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Myeloma
A 2024 Perspective
Based on what has happened in 2023

Sergio Giralt, MD
Melvin Berlin Family Chair in Myeloma Research
Deputy Head, Division of Hematologic Oncology
Professor of Medicine
Weill Cornell College of Medicine
Attending Physician, Adult BMT Service Memorial Sloan Kettering Cancer Center

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Biology

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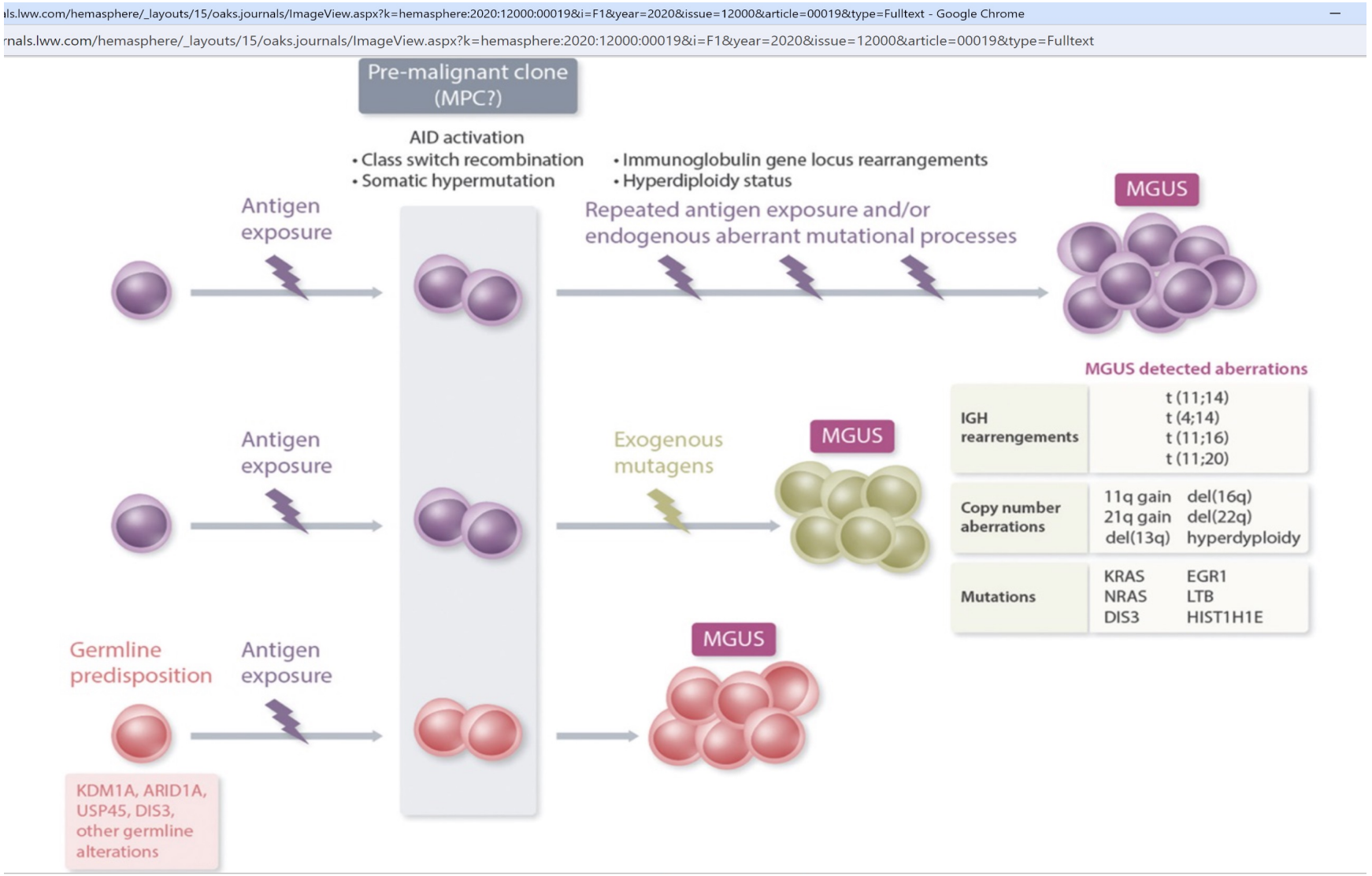
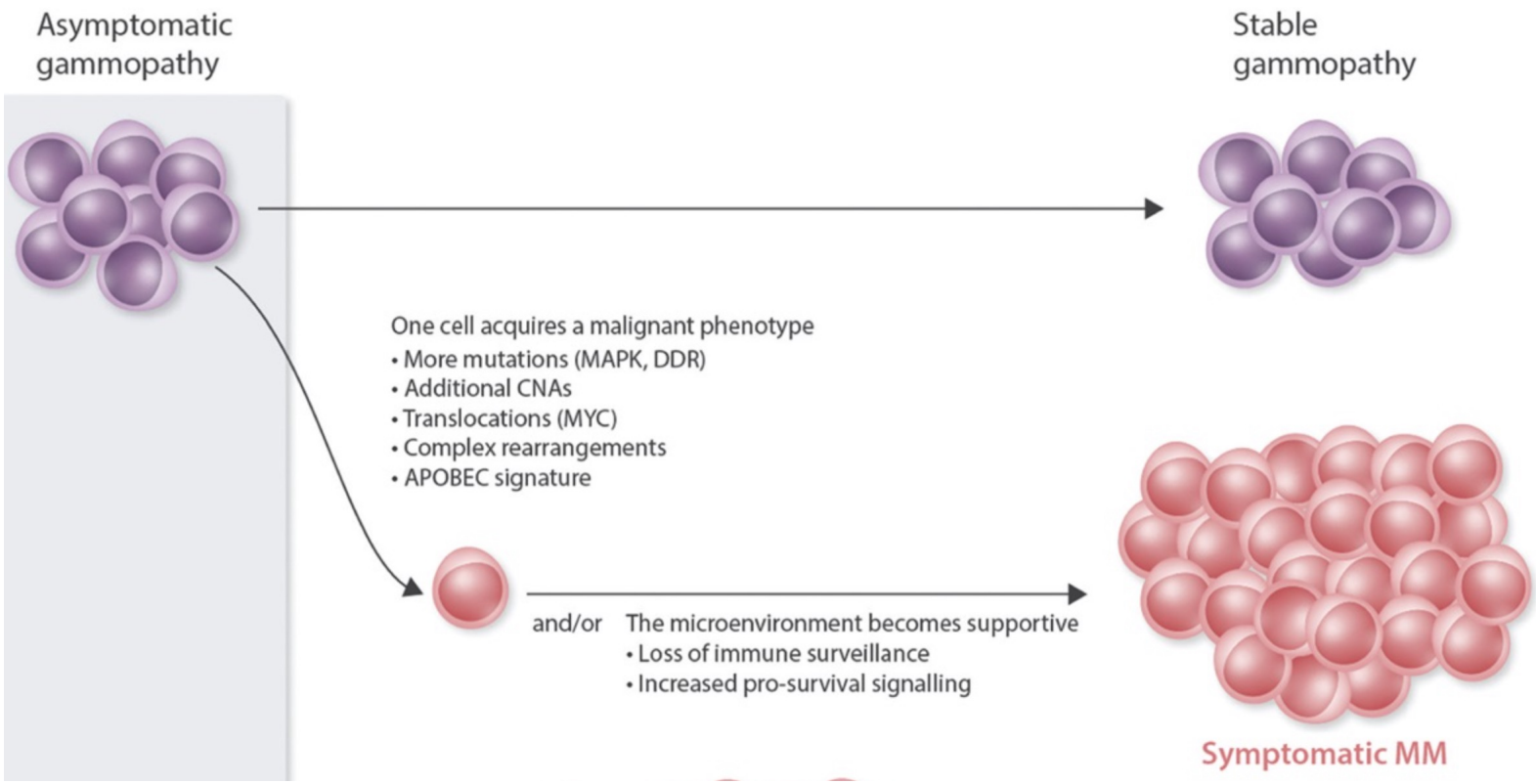
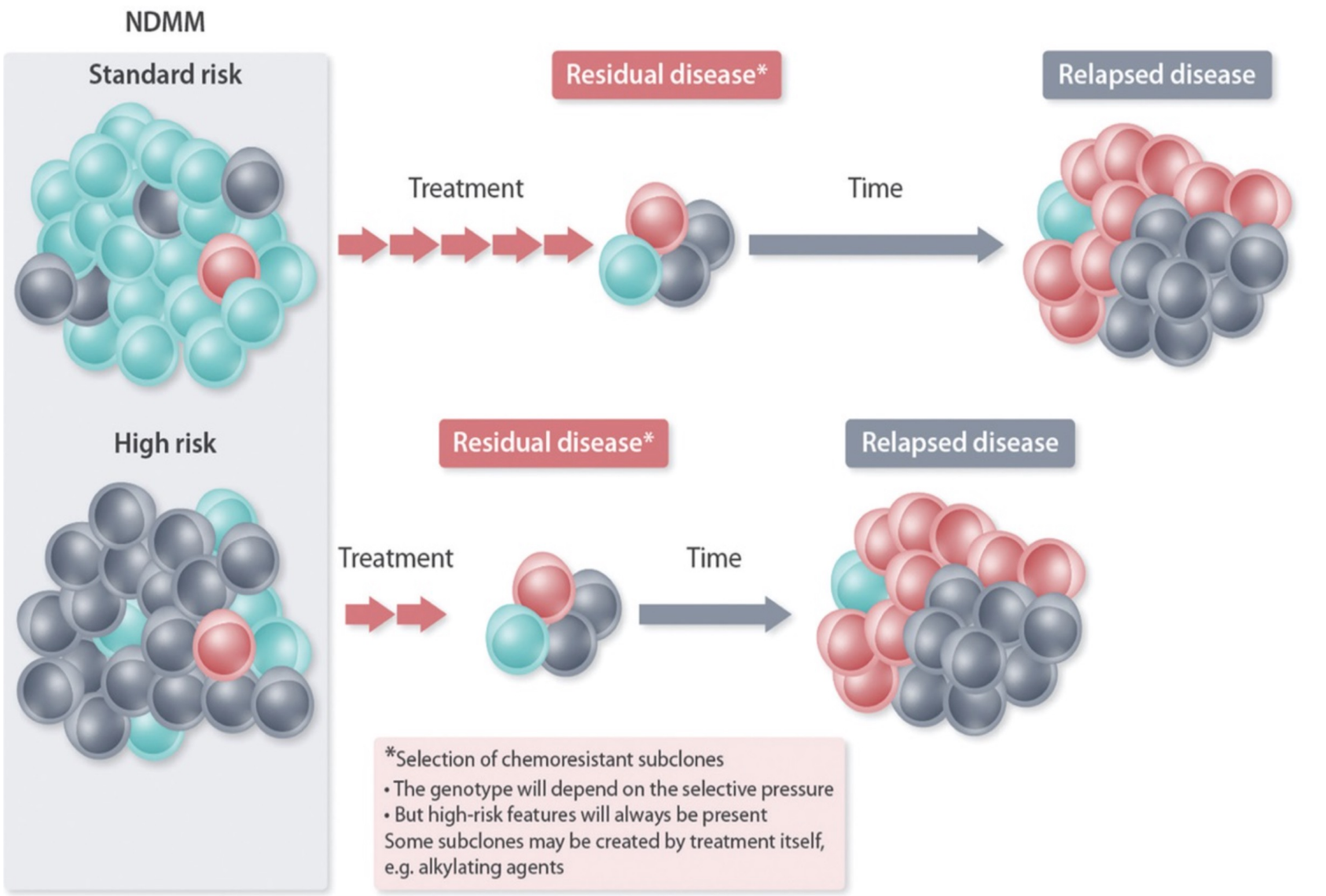



Asymptomatic gammopathy
Stable gammopathy
One cell acquires a malignant phenotype
• More mutations (MAPK, DDR)
• Additional CNAs
• Translocations (MYC)
• Complex rearrangements
• APOBEC signature
and/or
The microenvironment becomes supportive
• Loss of immune surveillance
• Increased pro-survival signalling
Symptomatic MM


NDMM
Standard risk
Residual disease*
Relapsed disease
Treatment
Time
High risk
Residual disease*
Relapsed disease
Treatment
Time
*Selection of chemoresistant subclones
• The genotype will depend on the selective pressure
• But high-risk features will always be present
Some subclones may be created by treatment itself, e.g. alkylating agents

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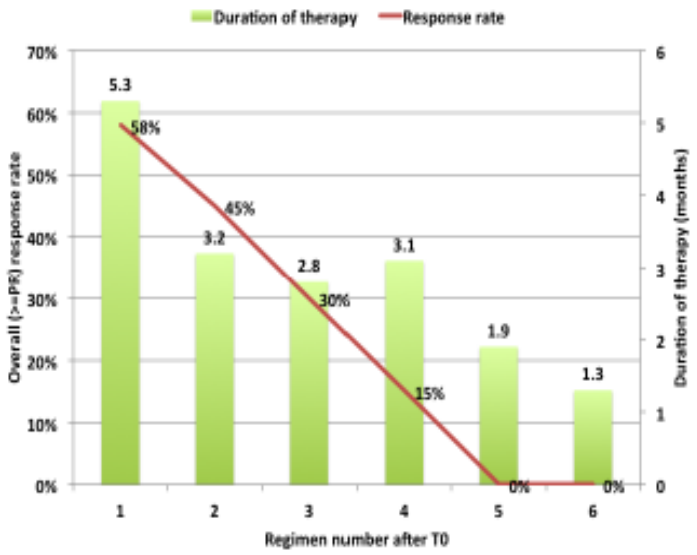
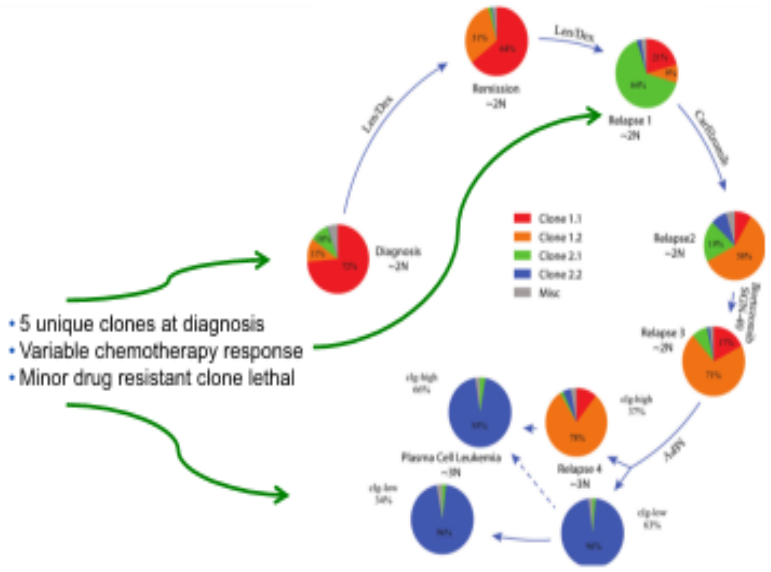
Development of Resistance





Kumar et al, 2004; Durie et al, 2012; Keats et al, 2012.

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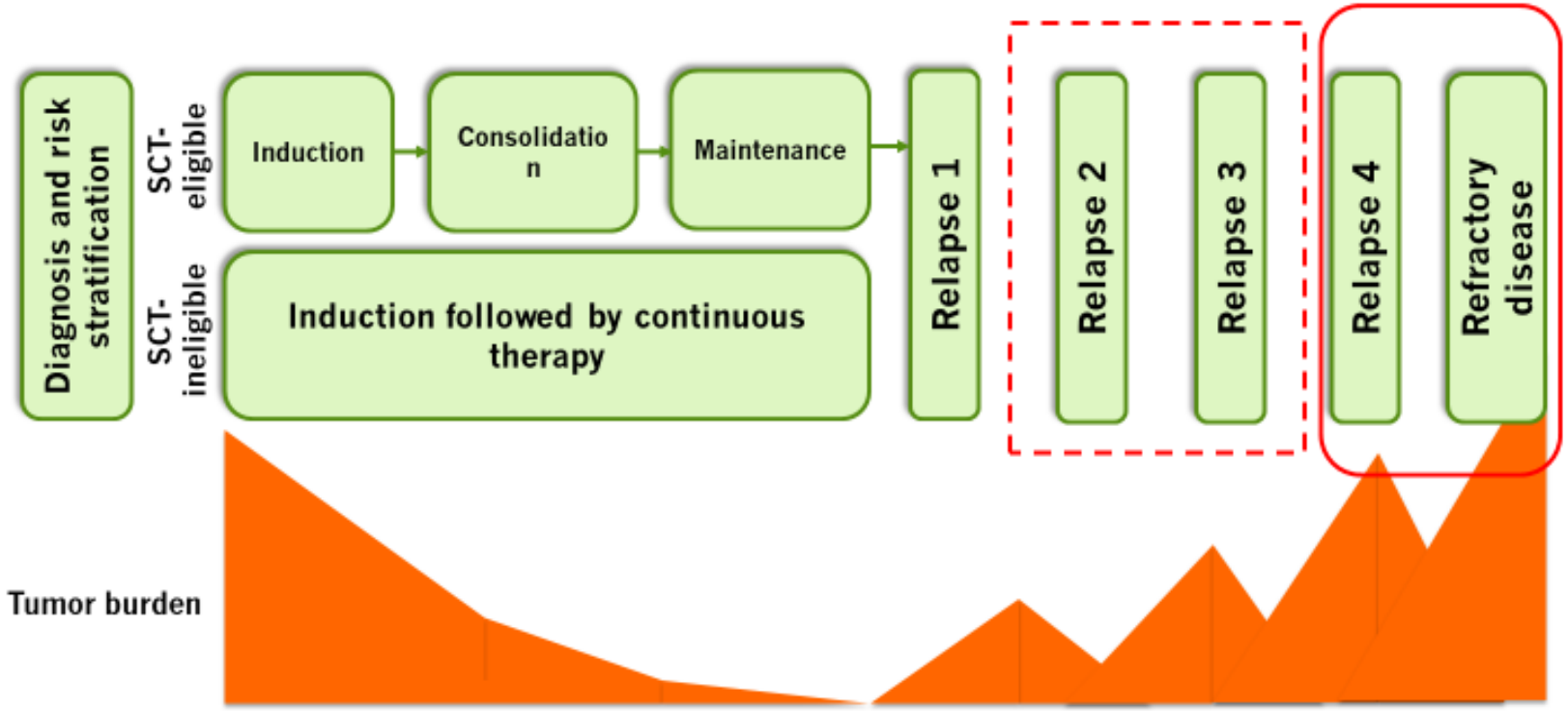
Myeloma Treatment Paradigm



Mayo Clinic, 2021.

