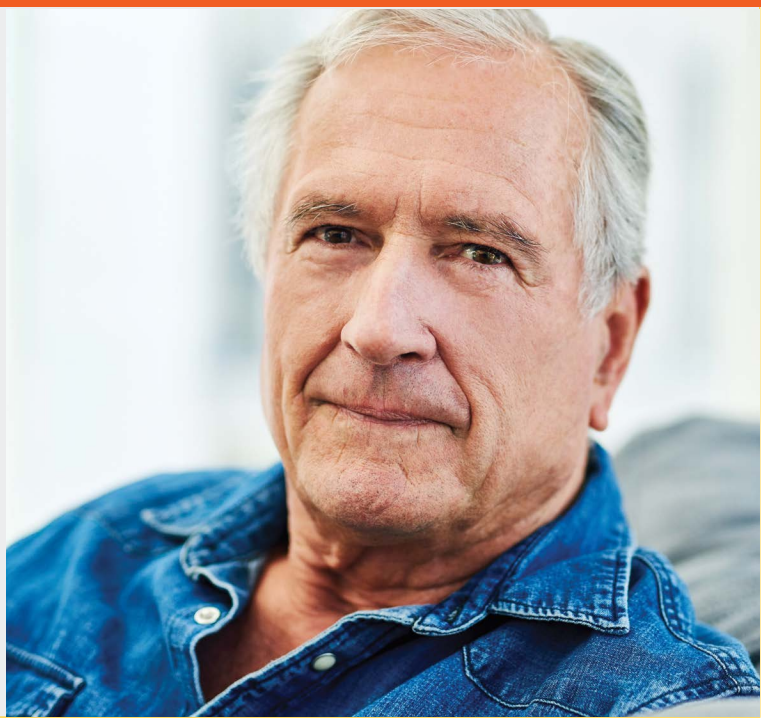
PATIENT CASE STUDY

FRANK
Age 75

Relapsed chronic lymphocytic leukemia (CLL) with unmutated IGHV and hypertension

- High risk: unmutated IGHV
- Comorbidity: hypertension
- ECOG performance status: 1
- Retired hardware store owner
- Proud grandfather of seven



Individual results may vary. This is not a real patient. This representation was not designed to imply efficacy for an individual patient subgroup.
ECOG=Eastern Cooperative Oncology Group.

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

IMPORTANT SAFETY INFORMATION ABOUT CALQUENCE® (acalabrutinib) capsules

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.

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

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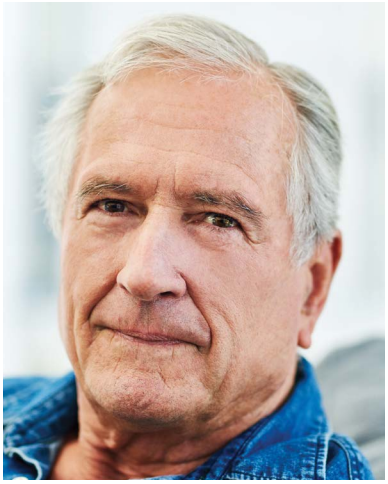
FRANK: AT A GLANCE

Relapsed/Refractory CLL



Frank was diagnosed with CLL during a routine checkup almost 3 years ago. Cytogenetic testing revealed that Frank had unmutated IGHV, a high-risk feature.[1] Due to his hypertension and age, he was given bendamustine and rituximab (BR), and since then had been in remission. Recently, though, he presented to his oncologist with worsening fatigue, weight loss, and anemia. After testing, his doctor confirmed that his disease had relapsed.[2] He and his doctor have many factors to consider as they decide on a new treatment.

"Finding out my CLL had relapsed—that was tough news to hear. Now my doctor and I have to consider my high-risk feature and my hypertension on top of that. I've been enjoying life since remission, and this time, I want a treatment that won't interfere with my lifestyle."

