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Calquence plus chemoimmunotherapy approved in the US for patients with previously untreated mantle cell lymphoma

Based on ECHO Phase III trial results which showed more than 16 months of progression-free survival improvement vs. chemoimmunotherapy alone

First and only BTK inhibitor approved for the 1st-line treatment of MCL in the US

AstraZeneca's *Calquence* (acalabrutinib) in combination with bendamustine and rituximab has been approved in the US for the treatment of adult patients with previously untreated mantle cell lymphoma (MCL) who are ineligible for autologous hematopoietic stem cell transplantation.

The approval was granted by the Food and Drug Administration (FDA) after securing Priority Review. It was based on results from the ECHO Phase III trial which were presented at the European Hematology Association 2024 Congress.

MCL is a rare and typically aggressive form of non-Hodgkin lymphoma (NHL), often diagnosed at an advanced stage.[1],[2] It is estimated that there are more than 21,000 patients diagnosed with MCL in the US, UK, France, Germany, Spain, Italy, Japan and China.[3]

Michael Wang, MD, Puddin Clarke Endowed Professor, Director of Mantle Cell Lymphoma Program of Excellence and principal investigator in the trial, said: "Managing this aggressive cancer requires maximising efficacy while maintaining tolerability, especially for elderly patients. Results from the pivotal ECHO trial highlight the promise of the acalabrutinib combination in defining a new standard of care, with today's approval underscoring the transformative potential of this regimen as a first-line treatment for older patients with mantle cell lymphoma."

Dave Fredrickson, Executive Vice-President, Oncology Haematology Business Unit, AstraZeneca, said: "With today's approval, *Calquence* provides a critical new treatment option to mantle cell lymphoma patients in the US, with *Calquence* proven to deliver nearly one and a half years of additional time without disease progression. This approval brings a new and effective treatment option to those living with this disease and further reinforces our belief in *Calquence* as a backbone therapy across multiple blood cancers."

Meghan Gutierrez, Chief Executive Officer, Lymphoma Research Foundation, said: "New treatment options have long been needed in the first-line treatment of mantle cell lymphoma in the US. Patients with this rare and often aggressive cancer can experience severe symptoms by the time they are diagnosed - having an effective therapy that can significantly improve outcomes for patients early in the treatment process is a much-needed advancement."

Results from the ECHO trial showed *Calquence* plus bendamustine and rituximab reduced the risk of disease progression or death by 27% compared to standard-of-care chemoimmunotherapy (hazard ratio [HR] 0.73; 95% confidence interval [CI] 0.57-0.94; p=0.016). Median PFS was 66.4 months for patients treated with the *Calquence* combination versus 49.6 months with chemoimmunotherapy alone.

This approval additionally converts *Calquence's* accelerated approval to a full approval for adult patients with MCL treated with at least one prior therapy, as granted by the FDA in October 2017.

The ECHO trial enrolled patients throughout the COVID-19 pandemic. After censoring for COVID-19 deaths, PFS was further improved in both arms, with the *Calquence* combination reducing the risk of disease progression or death by 36% (HR 0.64; 95% CI 0.48-0.84). Although OS data were not mature at the time of the analysis, when censored for COVID-19, a favourable trend was seen for OS (HR 0.75; 95% CI 0.53-1.04), despite 69% of patients in the chemoimmunotherapy arm receiving treatment with a BTK inhibitor on relapse or disease progression.

The safety and tolerability of *Calquence* was consistent with its known safety profile, and no new safety signals were identified.

The US regulatory submission was reviewed under Project Orbis, which provides a framework for concurrent submission and review of oncology medicines among participating international partners. As part of Project Orbis, *Calquence* plus chemoimmunotherapy is also under review by regulatory authorities in Australia, Canada, and Switzerland for the same indication. Regulatory applications are also under review in the EU, Japan, and other countries based on the ECHO results.

