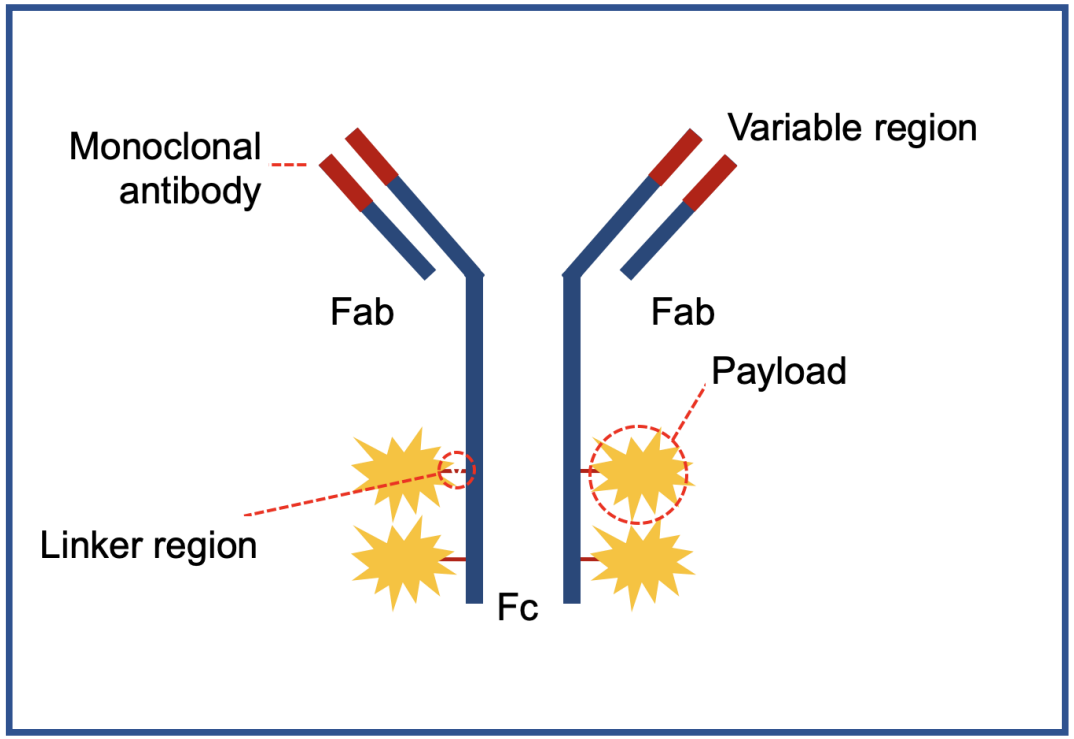
# Antibody Drug Conjugates

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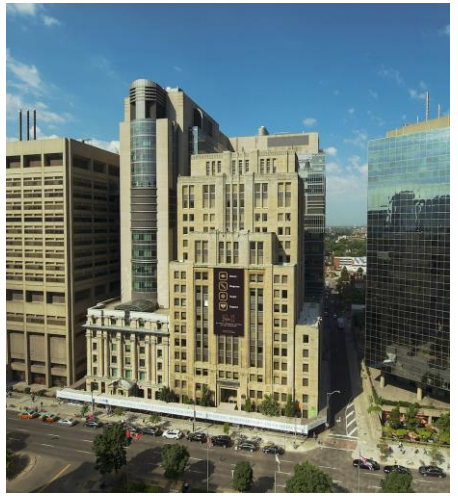

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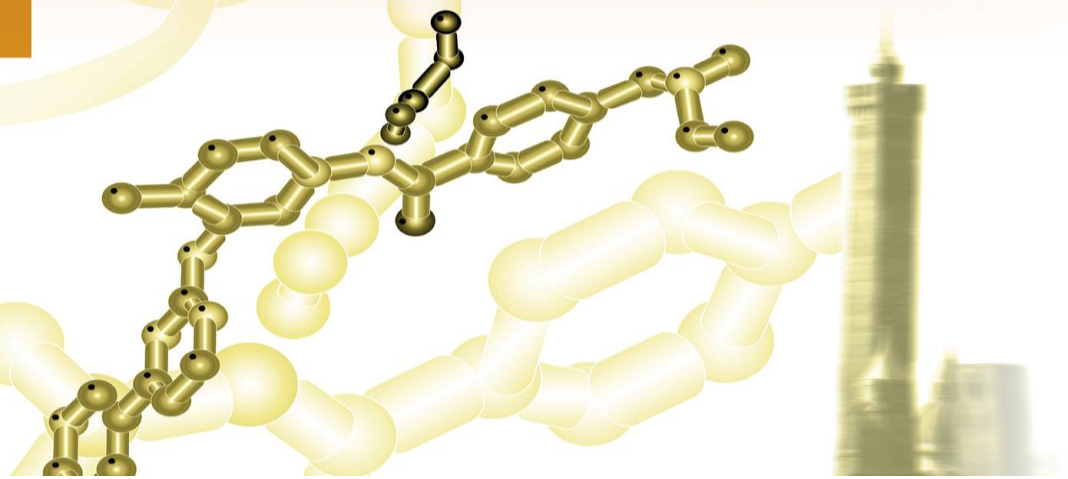


# New Drugs in Hematology

President: Pier Luigi Zinzani
Co-President: Michele Cavo

**Bologna,**
**Royal Hotel Carlton**
**January 15-17, 2024**

| Company name | Research support | Employee | Consultant | Stockholder | Speakers bureau | Advisory board | Other |
|---|---|---|---|---|---|---|---|
| GSK | Yes | No | Yes | No | No | Yes | No |
| Janssen | Yes | No | No | No | No | Yes | No |
| BMS/Celgene | Yes | No | Yes | No | No | Yes | No |
| Amgen | Yes | No | No | No | No | Yes | No |
| Pfizer | Yes | No | No | No | No | Yes | No |
| Genentech | Yes | No | No | No | No | No | No |
| Roche | Yes | No | Yes | No | No | Yes | No |
| Sanofi | No | No | No | No | No | Yes | No |
| K36 Therapeutics | Yes | No | Yes | No | No | No | No |

# Summary of antibody-drug conjugates developed for myeloma

| Agent | Target | Payload | Phase 1 Activity | Current Status |
|---|---|---|---|---|
| Indatuximab Ravtansine[1] | CD138 | DM4 | ORR 11%, SD 41% | Phase I/II completed |
| Lorvotuzumab mertansine[2] | CD56 | DM1 | ORR 5.7%, SD 43% (all doses) | Discontinued in myeloma |
| Milatuzumab–DOX [3] | CD74 | Doxorubicin | ORR 0%<br>stable disease 26% | Phase I completed |
| DFRF4539A [4] | FcRH5 | MMAE | 5% ORR, 49% SD | Development discontinued |
| Belantamab Mafodotin[5] | BCMA | MMAF | 60% ORR (54% ≥ VGPR) | Phase II completed. Granted FDA priority review |
| MEDI2228[6] | BMCA | PBD | ORR 65.9% at MTD | Phase 1, discontinued |
| AMG 224[7] | BMCA | DM1 | ORR 27% at selected dose (n=11) | Development discontinued |
| CC-99712 | BCMA | DM-1 like | NR | Phase 1, recruiting |
| HDP-101 | BMCA | amanitin | 4 pts dosed | Phase 1/2a, recruiting |
| STRO-001 | CD74 | MMAF | NR | Phase I, recruiting |
| SGN-CD48A | CD48 | MMAE | NR | Phase I, terminated |
| ABBV-838 | SLAMF7 | MMAE | NR | Phase I, terminated |
| STI-6129 | CD38 | Duostatin 5.2 | NR | Phase 1b/2a |

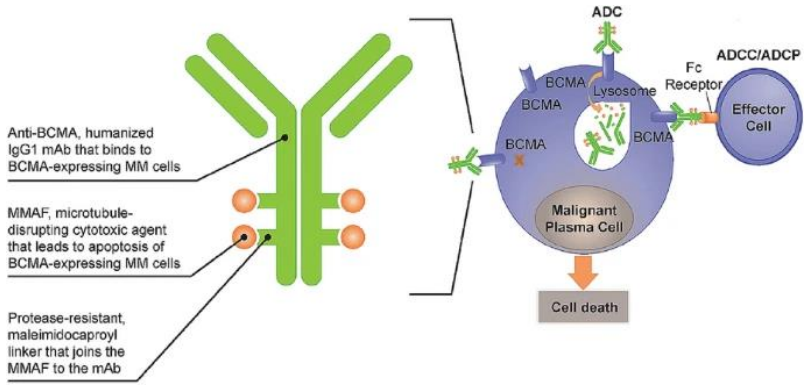
ADCs targeting BCMA validate the clinical activity of ADCs in myeloma

`monomethyl auristatin E (MMAE) and F ( MMAF);PBD, pyrrolobenzodiaezpine; maytansinoids DM1 and ravtansine (DM4); ORR, overall response rate; SD, stable disease, VGPR, very good partial response

; [1]Jagannath S et al, Clin Lymphoma Myeloma Leuk 2019;19:372; [2]Aliawadhi et al. Clin Lymphoma Myeloma Leuk 2019;[3]Kaufman et al, BrJHematol.2013;163:478; [4]Stewart AK et al, Blood Cancer J 2 019;9:17; [5]Trudel et. al. BCJ 20199:37; 6.* Kumar. ASH 2020. Abstr 179; 7. Lee HC et al, Leukemia. 2020; online ahead of print.

