

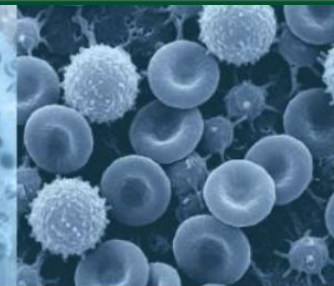
Newly Diagnosed Multiple Myeloma: Are We Done with Autologous Stem Cell Transplant?

Debate: Moving Away from Upfront Auto-SCT

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**2026 FLASCO CLINICAL
ONCOLOGY SERIES:**
MALIGNANT HEMATOLOGY



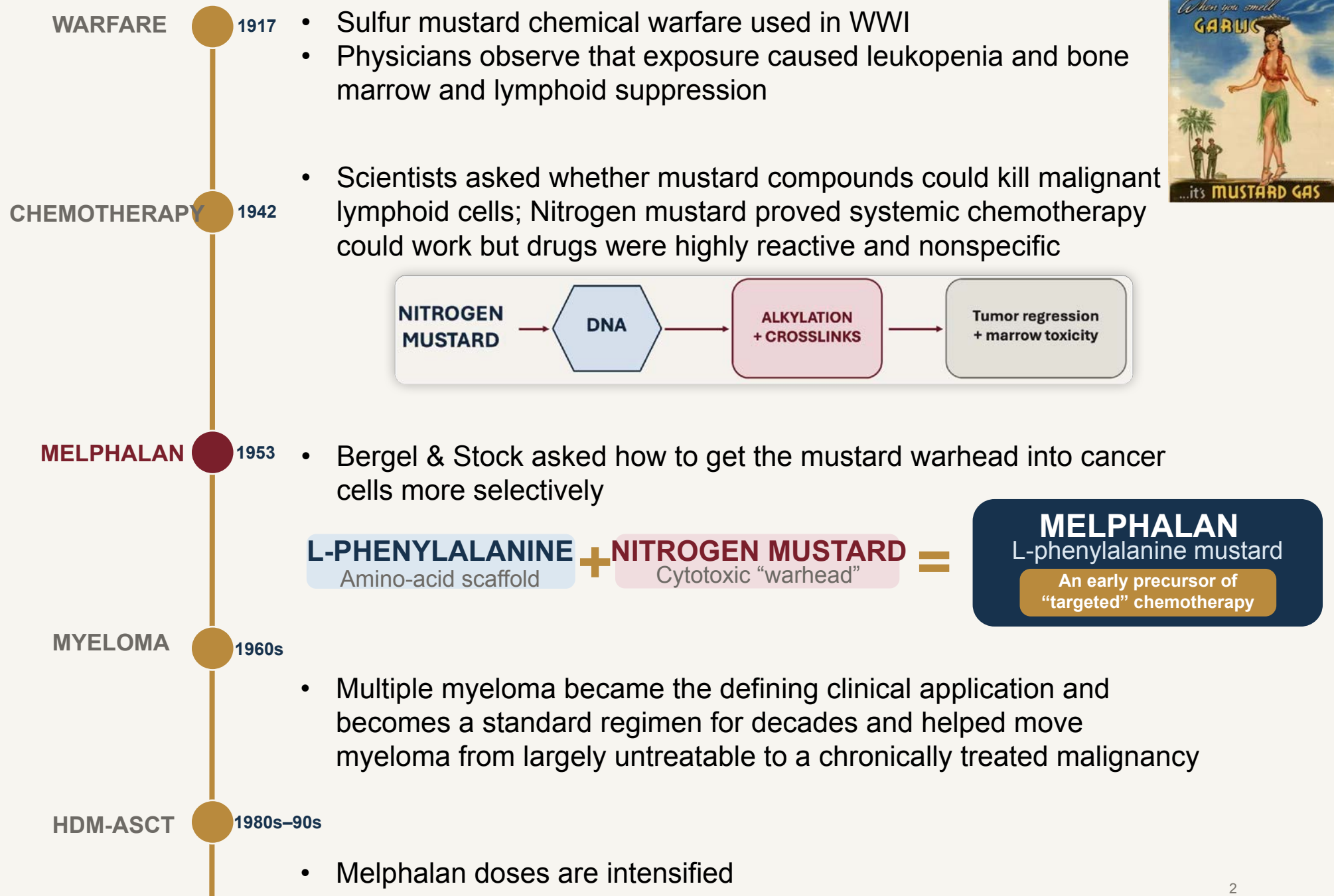
August 29, 2026: Precision Approaches in the Modern Era

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Assistant Director for Interventional Clinical Research,
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University of Miami, Miller School of Medicine



FROM MUSTARD GAS TO MELPHALAN

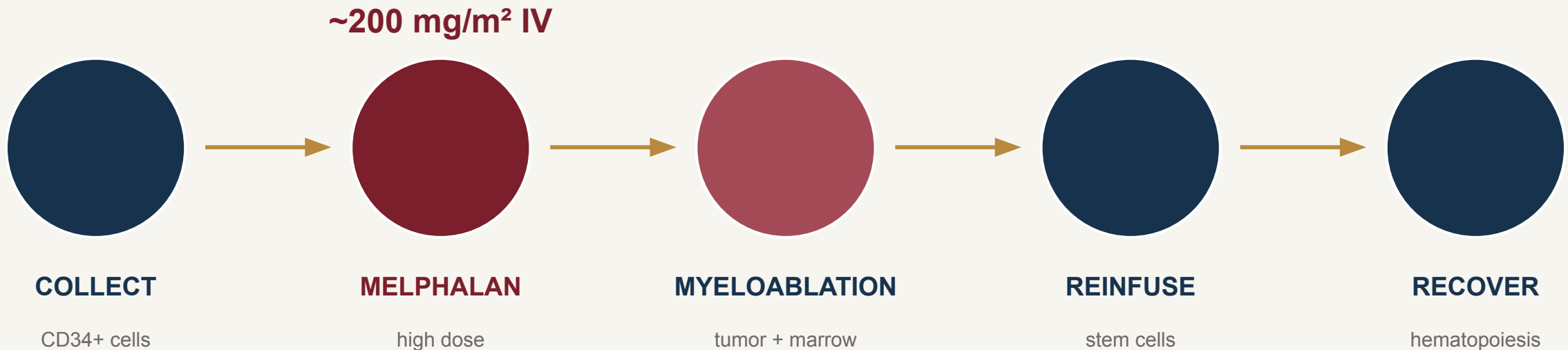
How a chemical-warfare observation became a backbone of multiple myeloma therapy



From war to bedside, marrow toxicity becomes a key feature: High-dose Melphalan with stem cell rescue (HDM-ASCT)

Stem-cell rescue allows melphalan dose intensity to be pushed higher

This transformed melphalan from a conventional oral alkylator into the conditioning backbone of autologous transplantation in myeloma.



