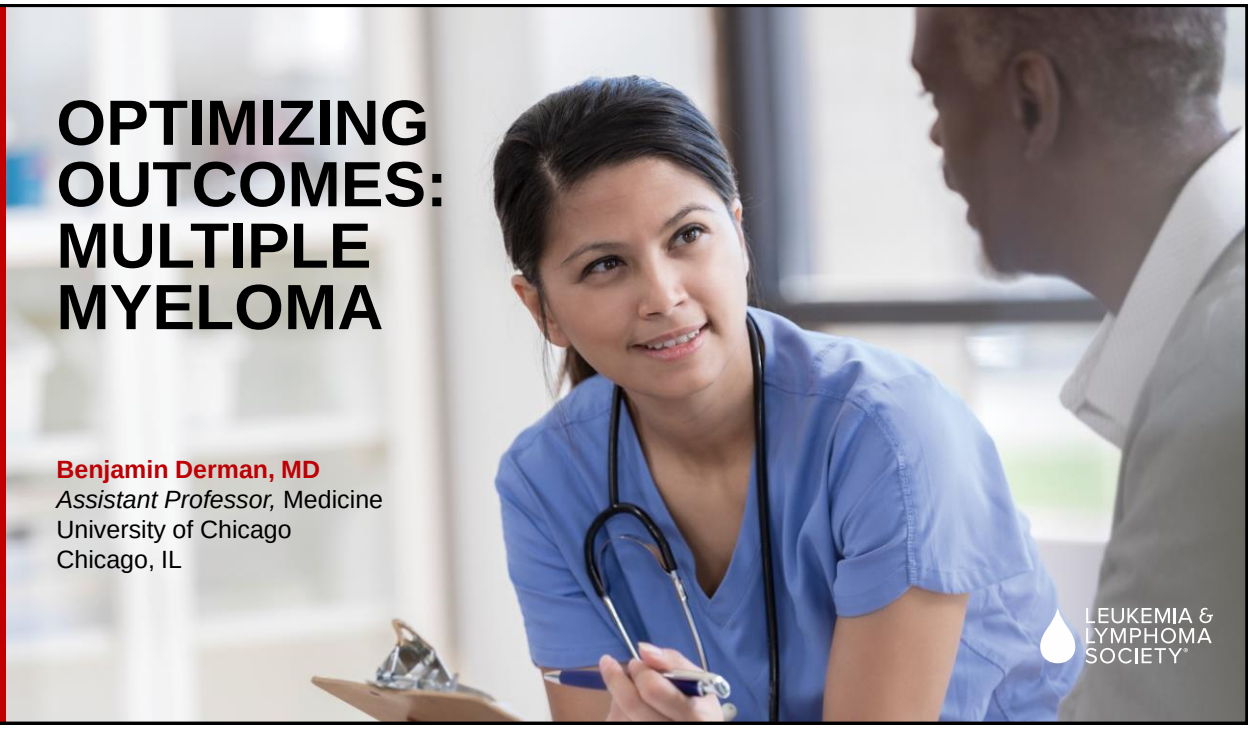
OPTIMIZING OUTCOMES: MULTIPLE MYELOMA



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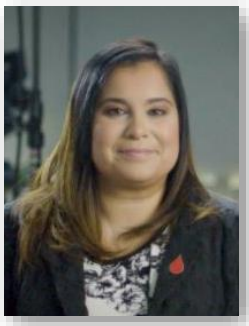
WELCOMING REMARKS

OPTIMIZING OUTCOMES: MULTIPLE MYELOMA



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OPTIMIZING OUTCOMES: MULTIPLE MYELOMA

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AT THE FOREFRONT
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What's New in Multiple Myeloma?

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October 25, 2023

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Disclosures

I declare advisory board fees Janssen and COTA, Inc.

I am an independent reviewer of a clinical trial for BMS.

I will be discussing off label and/or investigational use of therapies.

Objectives

- **Smoldering Myeloma**
  - To Treat or Not to Treat?
- **Newly Diagnosed Multiple Myeloma**
  - Quadruplets for all?
  - Stem cell transplant for all?
  - MRD as a decision aid?
- **Relapsed/Refractory Multiple Myeloma**
  - Bispecific antibodies
  - CAR T-cell therapy

Multiple Myeloma Diagnostic Criteria

MGUS	Smoldering Myeloma	Multiple Myeloma
• M protein < 3 g/dL • Clonal plasma cells in BM < 10% • No myeloma defining events	• M protein ≥ 3 g/dL (serum) *OR* ≥ 500 mg/24 hrs (urine) *AND/OR* • Clonal plasma cells in BM ≥ 10% - 60% *AND* • No myeloma defining events	• Underlying plasma cell proliferative disorder *AND* 1 or more myeloma defining events • ≥ 1 CRAB* feature • Clonal plasma cells in BM ≥ 60% • Serum free light chain ratio ≥ 100 • >1 MRI focal lesion ≥ 5mm

*__C__: Calcium elevation (> 11 mg/dL or > 1 mg/dL higher than ULN)
__R__: Renal insufficiency (creatinine clearance < 40 mL/min or serum creatinine > 2mg/dL)
__A__: Anemia (Hb < 10 g/dL or 2 g/dL < normal)
__B__: Bone disease (≥ 1 lytic lesions on skeletal radiography, CT, or PET-CT)

Rajkumar SV, et al. *Lancet Oncol.* 2014;15:e538-e548.
NCCN. Clinical Practice Guidelines in Oncology: Multiple Myeloma. (NCCN Guidelines®).

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Epidemiology of MGUS and SMM

Driven by MGUS

- **Risk increases with age**
- **More common in males**
- **Higher in African Americans (3x)**
  - **Risk of progression to MM =**
- **Higher if first-degree relatives (2.6x)**

Study	Prevalence of MGUS	Prevalence of Smoldering Myeloma
Kyle et al. NEJM 2006 (Mayo)	50-59: 1.7% ≥ 70: 5.3% ≥ 85: 7.5%	NR
iSTOPMM (Iceland)*	40-59: 2.3% 60-79: 6.2% ≥ 80: 12.3%	≥ 40: 0.53% ≥70: 1.08% ≥80: 1.59%
PROMISE (US, 'at-risk' group)^	40-49: 6% 50-59: 11% 60-69: 15% 70-79: 18% ≥80: 26%	NR

Kyle et al. N Engl J Med 2006; 354:1362-1369
Landgren et al. Blood; 2006 Feb 1;107(3):904-6
Landgren et al. Mayo Clin Proc; 2007 Dec;82(12):1468-73
Vachon et al. Blood; 2009 Jul 23;114(4):785-90

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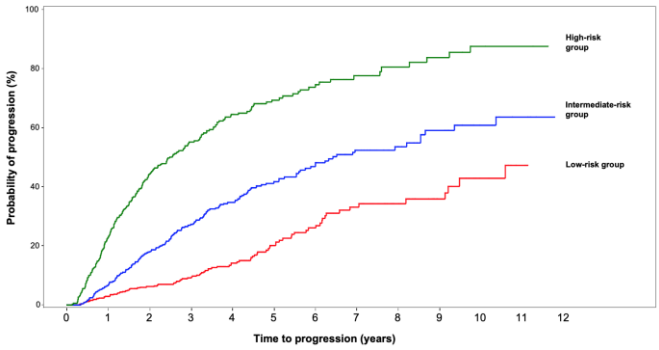
*Kristinsson et al. ASH 2021; abstract 156
*Thorsteinsdottir et al. ASH 2021; abstract 151; Nature Medicine 2023
^ El-Khoury et al. The Lancet Haematology 2022

2/20/20 Score

2/20/20 Score		
Risk Factors for SMM Progression	BM plasma cells > 20% M-protein > 2 g/dL sFLC ratio >20	
Risk Category (# of risk factors)	**Median Time to progression**	**Progression at 2 years**
Low (0)	110 months	10%
Intermediate (1)	68 months	26%
High (2-3)	29 months	47%

IMWG Validation



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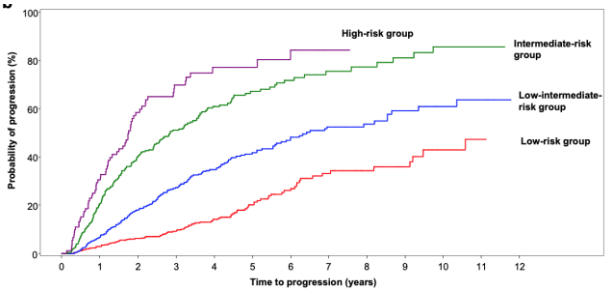
Lakshman et al. *BCJ* 2018 Jun 12;8(6):59
Mateos et al. *BCJ* 2020 Oct; 10(10): 102.

