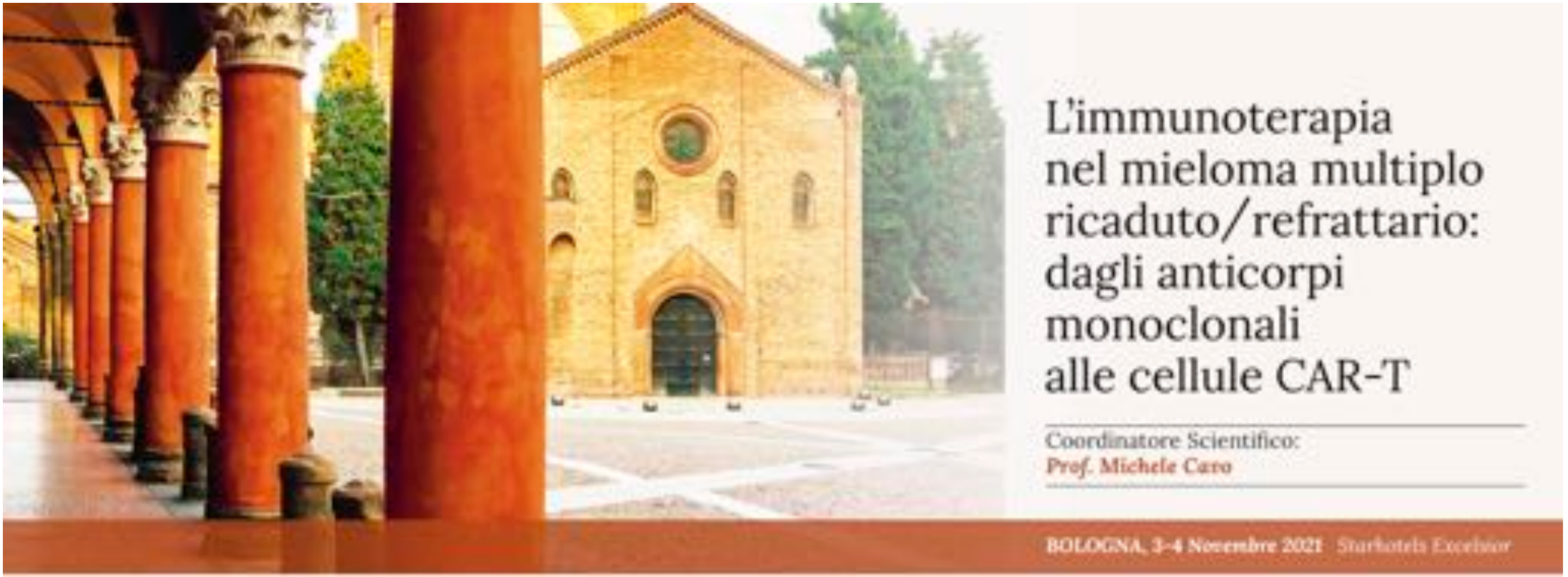
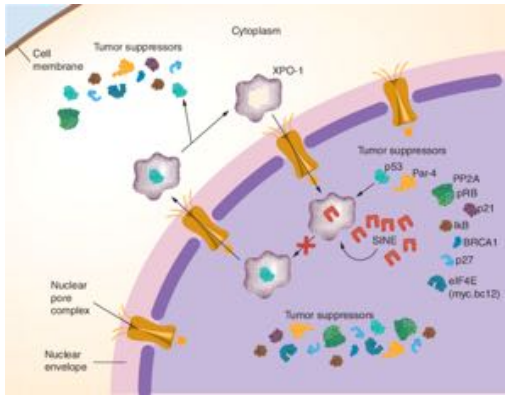


Terapia del paziente triplo-refrattario (IMiDs + PIs + anti CD38)

Eventi avversi e loro gestione

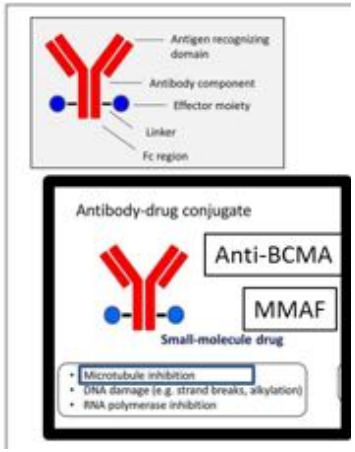
Paola Tacchetti
IRCCS Azienda Ospedaliero-Universitaria di Bologna
Istituto di Ematologia "Seràgnoli"

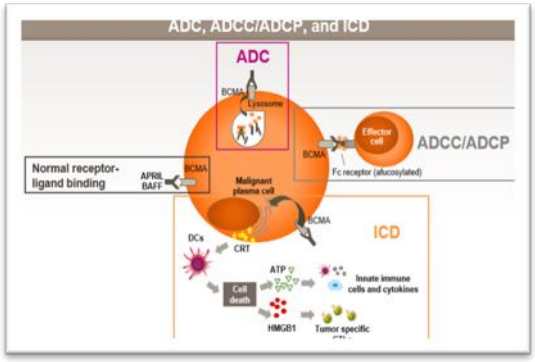
Selinexor and Belantamab Mafodotin for the Treatment of Triple Class Refractory MM



Selinexor-dex is approved by FDA in US and has received conditional approval by EMA CHMP for the treatment of MM pts who have received at least four prior therapies and whose disease is refractory to at least two PIs, two IMiDs, and an anti-CD38 moAb, and who have demonstrated PD on the last therapy

Chari A et al. NEJM 2019

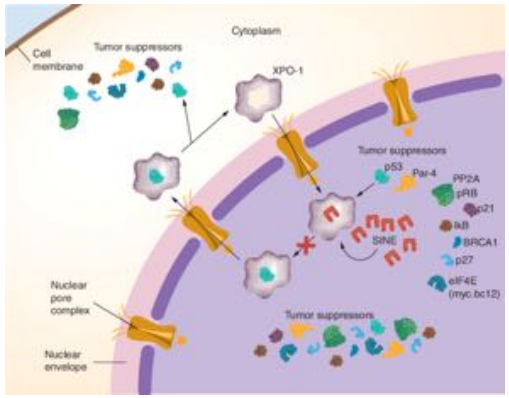




Belantamab mafodotin (2.5 mg/Kg every 3 weeks) has been approved by FDA and EMA for the treatment of adult patients with RRMM who have received at least four prior therapies and whose disease is refractory to at least one PI, one IMiDs, and an anti-CD38 MoAb, and have demonstrated PD on the last therapy

Lonial S et al. Lancet Oncol 2020

Selinexor and Belantamab Mafodotin for the Treatment of Triple Class Refractory MM



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Chari A et al. NEJM 2019

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STORM phase 2 trial: Treatment-Related Adverse Events

- **STORM phase II study**
- Sel 80 mg and Dexa 20 mg twice-weekly in a 28-day cycle
- 122 patients after a median of 7PL (59% pentarefractory and 100% three-drug class refractory)
- ORR 26%, including two pts in sCR and MR observed in 39% sustained across the different subgroups of patients
- Median PFS 3.7 m and OS of 8.6 m
- Safety profile: thrombocytopenia (54% G3-4) and some GI events (nausea 10% G3-4, anorexia 5% G3-4)

