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Multiple Myeloma: Update on Immune-Targeted Agents

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MLS Cleveland

CONFESSION

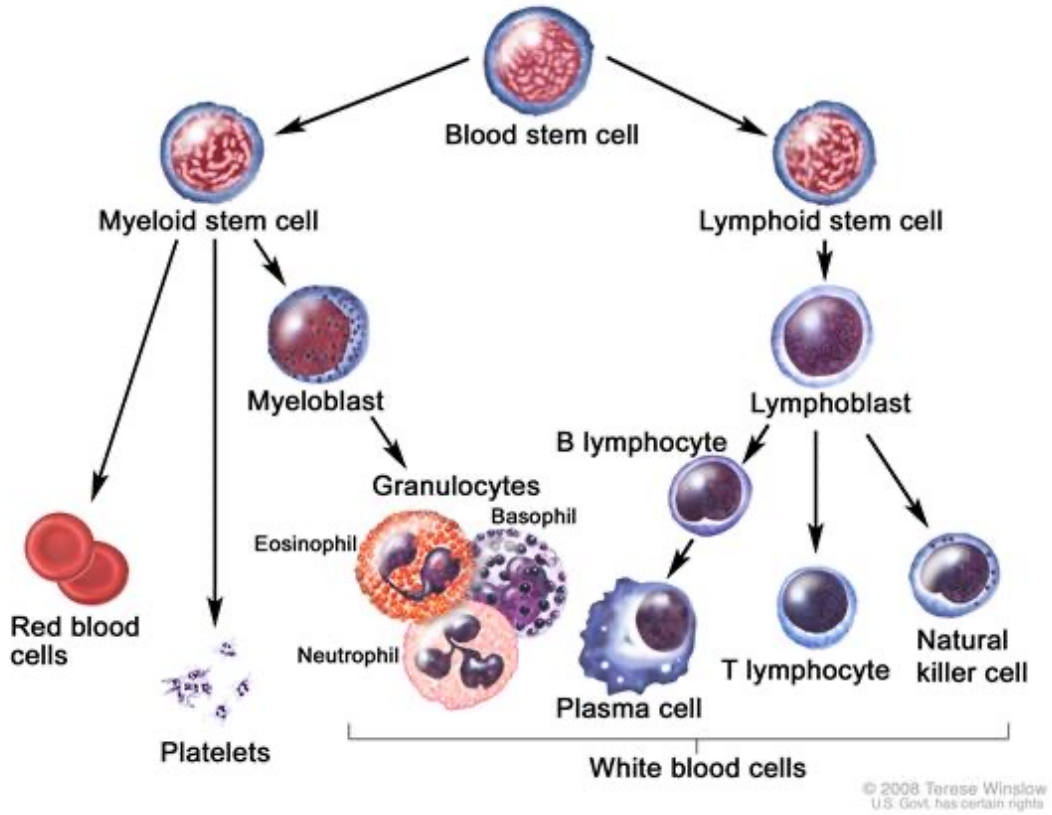
- Host of the Classical Music Clinic
- Sundays 1 pm Eastern on Clubhouse
- 3+ hours of classical music therapy
- https://www.clubhouse.com/@mxk214

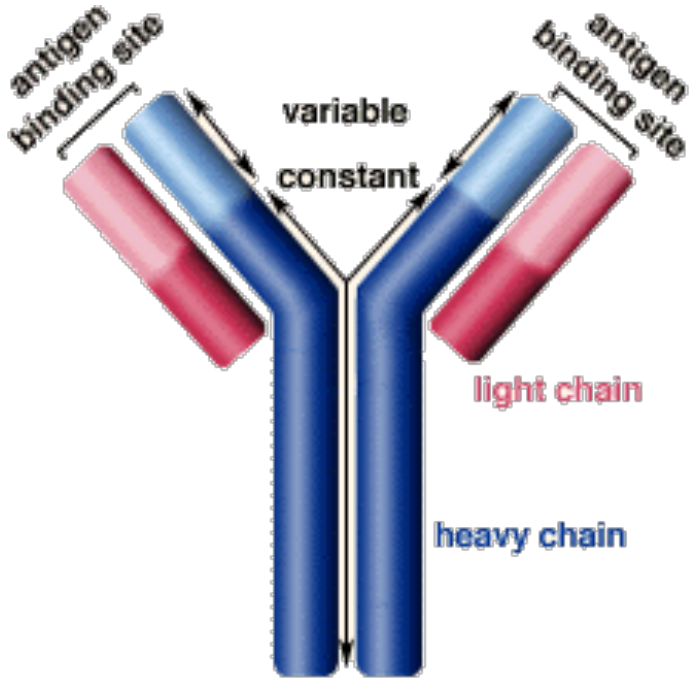
OBJECTIVES/OUTLINE

- Very good, but partial background
  - Basic pharmacology of anti-MM agents
- **Targeted agents: mechanisms, indications, outcomes**
  - Induction phase: RVD ± CD38 mabs
  - R/R disease: BiTE therapy
  - R/R disease: CAR T cells
- Conclusions and future directions
  - “Smoldering” questions in MM

PLASMA CELL DISEASES

Multiple myeloma is a malignancy of clonal plasma cells





Plasma cell = antibody factory

Molecular subtypes:

- Full Ig (“M-spike”), light chain, or oligo/non-secretory

MULTIPLE MYELOMA: The Toolbox

Major therapeutic drug classes in myeloma*:

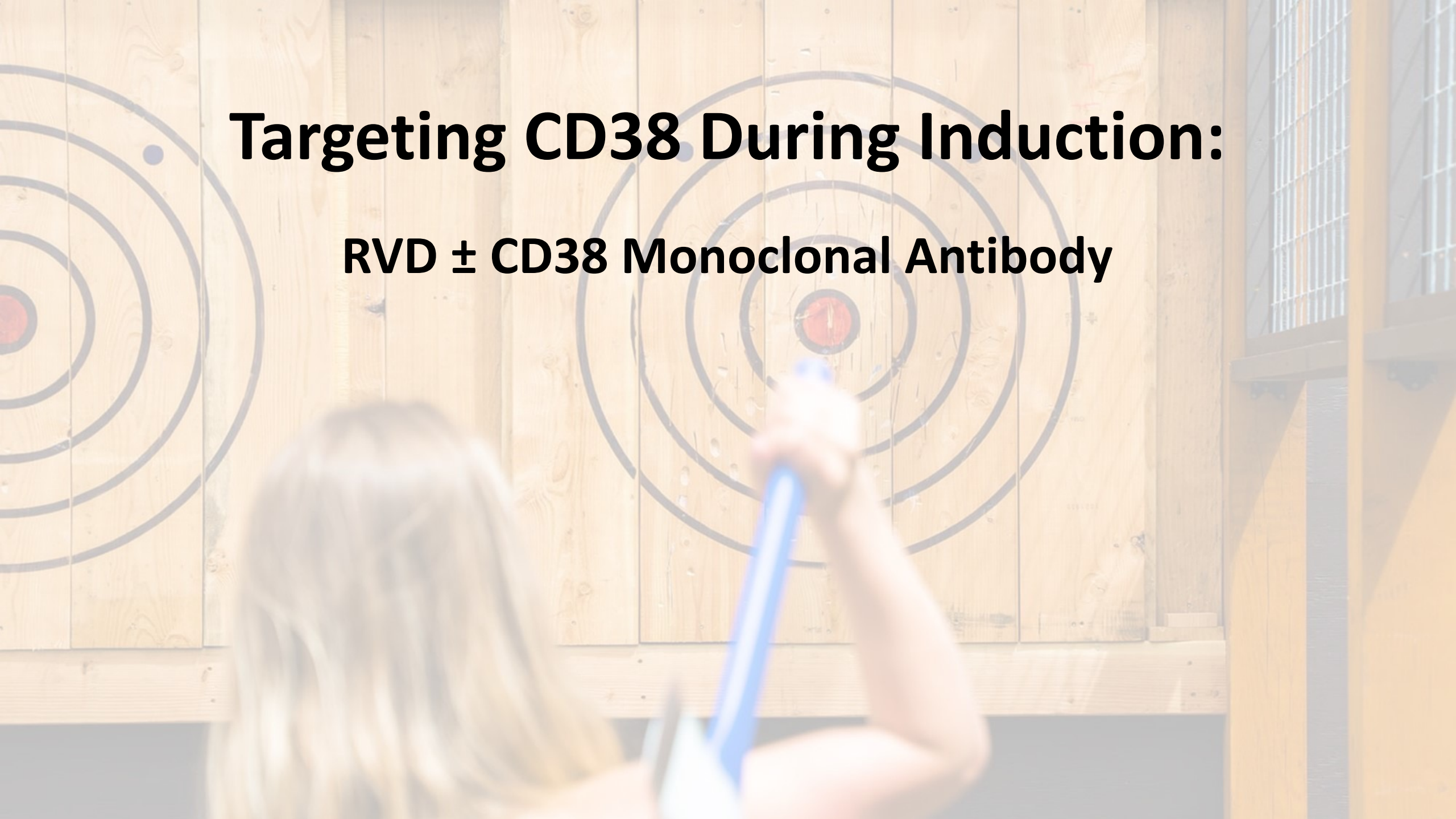
Class	Representative Agent(s)
Immunomodulator **(IMiD)**	lenalidomide, pomalidomide
Proteasome inhibitor **(PI)**	bortezomib, carfilzomib, ixazomib
Steroid	dexamethasone
Cytotoxic chemotherapy	cyclophosphamide, melphalan[1]
CD38 monoclonal antibody **(mab)**	daratumumab, isatuximab
Immunotherapy	
BiTEs (BCMA, GPRC5D)	teclistamab, talquetamab, elranatamab
CAR T cells (BCMA)	ide-cel, cilta-cel

*not an exhaustive list

1. Off-label indication in HCT

Targeting CD38 During Induction:

RVD ± CD38 Monoclonal Antibody



INDUCTION

Initial therapy to **induce response** and **stop end-organ damage**:

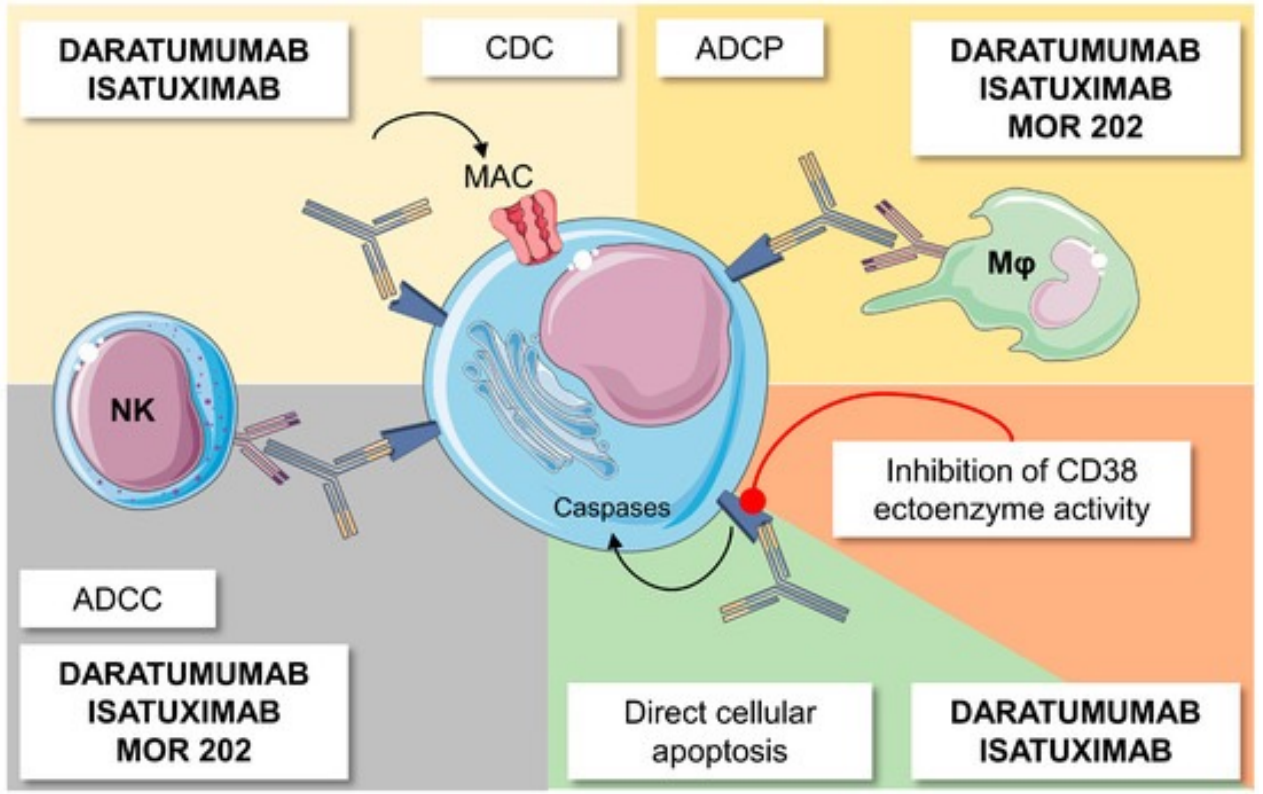
- "Triplet" seems to outperform "doublet"
- Transplant vs. non-transplant candidate
  - Attempt to transplant fit patients ≤ 75 years old
  - **RVD**: most common "fit patient" induction: lenalidomide (R), bortezomib (V) and dexamethasone (D)

Sources: Durie BG, et al. *Lancet* 2017; Facon T, et al. *Lancet Oncol* 2021

MECHANISM: Anti-CD38 monoclonal antibodies

Mechanisms of action:

- ADCC: antibody-dependent cell-mediated cytotoxicity
- CDC: complement-dependent cytotoxicity
- ADCP: antibody-dependent cellular phagocytosis
- Apoptosis
- Inhibit CD38 enzyme



Source: De Novellis D, et al. *Int J Mol Sci* 2023

INDUCTION: RVD + Targeting CD38

RVD:

- Lenalidomide (R), bortezomib (V), and dexamethasone (D)
- Standard-of-care triplet induction for fit patients (e.g. auto-HCT candidates) in US