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Diagnosis and Work Up

Assessment of MRD needs to be thought of from the moment of diagnosis

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2024
Multiple Myeloma

NCCN Guidelines Index
Table of Contents
Discussion

INITIAL DIAGNOSTIC WORKUP[a]

- History and physical (H&P) exam
- CBC, differential, and platelet count
- Peripheral blood smear
- Serum BUN/creatinine, electrolytes, liver function tests, albumin,[b] calcium, serum uric acid, serum LDH,[b] and beta-2 microglobulin[b]
- Creatinine clearance (calculated or measured directly)[c]
- Serum quantitative immunoglobulins, serum protein electrophoresis (SPEP), and serum immunofixation electrophoresis (SIFE)
- 24-h urine for total protein, urine protein electrophoresis (UPEP), and urine immunofixation electrophoresis (UIFE)
- Serum free light chain (FLC) assay
- Whole-body low-dose CT or FDG-PET/CT[d,e]
- Unilateral bone marrow aspirate and biopsy, including immunohistochemistry (IHC) and/or multi-parameter flow cytometry
- Plasma cell fluorescence in situ hybridization (FISH)[b] panel on bone marrow[f] [del(13), del (17p13), t(4;14), t(11;14), t(14;16), t(14:20), 1q21 gain/1q21 amplification[g], 1p deletion]
- NT-proBNP/BNP[h]

Useful In Certain Circumstances

- If whole-body low-dose CT or FDG-PET/CT is negative, consider whole-body MRI without contrast to discern smoldering myeloma from multiple myeloma (MM)
- Tissue biopsy to confirm suspected plasmacytoma
- Serum viscosity
- Hepatitis B and hepatitis C testing and HIV screening as required
- Echocardiogram
- Evaluation for light chain amyloidosis, if appropriate (NCCN Guidelines for Systemic Light Chain Amyloidosis)
- Single nucleotide polymorphism (SNP) array on bone marrow,[f] and/or next-generation sequencing (NGS) panel on bone marrow[f]
- Consider baseline clone identification and storage of aspirate sample for future minimal residual disease (MRD) testing by NGS
- Assess for circulating plasma cells as clinically indicated

CLINICAL FINDINGS

- Solitary plasmacytoma → Primary Treatment (MYEL-2)
- Smoldering myeloma (asymptomatic)[i] → Primary Treatment (MYEL-3)
- MM (symptomatic)[i] → Primary Treatment (MYEL-4)
- Monoclonal gammopathies of clinical significance
  - For Monoclonal Gammopathy of Renal Significance, see MGRS-1
  - For Monoclonal Gammopathy of Neurological Significance see MGNS-1

[a] Frailty assessment should be considered in older adults. See NCCN Guidelines for Older Adult Oncology.
[b] These tests are essential for R-ISS staging. See Disease Staging and Risk Stratification for Multiple Myeloma (MYEL-B).
[c] Management of Renal Disease in Multiple Myeloma (MYEL-K).

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Upfront Treatment

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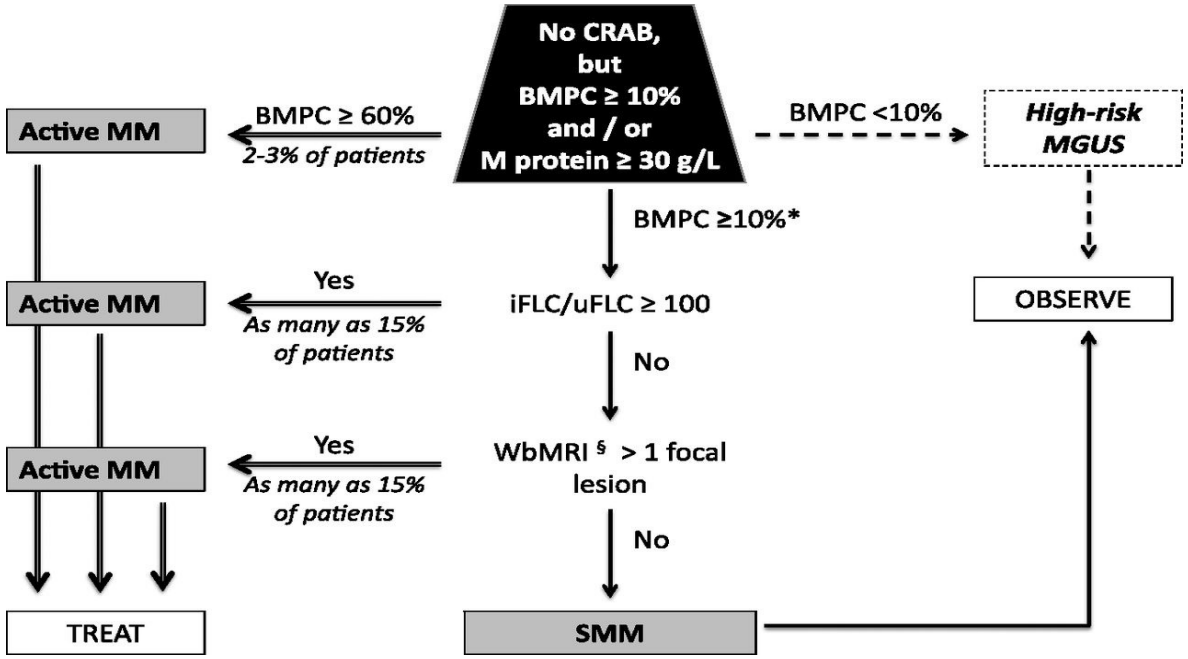
Treatment Indications



- *Consider including patients with the following FISH: deletion 17p, t(4;14), and 1q21 gains as active MM; this population could account for as many as 30% of SMM patients. §Consider using more than 1 fluorodeox.

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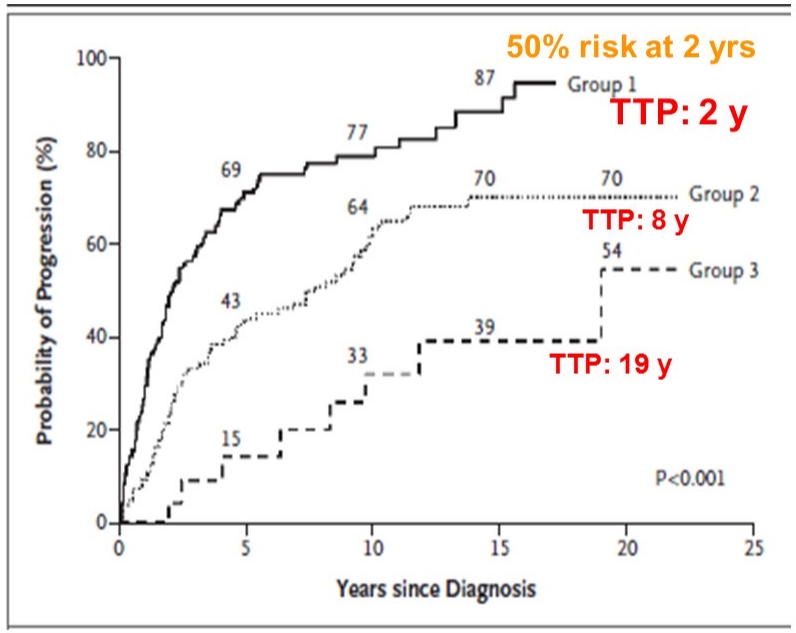
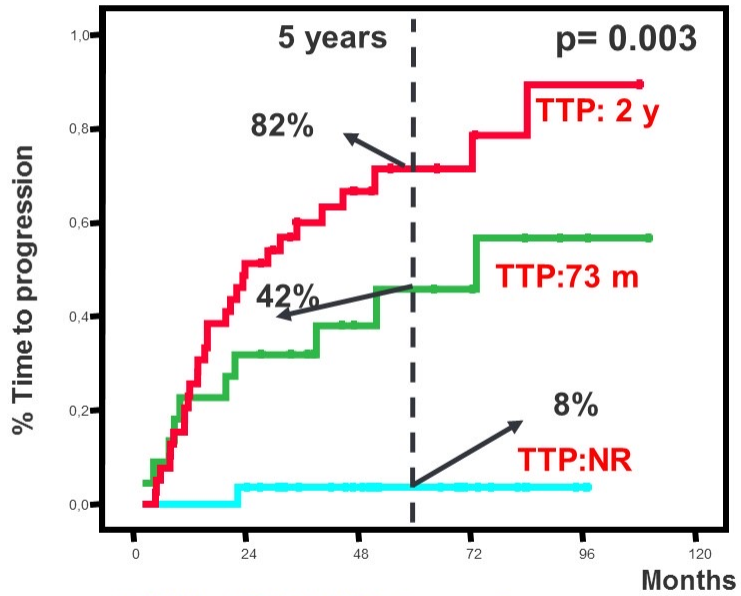
Mayo risk model
PCs BM infiltration and Serum M-component level



Group 1: *PCBM ≥ 10% + MC ≥ 3g/dl*
Group 2: *PCBM ≥ 10% + MC < 3g/dl*
Group 3: *PCBM < 10% + MC ≥ 3g/dl*

Kyle R. N Engl J Med 2007; 356:2582-90

Spanish model:
Aberrant PCs by immunophenotype plus immunoparesis



>95% aPC/BMPC + paresis
>95% aPC/BMPC or paresis
No adverse factors

Pérez E. Blood 2007; 110:2586-92

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Staging and Cytogenetic Risk-Assessment

Stage[1]	R-ISS[1]
I	Serum albumin ≥3.5 g/dL^{-1} Serum β2M <3.5 mg/L^{-1} No high-risk cytogenetics Normal LDH level
II	Not stage I or III
III	Serum β2M >5.5 mg/L^{-1} High-risk cytogenetics: t(4;14), t(4;16), or del(17p) or elevated LDH

Risk[2]	Features
Standard	Trisomies t(11;14) t(6;14)
High	t(4;14) t(14;16) t(14;20) Del(17p) *p53* mutation Gain/Amp 1q High plasma cell S-phase GEP high-risk signatures Circulating Plasma Cells Elevated LDH/EMD
Ultra-High Risk	2 or more features

1. Palumbo A, et al. *J Clin Oncol*. 2015;33:2863-2869; 2. Costa LJ, Usmani SZ. J Natl Compr Canc Netw. 2020;18(12):1730-1737.

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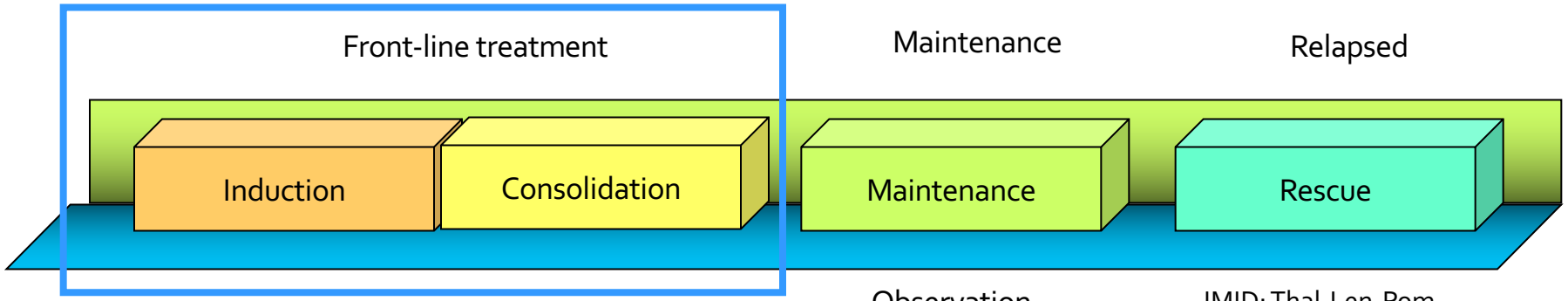
Induction Therapy has Changed Over the Last 40 Years



1980-VAD

1990 -IMID:Thal Dex

2000 Triplet IMID Proteosome Inhibitor Dex

2020 Quadruplet?

High Dose Melphalan
Auto SCT

Observation
IMID: Thal-Len
Proteosome Inh: Bor
Steroids: Dex-Pred
Antibodies

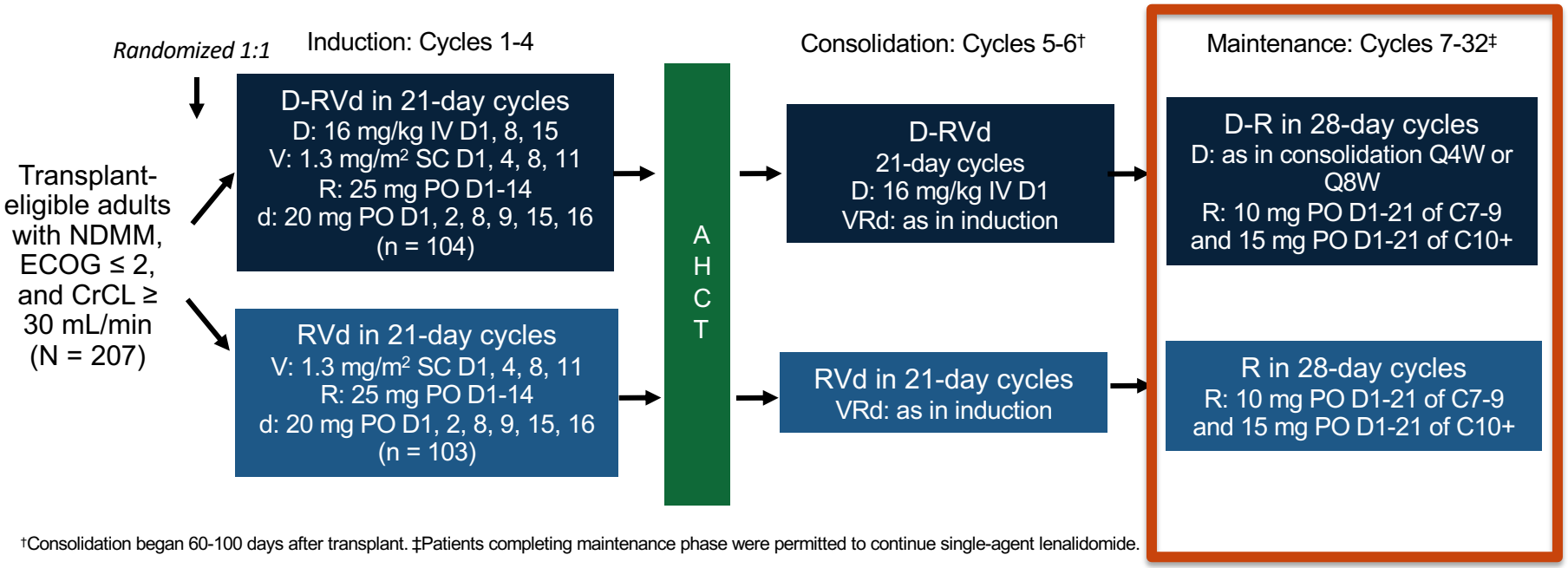
IMID: Thal-Len-Pom
Proteosome Inh: Bor-Car
Steroids: Dex-Pred
Alkylators: Mel-Cy-Benda
Antibodies
Investigational
CAR T Cells
Belantemab (anti BCMA drug conjugate)

[a]Transplant eligible patients.

Bor = bortezomib; Dex = dexamethasone; Dox = doxorubicin; Thal = thalidomide; Len = lenalidomide; SCT = stem-cell transplant; Pred = prednisone; Lipo/Dox = liposomal doxorubicin.

NCCN Clinical Practice Guidelines v2.2014.

GRIFFIN 2-yr Maintenance Update



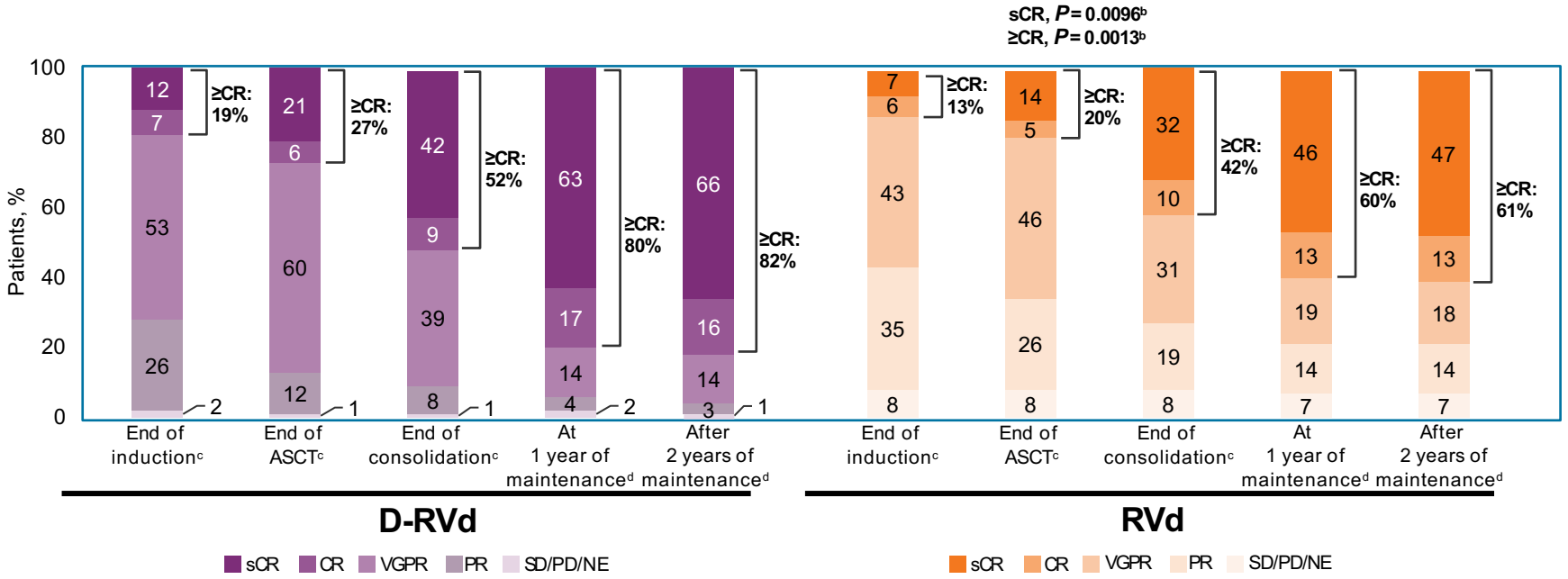
†Consolidation began 60-100 days after transplant. ‡Patients completing maintenance phase were permitted to continue single-agent lenalidomide.

