPH4102; An Anti-KIR3DL2 Monoclonal Antibody in Refractory Sézary Syndrome: Results From a Multicenter Phase 1 Trial

**I**PH4102 is a humanized antibody that binds to KIR3DL2, a member of the killer immunoglobulin-like receptors expressed on lymphocytes.<sup>1</sup> KIR3DL2 shows restricted expression on normal immune cells but is widely expressed on CTCL cells, with significantly increased expression on Sézary cells compared with lymphoid cells from healthy donors.

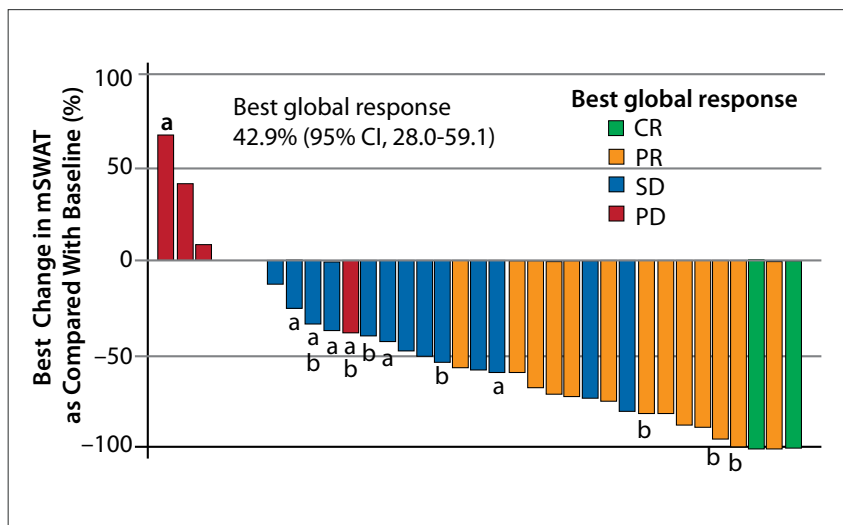
Preclinical studies have shown that IPH4102 mediates antitumor activity through antibody-dependent cellular cytotoxicity and phagocytosis.<sup>2</sup> In mice inoculated with CTCL tumor cells expressing KIR3DL2, treatment with IPH4102 improved survival and reduced tumor growth compared with controls. IPH4102 was also shown to kill Sézary cells *ex vivo*.

A first-in-human, phase 1 trial evaluated IPH4102 in patients with refractory CTCL.<sup>3</sup> The dose-escalation/expansion trial evaluated 10 dose levels of IPH4102, up to 10 mg/kg, in an accelerated 3 + 3 design. The study included all CTCL subtypes. Enrolled patients had received at least 2 prior systemic therapies. Skin disease assessments relating to quality of life were made using the Skindex-29 instrument.<sup>4</sup> Based on central testing, KIR3DL2 expression of at least 5% in the skin and/or blood was required for enrollment in the dose-escalation phase. Any level of KIR3DL2 expression was permitted for enrollment in the cohort expansion. IPH4102 was administered once per week for 4 weeks, then every 2 weeks for 10 administrations, followed by administration once every 4 weeks thereafter. The primary endpoint was safety. Key secondary endpoints included best global response, PFS, duration of response, quality of life, and biomarker analyses.

Thirty-five patients with Sézary syndrome were enrolled, 20 in the dose-escalation cohort and 15 in the

### ABSTRACT SUMMARY Evaluation of Maintenance Therapy in Cutaneous T-Cell Lymphoma Patients Receiving Total Skin Electron Beam Radiation Therapy

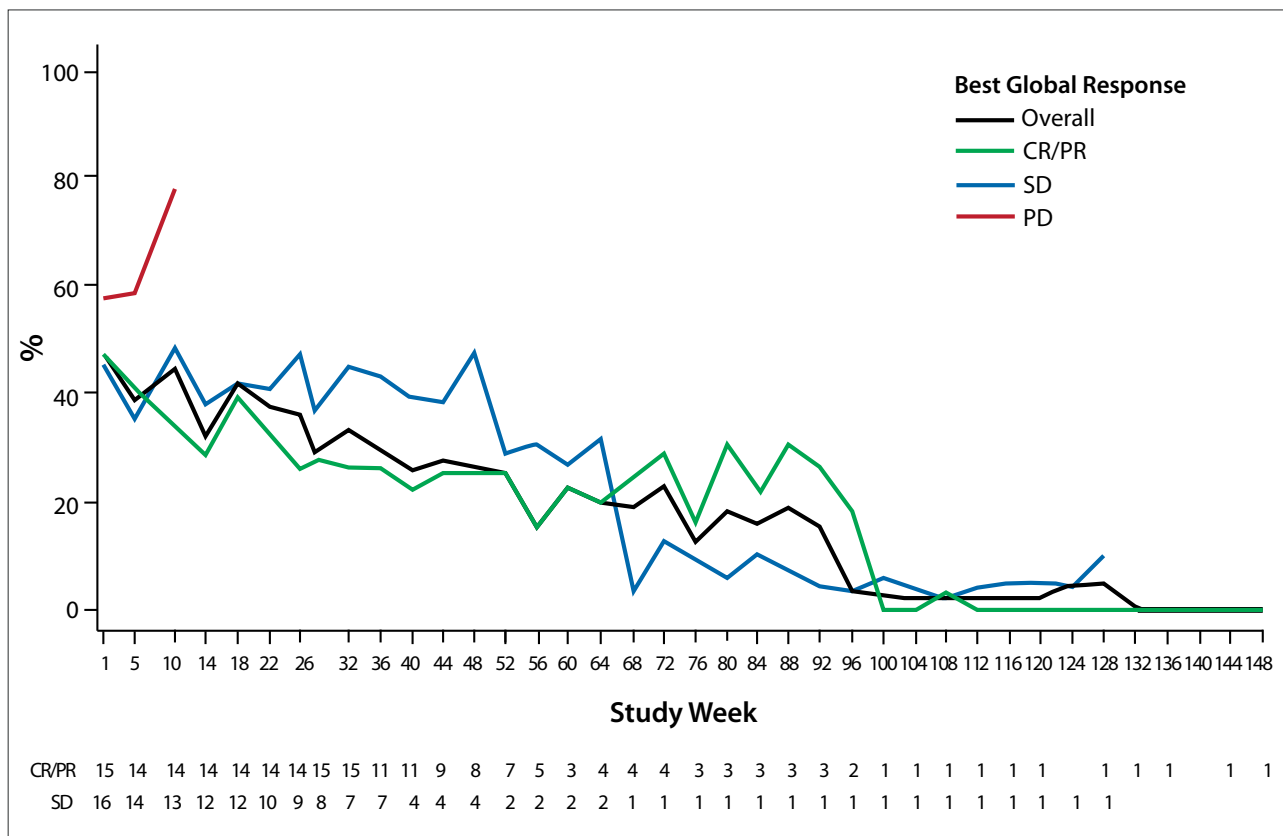
A retrospective, single-center study evaluated the relationship between maintenance treatment and survival in CTCL patients receiving treatment with total skin electron beam (TSEB) therapy (Abstract 1639). Among 101 patients who underwent TSEB, 43 also received maintenance treatment. Maintenance was administered concurrently with TSEB in 36% of patients and after TSEB in 34%. (The timing was unknown in 30%.) The most common maintenance therapies were bexarotene (29%), interferon (23%), and psoralen/ultraviolet A therapy (15%). The median PFS after TSEB was significantly prolonged in patients who received maintenance treatment vs those who did not (9.6 vs 6 months;  $P=.025$ ). Two-year PFS was 25% with maintenance treatment vs 9% without. The median overall survival was 4.2 years vs 2.5 years, respectively ( $P=.26$ ).



