NCI Cancer Center

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THE UNIVERSITY OF KANSAS HEALTH SYSTEM

Multiple Myeloma: Aiming Wisely with Targeted Agents

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August 19, 2023

CONFESSION

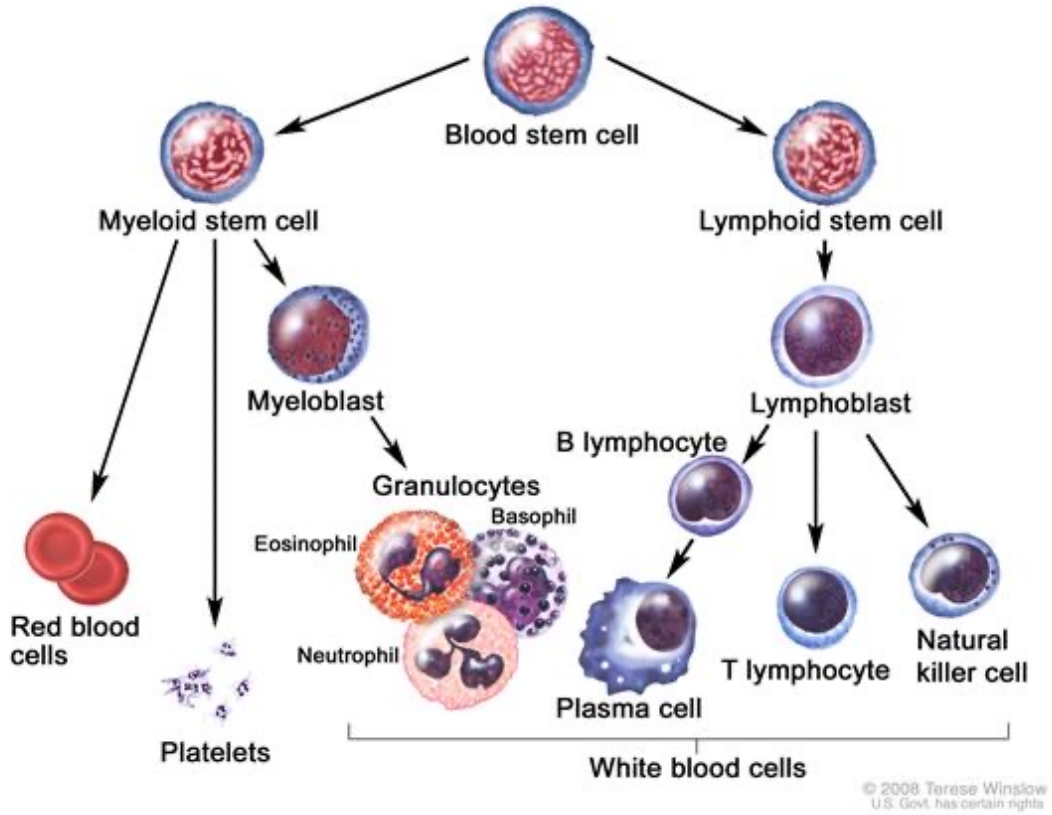
- Host of the Classical Music Clinic
- Sundays 1 pm Eastern on Clubhouse
- 3+ hours of classical music therapy
- https://www.clubhouse.com/@mxk214

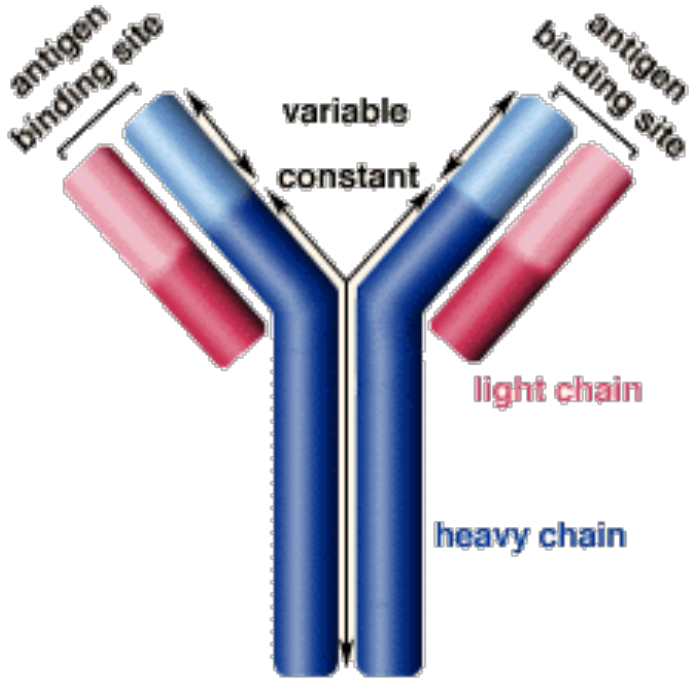
OBJECTIVES/OUTLINE

- 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
Steroid	dexamethasone
Cytotoxic chemotherapy	cyclophosphamide[1], melphalan[1]
CD38 monoclonal antibody **(mab)**	daratumumab, isatuximab
Immunotherapy	
BiTEs (BCMA, GPRC5D)	teclistamab, talquetamab[2]
CAR T cells (BCMA)	ide-cel, cilta-cel