RCTs adding CD38 mabs to RVD:

- GRIFFIN (phase II): RVD ± daratumumab[1]
- GMMG-HG7: RVD ± isatuximab[2]
- PERSEUS: RVD ± daratumumab[1]

1. FDA-approved 1st line or 2nd line+ with **other combinations**
2. FDA-approved 2nd line+ with **other combinations**

Sources: Goldschmidt H, et al. Lancet Haematol 2023; Sonneveld P, et al. NEJM 2024; Voorhees P, et al. *Blood* 2020

INDUCTION: RVD + Targeting CD38

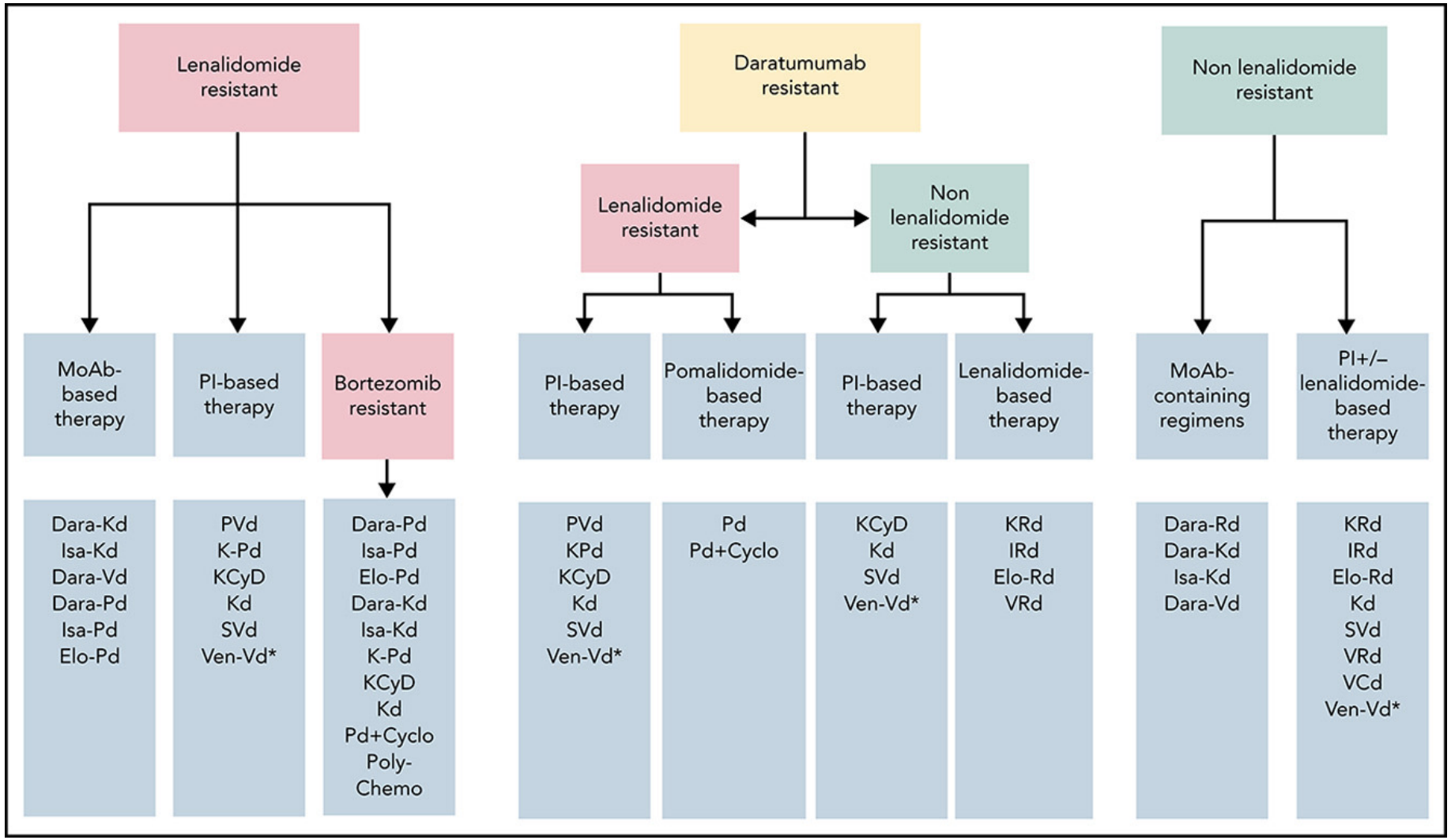
CD38 monoclonals added to RVD:

- Auto-HCT utilization is implicit
- Higher % MRD-negativity
- Deeper responses
- Toxicity not substantially increased
- Limited inclusion of:
  - Older patients
  - High-risk disease
  - Renal dysfunction
- Suboptimal auto-HCT in standard Rx arms (some studies)
- **Cost-effective? Implications for CD38 mab use in relapse?**

Aiming T-cells at Relapsed/Refractory Myeloma

BiTE therapy and CAR T cells

CHOICE OVERLOAD



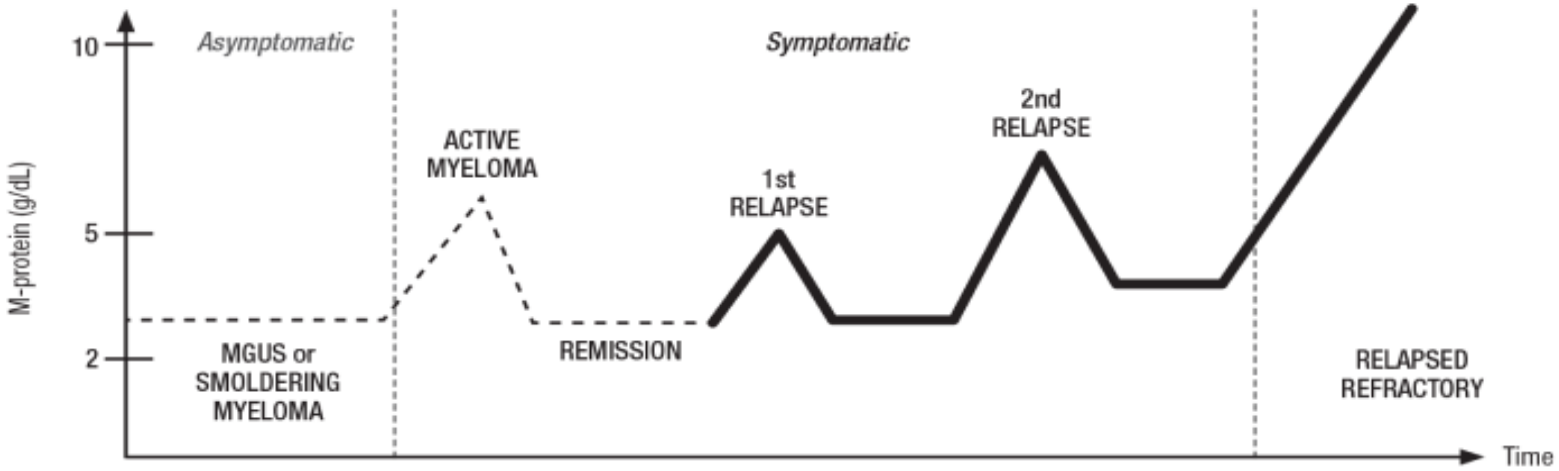
Source: Kastritis E, et al. *Blood* 2022

CHOICE OVERLOAD

RELAPSED/REFRACTORY DISEASE

Sequencing of therapies:

- Initiate new Rx with recurrence of paraprotein or CRAB
- Introduction of new agents or drug combinations
- Decreasing depth/duration of response
- Can new targeted therapies do better?



