▼This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION

BLENREP (belantamab mafodotin) powder for injection

BLENREP can cause changes in the corneal epithelium which may result in ocular symptoms such as changes in vision and dry eyes. Severe visual impairment and/or corneal ulcers can occur.

Ophthalmic exams should be conducted prior to each dose of BLENREP or more frequently as clinically indicated. If changes in vision or corneal signs are not observed at or before the sixth dose exam, the ophthalmic examination frequency may be reduced to approximately every 3 months and whenever clinically indicated. The examination includes visual acuity testing and slit lamp examinations by an eyecare professional. If ocular adverse reactions are noted, withhold BLENREP until improvement and resume, or permanently discontinue, based on severity. Ocular adverse reactions can recur after resuming BLENREP even if the dose is reduced (see section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS), 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and 4.2 DOSE AND METHOD OF ADMINISTRATION for management guidelines for these adverse reactions).

1 NAME OF THE MEDICINE

Belantamab mafodotin

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Belantamab mafodotin is an antibody-drug conjugate (ADC) that contains belantamab, an afucosylated humanised monoclonal IgG1k antibody specific for B cell maturation antigen (BCMA), produced using recombinant DNA technology in a mammalian cell line (Chinese Hamster Ovary) that is conjugated with maleimidocaproyl monomethyl auristatin F (mcMMAF).

Each vial contains 70 mg or 100 mg of belantamab mafodotin.

After reconstitution, the solution contains 50 mg per mL belantamab mafodotin.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

Powder for injection

Each vial contains belantamab mafodotin as a lyophilised white to yellow powder.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

BLENREP is indicated for the treatment of adults with relapsed or refractory multiple myeloma:

- in combination with bortezomib and dexamethasone in patients who have received at least one prior therapy; and
- in combination with pomalidomide and dexamethasone in patients who have received at least one prior therapy including lenalidomide.

4.2 DOSE AND METHOD OF ADMINISTRATION

Treatment with belantamab mafodotin should be initiated and supervised by physicians experienced in the treatment of multiple myeloma.

Method of administration

Belantamab mafodotin is a cytotoxic anticancer medicinal product. Proper handling procedures should be followed. Instructions on reconstitution and further dilution are provided below.

Belantamab mafodotin is administered as an intravenous infusion over approximately 30 minutes.

Product is for single use in one patient only. Discard any residue.

Use and Handling

Use aseptic technique for the reconstitution and dilution of the dosing solution.

Calculate the dose (mg), total volume (mL) of solution required and the number of vials needed based on the patient's actual body weight (kg).

<u>Reconstitution</u>

1. Remove the vial(s) of belantamab mafodotin from the refrigerator and allow to stand for approximately 10 minutes to reach room temperature.
2. Reconstitute each 70 mg vial with 1.4 mL of Sterile Water for Injection to obtain a final concentration of 50 mg/mL. Reconstitute each 100 mg vial with 2 mL of Sterile Water for Injection to obtain a final concentration of 50 mg/mL. Gently swirl the vial to aid dissolution. Do not shake.
3. Visually inspect the reconstituted solution for particulate matter and discoloration. The reconstituted solution should be a clear to opalescent, colourless to yellow to brown liquid. Discard the reconstituted vial if extraneous particulate matter other than translucent to white proteinaceous particles is observed.

<u>Dilution Instructions for Intravenous Use</u>

1. Withdraw the necessary volume for the calculated dose from each vial.
2. Add the necessary amount of belantamab mafodotin to the infusion bag containing 250 mL of sodium chloride 9 mg/mL (0.9%) solution for injection. Mix the diluted

solution by gentle inversion. The final concentration of the diluted solution should be between 0.2 mg/mL to 2 mg/mL. DO NOT SHAKE.
3. Discard any unused reconstituted solution of belantamab mafodotin left in the vial.

If the diluted solution is not used immediately, it may be stored in a refrigerator (2˚C to 8˚C) for up to 24 hours prior to administration. If refrigerated, allow the diluted solution to equilibrate to room temperature prior to administration. The diluted solution may be kept at room temperature (20˚C to 25˚C) for a maximum of 6 hours (including infusion time).

Administration Instructions

1. Administer the diluted solution by intravenous infusion over approximately 30 minutes using an infusion set made of polyvinyl chloride or polyolefin.
2. Filtration of the diluted solution is not required. However, if the diluted solution is filtered, polyethersulfone (PES) based filter is recommended.

Recommended Supportive Care

Patients should have an ophthalmic examination (including visual acuity and slit lamp examination) performed by an eye care professional, prior to each dose of BLENREP or more frequently as clinically indicated. If changes in vision or corneal signs are not observed at or before the sixth dose, ophthalmic exam frequency may be reduced to approximately every 3 months and whenever clinically indicated.

Physicians should encourage patients to inform them of any ocular symptoms. Additionally, they should advise patients to administer preservative-free artificial tears at least 4 times a day beginning on the first day of infusion and continuing until completion of treatment as this may reduce ocular symptoms (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

For patients with dry eye symptoms, additional therapies may be considered as recommended by their eye care professional.

Adults

Administration of belantamab mafodotin should be continued until disease progression or unacceptable toxicity.

Recommended dose

The recommended starting dose schedule of belantamab mafodotin in combination with other therapies is presented in Table 1.

Table 1. Recommended starting dose schedule in combination with other therapies

Combination regimen	Recommended starting dose schedule
With bortezomib and dexamethasone (BVd)[a] (Cycle length = 3 weeks)	2.5 mg/kg administered once every 3 weeks
With pomalidomide and dexamethasone (BPd) (Cycle length = 4 weeks)	Cycle 1: 2.5 mg/kg administered once Cycle 2 onwards: 1.9 mg/kg administered once every 4 weeks

[a] Belantamab mafodotin is administered from Cycle 1 until completion of treatment; bortezomib and dexamethasone are administered for the first 8 Cycles.

For dosing instructions of therapies administered in combination with belantamab mafodotin, refer to section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical trials and respective Prescribing Information, as appropriate.

Dose Modifications

The dosage of belantamab mafodotin should be individualised for each patient based on their condition through dose withholding and dose adjustments. Recommended dose modifications are provided in Tables 2 and 3 for adverse reactions.

Ocular events were graded based on ophthalmic examination findings that include the combination of corneal examination findings and best corrected visual acuity (BCVA).

The treating physician should review the patient's ophthalmic examination findings before dosing and determine the dose of belantamab mafodotin based on the results (Table 3). During the ophthalmic examination, the eye care professional should assess the following:

- The corneal examination finding(s) and the decline in BCVA.
- If there is a decline in BCVA, the relationship to belantamab mafodotin should be determined.
- The category grading for these examination findings and BCVA should be communicated to the treating physician.

The corneal examination findings may or may not be accompanied by changes in BCVA. Note: One eye may be more severely affected than the other. It is important for physicians to consider not only corneal examination findings but also visual acuity changes and reported symptoms as they evaluate dose delays and reductions.

Do not re-escalate the belantamab mafodotin dose after a dose reduction is made for ocular adverse reactions.

Table 2. Dose reduction schedule for belantamab mafodotin

	Combination with bortezomib and dexamethasone[a]	**Combination with pomalidomide and dexamethasone[a]**
Recommended starting dose schedule	2.5 mg/kg every 3 weeks	Cycle 1: 2.5 mg/kg administered once. Cycle 2 onwards: 1.9 mg/kg administered every 4 weeks
Reduced dose level 1	1.9 mg/kg every 3 weeks	1.9 mg/kg every 8 weeks
Reduced dose level 2	N/A	1.4 mg/kg every 8 weeks

N/A = Not applicable.

[a] Extended dosing intervals were observed during the clinical studies (see section 5.1 PHARMACODYNAMIC PROPERTIES, Tables 9 and 11).

Table 3. Dose modification guidelines for belantamab mafodotin-related adverse reactions

Adverse Reaction	Severity[a]	Recommended dose modifications
Ocular adverse reactions (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE)[b]	**Mild (Grade 1)** *Corneal examination finding(s)* Mild superficial punctate keratopathy with worsening from baseline, with or without symptoms *Change in BCVA* Decline from baseline of 1 line on Snellen Equivalent Visual Acuity.	Continue BLENREP at current dose per the judgment of the physician with close direct monitoring of the patient's clinical status.
	Moderate (Grade 2) *Corneal examination finding(s)* Moderate superficial punctate keratopathy, patchy microcyst-like deposits, peripheral sub-epithelial haze, or a new peripheral stromal opacity. *Change in BCVA* Decline from baseline of 2 lines (and Snellen Equivalent Visual Acuity not worse than 20/200). Or **Severe (Grade 3)** *Corneal examination finding(s)* Severe superficial punctate keratopathy, diffuse microcyst-like deposits involving the central cornea, central sub-epithelial haze, or a new central stromal opacity. *Change in BCVA* Decline from baseline of 3 or more lines (and Snellen Equivalent Visual Acuity not worse than 20/200).	Withhold treatment until improvement in both corneal examination findings and BCVA to mild severity or better. Resume treatment at reduced dose level 1 as per Table 2[c].

	Corneal Epithelial Defect or Change of BCVA of worse than 20/200 (Grade 4) *Corneal examination finding(s)* Corneal epithelial defect[d] *Change in BCVA* Decline to Snellen Equivalent Visual Acuity of worse than 20/200.	Withhold until improvement in both corneal examination findings and BCVA to mild severity or better. Resume treatment at reduced dose level 1 for BVd and reduced dose level 2 for BPd as per Table 2 if applicable. For worsening symptoms that are unresponsive to appropriate management, consider permanent discontinuation.
Pneumonitis (see section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS))	**Grade ≥3**	Permanently discontinue BLENREP.
Thrombocytopenia (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE)	**Grade 3**	No bleeding: • For patients on 2.5 mg/kg, reduce belantamab mafodotin to 1.9 mg/kg. For patients on 1.9 mg/kg or lower, continue at same dose[e]. With bleeding: • Withhold belantamab mafodotin until improvement to Grade 2 or better. For patients previously on 2.5 mg/kg, resume belantamab mafodotin at 1.9 mg/kg. For patients on 1.9 mg/kg or lower, resume at same dose. Consider additional supportive treatment (e.g., transfusion), as clinically indicated and per local practise.
	Grade 4	Withhold the dose and consider restarting if recovered to Grade 3 or better, and only if there is no active bleeding at the time of treatment restart. For patients previously on 2.5 mg/kg, resume belantamab mafodotin at 1.9 mg/kg. For patients on 1.9 mg/kg or lower, resume at same dose. • If thrombocytopenia is considered disease-related, is not

		accompanied by bleeding, and recovers with transfusion to >25 x 10^9/L, continuing treatment at the current dose may be considered.
Infusion-related reactions (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE)	**Grade 2**	Interrupt infusion and provide supportive treatment. Once symptoms resolve to Grade 1 or better, resume at a decreased infusion rate by at least 50%.
	Grade 3	Interrupt infusion and provide supportive treatment. Once symptoms resolve to Grade 1 or better, resume with premedication and at lower infusion rate extended to 2 to 4 hours. Any future infusion requires premedication.
	Grade 4	Permanently discontinue belantamab mafodotin • If anaphylactic or life-threatening infusion reaction, permanently discontinue the infusion and institute appropriate emergency care.
Other adverse reactions (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE)	**Grade 3**	Withhold belantamab mafodotin until improvement to Grade 1 or better. For patients previously on 2.5 mg/kg, resume belantamab mafodotin at 1.9 mg/kg. For patients on 1.9 mg/kg or lower, resume at same dose.
	Grade 4	Consider permanent discontinuation of belantamab mafodotin. If continuing treatment, withhold belantamab mafodotin until improvement to Grade 1 or better. For patients previously on 2.5 mg/kg, resume belantamab mafodotin at 1.9 mg/kg. For patients on 1.9 mg/kg or lower, result at same dose.