IMWG Logistic Regression Score

IMWG Score				
Score	**sFLC Ratio**	**M-protein (g/dL)**	**BM PC %**	**FISH studies**
0	0-10	0-1.5	0-15	
2	>10-25		>15-20	t(4;14), t(14;16), +1q, or del13q
3	>25-40	>1.5-3	>20-30	
4		>3		
5	>40		>30-40	
6			>40	



Risk Category (score)	Score	Progression at 2 years
Low	0-4	4%
Low-Intermediate	5-8	26%
Intermediate	9-12	51%
High	>12	73%

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Mateos et al. *BCJ* 2020 Oct; 10(10): 102

PANGEA Model: Another Way to Assess SMM

Example: BMBx 25%, sFLC ratio 30, M-spike 2.3 g/dL, creatinine 1, hgb 13

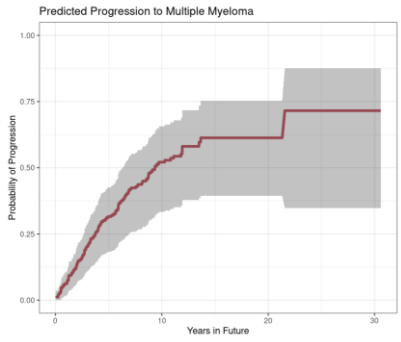
2/20/20 risk: mTTP 29 mos.

IMWG risk: 51% risk @ 2 yr

PANGEA Model:

Factors in plasma cell %, sFLC ratio, M-spike, creatinine, hemoglobin

Years in Future	Probability of Progression
1	6.2%
2	13.4%
5	31.6%
10	52.1%



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Reasons to Consider Treating (High-Risk) Smoldering Myeloma

- **Avoid end-organ damage from myeloma between visits**
- **Two studies showed that Lenalidomide increased the time to death or progression (PFS) compared to observation.**
- **One study showed lenalidomide increased survival (caveat: included old definition of SMM)**
- **Might we cure patients if treating earlier?**

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Responses with Len and Progression in Observation Arm

How many patients respond deeply to lenalidomide?

≥ Partial response: 50% (4% ≥ VGPR)

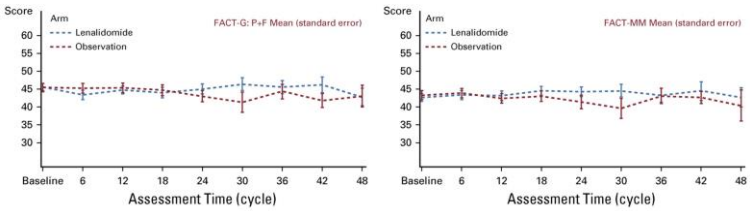
How many patients in observation arm had clinical progression?

Variable	Phase II Run In: Lenalidomide (n = 6 PD cases)	Phase III Randomized Trial: Lenalidomide (n = 7 PD cases)	Phase III Randomized Trial: Observation (n = 21 PD cases)	Phase III Randomized Trial: Total (n = 28 PD cases)
End organ				
Hypercalcemia	0 (0.0)	0 (0.0)	1 (4.8)	1 (3.6)
Anemia	2 (33.3)	4 (57.1)	8 (38.1)	12 (42.9)
Renal failure	0 (0.0)	0 (0.0)	3 (3%)	3 (10.7)
Bone lesion/soft-tissue plasmacytoma	4 (66.7)	3 (42.9)	11 (12%)	14 (50.0)

Unknown severity of renal failure
Unknown % with fractures

Is quality of life improved with lenalidomide?

No



Lonial et al. *JCO* 2020

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Reasons NOT TO Treat Smoldering Myeloma

- **Most patients in surveillance don't get end-organ damage**
  - **ECOG E3A06**: Only 12% in obs arm had bony disease & 3% w/kidney failure
- **Most patients had <50% response with Lenalidomide**
  - And only 50% achieved a response!
- **Quality of life was not improved with lenalidomide**
  - **ECOG E3A06:** >50% discontinued because of adverse events or withdrawal
- **Contemporary SMM patients differ from Mayo 2/20/20**
  - iSTOPMM: Median M-spike 0.62 g/dL vs 2 g/dL in Mayo cohort
  - iSTOPMM: Only 8% high-risk by 2/20/20 model
- **Smoldering myeloma is a genetically mature disease**
  - Most of the genetic changes in MM have already occurred in SMM
  - Do we really expect more cures? Need a curative strategy...

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GEM-CESAR

Eligibility (n = 90)

High-Risk SMM:
** M-spike ≥3 g/dL AND BMPC ≥ 10%
** M-spike ≥ 3 or BMPC ≥10% AND >95% aberrant PCs

Induction
6 x 28-Day Cycles
KRd
Carfilzomib
Lenalidomide
Dexamethasone

High-dose melphalan 200 mg/m^2 followed by **ASCT**

Consolidation
2 x 28-Day Cycles
KRd
Carfilzomib
Lenalidomide
Dexamethasone

Maintenance
24 x 28-Day Cycles
Rd
Lenalidomide
Dexamethasone

Included SLiM patients:
- **FLC ratio >100**: 33%
- **>1 focal lesion on MRI**: 20%
- **≥60% BMPC**: 8%

Patients with bone disease on CT or PET/CT at screening were excluded

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Mateos ASH 2022. Abstr 118. 15

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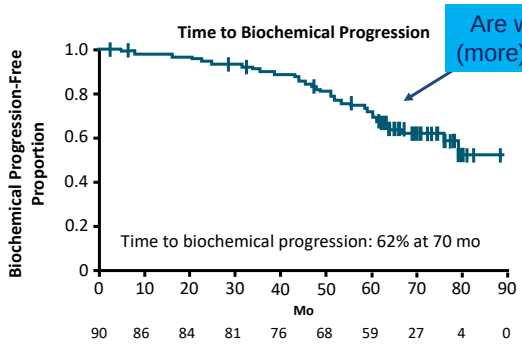
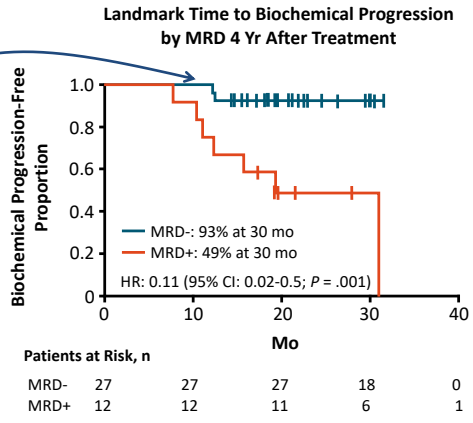
GEM-CESAR: MRD Status at 4 Years

Undetectable MRD, n (%)	4 Yr After ASCT (n = 58)
MRD negative at 10^{-5}	25 (43%)
MRD negative at 10^{-6}	28 (48%)

Evaluable patients included those discontinued earlier than the specific time point due to progressive or biochemical progressive disease.



Are we curing (more) patients?



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Mateos. ASH 2022. Abstr 118. 16

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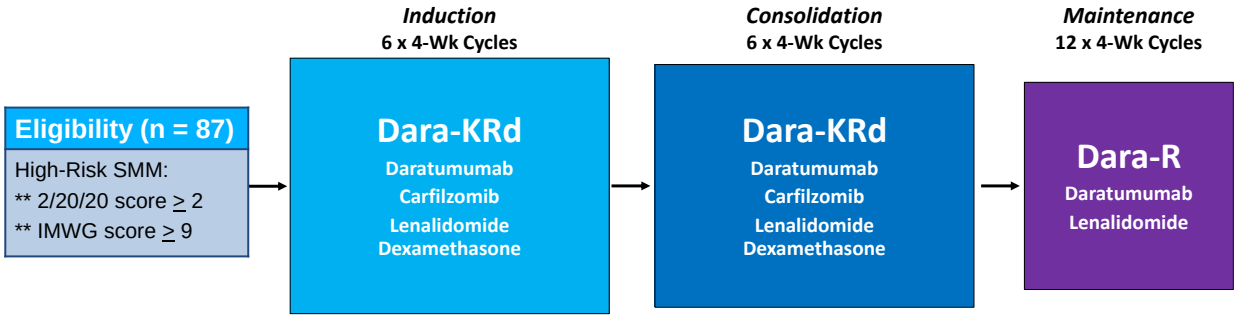
ASCENT



Patient Population	n (%)
IMWG 2/20/20 high-risk, n (%) ▪ M spike >2 g/dL ▪ FLC ratio >20 ▪ BMPCs >20%	59 (68%) 63 (72%) 27 (31%) 64 (74%)
IMWG score ≥9, n (%)	28 (32%)

