The first and only BTKi approved in 1L MCL*[1]

5.5 years mPFS†
with CALQUENCE + BR vs
4.1 years with placebo + BR‡[1]

(HR§=0.73 [95% CI: 0.57-0.94]; *P*‖=0.016)

*In combination with BR for patients ineligible for auto-HSCT in 1L MCL.

ECHO enrolled a substantial proportion of high-risk 1L MCL patients[1-3]

High-risk features included *TP53*m, Ki-67 ≥30%, blastoid/pleomorphic histology, and/or high-risk MIPI

ECHO study design: The Phase 3 ECHO trial evaluated CALQUENCE + bendamustine and rituximab (BR) vs placebo + BR in 598 patients ≥65 years with previously untreated MCL and no intention for transplant. Patients received 6 cycles of BR with either CALQUENCE 100 mg BID or placebo until disease progression or unacceptable toxicity. Crossover to CALQUENCE was allowed at disease progression. Maintenance rituximab was permitted in responders. Primary endpoint was IRC-assessed PFS; key secondary endpoints included ORR, OS, and safety.[1,2]

Patient characteristics at baseline, including high-risk features [n (%)][1-4]

	CALQUENCE + BR (n=299)	Placebo + BR (n=299)
Age, median (range), yr	71 (65-85)	71 (65-86)
≥75, n (%)	84 (28)	77 (26)
Male, n (%)	214 (72)	209 (70)
Race		
White	233 (78)	235 (79)
Asian	44 (15)	49 (16)
Black or African American	1 (0.3)	2 (0.7)
ECOG PS, n (%)		
1	129 (43)	132 (44)
2	12 (4)	23 (8)
Classic type histology, n (%)	238 (80)	243 (81)
Blastoid/pleomorphic histology, n (%)	41 (14)	38 (13)
Tumor bulk ≥5 cm, n (%)	112 (38)	113 (38)
Ann Arbor stage IV disease	251 (84)	263 (88)
sMIPI score, n (%)		
Low risk	99 (33)	101 (34)
Intermediate risk	128 (43)	125 (42)
High risk	72 (24)	73 (24)
Extranodal disease, n (%)	264 (88)	277 (93)
TP53 status, n (%)¶		
Unmutated	97 (32)	83 (28)
Mutated	22 (7)	29 (10)
Ki-67 index, n (%)		
<30%	133 (45)	126 (42)
≥30%	139 (47)	147 (49)
Total high-risk	187 (63)	183 (61)

MCL patient case

David

Not a real CALQUENCE patient.

Presentation
- Male, 73 years old
- Night sweats, fatigue, and weight loss of 20 pounds in 5 months
- Comorbidities: controlled hypertension (ACEi), benign prostatic hyperplasia (controlled on alpha-blocker)

Workup
- PET/CT showed diffuse lymphadenopathy in the abdomen and chest with hypermetabolic activity in the spleen (SUV of 12)
- IR-guided biopsy confirmed mantle cell lymphoma (Ann Arbor stage IV) *SOX-11*+, Ki-67 of 50%, and complex karyotype without del(17p) by cytogenetics, and wild-type *TP53*
- Pathologically confirmed MCL, ineligible for auto-HSCT; ECOG PS 2

†At interim analysis, mPFS was 66.4 months (95% CI: 55.1-NE) with CALQUENCE + BR vs 49.6 months (95% CI: 36.0-64.1) with placebo + BR.[1] ‡At 49.8-month median follow-up (range: 0.0-77.3 months).[1,2,4] §Based on a stratified Cox proportional-hazards model for HR (95% CI).[1] ‖Estimated based on a stratified log-rank test for *P* value, with an alpha level of 0.039 derived by the O'Brien-Fleming method.[1] ¶All other patients in the CALQUENCE (n=180) and placebo (n=187) groups had unknown *TP53* mutation status.[3]

