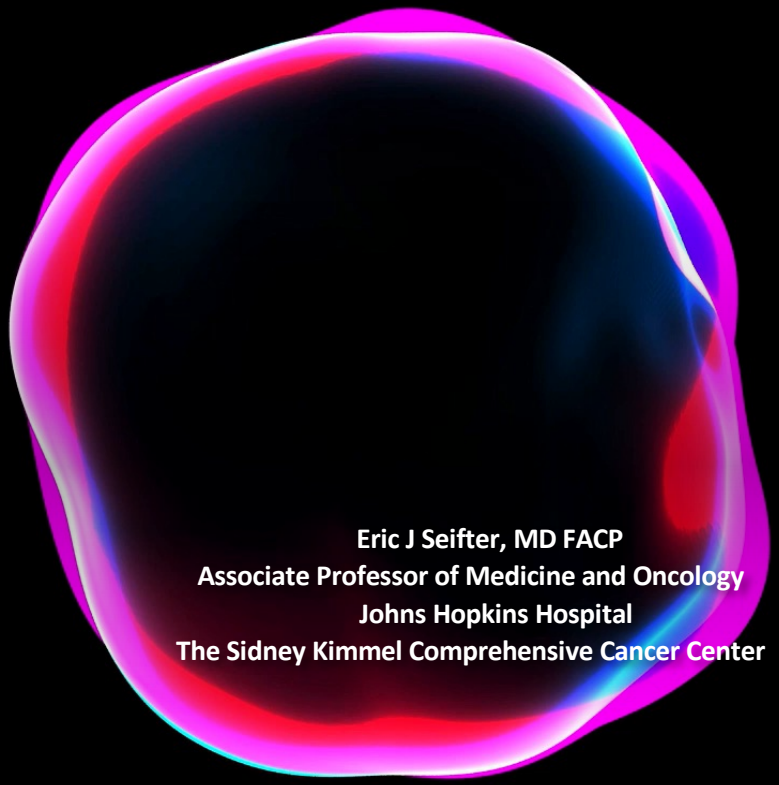
Myeloma & Plasma Cell Dyscrasia



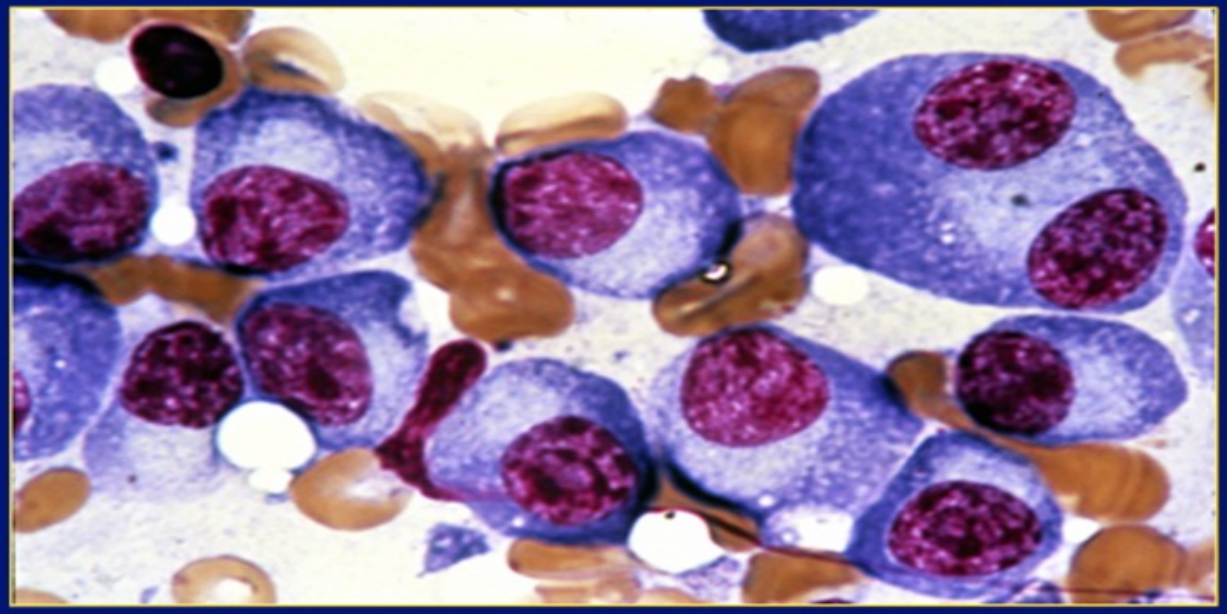
Eric J Seifter, MD FACP
Associate Professor of Medicine and Oncology
Johns Hopkins Hospital
The Sidney Kimmel Comprehensive Cancer Center

American Society *of* Hematology

Helping hematologists conquer blood diseases worldwide

No disclosures: I have been "Pharma-Free" since 2002

MM Plasma Cells



Myeloma numbers

2nd	• 2nd most common blood cancer
2.1%	• 2.1% of all new cancer cases in the USA
32,270	• New cases of MM in 2020
140,779	• People living with MM - Rising yearly

https://seer.cancer.gov/statfacts/html/mulmy.html
Siegel. CA Cancer J Clin 2019

Every medical lecture must answer 2 questions:

- Why this topic?
- Why right now?

And parenthetically: Why me?

NEW YORK TIMES June 5, 2025

From No Hope to a Potential Cure for a Deadly Blood Cancer

by Gina Kolata (doyenne of science journalists)

Multiple myeloma is considered incurable, but a third of patients in a Johnson & Johnson clinical trial have lived without detectable cancer for years after facing certain death. These results, in patients whose situation had seemed hopeless, has led some battle-worn American oncologists to dare to say the words "potential cure."

IS THIS CLICKBAIT HYPERBOLE or FOR REAL?

Myeloma Work-Up

Serum/urine IEP (immunofixation or immunoelectrophoresis): IgG, IgA, (rarely IgD, IgE)

IgM almost never myeloma: may become lymphoplasmacytic lymphoma (Waldenstrom's macroglobulinemia) which is a low grade lymphoma (lymphadenopathy/splenomegaly, but almost never lytic bone lesions)

Also identifies associated light chain: kappa or lambda 2-4% non-secretory, 20% light chain only

Free kappa/lambda + ratio: quantifies kappa or lambda light chain partner (rarely neither)

SPEP: M protein quantification: mg/dl or g/dl

Serum Immunoglobulin Quantification: mg/dl or g/dl > 3 g/dl is high, ? Immunoparesis

Urine PEP (UPEP): mg/dl protein + % M-protein **abst 81 ASH 2024 Banerjee R et al Fred Hutch** 24 hour urine unhelpful ≥99.5% of the time (IMWG) EXCEPT for AL amyloidosis, MGRS, or urine-only response

Beta-2 microglobulin (less helpful if creat >2.0)

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Bone Marrow Biopsy/Aspirate

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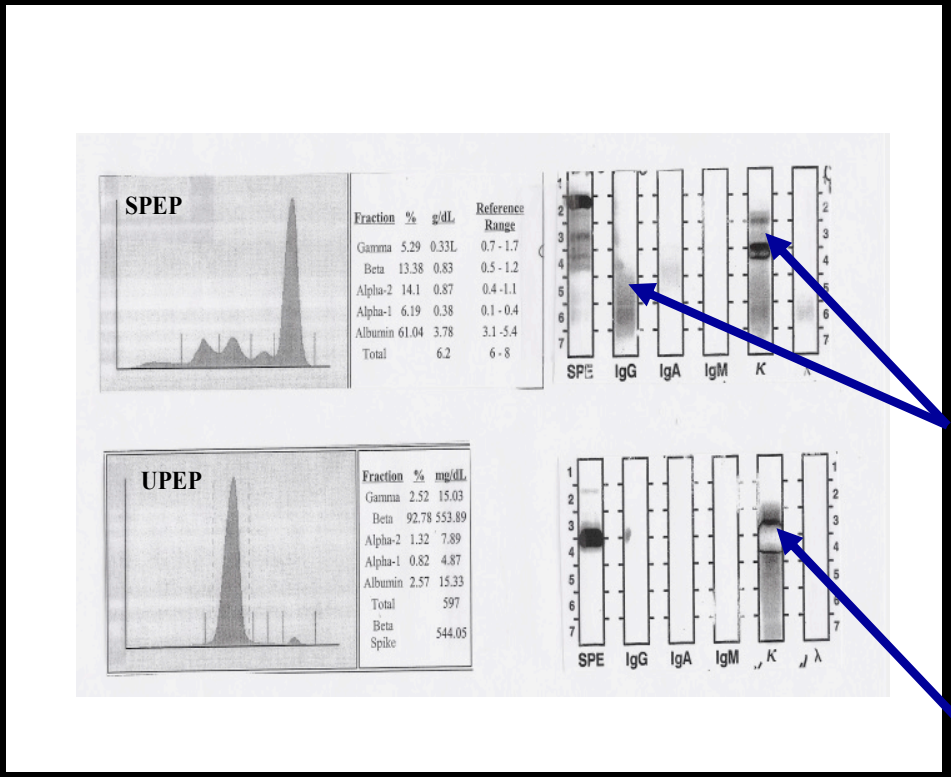
Immunofixation showing IgG kappa in serum and kappa in urine



These are M proteins because they are monoclonal

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New Reference Intervals for Serum Free Light Chains

eGFR	Kappa mg/L	Lambda mg/L	FLC ratio
≥ 60	7.0 - 32.0	5.0 - 22.0	0.66 - 2.10
45-59	10.0 – 47.0	9.1 – 39.2	0.64 – 1.92
30-44	12.5 – 70.8	10.9 – 52.8	0.68 – 2.06
<30	17.8 – 117.3	14.5 – 94.4	0.67 – 2.17

Abst 542 ASH 2021 Long TE et al Iceland

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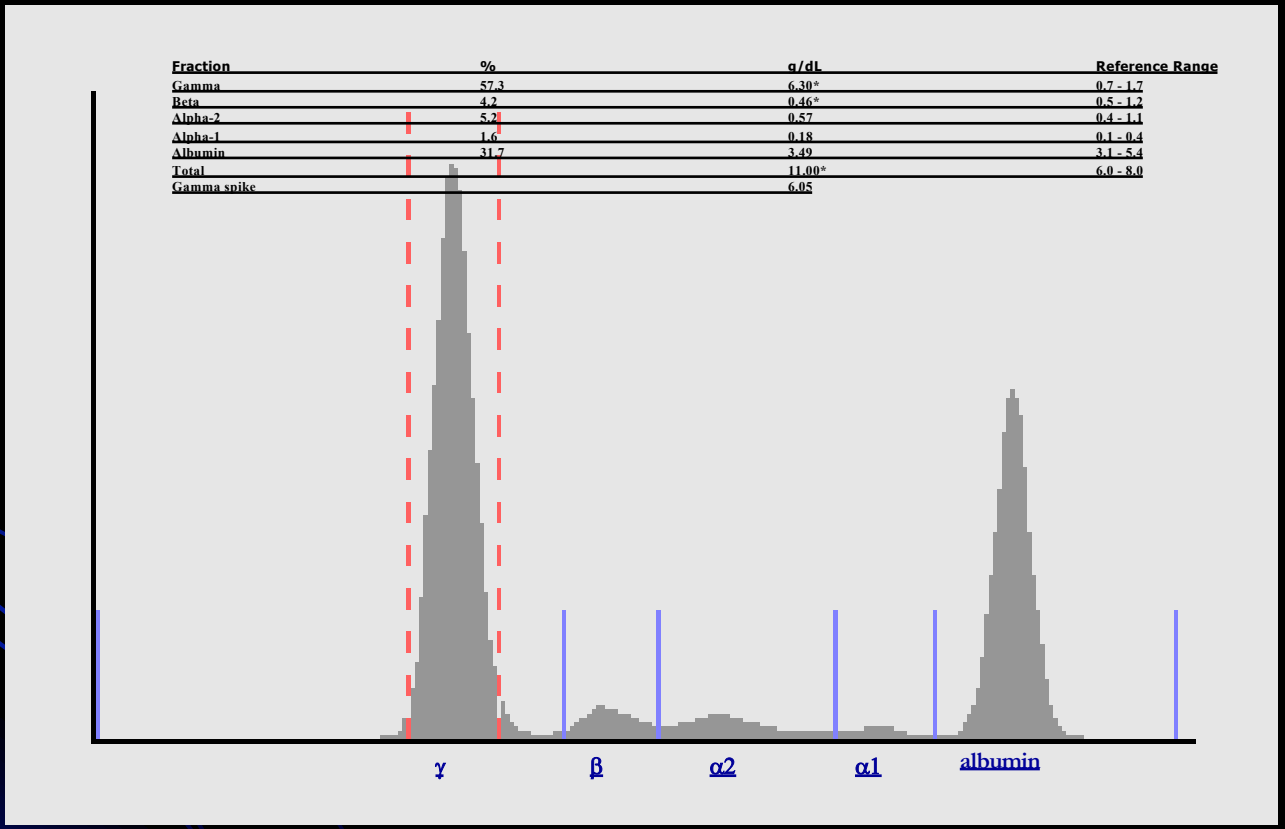
Serum protein electrophoresis in MM (classic “goal post” appearance)



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SCREENING FOR MGUS

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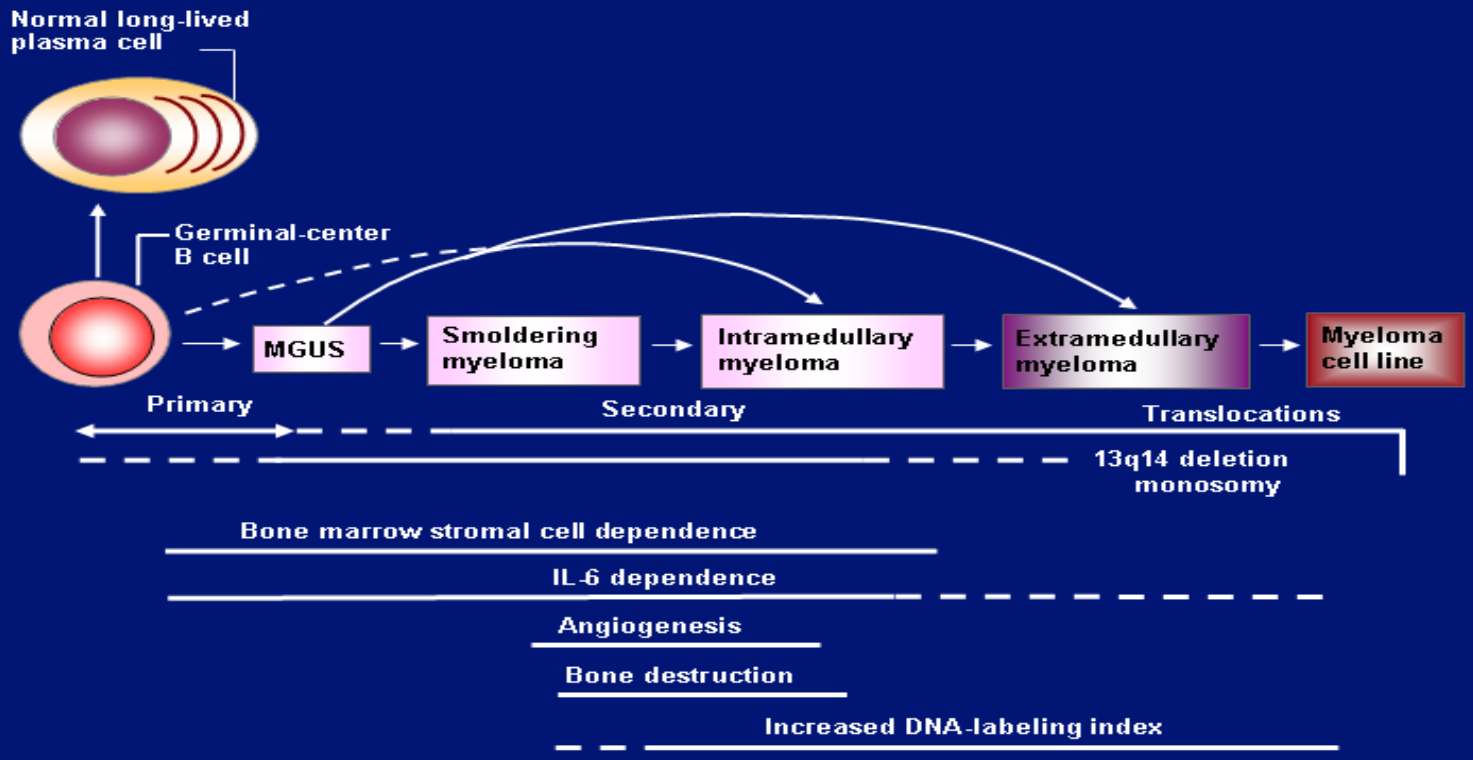
Pathogenesis of MM