BCVA = best corrected visual acuity; BPd = belantamab mafodotin with pomalidomide and dexamethasone; BVd = belantamab mafodotin with bortezomib and dexamethasone.

[a] Non-ocular adverse reactions were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE).

[b] Ocular adverse reaction severity is defined by the most severely affected eye as both eyes may not be affected to the same degree.

[c] If toxicity is identified prior to dosing Cycle 2 for belantamab mafodotin with pomalidomide and dexamethasone, dose at 1.9 mg/kg every 4 weeks.

[d] A corneal defect may lead to corneal ulcers. These should be managed promptly and as clinically indicated by an eye care professional.
[e] For belantamab mafodotin with bortezomib and dexamethasone, may consider reverting to previous dose, if appropriate once thrombocytopenia recovers to Grade 2 or better.

Children

The safety and efficacy of belantamab mafodotin have not been established in children less than 18 years of age.

Elderly

No dosage adjustment is required in patients over 65 years of age (see section 5.2 PHARMACOKINETIC PROPERTIES).

Renal impairment

No dose adjustment is required in patients with mild, moderate or severe renal impairment or kidney failure (eGFR <30 mL/min) (see section 5.2 PHARMACOKINETIC PROPERTIES).

Hepatic impairment

BLENREP should only be used in these patients if the potential benefits outweigh any potential risks (see section 5.2 PHARMACOKINETIC PROPERTIES).

No dose adjustment is required in patients with mild hepatic impairment (total bilirubin greater than ULN to ≤ 1.5 x ULN and any aspartate transaminase [AST] or total bilirubin ≤ ULN with AST > ULN). There are limited data in patients with moderate hepatic impairment and no data in patients with severe hepatic impairment to support a dose recommendation (see section 5.2 PHARMACOKINETIC PROPERTIES).

Body weight

BLENREP is dosed based on actual body weight and has been studied in patients with body weight 37-170 kg (see section 5.2 PHARMACOKINETIC PROPERTIES). For changes of body weight >10% during treatment, recalculate dose based on the actual body weight at the time of dosing.

4.3 CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 LIST OF EXCIPIENTS.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Ocular Adverse Reactions

Ocular adverse reactions (e.g., blurred vision, dry eye, eye irritation, and photophobia) have been reported with the use of belantamab mafodotin.

The most commonly reported corneal examination findings included superficial punctate keratopathy, microcyst-like epithelial changes and haze, with or without changes in visual acuity. These effects may be uncomfortable and/or painful. Clinically relevant changes in

visual acuity may be associated with temporary difficulty in driving or operating machinery. These events were typically of limited duration and resolved for most patients (97% for reading and 92% for driving), with a median time to resolution of approximately one month. Patients should be advised to avoid activities such as driving or operating machinery if visual symptoms occur and to report any changes in vision promptly.

Physicians should also encourage patients to inform them of any ocular symptoms. Patients should have an ophthalmic examination (including visual acuity and slit lamp examination), performed by an eye care professional, prior to each dose of BLENREP or more frequently as clinically indicated. If changes in vision or corneal signs are not observed at or before the sixth dose, ophthalmic exam frequency may be reduced to approximately every 3 months and whenever clinically indicated.

Patients should be advised to administer preservative-free artificial tears at least 4 times a day during treatment (see section 4.2 DOSE AND METHOD OF ADMINISTRATION). Patients should avoid using contact lenses until the end of treatment. Bandage contact lenses may be used under the direction of an ophthalmologist.

Patients experiencing corneal examination findings (keratopathies such as superficial punctate keratopathy or microcyst-like deposits) with or without changes in visual acuity may require a dose modification (delay and/or reduction) or treatment discontinuation based on severity of findings (see section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Cases of corneal ulcer (ulcerative and infective keratitis) have been reported (see section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)). These should be managed promptly and as clinically indicated by an eye care professional. Treatment with belantamab mafodotin should be interrupted until the corneal ulcer has healed (see section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Thrombocytopenia

Thrombocytopenic events (thrombocytopenia and platelet count decreased) were reported with belantamab mafodotin. Thrombocytopenia may lead to serious bleeding events, including gastrointestinal and intracranial bleeding.

Complete blood counts should be obtained at baseline and monitored during treatment, as clinically indicated. Patients experiencing Grade 3 or 4 thrombocytopenia or those on concomitant anticoagulant treatments may require more frequent monitoring and should be managed with a dose delay or dose reduction (see section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Supportive therapy (e.g., platelet transfusions) should be provided according to standard medical practice.

Infusion Reactions

Infusion-related reactions (IRR) have been reported with belantamab mafodotin. Most IRRs were Grade 1 or 2 and resolved within the same day (see section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)). If a grade 2 or higher IRR occurs during administration, reduce the infusion rate, or stop the infusion depending on the severity of the symptoms. Institute appropriate medical treatment and restart infusion at a slower rate, if the patient’s

condition is stable. If Grade 2 or higher IRR occurs, administer premedication for subsequent infusions (see section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Pneumonitis

Cases of pneumonitis, including fatal events, have been observed with belantamab mafodotin although a casual association has not been established. Evaluation of patients with new or worsening unexplained pulmonary symptoms (e.g., cough, dyspnoea) should be performed to exclude possible pneumonitis. In case of suspected Grade 3 or higher pneumonitis, belantamab mafodotin should be withheld. If Grade 3 or higher pneumonitis is confirmed, appropriate treatment should be initiated. Belantamab mafodotin should only be resumed after an evaluation of the benefit and risk.

Hepatitis B virus reactivation

Hepatitis B virus (HBV) reactivation can occur in patients treated with medicinal products directed against B cells, including BLENREP, and in some cases, may result in fulminant hepatitis, hepatic failure, and death. Patients with evidence of positive HBV serology must be monitored for clinical and laboratory signs of HBV reactivation as per clinical guidelines. In patients who develop reactivation of HBV while on BLENREP, treatment with BLENREP must be withheld and patients must be treated according to clinical guidelines.

Use in hepatic impairment

No formal studies have been conducted in patients with hepatic impairment (see section 5.2 PHARMACOKINETIC PROPERTIES).

Use in renal impairment

See section 5.2 PHARMACOKINETIC PROPERTIES.

Use in the elderly

Based on a population of patients aged 32 to 89 years, age was not a significant covariate in population pharmacokinetics analyses.

Paediatric use

No pharmacokinetic data are available in paediatric patients.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No formal drug interaction studies have been performed with belantamab mafodotin.

In vitro studies demonstrated that cys-mcMMAF is not an inhibitor, an inducer, or a sensitive substrate of cytochrome P450 enzymes, but is a substrate of organic anion transporting polypeptide (OATP)1B1 and OATP1B3, multidrug resistance-associated protein (MRP)1, MRP2, MRP3, bile salt export pump (BSEP), and a possible substrate of P-glycoprotein (P-gp).

Effect of other drugs on belantamab mafodotin

A population pharmacokinetic (PK) analysis was used to assess combination therapy on belantamab mafodotin ADC and cys-mcMMAF PK. Combination therapies with bortezomib, lenalidomide, pomalidomide and/or dexamethasone, did not affect the PK of ADC and cys-mcMMAF.

Effect of belantamab mafodotin on other drugs

For combination therapies with lenalidomide, bortezomib, and pomalidomide, PK profiles were evaluated in clinical trials and compared with historical data. The observed PK for lenalidomide, bortezomib, and pomalidomide suggested lack of impact of belantamab mafodotin on the PK of the included combination therapies.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No animal studies have been performed to evaluate the potential effects of belantamab mafodotin on reproduction. Based on findings in animal studies and the mechanism of action, belantamab mafodotin may impair fertility in females and males of reproductive potential.

Effects on male and female reproductive organs have been observed at doses of ≥ 10 mg/kg, which is approximately 4 times the exposure of the clinical dose. Luteinised non-ovulatory follicles were seen in the ovaries of rats after 3 weekly doses. Findings in male reproductive organs, that were adverse and progressed following repeat dosing in rat, included marked degeneration/atrophy of seminiferous tubules, associated with aspermia/hypospermia in the epididymides, that generally did not reverse following dosing cessation.

Women of child-bearing potential/Contraception in males and females

The pregnancy status of child-bearing women should be verified prior to initiating therapy with belantamab mafodotin. Women of child-bearing potential should use effective contraception during treatment with belantamab mafodotin and for 4 months after the last dose.

Men with female partners of child-bearing potential should use effective contraception during treatment with belantamab mafodotin and for 6 months after the last dose.

Use in pregnancy

(Category D)

There are no data from the use of belantamab mafodotin in pregnant women.

Based on the mechanism of action of the cytotoxic component monomethyl auristatin F (MMAF), belantamab mafodotin can cause embryo-fetal harm when administered to a pregnant woman. The cytotoxic component kills rapidly dividing cells, which would affect a developing embryo. There is also a potential risk of heritable changes via aneuploidy in female germ cells.

Human immunoglobulin G (IgG) is known to cross the placenta; therefore, belantamab mafodotin has the potential to be transmitted from the mother to the developing fetus.

Use in lactation

It is not known whether belantamab mafodotin is excreted into human milk. Immunoglobulin G (IgG) is present in human milk in small amounts. Since belantamab mafodotin is a humanised IgG monoclonal antibody, and based on the mechanism of action, it may cause serious adverse reactions in breastfed children. Women should be advised to discontinue breastfeeding prior to initiating treatment with belantamab mafodotin and for 3 months after the last dose.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Worsening of visual acuity has been reported in some patients treated with belantamab mafodotin during clinical studies (see sections 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)). Patients should be advised to use caution when driving or operating machinery as belantamab mafodotin may affect their vision.