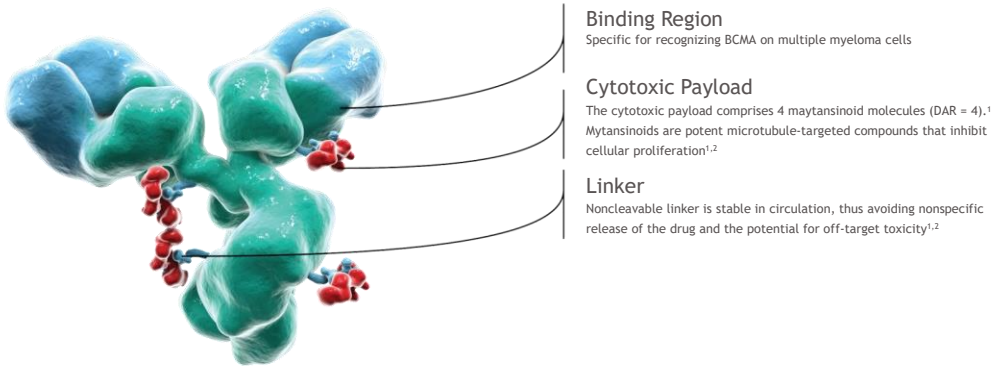
# BMCA-targeting ADCs currently undergoing evaluation in the clinic

## Belantamab Mafodotin



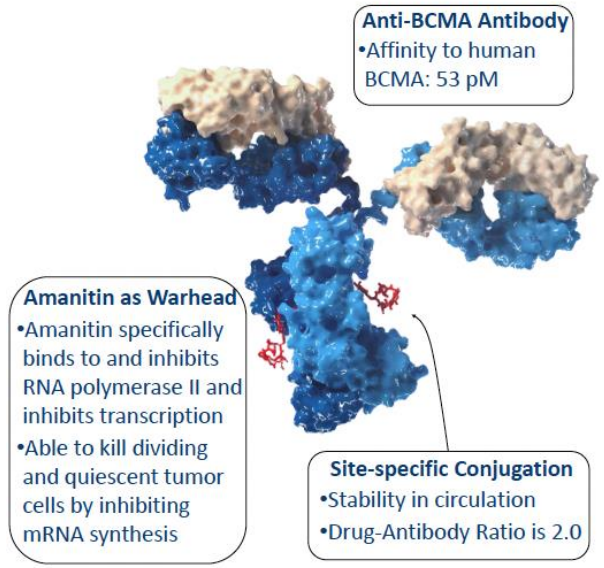

- Multimodal mechanisms[1]:
  - ✓ Direct cell kill via inhibition of microtubule polymerization
  - ✓ Afucosylation-enhanced ADCC/ADCP
  - ✓ Induces immunogenic cell death (ICD)
- Toxicities of MMAF-ADCs include:
  - ✓ Keratopathy
  - ✓ Thrombocytopenia
- In combination studies Phase II and III, first line and early relapse, Phase I novel combination in late RRMM

## CC-99712




- Toxicities of maytansinoid-ADCs include:
  - ✓ Peripheral neuropathy
  - ✓ Transaminitis
- First in human study +/- nirogacestat (GSI inhibitor), late RRMM-development discontinued 2023

## HDP-101




- del17p can cause haploinsufficiency of RNA polymerase II subunit A (POLR2A) resulting in reduced expression and enhance sensitivity to α-Amanitin[2]
- Potential for hepatoxicity
- Recruiting in first in human study, late RRMM[3]
  - 4 cohorts (11 pts) DLT evaluable-no DLTS observed
  - No signs of liver, renal, ocular toxicities or IRR
  - 1 pt in cohort 3 with SD x 14 cycles

Pts=patients

1) Tai. YT et al, Blood. 2014;123:3128; 2) Liu Y et al. Nature. 2015;520:697; 3) MS Raab, ASH 2023;3334a

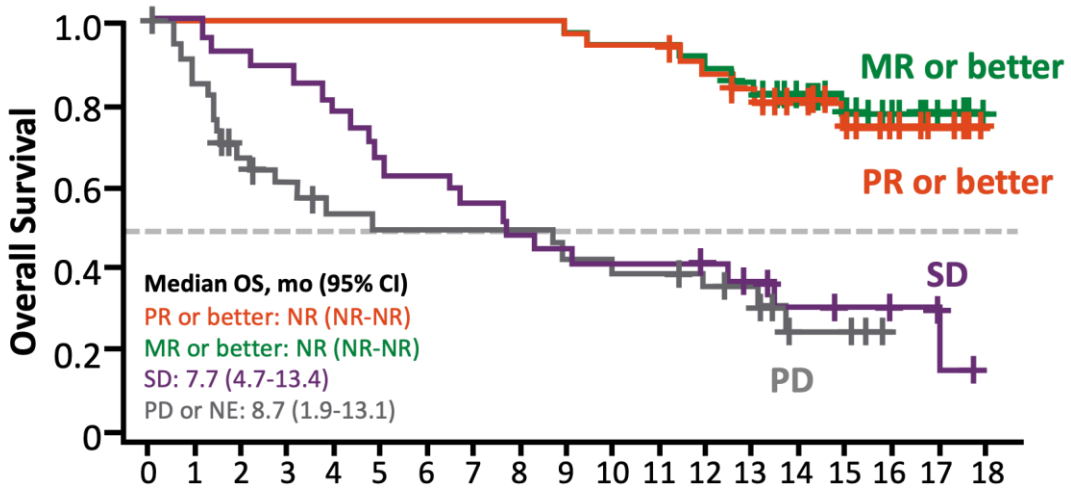
# DREAMM-2 Final Analysis: key efficacy and safety data (clinically meaningful benefit in responders)

| | Belantamab mafodotin | DREAMM-2 (2.5mg/kg cohort) phase II |
|---|---|---|
| Final analysis | | |
| **Patient Characteristics[1,2]** | **ITT population** | **N=97** |
| | **Median age,** years (IQR) | 65 (60-70) |
| | **ECOG PS 2,** n (%) | 16 (17) |
| | **High-risk cytogenetics,** n (%) | 41 (42) |
| | **Median prior lines of therapy**, n | 7 |
| | Triple refractory, n (%) | 97 (100) |
| **Efficacy outcomes*[1]** | | |
| | **ORR,** n (%) | 31 (32) |
| | ≥VGPR, n (%) | 18 (19) |
| | **Median time to response,** months | 1.5 |
| | **mDOR,** months | 12.5 |
| | **mPFS,** months | 2.8 |
| | **mPFS of patients achieving ≥VGPR,** months | 14.0 |
| | **mOS,** months | 15.3 |

| **Safety data[1]** | **AE (N=95)** | **Any grade, n (%)** | **Grade ≥3, n (%)** |
|---|---|---|---|
| | **Keratopathy†** | 67 (71) | 29 (31) |
| | **BCVA reduced to 20/50 or worse** | 46 (48) | N/A |
| | **Thrombocytopenia†** | 36 (38) | 21 (22) |
| | **Anemia†** | 26 (27) | 20 (21) |

- Median follow-up 12.5 months
- ORR 32%
- For patients that responded, responses were durable (mDOR=12.5 months)
- OS not reached for patients achieving minimal response (MR) or better

**Overall Survival by Response**




Most common toxicities keratopathy and thrombocytopenia

-ORR comparable high and standard risk patients

-No increased toxicity in patients with moderate renal dysfunction

-Patients with extramedullary disease did no derive the same benefit

AE: adverse event; BVCA: best-corrected visual acuity; mDOR: median duration of response; mOS: median overall survival; mPFS: median progression free survival; MR: minimal response; NE: not evaluable; ORR: overall response rate; PD: progressive disease; PR: partial response; SD: stable disease; VGPR: very good partial response

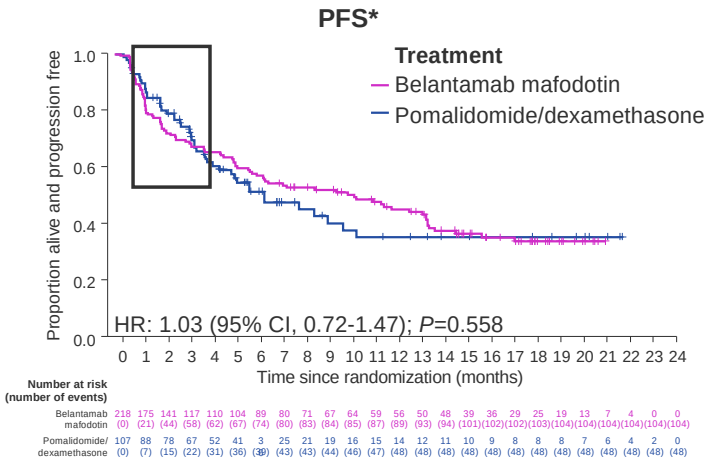

1) Nooka A et a l, ASH 2022; 3246z

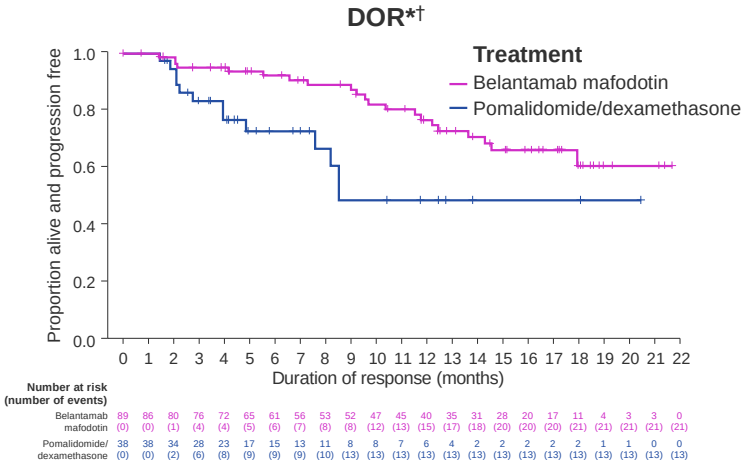
2) Lonial S et al. Cancer. 2021;127(22):4198-4212

# The DREAMM-3 trial of belantamab mafodotin monotherapy versus the doublet pom/dex did not meet its primary endpoint of superior PFS

| DREAMM-3 phase III | Belantamab mafodotin 21-day cycles | Pd 28-day cycles |
|---|---|---|
| **Patient characteristics** | | |
| **ITT population** | **n=218*** | **n=107†** |
| **Median age,** years (range) | 68 (43-86) | 68 (38-90) |
| **Extramedullary disease,** n (%) | 39 (18) | 19 (18) |
| **Median prior lines of therapy,** n (range) | 4 (2-12) | 3 (2-13) |
| Triple refractory, n (%) | 46 (21) | 22 (21) |
| **Efficacy outcomes** | | |
| **ORR,** % | 41 | 36 |
| ≥CR, % | 10 | 3 |
| ≥VGPR, % | 25 | 8 |
| **mDOR,** months | NR | 8.5 |
| **mPFS,** months | 11.2 | 7.0 |
| HR (95% CI) | 1.03 (0.72-1.47) | |
| **mOS,** months‡ | 21.2 | 21.1 |
| HR (95% CI) | 1.14 (0.77-1.68) | |

**No new safety signals** were noted in DREAMM-3, and the AEs observed were consistent with those expected for the individual agents

