Highlights from IMW2019
Bologna, 19-20 Novembre 2019

E’ possibile il ri-trattamento con anticorpi monoclonali?

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Disclosures for Mario Boccadoro, MD

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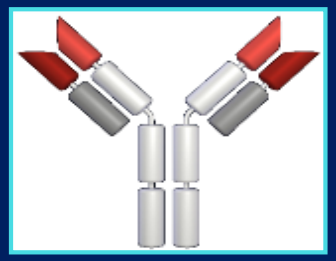
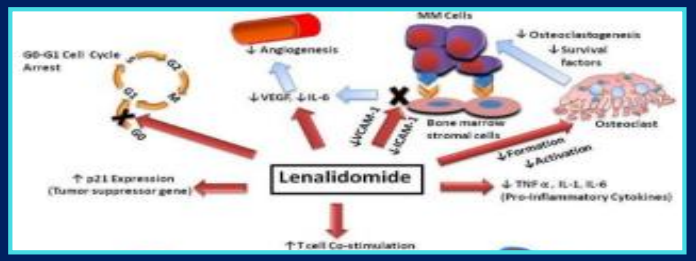
Presentation includes discussion of the off-label use of a drug or drugs

Immunotherapies Target Different Aspects of the Immune Environment in MM

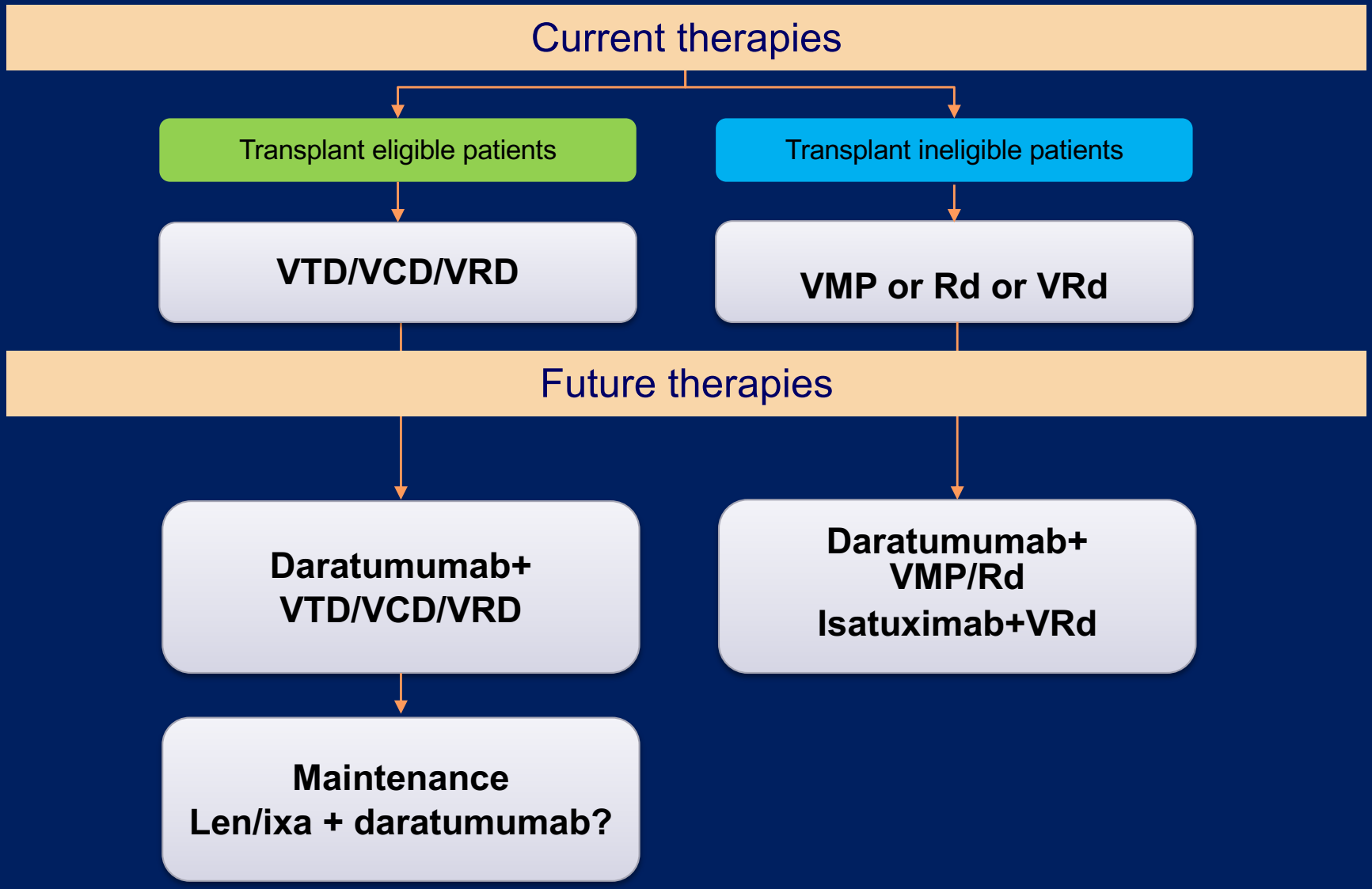
mAbs	Bispecific Antibody Therapies	Broad Immunomodulatory Effects	Vaccines	Adoptive Cellular Therapies
They target immune cells and/or tumor cells, with immunomodulatory effects	They target both immune cells and tumor cells	Multiple effects across immune system	They boost the activity of the immune system	Delivery of active immune cells
• CD38 • PD-1/PD-L1 • SLAMF7 • Antibody-drug conjugates	• Bispecific T-cell engagers • Bispecific NK-cell engagers • Bispecific antibodies	• IMiDs • Cytokines – Interleukins – Interferons	• Cell-based vaccines • Peptide-based vaccines	• Chimeric antigen receptors • Adoptive T cell and NK cell therapy • Allogeneic NK cells





