# ADC: sviluppo futuro

*Dr. Vittorio Montefusco*

Sistema Socio Sanitario
Regione Lombardia
ASST Santi Paolo e Carlo

LE NUOVE FRONTIERE DELL'IMMUNOTERAPIA PER LA CURA DEL

**MIELOMA MULTIPLO**

*dalla teoria alla pratica*

**TORINO 3-4 MARZO 2023**

# Disclosures of dr. Vittorio Montefusco

| Company name | Research support | Employee | Consultant | Stockholder | Speakers bureau | Advisory board | Other |
|---|---|---|---|---|---|---|---|
| Amgen | | | X | | X | X | |
| BMS/Celgene | X | | | | X | X | |
| Janssen | X | | | | X | X | |
| Sanofi | X | | | | X | X | |
| Takeda | | | | | X | X | |
| Kariopharm | | | | | | X | |
| GSK | | | | | X | X | |

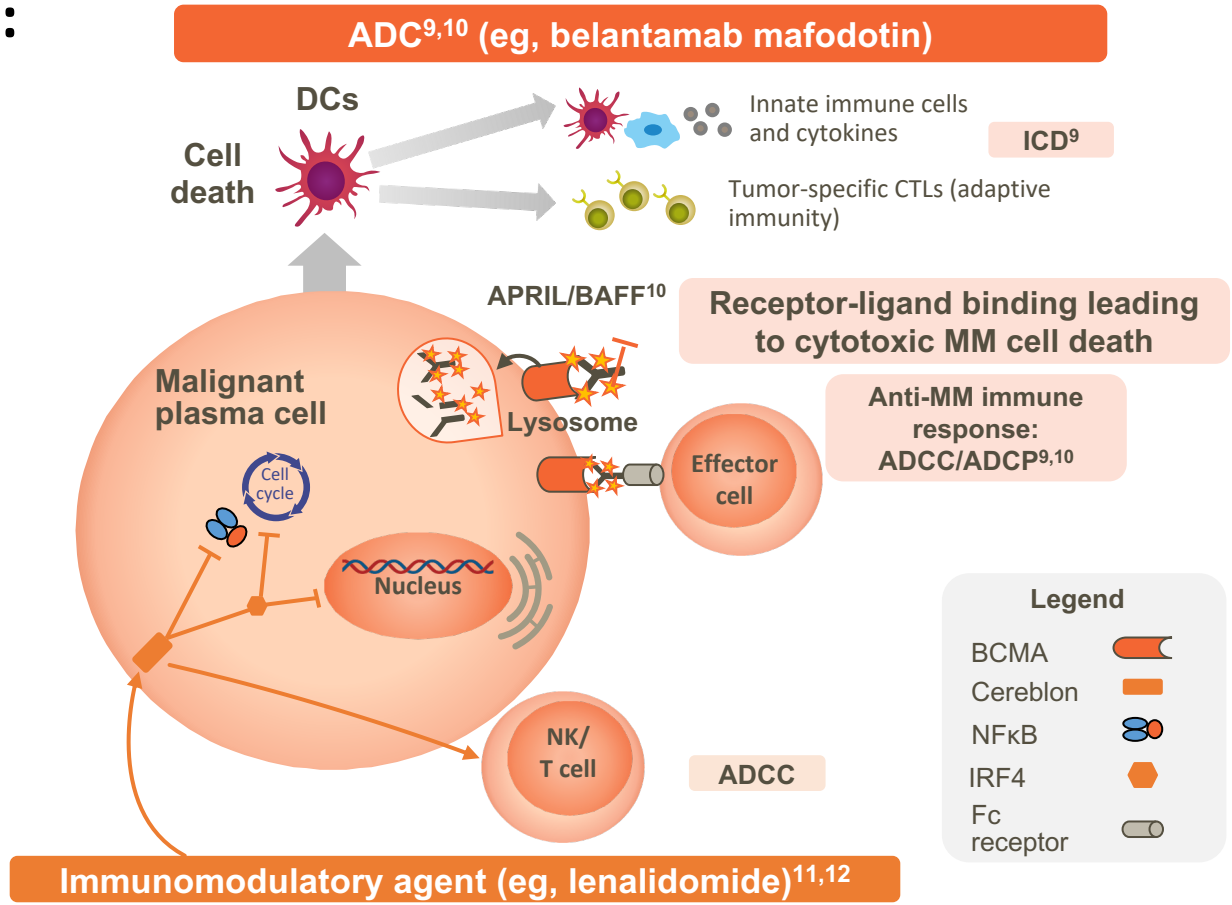
# POTENTIAL SYNERGISM BETWEEN BELANTAMAB AND IMiDs

## Belantamab acts through several mecanisms:

- Direct cell killing (MMAF)
- ADCC
- ADCP
- Complement activation

## IMiDs can synergize through:

- Immunomodulation
- Anti-inflammatory activity
- Anti-proliferative effect




This figure was created by GSK.


**1.** Terpos, E., et al. Presented at: American Society of Hematology Annual Meeting and Exposition; December 11-14, 2021; Atlanta, GA. Poster 2736. **2.** Lonial, S., et al. *Lancet Oncol*. 2020;21(2):207-221. **3.** Tai, YT, et al. *Blood.* 2014;123(20):3128-3138. 4.**.** Montes de Oca, R., et al. Presented at: European Hematology Association Congress; June 13-16, 2019; Amsterdam, Netherlands. Poster PF558. **5**. Cho, SF, et al. *Front Immunol*. 2018;9:1821. **6.** Bruins, WSC, et al. *Front Immunol*. 2020;11:1155. **7**. Armoiry, X, et al. *J Clin Pharm Ther*. 2008;33(3):219-226. **8**. Revlimid. Prescribing Information. Celgene Corporation; 2022. **9.** Montes de Oca, R., et al. *Mol Cancer Ther.* 2021;20(10):1941-1955. **10**. Tai, YT, Anderson KC. *Immunotherapy.* 2015;7(11):1187-1199. **11.** Shi, Q., Chen, L. *J Immunol Res*. 2017;2017:9130608. **12**. Quach, H., et al. *Leukemia*. 2010;24(1):22-32.

# BELANTAMAB - LENALIDOMIDE - DEXAMETHASONE

***A Phase 1/2, Dose and Schedule Evaluation Study to Investigate the Safety and Clinical Activity of Belantamab Mafodotin Administered in Combination with Lenalidomide and Dexamethasone in Transplant-Ineligible Patients with Newly Diagnosed Multiple Myeloma***

- Open-label, single-center, phase I/II study conducted in Greece
- The study aims to enroll 66 patients with TI-NDMM

**Part 1 – dose finding[1]**

**Part 1**
(36 patients randomized 1:1:1)

**Belantamab mafodotin**

- **Cohort 1:** 2.5mg/kg Q8W
- **Cohort 2:** 1.9mg/kg Q8W
- **Cohort 3:** 1.4mg/kg Q8W

**len:** 25mg/day PO, days 1-21 of every 28-day cycle

**dex:** 40mg/day PO or IV, days 1, 8, 15, 22 of every 28-day cycle[†]

**Until PD or unacceptable toxicity**

**Primary endpoint**

- **Part 1:** Belantamab mafodotin + len/dex safety, tolerability, RP2D

**Secondary endpoints:**

- Belantamab mafodotin + len/dex efficacy
- Ocular AE management
- PK profile
- Ocular AEs by OSDI