*not an exhaustive list

1. Off-label indication, 2. Pending FDA approval

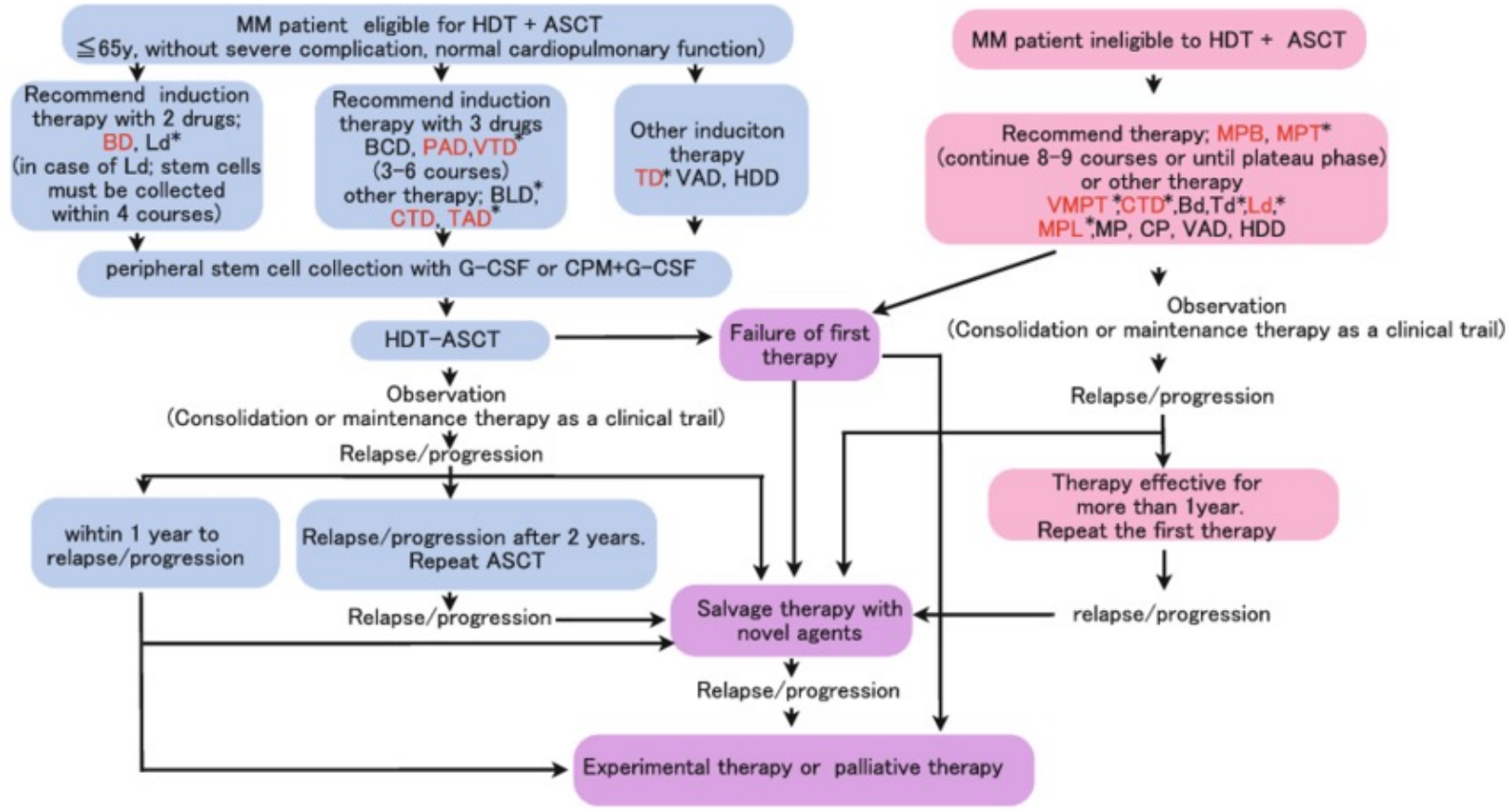
INDUCTION

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

CHOICE OVERLOAD



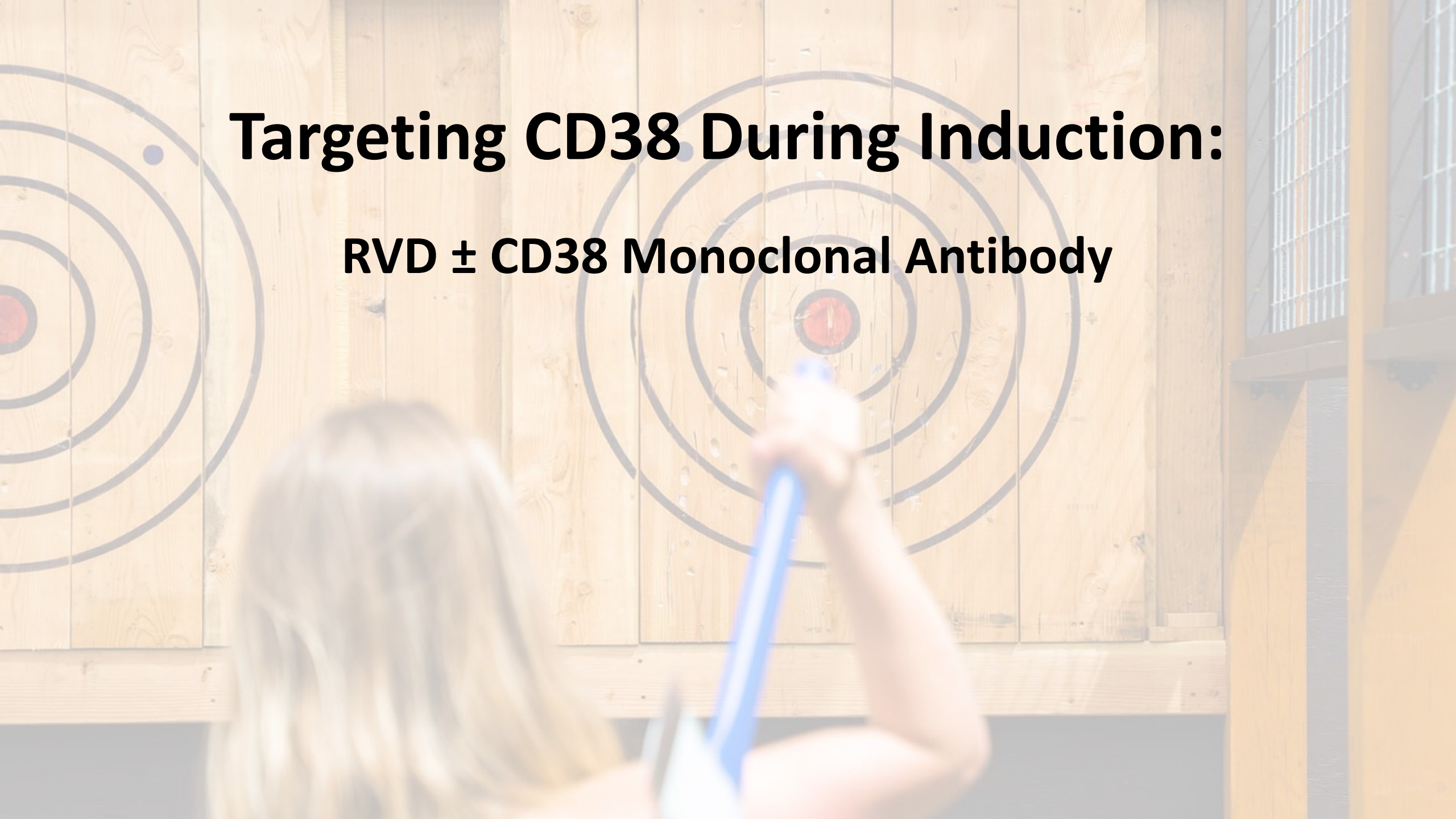
Preferred regimens
BOR/DEX (category 1)
BOR/Cy/DEX
BOR/doxorubicin/DEX (category 1)
BOR/LEN/DEX
BOR/THAL/DEX (category 1)
LEN/DEX (category 1)
BOR/DEX
LEN/low-dose DEX (category 1)
MEL/prednisone/BOR (MPB) (category 1)
MEL/prednisone/LEN (MPL) (category 1)
MEL/prednisone/THAL (MPT) (category 1)
BOR
LEN (category 1)
THAL (category 1)
Repeat primary induction therapy (if relapse at > 6 months)

