Press Release

Astellas Receives Approval from the European Commission for VYLOY™ (zolbetuximab) in Combination with Chemotherapy for Advanced Gastric and Gastroesophageal Junction Cancer

- Zolbetuximab is currently the first and only therapy approved in the European Union to target claudin 18.2, a biomarker positively expressed by 38% of patients with advanced gastric cancer[1,2] -

-Treatment with the claudin 18.2-targeted monoclonal antibody shown to significantly extend both progression-free survival and overall survival in Phase 3 trials[1,2] -

TOKYO, 20 September, 2024 – Astellas Pharma Inc. (TSE: 4503, President and CEO: Naoki Okamura, "Astellas") today announced that the European Commission (EC) has approved VYLOY™ (zolbetuximab) in combination with fluoropyrimidine- and platinum-containing chemotherapy for the first-line treatment of adult patients 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. The European Medicines Agency has recommended that zolbetuximab's designation as an orphan medicinal product be maintained in recognition of the poor survival outcomes associated with gastric and GEJ cancers.

Zolbetuximab is currently the first and only approved monoclonal antibody specifically designed to target gastric tumor cells that express the biomarker CLDN18.2, offering a more personalized approach to cancer treatment. In the zolbetuximab Phase 3 clinical trials, approximately 38% of adult patients with advanced and metastatic gastric and GEJ cancers had tumors that were CLDN18.2 positive.[1,2] By binding to CLDN18.2 expressed on tumor cell membranes, zolbetuximab results in antibody-dependent cellular cytotoxicity, complement dependent cytotoxicity and tumor growth inhibition.[3]

Zorana Maravic, Chief Executive Officer of Digestive Cancers Europe (DiCE):
"Sadly, due to similar symptoms to more common stomach conditions, gastric and gastroesophageal junction cancers are often diagnosed at the advanced or metastatic stage when treatment options have traditionally been relatively limited. Ensuring timely diagnosis, followed by personalized treatment and care, will be essential to better survival and quality of life for patients."

Moitreyee Chatterjee-Kishore, Ph.D., M.B.A., Senior Vice President and Head of Immuno-Oncology Development, Astellas:

“We are delighted to bring zolbetuximab, a first-in-class targeted treatment option, to patients in Europe where gastric and gastroesophageal cancers are the sixth leading cause of cancer-related death. With zolbetuximab, we’re entering a new era in precision medicine for these advanced cancers, underpinning our ongoing commitment to pioneering scientific discovery that can advance patient outcomes."

Data from the Phase 3 SPOTLIGHT and GLOW clinical trials, which supported the European Marketing Authorization, showed that treatment with zolbetuximab provided statistically significant improvements in progression-free survival (PFS) and overall survival (OS) compared to other standard of care chemotherapies in eligible patients with gastric and GEJ cancers.[1,2] In the SPOTLIGHT trial, a median PFS of 10.61 months was achieved with zolbetuximab plus mFOLFOX6 as first-line treatment, versus 8.67 months with placebo plus mFOLFOX6. The median OS was 18.23 months versus 15.54 months in the respective treatment groups.[1] Similar efficacy findings were seen in the GLOW trial where median PFS was 8.21 months versus 6.80 months, and median OS 14.39 months versus 12.16 months, with zolbetuximab plus CAPOX, compared to placebo plus CAPOX, respectively.[2] In both the SPOTLIGHT and GLOW trials, the incidence of serious treatment emergent adverse events (TEAEs) was similar in the zolbetuximab treatment groups compared to the controls. The most common all-grade TEAEs reported in the zolbetuximab treatment groups were nausea, vomiting and decreased appetite.[1,2]

The European Marketing Authorization for zolbetuximab is valid in all 27 EU member states as well as Iceland, Liechtenstein, and Norway, and is aligned to the recently updated ESMO Gastric Cancer Living Guidelines which state that the addition of zolbetuximab to chemotherapy can be considered for patients with CLDN18.2 positive, HER-2 negative tumors in the first-line metastatic disease setting.[4] Astellas is working closely with local regulatory authorities and health technology assessment bodies across the EU to ensure that patients who may gain benefit from zolbetuximab are able to access the novel treatment as soon as possible.

This regulatory approval for zolbetuximab follows the August 2024 approval by the UK Medicines and Healthcare products Regulatory Agency and the March 2024 approval by Japan’s Ministry of Health, Labour and Welfare.[5,6] Astellas has submitted further applications for zolbetuximab to other regulatory agencies around the world with reviews ongoing.

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

About Zolbetuximab

Zolbetuximab is a claudin 18.2-directed cytolytic antibody investigated in combination with fluoropyrimidine- and platinum-containing chemotherapy for the first-line treatment of adult patients 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. In both the SPOTLIGHT and GLOW Phase 3 clinical trials, approximately 38% of patients screened had tumors that were CLDN18.2 positive, defined as ≥75% of tumor cells demonstrating moderate to strong membranous CLDN18 immunohistochemical staining, assessed and confirmed using an in-vitro companion diagnostic test or medical device.[1,2] Astellas collaborated with Roche on the VENTANA® CLDN18 (43-14A) RxDx Assay that, upon approval, is intended to be used by a pathologist

or laboratory to identify patients eligible for targeted treatment with zolbetuximab.[7] This immunohistochemistry based companion diagnostic test is currently under review by the notified body.

As an investigational first-in-class monoclonal antibody (mAb), zolbetuximab targets and binds to CLDN18.2, a transmembrane protein expressed on cancer cells. In pre-clinical studies, zolbetuximab reduced the number of CLDN18.2-positive cells via antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity, leading to tumor growth inhibition.[3]

About Locally Advanced Unresectable Metastatic Gastric and Gastroesophageal Junction Cancer

Gastric and gastroesophageal junction (G/GEJ) cancers are known to be histologically similar, are recommended to be managed in the same way in treatment guidelines, and frequently display aligned responses to treatment.[2,8] Across Europe, over 135,000 new cases of G/GEJ cancer were diagnosed in 2022.[9] G/GEJ cancer is the sixth most common cause of cancer-related mortality in Europe, responsible for 95,431 deaths in 2022.[9,10] GEJ adenocarcinomas start in the first two inches (5 cm) where the esophagus joins the stomach.[11] The average five-year survival rate for patients in Europe with G/GEJ cancer is 26% across all stages of the disease, driving the need for new therapeutic options that can slow disease progression and extend lives.[12]

Because early-stage cancer symptoms frequently overlap with more common stomach-related conditions, G/GEJ cancers are often diagnosed in the advanced or metastatic stage, or once they have spread from the tumor's origin to other body tissues or organs.[13]

Early 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.[13,14] Signs of more advanced G/GEJ cancer can include unexplained weight loss, weakness and fatigue, sensation of food getting stuck in the throat while eating, vomiting blood or having blood in the stool.[13,14,15] Risk factors associated with G/GEJ cancer can include older age, male gender, family history, *H. pylori* infection, smoking, and gastroesophageal reflux disease (GERD).[16,17]

INVESTIGATIONAL STUDIES

About the 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) of 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.[1]

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.[1]

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

About the 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, including Japan. 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.[2]

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.[2]

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

Investigational Pipeline in CLDN18.2
An expanded Phase 2 trial of zolbetuximab in metastatic pancreatic adenocarcinoma is in progress and recruiting patients. 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 the 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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