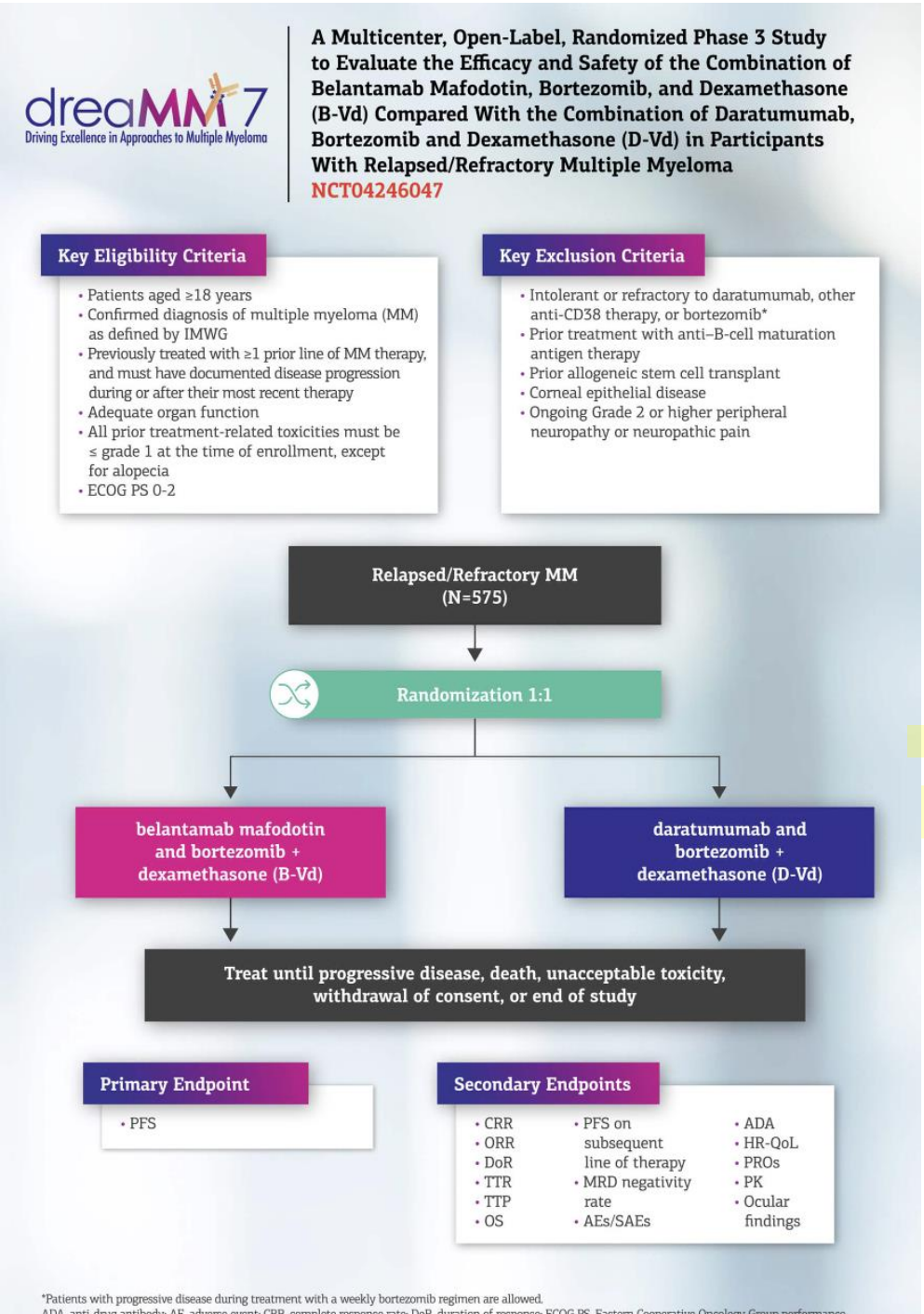



*Median follow-up time of 11.5 months (range, 0.6-24.2). †Median follow-up time of 10.8 months (range, 0.0-26.4). ‡At 37.5% maturity.

AE, adverse event; CR, complete response; ITT, intent-to-treat; mDOR, median duration of response; mOS, median overall survival; mPFS, median progression-free survival; MR, minimal response; NE, not evaluable; NR, not reached; ORR, overall response rate; PD, progressive disease; Pd, pomalidomide/dexamethasone; PR, partial response; RRMM, relapsed/refractory multiple myeloma; sCR, stringent complete response; SD, stable disease; VGPR, very good partial response.

Weisel K. Presented at: American Society of Clinical Oncology Annual Meeting; June 2-6, 2023; Chicago, IL. Presentation 8007.




# GSK announces positive results from DREAMM-7 head-to-head phase III trial for *Blenrep* in relapsed/refractory multiple myeloma

- *Blenrep* (belantamab mafodotin) plus BorDex showed statistically significant progression-free survival (PFS) benefit versus daratumumab plus BorDex
- Trial unblinded early based on Independent Data Monitoring Committee (IDMC) recommendation

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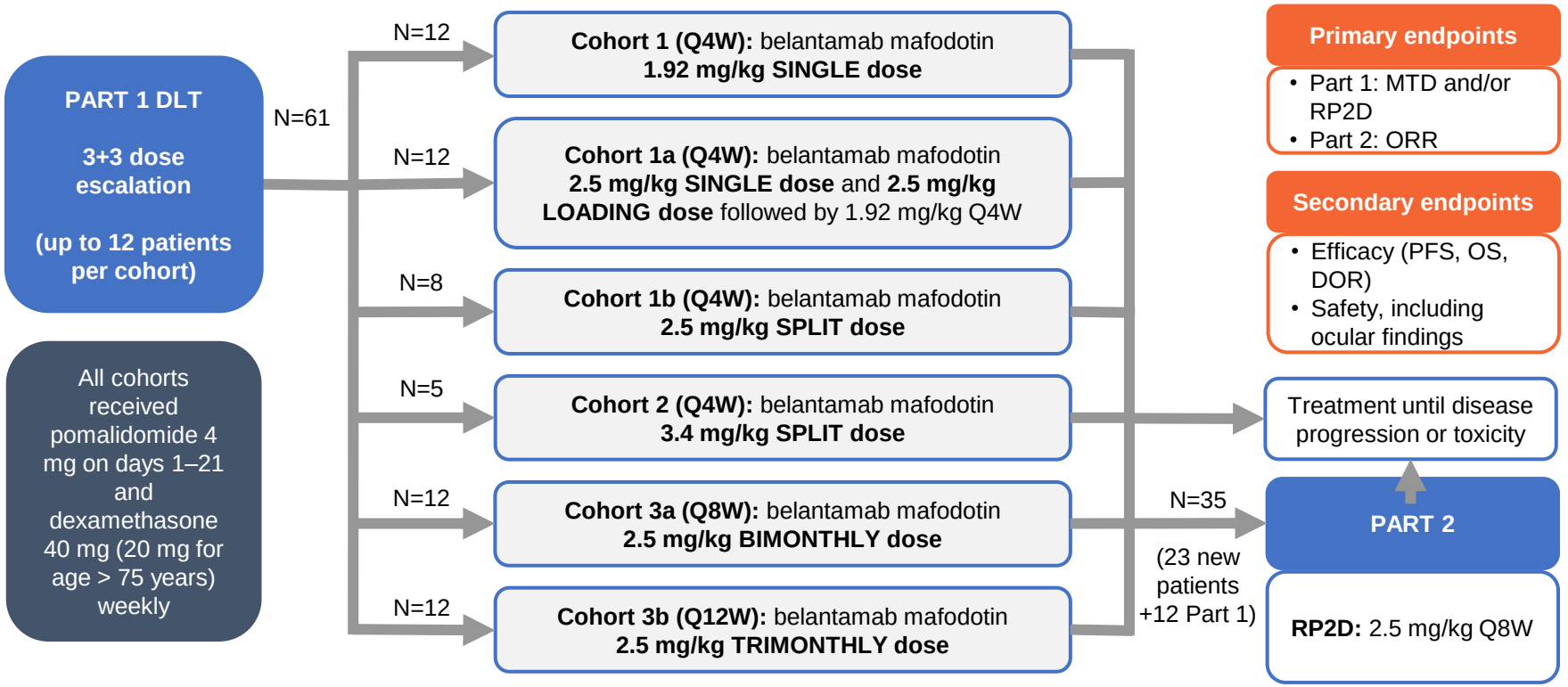
GSK plc (LSE/NYSE: GSK) today announced positive headline results from a planned interim efficacy analysis of the DREAMM-7 head-to-head phase III trial evaluating belantamab mafodotin as a second-line treatment for relapsed or refractory multiple myeloma. The trial met its primary endpoint of progression-free survival (PFS) and showed that belantamab mafodotin when combined with bortezomib plus dexamethasone (BorDex) significantly extended the time to disease progression or death versus daratumumab plus BorDex, an existing standard of care for relapsed/refractory multiple myeloma. A strong and clinically meaningful overall survival (OS) trend with nominal p value < 0.0005 was also observed at the time of this analysis, and the trial continues to follow up for OS.

# The Algonquin study: two-part phase 1/2 trial evaluating the safety and efficacy of different doses and schedules of belantamab mafodotin + Pd in patients with RRMM




This figure was independently created by GSK from original data first presented in Trudel S et al. ASH. 2022.

## Key eligibility criteria

- ≥1 prior line of treatment
- Refractory to len and exposed or refractory to a proteasome inhibitor
- Refractory to last LoT

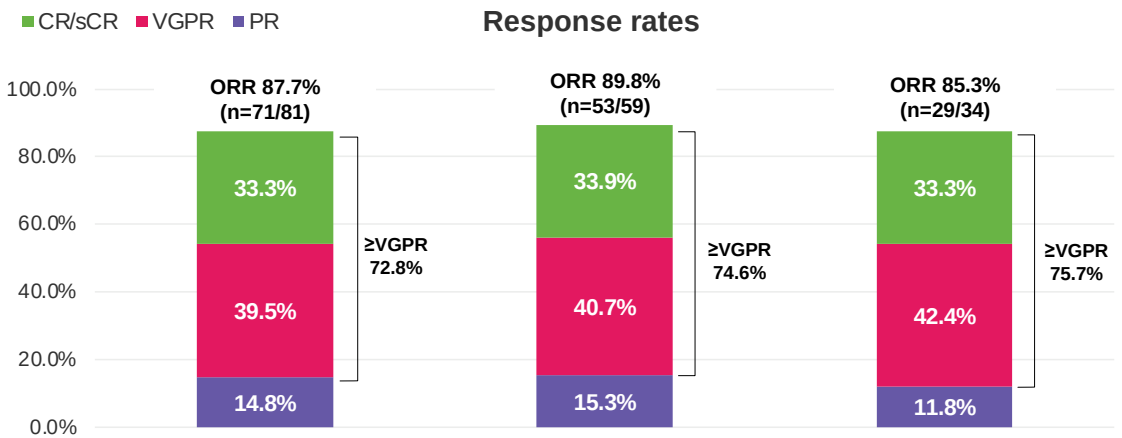
**Part 1 of the Algonquin study established a MTD of 2.5 mg/kg and a RP2D of 2.5mg/kg Q8W**

DLT, dose limiting toxicity; DOR, duration of response; MTD, maximum tolerated dose; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; pom/dex, pomalidomide/dexamethasone; QXW, every X weeks; RP2D, recommended phase 2 dose; RRMM, relapsed/refractory multiple myeloma.