Table 3. Adverse Events That Emerged during Treatment.*

Event	Grade 1	Grade 2	Grade 3	Grade 4	Total (N = 123)
			number (percent)		
≥1 Adverse event					123 (100)
Hematologic adverse events					
Thrombocytopenia	12 (10)	6 (5)	31 (25)	41 (33)	90 (73)
Anemia	7 (6)	22 (18)	53 (43)	1 (1)	83 (67)
Neutropenia	7 (6)	16 (13)	22 (18)	4 (3)	49 (40)
Leukopenia	8 (7)	16 (13)	17 (14)	0	41 (33)
Lymphopenia	2 (2)	4 (3)	10 (8)	4 (3)	20 (16)
Nonhematologic adverse events					
Fatigue	16 (13)	43 (35)	31 (25)	0	90 (73)
Nausea	34 (28)	42 (34)	12 (10)	0	88 (72)
Decreased appetite	22 (18)	41 (33)	6 (5)	0	69 (56)
Decreased weight	34 (28)	27 (22)	1 (1)	0	62 (50)
Diarrhea	32 (26)	15 (12)	9 (7)	0	56 (46)
Vomiting	22 (18)	21 (17)	4 (3)	0	47 (38)
Hyponatremia	18 (15)	0	26 (21)	1 (1)	45 (37)
Upper respiratory tract infection	3 (2)	23 (19)	2 (2)	0	28 (23)
Constipation	16 (13)	9 (7)	2 (2)	0	27 (22)
Dyspnea	11 (9)	11 (9)	5 (4)	0	27 (22)
Cough	14 (11)	7 (6)	0	0	21 (17)
Hypokalemia	10 (8)	3 (2)	8 (7)	0	21 (17)
Insomnia	13 (11)	6 (5)	2 (2)	0	21 (17)
Mental status changes	7 (6)	7 (6)	7 (6)	0	21 (17)
Pneumonia	0	8 (7)	10 (8)	1 (1)	21 (17)†
Dizziness	14 (11)	5 (4)	0	0	19 (15)
Pyrexia	11 (9)	8 (7)	0	0	19 (15)
Epistaxis	11 (9)	3 (2)	1 (1)	0	15 (12)
Fall	9 (7)	4 (3)	2 (2)	0	15 (12)
Hyperglycemia	2 (2)	3 (2)	8 (7)	0	13 (11)
Peripheral edema	8 (7)	3 (2)	2 (2)	0	13 (11)
Blurred vision	8 (7)	3 (2)	2 (2)	0	13 (11)

* Shown are events that occurred in at least 10% of the patients. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.[25]
† The total includes two events of grade 5.

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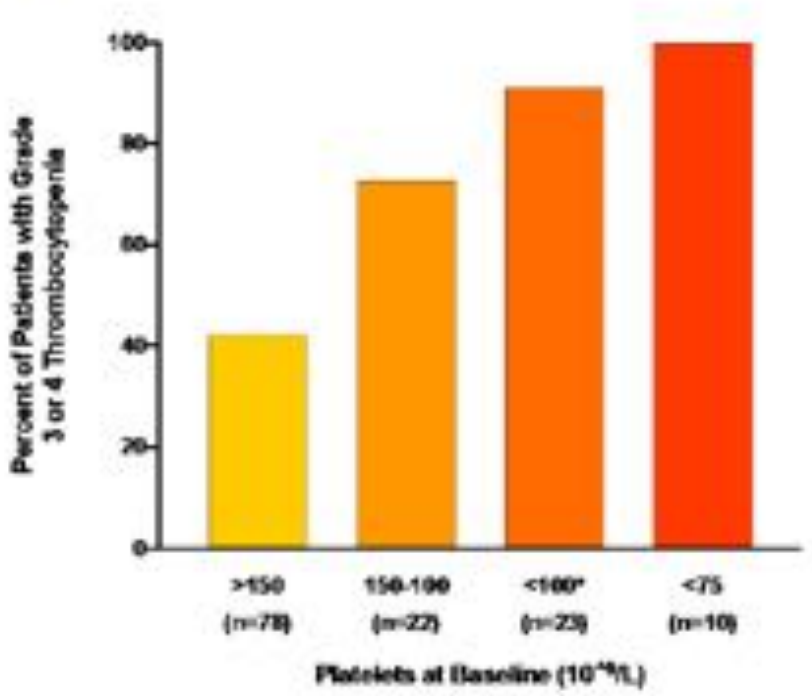
STORM: Relationship between the incidence of grade 3 or 4 thrombocytopenia and baseline platelet count



*Graded by CTCAE v4.03

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STORM: Serious Adverse Events

Table S6. Serious Adverse Events Occurring in ≥2% Patients

Adverse Event — n (%)	N=123	
	Treatment-emergent	Treatment-related[b]
Patient with ≥ 1 serious treatment emergent	78 (63.4)	39 (31.7)
Pneumonia	14 (11.4)	6 (4.9)
Sepsis	11 (8.9)	2 (1.6)
Anemia	4 (3.3)	1 (0.8)
Fatigue	4 (3.3)	3 (2.4)
General physical health deterioration	4 (3.3)	2 (1.6)
Hyponatremia	4 (3.3)	3 (2.4)
Mental status changes	4 (3.3)	1 (0.8)
Bacteremia	4 (3.3)	1 (0.8)
Asthenia	3 (2.4)	3 (2.4)
Pyrexia	3 (2.4)	0
Dehydration	3 (2.4)	3 (2.4)
Confusional state	3 (2.4)	1 (0.8)
Acute kidney injury	3 (2.4)	3 (2.4)

[a]Based on CTCAE v4.03

[b]Subset of treatment-emergent events. Relatedness per investigator assessment.

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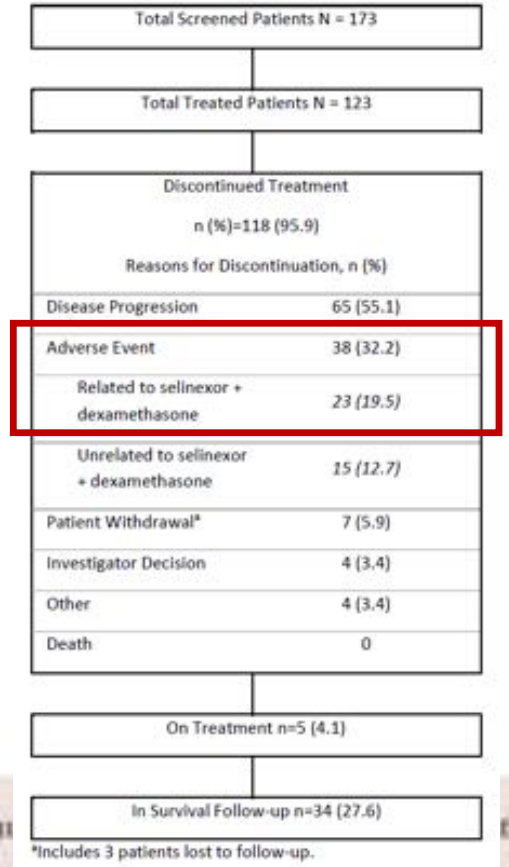
STORM: Adverse Events Leading to Dose Modification or Interruption

Adverse events leading to dose modification or interruption occurred in 80% of the patients, with the majority of events occurring in the first two cycles.

The most common adverse events leading to dose reduction or interruption were thrombocytopenia (in 43% of the patients), fatigue (in 16%), and neutropenia (in 11%).