Patients should be advised to avoid activities such as driving or operating machinery if visual symptoms occur and to report any changes in vision promptly.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical trial data

The safety of belantamab mafodotin was evaluated in 242 patients who received belantamab mafodotin in combination with bortezomib and dexamethasone in DREAMM-7. Adverse reactions leading to permanent discontinuation of any component of therapy occurred in 32% of patients, and 10% were due to ocular events including ocular adverse reactions, visual acuity changes or corneal examination findings. Adverse reactions leading to dose delay of any component of therapy occurred in 95% of patients and in 78% of patients with ocular events. Adverse reactions leading to dose reduction of any component of therapy occurred in 75% of patients and in 43% of patients with ocular events.

Serious adverse reactions occurred in 53% (n=129) of patients who received BLENREP. Serious adverse reactions that occurred in ≥2% of patients included pneumonia (12%), COVID-19 (5%), pyrexia (5%), COVID-19 pneumonia (3%), thrombocytopenia (3%) and anaemia (2%). Fatal adverse reactions occurred in 11% of patients. Adverse reactions leading to death in at least 1% of patients (i.e., ≥3 patients) who received BLENREP were pneumonia (3%) and COVID-19 (1%). Permanent discontinuation of BLENREP due to any adverse reaction occurred in 32% of patients. The most common adverse reactions (>3%) leading to permanent discontinuation of any component of BVd were ocular events (10%), peripheral sensory neuropathy (6%) and pneumonia (4%).

The safety of belantamab mafodotin was evaluated in 150 patients who received belantamab mafodotin in combination with pomalidomide and dexamethasone in DREAMM-8. Adverse reactions leading to permanent discontinuation of any component of therapy occurred in 19% of patients, and 11% were due to ocular events including ocular adverse reactions, visual acuity changes, or corneal examination findings. Adverse reactions leading

to dose delay of any component of therapy occurred in 91% of patients and in 83% of patients with ocular events. Adverse reactions leading to dose reduction of any component of therapy occurred in 63% of patients and in 59% of patients with ocular events.

Serious adverse reactions occurred in 67% (n=101) of patients who received BLENREP. Serious adverse reactions that occurred in ≥2% of patients included pneumonia (18%), COVID-19 pneumonia (11%), COVID-19 (7%), neutropenia (7%), urinary tract infection (3%), bronchitis (3%) and upper respiratory tract infection (2%). Fatal adverse reactions occurred in 13% of patients. Adverse reactions leading to death in 1% of patients (i.e., ≥2 patients), included COVID-19 pneumonia (3%), COVID-19 (1%) and pneumonia in 1% of patients. Permanent discontinuation of BLENREP due to any adverse reaction occurred in 19% of patients. Ocular adverse reactions were the most common reason for permanent discontinuation of any component of BPd (11%).

The safety of belantamab mafodotin as monotherapy (currently unapproved) was evaluated from pooled data in 312 patients who received belantamab mafodotin in DREAMM-2 and DREAMM-3. Adverse reactions leading to permanent discontinuation of belantamab mafodotin occurred in 14% of patients with 3% related to ocular events.

Table 4 summarises adverse drug reactions that occurred in patients receiving the recommended dose of belantamab mafodotin for all studied indications.

Adverse reactions are presented by system organ class (SOC) and by frequency. Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000) and very rare (< 1/10,000). Within each frequency grouping, where relevant, adverse reactions are presented in order of decreasing seriousness.

Table 4. Adverse reactions reported in multiple myeloma patients treated with belantamab mafodotin

System Organ Class	**Monotherapy**		**Combination with bortezomib and dexamethasone**		**Combination with pomalidomide and dexamethasone**	
	Toxicity grade		**Toxicity grade**		**Toxicity grade**	
	Any grade (%)	**Grade 3+4 (%)**	**Any grade (%)**	**Grade 3+4 (%)**	**Any grade (%)**	**Grade 3+4 (%)**
Infections and infestations						
Upper respiratory tract infection	5	<1	22	<1	28	2
COVID-19	9	1	26	5	39	6
Urinary tract infection	7	<1	10	2	16	4
COVID-19 pneumonia	<1	<1	3	2	13	7
Bronchitis	3	0	10	<1	10	3
Pneumonia	5	4	20	10	25	16
Blood and lymphatic system disorders						
Thrombocytopenia	43	28	88	73	54	38
Anaemia	28	17	20	9	25	11
Neutropenia	18	12	19	14	65	58
Leukopenia	11	3	11	5	10	6
Lymphopenia	10	7	14	8	9	5

System Organ Class	Monotherapy		Combination with bortezomib and dexamethasone		Combination with pomalidomide and dexamethasone	
	Toxicity grade		Toxicity grade		Toxicity grade	
	Any grade (%)	Grade 3+4 (%)	Any grade (%)	Grade 3+4 (%)	Any grade (%)	Grade 3+4 (%)
Febrile neutropenia	<1	<1	<1	<1	5	5
Immune system disorders						
Hypogammaglobulinaemia	<1	0	3	<1	7	1
Metabolism and nutrition disorders						
Decreased appetite	7	<1	10	<1	6	0
Psychiatric disorders						
Insomnia	4	0	16	1	14	1
Nervous system disorders						
Neuropathies[a]	3	<1	51	9	10	0
Eye disorders						
Corneal examination findings (including keratopathy)[b]	72	44	90	78	89	66
Visual acuity reduced[b]	62	32	90	59	91	61
Vision blurred	35	5	68	24	80	17
Dry eye	24	3	53	7	61	9
Foreign body sensation in eyes	18	<1	46	4	61	6
Photophobia	17	<1	50	3	46	3
Eye irritation	17	<1	45	5	51	4
Eye pain	12	<1	33	<1	33	2
Cataract	4	<1	21	7	28	8
Eye pruritus	1	0	2	0	3	<1
Visual impairment	5	4	11	5	15	10
Lacrimation increased	3	0	10	<1	6	<1
Diplopia	2	<1	5	0	5	<1
Ocular discomfort	2	<1	1	0	1	0
Corneal ulcer[c]	1	**<1**	<1	<1	2	2
Respiratory, thoracic and mediastinal disorders						
Cough	6	0	14	0	17	<1
Dyspnoea	6	<1	6	<1	17	1
Pneumonitis	<1	<1	0	0	<1	<1
Gastrointestinal disorders						
Nausea	16	0	16	<1	13	<1
Diarrhoea	11	<1	33	4	25	1
Constipation	7	0	20	<1	17	1
Vomiting	9	<1	7	<1	5	0
Hepatobiliary disorders						
Porto-sinusoidal vascular disorder[d]	-	-	<1	<1	<1	<1
Skin and subcutaneous tissue disorder						
Rash	2	0	3	0	7	<1
Musculoskeletal and connective tissue disorders						
Arthralgia	13	<1	10	0	9	1
Back pain	9	2	10	1	13	<1
Renal and urinary disorders						
Albuminuria[e]	1	0	5	<1	3	0

System Organ Class	Monotherapy		Combination with bortezomib and dexamethasone		Combination with pomalidomide and dexamethasone	
	Toxicity grade		Toxicity grade		Toxicity grade	
	Any grade (%)	Grade 3+4 (%)	Any grade (%)	Grade 3+4 (%)	Any grade (%)	Grade 3+4 (%)
General disorders and administration site conditions						
Pyrexia	20	2	19	<1	19	<1
Fatigue	11	1	20	4	28	6
Asthenia	4	<1	8	2	11	2
Investigations						
Increased gamma glutamyltransferase	10	3	16	10	7	3
Increased aspartate aminotransferase	16	2	15	2	11	3
Increased alanine aminotransferase	6	<1	20	6	17	2
Increased creatine phosphokinase	3	1	5	2	<1	0
Injury, poisoning and procedural complications						
Infusion-related reactions[f]	19	2	2	0	7	1

[a] Includes peripheral sensory neuropathy, neuropathy peripheral, neuralgia, polyneuropathy, peripheral motor neuropathy, sensory loss, peripheral sensorimotor neuropathy

[b] Based on ophthalmic examination findings

[c] Based on infective keratitis and ulcerative keratitis

[d] Signs or symptoms may include abnormal liver function tests, portal hypertension, varices and ascites.

[e] Includes albuminuria, albumin urine present, urine albumin/creatinine ratio increased, and microalbuminuria

[f] Includes events determined to be related to infusion. Infusion reactions may include pyrexia, chills, diarrhoea, nausea, asthenia, hypertension, lethargy, and tachycardia.

Ocular adverse reactions

Combination therapies

Across pooled datasets from 3 studies of belantamab mafodotin in combination with other therapies, DREAMM-6 (a Phase 1/2, open-label dose exploration study), DREAMM-7, and DREAMM-8 (n = 516), ocular adverse reactions occurred in 83% patients (n = 428) and the most common (> 25%) were reduced visual acuity (90%; 59% Grade 3 and 4) and corneal examination findings (89%; 71% Grade 3 and 4) based on the ophthalmic examination findings, blurred vision (62%; 17% Grades 3 and 4), dry eye (44%; 6% Grades 3 and 4), foreign body sensation in eyes (40%; 3% Grades 3 and 4); photophobia (37%; 2% Grades 3 and 4); eye irritation (35%; 4% Grades 3 and 4); and eye pain (27%; < 1% Grades 3 and 4).

Corneal examination findings (keratopathies such as superficial punctate keratopathy and microcyst-like deposits were reported based on the ophthalmic examination findings as Grade 1 in 5% of patients, Grade 2 in 14%, Grade 3 in 59%, and Grade 4 in 12%. Most visual acuity changes and corneal examination findings developed within receiving the first 2 doses (cumulative incidence of 75%).

DREAMM-7: Combination with bortezomib and dexamethasone

In the DREAMM-7 study, the most common adverse reactions (> 25%) included corneal examination findings (90%; 78% Grade 3 and 4) and reduced visual acuity (90%; 59% Grade 3 and 4) based on the ophthalmic examination findings, blurred vision (68%; 24% Grade 3 and 4), dry eye (53%; 7% Grade 3 and 4), photophobia (50%, 3% Grade 3 and 4), foreign body sensation in eyes (46%; 4% Grade 3 and 4), eye irritation (45%; 5% Grade 3 and 4), and eye pain (33%; < 1% Grade 3 and 4).

Corneal examination findings (keratopathies such as superficial punctate keratopathy and microcyst-like deposits) were reported based on the ophthalmic examination findings as Grade 1 in 4% of patients, Grade 2 in 9%, Grade 3 in 57%, and Grade 4 in 20%. Cases of corneal ulcer (ulcerative and infective keratitis) were reported with an incidence of < 1% (n = 2).