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Kumar. ASH 2022. Abstr 757. NCT03289299. 17

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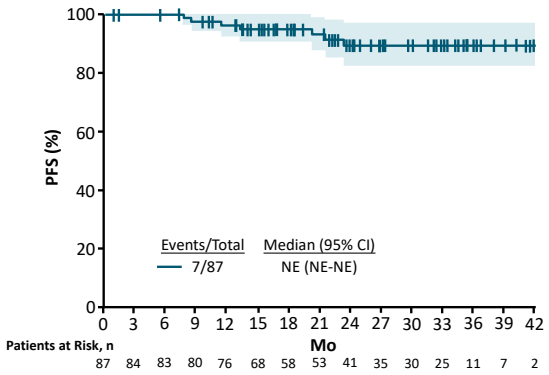
ASCENT: Responses

Median follow-up 26 months

- ***Response rate: 97%***
- ***Complete response: 64%***
- ***MRD negativity: 84% (n=73)***
- ***3-yr PFS rate: 89.9% (95% CI: 82.3%-98.3%)***



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Kumar. ASH 2022. Abstr 757. 18

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A Tale of Three High-Risk SMM Patients

55 year old female
- 40% BMPC
- M-spike 2.7 g/dL
- FLC ratio 30
- No high-risk cyto

65 year old female
- 50% BMPC
- M-spike 3 g/dL
- FLC ratio 25
- t(4;14)

74 year old male
- 30% BMPC
- M-spike 2 g/dL
- FLC ratio 45
- p53 deletion

All received ASCENT regimen

MRD-negative after 6 cycles Withdrew due to preference	MRD-negative at EOT	Best response VGPR at EOT Progressed → ASCT

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Ongoing Studies in Smoldering Myeloma

RANDOMIZED

Trial Identifier Primary Endpt	Intervention Arm	Control Arm
NCT04270409 (est. n=300) PFS	Isatuximab-Rd	Rd
DETER-SMM (est. n=288) OS/QoL	Daratumumab-Rd	Rd
AQUILA (est. n=390) PFS	Daratumumab	Observation
HO147SMM (est. n=120) PFS	KRd/R	Rd/R

NONRANDOMIZED

Trial Identifier	Intervention Arm
ASCENT	Dara-KRd x 12 → Dara-Rd x 12
GEM-CESAR	KRd x 6 → MEL/ASCT→KRd x 2 → Rd x 2 yr
CAR-PRISM	Cilta-cel
B-PRISM	Dara-VRd x 24
E-PRISM	Elo-Rd → Elo/R
NCT01572480	KRd x 8 → R x 12-24
NCT02960555	Isatuximab x 30
NCT02916771	Ixazomib-Rd x 9→ Ixa-R x 15
NCT04776395	Iberdomide

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Newly Diagnosed Multiple Myeloma

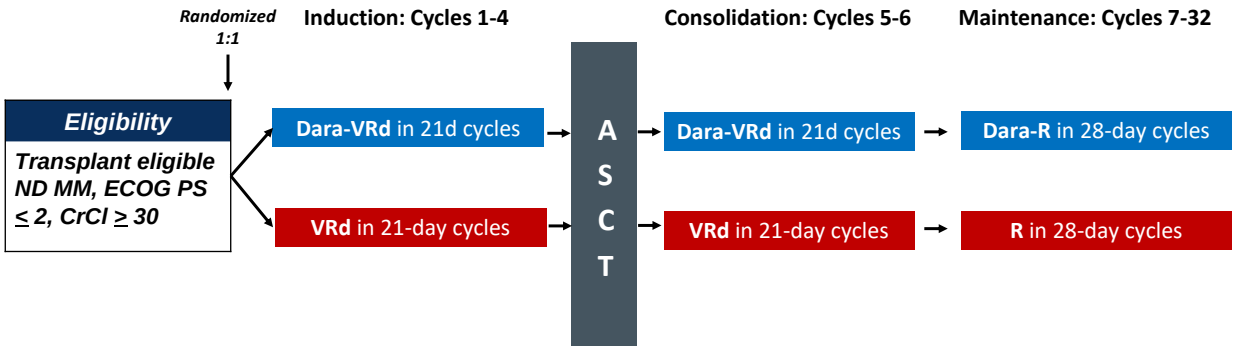
Myeloma Alphabet Soup

	Immunomodulatory Imides	Proteasome Inhibitors	Monoclonal antibodies	Alkylating Agents	Nuclear Exports	Bispecific antibodies	CAR T-Cell Therapy
Mechanism of Action	Binds to cereblon, and targets *of Ikaros & Aiolos for proteolysis*	Decreases degradation of misfolded proteins and pro-apoptotic factors	Anti-CD38 (Dara, Isa) and Anti-SLAMF7 (Elo) mAbs	Cross-link strands of DNA, leading to DNA strand breaks and abnormal base pairing	Inhibits XPO1, reactivates tumor suppressor proteins	Bind to CD3 on T-cells and target on myeloma cells	Adoptive T-cell therapy targeted toward specific antigens on cell surface (BCMA)
Drugs in Class	Lenalidomide (R) Pomalidomide (P)	Bortezomib (V) Carfilzomib (K) Ixazomib (I)	Daratumumab (Dara) Elotuzumab (Elo) Isatuximab (Isa)	Cyclophosphamide (Cy) Melphalan	Selinexor (S, X)	Teclistamab Elranatamab Talquetamab	Ide-cel Cilta-cel
Side Effects	Diarrhea (R>P) Cytopenias (P>R) Blood clots Birth defects 2nd Cancers	V: Neuropathy K: HTN, heart failure I: Neuropathy	Infusion reactions Infection	Cytopenias (more pronounced)	Cytopenias Fatigue (extreme) Diarrhea	Infections Cytopenias Skin/nail (talq) Taste (talq)	CRS ICANS HLH/MAS Cytopenias

d=dexamethasone (basic but has anti-myeloma effects)

GRIFFIN: Dara-VRd vs VRd (+ ASCT)

Trial Identifier: NCT02874742
Randomized in Induction: 207



Primary endpoint: sCR by end of consolidation with 1-sided α = 0.1
Secondary endpoints: MRD-negativity (NGS <10^{-5}), CR, ORR, > VGPR

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Voorhees et al *Blood* 2020 23

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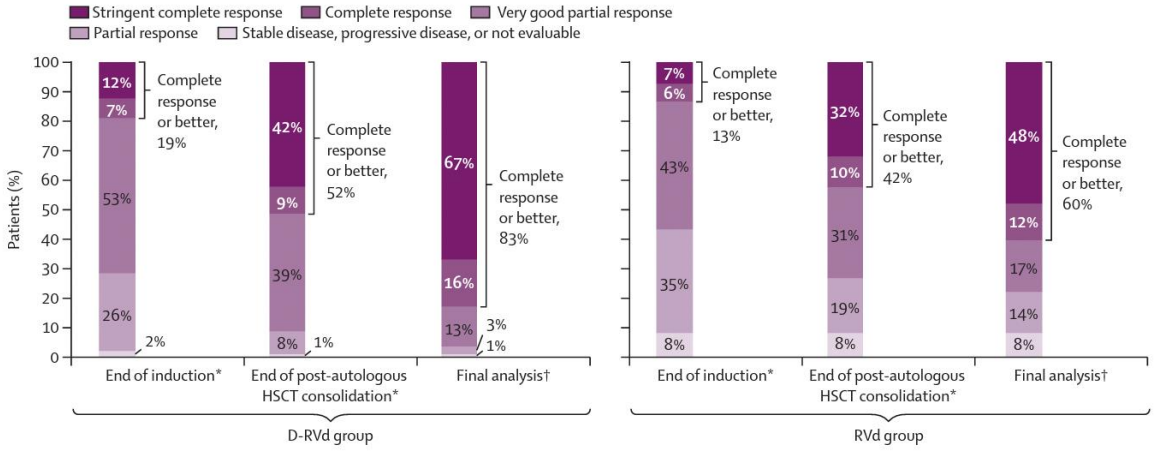
GRIFFIN: Primary Endpoint Was NOT Met…



sCR rate after transplant/consolidation: 42% vs 32% (hypothesis was 15% absolute difference)

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Voorhees et al. *Lancet Haematology* 2023 24