Primary endpoint: sCR by end of consolidation with 1-sided $\alpha = 0.1$

Key secondary endpoints: rates of MRD negativity, ORR, ≥VGPR, CR, PFS, OS

Laubach. ASH 2021. Abstr 79.

GRIFFIN: Responses Deepened Over Time



Response rates of sCR and ≥CR were greater for D-RVd versus RVd all time points, with the deepest responses occurring after 2 years of maintenance therapy

PR, partial response; SD/PD/NE, stable disease/progressive disease/not evaluable. [a]Data are shown for the response-evaluable population. [b]*P* values (2-sided) were calculated using the Cochran chi-square test. [c]Response rates are from the primary analysis cutoff (median follow-up: 13.5 mo), and the response-evaluable population included 196 patients (D-RVd, n = 99; RVd, n = 97). [d]Response rates for the maintenance phase were from the updated follow-up (median: 38.5 mo), and the response-evaluable population included 197 patients (D-RVd, n = 100; RVd, n = 97). Percentages may not add up due to rounding.

Laubach. ASH 2021. Abstr 79.

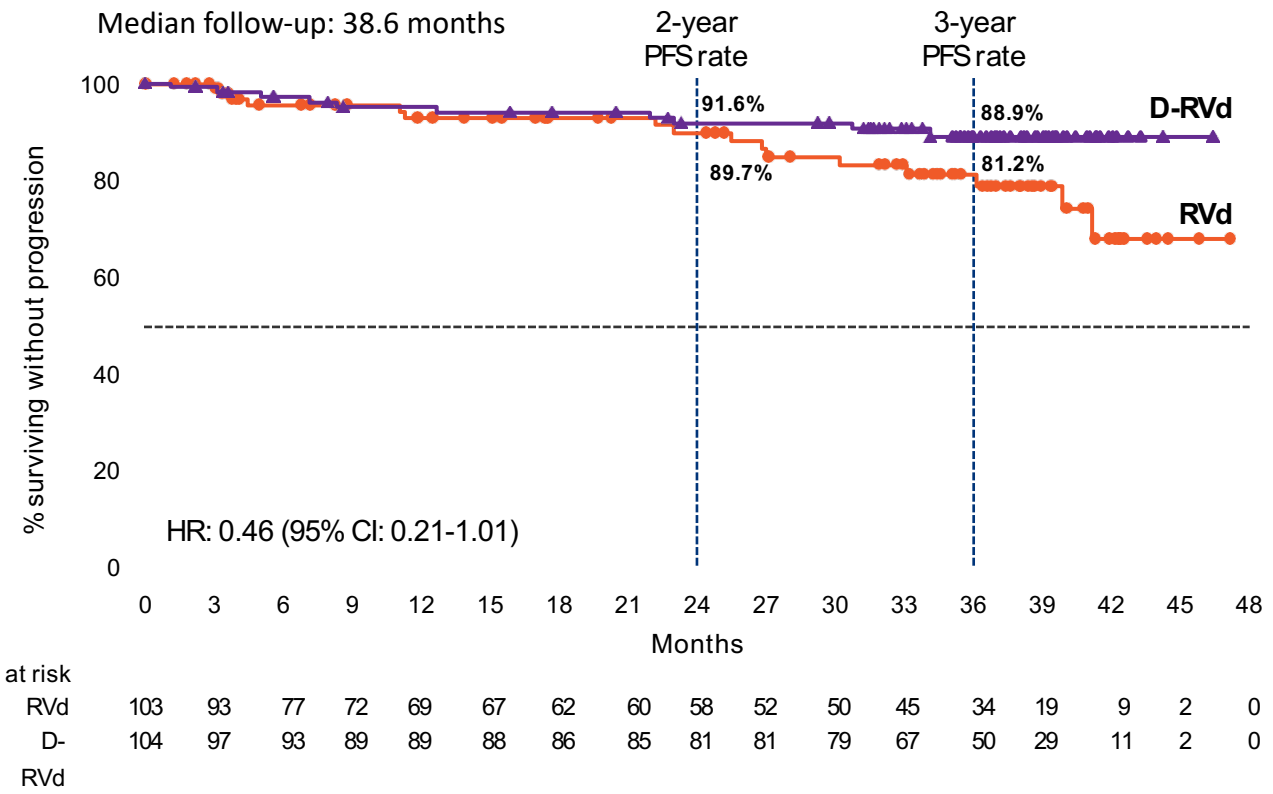
GRIFFIN 2-yr Maintenance Update

MRD Negativity After 24-Mo Maintenance, %	D-VRd (n = 104)	VRd (n = 103)	P Value
MRD at 10^{-5} threshold, % ▪ ITT population ▪ ≥CR	 64 78	 30 47	 <.0001 .0003
MRD at 10^{-6} threshold, % ▪ ITT population ▪ ≥CR	 36 43	 15 22	 .0007 .0121
Sustained MRD negativity lasting ≥12 mo, %	44.2	12.6	<.0001

Laubach. ASH 2021. Abstr 79.

GRIFFIN 2-yr Maintenance Update: PFS in ITT Population

- Median PFS was not reached in either group
- There is a positive trend toward improved PFS for D-RVd/DR vs RVd/R
- Separation of the PFS curves begins beyond 1 yr of maintenance and suggests a benefit of prolonged DR therapy



Laubach. ASH 2021. Abstr 79.

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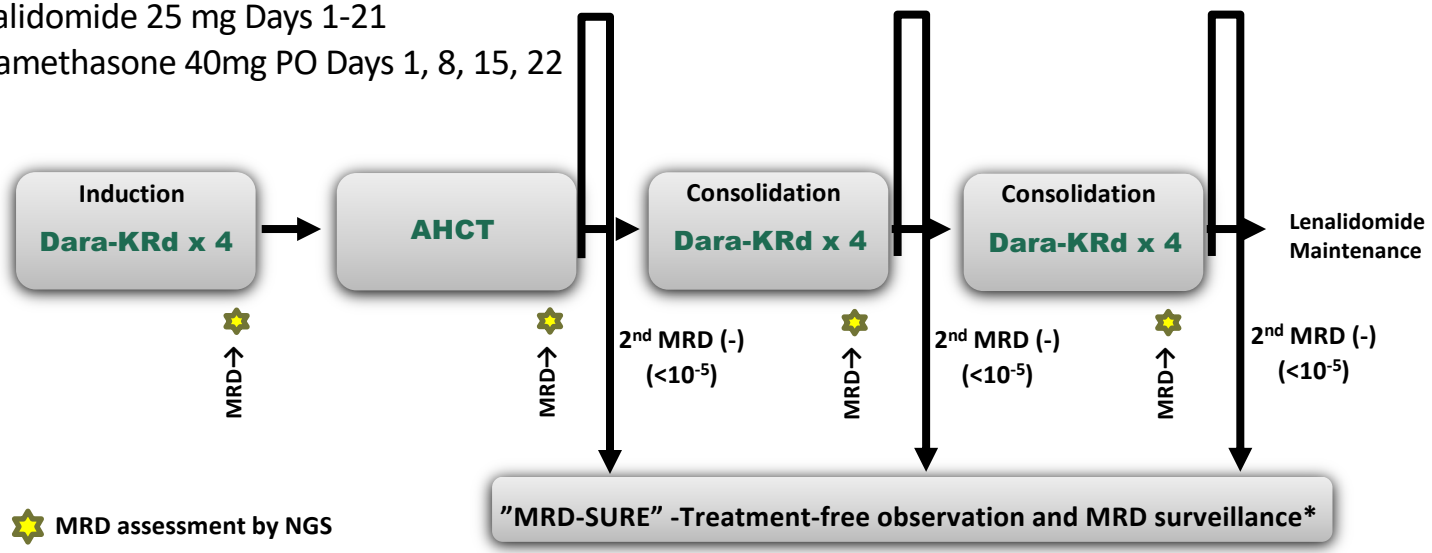
MASTER trial

Dara-KRd

- Daratumumab 16 mg/m^2 days 1, 8, 15, 22 (days 1,15 C 3-6; day 1 C >6)
- Carfilzomib (20) 56 mg/m^2 Days 1, 8, 15
- Lenalidomide 25 mg Days 1-21
- Dexamethasone 40mg PO Days 1, 8, 15, 22



*24 and 72 weeks after completion of therapy

Costa. ASH 2021. Abstr 481.

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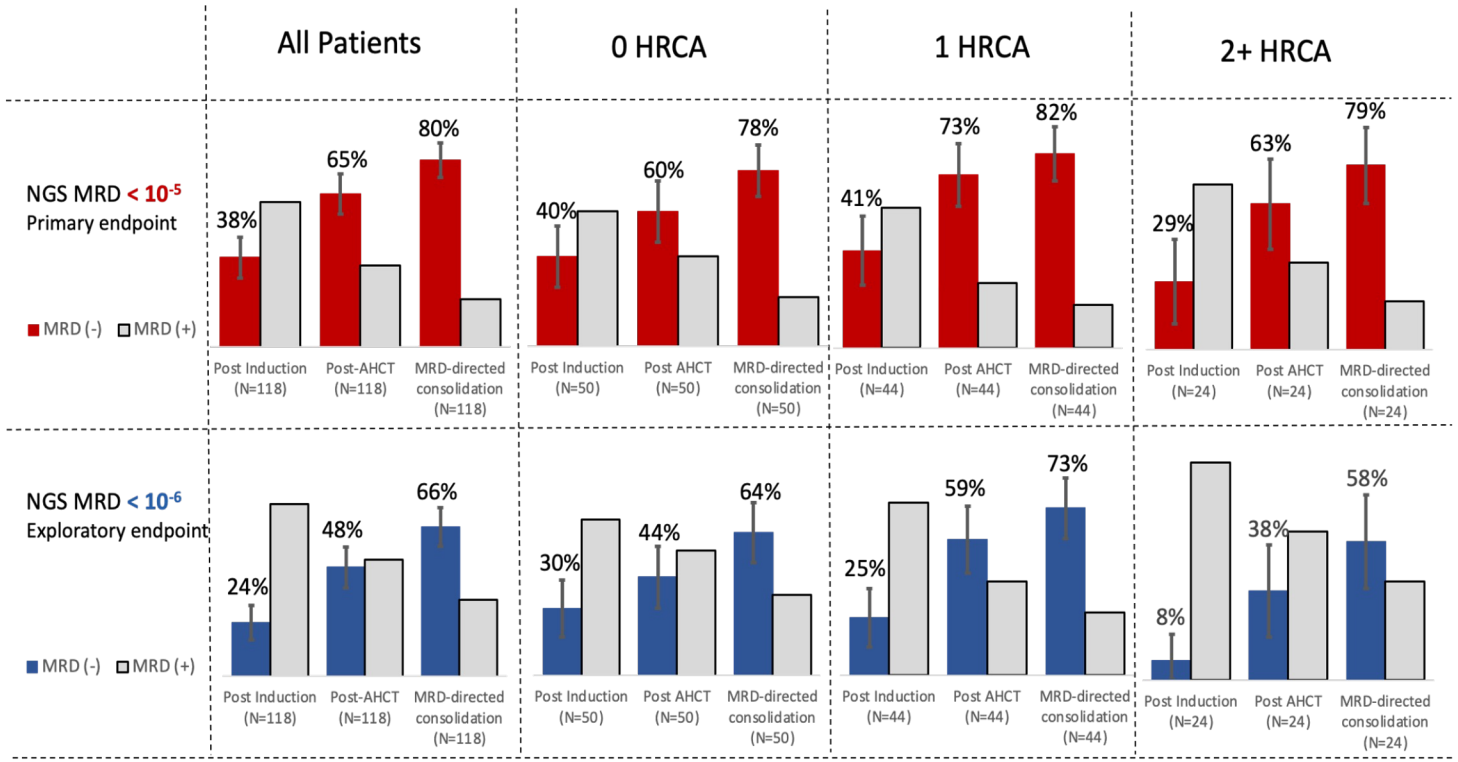
MASTER trial



HRCA = gain/amp 1q, t(4;14), t(14;16), t(14;20) or del(17p)

Costa. ASH 2021. Abstr 481.

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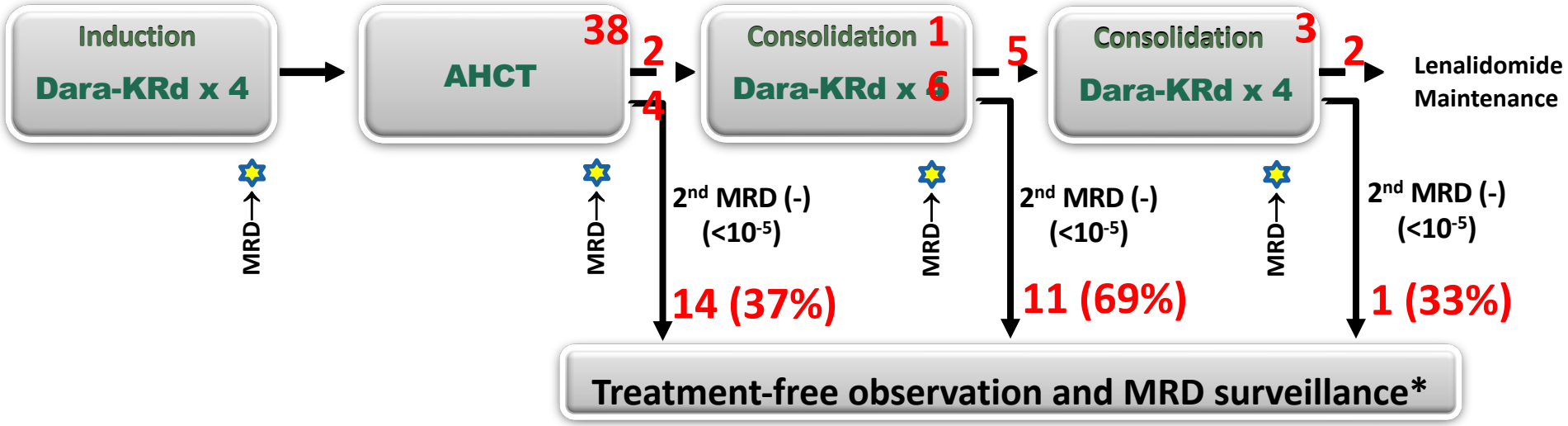
Observation/MRD surveillance

- 26 patients (19 SR, 7 HR) have reached confirmed MRD (-) and entered observation/MRD surveillance.
- Median follow up on observation 4.9 months (0.2-12.2) - <u>No relapse or resurgence of MRD</u>



*24 and 72 weeks after completion of therapy

MASTER trial

IFM 2009 Study design

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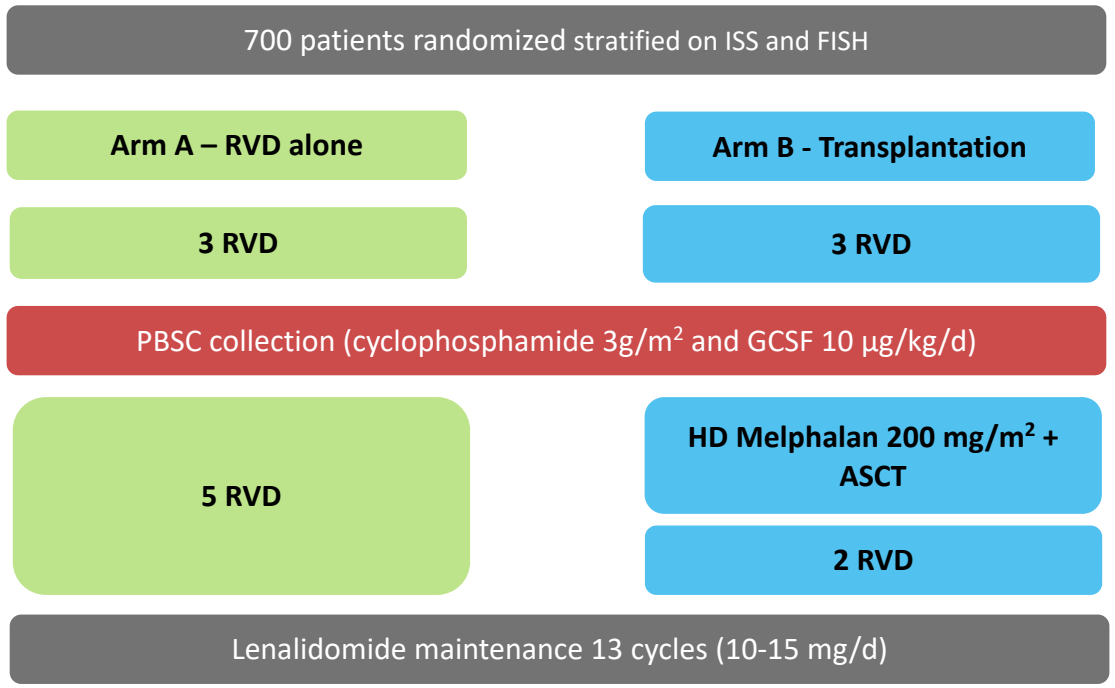

RVd 21d cycles
. Lenalidomide 25 mg/d: D1-D14
. Bortezomib 1.3 mg/m² D1, D4, D8, D11
. Dexamethasone 20 mg/d: D1, D2, D4, D5, D8, D9, D11, D12

Primary endpoint = PFS

Secondary endpoints
. ORR, MRD
. TTP
. OS
. Toxicity

M Attal et al, N Engl J Med 2017

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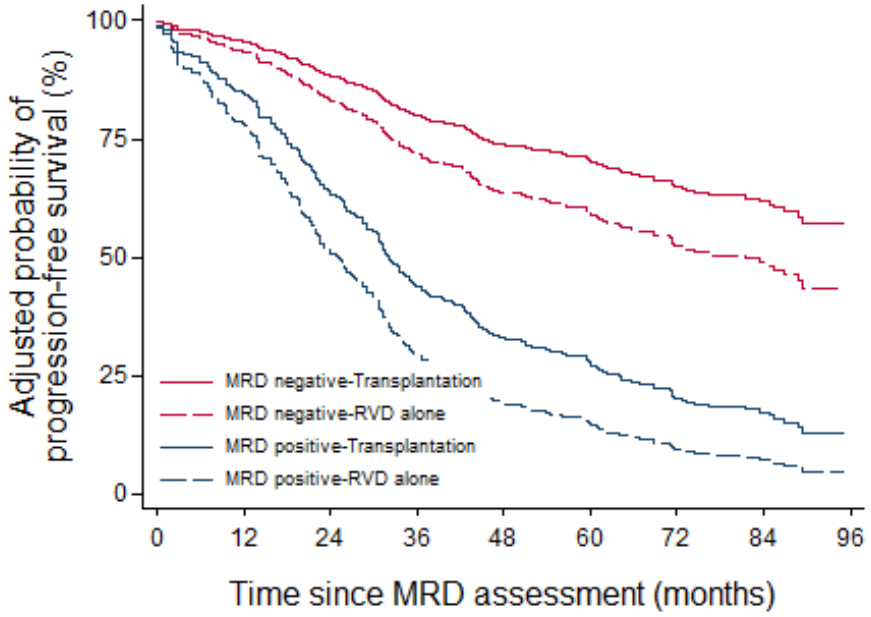
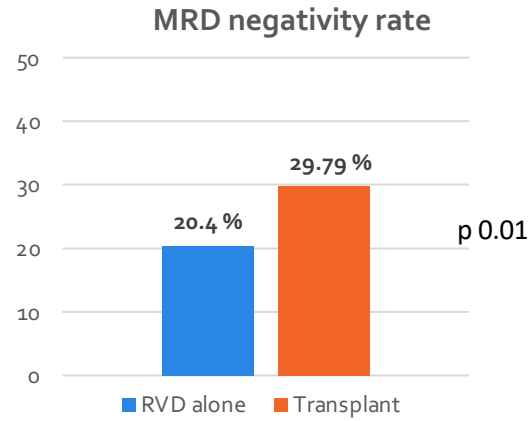
Subgroup analyses