Trudel S et al, Nat Med DOI 10.1038/s41591-023-02703-y

# Belantamab mafodotin plus Pom/Dex induced deep responses in patients with RRMM

| Baseline patient characteristics | All patients[a] N=87 | Part 1 patients n=61 | RP2D[b] patients n=38 |
|---|---|---|---|
| Median age, years (range) | 67 (36-85) | 64 (36-81) | 71 (38-85) |
| ECOG PS, n (%) | | | |
| 0 | 25 (28.7) | 20 (32.8) | 10 (26.3) |
| 1 | 55 (63.2) | 35 (57.4) | 26 (68.3) |
| 2 | 6 (6.9) | 6 (9.8) | 1 (2.7) |
| Missing | 1 (1.2) | 0 | 1 (2.7) |
| ISS stage III | 19 (21.8) | 10 (16.4) | 12 (31.6) |
| High-risk cytogenetics,[c] n (%) | 16 (18.4) | 14 (23) | 7 (18.5) |
| Median prior LOT, no. (range) | 3 (1-6) | 3 (1-5) | 3 (1-6) |
| **Prior therapies, n (%)** | | | |
| ASCT | 60 (69.0) | 49 (80.3) | 18 (47.4) |
| Lenalidomide | 87 (100.0) | 61 (100.0) | 38 (100.0) |
| PI | 87 (100.0) | 61 (100.0) | 38 (100.0) |
| Daratumumab | 58 (66.7) | 36 (59.0) | 30 (78.9) |
| **Refractory status, n (%)** | | | |
| Lenalidomide | 84 (96.6) | 58 (95.1) | 36 (94.7) |
| PI | 75 (86.2) | 53 (86.9) | 32 (84.2) |
| Daratumumab | 58 (66.7) | 36 (59.0) | 30 (78.9) |
| Triple-class refractory, n (%) | 48 (55.2) | 30 (49.2) | 24 (63.2) |




| Efficacy outcomes, n (%) | All patients[a] N=87 | Part 1 patients n=61 | RP2D[b] patients n=38 |
|---|---|---|---|
| Median follow-up, months[c] (range) | 14.5 (0.9-42.5) | 17.1 (0.9-42.5) | 13.9 (1.1-28.2) |

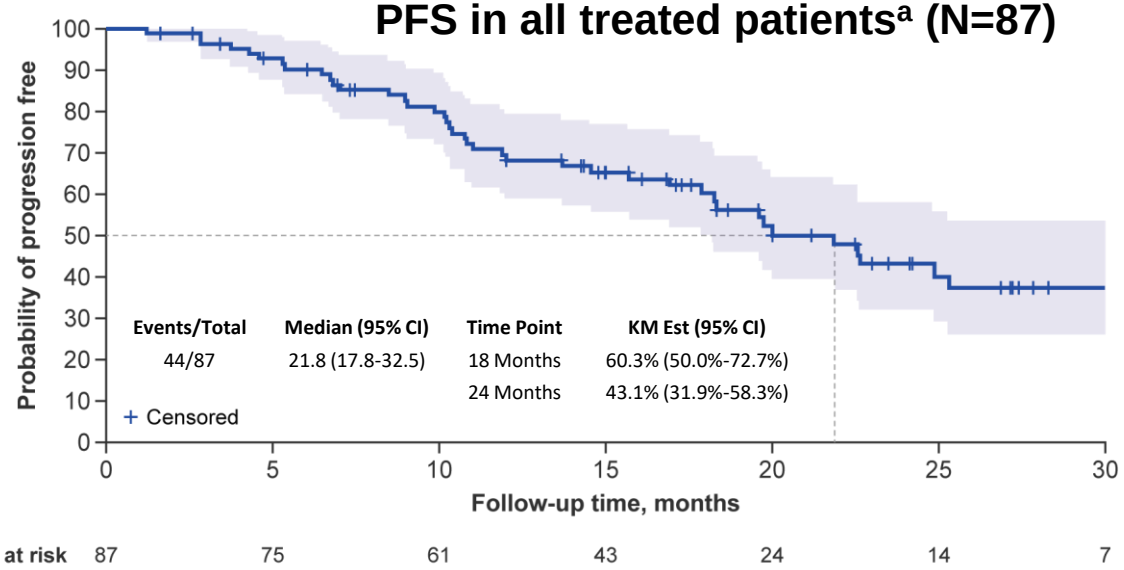
- 7 patients with confirmed ≥CR across all dosing cohorts had MRD assessment performed by multiparameter flow cytometry with sensitivity of $10^{-5}$
- 5 out of 7 achieved MRD negativity, including 3 of 4 patients treated at the RP2D

**Deep responses were demonstrated at the RP2D of 2.5 mg/kg Q8W, with ~1/3 of patients achieving ≥CR**

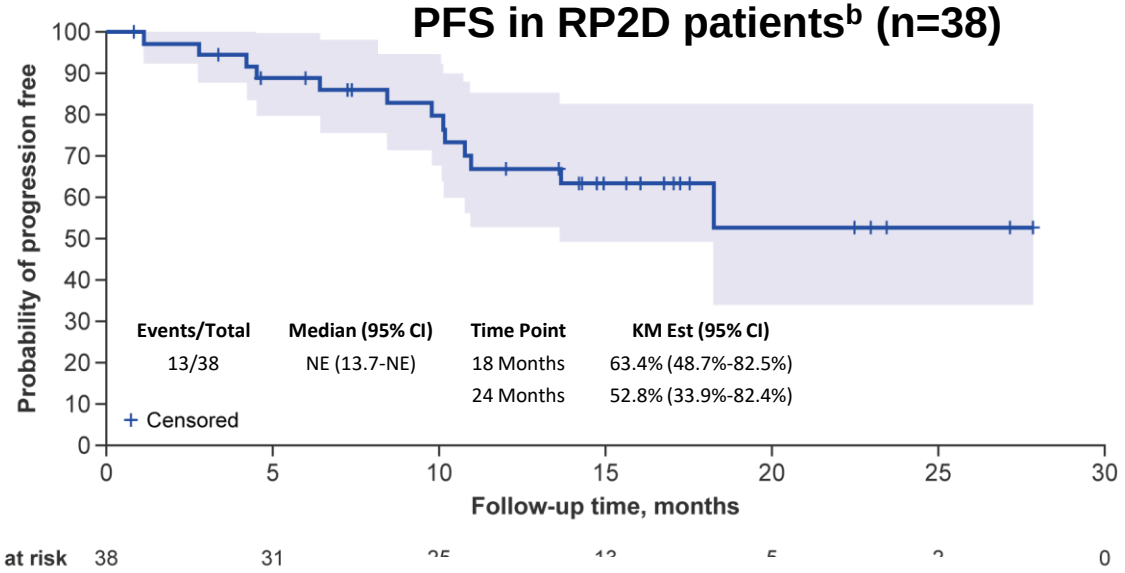
Trudel S et al, Nat Med DOI 10.1038/s41591-023-02703-y

# At the RP2D of 2.5 mg/kg Q8W, median PFS and OS has not yet been reached

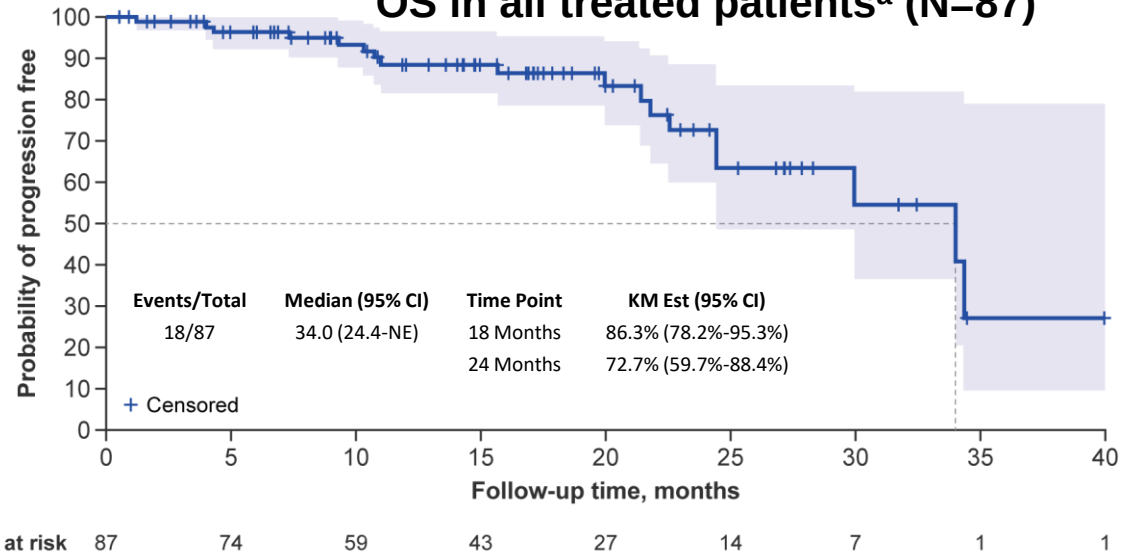
## PFS in all treated patients[a] (N=87)



