AstraZeneca

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Tagrisso extended disease-free survival regardless of prior adjuvant chemotherapy in early-stage EGFR-mutated lung cancer

Data at WCLC showed patients in the practice-changing ADAURA Phase III trial maintained their quality of life based on patient-reported outcomes

New data reinforce the ability of Tagrisso to penetrate the blood-brain barrier in patients with central nervous system metastases

Results from an exploratory analysis of the positive ADAURA Phase III trial showed AstraZeneca's *Tagrisso*(osimertinib) extended disease-free survival (DFS) in patients with epidermal growth factor receptor-mutated (EGFRm) non-small cell lung cancer (NSCLC) regardless of prior adjuvant chemotherapy treatment or stage of disease, building on the unprecedented primary DFS results for *Tagrisso* in the adjuvant setting announced last year. Results from ADAURA were presented during the 2020 World Conference on Lung Cancer (WCLC) hosted by the International Association for the Study of Lung Cancer (IASLC) and featured in the Press Programme.

In this exploratory analysis of the overall trial population, adjuvant *Tagrisso* reduced the risk of disease recurrence or death by 84% in patients who had been treated with prior adjuvant chemotherapy (based on a hazard ratio [HR] of 0.16, 95% confidence interval [CI] 0.10-0.26) and by 77% in patients who had not (HR 0.23; 95% CI 0.13-0.40). DFS benefits were similar across each stage of disease.

In addition, a separate exploratory post-hoc analysis of patient-reported outcomes in ADAURA showed that patients treated with *Tagrisso* maintained their quality of life, with no clinically meaningful differences in physical or mental health measures in the *Tagrisso* and placebo arms.

Yi-Long Wu, MD, FACS, Tenured Professor of the Lung Cancer Institute at Guangdong Provincial People's Hospital and Academy of Medical Sciences in Guangzhou, China, and a principal investigator in the ADAURA Phase III trial, said: "The overwhelming disease-free survival benefit in patients in ADAURA already supported the role of *Tagrisso* as a pioneering therapy in the adjuvant treatment of EGFR-mutated non-small cell lung cancer. This latest analysis shows the magnitude of that benefit is consistent with or without prior adjuvant chemotherapy, and regardless of disease stage, reinforcing the critical role of *Tagrisso* in this setting."

Dave Fredrickson, Executive Vice President, Oncology Business Unit, said: "These new data show that *Tagrisso* provides transformative benefits independent of prior chemotherapy treatment, preventing lung cancer from returning while allowing patients to sustain their quality of life. Following the recent approval of *Tagrisso* in the US in the adjuvant setting, we continue to work urgently with regulatory authorities globally to bring this new standard of care to patients with early-stage lung cancer."

Exploratory DFS analysis with and without chemotherapy (CTx)

OSI: Tagrisso; PBO: placebo

	Stage IB	**Stage II**	**Stage IIIA**	**Stage IB-IIIA**				
	OSI	**PBO**	**OSI**	**PBO**	**OSI**	**PBO**	**OSI**	**PBO**
With CTx	n=28	n=30	n=81	n=85	n=94	n=92	n=203	n=207
DFS events patients (%)	4 (14)	11 (37)	6 (7)	36 (42)	12 (13)	56 (61)	22 (11)	103 (50)
DFS HR (95% CI)	NC (NC, NC)	0.15 (0.06, 0.32)	0.13 (0.06, 0.23)	0.16 (0.10, 0.26)				
Without CTx	n=78	n=76	n=37	n=33	n=21	n=27	n=136	n=136
DFS events patients (%)	7 (9)	18 (24)	5 (14)	16 (48)	3 (14)	22 (81)	15 (11)	56 (41)
DFS HR (95% CI)	0.38 (0.15, 0.88)	0.20 (0.07, 0.52)	0.10 (0.02, 0.29)	0.23 (0.13, 0.40)				

In the ADAURA Phase III trial, chemotherapy use was balanced across the two treatment arms, with 60% of patients receiving prior adjuvant chemotherapy. In line with uptake observed in prior studies and clinical practice, younger patients (<70 years) and those with more advanced disease were more likely to have prior adjuvant chemotherapy.[1,2]Treatment with chemotherapy did not vary according to a patient's performance status.

