Better Health, Brighter Future

News Release

U.S. FDA Approves Takeda's ALUNBRIG® (brigatinib) as a First-Line Treatment Option for Patients Diagnosed with Rare and Serious Form of Lung Cancer

– ***Long-Term Results from the Phase 3 ALTA 1L Trial Established ALUNBRIG as a Superior First-Line Treatment Compared to Crizotinib for People with ALK+ Metastatic NSCLC, Including those with Brain Metastases***

Cambridge, Mass. & Osaka, Japan, May 22, 2020 – Takeda Pharmaceutical Company Limited (TSE:4502/NYSE:TAK) today announced that the U.S. Food and Drug Administration (FDA) approved ALUNBRIG (brigatinib) for adult patients with anaplastic lymphoma kinase-positive (ALK+) metastatic non-small cell lung cancer (NSCLC) as detected by an FDA-approved test. This approval expands ALUNBRIG's current indication to include the first-line setting. ALUNBRIG is a potent and selective next-generation tyrosine kinase inhibitor (TKI) designed to target ALK molecular alterations.

"We're extremely proud of the positive results ALUNBRIG has shown for newly diagnosed ALK+ NSCLC patients, particularly those with brain metastases," said Teresa Bitetti, President, Global Oncology Business Unit, Takeda. "Through a robust clinical development program and ongoing investigations across the NSCLC treatment landscape, Takeda is committed to uncovering solutions for people living with devastating forms of lung cancer in need of new options. We believe this approval for ALUNBRIG is a substantial step in the right direction and represents significant progress for Takeda's broader lung cancer portfolio."

The approval is based on results from the Phase 3 ALTA 1L trial, which is evaluating the safety and efficacy of ALUNBRIG compared to crizotinib in adult patients with ALK+ locally advanced or metastatic NSCLC who have not received prior treatment with an ALK inhibitor.

"Results from the ALTA 1L trial add brigatinib to the very short list of first-line treatment options for ALK+ lung cancer patients that have proven to be superior to crizotinib. Compared to crizotinib, brigatinib demonstrated superior efficacy, especially among those with brain metastases at baseline, and a low pill burden, at one pill a day, which is an important factor when we could be controlling disease for years," said Ross Camidge, MD, PhD, Joyce Zeff Chair in Lung Cancer Research, University of Colorado Cancer Center. "These data have established brigatinib's potential in the first-line setting, and I'm confident the FDA approval will open a new window of possibilities for physicians and their patients."

After more than two years of follow-up, results from the ALTA 1L trial showed ALUNBRIG demonstrated superiority over crizotinib, with significant anti-tumor activity observed, especially in patients with baseline brain metastases.

- ALUNBRIG reduced the risk of disease progression or death twofold compared with crizotinib (PFS hazard ratio = 0.49), with a 24-month median progression-free survival (PFS) as assessed by a blinded independent review committee (BIRC) versus 11 months for crizotinib.
- ALUNBRIG demonstrated a confirmed overall response rate (ORR) of 74% (95% CI: 66–81) for ALUNBRIG and 62% (95% CI: 53–70) for crizotinib as assessed by a BIRC.
- ALUNBRIG demonstrated a confirmed intracranial ORR for patients with measurable brain metastases at baseline of 78% (95% CI: 52–94) for patients treated with ALUNBRIG and 26% (95% CI: 10–48) for patients treated with crizotinib.

"As with many forms of lung cancer, ALK+ NSCLC is a complex and aggressive cancer that presents various treatment challenges for patients who are newly diagnosed, including those whose disease has spread to their brain," said Andrea Stern Ferris, President and CEO, LUNGevity Foundation. "Having this option for newly diagnosed patients is exciting news for the ALK+ NSCLC community and adds to the remarkable progress we have witnessed in lung cancer treatment over the past decade."

