NEWS RELEASE

CALQUENCE® (acalabrutinib) plus chemoimmunotherapy reduced the risk of disease progression or death by 27% vs. standard of care in patients with untreated mantle cell lymphoma in ECHO Phase III trial

6/16/2024

First and only BTK inhibitor to demonstrate favorable overall survival trend vs. standard-of-care chemoimmunotherapy in this setting

WILMINGTON, Del.--(BUSINESS WIRE)-- Positive results from the ECHO Phase III trial showed AstraZeneca's CALQUENCE® (acalabrutinib) in combination with bendamustine and rituximab demonstrated a statistically significant and clinically meaningful improvement in progression-free survival (PFS) and showed a favorable trend in overall survival (OS) compared to standard-of-care chemoimmunotherapy (bendamustine plus rituximab) in previously untreated patients with mantle cell lymphoma (MCL).

These results were presented today in a late-breaking oral presentation at the European Hematology Association (EHA) 2024 Hybrid Congress in Madrid, Spain (#LBA3439).

Results showed the CALQUENCE combination regimen 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 (n=299) versus 49.6 months with standard-of-care chemoimmunotherapy (n=299).

The secondary endpoint of OS showed a favorable trend for the CALQUENCE combination compared to standard-

of-care chemoimmunotherapy, further supporting the clinical benefit of this combination (HR 0.86; 95% CI 0.65-1.13; p=0.2743). 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.

The ECHO trial enrolled during the pandemic period, and a pre-specified analysis censoring for COVID-19-related deaths was conducted to assess the impact. 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; p=0.0017). Median PFS was not reached among patients treated with the CALQUENCE combination versus 61.6 months for standard-of-care chemoimmunotherapy (HR 0.64; 95% CI 0.48-0.84; p=0.0017). A favorable trend was seen for OS in this analysis for the CALQUENCE combination (HR 0.75; 95% CI 0.53-1.04; p=0.0797).

Michael Wang, MD, Puddin Clarke Endowed Professor, Director of Mantle Cell Lymphoma Program of Excellence, Co-Director of Clinical Trials at MD Anderson Cancer Center in Houston, US and principal investigator in the trial, said: “For people living with mantle cell lymphoma, a typically aggressive form of non-Hodgkin's lymphoma, the ECHO results offer promise of a new, effective treatment option for adults older than 65, who represent the majority of MCL patients. The improved progression-free survival seen in patients treated with the CALQUENCE combination compared to chemoimmunotherapy demonstrate its potential to change the standard of care as the only BTK inhibitor in this first-line setting.”

Susan Galbraith, Executive Vice President, Oncology R&D, AstraZeneca, said: “The ECHO trial data demonstrate important progress in improving outcomes for patients with mantle cell lymphoma. The 16.8 months of additional time patients can live without their disease progressing is highly clinically meaningful, together with a trend to improvement in overall survival. We therefore believe CALQUENCE plus chemoimmunotherapy will be an important new option for patients living with this disease.”

Summary of Results: ECHO

	CALQUENCE plus bendamustine and rituximab (n=299)	Placebo plus bendamustine and rituximab (n=299)
Median PFS (months)	66.4	49.6
PFS HR (95% CI)	0.73 (0.57-0.94)	
PFS p-value	0.0160	
OS HR (95% CI)	0.86 (0.65-1.13)	
OS p-value	0.2743	
Censoring for COVID-19 deaths		
Median PFS	NR	61.6
PFS HR (95% CI)	0.64 (0.48-0.84)	
PFS p-value	0.0017	
OS HR (95% CI)	0.75 (0.53-1.04)	
OS p-value	0.0797	

NR=Not reached

The safety and tolerability of CALQUENCE was consistent with its known safety profile, and no new safety signals were identified. Grade 3 or higher adverse events (AEs) due to any cause occurred in 88.9% (n=264) of patients treated with the CALQUENCE combination and 88.2% (n=262) of patients treated with standard-of-care chemoimmunotherapy, including Grade 3 or higher atrial fibrillation in 3.7% (n=11) and 1.7% (n=5) of patients, Grade 3 or higher hypertension in 5.4% (n=16) and 8.4% (n=25), Grade 3 or higher major bleeding in 2.0% (n=6) and 3.4% (n=10), and Grade 3 or higher infections in 41.1% (n=122) and 34.0% (n=101), respectively. Serious AEs and Grade 5 events were balanced across arms (69% [n=205] versus 62% [n=184], and 12.1% [n=36] versus 10.1% [n=30], respectively). AEs leading to discontinuation were observed in 10.4% (n=31) and 6.4% (n=19) of patients for the CALQUENCE combination and placebo arms respectively. AEs related to COVID-19 were seen in the trial, including Grade 5 events which occurred in 9.4% (n=28) of patients treated with the CALQUENCE combination and 6.7% (n=20) of patients treated with standard-of-care chemoimmunotherapy.

