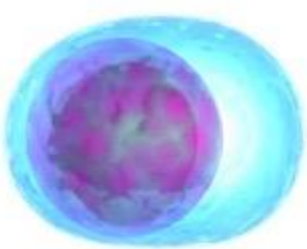
# Treatment of relapsed and refractory multiple myeloma

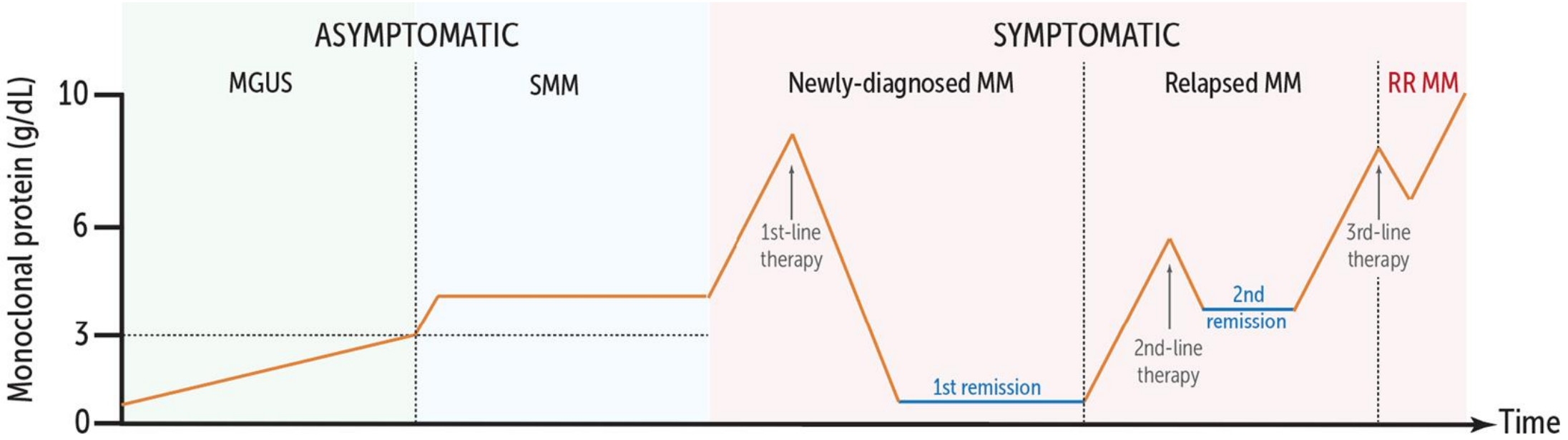
Nicolas Kint, MD PhD
University Hospital Ghent

BHS Educational Course
Saturday, 22nd April 2023



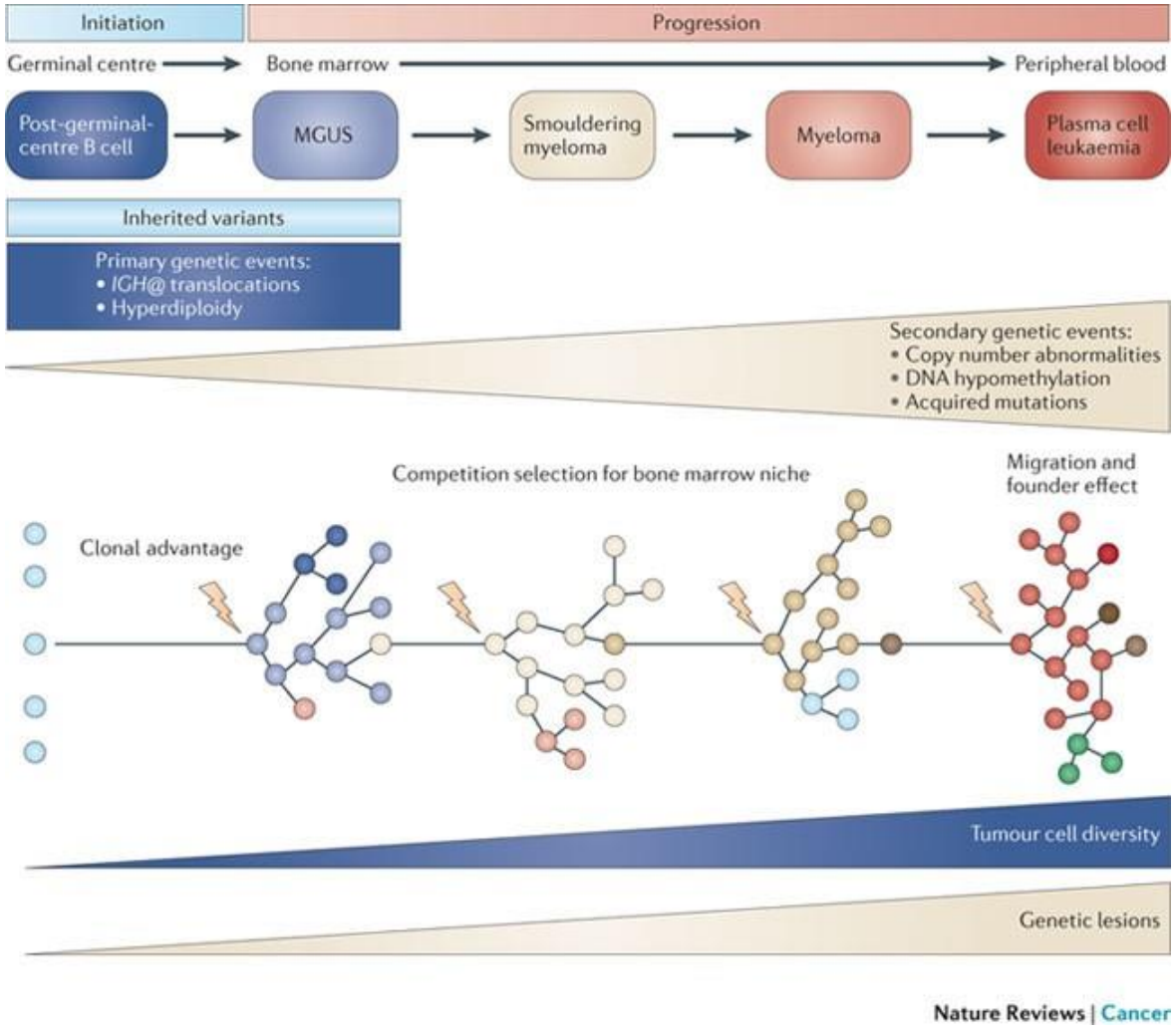
# Herakles and the Lernean Hydra

# The natural course of multiple myeloma




Ho M, Leukemia 2020

# The genetic architecture of MM



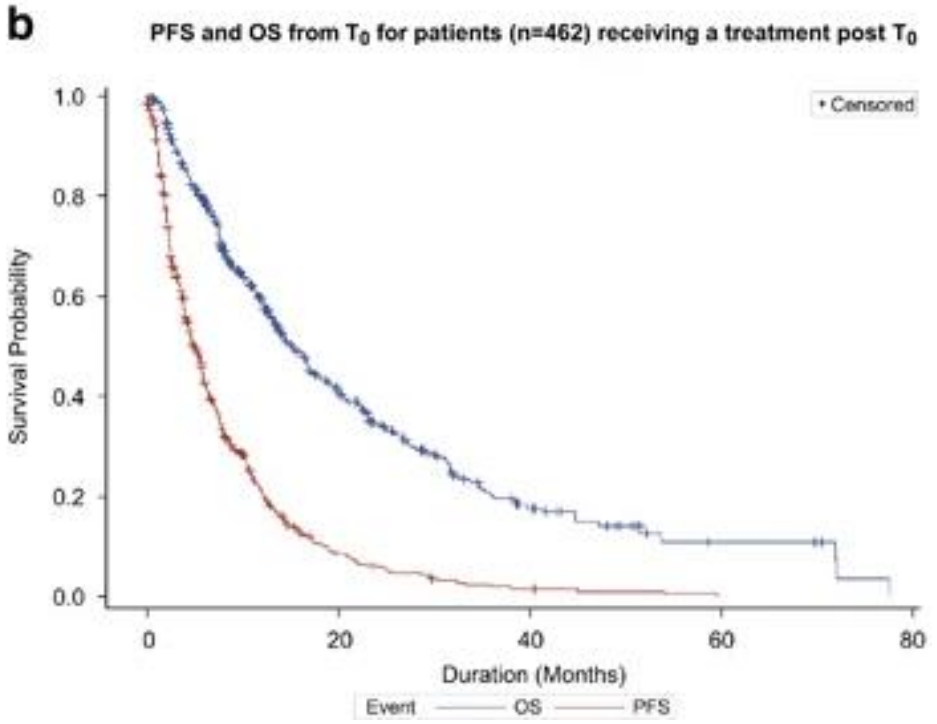

Morgan G et al. Nat Rev Cancer 2013

# Outcome of relapsed and refractory MM

Patients were:

- Refractory to a PI and an IMiD
- Exposed to alkylator agent

Median PFS: 5,0 mo
Median OS: 13,0 mo



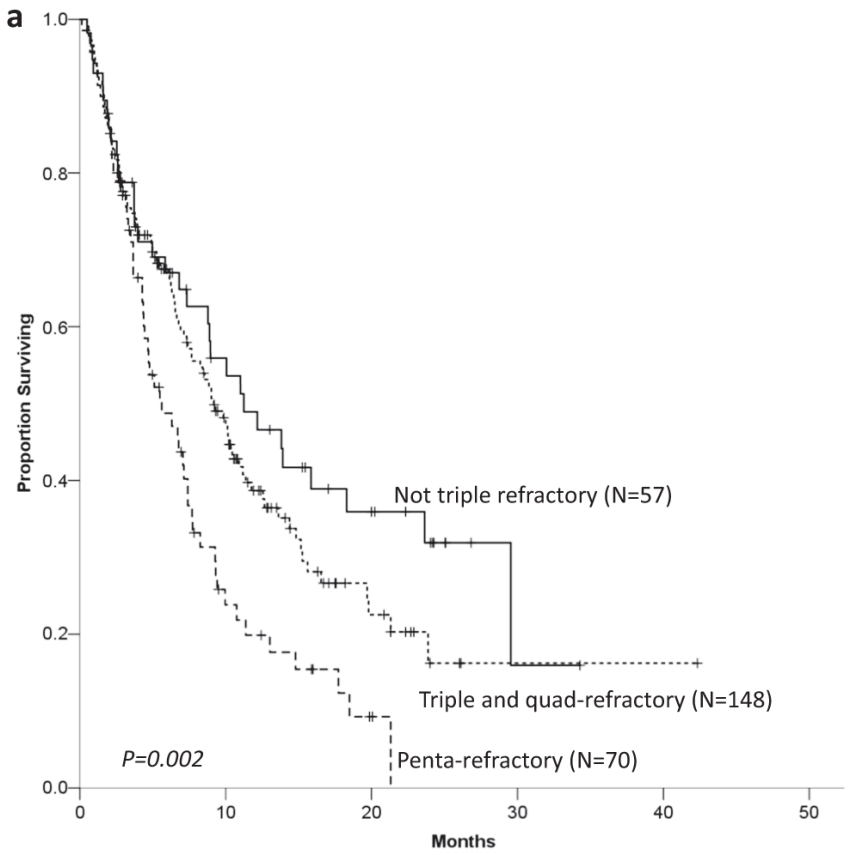

Kumar S, et al. Leukemia 2017

# Outcome of relapsed and refractory MM

N = 255

Median OS: 8,6 mo

Median OS in pentarefractory patients: 5,6 mo



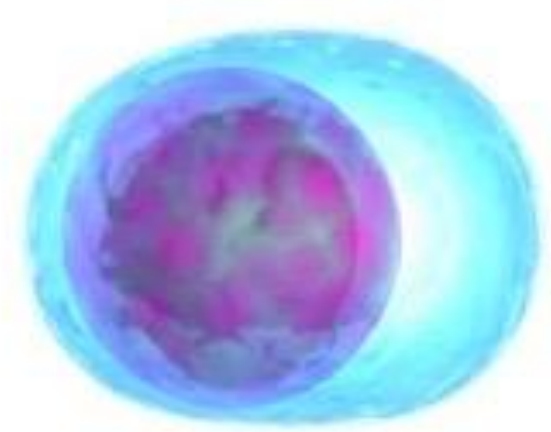

Gandhi et al. Leukemia 2019;33:2266

# Learning goals

1. Identification of a patient with relapsed and refractory MM
2. Knowledge of possible treatment options
3. Knowledge of the principles of treatment sequencing in R/R MM

# Course overview

1. Definitions
2. Conventional treatment classes and small molecule inhibitors
3. Antibody-drug conjugates
4. Immune therapy (bispecific antibodies and CAR T-cell therapy)
5. Conclusions



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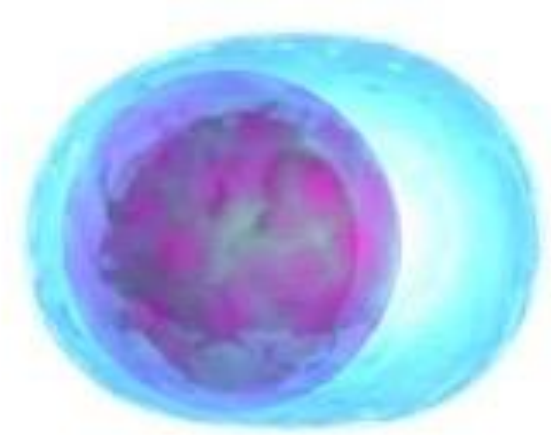
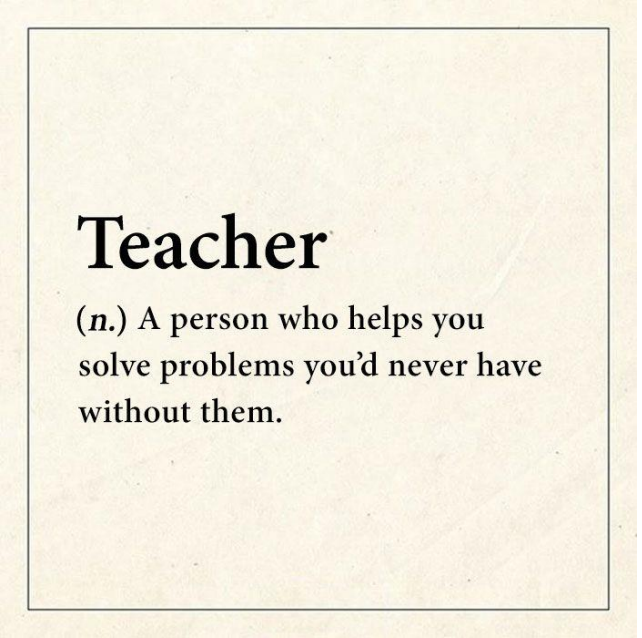


# Definition of relapse

Progressive disease is not (necessarily) synonymous with disease relapse

Several definitions are in order:

- Disease progression
- Clinical relapse
- Refractory disease
- (Progression from CR/MRD)



# IMS definition of disease progression

**Increase of > 25% from lowest response value** in any one or more of the following:

- Serum M-component and/or (the absolute increase must be > 0.5 g/dL)
- Urine M-component and/or (the absolute increase must be > 200 mg/24 h)
- Only in patients without measurable serum and urine M-protein levels; the difference between involved and uninvolved FLC levels. The absolute increase must be > 10 mg/dL
- Bone marrow plasma cell percentage; the absolute percentage must be > 10%
- Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas
- Development of hypercalcemia (corrected serum calcium > 11.5 mg/dL or 2.65 mmol/L) that can be attributed solely to the plasma cell proliferative disorder

Kumar S, Lancet Oncol 2016

# IMS definition of clinical relapse

Clinical relapse requires **one or more of direct indicators of increasing disease and/or end organ dysfunction (CRAB features)**. It is not used in calculation of time to progression or progression-free survival but is listed here as something that can be reported optionally or for use in clinical practice

- Development of new soft tissue plasmacytomas or bone lesions
- Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and at least 1 cm) increase as measured serially by the sum of the products of the cross-diameters of the measurable lesion
- Hypercalcemia (> 11.5 mg/dL) [2.65 mmol/L]
- Decrease in hemoglobin of > 2 g/dL [1.25 mmol/L]
- Rise in serum creatinine by 2 mg/dL or more [177 mmol/L or more]

Kumar S, Lancet Oncol 2016

# IMS definition of refractory disease

**Refractory disease**: disease that has become non-responsive or progressive on therapy or within 60 days of the last treatment in patients who had received an MR or better on prior therapy

**Primary refractory disease**: refractory disease in patients who have never achieved an MR with any therapy. These include patients who never achieve an MR or better, for whom there is no significant change in the M protein concentration and no evidence of clinical progression

Dimopoulos M, ESMO guidelines, Ann Oncol 2021

# Timing of treatment initiation

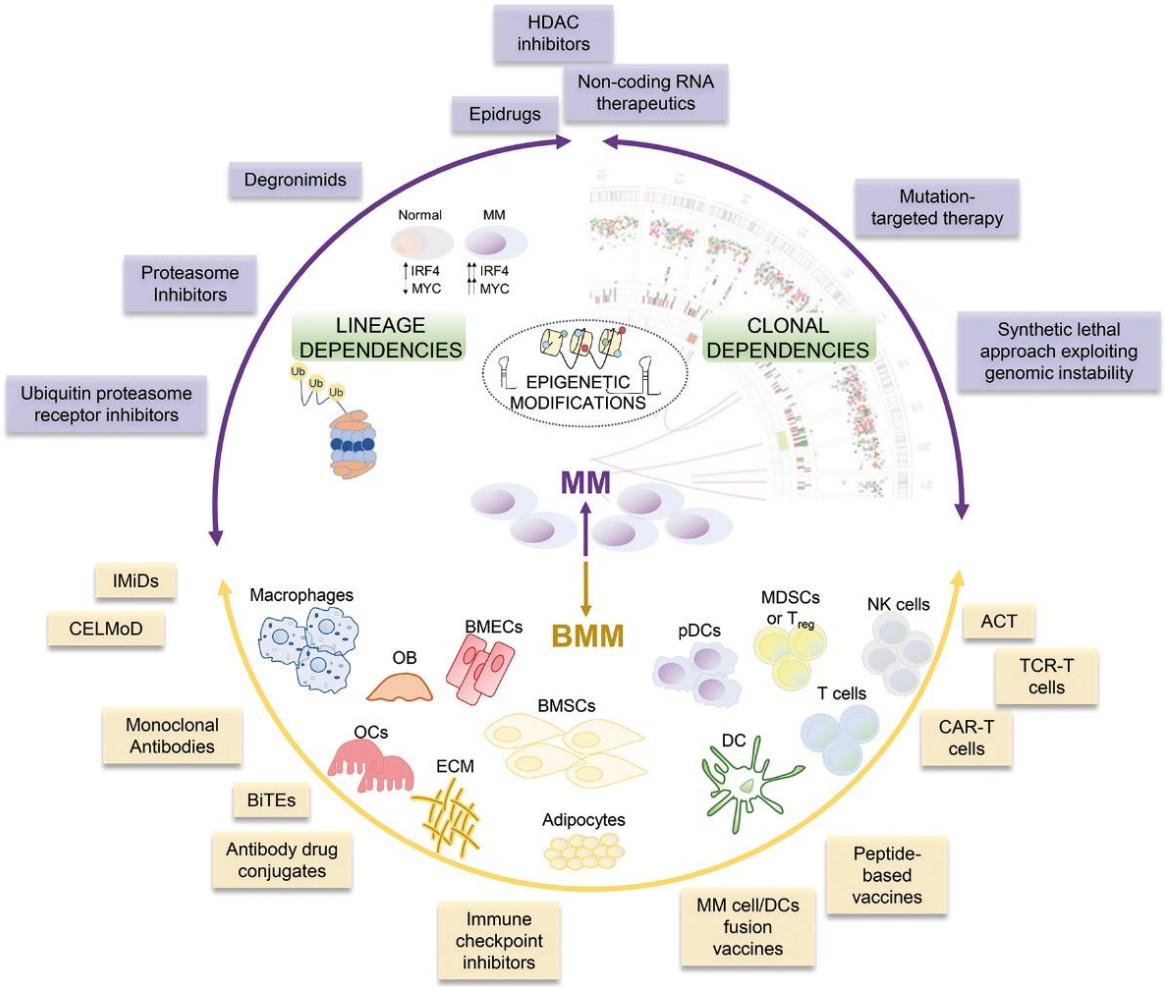
Biochemical progression does not always require immediate switch of treatment strategy (eg slowly progressive disease).