MGUS, monoclonal gammopathy of undetermined significance

Adapted with permission from Kuehl WM, Bergsagel PL. *Nat Rev Cancer*. 2002;2:175

MGUS

Best Model Calculator to Predict Progression of MGUS

Search:

“Pangea Model calculator MGUS”

pangeamodels.org

Rule out Monoglonal Gammopathy of Clinoical Significance:

- MGRS (renal)
- MGNS (neurological)
- Amyloidosis

QR CODE →

Defining Smoldering Myeloma

- First coined by Kyle and Greipp in 1980
  - Monoclonal gammopathy of reasonably high burden (compared to MGUS) but for whom "treatment should be withheld" given the lack of myeloma-defining events
- **Formal definition (any of below):**
  - Serum M-spike ≥ 3g/dL
  - Urinary monoclonal protein ≥ 500mg/24h
  - Bone marrow plasmacytosis 10-59%

SMOLDERING MULTIPLE MYELOMA

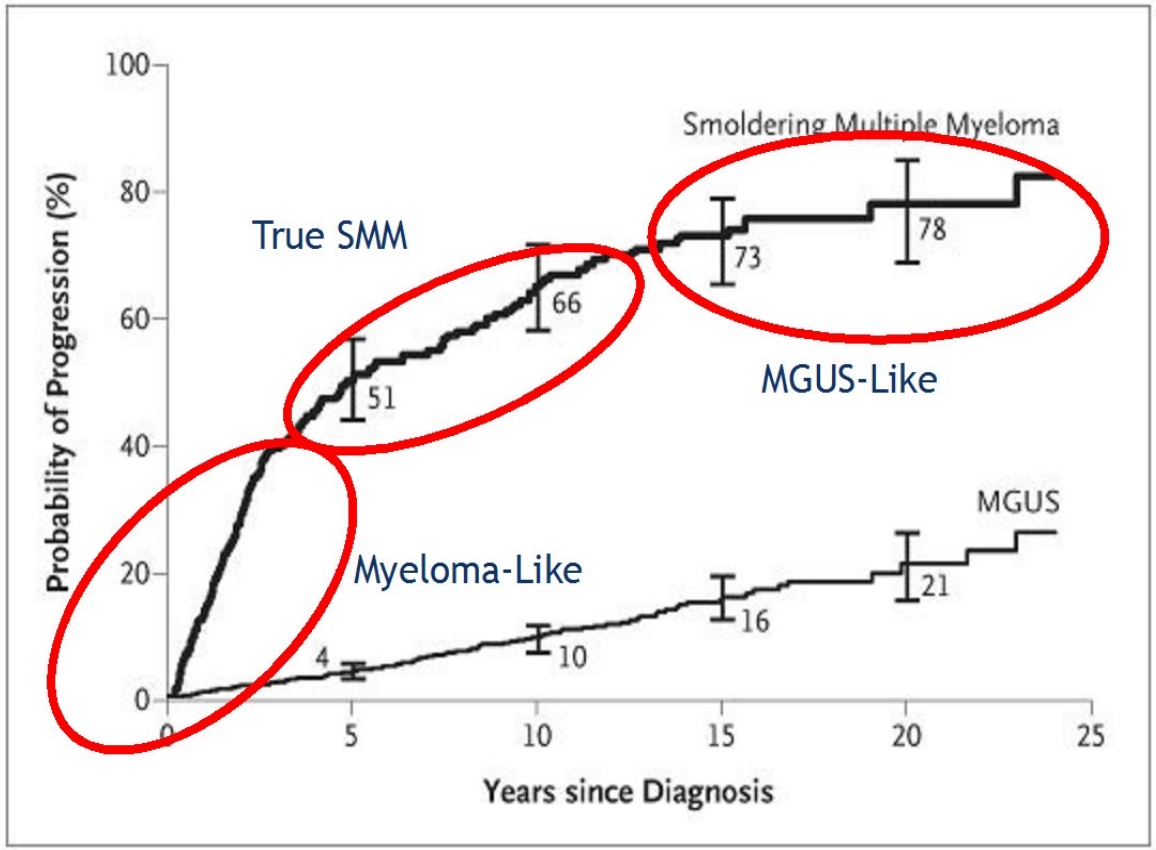
ROBERT A. KYLE, M.D.,
AND PHILIP R. GREIPP, M.D.

MULTIPLE myeloma is characterized by an increase of abnormal plasma cells in the bone marrow and monoclonal protein in the serum, often with osteolytic bone lesions. Its course is progressive: anemia, weakness, fatigue, fractures, bone pain, hypercalcemia, renal insufficiency, recurrent infections, bleeding, and deterioration lead to death. However, we have seen six patients with illnesses that met the criteria for the diagnosis of multiple myeloma[1] but have not had a progressive course. Although no chemotherapy was given, their condition has remained stable for five or more years. We designate these cases as "smoldering multiple myeloma." We wish to call attention to this group because smoldering multiple myeloma should be recognized, and treatment withheld.

PRESENTED BY:
Ben Derman, MD

Kyle and Greipp *NEJM* 1980 Jun 12;302(24)
Rajkumar et al. Lancet Oncol. 2014;15(12):e538–e548

Smoldering MM is a Heterogeneous disease



Kyle R et al. N Engl J Med 2007;356:2582-2590

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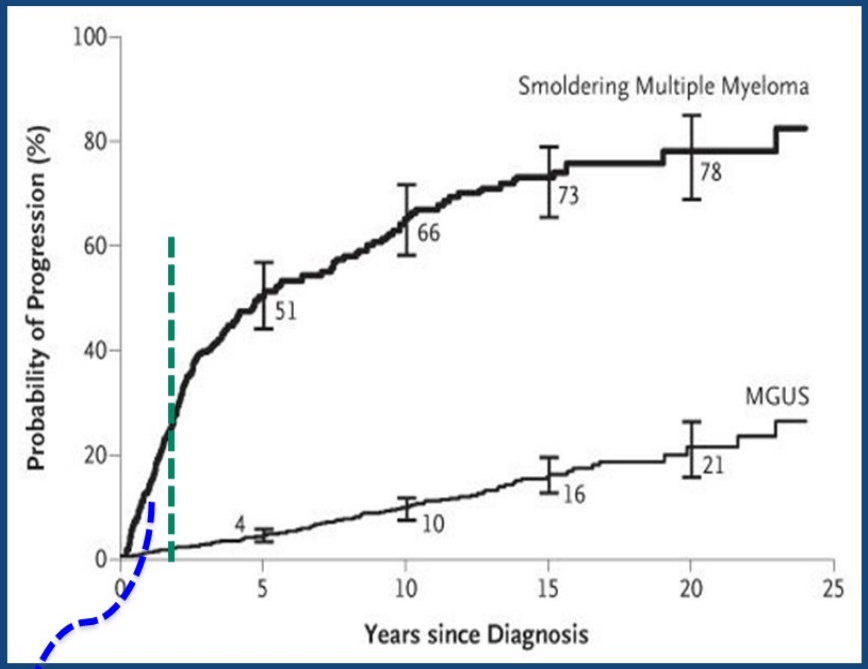
Redefining MM: A paradigm shift



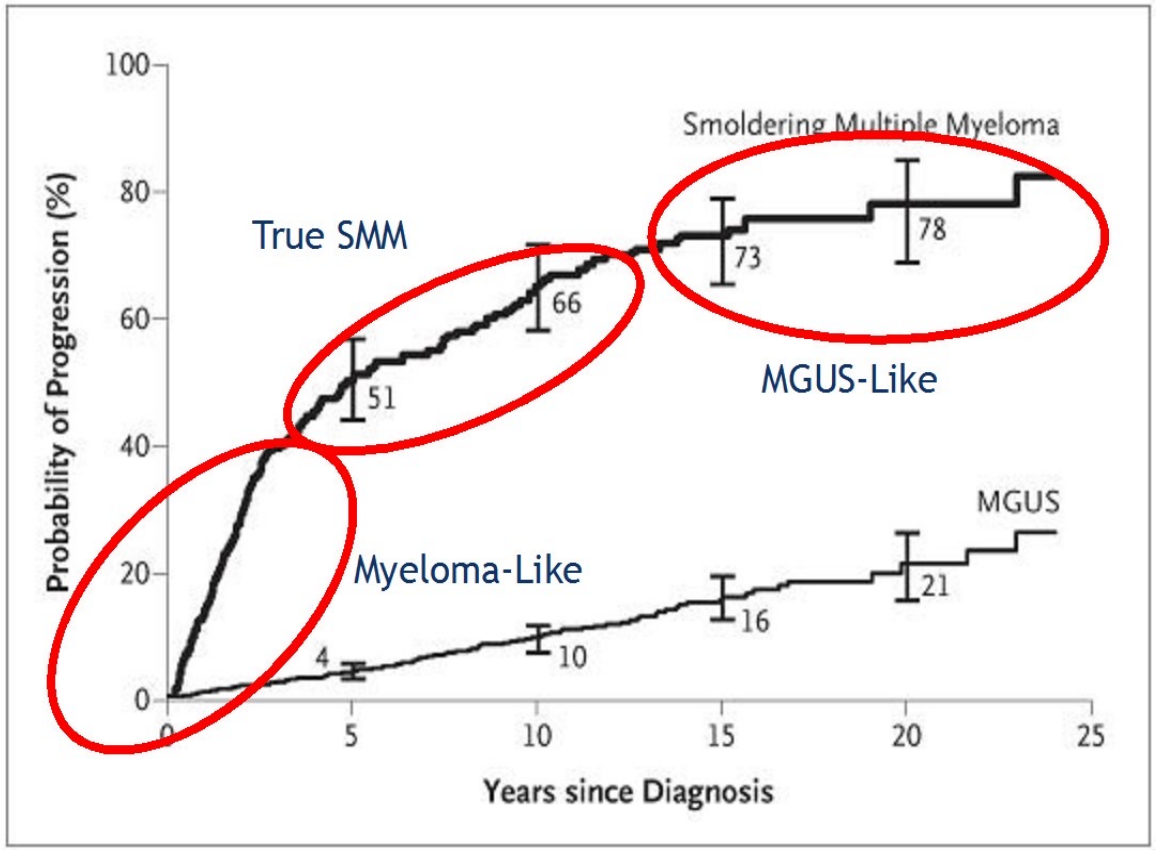
- Hyper**C**alcemia
- **R**enal Insufficiency
- **A**nemia
- **B**one Disease

- BMPC >= 60%
- >1 MRI lesions
- FLC ratio > 100

Predicts an 80% or more risk of progression in 2 years

High risk of progression: Redefine as MM?

Smoldering MM is a Heterogeneous disease



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Smoldering MM

IMWG 2/20/20 RULE

Serum M protein : >2 g/dl

Involved:uninvolved serum light chain >20

Bone marrow plasma cell infiltration >20%

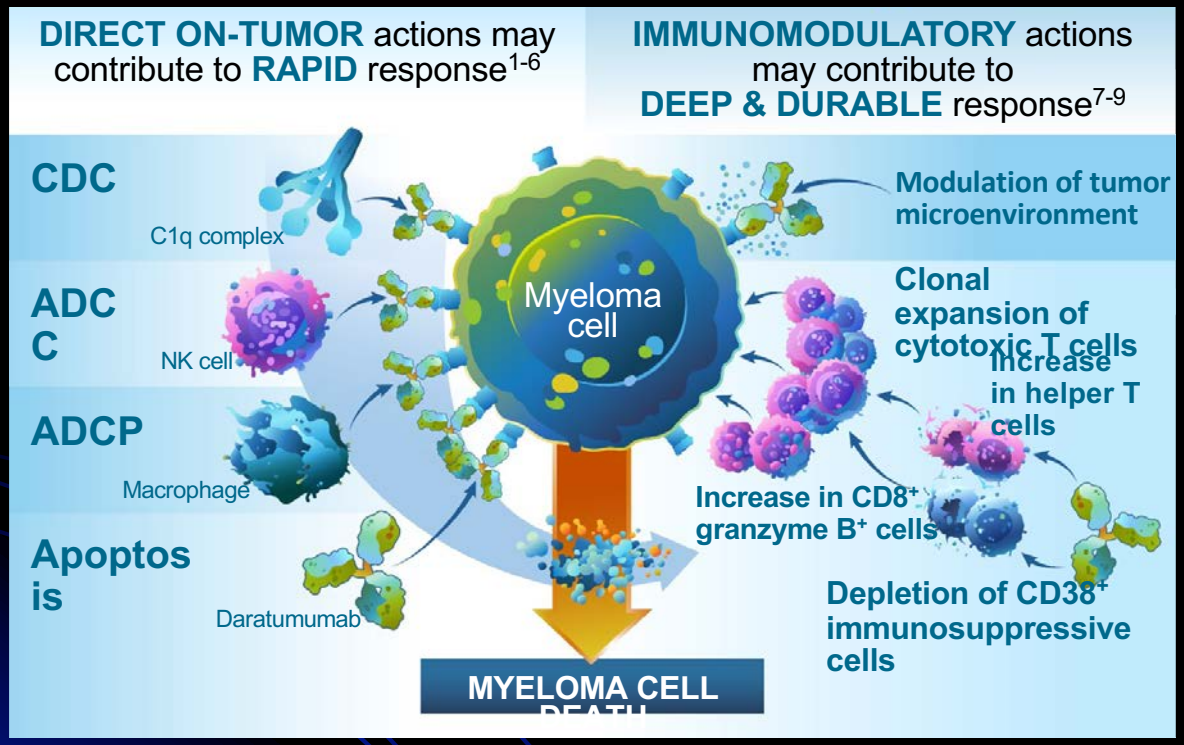
Chromosomal abnormality :

t(4;14), t(14;16), 1q + gain/amplification, del (13q)/monosomy 13 (?really)

??include del(17p)/TP53 mutations, t(14;20), del (1p32)

3-4 risk factors: HIGH RISK >50% chance progressing to myeloma in 2 years

Daratumumab (DARA)



Phase 3 Trials

- RRMM
  - D-Rd (POLLUX)
  - D-Vd (CASTOR)
  - D-Pd (APOLLO)*
  - D-Kd (CANDOR)*
- NDMM non-transplant
  - D-VMP (ALCYONE)
  - D-Rd (MAIA)
  - D-VRd (CEPHEUS)*
- NDMM transplant
  - D-VTd Part 1 (CASSIOPEIA)
  - D-VRd (PERSEUS)*
  - D-R maintenance (AURIGA)*

*Pending results.