A molecule conceived in 1953 remains central to myeloma transplantation more than seven decades later.

The debate has changed

The question is no longer whether ASCT works — it is whether every patient with NDMM still needs it upfront.

What ASCT still does

Prolongs PFS in NDMM

DETERMINATION: median PFS 67.5 vs 46.2 months with RVD-era therapy.

What it has not shown

No overall-survival advantage in DETERMINATION.

5-year OS: 80.7% with ASCT vs 79.2% without.

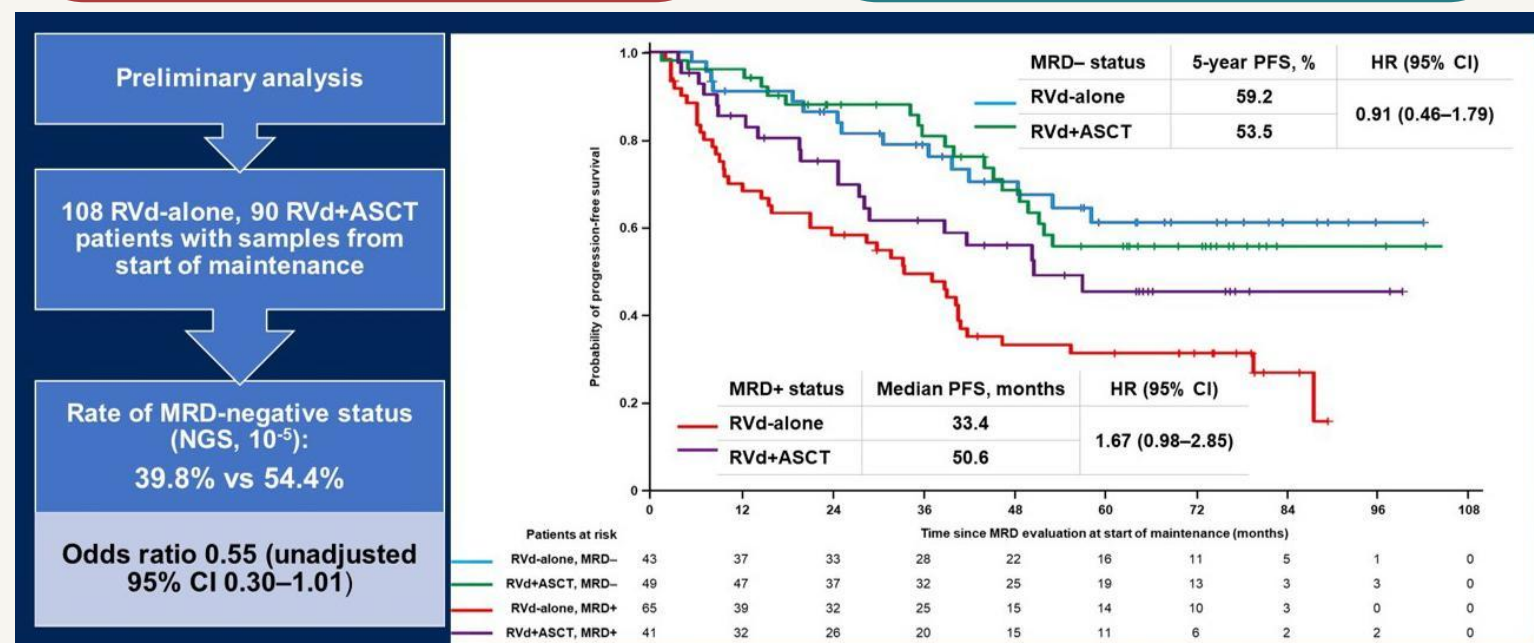
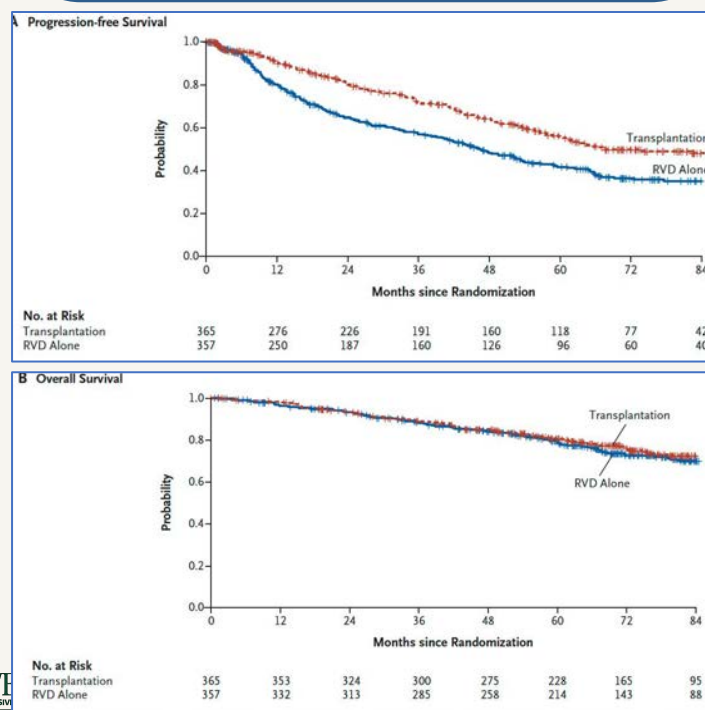
More grade ≥ 3 toxicity: 94.2% vs 78.2%.

What is different now

Dara-based quadruplets produce far deeper responses before transplant.

MRD at 10^{-6} can identify exceptionally deep responders.

CAR-T and bispecifics provide potent immune-based salvage options.



Melphalan has a biological price

A PFS gain is not free: high-dose alkylator exposure creates acute toxicity and long-term genotoxic risk.

Acute burden

Myeloablation → cytopenias, transfusions and infection risk.

Mucositis, GI toxicity, fatigue and weeks of functional disruption.

DETERMINATION: grade ≥ 3 adverse events were more frequent with ASCT.

Genotoxicity

Melphalan is a DNA-crosslinking alkylator.

Therapy-related MDS/AML is a recognized late complication after high-dose melphalan.

