Press Release

HUTCHMED and AstraZeneca Announce that TAGRISSO® Plus Savolitinib Demonstrated 49% Objective Response Rate in Lung Cancer Patients with High Levels of MET Overexpression and/or Amplification in SAVANNAH Phase II Trial

— MET is the most common biomarker in patients with EGFR-mutated lung cancer who develop resistance to targeted therapy —

— Global SAFFRON Phase III trial evaluating this combination is underway —

Hong Kong, Shanghai & Florham Park, NJ — Monday, August 8, 2022: HUTCHMED (China) Limited ("HUTCHMED") (Nasdaq/AIM: HCM, HKEX: 13) and AstraZeneca PLC ("AstraZeneca") (LON/STO/Nasdaq: AZN) today announce that preliminary results from the SAVANNAH Phase II trial showed that TAGRISSO® (osimertinib) plus savolitinib demonstrated an objective response rate ("ORR") of 49% (95% confidence interval ["CI"], 39-59%) in patients with epidermal growth factor receptor-mutated ("EGFRm") non-small cell lung cancer ("NSCLC") with high levels of mesenchymal epithelial transition ("MET") overexpression and/or amplification, defined as IHC90+ and/or FISH10+, whose disease progressed on treatment with TAGRISSO®.

The highest ORR was observed in patients with high levels of MET who were not treated with prior chemotherapy (52% [95% CI, 41-63%]). In patients whose tumors did not show high levels of MET, the ORR was 9% (95% CI, 4-18%). These results are being shared at the International Association for the Study of Lung Cancer (IASLC) 2022 World Conference on Lung Cancer (WCLC), taking place on August 6-9, 2022 in Vienna, Austria.

Savolitinib, marketed in China under the brand name ORPATHYS®, is an oral, potent and highly selective MET tyrosine kinase inhibitor ("TKI") being jointly developed and commercialized by AstraZeneca and HUTCHMED.

While EGFR-targeted therapy can provide a durable survival benefit to patients with EGFRm NSCLC, most will eventually develop resistance to their treatment, with MET being the most common resistance biomarker.[1] Among patients screened for enrolment in SAVANNAH, all of whom experienced disease progression on TAGRISSO®, 62% had tumors with MET overexpression and/or amplification, and more than one-third (34%) met the defined high MET level cut-off.

Myung-Ju Ahn, MD, PhD, Professor of Hemato-Oncology at the Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea, and Principal Investigator in the SAVANNAH Phase II trial, said: "Acquired resistance to targeted therapy and disease progression are difficult realities for most patients with EGFR-mutated NSCLC. These preliminary SAVANNAH results potentially support a novel approach for identifying patients with MET overexpression and/or amplification who are most likely to benefit from a MET-directed therapy, like savolitinib. They also suggest that with the right biomarker testing strategy, MET may be a more prevalent target among resistant patients than previously understood, supporting further investigation of the osimertinib plus savolitinib regimen."

Cristian Massacesi, Chief Medical Officer and Oncology Chief Development Officer, AstraZeneca said: "The current standard of care for patients with EGFR-mutated lung cancer who progress on targeted treatment is chemotherapy. The results from SAVANNAH suggest savolitinib added to TAGRISSO® at the time of disease progression could possibly provide these biomarker-selected patients with a potentially less toxic, more effective treatment option. We look forward to better understanding the potential of the TAGRISSO® plus savolitinib regimen in this trial and in the SAFFRON Phase III trial."

Weiguo Su, Chief Executive Officer and Chief Scientific Officer, HUTCHMED, said: "It is encouraging to see the savolitinib and TAGRISSO® combination regimen progress into a global Phase III study, SAFFRON, with a well-supported patient selection strategy that could benefit more patients than previously recognized. The preliminary results of the SAVANNAH study also affirm the role of molecular testing prior to initiating subsequent treatment for NSCLC patients who experience disease progression on an EGFR-targeted therapy. We are aligned in pursuing a selective, patient-centric approach in development efforts for savolitinib in this setting."

