BLA 761158: Belantamab mafodotin

Oncologic Drugs Advisory Committee Meeting

Introductory Comments

July 14, 2020

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Office of Oncologic Diseases

Approved Drugs for the Treatment of MM

- 12 drugs are approved for the treatment of relapsed or refractory multiple myeloma (MM).

- 7 new drugs or biologics have been approved since 2015, including a histone deacetylase (HDAC) inhibitor, an oral proteasome inhibitor, monoclonal antibodies (targeting CD38 and SLAMF7) and a nuclear export inhibitor.

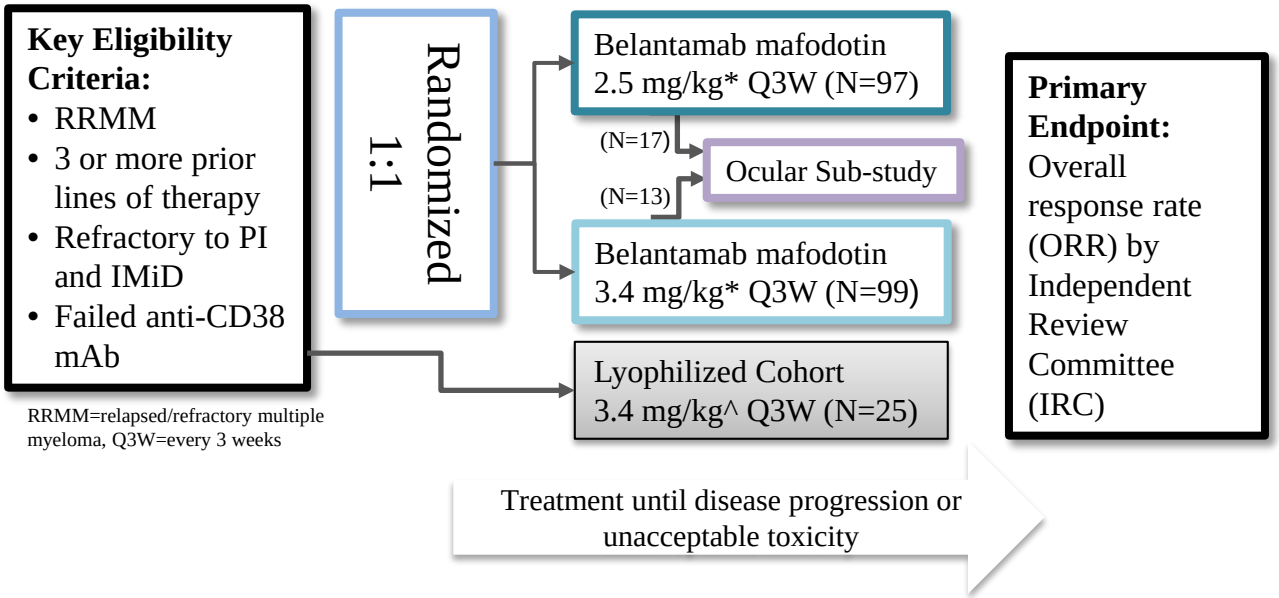
Belantamab mafodotin

Proposed Indication:

Belantamab mafodotin is a B-cell maturation antigen (BCMA)-directed antibody and microtubule inhibitor conjugate indicated for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least 4 prior therapies including an anti-CD38 monoclonal antibody (mAb), a proteasome inhibitor (PI), and an immunomodulatory agent (IMiD)

Study 205678 (DREAMM-2)

Two-arm, open label, multicenter study of two doses of belantamab mafodotin in patients with relapsed/refractory multiple myeloma



*Frozen liquid formulation; ^ 2.5 mg/kg lyophilized formulation proposed for marketing

DREAMM-2 Efficacy

Evaluable patient population at 2.5 mg/kg dose: 97

Primary Endpoint: ORR based on International Myeloma Working Group (IMWG) criteria by IRC

	2.5 mg/Kg^* N=97
ORR, n (%) (97.5% CI)	30 (31) (20.8, 42.6)
Best Response, n (%)	
sCR	2 (2)
CR	1 (1)
VGPR	15 (15)
PR	12 (12)

