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BEQALZI BECOMES FIRST BCL-2 INHIBITOR APPROVED FOR MANTLE CELL LYMPHOMA

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ABSTRACT

A recently licensed targeted anticancer drug called Beqalzi (sonrotoclax) is used to treat refractory or relapsed mantle cell lymphoma (MCL), a rare kind of non-Hodgkin lymphoma. It is a member of the BCL-2 inhibitor class, which functions by preventing the BCL-2 protein, which is essential for cancer cells to survive. Beqalzi causes apoptosis, or programmed cell death, and slows the growth of tumors by blocking this protein. In individuals who had previously undergone various treatments, such as BTK inhibitors, the medication has demonstrated encouraging clinical results. To reduce the possibility of tumor lysis syndrome (TLS), a potentially dangerous side effect, beqalzi is taken orally with a progressive dose increase. Its clearance signifies advancements in contemporary cancer treatment centered on selective action against malignant cells and offers a significant new targeted therapy option for cases of lymphoma that are challenging to treat. After at least two previous systemic treatments, including a BTK inhibitor, people with relapsed or refractory mantle cell lymphoma (MCL) may be treated with Beqalzi (generic name: sonrotoclax), an oral next-generation BCL-2 inhibitor. It promotes the programmed death of malignant lymphoma cells by specifically inhibiting the anti-apoptotic BCL-2 protein. Based on the findings of the phase 1/2 BGB-11417-201 clinical trial, which included patients with extensively pretreated MCL, the U.S. FDA granted the medication rapid approval in May 2026. Beqalzi had a 52% overall response rate in the research, with 16% of patients showing full responses and a median response duration of 15.8 months. Food and Drug Administration of the United States +2 To lower the risk of tumor lysis syndrome (TLS), a significant treatment-related safety issue, beqalzi is taken orally once day with food on a four-week dose ramp-up regimen. Fatigue, pneumonia, diarrhea, edema, fever, and upper respiratory infections are typical side effects. For patients with few therapeutic alternatives following the failure of previous medications, Beqalzi, the first BCL-2 inhibitor specifically licensed for mantle cell lymphoma, offers a major advancement in targeted therapy.

KEYWORDS: Beqalzi, Sonrotoclax, Non-Hodgkin Lymphoma, BCL-2 Inhibitor, Programmed Cell Death (Apoptosis), Tumor Lysis Syndrome (TLS), and Targeted Therapy.

INTRODUCTION

Adults with mantle cell lymphoma (MCL) that has returned or has not responded to treatment are treated with Beqalzi (sonrotoclax), a prescription cancer medication. Adults with refractory or relapsed mantle cell lymphoma are treated with beqalzi following at least two prior lines of systemic therapy, including Bruton's tyrosine kinase (BTK) inhibitor therapy.

Beqalzi is a BCL-2 inhibitor; BCL-2 is a protein that can help cancer cells survive. Beqalzi works by blocking BCL-2, which may help cancer cells die. Beqalzi was granted FDA accelerated approval on May 13, 2026, for adults with relapsed or refractory mantle cell lymphoma after at least two lines of systemic therapy, including a BTK inhibitor. FDA approval was based on the medicine response rate and how long responses lasted. In the main clinical trial, 52% of patients responded to Beqalzi, and the median duration of response was 15.8 months. Continued approval may depend on results from confirmatory clinical trial(s).

After at least two lines of systemic therapy, including a Bruton's tyrosine kinase (BTK) inhibitor, adult patients with relapsed or refractory mantle cell lymphoma (MCL) may be treated with BEQALZI, a BCL-2 inhibitor. Based on response durability and response rate, this indication is approved under accelerated approval. Verification and a description of the clinical benefit in confirmatory trials may be necessary for this indication's continued approval.

Dosage

Recommended dosage for mantle cell lymphoma

There is a 4-week ramp-up in BEQALZI dosage. The goal of the ramp-up dose regimen is to gradually lower the risk of TLS and tumor load (debulk).

Dose Ramp-Up Schedule for Four Weeks

Give BEQALZI orally once a day in accordance with the table's ramp-up dosage regimen.