Additional AstraZeneca data at EHA

In addition to these compelling data, AstraZeneca data at EHA 2024 shows how the Company is advancing a diverse and innovative pipeline spanning multiple modalities including next-generation T cell engagers, cell therapy and antibody drug conjugates, to enable the creation of novel combination regimens across a range of blood cancers.

Results from the ongoing Phase I, dose-escalation trial of AZD0486, a novel CD19xCD3 T cell engager, showed durable responses in patients with heavily pretreated relapsed/refractory follicular lymphoma with a median follow up of 11 months. Complete response rates of 84% were seen at doses of AZD0486 of 2.4 mg and above. Data also showed how cytokine release syndrome (CRS) events were effectively mitigated by the double step-up dosing schedule and no immune effector cell-associated neurotoxicity syndrome (ICANS) events were observed.

In an oral presentation, preliminary data was shared from an investigator-initiated trial of AstraZeneca's first hematology cell therapy, GC012F (AZD0120), in patients with transplant-eligible high-risk, newly diagnosed multiple myeloma. Early results showed that GC012F had an overall response rate of 100%, a minimal residual disease-negative stringent complete response rate of 95%, and was well tolerated. Grade 1-2 CRS was experienced by 27% (6/22) of patients and no ICANS or neurotoxicity was observed. GC012F is a novel BCMAxCD19 dual-targeting autologous chimeric antigen receptor T therapy (CAR-T) created using the next-day FasTCAR manufacturing platform pioneered by Gracell Biotechnologies, a wholly owned subsidiary of AstraZeneca.

INDICATIONS AND USAGE

CALQUENCE is a Bruton tyrosine kinase (BTK) inhibitor indicated for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy.

This indication is approved under accelerated approval based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

CALQUENCE is also indicated for the treatment of adult patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL).

IMPORTANT SAFETY INFORMATION ABOUT CALQUENCE® (acalabrutinib) tablets

Serious and Opportunistic Infections

Fatal and serious infections, including opportunistic infections, have occurred in patients with hematologic malignancies treated with CALQUENCE.

Serious or Grade 3 or higher infections (bacterial, viral, or fungal) occurred in 19% of 1029 patients exposed to CALQUENCE in clinical trials, most often due to respiratory tract infections (11% of all patients, including pneumonia in 6%). These infections predominantly occurred in the absence of Grade 3 or 4 neutropenia, with neutropenic infection reported in 1.9% of all patients. Opportunistic infections in recipients of CALQUENCE have included, but are not limited to, hepatitis B virus reactivation, fungal pneumonia, Pneumocystis jirovecii pneumonia, Epstein-Barr virus reactivation, cytomegalovirus, and progressive multifocal leukoencephalopathy (PML). Consider prophylaxis in patients who are at increased risk for opportunistic infections. Monitor patients for signs and symptoms of infection and treat promptly.

Hemorrhage

Fatal and serious hemorrhagic events have occurred in patients with hematologic malignancies treated with CALQUENCE. Major hemorrhage (serious or Grade 3 or higher bleeding or any central nervous system bleeding) occurred in 3.0% of patients, with fatal hemorrhage occurring in 0.1% of 1029 patients exposed to CALQUENCE in clinical trials. Bleeding events of any grade, excluding bruising and petechiae, occurred in 22% of patients.

Use of antithrombotic agents concomitantly with CALQUENCE may further increase the risk of hemorrhage. In clinical trials, major hemorrhage occurred in 2.7% of patients taking CALQUENCE without antithrombotic agents and 3.6% of patients taking CALQUENCE with antithrombotic agents. Consider the risks and benefits of antithrombotic agents when co-administered with CALQUENCE. Monitor patients for signs of bleeding.

Consider the benefit-risk of withholding CALQUENCE for 3-7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding.