Place video here

Median follow up	89.8 months





p 0.01

Transplant is superior to VRD alone, even in patients who achieved undetectable MRD at 10^{-6}

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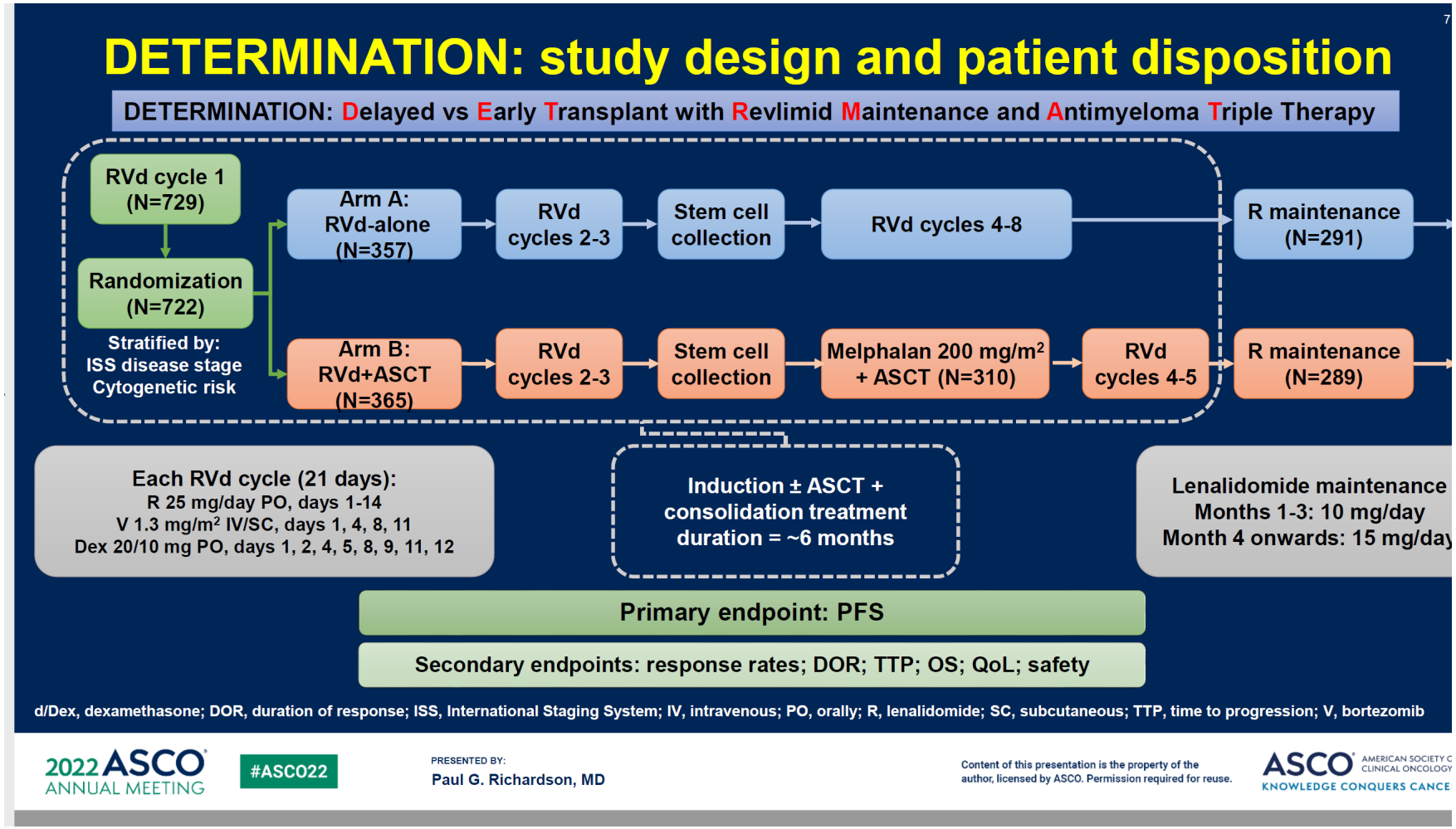
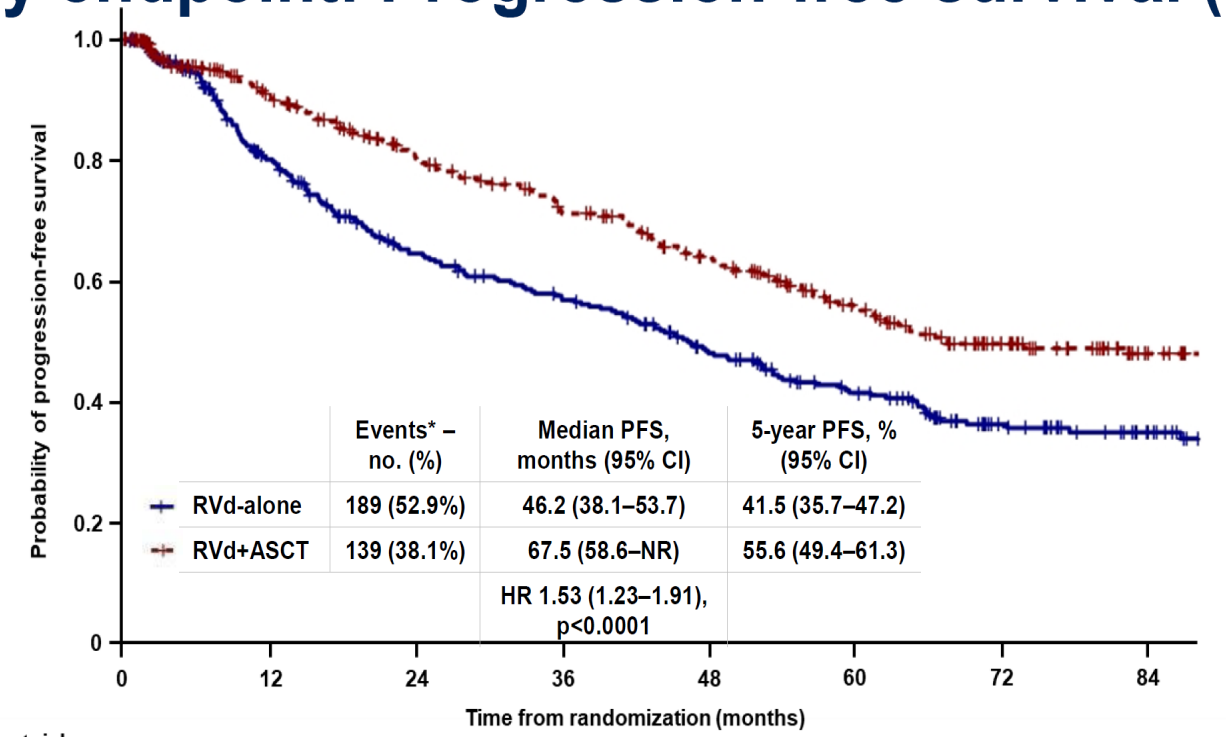
THE DETERMINATION STUDY



Primary endpoint: Progression-free survival (PFS)



	Events* – no. (%)	Median PFS, months (95% CI)	5-year PFS, % (95% CI)
RVd-alone	189 (52.9%)	46.2 (38.1–53.7)	41.5 (35.7–47.2)
RVd+ASCT	139 (38.1%)	67.5 (58.6–NR)	55.6 (49.4–61.3)
		HR 1.53 (1.23–1.91), p<0.0001	

Patients at risk

RVd-alone	357	250	187	160	126	96	60	40
RVd+ASCT	365	276	226	191	160	118	77	42

CI, confidence interval; HR, hazard ratio; Data cutoff: 12/10/21. *PFS events: disease progression or death.

PRESENTED BY: Paul G. Richardson, MD

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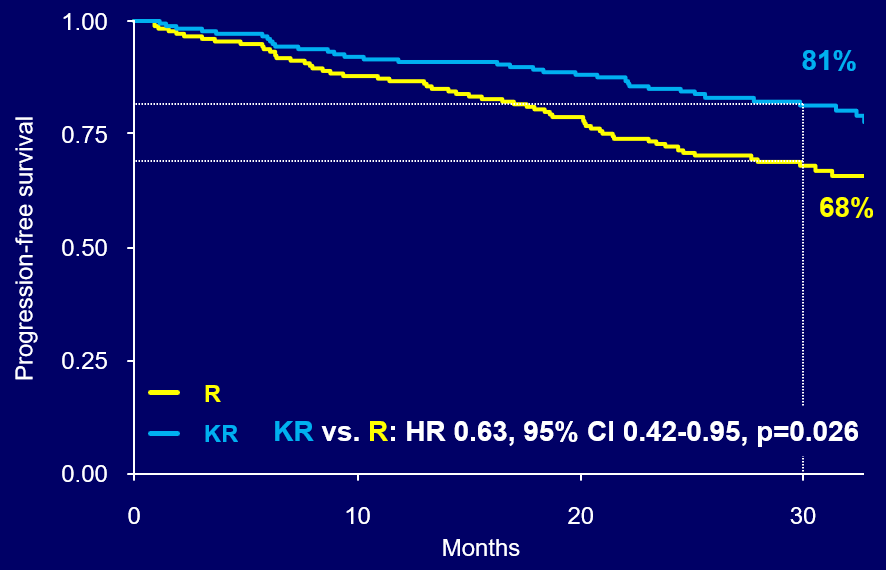
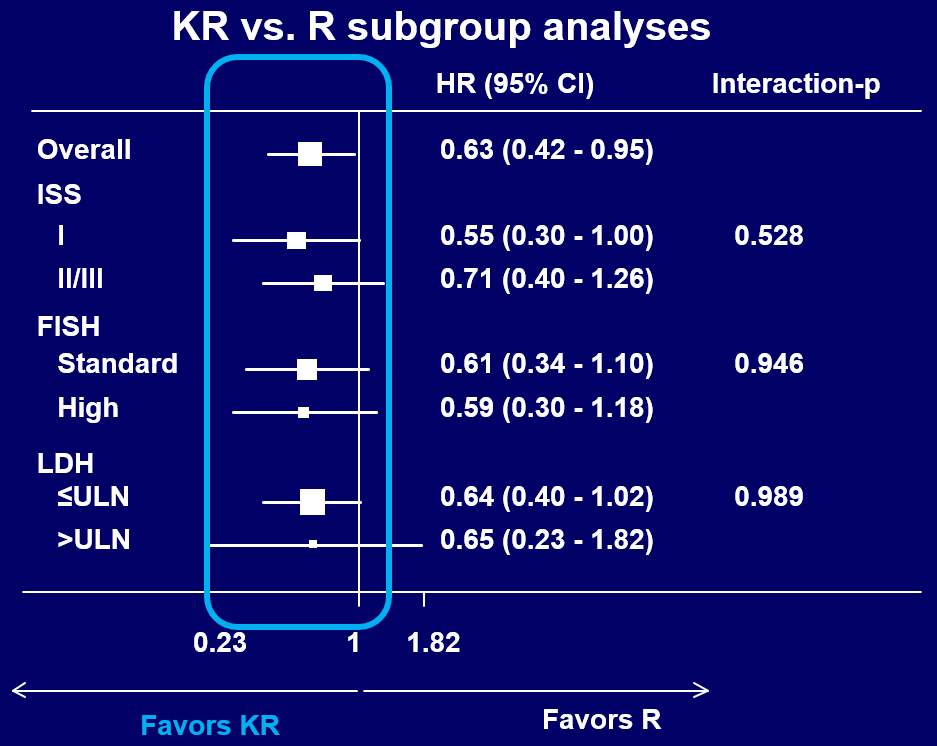
Progression-Free Survival: Random 2

Median follow-up from random 2: 31 months (26-36 months)





SIMILAR HR IN STANDARD-RISK AND HIGH-RISK PATIENTS TREATED WITH KR vs. R

Random 2, second randomization (maintenance treatment); PFS, progression-free survival; K, carfilzomib; R, lenalidomide; HR, hazard ratio; CI, confidence interval; p, p-value; ISS, International Staging System stage; FISH, fluorescence *in situ* hybridization; LDH, lactate dehydrogenase; ULN, upper limit of normal; KR, carfilzomib-lenalidomide maintenance; R, lenalidomide maintenance. 30-month PFS reported in the figure.

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Important Considerations

- Induction cycles: 4 versus 6
  - VRD standard and most cost effective for standard risk disease
  - If VGPR or better after 4 then stop?
  - If less than VGPR and not plateaued, then 6?
- Quads for all?
  - Strong data emerging for transplant eligible patients
  - May not be enough for high risk patients
- Multidrug maintenance
- Response-adaptive strategy in trials.
- Delaying transplant becoming more common
  - Not recommended for patients with high risk disease (survival benefit for transplant emerging)
  - Not recommended for patients less than 65 years of age
  - Not recommended for patients with less than a VGPR

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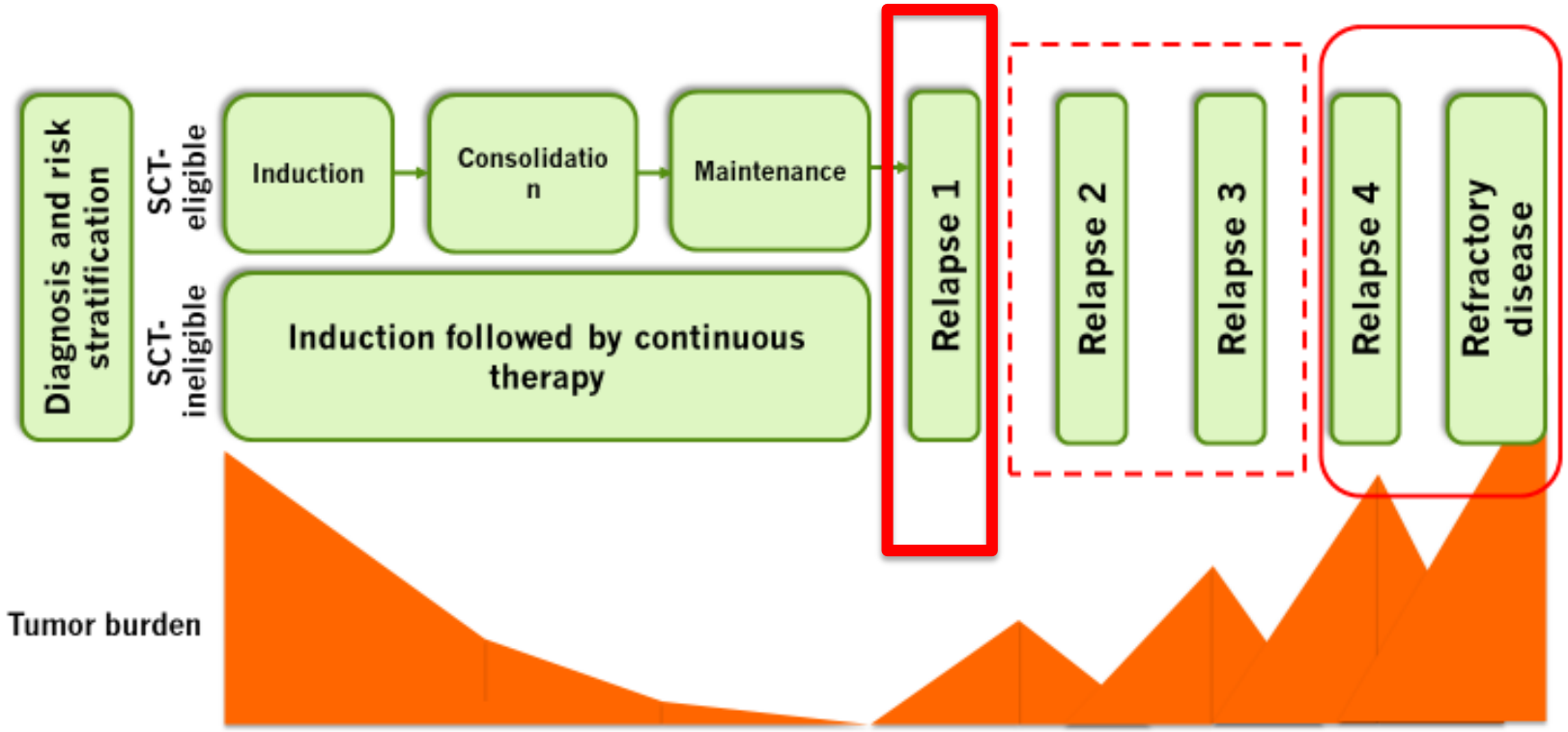
Myeloma Treatment Paradigm



Mayo Clinic, 2021.