1L=first-line; ACEi=angiotensin-converting enzyme inhibitors; auto-HSCT=autologous hematopoietic stem cell transplantation; BID=twice per day; BTKi=Bruton tyrosine kinase inhibitor; CI=confidence interval; del(17p)=deletion in the 17p chromosome; ECOG PS=Eastern Cooperative Oncology Group performance status; HR=hazard ratio; IR=interventional radiology; IRC=Independent Review Committee; Ki-67=antigen Kiel 67; MCL=mantle cell lymphoma; MIPI=Mantle Cell Lymphoma International Prognostic Index; mPFS=median progression-free survival; NE=not evaluable; ORR=overall response rate; OS=overall survival; PET-CT=positron emission tomography-computed tomography; PFS=progression-free survival; sMIPI=simplified Mantle Cell Lymphoma International Prognostic Index; *SOX-11*=SRY-Box Transcription Factor 11; SUV=standardized uptake value; *TP53*=tumor protein p53; *TP53*m=tumor protein p53 mutation.

INDICATION AND USAGE

CALQUENCE is a Bruton tyrosine kinase inhibitor indicated in combination with bendamustine and rituximab (BR) for the treatment of adult patients with previously untreated mantle cell lymphoma (MCL) who are ineligible for autologous hematopoietic stem cell transplantation (HSCT).

SELECT SAFETY INFORMATION

Serious adverse events, including fatal events, have occurred with CALQUENCE, including serious and opportunistic infections, hemorrhage, cytopenias, second primary malignancies, cardiac arrhythmias, and hepatotoxicity, including drug-induced liver injury. The most common adverse reactions (≥30%) are upper respiratory tract infection, diarrhea, headache, and musculoskeletal pain. The most common Grade 3 or 4 laboratory abnormalities (≥10%) are absolute neutrophil count decreased, uric acid increased, absolute lymphocyte count decreased, and platelets decreased.

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CALQUENCE®
acalabrutinib 100 mg tablets

Significantly longer mPFS with CALQUENCE + BR[1,2,5]

Demonstrated PFS superiority vs placebo + BR in ITT population

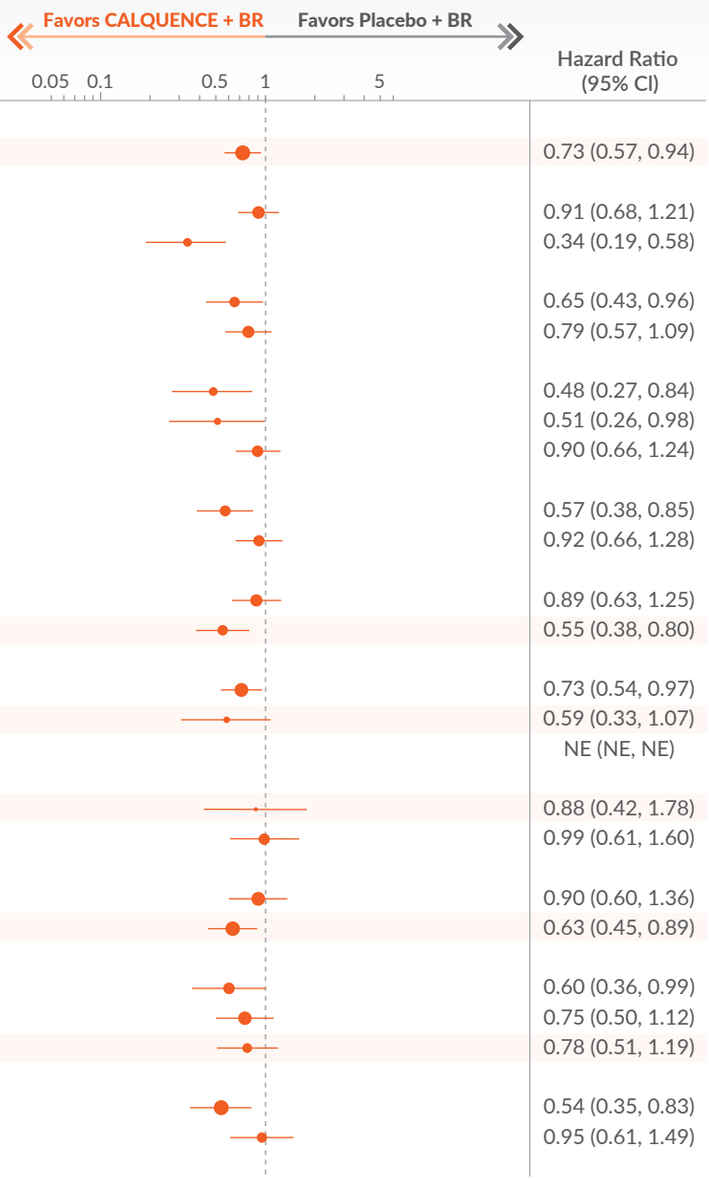
Progression-free survival, primary endpoint (ITT population)