mAb and BiTE figures: Adapted from Nagorsen D et al. *Leuk Lymph.* 2009;50:886–891. Lenalidomide figure: Attribution 2.0 Generic (CC BY 2.0). IMiD, immunomodulatory drug; I-O, immuno-oncology; mAb, monoclonal antibody; NK, natural killer; PD-1, programmed death receptor 1; PD-L1, programmed death ligand 1; SLAMF7, signaling lymphocytic activation molecule family member 7.

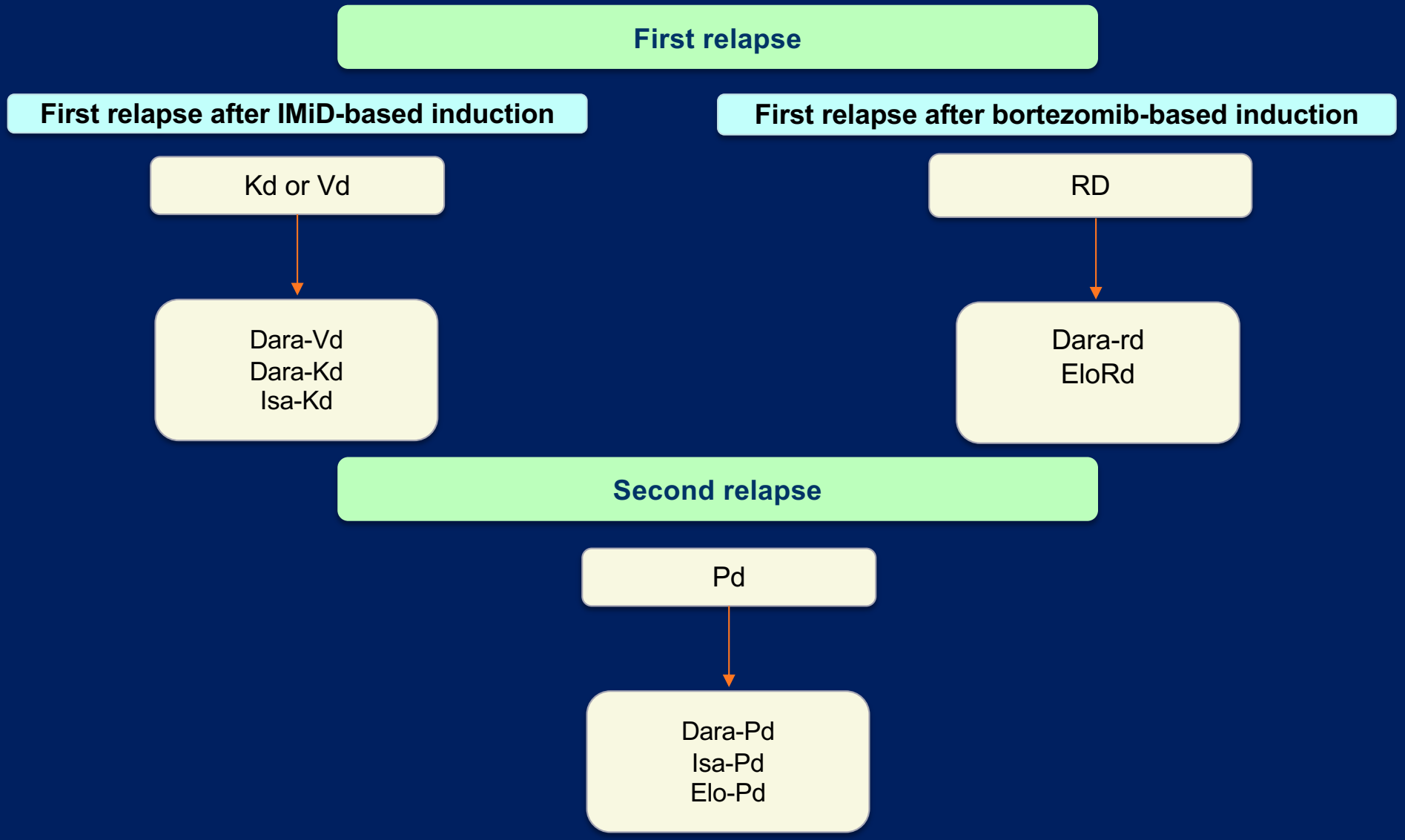
ESMO Guidelines for the management of NDMM



Virtually all patients will be exposed and/or refractory to an anti-CD38 monoclonal antibody after 1st line therapy

V: bortezomib; T: thalidomide; d: dexamethasone; C: cyclophosphamide; R/Len: lenalidomide; M, melphalan; Ixa: Ixazomib

