Belumosudil (Rezurock™) New Drug Update

August 2021

Nonproprietary Name	belumosudil
Brand Name	Rezurock
Manufacturer	Kadmon
Form	Oral tablet
Strength	200 mg
FDA Approval	July 16, 2021
Market Availability	Available
FDA Approval Classification	Breakthrough Therapy; Orphan Drug; Priority Review; Real-Time Oncology Review
FDB Classification- Specific Therapeutic Class (HIC3)	Immunosuppressives (Z2E)

INDICATION[1]

Belumosudil (Rezurock), a kinase inhibitor that targets Rho-associated coiled-coil kinase (ROCK2), is indicated for the treatment of patients ≥ 12 years of age with chronic graft-versus-host disease (cGVHD) following failure of ≥ 2 prior lines of systemic therapy.

PHARMACOKINETICS

The median time to maximum concentration following belumosudil administration was 1.26 to 2.53 hours. It has a mean bioavailability of 64%, and both the maximum concentration (which occurred 0.5 hours later) and overall exposure were increased by a high-fat and high-calorie meal; belumosudil should be administered with food. The mean volume of distribution of belumosudil is 184 L, and it is 99.9% bound to albumin. Belumosudil is metabolized by cytochrome p450 (CYP) 3A4 primarily, as well as CYP2C8, CYP2D6, and UGT1A9 to a lesser extent. It has a mean elimination half-life of 19 hours and a clearance of 9.83 L/hour. Belumosudil is excreted primarily in the feces (< 5% urine).

CONTRAINDICATIONS/WARNINGS

Belumosudil has no contraindications.

The only warning for belumosudil is embryo-fetal toxicity as it may cause fetal harm based on its mechanism of action and findings from animal studies. Females of reproductive potential and males with female partners of reproductive potential should use effective contraception during treatment and for ≥ 1 week following the last dose.

DRUG INTERACTIONS

Coadministration of belumosudil with a strong CYP3A inducer or a proton pump inhibitor (PPI) will decrease belumosudil exposure (potentially reducing effectiveness); a dose increase of belumosudil is required when coadministered with a strong CYP3A inducer or a PPI.

COMMON ADVERSE EFFECTS

The most common (incidence ≥ 20%, all grades) adverse reactions reported in clinical trials with belumosudil were infections (53%), asthenia (46%), nausea (42%), diarrhea (35%), dyspnea (33%), cough (30%), edema (27%), hemorrhage (23%), abdominal pain (22%), musculoskeletal pain (22%), headache (21%), and hypertension (21%).

The most common (incidence ≥ 20%, all grades) laboratory abnormalities reported in clinical trials with belumosudil were phosphate decreased, gamma glutamyl transferase increased, and lymphocytes decreased.

SPECIAL POPULATIONS

Pregnancy

Belumosudil can cause fetal harm when administered to a pregnant woman.

Pediatrics

The safety and effectiveness of belumosudil have been established in patients ≥ 12 years old.

Geriatrics

In clinical studies, there were no clinically meaningful differences in the safety and effectiveness of belumosudil in adults ≥ 65 years old compared to younger patients.

Hepatic Impairment

The pharmacokinetics of belumosudil in patients with severe hepatic impairment are not known.

Renal Impairment

No clinically significant differences in pharmacokinetics have been observed in patients with mild to moderate renal impairment (estimated glomerular filtration rate [eGFR] ≥ 30 mL/min/1.72m^2); its pharmacokinetics in patients with severe renal impairment are not known.

DOSAGES

The recommended dose of belumosudil is 200 mg orally once daily with a meal at approximately the same time each day until progression of cGVHD.

When coadministered with either a PPI or strong CYP3A inducer, the dose should be increased to 200 mg twice daily.

Total bilirubin, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) should be monitored at least monthly.

Dose adjustments (either temporary treatment holds or permanent discontinuation) for adverse effects are detailed in the product labeling.

CLINICAL TRIALS[2,3,4]

A literature search was performed using "belumosudil" and "chronic graft-versus-host disease."