27% **PFS risk reduction* with CALQUENCE + BR vs placebo + BR (HR=0.73 [95% CI: 0.57-0.94]; *P*=0.016)**

- mPFS was 66.4 months (95% CI: 55.1-NE) with CALQUENCE + BR vs 49.6 months (95% CI: 36.0-64.1) with placebo + BR at 49.8-month median follow-up[1]

Subgroup analysis of IRC-assessed PFS[2,5]

Subgroup	Number of Events/Patients: CALQUENCE + BR	Number of Events/Patients: Placebo + BR	Hazard Ratio (95% CI)
Overall			
Primary analysis	110/299	137/299	0.73 (0.57, 0.94)
Sex			
Male	93/214	94/209	0.91 (0.68, 1.21)
Female	17/85	43/90	0.34 (0.19, 0.58)
Age category, years			
<70	42/123	57/117	0.65 (0.43, 0.96)
≥70	68/176	80/182	0.79 (0.57, 1.09)
Geographic region			
North America	19/82	35/83	0.48 (0.27, 0.84)
Western Europe	14/46	24/46	0.51 (0.26, 0.98)
Other	77/171	78/170	0.90 (0.66, 1.24)
Baseline ECOG PS score			
0	42/156	60/140	0.57 (0.38, 0.85)
1 or 2	68/141	75/155	0.92 (0.66, 1.28)
Tumor bulk			
<5 cm	62/187	68/186	0.89 (0.63, 1.25)
≥5 cm	48/112	69/113	0.55 (0.38, 0.80)
MCL type			
Classic type	82/238	107/243	0.73 (0.54, 0.97)
Blastoid/pleomorphic variant	21/41	24/38	0.59 (0.33, 1.07)
Other	0/0	2/5	NE (NE, NE)
***TP53* mutation†**			
Positive	14/22	17/29	0.88 (0.42, 1.78)
Negative	36/97	31/83	0.99 (0.61, 1.60)
Ki-67			
<30%	45/133	47/126	0.90 (0.60, 1.36)
≥30%	56/139	80/147	0.63 (0.45, 0.89)
sMIPI score‡			
Low risk (0-3)	24/99	39/101	0.60 (0.36, 0.99)
Intermediate risk (4-5)	46/128	52/125	0.75 (0.50, 1.12)
High risk (6-11)	40/72	46/73	0.78 (0.51, 1.19)
COVID-19 vaccine status			
Yes	34/164	53/147	0.54 (0.35, 0.83)
No	39/76	40/79	0.95 (0.61, 1.49)



Exploratory analysis of prespecified subgroups. Study was not powered to show statistical significance across subgroups.

*Reduced risk of disease progression or death. †All other patients in the CALQUENCE (n=180) and placebo (n=187) groups had unknown *TP53* mutation status.[2] ‡Per interactive voice/web response system record.[2]
COVID-19=coronavirus 2019; ITT=intent-to-treat.

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 29% of 2,055 patients exposed to CALQUENCE in clinical trials, most often due to respiratory tract infections (18% of all patients, including pneumonia in 14%). These infections predominantly occurred in the absence of Grade 3 or 4 neutropenia, with neutropenic infection reported in 8% 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.