ESMO Guidelines for the management of RRMM



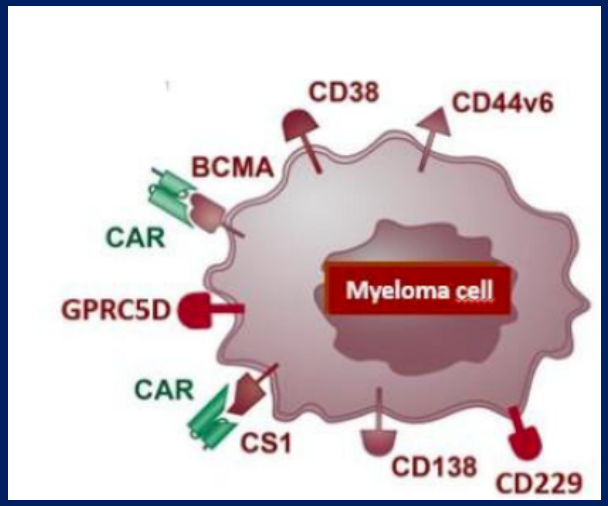
At relapse all best combinations are based on anti-CD38 mAbs

mAbs: monoclonal antibodies; K: carfilzomib; d: dexamethasone; V: bortezomib; Dara: daratumumab; R: lenalidomide; P: prednisone; Isa: Isatuximab; Elo: Elotuzumab

What is the optimal strategy?

Re-treatment with the same mAb product?

Different antigen target?



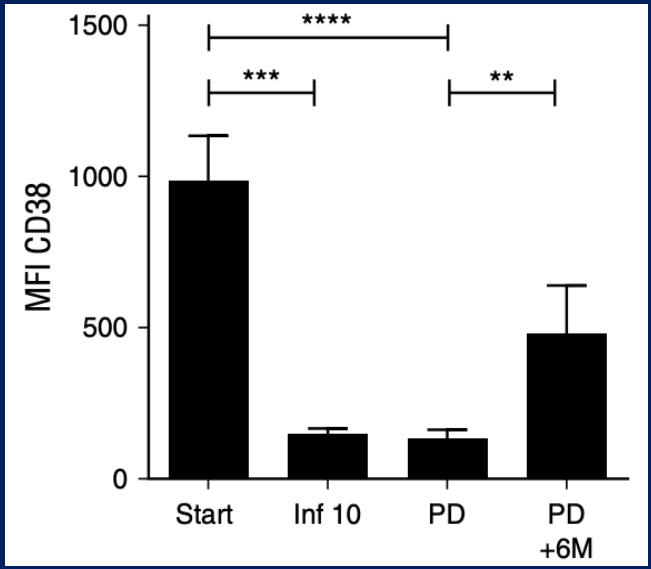
mAb: monoclonal antibody

CD38 clearance and re-appearance after anti-CD38 MAb exposure

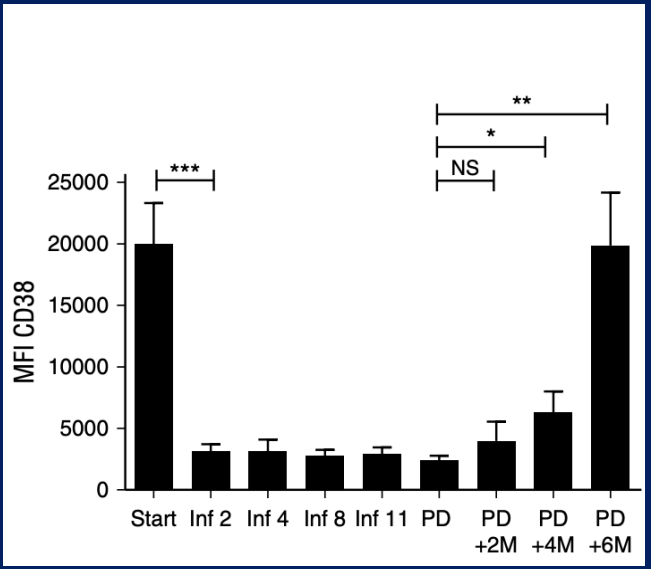
CD38 expression and complement inhibitors affect response and resistance to daratumumab therapy in myeloma

Inger S. Nijhof,[1,2] Tineke Casneuf,[3] Jeroen van Velzen,[4] Berris van Kessel,[1] Amy E. Axel,[5] Khaja Syed,[5] Richard W. J. Groen,[1] Mark van Duin,[6] Pieter Sonneveld,[6] Monique C. Minnema,[2] Sonja Zweegman,[1] Christopher Chiu,[5] Andries C. Bloem,[4] Tuna Mutis,[1] Henk M. Lokhorst,[1,2] A. Kate Sasser,[5] and Niels W. C. J. van de Donk[1]

CD38 expression on MM patients treated with daratumumab
N=21



CD38 expression on circulating MM cells
N=11



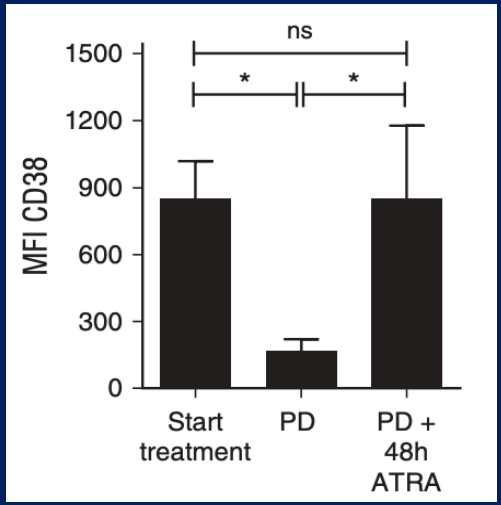
Nijhof I, et al. Blood. 2016 Aug 18;128(7):959-70