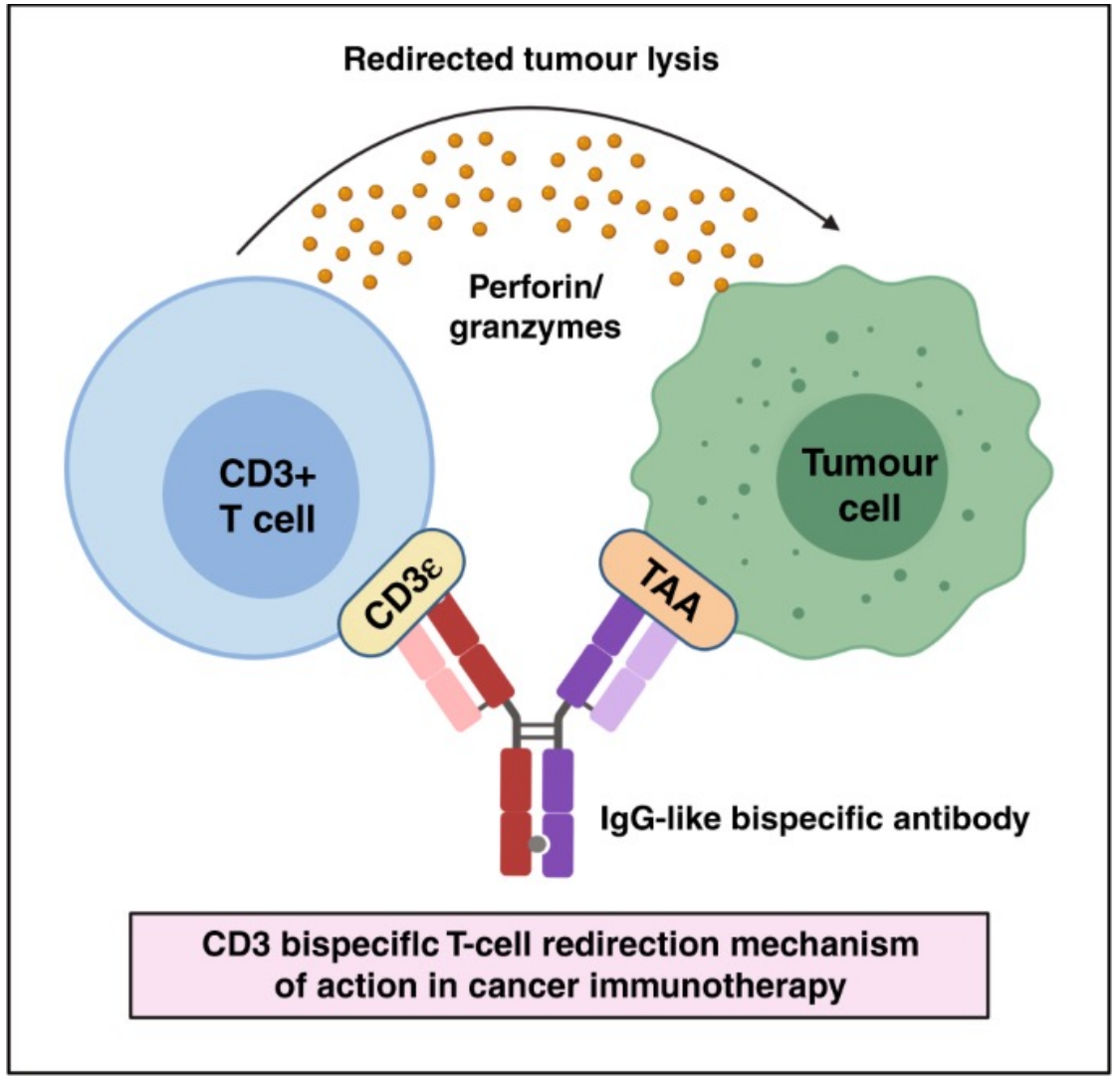
Variable timeline dependent on individual risk factors including genetic and phenotypic changes, depth and duration of response to therapy, persistence of a malignant multiple myeloma stem cell, and evolution of competing multiple myeloma clones

Source: Kurtin SE. *J Adv Pract Oncol*. 2013

T CELLS IN R/R MM: BiTES

Bi-Specific T-cell Engagers (BiTEs):

- Target CD3 on T-cells AND tumor antigen
- E.g., B-cell maturation antigen (**BCMA**): CD269, on B-cells and mature plasma cells
- Activate T-cell/facilitate immunological synapse → Lysis of target tumor cells



Sources: Singh A et al. *Br J Cancer* 2021; Tian Z et al. *J Hematol Oncol* 2021

BCMA BiTE IN R/R MM: Teclistamab

Majes-TEC1:

- Phase 1-2 trial of teclistamab, CD3-BCMA BiTE
- R/R disease
- N = 165
  - Age ≥ 18
  - ≥ 3 prior lines*, no prior BCMA
  - ECOG 0/1
  - **Admission and premeds for 3 step-up doses:** **CRS, ICANS, REMS**
  - Primary endpoint: ORR
  - Secondary endpoints: PFS, OS, MRD negativity, etc.

*FDA approval: ≥ 4 prior lines (including PI, IMiD, CD38)

Source: Moreau P et al. *NEJM*, 2022.

Majes-TEC1: Teclistamab

Study outcomes:

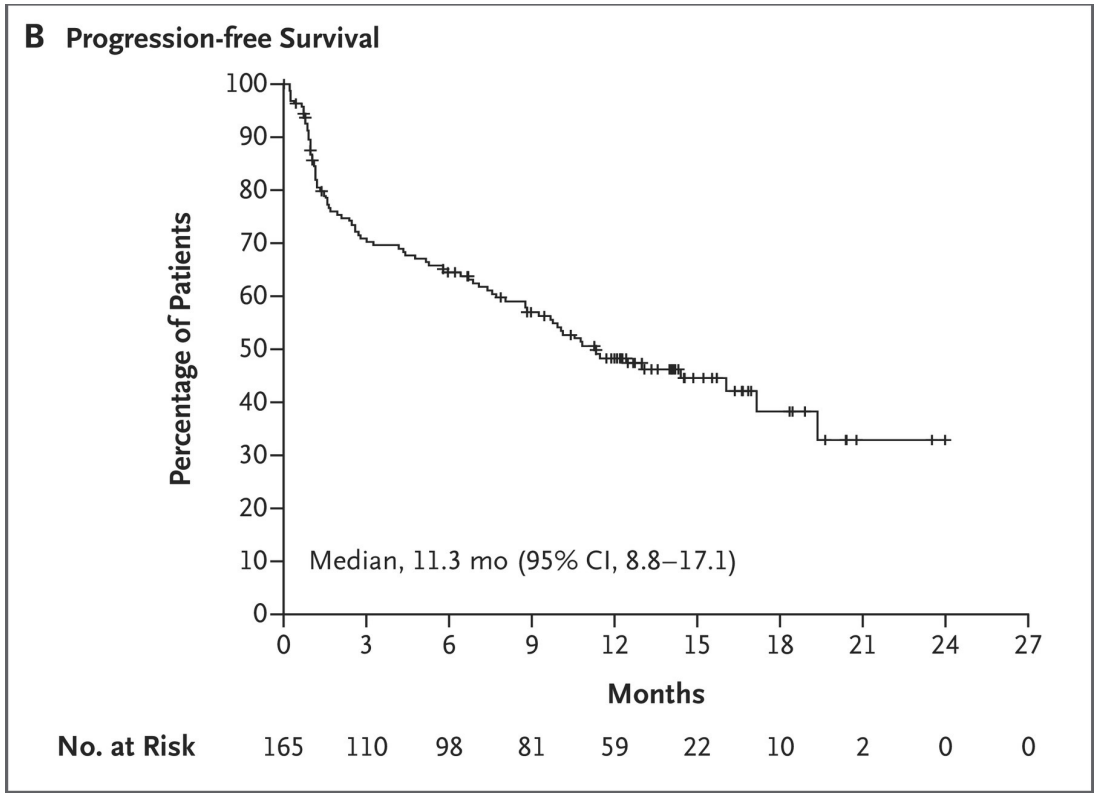
Cohort	Median age (y)	N	ORR (%)	≥ CR (%)	MRD - (%)	PFS (months)	OS (months)	Grade ≥3 CRS (%)	Grade ≥3 neuro (%)	Toxic discont. (%)
Teclistamab	64	165	63	39	27	11.3	18.3	1	1	1

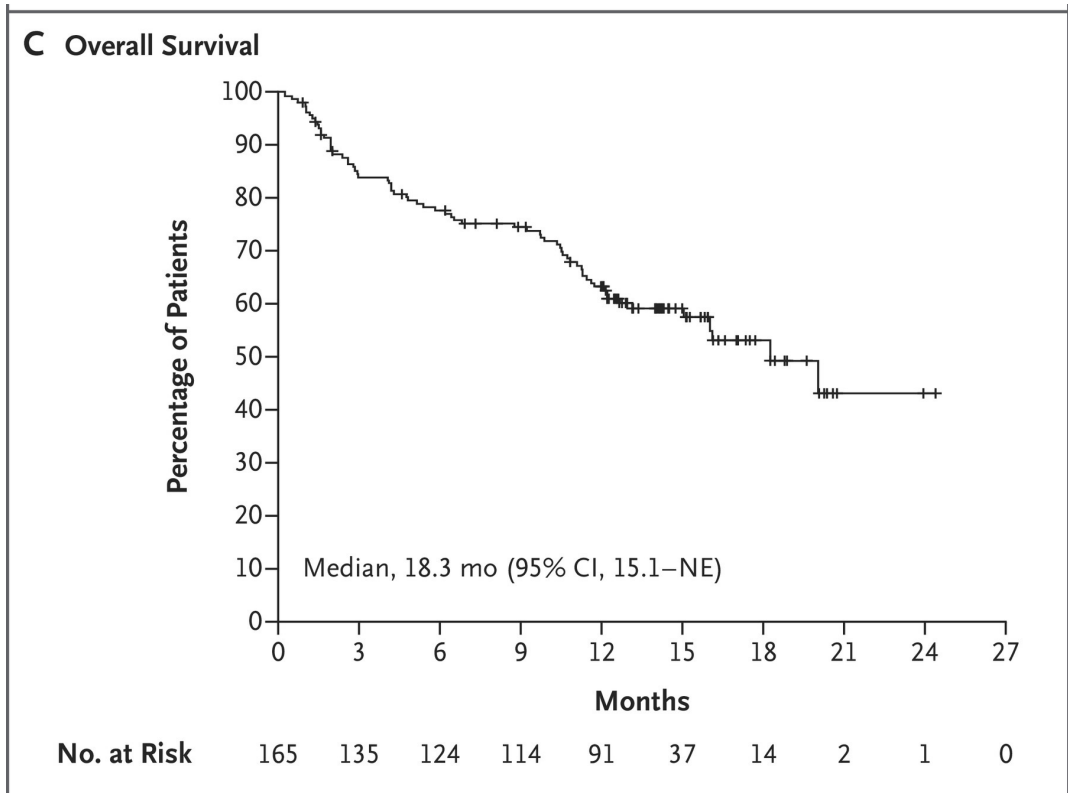
*Other tox: Grade 1-2 CRS 71%, grade 1-2 neuro 14%, grade ≥ 3 infection 45%

Source: Moreau P et al. *NEJM*, 2022

Majes-TEC1: Teclistamab

Survival curves:





Source: Moreau P et al. *NEJM*, 2022

GPRC5D BiTE in R/R MM: Talquetamab

MonumenTAL-1:

- Phase 1-2 trial of talquetamab, CD3-GPRC5D BiTE
- R/R disease
- N = 232
  - Age **≥** 18
  - R/R to established therapies, including IMiD and PI, Cr Cl ≥ 40
  - ECOG 0/1
  - **Admission and premeds for 1st dose:** **CRS, ICANS, REMS**
  - Primary endpoint: AEs
  - Secondary endpoints: RR, MRD negativity, etc.

Source: Chari A et al. *NEJM*, 2022.

MonumenTAL-1: Talquetamab

Study outcomes (updated):

Cohort	Median age (y)	N	ORR (%)	≥ VGPR (%)	MRD - (%)	PFS (months)	OS (months)	Grade ≥3 CRS (%)	Grade ≥3 neuro (%)	Toxic discont. (%)
Subcutaneous q week	64	288	74	59	11/16 with ≥ CR	7.5	n/a	1	0	5
Subcutaneous q 2 week		145	73	57		11.9	n/a	0	0	8

*Other tox: Grade 1-2 CRS 75-79%, grade 1-2 neuro 11%, grade ≥ 3 infection 16-26%

**Similar efficacy and toxicity for cohort with prior “T-cell redirection” (CAR-T, bispecific)

Source: Chari A et al. *NEJM*, 2022; Schinke C et al. ASCO 2023

BCMA BiTE in R/R MM: Elranatamab

MagnetisMM-3:

- Phase 2 trial of elranatamab, CD3-BCMA BiTE
- R/R disease
- N = 123 (cohort A)
  - Age ≥ 18
  - R/R disease (PI, IMiD, CD38)*, no prior BCMA (cohort A), Cr Cl ≥ 30, LVEF ≥ 40%
  - ECOG 0-2
  - **Admission and premeds for 2 step-up doses:** **CRS, ICANS, REMS**
  - Primary endpoint: ORR
  - Secondary endpoints: PFS, OS, MRD negativity, etc.

*FDA approval 8-14-23: ≥ 4 prior lines (including PI, IMiD, CD38)

Source: Lesokhin A et al. *NEJM*, 2022.

