Enhancing Immunotherapy in Myeloma

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The Future of Myeloma Immunotherapy

Delineate immune and tumor profiles before and after treatment to inform therapy

Scientifically-based combinations to both enhance efficacy and avoid resistance

Innovative strategies to improve efficacy, tolerability, and access

Earlier use of immunotherapies in NDMM and HR SMM

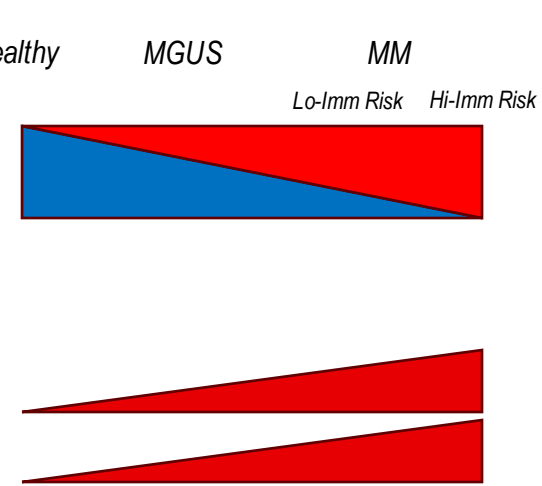
Goal will be to increase the cure fraction of myeloma

Alterations in Immune Microenvironment with Malignant Evolution

TCF1+ stem memory T cells
Naïve CD4/CD8 T cells
Naïve B cells

Functional ILC / NK cells

Functional DCs
M1 macrophages



Terminally differentiated T cells
Hyper-expanded T cell clones
Tregs

ILC / NK cell dysfunction

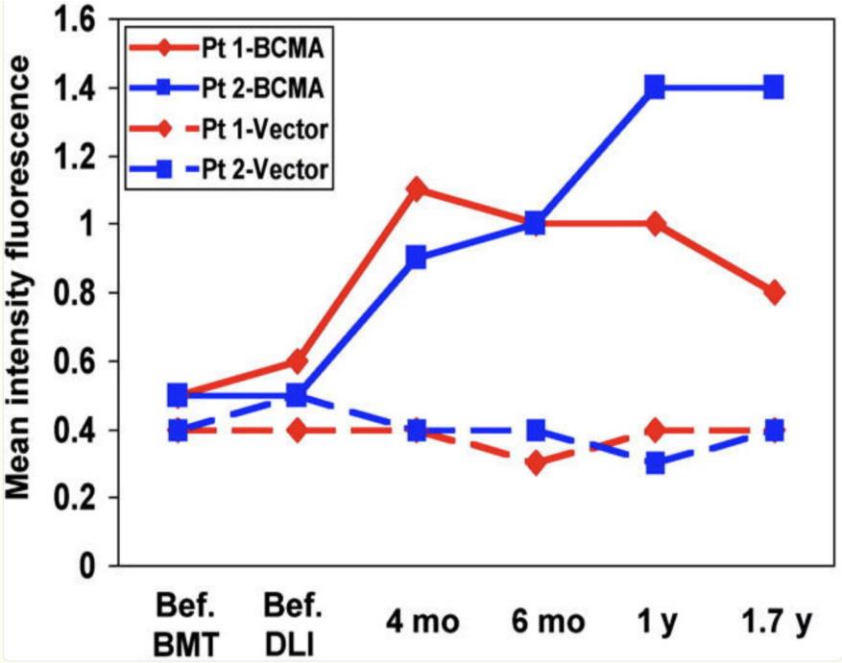
MDSC
DC dysfunction

Aging-associated changes

Inflammatory signaling

Dhodapkar and Paiva, Blood 2025: 146: 1041-50

Abs to BCMA Post DLI Persist and Mediate CDC/ADCC Against MM Cells



Belluci et al Blood 2005; 105: 3945-50

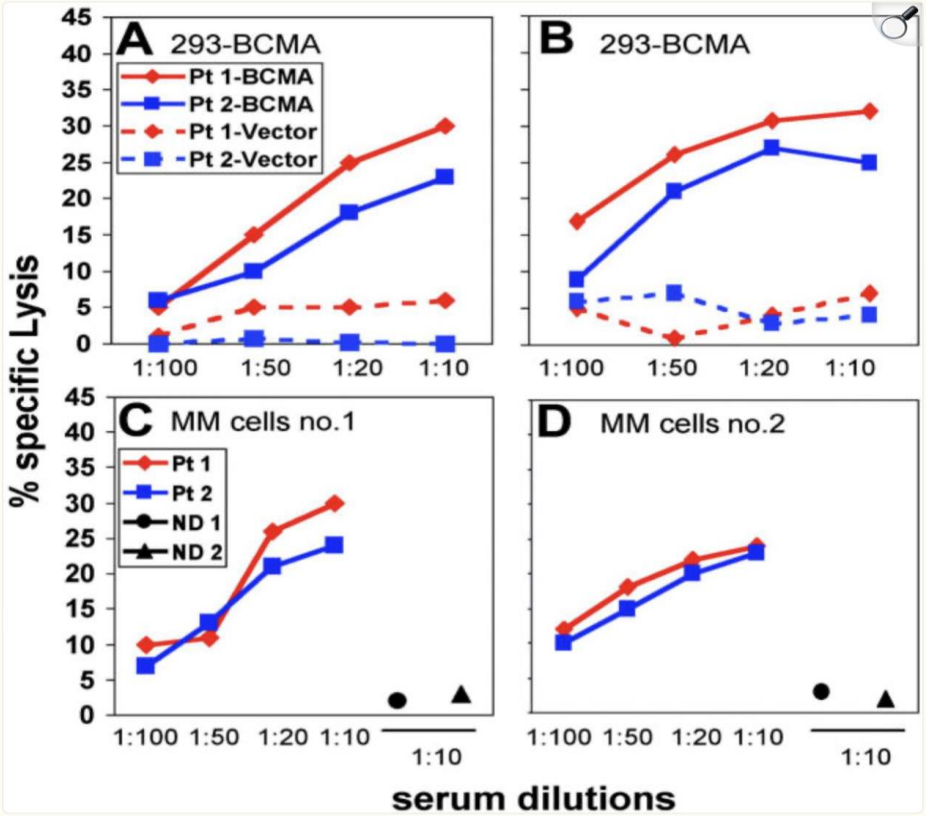
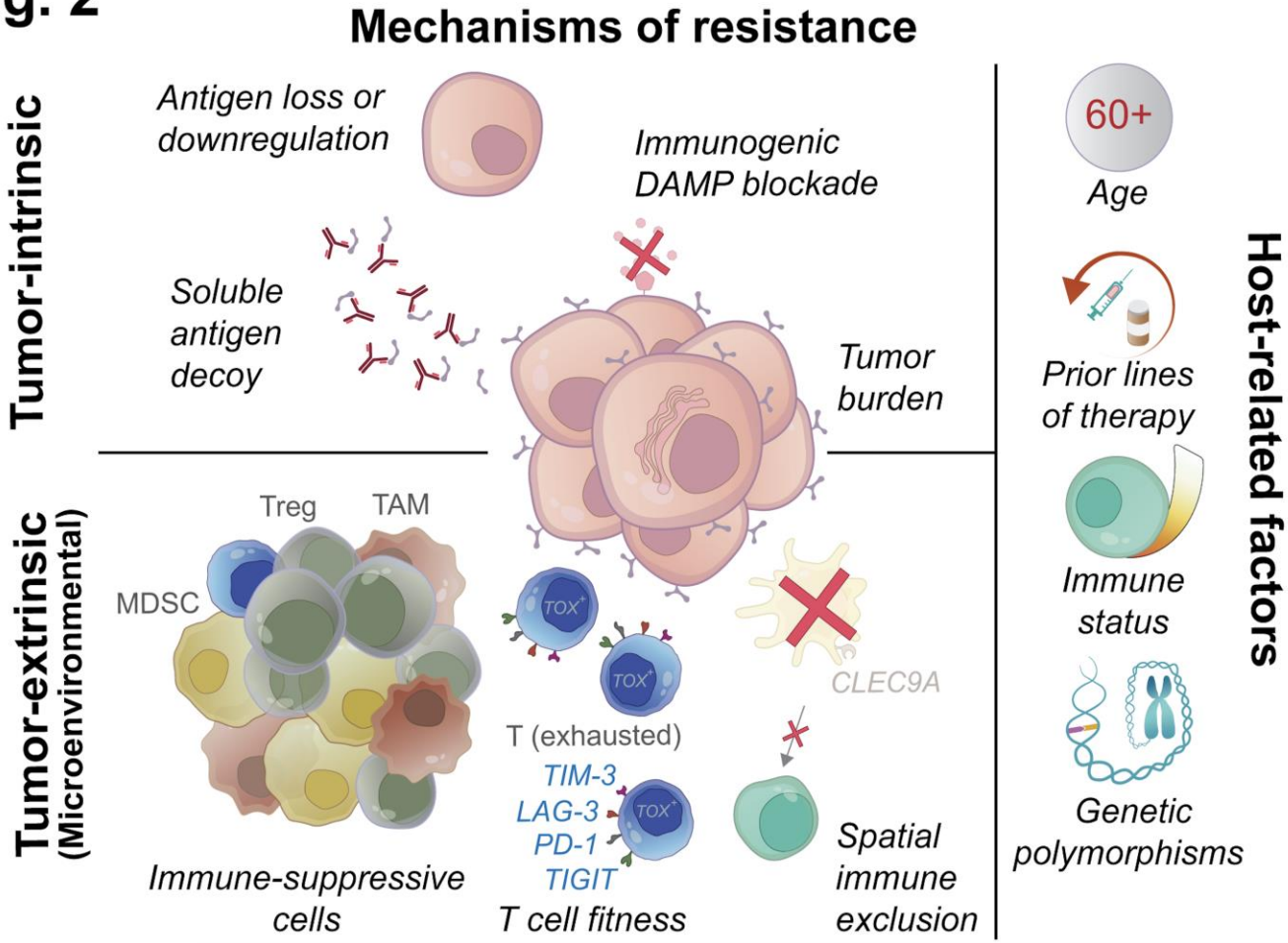
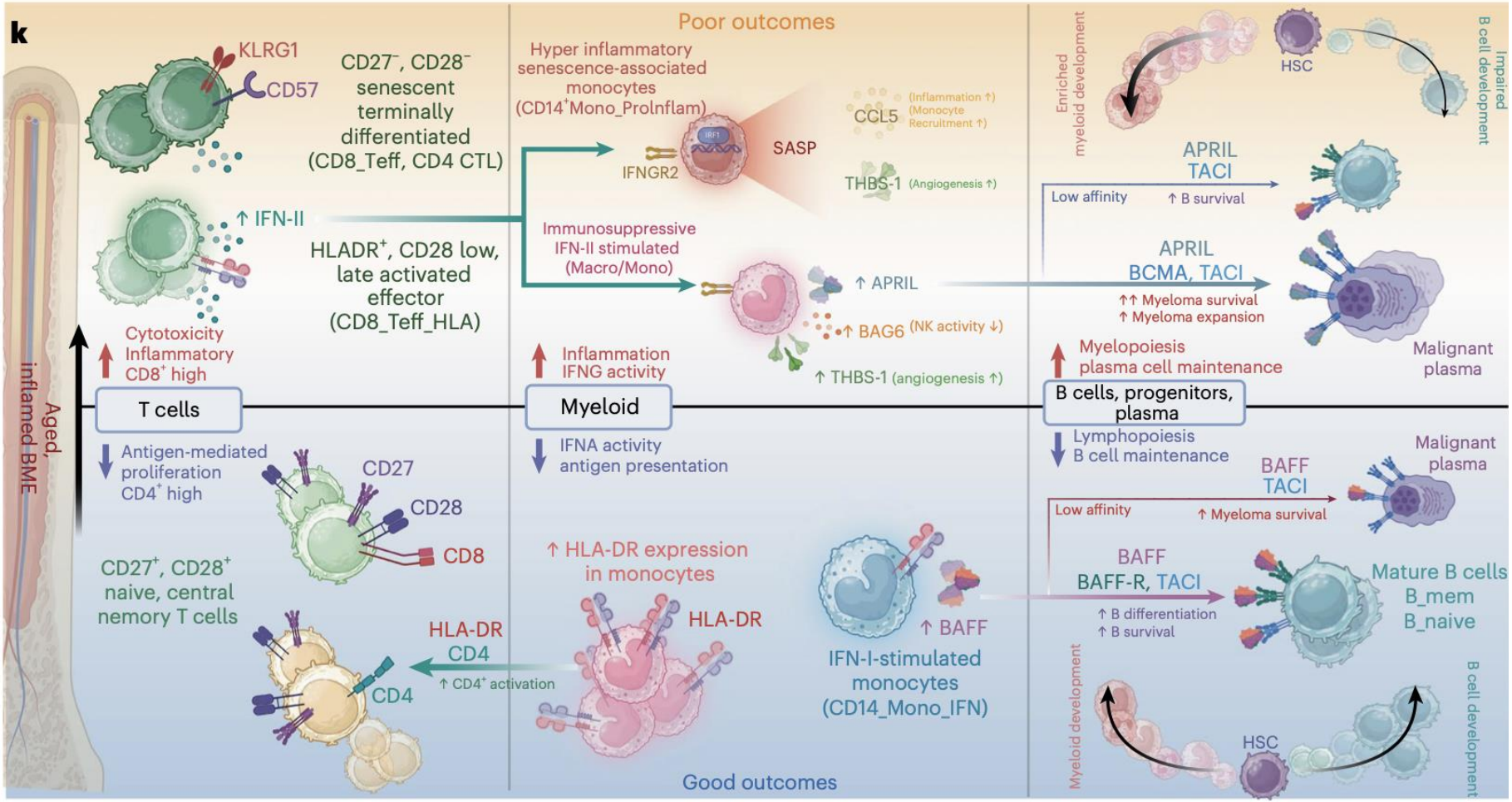