Increase expression of CD38 and anti-CD38 Mab activity with ATRA

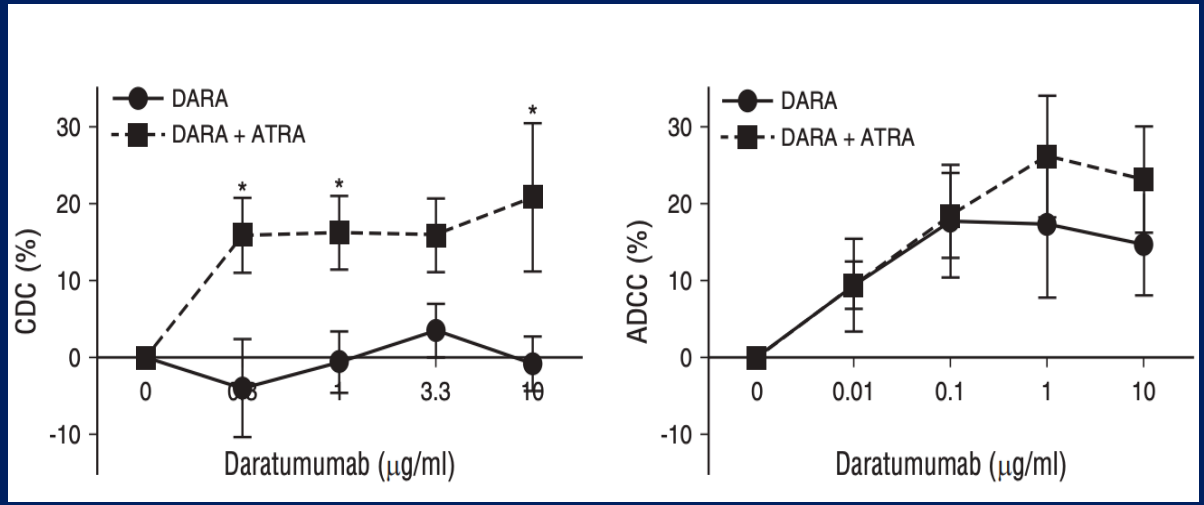
CD38 expression and complement inhibitors affect response and resistance to daratumumab therapy in myeloma

Inger S. Nijhof,[1,2] Tineke Casneuf,[3] Jeroen van Velzen,[4] Berris van Kessel,[1] Amy E. Axel,[5] Khaja Syed,[5] Richard W. J. Groen,[1] Mark van Duin,[6] Pieter Sonneveld,[6] Monique C. Minnema,[2] Sonja Zweegman,[1] Christopher Chiu,[5] Andries C. Bloem,[4] Tuna Mutis,[1] Henk M. Lokhorst,[1,2] A. Kate Sasser,[5] and Niels W. C. J. van de Donk[1]

CD38 expression on MM patients refractory to daratumumab exposed to ATRA
N=15



CDC and ADCC in MM patients refractory to daratumumab exposed to ATRA
N=15

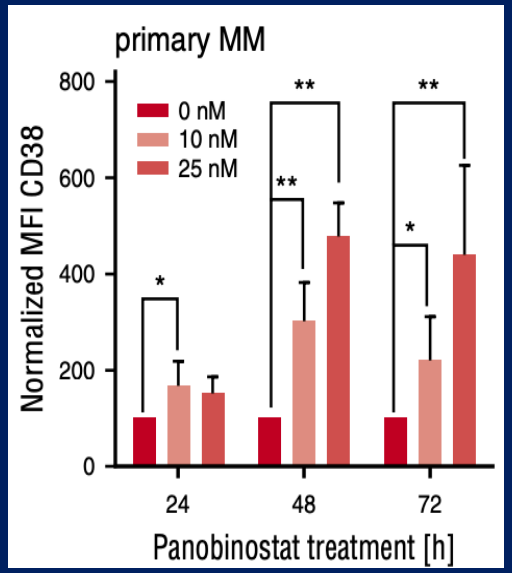


Nijhof I, et al. Blood. 2016 Aug 18;128(7):959-70

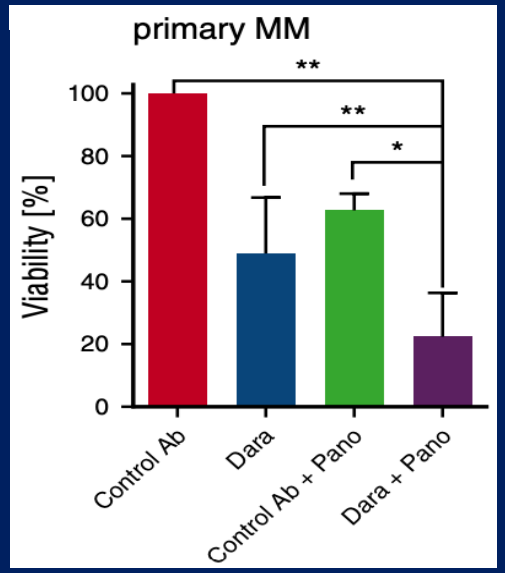
Panobinostat induces CD38 upregulation and augments the antimyeloma efficacy of daratumumab

Estefanía García-Guerrero,[1,2] Tea Gogishvili,[1] Sophia Danhof,[1] Martin Schreder,[1] Celine Pallaud,[3] Jose Antonio Pérez-Simón,[2] Hermann Einsele,[1] and Michael Hudecek[1]

CD38 expression on MM patients exposed or not to panobinostat
N=12



ADCC against primary myeloma cells with and without panobinostat treatment
N=54



Garcia-Guerrero E, et al. Blood. 2017 Jun 22;129(25):3386-3388

DNA methyltransferase inhibitors upregulate CD38 expression and enhance daratumumab efficacy in multiple myeloma

Authors:
Priya Choudhry[1], Margarette Mariano[2], Huimin Geng[1], Arun Wiita[1]

MM cell lines (RPMI-8226, MM.1S, XG-1, KMS12-PE) treated with two different DNMTis (5- Azacytidine and decitabine) assessed for CD38 cell surface expression by flow cytometry.