Table S3. Pre-specified Dose/Schedule Modifications for Adverse Events Related to Study Drug

	Dose Level	Selinexor Dosing
Dose Increase	1	100 mg twice-weekly (200 mg total per week)
Starting Dose	0	80 mg twice-weekly (160 mg total per week)
Dose Reduction	−1	60 mg twice-weekly (120 mg total per week)
	−2	100 mg total per week: 100 mg once weekly *OR* divided as 60 mg and 40 mg on separate days
	−3	80 mg total per week: 80 mg once weekly *OR* divided as 40 mg separate days
	−4	60 mg total per week: 60 mg once weekly *OR* divided as 40 mg and 20 mg on separate days
	−5	40 mg total per week: 40 mg once weekly *OR* divided as 20 mg on separate days



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Selinexor and backbone treatments of MM

SRd	SPd	SVd	SKd	SDd
Sel: 60mg QW Rev: 25mg QD Dex: 40mg QW	Sel: 60-80 mg QW Pom: 2-4mg QD Dex: 40mg QW	Sel: 100mg QW Vel: 1.3mg/m^2 QW Dex: 40mg QW (or 20mg BIW)	Sel: 80-100mg QW Kyp: 56-70mg/m^2 QW Dex: 40mg QW	Sel: 100mg QW Dar: 16mg/kg QW Dex: 40mg QW

S/Sel: Selinexor. R/Rev: Revlimid, d/Dex: Dexamethason, V/Vel: Velcade, K/Kyp: Kyprolis, D/Dar: Darzalex

Hashmi H and Green K. Curr Probl Cnacer 2021

BOSTON phase 3 trial: Treatment-Related Adverse Events

- **BOSTON phase III study: Once-per-week SVd versus twice-per-week Vd**
- Selinexor 100 mg once per week, bortezomib 1.3 mg/m² once per week, and dexamethasone 20 mg twice per week
- 402 pts (195 SVd, 207 Vd), 1-3 prior lines of tp
- ORR 76%, CR rate 17%
- Median PFS 14 m
- Safety profile: thrombocytopenia (54% G3-4) and some GI events (nausea 10% G3-4, anorexia 5% G3-4)

	Selinexor, bortezomib, and dexamethasone group (n=195)		Bortezomib and dexamethasone group (n=204)*	
	Any grade†	Grade 3–4	Any grade†	Grade 3–4
Haematological adverse events				
Thrombocytopenia	117 (60%)	77 (39%)	55 (27%)	35 (17%)
Anaemia	71 (36%)	31 (16%)	47 (23%)	20 (10%)
Neutropenia	29 (15%)	17 (9%)	12 (6%)	7 (3%)
Non-haematological adverse events				
Fatigue	82 (42%)	26 (13%)	37 (18%)	2 (1%)
Nausea	98 (50%)	15 (8%)	20 (10%)	0
Diarrhoea	63 (32%)	12 (6%)	51 (25%)	1 (<1%)
Peripheral neuropathy§	63 (32%)	9 (5%)	96 (47%)	18 (9%)
Decreased appetite	69 (35%)	7 (4%)	11 (5%)	0
Weight loss	53 (26%)	4 (2%)	25 (12%)	2 (1%)
Asthenia	48 (25%)	16 (8%)	27 (13%)	9 (4%)
Constipation	33 (17%)	0	35 (17%)	3 (1%)
Cough	35 (18%)	1 (1%)	30 (15%)	0
Insomnia	31 (16%)	2 (1%)	32 (16%)	4 (2%)
Back pain	30 (15%)	1 (1%)	29 (14%)	2 (1%)
Pneumonia¶	35 (18%)	24 (12%)	34 (17%)	23 (10%)
Pyrexia	30 (15%)	3 (2%)	22 (11%)	2 (1%)
Cataract	42 (22%)	17 (9%)	13 (6%)	3 (1%)
Vomiting	40 (21%)	8 (4%)	9 (4%)	0
Peripheral oedema	23 (12%)	1 (1%)	26 (13%)	0
Dyspnoea	18 (9%)	1 (1%)	27 (13%)	5 (2%)
Bronchitis	24 (12%)	3 (2%)	20 (10%)	1 (<1%)
Upper respiratory tract infection	35 (18%)	5 (3%)	30 (15%)	1 (<1%)

Grosicki S et al. N Engl Med 2019;
Dimopoulos MA, et al. ASCO 2020: abstract 8501

BOSTON: Effect of Age and Frailty on Tolerability

	<65 years		≥65 years		Nonfrail		Frail	
	XVd (n = 86)	Vd (n = 75)	XVd (n = 109)	Vd (n = 129)	XVd (n = 129)	Vd (n = 142)	XVd arm (n = 66)	Vd arm (n = 62)
Grade ≥ 3 Adverse Events, n (%)								
Thrombocytopenia	51 (59.3)	23 (30.7)	66 (60.6)	32 (24.8)	81 (62.8)	39 (27.5)	36 (54.5)	16 (25.8)
Anemia	35 (40.7)	18 (24.0)	36 (33.0)	29 (22.5)	46 (35.7)	32 (22.5)	25 (37.9)	15 (24.2)
Neutropenia	16 (18.6)	2 (2.7)	13 (11.9)	10 (7.8)	20 (15.5)	9 (6.3)	9 (13.6)	3 (4.8)
Leukopenia	7 (8.1)	0	3 (2.8)	3 (2.3)	6 (4.7)	2 (1.4)	4 (6.1)	1 (1.6)
Lymphopenia	5 (5.8)	3 (4.0)	6 (5.5)	1 (0.8)	10 (7.8)	4 (2.8)	1 (1.5)	0
Fatigue	34 (39.5)	13 (17.3)	48 (44.0)	24 (18.6)	55 (42.6)	28 (19.7)	27 (40.9)	9 (14.5)
Asthenia	20 (23.3)	10 (13.3)	28 (25.7)	17 (13.2)	24 (18.6)	18 (12.7)	24 (36.4)	9 (14.5)
Hyponatremia	7 (8.1)	2 (2.7)	8 (7.3)	1 (0.8)	10 (7.8)	3 (2.1)	5 (7.6)	0
Nausea	41 (47.7)	8 (10.7)	57 (52.3)	12 (9.3)	65 (50.4)	15 (10.6)	33 (50.0)	5 (8.1)
Vomiting	20 (23.3)	2 (2.7)	20 (18.3)	7 (5.4)	25 (19.4)	7 (4.9)	15 (22.7)	2 (3.2)
Diarrhea	34 (39.5)	16 (21.3)	29 (26.6)	35 (27.1)	43 (33.3)	33 (23.2)	20 (30.3)	18 (29.0)
Serious treatment-emergent adverse events	40 (46.5)	19 (25.3)	61 (56.0)	58 (45.0)	62 (48.1)	47 (33.1)	39 (59.1)	30 (48.4)
Dose Reduction	60 (69.8)	37 (49.3)	81 (74.3)	67 (51.9)	93 (72.1)	71 (50.0)	48 (72.7)	33 (53.2)
Discontinuation	11 (12.8)	7 (9.3)	30 (27.5)	25 (19.4)	28 (21.7)	22 (15.5)	13 (19.7)	10 (16.1)

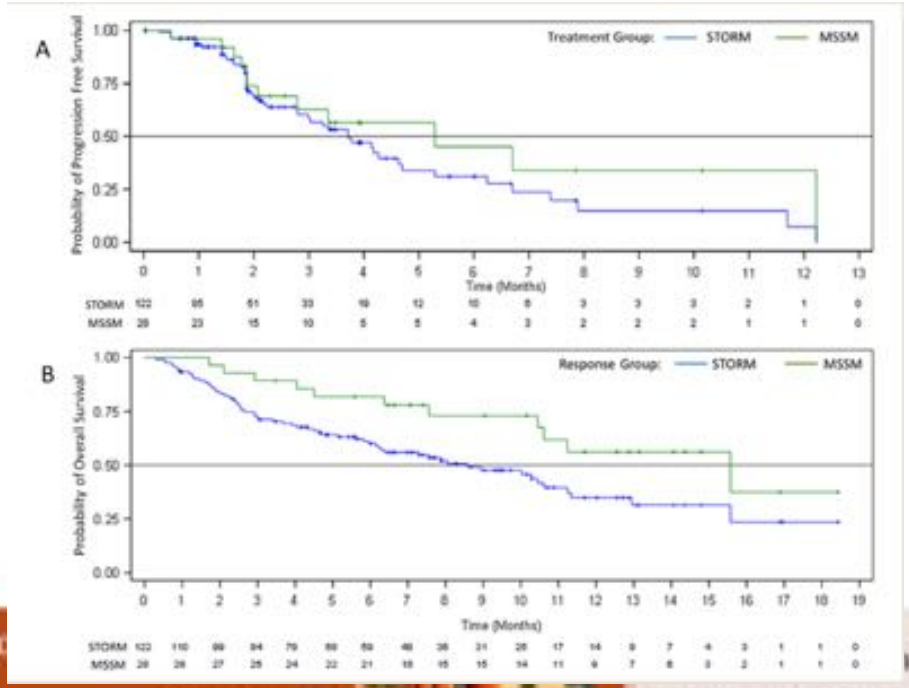
Auner HV et al. AJH 2021

STORM: Supporting Care

Tisch Cancer Institute at Mount Sinai School of Medicine (MSSM) strategy:
(1) aggressive multiagent prophylactic supportive care, (2) a phone call from the nursing team on day 3 of the cycle to assess study drug tolerability, (3) intravenous fluids based on severity of nausea, body weight loss and/or orthostatic changes, (4) hematologic monitoring and support