Fig. 2



Gulla, Anderson Blood Cancer Disc 2026: 7:176-94.

Immune Correlates of Clinical Outcome



Pilcher et al Nat Cancer 2026; 7:224-46.

Profiling Long Term MM Survivors

Small subset of patients with long term survival (≥ 10 years from diagnosis)

Connect MM Registry: favorable cytogenetics, younger age, good performance status, and ASCT treatment.

MRD- is associated with prolonged PFS and OS, but some MRD+ patients have long term survival.

Implicates tumor microenvironment and host immunity:

Immune Dysfunction: T and NK cell exhaustion, expansion of MDSCs, Tregs underly relapse and infection; conversely, immune restoration or reactivation evident in some long-term survivors.

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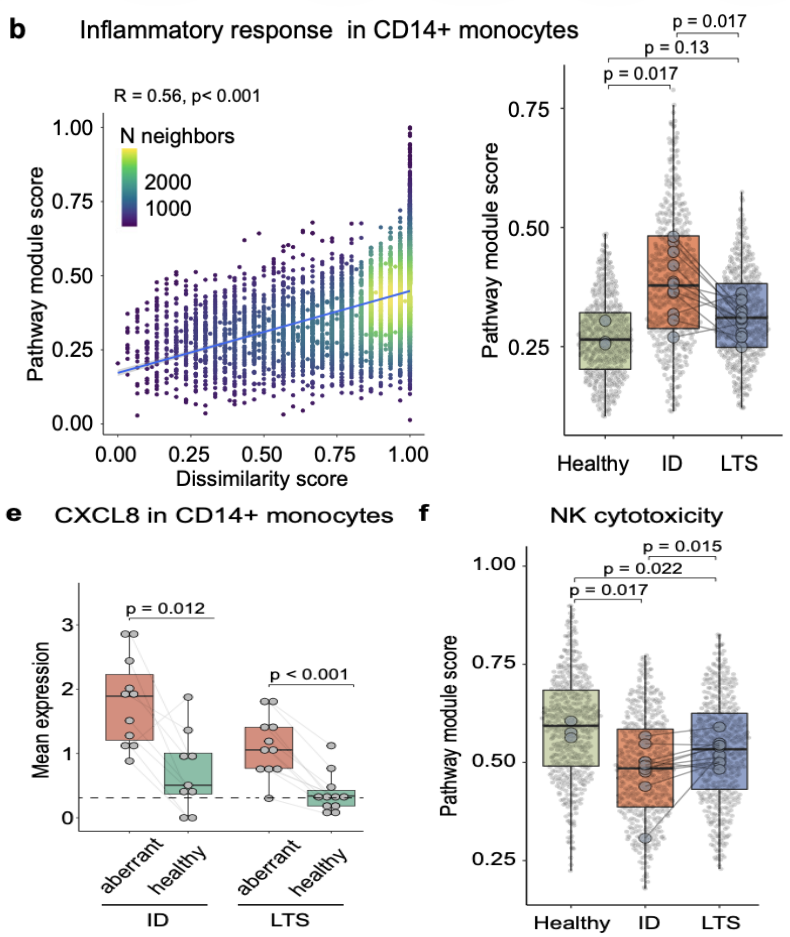
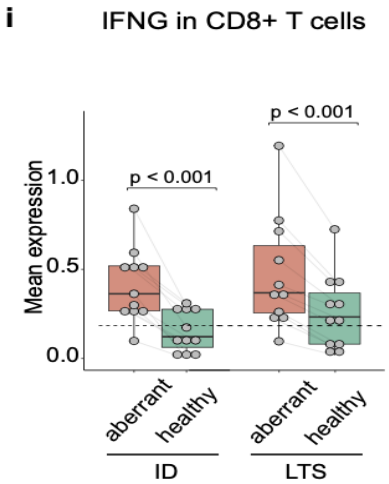
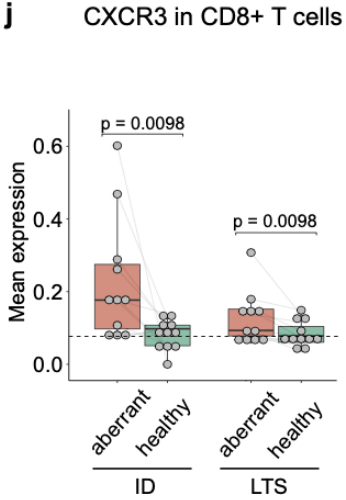
Terebelo HR et al CLML 2025;15: 58-66; Lutz et al Nat Comm 2024; 15: 10396;
Gorgun et al Blood 2013; 121: 2975-87; Prabhala et al Fron Immunol 2023; 13: 1271801

An Inflammatory Circuit Underlies Immune Remodeling During Active Disease and Long-Term Survival



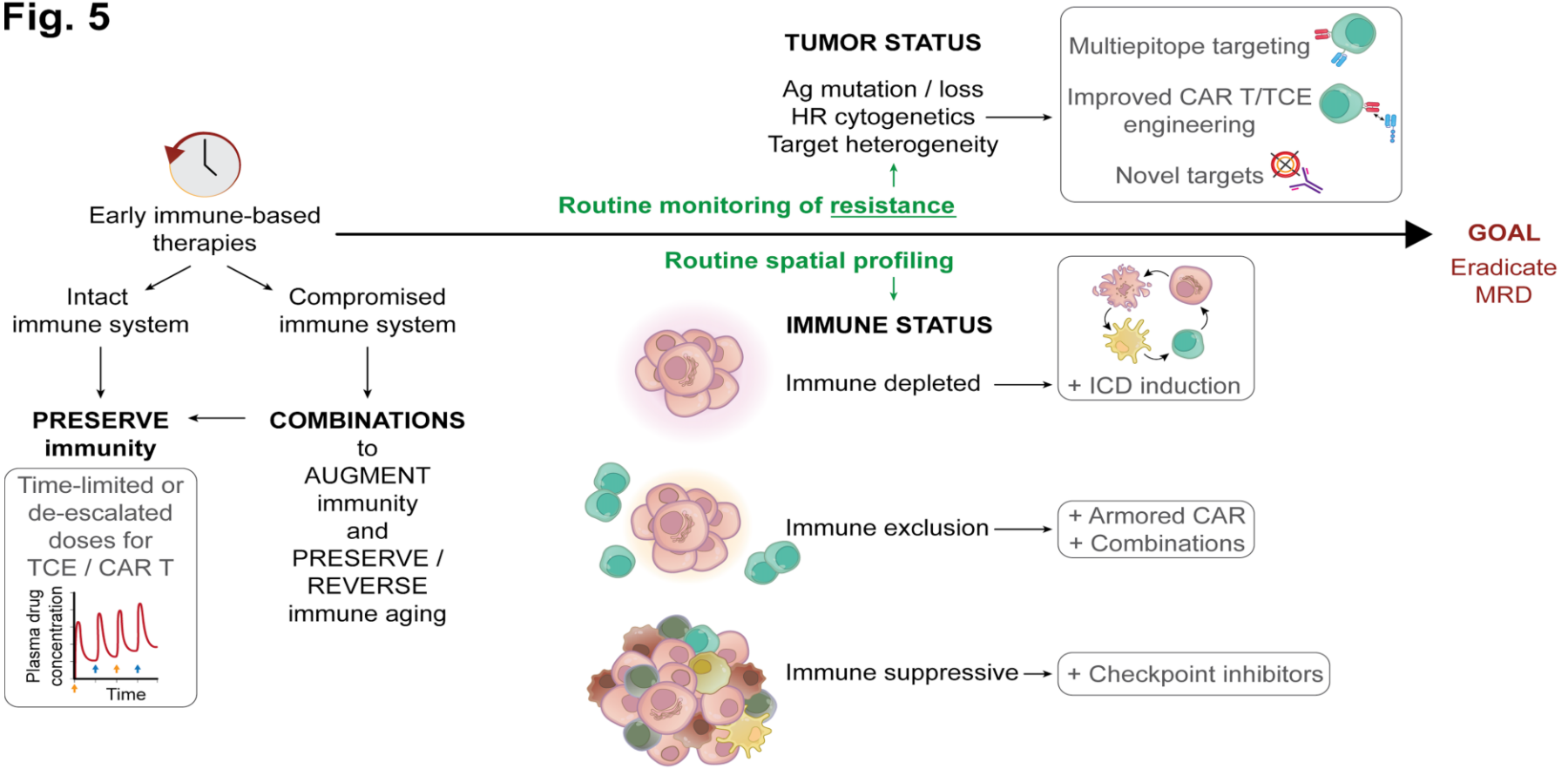




Lutz R et al Nat Comm 2024; 15: 10396

Profiling of Tumor and Host to Inform Therapy

Fig. 5



Gulla, Anderson Blood Cancer Disc 2026; 7: 176-94

Boosting CAR T Cell Efficacy by Blocking Proteasomal Degradation of Membrane Antigens

