Highlights from IMW 2021

1-2 febbraio 2022
Bologna
Royal Hotel Carlton

Immunoconiugati anti-BCMA

Immunoterapie effettrici del MM refrattario dopo ≥3 precedenti terapie

Coordinatore Scientifico
Michele CAVO

Comitato Scientifico
Michele CAVO
Maria Teresa PETRUCCI

DISCLOSURE

Maria Teresa Petrucci

Company name	Honoraria	Advisory board	Support for attending meetings and/or travel
Celgene- BMS	X	X	X
Janssen-Cilag	X	X	X
Takeda	X	X	X
Roche		X	
Amgen	X	X	X
GSK	X	X	
Karyopharm	X	X	
Sanofi	X	X	X

IMW21 18TH INTERNATIONAL MYELOMA WORKSHOP

Focus of This Talk

BCMA-targeting modalities

	Antibody-drug conjugate	T-cell activating strategies	
		CAR T-cell therapy	Bispecific antibody
			
Examples:	belantamab mafodotin	Ide-cel (bb2121) Cilta-cel	Teclistamab AMG701

BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor.
Cho SF et al. *Front Immunol.* 2018;9:1821. doi:10.3389/fimmu.2018.01821.

Atrium Health

IMW21 18TH INTERNATIONAL MYELOMA WORKSHOP

Immune therapy in myeloma: why focusing on BCMA?

- BCMA = B cell maturation antigen; member of TNFR superfamily
- Expressed by plasma cells and some mature B cells (overlaps with CD38)
- Universally expressed in MM and in a subset of lymphoma

Rodriguez-Otero P et al. *J Clin Med*. 2020;9(11) doi:10.3390/jcm9113577.

IMW21 18TH INTERNATIONAL MYELOMA WORKSHOP

Focus of This Talk

BCMA-targeting modalities

Antibody-drug conjugate	T-cell activating strategies	
	CAR T-cell therapy	Bispecific antibody
Examples: belantamab mafodotin	Ide-cel (bb2121) Cilta-cel	Teclistamab AMG701

BCMA, B-cell maturation antigen; CAR, [illegible] receptor.
Cho SF et al. *Front Immunol.* 2018;9:1821. doi:10.3389/fimmu.2018.01821.

Atrium Health

GAZZETTA UFFICIALE
DELLA REPUBBLICA ITALIANA

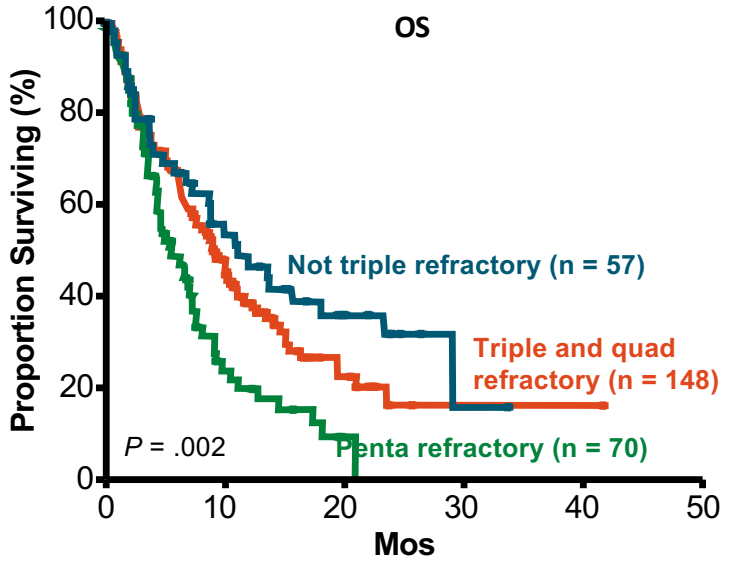
AGENZIA ITALIANA DEL FARMACO
DETERMINA 24 novembre 2021

Il medicinale BLENREP (belantamab mafodotin) è classificato come segue: indicazioni terapeutiche oggetto della negoziazione: «Blenrep» è indicato in monoterapia per il trattamento del mieloma multiplo nei pazienti adulti, che hanno ricevuto almeno quattro terapie precedenti e la cui malattia risulta refrattaria ad almeno un inibitore del proteasoma, un agente immunomodulatore e un anticorpo monoclonale anti-CD38 e che hanno mostrato progressione di malattia all'ultima terapia.

The Challenge of Treating Triple-Quad-Penta Class Refractory MM

- Retrospective analysis of 275 patients from 14 academic centers

Characteristic	Median OS, Mos	Description
Not triple refractory	11.2	Refractory to 1 CD38 mAb, but not to both PI and IMiD
Triple and quad refractory	9.2	Refractory to 1 CD38 mAb + 1 PI + 1 or 2 IMiDs
Penta refractory	5.6	Refractory to 1 CD38 mAb + 2 PIs + 2 IMiDs
Overall cohort	8.6	



- 249 patients received further treatment
  - ORR: 31%; mPFS: 3.4 mos; mOS: 9.3 mos

Gandhi. Leukemia. 2019;33:2266.

BCMA-targeted agents, the fourth pillar of treatment for MM, includes ADC therapy[1,2]

Nonexhaustive list

TREATMENT PILLARS FOR RRMM*

Immunomodulatory agents[3]	PIs[4]	Anti-CD38 mAbs[1,4]	BCMA-targeted agents[1,5]
Lenalidomide	Bortezomib	Daratumumab	Belantamab mafodotin
Pomalidomide	Carfilzomib	Isatuximab	Ide-cel
	Ixazomib		

*Other treatment options include anti-SLAMF7 treatments such as elotuzumab, amongst others.[1,6]

ADC, antibody-drug conjugate; BCMA, B-cell maturation antigen; CD, cluster of differentiation; ide-cel, idecabtagene vicleucel; mAb, monoclonal antibody; MM, multiple myeloma; PI, proteasome inhibitor; RRMM, relapsed/refractory multiple myeloma; SLAMF7, SLAM family member 7.

