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Tagrisso plus *Orpathys* demonstrated statistically significant and clinically meaningful improvements in progression-free and overall survival in MET-driven EGFR-mutated lung cancer after progression on *Tagrisso*

First global Phase III trial to show significant progression-free and overall survival benefits in this setting

SAFFRON trial results reinforce Tagrisso as the backbone therapy across EGFRm lung cancer

Positive high-level results from the SAFFRON Phase III trial showed *Tagrisso* (osimertinib) plus *Orpathys* (savolitinib) demonstrated a statistically significant and clinically meaningful improvement in both progression-free survival (PFS) and overall survival (OS) versus doublet platinum-based chemotherapy in patients with epidermal growth factor receptor-mutated (EGFRm) non-small cell lung cancer (NSCLC). Patients in the trial had tumours with high levels of MET overexpression or amplification and had progressed on prior treatment with *Tagrisso*.

Third-generation EGFR-tyrosine kinase inhibitors (TKIs) have significantly improved outcomes for patients with EGFRm NSCLC.[1] However, one in three patients' tumours will develop MET overexpression or amplification, one of the most common mechanisms of resistance on third-generation EGFR-TKIs.[1-2] MET-driven resistance is associated with poor prognosis, and there is a significant unmet need for effective and well-tolerated treatment options in later-line settings.[2]

Professor Shun Lu, Director of Shanghai Lung Cancer Center, Shanghai Chest Hospital, Shanghai Jiao Tong University School of Medicine and principal investigator of the trial, said: "These exciting results from SAFFRON represent a critical advance for patients with EGFR-mutated non-small cell lung cancer experiencing MET-driven resistance after osimertinib, a population with poor outcomes and no biomarker-directed treatment options available that are oral and well-tolerated. MET is one of the most common drivers of progression on targeted therapy in this setting, and these data underscore the potential impact of this novel osimertinib plus savolitinib combination and the urgency of MET testing to inform treatment decisions."

Susan Galbraith, Executive Vice President, Oncology Haematology R&D, AstraZeneca, said: "These data demonstrate the clear benefit of adding *Orpathys* to backbone therapy *Tagrisso* to address MET overexpression or amplification while maintaining EGFR suppression. By combining *Orpathys* and *Tagrisso*, with its established efficacy, safety profile and central nervous system protection, we aim to deliver the first biomarker-directed, all-oral option in this setting to patients across the globe. This further strengthens our leadership in EGFR-mutated lung cancer, reinforcing our strategy to improve patient outcomes across stages and through lines of therapy with novel combinations."

Weiguo Su, Chief Executive Officer and Chief Scientific Officer of HUTCHMED, said: "Overcoming MET-driven resistance after EGFR-TKI therapy has been a long-standing challenge in clinical practice. The SAFFRON global study further reinforces the robust efficacy previously demonstrated in the SACHI Phase III trial that supported approval in China, with the results providing clear evidence to support global registrations of the *Tagrisso* and *Orpathys* combination. We are grateful to everyone who supported this trial. Together with AstraZeneca, we look forward to potentially bringing this landmark treatment to patients around the world."

The safety profile for *Tagrisso* plus *Orpathys* was consistent with the known profiles of each medicine, and there were no new safety findings. These data will be presented at a forthcoming medical meeting and shared with global regulatory authorities.

Tagrisso plus *Orpathys* is approved in China for patients with locally advanced or metastatic EGFRm NSCLC with MET amplification after disease progression on EGFR-TKI therapy based on the SACHI Phase III trial.

Orpathys is being jointly developed by AstraZeneca and HUTCHMED and commercialised by AstraZeneca.

Notes

NSCLC and MET aberrations
Lung cancer is the leading cause of cancer death globally, accounting for almost one in four (23%) cancer deaths.[3] Lung cancer is broadly split into NSCLC and small cell lung cancer, with 80-85% of patients diagnosed with NSCLC.[4] Approximately 75% of NSCLC patients are diagnosed with advanced disease.[5] Additionally, about 10-15% of NSCLC patients in the US and Europe, and 30-40% of patients in Asia, have EGFRm NSCLC.[6-8]

MET is a tyrosine kinase receptor that has an essential role in normal cell development.[9] MET overexpression or amplification can lead to tumour growth and the metastatic progression of cancer cells.[9-10] An estimated 34% of tumours will develop high levels of MET overexpression or amplification after progression on a third-generation EGFR-TKI.[1]

SAFFRON
SAFFRON is a randomised, open-label, multi-centre, global Phase III trial studying the efficacy of *Orpathys* (300mg twice daily) added to *Tagrisso* (80mg once daily) versus doublet platinum-based chemotherapy in 338 patients with EGFRm, locally advanced or metastatic NSCLC with MET overexpression or amplification whose disease progressed following 1st- or 2nd-line treatment with *Tagrisso*. The trial enrolled patients in 230 centres across 29 countries, including in North America, Europe, South America and Asia. The primary endpoint is PFS and key secondary endpoints include OS and objective response rate.