Source: Watanabe R et al. *Int J Haematol*. 2013

CHOICE OVERLOAD

Targeting CD38 During Induction:

RVD ± CD38 Monoclonal Antibody



INDUCTION: Targeting CD38

“RVD”:

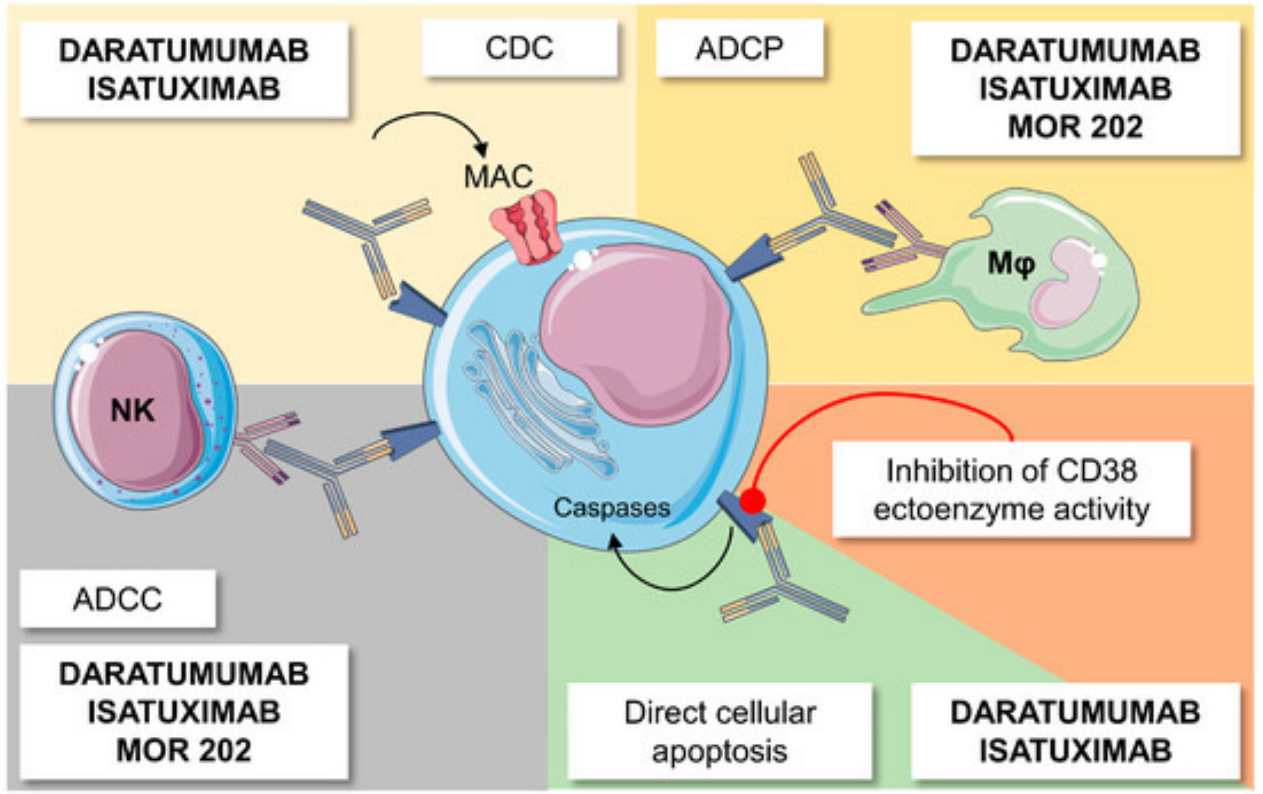
- Standard-of-care triplet induction for fit patients (e.g. auto-HCT candidates) in US
- Standard RVD utilizes a 21-day cycle:
  - R: lenalidomide 25 mg days 1-14
  - V: bortezomib IV or SC 1.3 mg/m^2 days 1, 4, 8, and 11
  - D: dexamethasone 160-320 mg per cycle.
- Excellent efficacy, RR 90 - 100% in first-line.
- Bortezomib-induced neuropathy in up to 80% (treatment-limiting)