In the DREAMM-7 study, 88% (212/242) of patients reported at least 1 corneal examination finding or BCVA-related event (Grade ≥2) in the BVd arm. Of patients who experienced an event, 91% (190/209) continued treatment on or after the onset of the first event and received a median of 8 additional doses (range: 1 to 52). For patients who continued treatment, 93% (177/190) achieved a response to therapy of partial response or better.

Table 5 includes a summary of ocular adverse reactions, decreased vision in patients with normal (Snellen equivalent visual acuity 20/25 or better in at least one eye) baseline, and corneal examination findings in DREAMM-7.

Table 5. Summary of BLENREP associated ocular adverse reactions in DREAMM-7.

	Ocular adverse reactions[a]	**Best Corrected Visual Acuity (BCVA)[b]**		**Corneal examination findings (Grade 2+ events)[c]**
		20/50 or worse for patients	**20/200 or worse for patients**	
Number of patients with event (%)	194 (80)	84 (35)	5 (2)	209 (86)
Median time to first onset (days)	42	79	105	43
Improvement of first event[d], n (%)	N/A	81 (96)	5 (100)	N/A
Resolution of first event[e], n (%)	88 (45)	78 (93)	4 (80)	180 (86)
Median time to resolution of first event (days)	51	63.5	86.5	106
Ongoing first event[e], n (%)	106 (55)	6 (7)	1 (20)	29 (14)
On treatment and follow-up ongoing, n (%)	28 (14)	1 (1)	-	-
Discontinued treatment and follow-up ongoing, n (%)	40 (21)	-	-	5 (2)
Discontinued treatment and follow-up ended, n (%)	38 (20)	5 (6)	1 (20)	24 (11)

N/A = Not applicable.

[a] Resolution of ocular adverse reactions was defined as time to being free from any ocular adverse reactions.

[b] Resolution of visual acuity was defined as time to 20/25 or better in at least one eye.
[c] Resolution of corneal examination findings was defined as time to Grade 1 or better based on the ophthalmic examination findings.
[d] Improvement was defined as bilateral improvement to better than 20/50, or 20/200.
[e] At the time of the data cut-off (7 October 2024).

DREAMM-8: Combination with pomalidomide and dexamethasone

In the DREAMM-8 study, the most common adverse reactions (> 25%) included reduced visual acuity (91%; 61% Grade 3 and 4) and corneal examination findings (89%; 66% Grade 3 and 4) based on the ophthalmic examination findings, blurred vision (80%; 17% Grade 3 and 4), dry eye (61%; 9% Grade 3 and 4), foreign body sensation in eyes (61%; 6% Grade 3 and 4), eye irritation (51%; 4% Grade 3 and 4), photophobia (46%; 3% Grade 3 and 4), eye pain (33%; 2% Grade 3 and 4) and cataract (28%, 8% Grade 3 and 4).

Corneal examination findings (keratopathies such as superficial punctate keratopathy and microcyst-like deposits) were reported based on the ophthalmic examination findings as Grade 1 in 6% of patients, Grade 2 in 17%, Grade 3 in 56% and Grade 4 in 10%. Cases of corneal ulcer (ulcerative keratitis) were reported with an incidence of 2% (n = 3).

In the DREAMM-8 study, 89% (133/150) of patients reported at least 1 corneal examination finding or BCVA-related event (Grade ≥ 2) in the BPd arm. Of patients who experienced an event, 92% (120/131) continued treatment on or after the onset of the first event and received a median of 5 additional doses (range: 1 to 21). For patients who continued treatment, 88% (106/120) achieved a response to therapy of partial response or better.

Table 6 includes a summary of ocular adverse reactions, decreased vision in patients with normal (Snellen equivalent visual acuity 20/25 or better in at least one eye) baseline, and corneal examination findings in DREAMM-8.

Table 6. Summary of BLENREP associated ocular adverse events in DREAMM-8.

	Ocular adverse reactions[a]	**Best Corrected Visual Acuity (BCVA)[b]**		**Corneal examination findings (Grade 2+ events)[c]**
		20/50 or worse for patients	**20/200 or worse for patients**	
Number of patients with event (%)	133 (89)	51 (34)	2 (1)	125 (83)
Median time to first onset (days)	29	112	N/A[d]	29
Improvement of first event[e], n (%)	N/A	49 (96)	2 (100)	N/A
Resolution of first event[f], n (%)	109 (82)	45 (88)	1 (50)	113 (90)
Median time to resolution of first event (days)	134.5	57	N/A[d]	88
Ongoing first event[f], n (%)	24 (18)	6 (12)	1 (50)	12 (10)
Treatment ongoing, n (%)	5 (4)	1 (2)	0	0

Discontinued treatment and follow-up ongoing, n (%)	6 (5)	1 (2)	0	4 (3)
Discontinued treatment and follow-up ended, n (%)	13 (10)	4 (8)	1 (50)	8 (6)

N/A = Not applicable.

[a] Resolution of ocular adverse reactions was defined as time to being free from any ocular adverse reactions.

[b] Resolution of visual acuity was defined as time to 20/25 or better in at least one eye.

[c] Resolution of corneal examination findings was defined as time to Grade 1 or better based on the ophthalmic examination findings.

[d] In patients with 20/200 or worse, two patients were reported. Time to first onset was 29 and 673 days. Both events improved to better than bilateral 20/200 by the data cut-off, of which 1 event resolved after 57 days.

[e] Improvement was defined as bilateral improvement to better than 20/50, or 20/200.

[f] At the time of the data cut-off (7 October 2024).

Monotherapy

Across pooled datasets from 2 studies of belantamab mafodotin as monotherapy, DREAMM-2 and DREAMM-3 (n = 312), ocular adverse events occurred in 67% patients (n = 210) and the most common adverse reactions (>25%) were blurred vision (35%; 5% Grade 3 and 4) and keratopathy (29%; 12% Grade 3 and 4).

Corneal examination findings were reported based on the ophthalmic examination findings as Grade 1 in 10% of patients, Grade 2 in 18%, Grade 3 in 37%, and Grade 4 in 8%. Most visual acuity changes and corneal examination findings (including keratopathy) developed within receiving the first 6 doses (cumulative incidence of 51%). Cases of corneal ulcer (ulcerative and infective keratitis) were reported with an incidence of 1% (n = 4).

Table 7 includes a summary of ocular adverse reactions, decreased visual acuity, and corneal examination findings in monotherapy studies.

Table 7. Belantamab mafodotin-associated ocular events in monotherapy studies[a]

	Ocular adverse reactions[b]	**Visual acuity[c]**		**Corneal examination findings (Grade 2+ events)[d]**
		BCVA to 20/50 or worse bilaterally	**BCVA to 20/200 or worse**	
Number of patients with event (%)	210 (67)	58 (19)	6 (2)	147 (47)
Median time to first onset (days)	37	62.5	83.5	43
Median time to resolution of first event (days)	102	33	32.5	66
Resolution of first event	54%	95%	67%	82%

[a] Ocular data for monotherapy is determined in the better eye unless otherwise specified.

[b] Resolution of ocular adverse reactions was defined as time to being free from any ocular adverse reactions.

[c] Resolution of visual acuity was defined as time to 20/25 or better in at least one eye.

[d] Resolution of corneal examination findings was defined as time to Grade 1 or better based on the ophthalmic examination findings.

Infusion-related reactions

Combination therapies

In the DREAMM-7 study, the incidence of IRR was 2% (n = 5). All IRRs are reported as Grade 1 (< 1%) and Grade 2 (1%).

In the DREAMM-8 study, the incidence of IRR was 7% (n = 11). Most IRRs were reported as Grade 1 (1%) and Grade 2 (5%) while 1% experienced Grade 3 IRRs. One patient discontinued treatment due to IRRs.

Monotherapy

In the DREAMM 2 and DREAMM 3 monotherapy studies, the incidence of IRR was 19% (n = 58). Most IRRs were reported as Grade 1 (7%) and Grade 2 (9%) while 2% experienced Grade 3 IRRs. Serious IRRs were reported by 3% of patients. One IRR event had a fatal outcome. No Grade 4 IRRs were reported.

Thrombocytopenia

Combination therapies

In the DREAMM-7 study, thrombocytopenic events (thrombocytopenia and platelet count decreased) occurred in 88% of patients (n = 212). Grade 2 thrombocytopenic events occurred in 10% of patients, Grade 3 in 26%, and Grade 4 in 47%. Clinically significant bleeding (≥ Grade 2) occurred in 7% of patients with concomitant low platelet levels (Grades 3 to 4).

In the DREAMM-8 study, thrombocytopenic events (thrombocytopenia and platelet count decreased) occurred in 54% of patients (n = 81). Grade 2 thrombocytopenic events occurred in 11% of patients, Grade 3 in 26%, and Grade 4 in 12%. Clinically significant bleeding (≥ Grade 2) occurred in 3% of patients with concomitant low platelet levels (Grades 3 to 4).

Monotherapy

In the DREAMM-2 and DREAMM-3 monotherapy studies, thrombocytopenic events (thrombocytopenia and platelet count decreased) occurred in 43% of patients (n = 135). Grade 2 thrombocytopenic events occurred in 8% of patients, Grade 3 in 17%, Grade 4 in 11%, and Grade 5 in <1%. Clinically significant bleeding (≥ Grade 2) bleeding events occurred in 12% of patients with concomitant low platelet levels (Grades 3 to 4).

Infections

Combination therapies

In the DREAMM-7 study, pneumonia was reported in 20% (n = 48) of patients with 12% reported as Grade ≥ 3. Seven patients had a pneumonia event with a fatal outcome.

In the DREAMM-8 study, pneumonia was reported in 25% (n = 38) of patients with 17% reported as Grade ≥ 3. Two patients had a pneumonia event with a fatal outcome.

Monotherapy

In DREAMM-2 and DREAMM-3 monotherapy studies, pneumonia was reported in 5% (n = 17) of patients with 4% reported as Grade ≥3, and most were Grade 3 (3%). Two patients had a pneumonia event with a fatal outcome.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

There has been no experience of overdosage with belantamab mafodotin in clinical studies.

There is no known specific antidote for overdose with belantamab mafodotin. If overdose is suspected, the patient should be monitored for any signs of symptoms of adverse reactions or effects, and appropriate standard of care measures should be instituted immediately.