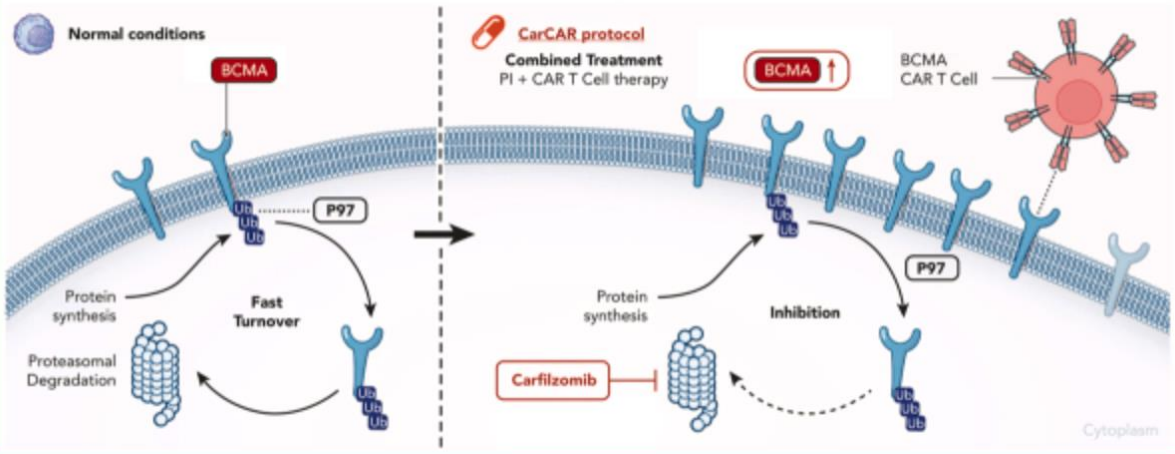
Context of Research

Loss or downregulation of antigen expression reduces CAR T cell efficacy

Aim of This Study

Unraveling the role of the ubiquitin-proteasome system in controlling antigen abundance in multiple myeloma

Findings



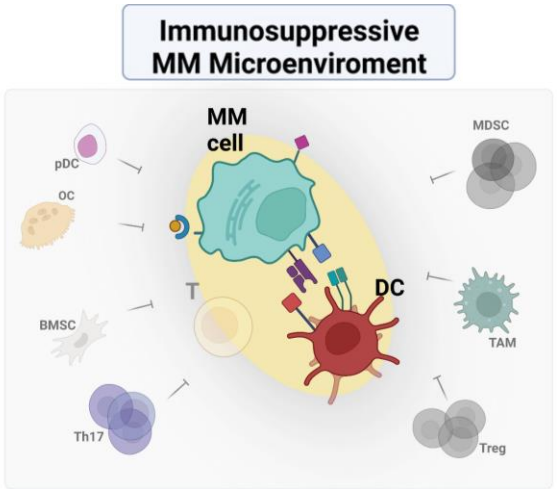
Conclusions: **BCMA antigen expression is controlled by the ubiquitin-proteasome system in a p97-dependent manner at the plasma membrane. Elevation of BCMA cell surface expression via proteasome inhibition augments and restores anti-BCMA CAR T cell activity.**

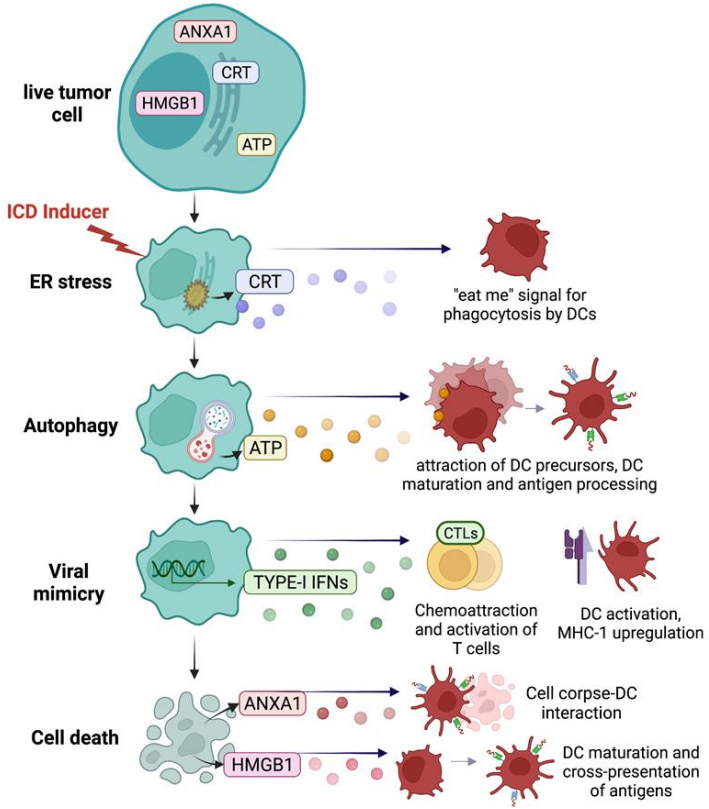
*Rieger et al. DOI: 10.1182/**blood**.2024027616*

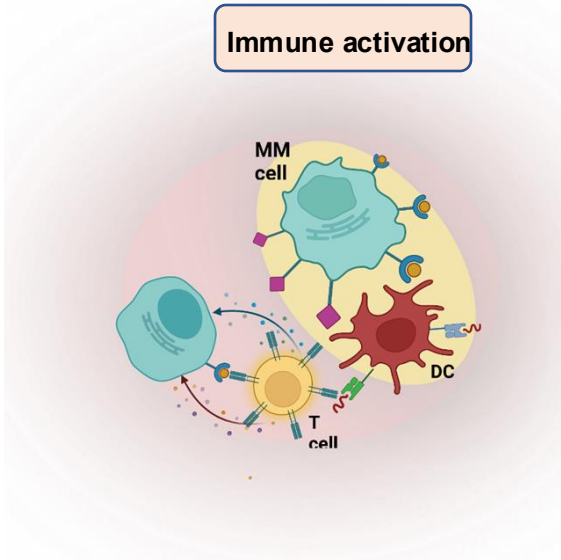
blood Visual Abstract

Bortezomib Triggers Immunogenic Cell Death in the Immunosuppressive MM Microenvironment

***Immunogenic cell death* (ICD)** → **Immune activation**

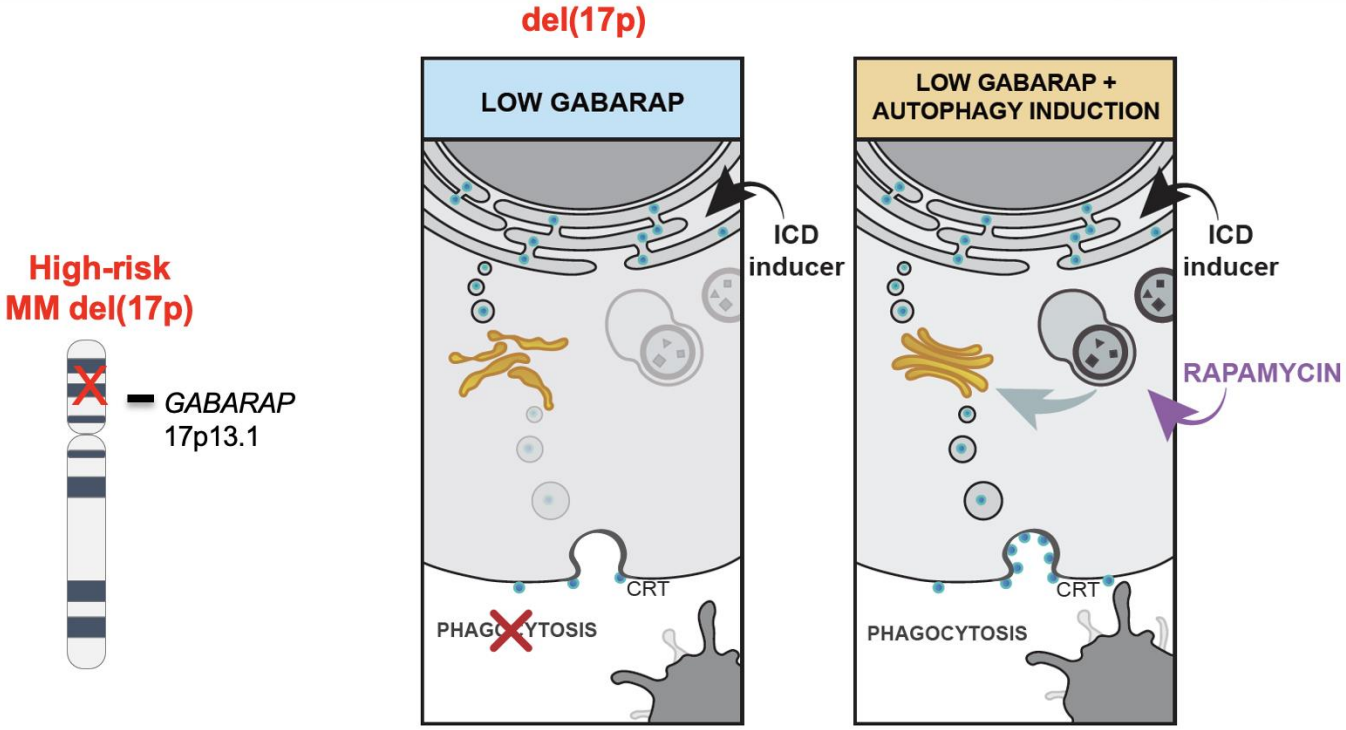






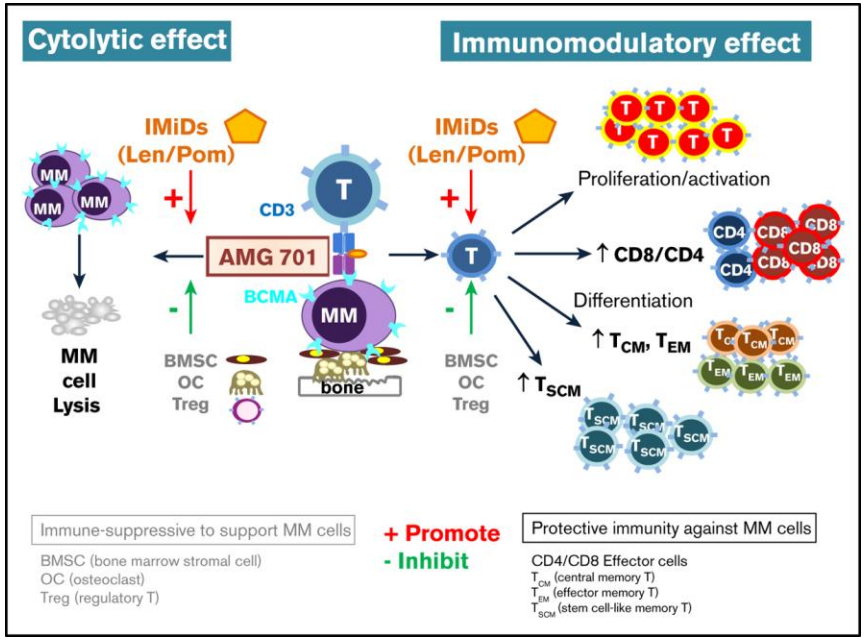
Johnstone M. et al Cells 2022
Gulla A, et al. Blood Cancer Discovery 2021; 2: 468-483.