About the ALTA 1L Trial

The Phase 3 ALTA 1L (**A**LK in **L**ung Cancer **T**rial of Brig**A**tinib in **1**st **L**ine) trial of ALUNBRIG in adults is a global, ongoing, randomized, open-label, comparative, multicenter trial, which enrolled 275 patients (ALUNBRIG, n=137, crizotinib, n=138) with ALK+ locally advanced or metastatic NSCLC who have not received prior treatment with an ALK inhibitor. Patients received either ALUNBRIG, 180 mg orally once daily with seven-day lead-in at 90 mg once daily, or crizotinib, 250 mg orally twice daily.

The median age was 58 years in the ALUNBRIG arm and 60 years in the crizotinib arm. Twenty-nine percent of patients had brain metastases at baseline in the ALUNBRIG arm versus 30% in the crizotinib arm. Twenty-six percent of patients received prior chemotherapy for advanced or metastatic disease in the ALUNBRIG arm versus 27% in the crizotinib arm.

Blinded independent review committee (BIRC)-assessed progression-free survival (PFS) was the major efficacy outcome measure. Additional efficacy outcome measures included confirmed overall response rate (ORR) per RECIST v1.1 and intracranial ORR.

The warnings and precautions for ALUNBRIG are: interstitial lung disease (ILD)/pneumonitis, hypertension, bradycardia, visual disturbance, creatine phosphokinase (CPK) elevation, pancreatic enzyme elevation, hyperglycemia and embryo-fetal toxicity.

In the ALTA 1L trial, serious adverse reactions occurred in 33% of patients receiving ALUNBRIG. The most

common serious adverse reactions other than disease progression were pneumonia (4.4%), ILD/pneumonitis (3.7%), pyrexia (2.9%), dyspnea (2.2%), pulmonary embolism (2.2%), and asthenia (2.2%). Fatal adverse reactions other than disease progression occurred in 2.9% of patients and included pneumonia (1.5%), cerebrovascular accident (0.7%), and multiple organ dysfunction syndrome (0.7%).

The most common adverse reactions in the ALTA 1L trial (≥10%) with ALUNBRIG were diarrhea (53%), rash (40%), cough (35%), hypertension (32%), fatigue (32%), nausea (30%), myalgia (28%), dyspnea (25%), abdominal pain (24%), and headache (22%).

About ALUNBRIG® (brigatinib)

ALUNBRIG is a potent and selective next-generation tyrosine kinase inhibitor (TKI) that was designed to target anaplastic lymphoma kinase (ALK) molecular alterations.

ALUNBRIG is currently approved in more than 40 countries, including the U.S., Canada and the European Union (EU), for the treatment of people living with ALK+ metastatic NSCLC who have taken the medicine crizotinib, but their NSCLC has worsened or they cannot tolerate taking crizotinib. ALUNBRIG is also approved in the EU as a monotherapy for the treatment of adult patients with ALK+ advanced NSCLC previously not treated with an ALK inhibitor.

ALUNBRIG received Breakthrough Therapy Designation from the FDA for the treatment of patients with ALK+ NSCLC whose tumors are resistant to crizotinib and was granted Orphan Drug Designation by the FDA for the treatment of ALK+ NSCLC, ROS1+ and EGFR+ NSCLC.

About ALK+ NSCLC

Non-small cell lung cancer (NSCLC) is the most common form of lung cancer, accounting for approximately 85% of the estimated 1.8 million new cases of lung cancer diagnosed each year worldwide, according to the World Health Organization.[1,2] Genetic studies indicate that chromosomal rearrangements in anaplastic lymphoma kinase (*ALK*) are key drivers in a subset of NSCLC patients.[3] Approximately three to five percent of patients with metastatic NSCLC have a rearrangement in the *ALK* gene.[4,5,6]

Takeda is committed to continuing research and development in NSCLC to improve the lives of the approximately 40,000 patients diagnosed with this serious and rare form of lung cancer worldwide each year.[7]

