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# MRD in Multiple Myeloma: From Biomarker to Clinical Decision Tool

## Transforming Myeloma and Redefining Drug Development

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May 15,  
2026*



**MYELOMA  
INSTITUTE**



@SylvesterCancer



# Disclosures

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- Honoraria/ad boards: AbbVie, Adaptive, Amgen, Binding Site, BMS, Celgene, GSK, Janssen, Pfizer, Sanofi
- Chairman for “Medscape Myeloma”: 2014-2025
- Chairman for “Myeloma Rounds in the US” (CME): 2023-ongoing
- Independent Data Monitoring Committee (IDMC): Merck, Janssen, Novartis, Arcellx

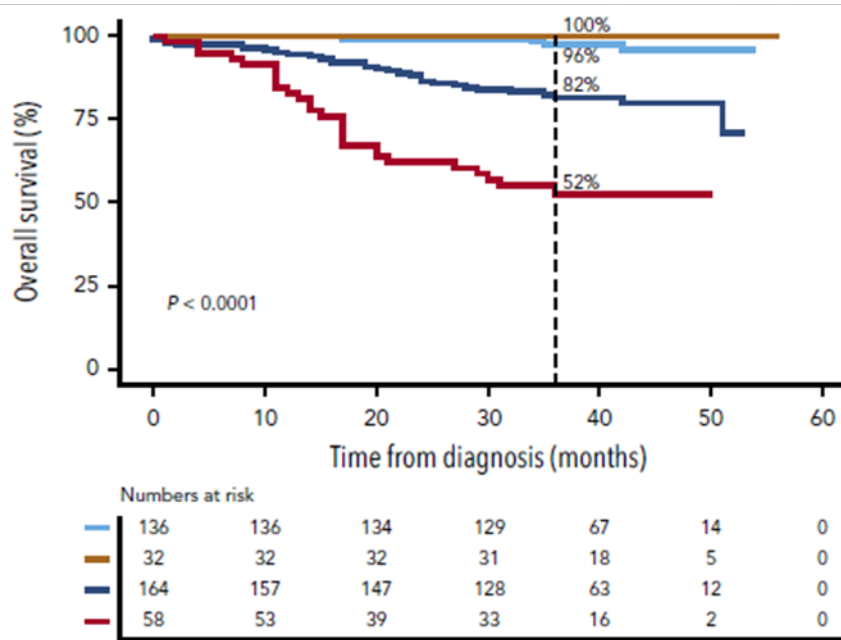
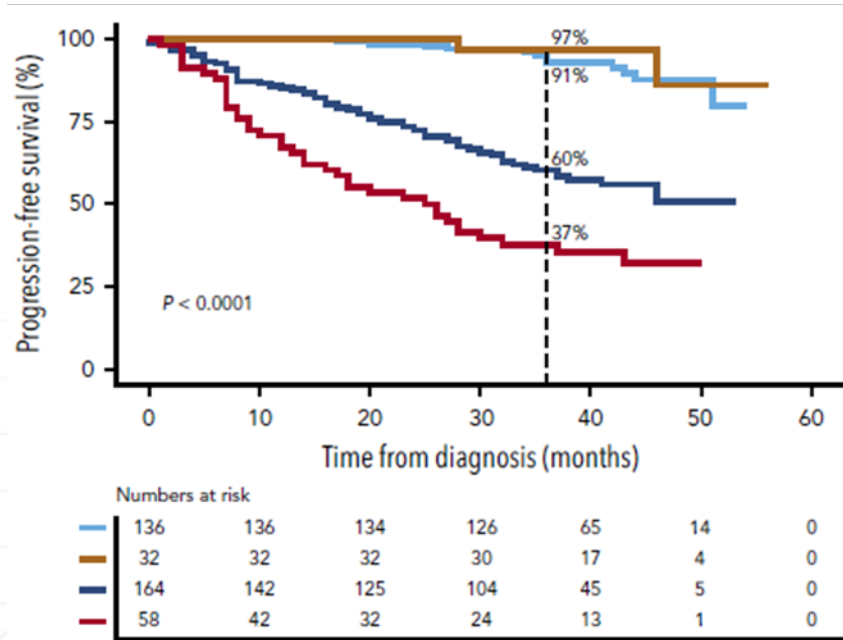
# Outline

- **How relevant is MRD in multiple myeloma?**
- **Accelerated drug approval**
- **MRD guided therapy and beyond**

# Multiple Myeloma

- Multiple myeloma has the 2<sup>nd</sup> highest incidence for blood malignancies, affecting over 36,000 Americans annually
- More than 190,000 individuals live with multiple myeloma in the U.S.
- The disease is genomically highly heterogeneous with 1000s of mutations detectable at diagnosis
- Although we lack established curative treatments for the disease, modern combination therapies allow high rates of patients to obtain deep and durable treatment responses (i.e., MRD negativity)

# MRD Negativity Predicts Outcomes, Independent of FISH Data



390 NDMM patients in the PETHEMA/GEM2012 MENOS65 trial were evaluated for MRD

300 patients had standard-risk cytogenetic abnormalities while 90 had high-risk MRD was assessed by EuroFlow MRD

Standard risk, MRD negative  
 Standard risk, MRD positive

High-risk, MRD negative  
 High-risk, MRD positive

# How to Assess MRD Status in a Myeloma Patient?

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## NCCN Guidelines Version 2.2026 Multiple Myeloma

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### RESPONSE CRITERIA FOR MULTIPLE MYELOMA (Revised based on the new criteria by International Myeloma Working Group [IMWG])

IMWG criteria for response assessment including criteria for minimal residual disease (MRD)	
Response Category <sup>a</sup>	Response Criteria
<b>IMWG MRD criteria (requires a complete response as defined below)</b>	
<b>Sustained MRD-negative</b>	MRD negativity in the marrow (next-generation flow [NGF], next-generation sequencing [NGS], or both) and by imaging as defined below, confirmed minimum of 1 year apart. Subsequent evaluations can be used to further specify the duration of negativity (eg, MRD-negative at 5 years). <sup>c</sup>
<b>Flow MRD-negative</b>	Absence of phenotypically aberrant clonal plasma cells by NGF <sup>c</sup> on bone marrow aspirates using the EuroFlow standard operation procedure for MRD detection in multiple myeloma (or validated equivalent method) with a minimum sensitivity of 1 in 10 <sup>5</sup> nucleated cells or higher.
<b>Sequencing MRD-negative</b>	Absence of clonal plasma cells by NGS on bone marrow aspirate in which presence of a clone is defined as less than two identical sequencing reads obtained after DNA sequencing of bone marrow aspirates using a validated equivalent method with a minimum sensitivity of 1 in 10 <sup>5</sup> nucleated cells <sup>d</sup> or higher.
<b>Imaging plus MRD-negative</b>	MRD negativity as defined by NGF or NGS plus disappearance of every area of increased tracer uptake found at baseline or a preceding FDG-PET/CT or decrease to less mediastinal blood pool standardized uptake value (SUV) or decrease to less than that of surrounding normal tissue. <sup>e</sup>
<b>Standard IMWG response criteria<sup>f</sup></b>	
<b>Stringent complete response</b>	Complete response as defined below plus normal FLC ratio <sup>g</sup> and absence of clonal cells in bone marrow biopsy by immunohistochemistry (κ/λ ratio ≤4:1 or ≥1:2 for κ and λ patients, respectively, after counting ≥100 plasma cells). <sup>h</sup>
<b>Complete response<sup>i</sup></b>	Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and <5% plasma cells in bone marrow aspirates.
<b>Very good partial response</b>	Serum and urine M-protein detectable by immunofixation but not on electrophoresis or ≥90% reduction in serum M-protein plus urine M-protein level <100 mg per 24 h.
<b>Partial response</b>	≥50% reduction of serum M-protein plus reduction in 24-h urinary M-protein by ≥90% or to <200 mg per 24 h. If the serum and urine M-protein are unmeasurable, a ≥50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria. If serum and urine M-protein are unmeasurable, and serum-free light assay is also unmeasurable, ≥50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma-cell percentage was ≥30%. In addition to these criteria, if present at baseline, a ≥50% reduction in the size (sum of the products of the maximal perpendicular diameters [SPD] of measured lesions <sup>j</sup> ) of soft tissue plasmacytomas is also required.
<b>Minimal response</b>	≥25% but ≤49% reduction of serum M-protein and reduction in 24-h urine M-protein by 50%–89%. In addition to the above listed criteria, if present at baseline, a 25%–49% reduction in SPD <sup>j</sup> of soft tissue plasmacytomas is also required.