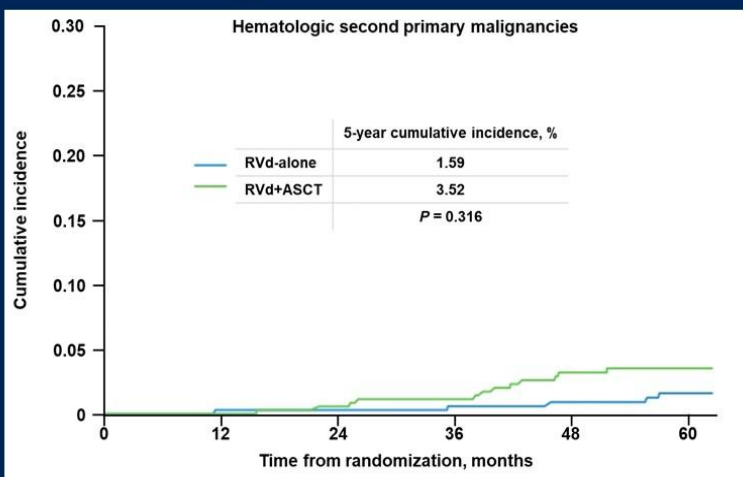
The relevant question in a patient with decades of expected survival: how much irreversible DNA damage is necessary?

The Practical

- We accept this toxicity when the incremental benefit is large.
- But modern induction is shrinking the incremental disease burden left for melphalan to eradicate.
- As benefit narrows, long-term toxicity matters more — not less.

5-year cumulative incidence of SPMs (RVd-alone vs RVd+ASCT):

- All : 9.7% vs 10.8%
- Invasive: 4.9% vs 6.5%
- Hematologic: 1.59% vs 3.52%



SPMs, %	RVd-alone (N=357)	RVd+ASCT (N=365)
Any	10.4	10.7
Any invasive SPM	5.3	6.8
Any hematologic SPM	2.5	3.6
ALL, n	7	3
AML/MDS, n	0*	10*
CLL/CML, n	2	0
Any solid tumor SPM	3.4	3.3
Any non-invasive solid tumor SPM	0	0.5
Any non-melanoma skin cancer	5.9	4.1

Richardson, ASCO

* $p=0.002$

The cost is more than the transplant bill

ASCT consumes patient time, caregiver time and specialized infrastructure — opportunity costs rarely appear on Kaplan–Meier curves

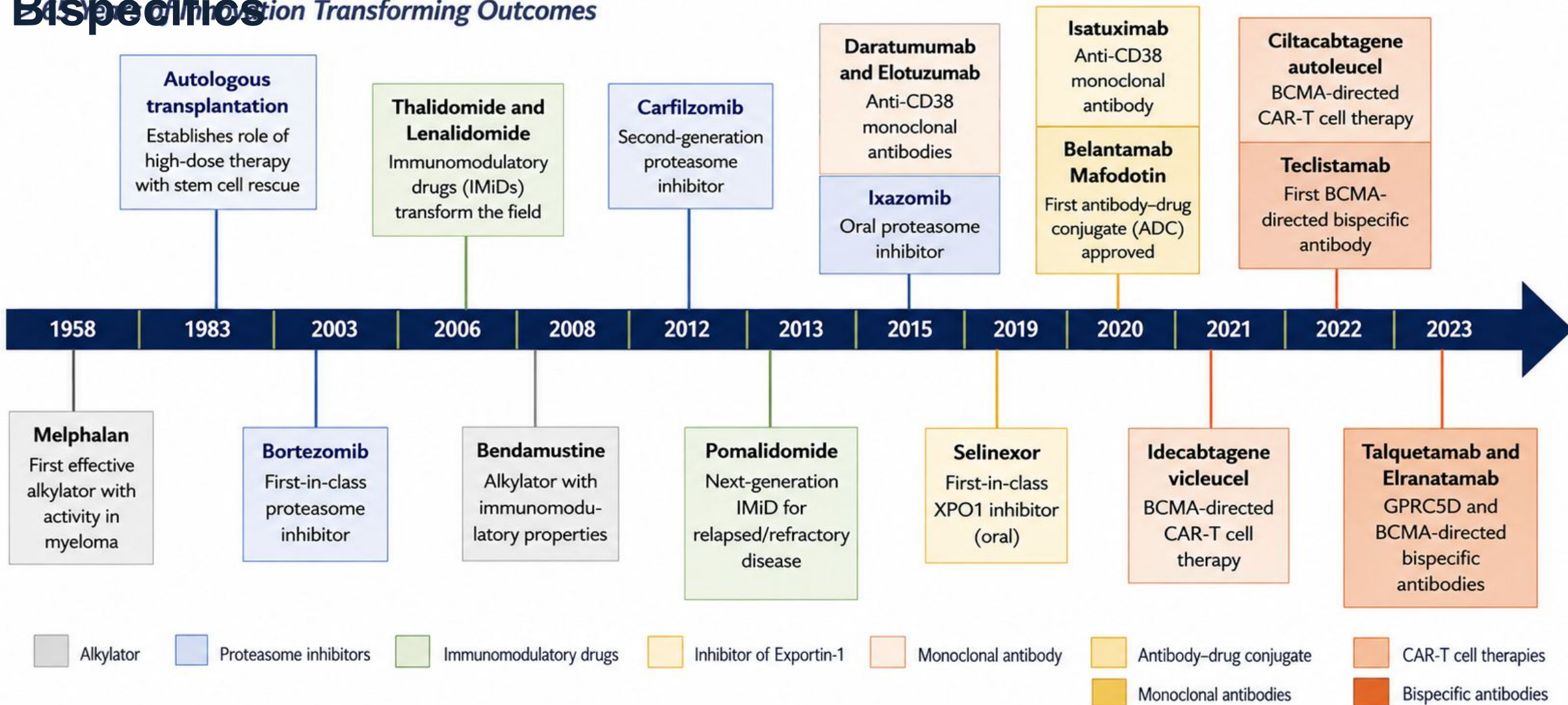


The image is a composite of three scenes illustrating the impact of ASCT. In the foreground, a man in a hospital bed covers his face with his hands, looking distressed, with an IV drip visible. In the background, a family (mother, father, and child) walks away down a long hospital hallway. A sign on the wall reads "One day at a time." with a heart symbol. A directional sign above the family points to the Transplant Unit, Infusion Center, Patient Rooms, and Family Lounge.