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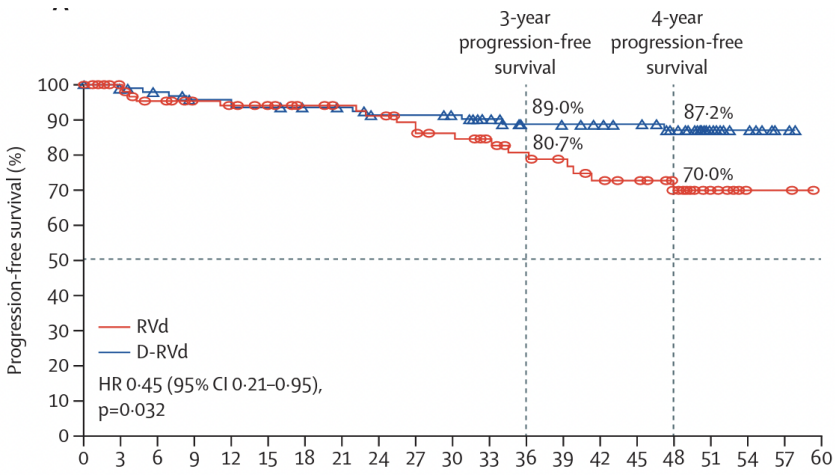
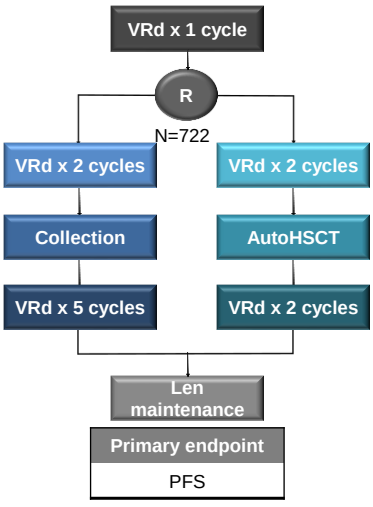
GRIFFIN: Progression Free Survival Favors Dara-VRd

PFS = time to progression or death

****This was not the main objective of the trial****



DETERMINATION: Early vs Delayed Stem Cell Transplant

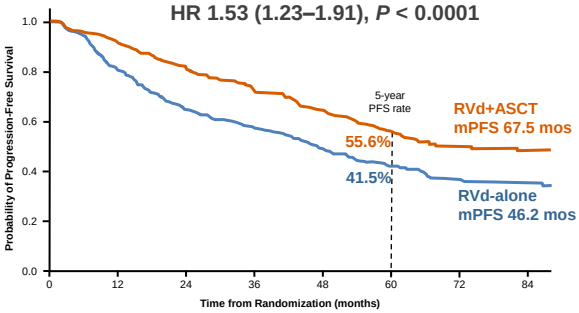


Outcome	VRd (n = 357)	AutoHSCT (n = 365)	*P*-Value
Response (%)			
PR or better	90	97.5	0.55
CR or better	42	46.8	0.99
MRD negative (10^{-5})	39.8	54.4	OR 0.55 (95% CI, 0.3 – 1.01)
Median duration of response	38.9m	56.4 m	HR, 1.45 (0.95% CI, 0.3 – 1.01)
Secondary primary malignancy	10.4%	10.7%	

DETERMINATION: Early Transplant Improved PFS, not OS

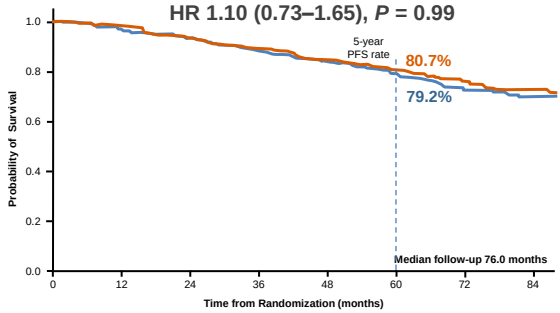
Progression-Free Survival

HR 1.53 (1.23–1.91), *P* < 0.0001



Overall Survival

HR 1.10 (0.73–1.65), *P* = 0.99



mPFS (months)	VRd	VRd + AutoHSCT	Hazard ratio
All	46.2	67.5	1.53 (95% CI 1.23–1.91)
Standard risk	53.2	82.3	1.38 (95% CI 1.07–1.79)
High risk	17.1	55.5	1.99 (95% CI 1.21–3.26)

Only 28% of patients on the VRd alone arm eventually underwent autoHSCT – authors attribute lack of OS difference to availability of novel therapies

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Richardson, et al. *NEJM.* 2022.

Patients with 2+ High-risk Features Need Better Therapies

Trial	Regimen	Estimated 3-year PFS
GRIFFIN (Dara-VRd)[2]	Dara-VRd x 4 → ASCT → Dara-VRd x 2 → Dara-R x 26	94% for 0 HRCA 91% for 1 HRCA **54% for 2+ HRCA**
MASTER[3]	Dara-KRd x 4 → ASCT → up to Dara-KRd x 8 → Off treatment	88% for 0 HRCA 79% for 1 HRCA **50% for 2+ HRCA**
OPTIMUM MUKnine[4]	Dara-CVRd x 6 → ASCT → Dara-VRd x 6→ Dara-VR x 12→Dara-R until progression	~75% overall
IFM 2018-04[5]	Dara-KRd x 6→ ASCT #1 → Dara-KRd x 4 → ASCT #2 → Dara-R x 2 years	~70% overall
GMMG-CONCEPT (ASCT-eligible)[6]	Isa-KRd x 6 → ASCT → Isa-KRd x 4 → Isa-KR x 26	69% overall 70% for 1 HRCA **55% for 2+ HRCA**
SWOG S1211 (Elo-VRd)[7]	Elo-VRd indefinitely	~45% overall
Elo-KRd[8]	Elo-KRd x 8 → MRD-guided Elo-KRd or Elo-Rd indefinitely	86% for 0 HRCA 61% for 1+ HRCA

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Key Takeaways from GRIFFIN and DETERMINATION

- ***Quadruplet therapy appears to be associated with improved PFS over triplet therapy, regardless of disease risk.***
- ***Transplant may still carry benefit for the right patient, especially those with high-risk disease.***
- ***Patients with 2 or more high risk cytogenetic abnormalities need better therapies!***

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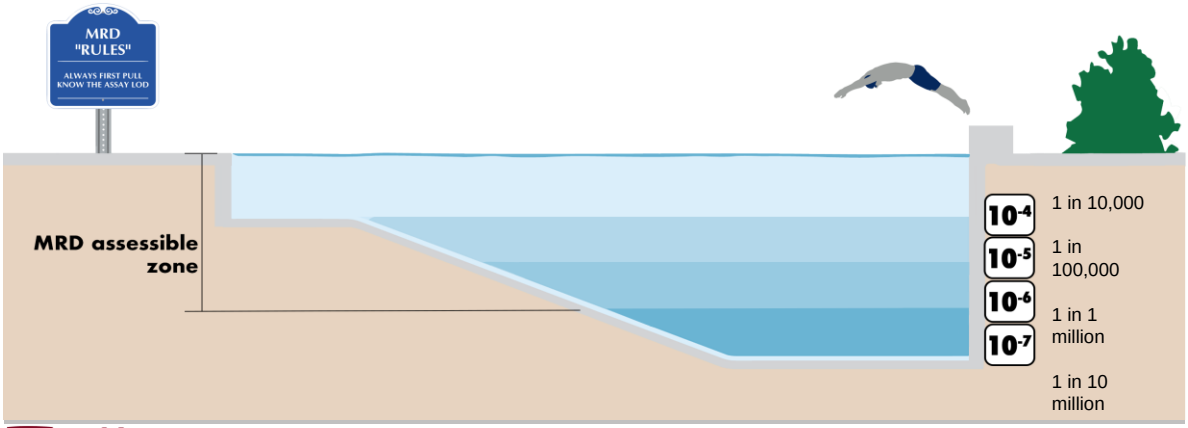
MRD = Measurable Residual Disease