1. Dimopoulos MA et al. *Hemasphere*. 2021;5(2):e528. doi:10.1097/HS9.0000000000000528 **2.** Becnel MR, Lee HC. *Ther Adv Hematol*. 2020. doi:10.1177/2040620720979813 **3.** Schjesvold F et al. *Future Oncol*. 2020;16(11):631-641. **4.** Chim CS et al. *Leukemia*. 2018;32:252-262. **5.** Abecma. Prescribing Information. Bristol-Myers Squibb Company; 2021. **6.** Moreau P et al. *Ann Oncol*. 2017;28(suppl 4):iv52-iv61.

IMW21 18TH INTERNATIONAL MYELOMA WORKSHOP

Belantamab mafodotin, a BCMA-targeted ADC, has a multimodal mechanism[1,2]

Belantamab mafodotin is a humanized, afucosylated, anti-BCMA monoclonal antibody conjugated to the microtubule inhibitor mafodotin[1]

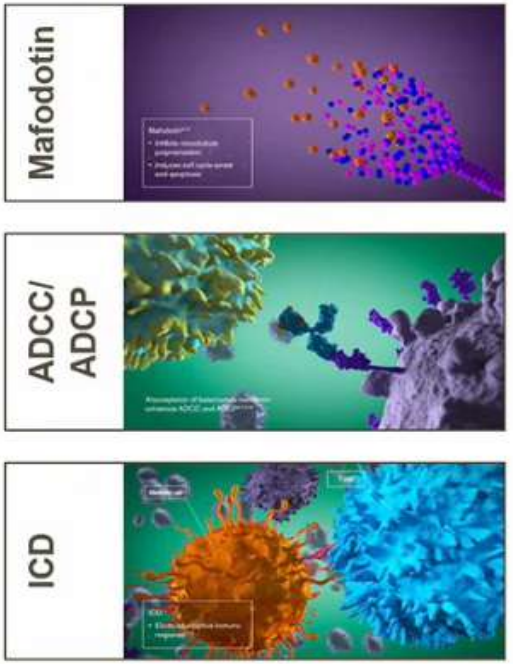
It specifically binds to BCMA and eliminates myeloma cells by a multimodal mechanism[1,3]:

- Delivers mafodotin to BCMA-expressing malignant plasma cells and inhibits microtubule polymerization resulting in immune-independent apoptosis

Immune-independent mechanism

- Enhances antibody-dependent cellular cytotoxicity and phagocytosis (ADCC/ADCP)
- Induces immunogenic cell death (ICD)

Immune-dependent mechanisms



IMW21 18TH INTERNATIONAL MYELOMA WORKSHOP

DREAMM-2: belantamab mafodotin monotherapy demonstrated deep and durable activity in a broad patient population[1,2]

Primary analysis data cutoff[3]: January 2020

Belantamab mafodotin — **DREAMM-2** (2.5mg/kg cohort)

Patient characteristics[3]

	Overall population N=97	HR cytogenetics n=41	Mild RI* n=48	Moderate RI* n=24
Median age, years (range)	**65** (60-70)	**67** (42-85)	**66** (40-85)	**69** (45-85)
Median prior lines of therapy (range)	**7** (3-21)	**6** (3-11)	**7** (3-12)	**7** (3-21)
Triple-refractory, n (%)	97 (100)	41 (100)	48 (100)	24 (100)

Efficacy outcomes[3]

[2.5mg/kg]	Overall population N=97	HR cytogenetics n=41	Mild RI* n=48	Moderate RI* n=24
ORR, n (%)	**31 (32)**	**12 (29)**	**16 (33)**	**8 (33)**
≥VGPR, n (%)	18 (19)	9 (22)	8 (17)	8 (33)
mDOR, months	**11.0**	**10.3**	**12.5**	**13.1**
mPFS, months	2.8	2.1	2.2	3.7
mOS, months	13.7	9.9	13.7	NR

Safety data for overall population[3]

AE†	Any grade, n (%)	Grade ≥3, n (%)
Any	93 (98)	80 (84)
Keratopathy‡§	**68 (72)**	**44 (46)**
Thrombocytopenia‖	36 (38)	21 (22)
Anemia	26 (27)	20 (21)

1. Dimopoulos MA et al. *Hemasphere*. 2021;5:2(e528). doi:10.1097/HS9.0000000000000528 **2.** Lonial S et al. *Lancet Oncol*. 2020;21(2):207-221. **3.** Lonial S et al. *Cancer*. 2021. doi:10.1002/cncr.33809 **4.** Lonial S et al. Presented at:

IMW21 18TH INTERNATIONAL MYELOMA WORKSHOP

Study design: first real-world data for belantamab mafodotin monotherapy

A retrospective real-world, multisite study in patients with RRMM who received ≥2 doses of belantamab mafodotin under the expanded access compassionate care program

N=67

Patients treated in EAP

- Belantamab mafodotin 3.4mg/kg
- Belantamab mafodotin 2.5mg/kg

Patients retrospectively included

Data were extracted from medical charts focusing on demographics, disease characteristics, prior treatment, and safety

Inclusion criteria

- All patients with RRMM who received ≥2 doses of belantamab mafodotin under the expanded access compassionate care program

Primary endpoint
- PFS

Secondary endpoints
- OS
- ORR
- Safety and tolerability

EAP, expanded access program; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; RRMM, relapsed/refractory multiple myeloma.
Shragai T, Lavi N, Gatt M, et al. Update of real-world experience with belantamab mafodotin monotherapy for relapsed/refractory myeloma via GSK expanded access program. Poster presented at: EHA Annual Meeting; June 9-17, 2021. Abstract 2853.

IMW21 18TH INTERNATIONAL MYELOMA WORKSHOP

A manageable safety profile is observed for single-agent belantamab mafodotin in the first real-world dataset

Heavily pretreated patients on belantamab mafodotin monotherapy were easily managed

- **74% of patients experienced resolution of symptoms** to grade 1 or 0 during follow-up

- **4 patients discontinued therapy** due to ocular AEs
- **No treatment-related deaths** were reported

Adverse event	N=67
Dose reduction, %	25
Ocular events,* %	65
Hematological toxicity,* %	11
Infection,* %	5
Non-ocular AEs, %	
Thrombocytopenia	39
Neutropenia	13
Infection	10
Elevated liver enzymes	10
Anemia	9

*Dose reduction due to ocular events, hematological toxicity, or infection.
AE, adverse event.