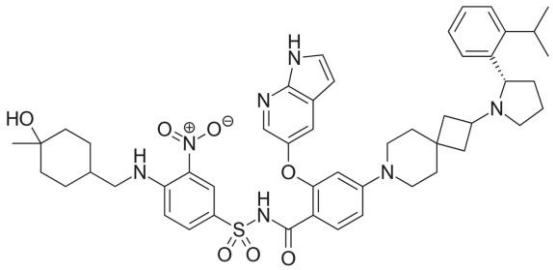
Table 1: Dosing Schedule for 4-Week Ramp-Up Phase

Week Number	Days	Daily Dose	Number of Tablets per Dose
Week 1	Days 1 to 3	1 mg	One 1 mg tablet
	Days 4 to 7	2 mg	Two 1 mg tablets
Week 2	Days 1 to 3	5 mg	One 5 mg tablet
	Days 4 to 7	10 mg	One 5 mg tablets
Week 3	Days 1 to 3	20 mg	Two 20 mg tablet
	Days 4 to 7	40 mg	Two 20 mg tablets
Week 4	Days 1 to 3	40 mg	One 80 mg tablet
	Days 4 to 7	160 mg	Two 80 mg tablets

Target dose week 5 and beyond

The recommended dosage of BEQALZI is 320 mg (four 80 mg tablets) given orally once day until the disease progresses or unacceptable toxicity occurs, following the completion of the 4-week ramp-up phase.

Structural Information:-(Beqalzi)



Sonrotoclax, marketed under the brand name Beqalzi, is a drug used to treat hematologic malignancies, namely small lymphocytic lymphoma (SLL) and chronic lymphocytic leukemia (CLL). It is a strong and specific BCL2 inhibitor that can overcome resistance brought on by BCL2 mutations, notably the G101V variation, which reduces the efficacy of venetoclax and other first-generation inhibitors.

Mechanism of action

More than 20 proteins that control the intrinsic apoptosis pathway and are essential to the equilibrium between cell survival and cell death are encoded by the B-cell lymphoma 2 (BCL2) gene family.

Both solid tumors and hematologic malignancies exhibit the highly controlled process of developing resistance to apoptosis.1,2 By reducing apoptosis, anti-apoptotic BCL2 has been demonstrated to increase the survival of malignant cells. The anti-apoptotic protein BCL2 is overexpressed as a result of BCL2 dysregulation, which modifies the ratio of pro-apoptotic BCL2 family members. Cell death signals in healthy cells cause BID and BIM to activate BAX and BAK. The pro-apoptotic proteins BAX and BAK oligomerize to cause

mitochondrial outer membrane permeabilization (MOMP), cytochrome c and second mitochondria-derived activator of caspase (SMAC) to be released from the mitochondria, and caspases to be activated, ultimately leading to cell death.