MRD = low levels of cancer cells



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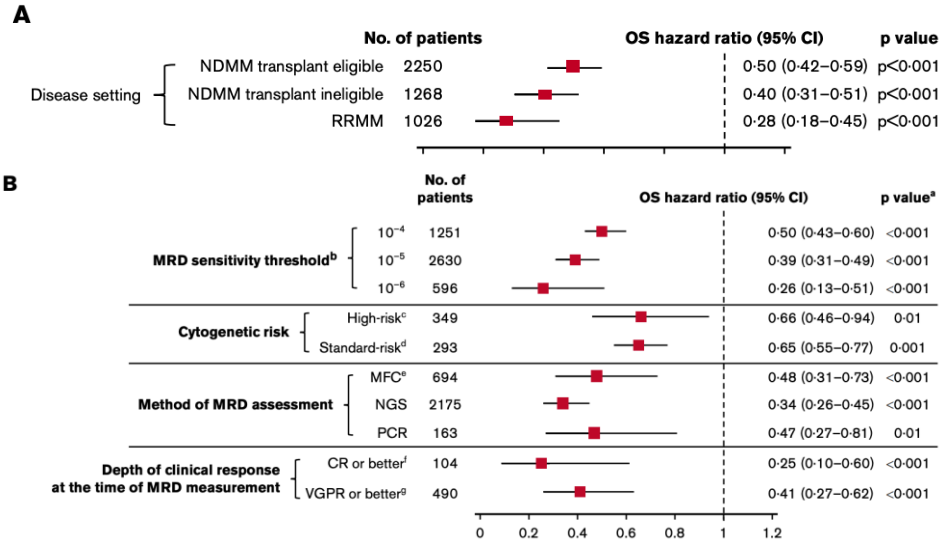
Derman and Fonseca. *Unpublished*

MRD is a Powerful Prognostic Tool



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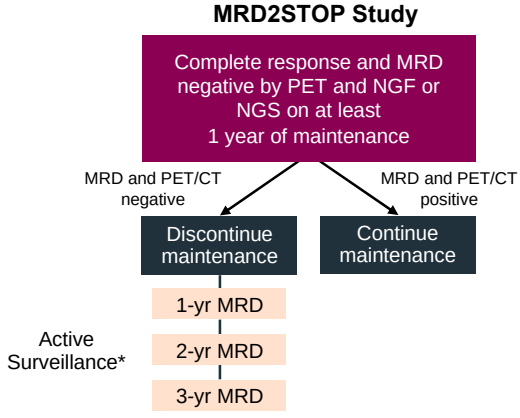
Munshi et al. *Blood Advances* 2020

MRD2STOP: Can MRD-Negativity Guide Discontinuation of Therapy?



- One year after stopping treatment: 84% remained MRD negative
- MRD resurgence occurred in 13% of patients (2 patients had resurgence of M protein and disease progression).
- MRD negativity (at 10^{-6} and 10^{-7}) is sustained even after discontinuation of maintenance therapy.

MRD-guided discontinuation of maintenance may carry significant cost savings.

*MRD assessment performed with PET, flow cytometry (10^{-5}), next-generation sequencing (10^{-6}), and CD138-selected next-generation sequencing (10^{-7})

Derman BA et al. *Blood*. 2022;140. Abstract 870.

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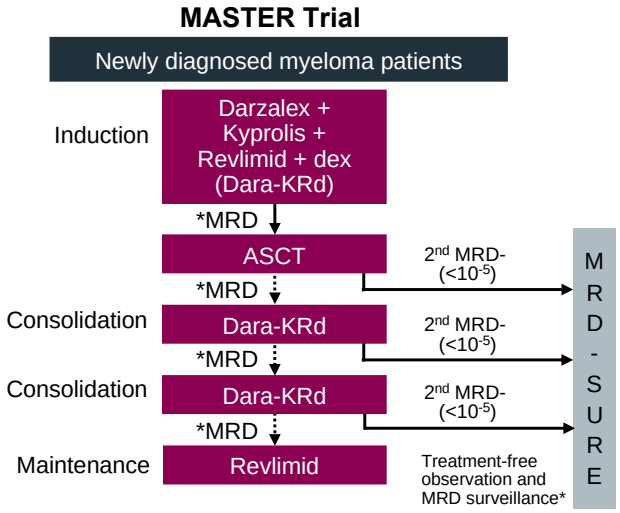
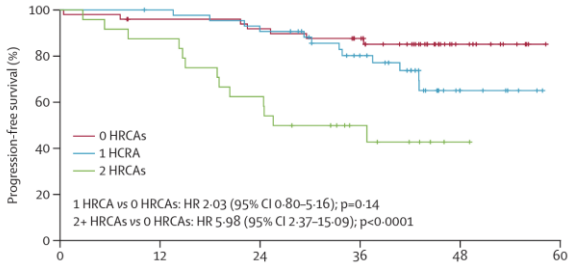
MASTER Trial: MRD Response-Adapted Treatment





71% of patients were able to stop treatment!
52% remained off treatment and MRD negative

Costa et al. *The Lancet Haematology* 2023

First…Some Terminology

- **Triple-class refractory** = Resistant to IMiD, PI, Anti-CD38 mAb
- **Penta-refractory** = Resistant to IMiD #1, IMiD #2, PI #1, PI #2, Anti-CD38 mAb
- **Lines of therapy** =
  - Anytime there is a change in therapy…except
  - Induction/transplant/consolidation/maintenance = 1 line

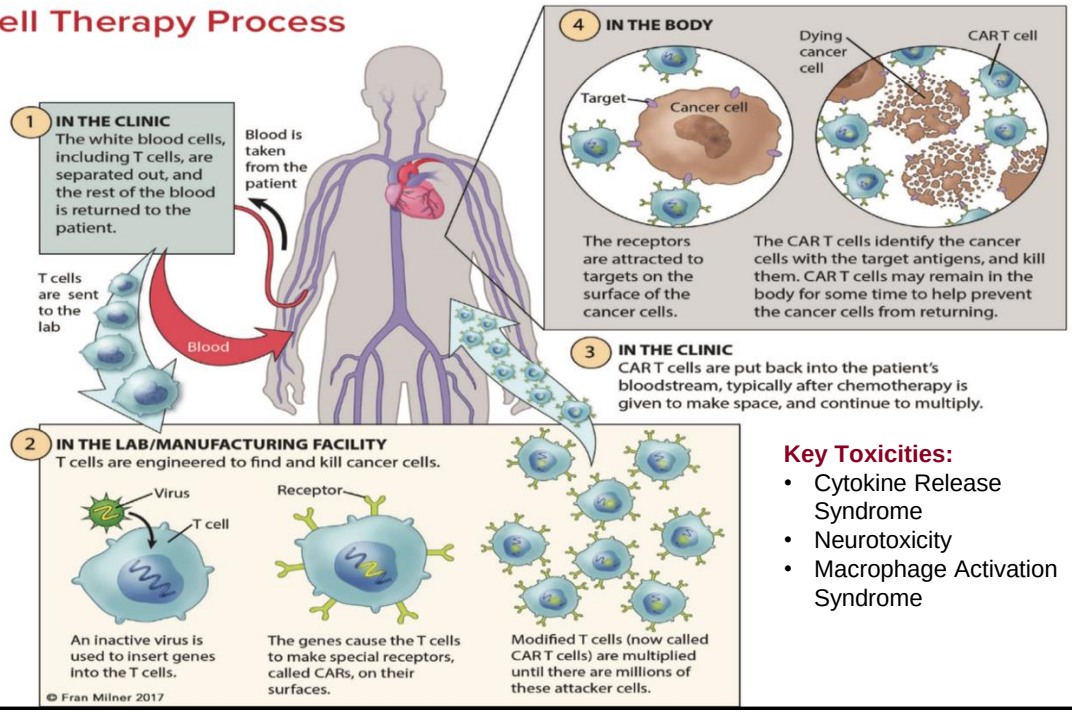
IMiD = lenalidomide, pomalidomide, thalidomide PI = bortezomib, carfilzomib, ixazomib Anti-CD38 = daratumumab, isatuximab

Relapsed/Refractory Multiple Myeloma

Recent FDA Approvals

Agent	Mechanism	Indication
Idecabtagene Vicleucel (ABECMA)	BCMA-directed CAR T-cell Therapy	4+ prior lines of therapy (triple-class exposed)
Ciltacabtagene Autoleucel (CARVYKTI)	BCMA-directed CAR T-cell Therapy	
Teclistamab (TECVAYLI)	BCMA-directed bispecific antibody	
Elrantamab (ELREXFIO)	BCMA-directed bispecific antibody	
Talquetamab (TALVEY)	GPRC5D-directed bispecific antibody	

CAR T-Cell Therapy Process



Key Toxicities:

- Cytokine Release Syndrome
- Neurotoxicity
- Macrophage Activation Syndrome

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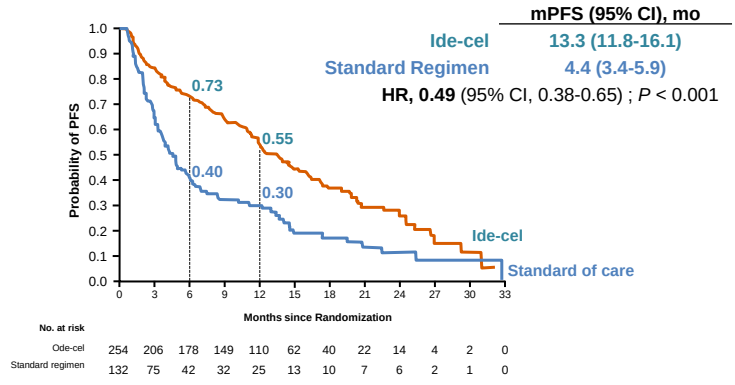
KarMMA-3: Ide-cel vs Standard of Care