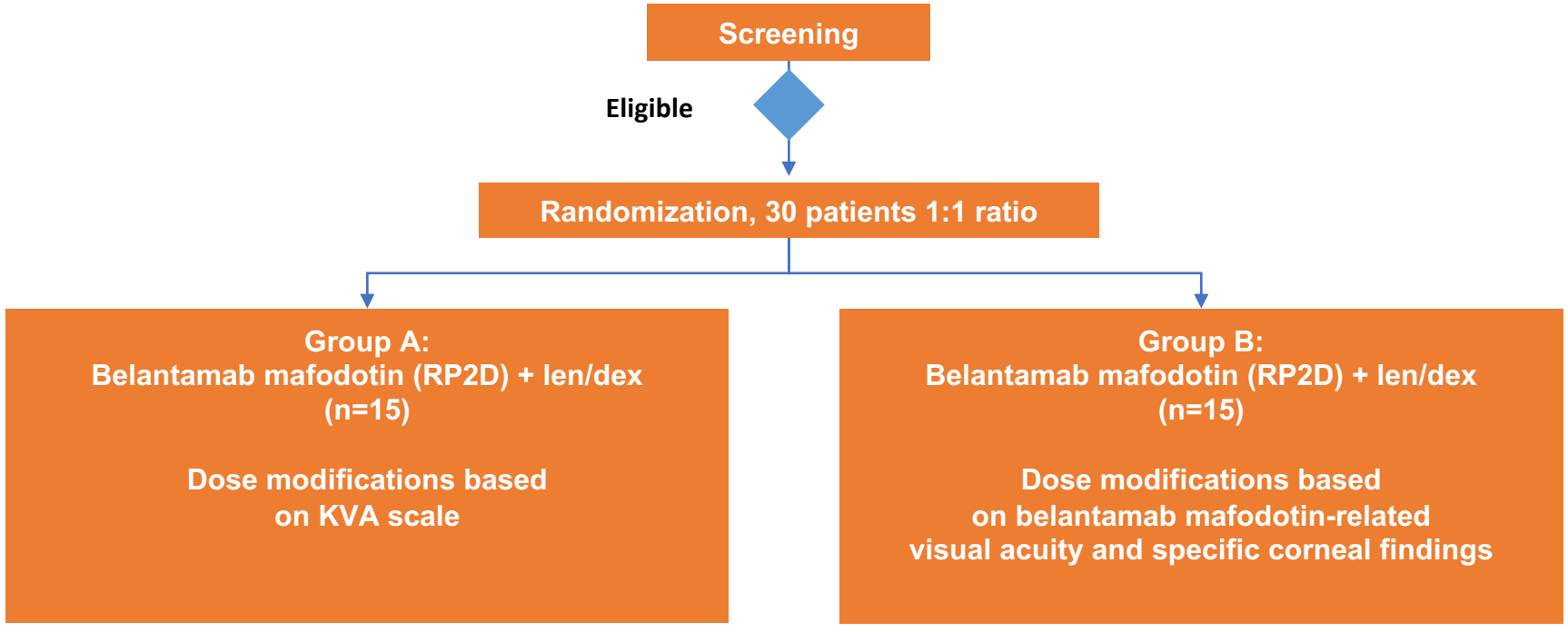
**Permitted dose modifications (mg/kg)**

| | Cohort 1 | Cohort 2 | Cohort 3 |
|---|---|---|---|
| **Dose +1[‡]** | 2.5 Q4W | 1.9 Q4W | 1.4 Q4W |
| **Starting dose** | **2.5 Q8W** | **1.9 Q8W** | **1.4 Q8W** |
| **Dose -1[‡]** | 2.5 Q12W | 1.9 Q12W | 1.4 Q12W |

Terpos E., et al. EHAC. 2022

# BELANTAMAB - LENALIDOMIDE - DEXAMETHASONE

## Part 2 – dose expansion

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# BELANTAMAB - LENALIDOMIDE - DEXAMETHASONE

| **Baseline characteristic**[2] | Cohort 1<br>belantamab mafodotin 2.5mg/kg Q8W + len/dex (n=12) | Cohort 2<br>**belantamab mafodotin** 1.9mg/kg **Q8W** + len/dex (n=12) | Cohort 3<br>belantamab mafodotin 1.4mg/kg **Q8W** + len/dex (n=12) |
|---|---|---|---|
| **Age**, years, median (min-max) | 75.0 (66.0-86.0) | 74.5 (68.0-82.0) | 69.0 (64.0-79.0) |
| **Gender**, n (%) | | | |
| Male | **8 (66.7)** | **5 (41.7)** | **6 (50.0)** |
| Female | 4 (33.3) | 7 (58.3) | 6 (50.0) |
| **ECOG PS**, n (%) | | | |
| 0 | 4 (33.3) | 3 (25.0) | 8 (66.7) |
| 1 | 6 (50.0) | 9 (75.0) | 4 (33.3) |
| 2 | 2 (16.7) | 0 | 0 |
| **Revised ISS stage**, n (%) | | | |
| I | 1 (8.3) | 2 (16.7) | 3 (25.0) |
| II | 9 (75.0) | 10 (83.3) | 8 (66.7) |
| III | 2 (16.7) | 0 | 1 (8.3) |
| **Lytic bone lesions**, n (%) | 7 (58.3) | 7 (58.3) | 5 (41.7) |
| **Presence of high-risk cytogenetics,*** n (%) | 1 (8.3) | 2 (16.7) | 0 |
| **IMWG frailty score, n (%)** | | | |
| Intermediate fitness (score=1) | 10 (83.3) | 11 (91.7) | 11 (91.7) |
| Frail (score ≥2) | 2 (16.7) | 1 (8.3) | 1 (8.3) |

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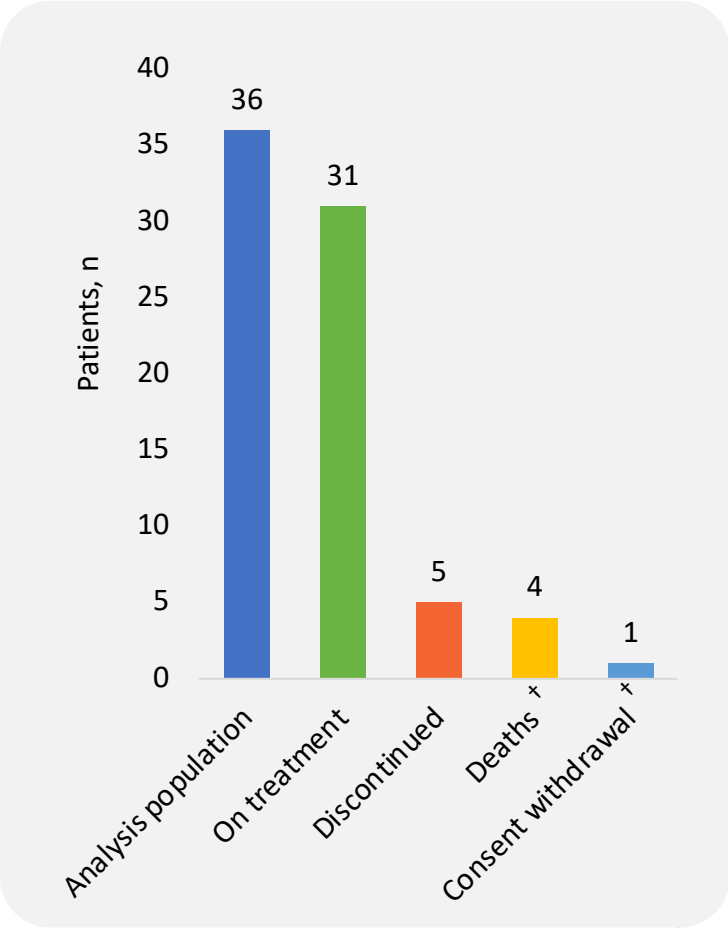
# BELANTAMAB - LENALIDOMIDE - DEXAMETHASONE

| | Cohort 1 belantamab mafodotin 2.5mg/kg Q8W + len/dex (n=12) | Cohort 2 belantamab mafodotin 1.9mg/kg Q8W + len/dex (n=12) | Cohort 3 belantamab mafodotin 1.4mg/kg Q8W + len/dex (n=12) |
|---|---|---|---|
| **Treatment exposure** | | | |
| Duration of therapy in months, median (range) | 10.1 (2.1-15.3) | 11.8 (6.5-17.5) | 10.0 (1.9-16.6) |
| Infusions, median (range) | 5.0 (2.0-6.0) | 5.0 (4.0-8.0) | 5.0 (2.0-9.0) |
| Follow-up time in months, median (range) | 11.0 (3.2-18.0) | 14.4 (8.8-17.8) | 10.9 (6.1-18.2) |
| Total number of cycles | 149 | 171 | 152 |
| **Treatment details** | | | |
| Number of planned doses | 80 | 86 | 81 |
| Dose skipped,* n (%) | 26 (32.5) | 18 (20.9) | 16 (19.8) |
| Dose infused, n (%) | 54 (67.5) | 68 (79.1) | 65 (80.2) |
| Intended dose intensity (mg/kg/Q4W) | 1.25 | 0.95 | 0.7 |
| Actual dose intensity (mg/kg/Q4W), median (range) | 1.0 (0.5-1.7) | 0.8 (0.6-1.0) | 0.6 (0.5-0.7) |
| Relative dose intensity (%), median (range) | 73.8 (40.2-102.4) | 80.0 (55.5-100.0) | 79.9 (67.1-100.0) |