**Figure 6.** Best change in mSWAT score among patients treated with IPH4102 in a phase 1 trial. CR, complete response; mSWAT, modified Severity Weighted Assessment Tool; PD, progressive disease; PR, partial response; SD, stable disease. <sup>a</sup>Patients with large-cell transformation. <sup>b</sup>Patients pretreated with mogamulizumab. Adapted from Bagot M et al. ASH abstract 684. *Blood*. 2018;132(suppl 1).<sup>3</sup>

expansion cohort. Their median age was 70 years (range, 37-90 years). Based on central testing of frozen tissue, 20% of patients had evidence of large-cell transformation. KIR3DL2 expression was observed in the skin of 77% of patients and in the blood of 94%. The median time from the diagnosis of Sézary syndrome was 23 months (range, 6-268 months). The median number of prior therapies was 2 (range, 1-9). Prior treatments included an HDAC inhibitor in 37% and mogamulizumab in 20%.

The maximum tolerated dose was not reached. The recommended phase 2 dose was 750 mg. The ORR was 42.9% (95% CI, 28.0%-59.1%). The best change in mSWAT score is shown in Figure 6, and the best global response is shown in Figure 7. The median duration of response was



**Figure 7.** Best global response among patients treated with IPH4102 in a phase 1 trial. CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease. Adapted from Bagot M et al. ASH abstract 684. *Blood*. 2018;132(suppl 1).<sup>3</sup>

13.8 months (95% CI, 7.2 months to not reached), and the median PFS was 11.7 months (95% CI, 8.1 months to not reached). Among 28 Sézary syndrome patients without large-cell transformation, the ORR was 53.6% (95% CI, 35.8%-70.5%), the median duration of response was 13.8 months (95% CI, 7.2 months to not reached), and the median PFS was 12.8 months (95% CI, 8.2 months to not reached). Among the 7 patients who had received prior treatment with mogamulizumab, the ORR was 42.9% (95% CI, 15.8-75.0 months), the median duration of response was 13.8 months (95% CI, 7.2 months to not reached), and the median PFS was 16.8 months (95% CI, 8.1 months to not reached). Based

on measures of symptoms as well as emotional and functional scores, patients with a CR, PR, or stable disease showed marked improvement during the course of the study. Pruritus scores improved not only in patients with a CR or PR, but also in patients with stable disease. Exploratory studies showed corresponding decreases in aberrant T cells and reductions in the level of KIR3DL2-positive, CD4-positive T cells during treatment with IPH4102.

The most common AEs of any grade were peripheral edema (29%), asthenia (26%), and fatigue (23%). The only grade 3/4 AE considered definitely related to treatment was lymphopenia, which occurred in 2

patients (6%). Four patients developed 5 AEs of grade 3 or higher that were considered possibly related to treatment, including grade 5 hepatitis, grade 4 sepsis, grade 3 lymphopenia, and grade 3 hypotension.

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## Evaluation of Symptom and Side Effect Bother in Cutaneous T-Cell Lymphoma Patients Treated With Mogamulizumab or Vorinostat

CTCL presents as patches, plaques, tumors, or erythroderma and may be accompanied by pruritus.<sup>1,2</sup> Advanced CTCL is typically associated with significant morbidity and impaired quality of life.<sup>3,4</sup> The MAVORIC trial protocol included preplanned analyses of patient-reported outcomes gleaned from the Functional Assessment of Cancer Therapy-General (FACT-G), Skindex-29, and 2 measures of pruritus: EQ-5D-3L and ItchyQoL.<sup>5</sup> The results from these questionnaires showed a greater improvement in quality of life at 6 months with mogamulizumab vs vorinostat ( $P<.05$ ).

Patient-reported outcomes collected during the MAVORIC trial were analyzed for changes during the course of treatment.<sup>6</sup> Individual symptom items captured by Skindex-29 and toxicity items in FACT-G were evaluated with longitudinal generalized estimation equations using data through cycles 5 or 6. Baseline characteristics were generally well-balanced between

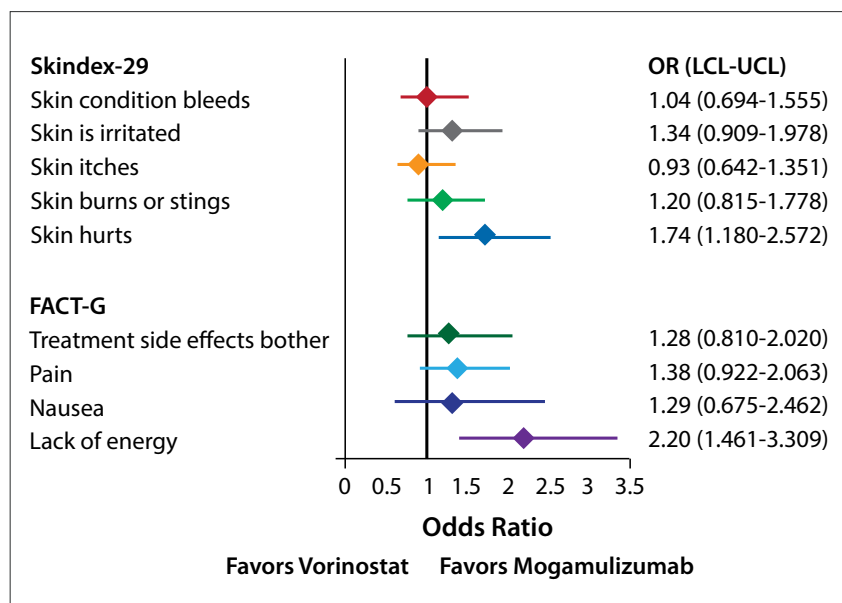
the mogamulizumab and vorinostat arms of the MAVORIC trial.

