Press Release

Astellas' VYLOY™ (zolbetuximab-clzb) Approved by U.S. FDA for Treatment of Advanced Gastric and GEJ Cancer

- VYLOY is the first and only CLDN18.2-targeted treatment approved in the U.S. for adults with advanced gastric and gastroesophageal junction cancer whose tumors are CLDN18.2 positive -

TOKYO, Oct. 18, 2024 – Astellas Pharma Inc. (TSE: 4503, President and CEO: Naoki Okamura, "Astellas") today announced that the U.S. Food and Drug Administration (FDA) has approved VYLOY™ (zolbetuximab-clzb) in combination with fluoropyrimidine- and platinum-containing chemotherapy for the first-line treatment of adults with locally advanced unresectable or metastatic human epidermal growth factor receptor 2 (HER2)-negative gastric or gastroesophageal junction (GEJ) adenocarcinoma whose tumors are claudin (CLDN) 18.2 positive as determined by an FDA-approved test.[1] VYLOY is the first and only CLDN18.2-targeted therapy approved in the U.S.

In the SPOTLIGHT and GLOW clinical trials, approximately 38% of patients screened had tumors that were CLDN18.2 positive.[2,3] CLDN18.2 positivity is defined as ≥75% of tumor cells demonstrating moderate to strong membranous CLDN18 immunohistochemical staining, as determined by the VENTANA® CLDN18 (43-14A) RxDx Assay from Roche.[2,3] Astellas collaborated with Roche on the newly approved immunohistochemistry (IHC) companion diagnostic (CDx) test to identify patients who may be eligible for VYLOY.[4]

Moitreyee Chatterjee-Kishore, Ph.D., M.B.A., Senior Vice President and Head of Immuno-Oncology Development, Astellas
"The approval of VYLOY as the first and only targeted therapy for CLDN18.2-positive patients in the U.S. further delivers on our relentless pursuit of scientific progress for devastating diseases like gastric and GEJ cancers, which are often only discovered at the advanced stage. This achievement is the result of years of dedicated research and development focused on targeting a novel biomarker, and we are grateful to the patients, investigators, and Astellas team members who have made this important advancement for patients a reality."

Samuel J. Klempner, M.D., Associate Professor, Harvard Medical School, Medical Oncologist at Massachusetts General Hospital, Boston
"While there have been advances in the first-line treatment of locally advanced unresectable and metastatic gastric and GEJ cancers in the last several years, there is still a tremendous unmet need among our patients. The approval of VYLOY, based on the pivotal Phase 3 SPOTLIGHT and GLOW trials, brings forward a novel biomarker and new therapy for patients whose tumors are CLDN18.2 positive, and for those on the frontlines of treatment decision-making."

The approval is based on results from the Phase 3 SPOTLIGHT and GLOW clinical trials.[2,3] The SPOTLIGHT study evaluated VYLOY plus mFOLFOX6 (a combination chemotherapy regimen that includes oxaliplatin, leucovorin, and fluorouracil) compared to placebo plus

mFOLFOX6. The GLOW study evaluated VYLOY plus CAPOX (a combination chemotherapy regimen that includes capecitabine and oxaliplatin) compared to placebo plus CAPOX. Both trials met their primary endpoint, progression-free survival (PFS), as well as a key secondary endpoint, overall survival (OS), in patients treated with VYLOY plus chemotherapy compared to placebo plus chemotherapy. Across the SPOTLIGHT and GLOW trials, the most common all-grade treatment-emergent adverse events (TEAEs) reported in the VYLOY treatment arms were nausea, vomiting and decreased appetite.[2,3]

An FDA-approved test is used to identify patients who may be eligible for VYLOY.[1] The VENTANA CLDN18 (43-14A) RxDx Assay from Roche is an FDA-approved IHC test used to help determine CLDN18.2 status. Testing is available in the U.S. at multiple reference laboratories nationwide and is expected to expand to additional laboratories over time. To see where testing for CLDN18.2 status is available, please visit VYLOYhcp.com.*

Following today's FDA decision, VYLOY is now approved in five markets worldwide — Japan, the United Kingdom, the European Union, South Korea and the U.S. Japan's Ministry of Health, Labour and Welfare approved VYLOY for use on March 26, 2024, representing the first global approval of this treatment. In August, VYLOY was approved by the UK Medicines and Healthcare products Regulatory Agency. In September, the European Commission granted marketing authorization to VYLOY in the European Union, and the Ministry of Food and Drug Safety approved the therapy in South Korea. Astellas has submitted other applications for VYLOY to regulatory agencies around the world, with reviews ongoing.