Exceptions (not exhaustive):

- Initial highly symptomatic presentation (eg severe renal insufficiency)
- Rapid biochemical progression, light chain disease
- Development of new bone lesions
- High-risk disease

# What type of treatment to choose?

# A large scope of treatment modalities for MM




Gulla A, Haematologica 2020

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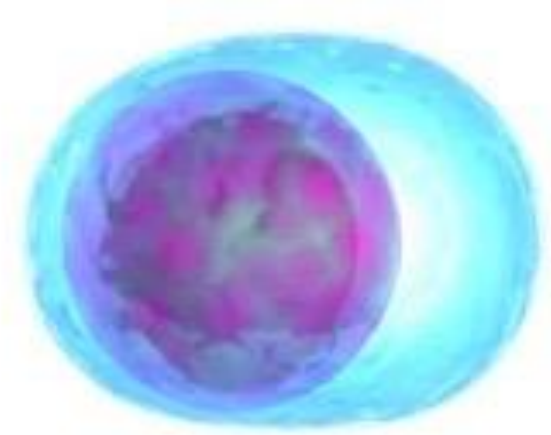
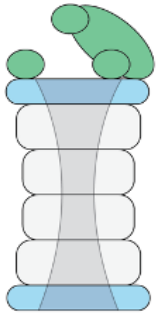
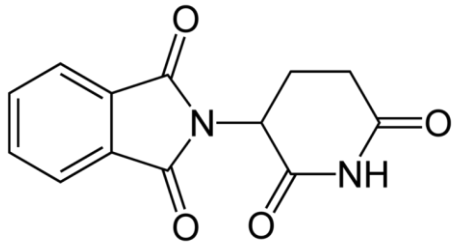


# Conventional classes of treatment

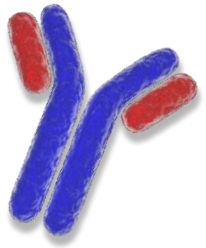
Proteasome inhibitors:
- Bortezomib
- Carfilzomib
- Ixazomib






Immunomodulatory Drugs (IMiDs):
- Thalidomide
- Lenalidomide
- Pomalidomide

Monoclonal antibodies:
- Daratumumab
- Isatuximab
- Elotuzumab



Chemotherapy
- Alkylators
- DCEP/DT-PACE/ VTD-PACE

# Definition of class-refractory disease

**Triple or quad refractory:** refractory to 1 CD38 mAb + 1 PI + 1 or 2 IMiDs, or 1 CD38 MoAB + 1 or 2 PIs + 1 IMiD

**Penta refractory:** refractory to 1 CD38 MoAB + 2 PIs + 2 IMiDs

**‘Triple class refractory’**: refractory to at least one PI, one IMiD and one anti-CD38 mAb

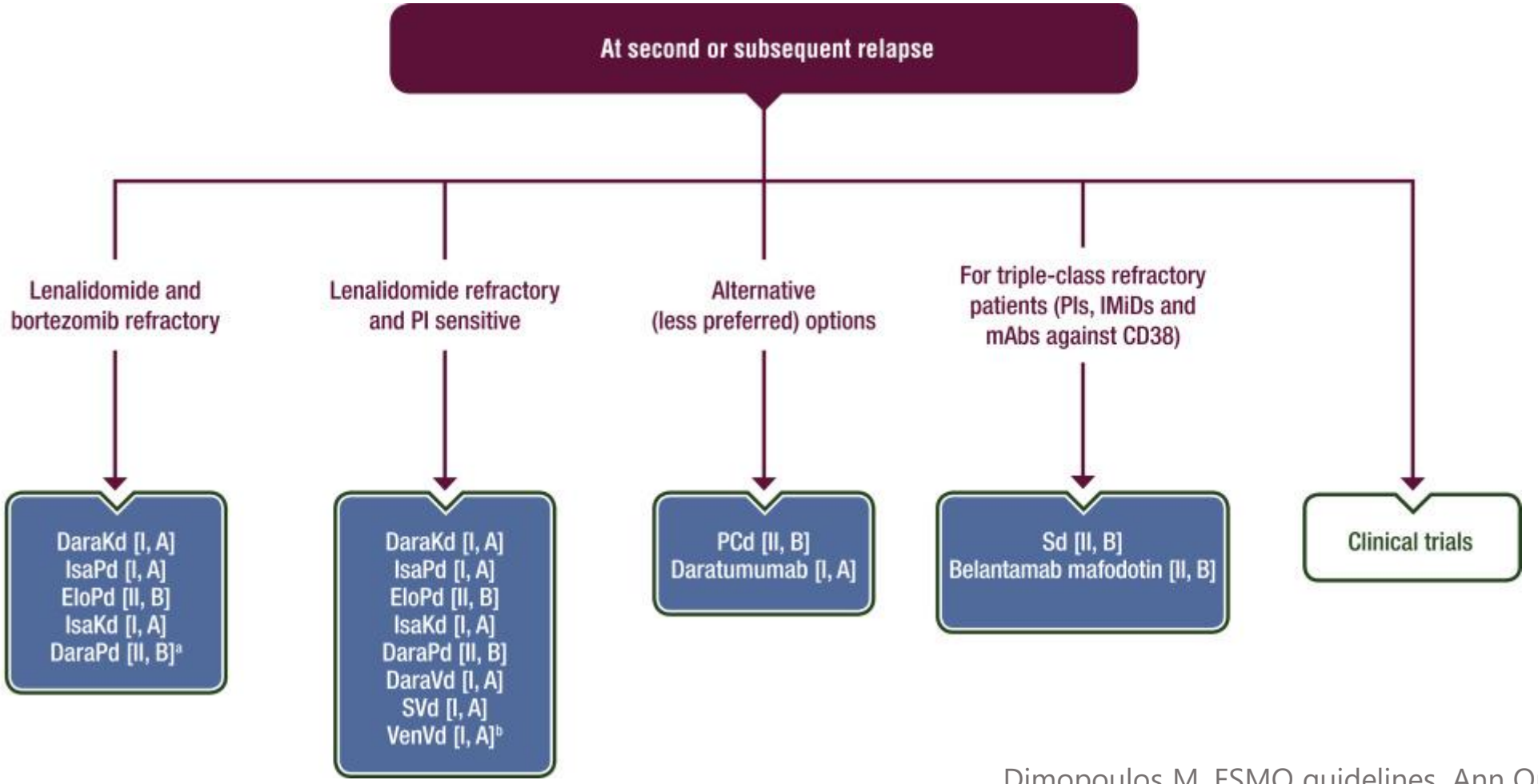
# Treatment sequencing: a game of chess?

Many (, many, many) different options

At relapse, next line of treatment is determined by:

- Prior treatments: type and response
- Patient status and comorbidities
  - Fitness?
  - Comorbidities?
  - Hematopoietic reserve?
- Disease characteristics
  - Rapid relapse?
  - Extramedullary disease?
- Reimbursement criteria

# Treatment at subsequent relapse




Dimopoulos M, ESMO guidelines, Ann Oncol 2021

# Combination treatment at (late) relapse

Several combinations (also, see course prof. M.C. Vekemans).

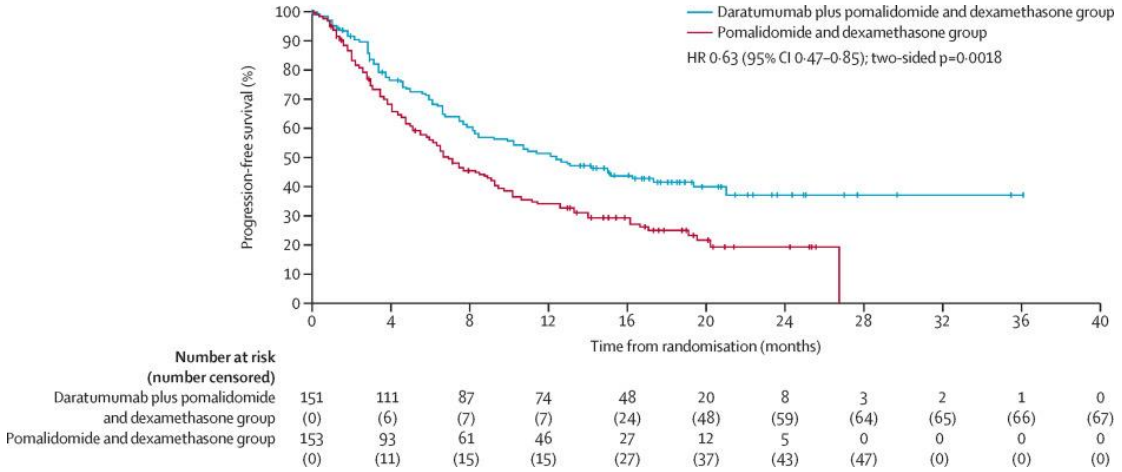
Examples:

- Daratumumab-carfilzomib-dexamethasone (Dara-Kd) (CANDOR)
- Isatuximab-carfilzomib-dexamethasone (Isa-Kd) (IKEMA)
- Daratumumab-pomalidomide-dexamethasone (Dara-Pd) (APOLLO)
- Isatuximab-pomalidomide-dexamethasone (Isa-Pd) (ICARIA)
- Elotuzumab-pomalidomide-dexamethasone (Elo-Pd) (ELOQUENT-2)

# Anti-CD38 mAb + pomalidomide/dexamethasone

**APOLLO trial**

Dara-pom-dex vs pom-dex



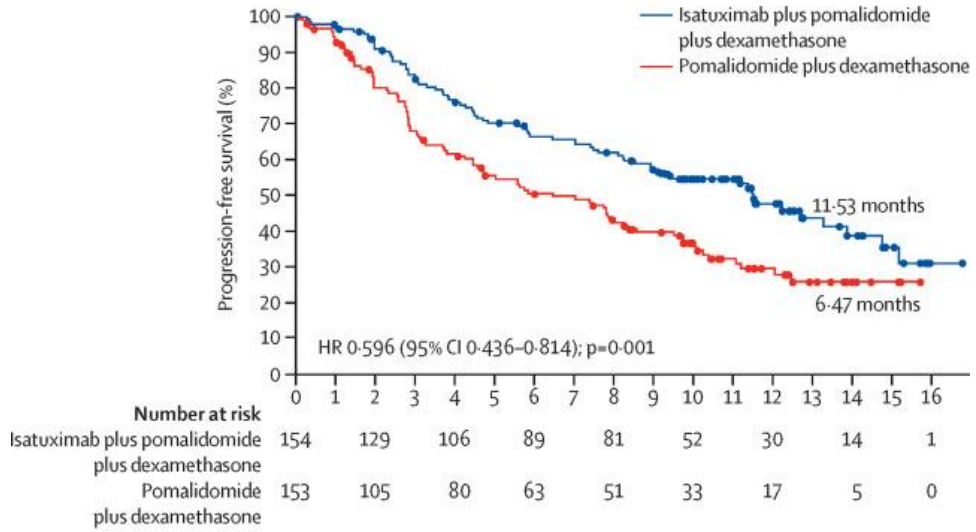

At least one prior line of treatment, including len and PI

Median PFS: 12,4 mo vs 6,9 mo (p = 0,0018)

Dimopoulos M et al, Lancet 2021

**ICARIA trial**

Isa-pom-dex vs pom-dex




At least two prior lines of treatment, including len and PI

Median PFS: 11,5 mo vs 6,5 mo (p = 0,001)

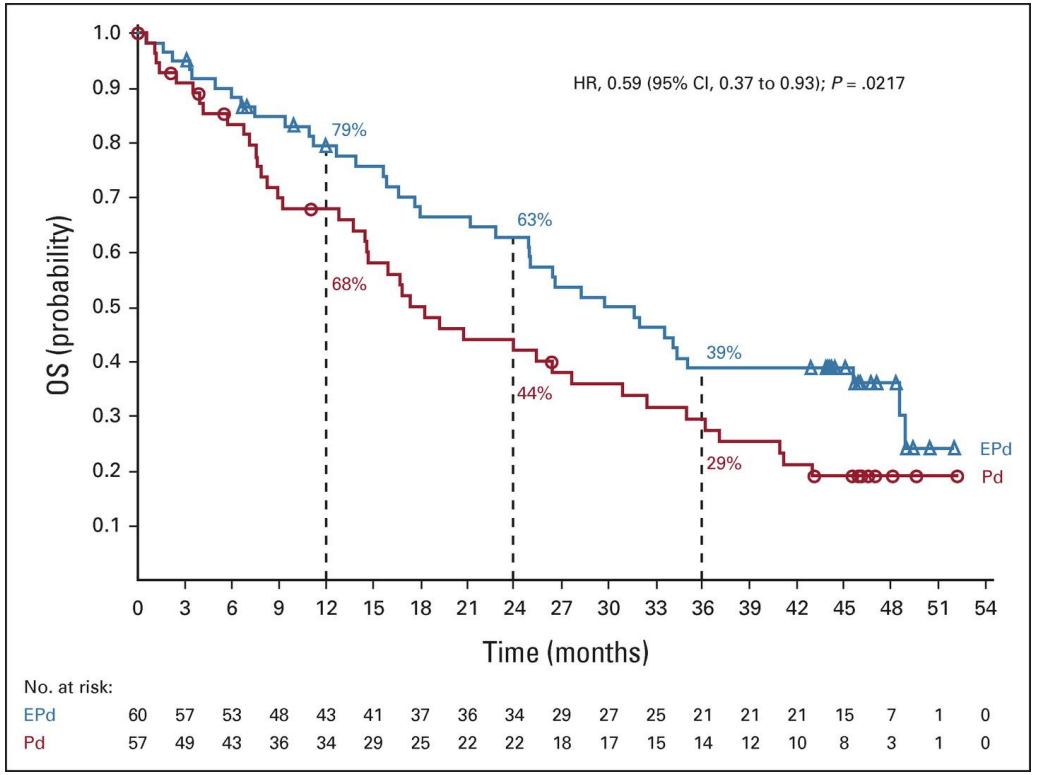
Richardson P et al, Lancet 2019

# Elotuzumab-pomalidomide-dexamethasone ELOQUENT-3 trial

Elotuzumab-pomalidomide-dexamethasone
vs Pomalidomide-dexamethasone

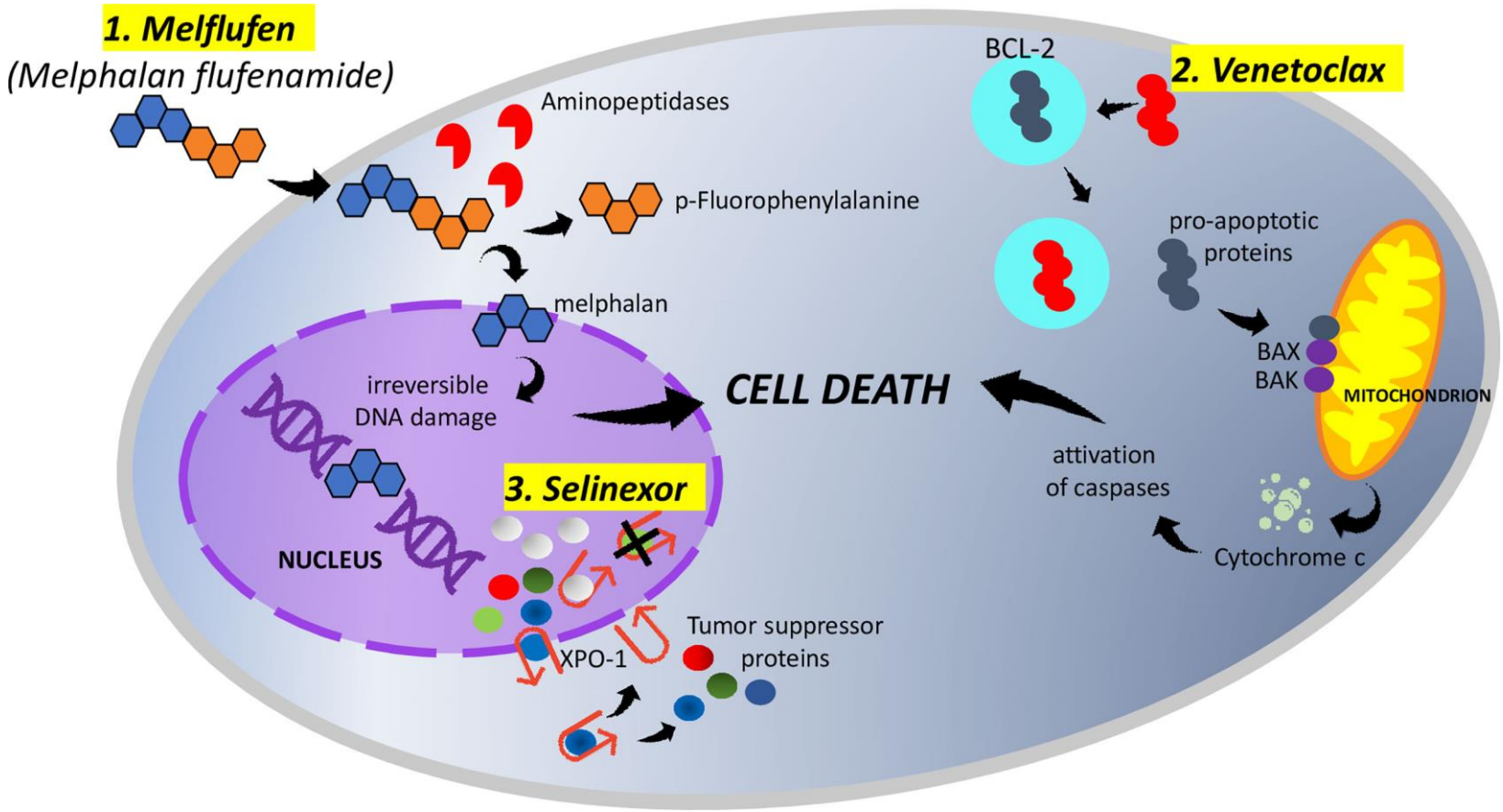
At least two prior lines of treatment,
refractory to PI and lenalidomide