Cytopenias

Grade 3 or 4 cytopenias, including neutropenia (23%), anemia (8%), thrombocytopenia (7%), and lymphopenia (7%), developed in patients with hematologic malignancies treated with CALQUENCE. Grade 4 neutropenia developed in 12% of patients. Monitor complete blood counts regularly during treatment. Interrupt treatment, reduce the dose, or discontinue treatment as warranted.

Second Primary Malignancies

Second primary malignancies, including skin cancers and other solid tumors, occurred in 12% of 1029 patients exposed to CALQUENCE in clinical trials. The most frequent second primary malignancy was skin cancer, reported in 6% of patients. Monitor patients for skin cancers and advise protection from sun exposure.

Cardiac Arrhythmias

Serious cardiac arrhythmias have occurred in patients treated with CALQUENCE. Grade 3 atrial fibrillation or flutter occurred in 1.1% of 1029 patients treated with CALQUENCE, with all grades of atrial fibrillation or flutter reported in 4.1% of all patients. Grade 3 or higher ventricular arrhythmia events were reported in 0.9% of patients. The risk may be increased in patients with cardiac risk factors, hypertension, previous arrhythmias, and acute infection. Monitor for symptoms of arrhythmia (eg, palpitations, dizziness, syncope, dyspnea) and manage as appropriate.

Hepatotoxicity, Including Drug-Induced Liver Injury

Hepatotoxicity, including severe, life-threatening, and potentially fatal cases of drug-induced liver injury (DILI), has occurred in patients treated with Bruton tyrosine kinase inhibitors, including CALQUENCE.

Evaluate bilirubin and transaminases at baseline and throughout treatment with CALQUENCE. For patients who develop abnormal liver tests after CALQUENCE, monitor more frequently for liver test abnormalities and clinical signs and symptoms of hepatic toxicity. If DILI is suspected, withhold CALQUENCE. Upon confirmation of DILI, discontinue CALQUENCE.

ADVERSE REACTIONS

The most common adverse reactions (≥20%) of any grade in patients with relapsed or refractory MCL were anemia,* thrombocytopenia,* headache (39%), neutropenia,* diarrhea (31%), fatigue (28%), myalgia (21%), and bruising (21%). The most common Grade ≥3 non-hematological adverse reaction (reported in at least 2% of patients) was diarrhea (3.2%).

*Treatment-emergent decreases (all grades) of hemoglobin (46%), platelets (44%), and neutrophils (36%) were based on laboratory measurements and adverse reactions.

Dose reductions or discontinuations due to any adverse reaction were reported in 1.6% and 6.5% of patients, respectively. Increases in creatinine to 1.5 to 3 times the upper limit of normal (ULN) occurred in 4.8% of patients.

The most common adverse reactions (≥30%) of any grade in patients with CLL were anemia,* neutropenia,* thrombocytopenia,* headache, upper respiratory tract infection, and diarrhea.

*Treatment-emergent decreases (all grades) of hemoglobin, platelets, and neutrophils were based on laboratory measurements and adverse reactions.

In patients with previously untreated CLL exposed to CALQUENCE, fatal adverse reactions that occurred in the absence of disease progression and with onset within 30 days of the last study treatment were reported in 2% for each treatment arm, most often from infection. Serious adverse reactions were reported in 39% of patients in the CALQUENCE plus obinutuzumab arm and 32% in the CALQUENCE monotherapy arm, most often due to events of pneumonia (7% and 2.8%, respectively).

Adverse reactions led to CALQUENCE dose reduction in 7% and 4% of patients in the CALQUENCE plus obinutuzumab arm (N=178) and CALQUENCE monotherapy arm (N=179), respectively. Adverse events led to discontinuation in 11% and 10% of patients, respectively. Increases in creatinine to 1.5 to 3 times ULN occurred in 3.9% and 2.8% of patients in the CALQUENCE combination arm and monotherapy arm, respectively.

In patients with relapsed/refractory CLL exposed to CALQUENCE, serious adverse reactions occurred in 29% of patients. Serious adverse reactions in >5% of patients who received CALQUENCE included lower respiratory tract infection (6%). Fatal adverse reactions within 30 days of the last dose of CALQUENCE occurred in 2.6% of patients, including from second primary malignancies and infection.