	Ide-cel (n=225)	SOC (n=126)
Median lines of therapy	3	3
Extramedullary Disease	24%	24%
HR Cytogenetics	42%	46%
Triple-class Refractory	65%	67%
Penta-refractory	6%	4%

SOC regimens (n=132):
43 Dara-Pd
30 Kd
30 Elo-Pd
22 Ixa-Rd
7 Dara-Vd



Rodriguez-Otero et al. *NEJM 2023*

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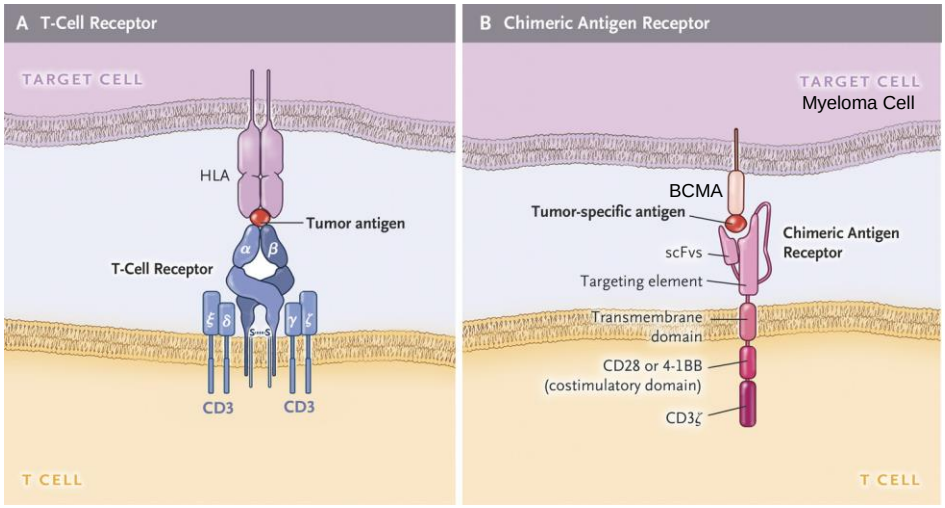
BCMA-Directed CAR T-cell Therapy



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June and Sadelain *NEJM* 2018

KarMMA-3: Ide-cel Toxicity

	Ide-cel	SOC
Neutropenia	78%	44%
Infections **Gr 3-5**	58% 28%	54% 20%
CRS	88% (most grade 1-2)	-
Neurotoxicity	15% (most grade 1-2)	-
Deaths All-cause G5 AEs Infection-related Treatment-related	30% 14% 5% 3%	26% 6% 5% 1%

**19/254 (7.5%) patients in the ide-cel group did not receive CAR T-cells due to death, manufacturing failure, or MD withdrawal

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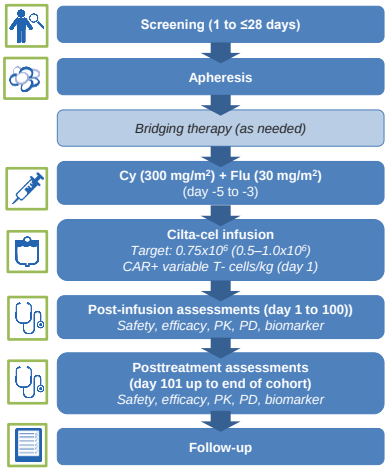
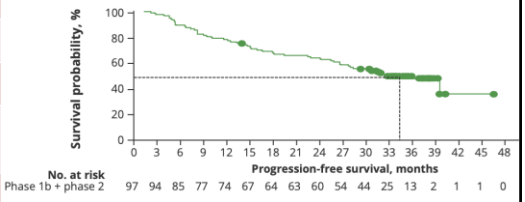
Rodriguez-Otero et al. *NEJM 2023*

CARTITUDE-1: Ciltacabtagene Autoleucel (CARVYKTI)



	All dose groups (n=97)
ORR	97.9%
CR/sCR	82.5%
mDOR	33.9 months
MRD (-)	91.8% at 10^{-5} 75% at 10^{-6}
mPFS	34.9 months
mOS	NR (36 mo OS 63%)



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Martin T, et al. *Blood*. 2021;138(supplement 1):549; Berdeja JG, et al. *Lancet*. 2021;398(10297):314-324; Martin et al. *JCO* 2022; Lin et al. *JCO 2023 (ASCO)*.

Cilta-Cel Side Effects

- ***Low blood counts are common***
- ***Cytokine Release Syndrome (CRS): 92%***
- ***Second Cancers: 23% (10% hematologic malignancies)***
- ***Neurologic changes: 20.6% total (10% severe)***
  - ICANS: 16%
  - Parkinsonism: 5 patients (5%), median onset 43 days
    - Resolution in only 50%
    - Mitigation strategies
      - Reduce tumor burden prior to infusion (optimize bridging)
      - Early aggressive CRS/ICANS management
  - Bell's palsy

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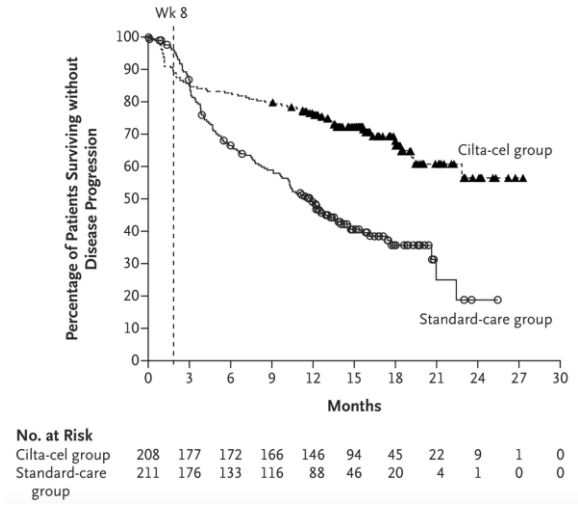
CARTITUDE-4: Cilta-Cel vs Standard of Care (DPd/VPd)

Median follow-up 15.9 months	Cilta-cel (n=208)	SOC (n=211)
Median lines of therapy	2 (1-3)	2 (1-3)
Extramedullary Disease	21%	217%
HR Cytogenetics	59%	63%
Triple-class Refractory	14%	16%
Penta-exposed	7%	5%
ORR	ITT: 84.6% As-tx: 99.4%	67.3%
MRD-Neg (10^{-5})	ITT: 61% As-tx: 72%	16%
Median DOR	NR	16.6 mos.



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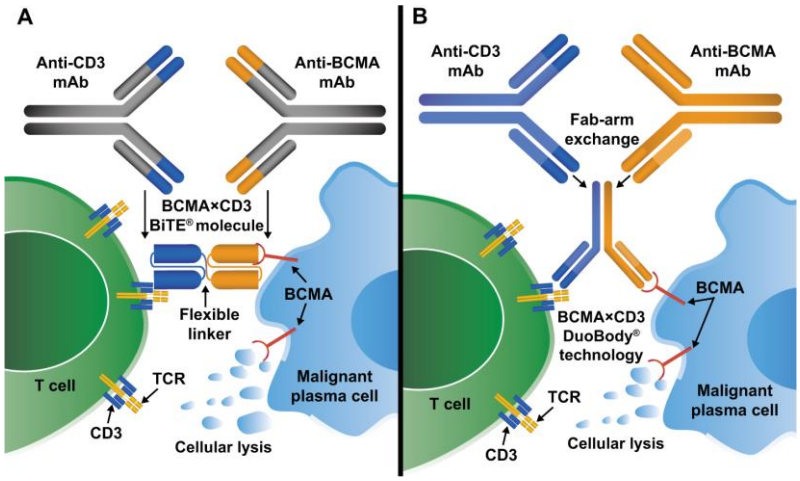
San-Miguel et al. *NEJM 2023*

