Clinical summary of DREAMM-2: a phase 2 study of BLENREP in relapsed or refractory multiple myeloma[1]

Adapted from: Lonial S, Lee HC, Badros A, et al. *Lancet Oncol.* 2020;21(2):207-221. doi:10.1016/S1470-2045(19)30788-0

Study design: Driving Excellence in Approaches to Multiple Myeloma (DREAMM-2): an open-label, phase 2 study of BLENREP with 2 parallel dosing cohorts of patients with relapsed/refractory multiple myeloma who had previously received 3 or more anti-myeloma therapies, including an anti-CD38 monoclonal antibody, and who were refractory to an immunomodulatory agent and a proteasome inhibitor. Patients were included if they had undergone autologous stem cell transplant or were considered transplant ineligible, and if they had measurable disease by International Myeloma Working Group (IMWG) criteria. Patients with renal impairment and history of cytopenia (without active conditions) were eligible. The majority of patients were White (74%) and had received prior autologous stem cell transplantation (87%). Patients were randomized to receive either BLENREP 2.5 mg/kg or 3.4 mg/kg by intravenous infusion every 3 weeks until disease progression or unacceptable toxicity. The efficacy outcome analysis is based upon the results obtained with the recommended dosage of 2.5 mg/kg (N=97). Primary endpoint was overall response rate as evaluated by an Independent Review Committee based on the IMWG Uniform Response Criteria for Multiple Myeloma; secondary endpoints included duration of response and time to first response.[1,2]

DREAMM-2 evaluated BLENREP in heavily pretreated patients[1-3]

Patient characteristics	N=97
Age (yr), median (range)	65.0 (39-85)
Gender, n (%)	Male, 51 (53%) Female, 46 (47%)
ISS disease stage at screening, n (%) Stage I Stage II Stage III Unknown	 21 (22%) 33 (34%) 42 (43%) 1 (1%)
ECOG performance status of 2 (%)	16%
Median previous lines of therapy	7[a]
Patients with high-risk cytogenetics,[b] n (%)	26 (27%)

ECOG=Eastern Cooperative Oncology Group; ISS=International Staging System.
[a]Range: 3 to 21.
[b]Any of the following cytogenetics: t[4;14], t[14;16], and 17p13del.

INDICATION

BLENREP is indicated for the treatment of adults with relapsed or refractory multiple myeloma who have received at least 4 prior therapies, including an anti-CD38 monoclonal antibody, a proteasome inhibitor, and an immunomodulatory agent.

This indication is approved under accelerated approval based on response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

IMPORTANT SAFETY INFORMATION

WARNING: OCULAR TOXICITY

BLENREP caused changes in the corneal epithelium resulting in changes in vision, including severe vision loss and corneal ulcer, and symptoms such as blurred vision and dry eyes.

Conduct ophthalmic exams at baseline, prior to each dose, and promptly for worsening symptoms. Withhold BLENREP until improvement and resume or permanently discontinue based on severity.

Because of the risk of ocular toxicity, BLENREP is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the BLENREP REMS.

WARNINGS AND PRECAUTIONS

Ocular Toxicity: Ocular adverse reactions occurred in 77% of the 218 patients in the pooled safety population. Ocular adverse reactions included keratopathy (76%), changes in visual acuity (55%), blurred vision (27%) and dry eye (19%). Among patients with keratopathy (n = 165), 49% had ocular symptoms, 65% had clinically relevant visual acuity changes (decline of 2 or more lines on Snellen Visual Acuity in any eye), and 34% had both ocular symptoms and visual acuity changes.

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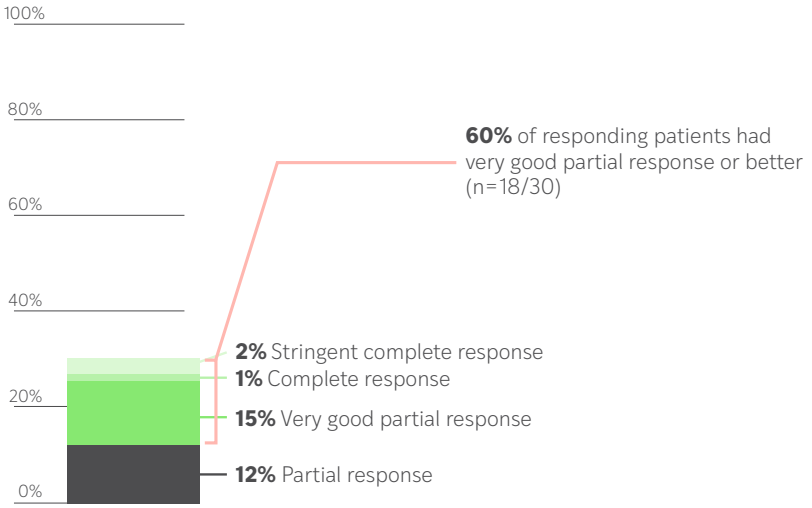
31% overall response rate in a heavily pretreated patient population[2]