Source: FDA Analysis

sCR: stringent complete response, CR: complete response, VGPR: very good partial response, PR: partial response

^Primary Analysis: Data cut-off: June 21,2019; Median duration of follow-up:6.3 months; *Frozen liquid formulation

Median Duration of Response: Not Reached [95% CI: ---, ---]

DREAMM-2: Safety

	2.5 mg/kg (N=95)		3.4 mg/kg (N=99)	
	n	%	n	%
Keratopathy~	67	71	77	76
Thrombocytopenia*^	33	35	58	59
Anemia*	23	24	37	37
Nausea	23	24	32	32
Pyrexia	21	22	25	25
Vision blurred^	21	22	30	30
Infusion related reaction	20	21	16	16
Fatigue*	19	20	34	34
Dry Eye^	13	14	21	21
AST increased*^	19	20	24	24
Lymphopenia*^	19	20	17	17
Upper Respiratory tract infection^	10	11	25	25
Neutropenia*^	13	14	26	26
Vomiting	7	7	20	20

Source: FDA Analysis (Treatment emergent adverse events≥20% of Patients in either dose) data cut-off June 21,2019;
^ FDA Grouped preferred terms; ~ Based on ocular exams and study specific Keratopathy Visual Acuity (KVA) scale
**Rates based on laboratory dataset (2.5mg/kg,3.4 mg/kg): Platelets decreased:62%,74%; hemoglobin decreased:32%,44%; AST increased:57%,69%;neutrophils decreased:28%,46%; lymphocytes decreased:49%,46%*

Issue: Ocular Toxicity

- Known risks
  - Keratopathy was the most frequent adverse event
    - 44% had severe keratopathy
    - Associated with decreased visual acuity and severe vision loss in some patients
    - Interference with patients' activities of daily living and driving and reading abilities
  - Symptoms not always present despite findings on ophthalmic exam
  - This toxicity is unique among anti-MM agents

Issue: Ocular Toxicity

- Uncertainties
  - The mechanism of ocular toxicity with belantamab mafodotin is not completely understood
  - Dose modification primary strategy to mitigate ocular toxicity
    - Recurrent and persistent ocular toxicity despite dose modifications
  - Inadequate characterization of reversibility and severity of ocular toxicity
    - High proportion of patients had keratopathy that was unresolved as of the last follow-up

Discussion

- Discuss whether the risk of ocular toxicity has been adequately characterized in Study 205678 (DREAMM-2) to allow for an assessment of the benefit-risk profile.

- Discuss the impact of ocular toxicity on the benefit-risk profile for belantamab mafodotin.

Voting Question

Does the demonstrated benefit of belantamab mafodotin outweigh the risks in the proposed patient population with multiple myeloma?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Discussion Topics