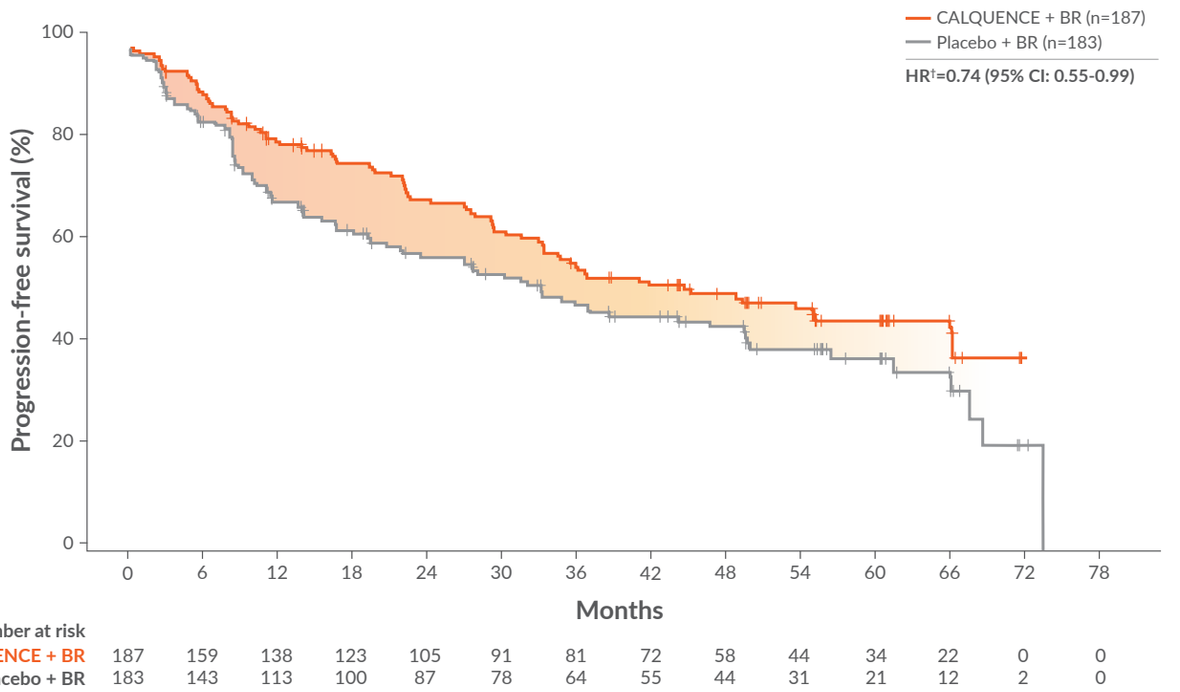
Hemorrhage

Fatal and serious hemorrhagic events have occurred in patients treated with CALQUENCE. Major hemorrhage (serious or Grade 3 or higher bleeding or any central nervous system bleeding) occurred in 4.7% of patients, with fatal hemorrhage occurring in 0.1% of 2,055 patients exposed to CALQUENCE in clinical trials. Bleeding events of any grade, excluding bruising and petechiae, occurred in 39% of patients.

Consistent PFS results observed in patients with high-risk disease[2,5]

PFS in high-risk 1L MCL ineligible for auto-HSCT*[2]

Progression-free survival, exploratory analysis (high-risk population)[4]



Number at risk													
CALQUENCE + BR	187	159	138	123	105	91	81	72	58	44	34	22	0	0
Placebo + BR	183	143	113	100	87	78	64	55	44	31	21	12	2	0

- High-risk disease was defined as any of the following: high-risk MIPI (6-11), Ki-67 index ≥30%, blastoid/pleomorphic histology, or *TP53* mutation[4]
- mPFS was 49.5 months with CALQUENCE + BR and 33.2 months with placebo + BR[4]

The analysis was exploratory and not formally tested.

*At 49.8-month follow-up (range: 0.0-77.3 months).[1,2,5] †Based on a stratified Cox proportional-hazards model for HR (95% CI).[1]

IMPORTANT SAFETY INFORMATION ABOUT CALQUENCE® (acalabrutinib) tablets (cont'd)

Hemorrhage (cont'd)

Use of antithrombotic agents concomitantly with CALQUENCE may further increase the risk of hemorrhage. In clinical trials, major hemorrhage occurred in 5% of patients taking CALQUENCE without antithrombotic agents and 3.2% 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 to 7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding.