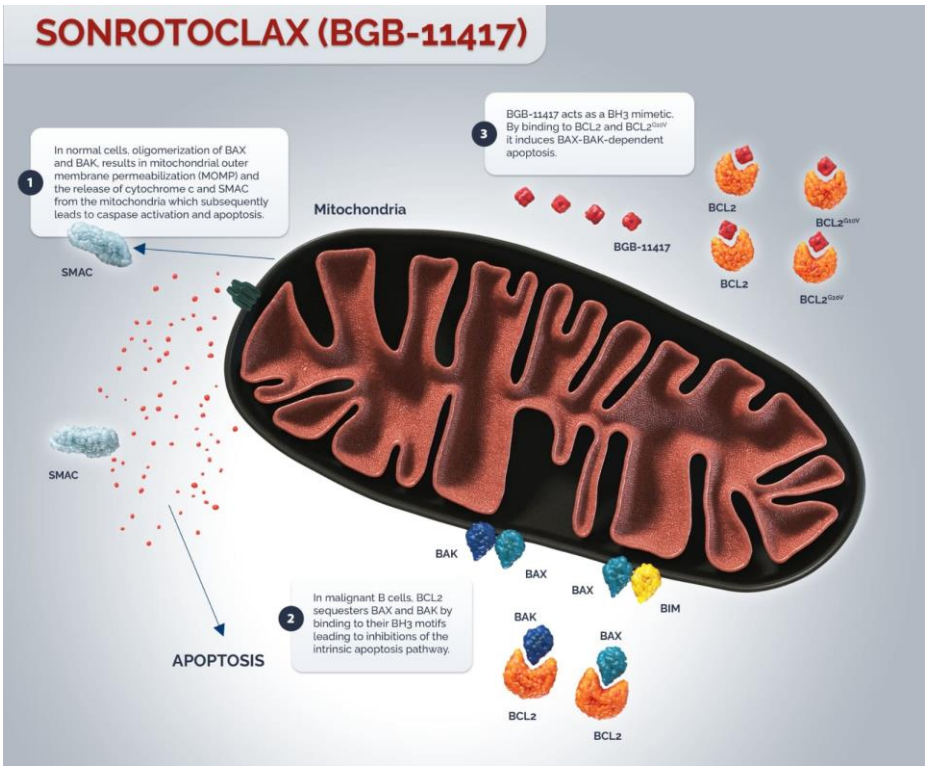


FIG: mechanism of action on Beqalzi (Sonrotoclax)

By attaching to the BH3 motifs of pro-apoptotic proteins including BAX and BAK, anti-apoptotic BCL2 inhibits the intrinsic apoptosis pathway.

Sonrotoclax functions as a mimic of BH3. It causes BAX-BAK-dependent apoptosis by attaching to BCL2. A well-established target for B-cell cancers is BCL2. Recurrent G10V mutations in BCL2 have been shown to mediate resistance to BCL2 inhibitors with long-term therapy. Sonrotoclax significantly suppressed both wildtype and G10V-mutant BCL2.3 in preclinical investigations.

Pharmacodynamic

Pharmacodynamic Effects Tumor Reduction: Patients have strong and quick tumor debulking when BCL-2 is specifically inhibited. Lymphocyte Depletion: Beqalzi usually causes a quantitative decrease in peripheral blood lymphocytes, including B cells and T cells, since BCL-2 is necessary for the survival of both malignant and normal lymphocytes. Biomarkers and Clinical Pharmacodynamics Dose Ramping: Because of the drug's strong potency and quick initiation of tumor-killing activity, beginning treatment may cause the tumor cells to break down quickly, raising the risk of tumor lysis syndrome (TLS). A rigorous 4-week dose ramp-up phase is used to progressively remove the tumor load in order to lessen this Secondary Cytopenias: Bone marrow homeostasis is naturally impacted by the mechanism, which may result in on-target hematologic toxicities including severe neutropenia or thrombocytopenia. Impact of Pharmacokinetics on Dynamics Sonrotoclax, in contrast to prior generation BCL-2 inhibitors, has a short systemic half-life and minimal or no drug accumulation, giving doctors more control over the management of unfavorable on-target side effects such TLS or neutropenia.

Pharmacokinetic

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1.9 months is the median time to response (TTR).

Median duration of response (DOR): 15.8 months (95% CI, 7.4 months-NE) at a median response follow-up of 11.9 months (has yet to reach full maturity)

Safety: Sonrotoclax monotherapy was generally well tolerated.

The ongoing confirmatory CELESTIAL-RRMCL trial (NCT06742996) must establish clinical benefit in order for this indication to remain approved. Sonrotoclax received Fast Track Designation, Orphan Drug Designation, and Breakthrough Therapy Designation (BTD) from the U.S. FDA for this indication.

Absorption
4 hours is the peak plasma time (Tmax).
The impact of food
Low-fat meal (~333–500 calories, 25% fat calories): AUC increased 1.5 times and Cmax increased 1.5 times.
High-fat meal (1,000 calories, 50% fat): AUC increased 2.5 times and Cmax increased 2.4 times.

