AstraZeneca and MedImmune, its global biologics research and development arm, today announced that the US Food and Drug Administration (FDA) has approved LUMOXITI™ (moxetumomab pasudotox-tdfk), a first-in-class CD22-directed cytotoxin, for the treatment of adult patients with relapsed or refractory hairy cell leukemia (HCL) who have received at least two prior systemic therapies, including treatment with a purine nucleoside analog. LUMOXITI is not recommended in patients with severe renal impairment (CrCl ≤ 29 mL/min).[i]

HCL is a rare, chronic, and slow-growing blood cancer.[ii],[iii] While many patients with hairy cell leukemia experience a remission with current treatments, 30% to 40% will relapse five to ten years after their first treatment.[iv] For some patients, the duration of response diminishes after repeated lines of therapy.[v],[vi] With very few treatments available, there remains significant unmet medical need for people with relapsed or refractory HCL. [2,4] LUMOXITI is the first new FDA-approved therapy for patients with relapsed or refractory HCL in over 20 years.[vii] We look forward to making LUMOXITI available to appropriate HCL patients as soon as possible.

The approval of LUMOXITI is based on data from the Phase III single-arm, open-label '1053' trial of LUMOXITI monotherapy in 80 patients who have received at least two prior therapies, including a purine nucleoside analog.[viii] The approval and these data demonstrate the potential impact that LUMOXITI could have on the management of patients with previously treated HCL.

Summary of key results from the trial, as determined by a blinded independent central review:

- The Phase III '1053' clinical trial findings showed a 30% (95% confidence interval [CI]: 20, 41) durable complete response (CR) rate (primary endpoint), defined as patients who achieved complete response with hematologic remission for a duration of more than 180 days. The findings also found a 75% (95% CI: 64, 84) overall response rate (ORR), a 41% (95% CI: 30, 53) CR rate, a 34% (95% CI: 24, 45) partial response rate, and an 80% hematologic remission rate. The median time to hematologic remission was 1.1 months (range: 0.2 to 13).1 At data cut-off, the median duration of complete response was not yet reached after a median 16.7 months of follow-up (2-49 months).[1] An independent review committee assesses responses.

- Capillary leak syndrome (CLS) and hemolytic uremic syndrome (HUS), including life-threatening cases of each, have been reported among patients

treated with LUMOXITI. In the combined safety database of 129 HCL patients treated with LUMOXITI, Grade 3 or 4 CLS occurred in 1.6% and 2% of patients respectively. Grade 3 or 4 HUS occurred in 3% and 0.8% of patients respectively1

- In the '1053' trial of 80 patients, the most common Grade 3 or 4 adverse reactions (reported in at least ≥ 5% of patients) were hypertension, febrile neutropenia, and HUS. HUS was the most common adverse reaction leading to discontinuation (5%). The most common adverse reactions (≥ 20%) of any grade were infusion-related reactions (50%), peripheral edema (39%), nausea (35%), fatigue (34%), headache (33%), pyrexia (31%), constipation (23%), anemia (21%), and diarrhea (21%).
- The most common laboratory abnormalities (≥ 20%) of any grade were creatinine increased, ALT increased, hypoalbuminemia, AST increased, hypocalcemia, hypophosphatemia, hemoglobin decreased, neutrophil count decreased, hyponatremia, blood bilirubin increased, hypokalemia, GGT increased, hypomagnesemia, platelet count decreased, hyperuricemia, and alkaline phosphate increased.[1]

The recommended dose of LUMOXITI is 0.04 mg/kg, administered as an intravenous infusion over 30 minutes on days 1, 3, and 5 of each 28-day cycle up to 6 cycles, disease progression, or unacceptable toxicity[1]

Select Important Safety Information, including Boxed WARNING, Patient Information (Medication Guide), and Instructions for Use about LUMOXITI.

IMPORTANT SAFETY INFORMATION, INCLUDING BOXED WARNING[1]

WARNING: CAPILLARY LEAK SYNDROME and HEMOLYTIC UREMIC SYNDROME

- Capillary Leak Syndrome (CLS), including life-threatening cases, occurred in patients receiving LUMOXITI. Monitor weight and blood pressure; check labs, including albumin, if CLS is suspected. Delay dosing or discontinue LUMOXITI as recommended *[see Dosage and Administration (2.3) and Warnings and Precautions (5.1)].*
- Hemolytic Uremic Syndrome (HUS), including life-threatening cases, occurred in patients receiving LUMOXITI. Monitor hemoglobin, platelet count, serum creatinine, and ensure adequate hydration. Discontinue LUMOXITI in patients with HUS *[see Dosage and Administration (2.3) and Warnings and Precautions (5.2)].*

LUMOXITI has been approved under FDA Priority Review, a designation granted to medicines that the FDA determines have the potential to provide significant improvements in the safety or effectiveness of the treatment, diagnosis, or prevention of serious conditions when compared to standard applications.[ix] This designation and

approval demonstrates progress against our vision of being a scientific leader in hematology by helping to transform care and drive toward a cure for people with life-threatening blood cancers. This is the second FDA approval for AstraZeneca in hematology within one year and as such underscores our commitment to bringing novel therapies to patients most in need.