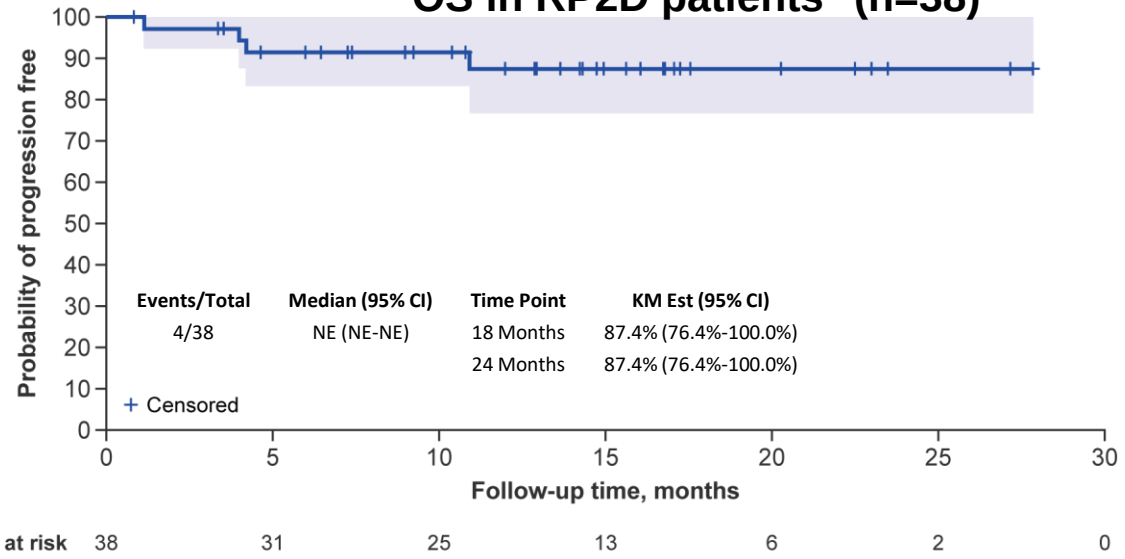

## PFS in RP2D patients[b] (n=38)




## OS in all treated patients[a] (N=87)




## OS in RP2D patients[b] (n=38)




**At the RP2D of 2.5 mg/kg Q8W, estimated 2-year PFS was 52.8% at a median follow-up of 13.9 months**

PFS, progression-free survival; OS, overall survival; RP2D, recommended part 2 dose (2.5 mg/kg Q8W)

Trudel S et al, Nat Med DOI 10.1038/s41591-023-02703-y

# The safety profile of belantamab mafodotin plus Pom/Dex in ALGONQUIN was consistent with the individual agents

| Any grade AE in ≥20% of patients, n (%) | All patients[a] N=87 | Part 1 patients n=61 | RP2D[b] patients n=38 |
|---|---|---|---|
| Decreased visual acuity | 68 (78.2) | 51 (83.6) | 27 (71.1) |
| Keratopathy | 62 (71.3) | 48 (78.7) | 25 (65.8) |
| Fatigue | 52 (59.8) | 38 (62.3) | 22 (57.9) |
| Infection | 44 (50.6) | 31 (50.8) | 18 (47.4) |
| Neutropenia | 43 (49.4) | 35 (57.4) | 15 (39.5) |
| Thrombocytopenia | 38 (43.7) | 32 (52.5) | 15 (39.5) |
| Diarrhea | 30 (34.5) | 24 (39.3) | 11 (28.9) |
| Fever | 26 (29.9) | 22 (36.1) | 6 (15.8) |
| Peripheral edema | 28 (32.2) | 21 (34.4) | 13 (34.2) |
| Constipation | 26 (29.9) | 21 (34.4) | 11 (28.9) |

| Grade 3-4 AE in ≥5% of patients, n (%) | All patients[a] N=87 | Part 1 patients n=61 | RP2D[b] patients n=38 |
|---|---|---|---|
| Keratopathy | 48 (55.2) | 35 (57.4) | 20 (52.6) |
| Decreased visual acuity | 38 (43.7) | 30 (49.2) | 15 (39.5) |
| Neutropenia | 36 (41.4) | 28 (45.9) | 14 (36.8) |
| Thrombocytopenia | 29 (33.3) | 24 (39.3) | 13 (34.2) |
| Infection | 18 (20.7) | 15 (24.6) | 3 (7.9) |
| Fatigue | 10 (11.5) | 9 (14.8) | 2 (5.3) |
| Diarrhea | 4 (4.6) | 3 (4.9) | 3 (7.9) |

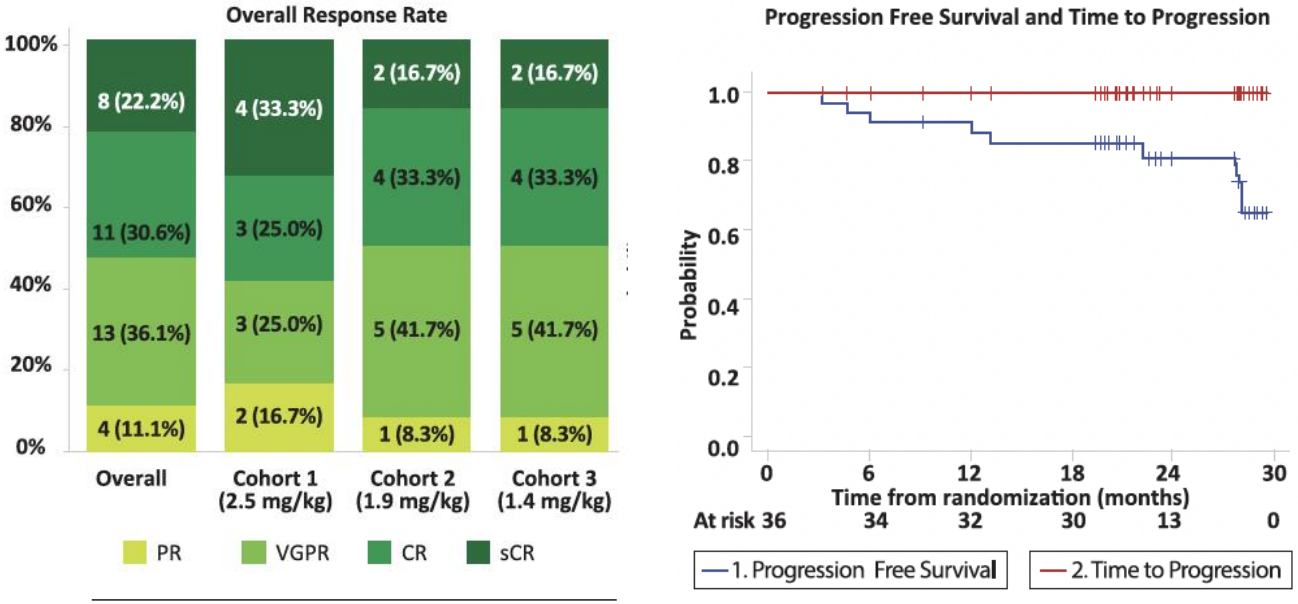
The safety profile of belantamab mafodotin plus Pom/Dex was consistent with the individual agents, grade ¾ decreased visual acuity reported in 39.5% while risk of grade 3-4 infection at the RP2D was low

[a]Includes patients from Part 1 (all cohorts) and Part 2. [b]2.5 mg/kg Q8W; includes 12 patients in Part 1 and 26 in Part 2.
AE, adverse event; ALT, alanine transaminase; BCVA, best corrected visual acuity; Pom/Dex, pomalidomide/dexamethasone; Q8W, every 8 weeks; RP2D, recommended phase 2 dose.

Trudel S et al, Nat Med DOI 10.1038/s41591-023-02703-y

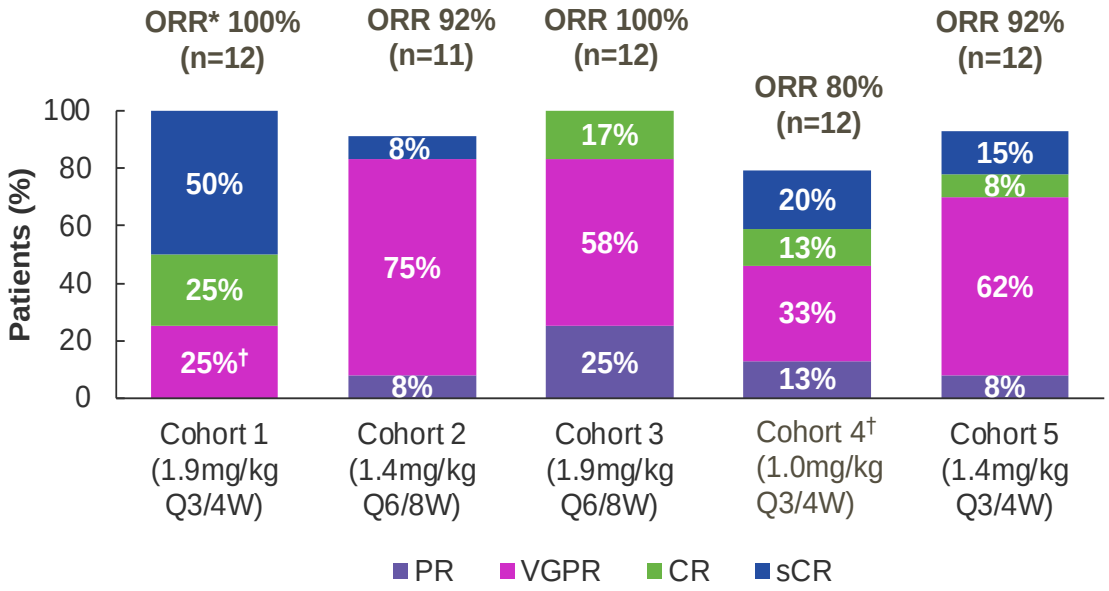
# Belantamab mafodotin combinations in NDMM demonstrate high overall response rates and depth of response

## Belantamab Mafodotin Administered in Combination with Lenalidomide and Dexamethasone in Transplant-Ineligible NDMM




Q8W dosing

## DREAMM-9: Phase 1 Study of Belantamab Mafodotin in Combination with VRD in Transplant Ineligible NDMM




*Based on best confirmed response by the investigator; †Cohort 4 safety population N=4.

