IN BOTH TN AND R/R CLL

CALQUENCE HAS BEEN STUDIED IN THREE PHASE 3 TRIALS WITH UP TO 5 YEARS OF LONG-TERM FOLLOW-UP DATA[1-3]

~800 patients were included, of which more than 500 had high-risk features[1-5]

		High-risk feature (>500 patients)				
Clinical trial	**Trial arm**	**17p deletion** n (%)	***TP53* mutation** n (%)	**11q deletion** n (%)	***IGHV* unmutated** n (%)	**Median follow-up duration (months)**
ELEVATE-TN[1,4]	CALQUENCE n=179	16 (9)	19 (11)	31 (17)	119 (66)	58.2
	CALQUENCE + obinutuzumab n=179	17 (10)	21 (12)	31 (17)	103 (58)	
ELEVATE-RR[2]	CALQUENCE n=268	121 (45)	100 (37)	167 (62)	220 (82)	40.9
ASCEND[3,5]	CALQUENCE n=155	28 (18)	39 (26)	39 (25)	109 (70)	46.5
	Total n=781	**182 (23)**	**179 (23)**	**268 (34)**	**551 (71)**	

More than 60% of patients in CALQUENCE clinical trials had at least one high-risk genomic feature, which reflects the overall CLL patient population.[1-6]

IN TREATMENT-NAIVE CLL

ELEVATE-TN Study Design[1,7]

ELEVATE-TN was a Phase 3, randomized, multicenter, open-label study that enrolled 535 patients aged ≥65 years, or 18–65 years with comorbidities (Cumulative Illness Rating Scale-Geriatric score >6 and/or creatinine clearance 30–69 mL/min by Cockcroft-Gault), who had treatment-naive CLL requiring treatment.[7] Patients were randomized 1:1:1 to receive either CALQUENCE + obinutuzumab (n=179), CALQUENCE monotherapy (n=179), or GClb (maximum 6 cycles) (n=177).[7] Patients received CALQUENCE 100 mg orally approximately every 12 hours until disease progression or unacceptable toxicity for either CALQUENCE + obinutuzumab or CALQUENCE monotherapy arms.[1,7]

The primary endpoint was PFS* for CALQUENCE + obinutuzumab vs GClb. Select secondary endpoints were IRC-assessed PFS for CALQUENCE monotherapy vs GClb, INV-assessed PFS, ORR, OS, and safety.[1] Crossover to CALQUENCE monotherapy was permitted in patients who progressed on GClb.[1]

IN RELAPSED/REFRACTORY CLL

ELEVATE-RR Study Design[2]

ELEVATE-RR was a randomized, multicenter, open-label, Phase 3 trial of CALQUENCE vs ibrutinib in 533 patients with R/R CLL with the presence of 17p deletion and/or 11q deletion. Patients were randomized 1:1 to receive either CALQUENCE 100 mg orally approximately every 12 hours (n=268) or ibrutinib 420 mg orally once daily (n=265) until disease progression or unacceptable toxicity.[2]

The primary endpoint was IRC-assessed PFS (non-inferiority†; tested after ~250 events). Secondary endpoints included incidence of any grade atrial fibrillation, incidence of Grade ≥3 infections, incidence of Richter's transformation, and OS.[2]

ASCEND Study Design[3,7]

ASCEND was a Phase 3, open-label, randomized, multicenter trial in 310 patients with R/R CLL. Patients received either CALQUENCE monotherapy 100 mg approximately every 12 hours until disease progression or unacceptable toxicity (n=155), or investigator's choice of IdR or BR (n=155).[7]

Primary endpoint at the interim analysis (median follow-up of 16.1 months) was IRC-assessed PFS. After the interim analysis at 16.1-month median follow-up, PFS was INV-assessed only. Select secondary endpoints were ORR, OS, and safety.[3,7]

*The primary endpoint was IRC-assessed PFS for CALQUENCE + obinutuzumab vs GClb. After the interim analysis at 28.3-month median follow-up, PFS was INV-assessed only.[1,7]
†Derivation of the non-inferiority margin (upper bound of two-sided 95% CI <1.429) was based on the results of one ibrutinib study. Therefore, it may be difficult to verify the constancy assumption of the historical control.[2]
BR=bendamustine + rituximab; CLL=chronic lymphocytic leukemia; GClb=obinutuzumab + chlorambucil; INV=investigator; IdR=idelalisib + rituximab; IRC=Independent Review Committee; ORR=overall response rate; OS=overall survival; PFS=progression-free survival; R/R=relapsed/refractory; TN=treatment-naive.