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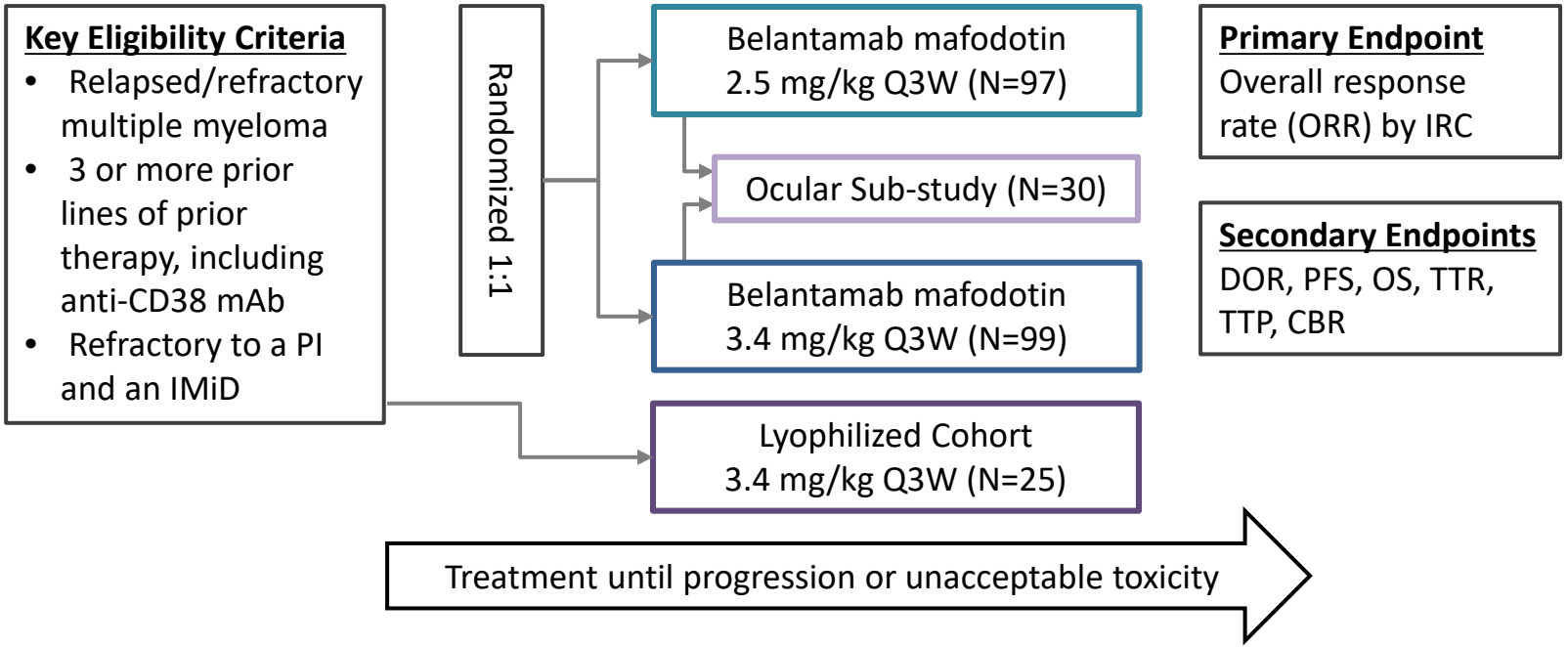
DREAMM-2 Trial Design



PI=proteasome inhibitor, IMiD=immunomodulatory agent, mAb=monoclonal antibody, Q3W=every 3 weeks, IRC=Independent Review Committee, DOR=duration of response, PFS=progression-free survival, OS=overall survival, TTR=time-to-response, TTP=time-to-progression, CBR=clinical benefit rate

Source: FDA

DREAMM-2 Efficacy Summary

	2.5 mg/kg (N=97)	3.4 mg/kg (N=99)
ORR*, n (%) [97.5% CI]	30 (31) [20.8, 42.6]	34 (34) [23.9, 46]
Best Response, n (%) sCR CR VGPR PR	 2 (2) 1 (1) 15 (15) 12 (12)	 3 (3) 0 17 (17) 14 (14)
Median Duration of Response, months Median [95% CI] Response ≥6 months	 NR [NR, NR] 70%	 NR [4.9, NR] 64%
Median PFS, months [95% CI]	2.9 [2.1, 3.7]	4.9 [2.3, 6.2]
Overall Survival	Not mature at time of data analysis	

*Median follow-up 6.3 months; ORR=overall response rate, NR=Not Reached, CI=confidence interval, sCR=stringent complete response, CR=complete response, VGPR=very good partial response, PR=partial response, PFS=progression-free survival

Source: FDA Analysis

Key Safety Issue: Ocular Toxicity

- High incidence of ocular toxicity, including severe events
- Decreased visual acuity, including severe vision loss
- Absence of ocular symptoms despite findings on exam
- Frequent need for dose modifications due to ocular toxicity
- Recurrent and unresolved events of ocular toxicity

