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

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# Study Leadership



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*Lead Principal Investigator*

**Professor, Medicine**

**Expertise:** Multiple Myeloma,  
Early Drug Development,  
Biomarker Development, MRD  
Assays



**Sean Devlin, Ph.D**

*Lead Study Statistician*

**Associate Attending, Biostatistics**

**Expertise:** Clinical Trial Design,  
Evaluation of Prognostic Models

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



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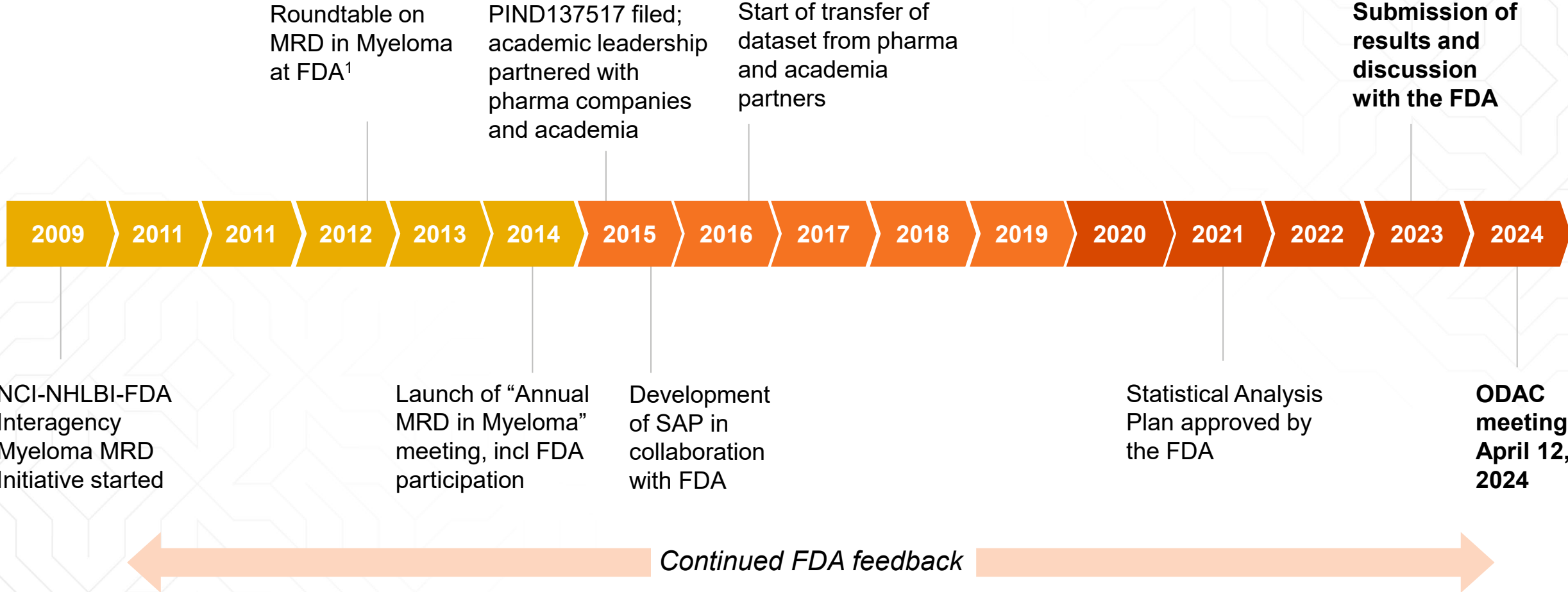
abbvie

# Focus for Today

- For multiple myeloma, no established curative therapy is yet available
- The most effective treatment is in the first line
- With current endpoints (PFS and OS), studies for patients with newly diagnosed multiple myeloma are taking a long time to mature. **New effective therapies are unavailable to patients for more than 10 years, while waiting for studies to mature**

**Can MRD serve as an objective and reliable early endpoint for accelerated approval in multiple myeloma, to facilitate patients' access to new drugs?**