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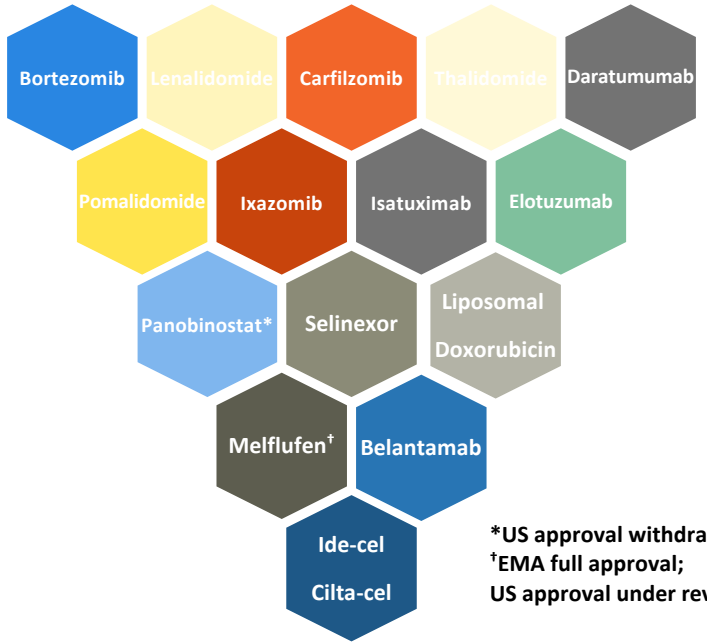
Multiple Novel Agents Now Available to Treat Newly Diagnosed and Relapsed/Refractory Myeloma in 2022

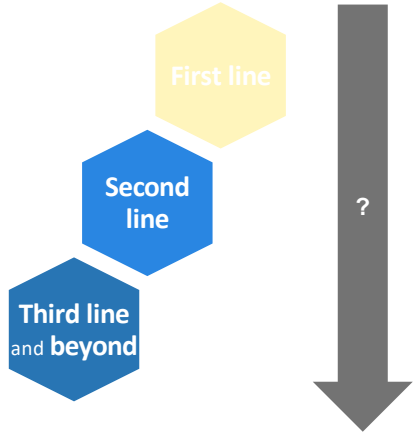
Previously up to 16 but now 14 approved novel agents in MM—with more coming



*US approval withdrawn.
†EMA full approval;
US approval under review.

Adapted from Laubach. Leukemia. 2016;30:1005. Moreau. Lancet Oncol. 2021;22:e105.

How do we sequence and strategize therapies to ensure the best outcomes for our patients?



Teclistimab

Talquetemab

Elranatemab in 2023

CCO

Slide credit: clinicaloptions.com

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Selecting Treatment for R/R MM: General Principles

Patient	Disease	Treatment	Regimen
▪ Age/frailty ▪ Performance status ▪ Lifestyle ▪ Patient preference ▪ Caregiver support ▪ Comorbidities – Renal status – Neuropathy – Cardiac – Diabetes – Cytopenias	▪ Disease burden: ISS – Rate of progression – Marrow burden – CRAB symptoms – Extramedullary disease ▪ Biology – LDH – Cytogenetics • t(4;14) • del(17p) • t(14;16) • amp(1q) • t(11;14)	▪ Toxicity – Myelosuppression – Infections – Neuropathy – Secondary cancers – Ocular toxicity ▪ Cost ▪ Administration route ▪ Relapsed vs refractory ▪ Depth/duration of response to prior treatment	▪ Triplet* (eg, KRd) is preferred over doublet ▪ Include ≥1 agent from new or non-refractory class ▪ Previously used agents may be effective in different combinations ▪ Treat to maximum response ▪ Maintain on ≥1 agent until progression or intolerability

Laubach. Leukemia. 2016;30:1005. NCCN. clinical practice guidelines in oncology: multiple myeloma. v.5.2022. nccn.org.
Sanchez. Expert Rev Hematol. 2020;13:943. Sonneveld. 2016;101:396.

Slide credit: clinicaloptions.com

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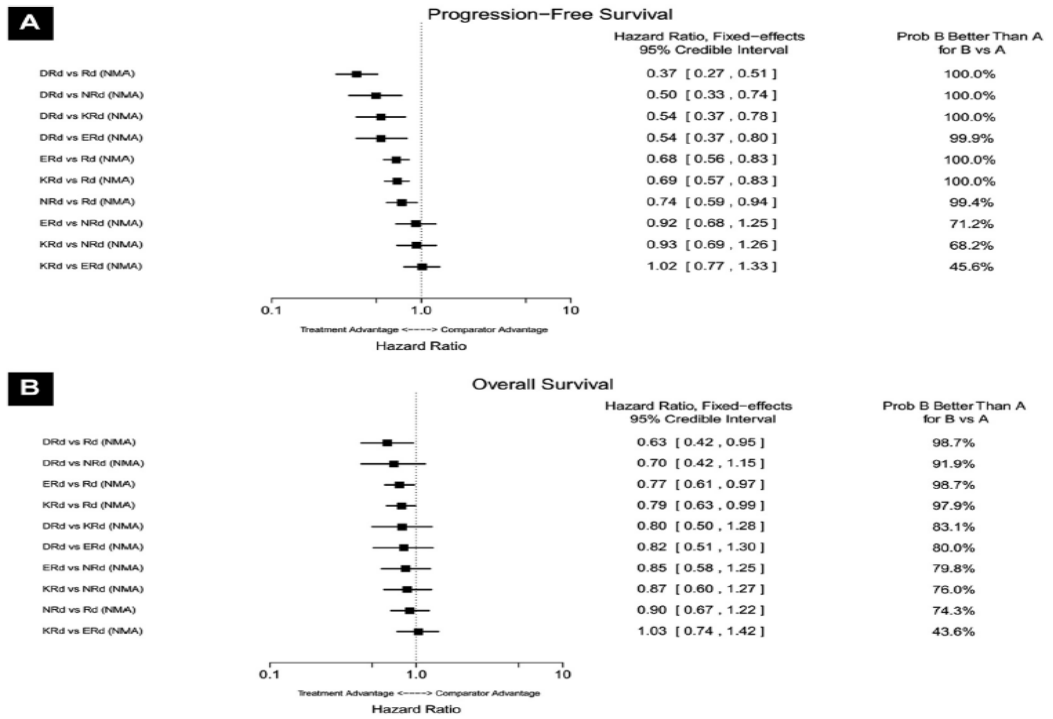
A Comparison of the Efficacy of Immunomodulatory-containing Regimens in Relapsed/Refractory Multiple Myeloma: A Network Meta-analysis

Meletios Athanasios Dimopoulos,[1] Jonathan L. Kaufman,[2] Darrell White,[3] Gordon Cook,[4] Maria Rizzo,[5] Yingxin Xu,[6] Kyle Fahrbach,[6] Maren Gaudig,[7] Mary Slavcev,[8] Lindsay Dearden,[8] Annette Lam[8]

CD 38 mab Naïve patients should preferentially receive a CD38 mab containing salvage regimen
Triplets better than doublets
Quadruplets not extensively explored



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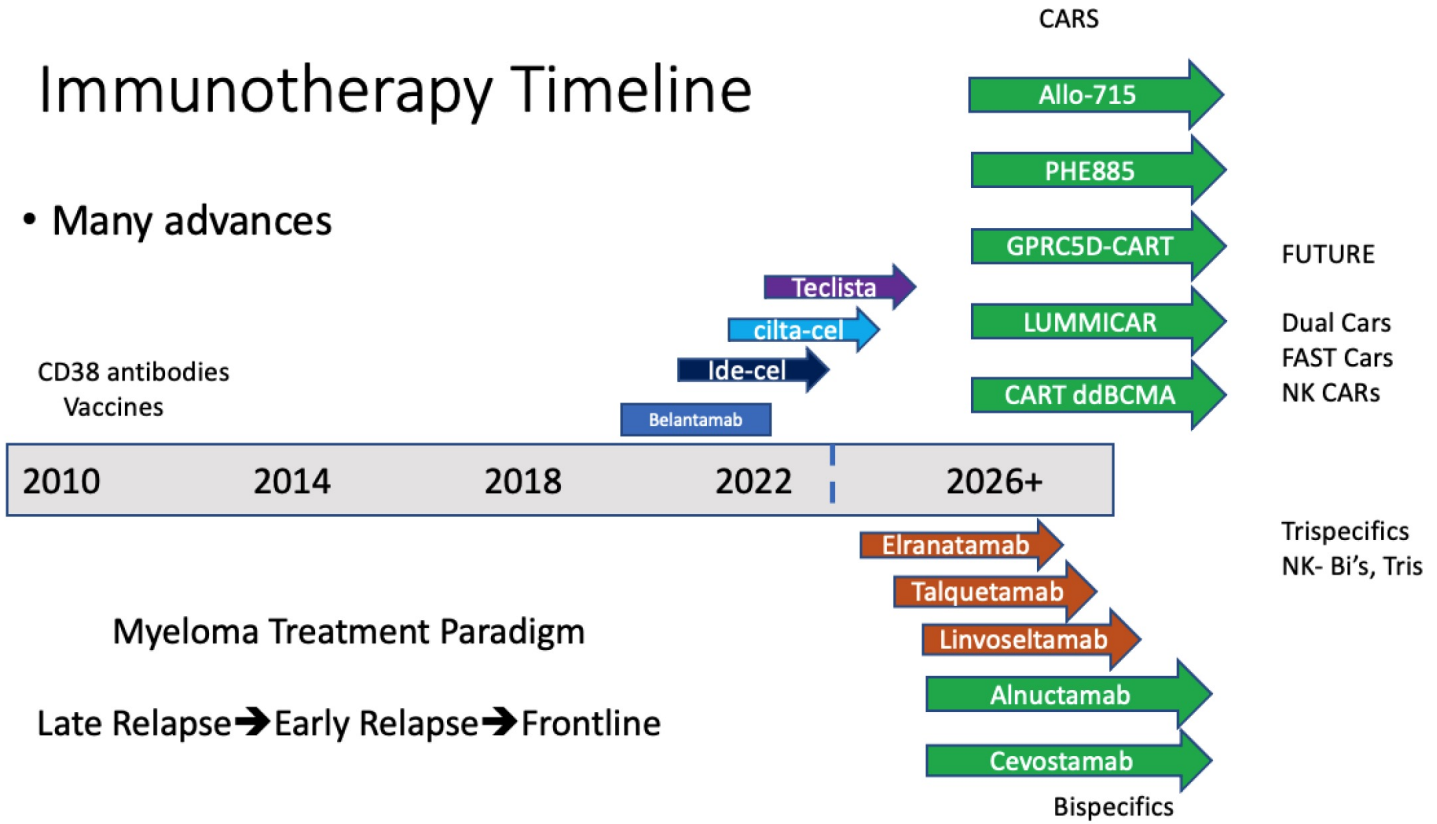
Immunotherapy Timeline

- Many advances



Myeloma Treatment Paradigm

Late Relapse➔Early Relapse➔Frontline

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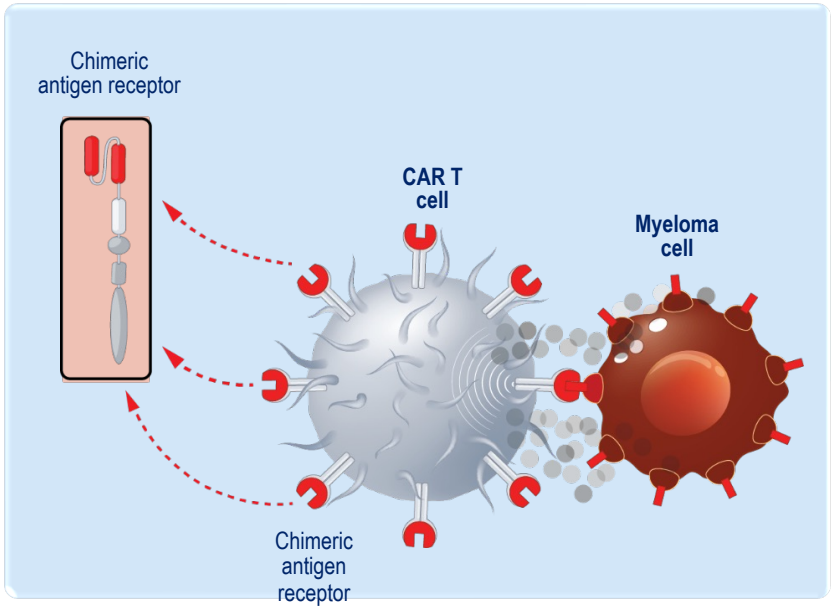
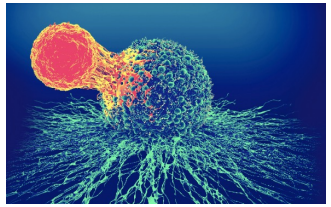
The Promise of T-cell Redirection

- Genetically modified T cells designed to recognize specific proteins on MM cells
- CAR T cells are activated once in contact with the MM cell and can destroy the MM cell
- CAR T cells can persist for long periods of time in the body
- CAR T cells are created from a patient's own blood cells, but the technology is evolving to develop "off-the-shelf" varieties





CAR, chimeric antigen receptor; MM, multiple myeloma

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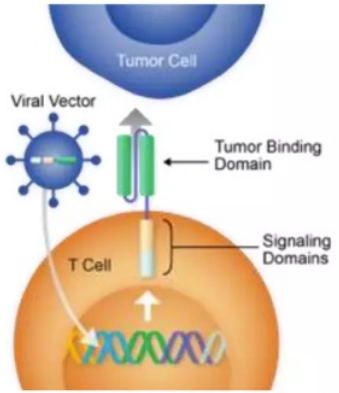
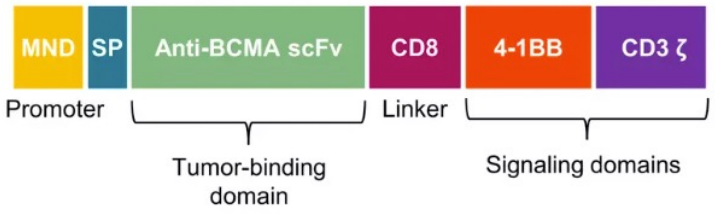
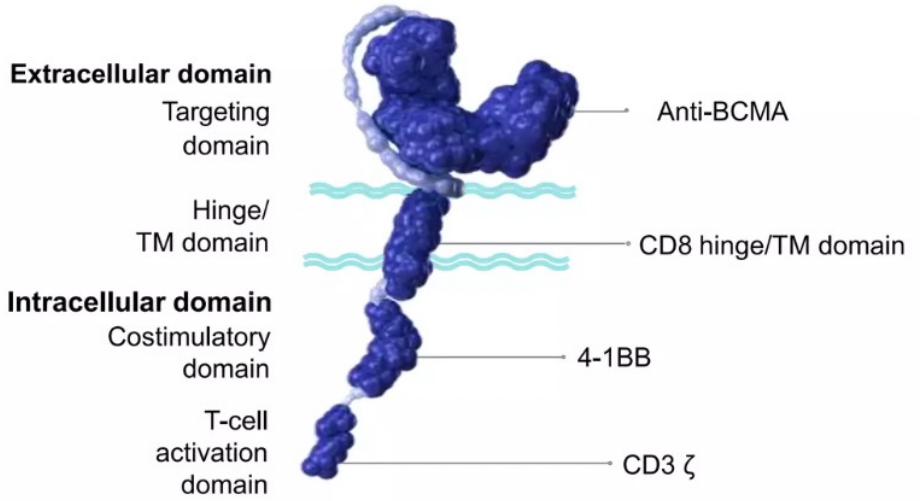
KarMMa-1: Phase 2 Study of Ide-cel in Patients with RRMM



Ide-Cel CAR Design





Ide-cel is a second-generation CAR construct

- **Autologous** T cells transduced with a lentiviral vector encoding CAR specific for BCMA
- Targeting domain: **anti-BCMA**
- Costimulatory domain: **4-1BB**
- T-cell activation domain: **CD3 ζ**

4-1BB associated with less toxicity and more durable CAR T-cell persistence than CD28 costimulatory domain

Munshi et al. ASCO 2020.

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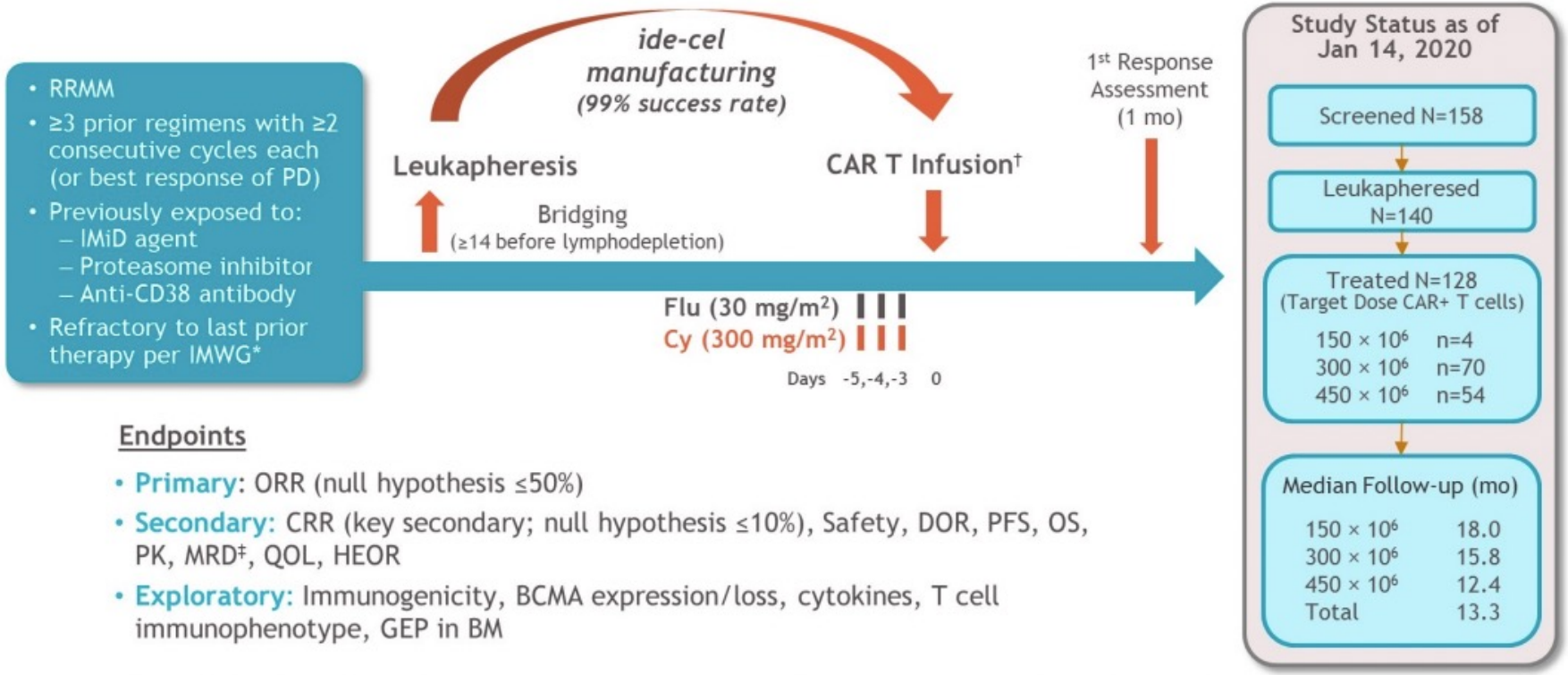
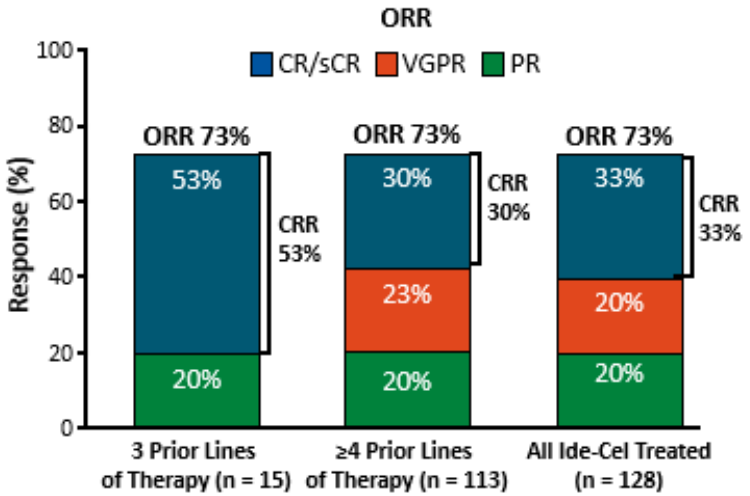
KarMMa-1: Phase 2 Study of Ide-cel in Patients with RRMM



Munshi et al. ASCO 2020.