The safety and tolerability of*Tagrisso*was consistent with previous trials in the metastatic EGFRm NSCLC setting. Adverse events at Grade 3 or higher from all causes occurred in 20% of patients in the *Tagrisso* arm versus 13% in the placebo arm as assessed by investigators.

Primary results of ADAURA, which were published in The New England Journal of Medicine in September 2020, showed adjuvant treatment with *Tagrisso* reduced the risk of disease recurrence or death by 83% (HR 0.17; 95% CI 0.12-0.23; p<0.0001) among patients with Stage II and IIIA EGFRm NSCLC and, as shown in a prespecified exploratory analysis, demonstrated a clinically meaningful improvement in central nervous system (CNS) DFS compared to placebo.

Additional *Tagrisso* highlights at WCLC

In addition to these ADAURA analyses, several other presentations and posters for *Tagrisso* across lung cancer settings and in novel combinations were featured during WCLC, including:

- Results from the ODIN BM Phase I trial, which support the efficacy and uniform brain penetration of *Tagrisso*in patients with CNS metastases as reported in previous clinical trials. This trial used a micro dose of intravenous *Tagrisso* detectable on PET scans, which showed rapid, high and widespread brain exposure of *Tagrisso* in both the healthy tissue and CNS metastases of four patients with EGFRm NSCLC. Results also showed that *Tagrisso* markedly reduced CNS metastases in patients following three to four weeks of daily oral treatment
- Final results from two expansion cohorts of the TATTON Phase Ib trial, which support the potential of *Tagrisso* plus savolitinib, a selective inhibitor of mesenchymal epithelial transition (c-MET) factor receptor tyrosine kinase, to overcome MET-based resistance in patients with NSCLC whose disease has progressed on prior EGFR-tyrosine kinase inhibitor (TKI) treatment. The safety profile of *Tagrisso* plus savolitinib was consistent with previous reports. The combination is currently being tested in the ongoing SAVANNAH and ORCHARD Phase II trials
- The design of a Phase I study exploring *Tagrisso* in combination with patritumab deruxtecan (U3-1402) in patients with locally advanced or metastatic EGFRm NSCLC who progressed during or after prior treatment with *Tagrisso* alone[3]
- The design of the NeoADAURA Phase III trial testing the benefit of treating patients with resectable Stage II-IIIB NSCLC with neoadjuvant *Tagrisso* as monotherapy or in combination with a choice of standard platinum-based chemotherapies versus chemotherapy with placebo. Patient recruitment for this trial is

ongoing

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Tagrisso was recently approved in the US for the adjuvant treatment of adult patients with early-stage EGFRm NSCLC after tumour resection with curative intent based on the ADAURA Phase III trial. This indication is under priority review in China and regulatory review in the EU; additional global submission discussions are ongoing. *Tagrisso* is also approved for the 1st-line treatment of patients with locally advanced or metastatic EGFRm NSCLC and for the treatment of locally advanced or metastatic EGFR T790M mutation-positive NSCLC in the US, Japan, China, the EU and many other countries around the world.

Lung cancer

Lung cancer is the leading cause of cancer death among both men and women, accounting for about one-fifth of all cancer deaths.[4] Lung cancer is broadly split into NSCLC and small cell lung cancer, with 80-85% classified as NSCLC.[5] The majority of all NSCLC patients are diagnosed with advanced disease while approximately 25-30% present with resectable disease at diagnosis.[6-8]Early-stage lung cancer diagnoses are often only made when the cancer is found on imaging for an unrelated condition.[9,10]

For patients with resectable tumours, the majority of patients eventually develop recurrence despite complete tumour resection and adjuvant chemotherapy.[11]

Approximately 10-15% of NSCLC patients in the US and Europe, and 30-40% of patients in Asia have EGFRm NSCLC.[12-14]These patients are particularly sensitive to treatment with an EGFR-TKI which blocks the cell-signalling pathways that drive the growth of tumour cells.[15]

ADAURA

ADAURA is a randomised, double-blind, global, placebo-controlled Phase III

trial in the adjuvant treatment of 682 patients with Stage IB, II and IIIA EGFRm NSCLC following complete tumour resection and adjuvant chemotherapy as indicated. Patients were treated with *Tagrisso* 80mg once-daily oral tablets or placebo for three years or until disease recurrence.