# History of This MRD Initiative



<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

# Multiple Myeloma, Unmet Medical Need, and Role of MRD



**C. Ola Landgren, M.D., Ph.D**

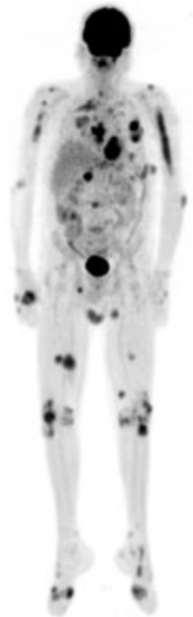
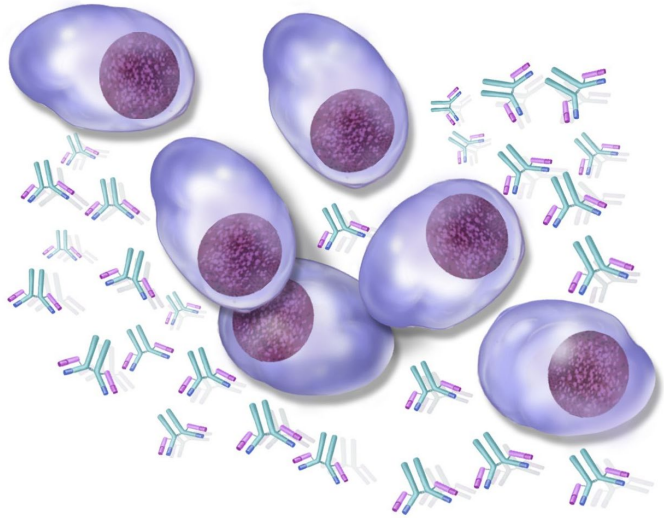
*Lead Principal Investigator*

**Professor, Medicine**

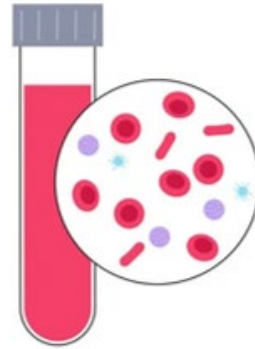
**Expertise:** Multiple Myeloma,  
Early Drug Development,  
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Assays

# Multiple Myeloma Background

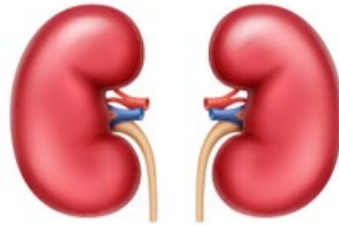
## Myeloma cells and monoclonal proteins



*Lytic bone lesions*



*Anemia*



*Renal failure*



*Immunosuppression and infections*



*Hypercalcemia*

- In the U.S. more than 35,700 new multiple myeloma cases are diagnosed annually; over 170,000 individuals are living with the disease
- Blacks have a 2-fold higher incidence of multiple myeloma, and ~10 years earlier age of onset (compared to Caucasians)
- New therapeutic approaches have resulted in substantial improvements in PFS for patients with newly diagnosed and relapsed/refractory multiple myeloma
- Despite numerous new drug approvals in recent years, there is no established curative therapy, reflected in over 12,500 deaths in the U.S. in 2023

# Treatment Landscape for Newly Diagnosed Multiple Myeloma

NCCN National Comprehensive Cancer Network® **NCCN Guidelines Version 3.2024 Multiple Myeloma** [NCCN Guidelines Index](#) [Table of Contents](#) [Discussion](#)

PRIMARY THERAPY FOR TRANSPLANT CANDIDATES <sup>a-d</sup>
<b>Preferred Regimens</b> <ul style="list-style-type: none"> <li>• Bortezomib/lenalidomide/dexamethasone (category 1)</li> <li>• Carfilzomib/lenalidomide/dexamethasone<sup>k</sup></li> </ul>
<b>Other Recommended Regimens</b> <ul style="list-style-type: none"> <li>• Daratumumab/lenalidomide/bortezomib/dexamethasone</li> </ul>
<b>Useful in Certain Circumstances</b> <ul style="list-style-type: none"> <li>• Bortezomib/cyclophosphamide/dexamethasone<sup>e</sup></li> <li>• Bortezomib/doxorubicin/dexamethasone</li> <li>• Carfilzomib/cyclophosphamide/dexamethasone<sup>e,f,k</sup></li> <li>• Daratumumab/bortezomib/thalidomide/dexamethasone</li> <li>• Daratumumab/bortezomib/cyclophosphamide/dexamethasone</li> <li>• Daratumumab/carfilzomib/lenalidomide/dexamethasone<sup>k</sup></li> <li>• Dexamethasone/thalidomide/cisplatin/doxorubicin/cyclophosphamide/etoposide/bortezomib<sup>g</sup> (VTD-PACE)</li> <li>• Isatuximab-irfc/lenalidomide/bortezomib/dexamethasone</li> </ul>
<b>MAINTENANCE THERAPY</b> <b>Preferred Regimens</b> <ul style="list-style-type: none"> <li>• Lenalidomide<sup>h</sup> (category 1)</li> </ul> <b>Other Recommended Regimens</b> <ul style="list-style-type: none"> <li>• Bortezomib</li> </ul> <b>Useful in Certain Circumstances<sup>z</sup></b> <ul style="list-style-type: none"> <li>• Bortezomib/lenalidomide<sup>l</sup></li> <li>• Carfilzomib/lenalidomide<sup>l</sup></li> <li>• Daratumumab ± lenalidomide<sup>l</sup></li> <li>• Ixazomib (category 2B)<sup>l</sup></li> </ul>