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### IMWG MRD criteria\*:

- Flow MRD-negative
- Sequencing MRD-negative
- Sustained MRD-negative
- Imaging plus MRD-negative

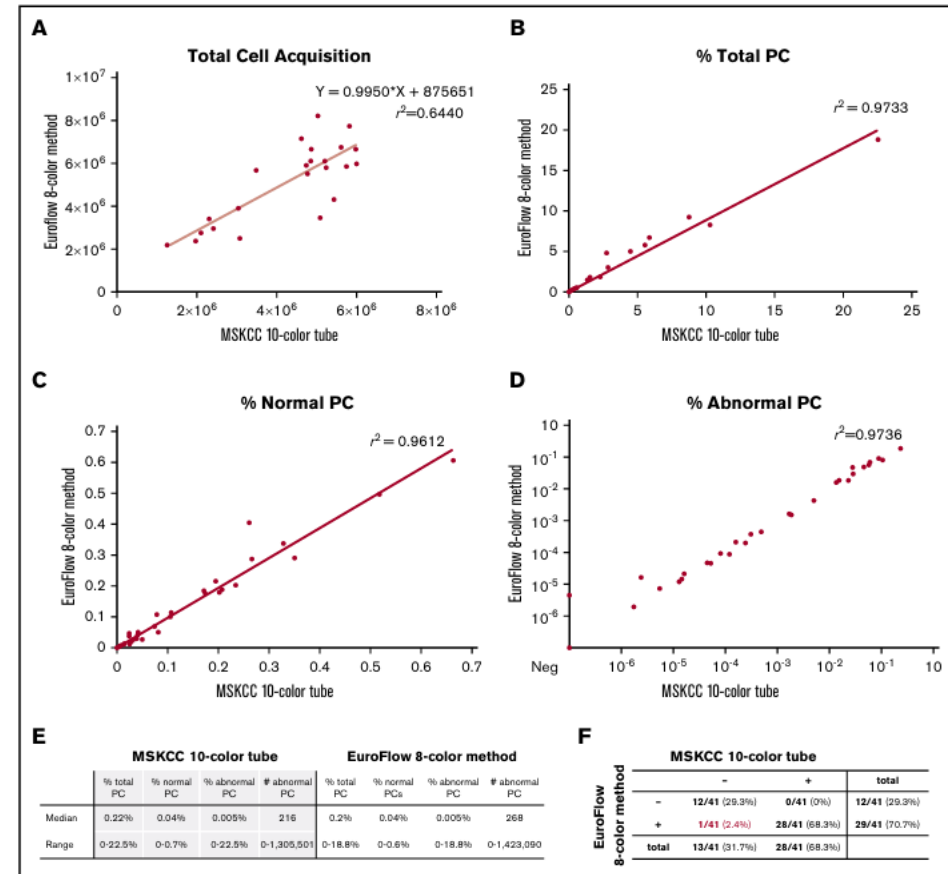
\*Requires a complete response (i.e., negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and <5% plasma cells in bone marrow aspirates)

# Multi-Color Flow Cytometry MRD

**European approach.** The EuroFlow 8-color 2-tube method uses surface-only staining in 1 tube that consists of individually added antibodies and a separate tube that uses a 2-step procedure of surface staining followed by cytoplasmic light chain staining

**U.S. approach.** The MSKCC 10-color single-tube MRD method uses EuroFlow bulk lysis followed by surface antibody staining, which consists of a surface antibody cocktail of CD117, CD19, CD138, CD81, CD56, CD38, CD27, and CD45, followed by fixation and/or permeabilization and staining with anti-K fluorescein isothiocyanate and anti-L phycoerythrin antibodies

Overall concordance between the 2 tests is 98%

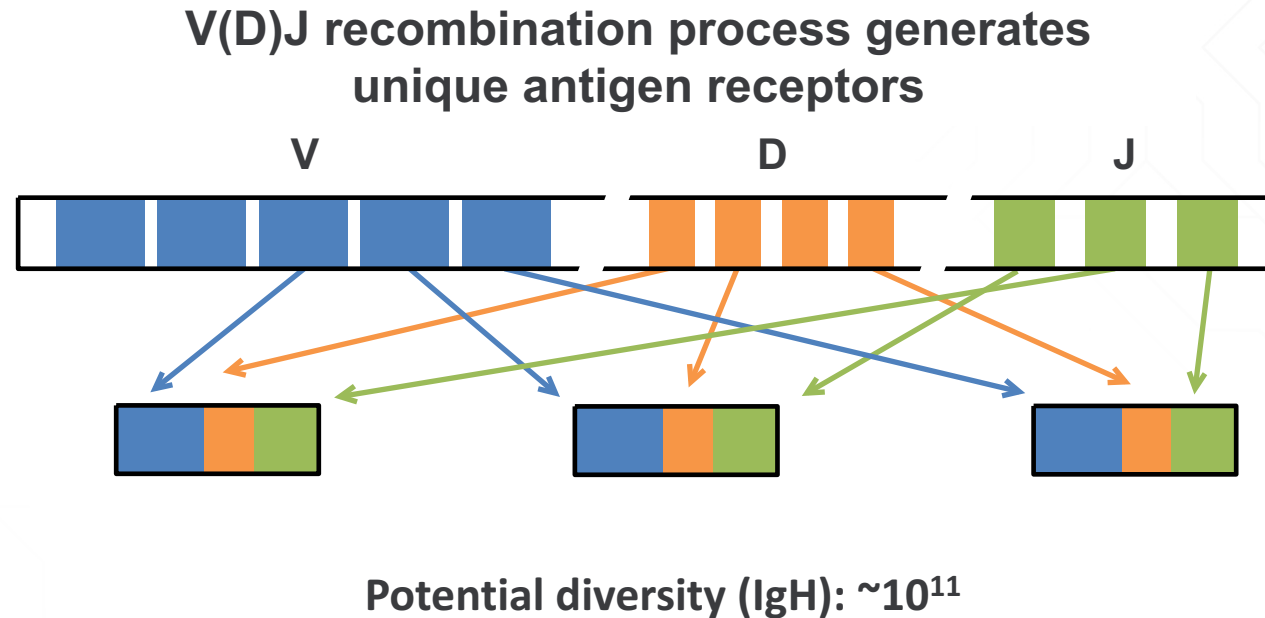


**Figure 1.** Comparison of MSKCC single 10-color tube and EuroFlow two 8-color tubes. (A) Total cell acquisition, percentage of (B) total plasma cells (PCs), (C) normal plasma cells, and (D) abnormal plasma cells, along with (E-F) tables containing a summary of the data.