5-Azacytidine and Decitabine treatment induced a **1.2-2 fold increase** in CD38 surface expression in a dose-dependent manner across MM cell lines

Choudhry P, et al. Leukemia. 2019 Oct 8. doi: 10.1038/s41375-019-0587-5 [Epub]

Practical considerations and role of Daratumumab retreatment for relapsed refractory Multiple Myeloma

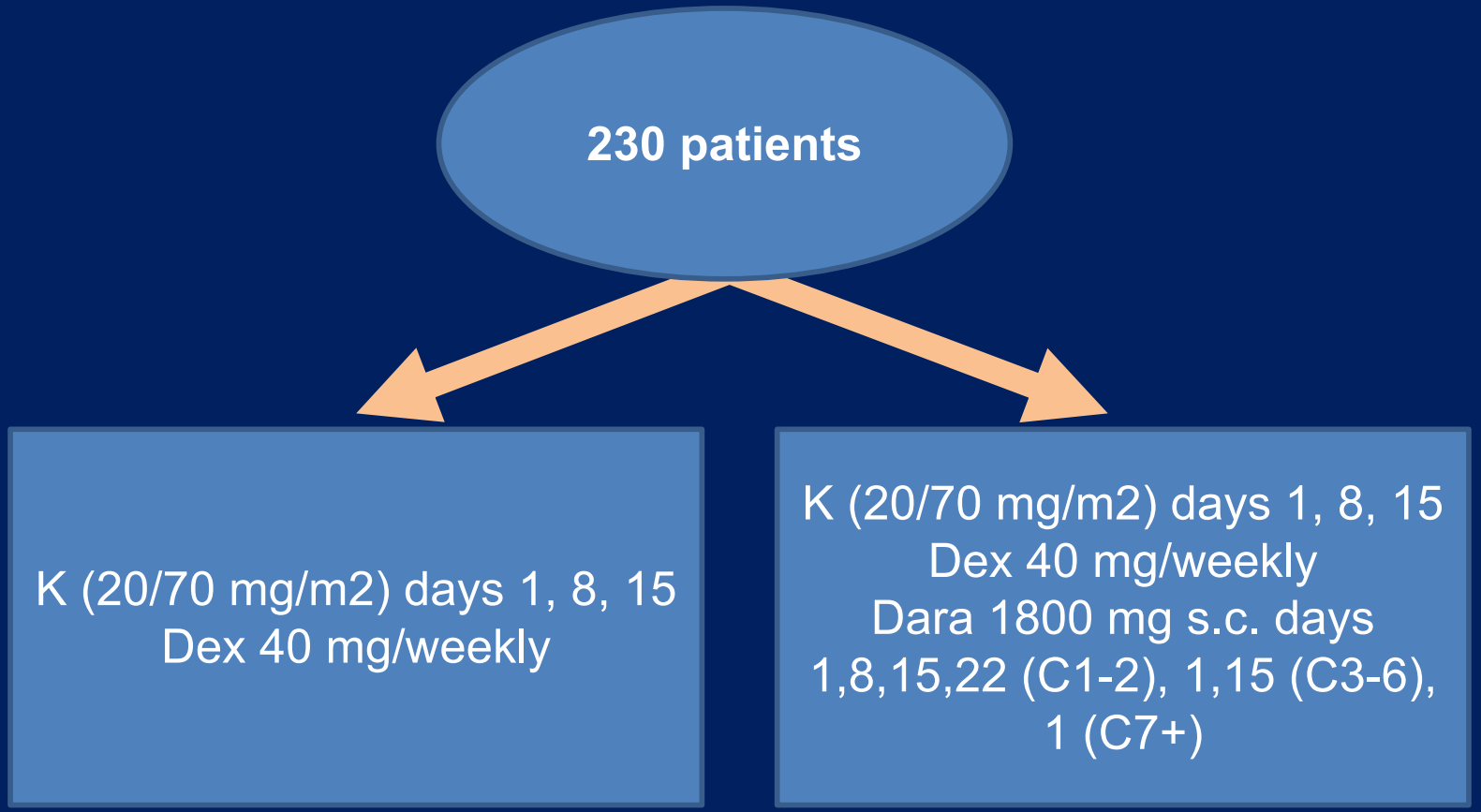
- 125 MM patients analyzed → 19 had a daratumumab therapy break longer than 8 weeks (8-133 weeks) → 8 due to PD
- 8 patients who progressed on a daratumumab-based regimen and had subsequent different therapies (n° 1-7 lines) received re-treatment with daratumumab
- Prior daratumumab response 3/8 → re-treatment daratumumab response 1/8