Source: Joseph NS, et al. *J Clin Oncol* 2020; Richardson PG, et al. *Blood* 2010

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: Targeting CD38

GRIFFIN:

- Phase 1 → phase 2 RCT of **RVD ± daratumumab**
- Phase 2: N = 207
  - Age 18-70, auto-HCT candidates
  - Excluded GFR < 30 or calcium > 14
  - Randomized: ± dara during induction, consolidation, and maintenance
  - **Primary endpoint: sCR by end of post-HCT consolidation***
  - Secondary endpoint: MRD negativity

*Addressed impact of dara on IFE assessment of sCR/CR

Source: Voorhees P, et al. *Blood* 2020

GRIFFIN: RVD ± daratumumab

Study outcomes

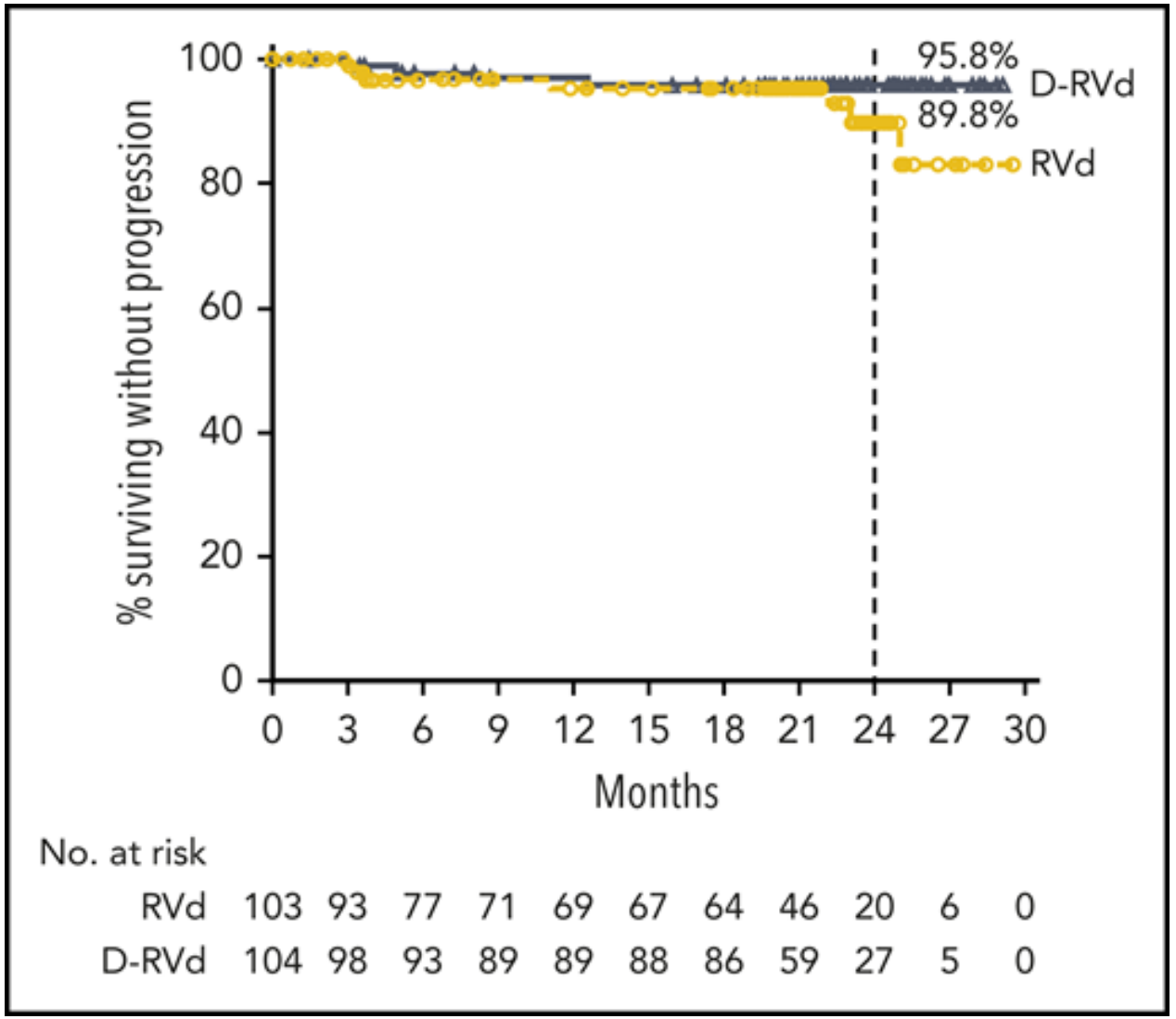
GRIFFIN	Median age (y)	N	ORR (%)	sCR (%)*	MRD - (%)	2-year PFS (%)	Auto-HCT (%)	PMN grade ≥3 (%)	Serious AE (%)	Overall discont. (%)
RVD + daratumumab	59	104	99	**42**	**51**	96	90	41	39	16
RVD	61	103	**92**	**32**	**20**	90	**76**	22	51	**43**

*reported **1-sided** P = 0.07 (2-sided P = 0.14) for sCR, primary endpoint

Source: Voorhees P, et al. Blood 2020

GRIFFIN: RVD ± daratumumab

Progression-free survival (PFS):



Source: Voorhees P, et al. Blood 2020

INDUCTION: Targeting CD38

GMMG-HD7:

- Part I: phase 3 RCT of **RVD** induction **± isatuximab**
- N = 660
  - Age 18-70, auto-HCT candidates
  - Excluded GFR < 30 or calcium > 14
  - Randomized: ± isa during induction (RVD x 3*)
  - **Primary endpoint: MRD negativity (flow) after induction**
  - Secondary endpoint: response rates, toxicity
- Part II: lenalidomide ± isatuximab maintenance, will assess PFS**

*RVD cycle length 42 days (= 6 cycles of 21-day RVD)