Within 6 treatment cycles, the patients treated with mogamulizumab were more likely to experience a 1-grade improvement in painful skin (odds ratio [OR], 1.74; 95% CI, 1.180-2.572;  $P=.0216$ ), side effect bother (OR, 1.28; 95% CI, 0.810-

2.020;  $P=.0122$ ), and lack of energy (OR, 2.20; 95% CI, 1.461-3.309;  $P=.0505$ ; Figure 8). Items that showed potential improvement with mogamulizumab over vorinostat included general cancer pain (OR, 1.38; 95% CI, 0.922-2.063;  $P=.0799$ ) and irritated skin (OR, 1.34; 95% CI, 0.909-1.978;  $P=.2176$ ). The results suggested that,

### ABSTRACT SUMMARY ARGX-110 for Treatment of CD70-Positive Advanced Cutaneous T-Cell Lymphoma in a Phase 1/2 Clinical Trial

Cusatuzumab (ARGX-110), a glycoengineered antibody that binds to CD70, was evaluated in an open-label, single-arm phase 1/2 study of patients with CTCL (Abstract 1627). The study included 27 heavily pretreated patients, whose median age was 67 years (range, 25-84 years). Among 26 evaluable patients, the ORR was 23%. Responses included 1 CR and 5 PRs, and 8 patients had stable disease. The CR occurred in an 84-year-old patient with subcutaneous panniculitis-like T-cell lymphoma. After 4 doses of cusatuzumab at 1 mg/kg every 3 weeks, the patient's proportion of neoplastic cells decreased. A CR was achieved at cycle 17, with a dose of cusatuzumab at 5 mg/kg every 6 weeks. Cusatuzumab was generally well-tolerated. Common treatment-emergent AEs included pyrexia (30.8% during phase 1) and asthenia (21.4% during phase 2).



**Figure 8.** The probability of observing a 1-point categorical improvement on individual items throughout cycle 5 or cycle 6 using a generalized estimating equation in patients treated with mogamulizumab or vorinostat in the phase 3 MAVORIC trial. FACT-G, Functional Assessment of Cancer Therapy–General; LCL, lower confidence limit; MAVORIC, Study of KW-0761 Versus Vorinostat in Relapsed/Refractory CTCL; OR, odds ratio; UCL, upper confidence limit. Adapted from Hudgens S et al. ASH abstract 3592. *Blood*. 2018;132(suppl 1).<sup>6</sup>

over the course of treatment, mogamulizumab provided a symptom benefit that was superior to that of vorinostat.

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## Phase 1/2 Trial of Durvalumab and Lenalidomide in Patients With Cutaneous T-Cell Lymphoma: Preliminary Results of Phase I Results and Correlative Studies

Many cancer types are characterized by the presence of exhausted T cells within the tumor microenvironment.<sup>1</sup> T-cell exhaustion often involves overexpression of inhibitory receptors such as programmed death 1 (PD-1) on the T cell and concomitant overexpression of the ligand (PD-L1) on tumor cells. By increasing the expression of PD-L1, tumors avoid immune surveillance and elimination. A study of primary T cells from CTCL skin biopsies showed increased PD-1 expression on CD4-positive T cells compared with skin from healthy donors.<sup>2</sup> Genome-wide mRNA expression analysis showed that checkpoint inhibition

mRNA expression was increased in CTCL stage T3/T4 samples compared with earlier-stage samples. Durvalumab is a human monoclonal antibody that binds to PD-L1, preventing its engagement with PD-1.<sup>3</sup> In a xenograft mouse model containing coimplanted human T cells, durvalumab inhibited tumor growth through a mechanism that was dependent on the presence of T cells.

A phase 1/2 trial evaluated the combination of durvalumab with or without lenalidomide in patients with CTCL.<sup>4</sup> Patients were enrolled in sequential cohorts to receive a fixed dose of durvalumab (1500 mg every 4 weeks) either alone or in combination

with escalating doses of lenalidomide (up to 20 mg daily). Serial skin and blood samples were collected to evaluate the impact of treatment on the tumor microenvironment. Objectives of the ongoing study are to evaluate the correlation between clinical response and resistance by evaluating PD-1 clustering at the single molecular level and to assess the expression of PD-L1 and inducible T-cell costimulator (ICOS) on both pretreatment primary cells from skin explants and formaldehyde-fixed, paraffin-embedded skin tissue from clinical trial participants.

The 9 enrolled patients had a median age of 54 years (range, 29-59

years), and 7 were male. One patient had stage IIB disease, 7 had stage II disease, and 1 had stage IIIA disease. Eight patients had mycosis fungoides and 1 had aggressive cytotoxic CTCL. Patients had received a median of 3 prior systemic therapies and a median of 4 prior skin-directed treatments. The median follow-up was 7 months (range, 1 to 18+ months).

As measured by the mSWAT, 7 patients showed improved skin disease, including 2 patients who achieved a PR with greater than 90% improvement by mSWAT. Three patients experienced disease progression, and 5 patients remained on treatment. Peripheral blood mononuclear cells were harvested from a patient with Sézary syndrome and then incubated with durvalumab plus lenalidomide

for 72 hours. Immunoblotting showed a small decrease in PD-L1 expression. This patient's cells were also depleted of CD3-positive T cells and then stimulated with interferon- $\gamma$ , which led to increased expression of PD-L1 and ICOS. Exposure to lenalidomide and durvalumab inhibited the expression of PD-L1 and ICOS. Exposure to lenalidomide was associated with decreased expression of pSTAT3, and exposure to durvalumab was associated with decreased expression of pSTAT1. The combination of lenalidomide plus durvalumab will be further evaluated in CTCL patients in the phase 2 portion of the trial.

Nonhematologic AEs of any grade included tumor flare reaction (n=9), other skin reactions (n=6), fatigue (n=5), rash (n=4), and skin

pain (n=3). Hematologic AEs included leukopenia (n=5) and anemia (n=3). A grade 3 maculopapular rash occurred in 1 patient. All other AEs were grade 1/2. No serious AEs or dose-limiting toxicities occurred.

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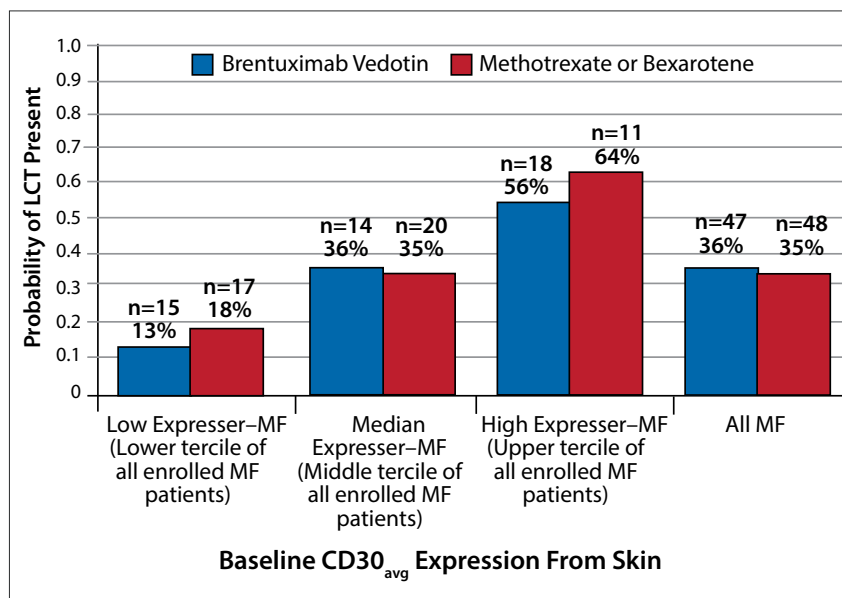
## Superior Clinical Benefit of Brentuximab Vedotin in Mycosis Fungoides Versus Physician's Choice Irrespective of CD30 Level or Large Cell Transformation Status in the Phase 3 ALCANZA Study