Triggering Autophagy (Rapamycin) with Immunogenic Cell Death (ICD) Inducer (Bortezomib) Induces ICD in *GABARAP*^{low} (del17p) High Risk MM

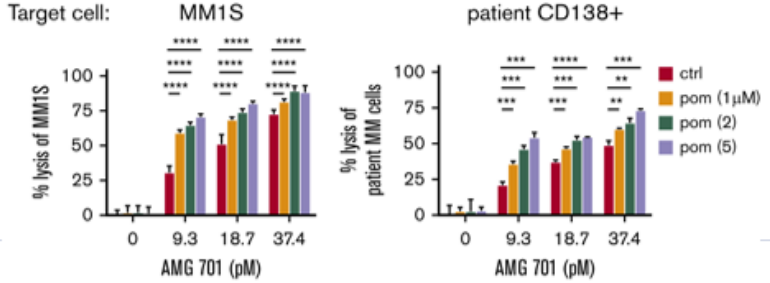


Gulla et al Blood 2024: 143: 2612-26

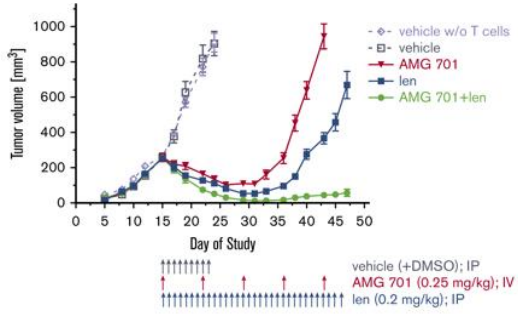
Combinations: Lenalidomide and Pomalidomide Enhance Cytotoxicity of Bispecific T Cell Engager in MM



IMiD pretreatment enhanced potency of AMG 701–induced T cytotoxicity against MM cells

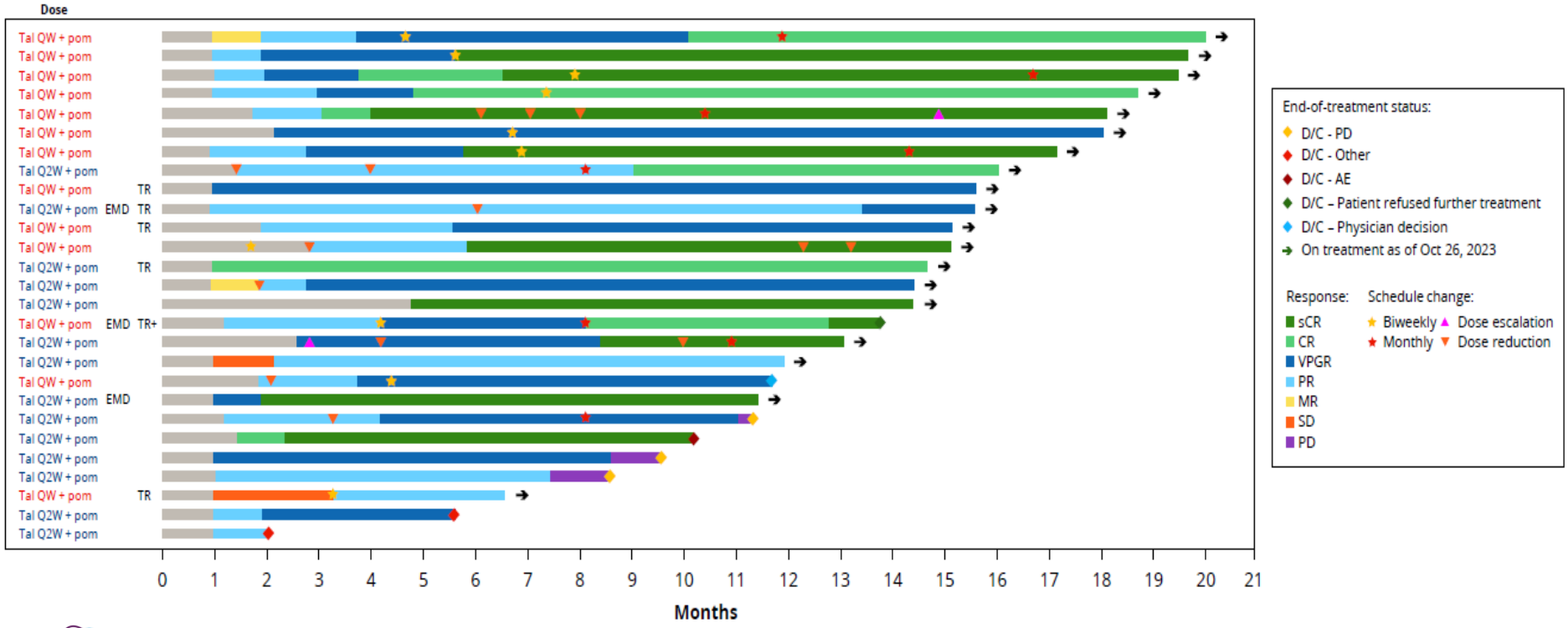


AMG 701 combination treatment with lenalidomide effectively prevented myeloma regrowth in vivo



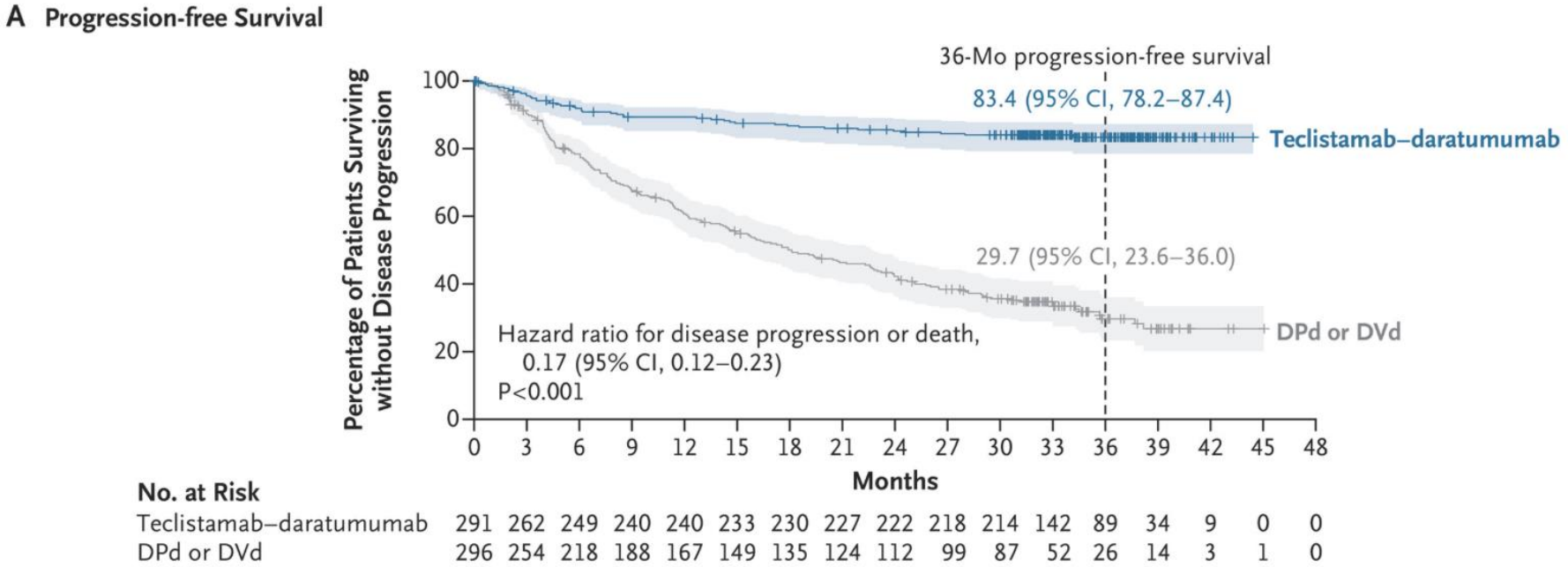
Cho SF et al. Blood Adv 2020; 17: 4195–4207.

Talquetamab GPRC5D Bispecific T Cell Engager/ Pomalidomide



Matous J et al. ASH 2023

MajesTEC-3: Dara Tec vs DPd or DVd (1-3 lines prior therapy)



Dara Depletes Treg and Augments Tec Anti MM Activity

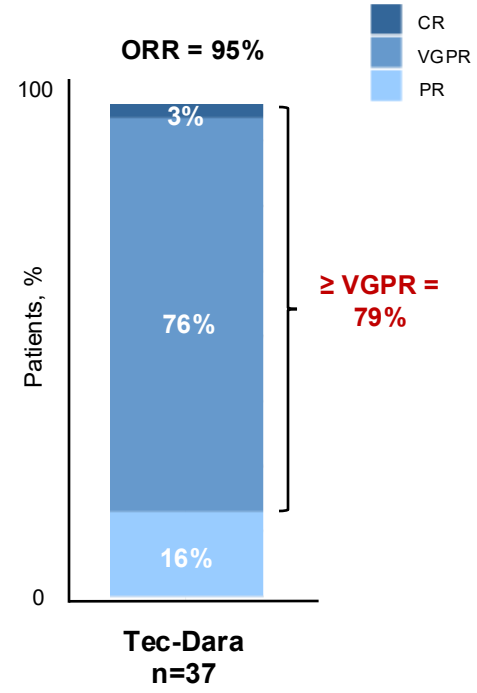
FDA Approved 3/5/26

Costa et al NEJM 2026; 394: 739-52.