Astellas has already reflected the impact from this approval in its financial forecast for the current fiscal year ending March 31, 2025.

*VYLOYhcp.com is in the process of being deployed. If you cannot access the site right away, please try again soon.

About VYLOY™ (zolbetuximab-clzb)
VYLOY™ (zolbetuximab-clzb) is a claudin 18.2-directed cytolytic antibody that is approved by the U.S. Food and Drug Administration (FDA) in combination with fluoropyrimidine- and platinum-containing chemotherapy for the first-line treatment of adults with locally advanced unresectable or metastatic human epidermal growth factor receptor 2 (HER2)-negative gastric or gastroesophageal junction (GEJ) adenocarcinoma whose tumors are claudin (CLDN) 18.2 positive as determined by an FDA-approved test. As a first-in-class monoclonal antibody (mAb), VYLOY targets and binds to CLDN18.2, a transmembrane protein. VYLOY depletes CLDN18.2-positive cells via antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC).[1]

VYLOY (zolbetuximab-clzb) U.S. Indication & Important Safety Information

INDICATION
VYLOY, in combination with fluoropyrimidine- and platinum-containing chemotherapy, is indicated for the first-line treatment of adults with locally advanced unresectable or metastatic human epidermal growth factor receptor 2 (HER2)-negative gastric or gastroesophageal junction (GEJ) adenocarcinoma whose tumors are claudin (CLDN) 18.2 positive as determined by an FDA-approved test.

IMPORTANT SAFETY INFORMATION

Warnings and Precautions

Hypersensitivity reactions, including serious anaphylaxis reactions, and serious and fatal infusion-related reactions (IRR) have been reported in clinical studies when VYLOY has been administered. **Any grade hypersensitivity reactions**, including anaphylactic reactions, occurring with VYLOY in combination with mFOLFOX6 or CAPOX was 18%. **Severe (Grade 3 or 4) hypersensitivity reactions**, including anaphylactic reactions, occurred in 2% of patients. Seven patients (1.3%) permanently discontinued VYLOY for hypersensitivity reactions, including two patients (0.4%) who permanently discontinued VYLOY due to anaphylactic reactions. Seventeen (3.2%) patients required dose interruption, and three patients (0.6%) required infusion rate reduction due to hypersensitivity reactions. **All grade IRRs** occurred in 3.2% in patients administered VYLOY in combination with mFOLFOX6 or CAPOX. Severe (Grade 3) IRRs occurred in 2 (0.4%) patients who received VYLOY. An IRR led to permanent discontinuation of VYLOY in 2 (0.4%) patients and dose interruption in 7 (1.3%) patients. The infusion rate was reduced for VYLOY for 2 (0.4%) patients due to an IRR. Monitor patients during infusion with VYLOY and for 2 hours after completion of infusion or longer if clinically indicated, for hypersensitivity reactions with symptoms and signs that are highly suggestive of anaphylaxis (urticaria, repetitive cough, wheeze and throat tightness/change in voice). Monitor patients for signs and symptoms of IRRs including nausea, vomiting, abdominal pain, salivary hypersecretion, pyrexia, chest discomfort, chills, back pain, cough and hypertension. If a severe or life-threatening hypersensitivity or IRR reaction occurs, discontinue VYLOY permanently, treat symptoms according to standard medical care, and monitor until symptoms resolve. For any Grade 2 hypersensitivity or IRR, interrupt the VYLOY infusion until Grade ≤1, then resume at a reduced infusion rate for the remaining infusion. Follow Grade 2 management for Grade 3 infusion-related nausea and vomiting. Premedicate the patient with antihistamines for the subsequent infusions, and closely monitor the patient for symptoms and signs of a hypersensitivity reaction. The infusion rate may be gradually increased as tolerated.

