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Resistance to Bispecific Antibodies in MM

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Disclosures

- Research funding: Abbvie, Amgen, BMS/Celgene, GSK, Gilead, Gracell Therapeutics, Janssen, K36 Therapeutics.

- Consulting: Abbvie, Amgen, BMS/Celgene, Galapagos, Genentech, GSK, Janssen, Pfizer, Regeneron, Sanofi, Takeda.

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NDMM: Principles of Therapy in 2026

- Picking the right strategy that gives the highest likelihood of the best depth of response in the first year of diagnosis is extremely important for survival outcomes.
  - MRD 10^{-5} >> MRD 10^{-6} >> Sustained MRD 10^{-6}
- Optimize induction, consolidation and maintenance based on:
  - Disease biology (what kind?).
  - Disease burden (how much?).
  - Patient characteristics (PS, co-morbidities, frailty).
  - Patient preference.
- Never under-treating high-risk disease.
- Supportive care measures: bone health, infection prevention, pain management, physical therapy and rehabilitation, mental health.

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Towards Curing Multiple Myeloma (2026)

- Comprehensively study the molecular and immunobiology of disease evolution and progression in MM.
  - Recognize 'real' myeloma at the smoldering stage and intervene early for a defined duration of time.
  - Pick different strategies for different disease biology and immune status.
  - Incorporate frailty assessments in this algorithm (Cure vs Control).
  - Optimize sequencing of existing therapies and incorporation of select novel MoAs based on disease biology.
- Accurately assess sustained minimal residual disease (MRD) negativity.
  - Utilize novel imaging and novel peripheral blood assessments.
- Use MRD assessments guide treatment time and treatment strategy.
  - Use Sustained MRD to stop treatment.
- Pay attention to supportive care.
  - Address both short-term and long-term sequelae of treatments.

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SMM and MGUS pooled analysis

374 patients with SMM/MGUS with available WGS or WES

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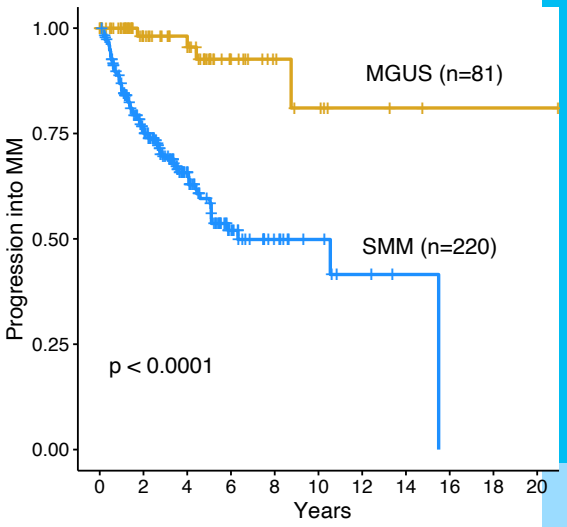
Features	Training (n=277)	Validation (n=97)
Age (years)	66 (32-90)	66 (34-87)
Sex (Male)	57%	50%
Race (European)	86%	71%
Disease stage		
MGUS	72 (26%)	17 (17%)
SMM	205 (84%)	80 (83%)
Bone marrow plasma cell	15% (0.5-55)	12.5% (2-50)
M-spike (g/dl)	1.35 (0-4.4)	1.53 (0-4.6)
Abnormal Free Lite ratio	76.50%	89.60%
IMWG 2/20/20		
Low	51 (31.6%)	30 (40%)
Int	61 (37.9%)	
High	49 (30.5%)	21 (28%)
Intervention clinical trials	62 (22%)	0
Median follow up	40 months	61 months



All data were generated using MGP pipeline: https://github.com/pblaney/mgp1000

Plasma cell clonality and potential contamination was assessed by integrating CNV, SNV, presence of oncogenic rearrangement and/or productive V(D)J in the immunoglobulin regions

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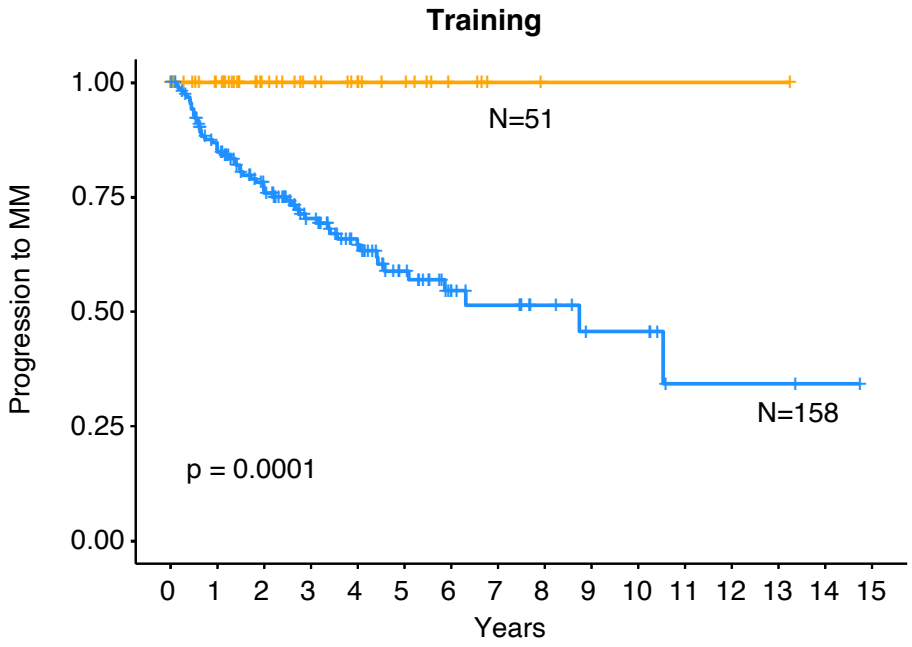
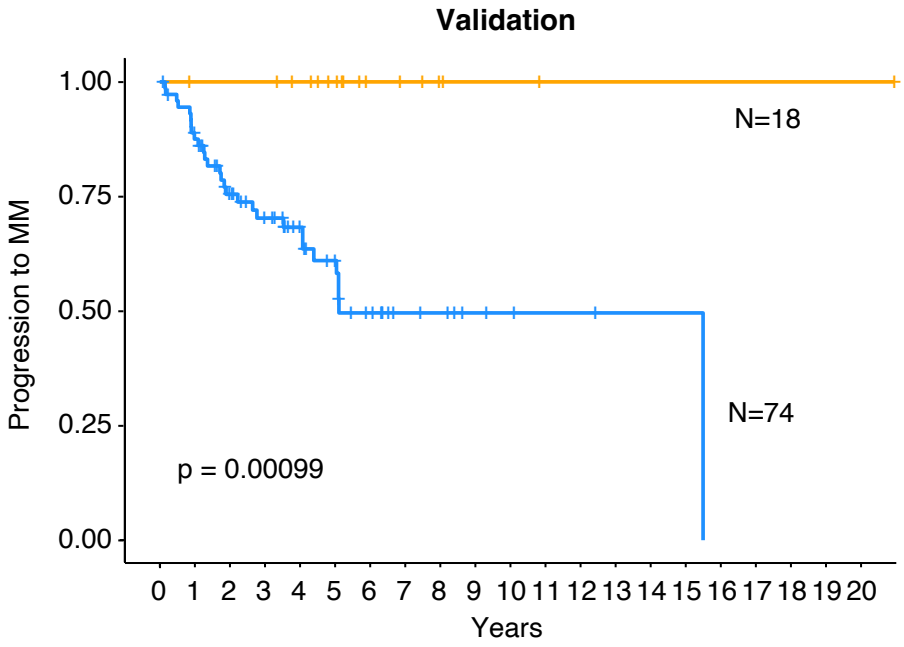
Clinical impact of malignant transformation