Questions or requests for more information may arise as news of this approval begins to travel among patients, healthcare professionals, and the general public. View the full press release here issued by AstraZeneca announcing the FDA approval for your reference.

WARNINGS AND PRECAUTIONS

- **Capillary leak syndrome (CLS)**, including life-threatening cases, has been reported among patients treated with LUMOXITI and is characterized by hypoalbuminemia, hypotension, symptoms of fluid overload, and hemoconcentration. In the combined safety database of HCL patients treated with LUMOXITI, CLS occurred in 34% (44/129) of patients, including Grade 2 in 23% (30/129), Grade 3 in 1.6% (2/129), and Grade 4 in 2% (3/129).

  Most cases of CLS occurred in the first 8 days (range: 1 to 19) of a treatment cycle, however, cases have also been reported on other days throughout the cycle. The median time to resolution of CLS was 12 days (range: 1 to 53). Monitor patient weight and blood pressure prior to each LUMOXITI infusion and as clinically indicated during treatment. Assess patients for signs and symptoms of CLS, including weight gain (increase in 5.5 pounds (2.5 kg) or ≥ 5% from Day 1 of current cycle), hypotension, peripheral edema, shortness of breath or cough, and pulmonary edema and/or serosal effusions. In addition, the following changes in laboratory parameters may help identify CLS: hypoalbuminemia, elevated hematocrit, leukocytosis, and thrombocytosis. CLS may be life-threatening or fatal if treatment is delayed. Counsel patients to seek immediate medical attention should signs or symptoms of CLS occur at any time. Patients who develop CLS should receive appropriate supportive measures, including concomitant oral or intravenous corticosteroids, and hospitalization as clinically indicated. Withhold LUMOXITI for Grade 2 CLS until resolution, and permanently discontinue for Grade ≥ 3 CLS.

- **Hemolytic Uremic Syndrome (HUS)**, including life threatening cases, has been reported in patients treated with LUMOXITI and is characterized by the triad of microangiopathic hemolytic anemia, thrombocytopenia, and progressive renal failure. In the combined safety database of HCL patients treated with LUMOXITI, HUS occurred in 7% (9/129) of patients, including Grade 3 in 3% (4/129) and Grade 4 in 0.8% (1/129).

Most cases of HUS occurred in the first 9 days (range: 1 to 16) of a treatment cycle, however, cases have also been reported on other days throughout the cycle. The median time to resolution of HUS was 11.5 days (range: 2 to 44). All cases resolved, including those who discontinued LUMOXITI.
Avoid LUMOXITI in patients with prior history of severe thrombotic microangiopathy (TMA) or HUS. Administer prophylactic intravenous fluids before and after LUMOXITI infusions. In Study 1053, patients with a platelet count ≥ 100,000/mm^3 received low-dose aspirin on Days 1 through 8 of each 28-day cycle for prophylaxis of thrombosis.
Monitor blood chemistry and complete blood counts prior to each dose and on Day 8 of each treatment cycle. Monitoring mid-cycle is also recommended. Consider the diagnosis of HUS in patients who develop hemolytic anemia, worsening or sudden onset of thrombocytopenia, increase in creatinine levels, elevation of bilirubin and/or LDH, and have evidence of hemolysis based on peripheral blood smear schistocytes.

The events of HUS may be life-threatening if treatment is delayed with increased risk of progressive renal failure requiring dialysis. If HUS is suspected initiate appropriate supportive measures, including fluid repletion, hemodynamic monitoring, and consider hospitalization as clinically indicated. Discontinue LUMOXITI in patients with HUS.

- **Renal Toxicity** has been reported in patients treated with LUMOXITI therapy. In the combined safety database of HCL patients treated with LUMOXITI, 26% (34/129) reported adverse events of renal toxicity, including acute kidney injury (2.3%), renal failure (2.3%), renal impairment (1.6%), serum creatinine increased (17%), and proteinuria (8%). Grade 3 acute kidney injury occurred in 1.6% (2/129) of patients.