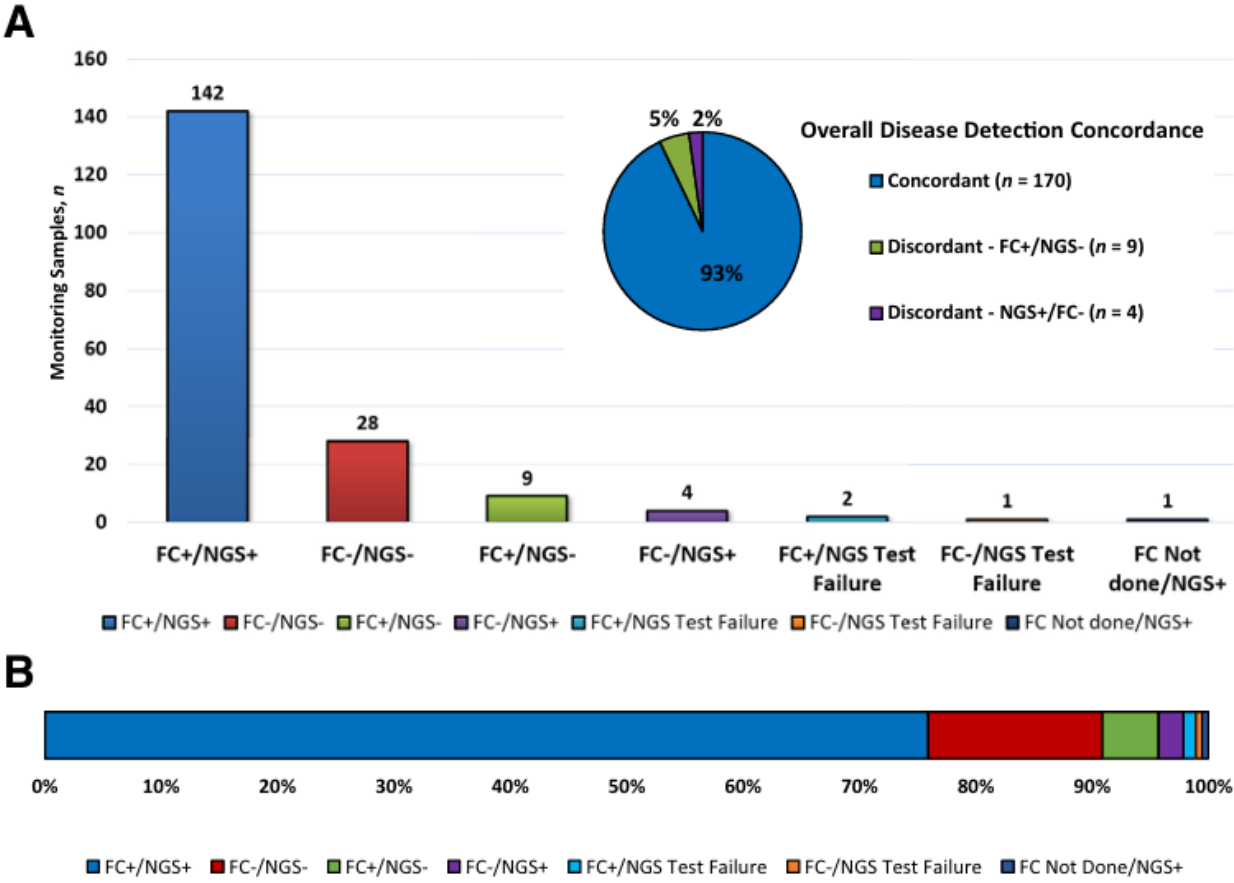
# clonoSEQ (NGS): FDA-Cleared MRD Myeloma Testing

**Identifies and quantifies specific DNA sequences associated with malignant B or T cells**

- DNA is extracted from the patient sample. PCR is used to amplify specific B- or T-cell receptor sequences, including Variable, Diversity, and Joining gene segments
- Using NGS, dominant cancer associated DNA sequences are identified
- These sequences are tracked to monitor MRD over time; sensitivity  $10^{-6}$



# NGS and Multi-Color Flow Cytometry MRD in Parallel



**Figure 6** Comparison of residual disease detection among 187 monitoring samples by flow cytometry (FC) and next-generation sequencing (NGS) assay. Results represented by a bar graph (A). Also shown is the percentage of cases with concordant and discordant residual disease status by the two assays. Results represented as cumulative percentage of total number of cases (B).

# Outline

- How relevant is MRD in multiple myeloma?
- Accelerated drug approval
- MRD guided therapy and beyond

# How Will MRD Testing Be Used in Multiple Myeloma?

## Opportunities

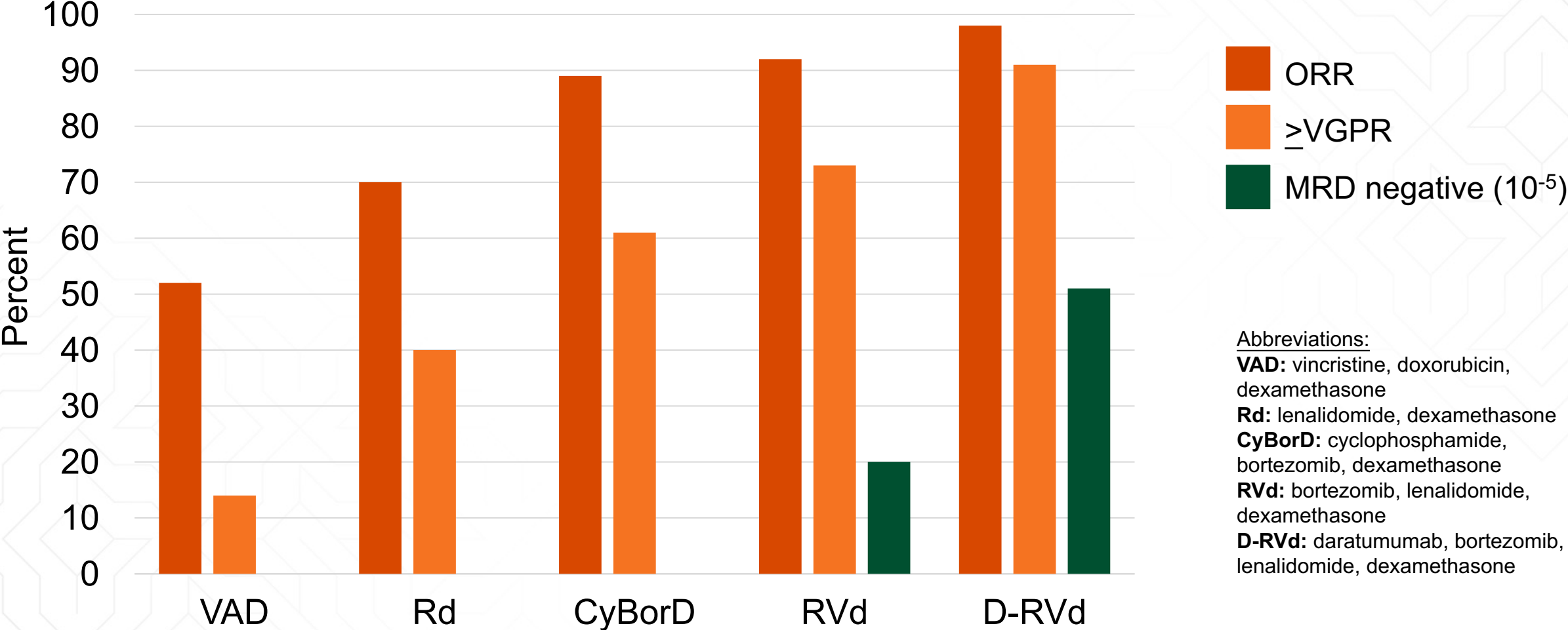
- Shortened drug development by 5 to 10+ years for individual drugs
- More new drugs will be developed for treatment of earlier lines
- Higher speed of change for the field overall