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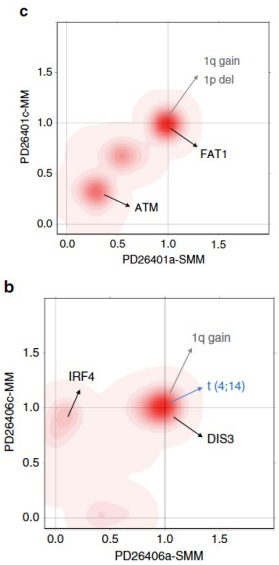
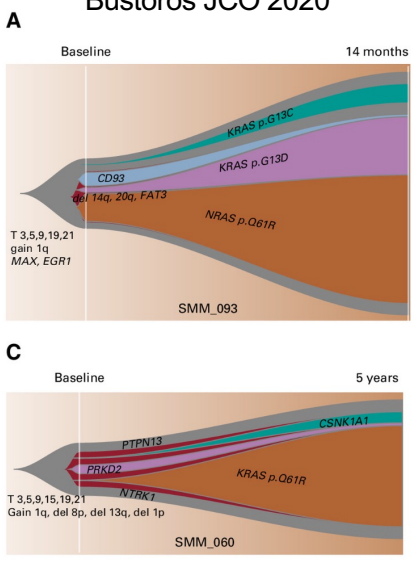
Clonal evolution from SMM to MM

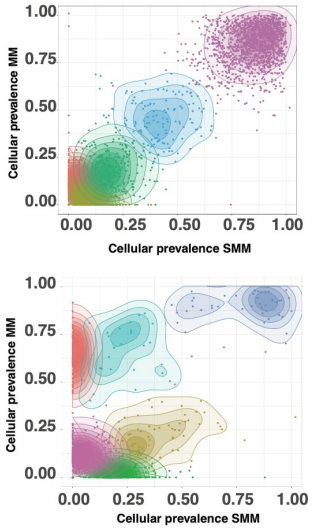
Bolli*, Maura* et al. Nat Comm 2018



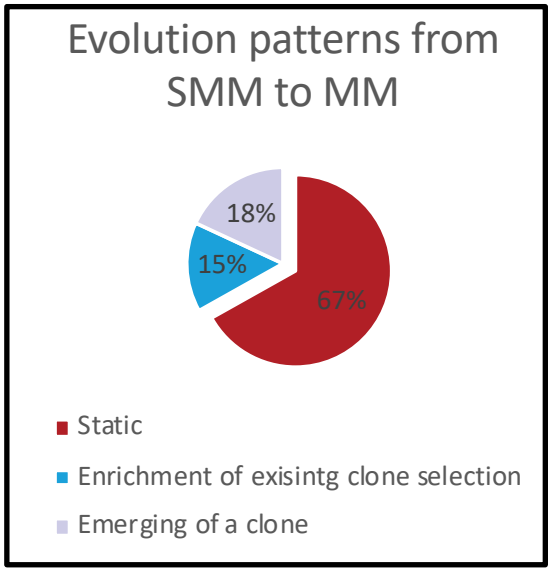
Bustoros JCO 2020



Samur JCO 2025



Samur JCO 2025



82% of SMM patients progress to MM have already detectable subclones at SMM diagnosis with **minimal** changes

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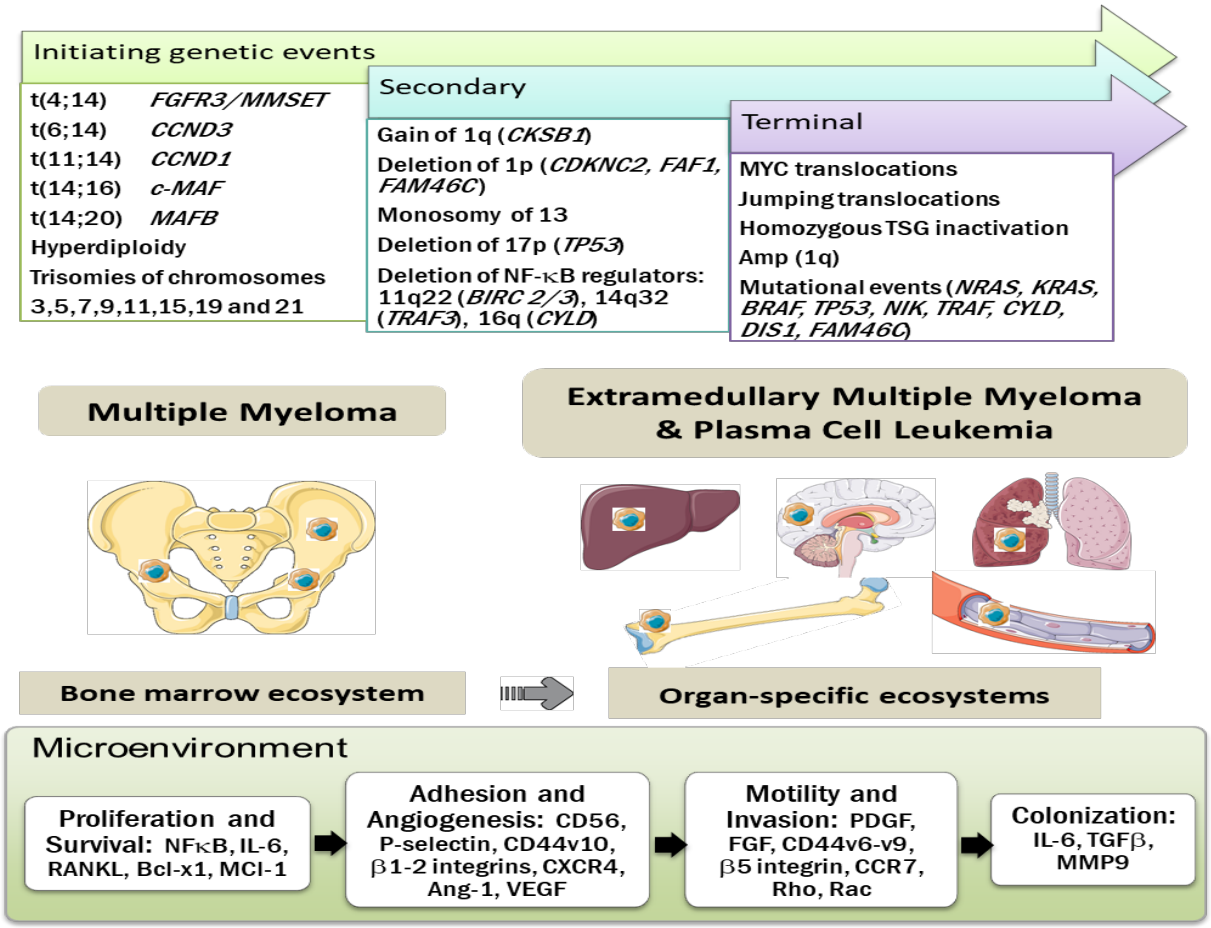
MM Cell Survival Outside the BM Microenvironment Portends Poor Prognosis



Bhutani M et al. *Leukemia 2020.*

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Bispecific Antibodies in MM

- BCMA : Teclistamab, Elranatamab, Linvoseltamab, Etentamig, Alnuctamab
- GPRC5D: Talquetamab, Forimtamig
- FcRH5: Cevostamab