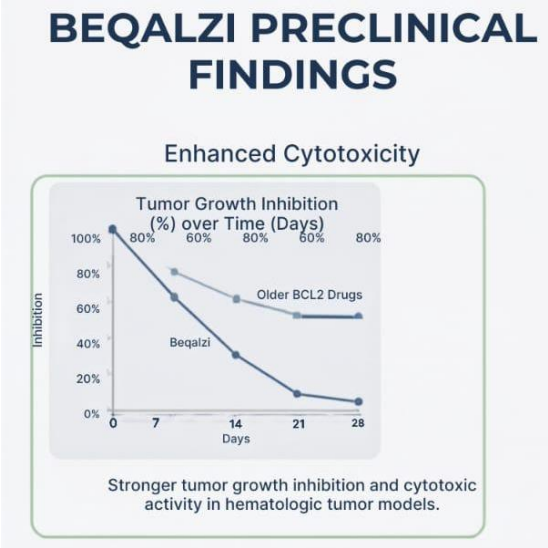
Distribution
99% protein binding
Vd: 482 L
Blood to plasma ratio: 0.6-0.7%
The metabolism mostly metabolized by CYP3A, with CYP2C8 playing a minor role.

Removal
Half-life: four to six hours

94 L/hr of clearance

Urine 28% (<0.04% unchanged); feces 86% (<19.5% unchanged)

Pre-clinical Trial



Preclinical Results Enhanced Cytotoxicity: Compared to earlier BCL2 medications, Beqalzi demonstrated greater tumor growth suppression and cytotoxic effect in laboratory tests across hematologic tumor types. Enhanced Selectivity: It showed a distinct pharmacokinetic and pharmacodynamic profile with no drug buildup and strong specificity for BCL2. Pharmacological Advantage: Preclinical models demonstrated a reduced half-life, which enhances overall medication tolerability and streamlines the treatment of tumor lysis syndrome.

Clinical Trial

Key Clinical Trials Overview

Trial ID / Name	Phase	Indication	Design / Key Features	Status / Notes
BGB-11417-201 (NCT05471843)	1/2	R/R MCL (post BTKi + anti-CD20)	Single-arm, monotherapy, RP2D 320 mg QD after ramp-up	Pivotal for FDA approval; primary analysis presented at ASH 2025
CELESTIAL-RRMCL (NCT06742996)	3	R/R MCL	Randomized: Sonrotoclax + zanubrutinib vs placebo + zanubrutinib	Confirmatory trial (ongoing)
BGB-11417-101 (NCT04277637)	1/1b	CLL/SLL, WM, other B-cell malignancies	Monotherapy or + zanubrutinib / obinutuzumab	Ongoing; promising data in CLL/WM
Other CELESTIAL trials	3	CLL, WM, MM, etc.	Combinations (often + BTKi)	Ongoing / planned

Efficacy Data from Pivotal Trial (BGB-11417-201, n=103 at 320 mg QD)

Endpoint	Result	95% CI / Notes
Overall Response Rate (ORR)	52% (52.4%)	42–62%
Complete Response (CR) Rate	16% (15.5%)	9.1–24%
Median Time to Response	1.9 months	Range: 1.6–6.2 months
Median Duration of Response (DOR)	15.8 months	7.4 – NE (maturing; median follow-up ~11.9–14.2 months)
Activity	Seen in high-risk subgroups (e.g., TP53 mutated)	-

FDA-approved pivotal trial: Phase 1/2 BGB-11417-201 (NCT05471843)

Design: Adults with R/R MCL who had previously received anti-CD20 treatment and a BTK inhibitor were included in this single-arm, open-label, multicenter study. included dose expansion and escalation; 320 mg once daily following ramp-up was the recommended phase 2 dose (RP2D).

Patients: Of the 125 participants, 103 patients at 320 mg provided the majority of the efficacy data.

Key Efficacy Findings (Lugano criteria, independent review)
52% (95% CI: 42-62%) was the overall response rate (ORR).
16% (95% CI: ~9-24%) of responses were complete (CR).

1.9 months was the median response time.

At a median follow-up of approximately 11.9–14.2 months (maturing), the median duration of response (DOR) was 15.8 months.

High-risk subgroups exhibit activity (e.g., TP53 mutant).

Safety: Generally accepted. Fatigue, infections (like pneumonia), and hematologic toxicities (like neutropenia) were common problems. Low rates of treatment discontinuation due to adverse events; ~37% of serious adverse events. Other than class effects, there are no significant new warning signs.
At ASH 2025, data were given.

Phase 3 CELESTIAL-RRMCL Confirmatory Trial (NCT06742996)
Sonrotoclax + zanubrutinib (Brukinsa) vs. placebo + zanubrutinib in R/R MCL was compared in a randomized experiment.

ongoing; the main completion is anticipated around 2028. For complete approval, this will verify clinical benefit.