ALUNBRIG IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Interstitial Lung Disease (ILD)/Pneumonitis: Severe, life-threatening, and fatal pulmonary adverse reactions consistent with interstitial lung disease (ILD)/pneumonitis have occurred with ALUNBRIG. In the ALUNBRIG arm of trial ALTA 1L (180 mg once daily), ILD/pneumonitis occurred in 5.1% of patients

receiving ALUNBRIG. ILD/pneumonitis occurred within 8 days of initiation of ALUNBRIG in 2.9% of patients, with Grade 3 to 4 reactions occurring in 2.2% of patients. In Trial ALTA, ILD/pneumonitis occurred in 3.7% of patients in the 90 mg group (90 mg once daily) and 9.1% of patients in the 90→180 mg group (180 mg once daily with 7-day lead-in at 90 mg once daily). Adverse reactions consistent with possible ILD/pneumonitis occurred early within 9 days of initiation of ALUNBRIG (median onset was 2 days) in 6.4% of patients, with Grade 3 to 4 reactions occurring in 2.7%. Monitor for new or worsening respiratory symptoms (e.g., dyspnea, cough, etc.), particularly during the first week of initiating ALUNBRIG. Withhold ALUNBRIG in any patient with new or worsening respiratory symptoms, and promptly evaluate for ILD/pneumonitis or other causes of respiratory symptoms (e.g., pulmonary embolism, tumor progression, and infectious pneumonia). For Grade 1 or 2 ILD/pneumonitis, either resume ALUNBRIG with dose reduction after recovery to baseline or permanently discontinue ALUNBRIG. Permanently discontinue ALUNBRIG for Grade 3 or 4 ILD/pneumonitis or recurrence of Grade 1 or 2 ILD/pneumonitis.

Hypertension: In the ALUNBRIG arm of trial ALTA 1L (180 mg once daily), hypertension was reported in 32% of patients receiving ALUNBRIG; Grade 3 hypertension occurred in 13% of patients. In ALTA, hypertension was reported in 11% of patients in the 90 mg group who received ALUNBRIG and 21% of patients in the 90→180 mg group. Grade 3 hypertension occurred in 5.9% of patients overall. Control blood pressure prior to treatment with ALUNBRIG. Monitor blood pressure after 2 weeks and at least monthly thereafter during treatment with ALUNBRIG. Withhold ALUNBRIG for Grade 3 hypertension despite optimal antihypertensive therapy. Upon resolution or improvement to Grade 1, resume ALUNBRIG at the same dose. Consider permanent discontinuation of treatment with ALUNBRIG for Grade 4 hypertension or recurrence of Grade 3 hypertension. Use caution when administering ALUNBRIG in combination with antihypertensive agents that cause bradycardia.

Bradycardia: In the ALUNBRIG arm of trial ALTA 1L (180 mg once daily), heart rates less than 50 beats per minute (bpm) occurred in 8.1% of patients receiving ALUNBRIG. Grade 3 bradycardia occurred in 1 patient (0.7%). In ALTA, heart rates less than 50 beats per minute (bpm) occurred in 5.7% of patients in the 90 mg group and 7.6% of patients in the 90→180 mg group. Grade 2 bradycardia occurred in 1 (0.9%) patient in the 90 mg group. Monitor heart rate and blood pressure during treatment with ALUNBRIG. Monitor patients more frequently if concomitant use of drug known to cause bradycardia cannot be avoided. For symptomatic bradycardia, withhold ALUNBRIG and review concomitant medications for those known to cause bradycardia. If a concomitant medication known to cause bradycardia is identified and discontinued or dose adjusted, resume ALUNBRIG at the same dose following resolution of symptomatic bradycardia; otherwise, reduce the dose of ALUNBRIG following resolution of symptomatic bradycardia. Discontinue ALUNBRIG for life-threatening bradycardia if no contributing concomitant medication is identified.