 Patient	 Caregiver	 Health system
Mobilization and collection	Transportation and monitoring	Apheresis capacity
Hospital/outpatient transplant visits	Time away from work	Transplant beds / daily clinic
Lost work and travel	Infection precautions	Blood products and supportive care
Weeks of reduced function	Uncompensated caregiving	Specialized transplant workforce

Evolution of Myeloma Therapies: From Melphalan to Bispecifics

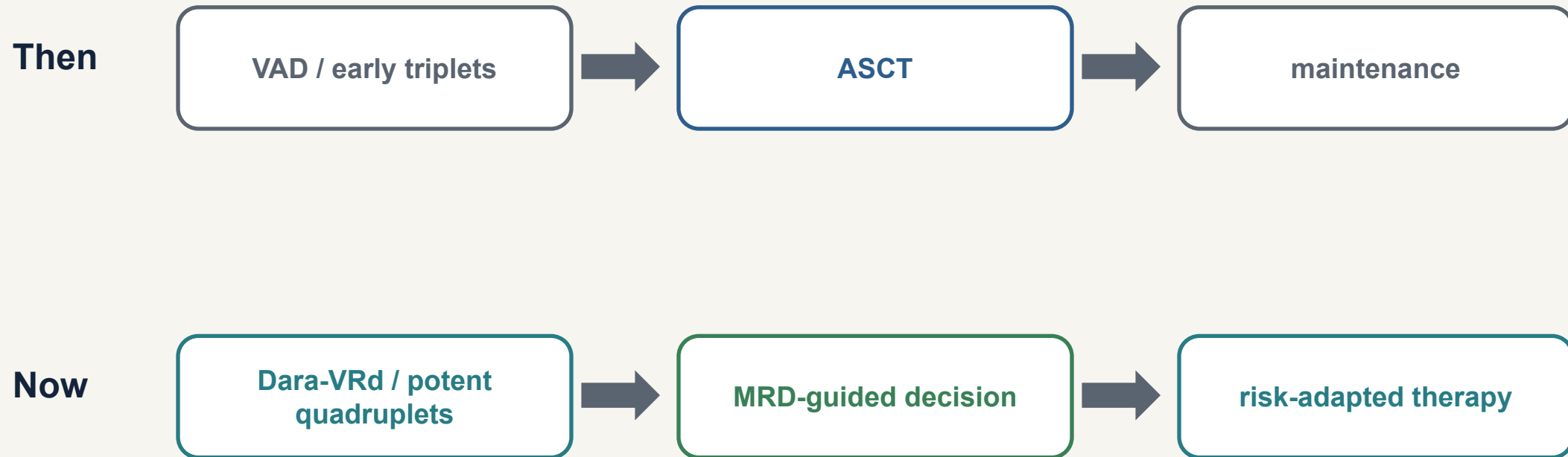
Apace of Innovation Transforming Outcomes



A relentless pace of innovation has expanded options and improved outcomes for patients with multiple myeloma.

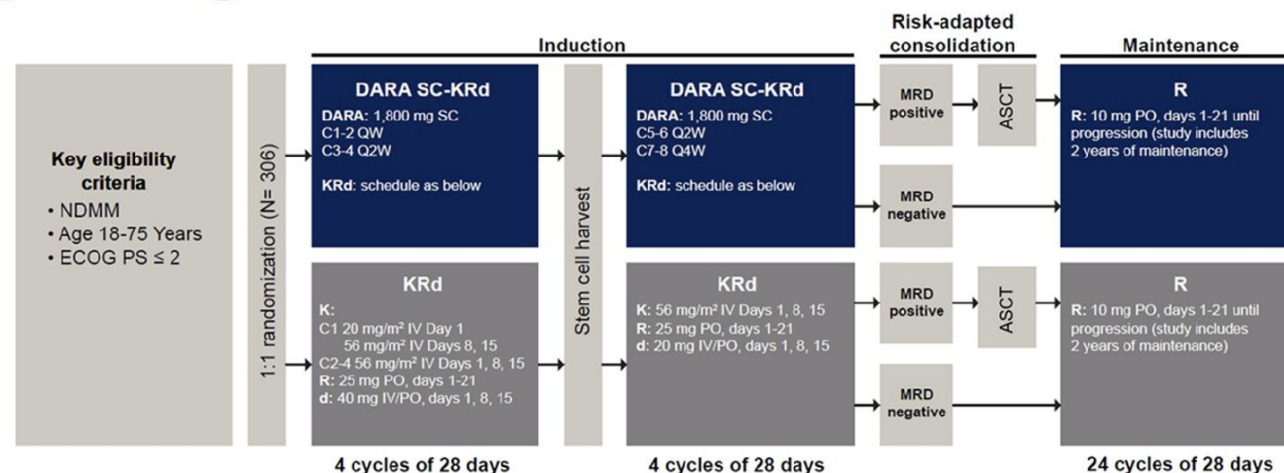
We are using a 1990s solution after a 2020s induction

Modern induction has moved much closer to the depth once uniquely provided by high-dose melphalan.



Quadruplet efficacy in 2026

Study Design of ADVANCE Clinical Trial



Primary endpoint: Overall MRD negativity rate ≥VGPR

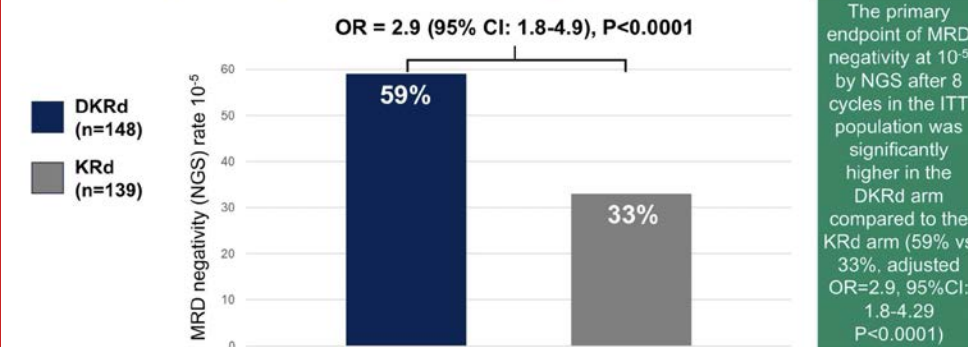
Key secondary endpoints: PFS, EFS, ≥CR, OS, Safety, MRD negativity rate in peripheral blood

MRD negativity rate was defined as the proportion of patients who achieved both MRD negativity and ≥VGPR in the ITT population. Patients who were not evaluable for MRD testing were considered MRD positive.

Transplant-eligible patients with MRD ≥10⁻⁵ by NGS after combination therapy were recommended to proceed with high-dose melphalan chemotherapy followed by autologous stem cell transplant (ASCT)

ECOG PS, Eastern Cooperative Oncology Group performance status; C, carfilzomib; IV, intravenous; R, lenalidomide; PO, oral; d, dexamethasone; DARA SC (DARA 1,800 mg co-formulated with recombinant human hyaluronidase PH20 [HuPH20, 2,000 U/mL; ENHANZE® drug delivery technology, Halozyme, Inc, San Diego, CA, USA]); QW, weekly; Q2W, every 2 weeks; Q4W, every 4 weeks; ASCT, Autologous stem cell transplantation; y, year; PR, partial response; ITT, intention to treat; CR, complete response; ISS, International Staging System; IMWG, International Myeloma Working Group; *Stratified by ISS stage and age. †MRD was assessed using the conoSEQ assay (Adaptive Biotechnologies, Seattle, WA, USA) using bone marrow aspirate samples obtained at baseline, at the time of suspected ≥CR, end of induction, and at end of C12 and C24 maintenance. ‡Response and disease progression were assessed based on IMWG response criteria. Overall, the MRD negativity rate was defined as the proportion of patients who achieved both MRD negativity (10⁻⁴ threshold) and ≥CR at any time. ClinicalTrials.gov Identifier: NCT04268498. Accessed April 9, 2025.