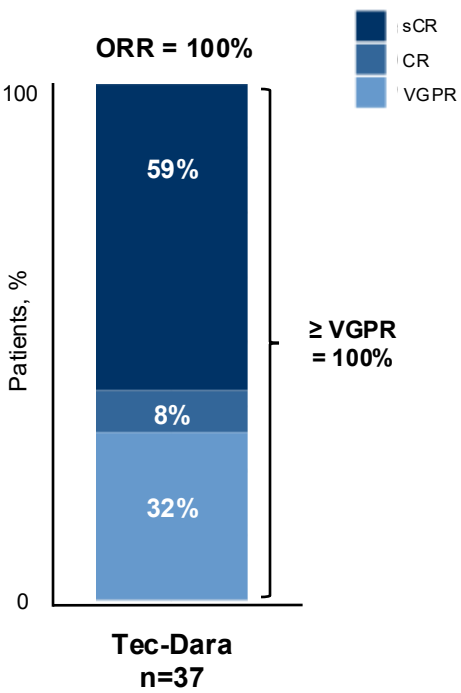
Tec-Dara in TNE NDMM Response

At median followip 10.3 months, no progression or deaths

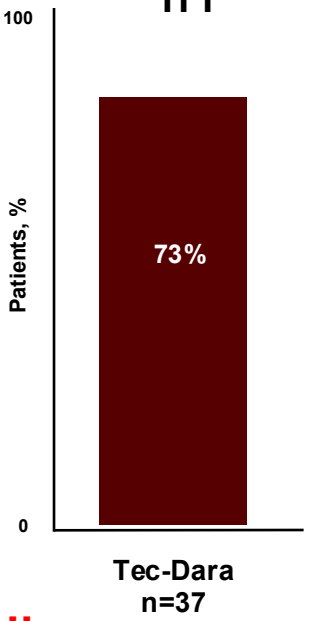
VGPR rate after 4 cycles*



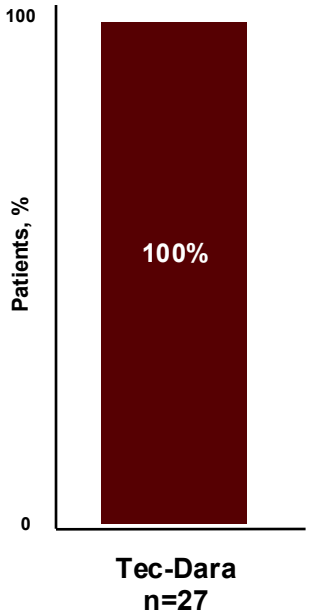
Best response rate



MRD by NGS 10^{-6} at 6 months ITT



MRD by NGS 10^{-6} at 6 months Evaluable samples

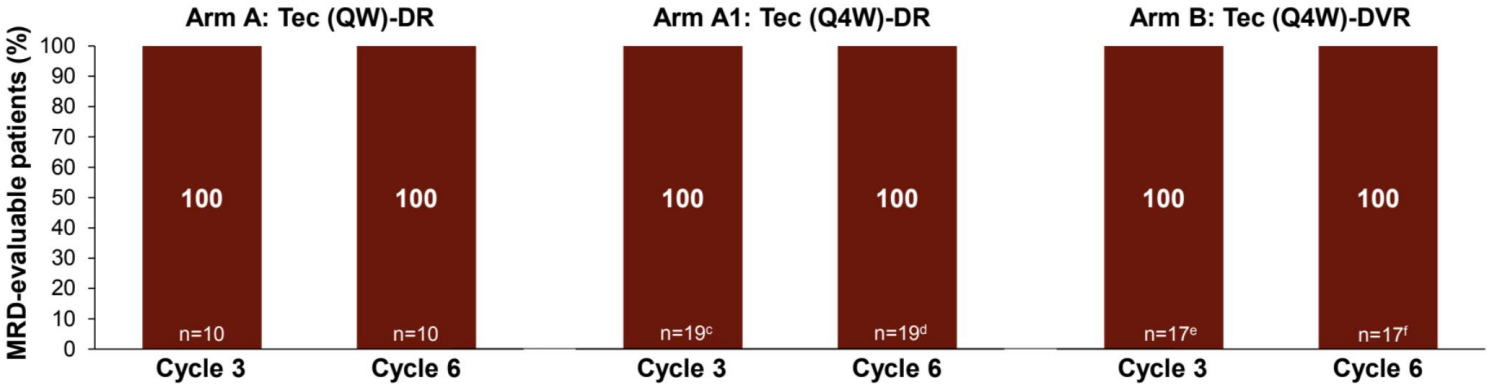


increased terminal effector memory T cells, decreased Tregs and NK cells at 6 mo

Manier et al ASH 2025

GMMG-HD10/DSMM-XX/MajesTEC-5: MRD Negativity (10^{-5})[a] in the MRD-Evaluable Analysis Set

- MRD-evaluable population: all patients with an available MRD test (positive or negative)[b]
  - Only 1 patient was not evaluable for MRD throughout induction (Cycle 3 or 6) due to discontinuation before Cycle 3



With completion of induction, 100% MRD negativity (10^{-5}) continues to be observed in MRD-evaluable patients, regardless of depth of response

[a]MRD-negativity rate was defined as the proportion of patients who achieved MRD negativity (10^{-5}) per NGF, regardless of response (ie, not all patients achieved CR). [b]Excluding those who were not tested, indeterminate, or had no baseline clone detected (NGS). [c]One patient was not tested. [d]One patient had discontinued after completing Cycle 3. [e]One patient was not tested, and 1 had discontinued before completing Cycle 3. [f]One patient had discontinued before completing Cycle 3, and 1 had an indeterminate result. CR, complete response; D, daratumumab; DSMM, Deutsche Studiengruppe Multiples Myelom; GMMG, German-speaking Myeloma Multicenter Group; MRD, minimal residual disease; NGF, next-generation flow cytometry; NGS, next-generation sequencing; QW, weekly; Q4W, every 4 weeks; R, lenalidomide; Tec, teclistamab; V, bortezomib.

Presented by MS Raab at the 22nd International Myeloma Society (IMS) Annual Meeting; September 17-20, 2025; Toronto, Canada

Rabb et al IMS 2025

Cross-Program Efficacy Summary of Trispecific Antibodies

Program	ORR	≥CR	MRD data	DLT / MTD	Efficacy in prior BCMA / GPRC5D	Efficacy in prior CAR-T /TCE
ISB2001 (BCMA x CD38 x CD3)	**79%** (all patients at ≥50 µg/kg)	30% (all patients at ≥50 µg/kg)	75% MRD-negative among evaluable patients with ≥CR (6/8) at 10^{-5}	No DLTs; MTD not reached	ORR 73% after prior BCMA	ORR 71% after CAR-T/bispecific
Ramantamig (JNJ-5322) (BCMA x GPRC5D x CD3)	**86.1%** (all pts, RP2D) **100%** (BCMA/GPRC5D-naïve, RP2D)	75% (all pts, RP2D) 88.9% (BCMA/GPRC5D-naïve, RP2D)	100% MRD-negative in evaluable RP2D patients at 10^{-5} (10/10) and 10^{-6} (7/7)	DLTs observed; RP2D selected	ORR 55% in exposed cohorts	Not reported
IBI3003 (BCMA x GPRC5D x CD3	**83.3%** (all patients at ≥120 µg/kg)	CR 16.7%	100% MRD-negative in patients with ≥CR (4/4), by NGS at 10^{-5}	DLTs in 2 pts; MTD not reached	ORR 77.8% after BCMA/GPRC5D	Not reported

Safety and efficacy data are derived from different patient populations across first-in-human Phase 1 studies and are not intended for cross-trial comparisons

International Myeloma Society

Quach et al. ASH 2024, *Blood* (2024) 144 (Supplement 1): 1026; Quach et al. ASCO 2025 *J Clin Oncol* (2025) **43** (supplement 16): 7514; van de Donk NW, et al. *ASCO 2025*,J Clin Oncol. 2025;43(16_suppl):7505; Popat, R et al. EHA 2025, abstract S100; Krishnan, A.Y et al. ASH 2025. *Blood* (2025) 146 (Supplement 1): 4042; Li, J et al. ASH 2025; *Blood* (2025) 146 (Supplement 1): 702

Quach IMS-IEC 2026

Selected Examples of Dual-Target CAR T in MM

Banerjee IMS 2025

BCMA & CD19		BCMA & GPRC5D
GC012F (AZD0120)[1]		Bispecific CARs[2]
Single-stalk with two scFv[3]	**Design**	Single-stalk with two scFv
Phase 1, n = 29 infused	**RRMM study**	Phase 1, n = 21 infused
97% TC-exposed, 90% ≥1 HRCA	**Population**	>50% TC-exposed, 48% ≥1 HRCA
ORR 93%, 100% MRD negative (10^{-6}), median PFS 38.0 months	**Efficacy**	ORR 86%, 81% MRD negative (10^{-5}), 10-month PFS 67% (84% at higher DL)
Overnight manufacturing with in vivo CAR T expansion	**Claim to fame**	Demonstrated efficacy with both 'double-positive' or 'single-positive' clones
'Carpooled' CD19 and BCMA doesn't add much beyond BCMA alone[3]	**Other strategies**	BMS-986453 with a different single-stalk design; phase 1 trial underway in USA[4]

The investigational therapies mentioned on this slide are not currently approved in any market and have not been evaluated by any regulatory agency as safe or effective for multiple myeloma.
BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; DL, dose level; HRCA, high-risk cytogenetic abnormality; MRD, measurable residual disease; ORR, overall response rate; PFS, progression-free survival; RRMM, relapsed/refractory multiple myeloma; scFv, single-chain variable fragment; TC, triple-class; USA, United States of America.

1. Du J, et al. Presented at ASCO; June 2-6, 2023; Chicago, IL, USA. Abstract #8005. **2.** Zhou D, et al. *Lancet Haematol*. 2024;11(10):e751-e760. **3.** Garfall AL, et al. *Blood Cancer Discov*. 2023;4(2):118-1336.
4. ClinicalTrials.gov. Available at https://clinicaltrials.gov/study/NCT06153251. Accessed August 28, 2025.

ESO-T101 In Vivo MM CAR T: A Nanobody-Targeted, Immune-Shielded Lentiviral Vector

1. A humanised anti-B-cell maturation antigen (BCMA) single-domain-antibody CAR.

2. Pivotal residues in vesicular stomatitis virus glycoprotein G mutated to circumvent lentivirus's extensive tropism to mammalian cells,

3. Viral membrane engineered to overexpress CD47 to suppress phagocytosis and an anti-T-cell receptor nanobody to attain T-cell targeting.

4. Major histocompatibility complex class-I knocked out to mitigate immunogenicity.

5. CAR: T cell-specific synthetic promoter, anti-BCMA variable domain of heavy chain, human CD8 hinge and transmembrane domains, 4–1BB costimulatory and CD3 zeta activation domains

An et al Nat Med 2026; 32: 1257-66

In Vivo Generation of Anti-BCMA CAR-T Cells in RRMM : A Phase 1 Study

ESO-T01: a nanobody-directed, immune-shielded lentiviral vector encoding humanized anti-BCMA CAR

ESO-T01 0.2×10^9 transduction units IV without leukapheresis, ex vivo manufacturing or lymphodepleting chemotherapy.