**B**rentuximab vedotin is approved in the United States for the treatment of CD30-positive lymphoproliferative diseases, including previously treated primary cutaneous anaplastic large cell lymphoma and CD30-expressing mycosis fungoides.<sup>1</sup> The international, open-label phase 3 ALCANZA trial (A Phase 3 Trial of Brentuximab Vedotin [SGN-35] Versus Physician's Choice [Methotrexate or Bexarotene] in Participants With CD30-Positive Cutaneous T-Cell Lymphoma) evaluated the efficacy and safety of brentuximab vedotin vs conventional therapy in previously treated patients with CD30-positive primary cutaneous anaplastic large cell lymphoma or mycosis fungoides.<sup>2</sup> Patients randomly assigned to the experimental arm received brentuximab vedotin (1.8 mg/kg) once every 3 weeks for up to 16 cycles of 3 weeks each. Patients in

the control arm received their physician's choice of methotrexate (5-50 mg once per week) or bexarotene (200 mg/m<sup>2</sup> daily) for up to 48 weeks. The study randomly assigned 66 patients to brentuximab vedotin and 65 to the physician's choice of treatment. After a median follow-up of 22.9 months, an objective global response lasting at least 4 months was achieved by 56.3% of patients in the brentuximab vedotin arm vs 12.5% of patients in the physician's choice arm ( $P < .0001$ ), achieving the primary endpoint. Median PFS was also superior with brentuximab vedotin (16.7 vs 3.5 months;  $P < .0001$ ).

A post hoc analysis of patients with mycosis fungoides from the ALCANZA trial was conducted, with a focus on patients with large-cell transformed (LCT) mycosis fungoides.<sup>3</sup> LCT mycosis fungoides is characterized by the presence of large cells

with enlarged nuclei, and the diagnosis is made when the biopsy of a mycosis fungoides lesion shows the presence of at least 25% large cells.<sup>4</sup> LCT mycosis fungoides carries a poor prognosis and a mean 5-year survival of less than 20%. Although CD30 expression is more common in LCT mycosis fungoides compared with untransformed mycosis fungoides, the expression is variable.<sup>5</sup> The objectives of the post hoc analysis were to determine the proportion of mycosis fungoides patients with LCT mycosis fungoides, to measure the efficacy of brentuximab vedotin in patients with LCT mycosis fungoides, and to evaluate the efficacy and safety of brentuximab vedotin according to transformed status and CD30 expression levels. The ALCANZA trial enrolled 50 mycosis fungoides patients into each treatment arm, and 48 per arm were evaluable for LCT status. In



**Figure 9.** Baseline levels of CD30 expression corresponded to the probability of LCT mycosis fungoides in the phase 3 ALCANZA trial of brentuximab vedotin vs physician's choice of treatment. ALCANZA, A Phase 3 Trial of Brentuximab Vedotin [SGN-35] Versus Physician's Choice (Methotrexate or Bexarotene) in Participants With CD30-Positive Cutaneous T-Cell Lymphoma; LCT, large cell transformed; MF, mycosis fungoides. Adapted from Kim YH et al. ASH abstract 1646. *Blood*. 2018;132(suppl 1).<sup>3</sup>

#### ABSTRACT SUMMARY Long-Term Outcome of Reduced Intensity Conditioning Allogeneic Hematopoietic Stem Cell Transplantation in Patients With Mycosis Fungoides and Sézary Syndrome: The Milan Experience

Long-term results from reduced intensity conditioning followed by allogeneic stem cell transplant were reported for 40 patients with mycosis fungoides or Sézary syndrome (Abstract 4655). Sources of stem cells included peripheral blood (87.5%), bone marrow (10%), and cord blood (2.5%). Full donor chimerism was achieved in 86% of evaluable patients (32/37), after a median of 2 months (range, 1-12 months). A CR was reported in 72% (28/39). The median follow-up exceeded 6.5 years. At the most recent follow-up (median, 80 months), 19 patients were alive, and 95% of these patients had maintained a CR. Seven patients (17%) died from transplant-related causes, including 5 who were in a CR. Five-year overall survival for the 40 patients was 52% (95% CI, 34%-70%), and 5-year disease-free survival was 43% (95% CI, 12%-51%). Five-year disease-free survival was 72% in patients with Sézary syndrome vs 30% in those with mycosis fungoides.

each arm, 17 patients (35%) had LCT mycosis fungoides. LCT was observed most frequently in patients with stage IIB disease.

Based on at least 2 biopsies taken at a single time point, median CD30

expression levels varied. In the physician's choice arm, the median level of CD30 expression was 15.0% (range, 1.0%-71.7%) in patients without LCT vs 35.0% (range, 6.3%-97.5%) in patients with LCT. In the brentux-

imab vedotin arm, the median CD30 expression level was 15.0% (range, 3.8%-70.0%) in patients without LCT vs 50.0% (range, 3.0%-95.0%) in patients with LCT. LCT mycosis fungoides was less common among patients with low levels of CD30 expression (13%-18%) and was most common among patients with higher levels of CD30 expression (56%-64%; Figure 9). Patients with LCT mycosis fungoides were more likely to achieve an ORR lasting at least 4 months compared with LCT-negative patients, both in the brentuximab vedotin arm (65% vs 39%) and in the standard treatment arm (18% vs 6%). Median PFS was superior with brentuximab vedotin vs physician's choice in patients with LCT mycosis fungoides (15.5 vs 2.8 months) and in those without LCT (16.1 vs 3.5 months). Among LCT mycosis fungoides patients treated with brentuximab vedotin, those who achieved an ORR lasting at least 4 months had a higher median level of CD30 expression (65%) compared with patients who did not attain an ORR lasting at least 4 months (20%). In both treatment arms, the presence of LCT mycosis fungoides did not impact the rate of AEs, including AEs of grade 3 or higher, drug-related AEs of grade 3 or higher, or serious AEs.