Further management should be as clinically indicated or as recommended by the national poisons centre, where available.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

ATC code

L01FX15

Mechanism of action

Belantamab mafodotin is a humanised IgG1 kappa monoclonal antibody conjugated with a cytotoxic agent, maleimidocaproyl monomethyl auristatin F (mcMMAF). Belantamab mafodotin binds to cell surface BCMA and is rapidly internalised. Once inside the tumour cell, the cytotoxic agent (cys-mcMMAF) is released disrupting the microtubule network, leading to cell cycle arrest and apoptosis. The antibody also enhances recruitment and activation of immune effector cells, killing tumour cells by antibody-dependent cellular cytotoxicity and phagocytosis. Apoptosis induced by belantamab mafodotin is accompanied by markers of immunogenic cell death, which may contribute to an adaptive immune response to tumour cells.

Pharmacodynamic effects

For BVd and BPd combination therapies, higher belantamab mafodotin Cycle 1 exposure was associated with higher probability of response [e.g., very good partial response (VGPR+)] and higher incidence of some safety adverse reactions (e.g., Grade ≥ 2 corneal examination findings). For most of the range of belantamab mafodotin Cycle 1 exposure, the

probability of VGPR or better was higher than the probability of ocular adverse reactions and BCVA-related endpoints.

Immunogenicity

The incidence of anti-belantamab mafodotin antibodies (ADAs) was consistently low in patients treated with belantamab mafodotin in combination therapies with no observed clinical impact on pharmacokinetics, safety, and efficacy.

In pivotal combination therapy studies (DREAMM-7 AND DREAMM-8) and the combination therapy supportive study (DREAMM-6), 3% of patients (15/515) tested positive for treatment emergent ADAs. Two patients tested positive for neutralising anti-belantamab mafodotin antibodies (NAb).

Clinical trials

DREAMM-7: Combination with bortezomib and dexamethasone

DREAMM-7 was an open-label, Phase III, multicentre study which evaluated belantamab mafodotin in combination with bortezomib and dexamethasone (BVd) compared with daratumumab, bortezomib and dexamethasone (DVd) in patients with relapsed or refractory multiple myeloma (MM).

Eligible patients had a confirmed diagnosis of MM as defined by International Myeloma Working Group (IMWG) criteria, had previously been treated with at least 1 prior line of MM therapy and must have had documented disease progression during or after their most recent therapy.

Patients were randomised in a 1:1 ratio. In the BVd arm (n = 243), patients received belantamab mafodotin 2.5 mg/kg by intravenous infusion (IV) every 3 weeks on day 1 of each Cycle; bortezomib 1.3 mg/m^2 (subcutaneously) on days 1, 4, 8, and 11 of Cycles 1 to 8 (21-day Cycles); and dexamethasone 20 mg (IV or orally) on the day of, and the day after, bortezomib treatment. In the DVd arm (n = 251), patients received daratumumab 16 mg/kg (IV) in 21-day Cycles: every week for Cycles 1 to 3 and every 3 weeks for Cycles 4 to 8. Dexamethasone and bortezomib schedules were the same in both arms for the first 8 Cycles. Treatment continued in both arms until disease progression, death, unacceptable toxicity, withdrawal of consent, or study end.

A total of 494 patients were evaluated for efficacy in DREAMM-7. Baseline demographics and characteristics were similar across both arms. Baseline characteristics for the BVd arm (n = 243) were: median age: 65 years (35% aged 65 to 74 years and 15% aged 75 years or older); 53% male, 47% female; 85% White, 12% Asian, 3% Black; R-ISS stage at screening I (42%), II (53%), III (4%); 28% high cytogenetics risk, median number of 1 prior line of therapy; 5% with extramedullary disease (EMD) present; and of those who received treatment (n = 242), Eastern Cooperative Oncology Group Performance Status (ECOG PS) 0 (50%), 1 (46%), or 2 (4%). In the BVd arm, 90% of patients received prior proteasome inhibitor therapy (bortezomib, carfilzomib, ixazomib), 81% of patients received prior immunomodulator therapy (lenalidomide, thalidomide, pomalidomide), 1% of patients received prior daratumumab therapy, and 67% of patients who previously received autologous stem cell transplantation (ASCT). There were 9% of patients refractory to proteasome inhibitor therapy and 39% of patients refractory to immunomodulator therapy.

The primary endpoint was progression-free survival (PFS) as evaluated by a blinded Independent Review Committee (IRC) based on the IMWG criteria for multiple myeloma.

Patients treated with belantamab mafodotin in combination with bortezomib and dexamethasone had a statistically significant improvement in PFS, overall survival (OS), and minimal residual disease (MRD) negativity rate in the overall population compared with daratumumab, bortezomib and dexamethasone.

Efficacy results at the time of the first interim analysis (data cut-off 2 October 2023) except OS where data are presented from the second interim analysis data cut-off 7 October 2024) are presented in Table 8 and Figures 1 and 2.

Table 8. Efficacy results of belantamab mafodotin in DREAMM-7

	Belantamab mafodotin plus bortezomib and dexamethasone (BVd)[a] n = 243	**Daratumumab plus bortezomib and dexamethasone (DVd)[a] n = 251**
Progression-free survival (PFS)[b]		
Number (%) of patients with event	91 (37)	158 (63)
Median in months (95% CI)[c]	36.6 (28.4, NR)	13.4 (11.1, 17.5)
Hazard ratio (95% CI)[d]	0.41 (0.31, 0.53)	
p-value[e]	<0.00001	
Probability of PFS at 18 months (95% CI)[f]	69% (62, 75)	43% (36, 49)
Overall survival (OS)		
Number (%) of patients with event	68 (28)	103 (41)
Median in months (95% CI)[c]	NR (NR, NR)	NR (41, NR)
Hazard ratio (95% CI)[d]	0.58 (0.43, 0.79)	
p-value[e]	0.00023	
Probability of OS at 24 months (95% CI)[f]	79% (73, 84)	67% (61, 73)
Probability of OS at 36 months (95% CI)[f]	74% (68, 79)	60% (54, 66)
Duration of response (DOR)[b,g]		
Number of responders	201	179
Number (%) of responders: follow-up ongoing	106 (53%)	52 (29%)
Median in months (95% CI)[d]	35.6 (30.5, NR)	17.8 (13.8, 23.6)
Minimal residual disease (MRD) negativity rate[b,h,i]		
Percent of patients (95% CI)	24.7% (19.4, 30.6)	9.6% (6.2, 13.9)
p-value[j]	<0.00001	

CI = Confidence interval; NR = Not Reached.

[a] Efficacy data are based on the intent-to-treat (ITT) population, except DOR which is based on responders only.

[b] Response was based on IRC per IMWG criteria.

[c] By Brookmeyer and Crowley method.

[d] Based on stratified Cox regression model.

[e] One-sided p-value based on stratified log-rank test.

[f] By Kaplan-Meier method.

[g] For patients with a partial response or better.

[h] For patients with a complete response or better.
[i] Assessed by NGS at 10-5 threshold.
[j] Two-sided p-value based on stratified Cochran-Mantel-Haenszel test.

The PFS of BVd was maintained in all pre-specified subgroups including patients with high-risk cytogenetics [HR 0.36 (95% CI 0.22, 0.58); median PFS 33.2 months for BVd and 10.5 months for DVd], those exposed to lenalidomide [HR 0.33 (95% CI 0.23, 0.48); median PFS was not reached for BVd and 10.4 months for DVd] or refractory to lenalidomide [HR 0.37 (95% CI 0.24, 0.56); median PFS 25 months for BVd and 8.6 months for DVd].