5 patients (median 3 lines prior therapy): 4 CRS (3 gr 3,1 gr2), cytopenias, transient transaminitis, infections (3 gr 2), ICANS 1 pt died w SCCS

Responses: 3 sCR, 4/4 MRD-(10^{-5}) at d60

Conclusion; preliminary evidence of safety and efficacy of in vivo immune-shielded vector

An et al Nat Med 2026; 32: 1257-66.

iGPS particle

Kelonia ASH 2025

100% MRD)-negative response rate across four patients
MRD-responses maintained at 3 mo in 2 patients

Robust CAR-T cell expansion reaching up to 85% of circulating T cells, similar to *ex vivo* therapies despite no lymphodepleting chemotherapy

Persistent memory CAR-T in all patients at 3 mo

Favorable toxicity profile: with no CRS $\geq$ grade 3, no ICANS or delayed neurotoxicity
Lower cytopenias than *ex vivo* CAR-T cells.

Three of the four patients were treated at 2×10^7 IU/kg. The fourth patient received lower dose of 6×10^6 IU/kg and achieved an MRD-response at month 1.

All four patients remain in IMWG response including CR, with the longest F/U 5 mo

Harrison, Ho et al ASH 2025

Kelonia Update ASCO 2026

18 patients, all MRD- at one month, 6 patients at ≥ 4mo remain MRD-(4sCR, 2 VGPR)

Robust expansion and persistence of CART in PB

No infusion reactions, 16/18 pts CRS (all Gr1-2), 2 pts ICANS
Limited cytopenias and Gr3-4 infections

Plans: Phase I study to define dose, then go to phase III

Future of CAR T Cell Therapy

In vivo CAR-T cell therapy – current status

- Clinical PoC with LV and LNP in vivo CAR-Ts in pts with MM and SLE
- Transient CAR expression with mRNA-loaded LNPs

What are the ***fear factors*** associated with using in vivo CAR-Ts?

- Acute toxicity after infusion of LV
- Concerns of off-target cell/tumor cell transduction
- Limited insights into vector dosing, limited ability for vector & CAR-T tracking

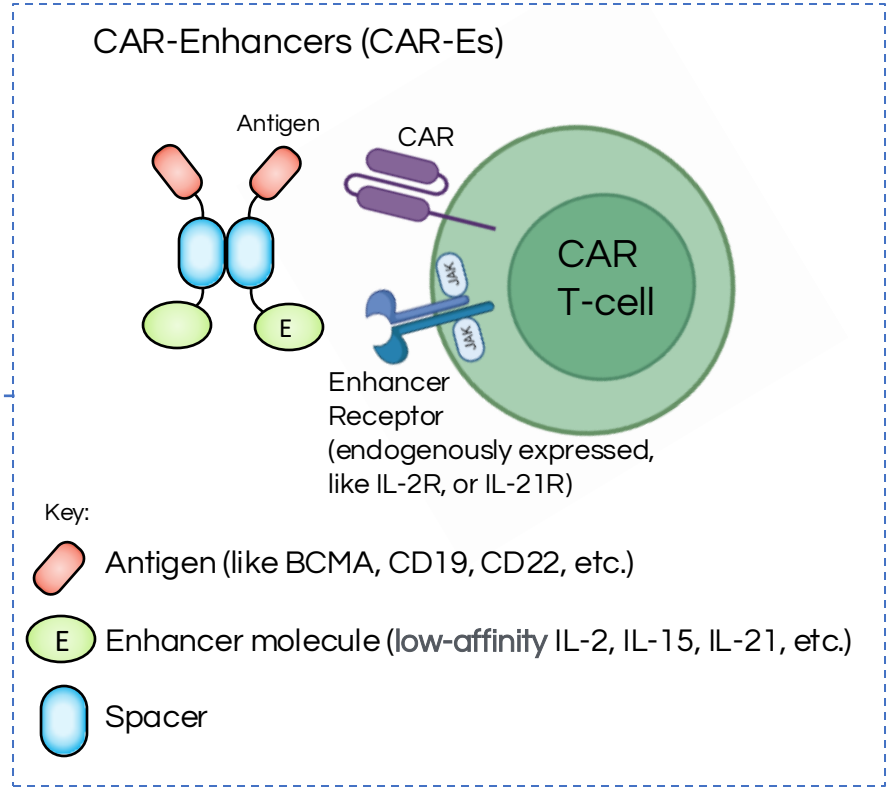
Can ***bedside CAR-T*** be used ***ad interim*** or even ***in lieu*** of in vivo CAR-Ts?

- Integration of T cell selection, gene-transfer and QC into <2 hour process
- Remove off-target cells, customize composite cell products (e.g. T+NK)
- Save on vector, prevent systemic response to vector

CAR-Enhancer (CAR-E) Molecules Selectively Target CAR T cells, Enhance Function and Drive Memory Cell Generation

The CAR-E platform:

- **Uses an off-the-shelf antigen to target the CAR molecule.**
- **Allows targeting any CAR T cells**
- **Uses a human self-protein to target CAR cells (no or low immunogenicity).**
- **Potential synergy between the CAR and Enhancer molecule may drive generation of memory CAR T cells**



NB: CAR-E Administered Two Weeks Post CAR-T Infusion Leads to Complete Tumor Clearance and Functional Memory CAR T-Cell Generation

Dana-Farber Cancer Institute

Rakhshandehroo et al Nat Biotechnology 2024

BCMA-Targeted Therapeutic mRNA Vaccine for Multiple Myeloma

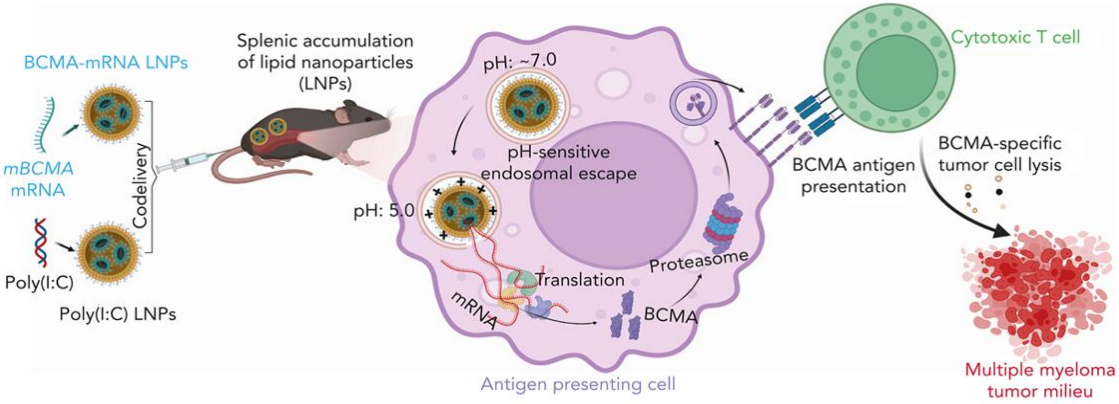
Context of Research

Multiple myeloma is an incurable plasma cell neoplasm for which the BCMA protein has been identified as a promising therapeutic target

Aim of This Study

To develop a therapeutic mRNA vaccine targeting BCMA, consisting of *BCMA* mRNA packaged in lipid nanoparticles in combination with an adjuvant

Findings



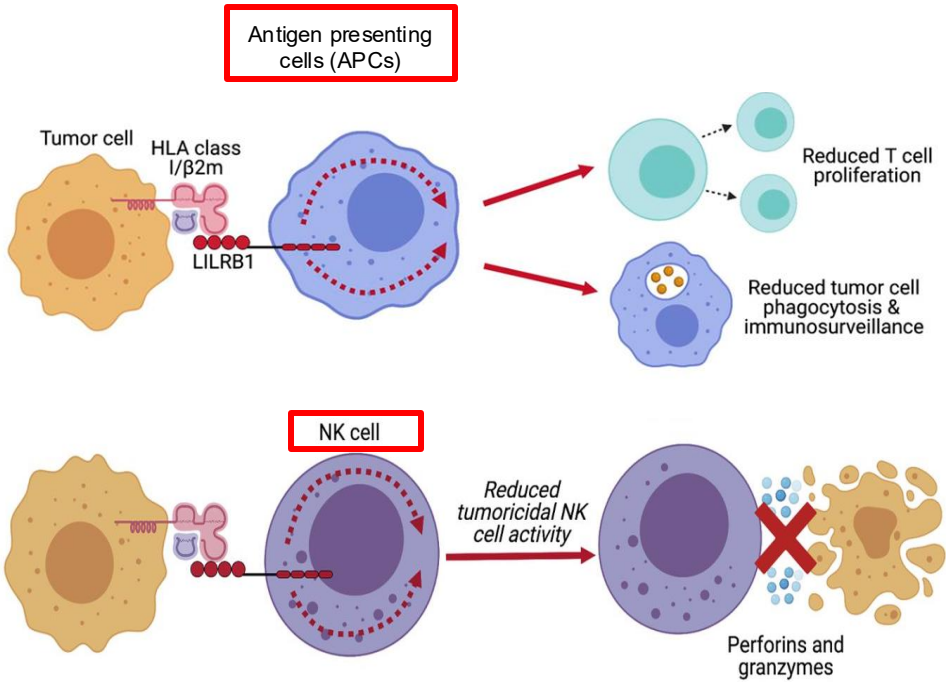
Conclusions: **BCMA-mRNA lipid nanoparticles efficiently deliver the mRNA to antigen-presenting cells, where BCMA antigens are processed and presented on the cell surface, priming BCMA-specific T cells for an effective immune response against myeloma. The BCMA-specific immune response was further elicited by combinational treatment with Poly(I:C).**

*Dutta et al. DOI: 10.1182/**blood**.2025028597*

blood Visual Abstract

Dutta et al BLOOD 2025; 146: 2322-35.