Adverse Events in DREAMM-2

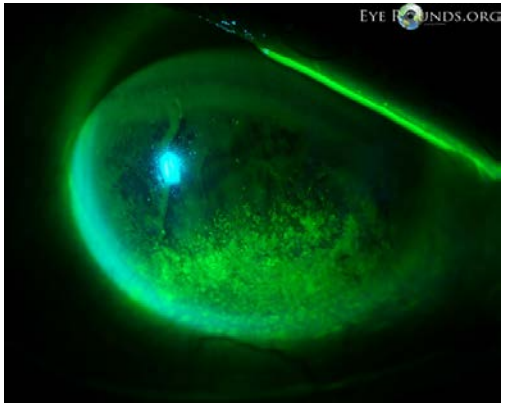
Adverse Event Term	2.5 mg/kg (N=95), n (%)	3.4 mg/kg (N=99), n (%)
Any adverse event	93 (98)	99 (100)
Keratopathy†	67 (71)	76 (77)
Thrombocytopenia*♦	33 (35)	58 (59)
Anemia♦	23 (24)	37 (37)
Nausea	23 (24)	32 (32)
Pyrexia	21 (22)	25 (25)
Blurred vision*	21 (22)	30 (30)
Infusion-related reaction$^{\Delta}$	20 (21)	16 (16)
Fatigue*	19 (20)	34 (34)
AST increased♦	19 (20)	24 (24)
Lymphopenia*♦	19 (20)	17 (17)
Dry eye*	13 (14)	21 (21)
Neutropenia*♦	13 (14)	26 (26)
Upper respiratory tract infection*	10 (11)	25 (25)
Vomiting	7 (7)	20 (20)

† Based on Keratopathy Visual Acuity (KVA) Scale
* Includes grouped terms
♦ Based on adverse event capture; rates are higher based on laboratory data
$^{\Delta}$ Based on terms considered by investigator to be part of an infusion-related reaction

Source: FDA Analysis

Mechanism of Ocular Toxicity

- Mechanism not completely understood; class effect for MMAF-containing ADCs
- Keratopathy: damage to the corneal epithelium; risk of corneal ulcers
- Ophthalmic exams at baseline and prior to each dose in DREAMM-2
- Dose modifications are the primary mitigating strategy
- Topical corticosteroids showed no impact in DREAMM-2 ocular sub-study



Source: *https://webeye.ophth.uiowa.edu/eyeforum/atlas/pages/Punctate-epithelial-erosions/Exposure-PEE-LRG.jpg*

ADC=antibody-drug conjugate, MMAF=monomethyl auristatin F (mafodotin)

DREAMM-2 Ocular Toxicity Grading Scales

Grade	KVA Scale*		CTCAE Grading
	Corneal Exam	Visual Acuity	Eye Disorders - Other
1	• Mild superficial keratopathy	• Change of 1 line from baseline	• Asymptomatic or mild symptoms • Intervention not indicated
2	• Moderate punctate keratopathy • Mild/patchy microcysts • Mild/patchy epithelial/stromal edema • Sub-epithelial haze (peripheral) • Active stromal opacity (peripheral)	• Change of 2-3 lines from baseline, and • Not worse than 20/200	• Moderate • Minimal intervention indicated • Limiting IADL
3	• Severe punctate keratopathy • Diffuse microcysts • Diffuse epithelial/stromal edema • Sub-epithelial haze (central) • Active stromal opacity (central)	• Change of more than 3 lines from baseline, and • Not worse than 20/200	• Severe or medically significant, but not immediately sight-threatening • Hospitalization indicated • Disabling • Limiting ADL
4	• Corneal ulcer	• Worse than 20/200	• Sight-threatening consequences • Urgent intervention indicated • Blindness (20/200 or worse) in affected eye

*Overall grade based on most severe finding on corneal or visual acuity exam

KVA=Keratopathy Visual Acuity, CTCAE=Common Terminology Criteria for Adverse Events, ADL=Activities of daily living, IADL=Instrumental ADL

Comparison of Ocular Toxicity Grading Scales

	2.5 mg/kg (N=95)	
Grade	**KVA***	**CTCAE**
All Grades	67 (71)	67 (71)
1	8 (8)	12 (13)
2	17 (18)	29 (31)
3	42 (44)	26 (27)
4	0†	0

*Based on grading of keratopathy identified on ophthalmic exam (corneal exam component of KVA scale)

†Two patients had Grade 4 events based on visual acuity changes

KVA= Keratopathy Visual Acuity scale, CTCAE=Common Terminology Criteria for Adverse Events