MM: multiple myeloma; PD: progressive disease; DARA: daratumumab

Kim E.B., et al. Clin Lymp Myeloma & Leukemia - IMW 2019. SP 109

Daratumumab Retreatment in Participants With Multiple Myeloma Who Have Been Previously Treated With Daratumumab Intravenous (Dara-IV)

Phase II, randomized study in RRMM pts who had 1 or 2 prior line(s) of treatment including a line containing Daratumumab-IV

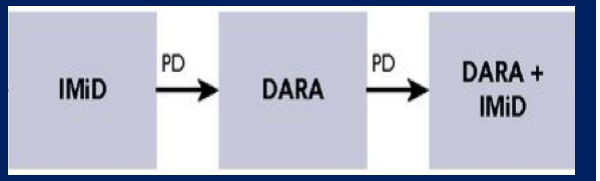


RRMM: relapsed/refractory multiple myeloma; K: carfilzomib; Dex: dexamethasone; Dara: daratumumab

https://clinicaltrials.gov/ NCT03871829

The addition of IMiDs for patients with daratumumab-refractory multiple myeloma can overcome refractoriness to both agents

RRMM patients



	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Sex	Male	Female	Female	Male	Male	Male
Age, y	58	79	51	60	58	66
MM subtype	IgGκ	IgGκ	IgGκ	λLC/BJ	IgGκ	κ LC
Prior ASCT	Yes	No	Yes	Yes	Yes	Yes
ISS prior to addition of IMiD to Dara	1	2	2	3	1	3
Time from diagnosis, y	11	8	8	6	9	4.5
Lines of prior therapies	13	8	4	4	3	4
Time from last exposure to IMiD to Dara/IMiD (mo)	13.2	16.3	20.7	15.8	37.1	13.9
Pomalidomide refractory	Yes, at 4 mg with weekly dexamethasone 40 mg	Yes, at 4 mg with weekly dexamethasone 20 mg and cyclophosphamide 50	Yes, at 4 mg with weekly dexamethasone 40 mg	No	No	Yes, at 4 mg with weekly dexamethasone 20 mg
Lenalidomide refractory	Yes, at 25 mg with weekly dexamethasone 40 mg	Yes, at 25 mg with weekly dexamethasone 40 mg	Yes, at 25 mg with weekly dexamethasone 40 mg	Yes, at 25 mg with weekly dexamethasone 40 mg	Yes, at 25 mg with weekly dexamethasone 40 mg	Yes, at 25 mg with weekly dexamethasone 40 mg
Best response to prior and current therapies						
Dara monotherapy duration, (mo)	11	17	6	6	10	8
Dara-IMiD-DEX	PD	MR	MR	VGPR	PR	VGPR
Dara + IMiD PFS, mo	2	3, ongoing	3, ongoing	4.5, ongoing	8, ongoing	8

ORR in IMID + daratumumab refractory pts: 67%

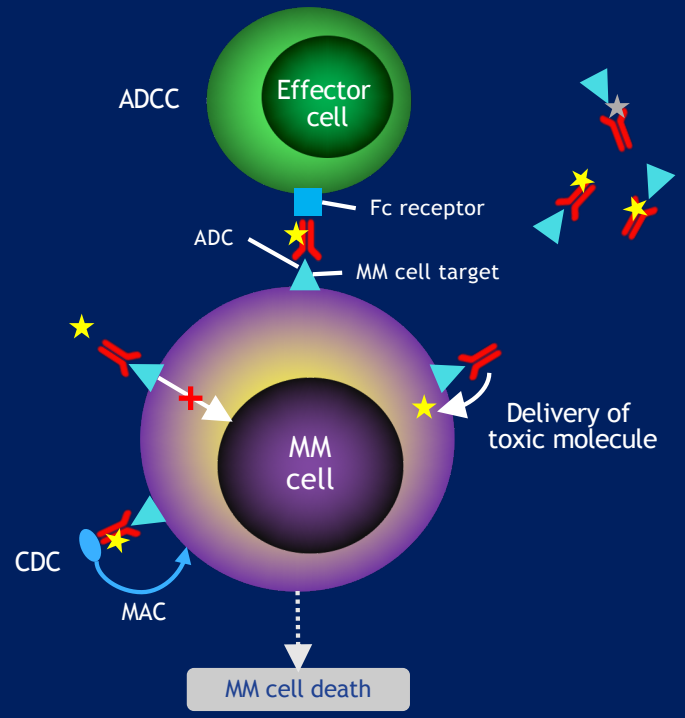
Gavriatopoulou M et al Blood 2018 131:464-467

RRMM: relapsed/refractory multiple myeloma; IMID: immunomodulatory drug; DARA: daratumumab; PD: progressive disease; ASCT: autologous stem cell transplantation; BJ: Bence Jones; BTZ: bortezomib; PFS: progression-free survival; SD: stable disease; VGPR: very good partial response; ORR: overall response rate.