Shragai T, Lavi N, Gatt M, et al. Update of real-world experience with belantamab mafodotin monotherapy for relapsed/refractory myeloma via GSK Expanded Access Program. Poster presented at: EHA Annual Meeting; June 9-17, 2021. Abstract 2853.

IMW21 18TH INTERNATIONAL MYELOMA WORKSHOP

Higher ORR in less heavily pretreated patients in DREAMM-1 suggests better efficacy with belantamab mafodotin in earlier lines of therapy[1,2]

Efficacy endpoint	DREAMM-1[1] Overall N=35	DREAMM-1[1] Patients without prior daratumumab treatment n=21	DREAMM-1[1] Patients with prior daratumumab treatment* n=13	DREAMM-2[2] Overall, triple-class refractory N=97
ORR	60% (95% CI: 42.1-76.1)	71.4% (95% CI: 47.8-88.7)	38.5% (95% CI: 13.9-68.4)	32% (97.5% CI: 21.7-43.6)

Patients without prior daratumumab treatment responded better than those exposed to daratumumab and who were triple-class refractory to immunomodulatory agents, PIs, and anti-CD38 mAbs[1,2]

*Daratumumab+PI+immunomodulatory agent.[1]
CD, cluster of differentiation; mAb, monoclonal antibody; ORR, overall response rate; PI, proteasome inhibitor.
1. Trudel S et al. *Blood Cancer J.* 2019;9(4):37. doi:10.1038/s41408-019-0196-6 **2.** Lonial S et al. *Cancer.* 2021. doi:10.1002/cncr.33809

IMW21 18TH INTERNATIONAL MYELOMA WORKSHOP

DREAMM-3: confirmatory phase III study evaluating belantamab mafodotin monotherapy in earlier lines of treatment

Inclusion criteria[1]

- Histologically or cytologically confirmed diagnosis of MM as defined by IMWG
- ECOG performance status of 0-2
- Undergone autologous stem cell transplant, if eligible
- ≥2 prior lines of antimyeloma therapy, including PI and immunomodulatory drug
- Disease progression on or within 60 days of completion of last therapy
- Prior treatment-related toxicities grade ≤1, except alopecia & peripheral neuropathy

Key exclusion criteria[1]

- Prior anti-BCMA or pomalidomide therapy
- Prior allogenic stem cell transplant
- Presence of active renal condition; HIV infection; presence of HbsAg/HbcAb

Open label, randomized, multicenter study (N=380)

1:2

- Belantamab mafodotin 2.5mg/kg Q3W
- Pomalidomide 4mg + dexamethasone 40mg or 20mg

Ocular substudy[2]

To explore BCLs as possible management of belantamab mafodotin–related corneal events

Estimated primary completion date: December 9, 2021

Endpoints[1]

Primary:

- PFS

Secondary:

- OS
- CBR
- ORR
- DOR
- TTR
- TTP
- Number of pts with AEs
- Changes in hematological parameters
- Number of pts with abnormal ocular findings
- Number of pts with ADAs against belantamab mafodotin

ADA, anti-drug antibody; AE, adverse event; BCL, bandage contact lens; BCMA, B-cell maturation antigen; CBR, clinical benefit rate; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; HbcAb, hepatitis B core antibody; HbsAg, hepatitis B surface antigen; HIV, human immunodeficiency virus; IMWG, International Myeloma Working Group; MM, multiple myeloma; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PI, proteasome inhibitor; pts, participants; Q3W, every 3 weeks; TTP, time to progression; TTR, time to response.

1. Study of single agent belantamab mafodotin versus pomalidomide plus low-dose dexamethasone (pom/dex) in participants with relapsed/refractory multiple myeloma (RRMM). ClinicalTrials.gov identifier: NCT04162210. Updated November 19, 2021. Accessed August 4, 2021. https://clinicaltrials.gov/ct2/show/NCT04162210 2. EU Clinical Trials Register. Accessed April 8, 2021. https://www.clinicaltrialsregister.eu/ctr-search/trial/2018-004252-38/GB

IMW21 18TH INTERNATIONAL MYELOMA WORKSHOP

ALGONQUIN: study rationale for belantamab mafodotin in combination with SOC in earlier lines of RRMM therapy

There is an urgent need to improve outcomes in patients treated with pomalidomide and dexamethasone[1]

Patients treated with pomalidomide and dexamethasone have an **ORR of only 30%** and a **PFS of 4 months[2]**

Conventional IgG functions of belantamab mafodotin could be enhanced by the **ability of pomalidomide to augment T-cell– and NK-cell–mediated immunity** (including ADCC and ADCP)[2]

ADCC, antibody-dependent cellular cytotoxicity; ADCP, antibody-dependent cellular phagocytosis; IgG, immunoglobulin G; NK, natural killer; ORR, overall response rate; PFS, progression free survival; RRMM, relapsed/refractory multiple myeloma; SOC, standard of care.