Source: FDA Analysis

Incidence and Severity of Keratopathy

	2.5 mg/kg (N=95) n (%)	3.4 mg/kg (N=99) n (%)	3.4 mg/kg Lyophilized (N=24) n (%)
Adverse event category*			
Any grade keratopathy	67 (71)	76 (77)	22 (92)
Grade ≥2 keratopathy	59 (62)	70 (71)	20 (91)
Grade 3-4 (severe) keratopathy	42 (44)	41 (41)	17 (77)
Serious keratopathy†	0	0	1 (5)
Other characteristics*			
Median time to onset (Grade ≥2), days (range)	36 (19-143)	22.5 (9-150)	22.5 (18-62)
Recurrent (>1) events (Grade ≥2)	23 (39)	23 (33)	2 (10)

*Based on grading of keratopathy identified on ophthalmic exam (corneal exam component of KVA scale)
†Designated as "serious" based on adverse event capture (CTCAE scale)

Source: FDA Analysis

Decreased Visual Acuity

Decrease in Best-Corrected Visual Acuity (BCVA)	2.5 mg/kg (N=95) n (%)	3.4 mg/kg (N=99) n (%)
Any worsening (≥1 line decrease)	50 (53)	48 (48)
Severe worsening (>3 line decrease)	25 (26)	22 (22)
Unilateral 20/50 or worse	18 (19)	17 (17)
Bilateral 20/50 or worse*	16 (17)	17 (17)
Unilateral 20/200 or worse	5 (5)	6 (6)
Bilateral 20/200 or worse†	1 (1)	2 (2)

*Level at which an individual may not be legally able to drive

†Level meets the definition of legal blindness in the U.S.

BCVA=best corrected visual acuity

Source: FDA Analysis

Patients with Severe Vision Loss

Patient #1	Baseline		Week 4	Day 42 (EOT)
Visual Acuity	R	>20/400	>20/400	>20/400
	L	20/80	20/200	20/60
Dose	2.5 mg		2.5 mg	

Patient #2	Baseline		Week 4	Week 7	Day 56	Week 10	Week 13	Week 16	Week 19	Week 22	Day 168 (EOT)	Day 227 (F/U)
Visual Acuity	R	20/40	20/30	20/50	20/400	20/80	20/70	20/50	20/80	20/60	20/50	20/30
	L	20/20	20/20	20/70	>20/400	>20/400	20/100	20/50	20/50	20/50	20/30	20/25
Dose	3.4 mg		3.4 mg									
Keratopathy				Grade 3	Grade 3	Grade 3	Grade 3	Grade 3	Grade 2	Grade 3		

Patient #3	Baseline		Week 4	Day 36	Day 45	Week 10	Day 85 (EOT)	Day 141	Day 232	Day 288 (F/U)
Visual Acuity	R	20/25	20/32	20/40	20/160	20/320	20/125	20/63	20/25	20/32
	L	20/20	20/25	20/50	20/100	>20/400	20/100	20/32	20/25	20/25
Dose	3.4 mg		3.4 mg							
Keratopathy			Grade 1	Grade 2	Grade 3	Grade 3	Grade 2	Grade 2	Grade 2	

R=right eye, L=left eye, EOT=end of treatment, F/U=follow-up

Source: FDA Analysis

Ocular Symptoms in Patients with Keratopathy

Adverse Event	2.5 mg/kg (N=95) n (%)	3.4 mg/kg (N=99) n (%)
Patients with keratopathy	67 (71)	76 (77)
Symptoms in patients with keratopathy		
Any ocular symptoms*	29 (43)	42 (55)
Blurred vision	21 (31)	29 (38)
Dry eye	12 (18)	18 (24)
Photophobia	3 (4)	5 (7)
Eye pain	1 (1)	3 (4)

*Includes preferred terms diplopia, dry eye, eye irritation, eye pain, eye pruritus, foreign body sensation in eyes, lacrimation increased, ocular discomfort, ocular hyperemia, photophobia, vision blurred, visual acuity reduced, and visual impairment

Source: FDA Analysis

Dose Modifications Due to Keratopathy

Dose Modifications*	2.5 mg/kg (N=95) n (%)	3.4 mg/kg (N=99) n (%)
Any dose modification	45 (47)	50 (51)†
Dose interruption/delays	45 (47)	48 (48)
Dose reduction	22 (23)	27 (27)
Permanent discontinuationΔ	2 (2)	3 (3)