CDC, complement-dependent cytotoxicity; ADCC, antibody-dependent cellular cytotoxicity; NK, natural killer; ADCP, antibody-dependent cellular phagocytosis; RRMM, relapsed/refractory multiple myeloma; D, daratumumab; R, lenalidomide; d, dexamethasone; V, bortezomib; P, pomalidomide; K, carfilzomib; NDMM, newly diagnosed multiple myeloma; MP, melphalan and prednisone; T, thalidomide.

1. DARZALEX® US PI; 2019. 2. Liszewski MK, et al. *Adv Immunol*. 1996;61:201-283. 3. Debets JM, et al. *J Immunol*. 1988;141(4):1197-1201. 4. Overdijk MB, et al. *mAbs*. 2015;7(2):311-321. 5. Lokhorst HM, et al. *N Engl J Med*. 2015;373(13):1207-1219. 6. Plesner T, et al. *Blood*. 2012;120:73. 7. Krejcik J, et al. *Blood*. 2016;128(3):384-394. 8. Adams HC III, et al. *Cytometry A*. 2019;95(3):279-289. 9. Chiu C, et al. Poster presented at: ASH 2016; San Diego, CA.

Smoldering MM

Dimopoulos MA AQUILA trial NEJM 392:1777-1788, 2025

390 pts (BM% 10-49% + 1 of following: M protein ≥3g/dl, immunoparesis x 2, FLC 8-99, IgA, BM%50-59)

IMWG 2020 high risk: benefit regardless of age: Voorhees P et al abst 372 ASH 2025

Median f/u: 65.2 months

	Daratumumab	W+W	
5 yr PFS	63.1%	40.8%	HR 0.49 (0.36- 0.67) p < .0001
5 yr PFS(IMWG-HR)	60.4%	23.6%	
5 yrTTNT(IMWG-HR)	HR 0.39 95% CI 0.25-0.62		
Med TTProg	44.1 mo	17.8 mo	HR 0.51 (0.40-0.66)
5 yr OS	93%	86%	HR 0.52 (0.27-0.98) p=NS

QOL (3 tests) : No differences

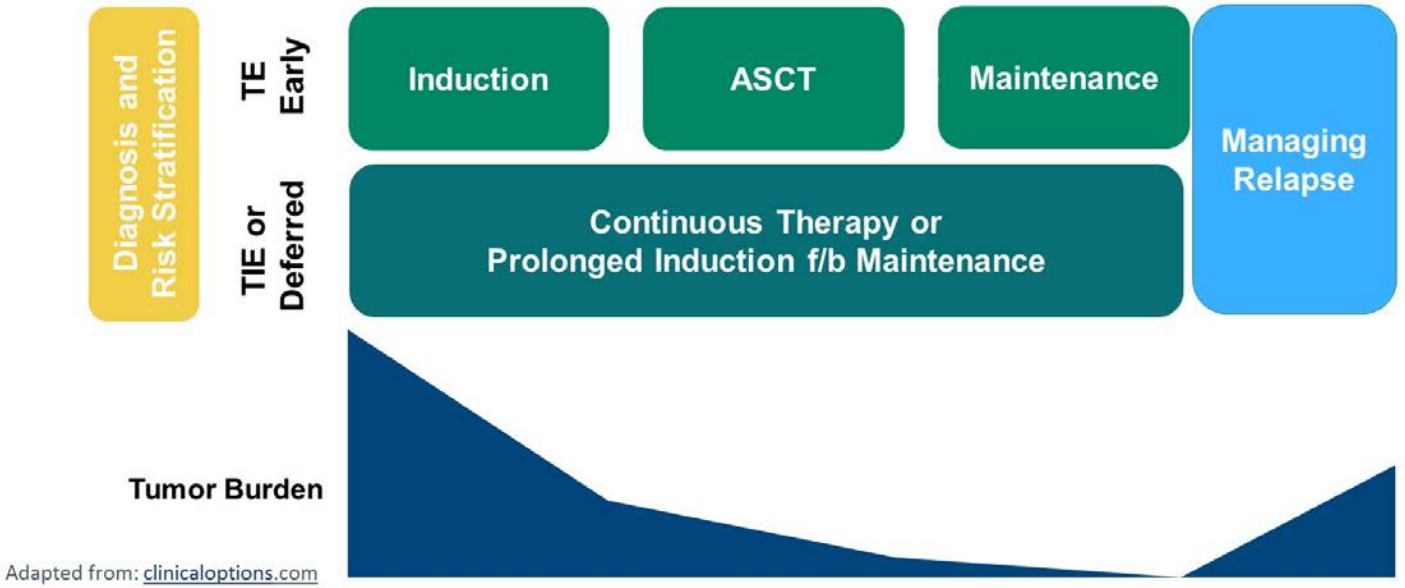
MY TAKE:

No significant differences in OS and QOL.

But the delay of progression may particularly benefit older less fit patients and there is no decrement in OS implementing the full dose MM therapy later.

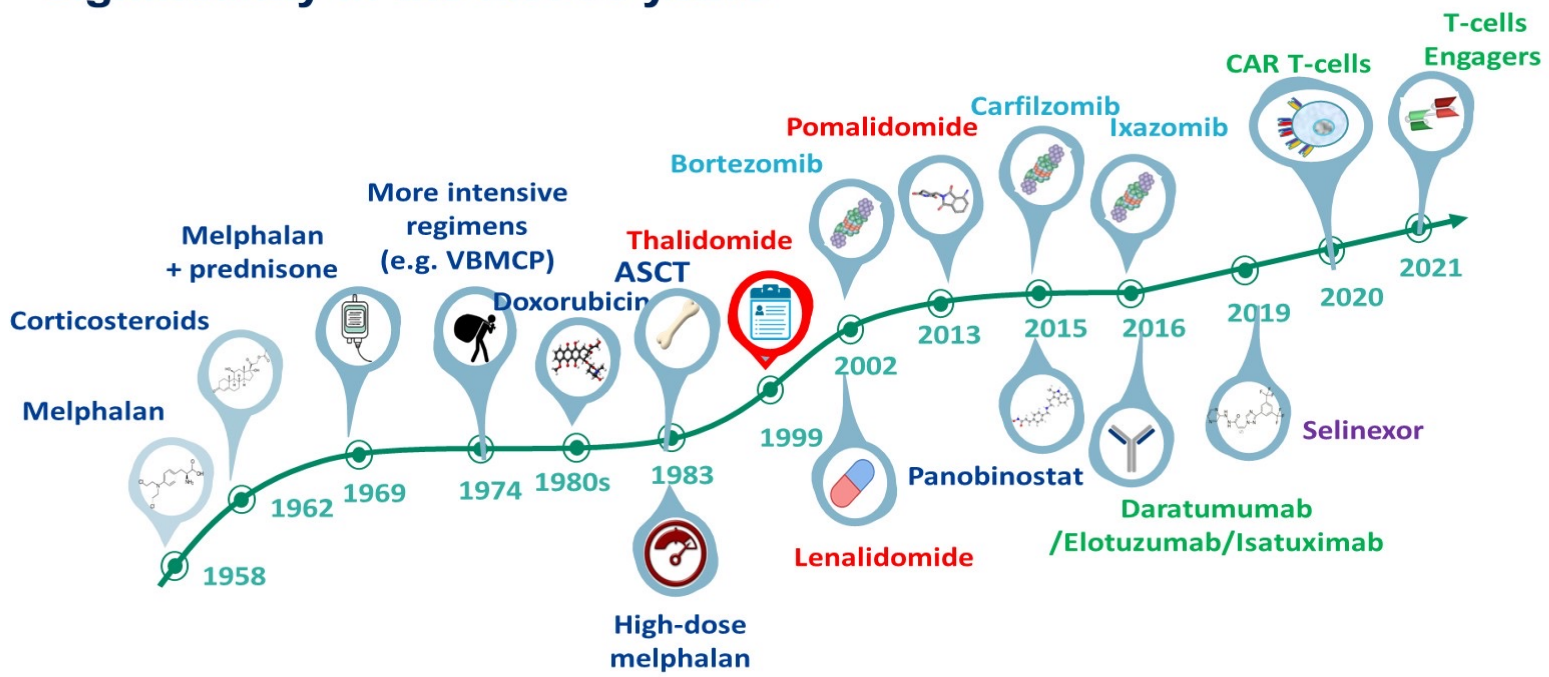
CHANGE IN SOC: Higher risk SMM should be treated with DARA

MM Treatment Paradigm



Adapted from: clinicaloptions.com

The multiple myeloma treatment landscape has changed significantly in the last 50 years



Isatuximab: 2024 first line (Dara “wannabe” ant-CD38 MoAb)

Belantamab mafadotin: 2025 relapsed (anti-BCMA ADC)

Median Survival MM

Prior to 1990s: 3 years chemo + steroids

1990 to 2000: 5 years better chemo +AutoSCT

2000 to 2010: 7 years chemo + AutoSCT + Bortezomib (Velcade; PROTEOSOME INHIBITOR)+ Lenalidomide (Revlimid; Cereblon binder, IMiDs) + zoledronate/denosumab (OSTEOCLAST INHIBITOR)

2010 to 2020: 9 years Added Lenalidomide maintenance
Pomalidomide (upgrade of lenalidomide; Cereblon binder, IMiDs)
Carfilzomib (upgrade of Bortezomib; PROTEOSOME INHIBITOR)

2020 on: 12+ years Added Daratumumab (anti-CD38 MoAb)
CAR T-Cells or Bispecific Antibodies (anti-BCMA)
Belantamab mafadotin (ADC to BCMA)
Venetoclax (BCL2 inhibition) for t(11;14)

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2000 to 2010: 7 years chemo + AutoSCT + Bortezomib (Velcade; PROTEOSOME INHIBITOR)+ Lenalidomide (Revlimid; Cereblon binder, IMiDs) + zoledronate/denosumab (OSTEOCLAST INHIBITOR)

2010 to 2020: 9 years Added Lenalidomide maintenance
Pomalidomide (upgrade of lenalidomide; Cereblon binder, IMiDs)
Carfilzomib (upgrade of Bortezomib; PROTEOSOME INHIBITOR)

2020 on: 12+ years Added Daratumumab (anti-CD38 MoAb)
CAR T-Cells or Bispecific Antibodies (anti-BCMA)
Belantamab mafadotin (ADC to BCMA)
Venetoclax (BCL2 inhibition) for t(11;14)

Newly Diagnosed Multiple Myeloma (NDMM) →

Induction Therapy (first-line)

“Everything But the Kitchen Sink”

Current Standard Therapy MM: DVRd

- Daratumumab: Anti-CD38 Monoclonal Antibody
- Bortezomib / Velcade: Proteosome inhibitor
- Lenalidomide / Revlimid: Cereblon binds to lenalidomide to form an E3 ubiquitin ligase complex that destroys cancer-driving proteins like Ikaros and Aiolos
- dexamethasone

ND MM

Sonneveld P et al N Eng J Med 390:301-313, 2024 **Perseus Trial**

NDMM 709 pts < age 70 randomized to D-VRd versus VRd Med f/u 47.5 mo Dara SC

	Dara-VRd	VRd	
4 yr PFS	84.3%	67.7%	HR 0.42 0.30-0.59, p<.0001
4 yr OS	90.4%	87.6%	p=NS

Zweeman S et al abst 362 ASH 2024 **Cepheus Trial**

NDMM 395 pts (≥age 70,comorbidities,noASCT) randomized to D-VRd vs VRd Med f/u 58.7 mo

	Dara-VRd	VRd	
2 yr MRD – (6 logs)	32.0%	15.7%	HR 0.40 0.24-0.64, p=.0001

Dara-VRd can be given at all ages (for private insurance say “transplant eligible”)

Newly Diagnosed Multiple Myeloma (NDMM) →

? CONSOLIDATION with AutoSCT

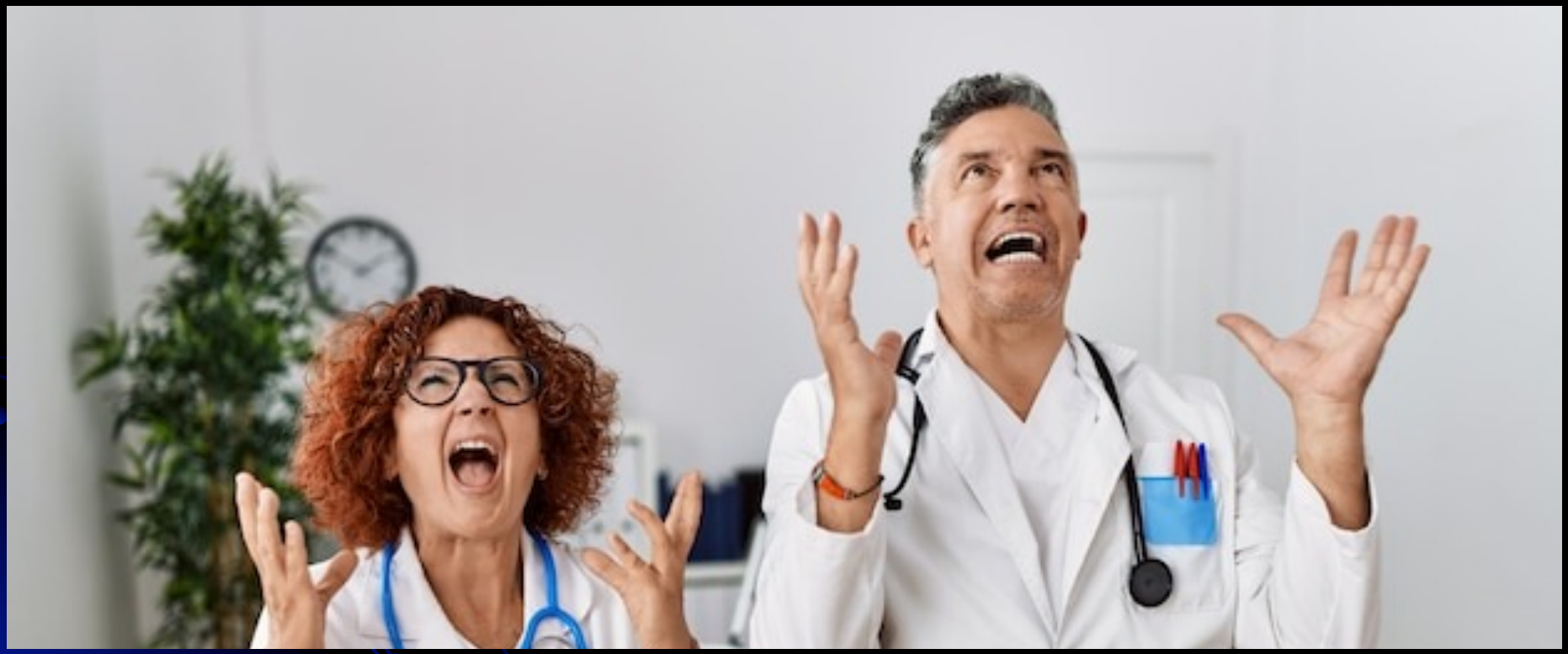
Newly Diagnosed Multiple Myeloma (NDMM) →

? CONSOLIDATION with AutoSCT

or as I might rephrase it:

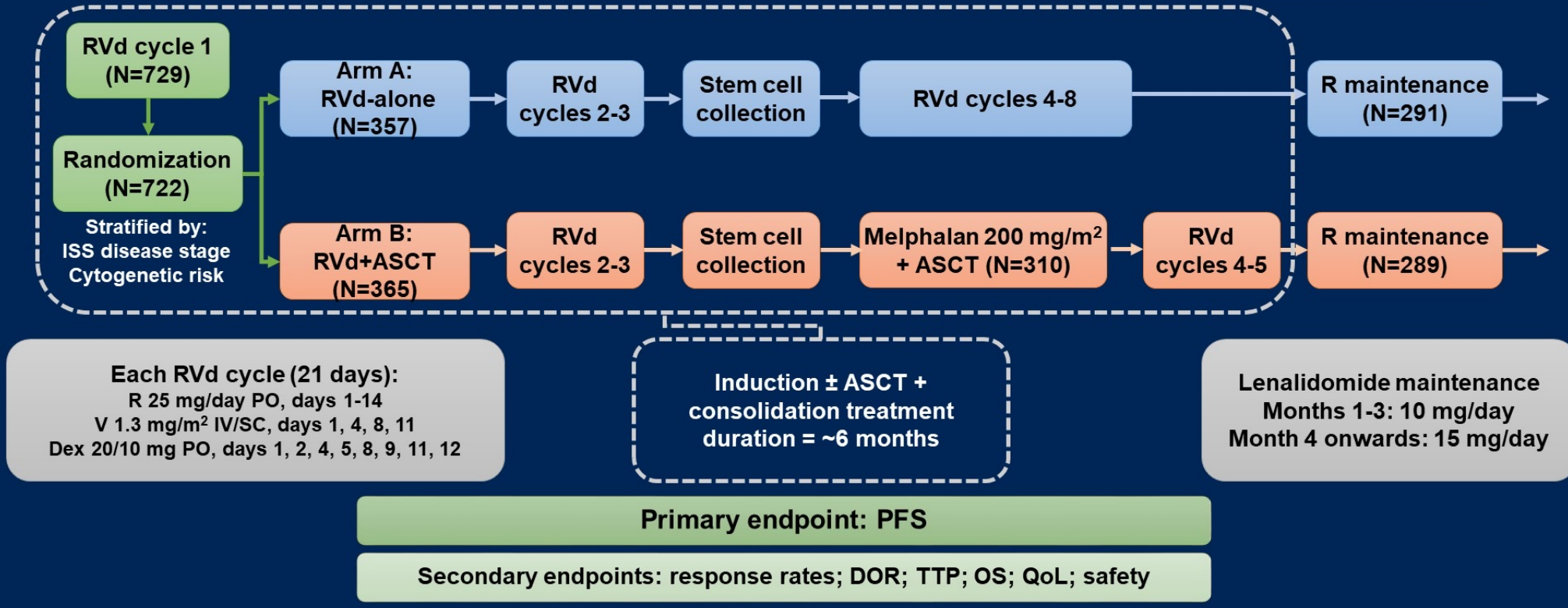
Can we finally get rid of Autologous SCT?

RESPONSE OF TRANSPLANT ONCOLOGISTS



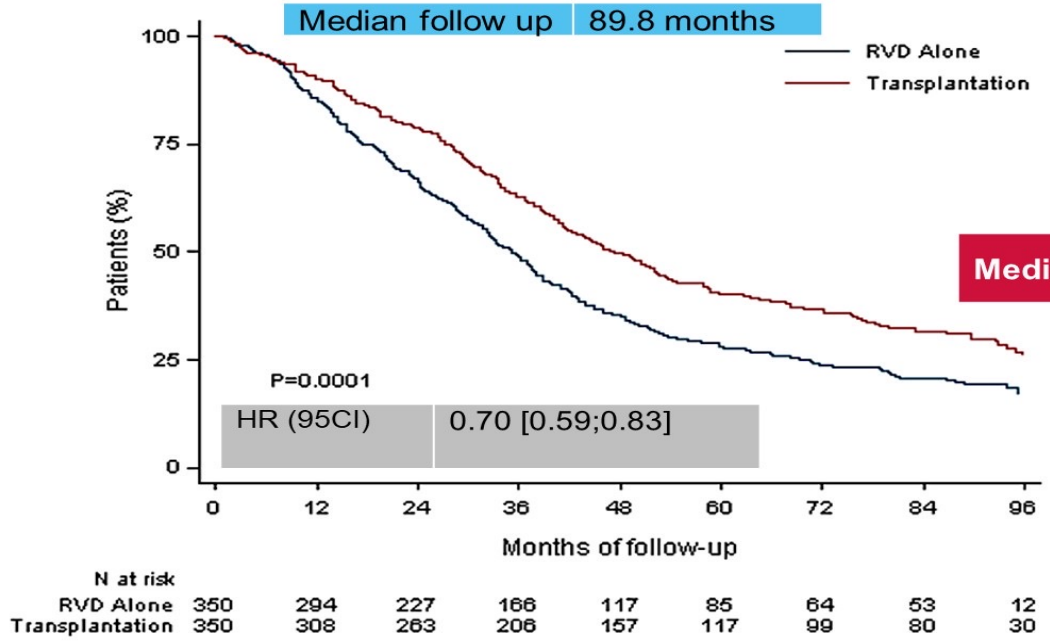
DETERMINATION: study design and patient disposition

DETERMINATION: Delayed vs Early Transplant with Revlimid Maintenance and Antimyeloma Triple Therapy



d/Dex, dexamethasone; DOR, duration of response; ISS, International Staging System; IV, intravenous; PO, orally; R, lenalidomide; SC, subcutaneous; TTP, time to progression; V, bortezomib

Updated PFS (primary endpoint)



Median PFS 47.3 months (Transplantation, arm B)

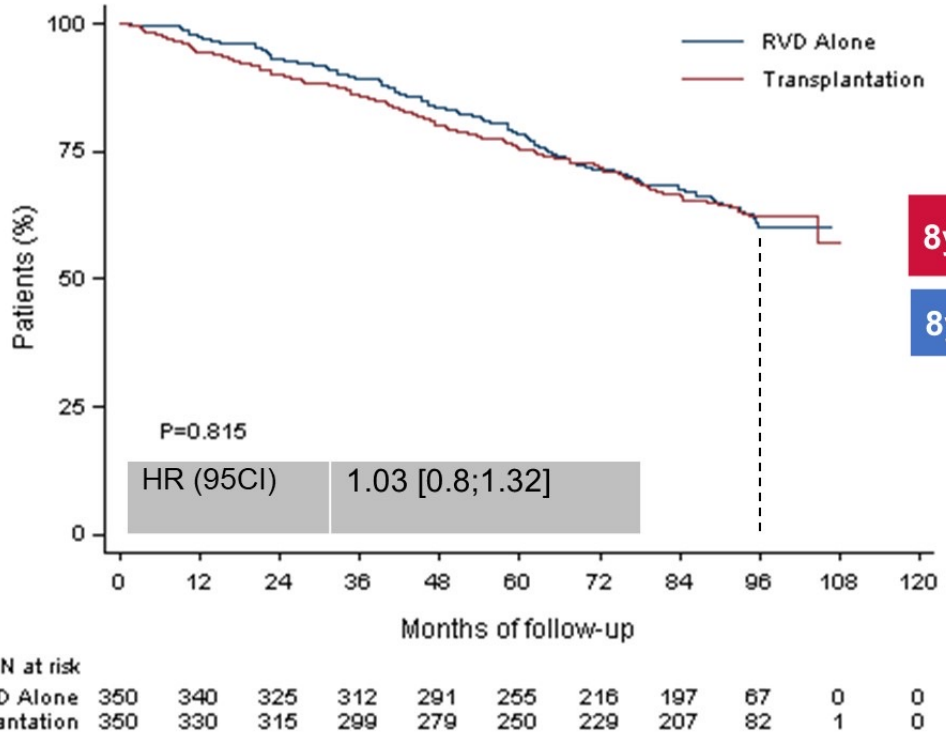
Median PFS 35 months (RVD alone, arm A)

30% reduction in the risk of progression or death in patients receiving transplant

In the NEJM paper: PFS 67.5 months versus 46.2 months (HR 1.53 95%CI 1.23-1.91, p<.0001) with median follow-up of 76 months.

OS

Median follow up	89.8 months



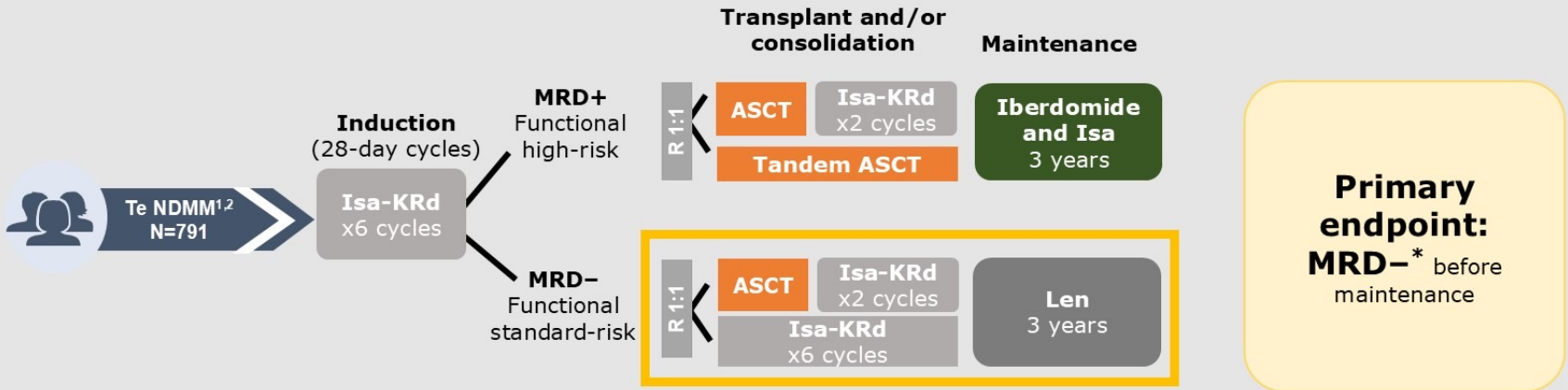
8y-OS 62.2% (Transplantation, arm B)

8y-OS 60.2% (RVD alone, arm A)

More than 60% of the patients in the two arms are alive after 8 years of follow-up

MIDAS: Can ASCT be omitted if MRD– is achieved post-induction?

MIDAS[1–3]: Can MRD status post-induction be used to guide treatment decisions?



Can transplant be omitted if MRD– is achieved post-induction?

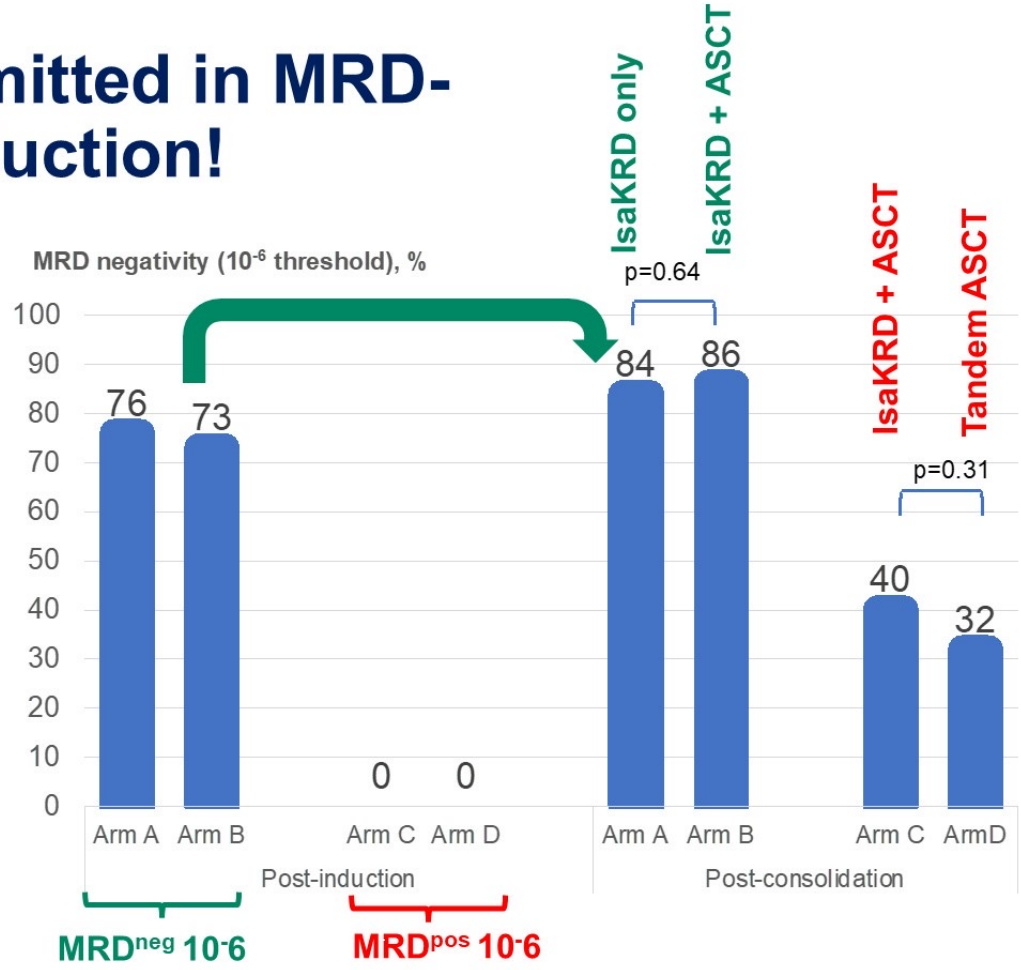
The response-adapted approach in MIDAS could help to elucidate the value of ASCT in the advent of CD38 mAb-based quadruplet regimens[2,3]

*At a sensitivity of 10^{-6} for HDT/ASCT vs Isa-KRd comparison and a sensitivity of 10^{-5} for the tandem ASCT vs single ASCT comparison.

1. ClinicalTrials.gov. NCT04934475 [Accessed Apr 2025]; 2. Perrot A, et al. Blood. 2025:blood.2024026230. doi: 10.1182/blood.2024026230. Epub ahead of print; 3. Helwick C. The ASCO poster. Available at: https://ascopost.com/issues/november-10-2024/evolving-role-of-mrd-status-in-multiple-myeloma/ [Accessed Apr 2025].

PRESENTED BY: Suzanne Lentzsch MD, PhD

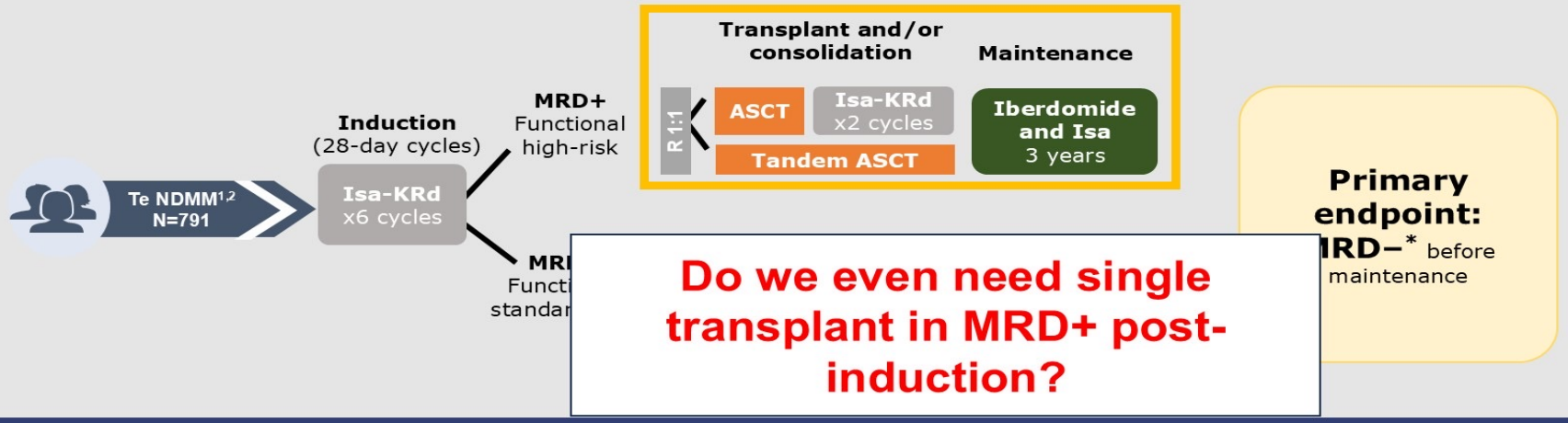
MIDAS:
YES, ASCT be omitted in MRD-patients post-induction!