Based on laboratory findings, during treatment, serum creatinine increased by two or more grades from baseline in 22% (29/129) of patients, including increases of Grade 3 in 1.6% (2/129) of patients. At the end of treatment, serum creatinine levels remained elevated at 1.5- to 3-times the upper limit of normal in 5% of patients. Patients who experience HUS, those ≥ 65 years of age, or those with baseline renal impairment may be at increased risk for worsening of renal function following treatment with LUMOXITI.
Monitor renal function prior to each infusion of LUMOXITI, and as clinically indicated throughout treatment. Delay LUMOXITI dosing in patients with Grade ≥ 3 elevations in creatinine, or upon worsening from baseline by ≥ 2 grades.

- **Infusion Related Reactions** occurred in patients treated with LUMOXITI, and were defined as the occurrence of any one of the following events on the day of study drug infusion: chills, cough, dizziness, dyspnea, feeling hot, flushing, headache, hypertension, hypotension, infusion related reaction, myalgia nausea, pyrexia, sinus tachycardia, tachycardia, vomiting, or wheezing. In Study 1053, infusion related reactions occurred in 50% (40/80) of patients, including Grade 3 events in 11% (9/80) of patients. The most

frequently reported infusion related events were nausea (15%), pyrexia (14%), chills (14%), vomiting (11%), headache (9%), and infusion related reaction (9%).
Infusion related reactions may occur during any cycle of treatment with LUMOXITI. Premedicate with antihistamines and antipyretics prior to each LUMOXITI dose. If a severe infusion related reaction occurs, interrupt the LUMOXITI infusion and institute appropriate medical management. Administer an oral or intravenous corticosteroid approximately 30 minutes before resuming, or before the next LUMOXITI infusion.

- **Electrolyte Abnormalities:** In the combined safety database of HCL patients treated with LUMOXITI, electrolyte abnormalities occurred in 57% (73/129) of patients with the most common electrolyte abnormality being hypocalcemia occurring in 25% of patients. Grade 3 electrolyte abnormalities occurred in 14% (18/129) of patients and Grade 4 electrolyte abnormalities occurred in 0.8% (1/129) of patients. Electrolyte abnormalities co-occurred in the same treatment cycle with CLS, HUS, fluid retention, or renal toxicity in 37% (48/129) of patients.
Monitor serum electrolytes prior to each dose and on Day 8 of each treatment cycle. Monitoring mid-cycle is also recommended.

ADVERSE REACTIONS

- Most common non-laboratory adverse reactions (≥ 20%) of any grade were infusion related reactions (50%), edema peripheral (39%), nausea (35%), fatigue (34%), headache (33%), pyrexia (31%), constipation (23%), anemia (21%), and diarrhea (21%). The most common Grade 3 or 4 adverse reactions (reported in at least ≥ 5% of patients) were hypertension, febrile neutropenia, and HUS.

- Most common laboratory abnormalities (≥ 20%) of any grade were creatinine increased, ALT increased, hypoalbuminemia, AST increased, hypocalcemia, hypophosphatemia, hemoglobin decreased, neutrophil count decreased, hyponatremia, blood bilirubin increased, hypokalemia, GGT increased, hypomagnesemia, platelet count decreased, hyperuricemia, and alkaline phosphate increased.

- Adverse reactions resulting in permanent discontinuation of LUMOXITI occurred in 15% (12/80) of patients. The most common adverse reaction leading to LUMOXITI discontinuation was HUS (5%). The most common adverse reaction resulting in dose delays, omissions, or interruptions was pyrexia (3.8%).

SPECIFIC POPULATIONS

- **Pregnancy:** There are no available data on LUMOXITI use in pregnant women to inform a drug-associated risk of major birth defects and miscarriage. Advise pregnant women of the potential risk to a fetus.

- **Lactation**: Advise women not to breastfeed.

- **Geriatric Use:** Exploratory analyses suggest a higher incidence of adverse reactions leading to drug discontinuation (23% versus 7%) and renal toxicity (40% versus 20%) for patients 65 years of age or older as compared to those younger than 65 years.

- [LUMOXITI™ (moxetumomab pasudotox-tdfk) for Injection (NDC 0310-4700-01)
    - Sterile, preservative-free, white to off-white lyophilized powder supplied in individually boxed single-dose vials
    - Each vial delivers a range of 0.9-1.1 mg moxetumomab pasudotox. The actual strength (in mg) varies per vial and is printed on every LUMOXITI carton and vial label
- IV Solution Stabilizer (NDC 0310-4715-11)
    - Sterile, preservative-free, colorless to slightly yellow, clear solution free from visible particles supplied in individually boxed single-dose vials
    - Each vial contains 1 mL solution]

Please see the Product Information sheet attached.

Please see complete Prescribing Information, including Boxed WARNING, Patient Information (Medication Guide), and Instructions for Use

[1] LUMOXITI™ (moxetumomab pasudotox-tdfk) [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP. 2018.

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