*Based on keratopathy by CTCAE scale

†71% in the 3.4 mg/kg lyophilized cohort (N=24)

Δ Discontinuations that occurred were due to Grade 2 or 3 keratopathy

Source: FDA Analysis

Outcomes of Keratopathy

	Primary Analysis 2.5 mg/kg (N=95) n (%)	90-Day Update 2.5 mg/kg (N=95) n (%)
Any grade keratopathy*	67 (71)	68 (72)†
Grade ≥2 keratopathy	59 (62)	60 (63)
Recovery rate (Grade ≥2 events)	24 (41)	29 (48)
Not resolved, treatment ongoing	17 (29)	13 (22)
Not resolved, follow-up ongoing	4 (7)	3 (5)
Not resolved, follow-up ended$^{\Delta}$	14 (24)	15 (25)
Median time to resolution (Grade ≤1), days (range)	62 (11-193)	78 (11-232)

*Based on grading of keratopathy identified on ophthalmic exam (corneal exam component of KVA scale)

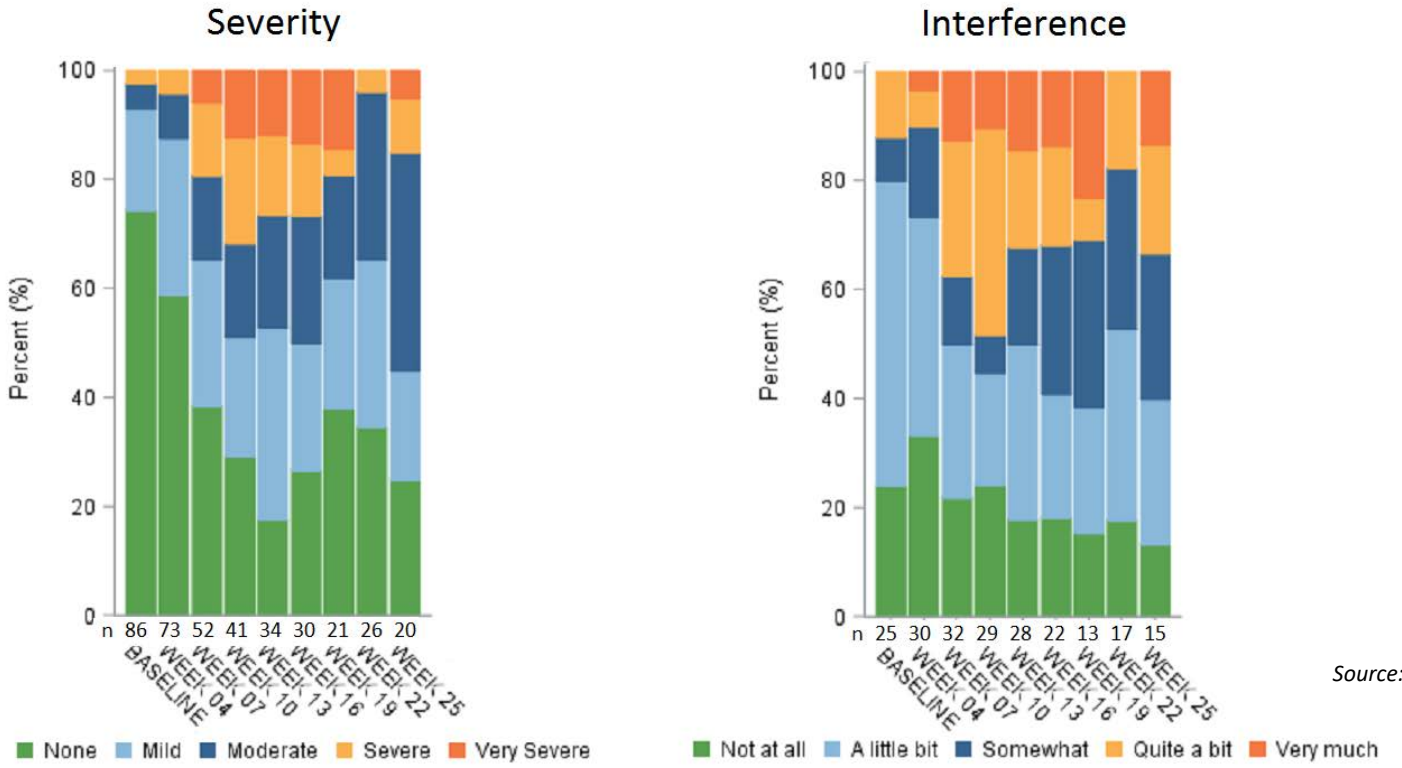
†Includes a Grade 4 keratopathy event of bilateral corneal ulcers in 1 patient