# FDA Initiatives to Help Multiple Myeloma Drug Development

- **Implementation of Accelerated Approval pathway** whereby approval may be granted based on intermediate endpoints reasonably likely to predict clinical benefit and can be measured earlier than disease progression or death
- **Launching of Project FrontRunner** to encourage development of treatments that may benefit patients in an earlier stage of their disease, rather than the usual sequential approach of first seeking approval for patients in the relapsed/refractory setting who have received numerous prior lines of therapy
- For multiple myeloma, overall response rate (ORR) has been identified as an intermediate endpoint reasonably likely to predict clinical benefit and the basis for accelerated approval. However, in newly diagnosed multiple myeloma ORR is challenging to use as an endpoint

# Treatment Responses in Newly Diagnosed Multiple Myeloma

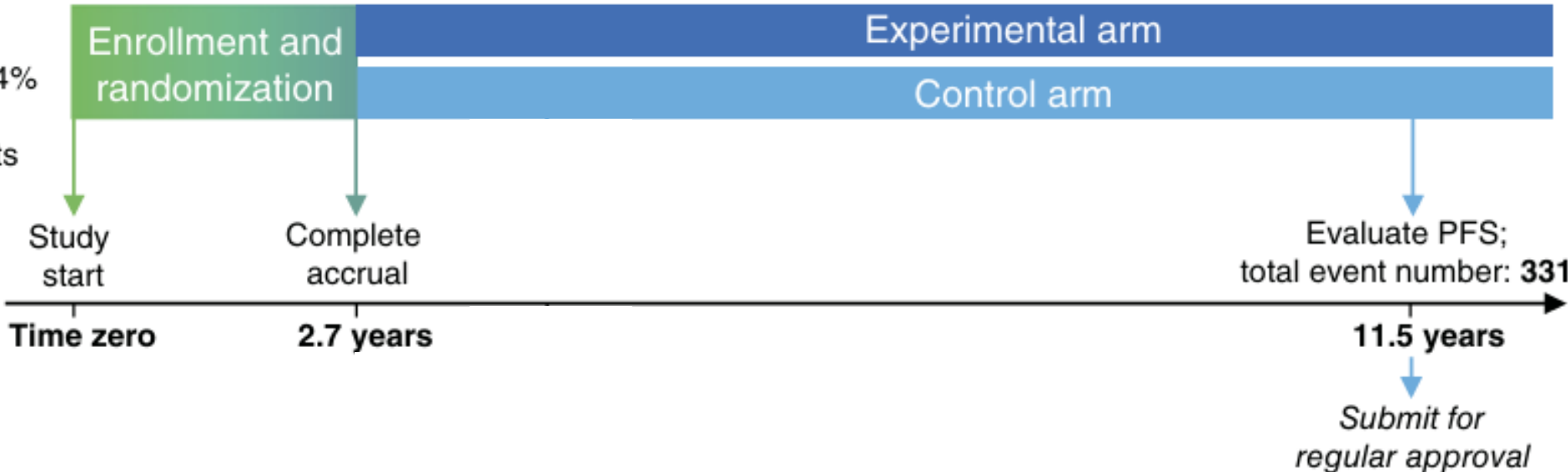


**Abbreviations:**  
**VAD:** vincristine, doxorubicin, dexamethasone  
**Rd:** lenalidomide, dexamethasone  
**CyBorD:** cyclophosphamide, bortezomib, dexamethasone  
**RVd:** bortezomib, lenalidomide, dexamethasone  
**D-RVd:** daratumumab, bortezomib, lenalidomide, dexamethasone

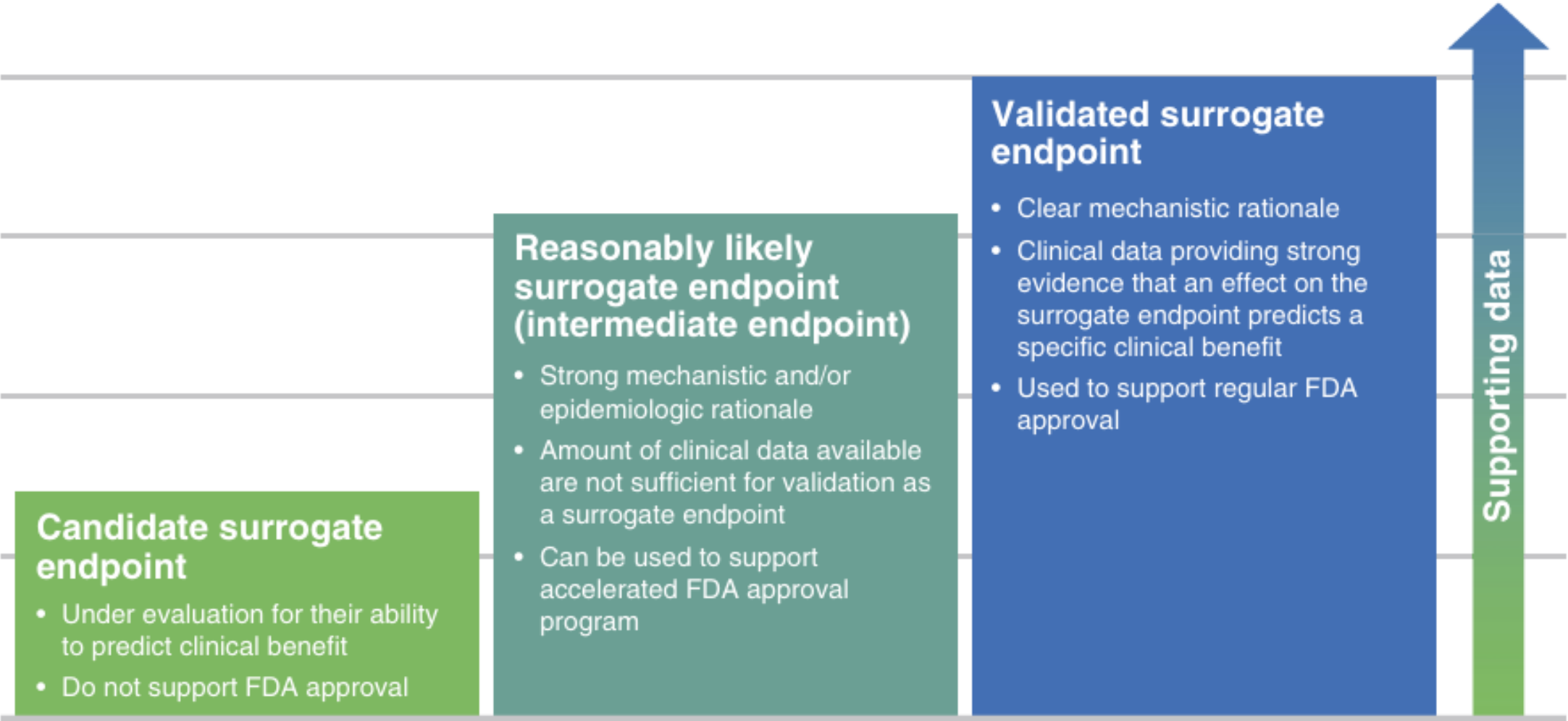
# MRD as Early Endpoint in Myeloma: To Save Many Lives!