80.2% of planned doses were infused in Cohort 3 (1.4mg/kg Q8W + len/dex)

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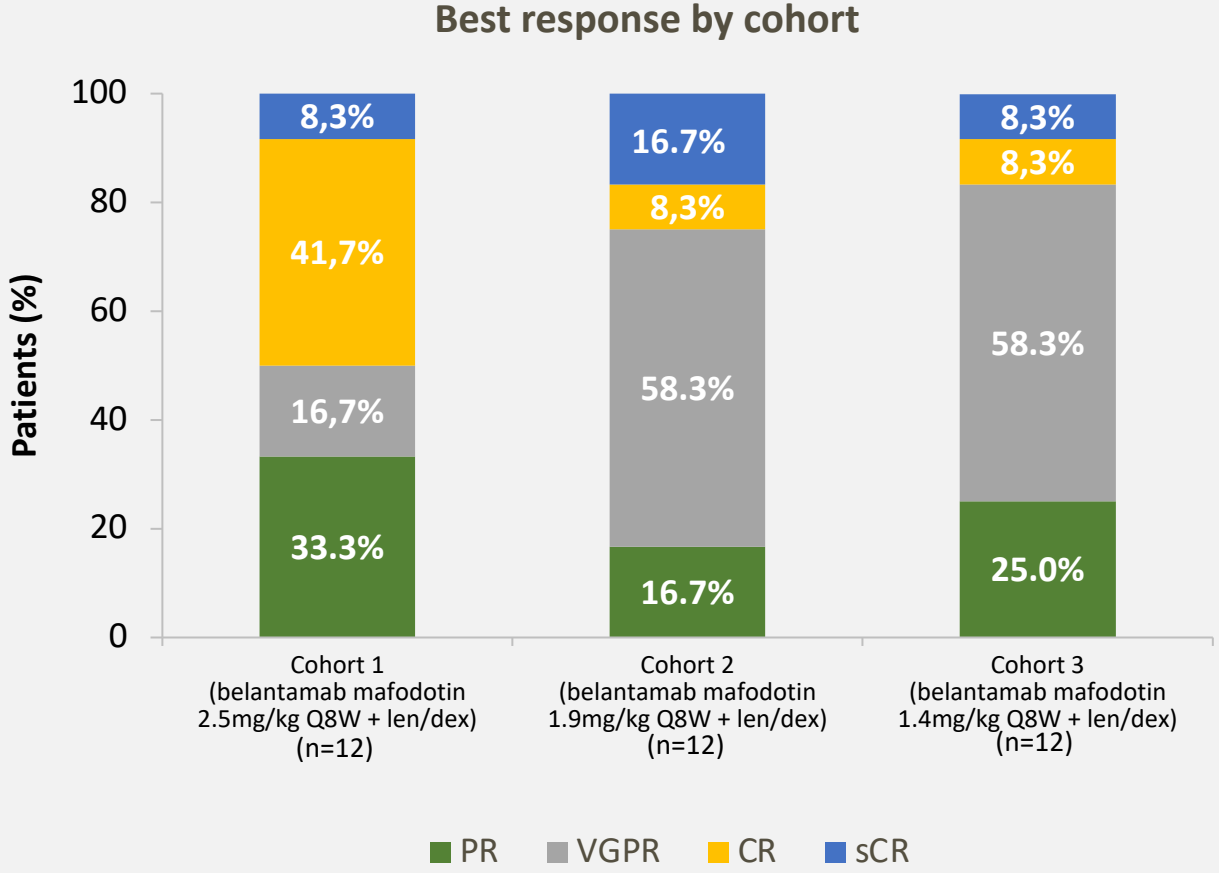
# BELANTAMAB - LENALIDOMIDE - DEXAMETHASONE

- Median time in months (range) to first response:
  - Cohort 1: 1.1 months (1.0-2.1)
  - Cohort 2: 1.0 months (0.9-3.8)
  - Cohort 3: 1.0 months (1.0-2.0)
- DoR event-free rate over the 11.9 months of follow-up was 100.0% in all 3 cohorts

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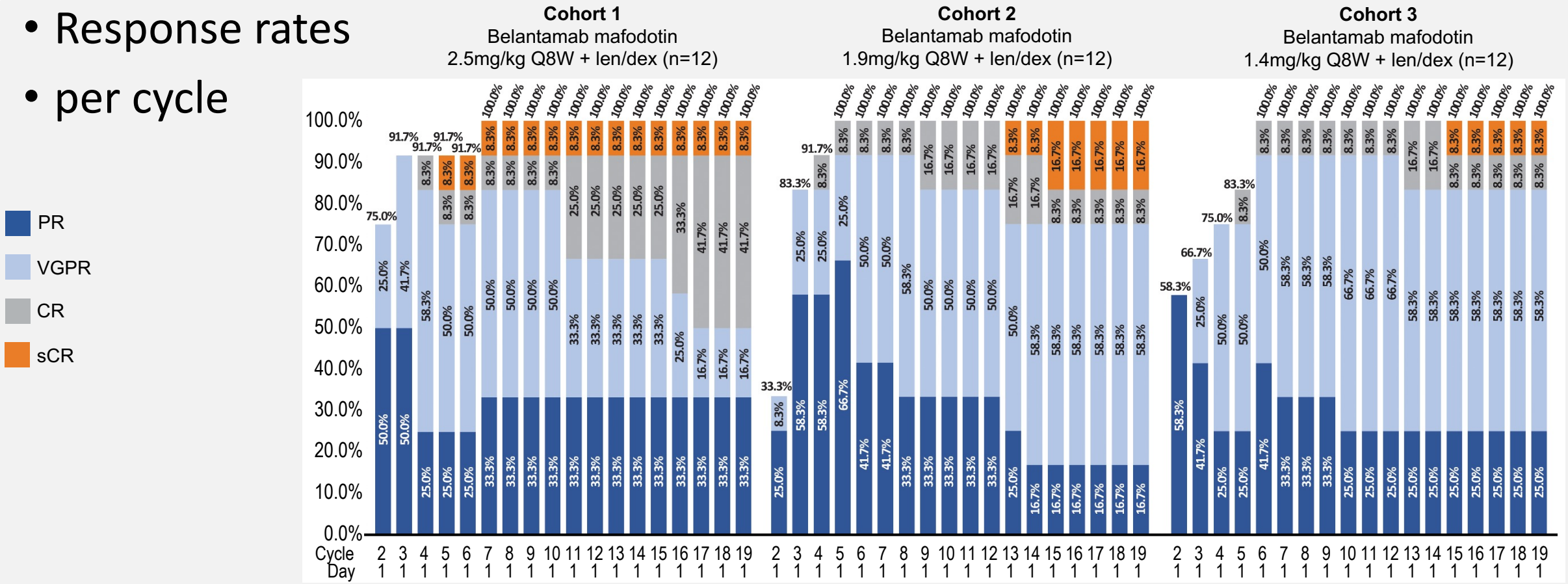
# BELANTAMAB - LENALIDOMIDE - DEXAMETHASONE