Clinically meaningful and durable responses observed in a patient population with a median 7 prior therapies[2]

Overall Response Rate: 31% (N = 30/97; 97.5% CI: 21%, 43%)



at 6 months of follow-up[1]

- Median time to first response was 1.4 months (95% CI: 1.0, 1.6).[2]
- 73% of responders had a duration of response ≥6 months at the time of data cutoff.[2]

IMPORTANT SAFETY INFORMATION *(CONT'D)*

WARNINGS AND PRECAUTIONS *(CONT'D)*

Keratopathy: Keratopathy was reported as Grade 1 in 7% of patients, Grade 2 in 22%, Grade 3 in 45%, and Grade 4 in 0.5% per the KVA scale. Cases of corneal ulcer (ulcerative and infective keratitis) have been reported. Most keratopathy events developed within the first 2 treatment cycles (cumulative incidence of 65% by Cycle 2). Of the patients with Grade 2 to 4 keratopathy (n = 149), 39% recovered to Grade 1 or lower after median follow-up of 6.2 months. Of the 61% who had ongoing keratopathy, 28% were still on treatment, 9% were in follow-up, and in 24% the follow-up ended due to death, study withdrawal, or lost to follow-up. For patients in whom events resolved, the median time to resolution was 2 months (range: 11 days to 8.3 months).

Visual Acuity Changes: A clinically significant decrease in visual acuity of worse than 20/40 in the better-seeing eye was observed in 19% of the 218 patients and of 20/200 or worse in the better-seeing eye in 1.4%. Of the patients with decreased visual acuity of worse than 20/40, 88% resolved and the median time to resolution was 22 days (range: 7 days to 4.2 months). Of the patients with decreased visual acuity of 20/200 or worse, all resolved and the median duration was 22 days (range: 15 to 22 days).

Monitoring and Patient Instruction: Conduct ophthalmic examinations (visual acuity and slit lamp) at baseline, prior to each dose, and promptly for worsening symptoms. Perform baseline examinations within 3 weeks prior to the first dose. Perform each follow-up examination at least 1 week after the previous dose and within 2 weeks prior to the next dose. Withhold BLENREP until improvement and resume at same or reduced dose, or consider permanently discontinuing based on severity. Advise patients to use preservative-free lubricant eye drops at least 4 times a day starting with the first infusion and continuing until end of treatment. Avoid use of contact lenses unless directed by an ophthalmologist. Changes in visual acuity may be associated with difficulty for driving and reading. Advise patients to use caution when driving or operating machinery. BLENREP is only available through a restricted program under a REMS.

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Permanent discontinuation due to an adverse reaction occurred in 8% of patients who received BLENREP[2]

The most frequent adverse reaction resulting in permanent discontinuation was keratopathy (2.1%)[2]

- The most common adverse reactions (≥20%) were keratopathy, decreased visual acuity, nausea, blurred vision, pyrexia, infusion-related reactions, and fatigue. The most common Grade 3 or 4 (≥5%) laboratory abnormalities were platelets decreased, lymphocytes decreased, hemoglobin decreased, neutrophils decreased, creatinine increased, and gamma-glutamyl transferase increased.[2]
- Serious adverse reactions occurred in 40% of patients who received BLENREP. Serious adverse reactions in >3% of patients included pneumonia (7%), pyrexia (6%), renal impairment (4.2%), sepsis (4.2%), hypercalcemia (4.2%), and infusion-related reactions (3.2%). Fatal adverse reactions occurred in 3.2% of patients, including sepsis (1%), cardiac arrest (1%), and lung infection (1%).[2]
- No permanent loss of vision was reported in the DREAMM-2 study.[1]

Adverse events were managed with supportive care and dose modifications

- Dosage interruptions due to an adverse reaction occurred in 54% of patients who received BLENREP. Adverse reactions which required a dosage interruption in >3% of patients included keratopathy (47%), blurred vision (5%), dry eye (3.2%), and pneumonia (3.2%).[2]
- Dose reductions due to an adverse reaction occurred in 29% of patients. Adverse reactions which required a dose reduction in >3% of patients included keratopathy (23%) and thrombocytopenia (5%).[2]

IMPORTANT SAFETY INFORMATION *(CONT'D)*

WARNINGS AND PRECAUTIONS *(CONT'D)*

Thrombocytopenia: Thrombocytopenia occurred in 69% of 218 patients in the pooled safety population, including Grade 2 in 13%, Grade 3 in 10%, and Grade 4 in 17%. The median time to onset of the first thrombocytopenic event was 26.5 days. Thrombocytopenia resulted in dose reduction, dose interruption, or discontinuation in 9%, 2.8%, and 0.5% of patients, respectively. Grade 3 to 4 bleeding events occurred in 6% of patients, including Grade 4 in 1 patient. Fatal adverse reactions included cerebral hemorrhage in 2 patients. Perform complete blood cell counts at baseline and during treatment as clinically indicated. Consider withholding and/or reducing the dose based on severity.