Median OS: 29,8 mo vs 17,4 mo (p = 0,0217)



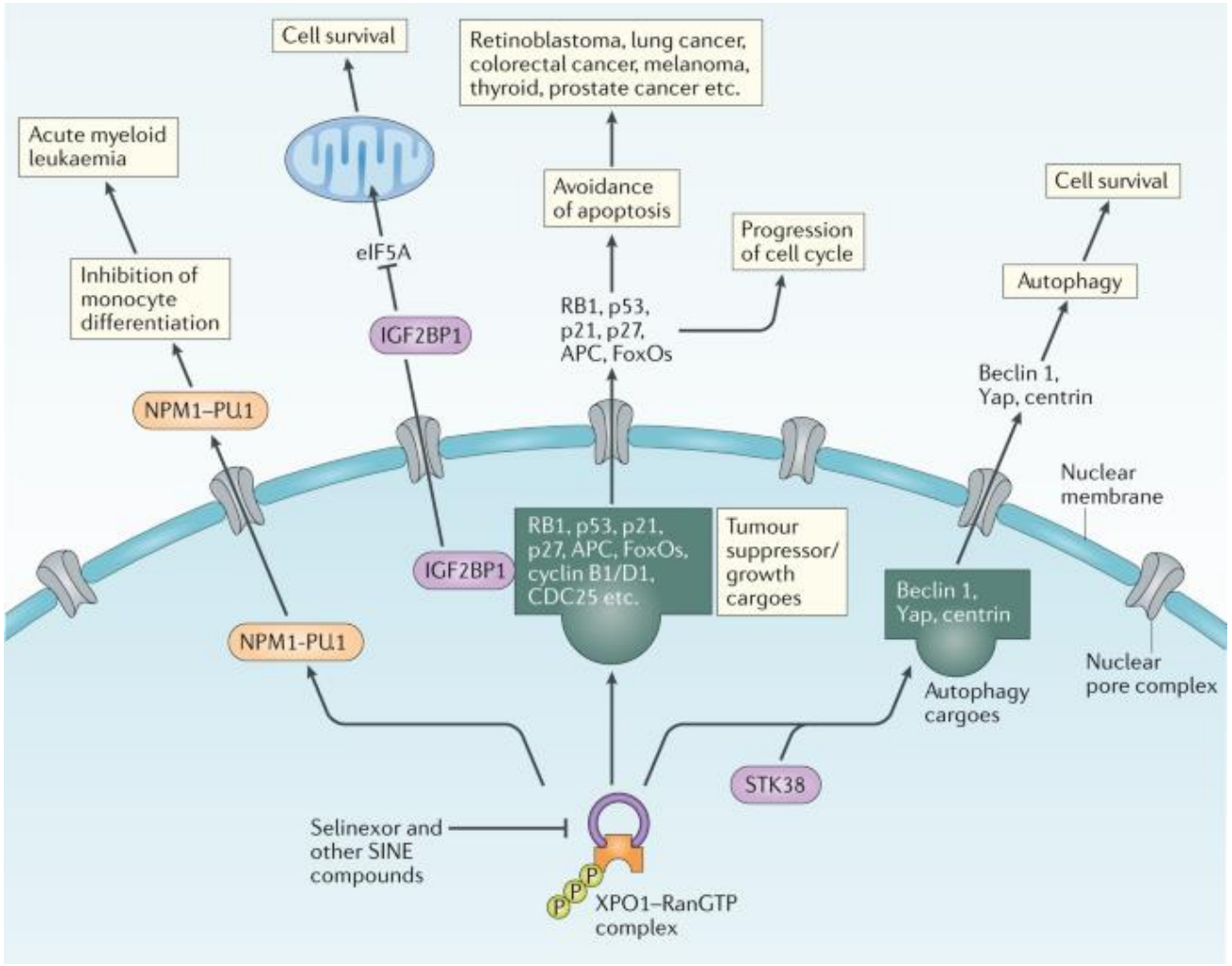

Dimopoulos M et al, JCO 2023

# Other small molecules




Sgherza N, Frontiers in Oncology 2021

# Selinexor



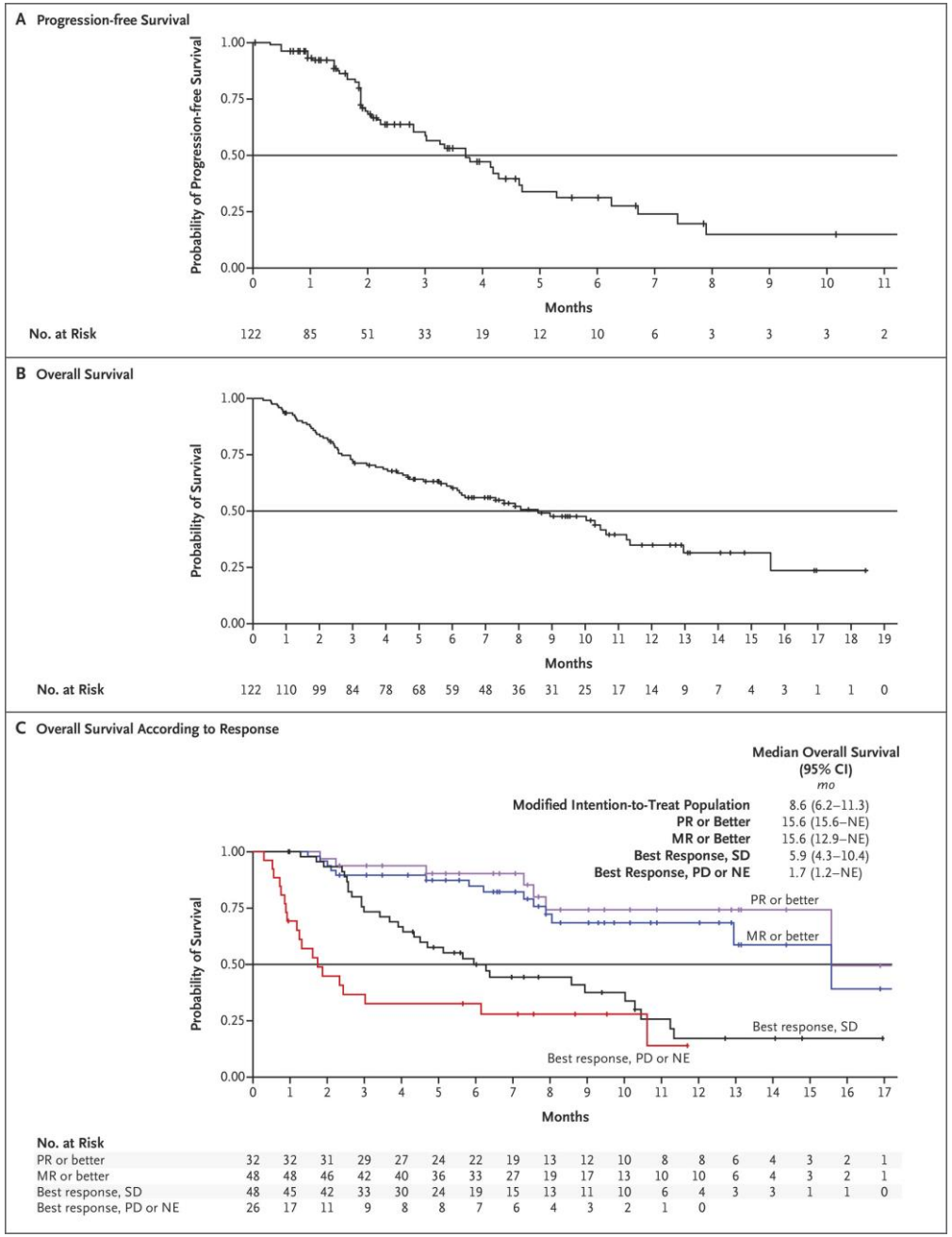

Asmi A, Nat Rev Clin Oncol 2020

# STORM trial

n = 122

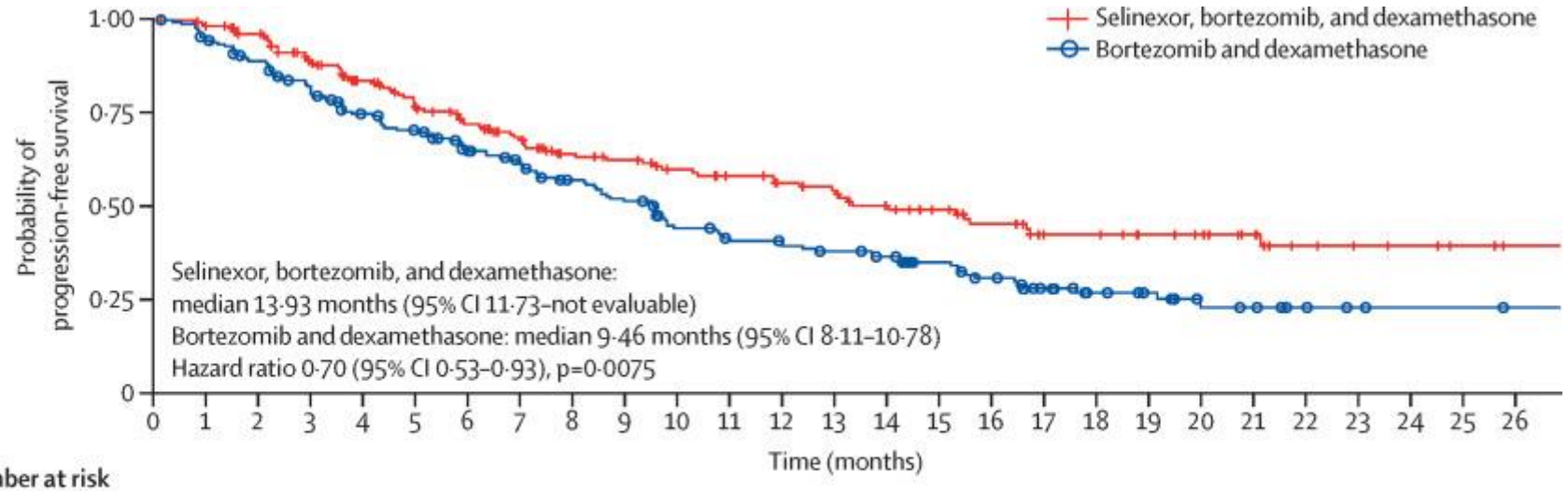
Triple class refractory (at least one proteasome inhibitor, one immunomodulatory agent, and daratumumab)

ORR: 39%
Median PFS: 3.7 mo
Median OS: 8.6 mo




Chari A, NEJM 2019

# SVd: BOSTON trial




| Number at risk (number censored) | | | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Selinexor, bortezomib, and dexamethasone | 195 (0) | 187 (5) | 175 (12) | 152 (21) | 135 (31) | 117 (37) | 106 (42) | 89 (50) | 79 (57) | 76 (59) | 69 (63) | 64 (66) | 57 (71) | 51 (73) | 45 (76) | 41 (80) | 35 (83) | 27 (89) | 26 (90) | 22 (94) | 19 (97) | 14 (102) | 9 (106) | 7 (108) | 6 (109) | 4 (111) | 2 (113) |
| Bortezomib and dexamethasone | 207 (0) | 187 (8) | 175 (10) | 152 (15) | 138 (20) | 127 (22) | 111 (29) | 100 (32) | 90 (37) | 81 (37) | 66 (41) | 59 (43) | 56 (44) | 53 (45) | 49 (47) | 42 (52) | 35 (55) | 26 (60) | 20 (65) | 16 (69) | 10 (73) | 8 (75) | 5 (78) | 4 (79) | 3 (80) | 3 (80) | 2 (81) |

Grosicki S et al, JCO 2020

# Other small molecule inhibitors

- CelMoDs: iberdomide, mezigdomide
- Venetoclax (BELLINI trial): in t(11;14) MM, but…
- Melflufen flufenamide
- Panobinostat-bortezomib-dexamethasone (PANORAMA trials)

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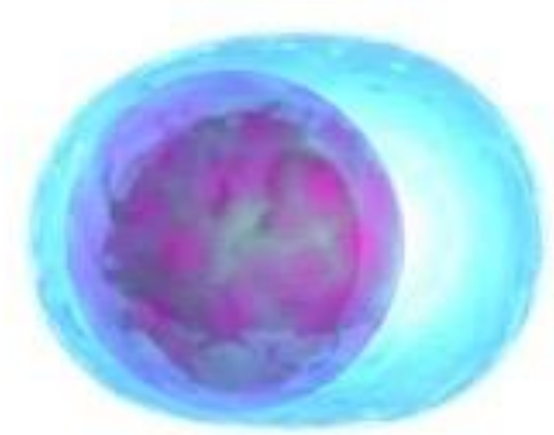
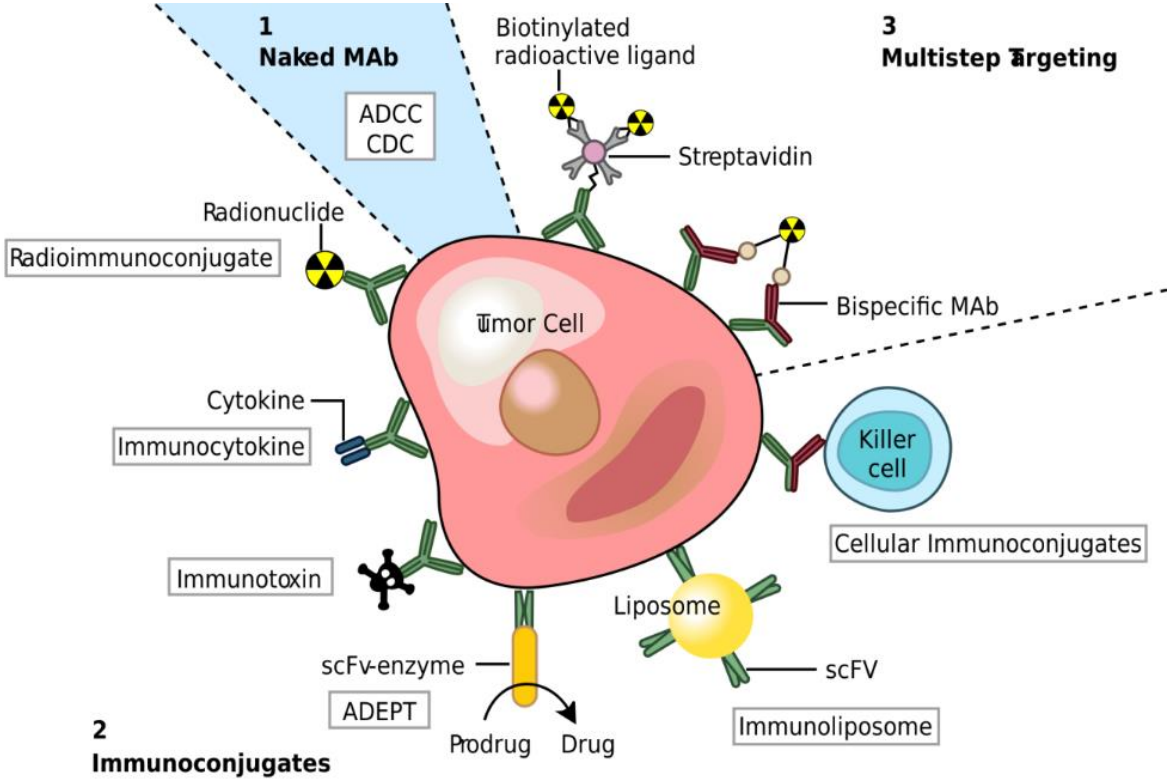
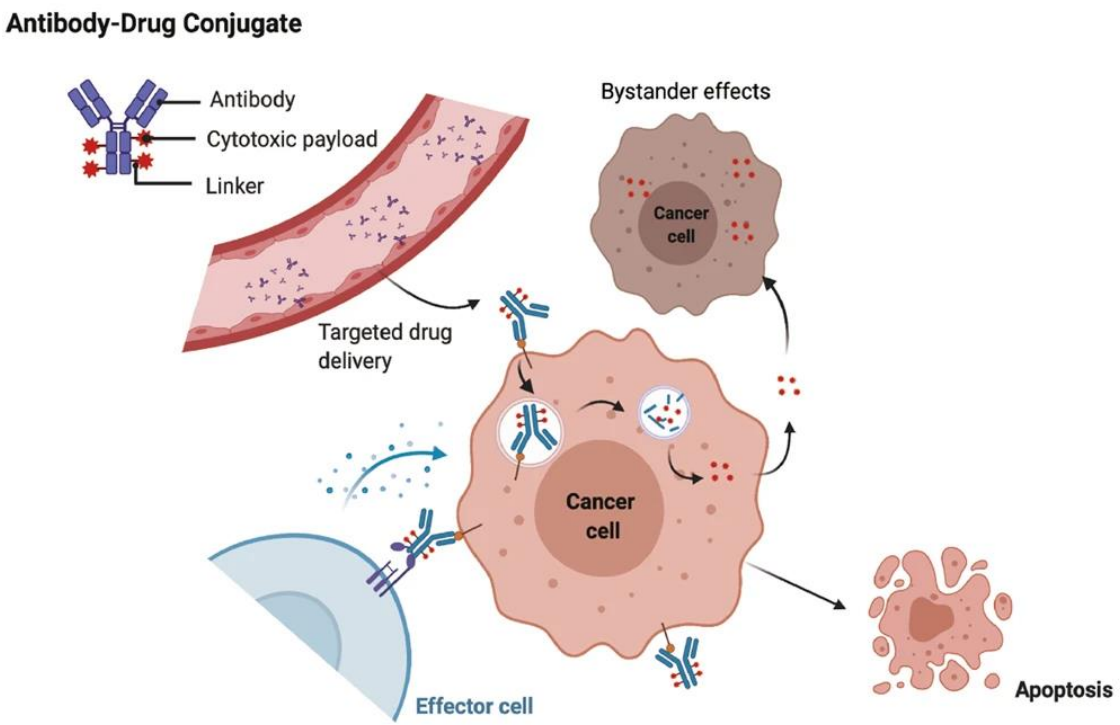