- Response rates
- per cycle



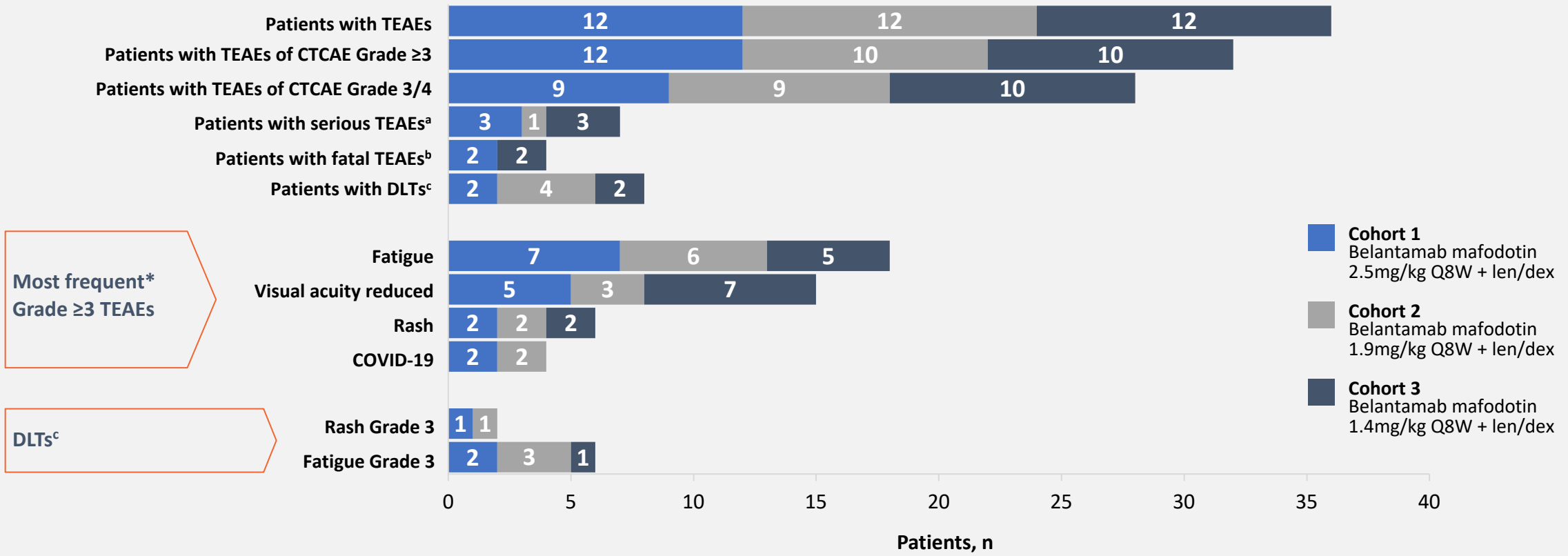

**Cohort 1 ≥VGPR, n (%) : 8 (67%)**

**Cohort 2 ≥VGPR, n (%) : 10 (83%)**

**Cohort 3 ≥VGPR, n (%) : 9 (75%)**

Terpos E., et al. ASH. 2022

# BELANTAMAB - LENALIDOMIDE - DEXAMETHASONE




This figure was first presented in Terpos, E., et al. ASH. 2022.

Most frequent Grade ≥3 TEAEs were fatigue, reduced visual acuity, rash, and COVID-19

Terpos E., et al. ASH. 2022

# BELANTAMAB - LENALIDOMIDE - DEXAMETHASONE

- Across all cohorts, no keratopathy higher than Grade 2 was observed
- Cohorts 2 and 3 showed no ocular symptoms higher than Grade 2
- Cohort 2 had a low occurrence of Grade 3-4 visual acuity reduction
- No Grade 4 ocular adverse events were observed

| Ocular assessments | Cohort 1 belantamab mafodotin 2.5mg/kg Q8W + len/dex (n=12) | Cohort 2 belantamab mafodotin 1.9mg/kg Q8W + len/dex (n=12) | Cohort 3 belantamab mafodotin 1.4mg/kg Q8W + len/dex (n=12) |
|---|---|---|---|
| **Ocular symptoms** | | | |
| Grade 0-1 | 96 (73.8%) | 123 (85.4%) | 101 (79.5%) |
| Grade 2 | 32 (24.6%) | 21 (14.6%) | 26 (20.5%) |
| Grade 3-4 | 2 (1.5%) | 0 (0.0%) | 0 (0.0%) |
| **Keratopathy** | | | |
| Grade 0-1 | 115 (87.1%) | 133 (91.1%) | 117 (92.1%) |
| Grade 2 | 17 (12.9%) | 13 (8.9%) | 10 (7.9%) |
| Grade 3-4 | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| **Visual acuity reduced** | | | |
| Grade 0-1 | 58 (44.3%) | 94 (64.8%) | 86 (67.7%) |
| Grade 2 | 59 (45.0%) | 44 (30.3%) | 31 (24.4%) |
| Grade 3-4 | 14 (10.7%) | 7 (4.8%) | 10 (7.9%) |

Belantamab doses skipped due to ocular AEs per the total number of planned administrations were 26/80 (**32.5%**), 18/86 (**20.9%**), and 16/81 (**19.8%**) in cohorts 1, 2, and 3, respectively.

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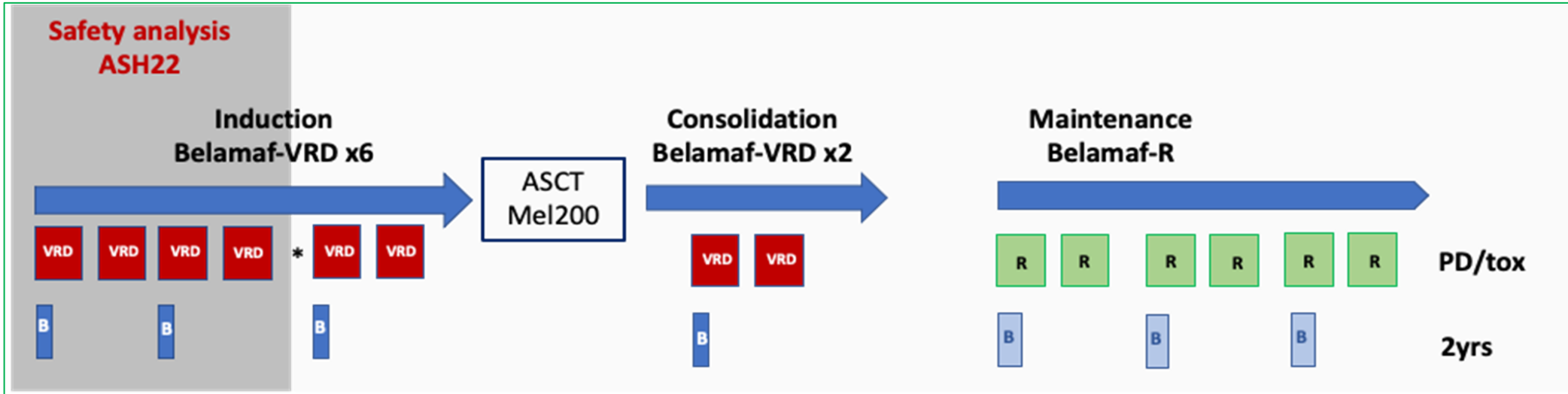
# BELANTAMAB - VRd

**GEM-BELA-VRd is the first trial to evaluate belantamab mafodotin + bor/len/dex in NDTE MM**




*VRD (bortezomib 1.3 mg/m2 (subcutaneous) on days 1, 4, 8, and 11 of each cycle; lenalidomide 25 mg/d on days 1 to 21; and dexamethasone 40 mg on days 1 to 4 and 9 to 12) at 4-week intervals for 6 cy.*

*R (Lenalidomide 10 mg/day on days 1-28 continuously (may increase up to 15 mg/day) until disease progression or patient withdrawal.*

*Belantamab 2.5 mg/kg iv every 8 wks (on day 1 of cycles 1, 3 and 5 of induction and on day 1 of cycle 1 of consolidation)*

*Belantamab 1.9 mg/kg iv every 8 wks until disease progression, patients withdrawal, death or up to two years as maintenance*

* *Stem cell mobilization and collection*

Gonzalez-Calle, et al. ASH. 2022

# BELANTAMAB - VRd

**Second dose administration of belantamab mafodotin**

- Patients receiving full dose: 60%
- Patients at reduced dose (1.9 mg/kg): 22.5%
- Patients withdrawing treatment: 17.5%

## Methods:

50 patients were planned to be recruited in this clinical trial.