B2M/LILRB1 Targeting to Overcome Immunosuppression and Enhance Response to Immunotherapy in MM



T cell

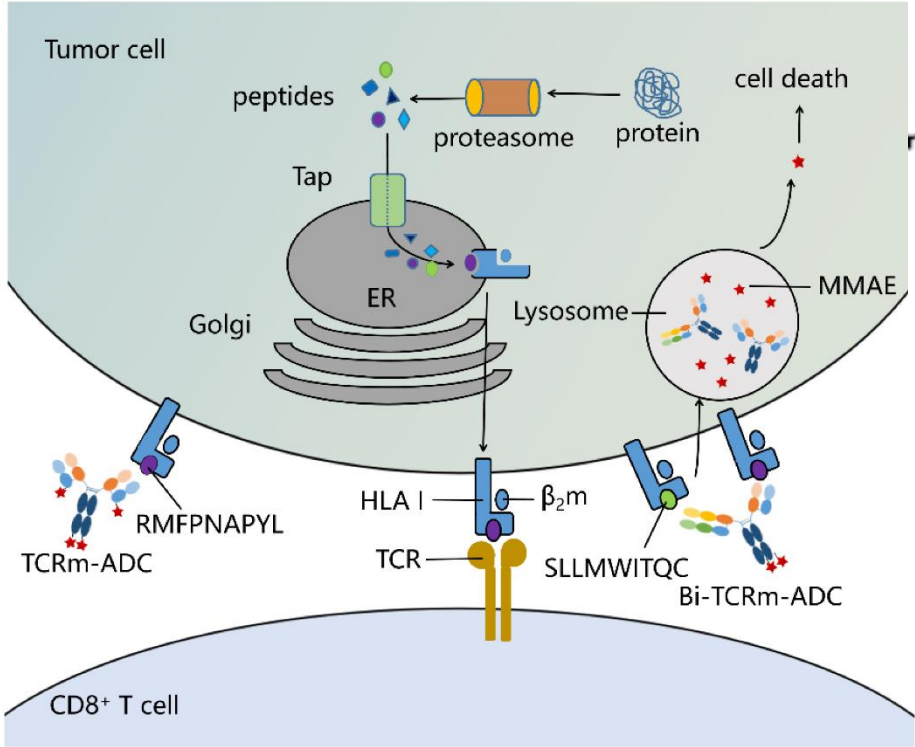
LILRB1 also expressed on T cells and acts as immune checkpoint inhibitor

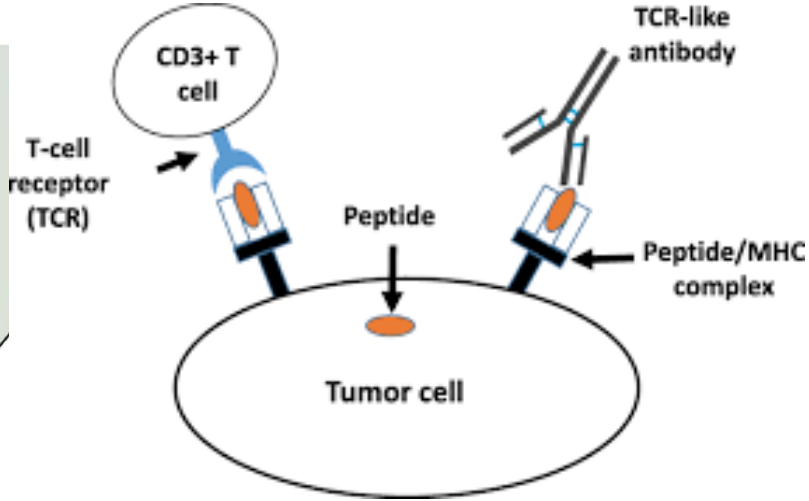
Targeting LILRB1 on APCs to enhance phagocytosis and trigger adaptive anti-MM response
Targeting LILRB1 on T and NK cells to enhance anti-MM responses

Adapted from Calvin D. De Louche, 2022

Turi M, Gulla A et al ASH 2025

TCR-Like Abs Targeting Intracellular Antigens (MZB1) in MM

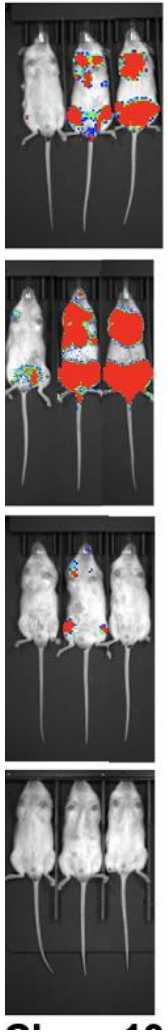




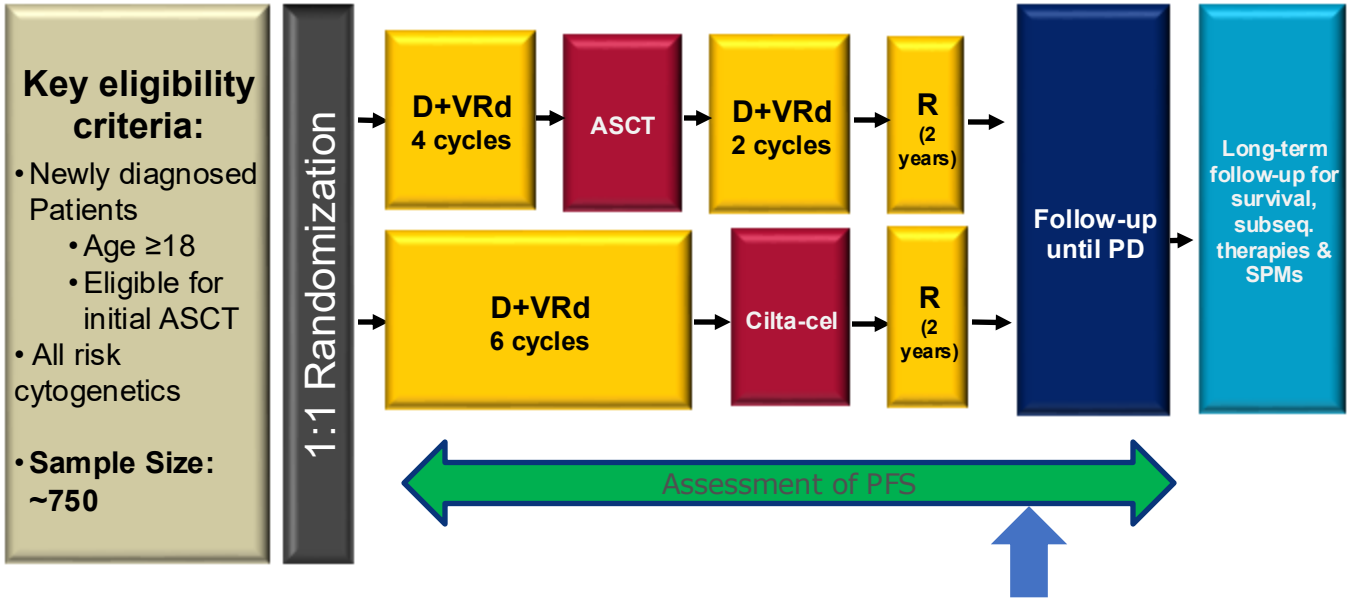
Screen for TCR-like Ab Against MZB1 Peptide in HLA2+

Use as naked Ab, BiTE, ADC, or CAR T

Fulciniti, Munshi ASH 2025



Cartitude 6 Randomized Phase 3 study in Newly Diagnosed, Transplant Eligible Patients vs ASCT



Stratification factors:
a) ISS staging
b) Cytogenetics
c) Age

Dual Primary endpoints:
PFS and Sustained MRD neg CR

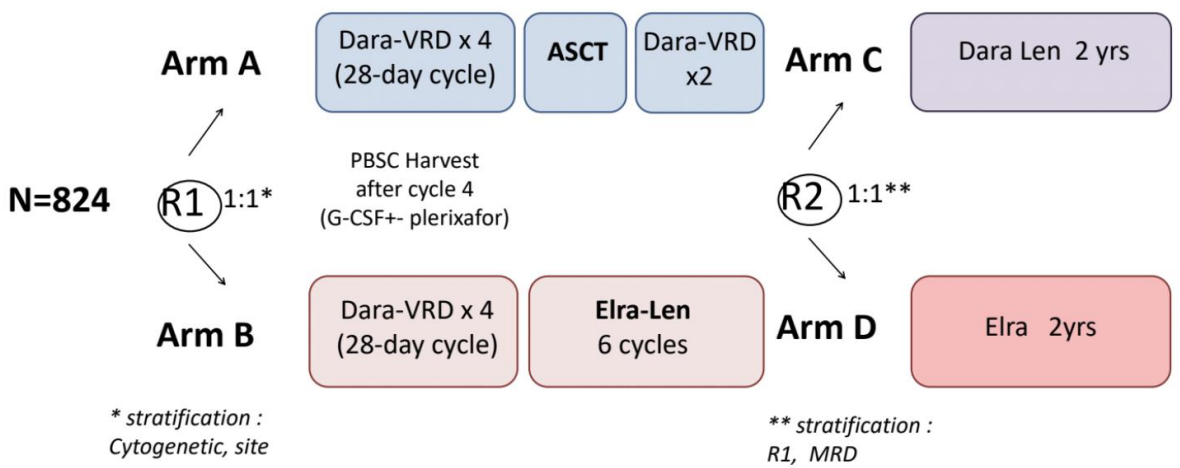
2. FIXED-DURATION BsAbs to replace ASCT in NDTEMM (study on-going, recruiting)

IFM 2025-01 – ELLEN

Population

- NDMM
- Transplant eligible

Study design



Objectives

- Primary :
- R1 : MRD (10-5) pre R2
- R2 : PFS

- Secondary:
Sustained MRD
OS
Safety
QoL
Rework

- Exploratory:
genomic, immuno, PET, Mass spec, CTCs

PIs : C Touzeau and A Perrot

Ciltacel in HR SMM: CAR-PRISM phase II trial

20 pts received 0.3-0.5 or >5.0 x 10^6 viable CAR T with no induction or bridging therapy (> 40% BM PC excluded)

No DLT; transient cytopenia (90% grade 3-4); CRS (100% grade 1-2)
Non ICANS neurotox: 4 CN palsies resolved, 3 persistent grade 1 symptoms

Median F/U 15.3 mo:
- **all MRD- at 10^{-6}**
- **16 pts w median F/U > 6 mo: all CR**
- **No progression**

Ciltacel induces rapid, deep, sustained MRD-responses in HR SMM with no induction therapy. Toxicity is consistent with Ciltacel in MM.

Nadeem et al Nat Med 2026, in press

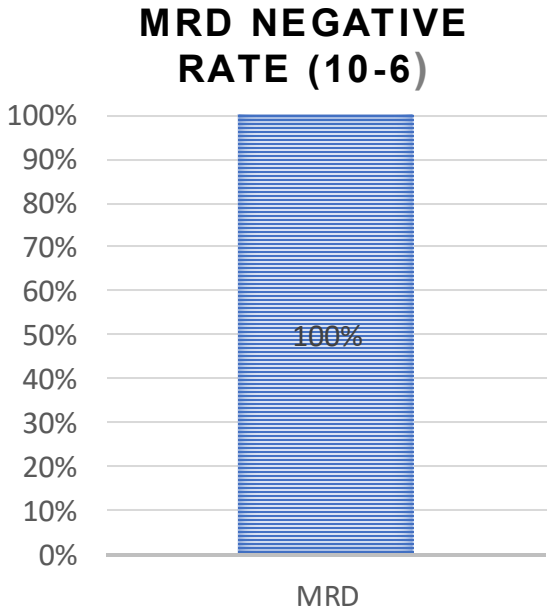
Fixed Duration Teclistamab in HR SMM (N=12); Can early treatment cure SMM?

TEC-treated Cohort (12 patients)

Best response	n	%
CR	10	83
VGPR	2	17
Overall response rate	12	100

- No patients have progressed on treatment.
- Stem cell collection was successful in all eligible patients with an average stem cell yield of 8.94 x 10^6 CD34+ cells/kg.

Nadeem et al ASH 2023 (abstr)



MRD-negativity rate at 10^{-5} is 100%

MRD-negativity rate at 10^{-6} is 100%

Average time to MRD-4.25 cycles

Conclusions and Future Directions

Three eras of myeloma bench to bedside progress targeting the tumor in its BM milieu:

1980 and Ongoing-Stem cell transplant

2000 and Ongoing- Novel agents (IMiDs, PIs, CD38MoAb)

2020 and Ongoing-Immune therapies (CAR T, BiTEs)

Progress to Date:

Rational combinations of ASCT, novel agents and immune therapies.