In this analysis, patients' MET overexpression and/or amplification levels were determined by two tests: immunohistochemistry ("IHC"), which detects if cancer cells have a particular protein or marker on their surface, and fluorescence in situ hybridization ("FISH"), which detects a specific DNA sequence from cancer cells. All patients in this analysis (n=193) had at least IHC50+ and/or FISH5+, and were treated with savolitinib 300mg once daily added to TAGRISSO® 80mg once daily following disease progression on TAGRISSO® alone.

Summary of efficacy results[i]:

Endpoint	All patients (IHC50+ and/or FISH5+; n=193)	Patients with high levels of MET[ii] (IHC90+ and/or FISH10+)		Patients with lower levels of MET[ii] (n=77)
		All (n=108)	No prior chemo (n=87)	
ORR, % (95% CI)	32 (26, 39)	49 (39, 59)	52 (41, 63)	9 (4, 18)
Median DoR[iii], months (95% CI)	8.3 (6.9, 9.7)	9.3 (7.6, 10.6)	9.6 (7.6, 14.9)	6.9 (4.1, 16.9)
Median PFS[iv], months (95% CI)	5.3 (4.2, 5.8)	7.1 (5.3, 8.0)	7.2 (4.7, 9.2)	2.8 (2.6, 4.3)
DCR[v], % (95% CI)	61 (53, 68)	74 (65, 82)	75 (64, 83)	43 (32, 55)

i. Analysis data cut-off: 27 August 2021
ii. Eight patients excluded from subgroup analyses due to invalid or missing test results
iii. DoR, duration of response
iv. PFS, progression-free survival
v. DCR, disease control rate

The safety profile of TAGRISSO® plus savolitinib was consistent with the known profiles of the combination and each treatment alone. No new safety signals were identified. Less than half (45%) of patients in this analysis experienced Grade 3 or higher adverse events ("AEs"), with those most frequently reported including pulmonary embolism, dyspnea, decreased neutrophil count and pneumonia. AEs attributable to savolitinib and leading to discontinuation occurred in 13% of patients.

The global SAFFRON Phase III trial will further assess the TAGRISSO® plus savolitinib combination versus platinum-based doublet chemotherapy in patients with EGFRm, MET-overexpressed and/or amplified, locally advanced or metastatic NSCLC following TAGRISSO®. Patients are being prospectively selected using the high MET level cut-off identified in SAVANNAH.

About NSCLC and MET aberrations

Lung cancer is the leading cause of cancer death among men and women, accounting for about one-fifth of all cancer deaths.[2] Lung cancer is broadly split into NSCLC and small cell lung cancer, with 80-85% classified as NSCLC.[3] The majority of NSCLC patients (approximately 75%) are diagnosed with advanced disease and approximately 10-15% of NSCLC patients in the U.S. and Europe and 30-40% of patients in Asia have EGFRm NSCLC.[4,5,6,7]

MET is a tyrosine kinase receptor that has an essential role in normal cell development.[8] MET overexpression and/or amplification can lead to tumor growth and the metastatic progression of cancer cells, and is the primary mechanism of acquired resistance to EGFR TKIs for metastatic EGFR-mutated NSCLC. [8,9] The prevalence of MET depends on the sample type, detection method and assay cut-off used.[10]

About SAVANNAH

SAVANNAH is an ongoing global, randomized, single-arm Phase II trial studying the efficacy of savolitinib added to TAGRISSO® in patients with EGFRm, locally advanced or metastatic NSCLC with MET overexpression and/or amplification who progressed following treatment with TAGRISSO®. Patients were treated with savolitinib 300 or 600 mg once-daily (QD) or 300 mg twice-daily, in combination with oral osimertinib 80 mg QD.

The trial has enrolled 294 patients to date in more than 80 centers globally, including centers in the U.S., Canada, Europe, South America and Asia. The primary endpoint is ORR. Key secondary endpoints include PFS, DoR and safety.

About TAGRISSO®

TAGRISSO® (osimertinib) is a third-generation, irreversible EGFR-TKI with proven clinical activity in NSCLC, including against central nervous system metastases. TAGRISSO® (40mg and 80mg once-daily oral tablets) has been used to treat approximately 575,000 patients across indications worldwide and AstraZeneca continues to explore TAGRISSO® as a treatment for patients across multiple stages of EGFRm NSCLC.

