PATIENT CASE STUDY

ELLEN
Age 73

Previously untreated chronic lymphocytic leukemia (CLL) with high-risk features

- High risk: 17p deletion, unmutated IGHV
- ECOG performance status: 0
- Retired lawyer
- Active grandmother

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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ELLEN: AT A GLANCE

No prior treatment

Ellen was diagnosed with CLL during a routine checkup. In follow-up testing, her doctor determined she also had a 17p deletion and unmutated IGHV, high-risk cytogenetics that can make her disease more challenging to treat.[1] As she and her doctor prepare to choose a treatment, it will be important to determine how these high-risk features factor into the decision.

"It was scary to learn I had CLL, and even scarier when my doctor told me I have high-risk features. I'm hoping for a treatment that works for me, so I can live on my terms. I have a busy life, and I don't want that to change."

ELEVATE-TN evaluated 535 patients with previously untreated CLL*[2,3]

SELECT BASELINE CHARACTERISTICS	CALQUENCE + OBINUTUZUMAB (%) n=179	CALQUENCE MONOTHERAPY (%) n=179	OBINUTUZUMAB + CHLORAMBUCIL (GClb) (%) n=177
Female sex	38	38	40
ECOG performance status 0-1	94	92	94
Cytogenetics/FISH category			
17p deletion	10	9	9
11q deletion	17	17	19
TP53 mutation	12	11	12
Unmutated IGHV	58	67	66
Complex karyotype (≥3 abnormalities)	16	17	18

*ELEVATE-TN was a Phase 3, open-label, randomized, multicenter trial in patients with previously untreated CLL (N=535). Patients were randomized 1:1:1 into 3 arms to receive CALQUENCE + obinutuzumab, CALQUENCE monotherapy, or GClb. The primary endpoint was progression-free survival (PFS) as assessed by an Independent Review Committee. Patients receiving CALQUENCE were given 100 mg twice daily until disease progression or unacceptable toxicity. Refer to the obinutuzumab prescribing information for recommended obinutuzumab dosing information.[3,4]

FISH=fluorescence in situ hybridization.

CONSIDER **CALQUENCE** FOR PATIENTS LIKE ELLEN WITH PREVIOUSLY UNTREATED 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 PREVIOUSLY UNTREATED CLL, CALQUENCE SIGNIFICANTLY IMPROVED PFS BOTH IN COMBINATION WITH OBINUTUZUMAB AND AS A MONOTHERAPY*†[3]

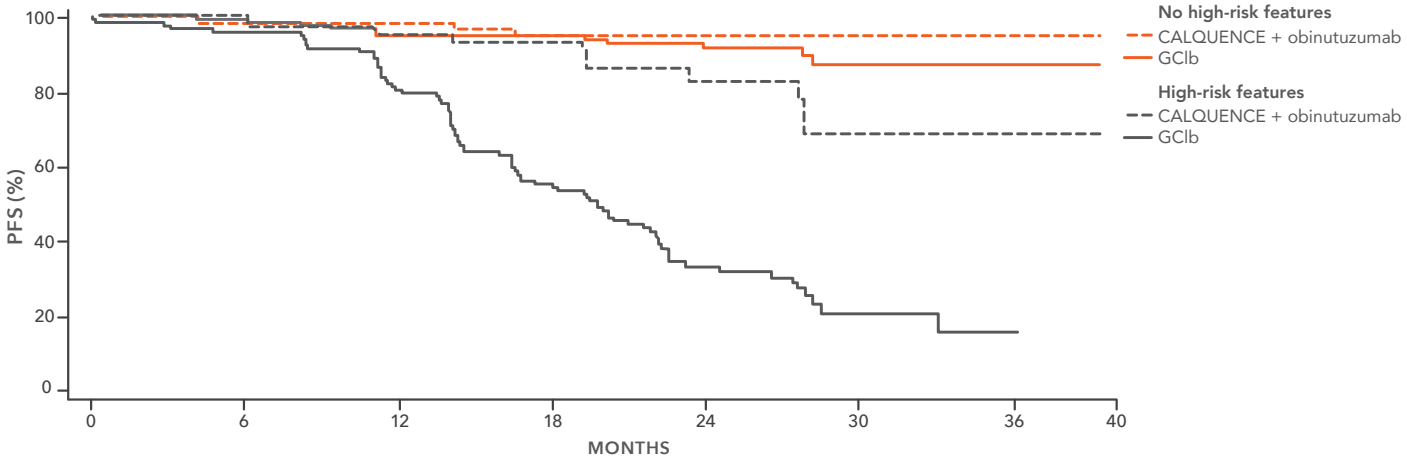
CALQUENCE + obinutuzumab:

- **90% relative risk reduction in disease progression or death** (HR=0.10‡ [95% CI: 0.06-0.17], *P*<0.0001§) vs GClb
  - Median PFS was not reached vs 22.6 months (95% CI: 20-28) with GClb

CALQUENCE monotherapy:

- **80% relative risk reduction in disease progression or death** (HR=0.20‡ [95% CI: 0.13-0.30], *P*<0.0001§) vs GClb
  - Median PFS was not reached (95% CI: 34-NE) vs 22.6 months (95% CI: 20-28) with GClb

CALQUENCE + OBINUTUZUMAB DEMONSTRATED CONSISTENT PFS FOR PATIENTS WITH OR WITHOUT A HIGH-RISK FEATURE†[2]



Exploratory analysis of prespecified subgroups. Study not powered to show statistical significance across subgroups. High-risk features include unmutated IGHV, 17p deletion, TP53 mutation, and 11q deletion.[2]

*Per 2008 International Workshop on CLL criteria.

†At median 28.3-month follow-up, the number of events in each arm was 14 (8%) for CALQUENCE + obinutuzumab, 26 (15%) for CALQUENCE monotherapy, and 93 (53%) for GClb.[3]

‡Based on a stratified Cox proportional-hazards model. Both hazard ratios are compared with the GClb arm.[3]

§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.[3]

CI=confidence interval; HR=hazard ratio; NE=not estimable.

SELECT SAFETY INFORMATION[3]

- The most common adverse reactions (≥30%) of any grade in patients with 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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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.

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

References: 1. Strati P, Jain N, O'Brien S. Chronic lymphocytic leukemia: diagnosis and treatment. *Mayo Clin Proc.* 2018;93(5):651-664. **2.** Data on File, REF-64711. AstraZeneca Pharmaceuticals LP. **3.** CALQUENCE [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2019. **4.** Elevate CLL TN: study of obinutuzumab + chlorambucil, acalabrutinib (ACP-196) + obinutuzumab, and acalabrutinib in subjects with previously untreated CLL. ClinicalTrials.gov identifier: NCT02475681. https://clinicaltrials. gov/ct2/show/NCT02475681. Updated October 14, 2019. Accessed November 15, 2019.

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