Infusion-Related Reactions: Infusion-related reactions occurred in 18% of 218 patients in the pooled safety population, including Grade 3 in 1.8%. Monitor patients for infusion-related reactions. For Grade 2 or 3 reactions, interrupt the infusion and provide supportive treatment. Once symptoms resolve, resume at a lower infusion rate. Administer premedication for all subsequent infusions. Discontinue BLENREP for life-threatening infusion-related reactions and provide appropriate emergency care.

Embryo-Fetal Toxicity: Based on its mechanism of action, BLENREP can cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with BLENREP and for 4 months after the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with BLENREP and for 6 months after the last dose. Pregnancy testing is recommended for females of reproductive potential prior to initiating BLENREP.

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BLENREP safety profile

Adverse reactions (any grade) reported in ≥10% of patients (N=95) who received BLENREP in DREAMM-2[2]

Adverse Reactions	BLENREP N=95	
	All Grades (%)	Grades 3-4 (%)
Eye disorders		
Keratopathy[a]	71	44
Decreased visual acuity[b]	53	28
Blurred vision[c]	22	4
Dry eyes[d]	14	1
Gastrointestinal disorders		
Nausea	24	0
Constipation	13	0
Diarrhea	13	1
General disorders and administration site conditions		
Pyrexia	22	3
Fatigue[e]	20	2
Procedural complications		
Infusion-related reactions[f]	21	3
Musculoskeletal and connective tissue disorders		
Arthralgia	12	0
Back pain	11	2
Metabolic and nutritional disorders		
Decreased appetite	12	0
Infections		
Upper respiratory tract infection[g]	11	0

- The most common Grade 3 or 4 laboratory abnormalities (≥5%) were platelets decreased, lymphocytes decreased, hemoglobin decreased, neutrophils decreased, creatinine increased, and gamma-glutamyl transferase increased.[2]

[a]Keratopathy was based on slit lamp eye examination, characterized as corneal epithelium changes with or without symptoms.
[b]Visual acuity changes were determined upon eye examination.
[c]Blurred vision included diplopia, vision blurred, visual acuity reduced, and visual impairment.
[d]Dry eyes included dry eye, ocular discomfort, and eye pruritus.
[e]Fatigue included fatigue and asthenia.
[f]Infusion-related reactions included infusion-related reaction, pyrexia, chills, diarrhea, nausea, asthenia, hypertension, lethargy, tachycardia.
[g]Upper respiratory tract infection included upper respiratory tract infection, nasopharyngitis, rhinovirus infections, and sinusitis.

IMPORTANT SAFETY INFORMATION *(CONT'D)*

ADVERSE REACTIONS

The pooled safety population described in *Warnings and Precautions* reflects exposure to BLENREP at a dosage of 2.5 mg/kg or 3.4 mg/kg (1.4 times the recommended dose) administered intravenously once every 3 weeks in 218 patients in DREAMM-2. Of these patients, 194 received a liquid formulation (not the approved dosage form) rather than the lyophilized powder.

Patients received BLENREP at the recommended dosage of 2.5 mg/kg administered intravenously once every 3 weeks (n = 95). Permanent discontinuation due to an adverse reaction occurred in 8% of patients who received BLENREP; keratopathy (2.1%) was the most frequent adverse reaction resulting in permanent discontinuation. Dosage interruptions due to an adverse reaction occurred in 54% of patients who received BLENREP. Adverse reactions which required a dosage interruption in >3% of patients included keratopathy (47%), blurred vision (5%), dry eye (3.2%), and pneumonia (3.2%). Dose reductions due to an adverse reaction occurred in 29% of patients. Adverse reactions which required a dose reduction in >3% of patients included keratopathy (23%) and thrombocytopenia (5%).

The most common adverse reactions (≥20%) were keratopathy (71%), decreased visual acuity (53%), nausea (24%), blurred vision (22%), pyrexia (22%), infusion-related reactions (21%), and fatigue (20%). The most common Grade 3 or 4 (≥5%) laboratory abnormalities were lymphocytes decreased (22%), platelets decreased (21%), hemoglobin decreased (18%), neutrophils decreased (9%), creatinine increased (5%), and gamma-glutamyl transferase increased (5%).