## Example in newly diagnosed multiple myeloma

- Expected 4-year PFS: 84% for SOC (HR, 0.70)  
Sample size: 960 patients
- Accrual rate: 30 patients/month



# Definitions of Surrogate Endpoints



# Developing MRD As a Regulatory Endpoint: My Reflections...



Choosing a Solution



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# Evaluating Minimal Residual Disease as an Intermediate Clinical Endpoint for Multiple Myeloma: The EVIDENCE Meta-Analysis

PIND 137517: ODAC Meeting 12 Apr 24

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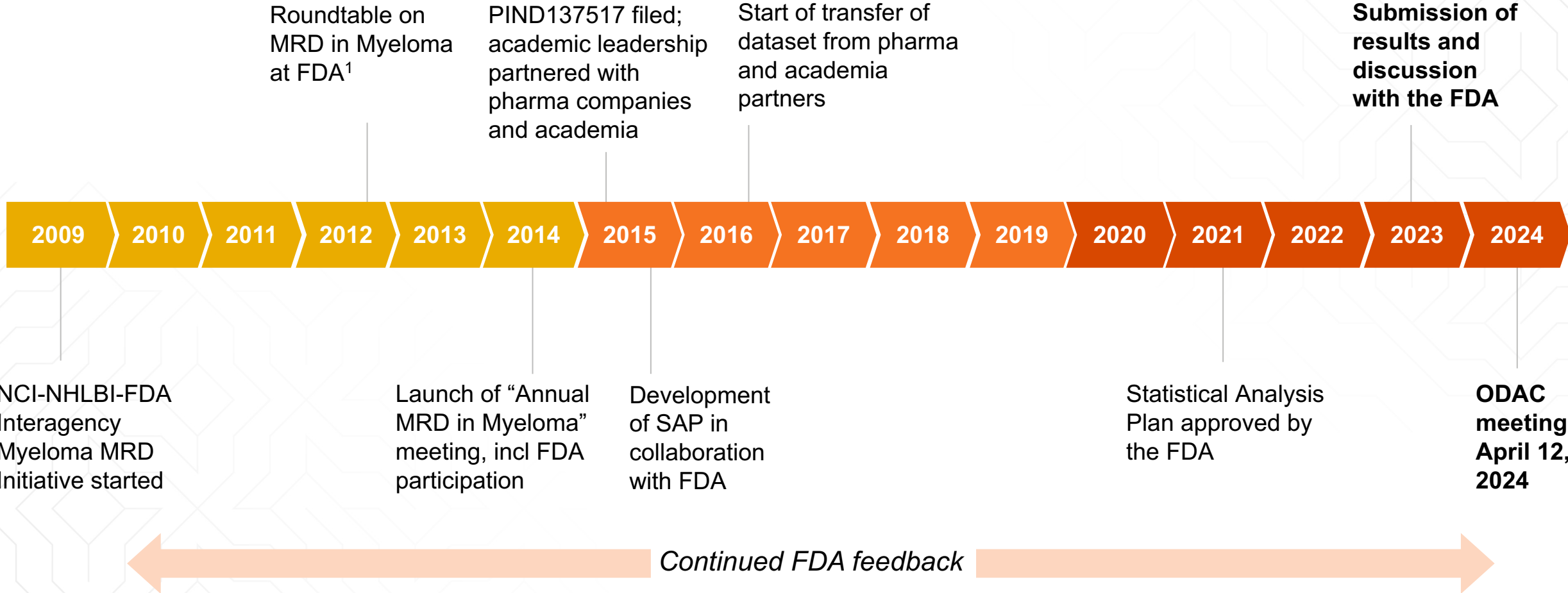
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# Development of EVIDENCE Meta-Analysis

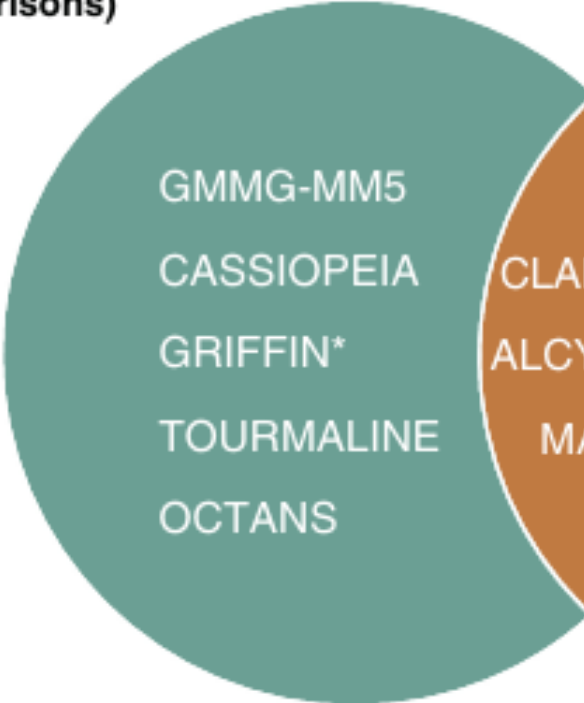


<sup>1</sup> Landgren O, Gormley N, Turley D, Owen RG, Rawstron A, Paiva B, Barnett D, Arroz M, Wallace P, Durie B, Yuan C, Dogan A, Stetler-Stevenson M, Marti GE. Flow cytometry detection of minimal residual disease in multiple myeloma: Lessons learned at FDA-NCI roundtable symposium. Am J Hematol. 2014;89(12):1159-60



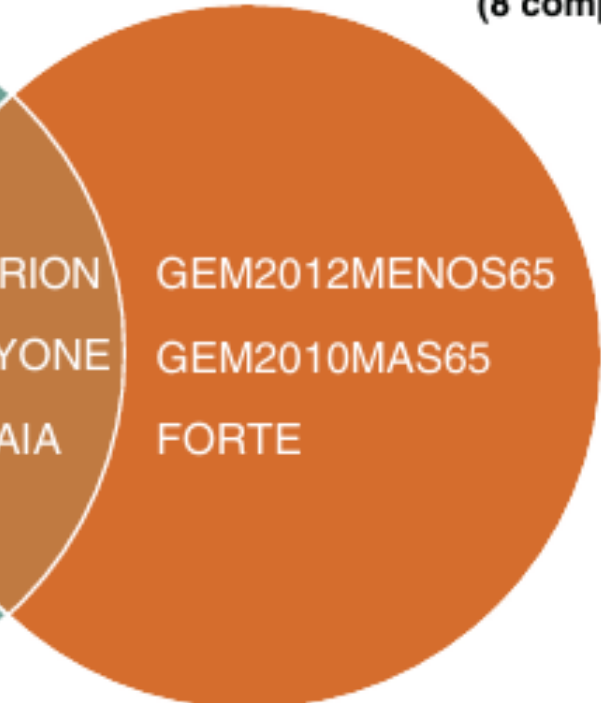
# Newly Diagnosed Multiple Myeloma Studies Included in EVIDENCE Meta-Analysis and I2TEAMM study: 12m MRD negative CR at $10^{-5}$ threshold