In Phase III trials, TAGRISSO® is being investigated in the neoadjuvant resectable setting (NeoADAURA), in the Stage IA2-IA3 adjuvant resectable setting (ADAURA2), in the Stage III locally advanced unresectable setting following chemoradiation therapy (LAURA), and in combination with chemotherapy in the advanced setting (FLAURA2). AstraZeneca is also researching ways to address tumor mechanisms of resistance through the SAVANNAH and ORCHARD Phase II trials, and the SAFFRON Phase III trial, which test TAGRISSO® given concomitantly with savolitinib, an oral, potent and highly selective MET TKI, as well as other potential new medicines.

About Savolitinib

Savolitinib is an oral, potent and highly selective MET TKI that has demonstrated clinical activity in advanced solid tumors. It blocks atypical activation of the MET receptor tyrosine kinase pathway that occurs because of mutations (such as exon 14 skipping alterations or other point mutations), gene amplification or protein overexpression.

Savolitinib is marketed in China under the brand name ORPATHYS® for the treatment of patients with NSCLC with MET exon 14 skipping alterations who have progressed following prior systemic therapy or are unable to receive chemotherapy. It is currently under clinical development for multiple tumor types, including lung, kidney and gastric cancers, as a single treatment and in combination with other medicines.

About AstraZeneca and HUTCHMED collaboration

In 2011, AstraZeneca and HUTCHMED entered a global licensing and collaboration agreement to jointly develop and commercialize savolitinib. Joint development of savolitinib in China is led by HUTCHMED, while AstraZeneca leads development outside of China. HUTCHMED is responsible for the marketing authorization, manufacturing and supply of savolitinib in China. AstraZeneca is responsible for the commercialization of savolitinib in China and worldwide. Sales of savolitinib are recognized by AstraZeneca.

About AstraZeneca in lung cancer

AstraZeneca is working to bring patients with lung cancer closer to cure through the detection and treatment of early-stage disease, while also pushing the boundaries of science to improve outcomes in the resistant and advanced settings. By defining new therapeutic targets and assessing innovative approaches, the Company aims to match medicines to the patients who can benefit most.

The Company's comprehensive portfolio includes leading lung cancer medicines and the next wave of innovations including TAGRISSO® (osimertinib) and IRESSA® (gefitinib); IMFINZI® (durvalumab) and tremelimumab; ENHERTU® (trastuzumab deruxtecan) and datopotamab deruxtecan in collaboration with Daiichi Sankyo; ORPATHYS® (savolitinib) in collaboration with HUTCHMED; as well as a pipeline of potential new medicines and combinations across diverse mechanisms of action.

AstraZeneca is a founding member of the Lung Ambition Alliance, a global coalition working to accelerate innovation and deliver meaningful improvements for people with lung cancer, including and beyond treatment.

About AstraZeneca in oncology

AstraZeneca is leading a revolution in oncology with the ambition to provide cures for cancer in every form, following the science to understand cancer and all its complexities to discover, develop and deliver life-changing medicines to patients.

The Company's focus is on some of the most challenging cancers. It is through persistent innovation that AstraZeneca has built one of the most diverse portfolios and pipelines in the industry, with the potential to catalyze changes in the practice of medicine and transform the patient experience.

AstraZeneca has the vision to redefine cancer care and, one day, eliminate cancer as a cause of death.

About AstraZeneca

AstraZeneca (LSE/STO/Nasdaq: AZN) is a global, science-led biopharmaceutical company that focuses on the discovery, development, and commercialization of prescription medicines in Oncology, Rare Diseases, and BioPharmaceuticals, including Cardiovascular, Renal & Metabolism, and Respiratory & Immunology. Based in Cambridge, UK, AstraZeneca operates in over 100 countries and its innovative medicines are used by millions of patients worldwide. Please visit astrazeneca.com and follow the Company on Twitter @AstraZeneca.

About HUTCHMED

HUTCHMED (Nasdaq/AIM: HCM; HKEX: 13) is an innovative, commercial-stage, biopharmaceutical company. It is committed to the discovery and global development and commercialization of targeted therapies and immunotherapies for the treatment of cancer and immunological diseases. It has more than 4,900 personnel across all its companies, at the center of which is a team of about 1,800 in oncology/ immunology. Since inception it has advanced 13 cancer drug candidates from in-house discovery into clinical studies around the world, with its first three oncology drugs now approved and marketed in China. For more information, please visit: www.hutch-med.com or follow us on LinkedIn.