The trial enrolled patients in more than 200 centres across more than 20 countries, including the US, in Europe, South America, Asia and the Middle East. The primary endpoint was DFS in Stage II and IIIA patients and a key secondary endpoint was DFS in Stage IB, II and IIIA patients.

The data readout was originally anticipated in 2022. In April 2020, an Independent Data Monitoring Committee recommended for the trial to be unblinded two years early based on a determination of overwhelming efficacy. Investigators and patients continue to participate and remain blinded to treatment. The trial will continue to assess overall survival.

Tagrisso

Tagrisso (osimertinib) is a third-generation, irreversible EGFR-TKI with clinical activity against CNS metastases.

Tagrisso (40mg and 80mg once-daily oral tablets) is approved in many countries around the world, including the US, Japan, China and in the EU, for the 1st-line treatment of EGFRm advanced NSCLC and EGFR T790M mutation-positive advanced NSCLC. *Tagrisso* is also approved in the US and several other countries for the adjuvant treatment of adults with early-stage EGFRm NSCLC after tumour resection, with further global submissions ongoing.

Tagrisso has been used to treat approximately 215,000 patients across indications worldwide.

AstraZeneca in lung cancer

AstraZeneca has a comprehensive portfolio of approved and potential new medicines in late-stage development for the treatment of different forms of lung cancer spanning different histologies, several stages of disease, lines of therapy and modes of action.

AstraZeneca aims to address the unmet needs of patients with EGFRm tumours as a genetic driver of disease with the approved medicines *Iressa* (gefitinib) and *Tagrisso* and its ongoing LAURA, NeoADAURA and FLAURA2 Phase III trials. AstraZeneca is committed to addressing tumour mechanisms of resistance through the ongoing SAVANNAH and ORCHARD Phase II trials, which test *Tagrisso* in combination with savolitinib, a selective inhibitor of c-MET receptor tyrosine kinase, along with other potential new medicines.

AstraZeneca in oncology

AstraZeneca has a deep-rooted heritage in oncology and offers a quickly growing portfolio of new medicines that has the potential to transform patients' lives and the Company's future. With seven new medicines launched between 2014 and 2020, and a broad pipeline of small molecules and biologics in development, the Company is committed to advance oncology as a key growth driver for AstraZeneca focused on lung, ovarian, breast and blood cancers.

By harnessing the power of six scientific platforms – Immuno-Oncology, Tumour Drivers and Resistance, DNA Damage Response, Antibody Drug Conjugates, Epigenetics, and Cell Therapies – and by championing the development of personalised combinations, AstraZeneca has the vision to redefine cancer treatment, and one day, eliminate cancer as a cause of death.

AstraZeneca

AstraZeneca (LSE/STO/Nasdaq: AZN) is a global, science-led biopharmaceutical company that focuses on the discovery, development and commercialisation of prescription medicines, primarily for the treatment of diseases in three therapy areas - Oncology, 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.

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References

Om AstraZeneca

AstraZeneca är ett globalt, innovationsdrivet bioläkemedelsföretag med fokus på forskning, utveckling och marknadsföring av receptbelagda läkemedel, primärt för behandling av sjukdomar inom tre huvudsakliga terapiområden: cancer, kardiovaskulära sjukdomar, njursjukdomar och metabola sjukdomar och sjukdomar i andningsvägarna. AstraZeneca bedriver verksamhet i över 100 länder och dess innovativa läkemedel används av miljontals patienter över hela världen.

Mer information finns på: www.astrazeneca.com och www.astrazeneca.se. Du kan även följa oss på twitter https://twitter.com/AstraZenecaSE

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