**EVIDENCE**  
(9 comparisons)



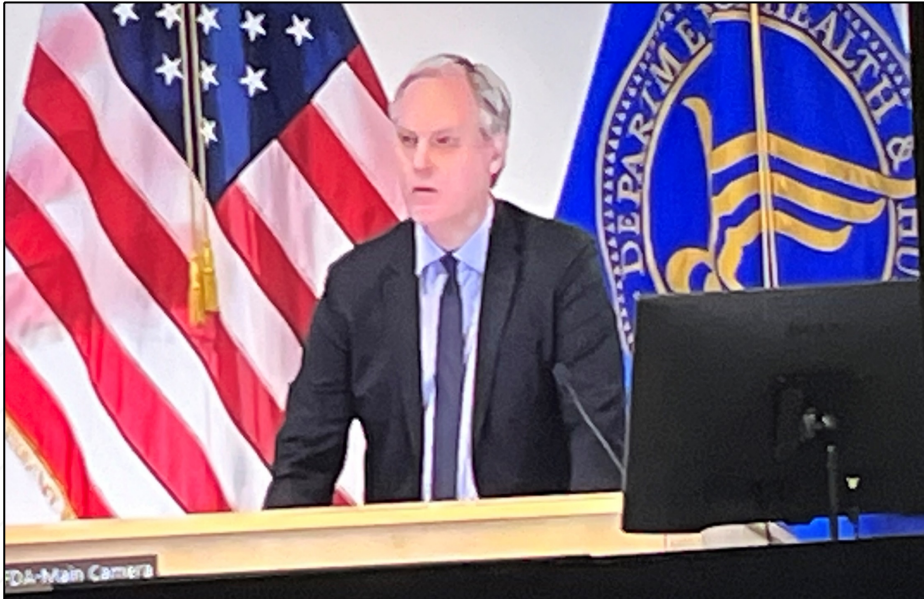
N = 6965

**I<sup>2</sup>TEAMM**  
(8 comparisons)



N = 6325

\*Included in 9m MRD negative CR analysis for I2TEAMM, and sensitivity analysis in EVIDENCE

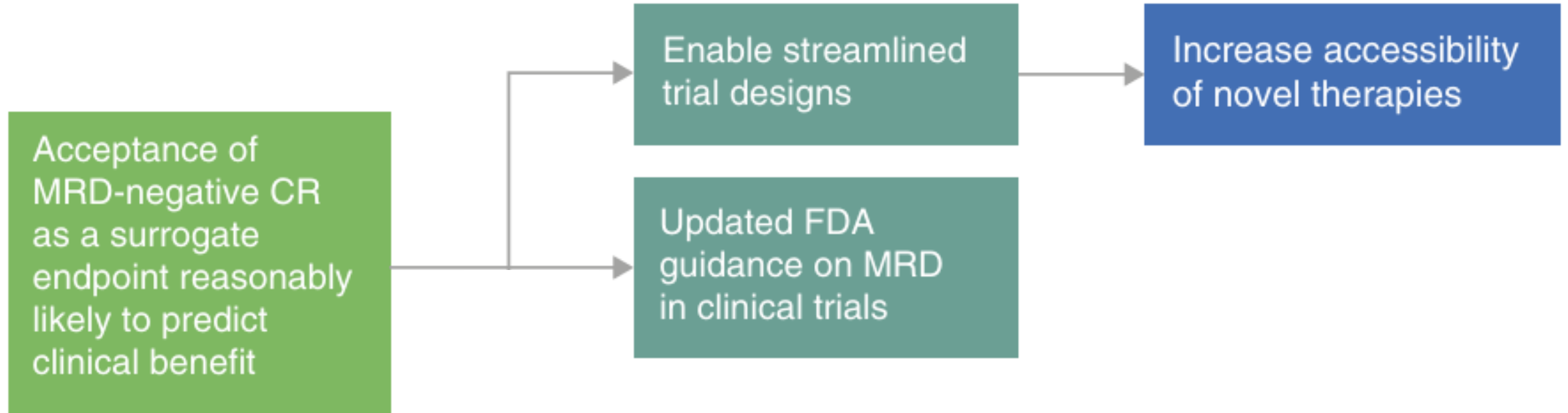


<b>Yes</b>	<b>12</b>	<b>4/12/2024</b>	
<b>No</b>	<b>0</b>	<b>3:05:45 PM</b>	
<b>Abstain</b>	<b>0</b>		
<b>Non-Vote Member</b>	<b>0</b>		
<b>Yes</b>	<b>Vote: 12</b>		
Christopher Hourigan	Christopher Lieu	David Mitchell (CR)	Grzegorz Nowakowski ...
Jorge Nieva	Mark Conaway	Matthew Maurer	Michael Riotto
Neil Vasani	Ranjana Advani	Ravi Madan	Thomas Martin
<b>No</b>	<b>Vote: 0</b>		
<b>Abstain</b>	<b>Vote: 0</b>		
<b>No-Voting</b>	<b>Total: 0</b>		

# FIERCE 50 Breakthroughs Honoree 2024 Award in NYC



# What Are the Implications of All This Work?



# Miami Myeloma MRD Meetings: 13<sup>th</sup> Annual Meeting in 2026

- 30 speakers
- 100 attendees in-person
- 850 attendees virtually



# 13<sup>th</sup> Annual Miami Myeloma MRD 2026 Meeting

Hosted by:



Official Media Partner:



In collaboration with:



Florida Society of Clinical Oncology

# ~~Miami Memo On MRD 2027~~

- Expansion from **myeloma only** → **include all hematologic malignancies**, e.g., myeloma, CLL, lymphoma, AML, MPNs
- Also include **solid tumors**, e.g., bladder cancer, breast cancer, lung cancer, colorectal cancer
- All types of **novel MRD technologies** are welcome
- Open for **academia, pharma, FDA, and patients**
- Plan for a **2-day meeting in Miami + virtually**

**DRAFT**

# Outline

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# How Will MRD Testing Be Used in Multiple Myeloma?

## Opportunities

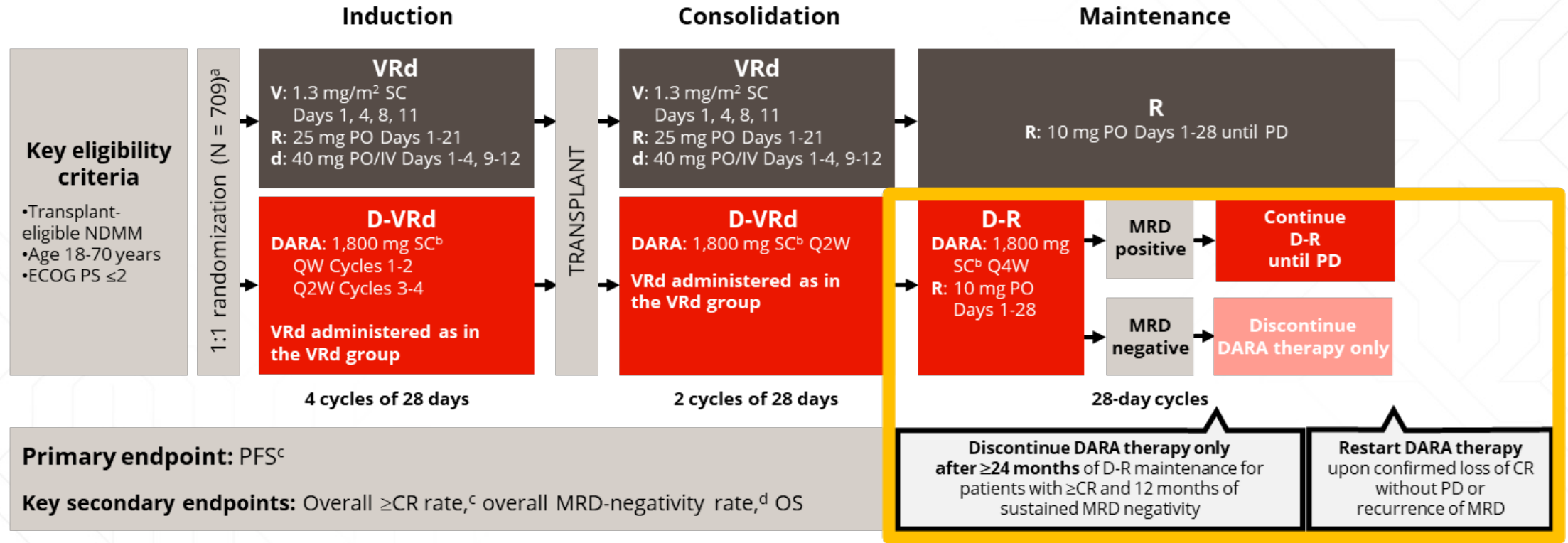
- Shortened drug development by 5 to 10+ years for individual drugs
- More new drugs will be developed for treatment of earlier lines
- Higher speed of change for the field overall