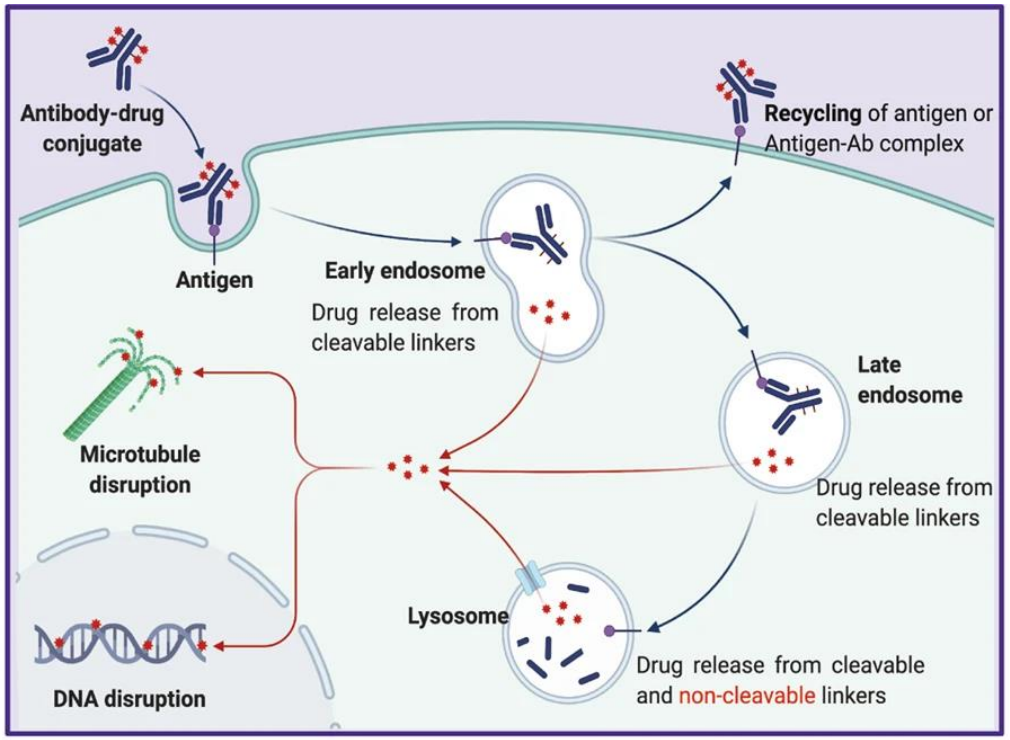
# Monoclonal antibodies: novel strategies




Carter P, Nature Reviews in Medicine 2001
Adapted by Nabi J, World Journal of Pharmaceutical Research 2020

# Antibody-drug conjugates
# Belantamab mafodotin (Belamaf)

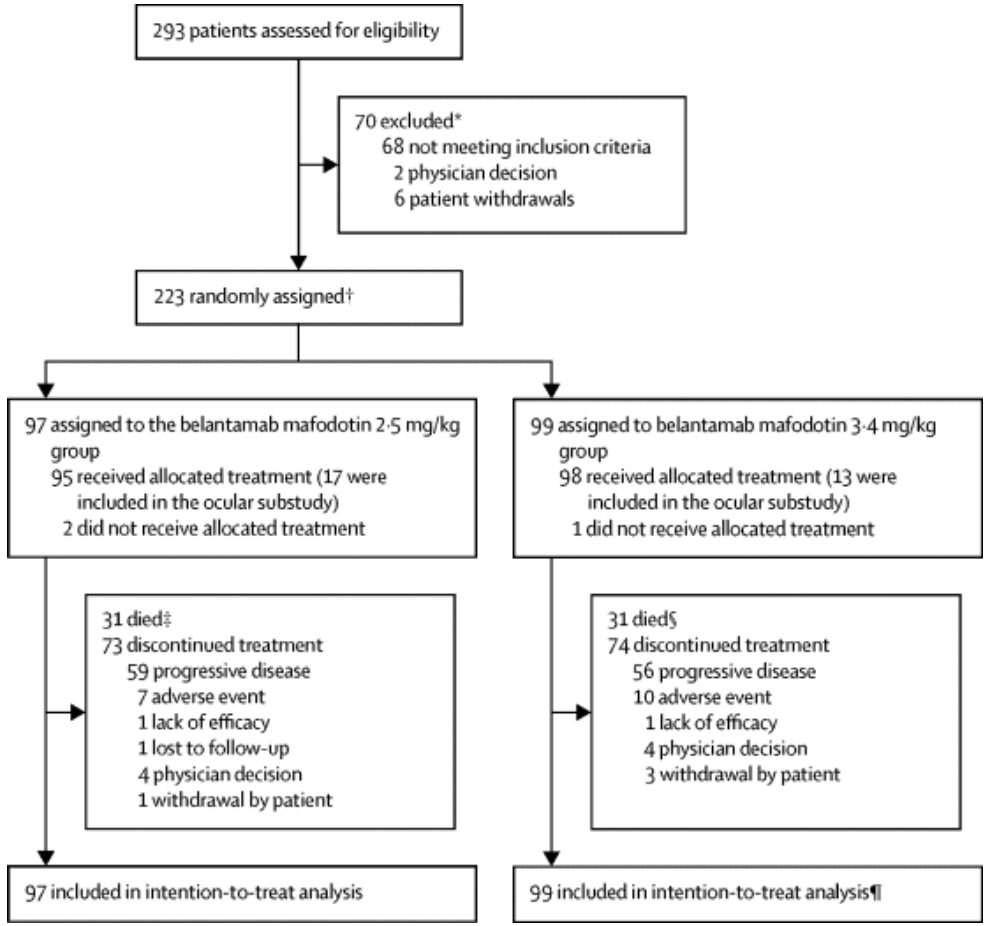



Belantamab mafodotin: anti-BCMA

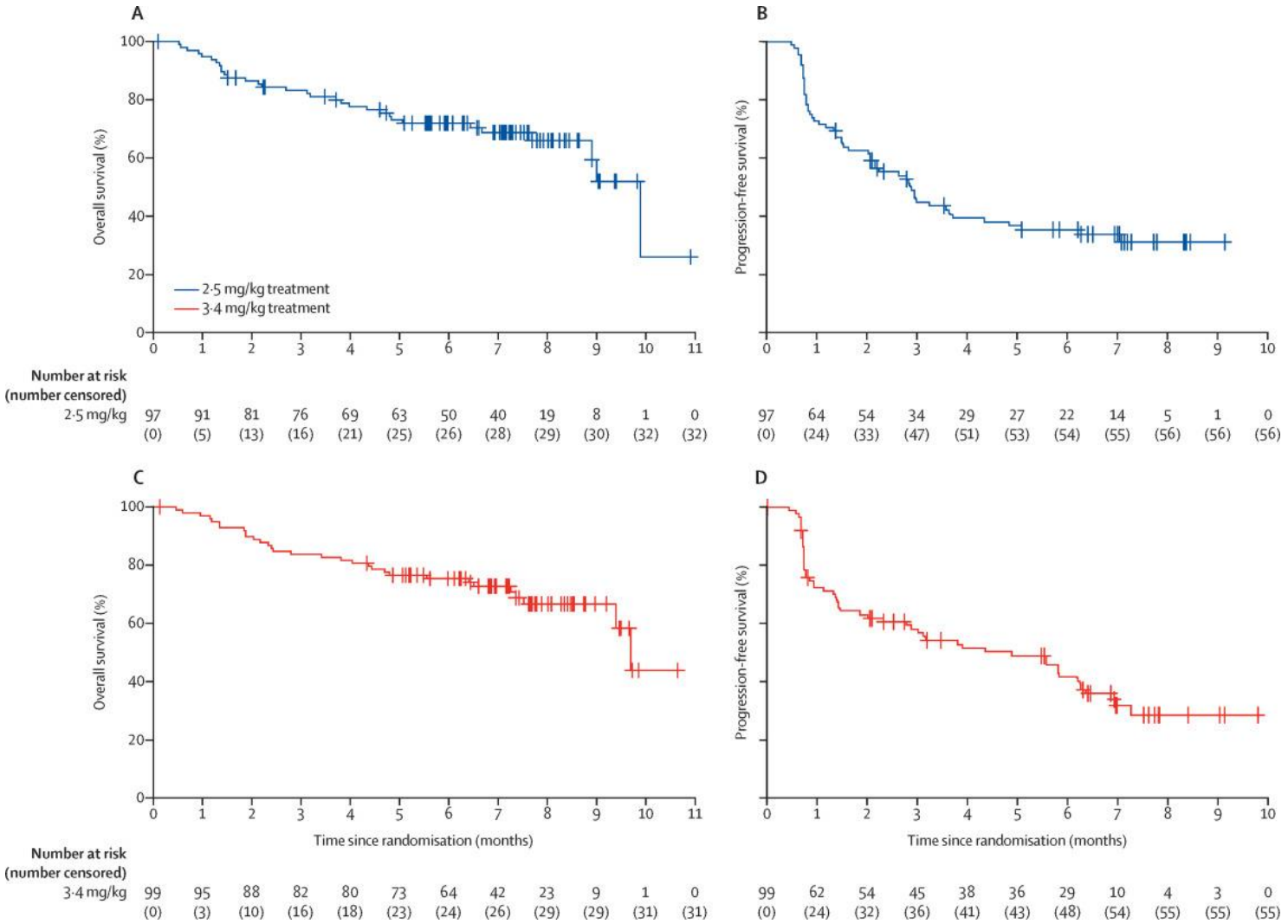
Fu Z et al. Signal Transduction and Targeted Therapy, 2022

# Belantamab mafodotin: DREAMM-2




Lonial S, Lancet Oncol 2019

# Belantamab-mafodotin




ORR: 32%
Median PFS: 2.8 mo

Side effects:
- Keratopathy
- Hematologic toxicity

Inferior responses in extramedullary disease

Lonial S, Lancet Oncol 2019

# Belantamab-mafodotin + pomalidomide/dexamethasone

Table 1: Safety and efficacy by dosing cohort and across all cohorts

| | All pts | 1.92 Q4W | 2.5 (SINGLE and SPLIT) Q4W | 2.5 Q8W | 2.5 Q12W | 3.4 SPLIT |
|---|---|---|---|---|---|---|
| Any ≥Gr 3 TEAE, n (%) | n=51 | n=6 | n=6 | n=23 | n=12 | n=4 |
| Keratopathy | 28 (54.9%) | 2 (33.3%) | 5 (83.3%) | 12 (52.2%) | 7 (58.3%) | 2 (50.0%) |
| Neutropenia | 19 (37.3%) | 3 (50.0%) | 2 (33.3%) | 8 (34.8%) | 5 (41.7%) | 1 (25.0%) |
| Thrombocytopenia | 14 (27.5%) | 3 (50.0%) | 1 (16.7%) | 7 (30.4%) | 2 (16.7%) | 1 (25.0%) |
| Decreased BCVA | 12 (23.5%) | 0 (0%) | 2 (33.3%) | 3 (13.0%) | 6 (50.0%) | 1 (25.0%) |
| | | | | | | |
| | n=50 | n=6 | n=6 | n=24 | n=11 | n=3 |
| ORR, n (%) | 43 (86.0%) | 5 (83.3%) | 6 (100%) | 20 (83.3%) | 10 (91.0%) | 2 (66.7%) |
| > VGPR | 30 (60.0%) | 3 (50.0%) | 4 (66.7%) | 15 (62.5%) | 6 (54.5%) | 2 (66.7%) |
| sCR/CR | 8 (16.0%) | 1 (16.7%) | 1 (16.7%) | 4 (16.7%) | 2 (18.2%) | 0 (0%) |
| | | | | | | |
| mPFS (95% CI), months | 15.6 (12.9-NYR) | 12.4 (6.2-NYR) | | 15.6 (13.6-NYR) | | |
| Follow-up, median, months | 5.7 (0.5-29.9) | 15.3 (1.8-29.9) | | 5.7 (0.5-16.6) | | |

Trudel S et al, Blood (2022) 140 (Supplement 1): 7306–7307.

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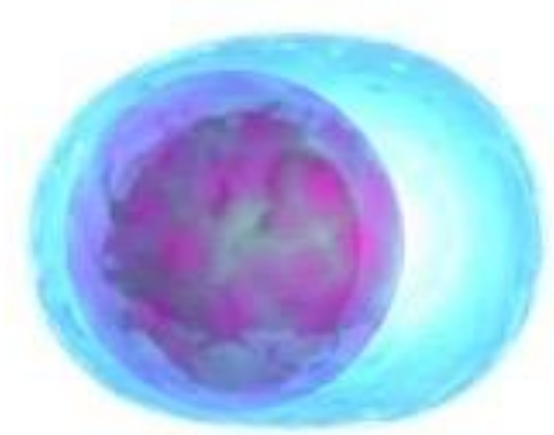
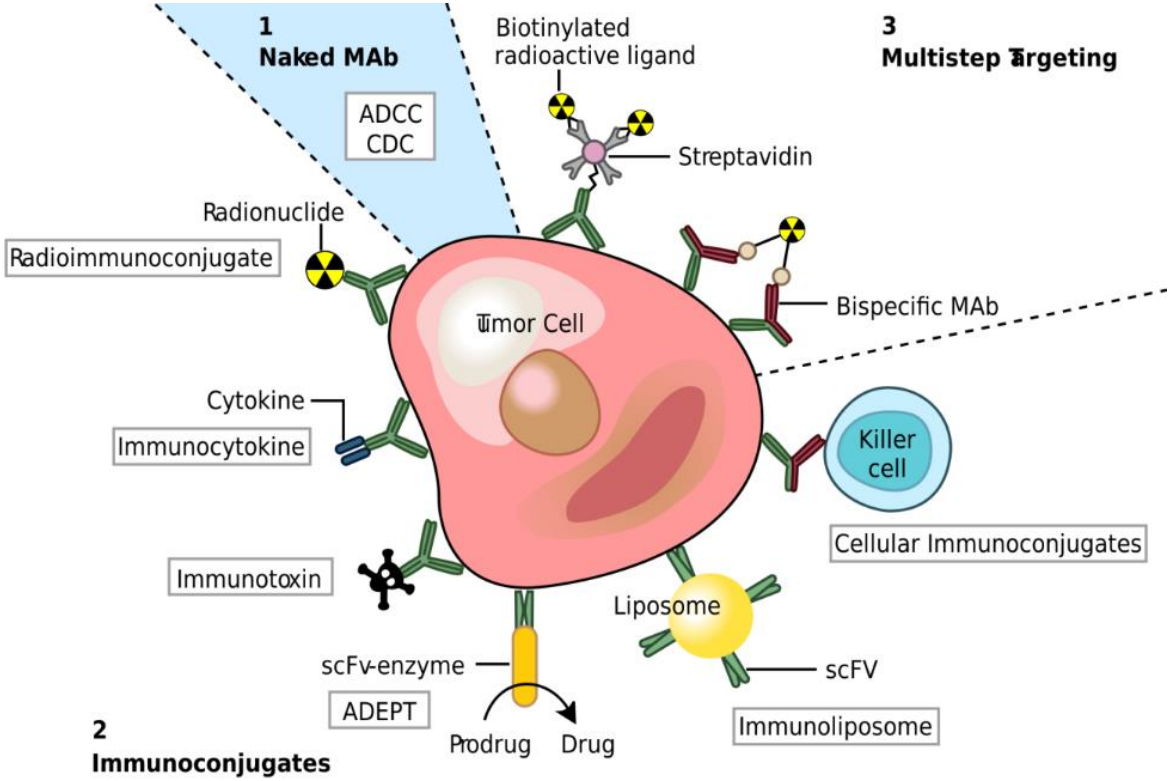


# Monoclonal antibodies: novel strategies




Carter P, Nature Reviews in Medicine 2001
Adapted by Nabi J, World Journal of Pharmaceutical Research 2020

# Monoclonal antibodies: bispecific Ab

Examples of bispecifics in myeloma:

Anti-BCMA x CD3:
- Teclistamab
- Elranatamab

Anti-GPRC5D x CD3:
- Talquetamab

And many others under investigation (eg anti-FcRH5 x CD3 – cevostamab)