Primary Endpoint: MRD Neg 10⁻⁵ in ITT Population



Abbreviations: Daratumumab, carfilzomib, lenalidomide and dexamethasone (DKRd); carfilzomib, lenalidomide and dexamethasone (KRd); next generation sequencing (NGS); MRD negativity refers to negative 10⁻⁵ by NGS in the intention to treat (ITT) population

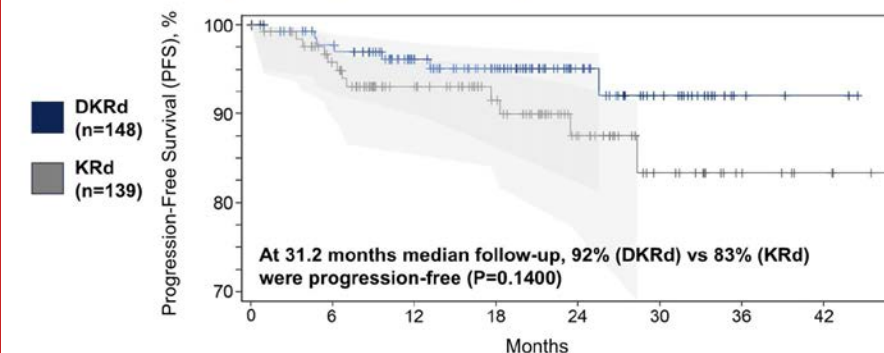
2025 ASCO ANNUAL MEETING

#ASCO25

PRESENTED BY: C. Ola Landgren, M.D., Ph.D., Chief of Myeloma Division & Sylvester Myeloma Institute, University of Miami

ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY KNOWLEDGE CONQUERS CANCER

Secondary Endpoint: Progression-Free Survival



Abbreviations: Daratumumab, carfilzomib, lenalidomide and dexamethasone (DKRd); carfilzomib, lenalidomide and dexamethasone (KRd); next generation sequencing (NGS); PFS=progressive disease or death – whichever came first

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Quadruplet efficacy in 2026

IMROZ: VRd +/-Isa, TI-NDMM

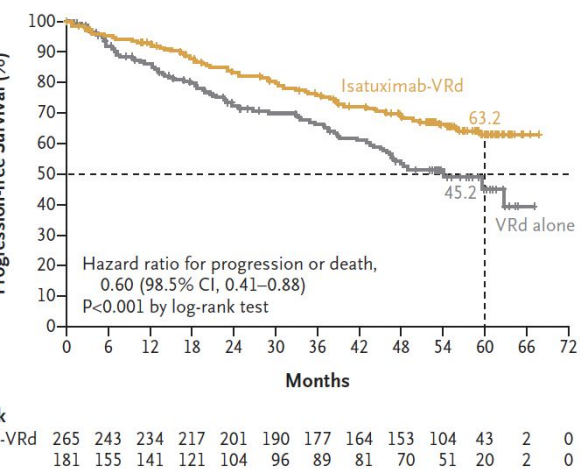
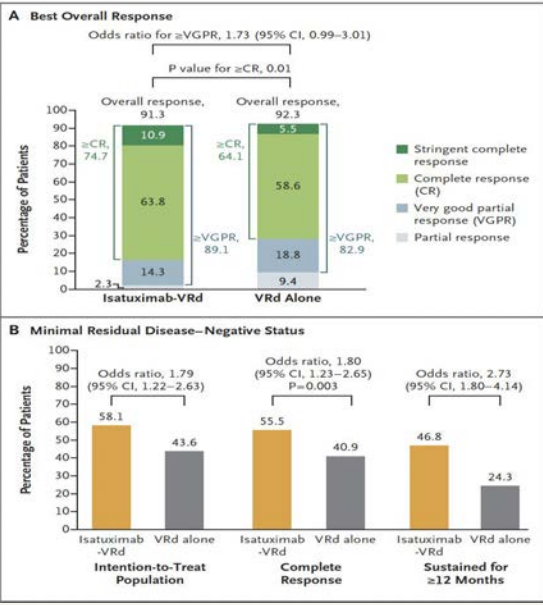
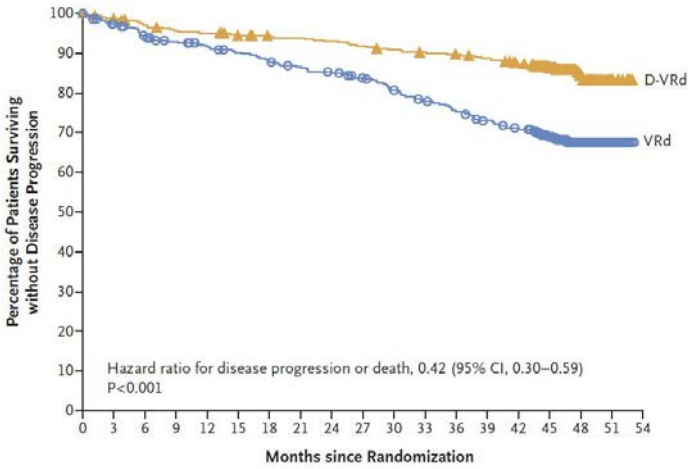


Figure 1. Progression-free Survival (Intention-to-Treat Population).