1. Trudel S et al. Presented at: ASH Annual Meeting and Exposition; December 5-8, 2020. 2. Nalley C. Oncol Times. 2021;43(S4):20. doi:10.1097/01.COT.0000735196.51054.e5

IMW21 18TH INTERNATIONAL MYELOMA WORKSHOP

ALGONQUIN: study design

A phase I/II, two-part, multicenter, dose-escalation study evaluating belantamab mafodotin in combination with pomalidomide and dexamethasone (B-Pd) in patients with RRMM[1-3]

Inclusion criteria
- ≥1 prior LOT
- Refractory to lenalidomide and exposed or refractory to a PI
- ECOG PS 0-2

All cohorts received pomalidomide 4mg on days 1-21 and dexamethasone 40mg (20mg for age >75 years) weekly

Part 1 DLT
3 + 3 dose escalation
(up to 12 patients per cohort)

N=37

- n=12 → **Cohort 1 (Q4W)**: belantamab mafodotin **1.92mg/kg SINGLE dose***
- n=12 → **Cohort 1a (Q4W)**: belantamab mafodotin **2.5mg/kg SINGLE dose* and 2.5mg/kg LOADING dose followed by 1.92mg/kg Q4W†**
- n=8 → **Cohort 1b (Q4W)**: belantamab mafodotin **2.5mg/kg SPLIT dose**
- n=5 → **Cohort 2 (Q4W)**: belantamab mafodotin **3.4mg/kg SPLIT dose†**

Currently enrolling → **Cohort 3 (Q8W, Q12W)**: belantamab mafodotin **2.5mg/kg Q8W OR 2.5mg/kg Q12W**

Part 2
N=35
(23 new patients +12 from part 1)
→ **RP2D**

Treatment until disease progression or toxicity‡

Primary endpoints
- **Part 1:** MTD and/or RP2D
- **Part 2:** ORR

Secondary endpoints
- Efficacy (PFS, OS, DOR)
- Safety, including ocular findings

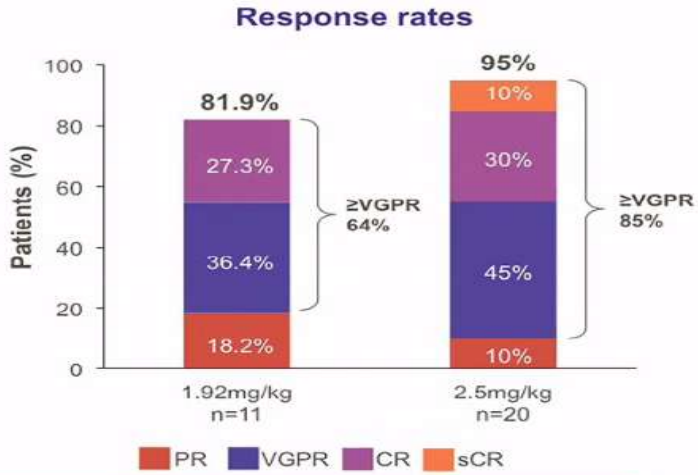
*SINGLE belantamab mafodotin IV on day 1.1 ‡SPLIT doses of belantamab mafodotin IV equally on days 1 and 8.1 ‡Nine patients had discontinued treatment as of November 2020.2
DLT, dose-limiting toxicity; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; IV, intravenous; LOT, line of therapy; MTD, maximum tolerated dose; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PI, proteasome inhibitor; Q4W, every 4 weeks; Q8W, every 8 weeks; Q12W, every 12 weeks; RP2D, recommended phase 2 dose; RRMM, relapsed/refractory multiple myeloma.
1. Trudel S et al. Abstract presented at: ASH Annual Meeting and Exposition; December 5-8, 2020. Abstract 725. Accessed February 22, 2021. https://ash.confex.com/ash/2020/webprogram/Paper134836.html 2. Trudel S et al. Presented at: ASH Annual Meeting and Exposition; December 5-8, 2020. 3. Multi-center study of GSK2857916 in combination with pomalidomide and dex. ClinicalTrials.gov identifier: NCT03715478. Updated August 10, 2020. Accessed February 8, 2021. https://clinicaltrials.gov/ct2/show/NCT03715478

IMW21 18TH INTERNATIONAL MYELOMA WORKSHOP

ALGONQUIN part 1: patients have maintained deep and durable responses across all cohorts

Patient characteristics	N=32
Median age, years (range)	**64** (36-81)
Median prior lines of therapy (range)	**3** (1-5)
Double refractory,* n (%)	24 (75)
Triple refractory,† n (%)	10 (31.2)

Efficacy outcomes	All cohorts (N=32)	1.92-mg/kg cohort (n=12)	2.5-mg/kg cohorts (n=20)
ORR, n (%)	**28/31**‡ (90)	**9/11**‡ (82)	**19/20** (95)
mPFS, months (95% CI)	**24.9** (14.5-NR)	**16.2** (8.72-NR)	**25.3** (13.09-NR)



Belantamab mafodotin 1.92mg/kg and 2.5mg/kg in combination with Pd resulted in high efficacy, with 64% and 85% of patients achieving ≥VGPR, respectively

*Refractory to lenalidomide and a proteasome inhibitor. †Refractory to lenalidomide, a proteasome inhibitor, and daratumumab. ‡11 patients in the 1.92-mg/kg cohort were evaluable for response.
CR, complete response; mPFS, median progression-free survival; NR, not reached; ORR, overall response rate; Pd, pomalidomide/dexamethasone; PR, partial response; sCR, stringent complete response; VGPR, very good partial response.
Trudel S et al. Poster presented at: 18th IMW; September 8-11, 2021; Vienna, Austria. Abstract 1082298.

IMW21 18TH INTERNATIONAL MYELOMA WORKSHOP

ALGONQUIN part 1*: belantamab mafodotin given in combination with Pd demonstrates a manageable safety profile consistent with the individual agents

AE	1.92mg/kg (cohort 1) n=12		2.5mg/kg (cohorts 1a-b) n=20	
	Any grade n (%)	≥Grade 3 n (%)	Any grade n (%)	≥Grade 3 n (%)
Keratopathy†	11 (91.7)	5 (41.7)	20 (100)	14 (70)
Blurred vision	10 (83.3)	4 (33.4)	18 (90)	9 (45)
Neutropenia	7 (58.3)	6 (50)	13 (65)	10 (50)
Thrombocytopenia	7 (58.3)	5 (41.7)	9 (45)	4 (20)

While keratopathy and blurred vision were the most frequently reported AEs, no patients discontinued treatment due to ocular events in either dose cohort

*MTD established as 2.5mg/kg SINGLE (day 1) and 2.5mg/kg SPLIT (1.25mg/kg on days 1 and 8) Q4W in combination with standard dosing of pomalidomide and dexamethasone. Alternative dosing schedules are under evaluation to further optimize efficacy/safety profile.[2] †Keratopathy including superficial punctate keratopathy and/or microcyst-like epithelial changes.[3]
AE, adverse event; MTD, maximum tolerated dose; Pd, pomalidomide/dexamethasone; Q4W, every 4 weeks.
1. Trudel S et al. Poster presented at: 18th IMW: September 8-11, 2021; Vienna, Austria. Abstract 1082298. **2.** Trudel S et al. Presented at: ASH Annual Meeting and Exposition; December 5-8, 2020. **3.** Popat R et al. Abstract presented at: ASH Annual Meeting and Exposition; December 5-8, 2020. Abstract 1419.