Patients were prospectively selected for SAFFRON using the high MET level cut-offs identified in the SAVANNAH Phase II trial. In SAVANNAH, MET overexpression 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 hybridisation (FISH), which detects a specific DNA sequence from cancer cells.

Orpathys
Orpathys (savolitinib) is an oral, potent and highly selective MET-TKI that has demonstrated clinical activity in advanced solid tumours. 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.

Orpathys is approved in China for the treatment of adult patients with locally advanced or metastatic NSCLC with MET exon 14 skipping alteration, representing the first selective MET inhibitor approved in China. *Orpathys* also received a conditional approval in China for the treatment of patients with locally advanced or metastatic gastric cancer or gastroesophageal junction adenocarcinoma with MET amplification who have failed at least two prior systemic treatments.
Orpathys in combination with *Tagrisso* is approved in China for patients with locally advanced or metastatic EGFRm-positive non-squamous NSCLC with MET amplification after disease progression on EGFR-TKI therapy based on the SACHI Phase III trial. The combination was also granted a temporary authorisation in Switzerland for the treatment of patients with locally advanced or metastatic EGFRm NSCLC and high levels of MET overexpression or amplification who progressed on prior treatment with *Tagrisso.* This was based on results from the global SAVANNAH Phase II trial.
Tagrisso
Tagrisso (osimertinib) is a third-generation, irreversible EGFR-TKI with proven clinical activity in NSCLC, including the treatment of central nervous system metastases. *Tagrisso* (40mg and 80mg QD oral tablets) has been used to treat more than one million patients across its indications worldwide and AstraZeneca continues to explore *Tagrisso* as a treatment for patients across multiple stages of EGFRm NSCLC.

Tagrisso is approved as monotherapy in more than 120 countries including the US, EU, China and Japan. Approved indications include for 1st-line treatment of patients with locally advanced or metastatic EGFRm NSCLC, locally advanced or metastatic EGFR T790M mutation-positive NSCLC, adjuvant treatment of early-stage EGFRm NSCLC and locally advanced, unresectable NSCLC

following platinum-based chemoradiation therapy. *Tagrisso* is also approved in combination with chemotherapy in more than 80 countries, including the US, EU, China and Japan, for 1st-line treatment of patients with locally advanced or metastatic EGFRm NSCLC.

There is an extensive body of evidence supporting the use of *Tagrisso* in EGFRm NSCLC, and it is the only targeted therapy shown to improve patient outcomes across all stages of the disease.

In late-stage disease, *Tagrisso* demonstrated improved outcomes as monotherapy in the FLAURA Phase III trial and in combination with chemotherapy in the FLAURA2 Phase III trial. *Tagrisso* is also being investigated in this setting in combination with *Datroway* (datopotamab deruxtecan or Dato-DXd) in the TROPION-Lung14 and TROPION-Lung15 Phase III trials.

Tagrisso also showed improved outcomes in early-stage disease in the NeoADAURA and ADAURA Phase III trials and in locally advanced stages in the LAURA Phase III trial. As part of AstraZeneca's ongoing commitment to treating patients as early as possible in lung cancer, *Tagrisso* is also being investigated in the early-stage adjuvant resectable setting in the ADAURA2 Phase III trial.

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 investigating 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* and *Iressa* (gefitinib); *Imfinzi* (durvalumab) and *Imjudo* (tremelimumab); *Enhertu* (trastuzumab deruxtecan) and *Datroway* in collaboration with Daiichi Sankyo; *Orpathys* 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.

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 catalyse 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.

AstraZeneca
AstraZeneca (LSE/STO/NYSE: AZN) is a global, science-led biopharmaceutical company that focuses on the discovery, development, and commercialisation of prescription medicines in Oncology, Rare Disease, and BioPharmaceuticals, including Cardiovascular, Renal & Metabolism, and Respiratory & Immunology. Based in Cambridge, UK, AstraZeneca's innovative medicines are sold in more than 125 countries and used by millions of patients worldwide. Please visit astrazeneca.com and follow the Company on social media @AstraZeneca.

Contacts
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