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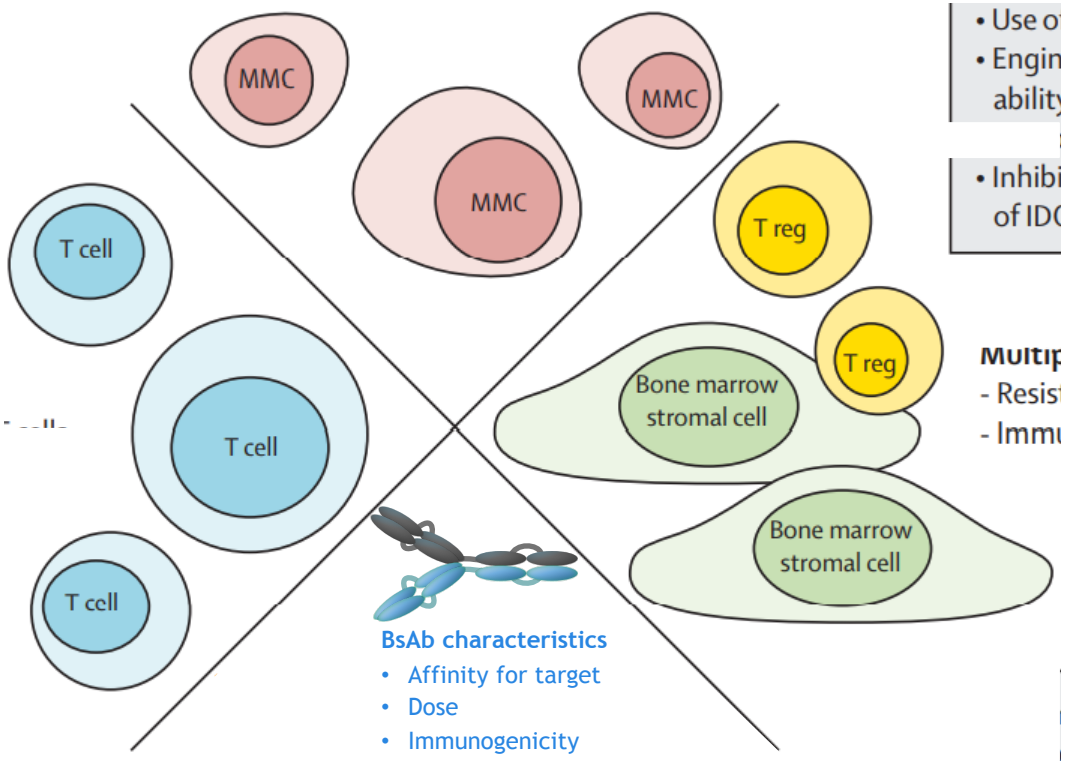
Mechanisms of resistance to BsAbs

Tumor-related features
- Antigen loss or diminished antigen expression
- Soluble BCMA (for BCMA BsAbs)
- Tumor load

- High-risk cytogenetic features
- Extramedullary disease
- Inhibitory receptors and ligands, which suppress T-cell function



T-cell characteristics
- T-cell frequency
- T-cell fitness

MM microenvironment-related factors
- BM stromal cells
- Immune suppressor cells

BsAb characteristics
- Affinity for target
- Dose
- Immunogenicity
- Dual targeting

BCMA, B-cell maturation antigen; BM, bone marrow; BsAb, bispecific antibody; IMiD, immunomodulatory drug; MMC, multiple myeloma cell; Tregs, regulatory T-cells

Adapted from: van de Donk N, Themeli M, Usmani SZ. Blood Cancer Discov 2021;2:302–18

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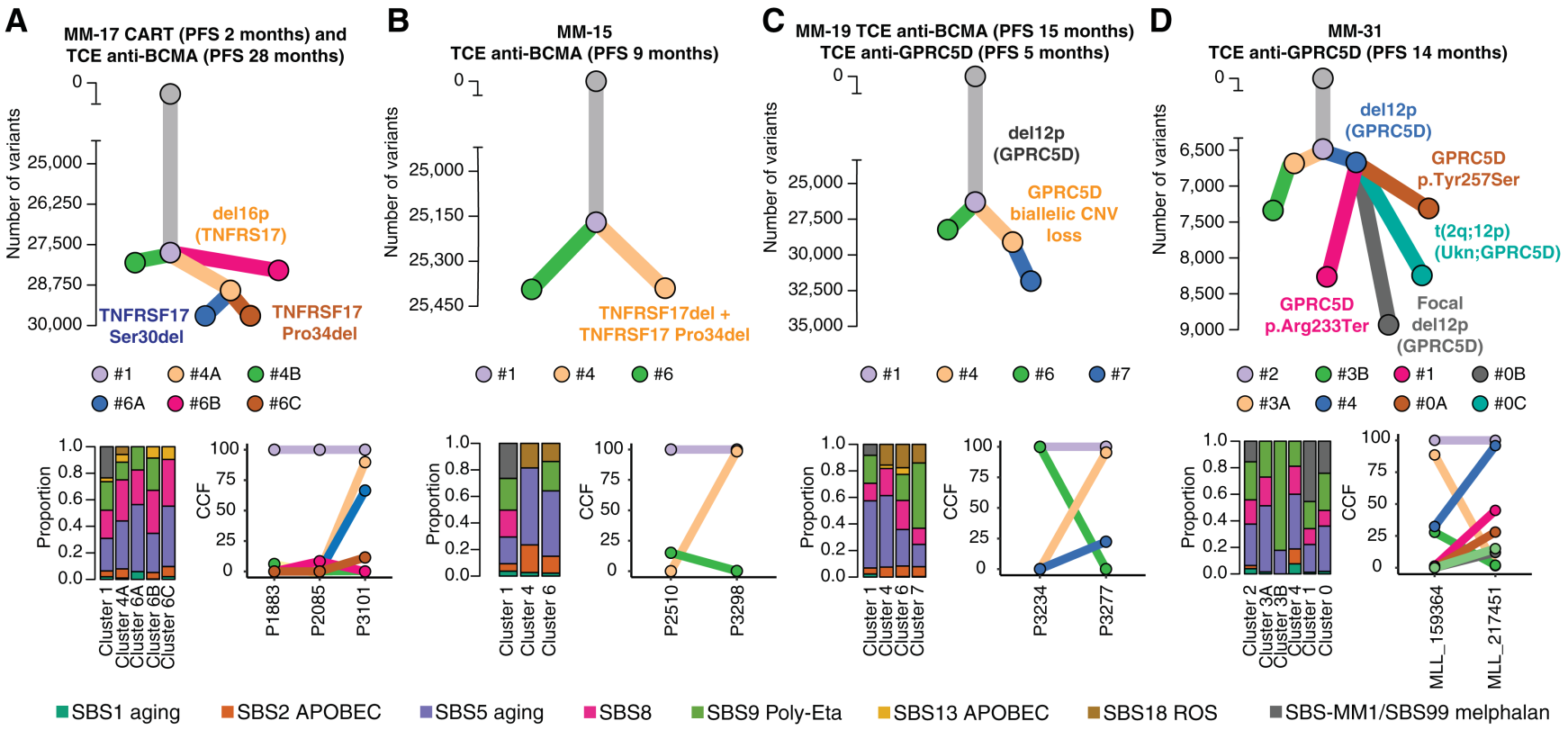
Timing Genomic Antigen Loss