IMW21 18TH INTERNATIONAL MYELOMA WORKSHOP

ALGONQUIN: study recap and future implications

- Belantamab mafodotin in combination with Pd **demonstrated deep and durable response rates**[1]
  - Both dose cohorts (1.92mg/kg and 2.5mg/kg) demonstrated high responses, with 64% and 85% of patients achieving ≥VGPR, and a mPFS of 16.2 and 25.3 months, respectively
- **No new safety signals were reported** with this combination[1]
  - The most frequent AEs observed were neutropenia, thrombocytopenia, and corneal events

- **ALGONQUIN dose-escalation study will help to inform**[2]
  - Mitigation strategies for corneal events associated with belantamab mafodotin
  - Appropriate dose selection for DREAMM-8, a phase III study evaluating belantamab mafodotin in combination with SOC doublet Pd vs PVd in 2L+ RRMM[2,3]
- **The RP2D will be presented at the ASH congress later this year**

2L, second line; AE, adverse event; ASH, American Society of Hematology; mPFS, median progression-free survival; Pd, pomalidomide/dexamethasone; PVd, pomalidomide/bortezomib/dexamethasone; RP2D, recommended phase 2 dose; RRMM, relapsed/refractory multiple myeloma; SOC, standard of care; VGPR, very good partial response.

1. Trudel S et al. Poster presented at: 18th IMW; September 8-11, 2021; Vienna, Austria. Abstract 1082298. **2.** Trudel S et al. Abstract presented at: ASH Annual Meeting and Exposition; December 5-8, 2020. Abstract 725. Accessed February 22, 2021. https://ash.confex.com/ash/2020/webprogram/Paper134836.html 3. Belantamab mafodotin plus pomalidomide and dexamethasone (Pd) versus bortezomib plus Pd in relapsed/refractory multiple myeloma (DREAMM 8). ClinicalTrials.gov identifier: NCT04484623. Updated July 19, 2021. Accessed August 11, 2021. https://www.clinicaltrials.gov/ct2/show/NCT04484623

IMW21 18TH INTERNATIONAL MYELOMA WORKSHOP

BCMA-targeted ADCs are currently under investigation in combination therapy with SOC and novel agents to enhance efficacy[1-3]

Preclinical data have shown promising synergistic combinability of BCMA-targeted ADC agents with the first **3 pillars of treatment for MM** (eg, immunomodulatory agents, PIs, and anti-CD38 mAbs) and **novel agents** (eg, gamma secretase inhibitors)

Unique MOAs of ADCs make them amenable to combination therapies[1-4]

Combinations with SOC agents can:

- Increase ADCC/ADCP activity (eg, immunomodulatory drugs, anti–PD-1)
- Enhance antitumor response via ICD (eg, anti–PD-1)
- Augment the degree of DNA damage and increase levels of MM cytotoxicity (eg, PIs, anti–CD-38 mAbs)

Synergism with novel agents can:

- Enhance MMAF-induced apoptosis (eg, gamma secretase inhibitors)

ADC, antibody-drug conjugate; ADCC, antibody-dependent cellular cytotoxicity; ADCP, antibody-dependent cellular phagocytosis; BCMA, B-cell maturation antigen; CD, cluster of differentiation; ICD, immunogenic cell death; mAb, monoclonal antibody; MM, multiple myeloma; MMAF, monomethyl auristatin F; MOA, mechanism of action; PD-1, programmed cell death protein 1; PI, proteasome inhibitor; SOC, standard of care.

1. Nooka AK et al. *Future Oncol*. 2021;17(16):1987-2003. **2.** Trudel S et al. Presented at: ASH Annual Meeting and Exposition; December 5-8, 2020. **3.** Xing L et al. *Clin Cancer Res*. 2021. doi:10.1158/1078-0432.CCR-21-1621 **4.** Xing L et al. *Leukemia*. 2020;34(8):2150-2162.

IMW21 18TH INTERNATIONAL MYELOMA WORKSHOP

Studies are in progress to further investigate belantamab mafodotin as monotherapy or a combination partner[1,2]

Monotherapy in the triple-class–refractory setting

DREAMM-2[*1]

Phase II study of belantamab mafodotin in RRMM patients - **ongoing**

DREAMM-12[*3]

Study of belantamab mafodotin in RRMM patients with renal impairment - **ongoing**

DREAMM-13[*4]

Study of belantamab mafodotin in RRMM patients with hepatic impairment - **ongoing**

Monotherapy in 3L+

DREAMM-3[*9]

Belantamab mafodotin vs Pd in RRMM patients - **ongoing**

Combination therapy with SOC in 1L+

DREAMM-6[*5]

Combo with Rd or Vd in RRMM - **ongoing**

DREAMM-7[*10]

Combo with Vd vs DaraVd in RRMM - **ongoing**

DREAMM-8[*11]

Combo with Pd vs PVd in RRMM - **ongoing**

ALGONQUIN[†6,12]

Combo with Pd in RRMM - **ongoing**

Combination therapy with novel agents

DREAMM-5[7]

Combo with feladilimab or nirogacestat or dostarlimab or GSK3174998 or isatuximab - **ongoing**

DREAMM-4[‡13]

Combo with pembrolizumab in RRMM - **ongoing**

Combination therapy in NDMM

DREAMM-9[*2]

Combo with VRd - **ongoing**

NCT04808037[§8]

Combo with Rd - **ongoing**

Key: **Alternative dosing schedule strategies to mitigate corneal events**[2,5-8]

Please refer to slide notes for footnotes, abbreviations, and references.
This information is intended for healthcare providers only. Compounds may be investigational. Inclusion in this presentation does not imply regulatory approval for these compounds or indications.