$^{\Delta}$Includes patients who either died or were lost to follow-up with persistent keratopathy at the final assessment

Source: FDA Analysis

Patient Reported Outcomes

PRO-CTCAE – Blurred Vision (2.5 mg/kg dose)



Source: FDA Analysis

Patient Reported Outcomes

- Limitations of PROs in DREAMM-2:
  - Suboptimal PRO completion rate for patients on trial
  - Many patients did not have the opportunity to respond to PRO questions because of disease progression, death, or discontinuation due to adverse events
  - DREAMM-2 not designed or powered to assess maintenance of Quality of Life

- Despite limitations, substantial proportion of patients reported severe visual symptoms with significant interference in usual/daily activities
  - 33% (27/83) reported “severe” or “very severe” blurred vision at any on-treatment time point
  - 45% (26/58) reported “quite a bit” or “very much” interference at any on-treatment time point

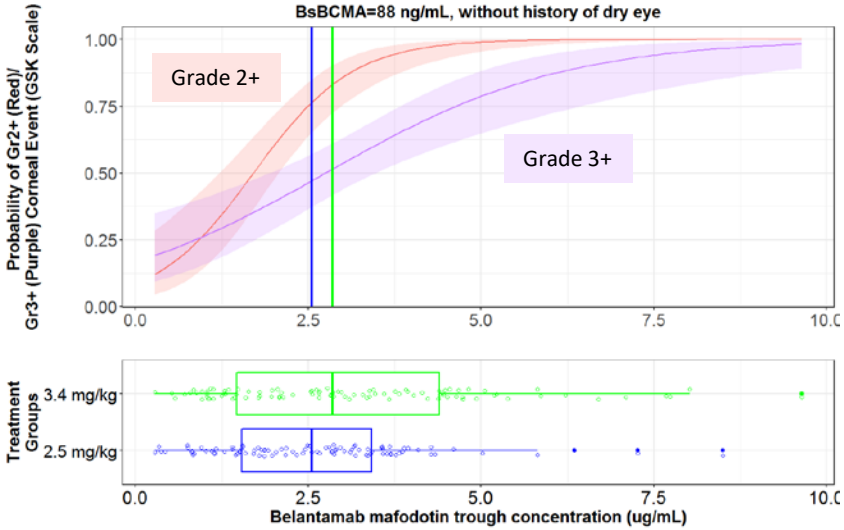
Additional Uncertainties

- Acceptability of the proposed 2.5 mg/kg dosage regimen
  - Rates and severity of ocular toxicity similar to 3.4 mg/kg dose
  - 47% required dose interruption due to ocular toxicity and 23% required dose reduction due to ocular toxicity
- Efficacy and safety in older patients
  - Median age 65 in 2.5 mg/kg cohort (median age at diagnosis 69 in U.S.)
  - ORR 8% (1/13) in patients ≥75 years in 2.5 mg/kg cohort
  - Higher rates of keratopathy and visual acuity changes in patients ≥65 years
- Safety of the lyophilized presentation
  - Keratopathy 92% vs. 77%; severe keratopathy 77% vs. 41% (3.4 mg/kg lyophilized vs. 3.4 mg/kg frozen)
  - No data with lyophilized presentation at 2.5 mg/kg dose proposed for marketing