Blood Cancer Discov. 2025;6(6):572-579. doi:10.1158/2643-3230.BCD-25-0005

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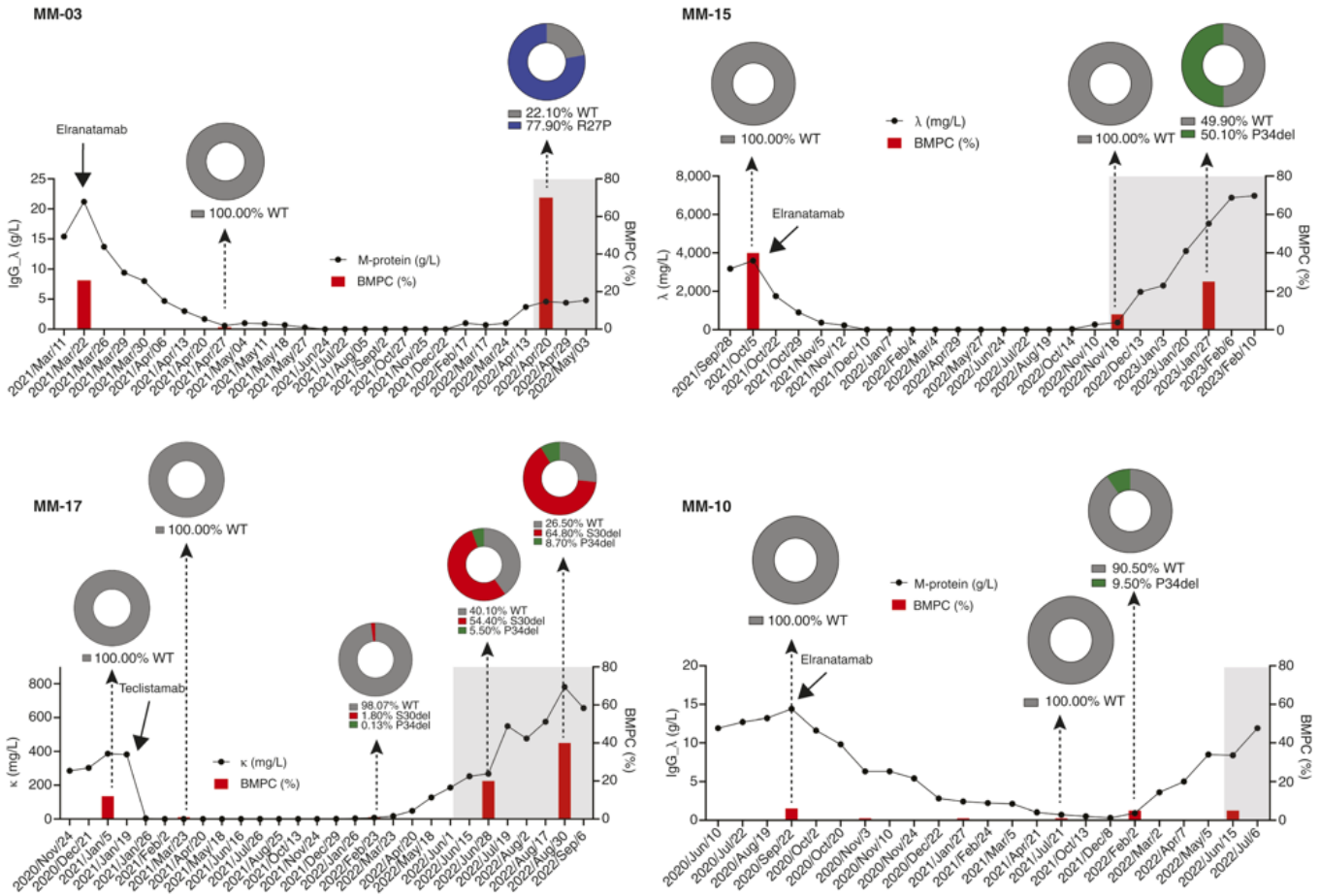
Timing Genomic Antigen Loss



Blood Cancer Discov. 2025;6(6):572-579. doi:10.1158/2643-3230.BCD-25-0005

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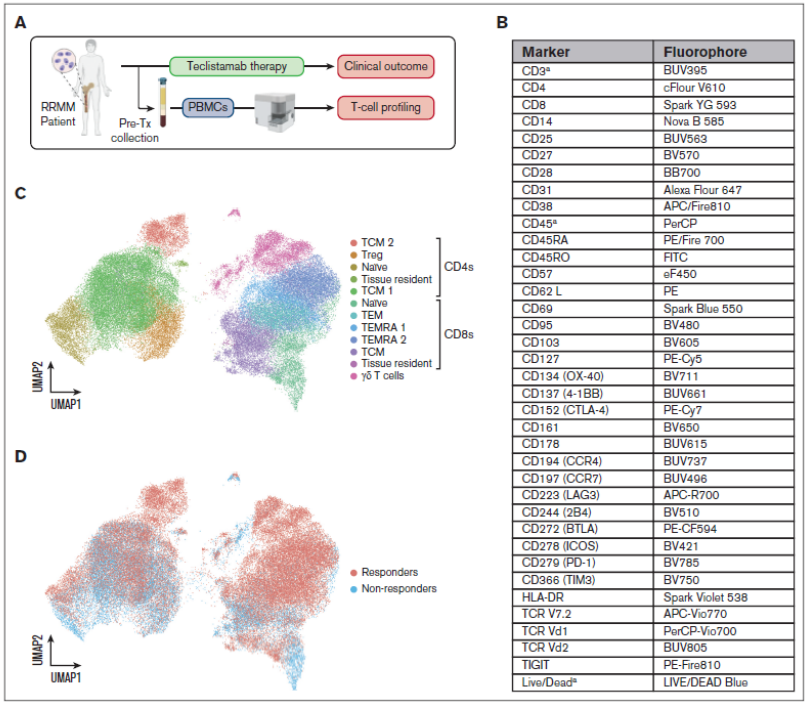
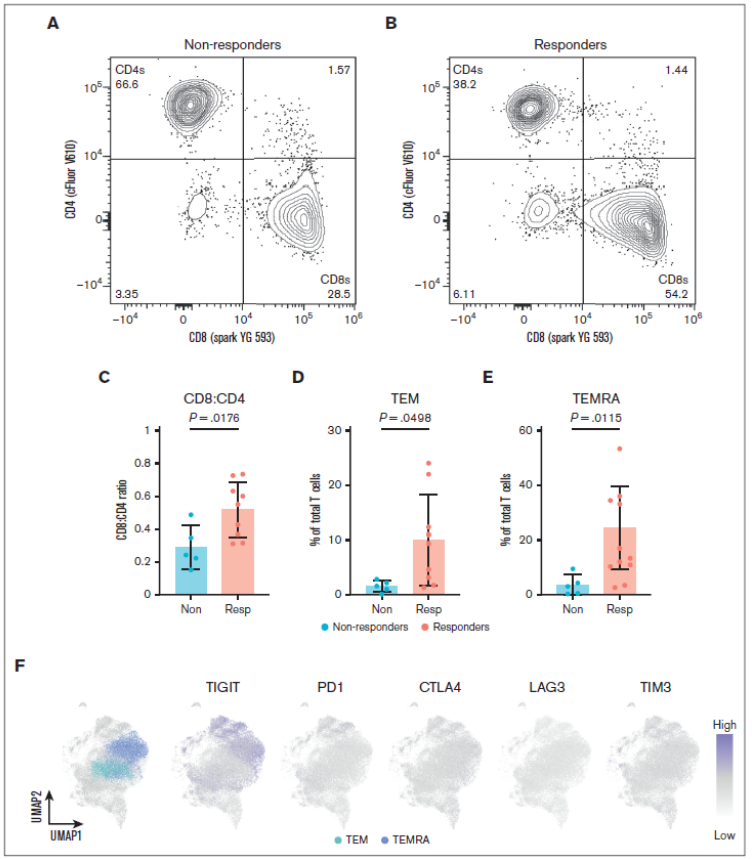
Translational Lessons from Teclistamab Use at MSKCC



B

Marker	Fluorophore
CD3[a]	BUV395
CD4	cFlour V610
CD8	Spark YG 593
CD14	Nova B 585
CD25	BUV563
CD27	BV570
CD28	BB700
CD31	Alexa Flour 647
CD38	APC/Fire810
CD45[a]	PerCP
CD45RA	PE/Fire 700
CD45RO	FITC
CD57	eF450
CD62 L	PE
CD69	Spark Blue 550
CD95	BV480
CD103	BV605
CD127	PE-Cy5
CD134 (OX-40)	BV711
CD137 (4-1BB)	BUV661
CD152 (CTLA-4)	PE-Cy7
CD161	BV650
CD178	BUV615
CD194 (CCR4)	BUV737
CD197 (CCR7)	BUV496
CD223 (LAG3)	APC-R700
CD244 (2B4)	BV510
CD272 (BTLA)	PE-CF594
CD278 (ICOS)	BV421
CD279 (PD-1)	BV785
CD366 (TIM3)	BV750
HLA-DR	Spark Violet 538
TCR V7.2	APC-Vio770
TCR Vd1	PerCP-Vio700
TCR Vd2	BUV805
TIGIT	PE-Fire810
Live/Dead[a]	LIVE/DEAD Blue



Peripheral blood regulatory T cells associate with teclistamab failure, whereas CD8+ effector T cells associate with teclistamab response.