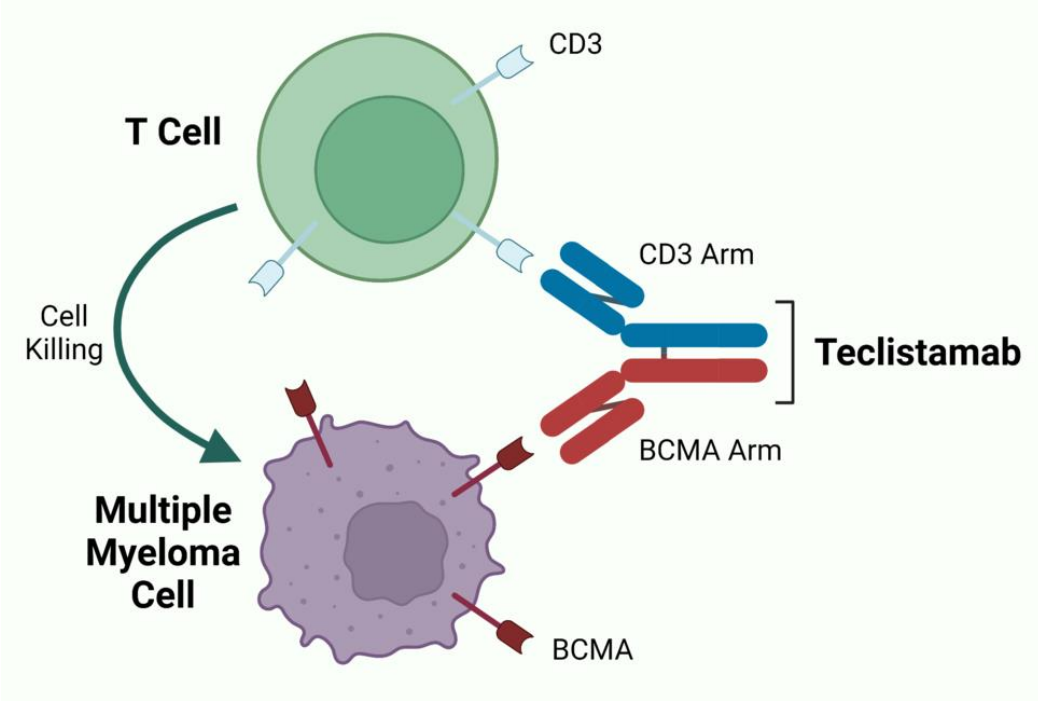
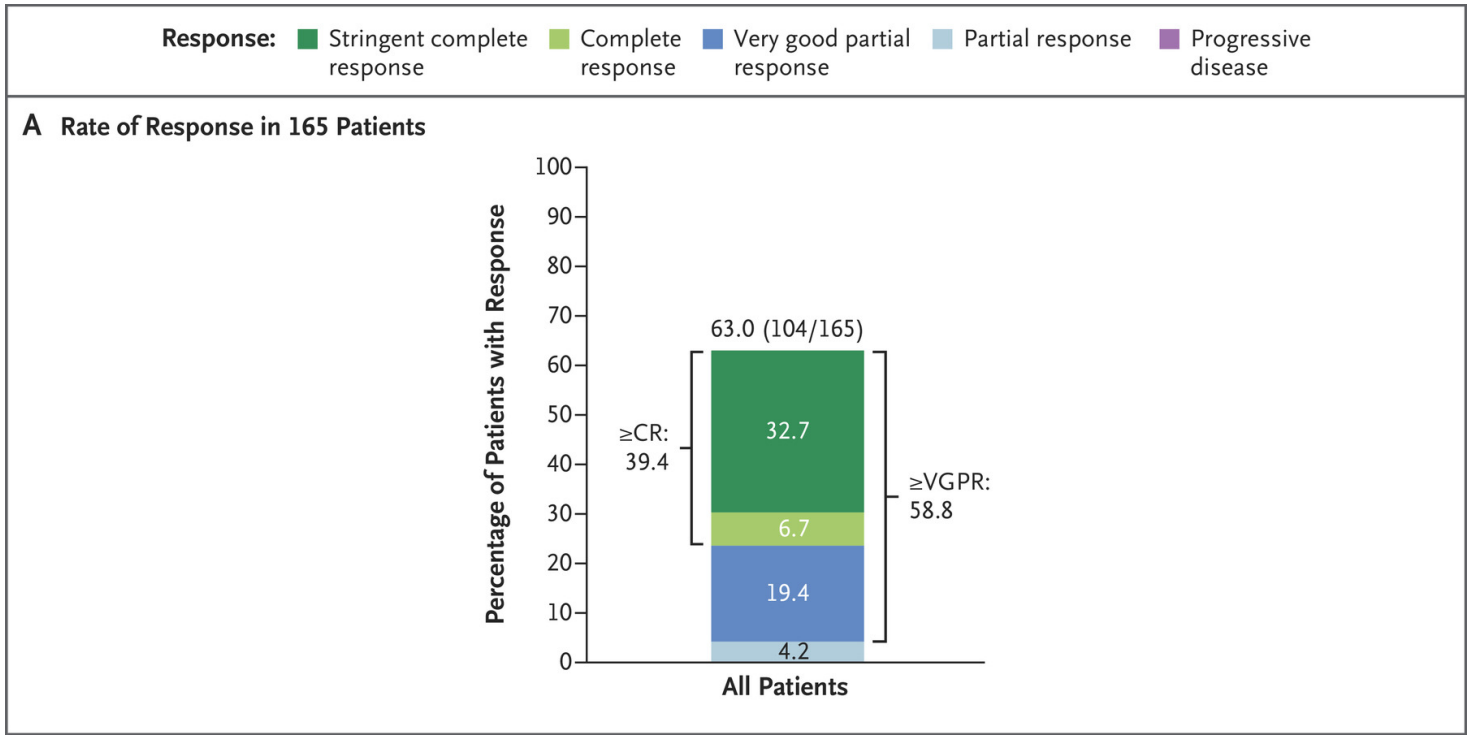


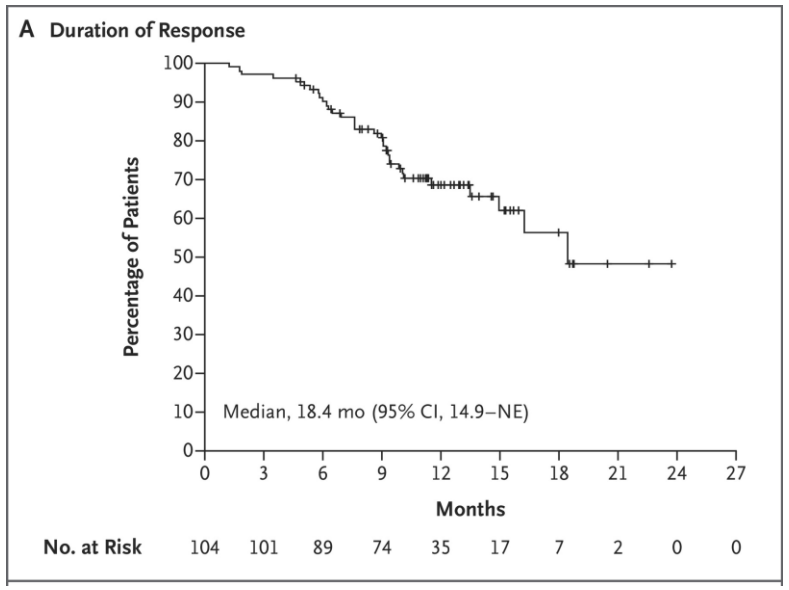

Image source: https://www.cancer.gov/news-events/cancer-currents-blog/2022/tecvayli-multiple-myeloma
Moreau P et al, NEJM 2022

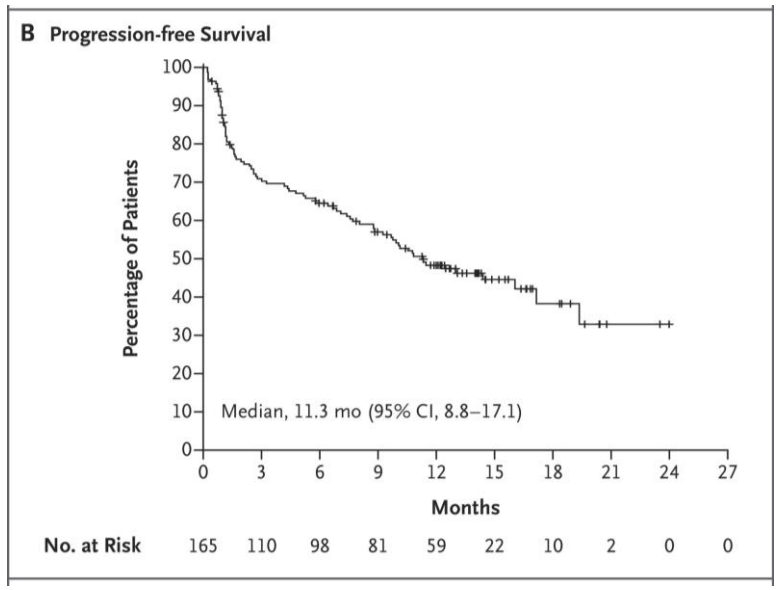
# Teclistamab

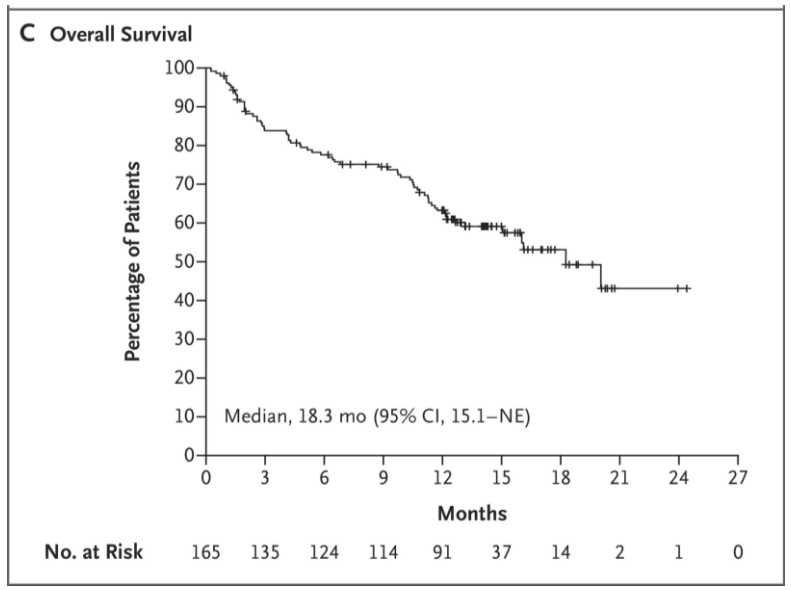



Moreau P et al. NEJM 2022

# Teclistamab




Moreau P et al. NEJM 2022

# Elranatamab

Anti-BCMA x CD3 bispecific

Similar response rates and safety to teclistamab based on current data (MagnetisMM-1, n = 55):

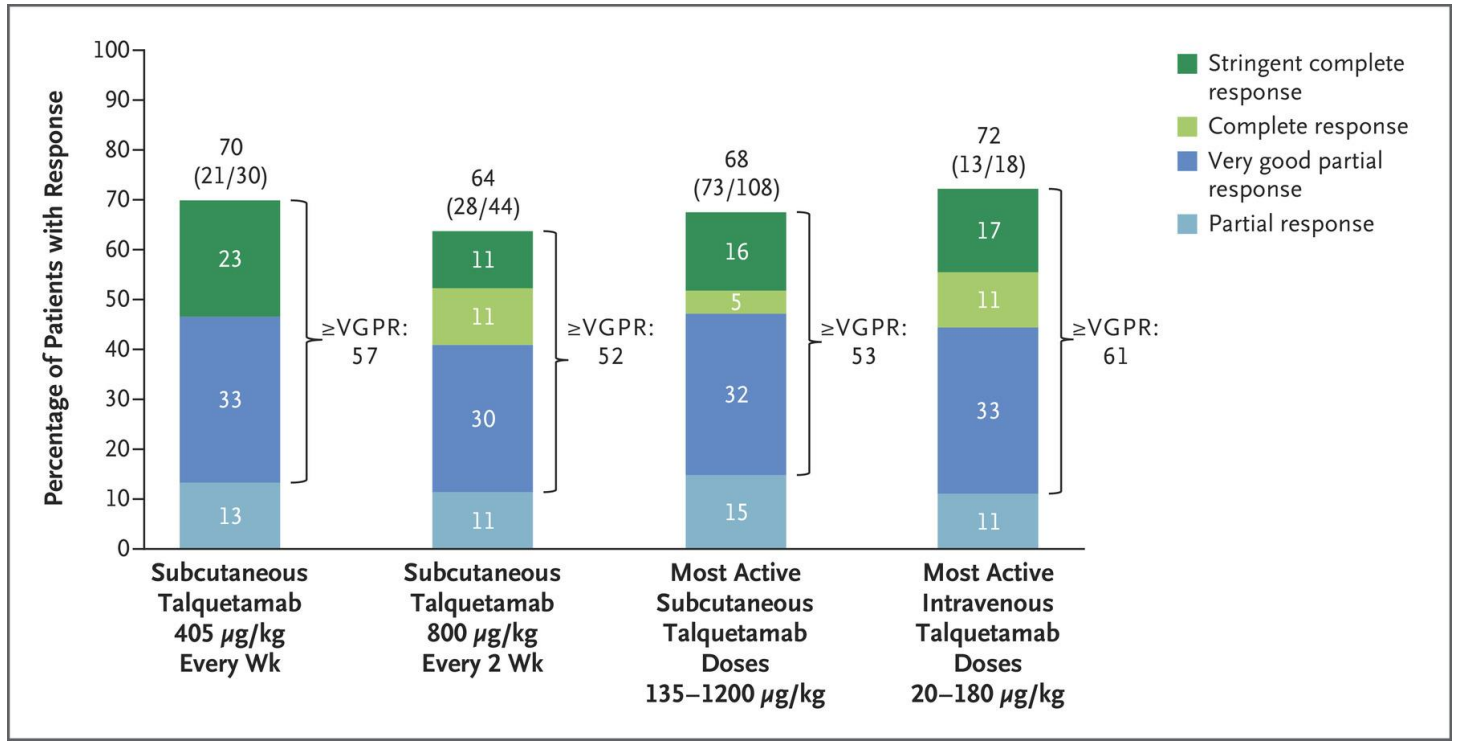
- ORR 64%
- CR or better in 38% of patients (100% MRD negative)

Raje N et al, Blood (2022) 140 (Supplement 1): 388–390.

# Talquetamab: MonumenTAL-1

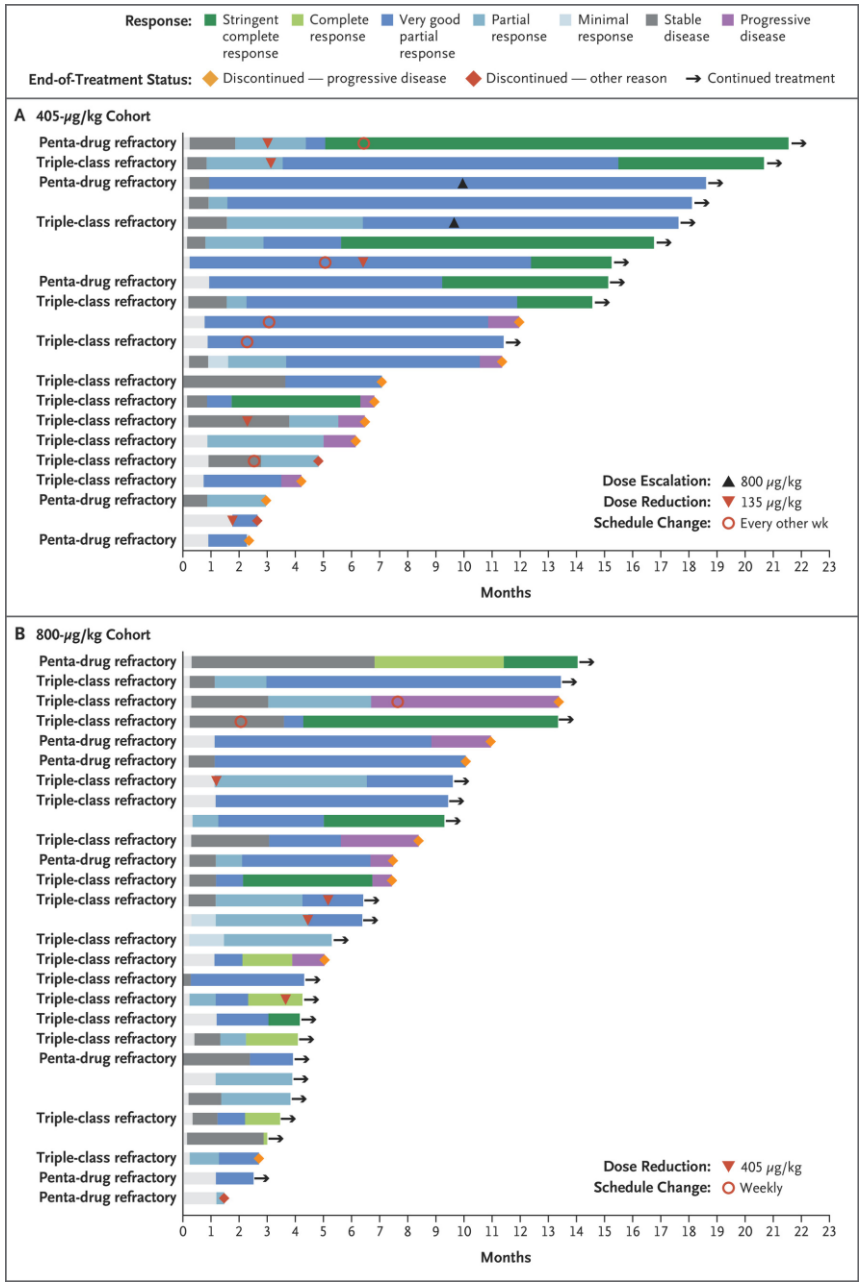
n = 288

R/R MM that had progressed with established therapies (median of six previous lines of therapy)