Severe Nausea and Vomiting. VYLOY is emetogenic. Nausea and vomiting occurred more often during the first cycle of treatment**. All grade nausea and vomiting** occurred in 82% and 67% respectively of patients treated with VYLOY in combination with mFOLFOX6 and 69% and 66% in combination with CAPOX, respectively. **Severe (Grade 3) nausea** occurred in 16% and 9% of patients treated with VYLOY in combination with mFOLFOX6 or CAPOX respectively. **Severe (Grade 3) vomiting** occurred in 16% and 12% of patients treated with VYLOY in combination with mFOLFOX6 or CAPOX. Nausea led to permanent discontinuation of VYLOY in combination with mFOLFOX6 or CAPOX in 18 (3.4%) patients and dose interruption in 147 (28%) patients. Vomiting led to permanent discontinuation of VYLOY in combination with mFOLFOX6 or CAPOX in 20 (3.8%) patients and dose interruption in 150 (28%) patients. Pretreat with antiemetics prior to each infusion of VYLOY. Manage patients during and after infusion with antiemetics or fluid replacement. Interrupt the infusion, or permanently discontinue VYLOY based on severity.

ADVERSE REACTIONS

Most common adverse reactions (≥15%): Nausea, vomiting, fatigue, decreased appetite, diarrhea, peripheral sensory neuropathy, abdominal pain, constipation, decreased weight, hypersensitivity reactions, and pyrexia.

Most common laboratory abnormalities (≥15%): Decreased neutrophil count, decreased leucocyte count, decreased albumin, increased creatinine, decreased hemoglobin, increased glucose, decreased lymphocyte count, increased aspartate aminotransferase, decreased platelets, increased alkaline phosphatase, increased alanine aminotransferase, decreased glucose, decreased sodium, increased phosphate, decreased potassium, and decreased magnesium.

SPOTLIGHT Study: **279 patients with locally advanced unresectable or metastatic HER2-negative gastric or GEJ adenocarcinoma whose tumors were CLDN18.2 positive who received at least one dose of VYLOY in combination with mFOLFOX6**

Serious adverse reactions occurred in 45% of patients treated with VYLOY in combination with mFOLFOX6; the **most common serious adverse reactions** (≥2%) were vomiting (8%), nausea (7%), neutropenia (2.9%), febrile neutropenia (2.9%), diarrhea (2.9%), intestinal obstruction (3.2%), pyrexia (2.5%), pneumonia (2.5%), respiratory failure (2.2%), pulmonary embolism (2.2%), decreased appetite (2.1%) and sepsis (2.0%). **Fatal adverse reactions** occurred in 5% of patients who received VYLOY in combination with mFOLFOX6 including sepsis (1.4%), pneumonia (1.1%), respiratory failure (1.1%), intestinal obstruction (0.7%), acute hepatic failure (0.4%), acute myocardial infarction (0.4%), death (0.4%), disseminated intravascular coagulation (0.4%), encephalopathy (0.4%), and upper gastrointestinal hemorrhage (0.4%). Permanent discontinuation of VYLOY due to an adverse reaction occurred in 20% of patients; the **most common adverse reactions leading to discontinuation** (≥2%) were nausea and vomiting. Dosage interruptions of VYLOY due to an adverse reaction occurred in 75% of patients; the **most common adverse reactions leading to dose interruption** (≥5%) were nausea, vomiting, neutropenia, abdominal pain, fatigue, and hypertension.