ROCKstar (KD025-213; NCT03640481): A phase 2, United States (US)-based, multicenter, randomized, open-label trial assessed the efficacy and safety of belumosudil in patients with cGVHD who have previously been treated with ≥ 2 lines of systemic therapy and require additional treatment. Patients with platelets < 50×10^9/L, an absolute neutrophil count (ANC) < 1.5×10^9/L, aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 3 × the upper limit of normal (ULN), a total bilirubin > 1.5 × ULN, a corrected QT interval using Fridericia's formula (QTcF) > 480 ms, an eGFR < 30 mL/min/1.73 m^2, or forced expiratory volume in 1 second (FEV_1) ≤ 39% were excluded. Eligible patients were randomized 1:1 to belumosudil 200 mg orally once daily or belumosudil 200 mg twice daily. Concomitant treatment with GVHD prophylaxis and standard care systemic cGVHD therapy with stable doses ≥ 2 weeks was permitted. Efficacy was evaluated using the overall response rate (ORR) through day 1 of cycle 7, including both complete response (CR) and partial response (PR) according to the 2014 National Institutes of Health (NIH) Response Criteria. At this time period, 66 patients were assigned once daily treatment (data on 65 patients available). At baseline, the median age was 53 years (range, 21 to 77 years), and 26% were ≥ 65 years old, 65% were male, 83% were White, and 9% were Black. The median number of prior lines of therapy was 3 (range, 2 to 6; 32% prior ibrutinib; 31% prior ruxolitinib), the median time from diagnosis was 25.3 months (range, 1.9 to 162.4 months), and 71% were considered to have severe cGVHD. The median global severity rating was 7 (range, 2 to 9), the median Lee Symptom Scale Score was 27 (range, 7 to 56), and the median corticosteroid dose at baseline was 0.19 prednisone equivalents/kg (range, 0.03 to 0.95). The median follow up was 14 months. Upon evaluation, the ORR was 75% (95% confidence interval [CI], 63 to 85; 6% CR; 69% PR). The median time to first response was 1.8 months (95% CI, 1 to 1.9), and the median duration of response (DOR) was 1.9 months (95% CI, 1.2 to 2.9). Of the patients who achieved response, 62% (95% CI, 46 to 74) had no death or new systemic therapy initiated for at least 12 months following response. An exploratory analysis also found at least a 7-point decrease in the Lee Symptom Scale summary score in 52% (95% CI, 40 to 65) of patients. Across both treatment groups, 12% discontinued belumosudil due to possible drug-related adverse effects.

OTHER DRUGS USED FOR CONDITION[5,6]

Several agents may be used for the treatment of cGVHD. Pharmacologic treatment options include select corticosteroids (e.g., prednisone), and these are generally considered the primary treatment for cGVHD. Other agents that may be used off-label for GVHD include calcineurin inhibitors (e.g., tacrolimus, cyclosporine), sirolimus, thalidomide, mycophenolate mofetil, azathioprine, and rituximab. Ibrutinib (Imbruvica®), an oral Bruton tyrosine kinase inhibitor, is approved for the treatment of cGVHD following ≥ 1 line of systemic therapy in adults. While not approved for cGVHD, ruxolitinib (Jakafi®), a Janus kinase inhibitor, is approved for the treatment of steroid-refractory acute GVHD.

PLACE IN THERAPY[7,8,9,10]

Graft-versus-host disease (GVHD) is an immune-mediated condition in patients who have received an allogeneic transplant in which the donated stem cells (graft) recognize the patient's body (host) as foreign and mount an immune response against the patient. Acute GVHD (aGVHD) generally involves a

syndrome of dermatitis, hepatitis, and enteritis and typically develops within 100 days following transplant. Chronic GVHD generally occurs after 100 days post-transplant, although there can be overlap with aGVHD and cGVHD. It can occur in patients with or without aGVHD, and consists of more diverse symptoms, including ocular (e.g., photophobia, irritation, dry eye), gastrointestinal (e.g., dry mouth, dysphagia, weight loss, ileus, diarrhea), pulmonary (e.g., obstructive lung disease, wheezing, dyspnea, chronic cough), neuromuscular (e.g., neuropathic pain, myalgia, optic neuritis), and joint (e.g., arthralgia, arthritis) symptoms. Patients may also have skin reactions, including maculopapular exanthema, lichenoid skin lesions or sclerodermatous thickening, and pruritus associated with jaundice. The occurrence of cGVHD varies depending on the transplant match, but the rate may be as high as 80%. Overall survival of cGVHD is 42%, but patients with a progressive onset of cGVHD have survival rates as low as 10%. Early recognition and treatment of cGVHD is key to limit disability and improve survival. The National Institutes of Health (NIH) has developed consensus criteria for cGVHD diagnostic and distinctive features as well as a scoring system to qualify disease severity.