Adverse reactions led to CALQUENCE dose reduction in 3.9% of patients (N=154), dose interruptions in 34% of patients, most often due to respiratory tract infections followed by neutropenia, and discontinuation in 10% of patients, most frequently due to second primary malignancies followed by infection. Increases in creatinine to 1.5 to 3 times ULN occurred in 1.3% of patients who received CALQUENCE.

DRUG INTERACTIONS

Strong CYP3A Inhibitors: Avoid co-administration of CALQUENCE with a strong CYP3A inhibitor. If these inhibitors will be used short-term, interrupt CALQUENCE. After discontinuation of strong CYP3A inhibitor for at least

24 hours, resume previous dosage of CALQUENCE.

Moderate CYP3A Inhibitors: Reduce the dosage of CALQUENCE to 100 mg once daily when co-administered with a moderate CYP3A inhibitor.

Strong CYP3A Inducers: Avoid co-administration of CALQUENCE with a strong CYP3A inducer. If co-administration is unavoidable, increase the dosage of CALQUENCE to 200 mg approximately every 12 hours.

SPECIFIC POPULATIONS

Based on findings in animals, CALQUENCE may cause fetal harm and dystocia when administered to a pregnant woman. There are no available data in pregnant women to inform the drug-associated risk. Advise pregnant women of the potential risk to a fetus.

Pregnancy testing is recommended for females of reproductive potential prior to initiating CALQUENCE therapy. Advise female patients of reproductive potential to use effective contraception during treatment with CALQUENCE and for 1 week following the last dose of CALQUENCE.

It is not known if CALQUENCE is present in human milk. Advise lactating women not to breastfeed while taking CALQUENCE and for 2 weeks after the last dose.

Avoid use of CALQUENCE in patients with severe hepatic impairment (Child-Pugh class C). No dosage adjustment of CALQUENCE is recommended in patients with mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment.

Please see full **Prescribing Information** , including **Patient Information**.

Notes

Mantle cell lymphoma

MCL is a rare and typically aggressive form of non-Hodgkin lymphoma (NHL), often diagnosed as a late-stage disease, resulting when B-lymphocytes mutate into malignant cells within a region of the lymph node known as the mantle zone.1,2 While MCL patients initially respond to treatment, patients do tend to relapse.3 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.3,4 It is estimated that there are more than 27,500 people living with MCL worldwide.5,6

ECHO

ECHO is a randomized, double-blind, placebo-controlled, multi-center Phase III trial evaluating the efficacy and safety of CALQUENCE plus bendamustine and rituximab compared to standard of care chemoimmunotherapy (bendamustine and rituximab) in adult patients at or over 65 years of age (n=635) with previously untreated MCL.7 Patients were randomized 1:1 to receive either CALQUENCE or placebo administered orally twice per day, on 28 day treatment cycles, plus bendamustine on days 1 and 2 and rituximab on day 1 of each cycle. After six cycles of induction therapy, all patients continued CALQUENCE or placebo in combination with bendamustine and rituximab, patients receive CALQUENCE or placebo plus maintenance rituximab for two years and then either CALQUENCE or placebo only until disease progression.7

The primary endpoint is PFS assessed by an Independent Review Committee and key secondary endpoints include OS, overall response rate (ORR), duration of response (DoR) and time to response (TTR).7 The trial includes 27 countries across North and South America, Europe, Asia and Oceania.7

The ECHO trial enrolled patients from May 2017 to March 2023, continuing through the COVID-19 pandemic. Patients with blood cancer remain at a disproportionately high risk of severe outcomes from COVID-19, including hospitalization and death compared to the general population.8

CALQUENCE

CALQUENCE (acalabrutinib) is a next-generation, selective inhibitor of Bruton's tyrosine kinase (BTK). CALQUENCE binds covalently to BTK, thereby inhibiting its activity.9 In B-cells, BTK signaling 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 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 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 program, 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, diffuse large B-cell lymphoma and follicular lymphoma.

AstraZeneca in hematology

AstraZeneca is pushing the boundaries of science to redefine care in hematology. Our goal is to help transform the lives of patients living with malignant, rare and other related hematologic 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 hematologic malignancies, expand our hematology 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 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.

AstraZeneca

AstraZeneca 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's innovative medicines are sold in more than 125 countries and used by millions of patients worldwide. Please visit **www.astrazeneca-us.com** and follow the Company on social media **@AstraZeneca**.

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US-90789 Last Updated 6/24

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Source: AstraZeneca