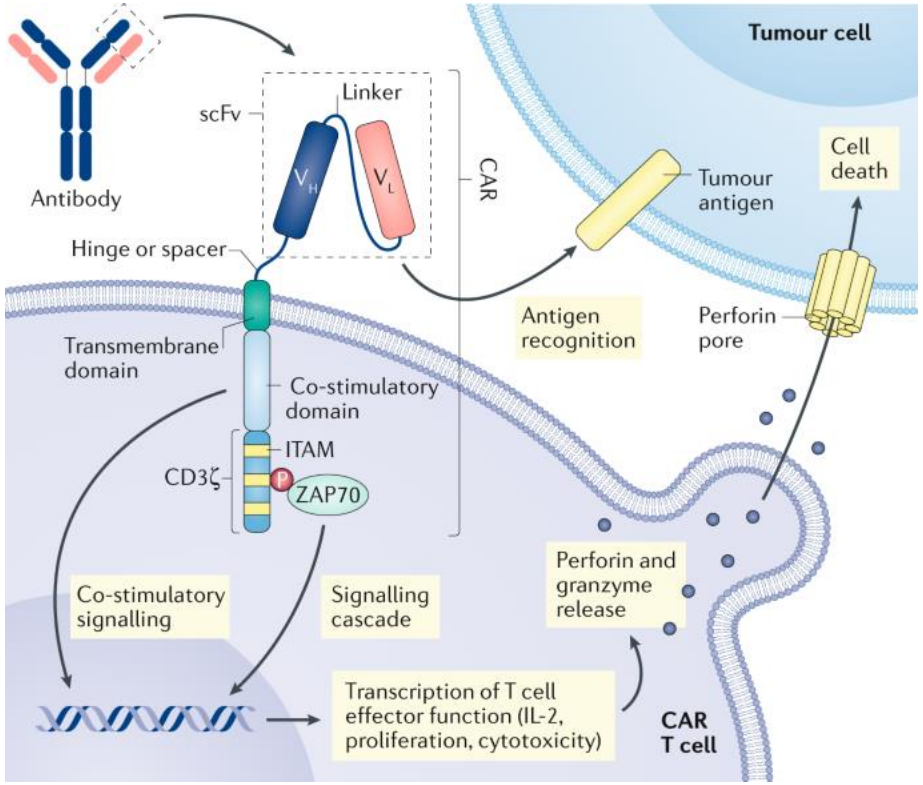

Chari A et al, NEJM 2022

# Talquetamab: MonumenTAL-1



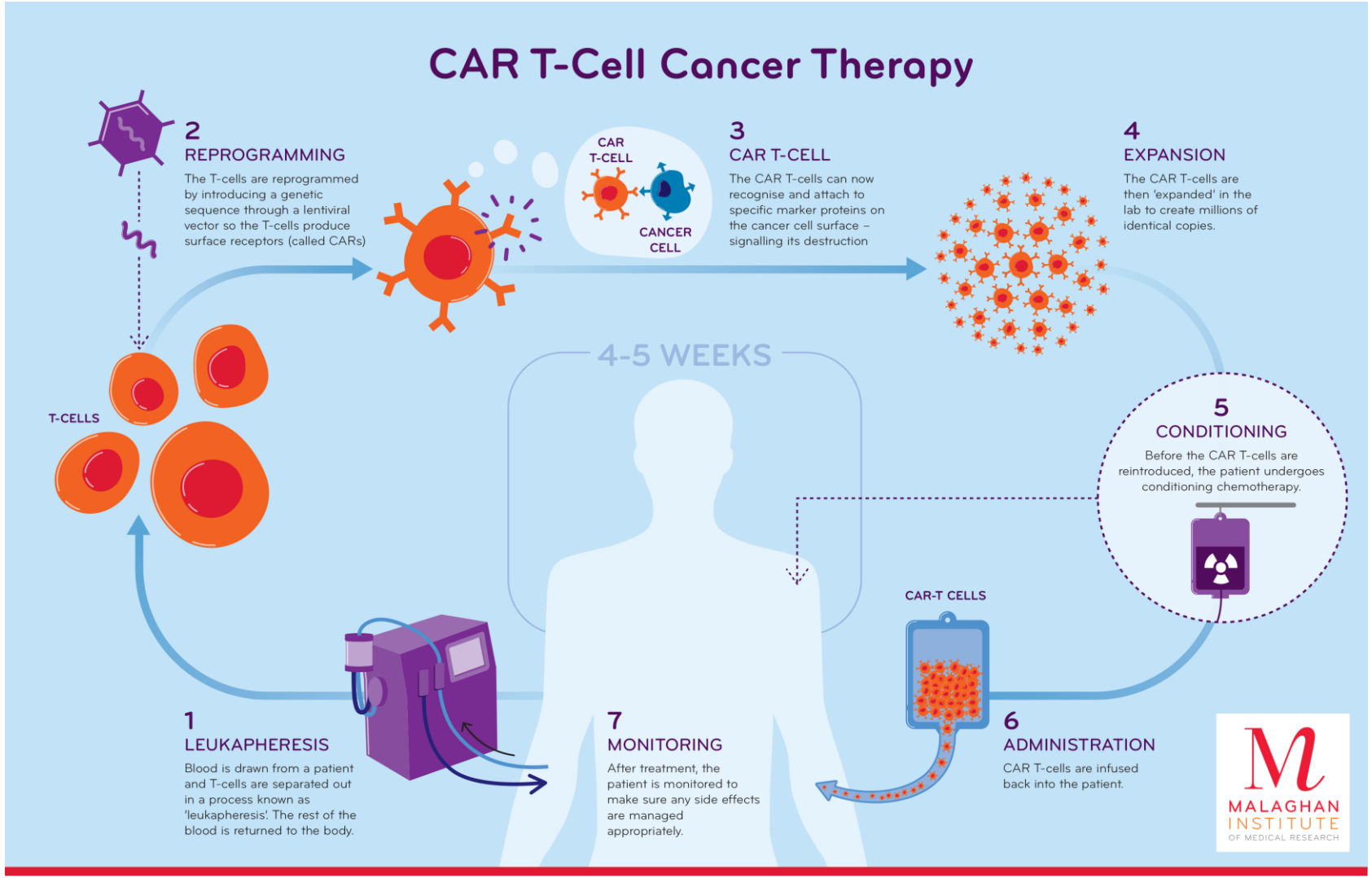

Chari A et al, NEJM 2022

# CAR T-cell therapy




RC Larson and MV Maus, Nature Rev Cancer, 2021

# CAR T-cell therapy



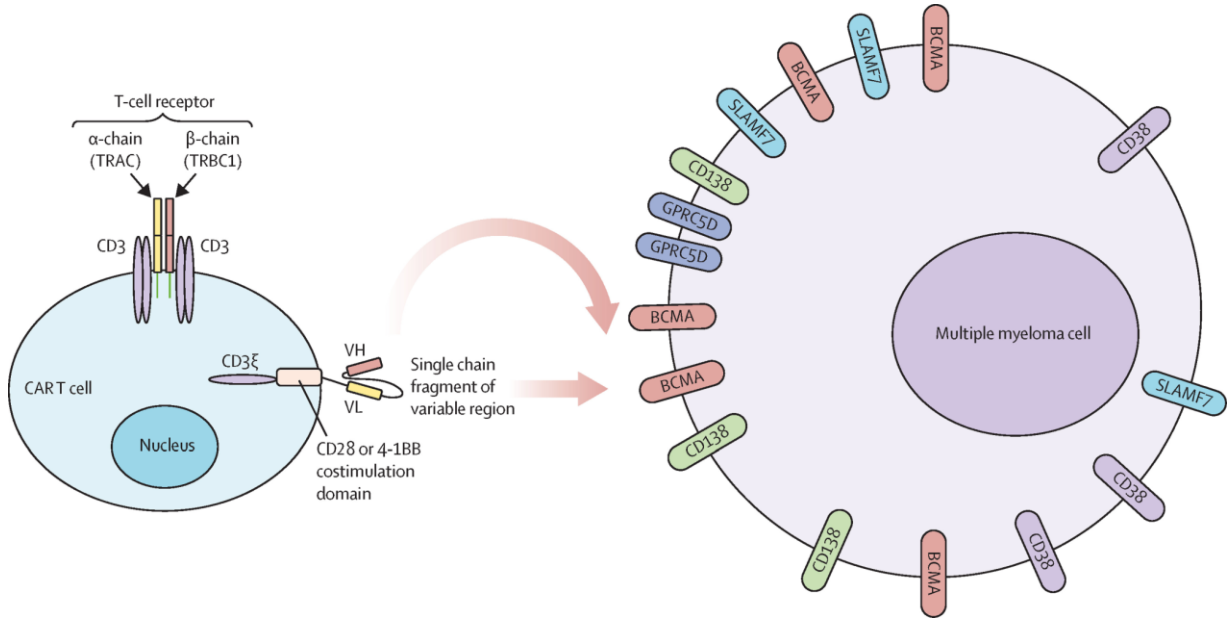

LG Rodríguez-Lobato, Front Oncol, 2020

# CAR T-cell therapy in MM

Prominent CAR constructs in MM:

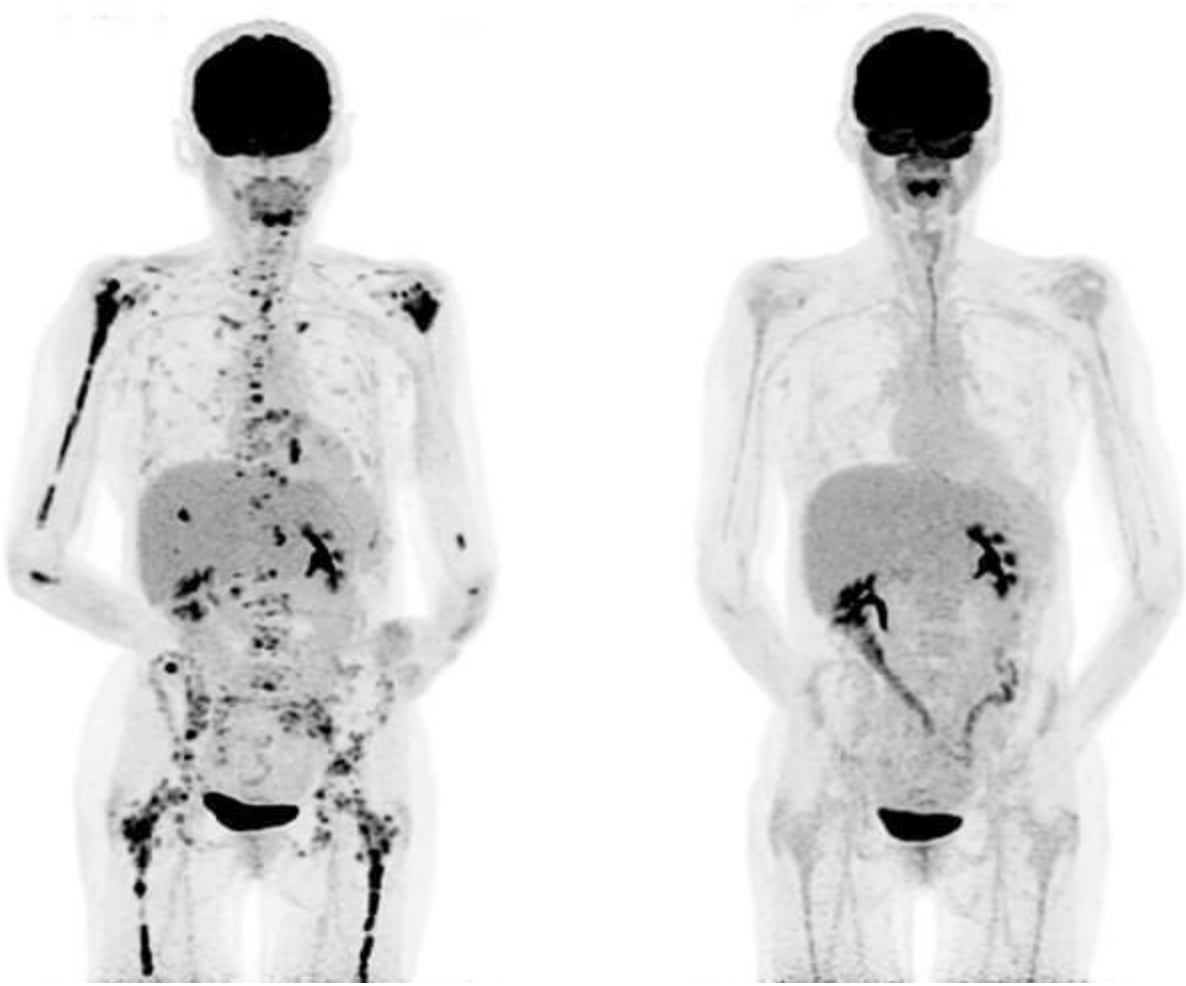
- Idecaptagene vicleucel (ide-cel)
- Ciltacaptagene autoleucel (cilta-cel)

Both are anti-BCMA



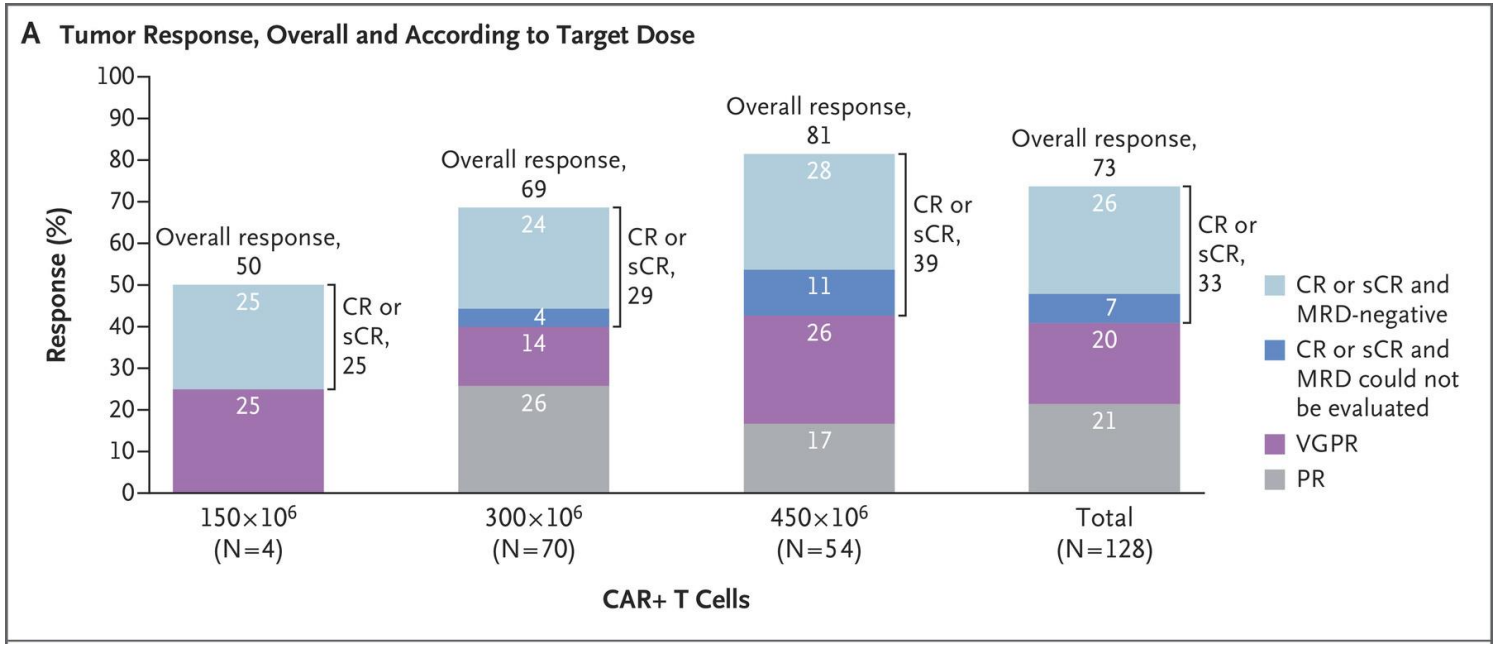

Van de Donk N, Lancet Haematology 2021

# Efficacy of CAR T treatment in MM



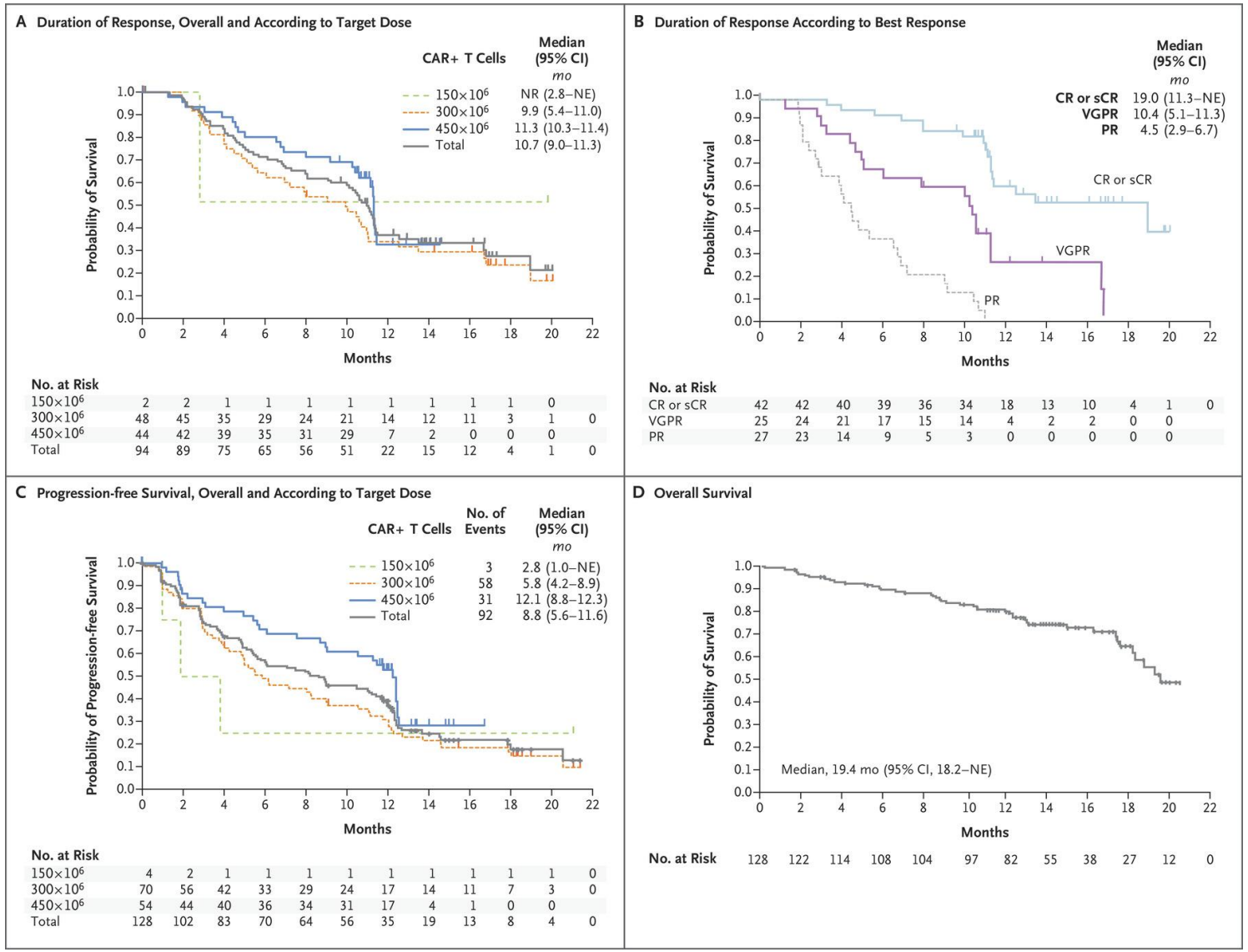
Source: https://www.cancer.gov/news-events/cancer-currents-blog/2017/car-t-cell-multiple-myeloma