IMW21 18TH INTERNATIONAL MYELOMA WORKSHOP

MEDI2228 rapidly internalizes into MM cells, leading to DNA damage and apoptosis of tumor cells[1,2]

MEDI2228 is a fully humanized antibody conjugated to a pyrrolobenzodiazepine (PBD) payload, tesirine[1-4]

- Once the agent is internalized in the MM cell, it cleaves and releases active PBD dimers
- The PBD dimers then cross-link the DNA, leading to apoptotic cell death
  - The dimers cause cell death in both rapidly dividing and more dormant cells

The ADC preferentially binds to membrane-bound BCMA, thereby delivering its payload specifically to MM cells[1]

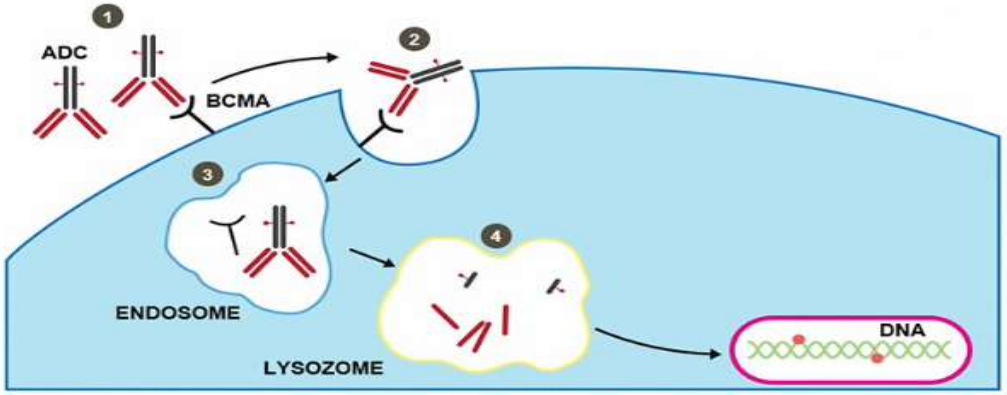


Figure adapted from Demel et al.[4]

ADC, antibody-drug conjugate; BCMA, B-cell maturation antigen; MM, multiple myeloma.

1. Cho SF et al. *Front Immunol.* 2018;9:1821. doi:10.3389/fimmu.2018.01821 **2.** Kinneer K et al. *Leukemia.* 2019;33(3):766-771. **3.** Xing L et al. *Leukemia.* 2020;34(8):2150-2162. **4.** Demel I et al. *Br J Haematol.* 2021;193(4):705-722.

IMW21 18TH INTERNATIONAL MYELOMA WORKSHOP

Phase I results for anti-BCMA ADC MEDI2228 in RRMM*

MEDI2228[1-3] — **Phase I** (actual enrollment N=107)

Patient characteristics

N=82
Median age, years (range): 69 (40-89)
Prior lines of therapy, range: 2-11
Triple refractory, n (%) 47 (57.3)

Efficacy outcomes

Dose in mg/kg	0.0125 (n=3)	0.025 (n=6)	0.05 (n=9)	0.10 (n=18)	MTD 0.14 (n=41)	0.2 (n=5)
ORR, n (%)	1 (33.3)	1 (16.7)	3 (33.3)	5 (27.8)	**27 (65.9)**	2 (40)
≥VGPR, n (%)	1 (33.3)	0 (0)	2 (22.2)	4 (22.2)	**11 (26.8)**	0 (0)
mDOR, months	--	--	--	--	**5.9**	--

Safety profile

Adverse event	Grades 1/2, n (%)	Grades 3/4, n (%)
Photophobia	**17 (41.5)**	**7 (17.1)**
Rash	13 (31.7)	0 (0)
Thrombocytopenia	3 (7.3)	10 (24.4)
Pleural effusion	9 (22.0)	1 (2.4)
GGT increased	2 (4.9)	8 (19.5)

*AstraZeneca has stopped development of MEDI2228 in MM.4
ADC, antibody-drug conjugate; BCMA, B-cell maturation antigen; GGT, gamma-glutamyltransferase; mDOR, median duration of response; MM, multiple myeloma; MTD, maximum tolerated dose; ORR, overall response rate; RRMM, relapsed/refractory multiple myeloma; VGPR, very good partial response.

1. MEDI2228 in subjects with relapsed/refractory multiple myeloma (MEDI2228). ClinicalTrials.gov identifier: NCT03489525. Updated May 24, 2021. Accessed August 4, 2021. https://clinicaltrials.gov/ct2/show/NCT03489525
2. Kumar SK et al. Presented at ASH Annual Meeting and Exposition; December 5-8, 2020. Abstract 179. 3. Kumar SK et al. Presented at: ASH Annual Meeting and Exposition; December 5-8, 2020. Poster 179. 4. Nick Taylor. AstraZeneca drops BCMA drug after seeing early clinical data. Fierce Biotech. Published April 30, 2021. https://www.fiercebiotech.com/biotech/astrazeneca-drops-bcma-drug-after-seeing-early-clinical-data

IMW21 18TH INTERNATIONAL MYELOMA WORKSHOP

AMG 224 ADC inhibits the assembly of microtubules, leading to tumor cell death[1-3]

AMG 224 is an ADC consisting of an antihuman BCMA-targeted IgG1 antibody[1]

- Conjugated to an antitubulin maytansinoid, (mertansine, DM1), via a non-cleavable linker
- Mertansine (DM1) is a potent microtubule-targeted cytotoxic agent[2,3]
- DM1 inhibits microtubule polymerization, resulting in antitumor effects