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## Mechanistic Analysis of Prolonged Negative Impacts of Anti-CCR4 Antibody Mogamulizumab on Regulatory T-Cell Homeostasis After Allogeneic Hematopoietic Stem Cell Transplantation

**A**TLL is a highly aggressive malignancy of CD4-positive cells caused by the human T-cell leukemia virus type 1.<sup>1</sup> The normal counterpart of ATLL cells is considered to be CD4+Foxp3+ regulatory T cells (Treg). After allogeneic hematopoietic stem cell transplant, Treg cells play a key role in suppressing graft-vs-host disease. Mogamulizumab binds to CCR4 and is used for the treatment of ATLL. Mogamulizumab depletes Treg cells for several months. A recent study of patients with aggressive ATLL evaluated the effect of mogamulizumab treatment prior to hematopoietic stem cell transplant.<sup>2</sup> The study included 996 patients who had undergone allogeneic hematopoietic stem cell transplant; 86 of these patients had received prior treatment with mogamulizumab. Among the latter patients, the final dose of mogamulizumab was administered at a median of 45 days prior to allogeneic hematopoietic stem cell transplant. The use of mogamulizumab before allogeneic hematopoietic stem cell transplant was associated with an increased risk of grade 3/4 acute graft-vs-host disease (relative risk, 1.80;  $P < .01$ ), and these patients were also more likely to be

refractory to systemic corticoid treatment for their graft-vs-host disease (relative risk, 2.09;  $P < .01$ ). One-year overall survival was also reduced in patients who had received prior treatment with mogamulizumab ( $P < .01$ ). Because Treg cells express CCR4, suppression of Treg cells by mogamulizumab and subsequent poor recovery may underlie the negative impact of mogamulizumab on allogeneic hematopoietic stem cell transplant.

A small study investigated the relationship between mogamulizumab and the activity of Treg cells in patients with ATLL.<sup>3</sup> The study included 3 patients who received mogamulizumab before allogeneic hematopoietic stem cell transplant, 1 patient who received mogamulizumab after transplant to treat early relapse of adult T-cell leukemia/lymphoma, and 2 patients who did not receive treatment with mogamulizumab. Peripheral blood samples were obtained before hematopoietic stem cell transplant and afterward (at 2, 4, 6, 8, and 12 weeks and every 3 months thereafter).

Peak levels of mogamulizumab were dependent on the total dose administered. Residual ATLL cells in the blood quickly decreased after

administration of mogamulizumab. After the final dose of mogamulizumab, levels of the antibody gradually declined, with an average estimated half-life of 11.2 days. A faster clearance rate was observed in a patient with high tumor burden (half-life, 5.2 days) and in a patient who received plasma (half-life, 8.4 days). Expansion of Treg cells failed in all 3 patients who had received prior treatment with mogamulizumab, but was successful in the patients who had not. Delayed recovery of Treg cells was observed for up to 30 months after mogamulizumab treatment, even when the antibody was no longer detectable.

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## Phase 1 Trial of Cobomarsen, an Inhibitor of Mir-155, in Cutaneous T-Cell Lymphoma

**M**icroRNAs are noncoding RNA molecules that regulate gene expression. Quantitative analysis of microRNA expression levels yielded an expression profile that distinguishes CTCL from benign skin disorders.<sup>1</sup> MicroRNA-155 is

overexpressed in CTCL skin lesions and is a regulator of several signaling pathways that are activated in CTCL cells, including the JAK/STAT, NF- $\kappa$ B, and phosphoinositide 3-kinase (PI3K) pathways. Cobomarsen is a 14-nucleotide locked nucleic acid that inhibits

the activity of miR-155.<sup>2</sup> In vitro studies showed that cobomarsen inhibited survival and increased apoptosis in CTCL cell lines.

A phase 1 study investigated the safety and tolerability of cobomarsen in patients with mycosis fungoides.<sup>3</sup>



The open-label, dose-ranging study evaluated intratumoral, subcutaneous, and intravenous administration of cobomarsen and characterized the drug's pharmacokinetic profile. During part A of the study, intralesional injections were administered at 75 mg per dose. Part B evaluated larger doses: 300 mg administered as a bolus injection, plus 600 mg and 900 mg administered as 2-hour infusions. The initial loading dose of cobomarsen was administered 3 times during week 1, followed by weekly dosing thereafter.

The 43 enrolled patients had a median age of 59 years, and two-thirds were male. Patients had biopsy-proven mycosis fungoides of stage I, II, or III. Patients with LCT mycosis fungoides were included. All patients were refractory or intolerant to standard therapy. During study participation, patients could continue to receive stable doses of standard therapy. The trial excluded patients with evidence of clinically meaningful visceral, nodal, or blood involvement of CTCL.

Twenty-five patients received cobomarsen in addition to other treatment and 18 received cobomarsen monotherapy. Patient enrollment into the various dosing cohorts is shown in Table 1. In patients treated up to 23 months, there was no evidence of immunosuppression. There were no consistent changes to T-cell or B-cell subsets, monocytes, or eosinophils. Increased levels of natural killer cells occurred in some patients treated with cobomarsen at 900 mg. Plasma concentration curves revealed a long terminal elimination phase. Cobomarsen showed linear kinetics, with dose-proportional increases in the maximum concentration and the area under the curve. No evidence of accumulation was observed at any of

**Table 1.** Dosing Cohorts in a Phase 1 Trial of Cobomarsen

	75 mg (n)	300 mg (n)	600 mg (n)	900 mg (n)
Intratumoral	6			
Subcutaneous		3	3	3
2-Hour Infusion		8	8	3
Intravenous Bolus		9		

Data from Foss FM et al. ASH abstract 2903. *Blood*. 2018;132(suppl 1).<sup>3</sup>

the doses tested and by any route of administration. Plasma trough values reached steady-state within 12 to 16 weeks of cobomarsen administration, consistent with a terminal half-life of approximately 2.5 to 3 weeks. Antidrug antibodies were detected in 3 patients, and these patients had increased trough values.

Gene expression analysis identified a profile encompassing 122 mRNAs that were regulated in common after treatment with cobomarsen. Pathways with altered expression included the PI3K/AKT, JAK/STAT, and NF- $\kappa$ B pathways, and expression of genes involved in apoptosis increased. Lesions from patients in part A of the study that were injected with cobomarsen had improved scores of Composite Assessment of Index Lesion Severity, and the proportion of tumor cell clones decreased by day 9. In most patients, expression of miR-155 was elevated compared with normal skin. The highest levels of miR-155 were observed in mycosis fungoides lesions with the highest density of neoplastic cells. Both intralesional and systemic treatment with cobomarsen led to a decrease in the expression of miR-155 to below detectable levels in most patients. The mSWAT score improved in 92% of patients (33/36). Fifty-two percent of patients who received more than 6

doses of cobomarsen had a PR, defined as a reduction of at least 50% in the mSWAT score. Among the 13 patients who achieved a PR, 69% maintained the response for at least 4 consecutive months. The mean duration of response was 259 days (range, 48 to 560+ days).

No serious AEs were attributed to cobomarsen. Four patients experienced 8 serious AEs, all of which were unrelated to study treatment. Thirty-nine patients (90.7%) reported at least 1 nonserious AE. The total number of reported AEs was 307, and 89.6% were grade 1/2. Among the 32 grade 3/4 AEs, 14 AEs in 6 patients were considered related to treatment with the study drug. Among all 43 patients, the most common AEs of any grade were fatigue (26%) and neutropenia (19%). Pruritus and tumor flare were each observed in 16% of patients.