## Opportunities

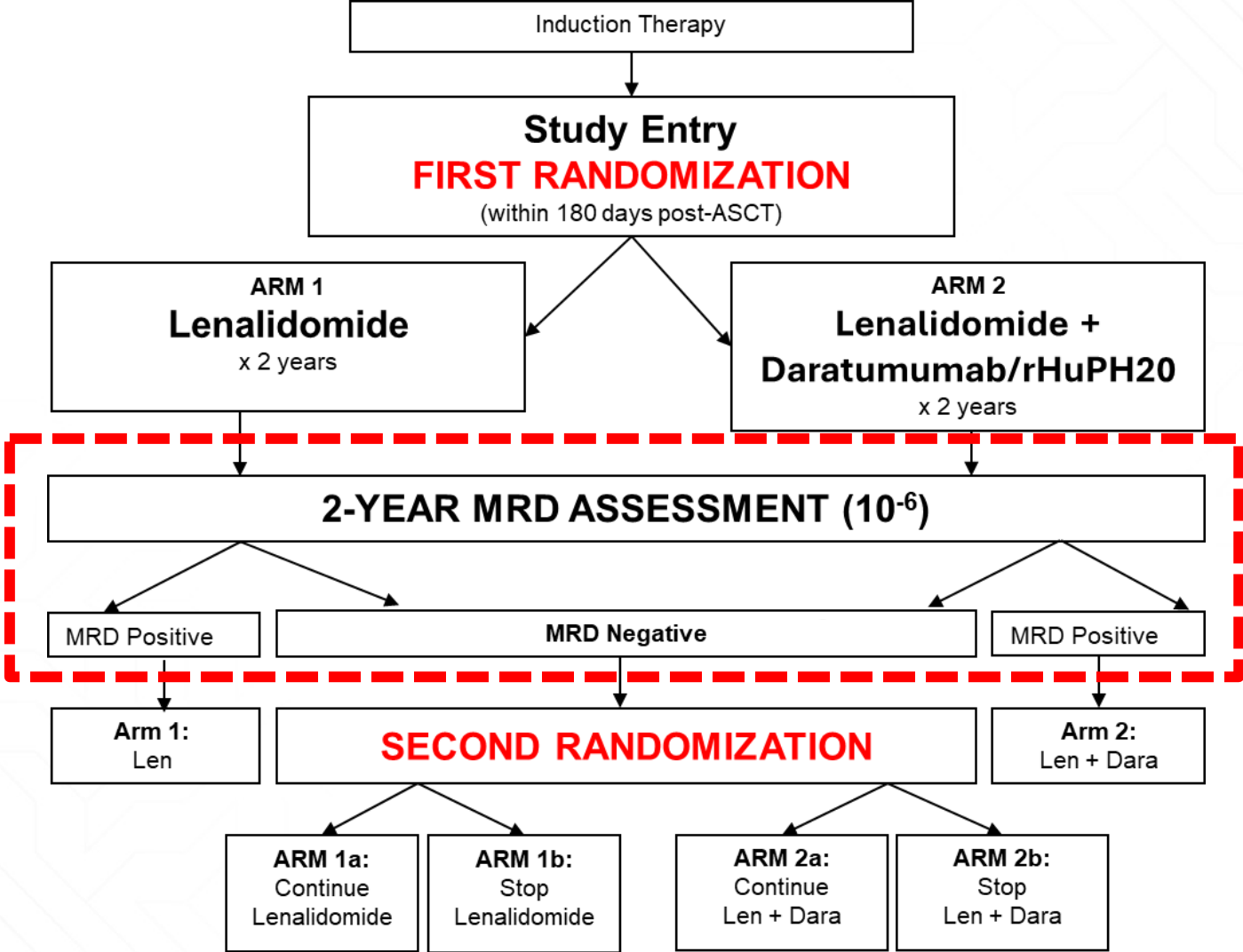
- Personalized clinical management of every patient, based on depth of response to therapy
- Identification of molecular relapse; will likely lead to earlier initiation of new therapy
- Patients with sustained MRD-negativity may go off therapy (indefinitely?)