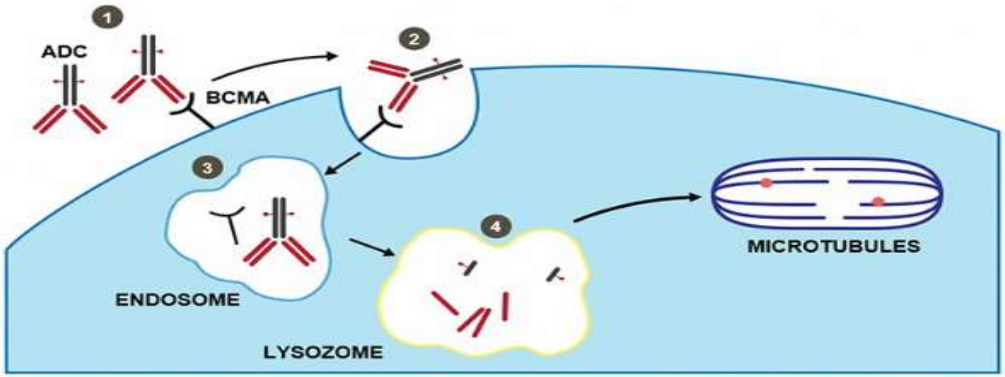


Figure adapted from Demel et al.[3]

ADC, antibody-drug conjugate; BCMA, B-cell maturation antigen; IgG1, immunoglobulin G1.

1. Lee HC et al. *Leukemia*. 2020. doi:10.1038/s41375-020-0834-9 **2.** O'Donnell EK, Raje NS. *Ther Adv Hematol*. 2017;8(20):41-53. **3.** Demel I et al. *Br J Haematol*. 2021;193(4):705-722.

IMW21 16TH INTERNATIONAL MYELOMA WORKSHOP

Phase I results for anti-BCMA ADC AMG 224 RRMM*

	AMG 224[1]	Phase I (actual enrollment N=42)	
Patient characteristics	**n=40**		
	Median age, years (range): 65 (46-82)		
	Median prior lines of therapy (range): 7 (2-11)		
	Double refractory, n (%)	13 (33)	
Efficacy outcomes	**Endpoints**	**Total (n=40)**	**Dose escalation cohort (n=29)**	**Dose expansion cohort 3mg/kg (n=11)**
	ORR, n (%)	9 (23)	6 (21)	3 (27)
	mDOR, months	--	14.7	--
Safety profile	**AEs in dose escalation cohort (n=29)**		**Grades 1/2, n (%)**	**Grades ≥3, n (%)**
	Thrombocytopenia		--	7 (24)
	Ocular†		**6 (21)**	**0**
	Anemia		--	6 (21)
	AEs in 3mg/kg dose expansion cohort (n=11)		**Grades 1/2, n (%)**	**Grades ≥3, n (%)**
	Thrombocytopenia		--	6 (55)
	Ocular‡		**4 (36)**	**0**
	Neutropenia		--	3 (27)
	Anemia		--	2 (18)

*Amgen deprioritized AMG 224 anti-BCMA ADC in 2017.[2] †Included dry eye, increased lacrimation, conjunctival hemorrhage, diplopia, eye irritation, eye pruritus, blurred vision, reduced visual acuity, visual impairment, and vitreous hemorrhage. ‡Included dry eye, increased lacrimation, and ocular hyperemia.[1]

1. Lee HC et al. *Leukemia*. 2020;35:255-258. **2.** ADC Review. AMG. Accessed August 5, 2021. https://www.adcreview.com/drugmap/amg-224-adc-bite/

Please refer to slide notes for abbreviations.

IMW21 18TH INTERNATIONAL MYELOMA WORKSHOP

Discussing the impact of ADCs on patient experience in triple-class–refractory MM

Is QOL impacted by ADC-associated adverse events in patients with triple-class–refractory multiple myeloma?

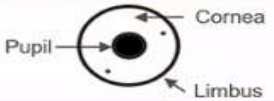
How can we successfully manage adverse events associated with ADCs (eg, corneal events)?

Can treatment efficacy be maintained with long-term management of ADC-associated adverse events?

ADC, antibody drug conjugate; MM, multiple myeloma; QOL, quality of life.
This information is intended for healthcare providers only. Compounds may be investigational. Inclusion in this presentation does not imply regulatory approval for these compounds or indications.

IMW21 18TH INTERNATIONAL MYELOMA WORKSHOP

Corneal exam findings (keratopathy*), together with BCVA changes, guide dose modifications of belantamab mafodotin

Corneal examination finding(s)†			Presentation of MECs†2	Corneal AE management
Severity†	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‖

Please refer to slide notes for footnotes, abbreviations, and reference.

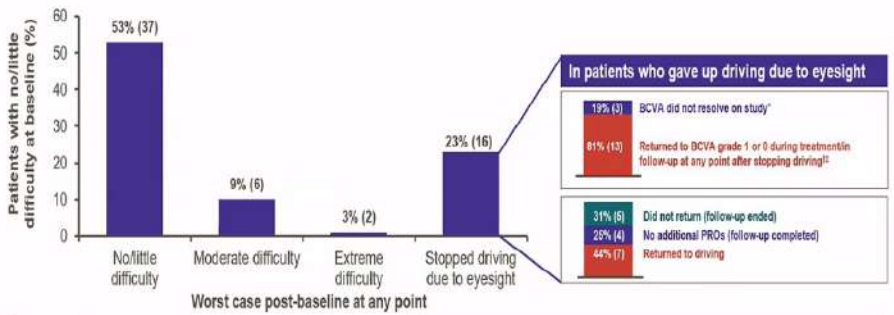
Highlights from IMW 2021

1-2 Febbraio 2022
Bologna
Royal Hotel Carlton

IMW21 18TH INTERNATIONAL MYELOMA WORKSHOP

Most patients in DREAMM-2 continued driving with little or no difficulty while on treatment with belantamab mafodotin

Worst case post-baseline shift in driving among patients with no/little difficulty at baseline (N=70)



Post-baseline assessments were missing for 6 patients (9%)