Firestone R et al. Blood Advances 2023
Firestone R et al, Blood 2024

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Mechanisms of resistance to BsAbs

Tumor-related features
- Antigen loss or diminished antigen expression
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- Tumor load

- High-risk cytogenetic features
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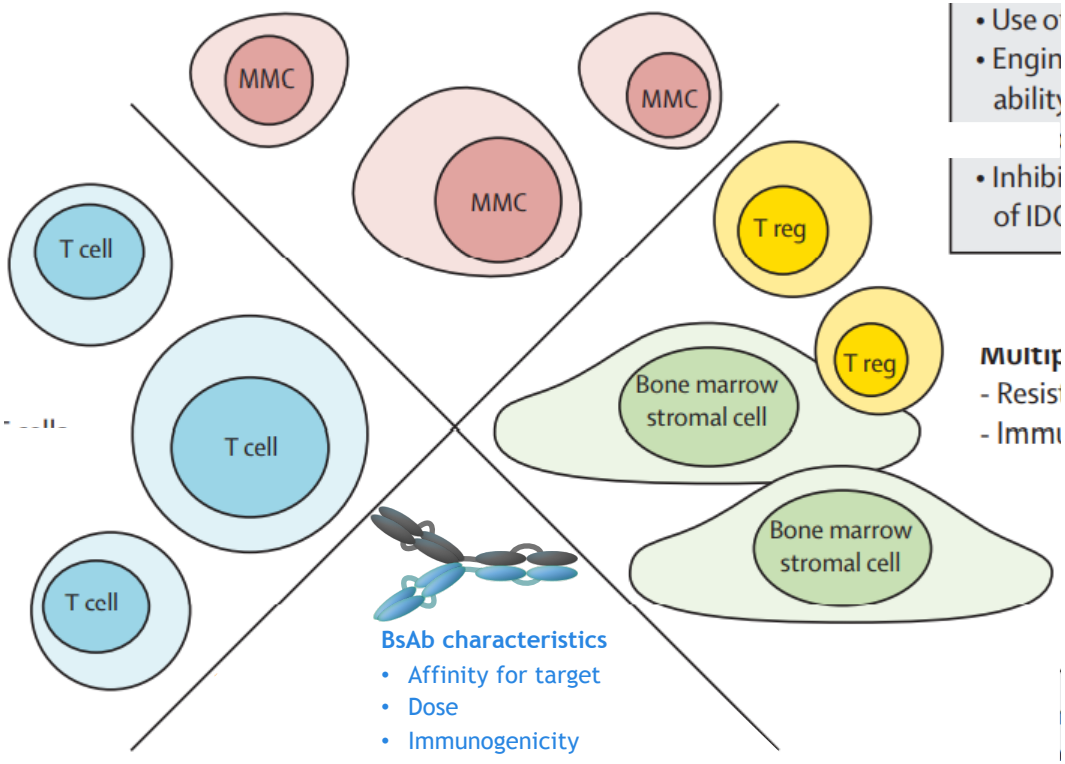

T-cell characteristics
- T-cell frequency
- T-cell fitness

MM microenvironment-related factors
- BM stromal cells
- Immune suppressor cells

IMiD/CelMOD, Check point inhibitors

CD38 antibody: Elimination of Tregs

BsAb characteristics
- Affinity for target
- Dose
- Immunogenicity
- Dual targeting

BCMA, B-cell maturation antigen; BM, bone marrow; BsAb, bispecific antibody; IMiD, immunomodulatory drug; MMC, multiple myeloma cell; Tregs, regulatory T-cells

Adapted from: van de Donk N, Themeli M, Usmani SZ. Blood Cancer Discov 2021;2:302–18

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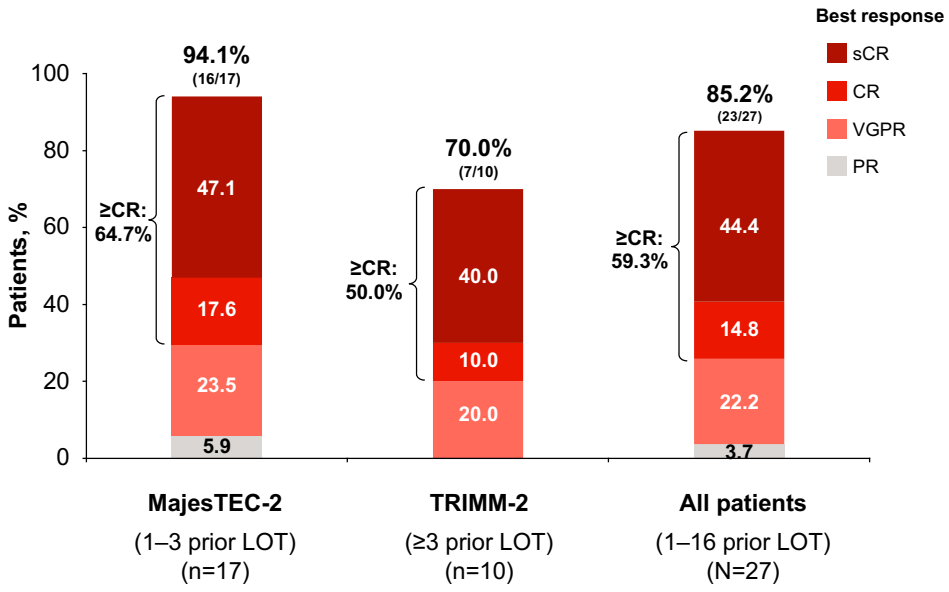
Phase 1b/2: Teclistamab + Dara SC + Pom

Tec-Dara-Pom in MajesTEC-2 and TRIMM-2: Response Rates



- Tec-Dara-Pom demonstrated rapid and deep responses across both cohorts
  - ORR: 85.2%
  - ORR: 72.7% in Dara-exposed patients[a]
- Deeper responses in 1–3 vs ≥3 prior LOT
  - ≥CR: 64.7% vs 50.0%
  - ≥VGPR: 88.2% vs 70.0%
- Median times to first and best response in all patients were 1.0 month and 3.2 months, respectively[b]

Response was assessed by investigators, based on International Myeloma Working Group criteria. Percentages were calculated with the number of patients in each group as the denominator. [a]n=8/11. [b]n=23.
CR, complete response; Dara, daratumumab; LOT, line of therapy; ORR, overall response rate; Pom, pomalidomide; PR, partial response; sCR, stringent complete response; Tec, teclistamab; VGPR, very good partial response.

Presented by A D'Souza at the 66th American Society of Hematology (ASH) Annual Meeting; December 7–10, 2024; San Diego, CA, USA

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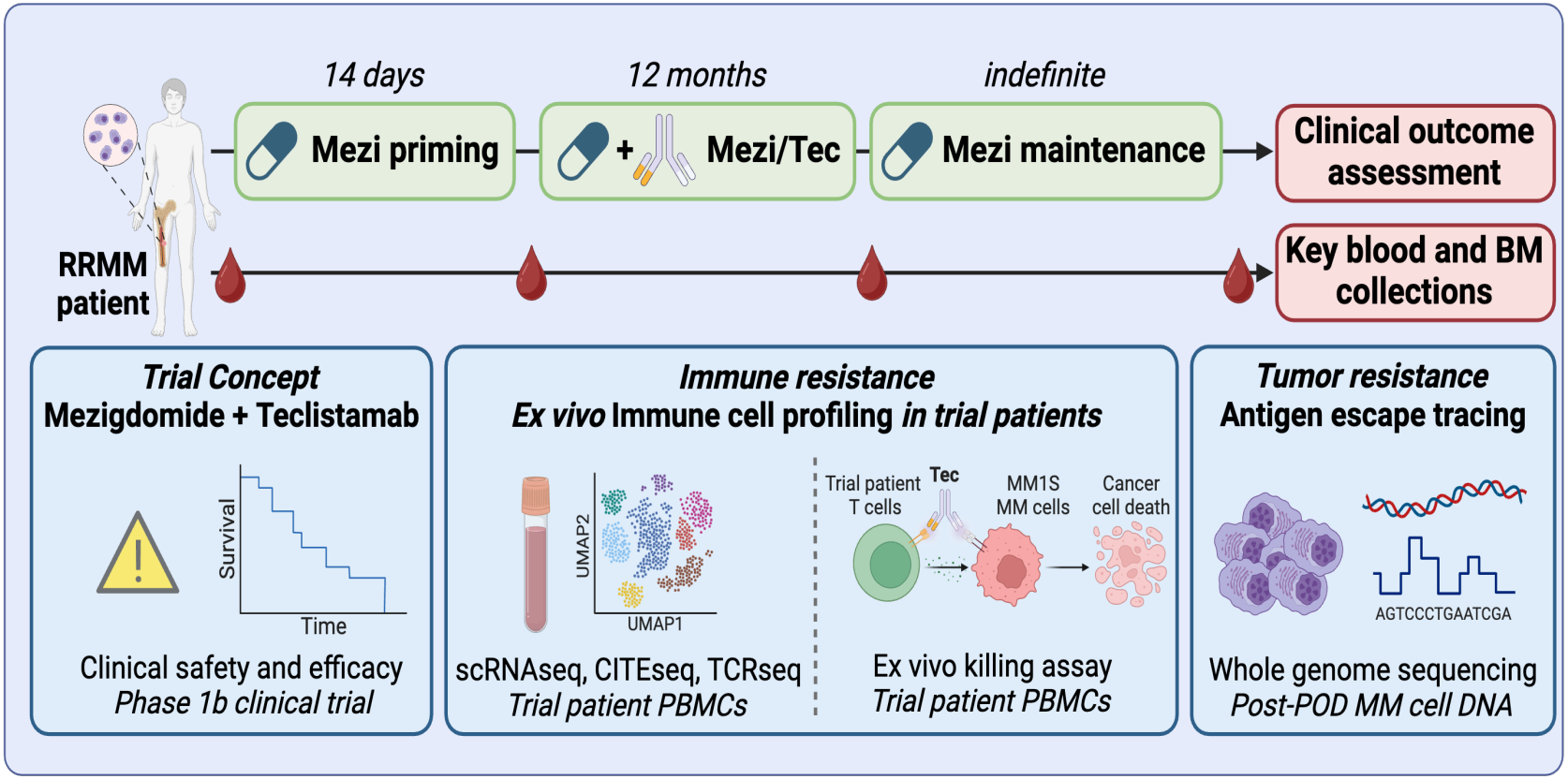
MATRIX