<sup>a</sup> Selected, but not inclusive of all regimens. The regimens under each preference category are listed by order of NCCN Category of Evidence and Consensus alphabetically.  
<sup>b</sup> [Supportive Care Treatment for Multiple Myeloma \(MYEL-H\)](#).  
<sup>c</sup> [General Considerations for Myeloma Therapy \(MYEL-F\)](#).  
<sup>d</sup> [Management of Renal Disease in Multiple Myeloma \(MYEL-K\)](#).  
<sup>e</sup> Preferred primarily as initial treatment in patients with acute renal insufficiency or those who have no access to proteasome inhibitor (PI)/lenalidomide/dexamethasone. Consider switching to PI/lenalidomide/dexamethasone after renal function improves.  
<sup>f</sup> Treatment option for patients with renal insufficiency and/or peripheral neuropathy.  
<sup>g</sup> Generally reserved for the treatment of aggressive MM.  
<sup>h</sup> There appears to be an increased risk for secondary cancers, especially with lenalidomide maintenance following transplant. The benefits and risks of maintenance therapy vs. secondary cancers should be discussed with patients.  
<sup>i</sup> Results from interim analyses of TOURMALINE MM3 and MM4 trials of ixazomib in the maintenance setting suggest a potential decrease in overall survival (OS).  
<sup>j</sup> Two drug maintenance recommended for high-risk MM.  
<sup>k</sup> Ixazomib may be substituted for carfilzomib in select patients.

**Note:** All recommendations are category 2A unless otherwise indicated.  
**Clinical Trials:** NCCN believes that the best management of cancer patients with access to investigational and/or emerging therapies should be sought. Patients are encouraged to talk to their health care provider about any of the clinical trials listed in this document for which they are eligible.

Version 3.2024 Continued

NCCN National Comprehensive Cancer Network® **NCCN Guidelines Version 3.2024 Multiple Myeloma** [NCCN Guidelines Index](#) [Table of Contents](#) [Discussion](#)

PRIMARY THERAPY FOR NON-TRANSPLANT CANDIDATES <sup>a-d</sup>
<b>Preferred Regimens</b> <ul style="list-style-type: none"> <li>• Bortezomib/lenalidomide/dexamethasone (category 1)</li> <li>• Daratumumab/lenalidomide/dexamethasone (category 1)</li> </ul>
<b>Other Recommended Regimens</b> <ul style="list-style-type: none"> <li>• Daratumumab/bortezomib/melphalan/prednisone (category 1)</li> <li>• Daratumumab/cyclophosphamide/bortezomib/dexamethasone</li> <li>• Carfilzomib/lenalidomide/dexamethasone<sup>k</sup></li> </ul>
<b>Useful in Certain Circumstances</b> <ul style="list-style-type: none"> <li>• Lenalidomide/low-dose dexamethasone (category 1)<sup>m</sup></li> <li>• Bortezomib/cyclophosphamide/dexamethasone<sup>e</sup></li> <li>• Bortezomib/dexamethasone</li> <li>• Bortezomib/lenalidomide/dexamethasone (VRD-lite) for frail patients</li> <li>• Carfilzomib/cyclophosphamide/dexamethasone<sup>f,k</sup></li> <li>• Lenalidomide/cyclophosphamide/dexamethasone</li> </ul>
<b>MAINTENANCE THERAPY</b> <b>Preferred Regimens</b> <ul style="list-style-type: none"> <li>• Lenalidomide (category 1)</li> </ul> <b>Other Recommended Regimens</b> <ul style="list-style-type: none"> <li>• Bortezomib</li> </ul> <b>Useful in Certain Circumstances</b> <ul style="list-style-type: none"> <li>• Bortezomib/lenalidomide<sup>l</sup></li> <li>• Ixazomib (category 2B)<sup>l</sup></li> </ul>