Serious adverse reactions occurred in 40% of patients who received BLENREP. Serious adverse reactions in >3% of patients included pneumonia (7%), pyrexia (6%), renal impairment (4.2%), sepsis (4.2%), hypercalcemia (4.2%), and infusion-related reactions (3.2%). Fatal adverse reactions occurred in 3.2% of patients, including sepsis (1%), cardiac arrest (1%), and lung infection (1%).

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Management considerations for ocular reactions before and during treatment[2]

Ophthalmic exams

- Conduct ophthalmic examinations (visual acuity and slit lamp) at baseline, prior to each dose, and promptly for worsening symptoms. Perform baseline examinations within 3 weeks prior to the first dose. Perform each follow-up examination at least 1 week after the previous dose and within 2 weeks prior to the next dose.

Eye drops

- Advise patients to use preservative-free lubricant eye drops at least 4 times a day, starting with the first infusion and continuing until end of treatment.

Avoid contact lenses

- Advise patients to avoid using contact lenses unless directed by an ophthalmologist.

Caution operating machinery

- Advise patients to use caution when driving or operating machinery, as BLENREP may adversely affect their vision.

BLENREP is available only through a restricted program under a REMS called the BLENREP REMS because of the risks of ocular toxicity.

Notable requirements of the BLENREP REMS include the following:

- Prescribers must be certified with the program by enrolling and completing training in the BLENREP REMS.
- Prescribers must counsel patients receiving BLENREP about the risk of ocular toxicity and the need for ophthalmic examinations prior to each dose.
- Patients must be enrolled in the BLENREP REMS and comply with monitoring.
- Healthcare facilities must be certified with the program and verify that patients are authorized to receive BLENREP.
- Wholesalers and distributors must only distribute BLENREP to certified healthcare facilities.

IMPORTANT SAFETY INFORMATION *(CONT'D)*

USE IN SPECIFIC POPULATIONS

Lactation: Because of the potential for serious adverse reactions in the breastfed child, advise women not to breastfeed during treatment with BLENREP and for 3 months after the last dose.

Females and Males of Reproductive Potential: Based on findings in animal studies, BLENREP may impair fertility in females and males.

Geriatric Use: Of the 218 patients who received BLENREP in DREAMM-2, 43% were aged 65 to less than 75 years and 17% were aged 75 years and older. Keratopathy occurred in 80% of patients aged less than 65 years and 73% of patients aged 65 years and older. Among the 95 patients who received BLENREP at the 2.5-mg/kg dose, keratopathy occurred in 67% of patients aged less than 65 years and 73% of patients aged 65 years and older.

Renal or Hepatic Impairment: The recommended dosage has not been established in patients with severe renal impairment (eGFR 15 to 29 mL/min/1.73 m^2) or end-stage renal disease (ESRD) with eGFR <15 mL/min/1.73 m^2 not on dialysis or requiring dialysis. The recommended dosage has not been established in patients with moderate or severe hepatic impairment (total bilirubin >1.5 × ULN and any AST).

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For the treatment of appropriate patients with relapsed/refractory multiple myeloma[2]

The first and only BCMA-targeting antibody-drug conjugate[2,4,5]

BLENREP targets B-cell maturation antigen (BCMA), a cell-surface protein expressed on myeloma cells, late-stage B cells, and plasma cells. BLENREP may also affect normal cells.[2,4,5]

31% overall response rate

(30/97; 97.5% CI: 21%, 43%) in a patient population with a median 7 prior therapies.[2]

Clinically meaningful and durable responses

- The majority of responders (60% [18/30]) achieved a clinically meaningful response with a VGPR or better.[2]
  - Of the 97 patients, 2 patients (2%) had an sCR, 1 (1%) had a CR, 15 (15%) had a VGPR, and 12 (12%) had a PR.[2]
- Median duration of response was not reached at 6 months.[2]
- 73% of responders had a duration of response ≥6 months.[2]

Most common adverse reactions (≥20%)

in patients who received the recommended dose included keratopathy (71%), decreased visual acuity (53%), nausea (24%), blurred vision (22%), pyrexia (22%), infusion-related reactions (21%), and fatigue (20%).[2]

CR=complete response; PR=partial response; sCR=stringent complete response; VGPR=very good partial response.

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References: 1. Lonial S, et al. *Lancet Oncol.* 2020;21(2):207-221. **2.** BLENREP Prescribing Information. **3.** Data on file, GSK. **4.** Tai Y-T, et al. *Blood.* 2014;123(20):3128-3138. **5.** Trudel S, et al. *Lancet Oncol.* 2018;19(12):1641-1653.

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