GLOW Study: **254 patients with locally advanced unresectable or metastatic HER2-negative gastric or GEJ adenocarcinoma whose tumors were CLDN18.2 positive who received at least one dose of VYLOY in combination with CAPOX**

Serious adverse reactions occurred in 47% of patients treated with VYLOY in combination with CAPOX; the **most common serious adverse reactions** (≥2%) were vomiting (6%), nausea (4.3%), decreased appetite (3.9%), decreased platelet count (3.1%), upper gastrointestinal hemorrhage (2.8%), diarrhea (2.8%), pneumonia (2.4%), pulmonary embolism (2.3%), and pyrexia (2.0%). **Fatal adverse reactions** occurred in 8% of patients who received VYLOY in combination with CAPOX including sepsis (1.2%), pneumonia (0.4%), death (0.8%), upper gastrointestinal hemorrhage (0.8%), cerebral hemorrhage (0.8%), abdominal infection (0.4%), acute respiratory distress syndrome (0.4%), cardio-respiratory arrest (0.4%), decreased platelet count (0.4%), disseminated intravascular coagulation (0.4%), dyspnea (0.4%), gastric perforation (0.4%), hemorrhagic ascites (0.4%), procedural complication (0.4%), sudden death (0.4%), and syncope (0.4%). Permanent discontinuation of VYLOY due to an adverse reaction occurred in 19% of patients; the **most common adverse reaction leading to discontinuation** (≥2%) was vomiting. Dosage interruption of VYLOY due to an adverse reaction occurred in 55% of patients; the **most common adverse reactions leading to dose interruption** (≥2%) were nausea, vomiting, neutropenia, thrombocytopenia, anemia, fatigue, infusion-related reaction, and abdominal pain.

SPECIFIC POPULATIONS

Lactation Advise lactating women not to breastfeed during treatment with VYLOY and for 8 months after the last dose.

For more information, please see the U.S. full Prescribing Information for VYLOY here.

About Locally Advanced Unresectable Metastatic Gastric and Gastroesophageal Junction Cancer

Gastric and gastroesophageal junction (G/GEJ) cancer is the fifth most commonly diagnosed cancer worldwide.[5] GEJ adenocarcinoma is a cancer that starts at the area where the

esophagus joins the stomach.[6] In the U.S., it is estimated that 130,263 people are living with G/GEJ cancer, classifying it as a rare disease.[7,8] In 2024, it is estimated that 26,890 people will be diagnosed with G/GEJ cancer and 10,880 will die from the disease in the U.S.[7] Signs and symptoms can include indigestion or heartburn, pain or discomfort in the abdomen, nausea and vomiting, bloating of the stomach after meals and loss of appetite.[9] Signs of more advanced G/GEJ cancer can include unexplained weight loss, weakness and fatigue, and vomiting blood or having blood in the stool.[10] Risk factors associated with gastric and GEJ cancer can include older age, male gender, family history, *H. pylori* infection, smoking, and gastroesophageal reflux disease (GERD).[11,12] Because early-stage gastric cancer symptoms frequently overlap with more common stomach-related conditions, G/GEJ cancer is often diagnosed in the advanced or metastatic stage, or once it has spread from the tumor's origin to other body tissues or organs.[10] The five-year relative survival rate for patients at the metastatic stage is 7%.[7]

INVESTIGATIONAL STUDIES

About SPOTLIGHT Phase 3 Clinical Trial

SPOTLIGHT is a Phase 3, global, multi-center, double-blind, randomized study, assessing the efficacy and safety of zolbetuximab plus mFOLFOX6 (a combination chemotherapy regimen that includes oxaliplatin, leucovorin, and fluorouracil) compared to placebo plus mFOLFOX6 as a first-line treatment in patients with locally advanced unresectable or metastatic HER2-negative gastric or GEJ adenocarcinoma whose tumors were CLDN18.2 positive. The study enrolled 565 patients at 215 study locations in the U.S., Canada, United Kingdom, Australia, Europe, South America, and Asia. The primary endpoint is progression-free survival (PFS) in participants treated with the combination of zolbetuximab plus mFOLFOX6 compared to those treated with placebo plus mFOLFOX6. Secondary endpoints include overall survival (OS), objective response rate (ORR), duration of response (DOR), safety and tolerability, and quality-of-life parameters.

Data from the SPOTLIGHT clinical trial were presented during the 2023 American Society of Clinical Oncology (ASCO) Gastrointestinal (GI) Cancers Symposium in an oral presentation on January 19, 2023, and were subsequently published in *The Lancet* on April 14, 2023.[2]

For more information, please visit clinicaltrials.gov under Identifier NCT03504397.