** not reported yet

Source: Goldschmidt H, et al. Lancet Haematol 2023

GMMG-HD7: RVD ± isatuximab

Outcomes, end of induction*:

GMMG-HD7	Median age (y)	N	ORR (%)	≥VGPR (%)	MRD - (%)	Auto-HCT (%)	PMN grade ≥3 (%)	Grade ≥3 AE (%)	Overall discont. (%)
RVD + isatuximab	59	331	90	77	**50**	92	23	63	5
RVD	60	329	**84**	61	**36**	**84**	7	61	**11**

*Long-term outcomes will be presented in future reports

Source: Goldschmidt H, et al. Lancet Haematol 2023

INDUCTION: Targeting CD38

CD38 monoclonals added to RVD:

- Higher % MRD-negativity
- Potentially deeper responses
- Toxicity not substantially increased
- Limited inclusion of:
  - Older patients
  - High-risk disease
  - Renal dysfunction
- Does the endpoint justify the means? Patient anxiety, health care $$$
- **No Rx change tied to MRD results**
- **Is MRD-negativity treatment-changing or merely prognostic?**

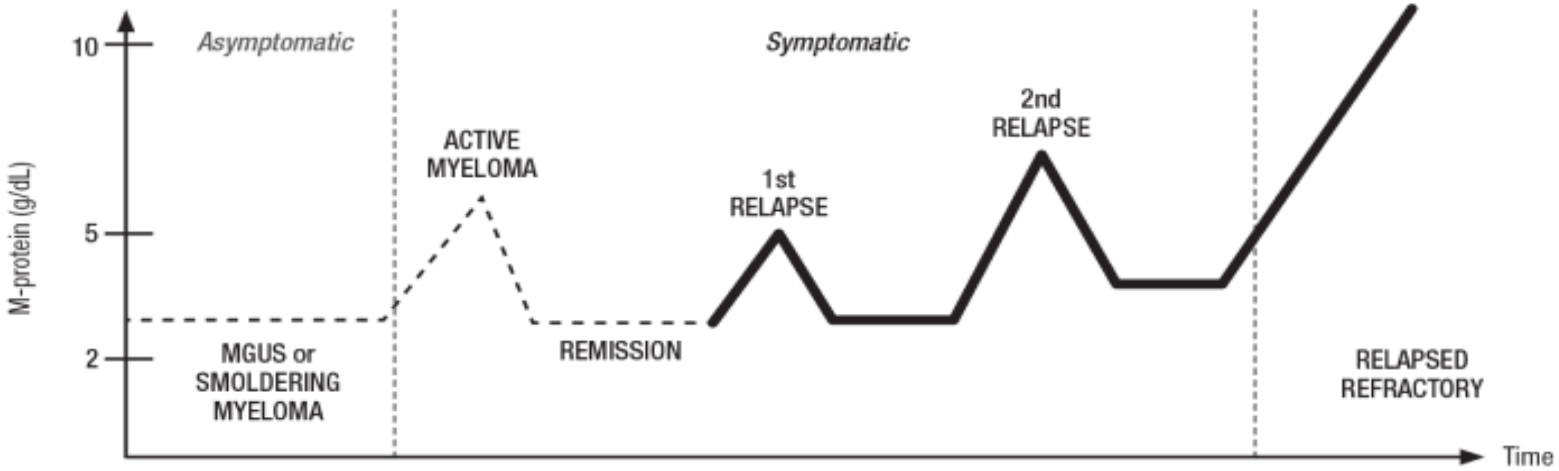
Aiming T-cells at Relapsed/Refractory Myeloma

BiTE therapy and CAR T cells

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?



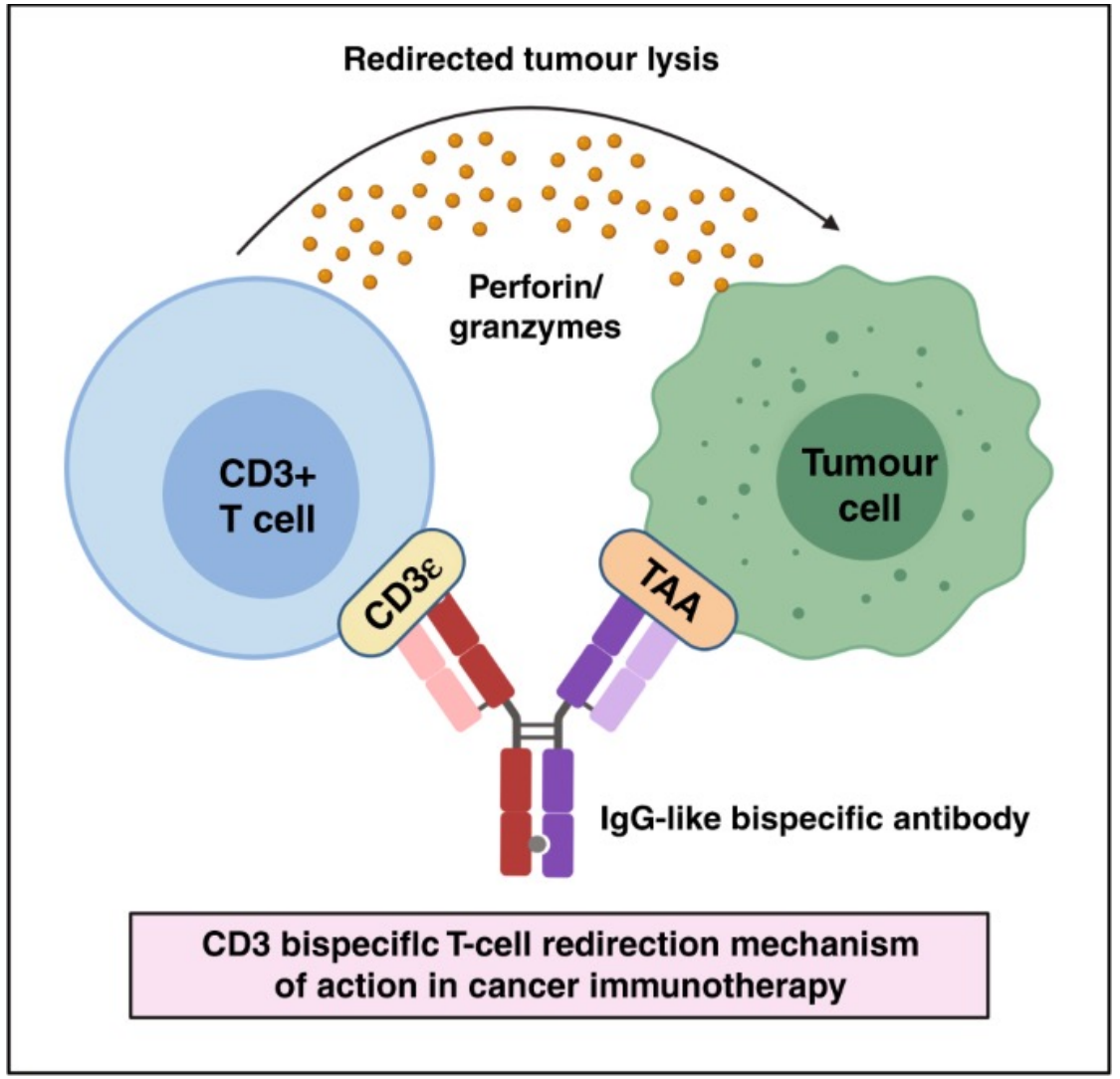
Variable timeline dependent on individual risk factors including genetic and phenotypic changes, depth and duration of response to therapy, persistence of a malignant multiple myeloma stem cell, and evolution of competing multiple myeloma clones