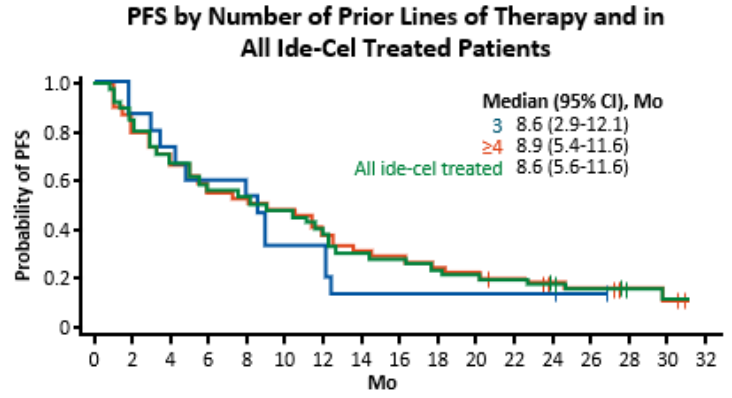
Memorial Sloan Kettering Cancer Center

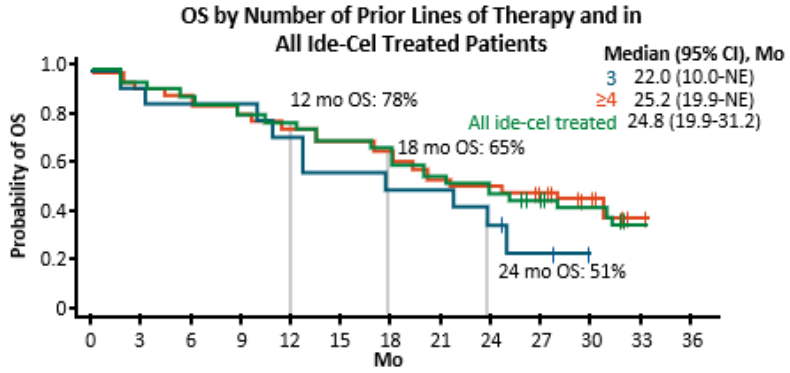
KarMMa-1: Survival Update



- ORR: 73%
- Median DoR: 10.9 mo

- Median PFS at 300 x 10^6 CAR T-cells was 5.8 mo vs 12.2 mo with 450 x 10^6 CAR T-cells
- Median OS in subgroups at high risk of progression (age ≥65 yr, extramedullary disease, triple refractory) was ≥20 mo
- Median OS in subgroup with R-ISS stage III disease was 8.8 mo

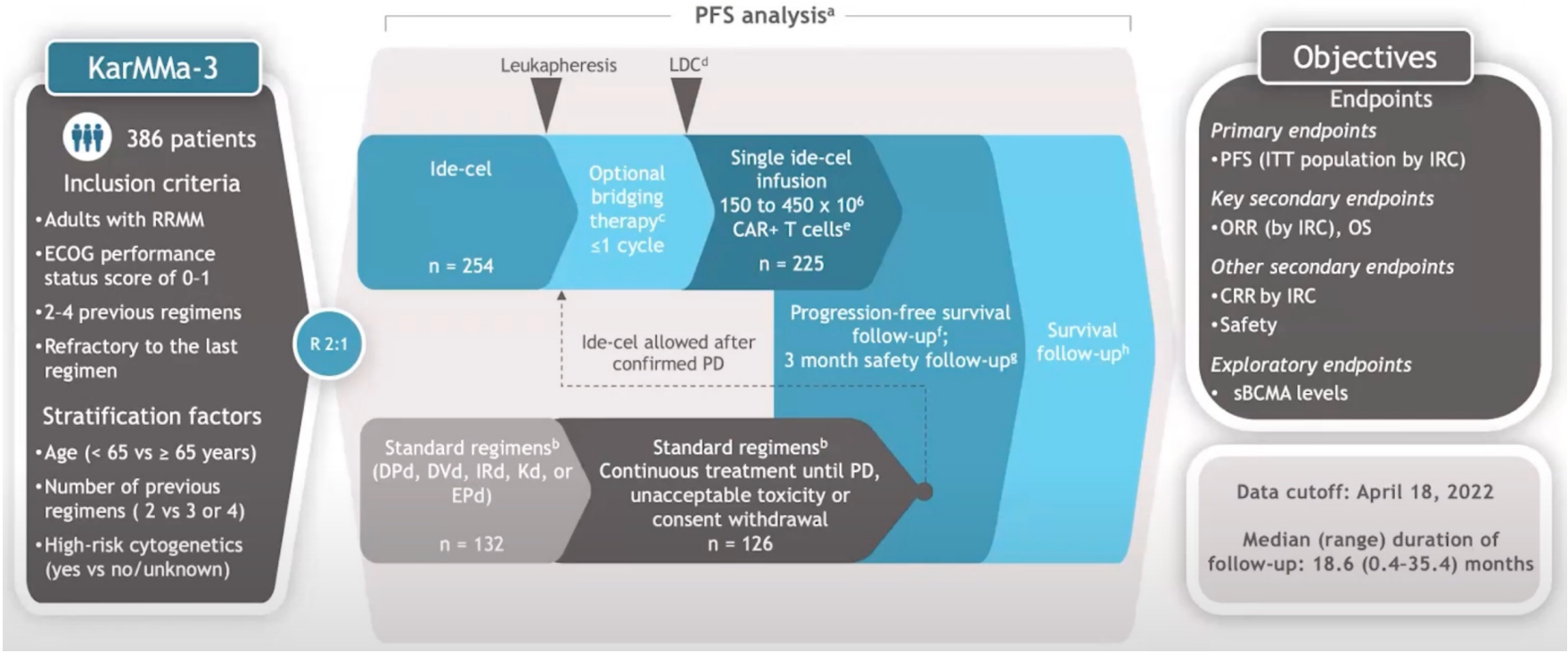




Anderson et al., ASCO 2021

Memorial Sloan Kettering Cancer Center

KarMMa-3: Ide-cel or Standard Regimens (DPd, DVd, IRd, Kd, EPd) in RRMM



Patel K et al. EHA 2023. Giralt S et al. ASTCT 2023. Rodriguez-Otero P et al. N Engl J Med 2023.

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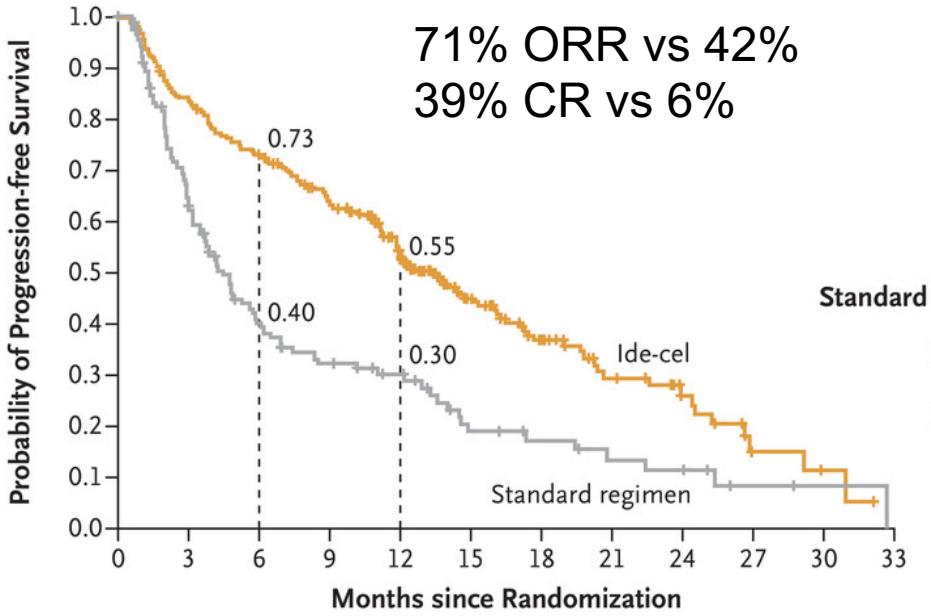
KarMMa-3: Ide-cel or Standard Regimens (DPd, DVd, IRd, Kd, EPd) in RRMM

71% ORR vs 42%
39% CR vs 6%



No. at Risk												
Ide-cel	254	206	178	149	110	62	40	22	14	4	2	0
Standard regimen	132	75	42	32	25	13	10	7	6	2	1	0

	Median Progression-free Survival (95% CI)
	mo
Ide-cel	13.3 (11.8–16.1)
Standard Regimen	4.4 (3.4–5.9)

Hazard ratio for disease progression or death, 0.49 (95% CI, 0.38–0.65)
P<0.001

Rodriguez-Otero P et al. N Engl J Med 2023.

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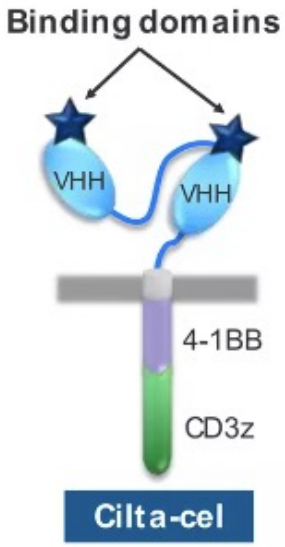
CARTITUDE-1: Phase 1/2 Study of Cilta-cel in Patients with RRMM

Key Eligibility Criteria

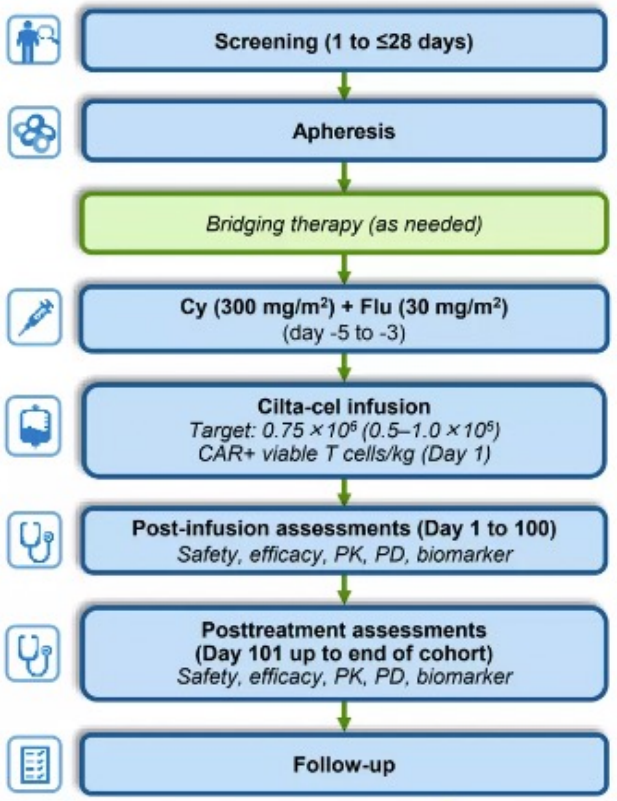
- Progressive MM per IMWG criteria
- ECOG PS ≤1
- ≥3 prior lines or double-refractory, prior PI, IMiD, and anti-CD38 mAb



2 BCMA-targeting single-domain antibodies designed to confer avidity

Median administered dose:
0.71×10^6 (range $0.51–0.95 \times 10^6$) CAR+ viable T cells/kg

Primary endpoints:
Phase 1b: Safety, confirm RP2D
Phase 2: ORR



Martin T et al, ASCO 2021, Berdeja et al, Lancet 2021

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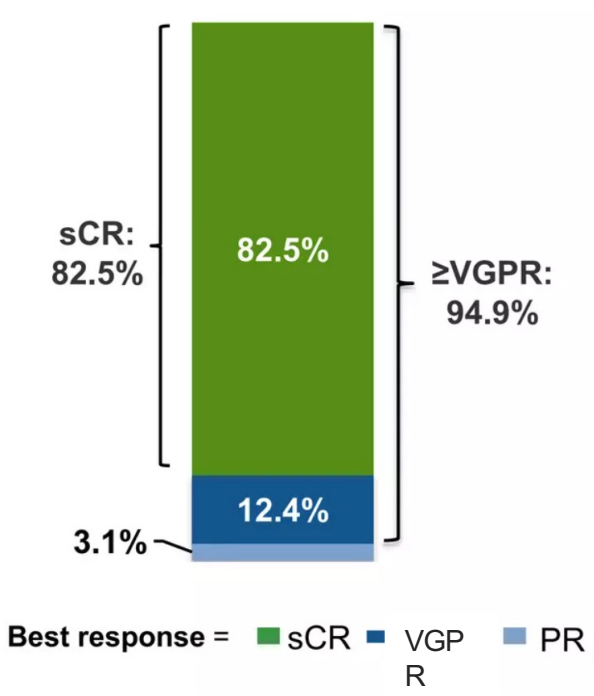
CARTITUDE-1: Efficacy



- Median time to first response was 1 month (range, 0.9–10.7)
- Median time to best response was 2.6 months (range, 0.9–17.8)
- Median time to CR or better was 2.9 months (range, 0.9–17.8)
- Median duration of response was not estimable (21.8 months–NE)

Responses deepened over time from the 1-year follow-up

Best response at any time	Median–1 year follow-up	Median–2 years follow-up
sCR, %	67	83

Martin T et al, ASCO 2021, Berdeja et al, Lancet 2021

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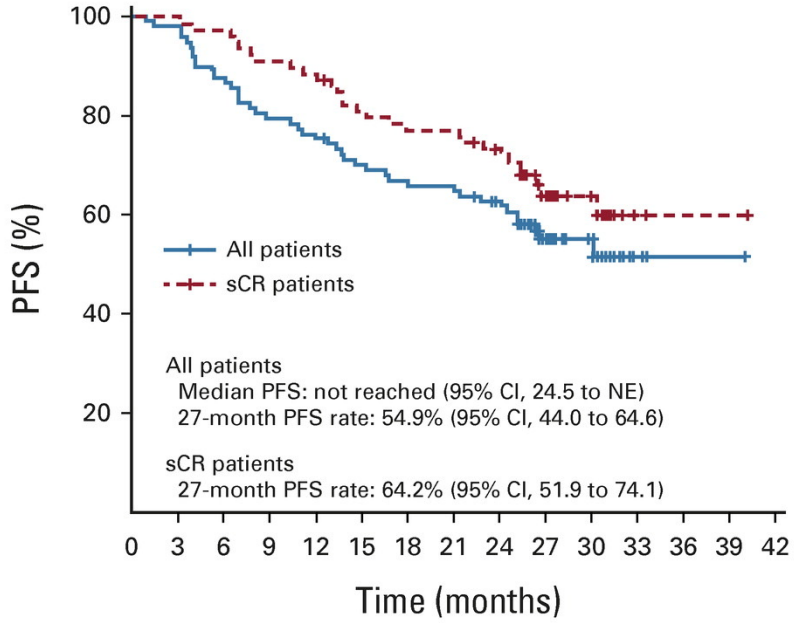
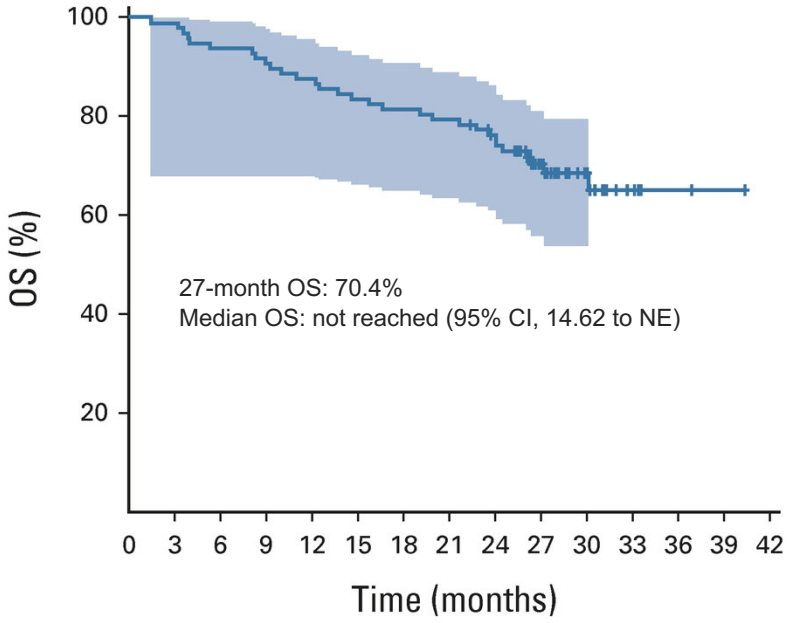
CARTITUDE-1: PFS and OS



No. at risk:

All patients	97	95	85	77	74	67	64	63	57	27	17	3	1	1	0
sCR patients	80	80	78	73	71	64	62	61	55	27	17	3	1	1	0



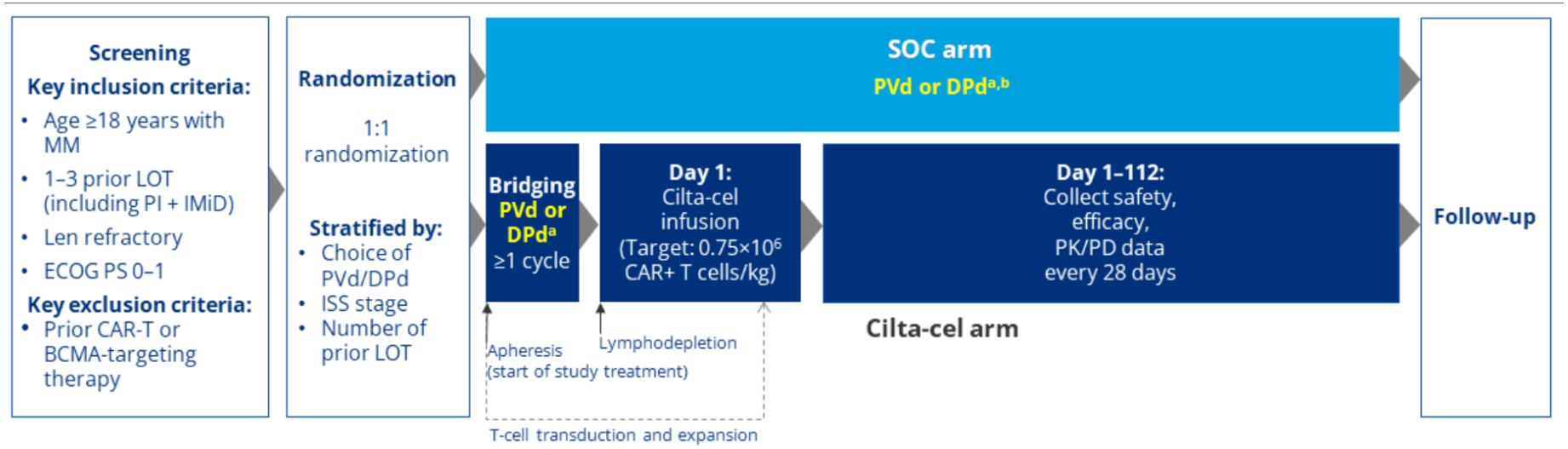
No. at risk:

	97	96	91	88	85	81	79	77	71	42	22	6	2	1	0

Martin T et al, J Clin Oncol 2023

Memorial Sloan Kettering Cancer Center

CARTITUDE-4: Cilta-cel or Standard of Care (PVd or DPd) in Lenalidomide-Refractory Multiple Myeloma



Primary endpoint
- PFS

Secondary endpoints
- Efficacy: ≥CR, ORR, MRD negativity, OS
- Safety
- PROs

Dhakal B et al. ASCO 2023. San-Miguel J et al. N Engl J Med 2023.