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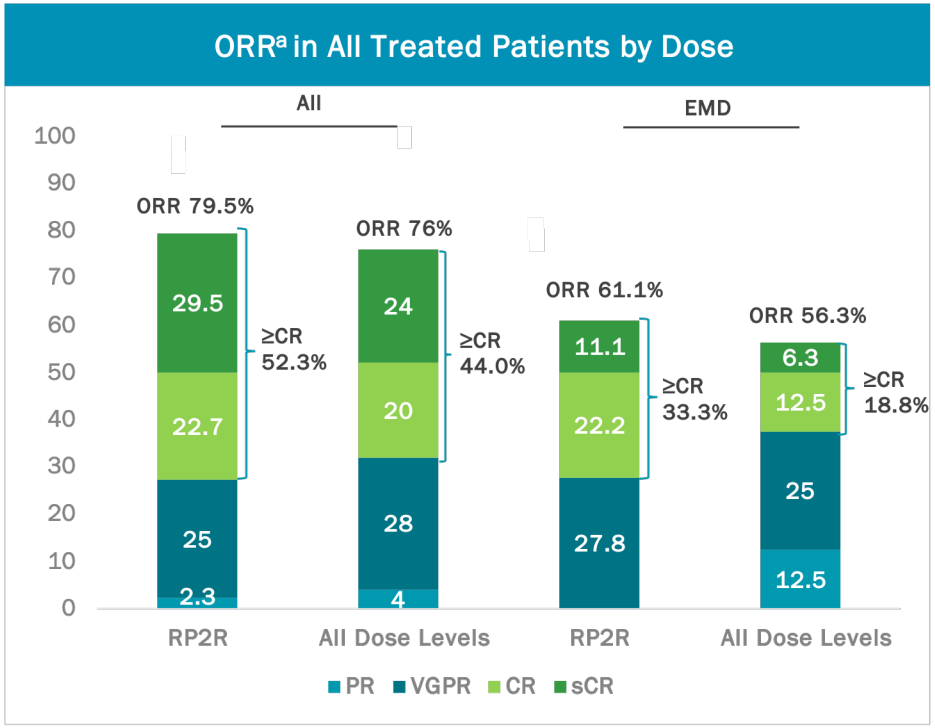
Phase 1b RedirecTT-1: Teclistamab + Talquetamab



All Patients	All Doses (n=50)	RP2R (n=44)
Median follow-up (range), mo	29.0 (0.5[b]-37.1)	18.2 (0.7-27.0)
Median time to first response (range), mo	2.1 (1.1-7.7)	1.4 (0.3-5.1)
12-mo mDOR rate, % (95% CI)	81.1 (18.9-NE)	91.0 (NE-NE)
12-mo mPFS rate, % (95% CI)	68.0 (14.6-NE)	73.7 (NE-NE)

Patients with EMD	All Doses (n=50)	RP2R (n=44)
Median follow-up (range), mo	18.7 (0.5[b]-33.8)	13.6 (0.7-25.9)
Median time to first response (range), mo	2.6 (2.1-3.8)	3.0 (1.4-5.1)
12-mo mDOR rate, % (95% CI)	55.6 (1.2-NE)	81.8 (5.95-NE)
12-mo mPFS rate, % (95% CI)	36.1 (2.5-15.3)	52.9 (2.4-NE)

Cohen YC, et al. IMS 2024. Abstract OA-03.

Presented by: Saad Z. Usmani, MD MBA FACP, @szusmani

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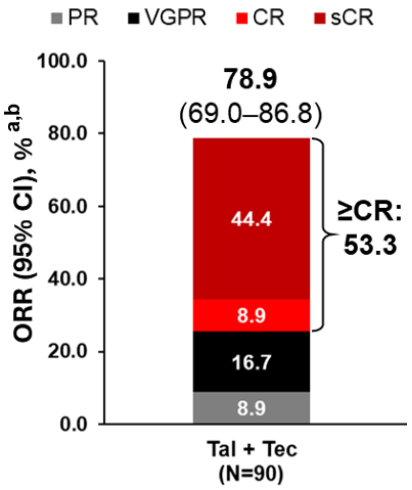
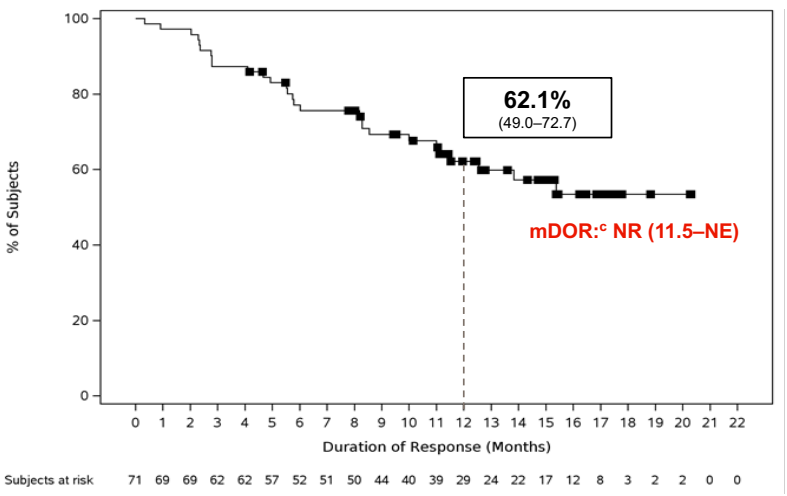
Phase 2 RedirecTT-1: Teclistamab + Talquetamab

RedirecTT-1 Phase 2 Tal + Tec: Response and DOR at 16.3 Months Median Follow-up





With additional ~4 months of follow-up, ORR remained high, median DOR was NR, and the estimated 12-month DOR rate was 62.1%

Data cut-off date: July 18, 2025. [a]ORR was assessed by independent review committee per IMWG criteria. [b]Due to rounding, individual response rates may not sum to the ORR. [c]At time of data cutoff, 43 (60.6%) patients were censored.
NE, not estimable; NR, not reported; PR, partial response; sCR, stringent complete response.