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
- 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:

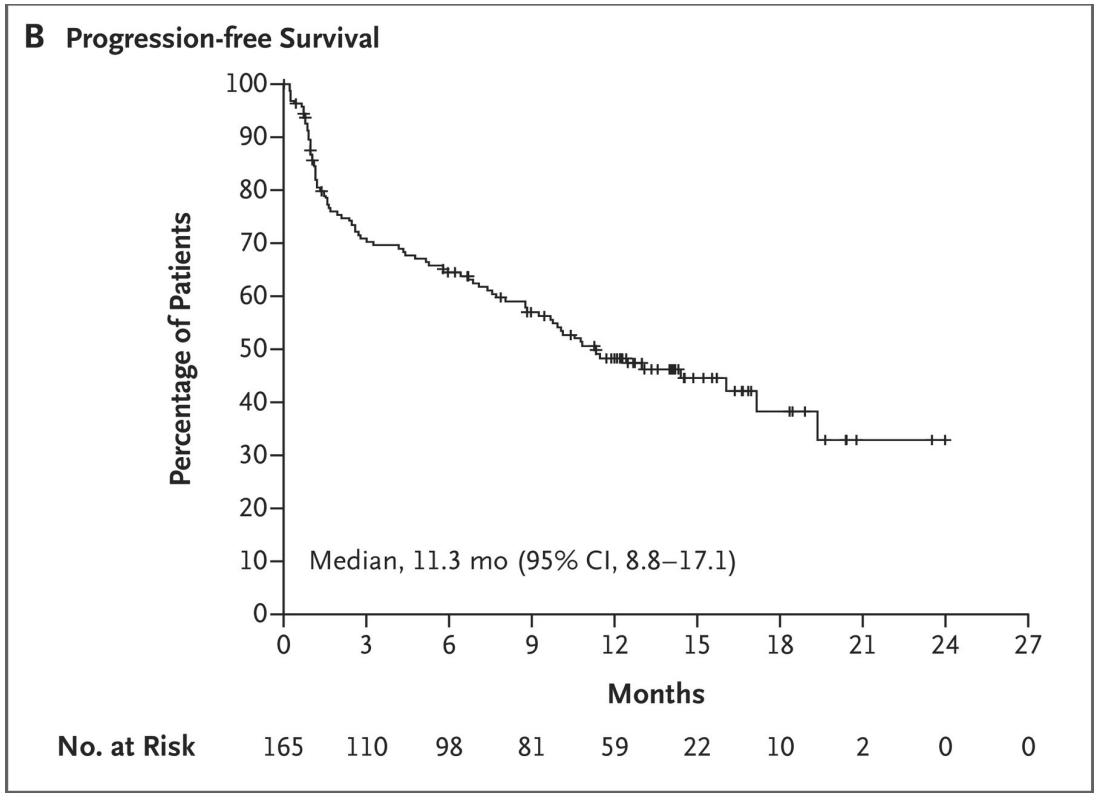
Cohort	Median age (y)	N	ORR (%)	≥ CR (%)	MRD - (%)	PFS (months)	OS (months)	Grade ≥3 CRS (%)	Grade ≥3 neuro (%)	Toxic discont. (%)
Teclistamab	64	165	63	39	27	11.3	18.3	1	1	1