Figure 1: Kaplan-Meier curve of progression-free survival per IRC in DREAMM-7

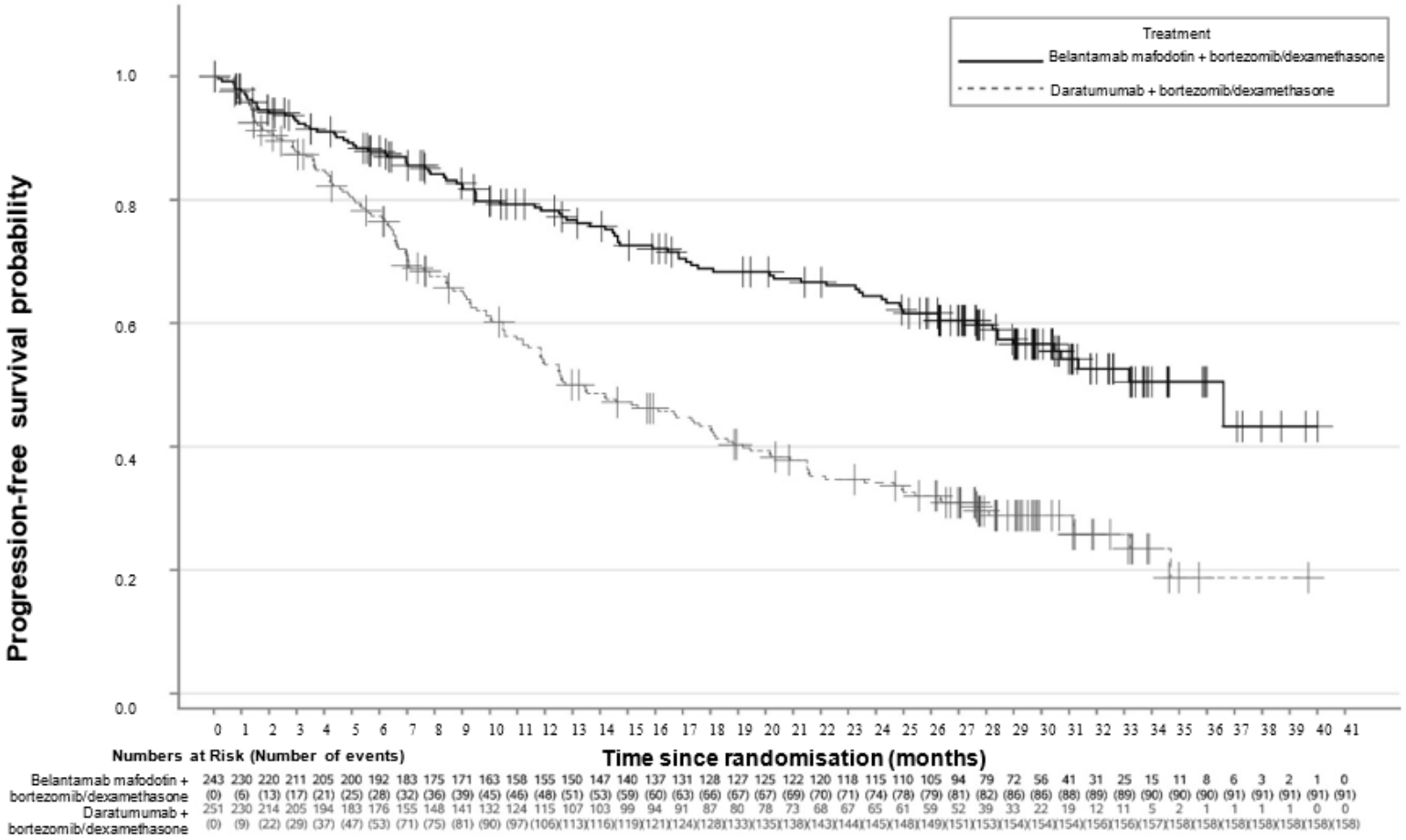
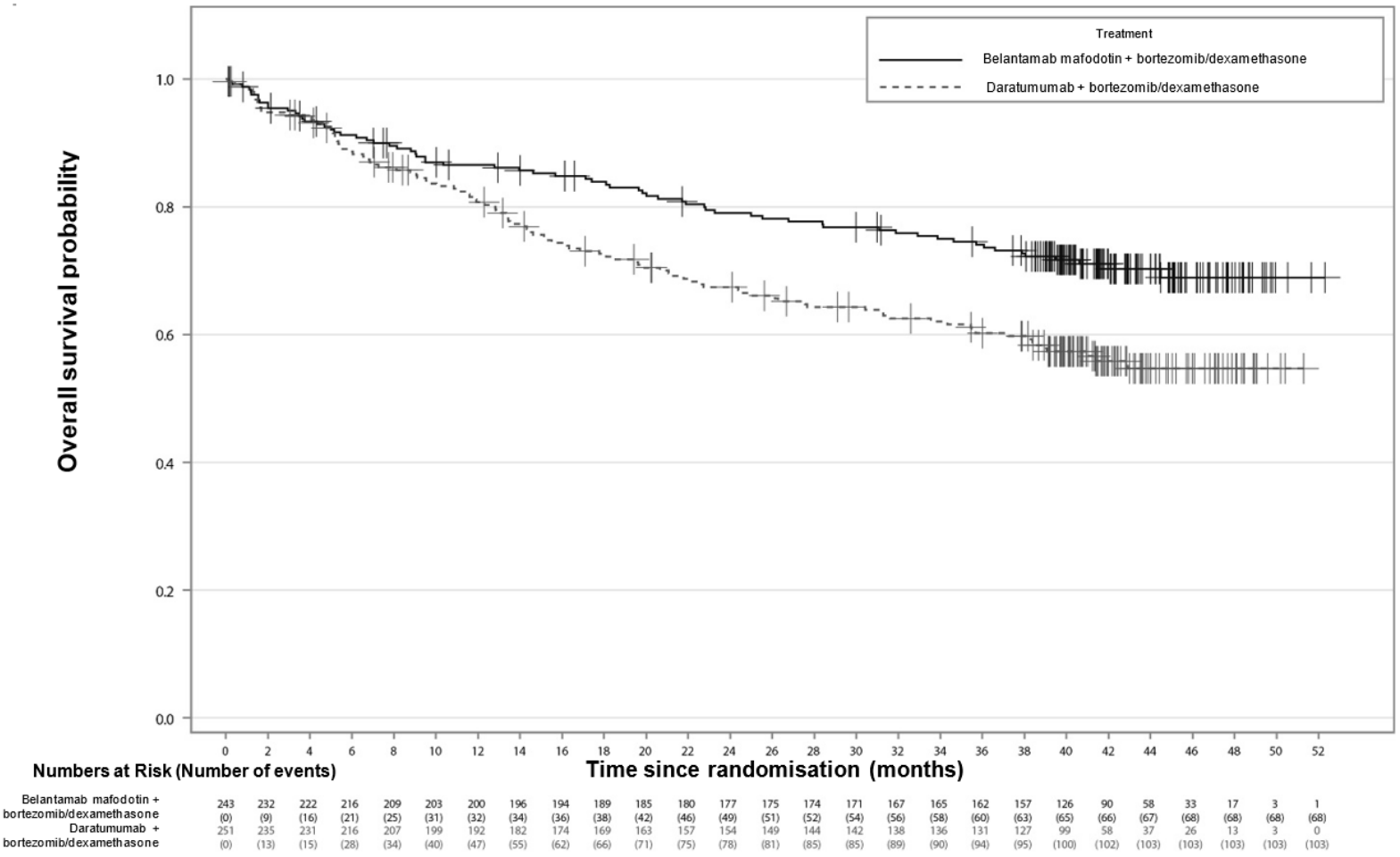


Figure 2: Kaplan-Meier curve of overall survival in DREAMM-7



Throughout the study, the recommended dose modifications, which included dose delays and reductions, managed adverse reactions and enabled patients to continue treatment. Due to dose adjustments in the DREAMM-7 study, the actual observed mean dose per patient was 2.2 mg/kg (median: 2.1 mg/kg) and the average dosing interval per patient was 7.2 weeks (median 5.7 weeks).Exposure to belantamab mafodotin observed during DREAMM-7 is presented in Table 9.

Table 9. Exposure to belantamab mafodotin in DREAMM-7

		Time intervals			
		0 to ≤ 6 months	**6 to ≤ 12 months**	**12+ months**	**Overall**
Number of patients		242	162	132	242
Number of infusions per patient	Mean	4.4	3.8	8.9	11.7
	Median (IQR)	4 (3, 6)	3 (2, 6)	6.5 (4, 13)	9 (4, 16)
Total number of doses		1133	577	1122	2832
Number of doses administered by dose level (%)	2.5 mg/kg	768 (68)	198 (34)	201 (18)	1167 (41)
	1.9 mg/kg	365 (32)	379 (66)	921 (82)	1665 (59)
Time between doses per patient (weeks)[a]	n	231	130	124	231
	Mean	4.8	6.8	10.9	7.2
	Median (IQR)	3.6 (3, 6)	4.7 (3, 8)	9.5 (5, 15)	5.7 (3, 10)

IQR = Interquartile range.

[a] Intervals for 0 to ≤ 6 months, > 6 to ≤ 12 months, and > 12 months, were calculated either by using days or days converted into months.

DREAMM-8: Combination with pomalidomide and dexamethasone

DREAMM-8 was an open-label, Phase III, multicentre study which evaluated belantamab mafodotin in combination with pomalidomide and dexamethosone (BPd) compared with pomalidomide, bortezomib, dexamethasone (PVd) in patients with relapsed or refractory multiple myeloma.

Eligible patients had a confirmed diagnosis of multiple myeloma (MM) as defined by IMWG criteria, had previously been treated with at least 1 prior line of MM therapy, including lenalidomide, and must have had documented disease progression during or after their most recent therapy.

Patients were randomised in a 1:1 ratio to receive either BPd or PVd, stratified by the number of prior lines of treatment, prior to exposure to bortezomib, prior anti-CD38 treatment and International Staging System (ISS) status. In the BPd arm (N = 155), patients received belantamab mafodotin 2.5 mg/kg (IV) once on day 1 in Cycle 1 (28-day Cycle) followed by belantamab mafodotin 1.9 mg/kg (IV) every 4 weeks on day 1 in Cycle 2 onwards (28-day Cycles); pomalidomide 4 mg (orally [PO]) administered on days 1 to 21 and dexamethasone 40 mg (PO) on Days 1, 8, 15, and 22 in all Cycles (28-day Cycles). In the PVd arm (N = 147), pomalidomide 4 mg (PO) was administered every 3 weeks on days 1 to 14 in all cycles (21-day Cycles); bortezomib 1.3 mg/m^2 was administered subcutaneously on days 1, 4, 8, and 11 in Cycles 1 to 8, and on days 1 and 8 in Cycle 9+ (21-day Cycles). Dexamethasone 20 mg (PO) was administered on the day of and the day after bortezomib. The dose level of dexamethasone in each arm was reduced by half in patients aged 75 years and older. Treatment in both arms continued until progressive disease, unacceptable toxicity, withdrawal of consent, initiation of another anticancer therapy, end of study or death.

A total of 302 patients with MM were evaluated for efficacy in DREAMM-8. Baseline demographics and characteristics were similar across both arms. Baseline characteristics for

the BPd arm (n = 155) were: median age: 67 years (46% aged 65 to 74 years and 12% aged 75 years or older); 64% male, 36% female; 86% White, 13% Asian, <1% Native Hawaiian or other Pacific Islander, <1% Mixed Race; ISS stage at screening I (60%), II (25%), III (14%); 34% high cytogenetic risk, median number of 1 prior line of therapy; 13% with EMD present; and of those who received treatment (n = 150), ECOG PS 0 (53%), 1 (45%), or 2 (3%). In the BPd arm, 100% of patients received prior immunomodulator therapy (lenalidomide, thalidomide), 90% of patients received prior proteasome inhibitor therapy (bortezomib, carfilzomib, ixazomib), 25% of patients received prior anti-CD38 therapy (daratumumab, isatuximab) and 64% of patients who previously received ASCT. There were 82% of patients refractory to immunomodulator therapy, 26% of patients refractory to proteasome inhibitor therapy, and 23% of patients refractory to anti-CD38 therapy.

The primary endpoint was Progression Free Survival (PFS) as evaluated by a blinded Independent Review Committee (IRC) based on the International Myeloma Working Group (IMWG) criteria for multiple myeloma.

Patients treated with belantamab mafodotin in combination with pomalidomide and dexamethasone had a statistically significant improvement in PFS in the overall population compared with pomalidomide, bortezomib and dexamethasone.

Efficacy results at the time of the first interim analysis (data cut-off 29 January 2024) are presented in Table 10 and Figures 3 and 4.

Table 10. Efficacy results of belantamab mafodotin in DREAMM-8

	Belantamab mafodotin plus pomalidomide and dexamethasone (BPd)[a] N = 155	Pomalidomide plus bortezomib and dexamethasone (PVd)[a] N = 147
Progression-free survival (PFS)[b]		
Number (%) of patients with event	62 (40)	80 (54)
Median in months (95% CI)[c,d,e]	NR (20.6, NR)	12.7 (9.1, 18.5)
Hazard ratio (95% CI)[f]	0.52 (0.37, 0.73)	
p-value[g]	<0.001	
Probability of PFS at 12 months (95% CI)[h]	71% (63, 78)	51% (42, 60)
Overall survival (OS)		
Number (%) of patients with event	49 (32)	56 (38)
Median in months (95% CI)[c]	NR (33, NR)	NR (25.2, NR)
Hazard ratio (95% CI)[f]	0.77 (0.53, 1.14)	
Probability of OS at 12 months (95% CI)[h]	83% (76, 88)	76% (68, 82)
Minimal residual disease (MRD) negativity rate[b,i,j]		
Percent of patients (95% CI)	23.9% (17.4, 31.4)	4.8% (1.9, 9.6)
Duration of response (DOR)[b,k]		
Number of responders	120	106
Number (%) of responders: follow-up ongoing[e]	66 (55)	33 (31)
Median in months (95% CI)[c]	NR (24.9, NR)	17.5 (12.1, 26.4)

CI = Confidence interval; NR = Not Reached.