Bispecific Antibodies: Bridging CD3 on T-cells with…

Targets on myeloma cells: BCMA, GPRC5D, FcRH5



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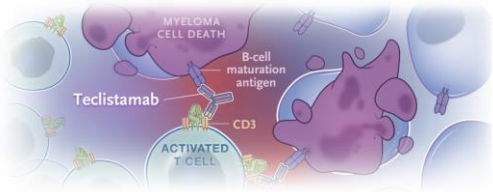
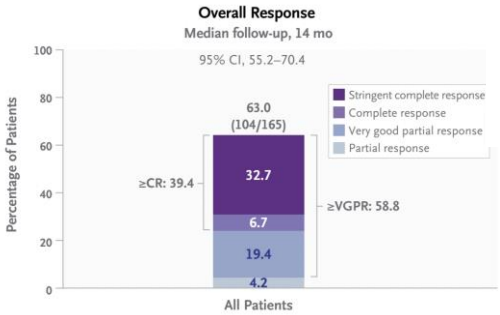
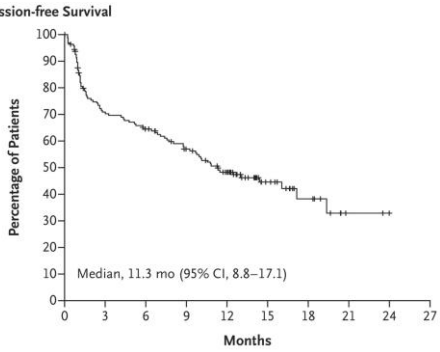
Shah et al. *Leukemia* 2020

MajesTEC-1: Teclistamab (BCMA x CD3)







	All doses (n=165)
ORR	63%
CR/sCR	39.4%
MRD (-)	27% at 10^{-5}
mDOR	18.4 months
mPFS	11.3 months
mOS	18.3 months

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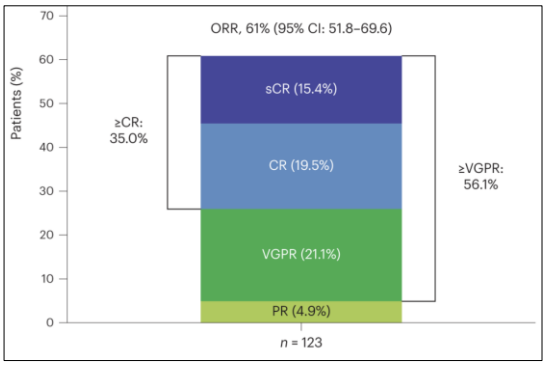
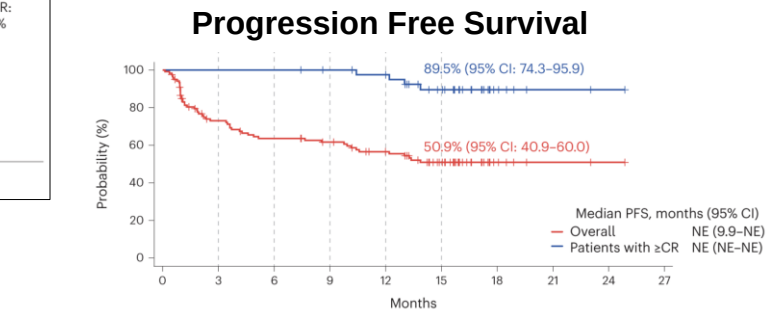
Moreau et al. *NEJM 2022*

MagnetisMM-3: Elranatamab (BCMA x CD3)





No. at risk

Overall	123	78	67	62	52	37	6	2	1	0
Patients with ≥CR	43	43	43	41	38	29	6	2	1	0

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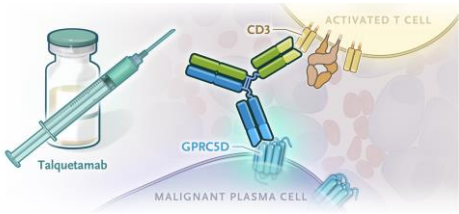
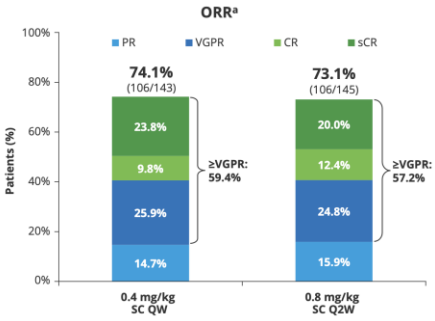
Lesohkin et al. *Nature Medicine* 2023

BCMA-Directed BsAb's: Infections are Common!

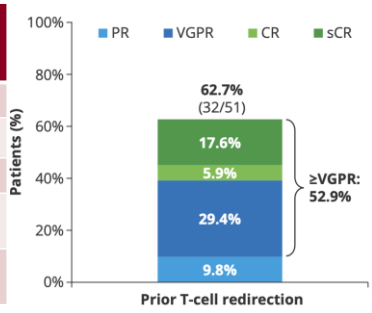
	Alnuctamab	Elranatamab	Linvoseltamab	ABBV-383	Teclistamab
Dose R2PD	30mg qW (SQ)	76mg weekly (SQ)	200mg qW/q2W	60mg IV q3W	1.5mg/kg SQ weekly
Total N	26	123	167	124	165
Median Age	63	68 (36-89)	64 (41-90)	58 (35-92)	64 (33-84)
Median prior lines	4	5	6	5	5
Triple Class Refract	96%	96.7%	90%	82%	78%
Efficacy					
ORR	**65%**	**61%**	**64% @ 200 mg**	**68% (n=49; ≥40mg doses)**	**63%**
≥VGPR	46%	NA	58%	54%	58.8%
Median DOR (mo)	NA	72% @ 12 mos.	NR (89% @ 6 mos.)	72.2% @ 12 mos.	18.4 mos.
Safety (Grade ¾)					
CRS	53% (0%)	58% (0%)	37% (1%)	57% (2%)	72% (0.6%)
Neurotoxicity	2% (0%)	3.4% (0%)	4% (0%)	2%	14.5% (0.6%)
Infection	**34% (9%)**	**67% (35%)**	**54% (29%)**	**41% (25%)**	**76% (45%)**
Neutropenia	37% (32%)	48% (48%)	20% (17%)	37% (34%)	71% (64%)
Reference	Wong et al. ASH 2022	Bahlis et al ASH 2022	Bumma et al. ASH 2022	D'Souza et al. JCO 2022	Moreau et al. NEJM 2022

MonumenTAL-1: Talquetamab (GPRC5D x CD3)





	0.4 mg/kg qW (n=143)	0.8 mg/kg q2W (n=145)
ORR	74%	73%
CR/sCR	34%	32%
mDOR	7.5 months	11.9 months
CRS	79% (2% G3+)	72% (1% G3+)
ICANS	11% (2% G3+)	10% (2% G3+)



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Chari et al. *ASH* 2022

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Talquetamab Safety

AEs (≥20% of any RP2D cohort), n (%)	0.4 mg/kg SC QW[a] (n=143) mFU, 11.0 months[b]		0.8 mg/kg SC Q2W[a] (n=145) mFU, 5.1 months[c]	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
CRS	113 (79.0)	3 (2.1)	105 (72.4)	1 (0.7)
Skin-related AEs[d]	80 (55.9)	0	98 (67.6)	1 (0.7)
Nail-related AEs[e]	74 (51.7)	0	63 (43.4)	0
Dysgeusia[f]	69 (48.3)	NA	67 (46.2)	NA
Rash-related AEs[g]	56 (39.2)	2 (1.4)	39 (26.9)	8 (5.5)
Weight decreased	57 (39.9)	3 (2.1)	47 (32.4)	2 (1.4)
Pyrexia	53 (37.1)	4 (2.8)	35 (24.1)	1 (0.7)
Asthenia	37 (25.9)	3 (2.1)	13 (9.0)	2 (1.4)
Dry mouth	36 (25.2)	0	53 (36.6)	0
Diarrhea	34 (23.8)	3 (2.1)	32 (22.1)	0
Dysphagia	34 (23.8)	0	33 (22.8)	3 (2.1)
Fatigue	32 (22.4)	5 (3.5)	29 (20.0)	1 (0.7)
Decreased appetite	25 (17.5)	2 (1.4)	29 (20.0)	2 (1.4)
Infections	57%	17%	51%	12%

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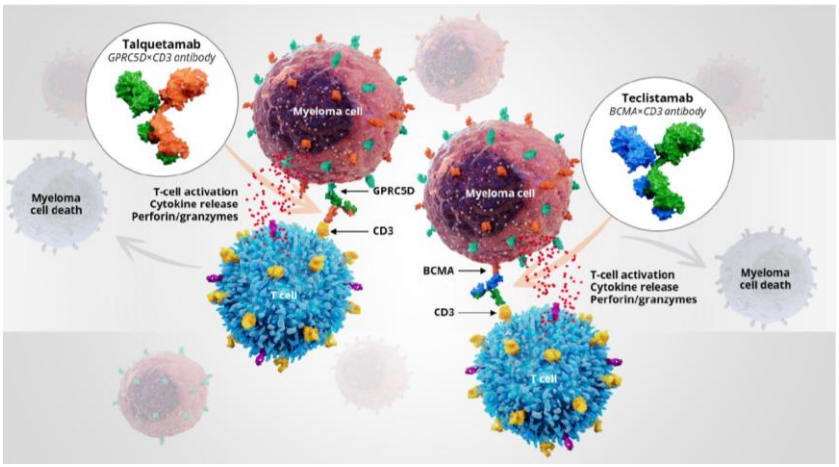
Chari et al. *ASH* 2022

RedirecTT-1: Can Bispecific Antibodies Be Combined?