Table 2 Response to Therapy (mITT Population)

Response, n (%)	MSSM (n = 28)	STORM (n = 122)
Overall Response Rate[a]	15 (53.6)	32 (26.2)



The MSSM cohort had:
- **more dose reductions** (67.9% vs. 50.5%)
- **less discontinuations** due to treatment-related AEs (3.6% vs. 25.3%)
- more prevalent simultaneous use of **multiple anti-emetic agents** (MSSM: 71.4%, non-MSSM: 50.1%)
- more prevalent use of **romiplostim** (MSSM: 32.1%, non-MSSM: 6.3%)

More frequent dose reductions, and prompter and more aggressive supportive care may have contributed to the lower discontinuation rate, longer duration therapy, and greater efficacy rates observed in the MSSM cohort.

Chari A et al. Clinical Lymphoma, Myeloma and Leukemia 2021

STORM: Supporting Care

Table 4 MSSM Supportive Care Algorithm

Identification/Implementation	• Educate patients regarding selinexor side-effects, prophylactic and responsive measures, and nutrition • Call patients once weekly • Weights at least weekly for first 8 wks, then as needed • CBC and chemistry at least weekly for first 8 wks, then as needed
Nausea/Emesis *Prophylaxis* *Treatment* *Preferred Second Antiemetic*	• Begin with 5-HT3 antagonist and 1 or 2 additional antiemetics on first d of selinexor in most patients* • Rapidly add second or third antiemetic if nausea occurs after first selinexor dose: 70% received second antiemetic with early initiation (day 2-3) • Recommend NK-1 antagonist as second agent for nausea/emesis
Fatigue/Asthenia	• Rule out hypovolemia, anemia, hypothyroidism, and adrenal insufficiency • Treat with methylphenidate (≥10 mg/d); monitor food and fluid intake
Thrombocytopenia	• When platelets are <50,000/μL, begin weekly romiplostim 10 mcg/kg subcutaneously after each once-weekly dose of selinexor

* NK-1 antagonist such as rolapitant (which has reduced interaction with dexamethasone) or aprepitant (with concomitant reduction of corticosteroid dose) OR olanzapine (2.5-5.0 mg po qhs continuous OR D2-antagonist are recommended on Day 1. Olanzapine is also effective in patients with anorexia and/or weight loss (data not shown).

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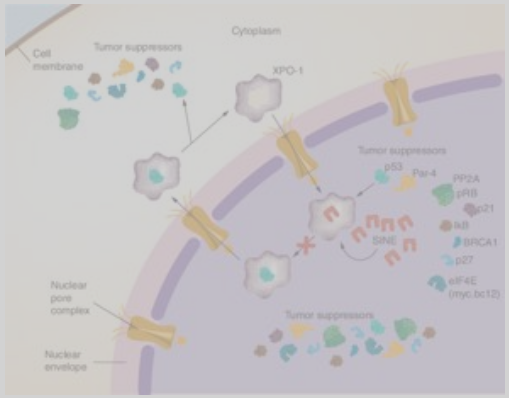
Selinexor and Belantamab Mafodotin for the Treatment of Triple Class Refractory MM



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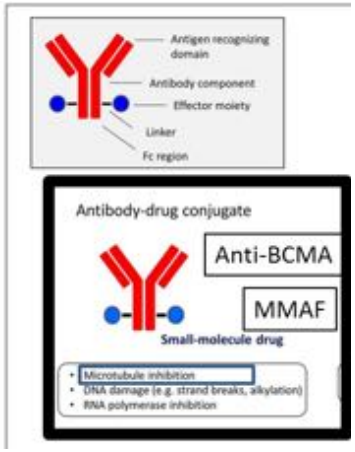
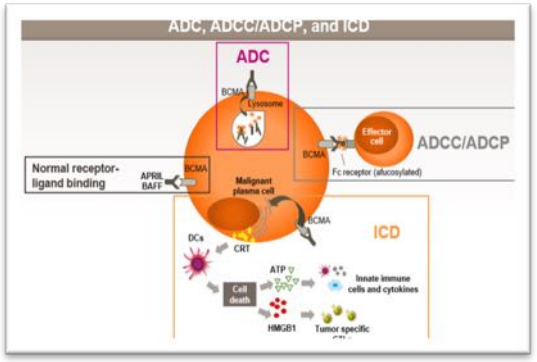
Chari A et al. NEJM 2019





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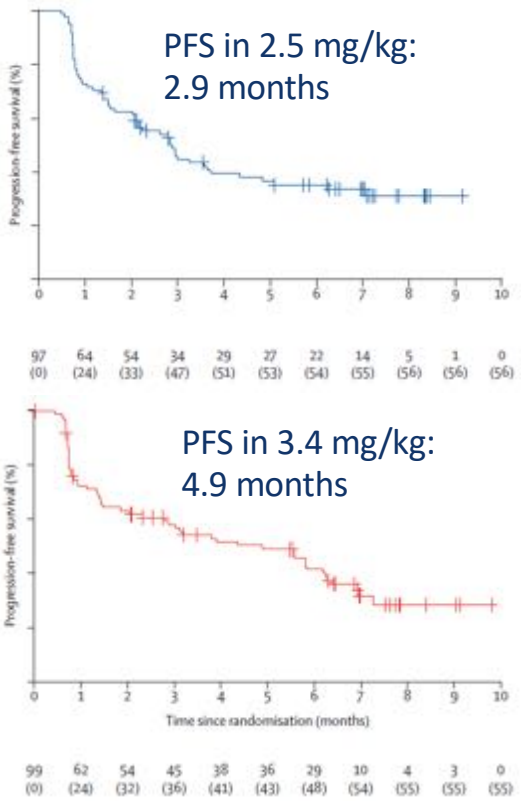
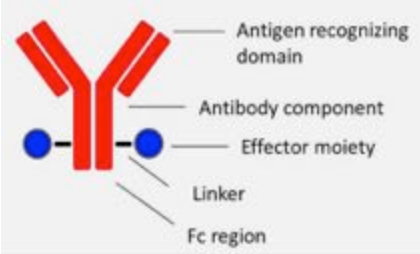
Lonial S et al. Lancet Oncol 2020

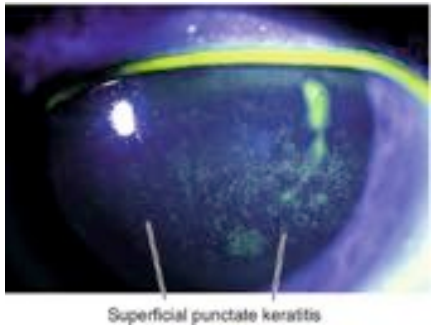
DREAMM2: Belantamab mafodotin

DREAMM2: patients with disease refractory to IMID/PI/CD38

DREAMM2	2.5 mg/kg every 3 week	3.4 mg/kg every 3 weeks
Prior lines (median)	7	6
≥PR (%)	31	34
≥VGPR (%)	19	20
≥grade 3 keratopathy (%)	27	21
≥grade 3 thrombocytopenia (%)	20	33
AEs leading to dose delay (%)	54	62
AEs leading to dose reductions (%)	29	41







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DREAMM-2 results: Safety from 13-month follow-up
Belantamab Mafodotin was generally tolerated with supportive care and dose modification

Event	Belamaf 2.5 mg/kg, N = 95: No. of Patients (%)	
	Any Grade	Grade ≥3
Any event	93 (98)	80 (84)
Eye examination finding		
Keratopathy[b]	68 (72)	44 (46)
Change in BCVA	51 (54)	29 (31)
Thrombocytopenia[c]	36 (38)	21 (22)
Anemia	26 (27)	20 (21)
Blurred vision[d]	24 (25)	4 (4)
Nausea	24 (25)	0 (0)
Pyrexia[e]	22 (23)	4 (4)
Aspartate aminotransferase increased	20 (21)	2 (2)
Infusion-related reaction[f]	20 (21)	3 (3)
Fatigue	15 (16)	2 (2)
Neutropenia[g]	14 (15)	10 (11)
Dry eye[h]	14 (15)	1 (1)
Hypercalcemia	14 (15)	7 (7)
Lymphocyte count decreased	13 (14)	12 (13)
Pneumonia	9 (9)	6 (6)

80 (84%) of patients in the safety population experienced Grade ≥3 events and these events were treatment-related in 54 (57%) of patients.