MIDAS: What is Missing?

Data not yet available

MIDAS[1–3]: Can MRD status post-induction be used to guide treatment decisions?



Do we even need single transplant in MRD+ post-induction?

We do not know whether MRD+ patients should receive single ASCT and what the is the QoL due to 12 cycles Isa-KRD

*At a sensitivity of 10^{-6} for HDT/ASCT vs Isa-KRd comparison and a sensitivity of 10^{-5} for the tandem ASCT vs single ASCT comparison.

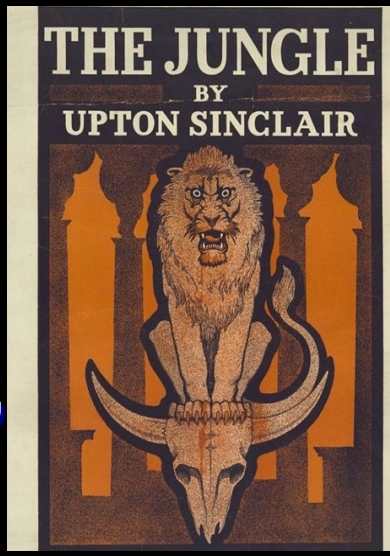
1. ClinicalTrials.gov. NCT04934475 [Accessed Apr 2025]; 2. Perrot A, et al. Blood. 2025:blood.2024026230. doi: 10.1182/blood.2024026230. Epub ahead of print; 3. Helwick C. The ASCO poster. Available at: https://ascopost.com/issues/november-10-2024/evolving-role-of-mrd-status-in-multiple-myeloma/ [Accessed Apr 2025].

Perrot A et al Measurable Residual Disease-Guided Therapy in Newly Diagnosed Myeloma N Engl J Med 393:425-437, 2025

Why won't transplanters give up ASCT for MM?

Upton Sinclair (1935)

"It is difficult to get a man to understand something, when his salary depends on his not understanding it."



Newly Diagnosed Multiple Myeloma (NDMM) →

Maintenance Therapy

LENALIDOMIDE MAINTENANCE

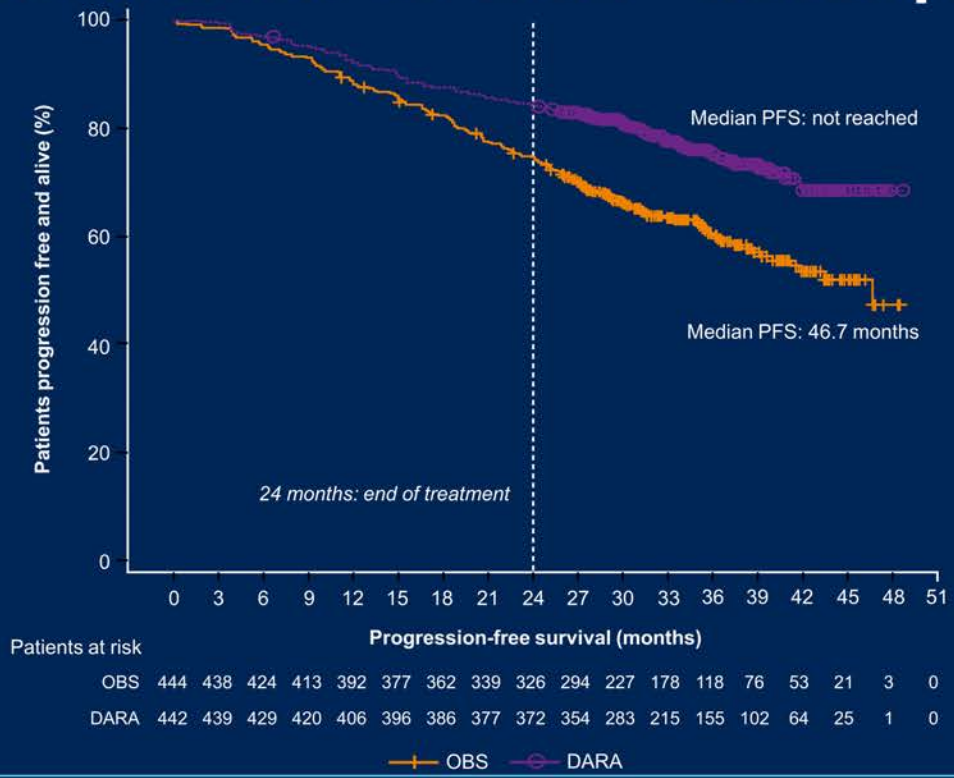
Most modern regimens incorporate lenalidomide maintenance (and more recently Daratumumab sc monthly + lenalidomide orally)

Takeaways for lenalidomide maintenance:

- PFS (med 53 mo vs 24 mo) HR .48 (.41-.55) JCO 35:3279-3289, 2017
- OS (7 yr OS 62% vs 50%) p=.001 JCO 35:3279-3289, 2017
- Increased MDS/AML with lenalidomide (5.3%) JCO 35:3279-3289, 2017
- MDS/AML mostly associated with Melphalan (and other alkylators) based on meta-analysis
- ?Less MDS/AML with pomalidomide

DARA Significantly Improved PFS From Second Randomization vs OBS - Cassopeia

Median follow-up: 35.4 months from second randomization



HR 0.53
(95% CI 0.42–0.68)
P<0.0001

CI, confidence interval; DARA, daratumumab; HR, hazard ratio; OBS, observation; PFS, progression-free survival.

MYELOMA MAINTENANCE

The Daratumumab randomized trials (Perseus, Cepheus) show a PFS advantage for DR (Dara + Revlimid/lenalidomide) maintenance over Revlimid alone.

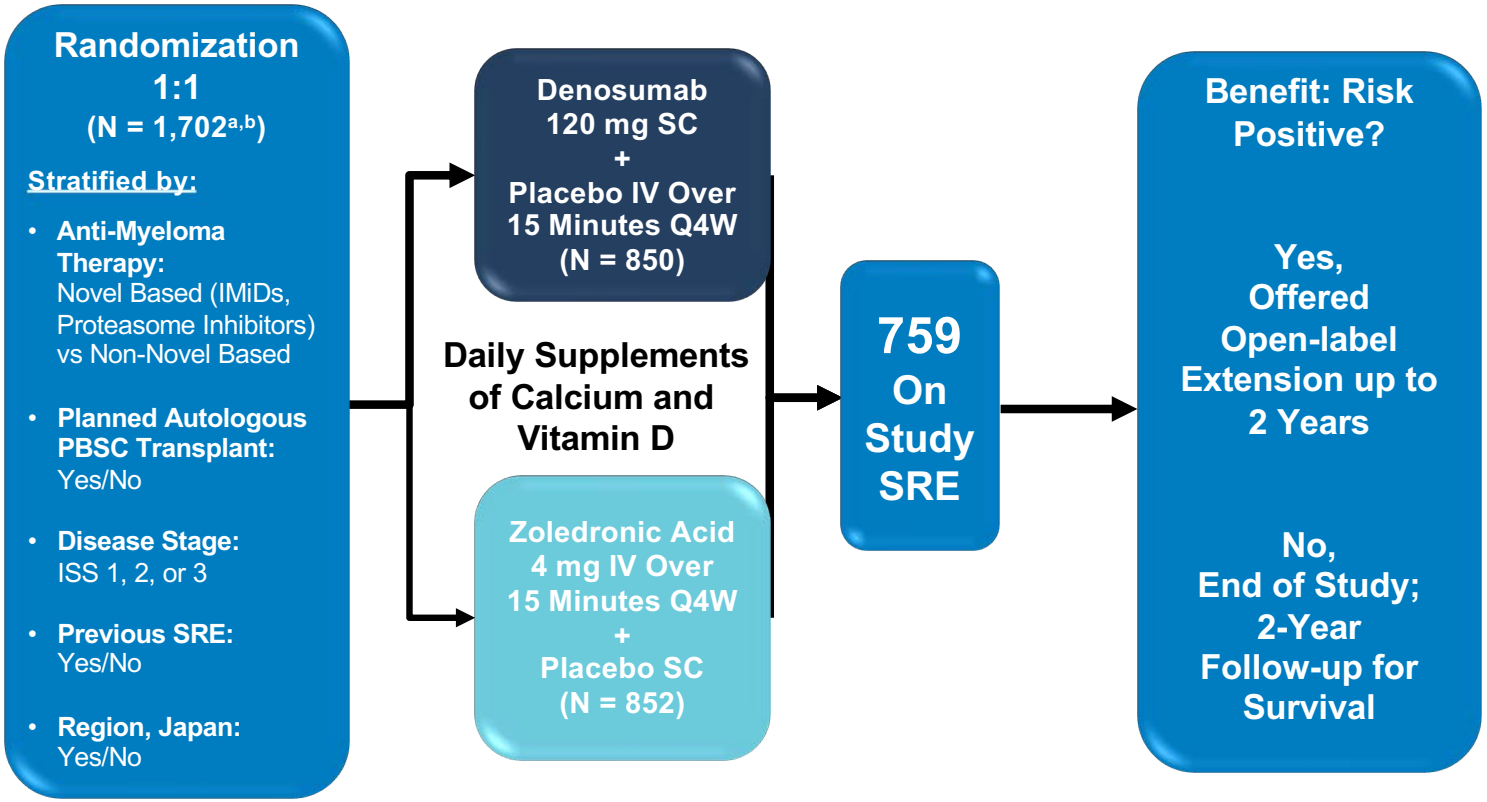
DR maintenance has become the new STANDARD OF CARE despite no OS advantage seen as yet (for the combo vs R alone).

Since Revlimid confers a 5% risk of MDS/AML, many clinicians stop it after 3 years in non-high risk patients with complete or near complete remission (in the absence of clinical trials).

Newly Diagnosed Multiple Myeloma (NDMM) →

Adjunctive Therapy

MM 20090482 Study Design



Study Endpoints:

Primary
- Time to the first on-study SRE (noninferiority)

Secondary
- Time to the first on-study SRE (superiority)
- Time to the first and subsequent on-study SRE
- Overall survival (OS)

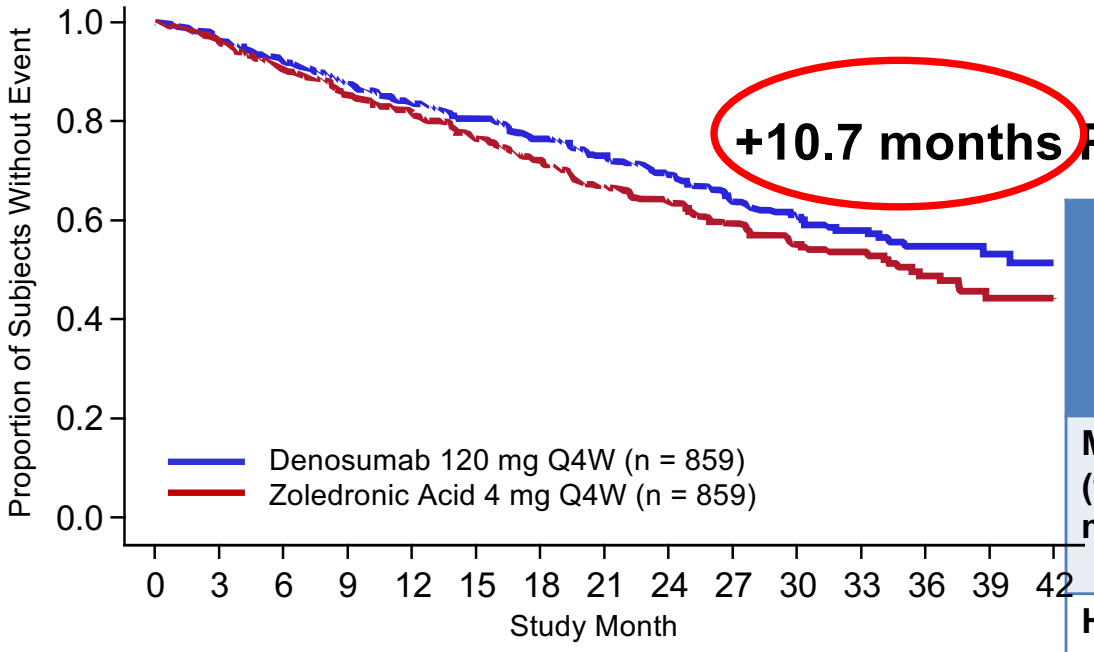
Exploratory
- Progression-free survival (PFS)

IMiD, Immunomodulatory imide drug; ISS, International Staging System; IV, intravenous; MM, multiple myeloma; PBSC, peripheral blood stem cell; Q4W, once every 4 weeks; SC, subcutaneous; SRE, skeletal-related event.

[a]Per protocol and Zometa® label, IV product was dose adjusted for baseline creatinine clearance and subsequent dose intervals were determined by serum creatinine levels. No SC dose adjustments were required. [b]Patients received at least one dose out of 1,718 enrolled.