About GLOW Phase 3 Clinical Trial

GLOW is a Phase 3, global, multi-center, double-blind, randomized study, assessing the efficacy and safety of zolbetuximab plus CAPOX (a combination chemotherapy regimen that includes capecitabine and oxaliplatin) compared to placebo plus CAPOX as a first-line treatment in patients with locally advanced unresectable or metastatic HER2-negative gastric or GEJ adenocarcinoma whose tumors were CLDN18.2 positive. The study enrolled 507 patients at 166 study locations in the U.S., Canada, United Kingdom, Europe, South America, and Asia. The primary endpoint is PFS in participants treated with the combination of zolbetuximab plus CAPOX compared to those treated with placebo plus CAPOX. Secondary endpoints include OS, ORR, DOR, safety and tolerability, and quality-of-life parameters.

Data from the GLOW study were initially presented at the March 2023 ASCO Plenary Series with an updated oral presentation at the 2023 ASCO Annual Meeting on June 3, 2023, and were subsequently published in *Nature Medicine* on July 31, 2023.[3]

For more information, please visit clinicaltrials.gov under Identifier NCT03653507.

Investigational Pipeline in CLDN18.2
A Phase 2 trial of zolbetuximab in metastatic pancreatic adenocarcinoma is in progress. The trial is a randomized, multi-center, open-label study, evaluating the safety and efficacy of investigational zolbetuximab in combination with gemcitabine plus nab-paclitaxel as a first-line treatment in patients with metastatic pancreatic adenocarcinoma with CLDN18.2 positive tumors (defined as ≥75% of tumor cells demonstrating moderate to strong membranous CLDN18 staining based on a validated immunohistochemistry assay). For more information, please visit clinicaltrials.gov under Identifier NCT03816163.

In addition to zolbetuximab, ASP2138 is under development in our Primary Focus Immuno-Oncology area and is currently recruiting patients. ASP2138 is a bispecific monoclonal antibody that binds to CD3 and CLDN18.2, and it is currently in a Phase 1/1b study in participants with metastatic or locally advanced unresectable gastric or GEJ adenocarcinoma or metastatic pancreatic adenocarcinoma whose tumors have CLDN18.2 expression. The safety and efficacy of the agent under investigation have not been established for the uses being considered. For more information, please visit clinicaltrials.gov under Identifier NCT05365581.

There is no guarantee that these agent(s) will receive regulatory approval and become commercially available for the uses being investigated.

About Astellas
Astellas Pharma Inc. is a pharmaceutical company conducting business in more than 70 countries around the world. We are promoting the Focus Area Approach that is designed to identify opportunities for the continuous creation of new drugs to address diseases with high unmet medical needs by focusing on Biology and Modality. Furthermore, we are also looking beyond our foundational Rx focus to create Rx+® healthcare solutions that combine our expertise and knowledge with cutting-edge technology in different fields of external partners. Through these efforts, Astellas stands on the forefront of healthcare change to turn innovative science into VALUE for patients. For more information, please visit our website at https://www.astellas.com/en.

Cautionary Notes
In this press release, statements made with respect to current plans, estimates, strategies and beliefs and other statements that are not historical facts are forward-looking statements about the future performance of Astellas. These statements are based on management's current assumptions and beliefs in light of the information currently available to it and involve known and unknown risks and uncertainties. A number of factors could cause actual results to differ materially from those discussed in the forward-looking statements. Such factors include, but are not limited to: (i) changes in general economic conditions and in laws and regulations, relating to pharmaceutical markets, (ii) currency exchange rate fluctuations, (iii) delays in new product launches, (iv) the inability of Astellas to market existing and new products effectively, (v) the inability of Astellas to continue to effectively research and develop products accepted by customers in highly competitive markets, and (vi) infringements of Astellas' intellectual property rights by third parties.

Information about pharmaceutical products (including products currently in development) which is included in this press release is not intended to constitute an advertisement or medical advice.

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