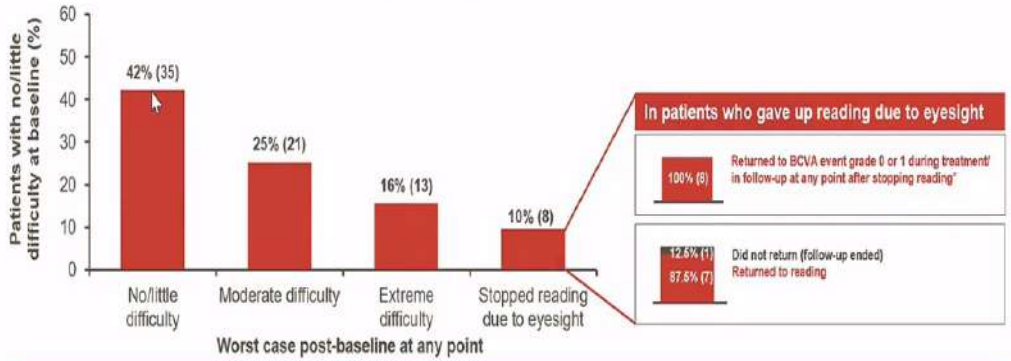
In the 23% (16) patients who stopped driving due to eyesight, time to onset of first occurrence was a median of 63.5 days

Of these patients who stopped driving, 81% (13) returned to a BCVA of grade 0 or 1 later during treatment/follow-up,†‡ with 44% (7) returning to driving on-study. Of the 56% (9) patients who did not return to driving, 44% (4) did not have a follow-up PRO assessment

Please refer to slide notes for abbreviations and references.
This information is intended for healthcare providers only. Compounds may be investigational. Inclusion in this presentation does not imply regulatory approval for these compounds or indications.

Additionally, many patients in DREAMM-2 continued reading with little or no difficulty while on treatment

Worst case post-baseline shift in reading among patients with no/little difficulty at baseline



Post-baseline assessments were missing for 8 patients (10%)

Time to first occurrence for patients who stopped reading due to eyesight was a median of 85 days. Of the 8 patients who stopped reading, 100% (8) returned to a BCVA of grade 0 or 1 later during treatment/follow-up,* with 87.5% (7) able to start reading again while in the study

Please refer to slide notes for abbreviations and references.
This information is intended for healthcare providers only. Compounds may be investigational. Inclusion in this presentation does not imply regulatory approval for these compounds or indications.

IMW21 18TH INTERNATIONAL MYELOMA WORKSHOP

Example questions to ask patients to facilitate reporting of new corneal AEs

During conversations with patients regarding the effects of their treatment, it may be helpful to ask the following questions regarding new corneal AEs they may be experiencing:

- **Are you finding it difficult to read during the day or at night due to your eyesight?**
- **Have you noticed any problems with your eyesight while driving?**
- **Do you have any problems with your eyes or vision when using a computer/tablet/phone or watching television?**
  - Have you needed to increase the font size on your devices so that you can see the text better?
- **Have you noticed any vision changes or other symptoms when you engage in any other activities that are important to you?**
- **Have you experienced any pain or discomfort in or around your eyes?**
- **Are your eyes more sensitive than usual to light?**
  - Have you needed to turn off the lights or wear sunglasses indoors because you were more sensitive to light?
- **Have you noticed any other symptoms related to your eyes or eyesight?**
  - Foreign body sensation?
  - Watering eyes?
  - Others (patient to indicate)

AE, adverse event.

Lonial S et al. *Blood Cancer J.* 2021;11:103.

Highlights from IMW 2021

1-2 Febbraio 2022
Bologna
Royal Hotel Carlton

IMW21 18TH INTERNATIONAL MYELOMA WORKSHOP

Summary

Belantamab mafodotin displays a multimodal MOA including immunogenic cell death[1]

- Belantamab mafodotin is an anti-BCMA mAb with **immune-dependent (ICD and ADCC/ADCP) and independent (MMAF) antitumor activity**
- Induction of ICD by belantamab mafodotin results in an **immune-dependent mechanism** that activates innate and adaptive immune cells

MEDI2228 and AMG 224 induce tumor cell apoptosis via different MOAs

- **MEDI2228's payload, PBD, cross-link DNA**, leading to apoptotic cell death through accumulation of DNA damage[2]
- **AMG 224** induces apoptosis through its payload by **inhibiting microtubule assembly**[3]

BCMA-targeted ADCs are amenable to combination therapies

- **BCMA-targeted ADCs can be combined with SOC**, to include the other 3 pillars of treatment for MM, **and novel agents**[4,5]
  - Belantamab mafodotin combos can **enhance ADCC/ADCP activity or increase antitumor response**[6]
  - MEDI2228 combos can **induce MM cytotoxicity and increase MM cell DNA damage**[7]

ADC, antibody-drug conjugate; ADCC, antibody-dependent cellular cytotoxicity; ADCP, antibody-dependent cellular phagocytosis; BCMA, B-cell maturation antigen; ICD, immunogenic cell death; mAb, monoclonal antibody; MM, multiple myeloma; MMAF, monomethyl auristatin F; MOA, mechanism of action; PBD, pyrrolobenzodiazepine; SOC, standard of care.

1. Montes De Oca R, Gupta I, Shelton C. Presented at: American Association for Cancer Research Annual Meeting; June 22-24, 2020. Poster 6711. **2.** Kinneer K et al. *Leukemia*. 2019;33(3):766-771. **3.** Demel I et al. *Br J Haematol*. 2021;193(4):705-722. **4.** Montes De Oca R, Gupta I, Shelton C. Poster presented at: American Association for Cancer Research Annual Meeting; June 22-24, 2020. Poster 6711. **5.** Nooka AK et al. *Future Oncol*. 2021;17(16):1987-2003. **6.** Trudel S et al. Poster presented at: ASH Annual Meeting and Exposition; December 5-8, 2020. **7.** Xing L et al. *Leukemia*. 2020;34(8):2150-2162.