B-Rd, belantamab mafodotin/lenalidomide/dexamethasone; B-VRd, belantamab mafodotin/bortezomib/lenalidomide/dexamethasone; CI, confidence interval; CR, complete response; MRD, minimal residual disease; NDMM, newly-diagnosed multiple myeloma; ORR, overall response rate; PR, partial response; Q3/4W, every 3 to 4 weeks; Q6/8W, every 6 to 8 weeks; sCR, stringent complete response; VGPR, very good partial response

1) Terpos E et al. ASH 2023 (Abstract 4765)

2) Usmani S et al. EHA 2022 (Abstract P942)

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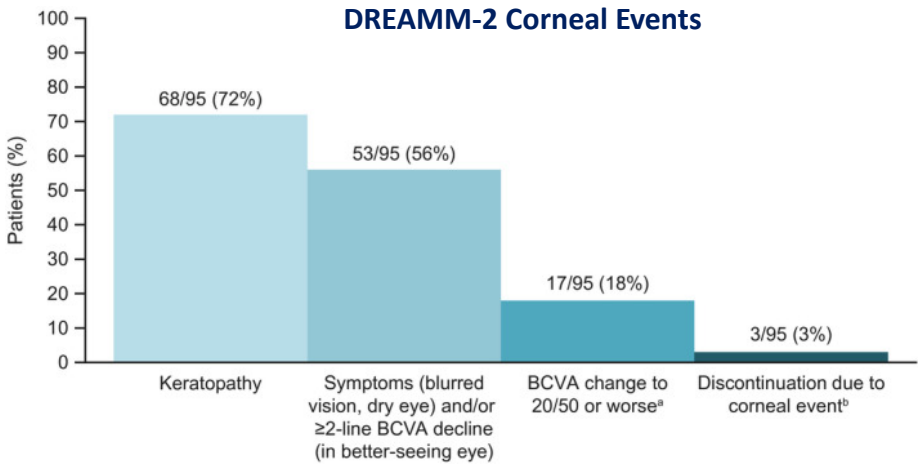
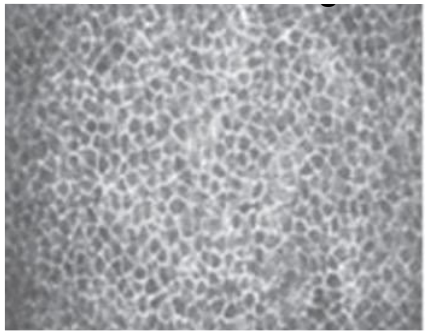
# Belantamab Mafodotin corneal event management

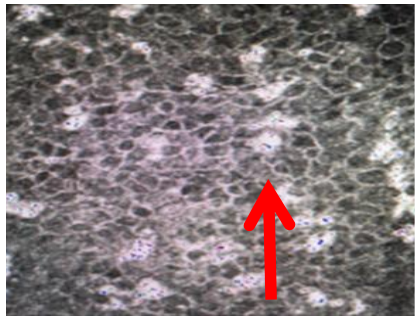
- The corneal events reported are common for MMAF-immunoconjugates
- Most commonly reported symptoms are blurred vision and dry eyes
- Increase drug exposure is associated with higher and earlier occurrence of keratopathy




**Keratopathy (MECs)-microcyst-like epithelia changes on slit lamp exam**



Normal corneal epithelial cells

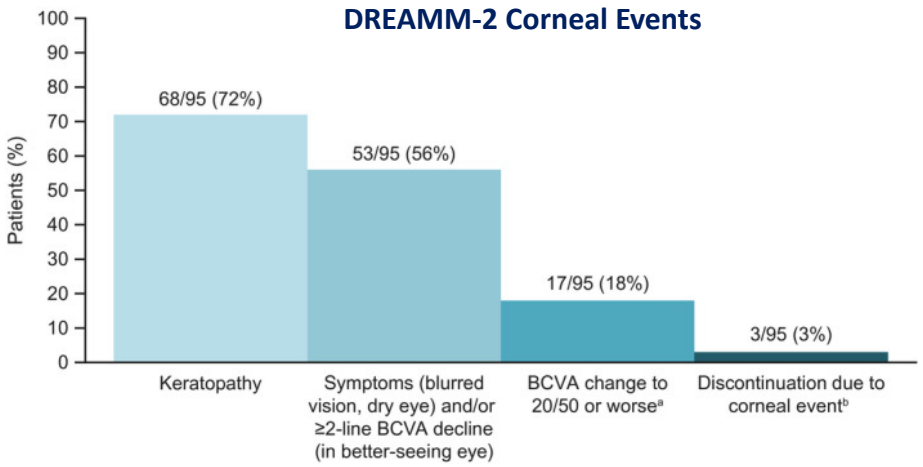


Deposits in epithelium

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

# Belantamab Mafodotin corneal event management

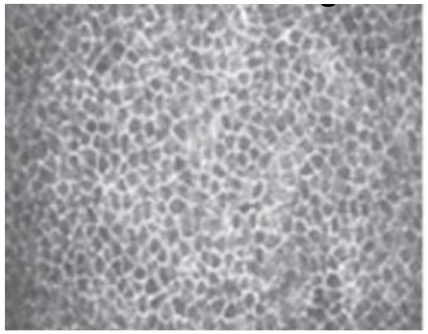
- The corneal events reported are common for MMAF-immunoconjugates
- Most commonly reported symptoms are blurred vision and dry eyes
- Increase drug exposure is associated with higher and earlier occurrence of keratopathy



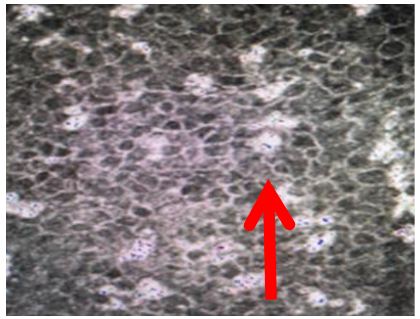

Mitigating ocular toxicity

- Eye exam at baseline and prior to each dose
- Preservative-free artificial tears for the duration of treatment
- Avoid use of contacts
- Dose reductions and delays if corneal AEs emerge

**Keratopathy (MECs)-microcyst-like epithelia changes on slit lamp exam**



Normal corneal epithelial cells



Deposits in epithelium

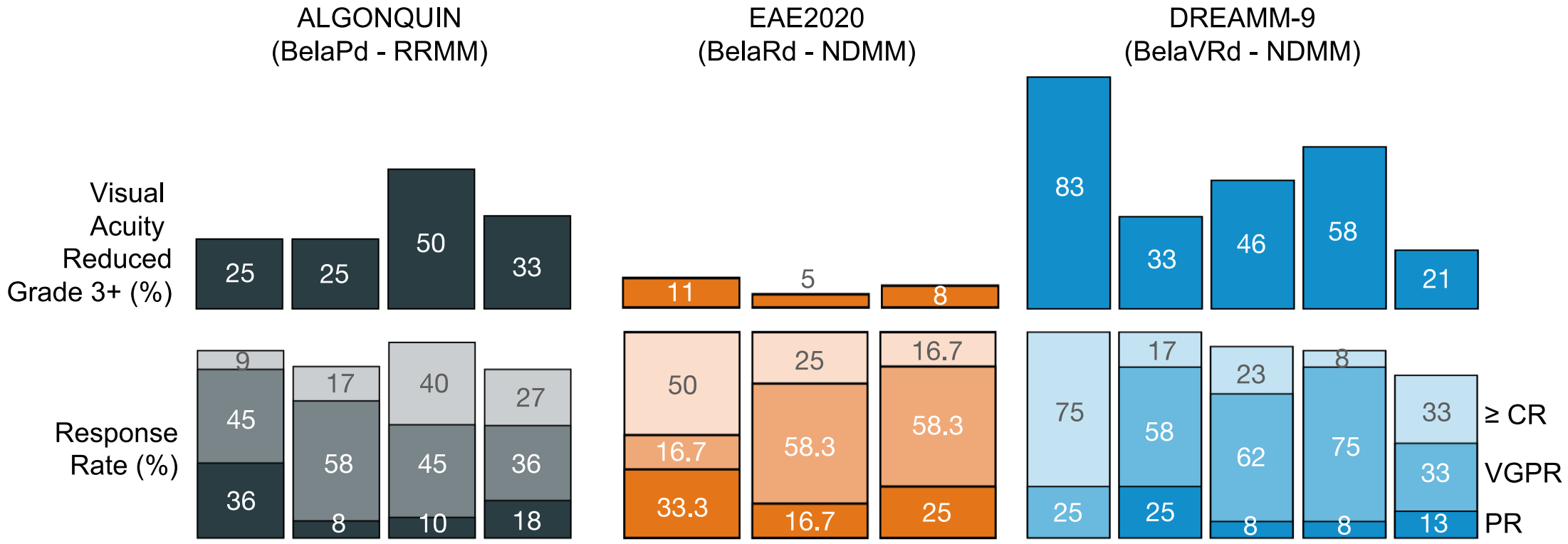
**Phase II DREAMM-2: Post Hoc Analysis—Outcomes With Prolonged Dose Delay**

| | 2.5 mg/kg (n = 16) |
|---|---|
| Maintained clinical benefit, n (%) | 14 (88) |
| ▪ Deepened response | 6 (38) |
| ▪ Maintained same response category | 6 (38) |
| ▪ Did not meet progression criteria* | 2 (13) |
| Developed PD, n (%) | 2 (13)† |

Prolonged delay defined as ≥ 3 treatment cycles (ie ≥ 9 weeks)

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

# Lower doses and longer dosing intervals results in lower incidence of ≥ grade 3 changes in vision




| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Total N | 12 | 12 | 20 | 12 | 12 | 12 | 12 | 12 | 12 | 13 | 12 | 15 |
| Dose (mg/kg) | 2.5 | 2.5 | 2.5 | 1.92 | 2.5 | 1.9 | 1.4 | 1.9 | 1.9 | 1.4 | 1.4 | 1 |
| Interval | Q12W | Q8W | Q4W | Q4W | Q8W | Q8W | Q8W | Q3/4W | Q6/8W | Q3/4W | Q6/8W | Q3/4W |
| **ORR (%)** | **91** | **83** | **95** | **82** | **100** | **100** | **100** | **100** | **100** | **92** | **92** | **80** |

BelaPd: belantamab mafodotin/pomalidomide/dexamethasone; BelaRd: belantamab mafodotin/revlimid/dexamethasone; BelaVRd: belantamab mafodotin/velcade/revlimid/dexamethasone; CR: complete response; ORR: overall response rate; PR: partial response; VGPR: very good partial response


1) Trudel S et al. ASH 2021 (Poster 1653)
2) Terpos E et al. EHA 2022 (Abstract S178)
3) Usmani S et al. EHA 2022 (Abstract P942)