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## Highlights in Cutaneous T-Cell Lymphoma From the 60th American Society of Hematology Annual Meeting: A Hematologist's Perspective

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**P**resentations on cutaneous T-cell lymphoma (CTCL) at the 60th American Society of Hematology (ASH) meeting offered valuable insight into the management of these patients. Several analyses examined the use of mogamulizumab. Other studies focused on novel approaches and biomarker-driven treatment strategies. A key theme across many of the studies was to identify characteristics associated with response to therapy.

### Mogamulizumab

A post hoc analysis by Dr Pier Luigi Zinzani evaluated how prior therapy impacted response to treatment with mogamulizumab in the phase 3 MAJORIC trial (Study of KW-0761 Versus Vorinostat in Relapsed/Refractory CTCL).<sup>1,2</sup> The MAJORIC trial met its primary endpoint. Progression-free survival was 7.7 months with mogamulizumab vs 3.1 months with vorinostat ( $P < .0001$ ).

Mogamulizumab is a monoclonal antibody that targets the chemokine receptor CCR4. The mechanism of action relies on antibody-dependent cellular cytotoxicity (ADCC). Pre-clinical studies suggested that histone deacetylase (HDAC) inhibitors can downregulate CCR4 and potentially suppress the activity of natural killer cells, which could negatively impact the ADCC mechanism of action.<sup>3</sup> In the analysis by Dr Zinzani, no prior treatments, including HDAC inhibitors, had a significant impact on responses or duration of response.<sup>1</sup> The immunologic activity of the drug had no impact, nor did the time from immediate prior systemic therapy. The

prior systemic treatment had been administered a median of 90 days before initiation of mogamulizumab. It will be interesting to see if a closer interval between the prior drug and mogamulizumab will impact the mechanism of action and resultant efficacy. Subsequent studies will assuredly look to identify synergistic combinations with mogamulizumab.

A post hoc analysis from Dr Martine Bagot evaluated data from the MAJORIC trial to identify the best responders.<sup>4</sup> Results from the MAJORIC trial, which appeared in the *Lancet Oncology*, found that treatment with mogamulizumab was associated with higher response rates and potentially more durable responses among patients with Sézary syndrome and other mycosis fungoides patients with blood involvement.<sup>2</sup> The post hoc analysis drew the same conclusion. There was significantly more benefit in patients with blood involvement, even at low levels (defined as B1 disease). Patients with Sézary syndrome seemed to have a longer-term benefit. Unsurprisingly, patients with better performance status also had better outcomes. The original report showed that patients with more blood disease had a better response. Mogamulizumab may have efficacy in all stages of disease, but it may be best suited for earlier use in patients with blood involvement. An interesting observation from the post hoc analysis was that there was no significant trend between outcome and the level of CCR4 expression. Therefore, there are currently no data to support checking a patient's level of CCR4 expression before consider-

ing treatment with mogamulizumab. More pertinent factors include the patient's disease stage, clinical characteristics, and the presence of any blood involvement.

The post hoc analysis by Dr Bagot also evaluated the safety of mogamulizumab. Infusion reaction is the most common adverse event seen with this therapy.<sup>4</sup> Longer treatment duration did not significantly increase the rate of adverse events. This important finding suggests that patients who respond to mogamulizumab can receive treatment for long periods without concern for cumulative toxicity.

A study by Dr Yasuhisa Sando evaluated the effect of mogamulizumab before or after transplant in patients with adult T-cell leukemia/lymphoma (ATLL).<sup>5</sup> Previous research has identified potential risks when mogamulizumab is administered before and after an allogeneic transplant.<sup>6</sup> This risk may relate to a decrease in regulatory T cells (Tregs), which is an on-target effect of mogamulizumab. In the context of an allogeneic transplant, a decrease in Tregs can increase the risk of graft-versus-host disease (GVHD). Patients with ATLL tend to have a poor prognosis, so despite the potential risks, allogeneic stem cell transplant should still be considered. However, close monitoring and further investigation are warranted. For CTCL, the implications are more limited. Mogamulizumab is approved for patients with relapsed or refractory mycosis fungoides or Sézary syndrome treated with 1 or more lines of therapy. The percentage of patients with CTCL who undergo transplant is very small. However, further research should

explore ways to potentially mitigate the increased risk of GVHD after an allogeneic transplant in patients treated with mogamulizumab. There may be novel conditioning regimens or donor sources that could be used in this setting to decrease the risk of GVHD.

A subanalysis of the MAVORIC trial evaluated the impact of mogamulizumab and vorinostat on symptoms related to CTCL.<sup>7</sup> The analysis identified better symptom control with mogamulizumab as compared with vorinostat. This improvement in symptoms is great for patients. Skin disease and pruritus can be a large burden and significantly impact the patient's quality of life. Mogamulizumab represents an important advance not only because it increases progression-free survival, but also because it improves symptoms and quality of life. This analysis suggests that mogamulizumab is a much better option for patients than vorinostat.

In conclusion, these studies on mogamulizumab suggest that it is safe overall and improves symptoms. Investigators are still learning which patients may benefit the most from treatment, and are also exploring synergistic combinations.

### Brentuximab Vedotin

Dr Youn Kim presented a post hoc analysis of the phase 3 ALCANZA trial (A Phase 3 Trial of Brentuximab Vedotin [SGN-35] Versus Physician's Choice [Methotrexate or Bexarotene] in Participants With CD30-Positive Cutaneous T-Cell Lymphoma), which compared brentuximab vedotin vs the physician's choice of treatment in patients with mycosis fungoides or primary cutaneous anaplastic large-cell lymphoma.<sup>8,9</sup> Brentuximab vedotin is an antibody-drug conjugate that targets CD30. The analysis by Dr Kim aimed to identify the relationship between the status of large-cell transformation and CD30 expression or clinical outcome. The study found that a higher level of CD30 expression may help predict response to brentuximab vedotin.

However, responses were also seen in patients with a low level of expression. This conclusion has been the same in other T-cell lymphomas.<sup>10</sup> In the setting of large-cell transformation, Dr Kim found that high CD30 expression was somewhat more common, but there were also low expressers. The analysis showed that brentuximab vedotin is safe, tolerable, and effective in patients with large-cell transformation, a population that historically has a poor prognosis. It suggests that brentuximab vedotin may be a good choice for patients with large-cell transformation, particularly those who are CD30-positive.

### Reduced Intensity Conditioning for Transplant

A study from Milan examined long-term outcome of a reduced-intensity conditioning regimen for allogeneic hematopoietic stem cell transplant in patients with mycosis fungoides or Sézary syndrome.<sup>11</sup> A similar study performed at MD Anderson Cancer Center suggested that this strategy is effective.<sup>12</sup> In the Milan experience, a complete response was seen in 28 of 39 evaluable patients (71%). This study reemphasized that allogeneic transplant remains a potentially curative option for patients, especially those who are young and fit or who have relapsed multiple times. The study identified a fair amount of infectious complications, which were likely related to T-cell depletion from pentostatin and antithymocyte globulins.