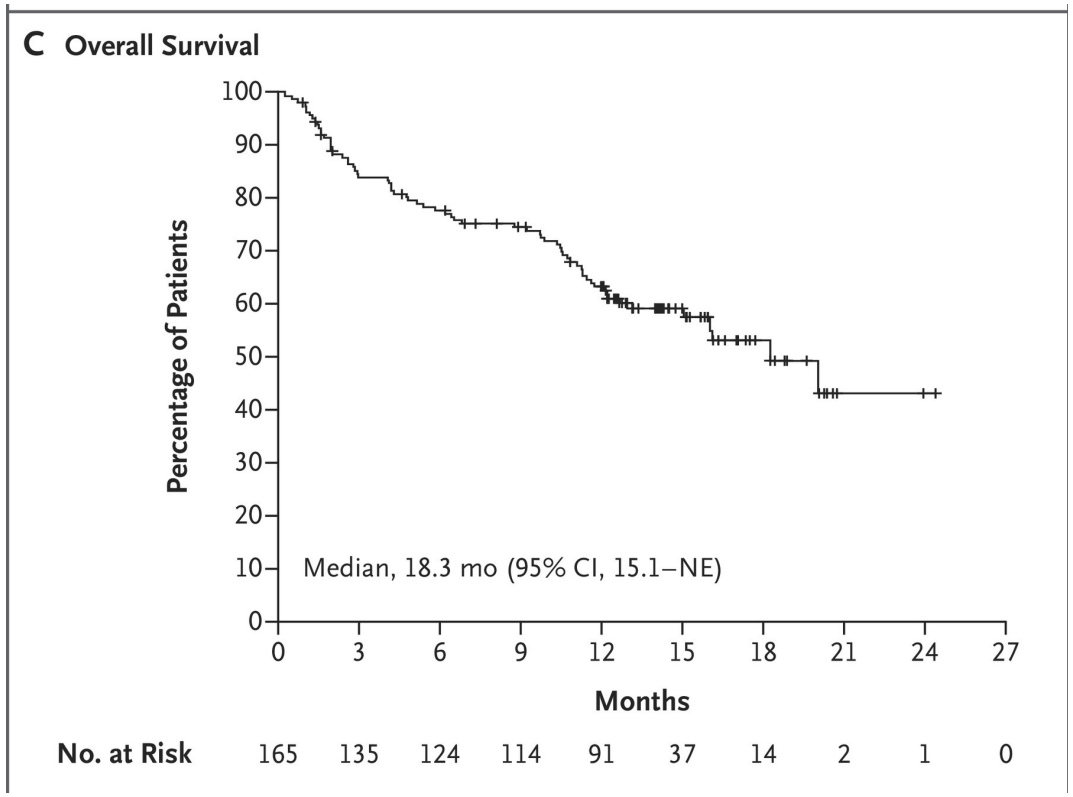
*Other tox: Grade 1-2 CRS 71%, grade 1-2 neuro 14%, grade ≥ 3 infection 45%

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

Majes-TEC1: Teclistamab

Treatment response:





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**
  - Primary endpoint: AEs
  - Secondary endpoints: RR, MRD negativity, etc.

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

MonumenTAL-1: Talquetamab

Study outcomes:

Cohort	Median age (y)	N	ORR (%)	≥ CR (%)	MRD - (%)	PFS (months)	OS (months)	Grade ≥3 CRS (%)	Grade ≥3 neuro (%)	Toxic discont. (%)
Subcutaneous	64	130	70	23	11/16 with ≥ CR	10.2 / 7.8	n/a	1	0	0.4
Intravenous	65	102	72	28		n/a	n/a	5	3	

*Other tox: Grade 1-2 CRS 59%, grade 1-2 neuro 6%, grade ≥ 3 infection 7%

**Responses and PFS reported for selected dose cohorts

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

BiTES IN R/R MM: Teclistamab

BCMA-targeted BiTE (teclistamab):

- 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
- Requires toxicity-monitoring admission but…
- Low rates of grade ≥3 CRS and ICANS
- Kaplan-Meier curve is linear: **treatment is palliative.**

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

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

BiTES IN R/R MM: Talquetamab

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- Requires toxicity-monitoring admission but…
- Low rates of grade ≥3 CRS and ICANS