# Understanding the impact of keratopathy on ADLs

## Extended dosing schedule for belantamab mafodotin has minimal impact on vision-related functioning

### Ocular Surface Disease Index (OSDI)

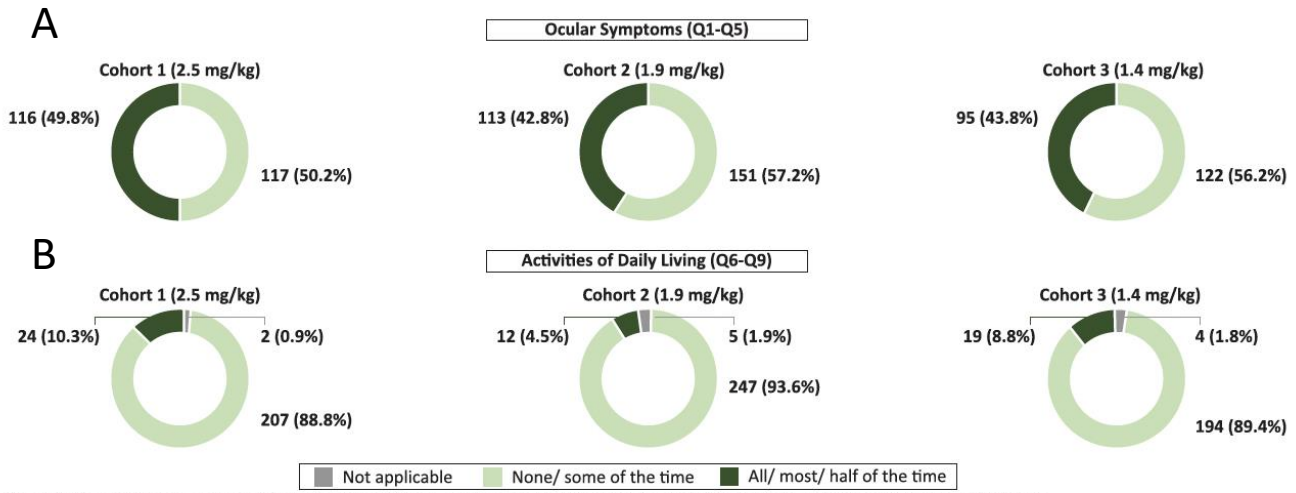
| Have you experienced any of the following *during the last week*? | All of the time | Most of the time | Half of the time | Some of the time | None of the time |
|---|---|---|---|---|---|
| 1. Eyes that are sensitive to light? | 4 | 3 | 2 | 1 | 0 |
| 2. Eyes that feel gritty? | 4 | 3 | 2 | 1 | 0 |
| 3. Painful or sore eyes? | 4 | 3 | 2 | 1 | 0 |
| 4. Blurred vision? | 4 | 3 | 2 | 1 | 0 |
| 5. Poor vision? | 4 | 3 | 2 | 1 | 0 |

Subtotal score for answers 1 to 5 (A)

| Have problems with your eyes limited you in performing any of the following *during the last week*? | All of the time | Most of the time | Half of the time | Some of the time | None of the time | N/A |
|---|---|---|---|---|---|---|
| 6. Reading? | 4 | 3 | 2 | 1 | 0 | N/A |
| 7. Driving at night? | 4 | 3 | 2 | 1 | 0 | N/A |
| 8. Working with a computer or bank machine (ATM)? | 4 | 3 | 2 | 1 | 0 | N/A |
| 9. Watching TV? | 4 | 3 | 2 | 1 | 0 | N/A |

Subtotal score for answers 6 to 9 (B)

### Belantamab Mafodotin Administered in Combination with Lenalidomide and Dexamethasone in Transplant-Ineligible NDMM




**Classification of the assessments in each category was based on the worst (most frequent) item among Q6-Q9 or Q1-Q5, as applicable**
**An assessment was classified as none of the time if all Q6-Q9 were none of the time or if some of the Q6-Q9 were none of the time and some were 'not applicable'.**
- **Ocular symptoms (Q1-5):** sensitivity to light, gritty eyes, sore or painful eyes, blurred vision, poor vision
- **ADL (Q6-9):** driving at night, reading, working with a computer or bank machine and watching TV

Q8W dosing

Nearly half of patients had symptoms all or most of the time BUT minority had problems with ADLs all or most of the time

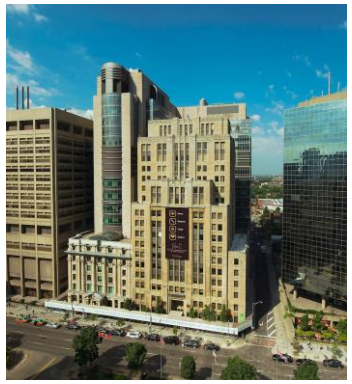
1) Terpos E et al. ASH 2023 (Abstract 4765)

# Summary

- **ADCs** have demonstrated limited anti-MM activity thus far with the exception of those targeting BMCA
- Combination studies are showing high ORR/≥VGPR and encouraging PFS with data superior to SOC and favourable when compared to bispecifics Abs and to the CART product, idecel
- Results of the Algonquin study to be confirmed with the DREAMM-8 Phase 3 trial (BelaPd vs PVd)
- Thus far **ADCs** have the advantage of fully outpatient administration and no risk of CRS and lower risk of infection compared to BMCA targeted bispecific Abs
- Studies exploring lower doses and extended schedules are demonstrating a reduction in the severity of corneal toxicity with minimal persistent effects on ADLs

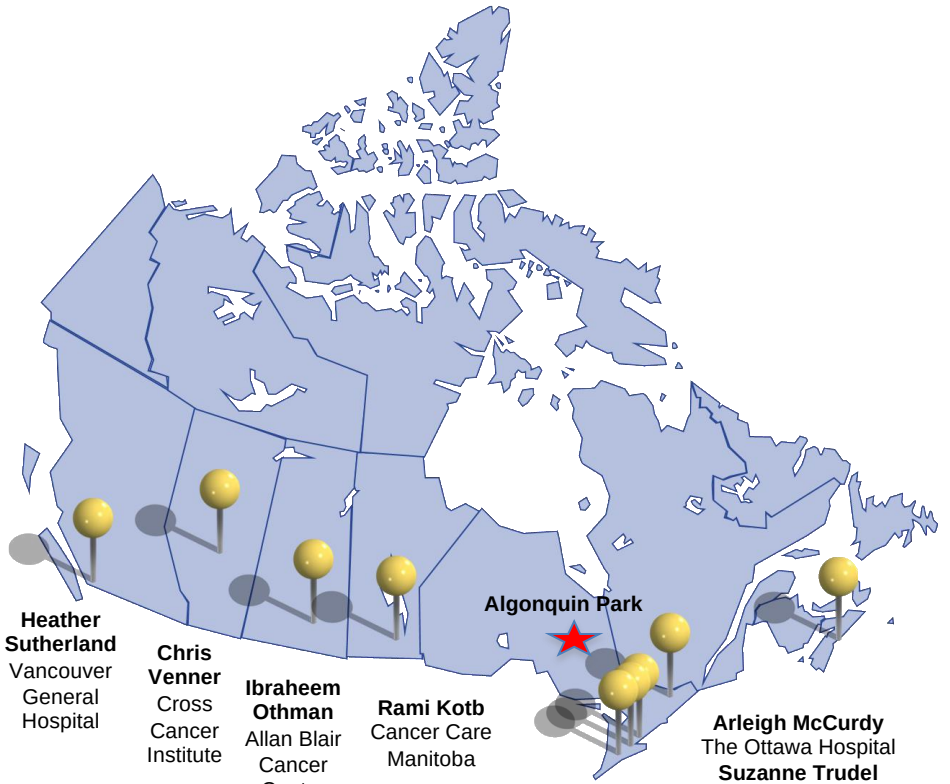
# Thank You

UHN Princess Margaret Cancer Centre



University of Toronto


## Algonquin Investigators




**Heather Sutherland**
Vancouver General Hospital

**Chris Venner**
Cross Cancer Institute

**Ibraheem Othman**
Allan Blair Cancer Centre

**Rami Kotb**
Cancer Care Manitoba

**Arleigh McCurdy**
The Ottawa Hospital

**Suzanne Trudel**
Princess Margaret Cancer Centre

**Hira Mian**
Juravinski Cancer Centre

**Martha Louzada**
London Health Sciences Centre

# No Evidence of BCMA Expression After Treatment With Belantamab Mafodotin (post hoc analysis of DREAMM-1 and DREAMM-2)

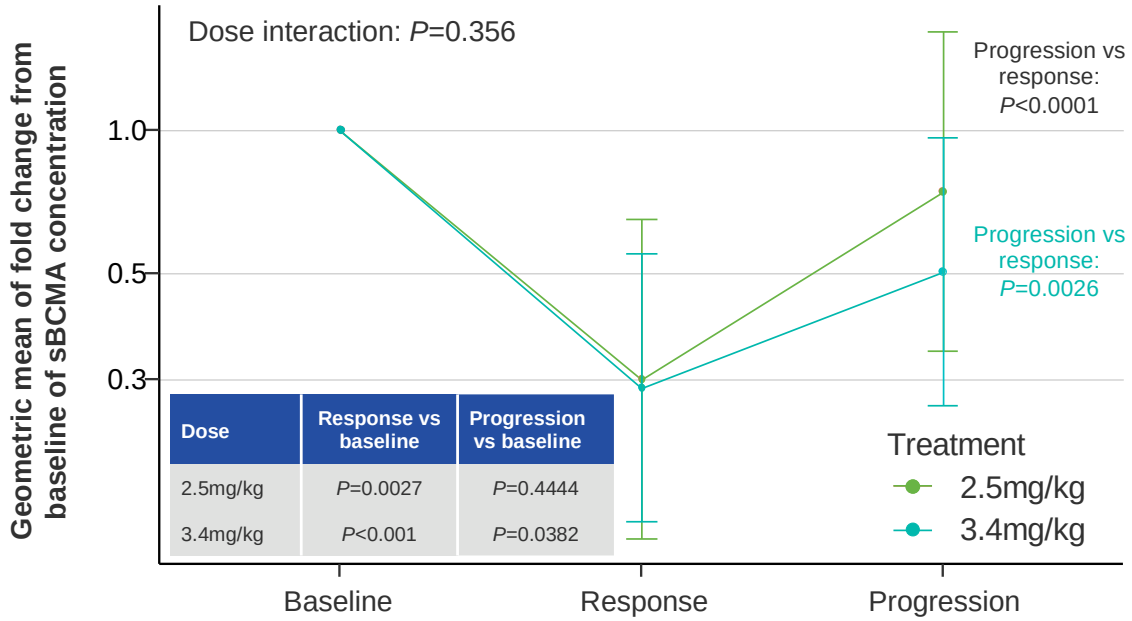
**Patients with detectable sBCMA levels by visit: all patients**

| Study | Visit | Percentage |
|---|---|---|
| DREAMM-1 | Baseline (n=75) | 100.0% |
| | At response (n=78) | 85.9% |
| | **At progression** (n=51) | **98.0%** |
| DREAMM-2 | Baseline (n=213) | 99.1% |
| | At response (n=217) | 97.2% |
| | **At progression** (n=183) | **98.9%** |

sBCMA levels were measurable (above LLOQ) upon progression in the vast majority of patients