References

1. Del MD, *et al.* Understanding the Mechanisms of Resistance in EGFR-Positive NSCLC: From Tissue to Liquid Biopsy to Guide Treatment Strategy. *Int J Mol Sci.* 2019;20(16): 3951.
2. World Health Organization. International Agency for Research on Cancer. All cancers fact sheet. Available at: https://gco.iarc.fr/today/data/factsheets/cancers/39-All-cancers-fact-sheet.pdf. Accessed July 2022.
3. American Cancer Society. What is Lung Cancer? Available at: https://www.cancer.org/cancer/lung-cancer/about/what-is.html. Accessed July 2022.
4. Knight SB, *et al.* Progress and prospects of early detection in lung cancer. *Open Biol.* 2017;7(9): 170070.
5. Keedy VL, *et al.* American Society of Clinical Oncology Provisional Clinical Opinion: Epidermal Growth Factor Receptor (EGFR) Mutation Testing for Patients with Advanced Non-Small-Cell Lung Cancer Considering First-Line EGFR Tyrosine Kinase Inhibitor Therapy. *J Clin Oncol.* 2011:29;2121-27.
6. Zhang Y, *et al*. The prevalence of EGFR mutation in patients with non-small cell lung cancer: a systematic review and meta-analysis. *Oncotarget*. 2016;7(48).
7. Szumera-Ciećkiewicz A, *et al*. EGFR Mutation Testing on Cytological and Histological Samples in 11. Non-Small Cell Lung Cancer: a Polish, Single Institution Study and Systematic Review of European Incidence. *Int J Clin Exp Pathol*. 2013:6;2800-12.
8. Uchikawa E, et al. Structural basis of the activation of c-MET receptor. Nat Commun. 2021;12(4074).
9. Wang Q, *et al.* MET inhibitors for targeted therapy of EGFR TKI-resistant lung cancer. *Journal of Hematology & Oncology.* 2019;63.
10. Coleman N, *et al*. Beyond epidermal growth factor receptor: MET amplification as a general resistance driver to targeted therapy in oncogene-driven non-small-cell lung cancer. *ESMO Open*. 2019;6(6).

Forward-Looking Statements

This press release contains forward-looking statements within the meaning of the "safe harbor" provisions of the U.S. Private Securities Litigation Reform Act of 1995. These forward-looking statements reflect HUTCHMED's current expectations regarding future events, including its expectations regarding the therapeutic potential of savolitinib for the treatment of patients with NSCLC, the further clinical development of savolitinib in this and other indications, its expectations as to whether clinical studies of savolitinib would meet their primary or secondary endpoints, and its expectations as to the timing of the completion and the release of results from such studies. Forward-looking statements involve risks and uncertainties. Such risks and uncertainties include, among other things, assumptions regarding the sufficiency of HUTCHMED's data to support New Drug Application approval of savolitinib for the treatment of patients with NSCLC in China, the U.S., E.U., Japan or other jurisdictions, the safety profile of savolitinib, the potential for savolitinib to become a new standard of care for patients with NSCLC and other types of cancer, its ability to implement and complete its further clinical development plans for savolitinib, the potential commercial launch of savolitinib in the U.S., E.U., Japan, China and other jurisdictions, the timing of these events, and the impact of the COVID-19 pandemic on general economic, regulatory and political conditions. In addition, as certain studies rely on the use of TAGRISSO® and IMFINZI® as combination therapeutics with savolitinib, such risks and uncertainties include assumptions regarding the safety, efficacy, supply and continued regulatory approval of TAGRISSO® and IMFINZI®. Existing and prospective investors are cautioned not to place undue reliance on these forward-looking statements, which speak only as of the date hereof. For further discussion of these and other risks, see HUTCHMED's filings with the U.S. Securities and Exchange Commission, on AIM and with The Stock Exchange of Hong Kong Limited. HUTCHMED undertakes no obligation to update or revise the information contained in this press release, whether as a result of new information, future events or circumstances or otherwise.

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