Cytopenias

CALQUENCE can cause Grade 3 or 4 cytopenias. Grade 3 or 4 cytopenias included absolute neutrophil count decreased (28%), absolute lymphocyte count decreased (10%), hemoglobin decreased (9%), and platelets decreased (9%) in 1,758 patients treated with CALQUENCE alone and in combination with obinutuzumab or venetoclax; Grade 4 neutropenia developed in 14% 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 16% of 2,055 patients exposed to CALQUENCE in clinical trials. The most frequent second primary malignancy was non-melanoma skin cancer, reported in 9% of patients, followed by other solid tumors in 8% (including melanoma, lung cancer, gastrointestinal cancers, and genitourinary cancers) and hematologic malignancies (1.1%). Fatal second primary malignancies occurred in 0.8% of patients. Monitor patients for the development of second cancers and advise protection from sun exposure.

Cardiac Arrhythmias

Fatal and serious cardiac arrhythmias have occurred in patients treated with CALQUENCE. Grade 3 or 4 atrial fibrillation or flutter was reported in 2.2% of 2,055 patients treated with CALQUENCE, with all grades of atrial fibrillation or flutter reported in 7% of all patients. Grade 3 or higher ventricular arrhythmia events were reported in 0.5% of patients, including fatal cases in 0.3% of all patients. The risk of arrhythmias 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

Previously Untreated Mantle Cell Lymphoma

The most common adverse reactions (≥15%) of any grade in patients with previously untreated MCL in the ECHO study who received CALQUENCE plus BR (n=297) were rash (47%), COVID-19 (38%), fatigue (37%), diarrhea (37%), pneumonia (31%), headache (31%), upper respiratory tract infection (30%), pyrexia (29%), cough (27%), vomiting (26%), constipation (25%), hemorrhage (20%), edema (20%), secondary primary malignancy (19%), dizziness (18%), arthralgia (18%), and dyspnea (17%).

Grade 4 laboratory abnormalities in >15% of patients treated with CALQUENCE plus BR include absolute lymphocyte count decreased (26%), absolute neutrophil count decreased (36%), and uric acid increased (17%).

Serious adverse reactions occurred in 69% of patients who received CALQUENCE plus BR. Serious adverse reactions reported in ≥2% of patients were pneumonia (23%; includes COVID-19 pneumonia), COVID-19 (20%; includes COVID-19 pneumonia),

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Safety was consistent with the established profile of CALQUENCE[1-3]

Most ARs were Grade 1 or 2 in the CALQUENCE + BR arm (n=297)

Most common ARs (≥15%) in patients who received CALQUENCE + BR (Any Grade/Grade ≥3) included rash* (47%/12%), COVID-19† (38%/13%), upper respiratory tract infection‡ (30%/0.7%), pneumonia§ (31%/17%), diarrhea (37%/3%), vomiting (26%/0.7%), constipation (25%/1%), fatigue (37%/3.7%), pyrexia (29%/2.4%), edema (20%/1.3%), headache (31%/1.7%), dizziness (18%/1%), cough (27%/0%), dyspnea (17%/1%), secondary primary malignancy‖ (19%/7%), arthralgia (18%/0.7%), and hemorrhage¶ (20%/1.7%).

- **Serious ARs** occurred in 69% of patients who received CALQUENCE plus BR. Serious ARs reported in ≥2% of patients were pneumonia (23%; includes COVID-19 pneumonia), COVID-19 (20%; includes COVID-19 pneumonia), second primary malignancy (7%), pyrexia (6%), rash (3.4%), febrile neutropenia (3.4%), atrial fibrillation (3%), sepsis (2.7%), and anemia (2.4%)[1]
- **Fatal ARs** that occurred within 30 days of the last study treatment were reported in 12% who received CALQUENCE plus BR, including COVID-19 (6%; includes COVID-19 pneumonia), pneumonia (1%), sepsis (0.3%), second primary malignancy (0.7%), and pneumonitis (0.3%)[1]
- **Grade 4 laboratory abnormalities** in >15% of patients treated with CALQUENCE + BR included decreased absolute lymphocyte count (26%), decreased absolute neutrophil count (36%), and increased uric acid (17%)[1]

Low rates of select cardiovascular AEs[3]

Events of clinical interest

	CALQUENCE + BR (n=297)		**Placebo + BR** (n=297)	
	Any Grade (%)	Grade ≥3 (%)	Any Grade (%)	Grade ≥3 (%)
Atrial fibrillation	7	4	4.4	1.7
Hypertension	12	6	16	8
Major bleeding#	2.4	2	5	3.4
Infections	78	41	71	34
Second primary malignancies (excluding nonmelanoma skin malignancy)	10	5	11	7

Values >5 are rounded to the nearest whole number.