Novel immunotherapies in MM

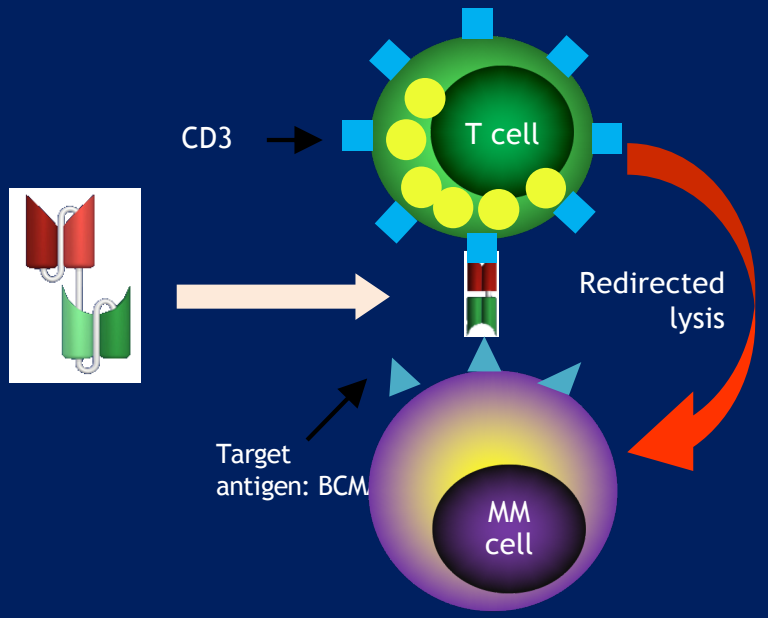
Antibody-drug conjugates[1]

MM cell-targeted mAbs conjugated with cytotoxic molecules or radioactive particles



Bispecific antibodies (BiTEs)[2]

Potential to overcome the limitations of immunosuppressive tumor microenvironment by redirecting T cells to kill tumor target cells

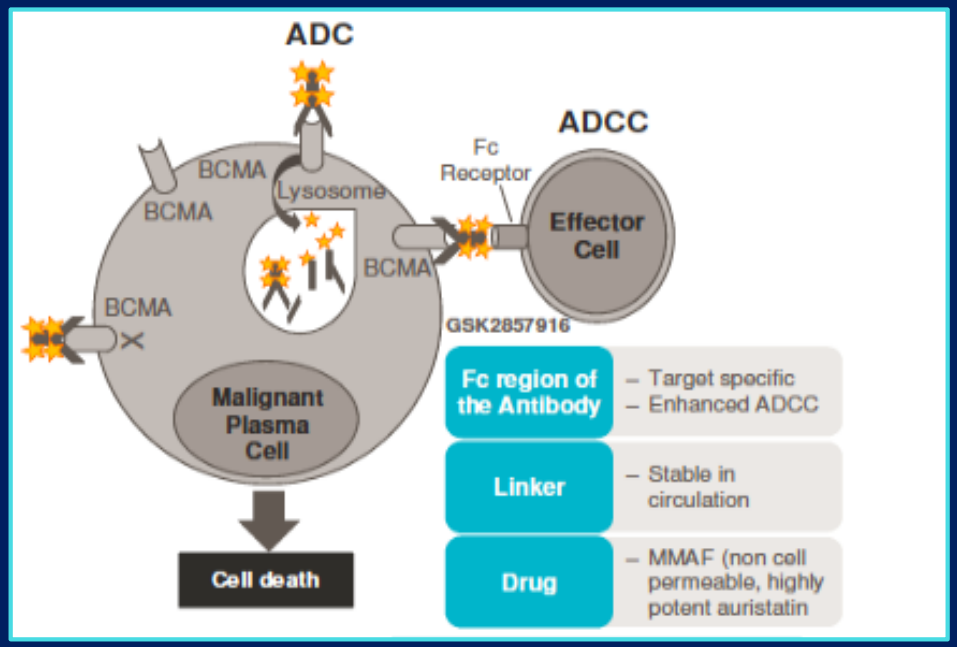


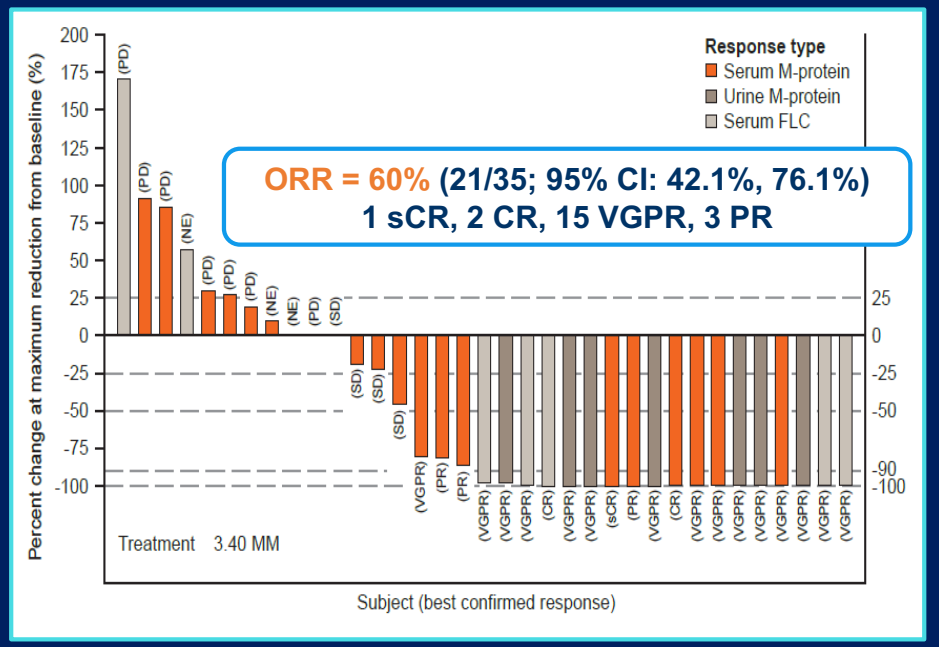
ADC, antibody-drug conjugate; ADCC, antibody dependent cell mediated cytotoxicity; BCMA, B-cell maturation antigen; BiTE, bispecific T-cell engager; CDC, complement-dependent cytotoxicity; mAb, monoclonal antibody;
MAC, membrane attack complex; MM, multiple myeloma; RRMM, relapsed/refractory multiple myeloma.