Visual Disturbance: In the ALUNBRIG arm of trial ALTA 1L (180 mg once daily), Grade 1 or 2 adverse reactions leading to visual disturbance including blurred vision, photophobia, photopsia, and reduced visual acuity were reported in 7.4% of patients receiving ALUNBRIG. In ALTA, adverse reactions leading to visual disturbance including blurred vision, diplopia, and reduced visual acuity, were reported in 7.3% of patients

treated with ALUNBRIG in the 90 mg group and 10% of patients in the 90→180 mg group. Grade 3 macular edema and cataract occurred in one patient each in the 90→180 mg group. Advise patients to report any visual symptoms. Withhold ALUNBRIG and obtain an ophthalmologic evaluation in patients with new or worsening visual symptoms of Grade 2 or greater severity. Upon recovery of Grade 2 or Grade 3 visual disturbances to Grade 1 severity or baseline, resume ALUNBRIG at a reduced dose. Permanently discontinue treatment with ALUNBRIG for Grade 4 visual disturbances.

Creatine Phosphokinase (CPK) Elevation: In the ALUNBRIG arm of trial ALTA 1L (180 mg once daily), creatine phosphokinase (CPK) elevation occurred in 81% of patients who received ALUNBRIG. The incidence of Grade 3 or 4 CPK elevation was 24%. Dose reduction for CPK elevation occurred in 15% of patients. In ALTA, CPK elevation occurred in 27% of patients receiving ALUNBRIG in the 90 mg group and 48% of patients in the 90 mg→180 mg group. The incidence of Grade 3-4 CPK elevation was 2.8% in the 90 mg group and 12% in the 90→180 mg group. Dose reduction for CPK elevation occurred in 1.8% of patients in the 90 mg group and 4.5% in the 90→180 mg group. Advise patients to report any unexplained muscle pain, tenderness, or weakness. Monitor CPK levels during ALUNBRIG treatment. Withhold ALUNBRIG for Grade 3 or 4 CPK elevation with Grade 2 or higher muscle pain or weakness. Upon resolution or recovery to Grade 1 CPK elevation or baseline, resume ALUNBRIG at the same dose or at a reduced dose.

Pancreatic Enzyme Elevation: In the ALUNBRIG arm of trial ALTA 1L (180 mg once daily), amylase elevation occurred in 52% of patients and Grade 3 or 4 amylase elevation occurred in 6.8% of patients. Lipase elevations occurred in 59% of patients and Grade 3 or 4 lipase elevation occurred in 17% of patients. In ALTA, amylase elevation occurred in 27% of patients in the 90 mg group and 39% of patients in the 90→180 mg group. Lipase elevations occurred in 21% of patients in the 90 mg group and 45% of patients in the 90→180 mg group. Grade 3 or 4 amylase elevation occurred in 3.7% of patients in the 90 mg group and 2.7% of patients in the 90→180 mg group. Grade 3 or 4 lipase elevation occurred in 4.6% of patients in the 90 mg group and 5.5% of patients in the 90→180 mg group. Monitor lipase and amylase during treatment with ALUNBRIG. Withhold ALUNBRIG for Grade 3 or 4 pancreatic enzyme elevation. Upon resolution or recovery to Grade 1 or baseline, resume ALUNBRIG at the same dose or at a reduced dose.

Hyperglycemia: In the ALUNBRIG arm of trial ALTA 1L (180 mg once daily), 56% of patients who received ALUNBRIG experienced new or worsening hyperglycemia. Grade 3 hyperglycemia, based on laboratory assessment of serum fasting glucose levels, occurred in 7.5% of patients. In ALTA, 43% of patients who received ALUNBRIG experienced new or worsening hyperglycemia. Grade 3 hyperglycemia, based on laboratory assessment of serum fasting glucose levels, occurred in 3.7% of patients. Two of 20 (10%) patients with diabetes or glucose intolerance at baseline required initiation of insulin while receiving ALUNBRIG. Assess fasting serum glucose prior to initiation of ALUNBRIG and monitor periodically thereafter. Initiate or optimize anti-hyperglycemic medications as needed. If adequate hyperglycemic control cannot be achieved with optimal medical management, withhold ALUNBRIG until adequate hyperglycemic control is achieved and consider reducing the dose of ALUNBRIG or permanently discontinuing ALUNBRIG.