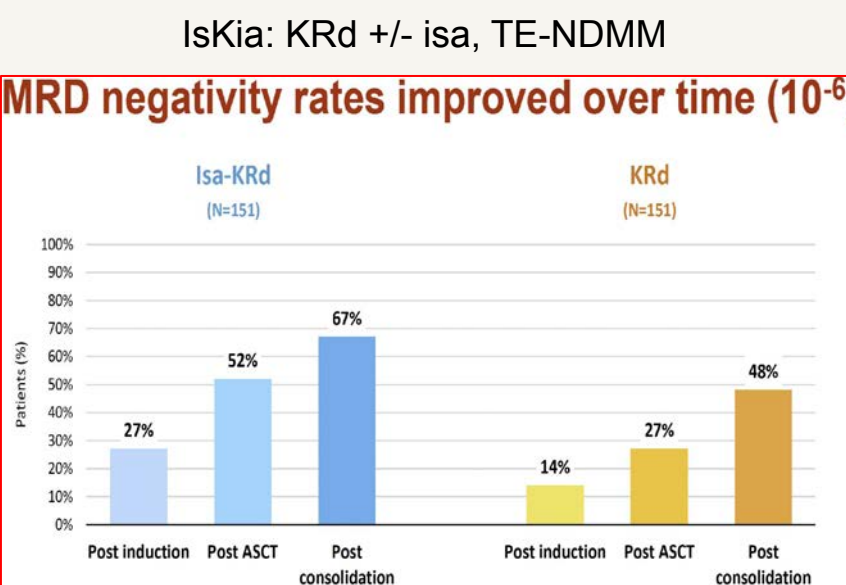
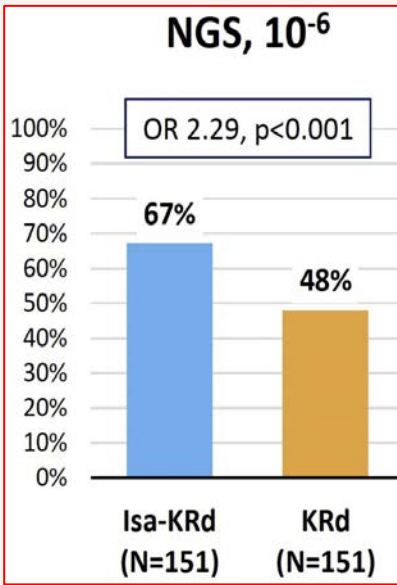
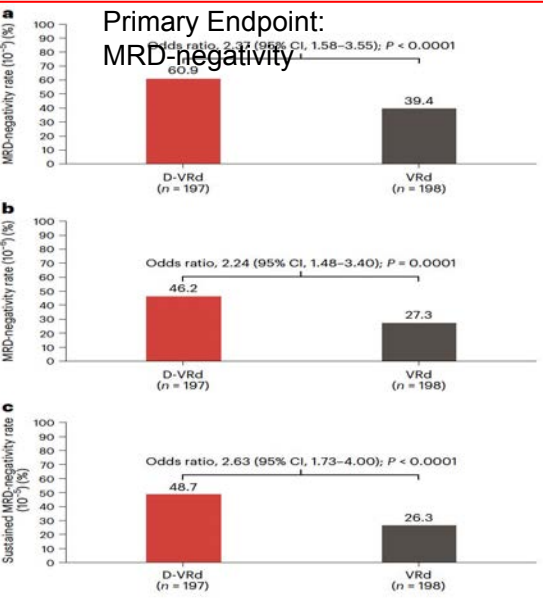
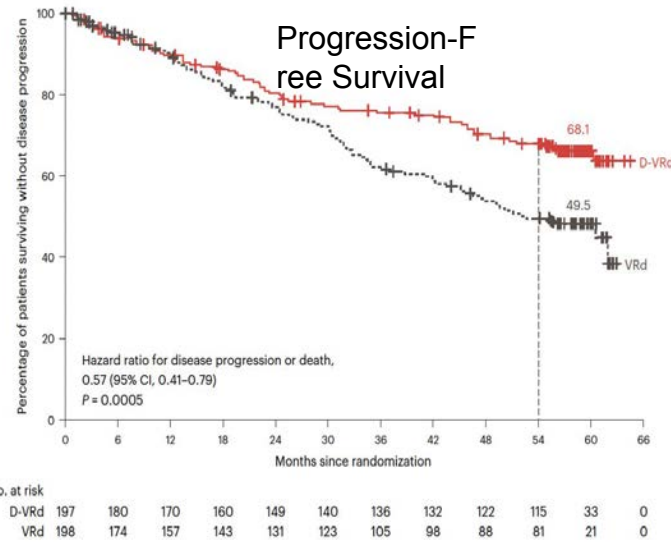


PERSEUS: VRd +/-Dara, TE-NDMM



	DARZALEX FASPRO-VRd (n=355)	VRd (n=354)
Overall response (sCR+CR+VGPR+PR), n (%)	338 (95.2%)	326 (92.1%)
Stringent complete response (sCR)	67 (18.9%)	46 (13.0%)
Complete response (CR)	91 (25.6%)	77 (21.8%)
Very good partial response (VGPR)	165 (46.5%)	168 (47.5%)
Partial response (PR)	15 (4.2%)	35 (9.9%)
CR or better (sCR+CR), n (%)	158 (44.5%)	123 (34.7%)
95% CI (%) [†]	(39.3%, 49.9%)	(29.8%, 40.0%)
MRD negativity rate ^{‡,§} , n (%)	204 (57.5%)	115 (32.5%)
95% CI (%) [†]	(52.1%, 62.7%)	(27.6%, 37.6%)
MRD negativity rate in patients with CR or better [§]		
Number of patients with CR or better	n=158	n=123
MRD negativity rate n (%)	121 (76.6%)	72 (58.5%)
95% CI (%) [†]	(69.2%, 82.9%)	(49.3%, 67.3%)

CEPHEUS: VRd +/- Dara, TI-NDMM



MRD creates an off-ramp from automatic transplant

A biologic endpoint can replace the binary label of “transplant eligible.”

~6 cycles modern quadruplet

MRD negative

What additional value does melphalan add after disease is already below 10^{-5} – 10^{-6} ?

Consolidate without ASCT, monitor MRD, preserve collected stem cells.

MRD positive

Residual disease identifies the patient who may actually need intensification.