Treatment of cGVHD depends on the organ systems affected and generally consists of corticosteroids (0.5 to 1 mg/kg prednisone equivalent; generally preferred initial therapy), although about 40% to 50% of patients develop steroid-refractory disease. Thus, other systemic pharmacologic agents and supportive care may also be initiated. The National Comprehensive Cancer Network (NCCN) updated their hematopoietic cell transplantation guidelines, which include recommendations for cGVHD, in late July 2021. For steroid refractory cGVHD, NCCN recommends abatacept, alemtuzumab, belumosudil, calcineurin inhibitors, etanercept, extracorporeal photopheresis (ECP), hydroxychloroquine, ibrutinib, imatinib, interleukin-2, low-dose methotrexate, mTOR inhibitors, mycophenolate mofetil, pentostatin, rituximab, and ruxolitinib; they state there is insufficient evidence to recommend a specific systemic agent over another, although data may be more supportive of one agent over another depending on the organ sites affected. The choice of treatment should consider prescriber and institutional preference, treatment toxicity, patient tolerability, prior treatment, drug interactions, and practical considerations (e.g., convenience, accessibility). Notably, NCCN encourages participation in clinical trials. Regarding belumosudil's ROCKstar study results, NCCN states that this agent appears promising as it was well tolerated and had clinically meaningful responses.

Belumosudil (Rezurock), aROCK2 inhibitor, provides a treatment option for patients ≥ 12 years of age with cGVHD following failure of ≥ 2 prior lines of systemic therapy and has demonstrated benefit and tolerability in a key phase 2 clinical trial. In steroid-refractory patients, it may compete with ibrutinib (Imbruvica) and other unlabeled medications that are used for the treatment of cGVHD.

SUGGESTED UTILIZATION MANAGEMENT

Anticipated Therapeutic Class Review (TCR) Placement	To be determined (TBD)
Clinical Edit	**Initial Approval Criteria** ▪ Patient is ≥ 12 years old; **AND** ▪ Patient is post-allogeneic stem cell transplant (generally 3 or more months); **AND** ▪ Patient has diagnosis of chronic graft-versus-host disease (cGVHD); **AND** ▪ Patient does not have histologic relapse of underlying cancer or post-transplant lymphoproliferative disease; **AND** ▪ Patient has failed ≥ 2 previous lines of systemic therapy for the treatment of cGVHD (e.g., corticosteroids, immunosuppressants); **AND** ▪ Belumosudil will be used in combination with stable doses of systemic therapies for GVHD which must include, but are not limited to, corticosteroids (examples of systemic therapies include calcineurin inhibitors [cyclosporine; tacrolimus], sirolimus, mycophenolate mofetil, methotrexate, rituximab); **AND** ▪ Patient will avoid concomitant therapy with all of the following: – Coadministration with proton-pump inhibitors (PPIs), or if therapy is unavoidable, the patient will be monitored closely for adverse reaction and dose modifications will be implemented; **AND** – Coadministration with strong CYP3A inducers (e.g., rifampin, carbamazepine, St. John's wort, etc.) or if therapy is unavoidable, the patient will be monitored closely for adverse reaction and/or dose modifications will be implemented; **AND** ▪ Belumosudil will not be used in combination with ibrutinib (subsequent therapy is allowed). **Renewal Criteria** ▪ Patient continues to meet the above criteria; **AND** ▪ Patient has not had unacceptable toxicity from the drug (e.g., grade 4 hepatotoxicity); **AND** ▪ Patient has a response to therapy with an improvement in ≥ 1 of the following: – Clinician assessments (e.g., NIH Skin Score, Upper GI Response Score, NIH Lung Symptom Score); **AND/OR** – Patient-reported symptoms (e.g., Lee Symptom Scale).
Quantity Limit	1 tablet/day (30 tablets/30 days) If belumosudil *must* be coadministered with either a proton pump inhibitor (PPI) or strong CYP3A inducer: 2 tablets/day (60 tablets/30 days)
Duration of Approval	Initial: 6 months; Renewal: 6 months
Drug to Disease Hard Edit	None

REFERENCES

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