NCT01345019

Improved Median PFS in the Denosumab Arm Warranted Further PFS Analysis



Denosumab 120 mg Q4W	859	789	703	583	501	411	329	269	214	157	125	82	57	35	14
Zoledronic Acid 4 mg Q4W	859	806	690	584	495	404	324	252	206	159	112	78	53	30	9

	Denosumab 120 mg Q4W (N = 859)	Zoledronic Acid 4 mg Q4W (N = 859)
Median PFS (95% CI), months	**46.09 (34–NE)**	**35.38 (30–NE)**
HR (95% CI)	**0.82 (0.68–0.99)**	
Descriptive *P*-value	**0.036**	

Supportive Care

- Proteasome inhibitors/anti-CD38 antibodies: Shingles prophylaxis
- IMiDs: blood clot prophylaxis
- Corticosteroids: consider GI prophylaxis
- Bone disease: zoledronic acid or denosumab (preferred if renal dysfunction)

  *pain control / interventions such as vertebroplasty / kyphoplasty
- Infection prophylaxis:
  - Vaccines (pneumococcal, yearly influenza, shingles)
  - Antibiotics are actively being studied
  - IVIG if recurrent life-threatening infections or IgG<400
- Social Work
- Palliative Care
- Physical Therapy & Rehabilitative Medicine

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Relapsed/Refractory Multiple Myeloma (NDMM) →

Second-Line Therapy and Beyond

NEW YORK TIMES June 5, 2025

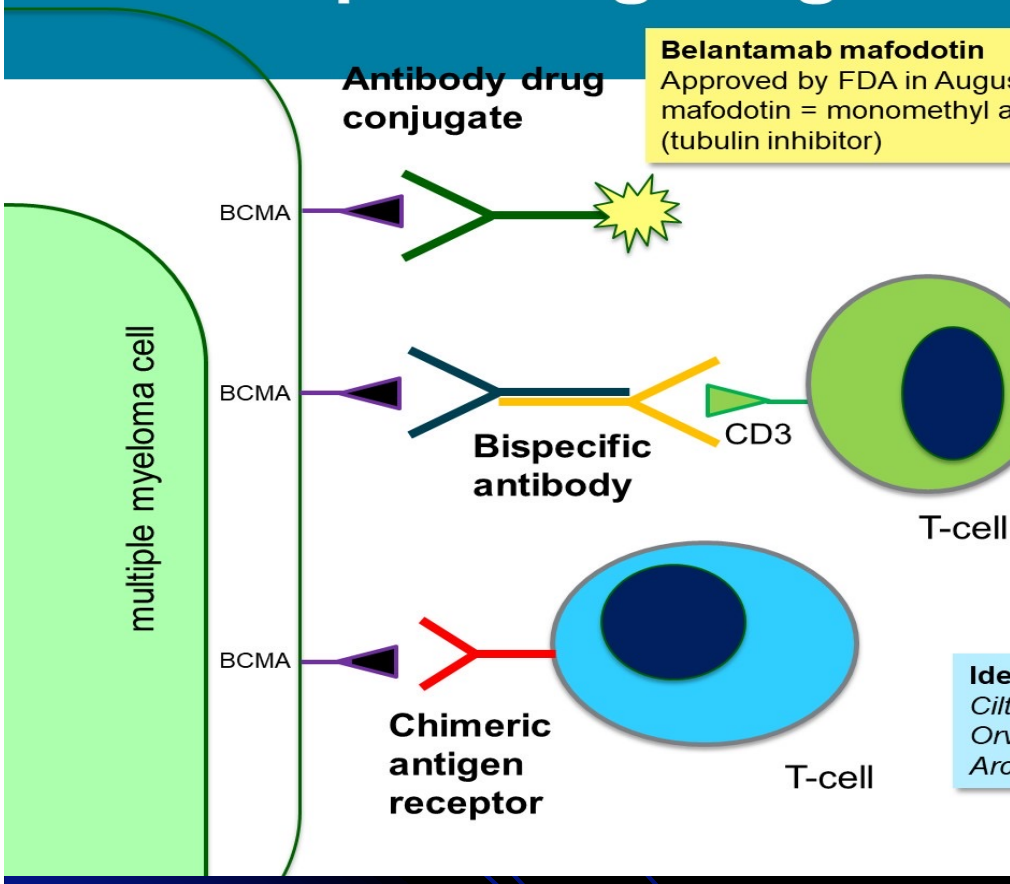
From No Hope to a Potential Cure for a Deadly Blood Cancer

by Gina Kolata (doyenne of science journalists)

Multiple myeloma is considered incurable, but a third of patients in a Johnson & Johnson clinical trial have lived without detectable cancer for years after facing certain death. These results, in patients whose situation had seemed hopeless, has led some battle-worn American oncologists to dare to say the words "potential cure."

IS THIS CLICKBAIT HYPERBOLE or FOR REAL?

Therapies targeting BCMA



Belantamab mafodotin
Approved by FDA in August 2020
mafodotin = monomethyl auristatin F (tubulin inhibitor)

BCMA = B cell maturation antigen

- Cell surface receptor expressed on plasma cells with higher expression on myeloma cells
- Plays role in B-cell maturation and differentiation
- Not expressed in other tissues

AMG 420
CC-93269
ASH 2019

Teclistamab
AMG 701
REGN5458
TNB-383B
Elranatamab (PF-06863135)
ASH 2020

Idecabtagene vicleucel (bb2121), approved March 2021
Ciltacabtagene autoleucel (LCAR-B38M)
Orvacabtagene autoleucel (JCARH125)
Arcellx and others

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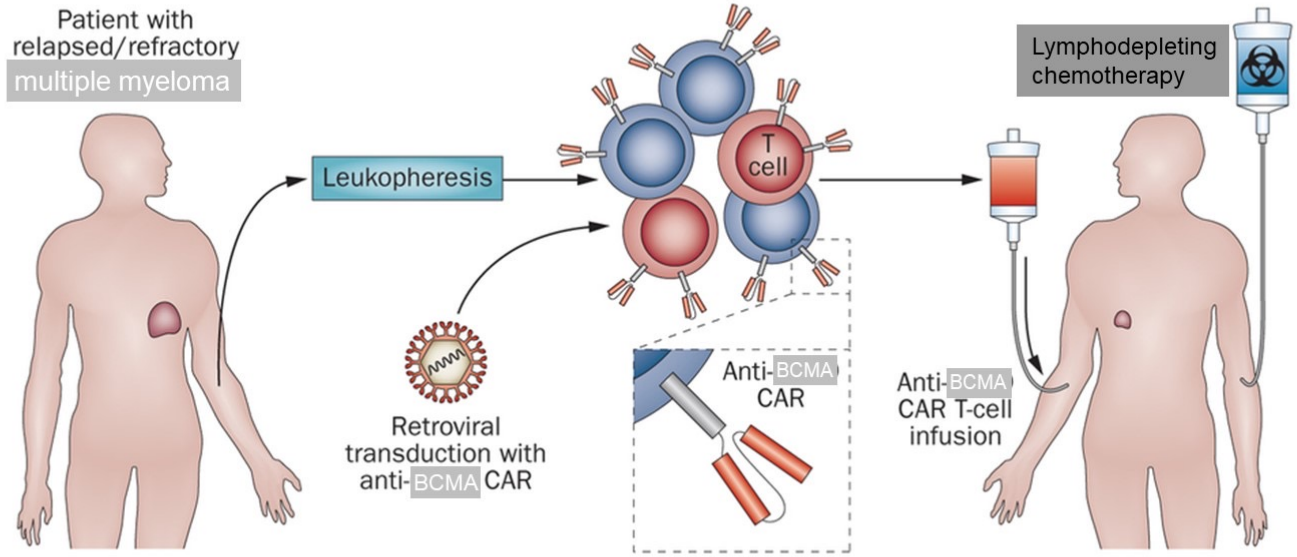
Treating CRS with tocilizumab (anti-IL6) and steroids
Treating ICANS with steroids and prophylactic Keppra

CAR T-cell Therapy



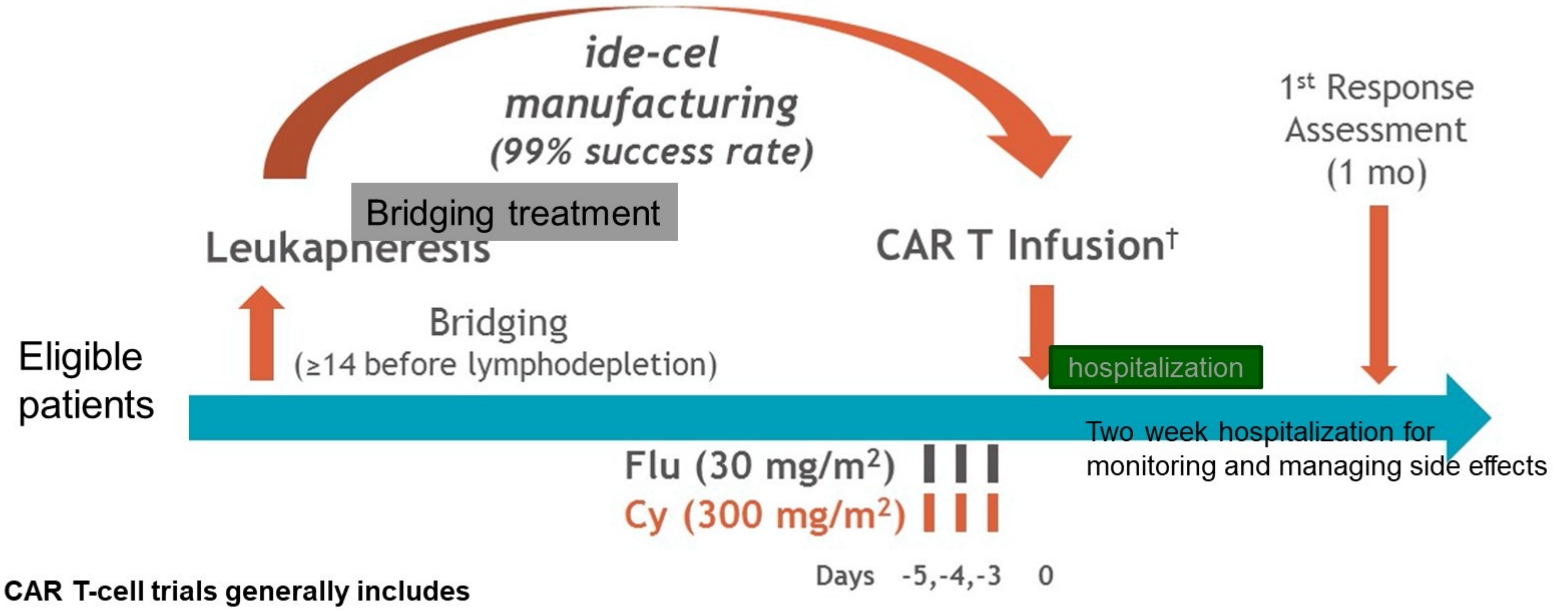
Klebanoff et al., *Nature Rev. Clin. Oncol* 2014

In ALL and lymphoma, patient's T-cells are collected and engineered to target CD19

In myeloma, CAR T-cells target myeloma-specific antigens, e.g. BCMA

ESPECIALLY GOOD FOR EXTRAMEDULLARY DISEASE

Schema of CAR T-cell treatment (ide-cel)



Eligibility for many CAR T-cell trials generally includes
≥3 prior lines of therapy, including a proteasome inhibitor, an IMiD, and daratumumab
Refractory to last line of therapy
Adequate hematologic function, renal function

One treatment followed by observation: **"one and done"**

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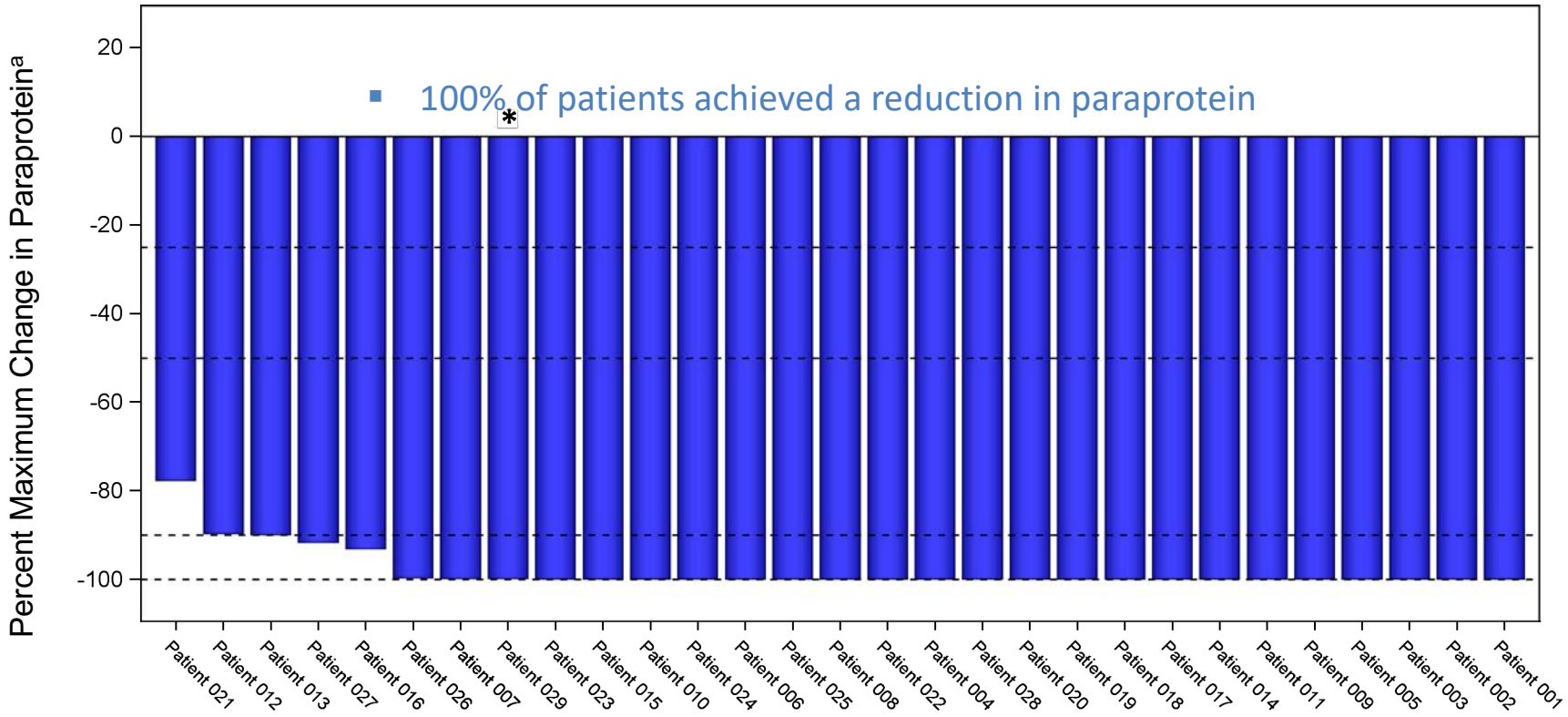
Results from CARTITUDE-1: A Phase 1b/2 Study of Cilta-cel, a B-Cell Maturation Antigen-Directed Chimeric Antigen Receptor T Cell Therapy in Relapsed/Refractory Multiple Myeloma (R/R MM)

Deepu Madduri et al abst 577 ASH 2019 and abst 177 ASH 2020

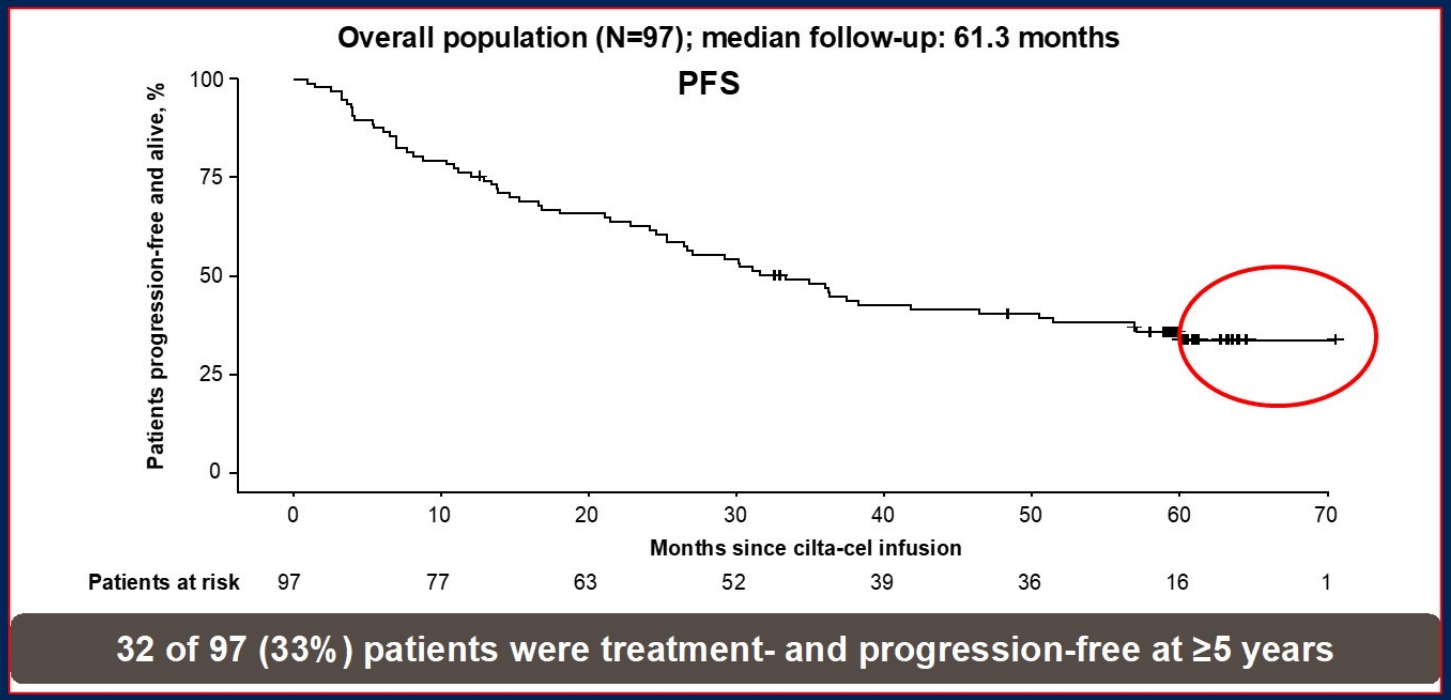
Jagannath S et al J Clin Oncol 43: 2766-2771, 2025

CARTITUDE-1 Efficacy: Tumor Burden Reduction



Treating CRS with tocilizumab (anti-IL6) and steroids
Treating ICANS with steroids and prophylactic Keppra

Late Line Ciltacel PFS– worth another look!
(please let that plateau continue forever!!!)