Only 3 (3%) SAEs were fatal (1 [1%] study treatment-related fatal events)

Lonial S et al. Cancer 2021

DREAMM-2 results: Safety from 13-month follow-up
There were no new safety concerns in patients with cytogenetics abnormalities

Most common AEs (occurring in ≥15%) and Grade ≥3 AEs (≥5%)

Patients with event, n (%)*	[illegible] (N=28)		[illegible] (N=41)		[illegible] (N=54)	
Any adverse event	25 (96)		39 (95)		54 (100)	
Treatment-related adverse event	23 (88)		34 (83)		50 (93)	
Any serious adverse event	11 (42)		19 (46)		21 (39)	
Most common adverse events	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Keratopathy†	17 (65)	12 (46)	25 (61)	15 (37)	43 (80)	32 (59)
Thrombocytopenia‡	11 (42)	8 (31)	17 (41)	12 (29)	19 (35)	9 (17)
Anemia	7 (27)	6 (23)	11 (27)	10 (24)	15 (28)	10 (19)
Nausea	5 (19)	0 (0)	11 (27)	0 (0)	13 (24)	0 (0)
Pyrexia	8 (31)	2 (8)	11 (27)	3 (7)	11 (20)	1 (2)
Infusion-related reaction§	7 (27)	3 (12)	10 (24)	3 (7)	10 (19)	0 (0)
Aspartate aminotransferase increased	7 (27)	0 (0)	9 (22)	1 (2)	11 (20)	1 (2)
Constipation	5 (19)	0 (0)	8 (20)	0 (0)	4 (7)	0 (0)
Blurred vision¶	6 (23)	0 (0)	8 (20)	0 (0)	16 (30)	4 (7)
Hypercalcemia	4 (15)	2 (8)	7 (17)	4 (10)	7 (13)	3 (6)
Neutropenia#	6 (23)	4 (15)	7 (17)	4 (10)	7 (13)	6 (11)
Back pain	4 (15)	0 (0)	6 (15)	1 (2)	6 (11)	1 (2)
Diarrhea	6 (23)	1 (4)	6 (15)	1 (2)	6 (11)	0 (0)
Hyperuricemia	2 (8)	2 (8)	6 (15)	3 (7)	3 (6)	0 (0)
Pneumonia	4 (15)	3 (12)	6 (15)	4 (10)	3 (6)	2 (4)
Leukopenia	4 (15)	3 (12)	5 (12)	3 (7)	4 (7)	1 (2)
Dry eye¶	3 (12)	1 (4)	5 (12)	1 (2)	9 (17)	0 (0)
Lymphocyte count decreased	4 (15)	4 (15)	4 (10)	4 (10)	9 (17)	8 (15)
Fatigue	1 (4)	0 (0)	4 (10)	1 (2)	11 (20)	1 (2)
Arthralgia	3 (12)	0 (0)	4 (10)	1 (2)	8 (15)	0 (0)
White blood cell decreased	4 (15)	1 (4)	4 (10)	1 (2)	3 (6)	1 (2)
Hypertension	1 (4)	0 (0)	3 (7)	1 (2)	6 (11)	3 (6)
Blood creatine phosphokinase increased	1 (4)	1 (4)	2 (5)	2 (5)	3 (6)	0 (0)
Blood creatinine increased	0 (0)	0 (0)	2 (5)	1 (2)	8 (15)	2 (4)
Hypophosphatemia	2 (8)	1 (4)	2 (5)	1 (2)	5 (9)	3 (6)
Lymphopenia	1 (4)	1 (4)	1 (2)	1 (2)	5 (9)	3 (6)

The safety profile of belantamab mafodotin in patients with cytogenetic abnormalities was comparable between subgroups. There were no new safety concerns

Lonial S et al. Cancer 2021

DREAMM-2 results: Safety from 13-month follow-up
There were no new safety concerns in patients with renal impairment

Most common AEs (occurring in ≥15%) and Grade ≥3 AEs (≥10%)

Patients with event, n (%)[a]	Normal renal function[b] (N=19)		Mild renal impairment[b] (N=49)		Moderate renal impairment[b] (N=24)	
Any adverse event	19 (100)		47 (96)		23 (96)	
Treatment related adverse event	19 (100)		43 (90)		19 (79)	
Any serious adverse event	8 (42)		17 (35)		12 (50)	
Most common adverse events	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Keratopathy[f]	18 (95)	14 (74)	34 (71)	24 (50)	15 (63)	9 (38)
Aspartate aminotransferase increased	5 (26)	2 (11)	13 (27)	0 (0)	2 (8)	0 (0)
Neutropenia[e]	5 (26)	2 (11)	5 (10)	4 (8)	3 (13)	3 (13)
Blurred vision[c]	5 (26)	1 (5)	15 (31)	2 (4)	4 (17)	1 (4)
Fatigue	5 (26)	0 (0)	9 (19)	1 (2)	1 (4)	1 (4)
Headache	5 (26)	0 (0)	3 (6)	0 (0)	2 (8)	0 (0)
Nausea	5 (26)	0 (0)	11 (23)	0 (0)	7 (29)	0 (0)
Thrombocytopenia[d]	4 (21)	2 (11)	19 (40)	9 (19)	10 (42)	7 (29)
Epistaxis	4 (21)	1 (5)	4 (8)	0 (0)	1 (4)	0 (0)
Blood alkaline phosphatase increased	4 (21)	0 (0)	5 (10)	2 (4)	0 (0)	0 (0)
Blood creatine phosphokinase increased	3 (16)	1 (5)	1 (2)	1 (2)	1 (4)	0 (0)
Gamma-glutamyltransferase increased	3 (16)	1 (5)	7 (15)	2 (4)	0 (0)	0 (0)
Leukopenia	3 (16)	0 (0)	3 (6)	2 (4)	2 (8)	1 (4)
Infusion-related reaction[g]	3 (16)	0 (0)	7 (15)	0 (0)	9 (38)	3 (13)
Back pain	3 (16)	0 (0)	7 (15)	1 (2)	2 (8)	1 (4)
Lymphocyte count decreased	3 (16)	2 (11)	8 (17)	8 (17)	2 (8)	2 (8)
Anemia	2 (11)	1 (5)	13 (27)	9 (19)	8 (33)	7 (29)
Pyrexia	2 (11)	0 (0)	9 (19)	0 (0)	10 (42)	3 (13)
Hypertension	2 (11)	0 (0)	2 (4)	0 (0)	5 (21)	4 (17)
Dry eye[h]	1 (5)	0 (0)	10 (21)	0 (0)	3 (13)	1 (4)
Decreased appetite	1 (5)	0 (0)	9 (19)	0 (0)	2 (8)	0 (0)
Arthralgia	1 (5)	0 (0)	8 (17)	1 (2)	3 (13)	0 (0)
Diarrhea	1 (5)	0 (0)	8 (17)	0 (0)	3 (13)	1 (4)
Hypercalcemia	1 (5)	0 (0)	6 (13)	3 (6)	5 (21)	3 (13)
Blood creatinine increased	1 (5)	0 (0)	2 (4)	0 (0)	5 (21)	1 (4)
Hyperuricemia	1 (5)	0 (0)	3 (6)	1 (2)	4 (17)	2 (8)
Constipation	0 (0)	0 (0)	4 (8)	0 (0)	8 (33)	0 (0)