# Idecaptagene vicleucel: KarMMa-1



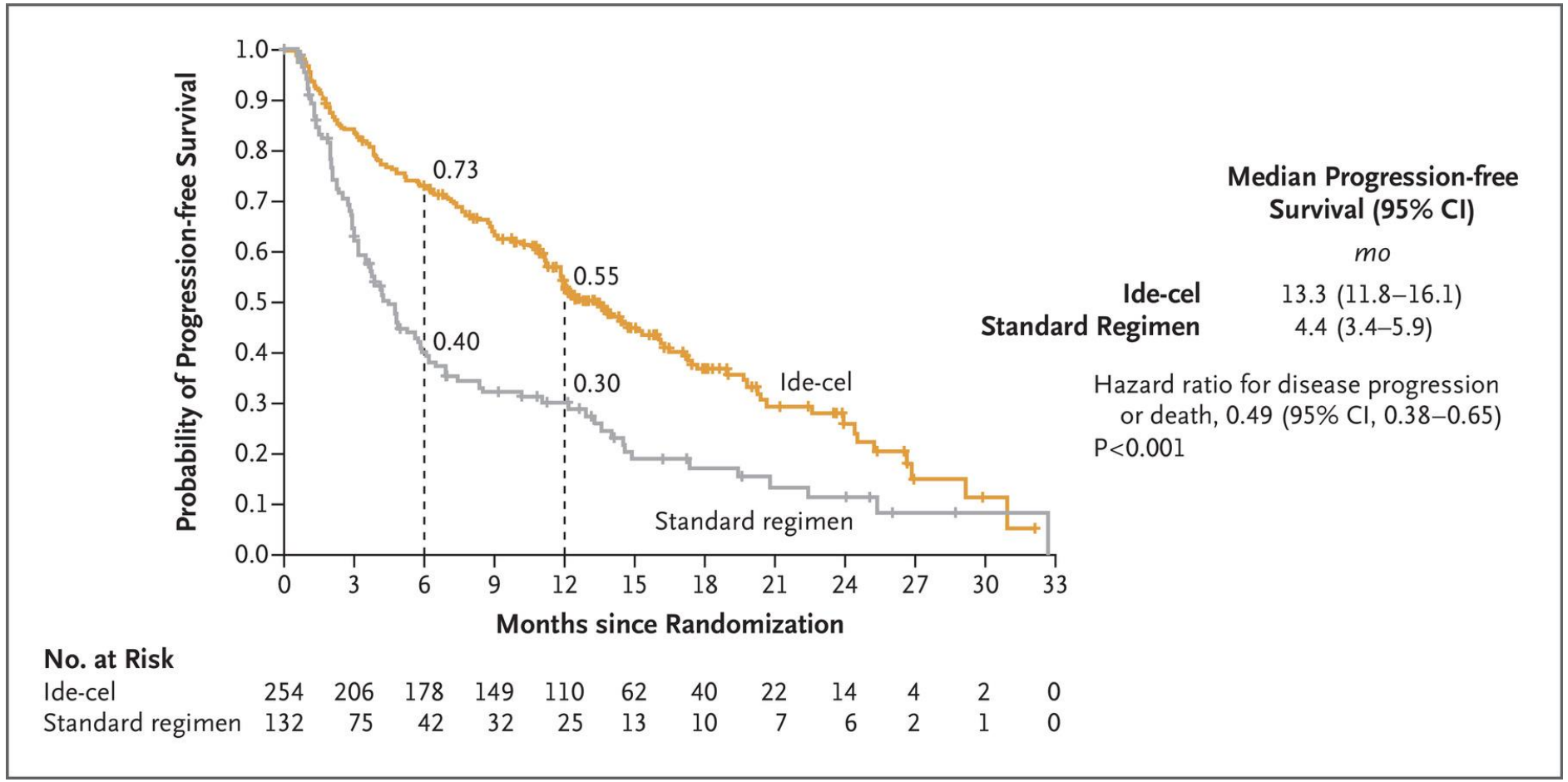

Munshi N et al. NEJM 2021

# Idecaptagene vicleucel: KarMMa-1



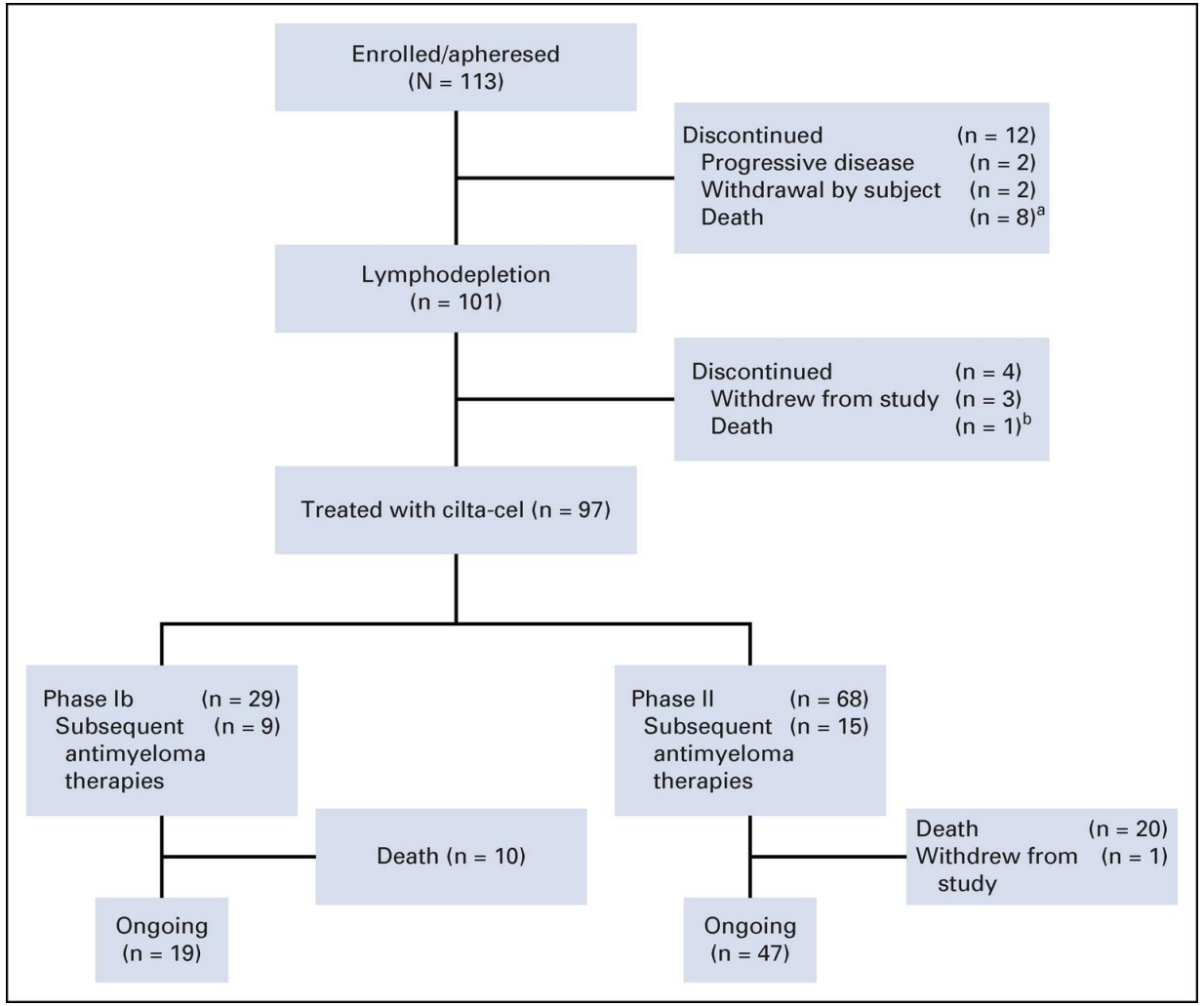

Munshi N et al. NEJM 2021

# Idecaptagene vicleucel vs SOC: KarMMa-3



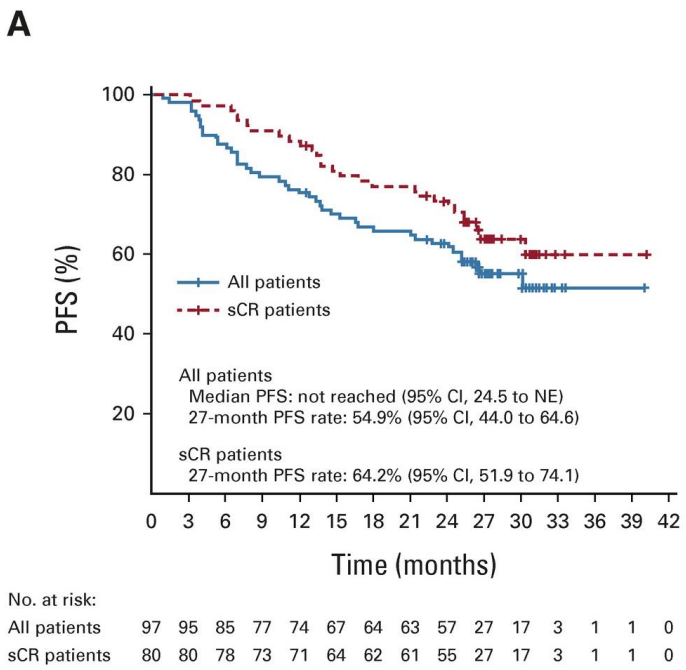

Rodriguez-Otero P, NEJM 2023

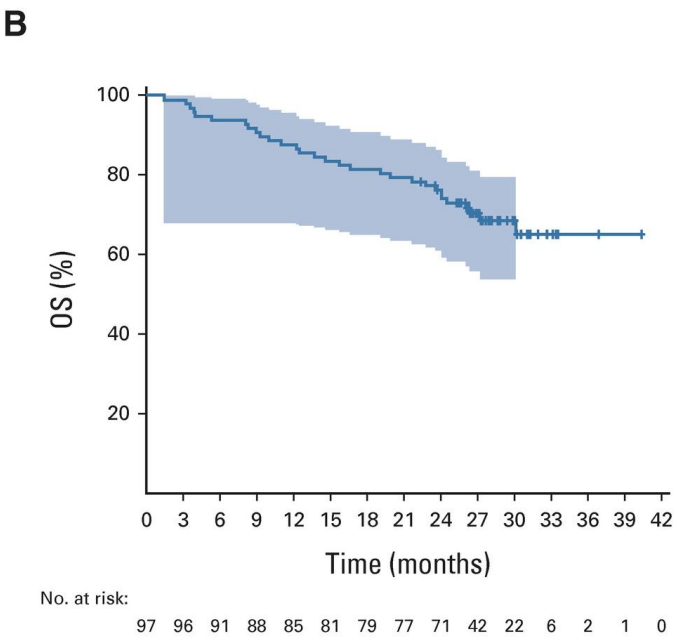
# Ciltacaptagene autoleucel: CARTITUDE-1

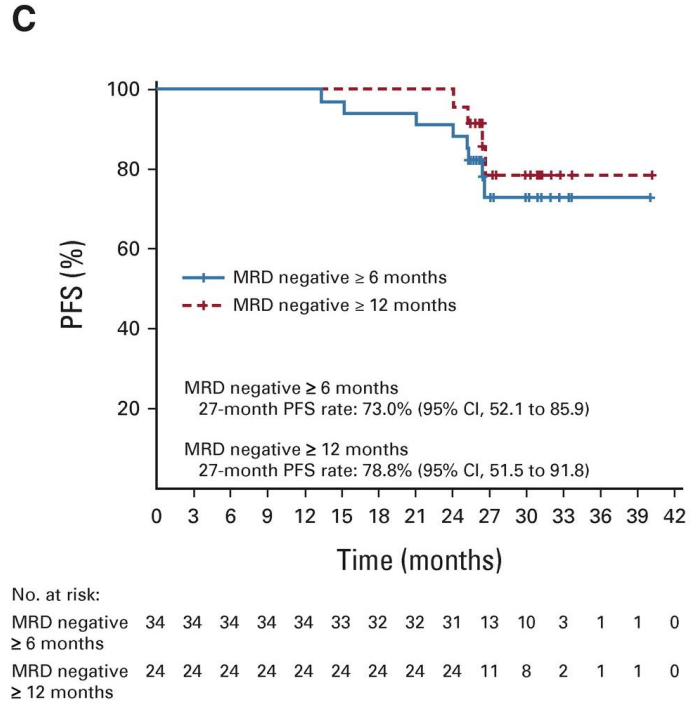



Martin T et al, JCO 2023

# Ciltacaptagene autoleucel: CARTITUDE-1




ORR: 97.9%

Martin T et al, JCO 2023

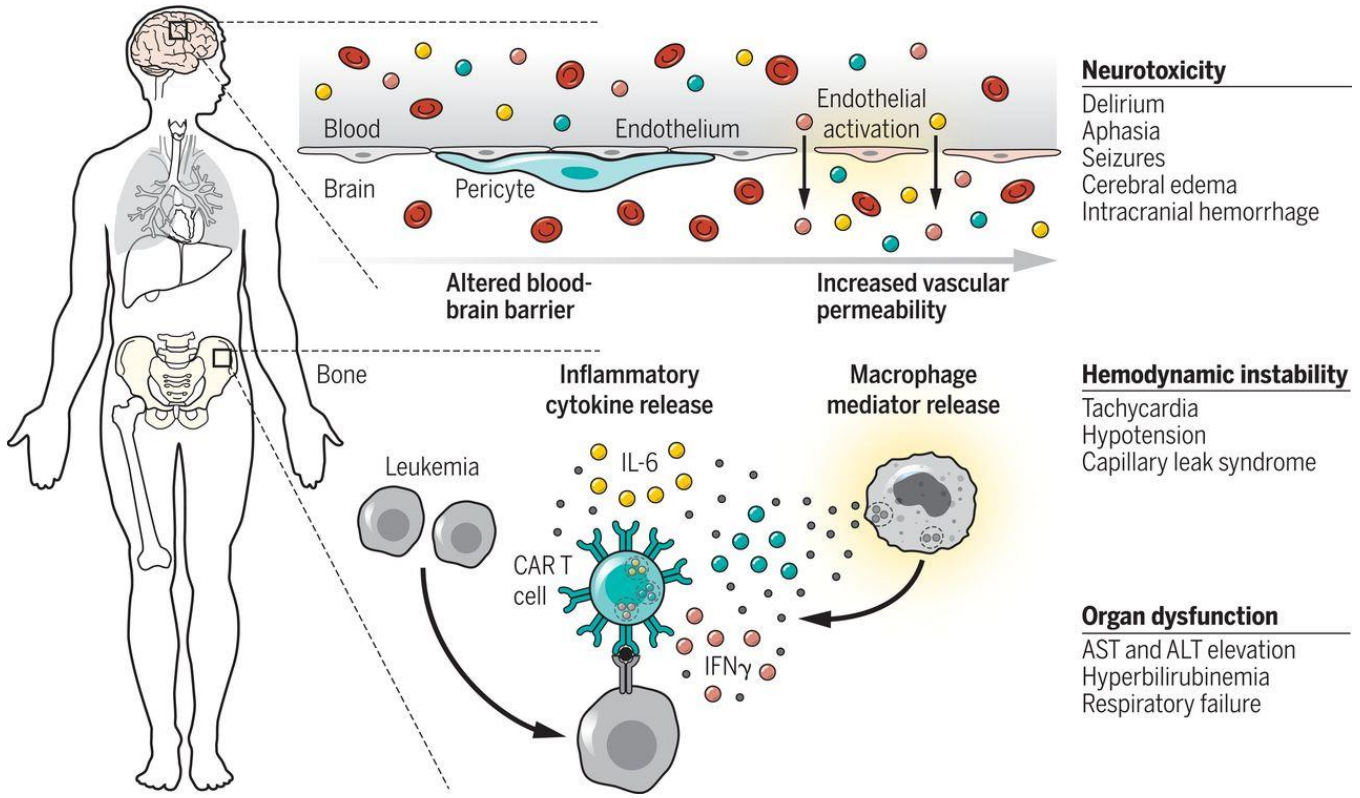
# Bispecifics and CAR T-cell therapy side effects

Cytokine release syndrome (CRS):
- In early phases of treatment
- Mostly grade 1-2 (manageable)

ICANS: rarely

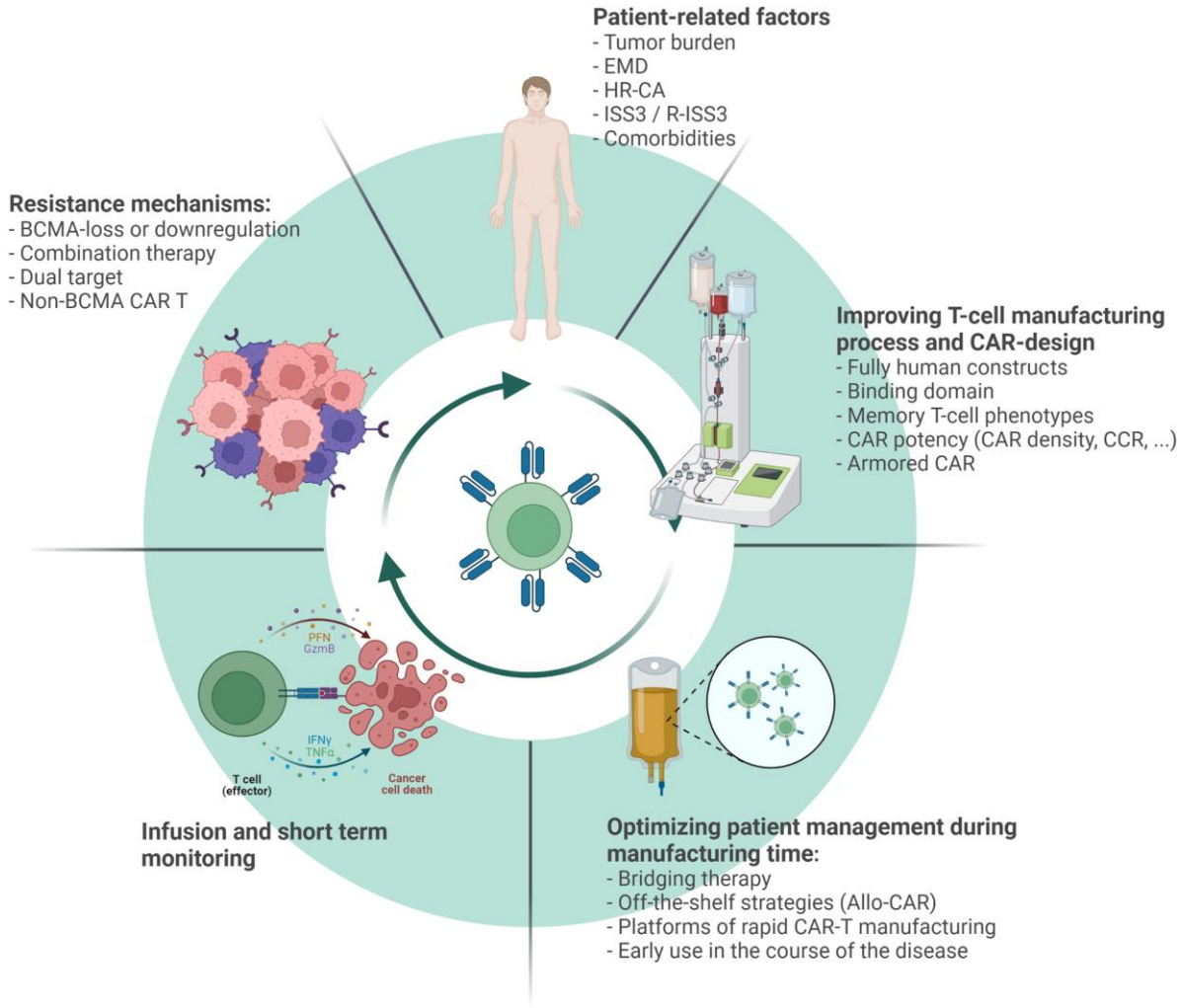
Opportunistic infections

Target-related AEs:
- Dysgeusia and dermatologic AEs (anti-GPRC5D)