**40 patients** had already completed the four induction cycles and were included in this analysis.

| Keratopathy by KVA scale | | |
|---|---|---|
| **Keratopathy** | **4 weeks from 1st belantamab mafodotin dose (C2 bor/len/dex)** | **4 weeks from 2nd planned belantamab mafodotin dose (C4 bor/len/dex)** |
| **None, n (%)** | **16 (40)** | **8 (20)** |
| **Any Grade, n (%)** | **24 (60.0)** | **32 (80.0)** |
| Mild | 12 (50.0) | 12 (37.5) |
| Moderate | 11 (45.8) | 17 (53.1) |
| Severe | 1 (4.2) | 3 (9.4) |

| Efficacy after 4 cycles of belantamab mafodotin and bor/len/dex (n=39/40) | |
|---|---|
| **Median follow-up, mo (range)** | **6 (3-12)** |
| **PFS, 6 mo[a], %** | **89.3** |
| **ORR[b], %** | **82.1 (32/39)** |
| **CR[c], n (%)** | **5/39 (12.8)** |
| MRD negativity, n (%) | 4/5 (80) |
| Not evaluable, n (%) | 1/5 (20) |

**Ocular side effects**
(any Grade vs Grade ≥3, CTCAEv4.0):

- Blurred vision (77.5% vs 27.5%)
- Eye irritation (57.5% vs 10%)
- Dry eye (50% vs 10%)
- Photophobia (25% vs 0%)

Gonzalez-Calle, et al. ASH. 2022

# BELANTAMAB – Dara-Rd

***A Phase 1/2, Dose and Schedule Evaluation Study to Investigate the Safety and Clinical Activity of Belantamab Mafodotin Administered in Combination with Dara, Len and Dex in Transplant-Ineligible Patients with NDMM***

**Part 1: Dose-finding in 2 cohorts (N=24, with 12 patients per cohort)**

R=1:1

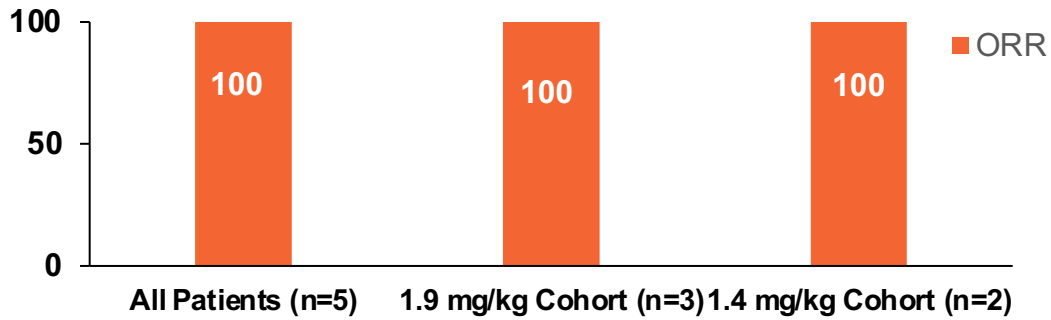
- **Belantamab mafodotin 1.4 mg/kg** (IV, every 8 weeks on day 1 of each cycle) **plus dara/len/dex**
- **Belantamab mafodotin 1.9 mg/kg** (IV, every 8 weeks on day 1 of each cycle) **plus dara/len/dex**

**Part 2: Dose expansion in 1 cohort (N=12)**

**Belantamab mafodotin RP2D plus dara/len/dex**

**No belantamab mafodotin dose reductions/delays** were reported

**Preliminary responses at a median follow-up of 1.3 months (range: 0.1-2.4)**




| Safety summary | All patients (N=11) |
|---|---|
| **Serious TEAEs** | 0 |
| Grade ≥3 infections | 0 |
| Grade ≥3 thrombocytopenia | 0 |

Terpos, et al. ASH, 2022

# BELANTAMAB – Dara-Rd

***Phase 2 Study of BeLAntamab Mafodotin as Pre- and Post-Stem Cell Transplant Consolidation and Maintenance (BLAST study) for Multiple Myeloma Patients in First Remission***

**Hypothesis: Incorporating reduced-frequency belantamab with len maintenance post-ASCT may improve MRD-negative rates and thereby improve long-term clinical outcomes while minimising ocular AEs**

**Single-centre, single-arm, phase 2 study with N=39 planned patients**

**STUDY POPULATION**

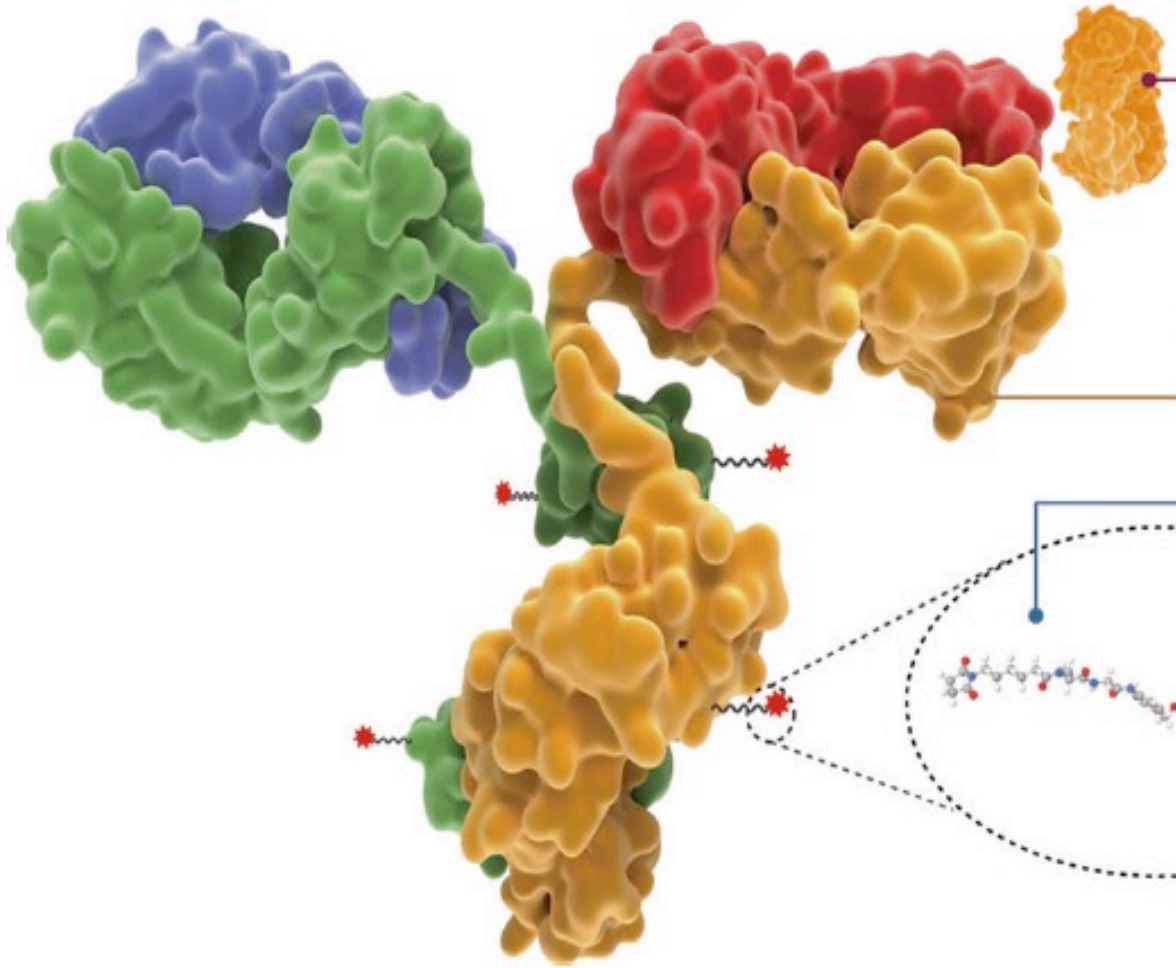
| Pre-ASCT period | | Transplant | Post-ASCT maintenance period |
|---|---|---|---|
| **2.5 mg/kg IV belantamab mafodotin on day –42** | **Stem cell mobilisation and collection[c] on day –14** | **ASCT on day 0** | **2.5 mg/kg IV belantamab mafodotin** (starting day +60 post-ASCT; every 3 months up to 2 years post ASCT)<br>**10 mg/day for 21/28 days len maintenance** (starting ~day +100; until PD) |