Embryo-Fetal Toxicity: Based on its mechanism of action and findings in animals, ALUNBRIG can cause fetal harm when administered to pregnant women. There are no clinical data on the use of ALUNBRIG in

pregnant women. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective non-hormonal contraception during treatment with ALUNBRIG and for at least 4 months following the final dose. Advise males with female partners of reproductive potential to use effective contraception during treatment and for at least 3 months after the last dose of ALUNBRIG.

ADVERSE REACTIONS

In ALTA 1L, serious adverse reactions occurred in 33% of patients receiving ALUNBRIG. The most common serious adverse reactions other than disease progression were pneumonia (4.4%), ILD/pneumonitis (3.7%), pyrexia (2.9%), dyspnea (2.2%), pulmonary embolism (2.2%), and asthenia (2.2%). Fatal adverse reactions other than disease progression occurred in 2.9% of patients and included pneumonia (1.5%), cerebrovascular accident (0.7%), and multiple organ dysfunction syndrome (0.7%).

In ALTA, serious adverse reactions occurred in 38% of patients in the 90 mg group and 40% of patients in the 90→180 mg group. The most common serious adverse reactions were pneumonia (5.5% overall, 3.7% in the 90 mg group, and 7.3% in the 90→180 mg group) and ILD/pneumonitis (4.6% overall, 1.8% in the 90 mg group and 7.3% in the 90→180 mg group). Fatal adverse reactions occurred in 3.7% of patients and consisted of pneumonia (2 patients), sudden death, dyspnea, respiratory failure, pulmonary embolism, bacterial meningitis and urosepsis (1 patient each).

The most common adverse reactions (≥25%) with ALUNBRIG were diarrhea (49%), fatigue (39%), nausea (39%), rash (38%), cough (37%), myalgia (34%), headache (31%), hypertension (31%), vomiting (27%), and dyspnea (26%).

DRUG INTERACTIONS

CYP3A Inhibitors: Avoid coadministration of ALUNBRIG with strong or moderate CYP3A inhibitors. Avoid grapefruit or grapefruit juice as it may also increase plasma concentrations of brigatinib. If coadministration of a strong or moderate CYP3A inhibitor cannot be avoided, reduce the dose of ALUNBRIG.
CYP3A Inducers: Avoid coadministration of ALUNBRIG with strong or moderate CYP3A inducers. If coadministration of moderate CYP3A inducers cannot be avoided, increase the dose of ALUNBRIG.
CYP3A Substrates: Coadministration of ALUNBRIG with sensitive CYP3A substrates, including hormonal contraceptives, can result in decreased concentrations and loss of efficacy of sensitive CYP3A substrates.

USE IN SPECIFIC POPULATIONS

Pregnancy: ALUNBRIG can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus.
Lactation: There are no data regarding the secretion of brigatinib in human milk or its effects on the breastfed infant or milk production. Because of the potential adverse reactions in breastfed infants, advise lactating women not to breastfeed during treatment with ALUNBRIG.
Females and Males of Reproductive Potential:

Pregnancy Testing: Verify pregnancy status in females of reproductive potential prior to initiating ALUNBRIG.

Contraception**:** Advise females of reproductive potential to use effective non-hormonal contraception during treatment with ALUNBRIG and for at least 4 months after the final dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with ALUNBRIG and for at least 3 months after the final dose.

Infertility: ALUNBRIG may cause reduced fertility in males.

Pediatric Use: The safety and effectiveness of ALUNBRIG in pediatric patients have not been established.