The safety profile of belantamab mafodotin in patients with renal impairment was comparable between subgroups. There were no new safety concerns

Lonial S et al. Cancer 2021

DREAMM-2 results: Safety from 13-month follow-up
There were no new safety concerns in patients with extramedullary disease

Most common AEs (occurring in ≥15%) and Grade ≥3 AEs (≥10%)

Patients with event, n (%)[a]	EMD (N=21)	
Any adverse event	21 (100)	
Treatment-related adverse event	19 (90)	
Any serious adverse event	10 (48)	
Most common adverse events	**Any Grade**	**Grade ≥3**
Keratopathy[b]	13 (62)	9 (43)
Anemia	9 (43)	7 (33)
Thrombocytopenia[c]	7 (33)	5 (24)
Pyrexia	6 (29)	0 (0)
Blood alkaline phosphatase increased	5 (24)	1 (5)
Fatigue	5 (24)	1 (5)
Hypercalcemia	5 (24)	4 (19)
Lymphocyte count decreased	5 (24)	4 (19)
Blurred vision[d]	4 (19)	1 (5)
Nausea	5 (24)	0 (0)
Aspartate aminotransferase increased	4 (19)	1 (5)
Hyperuricemia	4 (19)	2 (10)
Pain in extremity	4 (19)	0 (0)
Neutropenia[e]	3 (14)	3 (14)
Hypophosphatemia	3 (14)	2 (10)
Bone pain	2 (10)	2 (10)
Pneumonia	2 (10)	2 (10)
Dry eye[f]	2 (10)	0 (0)
Infusion related reaction[g]	2 (10)	0 (0)

The safety profile of belantamab mafodotin in patients with EMD was comparable to the overall population. There were no new safety concerns

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Patients receiving Belantamab Mafodotin for ≥ 12 months

	Patients Receiving 2.5 mg/kg ≥ 12 Months (N = 14)
Most Common Non-ocular Adverse Events, n (%)	
Nausea	7 (50)
Diarrhea	6 (43)
Arthralgia	5 (36)
Constipation	5 (26)
Infusion-related Reaction	5 (36)
Pyrexia	5 (36)

Nusea and diarrhea were among the most common non ocular adverse events

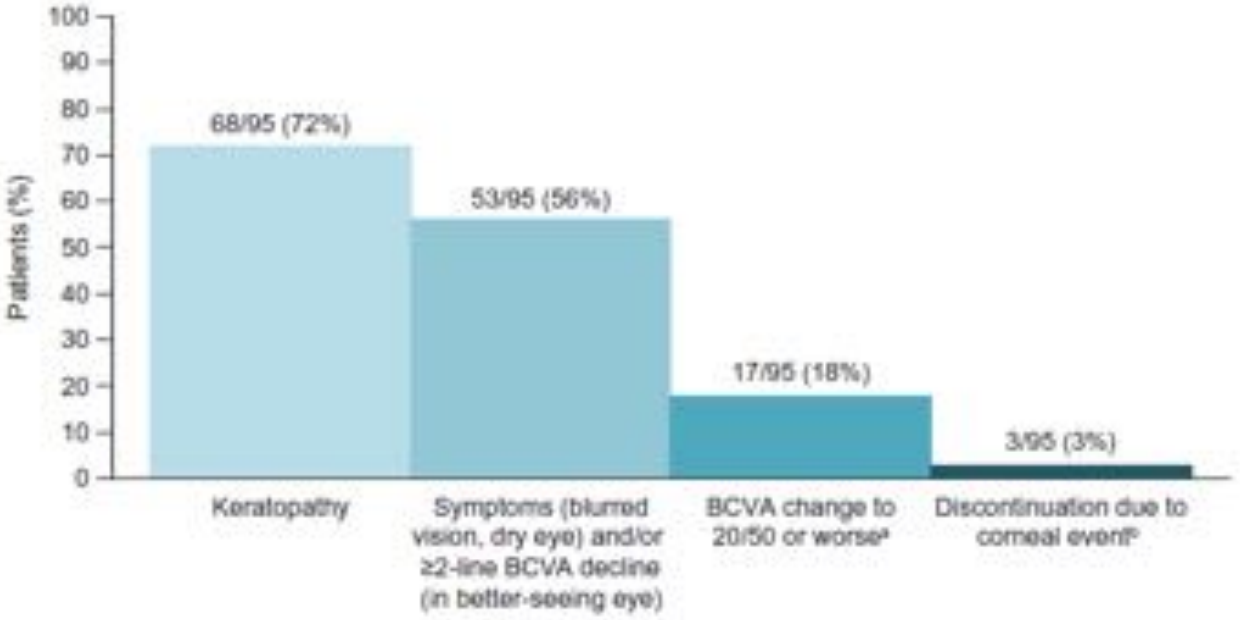
	Patients with drug-related ocular adverse events, n (%)	Patients with ocular adverse events leading to dose reduction, n (%)	Patients with ocular adverse events leading to dose delays, n (%)
Keratopathy	14 (100)	10 (71)	13 (93)
Vision blurred	8 (57)	1 (7)	3 (21)
Dry eye	5 (36)	0	1 (7)
Photophobia	3 (21)	0	0
Visual acuity reduced	3 (21)	0	0
Ocular discomfort	2 (14)	0	1 (7)
Visual impairment	2 (14)	0	0
Glaucoma	1 (7)	0	1 (7)
Retinal hemorrhage	1 (7)	0	1 (7)
Ulcerative keratitis	1 (7)	0	1 (7)
Vitreous detachment	1 (7)	0	0

Keratopathy and blurred vision were among the most common ocular symptoms and led to the most dose modifications

Lonial S et al. EHA 2021
Lonial S et al. IMW 2021

DREAMM-2 results: Safety from 13-month follow-up
Keratopathy can occur with or without symptoms

Frequency of corneal and vision-related events in patients treated with belamaf 2.5 mg/kg



- 82% of patients without clinically significant visual acuity change*
- No new safety signals observed at 13-month follow-up
- 1 patient developed a Grade 4 corneal ulcer[¶]

Lonial S et al. Cancer 2021

DREAMM-2 results: Safety from 13-month follow-up
Ocular Events: Recovery of Grade ≥2 keratopathy (MECs) in DREAMM-2

	Patients with keratopathy ≥ Grade 2 (N = 60)*
Median time to onset of first occurrence, days (range)	37 (19-147)
Median duration of first event, days (range)	86.5 (8-358)
Recovered from first occurrence, n (%) Median time to resolution, days	46 (77) 86.5
Recovered as of last follow-up, n (%)	29 (48)

84% of patients with Grade 3/4 keratopathy (MECs) events were improving or had recovered at last follow-up

Lonial S et al. Cancer 2021
Farooq AV et al. Ophtalmol Ther 2020

DREAMM-2 results: Safety from 13-month follow-up
Ocular Events: Recovery of changes in BCVA worse than 20/50 in the better seeing eye

	Belantamab mafodotin 2.5 mg/kg (N = 95)*	
	Bilateral BCVA of 20/50 or worse in the better seeing eye	Bilateral BCVA of 20/200 or worse in the better seeing eye
Patients, n (%)	17 (18)	1 (1)
Time to onset; median days (range)	66.0 (20-442)	21.0 (21-21)
Time to resolution; median days (range)	21.5 (7-64)	22.0 (22-22)
Resolved as of last assessment, n (%)	14 (82)	1 (100)