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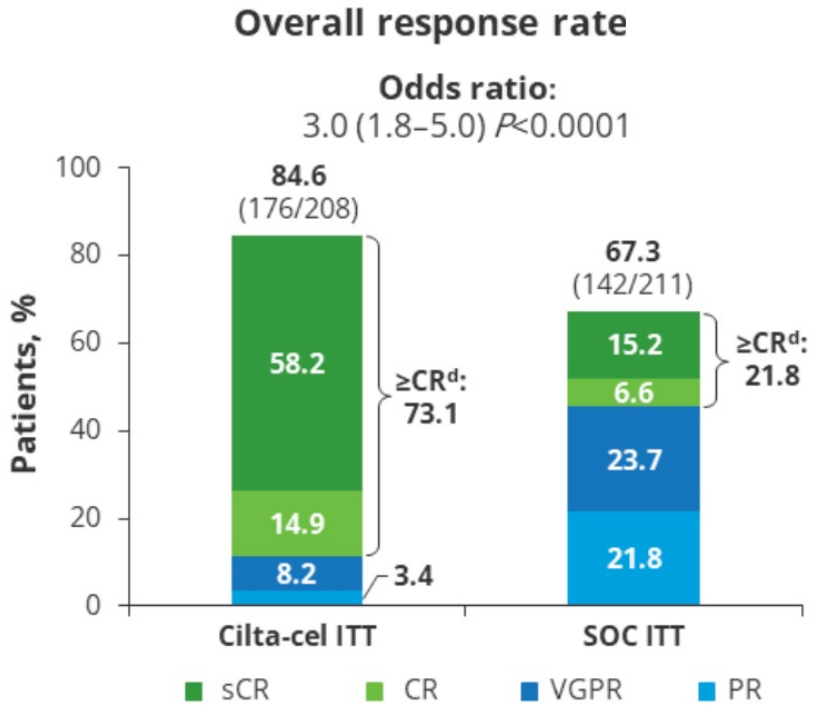
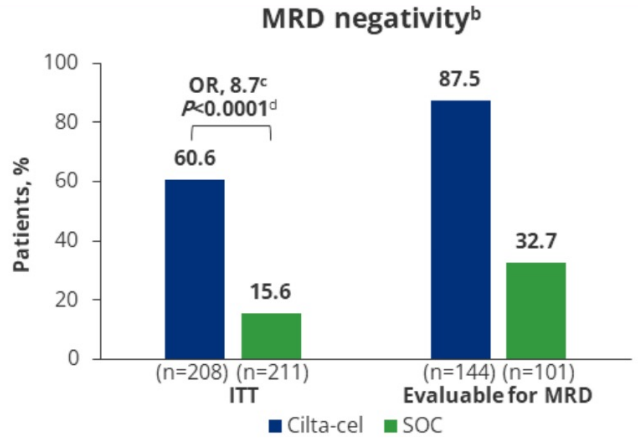
CARTITUDE-4: Cilta-cel or Standard of Care (PVd or DPd) in Lenalidomide-Refractory Multiple Myeloma



Outcome	Cilta-cel (N=208)	SOC (N=211)
12-month DOR rate, % (95% CI)	84.7 (78.1–89.4)	63.0 (54.2–70.6)
Duration of response, months median (95% CI)	NR	16.6 (12.9–NE)



Dhakal B et al. ASCO 2023. San-Miguel J et al. N Engl J Med 2023.

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CRS/Neurotoxicity Events with BCMA CAR T-cell Therapies

CRS and NT events were primarily grade 1/2 and manageable

	KarMMa[1] N = 128	CARTITUDE-1[2] N = 97
≥ 1 CRS event, n (%)	107 (84)	92 (95)
Grade 1/2	100 (78)	87 (95)
≥ Grade 3	7 (5)	5 (5)
Median onset (range), days	1 (1 – 12)	7 (1 – 12)
Median duration (range), days	5 (1 – 63)	4 (1 – 97)
≥ 1 NT event, n (%)	23 (18)	20 (21)
Grade 1/2	18 (12)	10 (10)
≥ Grade 3	5 (4)	10 (10)
ICANS any grade, %	-	17

Munshi et al. NEJM 2021; 384(8):705-716. Berdeja et al. Lancet 2021; 398:314

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RESEARCH SUMMARY

Teclistamab in Relapsed or Refractory Multiple Myeloma

Moreau P et al. DOI: 10.1056/NEJMoa2203478

CLINICAL PROBLEM

Effective therapies are lacking for relapsed or refractory multiple myeloma after standard treatment with immunomodulatory agents, proteasome inhibitors, and anti-CD38 antibodies. Teclistamab — a bispecific antibody that targets both CD3 expressed on the surface of T cells and B-cell maturation antigen expressed on myeloma cells — showed promising efficacy in a phase 1 dose-defining portion of the study.

CLINICAL TRIAL

Design: A phase 1–2, multinational study assessed the efficacy and safety of teclistamab in patients with relapsed or refractory multiple myeloma after at least three lines of therapy, including triple-class exposure to an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody.

Intervention: 165 adult patients received once-weekly subcutaneous injections of teclistamab at a dose of 1.5 mg per kilogram of body weight after receiving step-up doses of 0.06 mg and 0.3 mg per kilogram. The primary end point was overall response, which was defined as partial response or better according to International Myeloma Working Group criteria.

RESULTS

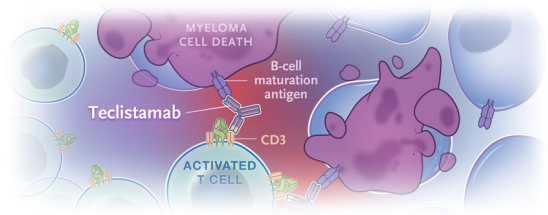
Efficacy: During a median follow-up period of 14 months, responses occurred in nearly two thirds of the patients, and complete responses in more than one third, despite extensive previous treatment. Responses were durable and deepened over time.

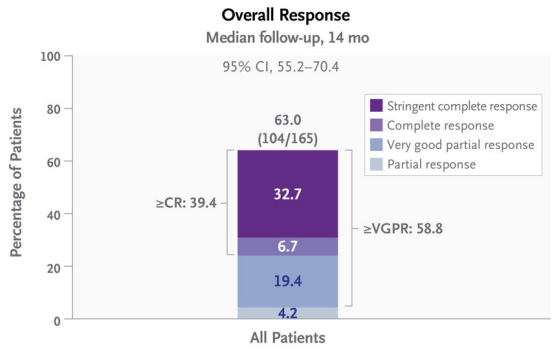
Safety: Adverse events occurred in all the patients, most of whom had a grade 3 or 4 event. Cytokine release syndrome (mostly low-grade), neutropenia, anemia, and thrombocytopenia were the most common adverse events, and infections were frequent. More than half the patients skipped a dose because of adverse events.

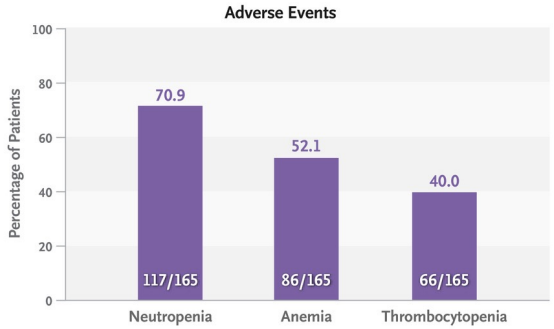
LIMITATION

- Comparison of teclistamab against other available therapies for relapsed or refractory multiple myeloma is limited to cross-trial comparisons.

Links: Full Article | NEJM Quick Take | Editorial







CONCLUSIONS

In patients with triple-class–exposed relapsed or refractory multiple myeloma, once-weekly subcutaneous teclistamab induced a high rate of lasting response.

The NEW ENGLAND JOURNAL of MEDICINE

RESEARCH SUMMARY

Talquetamab, a T-Cell–Redirecting GPRC5D Bispecific Antibody for Multiple Myeloma

Chari A et al. DOI: 10.1056/NEJMoa2204591

CLINICAL PROBLEM

Patients with triple-class–exposed relapsed or refractory multiple myeloma have a poor prognosis, and relapse is common even in those receiving the newest therapies. Talquetamab is a bispecific antibody that redirects T cells to mediate killing of myeloma cells expressing the receptor GPRC5D, which has not been previously targeted.

CLINICAL TRIAL

Design: A phase 1, open-label, multicenter, two-part study (part 1, dose-escalation phase; part 2, dose-expansion phase) evaluated the safety and efficacy of talquetamabin in order to select the recommended doses for a phase 2 study.

Intervention: 232 patients with heavily pretreated relapsed or refractory myeloma who had disease that had progressed with established therapies or who could not receive these therapies without unacceptable side effects received talquetamab intravenously (0.5 to 180 μg per kilogram of body weight, with or without step-up doses) or subcutaneously (5 to 1600 μg per kilogram, all with step-up doses). The primary end points included the frequency and type of dose-limiting toxic effects (study part 1 only) and adverse events. A key secondary end point was response.

RESULTS

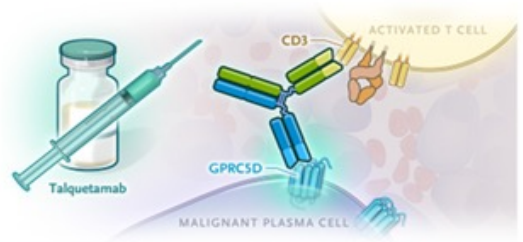
Safety: Four dose-limiting toxic effects occurred during dose escalation, including a grade 3 rash in a patient who had received talquetamab subcutaneously at a dose of 800 μg per kilogram every other week (one of the two phase 2 recommended doses). During a median follow-up of 11.7 months in the patients who received subcutaneous talquetamab at the 405-μg dose level and 4.2 months in those who received subcutaneous talquetamab at the 800-μg dose level, all patients had adverse events — most frequently cytokine release syndrome (grade 1 or 2 in all but one case), skin-related events, and dysgeusia. Most grade 3 or 4 adverse events were hematologic toxic effects.

Efficacy: Responses were substantial and deepened over time.

LIMITATIONS

- The dose groups included small numbers of patients.
- Follow-up times varied between the dose groups.

Links: Full Article | NEJM Quick Take | Science behind the Study

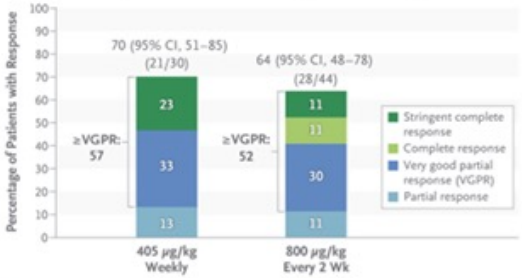


Adverse Events

Event	Talquetamab 405 μg Weekly (N=30)		Talquetamab 800 μg Every 2 Wk (N=44)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients (percent)			
Any adverse event	30 (100)	26 (87)	44 (100)	38 (86)
Cytokine release syndrome	23 (77)	1 (3)	35 (80)	0
Skin-related event*	20 (67)	0	31 (70)	1 (2)
Dysgeusia	19 (63)	NA	25 (57)	NA

* Skin-related adverse events included asteatotic eczema, dry skin, eczema, pruritus, exfoliation, fissures, hyperpigmentation, lesions, skin toxic effects, and ulcers. NA denotes not available.

Response to Subcutaneous Talquetamab Therapy



CONCLUSIONS

In patients with heavily pretreated relapsed or refractory myeloma, two different doses of subcutaneous talquetamab showed substantial antitumor effects and resulted in common adverse events of cytokine release syndrome, skin-related events, and dysgeusia that were primarily low grade.

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Summary of Trials With Bispecific Antibodies

	Teclistamab[1]	Elranatamab[2,3]	ABBV-383[4]	Linvoseltamab[5]	Talquetamab[6]	Cevostamab[7]
Target	BCMA	BCMA	BCMA	BCMA	GPCR5D	FcHR5
N	165	55	60	167 (all dose levels)	143 (QW dosing)	161
P2D	1500 µg/kg SC QW	76 mg SC QW	40 mg or 60 mg IV Q3W	200 mg IV QW, then Q2W	405 µg/kg SC QW 800 µg/kg SC Q2W	--
Prior lines, median (range)	5 (2-14)	5 (2-14)	5 (3-15)	6	5 (2-13)	6 (2-18)
Triple refractory, %	100	91	80	90	74	85
Penta refractory, %	70	--	--	--	29	68
Overall response, %	63	64	60	75 (at ≥ 200 mg)	73	57 (higher doses)
Complete response, %	39	38	29	38	29	8.4
DoR, mo	18.4 mo	17.1 mo	NR (median f/u: 8.4 mo)	NR	9.3 mo	11.5 mo
Infection, %	76	52	43	--	57	--
CRS, %	72	61	72	48	79	81
Neurotoxicity, %	15 (3 ICANS)	2.2 ICANS	--	--	10 ICANS	14.3 ICANS

1. Moreau. NEJM. 2022;387:495. 2. Raje. ASH 2022. Abstr 158. 3. Lesokhin. ASCO 2022. Abstr 8006.
4. Voorhees. ASH 2022. Abstr 1919. 5. Bumma. ASH 2022. Abstr 4555. 6. Chari. ASH 2022. Abstr 157. 7. Trudel. ASH 2021. Abstr 157.

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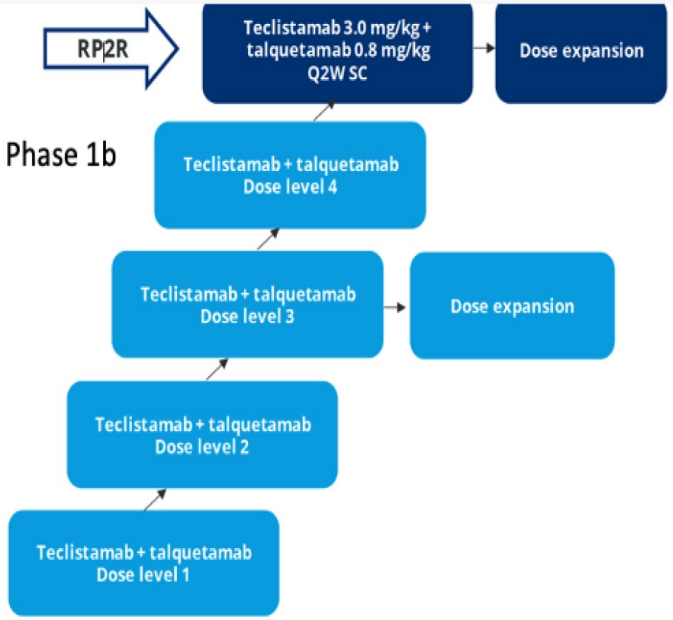
First Results From the RedirecTT-1 Study With Teclistamab + Talquetamab Simultaneously Targeting BCMA and GPRC5D in Patients With Relapsed/Refractory Multiple Myeloma

Yaël C Cohen[1], Daniel Morillo[2], Moshe Gatt[3], Michael Sebag[4], Kihyun Kim[5], Chang-Ki Min[6], Albert Oriol[7], Enrique M Ocio[8], Sung-Soo Yoon[9], María-Victoria Mateos[10], Michael P Chu[11], Paula Rodríguez-Otero[12], Irit Avivi[13], Yue Guo[14], Maria Krevvata[14], Michelle R Peterson[14], Melissa Beelen[14], Jill Vanak[14], Arnob Banerjee[14], Hila Magen[15]