Geriatric Use: Of the 359 patients enrolled in the ALTA 1L ALUNBRIG arm and in ALTA, 26.7% were 65 and older and 7.5% were 75 and older. No clinically relevant differences in safety or efficacy were observed between patients ≥65 years and younger patients.

Hepatic or Renal Impairment: No dose adjustment is recommended for patients with mild or moderate hepatic impairment or mild or moderate renal impairment. Reduce the dose of ALUNBRIG for patients with severe hepatic impairment or severe renal impairment.

Please see the full U.S. Prescribing Information for ALUNBRIG at www.ALUNBRIG.com

Takeda's Commitment to Oncology

Our core R&D mission is to deliver novel medicines to patients with cancer worldwide through our commitment to science, breakthrough innovation and passion for improving the lives of patients. Whether it's with our hematology therapies, our robust pipeline, or solid tumor medicines, we aim to stay both innovative and competitive to bring patients the treatments they need. For more information, visit www.takedaoncology.com.

About Takeda Pharmaceutical Company Limited

Takeda Pharmaceutical Company Limited (TSE:4502/NYSE:TAK) is a global, values-based, R&D-driven biopharmaceutical leader headquartered in Japan, committed to bringing Better Health and a Brighter Future to patients by translating science into highly-innovative medicines. Takeda focuses its R&D efforts on four therapeutic areas: Oncology, Rare Diseases, Neuroscience, and Gastroenterology (GI). We also make targeted R&D investments in Plasma-Derived Therapies and Vaccines. We are focusing on developing highly innovative medicines that contribute to making a difference in people's lives by advancing the frontier of new treatment options and leveraging our enhanced collaborative R&D engine and capabilities to create a robust, modality-diverse pipeline. Our employees are committed to improving quality of life for patients and to working with our partners in health care in approximately 80 countries.

For more information, visit https://www.takeda.com.

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The companies in which Takeda directly and indirectly owns investments are separate entities. In this press release, "Takeda" is sometimes used for convenience where references are made to Takeda and its subsidiaries in general. Likewise, the words "we", "us" and "our" are also used to refer to subsidiaries in general or to those who work for them. These expressions are also used where no useful purpose is served by identifying the particular company or companies.

Forward-Looking Statements

This press release and any materials distributed in connection with this press release may contain forward-looking statements, beliefs or opinions regarding Takeda's future business, future position and results of operations, including estimates, forecasts, targets and plans for Takeda. Without limitation, forward-looking statements often include words such as "targets", "plans", "believes", "hopes", "continues", "expects", "aims", "intends", "ensures", "will", "may", "should", "would", "could" "anticipates", "estimates", "projects" or similar expressions or the negative thereof. These forward-looking statements are based on assumptions about many important factors, including the following, which could cause actual results to differ materially from those expressed or implied by the forward-looking statements: the economic circumstances surrounding Takeda's global business, including general economic conditions in Japan and the United States; competitive

pressures and developments; changes to applicable laws and regulations; the success of or failure of product development programs; decisions of regulatory authorities and the timing thereof; fluctuations in interest and currency exchange rates; claims or concerns regarding the safety or efficacy of marketed products or product candidates; the impact of health crises, like the novel coronavirus pandemic, on Takeda and its customers and suppliers, including foreign governments in countries in which Takeda operates, or on other facets of its business; the timing and impact of post-merger integration efforts with acquired companies; the ability to divest assets that are not core to Takeda's operations and the timing of any such divestment(s); and other factors identified in Takeda's most recent Annual Report on Form 20-F and Takeda's other reports filed with the U.S. Securities and Exchange Commission, available on Takeda's website at: https://www.takeda.com/investors/reports/sec-filings/ or at www.sec.gov. Takeda does not undertake to update any of the forward-looking statements contained in this press release or any other forward-looking statements it may make, except as required by law or stock exchange rule. Past performance is not an indicator of future results and the results or statements of Takeda in this press release may not be indicative of, and are not an estimate, forecast, guarantee or projection of Takeda's future results.

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