# Phase 3 PERSEUS Study Design

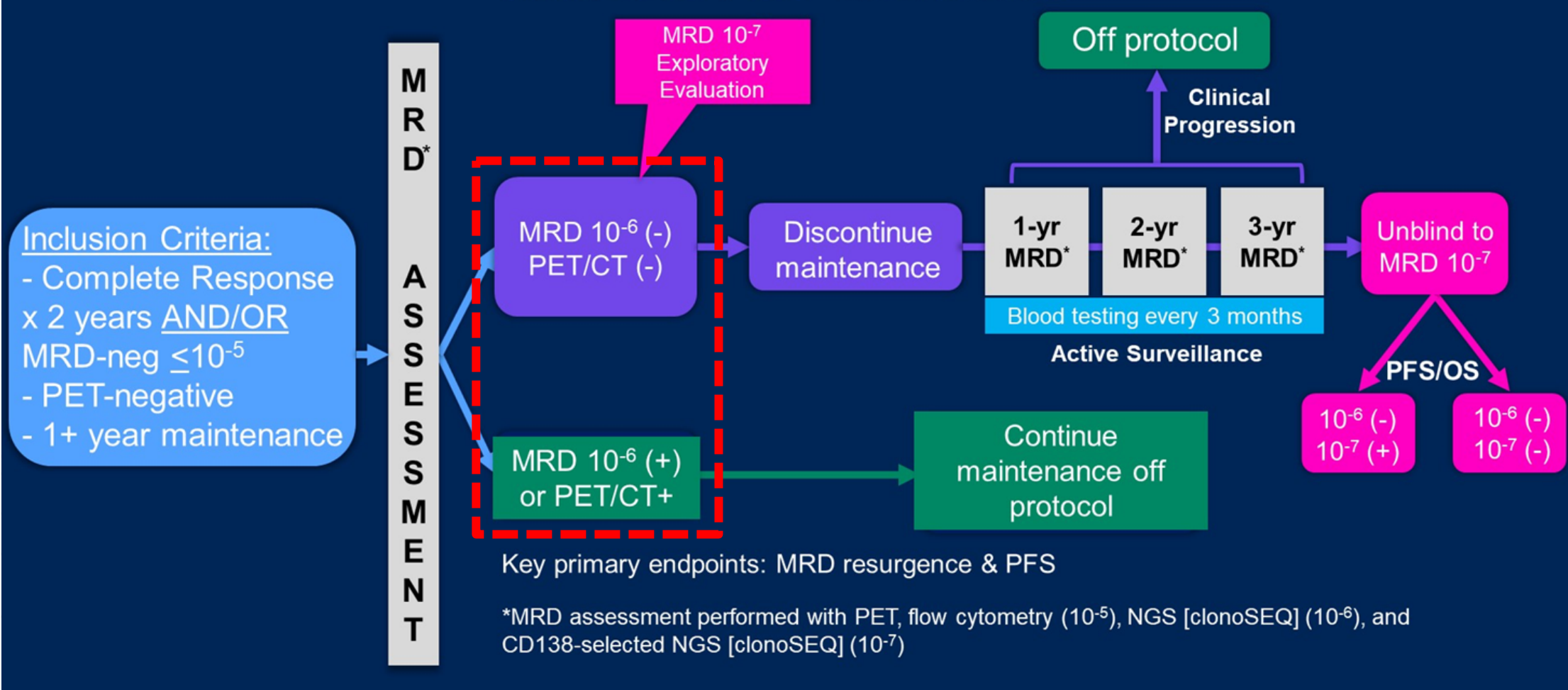


ECOG PS, Eastern Cooperative Oncology Group performance status; V, bortezomib; SC, subcutaneous; PO, oral; d, dexamethasone; IV, intravenous; QW, weekly; Q2W, every 2 weeks; PD, progressive disease; Q4W, every 4 weeks; MRD, minimal residual disease; OS, overall survival; ISS, International Staging System; rHuPH20, recombinant human hyaluronidase PH20; IMWG, International Myeloma Working Group; VGPR, very good partial response. <sup>a</sup>Stratified by ISS stage and cytogenetic risk. <sup>b</sup>DARA 1,800 mg co-formulated with rHuPH20 (2,000 U/mL; ENHANZE<sup>®</sup> drug delivery technology, Halozyme, Inc., San Diego, CA, USA). <sup>c</sup>Response and disease progression were assessed using a computerized algorithm based on IMWG response criteria. <sup>d</sup>MRD was assessed using the clonoSEQ assay (v.2.0; Adaptive Biotechnologies, Seattle, WA, USA) in patients with ≥VGPR post-consolidation and at the time of suspected ≥CR. Overall, the MRD-negativity rate was defined as the proportion of patients who achieved both MRD negativity (10<sup>-5</sup> threshold) and ≥CR at any time.

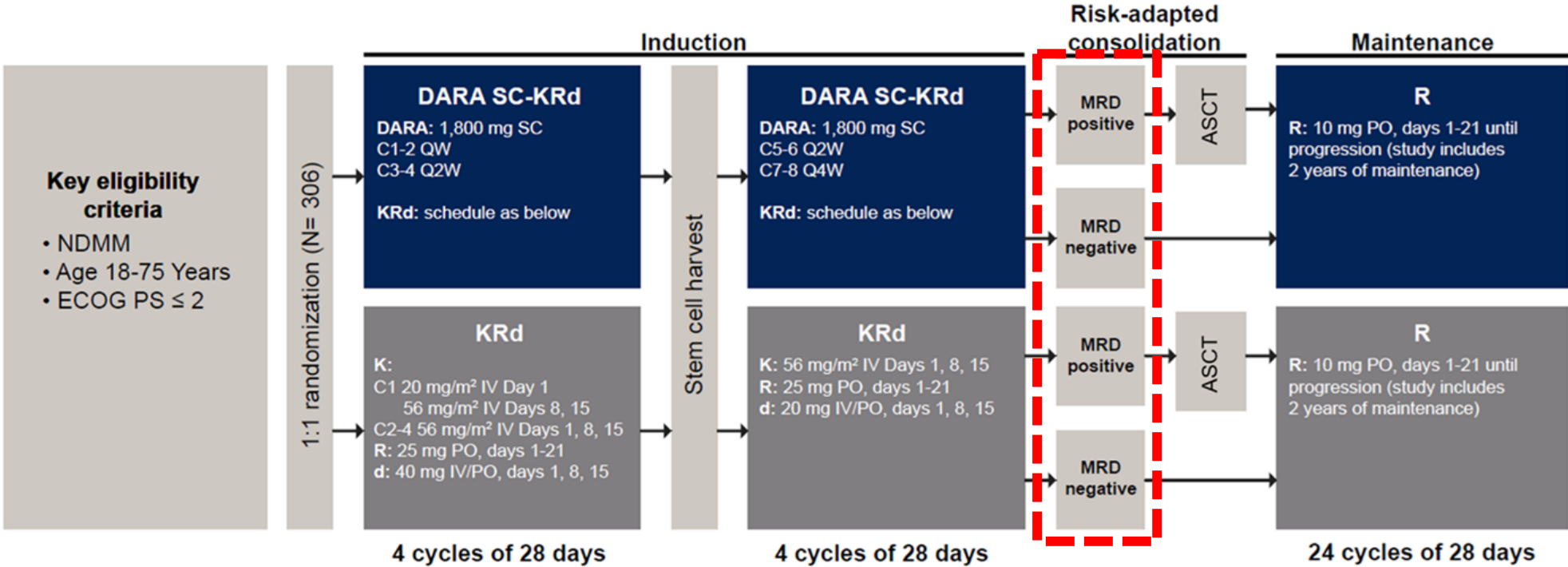
# Phase 3 DRAMMATIC Study Design



# Phase 2 MRD2STOP Study Design



# Phase 2 ADVANCE Study Design



**Primary endpoint:** Overall MRD negativity rate ≥VGPR

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

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

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.

# MRD Testing in Multiple Myeloma: Select Gaps

- Urgent need for blood-based MRD tests that are sensitive, reproducible, and widely available
- Need to update MRD guidelines (e.g., MRD negativity in patients with VGPR, strategies to better define focal/extramedullary disease, increased sensitivity)
- Integration of MRD and disease (and immune) profiling

# Patterns Across the Trials: Efficacy

Adding a 4<sup>th</sup> drug improves the MRD negativity rate and PFS, regardless of age and transplant status

	IMROZ trial		BENEFIT trial		PERSEUS trial	
<b>Combination regimen</b>	<u>I</u> sa-VRd	VRd	I <u>s</u> a-VRd	I <u>s</u> a-Rd	<u>D</u> ara-VRd, transplant	VRd, transplant
<b>Maintenance</b>	<u>I</u> sa-Rd	Rd	I <u>s</u> a-R	I <u>s</u> a-R	<u>D</u> ara-R	R
<b>Median age (range)</b>	72 (60-80)	72 (55-80)	74 (71-76)	73 (71-76)	61 (32-70)	59 (31-70)
<b>Transplant status</b>	Transplant Ineligible (TI)		Transplant Ineligible (TI)		Transplant Eligible (TE)	
<b>MRD negativity 10<sup>-5</sup> rate</b>	47% sust ≥12 mo	24% sust ≥12 mo	53% at 18 mo	26% at 18 mo	65% at 12 mo	39% at 12 mo
<b>PFS</b>	63% at 60 mo	45% at 60 mo	85% at 24 mo	80% at 24 mo	71% at 30 mo	56% at 30 mo

*I*sa = isatuximab, *d*ara = daratumumab, *V* = bortezomib, *R* = lenalidomide, *d* = dexamethasone

**Why are we still talking about TE and TI patients in the modern era???**

# Myeloma Program at Sylvester Comprehensive Cancer Center, University of Miami

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Multiple Myeloma  
Research Program Fund**



**Cannon Guzy  
Family Fund**



***And many, many more!***





# *Thank you for your attention!*

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