Learn more about the NCCN Guidelines® for CLL/SLL patients with high-risk features

CALQUENCE® acalabrutinib 100 mg tablets

INDICATION AND USAGE
CALQUENCE is a Bruton tyrosine kinase (BTK) inhibitor indicated for the treatment of adult patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL).

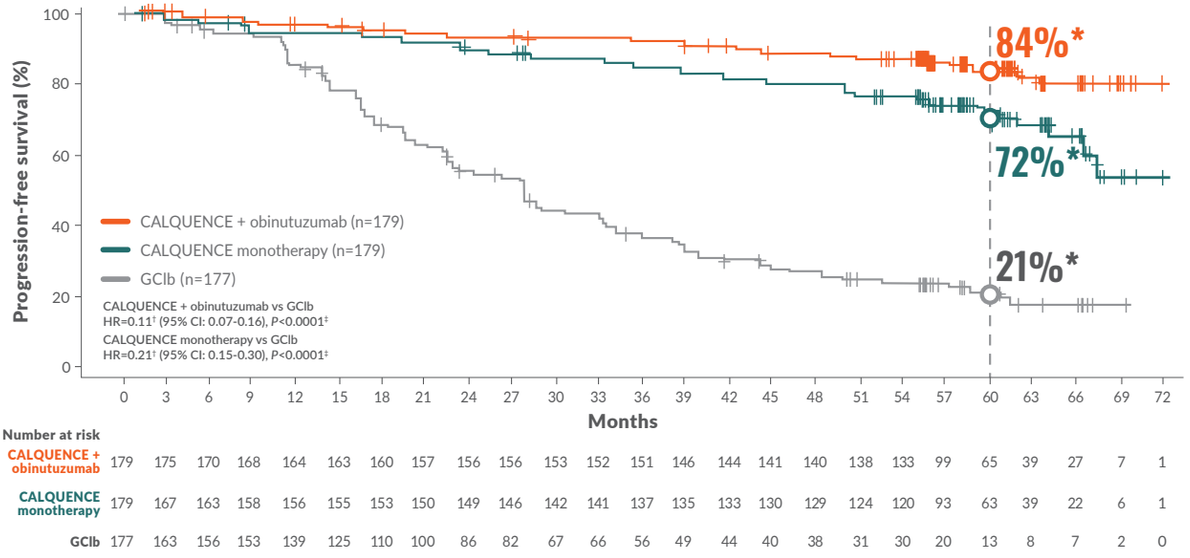
IMPORTANT SAFETY INFORMATION ABOUT CALQUENCE® (acalabrutinib) tablets
Serious and Opportunistic Infections
Fatal and serious infections, including opportunistic infections, have occurred in patients with hematologic malignancies treated with CALQUENCE.

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 jiroveci* 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.

Please see additional Important Safety Information throughout and full Prescribing Information, including Patient Information.

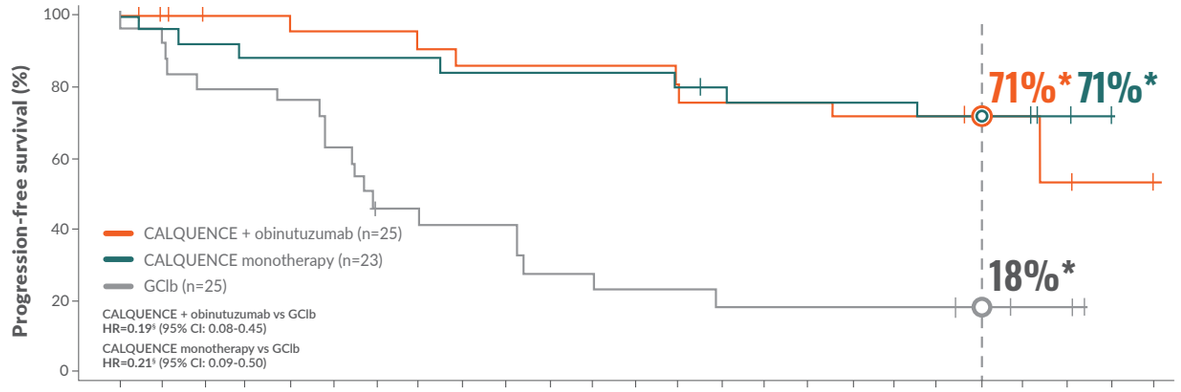
CALQUENCE with or without obinutuzumab delivered consistent PFS results, regardless of 17p deletion or *TP53* mutational status[1]