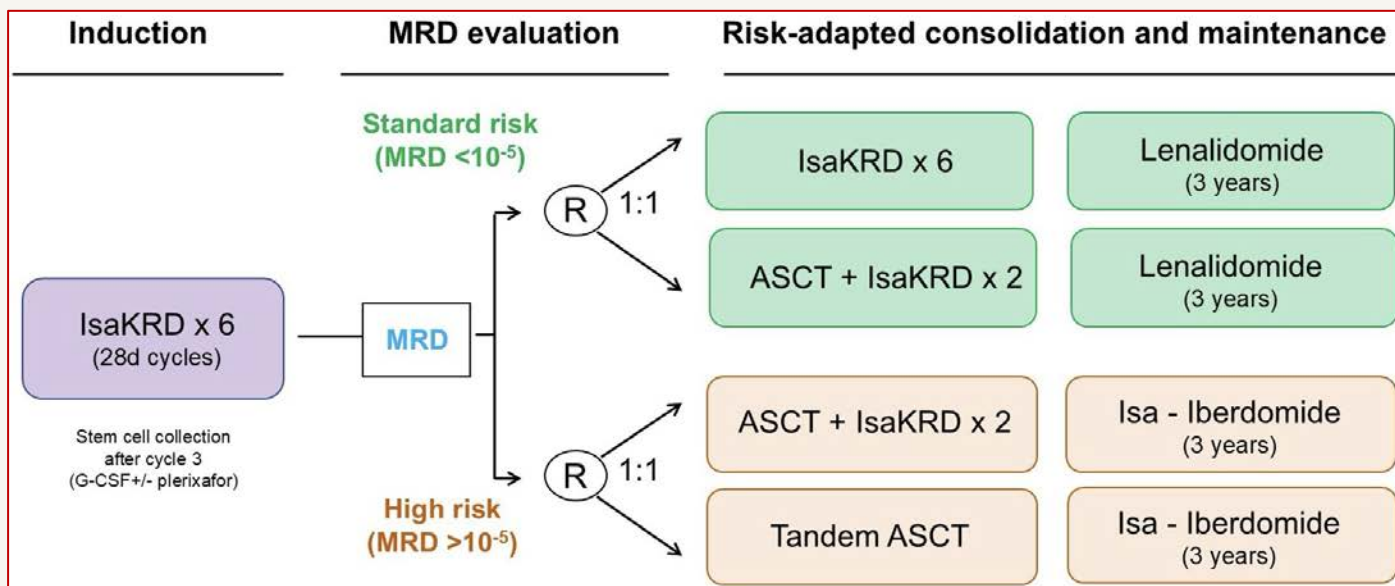
ASCT and/or next-generation immune therapy can be deployed selectively.

This is not “never transplant.” It is: collect now, transplant only if biology says it is needed

MIDAS: MRD-guided challenge to automatic –by default–

ASCT

After 6 cycles of Isa-KRd, consolidation was assigned by MRD status — asking whether ASCT adds depth after modern quads



Primary endpoint

Pre-maintenance MRD- at 10⁻⁶

MRD-negative cohort: ASCT did not deepen MRD

Pre-maintenance MRD- at 10⁻⁶: 86% with ASCT vs 84% with continued Isa-KRd.

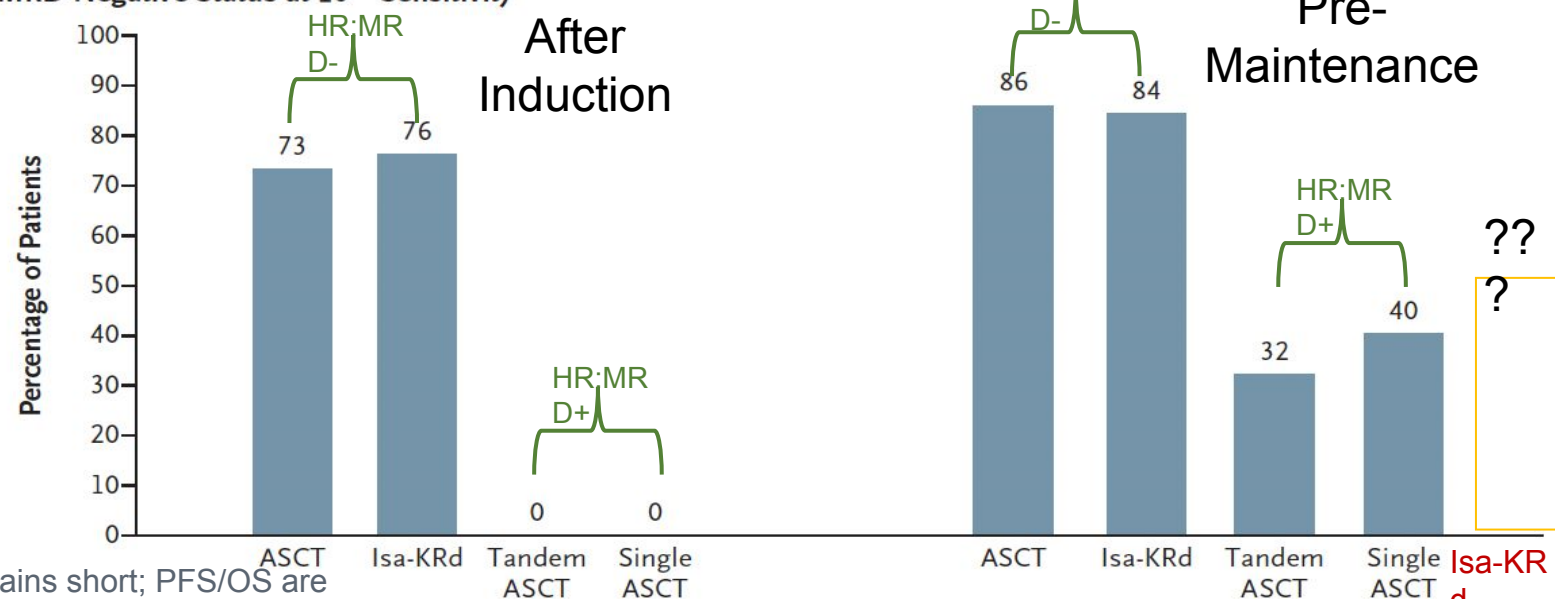
No significant difference: adjusted RR 1.02; P=0.64.

MRD-positive cohort: tandem ASCT did not outperform single ASCT + Isa-KRd

Pre-maintenance MRD- at 10⁻⁶: 32% with tandem ASCT vs 40% with single ASCT + Isa-KRd.

No significant difference: adjusted RR 0.82; P=0.31.

MRD-Negative Status at 10⁻⁶ Sensitivity



With unprecedented MRD negativity rates with quads why should all patients be automatically transplanted?

My colleagues may say....