The ASCEND trial evaluated CALQUENCE in patients with relapsed/refractory (R/R) CLL*[3-5]

SELECT BASELINE CHARACTERISTICS	CALQUENCE (%) n=155	INVESTIGATOR'S CHOICE OF IDELALISIB + RITUXIMAB (IR) OR BR (%) n=155
Male sex	70	65
ECOG performance status 0-1	88	87
Cytogenetics/FISH category		
17p deletion	18	14
11q deletion	25	29
TP53 mutation	25	22
Unmutated IGHV	77	82
Complex karyotype (≥3 abnormalities)	32	30

*A Phase 3, open-label, randomized, multicenter trial in patients with R/R CLL (N=310). Patients were randomized 1:1 to receive either CALQUENCE or the investigator's choice of IR or BR. Patients receiving CALQUENCE were given 100 mg twice daily until disease progression or unacceptable toxicity. The primary endpoint was progression-free survival (PFS) as assessed by an Independent Review Committee.[3,6]

FISH=fluorescence in situ hybridization.

CONSIDER CALQUENCE FOR PATIENTS LIKE FRANK WITH R/R CLL

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.

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.

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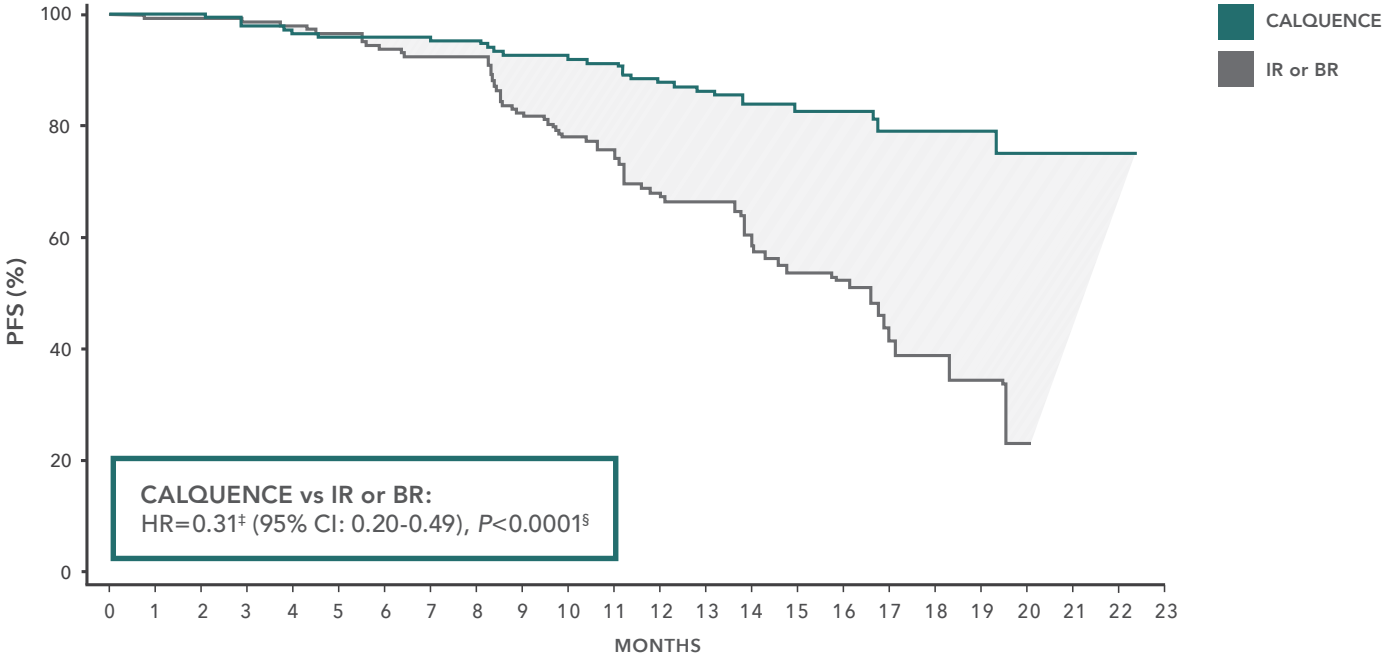
IN R/R CLL, CALQUENCE SIGNIFICANTLY IMPROVED PFS vs IR or BR*†[3]

CALQUENCE is the first and only BTKi monotherapy to demonstrate superior PFS against standard-of-care combinations, including novel agents, in R/R CLL.[3]