## Endpoints and other procedures

- **Primary:** MRD negativity rate at 12 mo post-ASCT (sensitivity of at least $10^{-6}$ assessed by NGS)
- **Secondary:** feasibility, safety, and tolerability of belantamab mafodotin; efficacy per IMWG-assessed responses and KM estimates of PFS and OS; MRD negativity rates at 3 and 24 mo post-ASCT; and impact of belantamab mafodotin on stem cell collection, hematopoietic reconstitution post-ASCT, and HRQoL
- Serial ophthalmologic exams, with belantamab mafodotin dose modifications and/or holds for ocular AEs[d]

Cohen, et al. ASH. 2022

# STRUCTURE OF AN ANTIBODY DRUG CONJUGATE

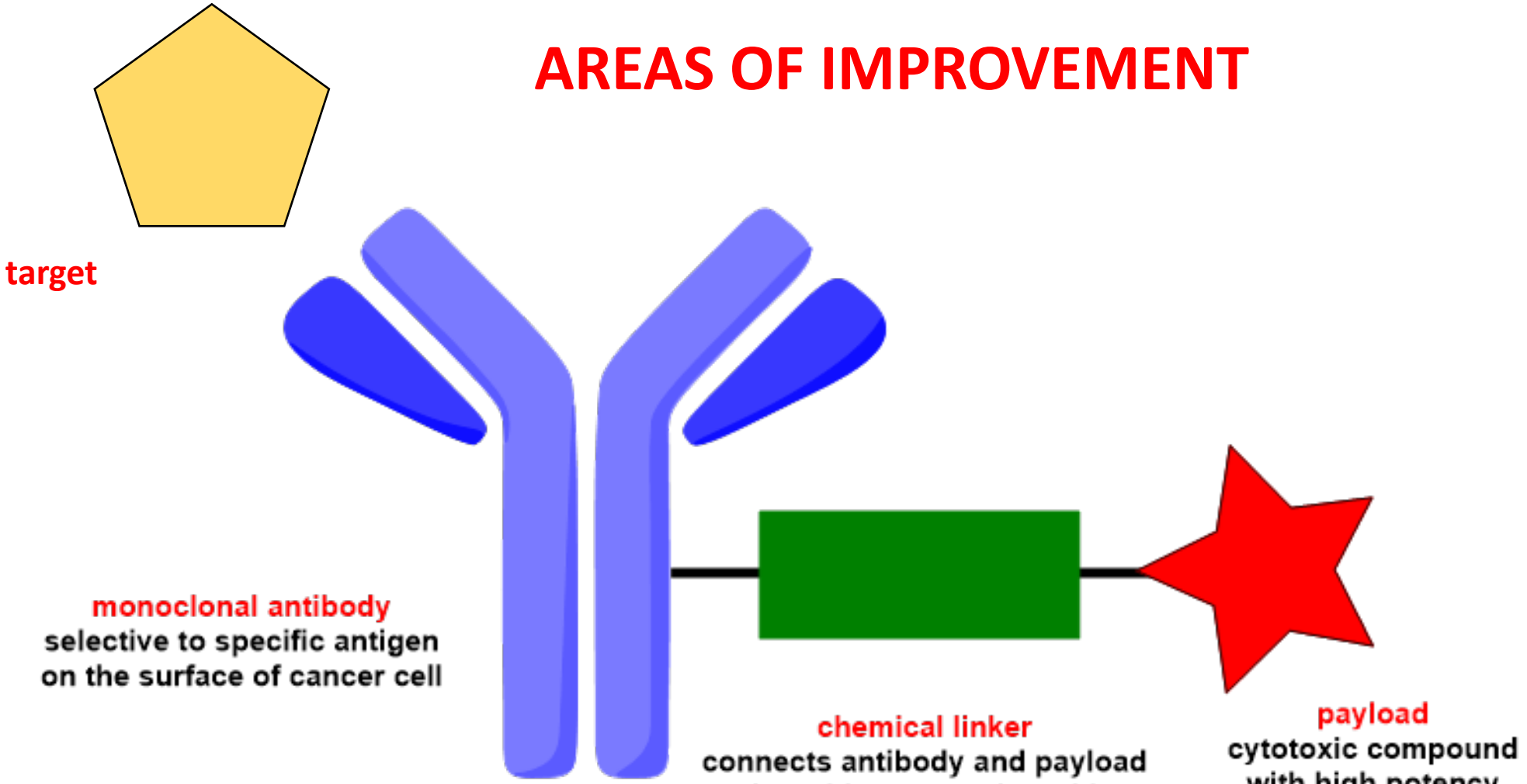


**Key functions**

| | |
|---|---|
| Target antigen | Recognition of target cancer cells |
| Antibody | Guidance system for cytotoxic drugs |
| Linker | Bridge between antibody and drugs and to control the release of drugs inside cancer cells |
| Cytotoxic drug | Warhead for destroying cancer cells |

Adapted from Zhiwen et al. Signal Transduction and Target Therapy 2022

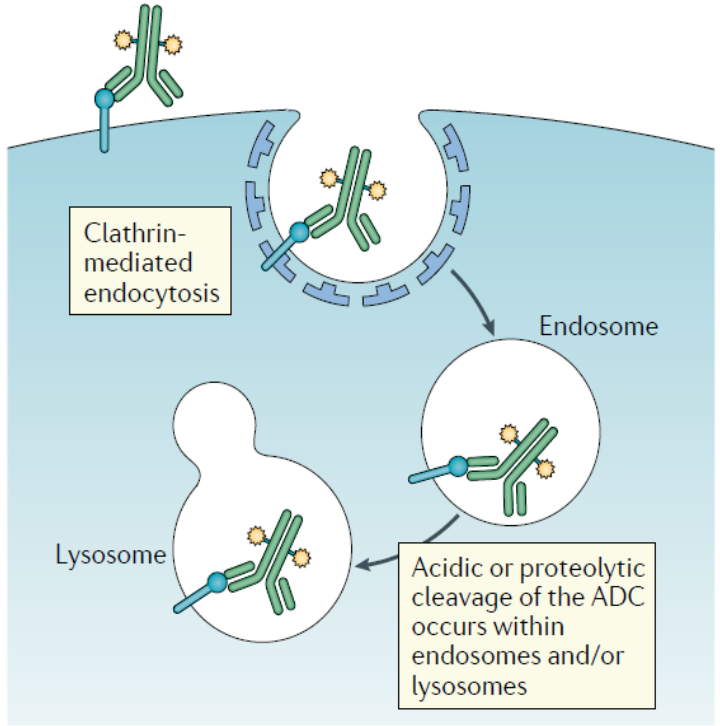
# AREAS OF IMPROVEMENT



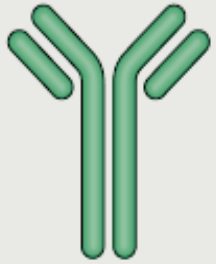
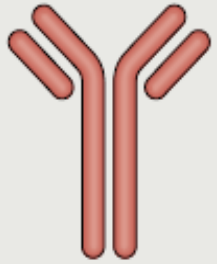
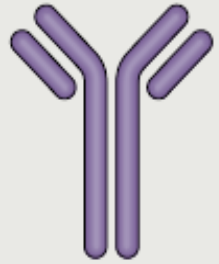
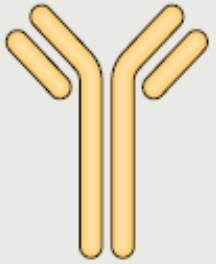
# Antigen

Target for ADC should be:

- Highly tumor-specific
- Absent in the bloodstreem
- Internalized
- Processed by lysosomes
- Actively replenished