There have been no reports of permanent vision loss to date

Lonial S et al. Cancer 2021
Farooq AV et al. Ophtalmol Ther 2020

DREAMM-2 results: Safety from 13-month follow-up
Dose Modifications and Discontinuations

n (%)	Belantamab Mafodotin 2.5 mg/kg (N = 95)
AEs leading to dose delays*	51 (54)
Dose delays due to keratopathy (MECs)	45 (47)
AEs leading to dose reductions	33 (35)
Dose reductions due to keratopathy (MECs)	24 (25)
AEs leading to permanent treatment discontinuation	9 (9)
Discontinuation due to keratopathy (MECs†)	1 (1)
Discontinuation due to patient-reported AEs/symptoms	2 (2)‡

This chart has been independently created by GSK from original data first presented in Lonial S et al. Cancer 2021

*Dose delays of any duration, including but not limited to delays >63 days
†an eye examination finding
‡ Blurred vision or change in BCVA (n = 1 each)

Most dose delays and reductions were due to keratopathy (MECs). Ocular symptoms were generally managed with frequent application of preservative-free lubricant eye-drops, and by dose modification (reduction and/or delay) or treatment discontinuation

Ocular symptoms continued to resolve with additional patient follow-up

Lonial S et al. Cancer 2021

DREAMM-2 results: Safety from 13-month follow-up
Clinical Outcomes with First Prolonged Dose Delays > 63 days

	Belantamab mafodotin 2.5 mg/kg (n=16)
Maintained a clinical benefit, n (%)	14 (88)
Deepened clinical response	6 (38)
Maintained the same response category	6 (38)
Did not meet progression criteria*	2 (13)
Developed progressive disease, n (%)	2 (13)†

This chart has been independently created by GSK from original data first presented in Lonial S et al. Cancer. 2021.

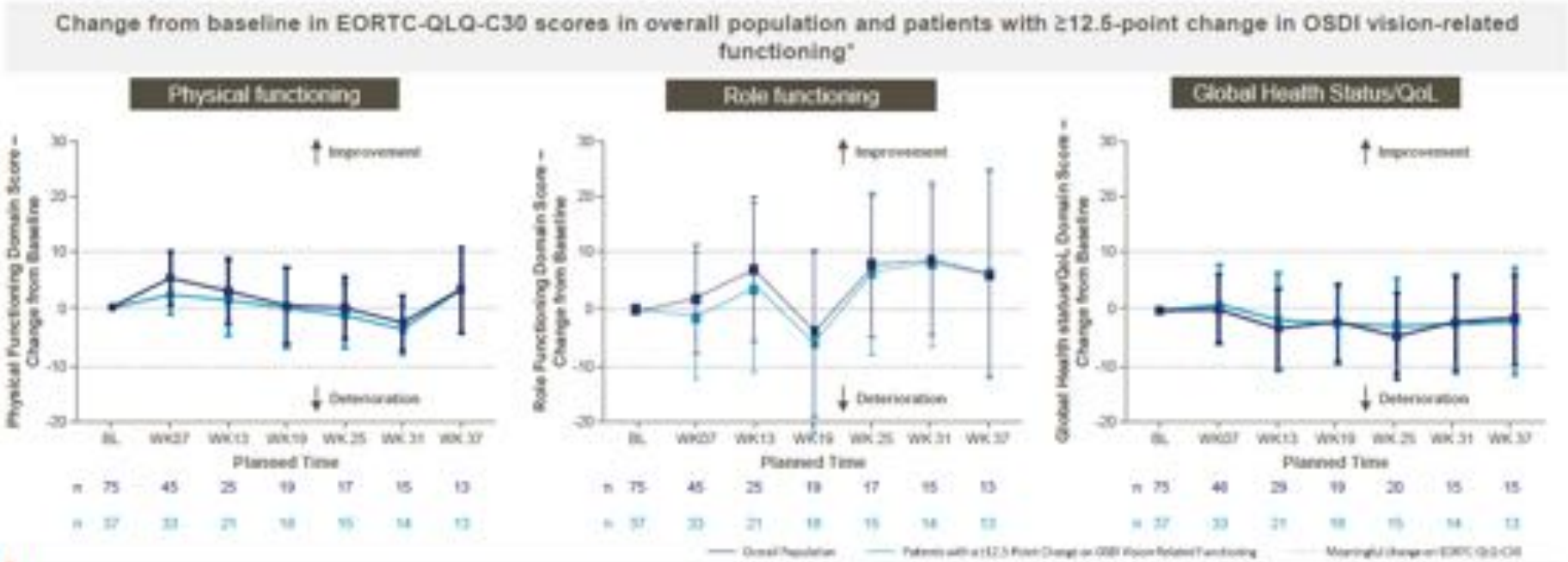
Percentages do not add up to 100% due to rounding. *Indicates patients with elevated paraproteins reported during the delays, though these elevated paraproteins did not meet progressive disease criteria; †1 patient developed progressive disease 6 weeks into delay and 1 patient developed progressive disease 3 weeks after delay; ‡1 patient developed progressive disease 6 weeks into the delay, 1 patient developed progressive disease 15 weeks into the delay, and 1 patient developed progressive disease 6 weeks after delay.

About half of patients in both cohorts had prolonged dose delays of more than 63 days.

Responses to belantamab mafodotin are durable despite dose modifications. Most patients continued to experience a clinical benefit during the delay, and some even deepened their response during the delay. Few patients had progressive disease

Lonial S et al. Cancer 2021

Effect on Disease Symptoms and Health-Related Quality of Life
EORTC-QLQ-C30 changes from baseline in patients with reduction in OSDI visual functioning



There was no change in overall patient-reported Global Health Status/QoL, Physical Functioning, or Role Functioning domain scores of the EORTC-QLQ-C30, even among patients with a minimal meaningful within-patient reduction in vision-related function by OSDI

These figures were first presented in Popat R et al. ASH. 2020.

*13-month follow-up; cut-off date January 31, 2020.

EORTC-QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire core 30; GHS = global health status; OSDI = Ocular Surface Disease Index; QoL = quality of life;

Popat R et al. Presented at the 62nd American Society of Hematology Annual Meeting. 2020.

ALGONQUIN: Belantamab mafodotin plus Pom-dex

Study design

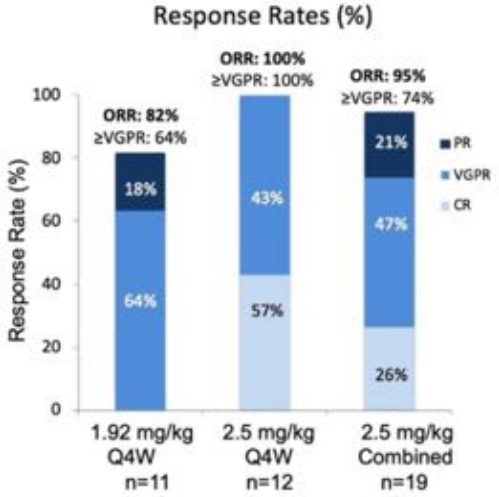
PART 1: DLT 3+3

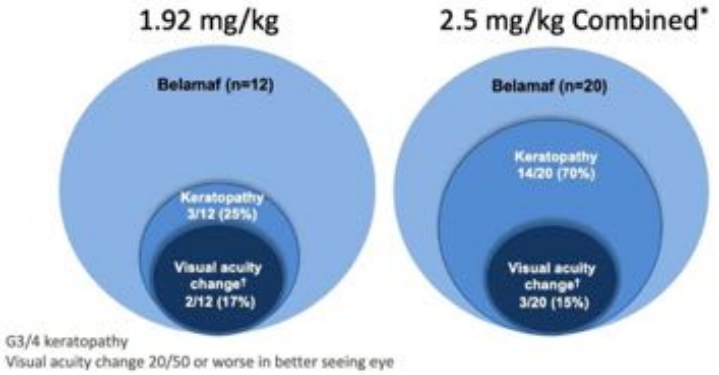
PART 1: RP2D determination phase ≤12 patients/cohort