[a] Efficacy data are based on the intent-to-treat (ITT) population, except DOR which is based on responders only.

[b] Response was based on IRC per IMWG criteria.

[c] By Brookmeyer and Crowley method.

[d] Median follow-up of 21.8 months.

[e] At the time of the data cut-off (29 JAN 2024).

[f] Based on stratified Cox regression model.

[g] One-sided p-value based on stratified log-rank test.

[h] By Kaplan-Meier method.

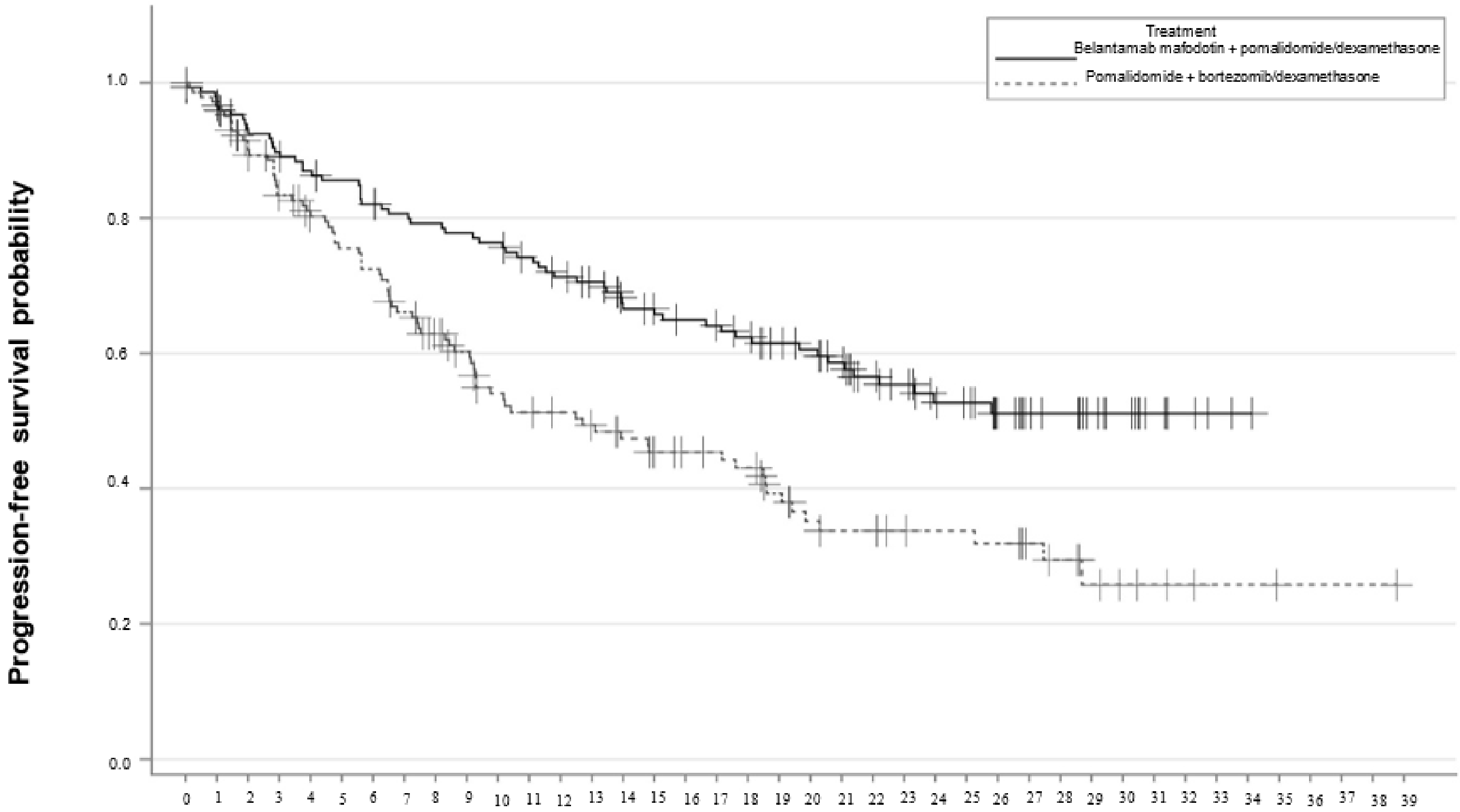
[i] For patients with a complete response or better.

[j] Assessed by NGS at 10-5 threshold.

[k] For patients with a partial response or better.

The PFS of BVd was maintained in all pre-specified subgroups including patients with high-risk cytogenetics [HR 0.57 (95% CI 0.34, 0.95); median PFS 17.6 months for BPd and 9.1 months for PVd], those refractory to lenalidomide [HR 0.45 (95% CI 0.31, 0.65); median PFS 24 months for BPd and 9.2 months for PVd] or refractory to anti-CD38 agents [HR 0.65 (95% CI 0.36, 1.18); median PFS 11.5 months for BPd and 6.4 months for PVd].

Figure 3: Kaplan-Meier curve of progression-free survival per IRC in DREAMM-8

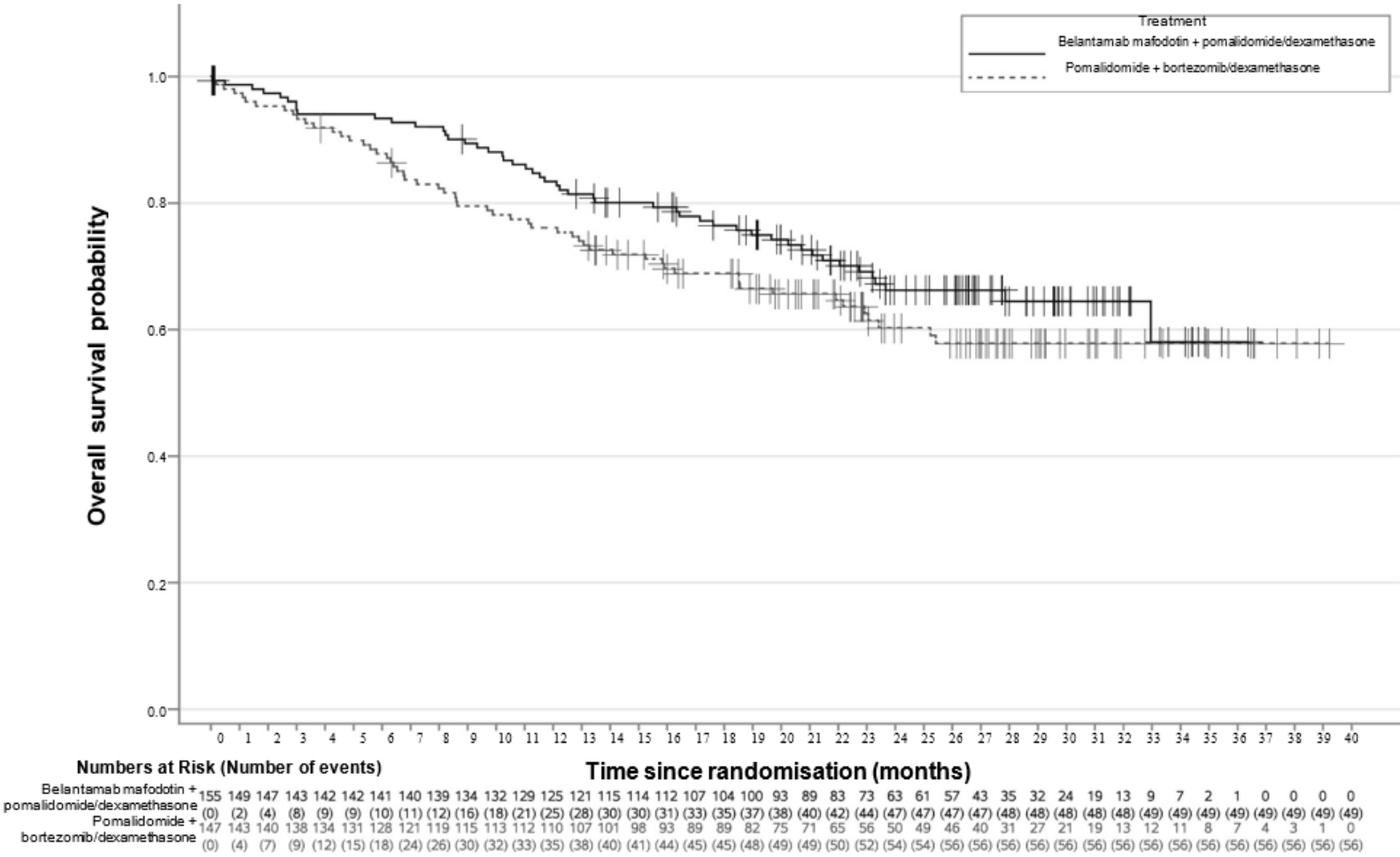


Numbers at Risk (Number of events)

	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
Belantamab mafodotin + pomalidomide/dexamethasone	155 (0)	143 (5)	135 (10)	130 (15)	125 (19)	122 (21)	117 (26)	113 (28)	111 (30)	109 (32)	107 (34)	102 (37)	97 (41)	93 (42)	82 (47)	80 (47)	77 (49)	75 (50)	72 (52)	67 (53)
Pomalidomide + bortezomib/dexamethasone	147 (0)	138 (4)	123 (14)	111 (23)	102 (27)	96 (33)	92 (37)	83 (45)	75 (49)	68 (52)	59 (59)	56 (62)	54 (62)	51 (64)	47 (66)	43 (68)	40 (68)	39 (68)	37 (70)	30 (73)

	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39
Belantamab mafodotin + pomalidomide/dexamethasone	64 (54)	59 (56)	50 (58)	45 (59)	38 (61)	36 (61)	28 (62)	23 (62)	21 (62)	16 (62)	13 (62)	8 (62)	4 (62)	2 (62)	1 (62)	0 (62)	0 (62)	0 (62)	0 (62)	0 (62)
Pomalidomide + bortezomib/dexamethasone	25 (76)	22 (77)	22 (77)	19 (77)	18 (77)	18 (77)	17 (78)	13 (78)	11 (79)	7 (80)	5 (80)	4 (80)	3 (80)	2 (80)	2 (80)	1 (80)	1 (80)	1 (80)	1 (80)	0 (80)

Figure 4: Kaplan-Meier curve of overall survival in DREAMM-8



Throughout the study, the recommended dose modifications, which included dose delays and reductions, managed adverse reactions and enabled patients to continue treatment. Due to dose adjustments in the DREAMM-8 study, the mean dose per patient was 2 mg/kg (median: 2 mg/kg) and the average dosing interval per patient was 9.5 weeks (median 8.7 weeks). Exposure to belantamab mafodotin observed during DREAMM-8 is presented in Table 11.