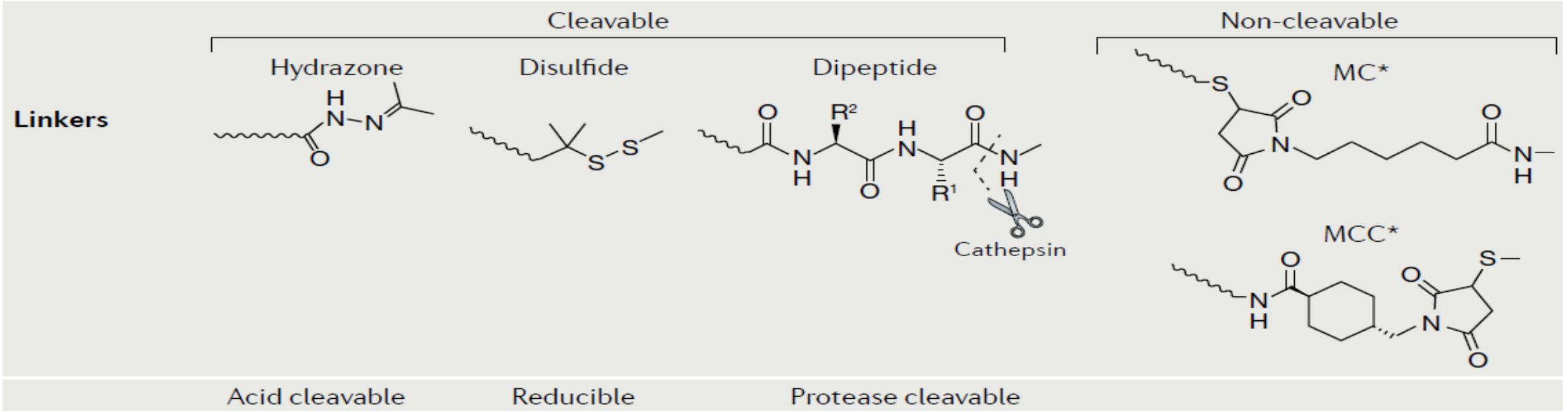


# The monoclonal Antibody

| Antibodies | IgG1 | IgG2 | IgG3 | IgG4 |
|---|---|---|---|---|
| |  |  |  |  |
| **Serum half-life** | 21 days | 21 days | 7–21 days | 21 days |
| **C1q binding** | Yes | Yes | Yes | No |
| **Fcγ avidity** | High | Low | High | Moderate |

Adapted from Drago et al. Nature Reviews 2021

# The Linker

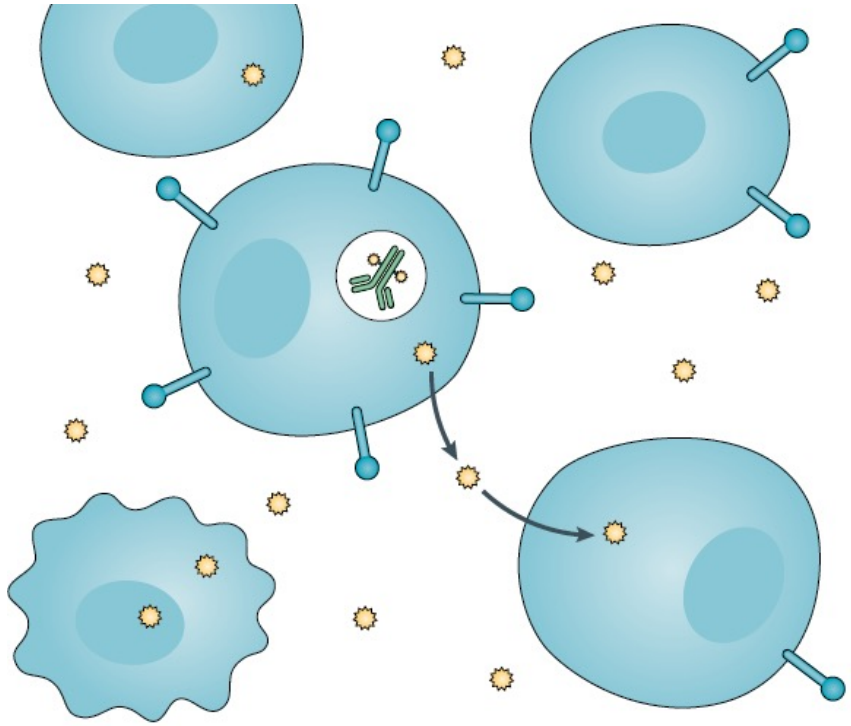



Clevable linkers:

- **Acid cleavable** → released in early endosomes, but also in the low pH tumor microenvironment
- **Reducible** → released in the cytoplasm, rich in glutathione
- **Protease cleavable** → released in late endosomes or lysosomes, but also in the protease-rich tumor microenvironment.

Adapted from Drago et al. Nature Reviews 2021

# The bystender effect



Payload release in the tumor microenvironment generates the bystander effect, wich is crucial to target tumor cells with low target expression.

The bystander effect can be obtained also by diffusion of lipophilic payloads across cell membranes.

# The Payload

| Payloads |  |  |  |  |
|---|---|---|---|---|
| | Auristatins | Maytansinoids | Calicheamicins | Camptothecins |
| | Anti-microtubule | Anti-microtubule | DNA cleavage | Topoisomerase 1 inhibition |

Only 2% of the administered dose reaches the tumor.

It is necessary to use highly potent cytotoxic drugs, active at sub-nanomolar concentrations.

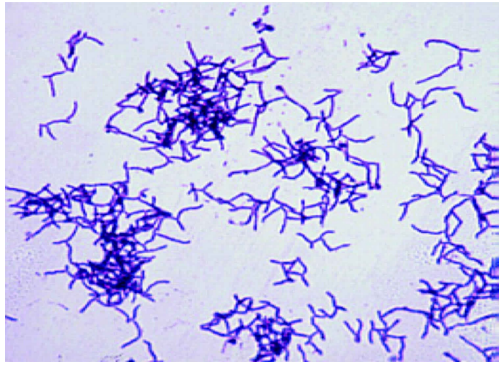
Adapted from Drago et al. Nature Reviews 2021