### Novel Treatment Strategies

A phase 1 trial from Dr Martine Bagot evaluated IPH4102, an anti-KIR3DL2 monoclonal antibody, in patients with Sézary syndrome.<sup>13</sup> The trial enrolled patients with KIR3DL2 expression; the dose-escalation phase required expression of 5% or higher in the skin and/or blood, and the cohort expansion permitted any level of expression. The study underscores a wider goal in the field of CTCL: to identify patients who will benefit from specific therapies

based not only on their clinical presentation, stage, and symptoms, but also biomarkers that predict response in the tumor tissue. Between 80% to 90% of patients with Sézary syndrome express KIR3DL2. Treatment with IPH4102 led to an overall response rate of 42.9%, which is an encouraging outcome in a biomarker-driven trial, particularly in patients with Sézary syndrome and large-cell transformation, who have a poor prognosis. Importantly, IPH4102 also improved quality-of-life indexes, including the Skindex. In CTCL, the aim of therapy should be not only to treat the disease, but also to improve the patient's quality of life. IPH4102 had a reasonable safety profile. This therapy will be evaluated in a large phase 2 trial, known as TELLOMAK (T-Cell Lymphoma Anti-KIR3DL2 Therapy) across several patient populations, including those with mycosis fungoides and Sézary syndrome.

Dr Bagot also presented a phase 1/2 study on cusatuzumab (ARGX-110), an antibody that blocks CD70 and CD27.<sup>14</sup> The trial enrolled patients with relapsed/refractory CTCL who were CD70-positive. Cusatuzumab showed some encouraging responses, with an overall response rate of 23%. Further studies should clarify any other on-target effects this drug might have when blocking this pathway. Enrollment in future clinical trials may be limited to patients in whom this pathway is pertinent.

A small phase 1/2 trial by Dr Christiane Querfeld evaluated the combination of durvalumab and lenalidomide among 9 patients with CTCL.<sup>15</sup> Skin disease improved in 8 patients, and the treatment appeared to be safe. This study included an analysis of expression panels of several immune checkpoint markers. Dr Querfeld evaluated markers in the tumor cells and tumor microenvironment to identify any association with outcome. Responders had detectable levels of programmed death ligand 1 and low expression of inducible T-cell costimulator.

Dr Francine Foss presented a phase 1 study of cobomarsen, an oligonucleotide drug that targets miR-155, in patients with mycosis fungoides.<sup>16</sup> The aim of targeting miR-155 is to block several signaling pathways that are active among patients with CTCL. In this study, cobomarsen was given via intratumoral, subcutaneous, and intravenous administration. The encouraging results showed that the modified Severity Weighted Assessment Tool (mSWAT) score improved in 92% of patients treated with systemic therapy. Treatment was well-tolerated. Cobomarsen will be studied in a phase 3 trial.

Dr Steven Horwitz presented a phase 2a study of cerdulatinib, a novel SYK/JAK inhibitor, in patients with relapsed/refractory CTCL or peripheral T-cell lymphoma.<sup>17</sup> Cerdulatinib inhibits the JAK/STAT pathway, which appears to be important in some T-cell lymphomas. The overall response rates were 34% in peripheral T-cell lymphoma and 26% in CTCL (29% in mycosis fungoides and 17% in Sézary syndrome). The use of cerdulatinib will be explored further, perhaps in combination with other therapies. It would seem intuitive that cerdulatinib would be most effective in patients whose lymphoma relies on the JAK/STAT pathway. Further analyses will likely examine characteristics of the responders, such as whether they were more reliant on the JAK/STAT pathway or had higher SYK upregulation in the tumor as compared with nonresponders. Cerdulatinib may also affect the microenvironment. It will be important to develop drugs that impact the microenvironment, and to understand how this strategy might be used to treat T-cell lymphomas.

A study by Dr Özlem Önder used mass spectrometry to evaluate the epiproteomic profile of patients with CTCL or Sézary syndrome.<sup>18</sup> This type of analysis will have broad implications across many different cancers, providing insight into how to identify

which patients will benefit from HDAC inhibitors and how to monitor response by identifying changes in the epiproteomic profile throughout treatment. Dr Önder found that alterations in H4K20 methylation are fairly common in patients with CTCL and Sézary syndrome. This finding has the potential to identify patients who will respond best to HDAC inhibitors. HDAC inhibitors are effective in CTCL overall, and they are very effective in certain subsets of CTCL and Sézary syndrome.

### Maintenance After Total Skin Electron Beam Therapy

A retrospective study by Dr Pamela Allen evaluated maintenance therapy after total skin electron beam therapy in patients with CTCL.<sup>19</sup> Use of maintenance therapy after total skin electron beam therapy is a common clinical strategy, based on anecdotal evidence suggesting that it appears to prolong response. This study showed that maintenance therapy nearly doubled progression-free survival.

### Disclosure

*Dr Haverkos has no real or apparent conflicts of interest to report.*

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## Highlights in Cutaneous T-Cell Lymphoma From the 60th American Society of Hematology Annual Meeting: A Dermatologist's Perspective

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**D**ermatologists often work closely with hematologists to treat patients with cutaneous T-cell lymphoma (CTCL). Several studies presented at the 60th American Society of Hematology (ASH) meeting have the potential to impact management. Studies evaluated the use of mogamulizumab, as well as novel treatments and strategies.

### Mogamulizumab

The randomized phase 3 MAVORIC trial (Study of KW-0761 Versus Vorinostat in Relapsed/Refractory CTCL) evaluated mogamulizumab, a CCR4 antibody, in patients with previously treated CTCL.<sup>1</sup> Treatment with mogamulizumab led to a median progression-free survival of 7.7 months, vs 3.1 months with vorinostat ( $P < .0001$ ). The objective response rate was 28% vs 5% ( $P < .0001$ ). A post hoc analysis of the MAVORIC trial evaluated the number of therapies that patients received before treatment with mogamulizumab.<sup>2</sup> The analysis found that the responses were the same regardless of whether patients were heavily pretreated or not. This finding speaks to the unique mechanism of action of mogamulizumab, which does not overlap with that of other therapies. Treatment with prior therapies did not predict or impede the response to mogamulizumab. This analysis provides the clinically important observation that basically any

patient may benefit from treatment with mogamulizumab.

A post hoc analysis of the MAVORIC trial from Dr Martine Bagot evaluated long-term clinical benefit with mogamulizumab.<sup>3</sup> Long-term treatment exposure was defined as lasting beyond 351 days. The primary goal of the analysis was to assess the safety and efficacy of mogamulizumab based on treatment exposure. The analysis found that long-term treatment with mogamulizumab was safe and well-tolerated. The main issue was drug eruption, a skin rash that was considered related to treatment. Drug eruption occurred in 20% of patients treated with long-term mogamulizumab. Thrombocytopenia was reported in 11.1%. All other side effects were observed in less than 10% of patients, and they tended to be low-grade.

The analysis also showed that benefit continued beyond 1 year, and was similar regardless of the patient's CCR4 expression status.<sup>3</sup> The global response rates were high in patients treated with mogamulizumab for longer periods. However, this improvement may not necessarily be attributable to the longer treatment duration. The study raises the question of whether these patients were preselected. They may have characteristics that would allow them to respond better to treatment with mogamulizumab. As mentioned, CCR4 expression status did not pre-

dict response, but there may be other factors. Based on this analysis, it is not known whether increased duration of mogamulizumab treatment led to long-term improvements, or whether patients who respond well to mogamulizumab were able to maintain treatment for a longer duration.