Long-term analysis: INV-assessed PFS[1]



Number at risk																									
CALQUENCE + obinutuzumab	179	175	170	168	164	163	160	157	156	156	153	152	151	146	144	141	140	138	133	99	65	39	27	7	1
CALQUENCE monotherapy	179	167	163	158	156	155	153	150	149	146	142	141	137	135	133	130	129	124	120	93	63	39	22	6	1
GClb	177	163	156	153	139	125	110	100	86	82	67	66	56	49	44	40	38	31	30	20	13	8	7	2	0

INV-assessed PFS in subgroup of patients with del(17p) and/or mutated *TP53*[1]



Number at risk																									
CALQUENCE + obinutuzumab	25	24	23	22	22	22	22	22	21	21	21	21	21	20	19	18	18	18	18	11	8	6	3	1	0
CALQUENCE monotherapy	23	22	21	21	20	20	20	19	18	18	18	18	18	17	16	16	16	15	15	12	8	8	3	2	1
GClb	25	21	19	19	18	15	10	9	9	9	6	6	5	5	4	4	4	4	4	4	3	2	2	0	0

At 58.2-month median follow-up

- The most common AEs (≥30%) of any grade in the CALQUENCE + obinutuzumab arm (n=178) were infection (79%), bleeding (49%), diarrhea (43%), headache (40%), arthralgia (34%), and neutropenia (34%). In the CALQUENCE monotherapy arm (n=179), the most common AEs (≥30%) of any grade were infection (75%), bleeding (44%), diarrhea (43%), and headache (39%)[1]
- Median duration of CALQUENCE exposure was 58.1 months for CALQUENCE + obinutuzumab and 58.0 months for CALQUENCE monotherapy. Median duration of exposure was 5.6 months for GClb[1]

At 28.3-month median follow-up (interim analysis)

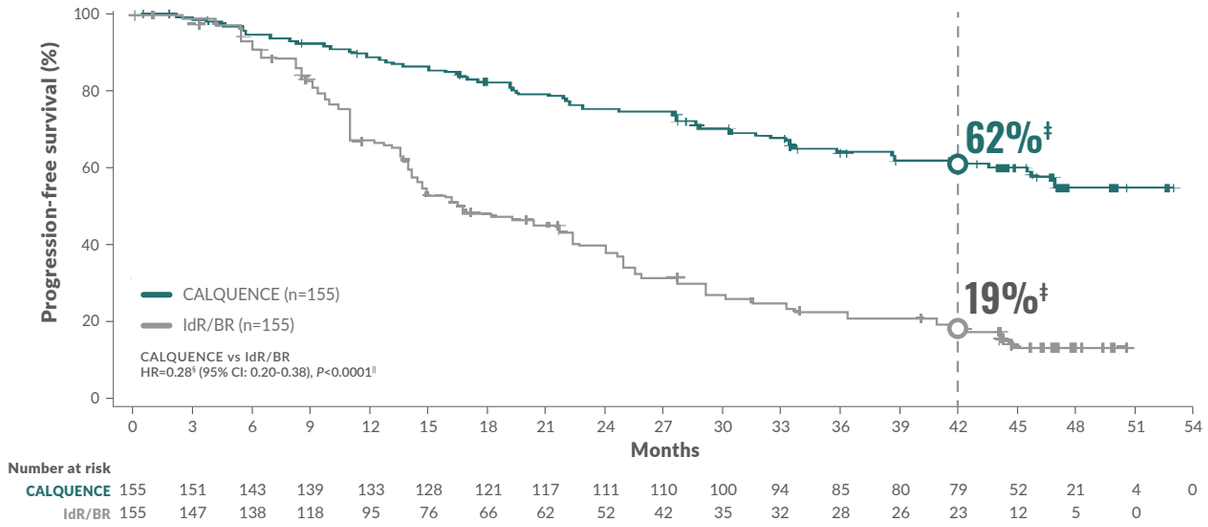
- There was a 90% risk reduction in IRC-assessed disease progression or death (HR=0.10‖; 95% CI: 0.06-0.17; *P*<0.0001¶) with CALQUENCE + obinutuzumab vs GClb and an 80% risk reduction (HR=0.20‖; 95% CI: 0.13-0.30; *P*<0.0001¶) with CALQUENCE monotherapy vs GClb[4,7]
  - Median PFS was not reached with CALQUENCE ± obinutuzumab vs 22.6 months with GClb[4]
- The most common ARs (≥30%) of any grade in the CALQUENCE + obinutuzumab arm (n=178) were infection (69%), neutropenia (53%), anemia (52%), thrombocytopenia (51%), headache (40%), diarrhea (39%), musculoskeletal pain (37%), fatigue (34%), and bruising (31%). In the CALQUENCE monotherapy arm (n=179), the most common ARs (≥30%) of any grade were infection (65%), anemia (53%), headache (39%), diarrhea (35%), musculoskeletal pain (32%), and thrombocytopenia (32%)[7]
- Median duration of exposure at interim analysis was 27.7 months in the CALQUENCE + obinutuzumab group and 27.7 months in the CALQUENCE monotherapy group[4]