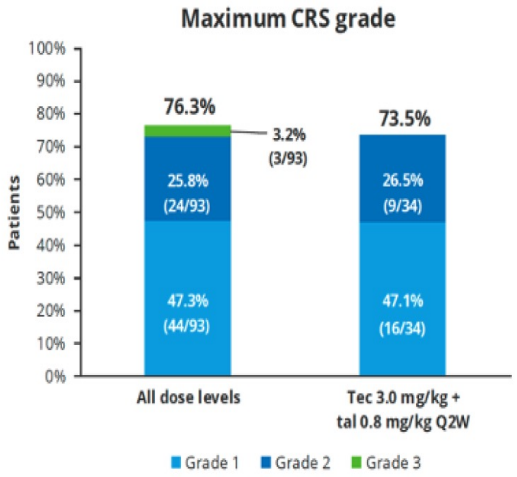


Eligibility
- TCE
- BCMA allowed

Characteristics
- 4 PLT, 80 refractory to last line
- 32% EMD
- 33% HR genetics

Toxicity
- Infection ~80% (Gr3/4 ~40-50%)
- CRS - ~75%
- ICANS ~4%

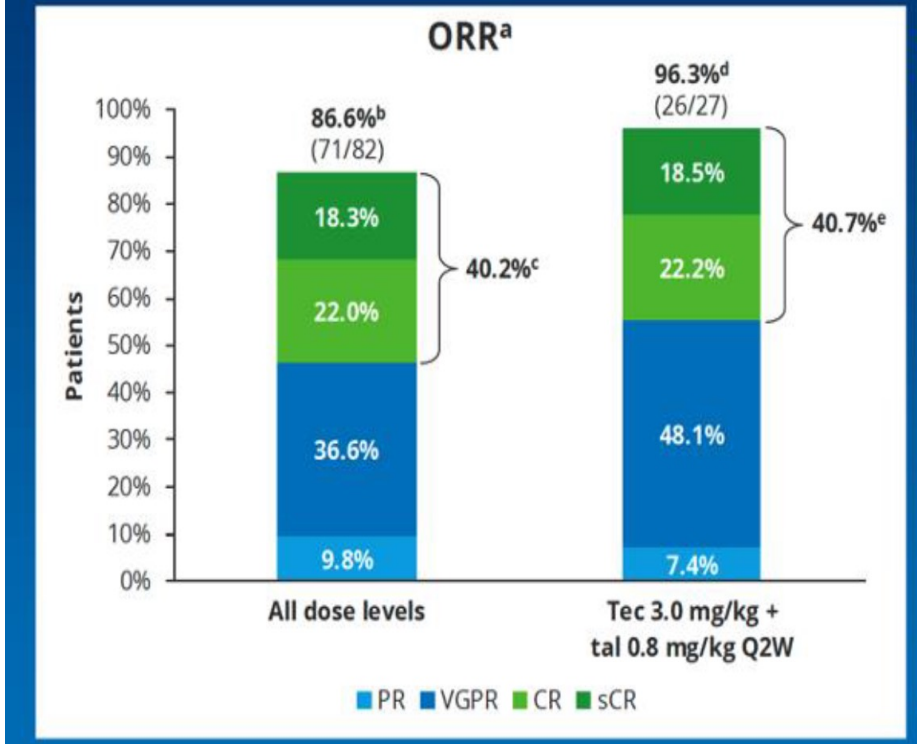
No unexpected tox
- Gr 3 >5%
  - Pneumonia
  - Fatigue
  - Heme Tox
    - Neutro
    - Plat
    - Anemia



Cohen et al. ASCO 2023

Memorial Sloan Kettering Cancer Center

RedirecTT-1: Efficacy



- ORR was high (86.6%) across all dose levels and 96.3% at the RP2R
- At data cut-off, 61% (57/93) of patients remained on treatment

	All dose levels (N=93)	Tec 3.0 mg/kg + tal 0.8 mg/kg Q2W (n=34)
Median follow-up, months (range)	13.4 (0.3–25.6)	8.1 (0.7–15.0)
Median DOR,[f] months (95% CI)	NE (NE–NE)	NE (NE–NE)
Median time to first response,[f] months (range)	1.97 (0–7.7)	1.48 (0–4.0)
Median time to best response,[f] months (range)	3.98 (1.1–15.7)	3.22 (1.4–10.7)
Median PFS,[g] months (95% CI)	20.9 (13.0–NE)	NE (9.9–NE)
9-month PFS rate[g] (95% CI)	70.1 (58.0–79.4)	77.1 (50.8–90.5)

Data cut-off date, March 16, 2023.
[a]Response was assessed by investigators, based on International Myeloma Working Group criteria; response-evaluable patients have received ≥1 study treatment and have ≥1 postbaseline response evaluation by investigator. [b]95% CI, 77.3–93.1%. [c]95% CI, 29.6–51.7%. [d]95% CI, 81.0–99.9%. [e]95% CI, 22.4–61.2%. [f]Includes patients with confirmed responses. [g]All treated patients. CR, complete response; DOR, duration of response; NE, not estimable; ORR, overall response rate; PFS, progression-free survival; PR, partial response; Q2W, every other week; RP2R, recommended phase 2 regimen; sCR, stringent complete response; VGPR, very good partial response.

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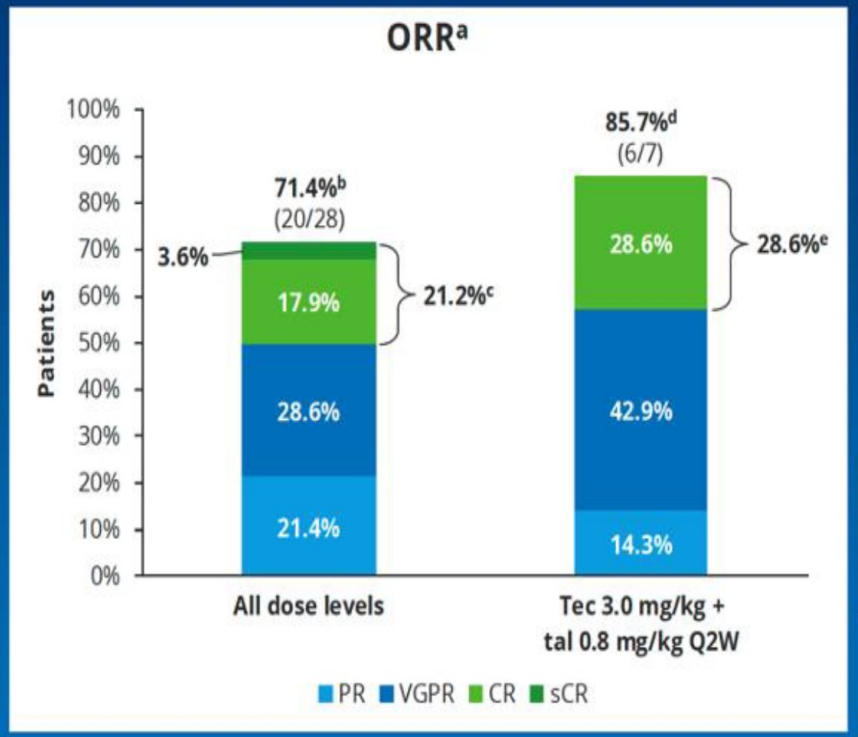
RedirecTT-1: High ORR in Extramedullary Disease



- All were soft tissue plasmacytomas
- At the RP2R (n=11):
  - Median follow-up, 7.2 mo (range 0.7–14.2)
  - 85.7% (6/7 evaluable) ORR
  - 28.6% (2/7 evaluable) ≥CR

	All dose levels (N=35)	Tec 3.0 mg/kg + tal 0.8 mg/kg Q2W (N=11)
Median DOR,[f] months (95% CI)	12.9 (4.17–NE)	NE (4.17–NE)
Median PFS,[g] months (95% CI)	6.1 (2.5–9.9)	9.9 (2.4–NE)

Data cut-off date, March 16, 2023.
[a]Response was assessed by investigators, based on International Myeloma Working Group criteria; response-evaluable patients have received ≥1 study treatment and have ≥1 postbaseline response evaluation by investigator. [b]95% CI, 51.3–86.8%. [c]95% CI, 8.3–41.0%. [d]95% CI, 42.1–99.6%. [e]95% CI, 3.7–71.0%. [f]Includes patients with confirmed responses. [g]All treated patients.
CR, complete response; DOR, duration of response; NE, not estimable; ORR, overall response rate; PFS, progression-free survival; PR, partial response; Q2W, every other week; RP2R, recommended phase 2 regimen; sCR, stringent complete response; VGPR, very good partial response.

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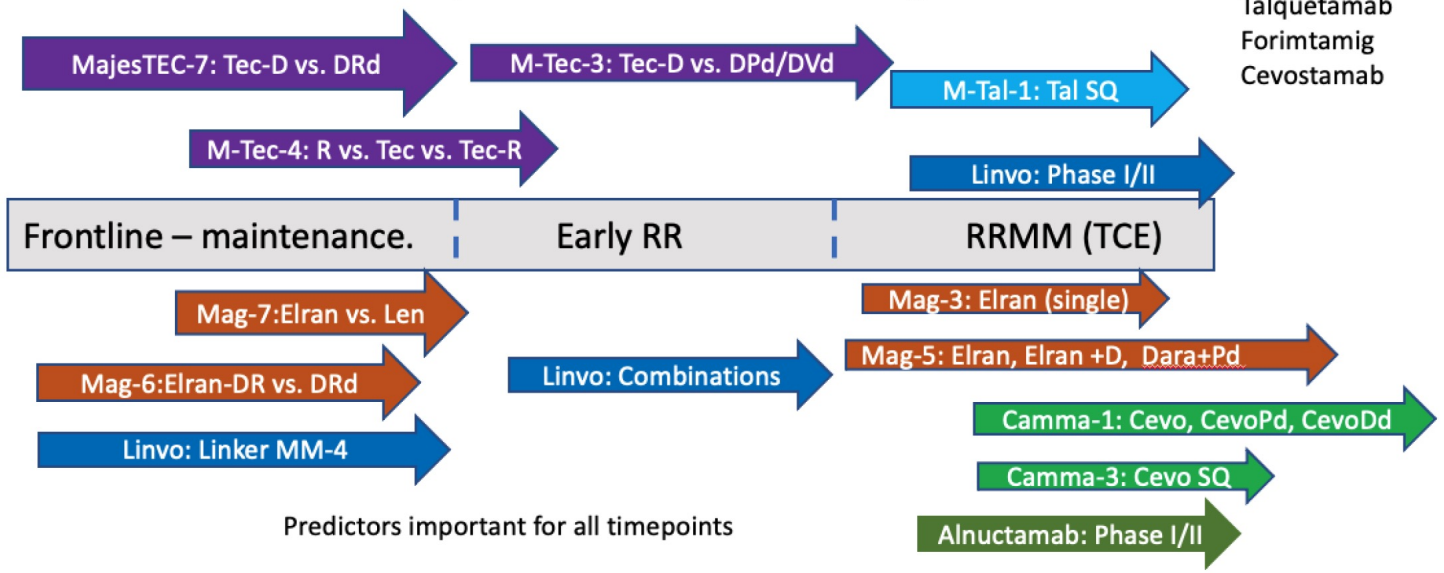
Immunotherapy Trials

Current and planned

- Myeloma Treatment Paradigm



BCMA
Teclistamab
Elranatamab
Linvoseltamab
Alnuctamab
ABBV-383
Non-BCMA
Talquetamab
Forimtamig
Cevostamab

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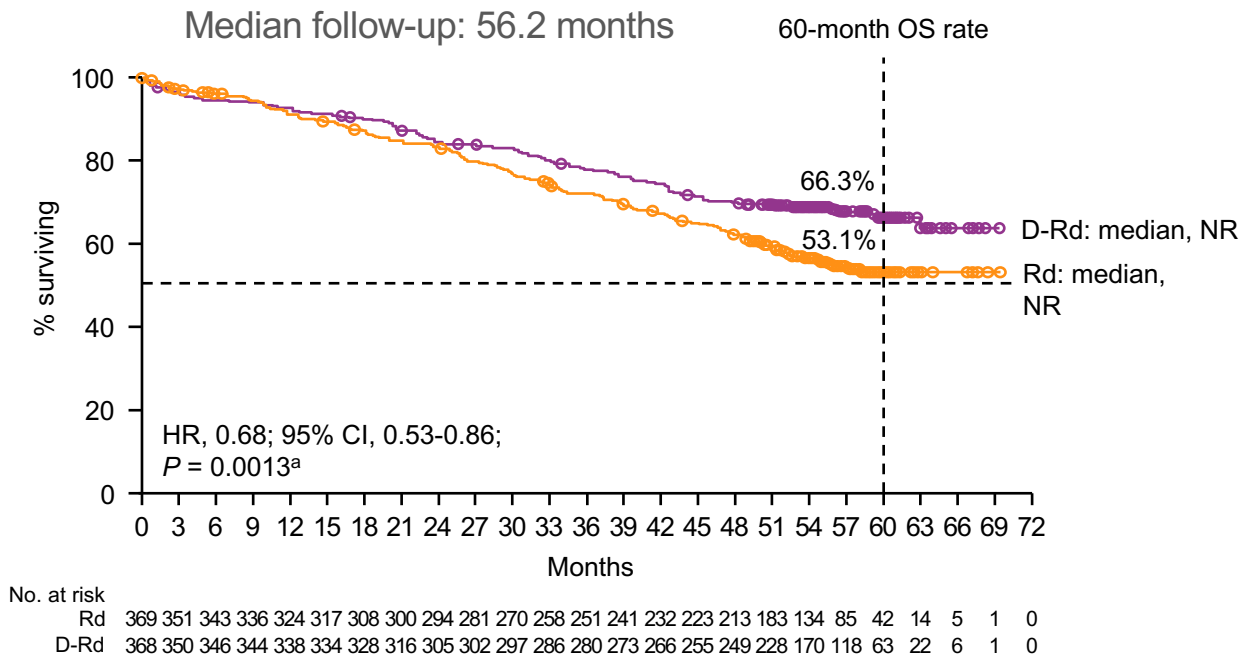
MAIA Phase III OS



D-Rd demonstrated a significant benefit in OS, with a 32% reduction in the risk of death, in patients with NDMM who are transplant ineligible

[a]*P* = 0.0013 is statistically significant, crossing the prespecified stopping boundary of *P* = 0.0414.

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Next Questions: Novel Immunotherapy, when?

Future treatment paradigms.....

SCT eligible

QUAD Induction (4-6 cycles) → CAR-T cell Vs. AutoSCT → Maintenance (CELMoD, Antibody)

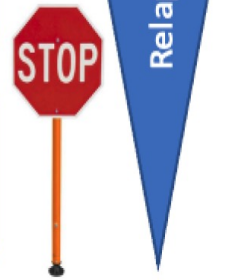
TI/CAR eligible

Tri/Quad Induction (4-6 cycles) → CAR BsAb + BsAb +/- partner → +/- Iber/BsAb Maintenance (1, 2 yr)

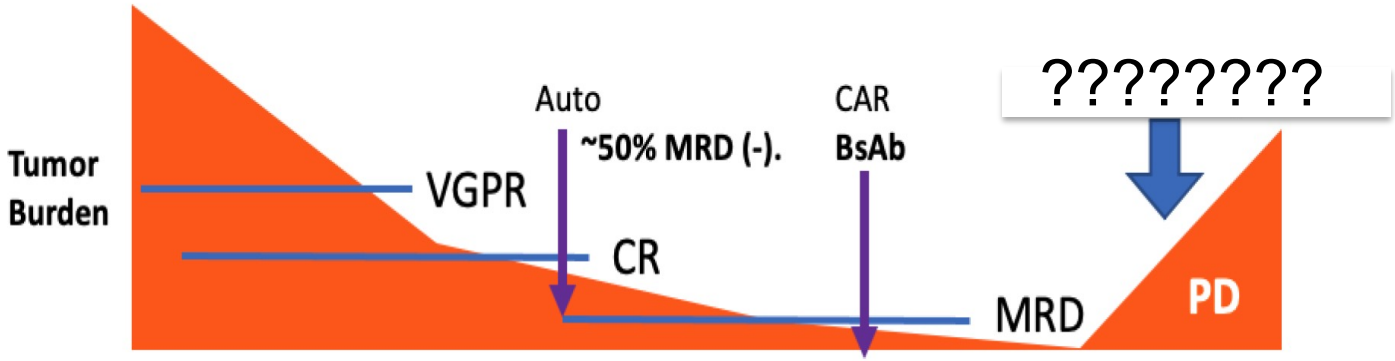
Frail

Triplet vs BsAb +/- partner(Cd38)

IMiD/CELMoD BsAb (different target)



- Trispecific
- AlloCAR
- NK CAR
- γδ CAR



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Conclusions

- The diagnosis, work up and treatment of myeloma has changed dramatically over the last 10 years.
- The therapeutic goal is to obtain deep remissions that translate into improved PFS and OS
- With combination therapy of IMIDS, Pis, MoAbs, BITES, autologous and allogeneic HCT as well as CAR T cells long term disease control and cures will be achievable in a substantial proportion of patients with MM.

MSKCC Myeloma Service

Saad Z. Usmani (Chief)
MM Immunotherapy
High-Risk Disease
Biology/Trials
Bispecific Antibodies
CAR T Cells
Checkpoint Inhibitors
Developmental Therapeutics

Sham Mailankody
MM
Immunotherapy
CAR T Cells

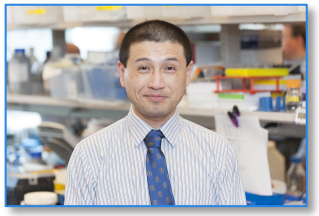
Malin Hultcrantz
MM Precursor Disease
Antibody drug conjugates
Genetics/MRD

Urvi Shah
Early Relapse
MM Precursor
Disease
Nutrition /CAR T cells

Alex Lesokhin
MM Immunotherapy
Bispecific Antibodies
Checkpoints Inhibitors
Neoantigens
Microbiota

Hani Hassoun
MM Supportive Care
Alliance Liaison
NDMM/RRMM Trials
Elderly and Frail

Neha Korde
NDMM Clinical Trials
MRD Directed therapy
Supportive Care



Sydney Lu
New molecular pathways
Mechanisms of resistance

Carlyn Tan
MM Precursor diseases
Supportive Care

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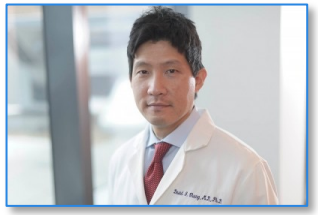
MSKCC Myeloma TCT Program

Sergio Giralt
Allo/Auto HCT for MM
New Regimens
CAR T Cells

David Chung
T Cell exhaustion
Auto HCT + Vaccines
MM Immunotherapies



Gunjan Shah
HCT Toxicities
Precision Drug Dosing
CAR T Cells
Salvage Auto and Allo HCT

Saad Z. Usmani
High-Risk Disease Biology/Trials
CAR T Cells
Auto HCT for MM

Michael Scordo
HCT Toxicities
Precision Drug Dosing
CAR T Cells

Heather Landau
Amyloidosis
HCT Toxicities
Homebound HCT
Precision Drug Dosing
Novel Regimens for Salvage Auto

Oscar Lahoud
Auto HCT and CAR T Cells
Post HCT Therapies

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Questions?

giralts@mskcc.org

7135045082