Presented by S Usmani at American Society of Hematology; December 6–9, 2025; Orlando, FL, USA

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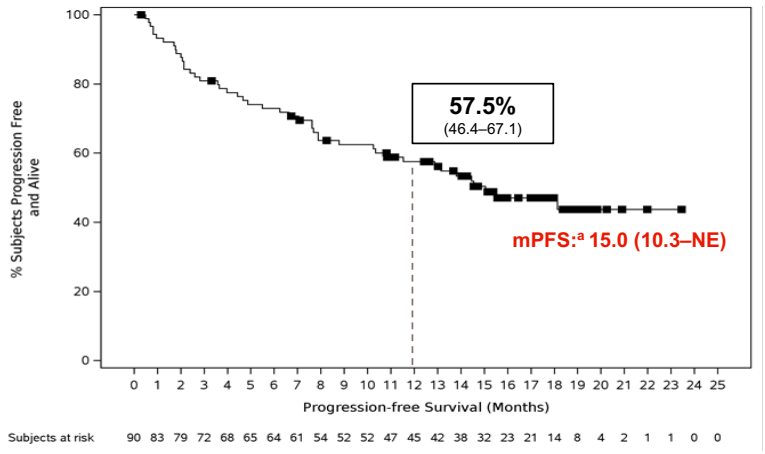
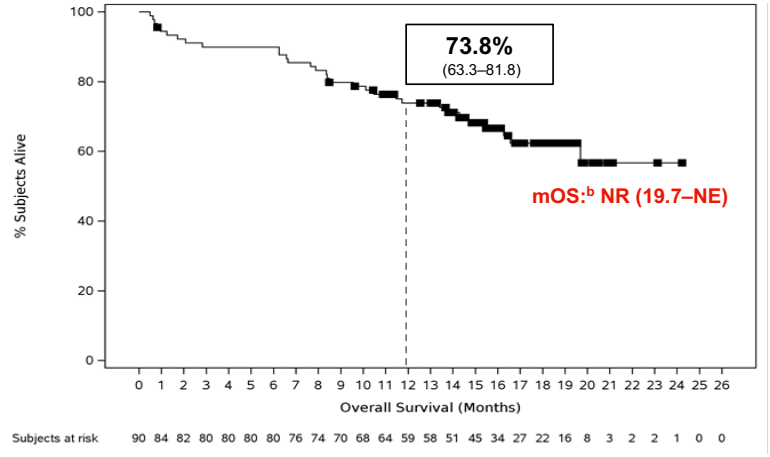
Phase 2 RedirecTT-1: Teclistamab + Talquetamab

RedirecTT-1 Phase 2 Tal + Tec: PFS and OS at 16.3 Months Median Follow-up





Estimated 12-month PFS rate was 57.5%

Estimated 12-month OS rate was 73.8%

Data cut-off date: July 18, 2025. [a]At time of data cutoff, 45 (50.0%) patients were censored for PFS. [b]At time of data cutoff, 59 (65.6%) patients were censored for OS.
mOS, median overall survival; mPFS, median progression free survival; OS, overall survival; PFS, progression free survival

Presented by S Usmani at American Society of Hematology; December 6–9, 2025; Orlando, FL, USA

Presented by: Saad Z. Usmani, MD MBA FACP, @szusmani

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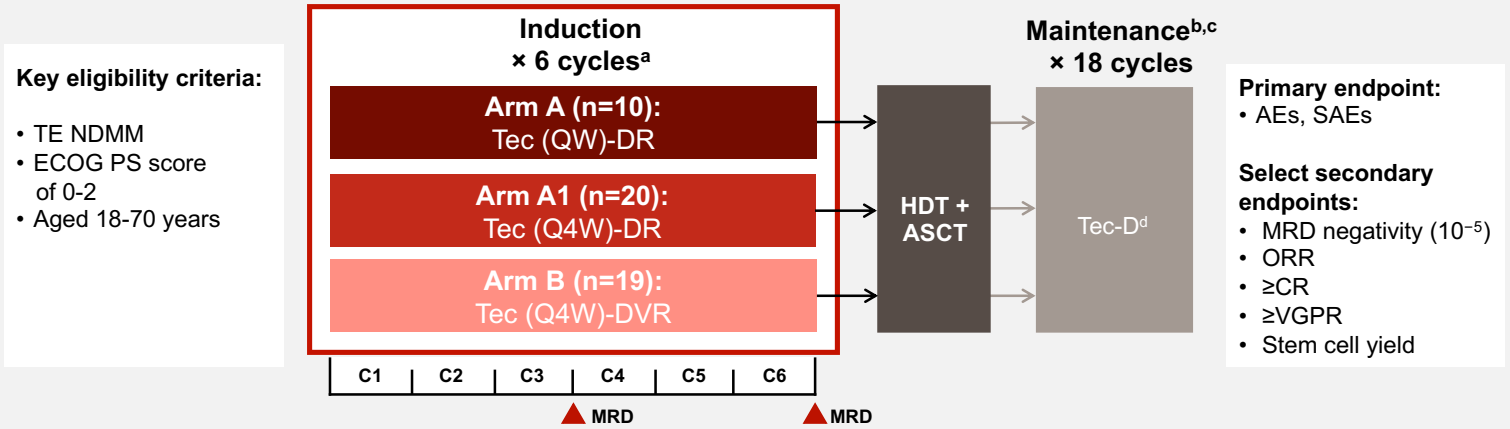
MajesTEC-5: Tec in Induction

GMMG-HD10/DSMM-XX/MajesTEC-5: Study Design



- Per protocol, MRD assessments by NGF were planned following completion of C3 and C6 in all patients
- Additional cohorts evaluating Tal and Tec/Tal combinations are also being investigated as part of this study

[a]Each cycle is 28 days. Dexamethasone was also administered in C1 and C2. Stem cell collection was planned after 3 cycles of induction. [b]Following maintenance therapy, patients could receive additional SoC maintenance treatment per institutional standard and local investigator decision. [c]Maintenance treatment can be discontinued when 12 months of sustained MRD negativity (10^{-5}) have been observed, beginning in induction. [d]Planned maintenance treatment in Arm A was Tec-DR. A protocol amendment permitted patients initially assigned to Tec-DR maintenance to receive Tec-D maintenance per investigator's choice (patients who started Tec-DR may have discontinued Len to receive Tec-D per investigator's choice).
AE, adverse event; ASCT, autologous stem cell transplant; C, Cycle; CR, complete response; D, daratumumab; ECOG PS, Eastern Cooperative Oncology Group performance status; GMMG/DSMM, German-speaking Myeloma Multicenter Group/Deutsche Studiengruppe Multiples Myelom; HDT, high-dose therapy; Len, lenalidomide; MRD, minimal residual disease; NDMM, newly diagnosed multiple myeloma; NGF, next-generation flow cytometry; ORR, overall response rate; QW, weekly; Q4W, every 4 weeks; R, lenalidomide; SAE, serious adverse event; SoC, standard-of-care; Tal, talquetamab; TE, transplant-eligible; Tec, teclistamab; V, bortezomib; VGPR, very good partial response.

Presented by MS Raab at the 66th American Society of Hematology (ASH) Annual Meeting and Exposition; December 7-10, 2024; San Diego, CA, USA

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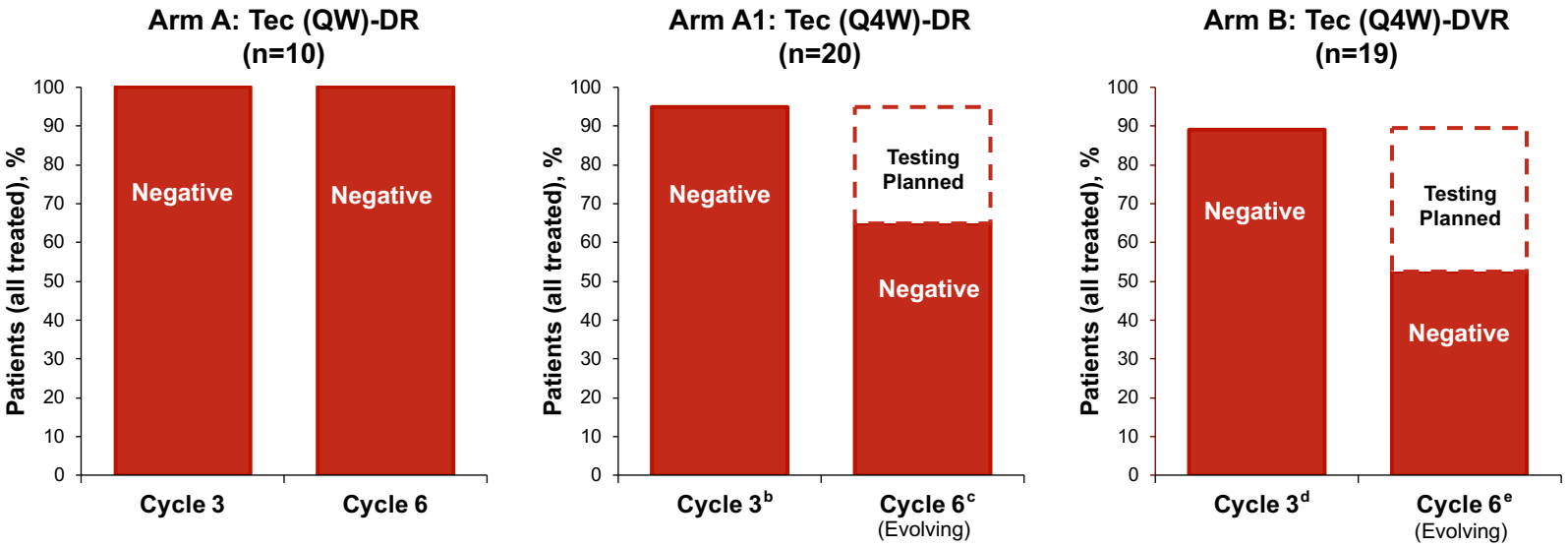
MajesTEC-5: : Tec in Induction