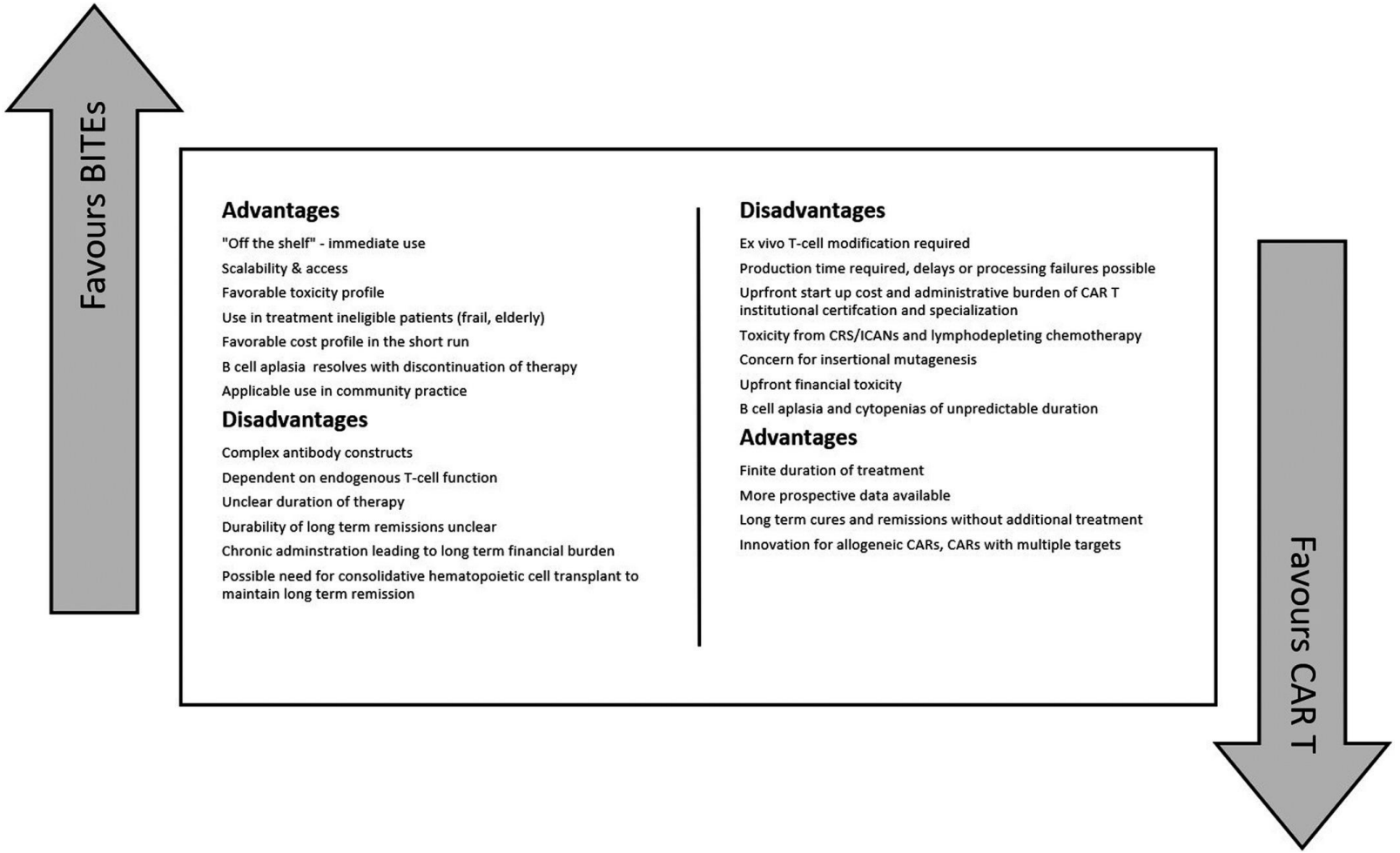

C. June et al, Science 2018

# Challenges in CAR T-treatment in MM



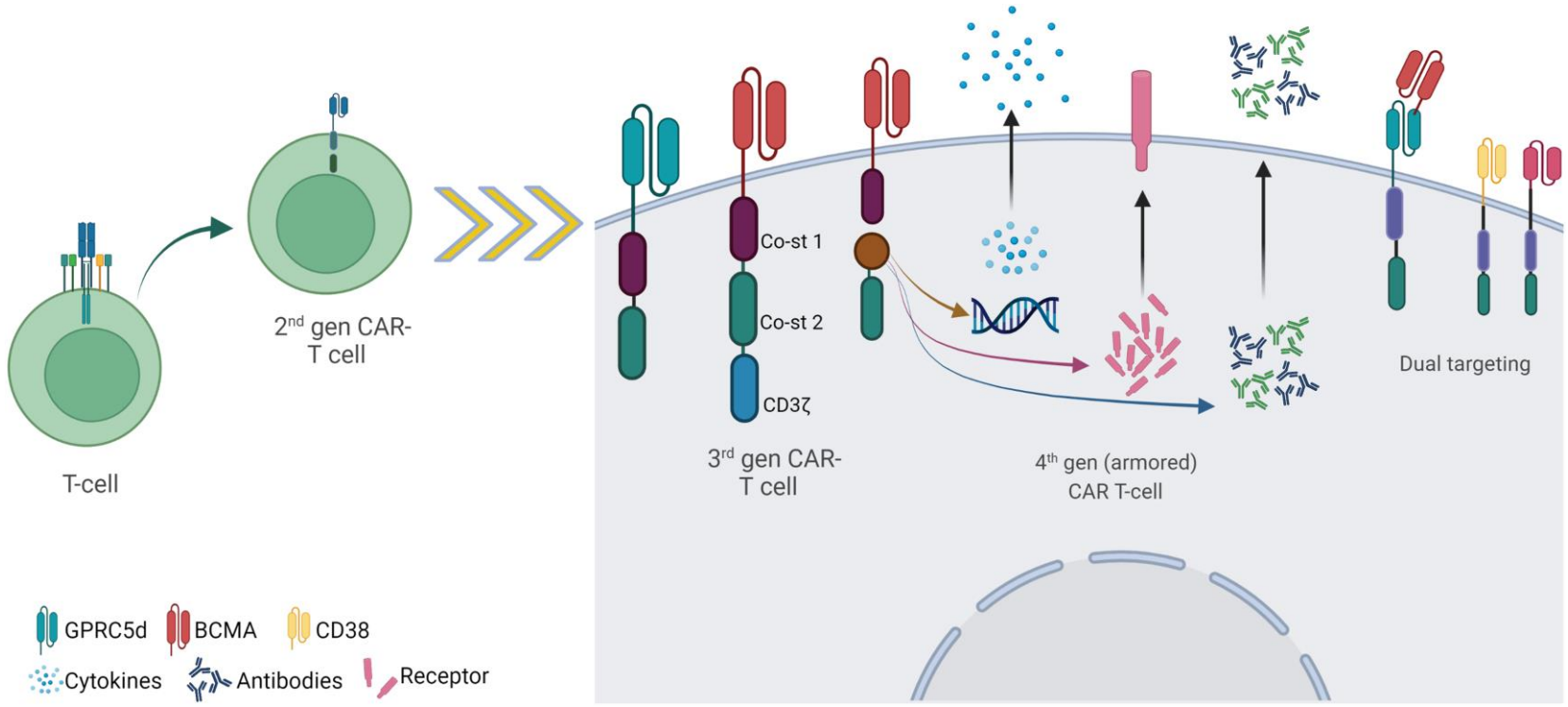

Rodriguez-Otero P, Hematology Am Soc Hematol Educ Program (2022) 2022 (1): 180–189.

# Bispecifics or CAR-T?



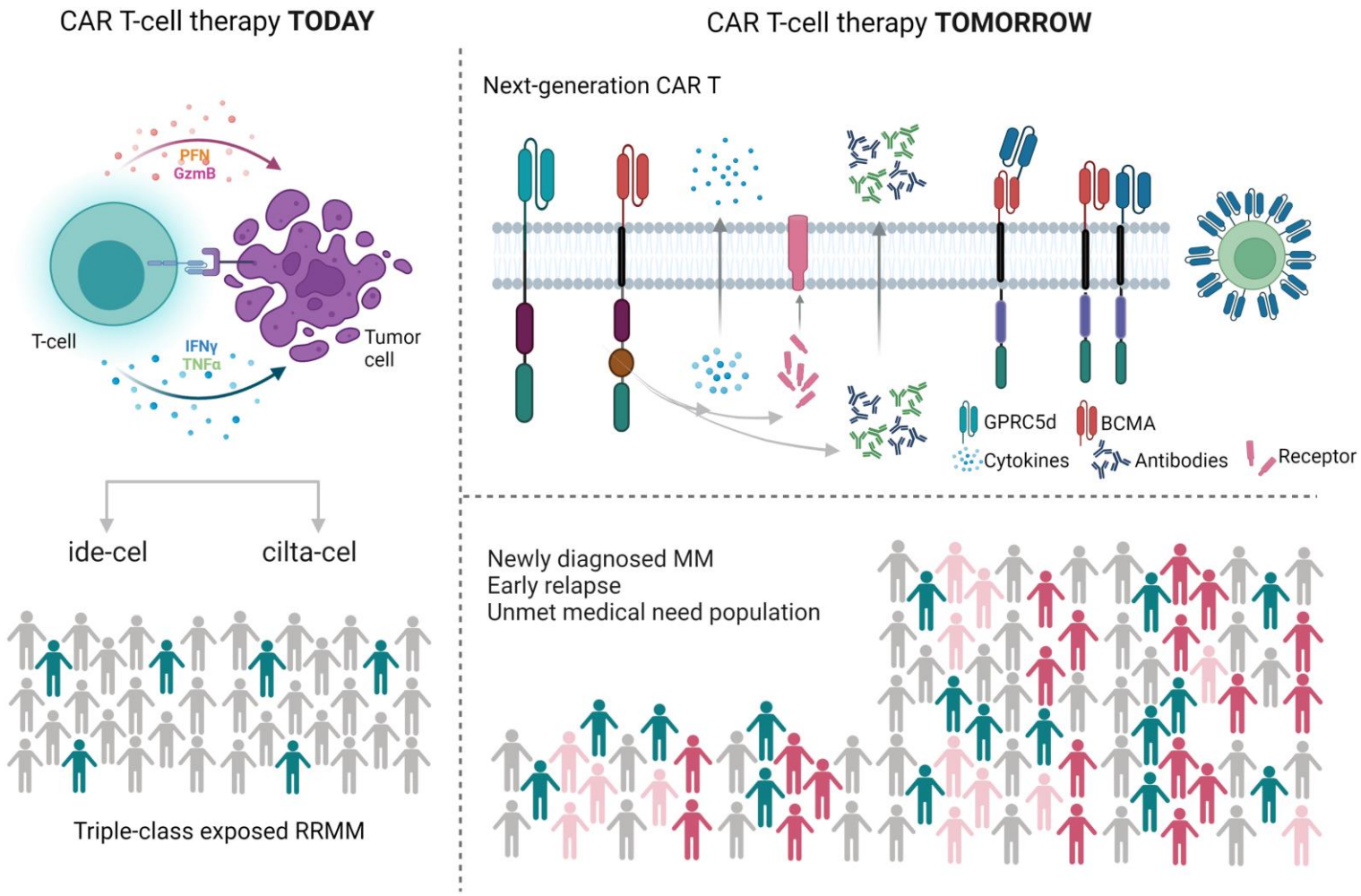

Patel A et al, Br J Haematol 2021

# The future of CAR T-cell therapy in MM




Rodriguez-Otero P, Hematology Am Soc Hematol Educ Program (2022) 2022 (1): 180–189.

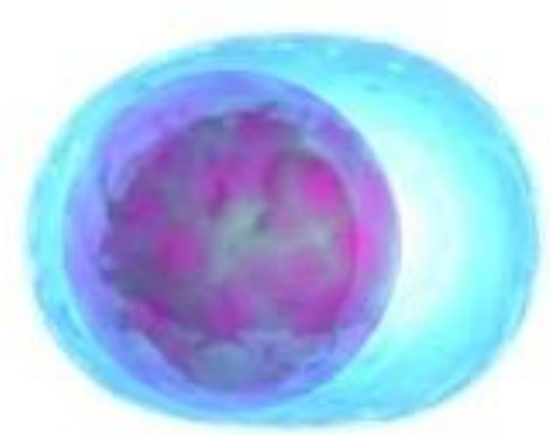
# The future of CAR T-cell therapy in MM




Rodriguez-Otero P, Hematology Am Soc Hematol Educ Program (2022) 2022 (1): 180–189.

# Course overview

1. Definitions
2. Conventional treatment classes and small molecule inhibitors
3. Antibody-drug conjugates
4. Immune therapy (bispecific antibodies and CAR T-cell therapy)
5. Best supportive care
6. Conclusions



# Best supportive care

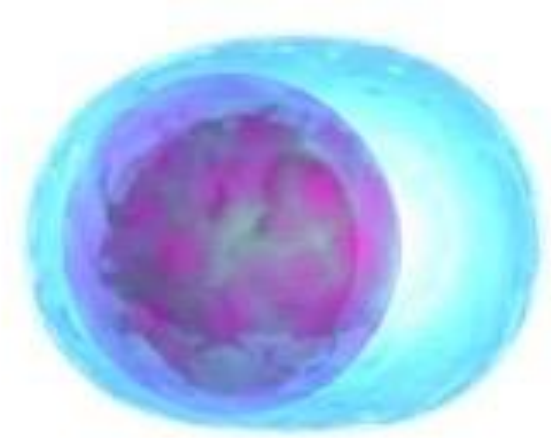
Active antimyeloma treatment is not always the best option!

Always discuss advance care planning with your patient, especially in the relapsed and refractory setting!


Image adapted from https://stories.northernhealth.ca/stories/advance-care-planning-takes-guesswork-out-your-care

# Course overview

1. Definitions
2. Conventional treatment classes
3. Antibody-drug conjugates and small molecules
4. Immune therapy (bispecific antibodies and CAR T-cell therapy)
5. Small molecules
6. Best supportive care
7. Conclusions



# Overview: trials in relapsed MM

| | Relapsed-refractory MM | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Clinical trial** | **POLLUX** | | | **ASPIRE** | | | **ELOQUENT-2** | | **TOURMALINE-MM1** | |
| Population | ITT | High risk | Early relapse | ITT | High risk | Early relapse | ITT | High risk | ITT | High risk |
| Treatment | DRd vs Rd | DRd vs Rd | | KRd vs Rd | KRd vs Rd | | EloRd vs Rd | EloRd vs Rd | IRd vs Rd | IRd vs Rd |
| **PFS (m)/HR** | **44.5 vs 17.5/0.44** | **26.8 vs 8.3/0.37** | **0.38** | **26.3 vs 17.3/0.69** | **23 vs 13.9/0.7** | **21.4 vs 10.7/0.7** | **19.4 vs 14.9/0.70** | **NA/0.72(del17p) NA/0.56 (t(4;14)** | **20.6 vs 14.7/0.74** | **21.4 vs 9.7/0.54** |
| **Clinical trial** | **CASTOR** | | **ENDEAVOR** | | **CANDOR** | | | **IKEMA** | | |
| Population | ITT | High risk | ITT | High risk | ITT | High risk | Early relapse | ITT | High risk | |
| Treatment | DVd vs Vd | DVd vs Vd | Kd vs Vd | Kd vs Vd | DKd vs Kd | DKd vs Kd | | IsaKd vs Kd | IsaKd vs Kd | |
| **PFS (m)/HR** | **16.7 vs 7.1/0.31** | **12.6 vs 6.2/0.41** | **18.7 vs 9.4/0.53** | **8.8 vs 6.0/0.7** | **28.6 vs 15.9/0.59** | **15.6 vs 5.6/0.49** | **CRrate 28 vs 3%** | **NR vs 19.1/0.53** | **NA/0.72** | |
| **Clinical trial** | **OPTIMISMM** | | **BOSTON** | | **ICARIA** | | **ELOQUENT-3** | | | |
| Population | ITT | High risk | ITT | High risk | ITT | High risk | ITT | High risk | | |
| Treatment | PVd vs Vd | PVd vs Vd | SVd vs Vd | SVd vs Vd | IsaPd vs Pd | IsaPd vs Pd | EloPd vs Pd | EloPd vs Pd | | |
| **PFS (m)/HR** | **11.2 vs 7.1/0.61** | **NA/0.56** | **11.2 vs 5.8/0.61** | **NA/0.67** | **11.5 vs 6.4/0.59** | **NA/0.66** | **10.3 vs 4.7/0.54** | **0.52** | | |
| **Clinical trial** | **STORM** | | **HORIZON** | | **DREAMM-2** | | **KARMMA-1** | | | |
| Population | ITT | High risk | ITT | High risk | ITT | High risk | ITT | High risk | | |
| Treatment | Sd | Sd | Melflufen-dex | Melflufen-dex | Belamaf | Belamaf | Ide-cel | Ide-cel | | |
| **PFS (m)/HR** | **3.7** | **3.3* and 4.6*** | **4.2** | **3.0** | **3.9** | **2.1** | **8.8** | **10.4** | | |

Mateos MV et al, ASH 2021

# Conclusions

The treatment of (relapsed) myeloma is in continuous evolution

Consider both patient and disease when choosing the next treatment step

Anti-BCMA treatments provide a major therapeutic opportunity in R/R MM

# Review questions

Multiple choice questions, one correct answer

The answer options ‘all of the above are correct/incorrect’ will **never** be applicable **for this course**

# A review question

You are following a currently 77-year old female patient with multiple myeloma (MM) IgG kappa. At diagnosis, she received the combination of bortezomib-melphalan-dexamethasone (VMP), which was stopped after 9 cycles because of worsening sensory neuropathy. The patient achieved a CR, and progressed three years later. She was then treated with carfilzomib-dexamethasone (Kd), and achieved PR, after which she was treated with daratumumab-lenalidomide-dexamethasone (DRd) until this moment.

She presents with worsening anemia (Hb 9.5 g/dL, compared to 13.6 g/dL four months prior) and biochemical progression. Bone marrow aspirate shows the presence of 36% plasma cells.

Which of the following pomalidomide-based options is the **least** preferable option, provided all have received regulatory approval?

a. Pomalidomide-cyclophosphamide-dexamethasone (IED)
b. Pomalidomide-bortezomib-dexamethasone (PVD)
c. Isatuximab-pomalidomide-dexamethasone (isa-pom-dex)
d. Belantamab mafodotin-pomalidomide-dexamethasone

# Thank you for your attention!