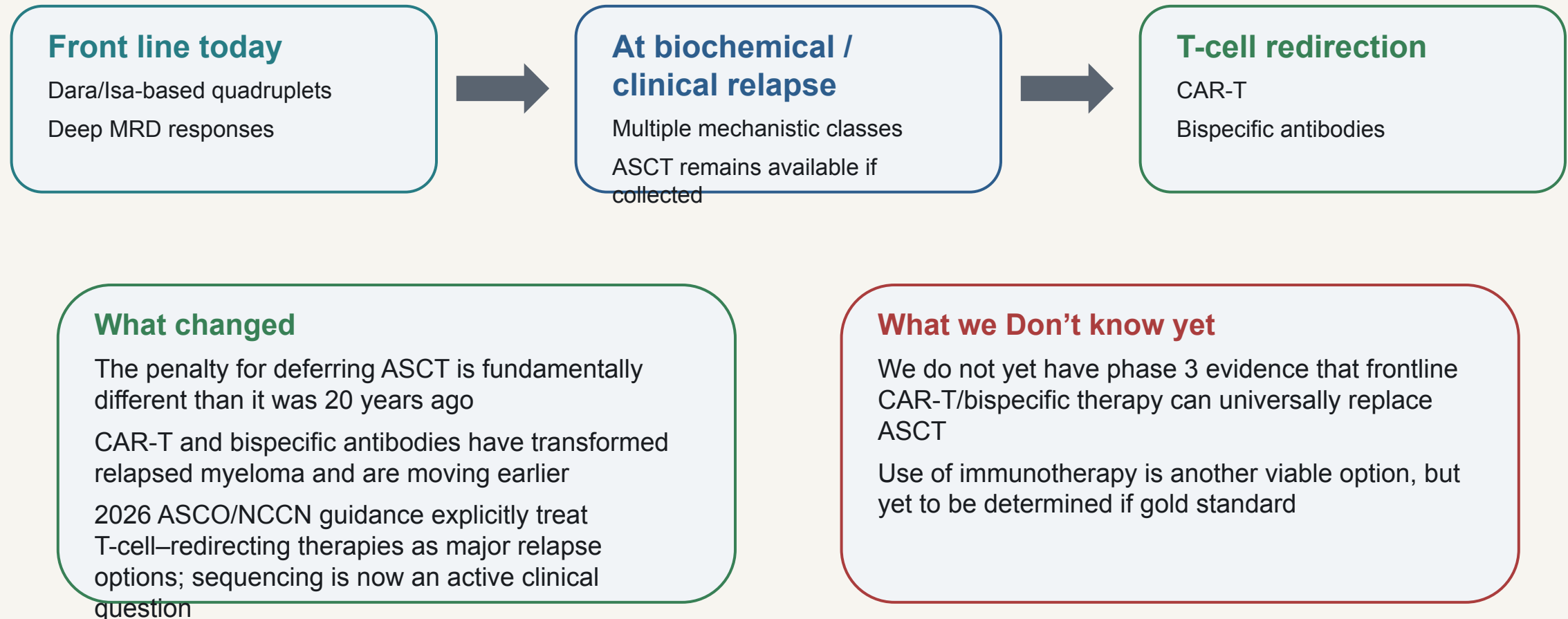
- ❑ “Randomized trials consistently show longer PFS with upfront ASCT.”
- ❑ “We have not yet proven non-inferiority of omission after modern quadruplets.”
- ❑ “Delayed transplant is not guaranteed to reproduce upfront benefit.”

I would say....

- ❑ Correct — ASCT is effective. The debate is necessity, not efficacy.
- ❑ Early trials used less effective induction than today’s Dara-based quads.
- ❑ No OS advantage emerged in DETERMINATION.
- ❑ Modern MRD lets us identify patients most likely to have little incremental benefit.
- ❑ Preserving stem cells keeps ASCT as a later option rather than exposing every patient upfront.

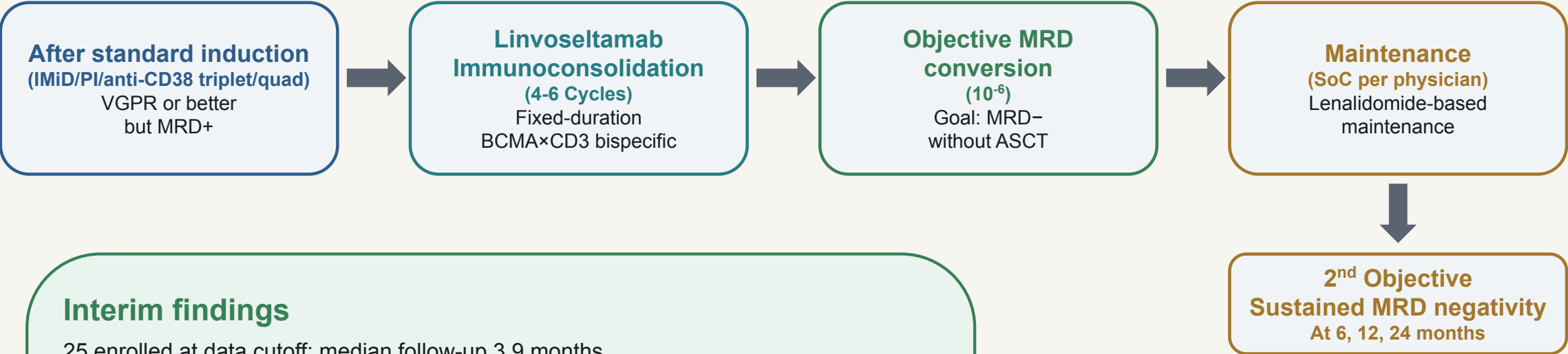
The therapeutic chessboard has changed

Deferring ASCT no longer means saving the only powerful rescue maneuver for later.



IMMUNOPLANT Study: immuno-consolidation as a transplant-sparing concept

A single-arm phase 2 study uses residual MRD after induction as the trigger for BCMA×CD3 bispecific consolidation.
University of Miami, Investigator-Sponsored Study



Interim findings

25 enrolled at data cutoff; median follow-up 3.9 months.

Overall Linvoseltamab Response by 6 Cycles
BM MRD negativity, n/N (%)
NGS <10⁻⁶ MRDneg: 18/18 (100; 95%CI: 81.5-100%)
Flow <10⁻⁵ MRDneg: 19/19 (100; 95%CI: 82.4-100%)

6-Month Post Linvo BMBx, N=10
BM MRD negativity, n (%)
NGS ≤10⁻⁶ MRDneg: 10 (100; 95%CI: 69.2-100%)
Flow ≤10⁻⁵ MRDneg: 10 (100; (95%CI: 69.15-100%)

Caveat: preliminary, single-arm and short follow-up — hypothesis-generating—

Summary:

ASCT is just another tool in the treatment armamentarium toolbox

It is a tool — not an automatic —by default— destination.

- The question should no longer be whether a patient is fit enough to receive melphalan 200 mg/m², but whether the patient's disease still requires it

1 Better induction

Quadruplets achieve unprecedented depth before transplant.



2 Better measurement

MRD tells us who has residual disease — and who may not need more cytotoxic therapy.



3 Better salvage

CAR-T and bispecific antibodies change the consequences of deferring ASCT.

Collect stem cells. Preserve the option. Stop treating transplant eligibility as a treatment indication.

Conclusions

- The historic triumph of melphalan was that more cytoreduction matters
- The modern challenge is knowing when enough cytoreduction is enough

Induce deeply

Use the best modern quadruplet.

Measure deeply

Use MRD to quantify what remains.

Escalate selectively

Reserve melphalan/ASCT for biology that still needs it.

The future is not “no transplant”
The future is no *unnecessary* transplant

Myeloma Institute at Sylvester Comprehensive Cancer



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Thank you

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