Uncertainty with the 2.5 mg/kg Dosage Regimen

DREAMM-1 Treatment Group (mg/kg)		0.03 (N=1)	0.06 (N=1)	0.12 (N=4)	0.24 (N=4)	0.48 (N=4)	0.96 (N=3)	1.92 (N=4)	2.5 (N=8)	3.4 (N=3)	4.6 (N=6)
Efficacy (INV)	**ORR, n (%)**	0	0	0	0	0	1 (33)	1 (25)	1 (13)	3 (100)	3 (50)
Eye Disorder	**Any grade, n (%)**	0	0	1 (25)	1 (25)	2 (50)	1 (33)	4 (100)	3 (38)	3 (100)	6 (100)
	Grade 2, n (%)	0	0	0	0	0	1 (33)	2 (50)	3 (38)	2 (67)	4 (67)
	Grade 3, n (%)	0	0	0	0	0	0	1 (25)	0	1 (33)	0

Exposure-Response Analysis for Ocular Toxicity in DREAMM-2*



Key Points:

- Lower doses/alternative dosing schedules have not been fully explored
- Higher trough exposure is associated with higher rates of ocular toxicity

*Adjusted analysis representing E-R relationships at baseline sBCMA 88 ng/mL
Blue and green lines represent the median C_{trough} for the 2.5 mg/kg and 3.4 mg/kg doses, respectively
INV=Investigator-assessed, ORR=overall response rate

Source: FDA Analysis

DREAMM-2 Ocular Toxicity Summary (2.5 mg/kg)

- High incidence of ocular toxicity, including severe events
  - Keratopathy in 71%
  - Severe (Grade 3-4) keratopathy in 44%
  - Similar incidence/severity in 2.5 mg/kg and 3.4 mg/kg cohorts
- Decreased visual acuity, including severe vision loss
  - 53% with ≥1-line decrease, 26% with >3-line decrease
  - 17% with worsening to ≥20/50 in the better eye (not able to legally drive)
  - 1 patient with worsening to ≥20/200 in the better eye (legal blindness)
  - Severe visual symptoms with interference in daily activities based on PROs
- Absence of ocular symptoms despite findings on exam
  - Ocular symptoms only present in 43% of patients with keratopathy
  - Concern that keratopathy may not be identified in absence of close monitoring

DREAMM-2 Ocular Toxicity Summary (2.5 mg/kg)

- Frequent need for dose modifications due to ocular toxicity
  - Dose interruption/delay due to keratopathy in 47%
  - Dose reduction due to keratopathy in 23%
- Recurrent and unresolved ocular toxicity
  - 39% of patients had more than 1 event of keratopathy
  - 52% with ongoing keratopathy at last assessment (9-month data)
    - 27% (16/60) remained on treatment or in active follow-up
    - 25% (15/60) had ongoing keratopathy when follow-up ended
- Additional uncertainties
  - Acceptability of the proposed 2.5 mg/kg dosage regimen
  - Efficacy and safety in older patients
  - Safety of the 2.5 mg/kg lyophilized presentation

Benefit-Risk Considerations

- Unmet medical need in patients refractory to major classes of anti-MM therapy
- First-in-class, anti-BCMA antibody-drug conjugate (novel mechanism of action)
- ORR 31% in heavily pre-treated population (median 7 prior lines, PI/IMiD-refractory, failed anti-CD38 mAb)
- High incidence/severity of ocular toxicity; impact on visual acuity and patients' daily activities
- Unique toxicity among anti-MM agents; no approved MMAF-containing ADCs
- Despite lower 2.5 mg/kg dose, close monitoring, and dose modifications, patients had recurrent and unresolved ocular toxicity
- Need for close monitoring to ensure dose modifications are implemented to prevent severe keratopathy/corneal ulcers

Risk Mitigation and Evaluation Strategy (REMS)

- REMS with elements to assure safe use (ETASU) proposed
  - Many patients are asymptomatic – risk mitigation measures needed to prevent/reduce the risk or severity of the risk
  - Risk is unique to this product and oncologists likely do not have experience managing ocular toxicities – labeling is unlikely sufficient

- If belantamab mafodotin is approved, a REMS with ETASU would be needed

Discussion Topics

- Discuss whether the risk of ocular toxicity has been adequately characterized in Study 205678 (DREAMM-2) to allow for an assessment of the benefit-risk profile.

- Discuss the impact of ocular toxicity on the benefit-risk profile for belantamab mafodotin.

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