An analysis of data from the MAVORIC trial evaluated symptoms and side effect bother in patients with CTCL treated with mogamulizumab or vorinostat.<sup>4</sup> The study showed that treatment with mogamulizumab was associated with a stronger likelihood of improvement in skin symptoms, side effect bother, and lack of energy vs vorinostat (odds ratio,  $>1.0$ ).

### Novel Strategies

Dr Steven Horwitz presented a study of the novel SYK/JAK inhibitor ceralutinib in patients with peripheral T-cell lymphoma (PTCL) and CTCL.<sup>5</sup> This type of therapy has not been evaluated in CTCL before. Abnormalities in the SYK/JAK signaling pathway are found in a small proportion of CTCL patients. However, a drug that targets this pathway would likely have high response rates in these patients. The trial enrolled 45 patients with PTCL and 29 patients with CTCL. At the time of the report, 27 patients with CTCL were evaluable for response. The overall response rate was 26%, consisting of a complete response in 7% and a partial response

in 19%. These results are impressive. Importantly, responses were seen in patients with mycosis fungoides (6 of 21 patients) and Sézary syndrome (1 of 6 patients). These patients experienced a dramatic improvement in pruritus.

Treatment with cerdulatinib was fairly well-tolerated. The rate of diarrhea was 3% among patients with CTCL, but cases appeared mild. There was an increase in lipase levels, but no cases of frank pancreatitis. No patients with CTCL reported abdominal pain (although it occurred in 9% of patients with PTCL).

Correlation studies are now evaluating which patients are most likely to benefit from cerdulatinib. A phase 2a trial is also being designed.

A phase 1/2 trial by Dr Christiane Querfeld evaluated the combination of durvalumab and lenalidomide in CTCL.<sup>6</sup> Dr Querfeld had previously piloted the use of lenalidomide in CTCL, showing some moderate responses.<sup>7</sup> The theory was that lenalidomide, as an immunomodulator, might improve outcomes with the programmed death 1 inhibitor durvalumab. The preliminary data, for only 9 patients, suggested that durvalumab and lenalidomide together had better clinical activity than either agent alone. Skin disease improved in 7 patients, with no serious adverse events. These preliminary results are promising. Correlative studies will attempt to identify any patient characteristics associated with response.

Dr Martine Bagot presented results of a first-in-human phase 1 study on IPH4102, an anti-KIR antibody, in patients with CTCL.<sup>8</sup> Dr Bagot presented results for 35 patients with Sézary syndrome, a large cohort for this rare disease. The response rate was 42.9%, and the drug was well-tolerated. There were some complete responses in the blood and lymph nodes. A complete response was seen in 2 patients (5.7%), and a partial response was seen in 13 patients (37.2%). An additional 45.7% of

patients had stable disease. An interesting finding was that responses were durable. The duration of response was 13.8 months, and some responses were still ongoing at the time of the report. The patients' quality of life also improved. IPH4102 will be evaluated in a larger phase 2 trial.

The novel therapy cobomarsen, an inhibitor of Mir-155, belongs to a new class of medications known as microRNA inhibitors. MicroRNA 155 may be involved in the pathogenesis of CTCL. Dr Francine Foss presented results of a phase 1 trial that evaluated cobomarsen administered intratumorally, subcutaneously, or intravenously to patients with mycosis fungoides (stages 1 to 3).<sup>9</sup> Cobomarsen had significant clinical efficacy. The modified Severity Weighted Assessment Tool (mSWAT) score improved in 92% of patients treated with the systemic formulation. Quality of life also improved. The responses were durable, with a mean duration of response of 259 days. The study reported few adverse events and no life-threatening conditions associated with treatment. The study did not reach the maximum tolerated dose.

A correlative study evaluated signatures of the histone deacetylase inhibitor romidepsin by using a novel strategy involving tandem mass spectrometry and quantitative proteomics.<sup>10</sup> This study defined some histone codes. In the future, this type of strategy may be used to select patients for treatment with histone deacetylase inhibitors or possibly to identify new biomarkers for novel therapeutic targets.

A phase 1/2 study by Dr Martine Bagot evaluated the novel agent cusatuzumab (ARGX-110) for the treatment of CD70-positive CTCL.<sup>11</sup> Cusatuzumab blocks signaling of CD70/CD27, which is needed for tumor cells to proliferate and survive. CD70 is expressed on lymphoma cells; it is considered a good target in cancer because it is not expressed by normal

cells. The overall response rate was 23% among 27 patients. In another 31% of patients, disease was stabilized.

### **Maintenance Therapy After Electron Beam Therapy**

A retrospective analysis by Dr Pamela Allen evaluated maintenance therapy after electron beam therapy.<sup>12</sup> Not surprisingly, the study found an increase in progression-free survival among patients treated with maintenance therapy. There was a trend toward an improvement in overall survival. This important study validates the current practice, as physicians typically use maintenance treatment after total skin electron beam therapy. A prospective study comparing maintenance vs no maintenance would be needed for confirmation.

### **Reduced-Intensity Conditioning Before Stem Cell Transplant**

Dr Francesco Onida presented a study of reduced-intensity conditioning before stem cell transplant in heavily pretreated patients with mycosis fungoides and Sézary syndrome.<sup>13</sup> Stem cell transplant is considered the only curative treatment for CTCL. This is an important study because a large percentage of CTCL patients who undergo stem cell transplant develop adverse events, including infections, graft-vs-host disease, and death. There is a need to improve outcomes and reduce the infectious side effects and overall toxicity. This study found that a reduced-intensity preconditioning regimen was effective and less toxic than the standard strategy. A complete response was seen in 71% of patients, which is high. After a median follow-up of 80 months, a complete response was maintained in 95% of patients.

### **Brentuximab Vedotin**

A study by Dr Youn Kim evaluated how the superior clinical benefit of brentuximab vedotin in mycosis fungoides reported in the ALCANZA

trial (A Phase 3 Trial of Brentuximab Vedotin [SGN-35] Versus Physician's Choice [Methotrexate or Bexarotene] in Participants With CD30-Positive Cutaneous T-Cell Lymphoma) corresponded to expression of CD30 molecules in large-cell transformation.<sup>14,15</sup> This important study reflects a real-life situation. It is sometimes necessary to treat patients who do not have large-cell transformation or who lack the level of CD30 expression required for enrollment in the ALCANZA trial. The analysis by Dr Kim found that while clinical responses were much higher in patients who expressed high levels of CD30 on their cells, there were still some clinical responses observed in patients who had lower CD30 expression. This critical finding shows that the level of CD30 expression is not an absolute predictor of response to brentuximab vedotin. Patients without large-cell transformation or with a lower level of CD30 expression may still benefit from treatment.

### Disclosure

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