In a pooled analysis of 2055 patients exposed to CALQUENCE, Grade ≥3 infections occurred in 29%, with neutropenic infection in 8%; major hemorrhage occurred in 4.7%, with fatal hemorrhage in 0.1%; fatal second primary malignancies occurred in 0.8%; Grade 3/4 atrial fibrillation or flutter in 2.2% and Grade ≥3 ventricular arrhythmia in 0.5%, including fatal cases in 0.3%. Among 1758 patients, Grade 3/4 cytopenias included absolute neutrophil count decreased (28%), absolute lymphocyte count decreased (10%), hemoglobin decreased (9%), and platelets decreased (9%), with Grade 4 neutropenia in 14%.[1]

See how you can offer your eligible patients with 1L MCL, including those with high-risk features, a chance to start strong at CALQUENCEhcp.com

*Includes rash, dermatitis, and other related terms.[1] †Includes the following fatal adverse reactions: n=24 for COVID-19.[1] ‡Includes upper respiratory tract infection, sinusitis, pharyngitis, and related terms.[1] §Includes pneumonia, terms containing pneumonia, and related infections. COVID-19 pneumonia is represented under both pneumonia and COVID-19.[1] ‖Includes terms related to malignant neoplasms including cutaneous neoplasms.[1] ¶Includes all terms containing hematoma or hemorrhage and related terms indicative of bleeding.[1] #Defined as any serious or Grade ≥3 hemorrhagic event, or Any Grade hemorrhagic event in the central nervous system.[1]
AEs=adverse events; ARs=adverse reactions.

IMPORTANT SAFETY INFORMATION ABOUT CALQUENCE® (acalabrutinib) tablets (cont'd)

ADVERSE REACTIONS (cont'd)

second primary malignancy (7%), pyrexia (6%), rash (3.4%), febrile neutropenia (3.4%), atrial fibrillation (3%), sepsis (2.7%), and anemia (2.4%). Fatal adverse reactions that occurred within 30 days of the last study treatment were reported in 12% who received CALQUENCE plus BR including COVID-19 (6%; includes COVID-19 pneumonia), pneumonia (1%), second primary malignancy (0.7%), sepsis (0.3%), and pneumonitis (0.3%).

Adverse reactions led to permanent discontinuation of CALQUENCE in 43%, dosage interruptions in 74%, and dosage reductions in 10% of patients. Adverse reactions that resulted in dosage modification in >10% included infections, cytopenias, rashes, and gastrointestinal toxicity. Adverse reactions which resulted in permanent discontinuation of CALQUENCE in ≥4% of patients included COVID-19 (includes COVID-19 pneumonia) and neutropenia.

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 Important Safety Information throughout, and full Prescribing Information, including Patient Information.

You may report side effects related to AstraZeneca products.

References: 1. CALQUENCE® (acalabrutinib) tablets [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2026. **2.** Wang M, Salek D, Belada D, et al. Acalabrutinib plus bendamustine-rituximab in untreated mantle cell lymphoma. *J Clin Oncol*. 2025;43(20):2276-2284. **3.** Wang M, Mayer J, Belada D, et al. Acalabrutinib plus bendamustine and rituximab in untreated mantle cell lymphoma: results from the phase 3, double-blind, placebo-controlled ECHO trial. Presented at: European Hematology Association (EHA) Annual Meeting; June 13-16, 2024; Madrid, Spain. **4.** Dreyling M, Zinzani PL, Pavlovsky MA, et al. Efficacy of rituximab-bendamustine with or without acalabrutinib in patients with untreated, high-risk mantle cell lymphoma: an analysis of the phase 3 ECHO trial. Presentation S233 presented at: European Hematology Association (EHA) Congress; June 12-15, 2025; Milan, IT. **5.** Data on File. REF-255868. AstraZeneca Pharmaceuticals LP.

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