MagnetisMM-3: Elranatamab

Study outcomes:

Cohort	Median age (y)	N	ORR (%)	≥ CR (%)	MRD - (%)	PFS (months)	OS (15 months)	Grade ≥3 CRS (%)	Grade ≥3 ICANS (%)	Toxic discont. (%)
Elranatamab	68	123	61	35	~21	15	57%	0**	0	14

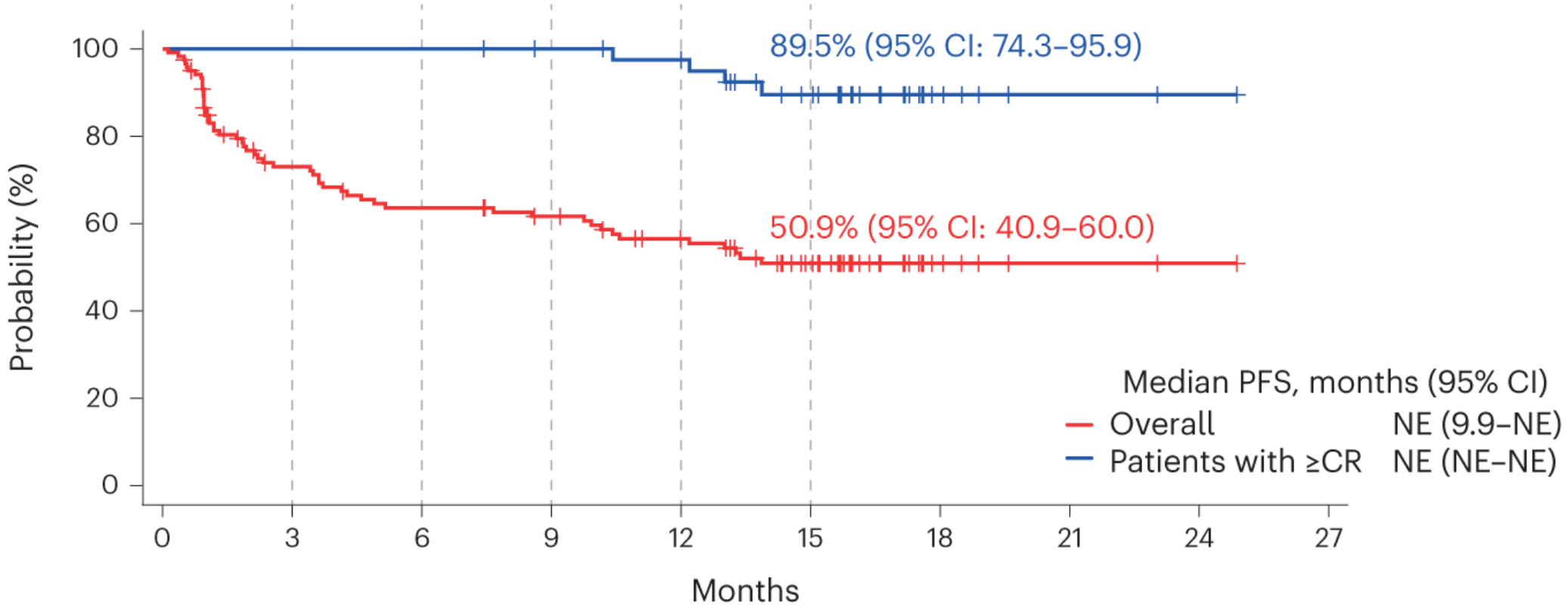
*Other tox: Grade 1-2 CRS 58%, grade 1-2 ICANS 3.4%, grade ≥ 3 infection 40%, grade 5 infection 6.5%; grade ≥ 3 neutropenia 49%

**grade 3 CRS 0.5% first report

Source: Lesokhin AM et al. *Nat Med*, 2023

MagnetisMM-3: Elranatamab

PFS, entire cohort (red) and CRs (blue):



Source: Lesokhin AM et al. *Nat Med*, 2023

BiTES IN R/R MM: Teclistamab, Talquetamab, and Elranatamab

BiTEs targeting BCMA and GPRC5D:

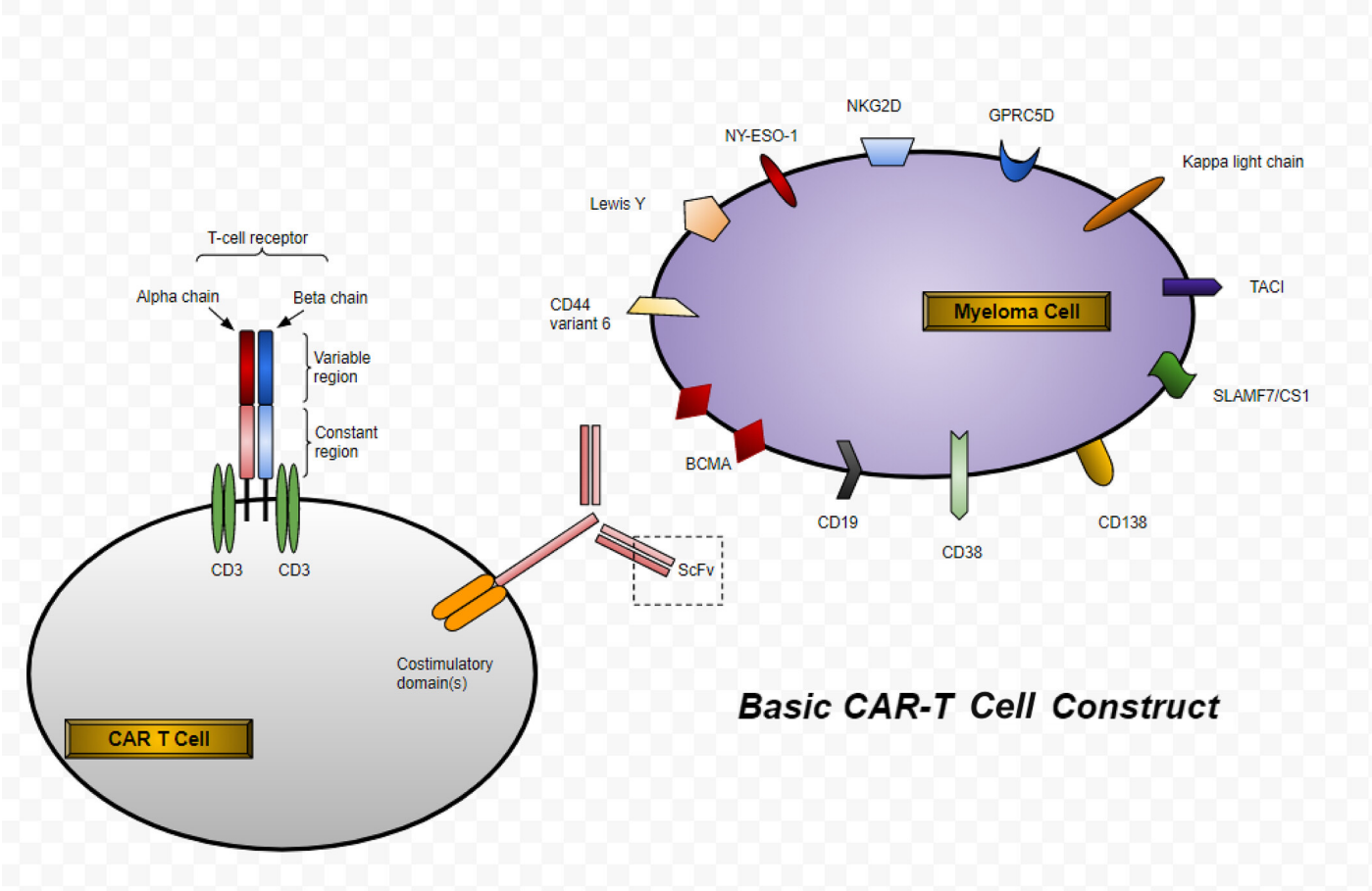
- Responses in triple-class and penta-refractory disease
- Some responses are deep
- Option for non-CAR T-cell candidates
- Reasonable inclusion of older and minority populations
- Require toxicity-monitoring admission(s) and premeds, but…
- Low rates of grade ≥3 CRS and ICANS
- Kaplan-Meier curves appear linear: **treatment is palliative.**