- **69% relative risk reduction in disease progression or death** (HR=0.31‡ [95% CI: 0.20-0.49], *P*<0.0001§) vs IR or BR
- At median 16.1-month follow-up, median PFS was not reached with CALQUENCE vs 16.5 months (95% CI: 14.0-17.1) with IR or BR[3]

IRC-assessed Progression-free Survival*†[3]



*Per 2008 International Workshop on CLL criteria.[3]
†At the time of analysis, the number of events in each arm was 27 (17%) for CALQUENCE and 68 (44%) for IR or BR.[3]
‡Based on a stratified Cox proportional-hazards model.[3]
§Based on a stratified log-rank test. The pre-specified type I error rate (α) for this interim analysis is 0.012 derived from a Lan-DeMets alpha spending function with O'Brien-Fleming boundary.[3]

BTKi=Bruton tyrosine kinase inhibitor; CI=confidence interval; HR=hazard ratio.

SELECT SAFETY INFORMATION[3]

- The most common adverse reactions (≥30%) of any grade in patients with previously untreated or relapsed/refractory CLL were anemia, neutropenia, thrombocytopenia, headache, upper respiratory tract infection, and diarrhea
- Adverse reactions led to discontinuation in 10% to 11% of CALQUENCE-treated patients

IMPORTANT SAFETY INFORMATION (Cont'd)

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 (e.g., 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.

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Consider **CALQUENCE** for patients like Frank with R/R CLL

IMPORTANT SAFETY INFORMATION (Cont'd)

ADVERSE REACTIONS (Cont'd)

*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 1.5 to 3 times the upper limit of normal 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), dosage 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 1.5 to 3 times the upper limit of normal occurred in 1.3% of patients who received CALQUENCE.

DRUG INTERACTIONS

Strong CYP3A Inhibitors: Avoid co-administration with a strong CYP3A inhibitor. If a strong CYP3A inhibitor will be used short-term, interrupt CALQUENCE.

Moderate CYP3A Inhibitors: When CALQUENCE is co-administered with a moderate CYP3A inhibitor, reduce CALQUENCE dose to 100 mg once daily.

Strong CYP3A Inducers: Avoid co-administration with a strong CYP3A inducer. If a strong CYP3A inducer cannot be avoided, increase the CALQUENCE dose to 200 mg approximately every 12 hours.

Gastric Acid Reducing Agents: If treatment with a gastric acid reducing agent is required, consider using an H2-receptor antagonist or an antacid. Take CALQUENCE 2 hours before taking an H2-receptor antagonist. Separate dosing with an antacid by at least 2 hours.

Avoid co-administration with proton pump inhibitors. Due to the long-lasting effect of proton pump inhibitors, separation of doses may not eliminate the interaction with CALQUENCE.

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 at least 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 at least 2 weeks after the final dose.

Avoid administration of CALQUENCE in patients with severe hepatic impairment. Dose modifications are not required for patients with mild or moderate hepatic impairment.

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

You may report side effects related to AstraZeneca products by clicking here.

References: 1. 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. **2**. Mir MA, Liu D, Patel SC, Rasool HJ. Chronic lymphocytic leukemia (CLL). Medscape website. https://emedicine.medscape.com/article/199313-overview. Updated October 22, 2019. Accessed December 2, 2019. **3**. CALQUENCE [package insert], Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2019. **4**. Ghia P, Pluta A, Wach M, et al. ASCEND phase 3 study of acalabrutinib vs investigator's choice of rituximab plus idelalisib (IDR) or bendamustine (BR) in patients with relapsed/refractory (R/R) chronic lymphocytic leukemia (CLL). Presented at: 24th European Hematology Society Congress; June 13-16, 2019; Amsterdam, the Netherlands. **5**. Data on File, REF-64711. AstraZeneca Pharmaceuticals LP. **6**. A study of acalabrutinib vs investigator's choice of idelalisib plus rituximab or bendamustine plus rituximab in R/R CLL. ClinicalTrials.gov identifier: NCT02970318. https://clinicaltrials.gov/ct2/show/NCT02970318. Updated August 16, 2019. Accessed November 14, 2019.

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