1. van de Donk NW, et al. Leukemia 2012;26:199–213;
2. Nagorsen D, et al. Leuk Lymph 2009;50:886–91.

BCMA antibody drug conjugated in MM DREAMM-1

- Humanized IgG1 anti-BCMA Ab conjugated to monomethyl auristatine-F
- BCMA is restricted to B cells at later stages of differentiation, broadly expressed on malignant PC
- DREAMM-1 Part 2: 90% double refractory to PI/IMiDs and 13% Dara-refractory





PFS: 7.9 (3.1-); DOR: NR

MM, multiple myeloma; BCMA, B Cell Maturation Antigen; DOR, duration of response; ORR, overall response rate; NR, not reported; PFS, progression-free survival; Dara, daratumumab; PC, plasma cells; PI, proteasome inhibitor; IMiD, immunomodulatory drug, CR, complete response; sCR, stringent CR; PR, partial response; VGPR, very good PR.

ORR

- In Daratumumab exposed (n=14): 42.9%
- in IMiD+PI refractory + Dara exposed (n=13): 38.5%

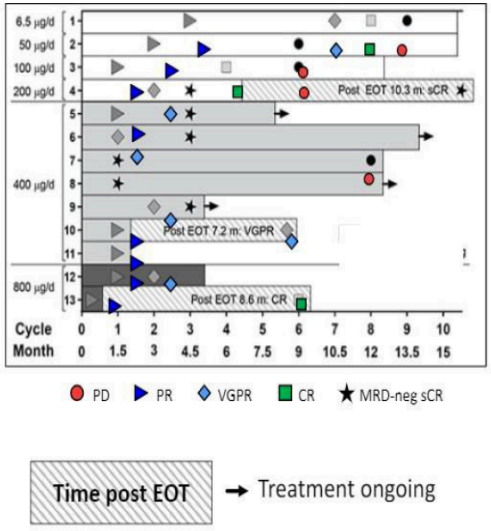
Trudel S et al. Lancet Oncol 2018; 19(12):1641-1653.

AMG420, an anti-BCMA BiTE in RRMM patients: results of a dose escalation FIH Phase 1 study

Efficacy

- Responses
  - *Overall*: 6 sCRs, 3 CRs, 2 VGPRs, 2 PRs
  - **At 400 µg/d: 70% response rate**
    - **5 MRD-negative sCRs, 1 VGPR, and 1 PR**
- Median time to any response: 1 month, with 9 of 13 patients responding in the first cycle
- Duration of response: 5.6-10.4 months
- 4 patients ongoing on treatment
- **As of July 2019, several responses lasted > 1 year**

Patients with RRMM responding to AMG 420



Efficacy

# Prior lines[1]	Baseline Bone Marrow PC%[2]	Dose µg/d × # cycles	Months of treatment	Best response
4 incl SCT×2	10	6.5 × 10	13.7	C8: CR
3 incl SCT×2	2	50 × 10	13.6	C3-C10: PR
3 incl SCT	2	100 × 7	9	C4-C5: CR
6 incl Dara	6	200 × 4	5.2	C3: MRD^{neg} sCR
3 incl SCTx2	3	400 × 4	4.6†	C3: MRD^{neg} sCR
4 incl SCT×2	25	400 × 7	10.2†	C3: MRD^{neg} sCR
6 incl SCT×2	60	400 × 7	9.0†	C1: MRD^{neg} sCR
2 incl SCT×2	80	400 × 6	8.8†	C1: MRD^{neg} sCR
4 incl SCT, Dara	80	400 × 1	1.0	End C1: PR
5 incl SCT×3	28	800 x 2, then 400 x 1	3.3	C2, C3: VGPR
5 incl SCTx2, Dara	0.2	800 × 1	0.5	C1: PR

4/10 patients were MRD-negative* at MTD

***MRD threshold used was 10^{-4} cells.**

RRMM, relapsed/refractory multiple myeloma; pts, patients; PLs, prior lines of therapy; IMiDs, immunomodulatory drugs; PI, proteasome inhibitors; Dara, daratumumab; Elo, elotuzumab; MTD, maximum tolerated dose; DLT, dose-limiting toxicity; CRS, cytokine release syndrome; FIH, first in human; PN, peripheral neuropathy; CR, complete response; MRD, minimal residual disease; PR, partial response; VGPR, very good PR.

Topp M., et al ASH 2018, abstract 101;
Einsele H., et al. IMW 2019, abstract OAB 029.

CONCLUSIONS

- Anti-CD38 mAbs will be the backbone of first-line regimens

- The role of retreatment with anti-CD38 still has to be elucidated
  - Biologically possible? Clinically unknown
  - Sequential use of different anti-CD38??? Dara→Dara; Dara-Isa

- Several other target antigens and compounds under development
  - ADC GSK
  - BiTEs

  } Effective in daratumumab exposed/refractory patients

Induction	Consolidation/maintenance	Relapse
Anti-CD38 mAb-based regimen	ADC/BiTEs: post induction/ASCT	ADC/BiTEs/CAR-T cells

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