Teclistamab
- Approved BCMAxCD3 BsAb
- Response rate 63%

Talquetamab
- GPRC5D-directed BsAb
- Response rate 74%



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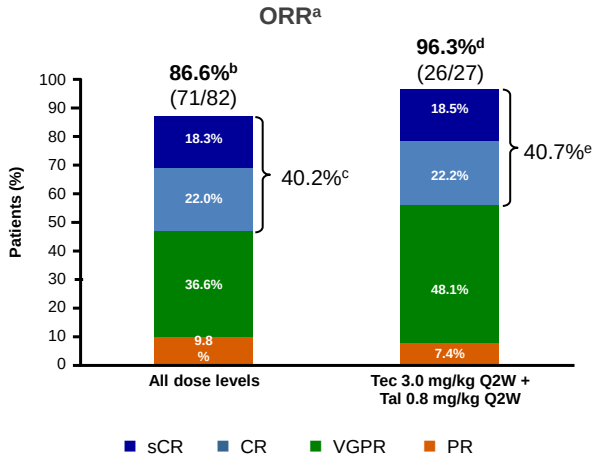
1. Fernandez de Larrea, et al. *Blood*. 2019;134 (suppl 1):136. 2. Moreau P, et al. *N Engl J Med*. 2022;387:495-505. 3. Chari A, et al. *Blood*. 2022;140(suppl1):384-7.
Figure from: Mateo's V, et al. EHA 2023: Abstract S190.

RedirecTT-1: Efficacy of Tec and Tal



	All dose levels (N=93)	Tec 3.0 mg/kg Q2W + Tal 0.8 mg/kg Q2W (n=34)
Median DOR[f], mos (95% CI)	NE (NE-NE)	NE (NE-NE)
Median PFS[g], mos (95% CI)	20.9 (13.0-NE)	NE (9.9-NE)
9-months PFS rate[g] (95% CI)	70.1 (58.0-79.4)	77.1 (50.8-90.5)

**For reference: mPFS with teclistamab alone: 11.3 mos.
mDOR with talquetamab alone: 9-12 mos.

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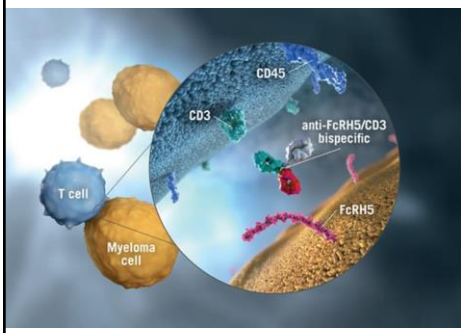
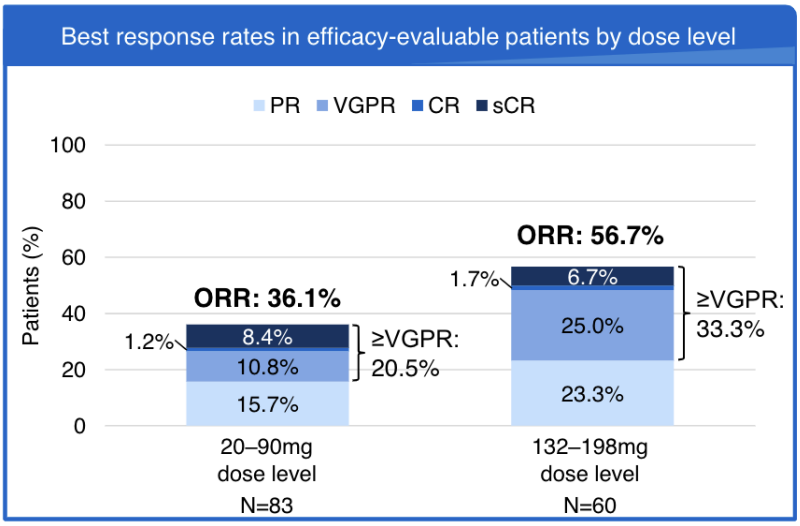
Mateo's V, et al. EHA 2023: Abstract S190.

FcRH5 x CD3 BsAb: Cevostamab





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https://www.mayoclinic.org/medical-professionals/cancer/news/tolerability-safety-and-deep-response-found-in-cevostamab-phase-1-trial/mac-20510681

Trudel *ASH* 2021

Bispecific Antibodies and CAR T-cell Therapy in Myeloma

	Bispecific Antibody Therapy	CAR T-cell Therapy
Availability / Speed	High / Quick (off the shelf)	Low / Slow (personalized)*
Lymphodepletion needed?	No	Yes (Flu/Cy or Benda)
Setting of infusion	Inpatient (5-10d) → Outpatient	Mostly inpatient (~14-21d)
Regulatory	REMS	Accreditation + REMS
Important toxicities	CRS & neurotoxicity Infections	CRS & neurotoxicity MAS/HLH Cytopenias / Infections B-cell aplasia
Dosing	Tec/Elra/Talq: qweekly→q2wk	"One and done"
Activity	High rates of response	High rates of response
Durability	Teclistamab: mPFS 11.3 months Elranatamab: mPFS ~15 mos.	Ide-cel: mPFS 13.3 months Cilta-cel: mPFS 34.9months
Combine with other agents	Likely	?

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*allo-CAR T can be off the shelf

Thank you!

@bdermanmd

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ASK A QUESTION
HIGHLIGHTS IN THERAPY: CHRONIC MYELOID LEUKEMIA

Ask a question by phone:

Press star (*) then the number 1 on your keypad.

Ask a question by web:

Click “Ask a question”

Type your question

Click “Submit”

Due to time constraints, we can only take one question per person. Once you’ve asked your question, the operator will transfer you back into the audience line.

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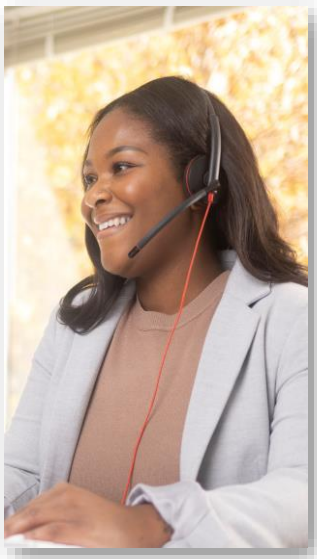

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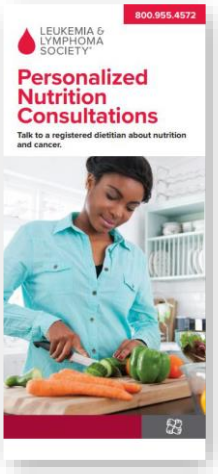

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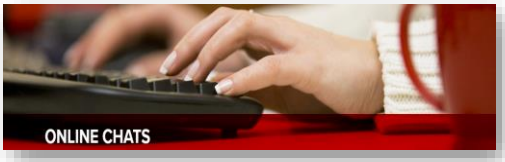

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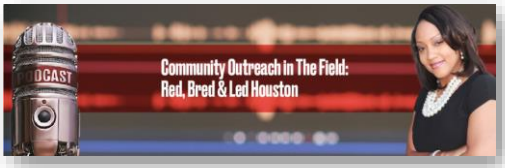

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The Bloodline with LLS is here to remind you that after a diagnosis comes hope. To listen to an episode, please visit **www.TheBloodline.org**

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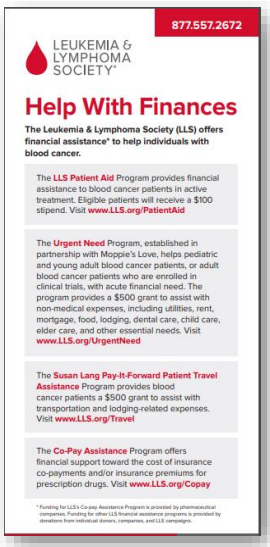

The Leukemia & Lymphoma Society (LLS) offers the following financial assistance programs to help individuals with blood cancers: **www.LLS.org/Finances**

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