The safety data presented include all patients (n=357) who received CALQUENCE in ELEVATE-TN, of which more than 60% had at least one high-risk cytogenetic feature.[1]

*Estimated PFS rate at 60 months.[1]
†Based on Cox proportional-hazards model stratified by del(17p) status (yes vs no based on interactive voice/web response system).[1]
‡Based on log-rank test stratified by del(17p) status (yes vs no based on interactive voice/web response system).[1]
§Based on an unstratified Cox proportional-hazards model. Hazard ratios are compared with the GClb arm.[1]
‖Based on a stratified Cox proportional-hazards model. Both HRs are compared with the GClb arm.[7]
¶Based on a stratified log-rank test, with an alpha level of 0.012 derived from alpha spending function by the O'Brien-Fleming method.[7]
AEs=adverse events; ARs=adverse reactions.

CALQUENCE demonstrated consistent PFS† results, including in patients with 17p deletion[3]

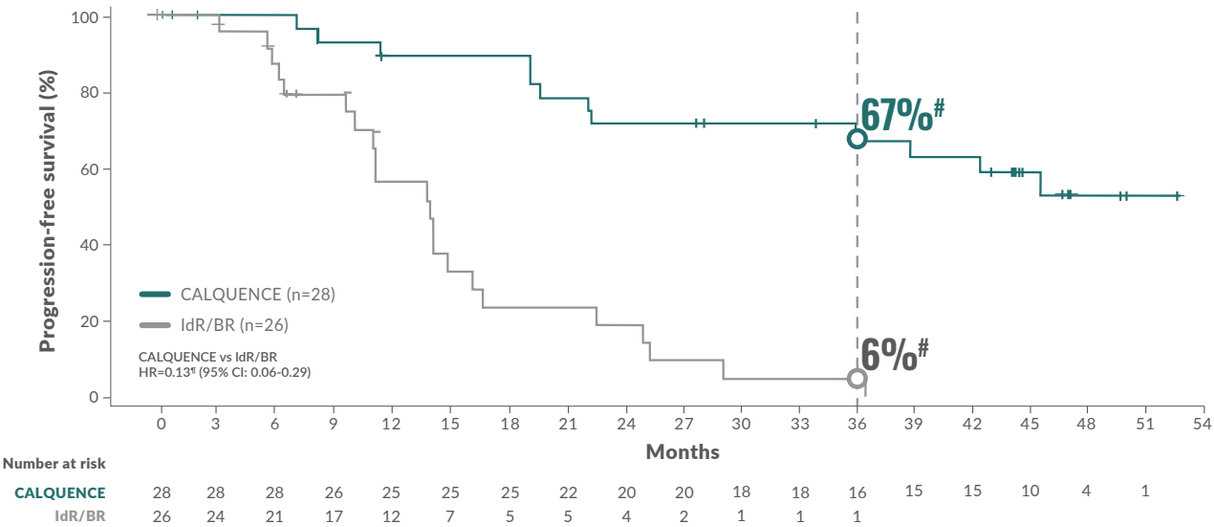
Long-term analysis: INV-assessed PFS[3]



Number at risk

CALQUENCE	155	151	143	139	133	128	121	117	111	110	100	94	85	80	79	52	21	4	0
IdR/BR	155	147	138	118	95	76	66	62	52	42	35	32	28	26	23	12	5	0	

INV-assessed PFS in subgroup of patients with del(17p)[3]



Number at risk

CALQUENCE	28	28	28	26	25	25	25	22	20	20	18	18	16	15	15	10	4	1	
IdR/BR	26	24	21	17	12	7	5	5	4	2	1	1	1						

At 46.5-month median follow-up

- The most common AEs (≥20%) of any grade in patients receiving CALQUENCE were infection (68%), hemorrhage (31%), neutropenia (24%), headache (23%), and diarrhea (21%)[3]
- The median duration of CALQUENCE exposure was 44.2 months (range: 1.1-54.2)[3]