Table 11. Exposure to belantamab mafodotin in DREAMM-8

		Time intervals			
		0 to ≤ 6 months	**> 6 to ≤ 12 months**	**> 12 months**	**Overall**
Number of patients		150	104	77	150
Number of infusions per patient	Mean	3.8	2.3	3.7	7.3
	Median (IQR)	4 (3, 5)	2 (1, 3)	3 (1, 5)	6 (4, 10)
Total number of doses		570	242	286	1098
Number of doses administered by dose level (%)	2.5 mg/kg	151 (26)	–	–	151 (14)
	1.9 mg/kg	415 (73)	235 (97)	267 (93)	917 (84)
	1.4 mg/kg	4 (<1)	7 (3)	19 (7)	30 (3)

Time between doses per patient (weeks)[a]	n	129	79	77	142
	Mean	5.3	11.9	14.2	9.5
	Median (IQR)	4.1 (4, 5)	11.8 (5, 16)	14.1 (10, 18)	8.7 (5, 13)

IQR = Interquartile range

[a] Intervals for 0 to ≤ 6 months, > 6 to ≤ 12 months, and > 12 months, were calculated either by using days or days converted into months.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Maximum concentration for belantamab mafodotin ADC occurred at or shortly after the end of infusion while cys-mcMMAF concentrations peaked ~24 hours after dosing.

Tables 12 and 13 describe the pharmacokinetics of belantamab mafodotin for 2.5 mg/kg doses on Cycle 1 Day 1 at the end of the first 3- and 4-week intervals.

Table 12. Belantamab mafodotin pharmacokinetics at the end of the first 3-week interval[a]

	AUC[b]	**C_{avg21}**	**C_{max}**	**C_{tau}**
ADC (%)	3950 µg•h/mL (30.6)	7.83 µg/mL (30.6)	43.7 µg/mL (22.1)	2.03 µg/mL (62.5)
cys-mcMMAF (%)	94.2 ng•h/mL (42.3)	0.243 ng/mL (42.4)	0.976 ng/mL (45.3)	–

ADC = antibody drug conjugate; AUC = Area under the curve; C_{avg21} = belantamab mafodotin average concentration over 21 days; C_{max} = maximum plasma concentration; C_{tau} = concentration at the end of a dosing interval.

[a] Data presented as geometric mean (%CV), based on population PK models.

[b] AUC for ADC is $AUC_{(0\text{-}21)days}$, and $AUC_{(0\text{-}7days)}$ for cys-mcMMAF.

Table 13. Belantamab mafodotin pharmacokinetics at the end of the first 4-week interval[a]

	AUC[b]	**C_{avg28}**	**C_{max}**	**C_{tau}**
ADC (%)	4504 µg•h/mL (25)	6.70 µg/mL (25)	47.1 µg/mL (18.9)	1.57 µg/mL (53)
cys-mcMMAF (%)	90.5 ng•h/mL (40.9)	0.182 ng/mL (42.7)	0.933 ng/mL (41.7)	–

ADC = antibody drug conjugate; AUC = Area under the curve; C_{avg28} = belantamab mafodotin average concentration over 28 days; C_{max} = maximum plasma concentration; C_{tau} = concentration at the end of a dosing interval.

[a] Data presented as geometric mean (%CV), based on population PK models.

[b] AUC for ADC is $AUC_{(0\text{-}28days),}$ and $AUC_{(0\text{-}7days)}$ for cys-mcMMAF.

Accumulation of belantamab mafodotin (ADC) was minimal to moderate as observed in clinical studies with a every 3 weeks dosing regimen.

Distribution

In vitro, cys-mcMMAF exhibited low protein binding (70% unbound at a concentration of 5 ng/mL) in human plasma in a concentration-dependent manner.

Based on the population PK analysis, the geometric mean (geometric CV%) for steady-state volume of distribution of belantamab mafodotin was 10.8 L (22%).

Metabolism

The monoclonal antibody portion of belantamab mafodotin is expected to undergo proteolysis to small peptides and individual amino acids by ubiquitous proteolytic enzymes. Cys-mcMMAF had limited metabolic clearance in human hepatic S9 fraction incubation studies.

Elimination

Based on the population PK analysis, the geometric mean (geometric CV%) belantamab mafodotin (ADC) initial systemic CL was 0.901 L/day (40%), and the elimination half-life was 13 days (26%). Following treatment, steady-state CL was 0.605 L/day (43%) or approximately 33% lower than initial systemic CL with an elimination half-life of 17 days (31%).

The fraction of cys-mcMMAF excreted in urine was not substantial (approximately 18% of the dose) after the Cycle 1 dose, with no evidence of other MMAF-related metabolites.

Belantamab mafodotin exhibits dose-proportional pharmacokinetics over the recommended dose range with a reduction in clearance over time.

Special patient populations

Children

No pharmacokinetic data are available in paediatric patients.

Elderly

Based on a population of patients aged 32 to 89 years, age was not a significant covariate in population pharmacokinetics analyses.

Renal impairment

In patients with severe renal impairment (eGFR: 15 to 29 mL/min), belantamab mafodotin C_{max} decreased by 23% and $AUC_{(0\text{-}tau)}$ decreased by 16% compared with patients with normal or mild renal impairment (eGFR ≥ 60 mL/min). For cys-mcMMAF, C_{max} and $AUC_{(0\text{-}168h)}$ decreased by 56% and 44%, respectively compared to patients with normal or mild renal impairment. Renal function (eGFR:12 to 150 mL/min) was not a significant covariate in population pharmacokinetic analyses that included patients with normal or mild, moderate, or severe renal impairment, or kidney failure.

Belantamab mafodotin is not expected to be removed via dialysis due to its molecular size. While free cys-mcMMAF may be removed via dialysis, cys-mcMMAF systemic exposure is very low and has not been shown to be associated with efficacy or safety endpoints based on exposure-response analysis.

Hepatic impairment

No formal studies have been conducted in patients with hepatic impairment. Hepatic function, as per National Cancer Institute Organ Dysfunction Working Group classification, was not a significant covariate in population pharmacokinetic analyses that included patients with normal hepatic function, mild (total bilirubin greater than ULN to ≤ 1.5 x ULN and any AST or total bilirubin ≤ ULN with AST > ULN) or moderate hepatic impairment (total bilirubin greater than 1.5 x ULN to ≤ 3 × ULN and any AST).

Body weight

Body weight (37 to 170 kg) was a significant covariate in population pharmacokinetic analyses, but this effect was not clinically relevant with the weight-proportional dosing regimen.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Belantamab mafodotin was genotoxic in an *in vitro* micronucleus screening assay in human lymphocytes, consistent with the pharmacological effect of cys-mcMMAF-mediated disruption of microtubules causing aneuploidy.

No definitive genotoxicity studies have been conducted with belantamab mafodotin.

Carcinogenicity

No carcinogenicity studies have been conducted with belantamab mafodotin.

Animal toxicology and/or pharmacology

In nonclinical studies, the principal adverse findings (directly related to belantamab mafodotin) in the rat and monkey, at exposures ≥ 1.2 times of the recommended clinical dose of 2.5 mg/kg, were elevated liver enzymes sometimes associated with hepatocellular necrosis at ≥ 10 and ≥ 3 mg/kg, respectively, and increases in alveolar macrophages associated with eosinophilic material in the lungs at ≥ 3 mg/kg (rat only). Most findings in animals were related to the cytotoxic drug conjugate, the histopathological changes observed in the testes and lungs, were not reversible in rats.

Single cell necrosis in the corneal epithelium and/or increased mitoses of corneal epithelial cells was observed in rat and rabbit. Inflammation of the corneal stroma correlating with superficial haze and vascularisation was observed in rabbits. Belantamab mafodotin was taken up into cells throughout the body by a mechanism unrelated to BCMA receptor expression on the cell membrane.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Sodium citrate dihydrate

Citric acid monohydrate

Trehalose dihydrate

Disodium edetate

Polysorbate 80

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

In the absence of compatibility studies, the reconstituted concentrate and diluted solution for infusion must not be mixed with other medicinal products.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store in the original container.

Store in a refrigerator (2˚C to 8˚C).

Do not freeze.

Reconstituted solution

The reconstituted solution can be stored for up to 4 hours at room temperature (20˚C to 25˚C) or stored in a refrigerator (2˚C to 8˚C) for up to 4 hours.

Do not freeze.

Diluted solution

If not used immediately, the diluted solution can be stored in a refrigerator (2˚C to 8˚C) prior to administration for up to 24 hours.

Do not freeze.

If refrigerated, allow the diluted solution to equilibrate to room temperature prior to administration.

The diluted infusion solution may be kept at room temperature (20˚C to 25˚C) for a maximum of 6 hours (including infusion time).

6.5 NATURE AND CONTENTS OF CONTAINER

Sterile lyophilised powder in a type I glass vial with bromobutyl rubber stopper and an aluminium overseal with a plastic removable cap.

The drug is supplied in a single use vial without a preservative.

Not all strengths, dose forms, pack sizes, container types may be distributed in Australia.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

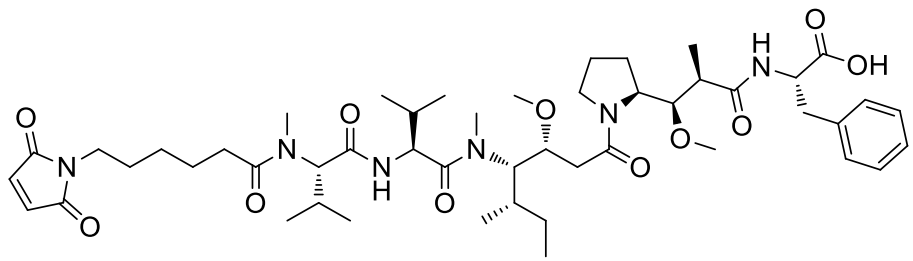
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

Belantamab mafodotin is an antibody-drug conjugate (ADC) that includes an IgG1 monoclonal antibody that contains sixteen (16) disulfide bonds, including four (4) interchain. Belantamab is partially reduced and conjugated with SGD-1269 at the interchain cysteine residues, resulting in belantamab mafodotin, which has a target drug-antibody ratio (DAR) of four (4).

SGD-1269



CAS number

2050232-20-5

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine

8 SPONSOR

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Abbotsford, Victoria, 3067

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9 DATE OF FIRST APPROVAL

17 November 2025

10 DATE OF REVISION

Not applicable

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
N/A	New Product Information

Version 1.0