Does not exclude functional loss

**Aggregate sBCMA at baseline, at response, and at PD**




sBCMA levels showed a pronounced drop during response but returned to near baseline upon progression

Lowther DE, et al. ASH 2022; 248a

# Emerging data supports the sequencing of T-cell redirecting therapies and ADCs

| | Tec[1] | Tec in non-TCE anti-BCMA exposed[2] | Elra[3] | Elra in non-TCE anti-BCMA exposed[4] | Cilta-cel[5] | CARTITUDE-2 Cohort C Cilta-cel after non-cellular anti-BCMA[6] |
|---|---|---|---|---|---|---|
| | **BMCA Targeting Agents** | | | | | |
| Median Follow-up, months | 23.0 | 12.5 | 14.7 | 11.3 | 33.4 | 18.0 |
| Total N | 165 | 40 | 123 | 87 | 97 | 20 |
| Median lines of therapy | 5 | 6 | 5 | 7 | 6 | 8 |
| Triple Class Refractory | 78% | 85% | 96.7% | 96.6 | 87.6 | 90% |
| Prior anti-BCMA ADC/CAR-T/both | NA | 72.5%/37.5%/10 % | NA | 67.8%/41.4%/9.2% | NA | 65%/35% (prior BsAb) |
| **Efficacy** | | | | | | |
| ORR (prior ADC/prior CAR-T) | 63.0% (NA) | 52% (55%/ 53%) | 61% (NA) | 46% (42%/53%) | 97.9% (NA) | 60% (62%/57% prior BsAb) |
| ≥VGPR | 59.4% | 47.5% | 56,1% | 42.5% | 94.8% | 55% |
| Median DoR, months (prior ADC/prior CAR-T) | 21.6 (NA) | NR (95% CI: 10.5 months to NE) | 71.5% at 15 months | 17.1 (13.6/NE) | 33.9 (NA) | 12.3 (13.3/8.2 prior BsAb) |

- Negative impact of prior BCMA targeted ADC/BsAb on BMCA targeting CAR-T cell therapy
- Modest impact or prior BMCA ADC on BCMA targeting BsAb therapy

DoR; duration of response; NA: not applicable; ORR: overall response rate; VGPR: very good partial response; BsAb: bispecific antibody; ADC: antibody drug conjugate);


1) Van de Donk N, et al, ASCO 2023
2) Touzeau C, et al. ASCO2023
3) Mohty M et al, ASCO 2023, 2
4) Nooka AK et al, ASCO 2023
5) Lin Y et al, ASCO 2023
6) Cohen AD et al, ASCO 2022,

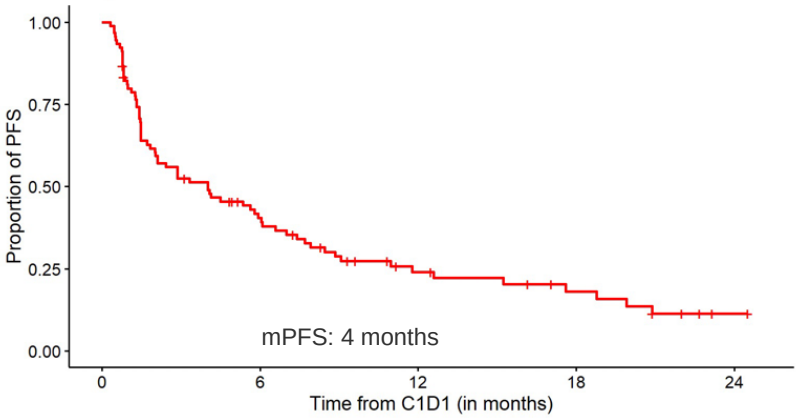
# Patients previously treated with BCMA-targeted ADC, bispecific, or CAR-T therapy responded to subsequent treatment with belantamab mafodotin

BCMA-targeted ADC, bispecific, or CAR-T therapy → BCMA-targeted ADC therapy

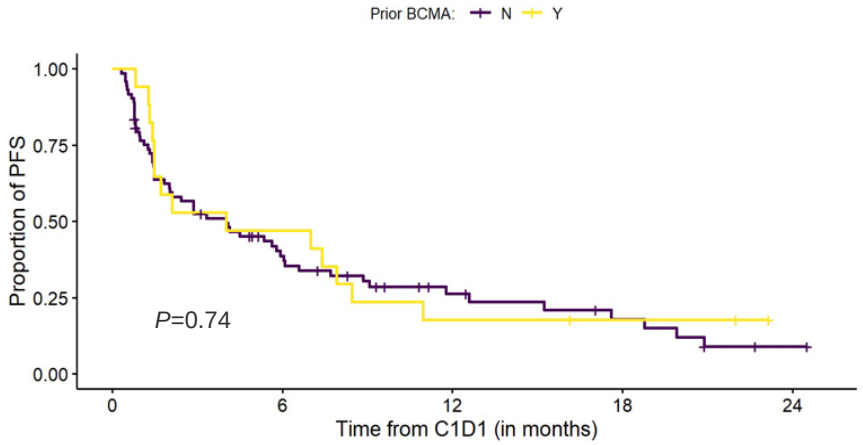
**Retrospective study:** single-center analysis of patients with RRMM* who received belantamab mafodotin after prior treatment with a BCMA-targeted therapy

| Patient characteristics | All patients (n=90) |
|---|---|
| Median prior LOTs, n (range) | 6 (2-14) |
| High-risk cytogenetics,† n (%) | 50 (61) |
| Prior treatment with a BCMA-targeted agent, n (%) | 17 (19) |
| CAR-T, n | 12 |
| Bispecific antibody, n | 6 |
| Belantamab mafodotin, n | 2 |

**PFS in total cohort**




**PFS in BCMA exposed versus unexposed**



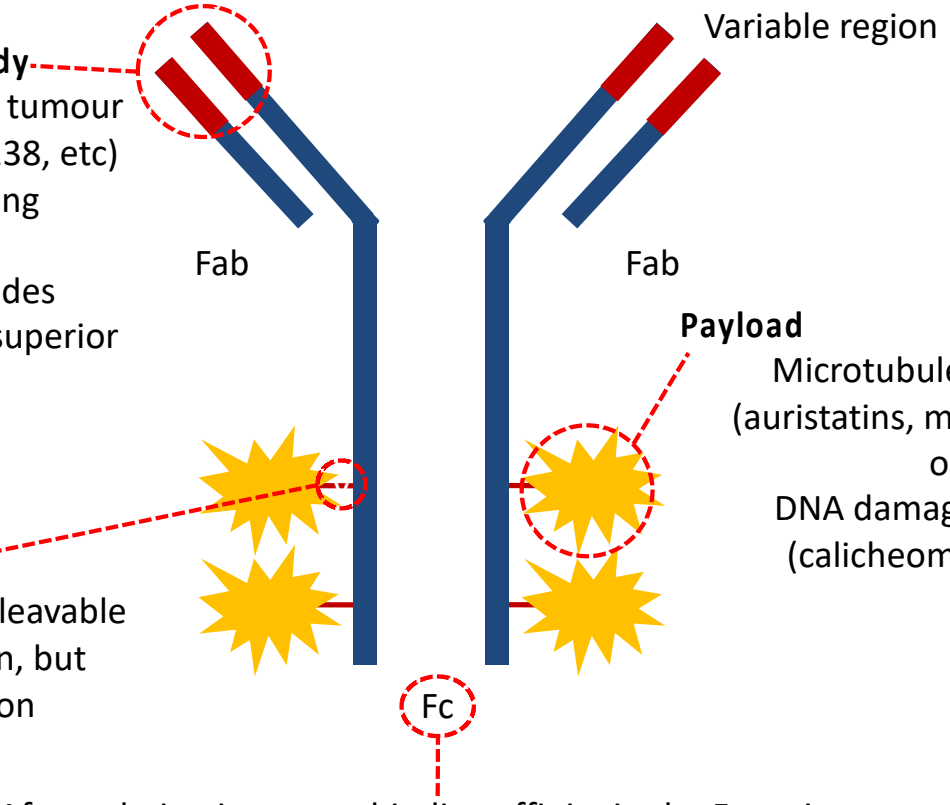

**The response to belantamab mafodotin was similar in those with prior BCMA exposure versus BCMA-naïve patients**

*Patients who completed ≥1 cycle of commercial belantamab mafodotin treatment outside clinical trials between October 1, 2020, and October 31, 2022, and had prior exposure to an immunomodulatory agent, a PI, and an anti-CD38 antibody. †Including 1q+, 1p-, t(4;14), t(14;16), and complex karyotype.

ADC, antibody-drug conjugate; BCMA, B-cell maturation antigen; C, cycle; CAR-T, chimeric antigen receptor T cell; CD, cluster of differentiation; D, day; LOT, line of therapy; mPFS, median progression-free survival; PFS, progression-free survival; PI, proteasome inhibitor; RRMM, relapsed/refractory multiple myeloma.

Hultcrantz M et al. Presented at: American Society of Hematology Annual Meeting and Exposition; December 10-13, 2022; New Orleans, LA.

# Structure of antibody-drug conjugates (ADCs)




**Monoclonal Antibody**
- High selectivity for tumour antigen (BCMA, CD138, etc)
- Internalizes following antigen binding
- IgG1 subtype provides longer half-life and superior ADCC activity

**Payload**

Microtubule inhibitors (auristatins, maytansinoids)
or
DNA damaging agents (calicheomicin, PBD)

**Linker Region**
- Cleavable or non-cleavable
- Stable in circulation, but releases payload upon internalisation

Afucosylation increases binding affinity in the Fc region, resulting in enhanced ADCC activity

Composed of **monoclonal antibodies (mAbs)** tethered to a **cytotoxic drug** (known as the "payload" or "warhead") via a **chemical linker**

Each of the components that make up ADCs will influence efficacy and toxicity

ADC: antibody drug conjugate; ADCC: antibody-dependent cellular cytotoxicity; Fab: fragment antigen binding; Fc: fragment crystallizable