At 16.1-month median follow-up (interim analysis)

- There was a 69% risk reduction in IRC-assessed PFS with CALQUENCE vs IdR/BR (HR=0.31** [95% CI: 0.20-0.49], *P*<0.0001††)[7]
  - Median PFS was not reached with CALQUENCE vs 16.5 months (95% CI: 14.0-17.1) with IdR/BR[7]
- The most common ARs (≥20%) of any grade in patients receiving CALQUENCE were infection (56%), neutropenia (48%), anemia (47%), thrombocytopenia (33%), lymphocytosis (26%), and headache (22%)[7]
- Median duration of exposure was 15.7 months (range: 1.1-22.4 months) in the CALQUENCE monotherapy arm[5,7]

The safety data presented include all patients (n=154) who received CALQUENCE in ASCEND, of which 70% had at least one high-risk cytogenetic feature.[3]

*Median follow-up of 46.5 months with CALQUENCE and 45.3 months with IdR/BR.[3]
†PFS was INV-assessed at median follow-up of ~4 years.[3]
‡Estimated PFS at 42 months.[3]
§Hazard ratio was based on stratified Cox proportional-hazards model, stratified by randomization stratification factors as recorded in an interactive voice/web response system.[3]
‖*P*-value was based on stratified log-rank test, stratified by randomization stratification factors as recorded in an interactive voice/web response system.[3]
¶Hazard ratios were based on unstratified Cox proportional-hazards model.[3]
#Because there were no IdR/BR–treated patients at risk by 42 months in the del(17p) subgroup, 42-month PFS rates were not available for that analysis.[3]
**Based on a stratified Cox proportional-hazards model.[7]
††Based on a stratified log-rank test, with alpha level of 0.012 derived from alpha spending function by the O'Brien-Fleming method.[7]

IMPORTANT SAFETY INFORMATION (cont'd)

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.

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CALQUENCE® acalabrutinib 100 mg tablets

Indication and Important Safety Information

INDICATION AND USAGE

CALQUENCE is a Bruton tyrosine kinase (BTK) inhibitor 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 jiroveci* 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.

Atrial Fibrillation and Flutter

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. 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.

ADVERSE REACTIONS

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 the upper limit of normal (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.

You are encouraged to report negative side effects of AstraZeneca prescription drugs by calling 1-800-236-9933. If you prefer to report these to the FDA, call 1-800-FDA-1088.

References: 1. Sharman JP, Egyed M, Jurczak W, et al. Acalabrutinib ± obinutuzumab vs obinutuzumab + chlorambucil in treatment naive chronic lymphocytic leukemia: 5-year follow-up of ELEVATE-TN. Poster presented at: American Society of Clinical Oncology (ASCO) Annual Meeting; June 3-7, 2022. Abs 7539. **2.** Byrd JC, Hillmen P, Ghia P, et al. Acalabrutinib versus ibrutinib in previously treated chronic lymphocytic leukemia: results of the first randomized phase III trial. *J Clin Oncol.* 2021;39(31):3441-3452 and supplementary appendix. **3.** Jurczak W, Pluta A, Wach M, et al. Acalabrutinib vs rituximab plus idelalisib or bendamustine in relapsed/refractory chronic lymphocytic leukemia: ASCEND results at ~4 years of follow-up. Poster presented at: American Society of Clinical Oncology (ASCO) Annual Meeting; June 3-7, 2022. Abs 7538. **4.** Sharman JP, Egyed M, Jurczak W, et al. Acalabrutinib with or without obinutuzumab versus chlorambucil and obinutuzumab for treatment naive chronic lymphocytic leukaemia (ELEVATE-TN): a randomised, controlled, phase 3 trial [published correction appears in *Lancet.* 2020;395(10238):1694]. *Lancet.* 2020;395(10232):1278-1291. **5.** Ghia P, Pluta A, Wach M, et al. ASCEND: phase III, randomized trial of acalabrutinib versus idelalisib plus rituximab or bendamustine plus rituximab in relapsed or refractory chronic lymphocytic leukemia. *J Clin Oncol.* 2020;38(25):2849-2861 and supplementary appendix. **6.** International CLL-IPI working group. An international prognostic index for patients with chronic lymphocytic leukaemia (CLL-IPI): a meta-analysis of individual patient data. *Lancet Oncol.* 2016;17(6):779-790. **7.** CALQUENCE® (acalabrutinib) tablets [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2022.