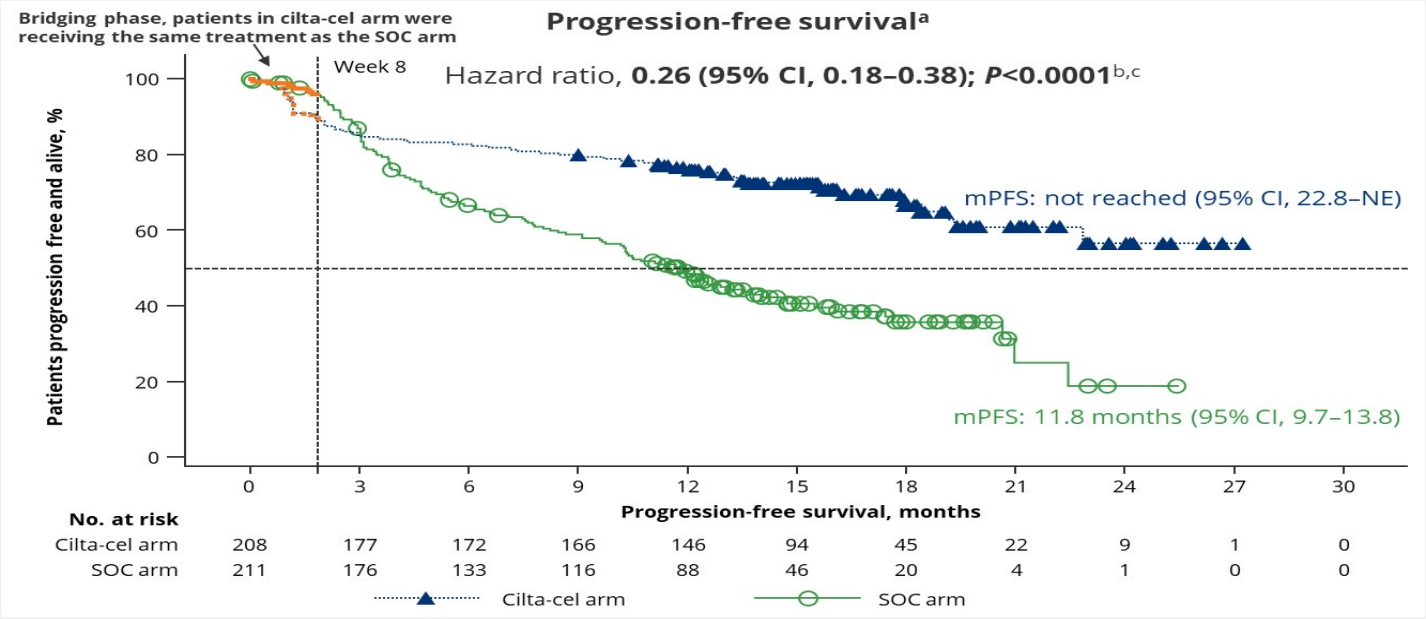


32 of 97 (33%) patients were treatment- and progression-free at ≥5 years

CARTITUDE-4:
Primary Endpoint – PFS (ITT Population)

Cilta-cel vs SOC

- 12-month PFS rate: 76% vs 49%
- SOC performed as expected



[a]Median follow-up, 15.9 months. [b]Constant piecewise weighted log-rank test. [c]Hazard ratio and 95% CI from a Cox proportional hazards model with treatment as the sole explanatory variable, including only progression-free survival events that occurred >8 weeks post randomization.
cilta-cel, ciltacabtagene autoleucel; HR, hazard ratio; ITT, intent-to-treat; mPFS, median progression-free survival; NE, not estimable; SOC, standard of care.

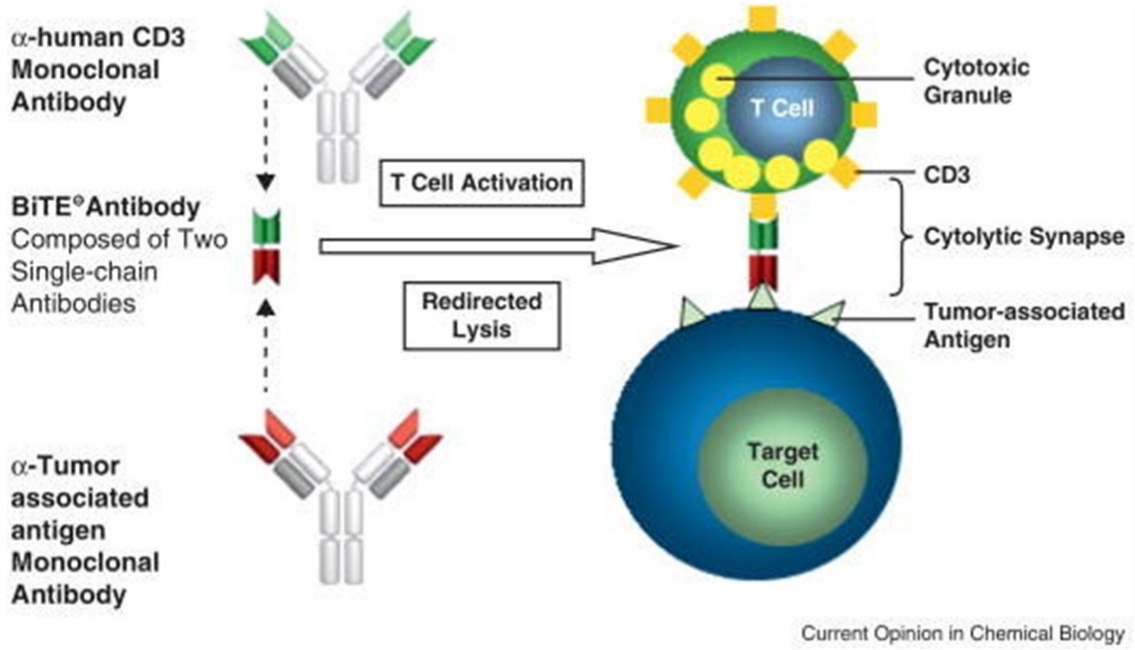
San-Miguel JS et al N Engl J Med 389:335-347, 2023

Cilta-cel (BCMA) CAR T-cell versus PVd or DPd in ≥ 2nd line

SIMILAR RESULTS for Ide-cel (BCMA) CAR T-cell versus SOC 3rd or 4th line

Rodriguez-Otero P et al N Engl J Med 388:1002-1014, 2023

Bispecific T-cell Engagers

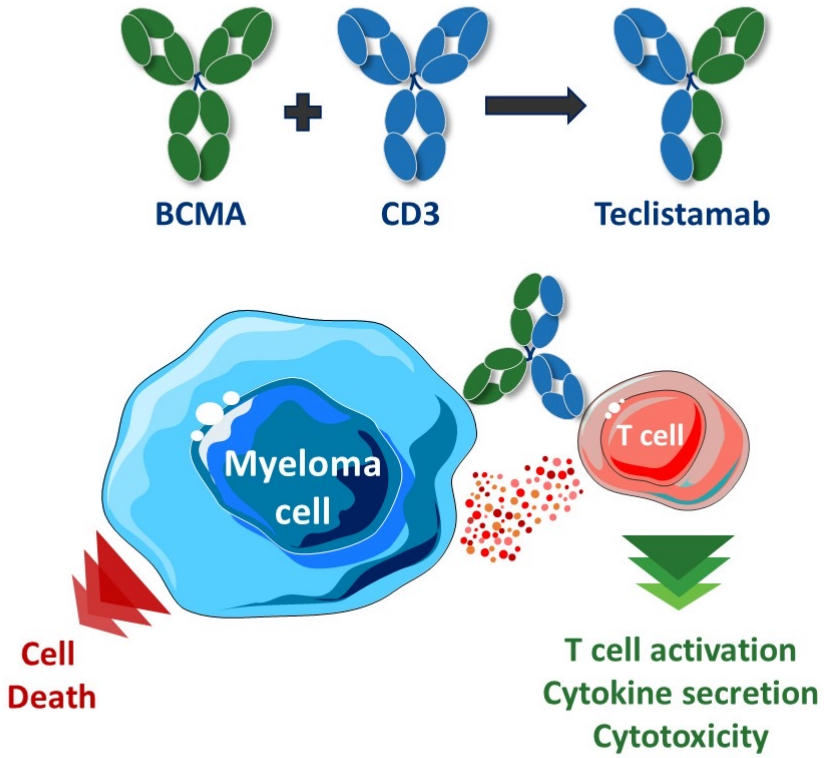


Current Opinion in Chemical Biology

MASSACHUSETTS GENERAL HOSPITAL CANCER CENTER

Teclistamab: BCMA × CD3 DuoBody® Antibody

- Prognosis is poor for patients who progress on available classes of therapies, with ORR ~30%, mPFS of ~3 months, and mOS between 6–11 months[1]
- Teclistamab (JNJ-64007957)[a] is a humanized BCMA × CD3 bispecific IgG-4 antibody that redirects $CD3^+$ T cells to BCMA-expressing myeloma cells
- Teclistamab induces T cell-mediated killing of myeloma cells from heavily-treated patients and in xenograft models[2-4]
- Updated results from an ongoing phase 1 study of teclistamab administered IV or SC in patients with RRMM (NCT03145181) are presented here[5]



1. Ghandi *Leukemia* 2019;33:2266. 2. Labrijn AF *PNAS*. 2013;110:5145. 3. Frerichs KA *Clin Cancer Res.* 2020;26:2203. 4. Pillarisetti K *Blood Adv.* 2020;4:4538. 5. Usmani SZ. *JCO* 2020:38 (Suppl) Abstract 100. BCMA, B-cell maturation antigen; IV, intravenously; mOS, median overall survival; mPFS, median progression-free survival; ORR, overall response rate; RRMM, relapsed and/or refractory multiple myeloma; SC, subcutaneously. [a]Includes technology licensed from GenMab.

Bispecifics

- **Teclistamab (BCMA)** B Cell Maturation Antigen
- **Talquetamab (GPRC5D)**

  G protein Class C Group 5 Member D
- **Elranatamab (BCMA)** B Cell Maturation Antigen
- **Treating CRS with tocilizumab (anti-IL6) and steroids**
- **Treating ICANS with steroids and prophylactic Keppra**

R/R MM

Mateos M-V et al LBA-6 ASH 2025 Costa LJ et al New Engl J Med 394: 739-752, 2026

R/R MM with 1 to 3 prior lines: 587 randomized to

Teclistamab + Daratumumab versus DPd/DVd BUT only 5% with prior Dara exposure

Med f/u 34.5 mo

	Tec + Dara	DPd/DVd	
3 yr PFS	83.4%	29.7%	**HR 0.17** (0.12-0.23) p<.0001
3 yr OS	83.3%	65.0%	**HR 0.46** (0.32-0.65) p<.0001
Still on original Rx	71.0%	28.0%	
MRD- (10/-5)	58.4%	17.1%	
TAE deaths	7.1%	5.9%	p=NS
CRS	60% (48% gr1-2, 12% gr3)		

Benefit for high-risk patients by ISS stage, FISH, soft tissue plasmacytomas

Infections: on T+D: 54% Gr 3,4 13 Gr5 deaths!

CHANGE IN SOC: These results are the best ever in this setting. “Off the shelf” therapy makes this easily accessible as an outpatient.

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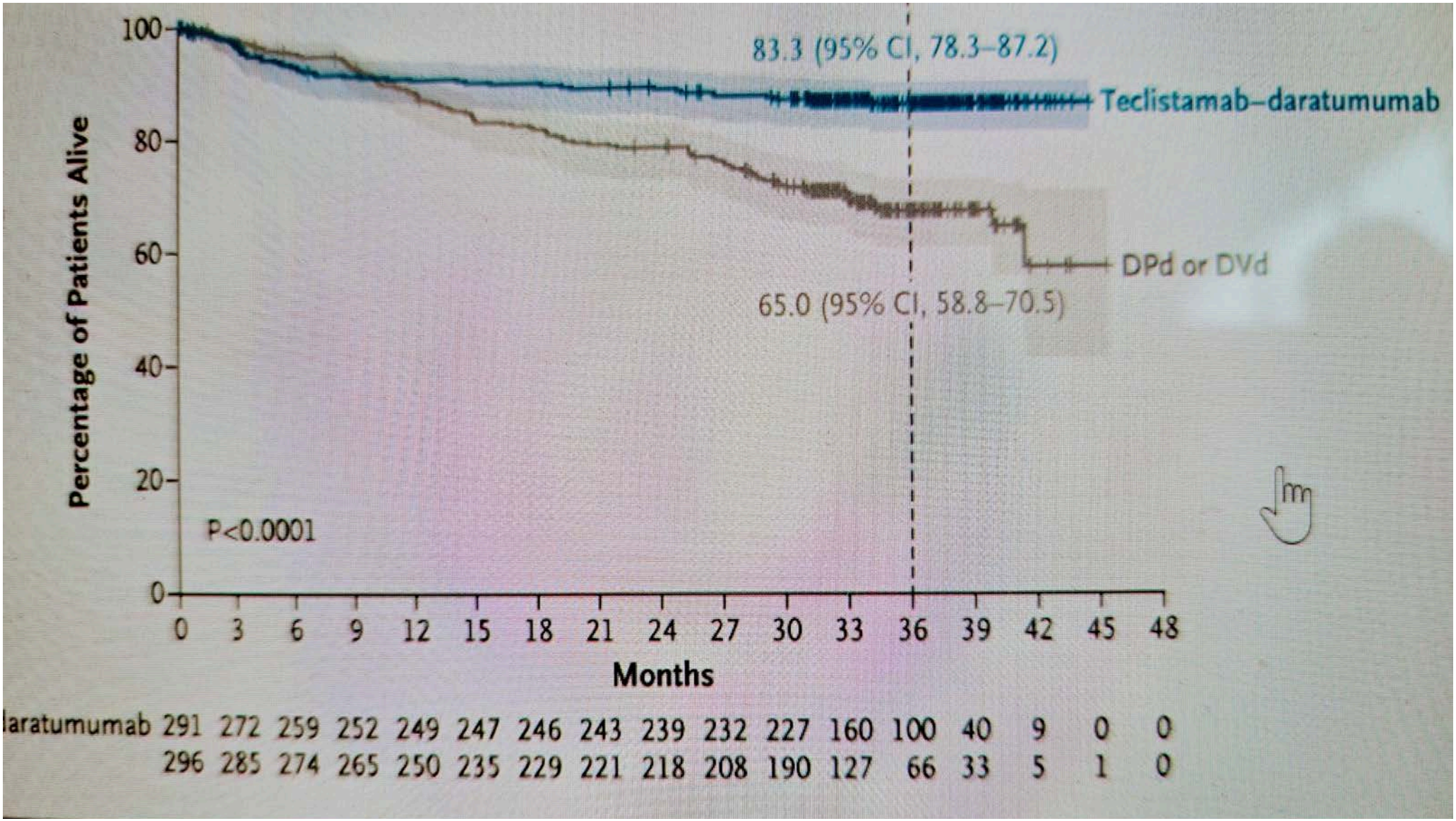