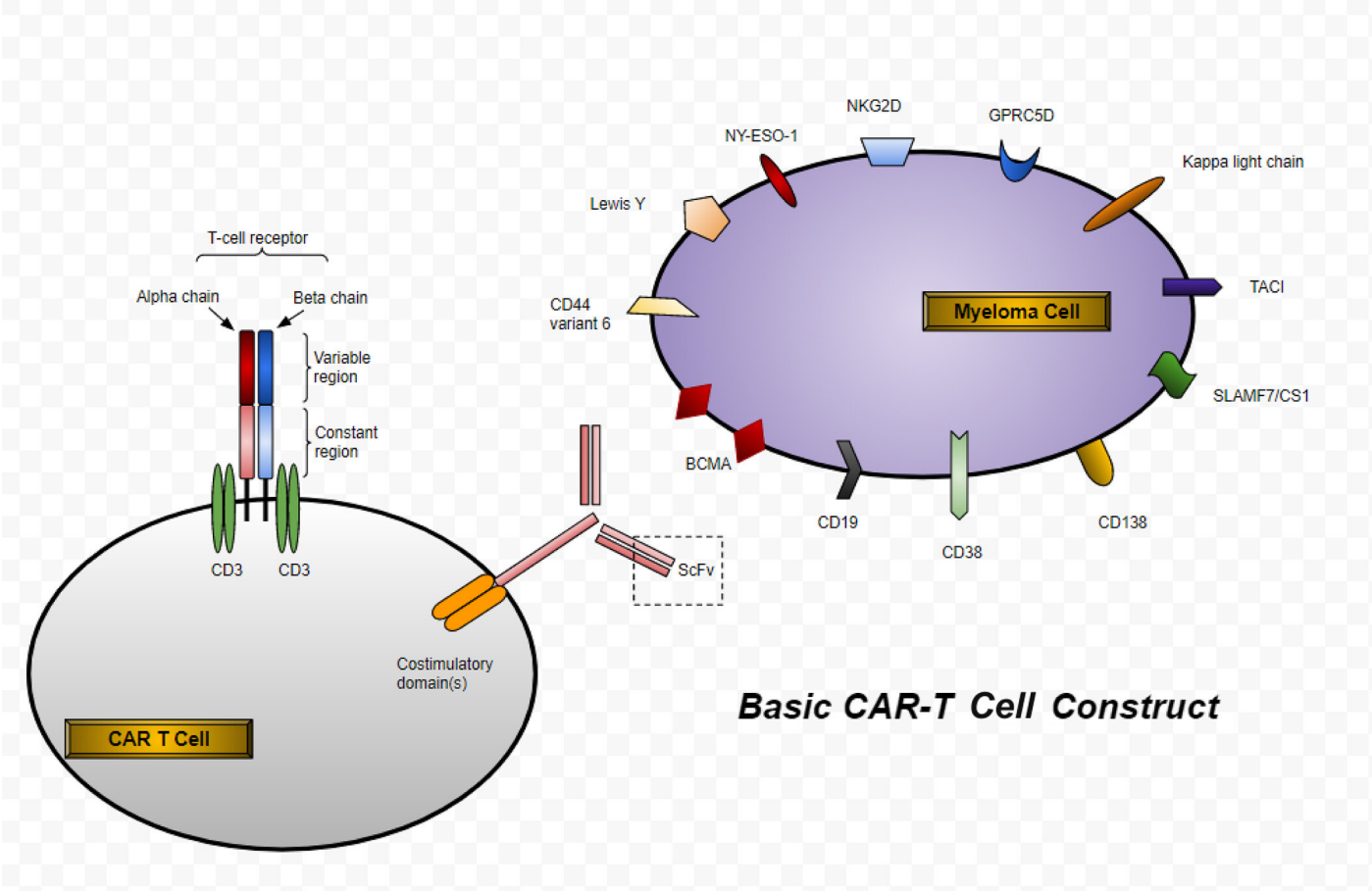
*Pending FDA approval

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

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	12	5	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

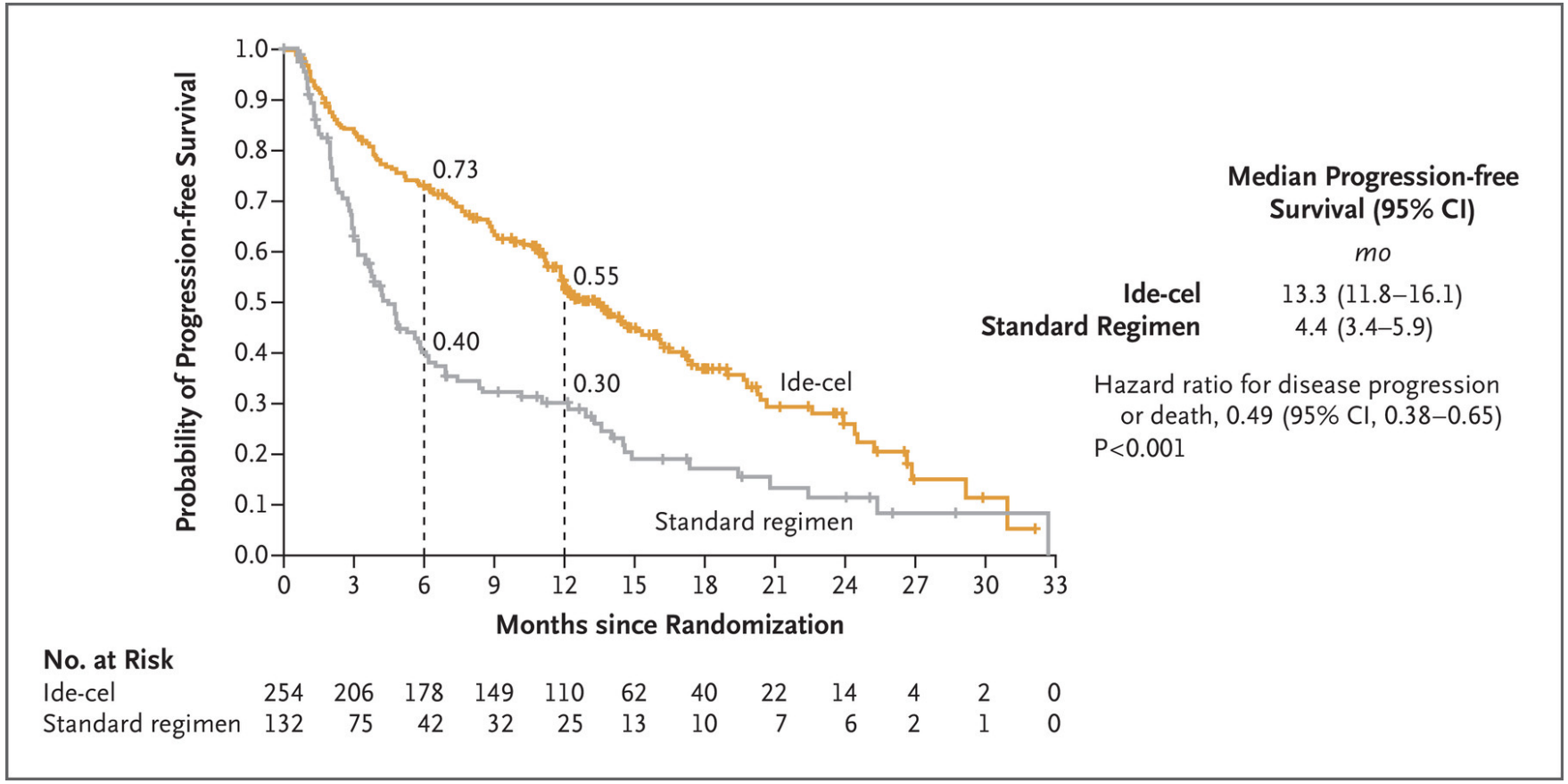
*OS data not mature at time of data cutoff

**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

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?
- Should **all** eligible patients receive auto-HCT?
- When and which targeted agents?
- What is the role of **CAR T cells** in MM?

CONCLUSIONS/FUTURE DIRECTIONS

Take-home points:

- CD38 mabs:
  - Increase MRD-negative rate, perhaps deepen response, *but*
  - Long-term outcomes are pending…
- 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
- Trial designs that link novel endpoints/MRD with *therapy decisions*

ACKNOWLEDGMENTS

Our patients and their families/caregivers

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- Kansas City VAMC Hem/Onc Division
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