Notes

Mantle cell lymphoma (MCL)

While MCL patients initially respond to treatment, patients do tend to relapse.[4] MCL comprises about 3-6% of non-Hodgkin lymphomas, with an annual incidence of 0.5 per 100,000 population in Western countries; in the US, it is estimated that approximately 4,000 new patients are diagnosed with MCL each year.4,[5]

ECHO

ECHO is a randomised, double-blind, placebo-controlled, multi-centre Phase III trial evaluating the efficacy and safety of *Calquence* plus bendamustine and rituximab compared to SoC

chemoimmunotherapy (bendamustine and rituximab) in adult patients at or over 65 years of age (n=635) with previously untreated MCL.[6] Patients were randomised 1:1 to receive either *Calquence* or placebo administered orally twice per day, continuously, until disease progression or unacceptable toxicity. Additionally, all patients received six 28-day cycles of bendamustine on days 1 and 2 and rituximab on day 1 of each cycle, followed by rituximab maintenance for two years if patients achieved a response after induction therapy.6

The primary endpoint is PFS assessed by an Independent Review Committee; other efficacy endpoints include OS, overall response rate (ORR), duration of response (DoR) and time to response (TTR).6 The trial was conducted in 27 countries across North and South America, Europe, Asia and Oceania.6

The ECHO trial enrolled patients from May 2017 to March 2023, continuing through the COVID-19 pandemic. Prespecified PFS and OS analyses censoring for COVID-19 deaths were conducted to assess the impact of COVID-19 on the study outcome in alignment with the FDA. 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.6,[7]

Calquence
Calquence (acalabrutinib) is a second-generation, selective inhibitor of Bruton's tyrosine kinase (BTK). *Calquence* binds covalently to BTK, thereby inhibiting its activity.[8] 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 85,000 patients worldwide[9] and is approved for the treatment of chronic lymphocytic leukaemia (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 for the treatment of adult patients with previously untreated MCL in the US, and in 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 multiple scientific platforms. Our acquisitions of Alexion, with expertise in rare, non-malignant blood disorders, and Gracell Biotechnologies Inc., pioneers of autologous cell therapies, expand our haematology pipeline and enable us to reach more patients with high unmet needs through the end-to-end discovery, 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
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References

1. Lymphoma Research Foundation. Mantle Cell Lymphoma. Available at: https://lymphoma.org/aboutlymphoma/nhl/mcl/. Accessed January 2025.
2. National Organization for Rare Disorders. Mantle Cell Lymphoma. Available at: https://rarediseases.org/rare-diseases/mantle-cell-lymphoma/. Accessed January 2025.
3. AstraZeneca 2024. Q3 2024 Financial Results. Available at: https://www.astrazeneca.com/investor-relations.html. Accessed January 2025.
4. Cheah C, Seymour J, Wang ML. Mantle cell lymphoma. *J Clin Oncol*. 2016;34(11):1256-1269. doi: 10.1200/JCO.2015.63.5904.
5. MD Anderson Cancer Center. What to know about mantle cell lymphoma. Available at: https://www.mdanderson.org/cancerwise/what-to-know-

about-mantle-cell-lymphoma-symptoms-diagnosis-and-treatment.h00-159385101.html. Accessed January 2025.
6. ClinicalTrials.gov. A Study of BR Alone Versus in Combination With Acalabrutinib in Subjects With Previously Untreated MCL. Available at: https://clinicaltrials.gov/study/NCT02972840. Accessed January 2025.
7. Dube S, et al. Continued Increased Risk of COVID-19 Hospitalisation and Death in Immunocompromised Individuals Despite Receipt of ≥4 Vaccine Doses: Updated 2023 Results from INFORM, a Retrospective Health Database Study in England. Poster P0409 at ECCMID 2024.
8. Wu J, Zhang M, Liu D. Acalabrutinib (ACP-196): a selective second-generation BTK inhibitor. *J Hematol Oncol*. 2016;9(21).
9. Data on File, REF-236261. AstraZeneca Pharmaceuticals LP.

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