*Current FDA approval for all MM BiTES: **≥** 4 prior lines (including PI, IMiD, CD38)

BCMA IN R/R MM: CAR T cells

Chimeric antigen receptor (CAR) T cells:

- Autologous CD8 T cells, engineered TCR
- T cells bind tumor antigen
- MHC-independent T cell activation
- **BCMA**; other targets in development
- Activate T cell and facilitate immunological synapse → Lysis of target tumor cells



Sources: Parikh RH and Lonial S. *CA Cancer J Clin* 2023; Wang Z et al. *Front Immunol* 2022

BCMA CAR T CELLS: Phase 2 pivotal studies

Idecabtagene vicleucel: triple class refractory, ≥ 3 prior lines, approval March 2021

KarMMa	Median age (y)	N	ORR (%)	≥ CR (%)	MRD - (%)	PFS (months)	OS (months)	Grade ≥3 CRS (%)	Grade ≥3 neuro (%)	Toxic deaths (%)
Ide-cel	61	128	73	33	26	8.8	19.4	5	3	2

Ciltacabtagene autoleucel: triple class refractory, ≥ 3 prior lines, approval February 2022

CARTITUDE-1	Median age (y)	N	ORR (%)	≥ CR (%)	MRD - (%)	12-month PFS (%)	12-month OS (%)	Grade ≥3 CRS (%)	Grade ≥3 neuro (%)	Toxic deaths (%)
Cilta-cel	61	97	98	82	92 (n=61)	77	89	5	12	6

*FDA approval: ≥ 4 prior lines, warnings for CRS, ICANS, HLH, cytopenias, REMS

Sources: Munshi NC et al. *NEJM* 2021; Martin T et al. *J Clin Oncol* 2023

IDE-CEL: Phase 3 vs standard therapy

Idecabtagene vicleucel vs standard therapy: triple class treated (66% refractory), 2-4 prior lines. Primary endpoint: PFS.*

KarMMa-3	Median age (y)	N	ORR (%)	≥ CR (%)	MRD - (%)	PFS (months)	Grade ≥3 overall (%)	Grade ≥3 CRS (%)	Grade ≥3 neuro (%)	Grade 5 event (%)
Ide-cel	63	254	71	39	20	**13.3**	93	5	3	14
Std Tx: DPD, DVD, IRD, KD, EPD	63	132	42	5	1	**4.4**	75	-	-	6

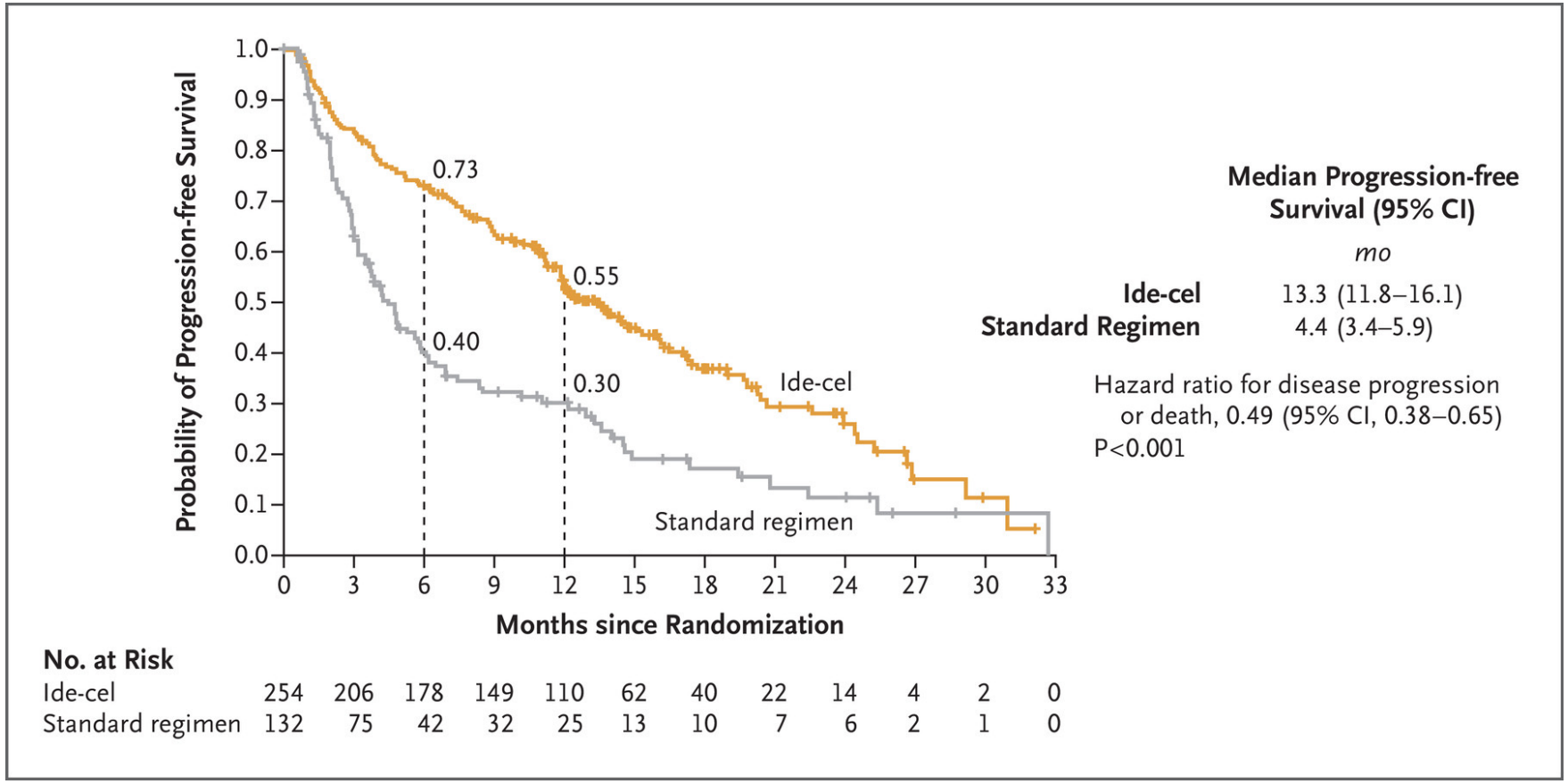
*OS data not mature at time of data cutoff

**DPD = 43, KD = 30, EPD = 30, IRD = 22, DVD = 7

Source: Rodriguez-Otero P et al. *NEJM* 2023

IDE-CEL: Phase 3 vs standard therapy

Idecabtagene vicleucel vs standard therapy: triple class treated (66% refractory), 2-4 prior lines. Primary endpoint: PFS.



