RNS Number : 1029Y
AstraZeneca PLC
29 July 2024

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Fixed-duration *Calquence* plus venetoclax, with or without obinutuzumab, significantly improved progression-free survival in 1st-line chronic lymphocytic leukaemia in AMPLIFY Phase III trial

Favourable trend in overall survival was also observed

Positive high-level results from an interim analysis of the AMPLIFY Phase III trial showed a fixed duration of AstraZeneca's *Calquence* (acalabrutinib) in combination with venetoclax, with or without obinutuzumab, demonstrated a statistically significant and clinically meaningful improvement in progression-free survival (PFS) compared to standard-of-care chemoimmunotherapy in previously untreated adult patients with chronic lymphocytic leukaemia (CLL).

For the secondary endpoint of overall survival (OS), a trend was observed in favour of *Calquence* in combination with venetoclax, with or without obinutuzumab, versus standard-of-care chemoimmunotherapy. The OS data were not mature at the time of this analysis and the trial will continue to assess OS as a key secondary endpoint.

CLL is caused by the abnormal production of white blood cells and is the most prevalent type of leukaemia in adults worldwide, with numbers anticipated to grow.[1-3] In the first-line setting, approximately 40,000 patients are treated with the current standard of care.[4] Although CLL is considered an incurable cancer, patients often live with the disease for many years, and may remain on continuous treatment.[5]

Jennifer R. Brown, MD, PhD, Director of the CLL Center of the Division of Hematologic Malignancies, Dana-Farber Cancer Institute, and the Worthington and Margaret Collette Professor of Medicine at Harvard Medical School, and principal investigator of the trial, said: "The AMPLIFY results demonstrate the potential of acalabrutinib and venetoclax with or without obinutuzumab to be effective and well-tolerated fixed-duration treatment options for patients with chronic lymphocytic leukaemia. This is an important advance in this setting as fixed-duration regimens allow those living with this chronic disease to take breaks from their treatment, thereby decreasing the possibility of long-term adverse events and drug resistance and improving quality of life."

Susan Galbraith, Executive Vice President, Oncology R&D, AstraZeneca, said: "The progression-free survival and overall survival results from the AMPLIFY Phase III trial demonstrate the potential of including a BTK inhibitor in a fixed-duration regimen and reinforce our leadership in advancing science for patients with chronic lymphocytic leukaemia. If approved, *Calquence* would become the only second-generation BTK inhibitor available as both a treat-to-progression and fixed-duration treatment, providing more options for patients and their healthcare providers."

The safety and tolerability were consistent with the known safety profile of each medicine. No new safety signals were identified, with low rates of cardiac toxicity observed.

The data will be presented at a forthcoming medical meeting and shared with global regulatory authorities.

Notes

CLL
In CLL, there is an accumulation of abnormal lymphocytes within the bone marrow and in blood and lymph nodes.[1] Although some people with CLL may not experience any symptoms at diagnosis, others may experience symptoms, such as weakness, fatigue, weight loss, chills, fever, night sweats, swollen lymph nodes and abdominal pain.[6] As the number of abnormal cells increases, there is less room within the marrow for the production of normal white blood cells, red blood cells and platelets. This could result in anaemia, infection and bleeding.[1] B-cell receptor signalling through BTK is one of the essential survival pathways for CLL.

AMPLIFY
AMPLIFY is a randomised, global, multi-centre, open-label Phase III trial evaluating the efficacy and safety of *Calquence* in combination with venetoclax with and without obinutuzumab compared to investigator's choice of chemoimmunotherapy in adult patients with previously untreated CLL without del(17p) or TP53 mutation.[7] Patients were randomised 1:1:1 to receive either *Calquence* in combination with venetoclax, *Calquence* in combination with venetoclax plus obinutuzumab for a fixed duration or standard-of-care chemoimmunotherapy.[7]

The primary endpoint is PFS in the *Calquence* and venetoclax arm as assessed by an Independent Review Committee (IRC) and PFS in this arm assessed by investigators (INV) is a key secondary endpoint. IRC and INV assessed PFS in the *Calquence,* venetoclax and obinutuzumab arm as a key secondary endpoint. Other key secondary endpoints include OS, event-free survival, overall response rate, duration of response and time to next treatment.[7] The trial includes 27 countries across North and South America, Europe, Asia and Oceania.[7]

The AMPLIFY trial enrolled patients from 2019 to 2021, continuing through the COVID-19 pandemic.[7] Patients with blood cancer remain at a disproportionately high risk of severe outcomes from COVID-19, including hospitalisation

and death compared to the general population.[8]

Calquence
Calquence (acalabrutinib) is a second-generation, selective inhibitor of Bruton's tyrosine kinase (BTK). *Calquence* binds covalently to BTK, thereby inhibiting its activity.[9] In B-cells, BTK signalling results in activation of pathways necessary for B-cell proliferation, trafficking, chemotaxis and adhesion.

Calquence has been used to treat more than 80,000 patients worldwide[10] and is approved for the treatment of CLL and small lymphocytic lymphoma (SLL) in the US and Japan, approved for CLL in the EU and many other countries worldwide and approved in China for relapsed or refractory CLL and SLL. *Calquence* is also approved in the US, China and several other countries for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy. *Calquence* is not currently approved for the treatment of MCL in Japan or the EU.

As part of an extensive clinical development programme, *Calquence* is currently being evaluated as a single treatment and in combination with standard-of-care chemoimmunotherapy for patients with multiple B-cell blood cancers, including CLL, MCL and diffuse large B-cell lymphoma.

AstraZeneca in haematology
AstraZeneca is pushing the boundaries of science to redefine care in haematology. Our goal is to help transform the lives of patients living with malignant, rare and other related haematologic diseases through innovative medicines and approaches that are shaped by insights from patients, caregivers and physicians.

In addition to our marketed products, we are spearheading the development of novel therapies designed to target underlying drivers of disease across six scientific platforms. Our recent acquisitions of Alexion, with expertise in rare, non-malignant blood disorders, and Gracell Biotechnologies Inc., focused on cell therapies for haematologic malignancies, expand our haematology pipeline and enable us to reach more patients with high unmet needs through the end-to-end development and delivery of novel therapies.

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/Nasdaq: AZN) is a global, science-led biopharmaceutical company that focuses on the discovery, development, and commercialisation of prescription medicines in Oncology, Rare Diseases, 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
For details on how to contact the Investor Relations Team, please click here. For Media contacts, click here.

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Adrian Kemp
Company Secretary
AstraZeneca PLC

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