**Monomethyl auristatin E (MMAE)**

**Monomethyl auristatin F (MMAF)**

*Dolabella Auricularia*

**Calicheamicins** →



*Actinomycetes bacteria*

**Camptothecin analogues** →

*Camptotheca Acuminata*

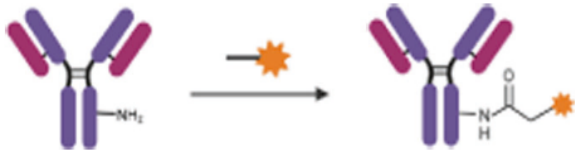
# Payload ligation

## Stochastic conjugation

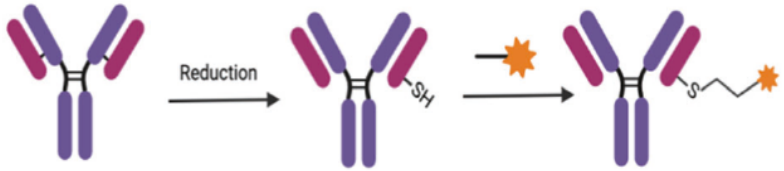
## Site-specific conjugation

## Enzyme-assisted ligation

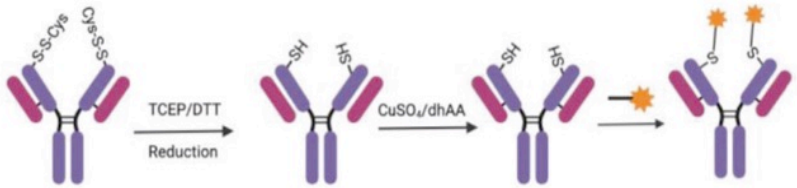
Lysine sites



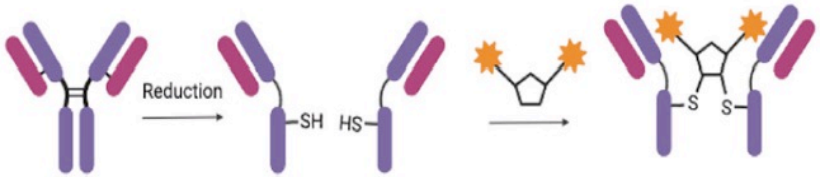

Reduced cysteine sites



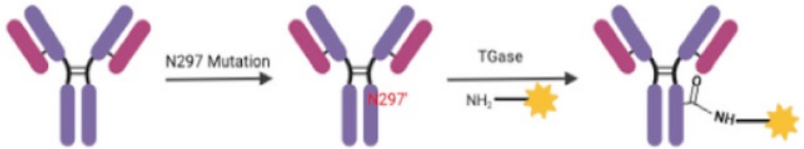

Engineered reactive cysteine residues




Disulfide re-bridging




Enzyme-assisted ligation



# Drug-to-Antibody Ratio (DAR)

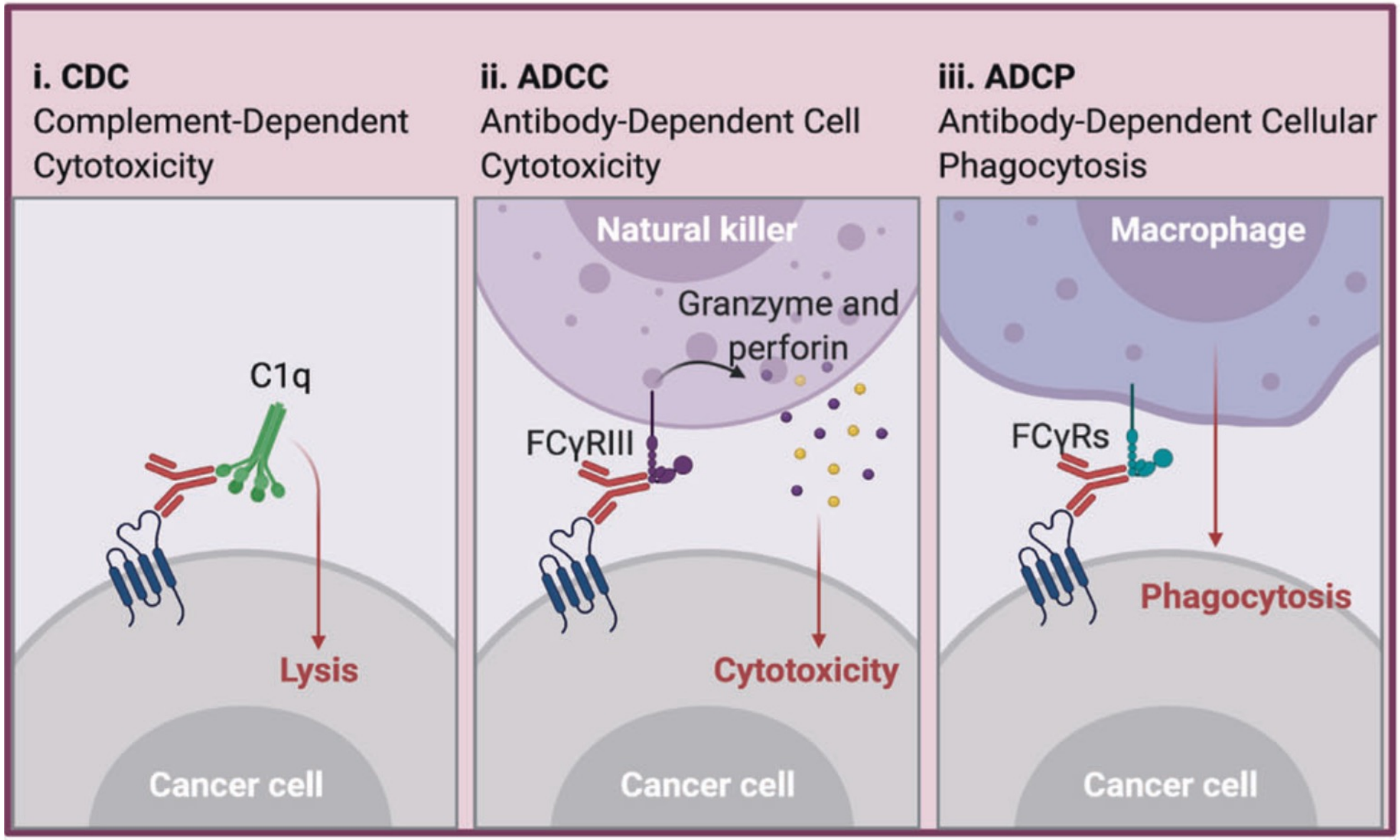
**The drug-to-antibody ratio is the average number of payload moyeties attached to each MoAb.**

Currently approved ADCs have DARs ranging from 2 to 8.

ADCs with high DARs are more potent in vitro, but can be cleared faster from the plasma by the liver, reducing ADC exposure and resulting in comparable activity to ADCs with lower DARs.

ADCs with high hydrophobic payloads have a faster hepatic clearance, but a better bystander activity.

# Immunomediated activity



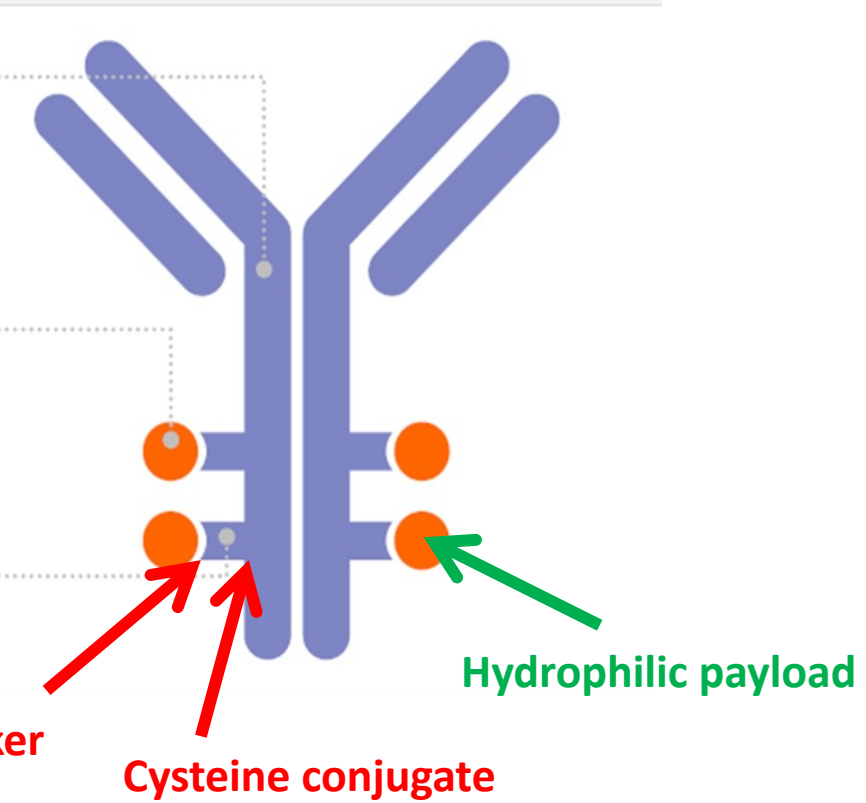
# ADCs in Hematology

| | Target Antigen | Isotype | Linker | Payload | DAR |
|---|---|---|---|---|---|
| Gemtuzumab Ozogamicin | CD33 | $IgG_4$ | Hydrazone | Ozogamicin | 2-3 |
| Belantamab Mafodotin | BCMA | $IgG_1$ | mc | MMAF | 4 |
| Brentuximab Vedotin | CD30 | $IgG_1$ | mc-VC-PABC | MMAE | 4 |
| Inotuzumab Ozogamicin | CD22 | $IgG_4$ | Hydrazone | MMAE | 5-7 |
| Polatuzumab Vedotin | CD79b | $IgG_1$ | mc-VC-PABC | CD79b | 3.5 |

# Belantamab Mafodotin

**Belantamab Mafodotin is a 3° generation ADC**

1. Afucosylated, humanized IgG1 anti-BCMA mAb
2. MMAF, a microtubule inhibitor
3. Protease-resistant maleimidocaproyl linker joining MMAF and the mAb




**Homogeneous DAR (1:4)**

**No extracellular payload release**

**No bystander effect**

Tai Y-T, et al. Blood 2014

# Improvements of ADC technology

**Improvements of :**

- **Target**
- **Bispecific or biparatopic MoAbs**
- **More stable cleaveble linkers**
- **Use of non-internalizing ADC to specifically target the tumor stroma, with a protease-mediated cleavage of the payload**
- **Dual payload, in order to limit drug resistance**
- **Use of hydrophobic payloads, to enhance the bystander effect**
- **Link of cytokines to ADC, to enhance the immuno-mediated killing**
- **Combination with checkpoint inhibitors.**

# Conclusions

**Belantamab Mafodotin is a 3° generation, first-in-class anti-BCMA ADC**

**Belantamab Mafodotin is highly active in MM**

**Dosage, schedule, and combinations optimization are ongoing**

**We are only in the early phase of ADC development**

# GRAZIE DELL'ATTENZIONE