100
80
60
40
20
0
Percentage of Patients Alive
83.3 (95% CI, 78.3–87.2)
Teclistamab–daratumumab
DPd or DVd
65.0 (95% CI, 58.8–70.5)
P<0.0001
0 3 6 9 12 15 18 21 24 27 30 33 36 39 42 45 48
Months
laratumumab 291 272 259 252 249 247 246 243 239 232 227 160 100 40 9 0 0
296 285 274 265 250 235 229 221 218 208 190 127 66 33 5 1 0

I have a dream……

One day we might eliminate all cytotoxics from curative or palliative therapy for most hematologic malignancies→ CLL, FL, WM, MZL, MM (almost), DLBCL (close), MCL (close), HL (half-way), AML/ALL (getting close)

- Multiple Myeloma (almost there if we toss out ASCT): Dara-VRd induction for now

- Teclistamab + Daratumumab is a good candidate for initial therapy (and is "off-the-shelf")

R/R MM

Kumar S et al abst 698 ASH 2025 Kumar S et al NEJM Dec 7, 2025

R/R MM with extramedullary plasmacytoma

Teclistamab + Talquetamab (anti-BCMA bispecific + anti GPRC5D bispecific)

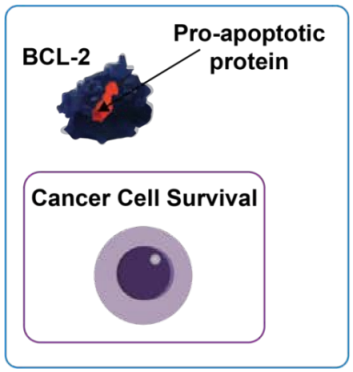
Phase I-II trial 90 pts Med f/u 12.6 mo med age 64 yrs

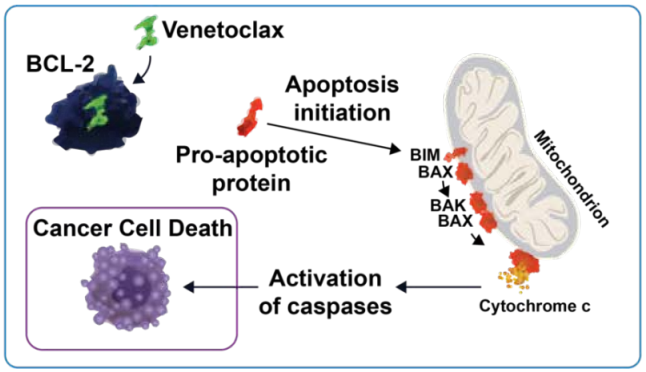
	Tec + Talq
ORR	79% (69-87)
1 yr PFS	61% (50-71)
Med PFS	15.4 months
1 yr OS	74% (63-83)
TAE deaths	11%
CRS/ ICANS	78% (100% gr1-2) / 12%

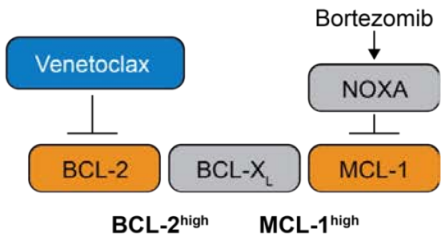
?CHANGE IN SOC: These results are the best ever in this setting. Quite toxic and we need to know the durability

Venetoclax for Myeloma

Venetoclax is a selective, orally available small-molecule BCL-2 inhibtor[1]; active in R/R MM[3]







Venetoclax (daily dose up to 1,200 mg) has an acceptable safety profile in R/R MM, predominantly in patients with t(11;14) abnormality and favorable BCL-2 family profile

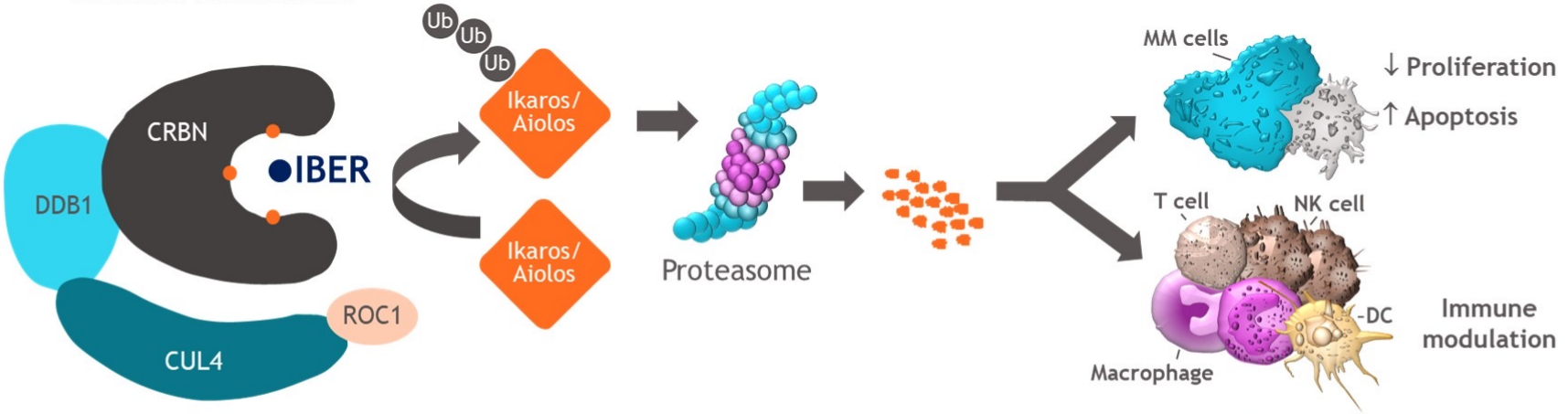
In contrast to the CLL experience, TLS appears to be uncommon in MM; ramp-up dosing has not been necessary

1. Roberts AW et al. *N Eng J Med*. 2015;374:311-322. 2. Punnoose E et al. *Mol Cancer Ther*. 2016;15:1132-1144. 3. Kumar S et al. *Blood*. 2017;130:2401-2409. **4. Kumar SK et al. Lancet 12;21 (12):1630-1642, 2020**

RETEST MARROW!

Iberdomide

- IBER is an oral, potent novel CRBN E3 ligase modulator (CELMoD) compound that co-opts CRBN to enable enhanced degradation of target proteins, including Ikaros and Aiolos[1,2]
  - IBER induces potent direct antimyeloma and immune-stimulatory activity in preclinical models[1]
  - IBER is active in LEN- and POM-resistant myeloma cell lines and enhances cell-mediated killing through immune stimulation[1,2]



CRBN, cereblon; CUL4, cullin 4; DC, dendritic cell; DDB1, DNA damage-binding protein 1; IBER, iberdomide; LEN, lenalidomide; MM, multiple myeloma; NK, natural killer; POM, pomalidomide; ROC1, regulator of cullins-1; E3 ubiquitin protein ligase; Ub, ubiquitin.

1. Matyskiela ME et al. *J. Med. Chem.* 2018;61:535-42. 2. Bjorklund CC, et al. *Leukemia*. 2020:34:1197-1201.

Median Survival MM

Prior to 1990s: 3 years chemo + steroids

1990 to 2000: 5 years better chemo +AutoSCT

2000 to 2010: 7 years chemo + AutoSCT + Bortezomib (Velcade; PROTEOSOME INHIBITOR)+ Lenalidomide (Revlimid; Cereblon binder,IMiDs) + zoledronate (OSTEOCLAST INHIBITOR)

2010 to 2020: 9 years Add Lenalidomide maintenance Pomalidomide (upgrade of lenalidomide; Cereblon binder, IMiDs)Carfilzomib (upgrade of Bortezomib; PROTEOSOME INHIBITOR)

2020 on: 12+ years Added Daratumumab (anti-CD38 MoAb)
CAR T-Cells or Bispecific Antibodies (anti-BCMA)
Belantamab mafadotin (ADC to BCMA)
Venetoclax (BCL2 inhibition) for t(11;14)

Do not undervalue better supportive measures and lead time bias (earlier Dx) to also account for improved survival.

Have we really found a cure? Or just a better delay?

NEW YORK TIMES June 5, 2025

From No Hope to a Potential Cure for a Deadly Blood Cancer

by Gina Kolata (doyenne of science journalists)

Multiple myeloma is considered incurable, but a third of patients in a Johnson & Johnson clinical trial have lived without detectable cancer for years after facing certain death. These results, in patients whose situation had seemed hopeless, has led some battle-worn American oncologists to dare to say the words "potential cure."

IS THIS CLICKBAIT HYPERBOLE or FOR REAL?

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CLICKBAIT HYPERBOLE, but I am willing to concede many more "functional cures"

Future Therapy for Multiple Myeloma

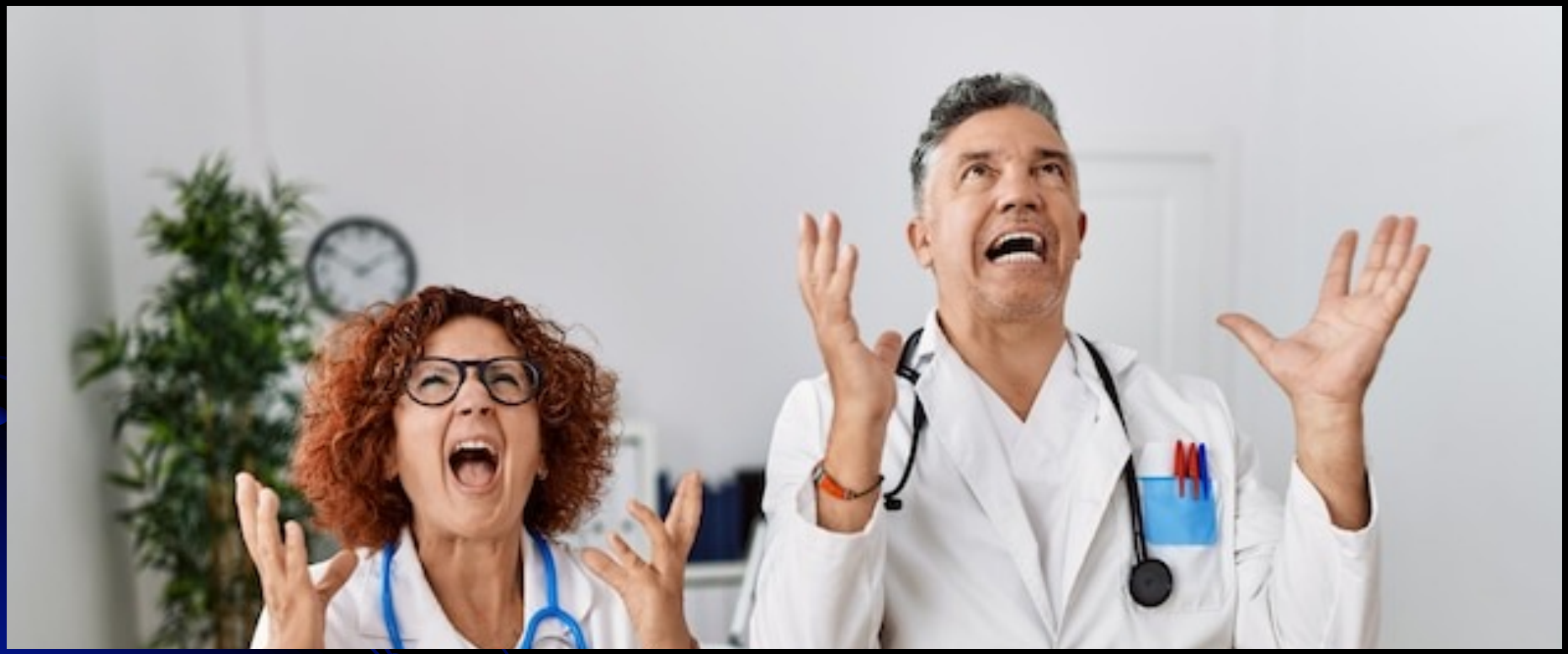
- CAR T-Cells or Bispecific T-Cell Engagers will be combined with Daratumumab and other elements of D-VRd for front-line therapy and new targets are being tested.

The oncologist's dilemma in immunotherapy for myeloma treatment

Future Therapy for Multiple Myeloma

- CAR T-Cells or Bispecific T-Cell Engagers will be combined with Daratumumab and other elements of D-VRd for front-line therapy and new targets are being tested.
- I am anticipating the imminent demise of cytotoxic chemotherapy and autoSCT for multiple myeloma.

RESPONSE OF TRANSPLANT ONCOLOGISTS



THE END

Maryland Hospital for the Insane 1849 (later Spring Grove)

QUESTIONS

High risk definitions

Kaiser MF et al J Clin Oncol 43: 2679-2691, 2025; Avet-Loiseau H et al J Clin Oncol 43:2739-2751, 2025; Spencer A Blood 146:1546-1549, 2025, Patel K and Facon T J Clin Oncol 43:2661-2663, 2025

High Risk (10-15% of myeloma patients requiring therapy)

- High beta 2-microglobulin $\geq$ 5.5 with creat < 1.2
- del(17p) with a > 20% clonal threshold or TP53mut by NGS
- t(4;14), t(14;16), or t(14;20) PLUS 1q+ (gain or amp) and/or del(1p32): now known as double-hit MM
- Monoallelic/biallelic del(1p32) PLUS 1q+ (gain or amp)

Special Consideration

- MM + Extramedullary disease/ Paramedullary disease
- Circulating plasma cells $\geq$2 to 5%: Primary plasma cell leukemia (1º or 2º)
- CNS involvement
- Chromothripsis (multiple genetic abnormalities/hyperdiploidy)
- Early relapse (<1.5 to 2 years) FUNCTIONAL HIGH RISK

CHECK PET-CT or WHOLE BODY MRI at least annually

RELAPSING MYELOMA

Indications to Start or Switch Therapy

- CRAB features
- Rapid rise in M protein
- High levels of free light chain
- with renal presentation
- High-risk cytogenetics with biochemical progression

Prognostic Factors

- Duration of initial response
- Acquisition of new abnormalities (1q amp, del17p)
- ISS/R-ISS
- Presence of EMD
- Circulating plasma cells

Goal of Treatment

- Triplet (2 active classes + dexamethasone) preferred over doublet
- With ≥ 1 agent from a new or nonrefractory class
- Treat to maximum response and maintain on ≥ 1 agent until progression or tolerability

MRD Biomarker
CLL or MM

Clinical validation as prognostic? YES

Clinical validation as potentially predictive? YES
(Ready for clinical trials)

Validation of clinical utility? NOT YET

This means using the biomarker to guide therapy to affect clinical outcomes such as OS, RFS, DFS, RR, or QOL

Should MRD negativity be the primary endpoint?

- Most trials have a goal of maximizing MRD negativity as a means of stopping therapy. But do we know that therapy should stop here?
- Perhaps maintenance therapy works best in MRD negative patients. Perhaps MRD + patients should receive more than lenalidomide + Dara maintenance.
- MRD testing should only be done in clinical trial settings until we have answers on how to act on its results.
- PET-CT scans add extra information beyond MRI alone (extramedullary and bone lesions, 12% positive when MRD –) to identify early relapsers