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



100% of evaluable patients achieved MRD negativity by C3; no patients were MRD positive

Data cutoff: September 30, 2024. [a]MRD-negativity rate was defined as the proportion of patients who achieved MRD negativity (10^{-5}), regardless of response. MRD was determined by NGF testing. [b]In Arm A1, 1 patient did not have bone marrow collected after C3. [c]In Arm A1, 1 patient did not have MRD testing (10^{-5}) after C6. [d]In Arm B, 1 patient was not tested at C3, but was MRD-negative at C6; 1 patient discontinued before C3 and had no on-study MRD testing. [e]In Arm B, 1 patient was MRD negative at 10^{-4} after C6 and was considered indeterminate and without available MRD testing (10^{-5}); 1 patient discontinued before C3 and had no on-study MRD testing.
C, Cycle; D, daratumumab; GMMG/DSMM, German-speaking Myeloma Multicenter Group/Deutsche Studiengruppe Multiples Myelom; MRD, minimal residual disease; NGF, next-generation flow cytometry; QW, weekly; Q4W, every 4 weeks; R, lenalidomide; Tec, teclistamab; V, bortezomib.

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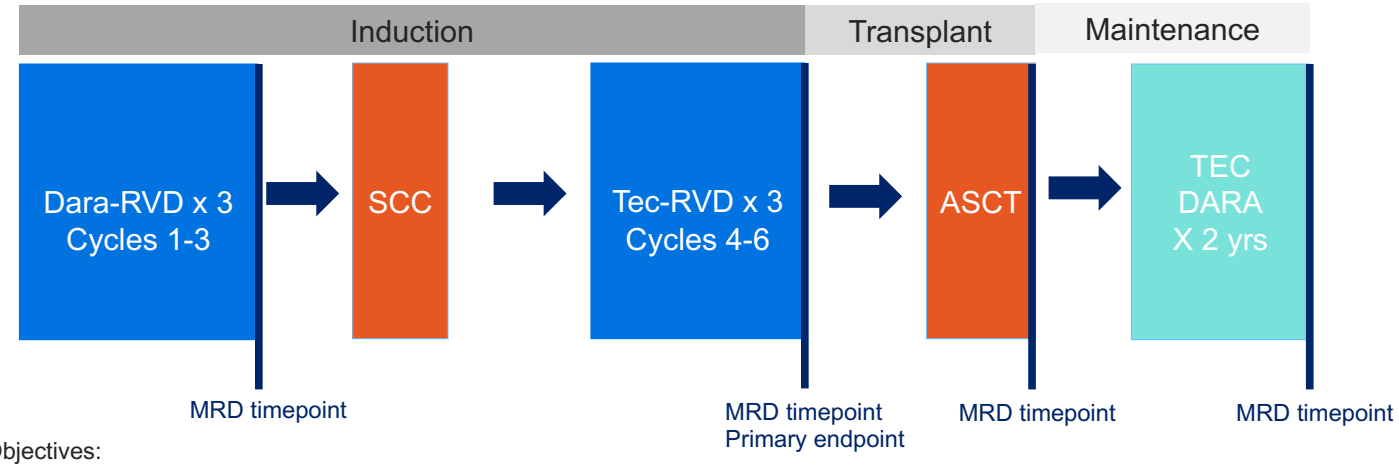
ALTITUDE – Standard Risk NDMM

ALTITUDE – ALTernating Induction Therapies to Achieve Undectable Disease Endpoints

Phase 1b/2 Alternating Dara-RVd – Teclistamab-RVd in Transplant Eligible Standard Risk Newly Diagnosed Multiple Myeloma



Objectives:
Primary Endpoints:
-Phase 1 - To evaluate the safety and tolerability of Tec-RVd
-Phase 2 – To evaluate MRD negativie rate of Dara-RVD x 3 cycles followed by Tec-RVD x 3 cycles
Secondary Endpoints:
-Safety and tolerability of Dara-TEC maintenance, response rates, sustained MRD negative rate after 12 and 24 months, HRQoL,PFS, EFS, and OS

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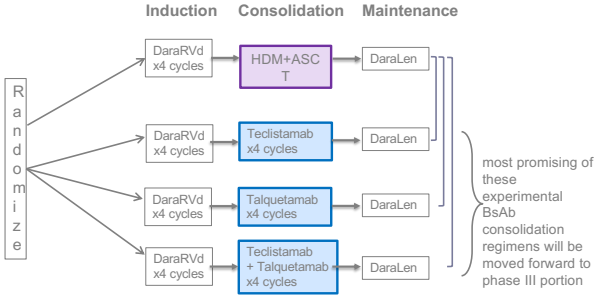
COBALT (*CO*mbination *B*ispecific *A*ntibodies in *L*ieu of *T*ransplant: **Standard Risk NDMM**

Phase II component

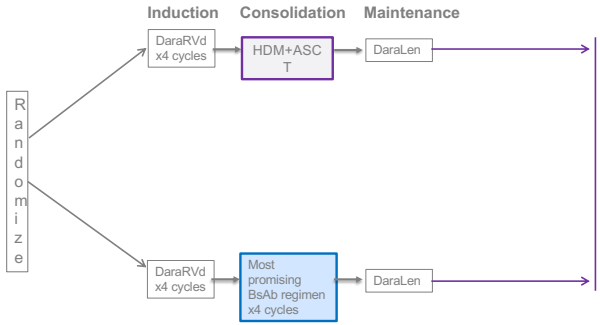


*all patients undergo stem cell collection post-induction and all undergo MRD assessments as per the original study schema (post-induction, post-consolidation, after 1 and 2 yrs of maintenance)

Primary Endpoint= MRD negativity (NGS) post-consolidation

Target improvement in MRD-neg rate to at least 60% (from 45%)
82% power, one-sided α = 0.08 for each comparison would require 50 patients/arm

Phase 3 component: compare control (ASCT) to the most promising BsAb arm from the phase 2 portion



*all patients undergo stem cell collection post-induction and all undergo MRD assessments as per the original study schema (post-induction, post-consolidation, after 1 and 2 yrs of maintenance)

Primary endpoint: PFS

Compare the ASCT and most promising BsAb arm to determine if experimental regimen significantly improves PFS
N=754 pts (377/arm)

85% power to detect a true HR of 0.50 or lower corresponding to 4-year PFS rates of 94% vs. 97%

1-sided α=0.025
accrual rate = 150 patients/year

Final analysis at 78 PFS events
Interim analyses at 33% and 67% PFS events

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Future Directions

- Rational combinations of bispecific antibodies in earlier lines of treatment to over resistance.

- Identifying antigen mutations:
  - Predicting risk of relapse will become more accurate using computational genomics and AI modeling.

- Improving T-cell redirection technology
  - Multi-antigen targeting, adding co-stimulatory domain, conditional activation, engineering bias/fusion constructs, etc.

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