D1 D8 D15 D21 C2D1 C3D1

POM 4 mg po	→				→					
Dex 40 mg po[a]	D	D	D	D	D	D	D	D	D	D
1.92/2.5 SINGLE iv	B				B				B	
2.5/3.4 SPLIT iv	B	B			B	B			B	B
BELAMAF loading iv	2.5				1.92				1.92	

TEAE, n (%)	Any grade	Grade ≥3
Keratopathy	28 (75.7)	19 (51.4)
Neutropenia	21 (56.8)	15 (40.5)
Thrombocytopenia	18 (48.6)	12 (32.4)
Decreased visual acuity	17 (45.9)	6 (16.2)
Fatigue	15 (40.5)	4 (10.8)





	1.92 mg/kg SINGLE	2.5 mg/kg Combined
Median dose holds/subject, n (range)	1 (0, 8)	5 (0, 16)

- **BELAMAF 1.92 mg/kg Q4W**
  - **≥ VGPR 64% and median PFS 14.1 months**
  - **Grade 3/4 keratopathy in 25% and ≤ 20/50 BCVA 17%**
- **BELAMAF 2.5 mg/kg (SINGLE Loading, SPLIT)**
  - **≥ VGPR 74% (100% for the 2.5 mg/kg Q4W) and not yet reached**
  - **Grade 3/4 keratopathy in 70% and ≤ 20/50 BCVA 15%**
- **Alternative dosing schedules are under evaluation to further optimize efficacy/safety profile**

Trudel S, et al. ASH 2020, Oral Abstract 725

Trudel S, et al. ASH 2020, Oral Abstract 725.

Management of Corneal Symptoms
Roles of the RRMM Patient Care Team

Multidisciplinary teams can improve care of patients with RRMM. A close collaboration between all team members can better inform treatment decisions and ensure best management of ocular symptoms

RRMM Patient Care Team Member	Roles Before Starting Treatment	Roles During Treatment
Hematologists/Oncologists	Educate the clinical care team and selves about corneal symptom risks and local label management strategies	Assess eye care examination report and decide appropriate treatment strategy based on local label corneal event guidelines Communicate with wider RRMM patient care team
Nurses, Nurse Practitioners, and Physician Assistants	Refer patient to an eye care professional Communicate with patient • Educate patient about avoiding contact lenses during treatment and exercising caution when driving or operating machinery • Make sure patient reports ocular symptoms	Regularly question patients about ocular symptoms and their impact on daily activities Communicate with patient about caregiver support for daily activities in case BCVA changes occur
Eye Care Professionals	Conduct baseline eye examination before starting treatment Obtain patients' clinical history on pre-existing ocular conditions, ocular surgery, or eye trauma. Make recommendations to hematologist/oncologist based on this history and whether it influences management	Communicate with hematologists/oncologists about corneal event grade/severity Echo to patients the importance of complying with supportive measures and being cautious when operating machinery or driving

The chart has been independently created by GSK from original data first presented in Lonial S et al. *Blood Cancer J.* 2021.

BCVA = best-corrected visual acuity; RRMM = relapsed/refractory multiple myeloma

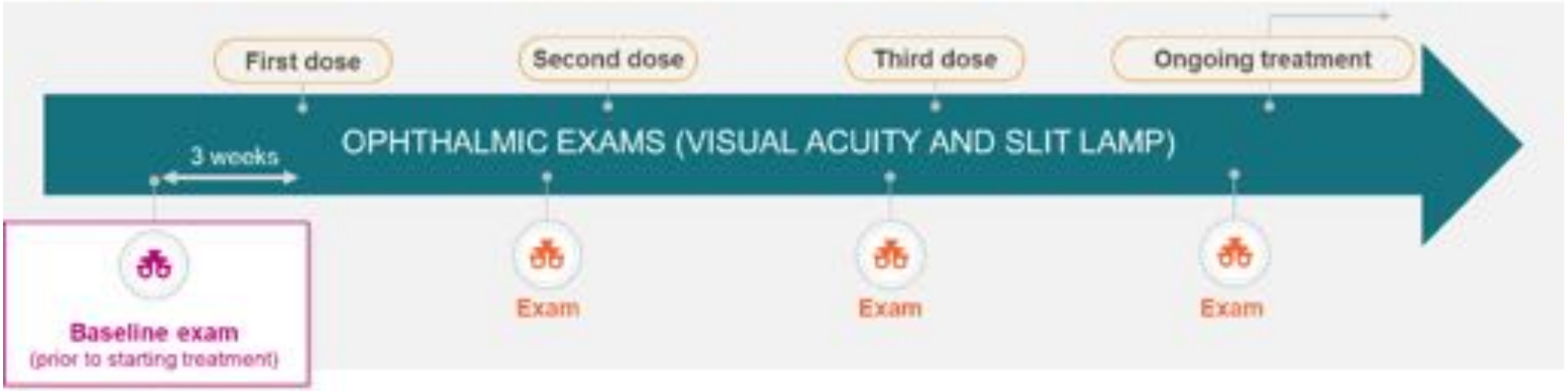
Lonial S et al. *Blood Cancer J.* 2021.

Characterization of Corneal Epitelial Findings: DREAMM-2 post-hoc analysis
Recommended Monitoring, Diagnosis, and Management Techniques

Proposed paradigm for monitoring based on the post hoc analysis of DREAMM-2 and an objective literature review

Monitoring

Conduct eye examinations (visual acuity and slit lamp microscopy) at baseline (up to 3 weeks before), prior to each cycle (up to 2 weeks before), and promptly for worsening symptoms



Corneal exam findings (keratopathy), together with BCVA changes, guide dose modifications of Belantamab Mafodotin

Severity[†]	Corneal examination finding(s)[‡]		Presentation of MECs[‡,2]	Corneal AE management
	Change in BCVA	Description	Example schematics by severity	Recommended dose modifications
Grade 1/ Mild	Decline from baseline of 1 line on Snellen VA test	**Mild superficial keratopathy**[*§] (documented worsening from baseline), with or without symptoms		**Continue treatment** at current dose
Grade 2/ Moderate	Decline from baseline of 2 or 3 lines (and Snellen VA not worse than 20/200)	**Moderate superficial keratopathy**[*§] with or without patchy MECs, subepithelial haze (peripheral), or a new peripheral stromal opacity	 Dots represent MECs	**Withhold treatment** until improvement and BCVA reduction is of mild severity or better Resume at reduced dose of 1.9mg/kg
Grade 3/ Severe	Decline from baseline of more than 3 lines (and Snellen VA not worse than 20/200)	**Severe superficial keratopathy**[*§] with or without diffuse MECs involving the central cornea, subepithelial haze (central), or a new central stromal opacity		**Withhold treatment** until improvement and BCVA reduction is grade 1/mild Resume at reduced dose of 1.9mg/kg[‡]
Grade 4/ Severe	Snellen VA worse than 20/200	**Corneal epithelial defect**, including corneal ulcers. These should be managed promptly and as clinically indicated by an eyecare professional	N/A	**Withhold treatment** until improvement and BCVA reduction is of mild severity or better. For worsening symptoms, **consider discontinuing** Resume at reduced dose of 1.9mg/kg[‡]

Lonial S. et al . Blood Cancer J 2021

Conclusions

- Sel and Belamaf are associated with **new safety concerns**
- **Trombocytopenia** is the most common hematological toxicity
- **Cytopenias, constitutional symptoms, gastrointestinal effects, and hyponatremia** are the major toxicities of Sel
- **Keratopathy** is the major toxicities of Belamaf
- Toxicities are in the majority of the cases manageable with **dose modifications and supporting care**
- As these are newer drugs with limited data, **continuous surveillance and monitoring** are warranted during the treatment course with early mitigation strategies.