Source: Rodriguez-Otero P et al. *NEJM* 2023

CILTA-CEL: Phase 3 vs standard therapy

Ciltacabtagene autoleucel vs standard therapy: lenalidomide-refractory, prior IMiD + PI, 1-3 prior lines (26% triple class exposed). Primary endpoint: PFS.*

CARTITUDE-4	Median age (y)	N	ORR (%)	≥ CR (%)	MRD - (%)	PFS (months)	Grade ≥3 overall (%)	Grade ≥3 CRS (%)	Grade ≥3 neuro (%)	Toxic deaths (%)
Cilta-cel	61.5	208	85	73	61	**23**	96	1	2.3	4.8
Std Tx: PVD, DPD	61	211	67	22	16	**12**	94	-	-	2.4

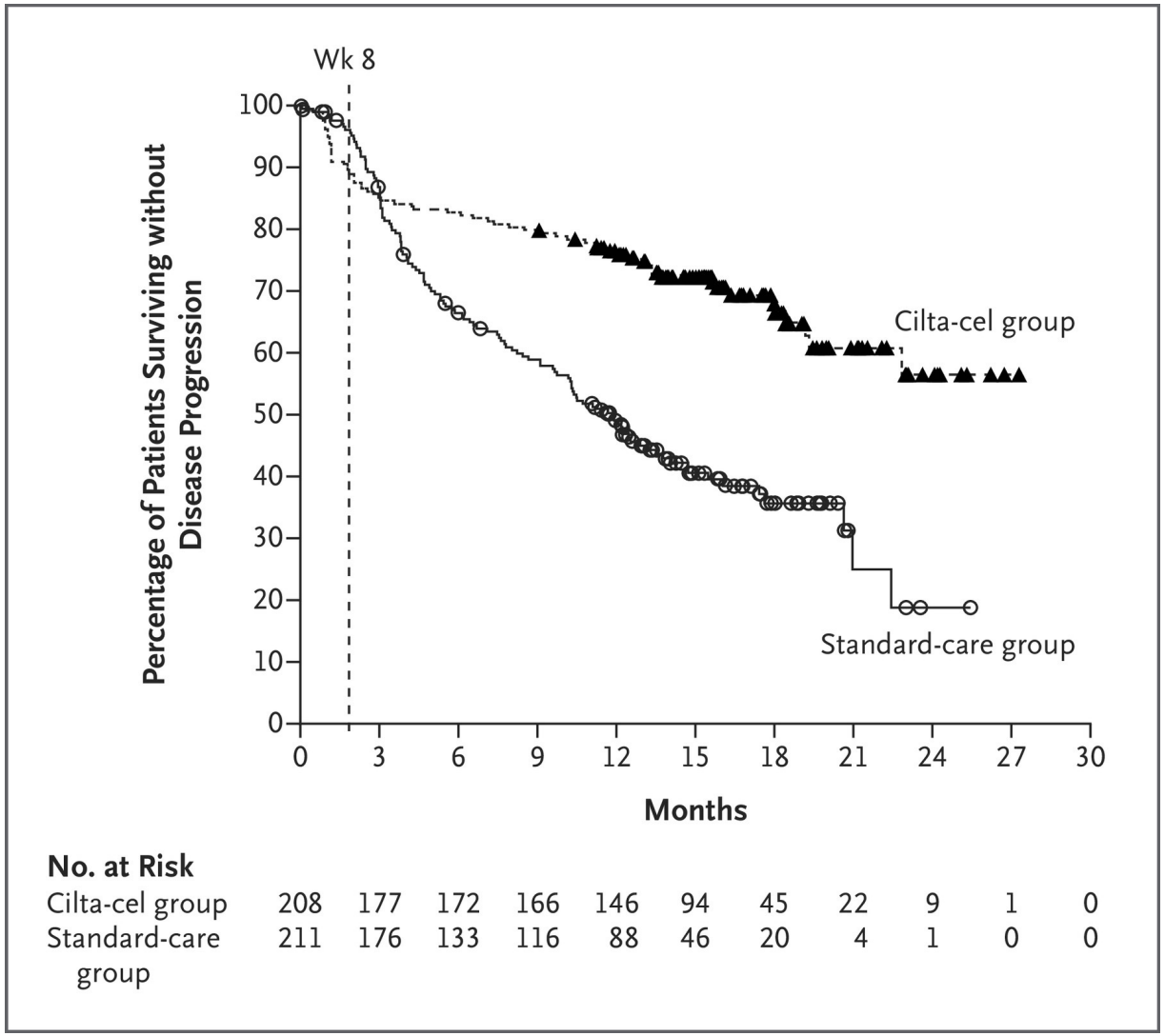
*OS data not mature at time of data cutoff

**DPD = 183, PVD = 28

Source: San-Miguel J et al. *NEJM* 2023

CILTA-CEL: Phase 3 vs standard therapy

Ciltacabtagene autoleucel vs standard therapy: lenalidomide refractory, 1-3 prior lines, 26% triple-class exposed. Primary endpoint: PFS.



Source: San-Miguel J et al. *NEJM* 2023

R/R MM: CAR T cells

Ide-cel and cilta-cel:

- Responses in triple class- and penta-refractory disease
- Some responses are deep
- Option for cellular therapy (more robust) candidates
- Limited inclusion of older populations
- Requires cellular therapy-capable facility due to…
- Appreciable rates of grade ≥3 CRS and ICANS
- Kaplan-Meier curve is linear: **treatment is palliative.**

*FDA approval: **≥** 4 prior lines (including PI, IMiD, CD38)

UNANSWERED QUESTIONS

Selected “smoldering topics” in MM:

- Ideal induction regimen? Triplet or quadruplet?
- Best treatment endpoint? **MRD** assessment?
- What is the optimal timing/sequencing of BiTEs and CAR T cells?
- Which is the optimal CAR T cell in MM, **ide-cel** or **cilta-cel**?

CONCLUSIONS/FUTURE DIRECTIONS

Take-home points:

- CD38 mabs:
  - Increase MRD-negative rate and deepen response
  - Seeing more use in 1st-line therapy
- BiTEs and CAR T cells buy time in heavily R/R MM, *but*
- Require specialized toxicity monitoring and/or centers

Future directions:

- Real-world datasets:
  - Multi-institution/health system studies of non-trial patients
  - CIBMTR database comparisons of CAR T products
- Trials that incorporate:
  - Novel sequencing and combinations
  - More permissive age, ECOG, and organ function criteria

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Our patients and their families/caregivers

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