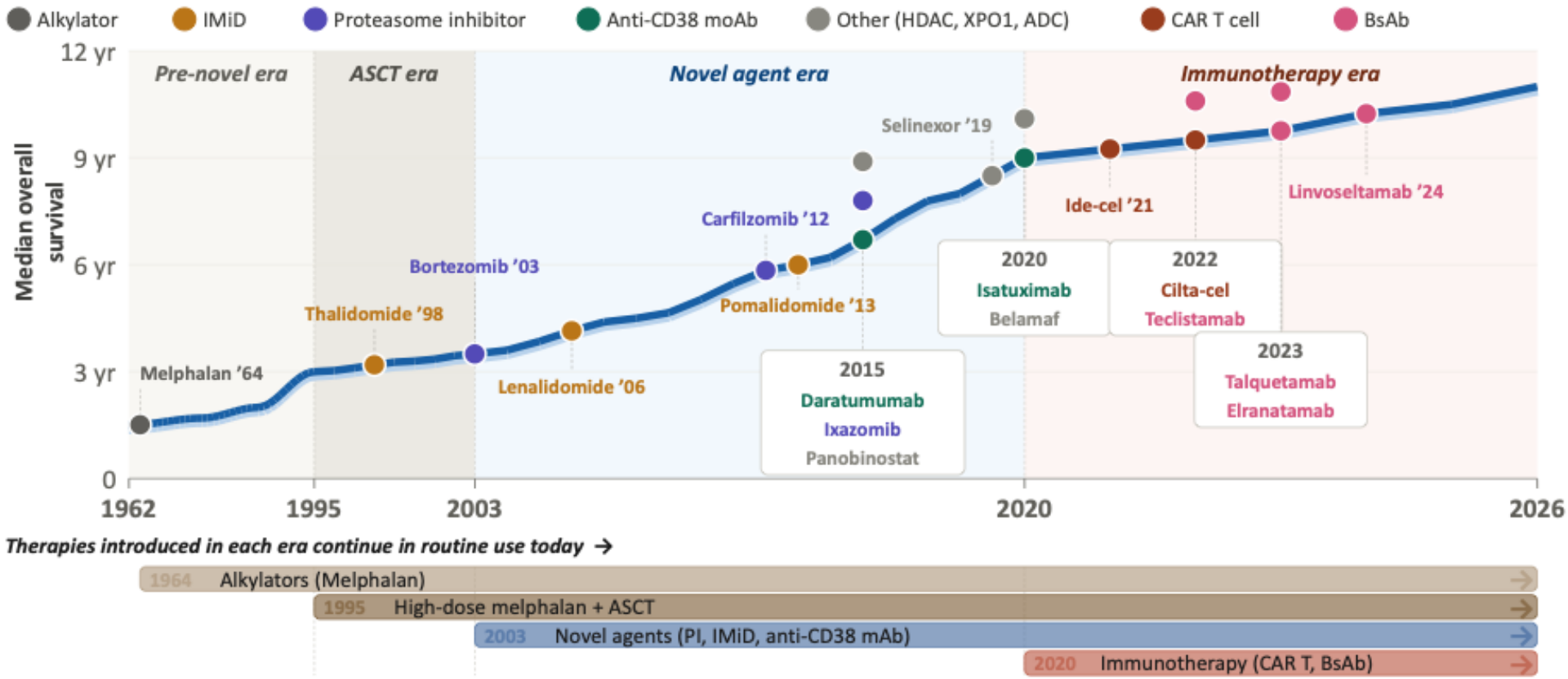
MRD-CR now achievable In NDMM and RRMM

In Future:

Profiling the tumor and host will inform use/assess response to novel combinations of targeted and immune therapies.

Combination targeted and immune therapy in NDMM and high risk SMM will induce durable MRD- response, allowing patients to be disease-free and off all therapy, with potential cure.

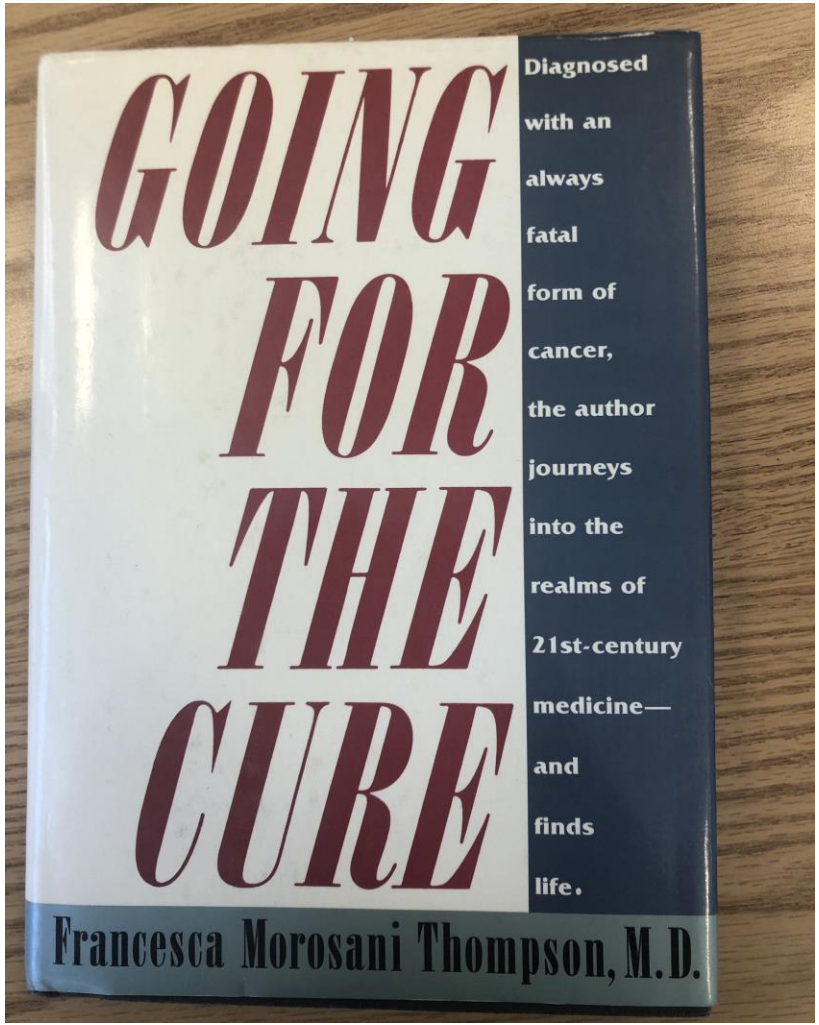
FDA Approved Treatments Markedly Prolong Median Overall Survival in Myeloma



Mouhieddine and Anderson, NEJM 2026

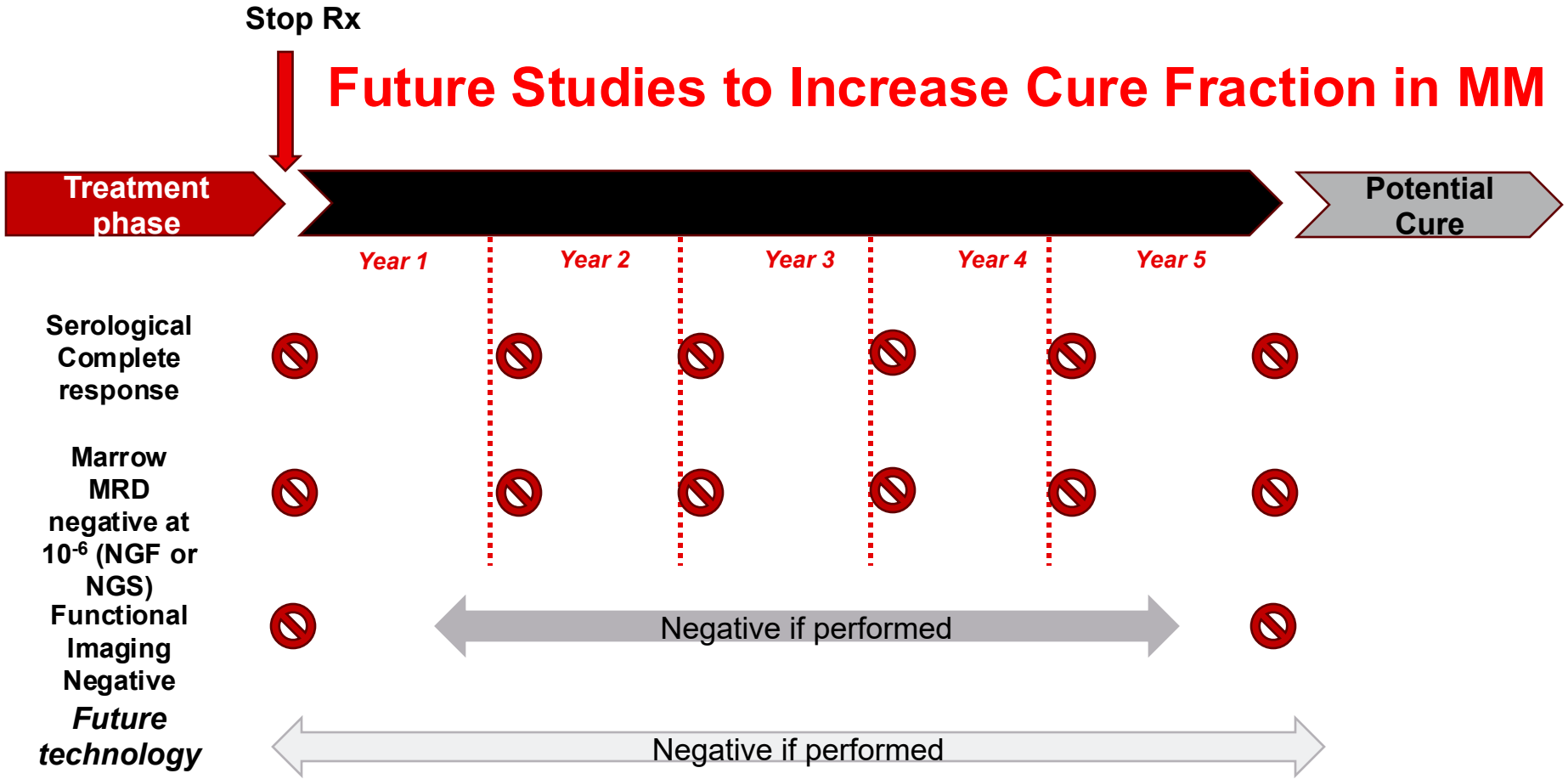
“Cure is Growing Old and Dying from Something Else”

Francesca Thompson, MD
1986



IMS Myeloma Cure Summit (2/26): Definitions, Metrics, and Milestones

Future Studies to Increase Cure Fraction in MM



2026 Waldenström Lifetime Achievement Award

This award is given to a researcher in recognition of their outstanding long-term contributions to the myeloma field.