Additional Significant Trials (Wider Development)

Phase 1/2 study BGB-11417-101 (NCT04277637): Sonrotoclax monotherapy or + zanubrutinib for CLL/SLL and other hematologic malignancies. demonstrated strong tolerance, profound responses (including high uMRD rates), and high ORR in combos, including in R/R and treatment-naïve conditions.

In CLL, Waldenstrom's macroglobulinemia, multiple myeloma, and other conditions, more Phase 3 trials (CELESTIAL program) are planned or in progress, frequently in conjunction with BTK inhibitors such as zanubrutinib.

Toxicity and Adverse effect
Tumor Lysis Syndrome (TLS): Rapid tumor cell disintegration can result in TLS, which can be fatal. This could happen as soon as four hours after the initial dose, during dose increases, or when the medication is restarted following a hiatus. In the pivotal trial, about 7% of patients experienced laboratory or clinical TLS. Impaired renal function and a high tumor burden (bulky disease, lymphocytosis, etc.) are risk factors. Risk evaluation, prophylaxis, electrolyte correction, regular lab monitoring (particularly in the early stages of treatment), and dose interruption when necessary are all part of management.

Serious Infections: May result in serious or lethal infections. 14% of patients had serious infections; 17% had Grade 3–4 infections (fatal in 2.6%). Pneumonia was the most frequent serious infection (10%). Keep an eye out for symptoms, think about prophylaxis (antibiotics, immunoglobulins according to recommendations), and modify dosage, stop, or stop as necessary.

Serious or severe cytopenias may result from neutropenia. 18% had grade 3–4 neutropenia (grade 4: 6%); 1.7% had febrile neutropenia. Regularly check total blood counts and adjust dosage according to severity.

Fetal damage may result from embryo-fetal toxicity (based on animal research and mechanism). During therapy and for a week following the final dose, use an

effective form of contraception (males with female partners and females with reproductive potential). Discourage nursing.

Adverse reaction

>10%

Lymphocyte decreased (66%)
Hemoglobin decreased (52%)
Neutrophils decreased (50%)
Calcium decreased (42%)
Uric acid increased (42%)
Platelets decreased (36%)
Glucose increased (35%)
Creatinine increased (32%)
Potassium decreased (30%)
Sodium decreased (29%)
Aspartate aminotransferase increased (27%)
Alkaline phosphatase increased (25%)
Alanine aminotransferase increased (22%)
Calcium increased (21%)
Pneumonia (16%)
Fatigue (16%)
Edema (14%)
Diarrhea (14%)
Upper respiratory tract infection (12%)

1-10%

Pyrexia (10%)
Constipation (10%)
Rash (10%)
Musculoskeletal pain (10%)
Contraindication:

Because BEQALZI may raise the risk of tumor lysis syndrome (TLS), it should not be used with powerful CYP3A inhibitors at beginning or during the ramp-up period.

Warning and precautions

BEQALZ Tumor Lysis Syndrome (TLS)I can cause rapid tumor reduction and changes in blood chemistries consistent with TLS, which may be serious or life-threatening and require prompt management. TLS can happen as soon as four hours after the initial dose, when the dose is increased, or when the treatment is restarted after a break. 7% of patients who adhered to the suggested dose ramp-up experienced laboratory or clinical TLS. Evaluate each patient's risk for TLS and start prophylactic measures, such as antihyperuricemics and proper hydration. Consider hospitalization with intravenous hydration and continuous monitoring for individuals who are at high risk of TLS. Keep a watchful eye on blood chemistries and act quickly to address any irregularities. When restarting BEQALZI for TLS, according to the prescribing information's dose adjustment recommendations.

CONCLUSION

Beqalzi is a significant development in the management of mantle cell lymphoma, a condition that is challenging to cure.

Significant tumor response rates were seen in clinical trials, and some patients experienced total remission.

The medication provides a targeted oral therapeutic option that might be more practical than other conventional cancer therapies.

However, regular medical supervision is necessary since it might induce dangerous adverse effects such tumor lysis syndrome, infections, and low blood cell counts.

Further research is still required to establish long-term benefits and safety because FDA approval was expedited.

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