<sup>a</sup> Selected, but not inclusive of all regimens. The regimens under each preference category are listed by order of NCCN Category of Evidence and Consensus alphabetically.  
<sup>b</sup> [Supportive Care Treatment for Multiple Myeloma \(MYEL-H\)](#).  
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<sup>f</sup> Treatment option for patients with renal insufficiency and/or peripheral neuropathy.  
<sup>g</sup> Results from interim analyses of TOURMALINE MM3 and MM4 trials of ixazomib in the maintenance setting suggest a potential decrease in OS.  
<sup>h</sup> Dual maintenance recommended for high-risk MM.  
<sup>i</sup> Ixazomib may be substituted for carfilzomib in select patients.  
<sup>j</sup> Continuously until progression. Benboubker L, Dimopoulos MA, Dispenzieri A, et al. Lenalidomide and dexamethasone in transplant-ineligible patients with myeloma. N Engl J Med 2014;371:906-917.  
<sup>k</sup> Ixazomib may be substituted for carfilzomib in select patients.  
<sup>l</sup> Two drug maintenance recommended for high-risk MM.  
<sup>m</sup> Ixazomib may be substituted for carfilzomib in select patients.

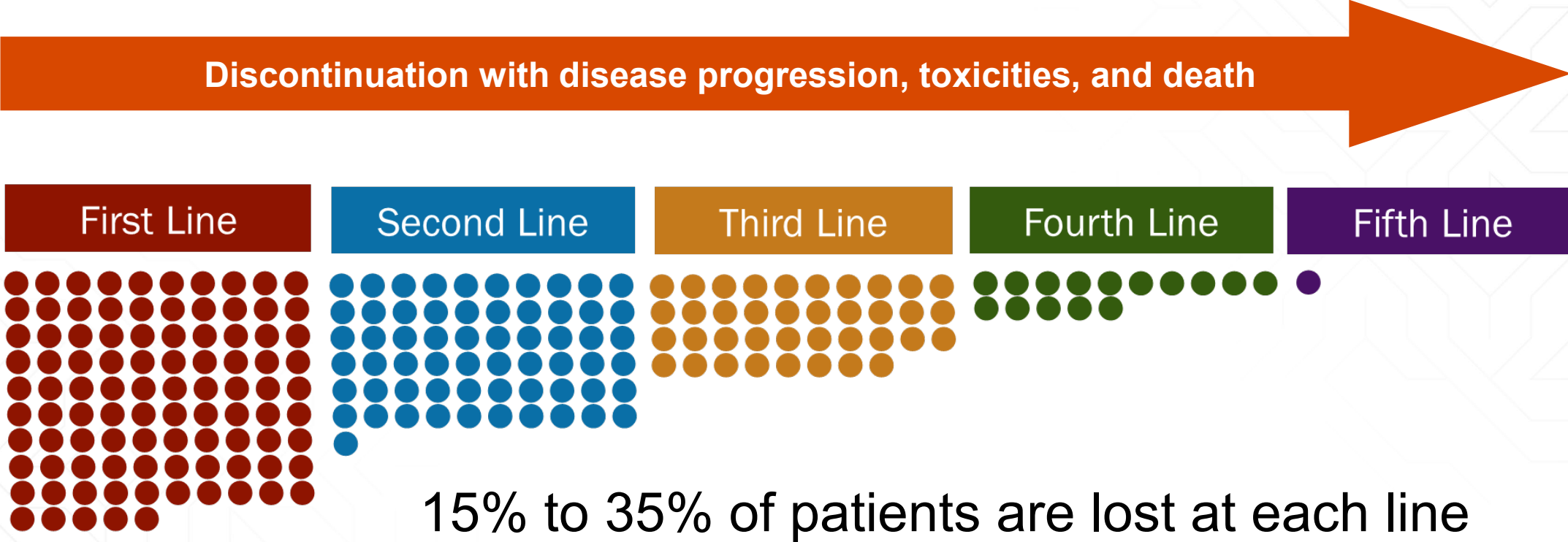
**Note:** All recommendations are category 2A unless otherwise indicated.

Version 3.2024 Continued

There remains a significant and critical unmet need for new therapeutic options to better control the disease, provide deep and sustained responses, safely deliver long-term clinical benefits, and to seek curative treatments



# Large Numbers of Patients are Lost at Each Line



**The most effective treatment happens in the first line of therapy**

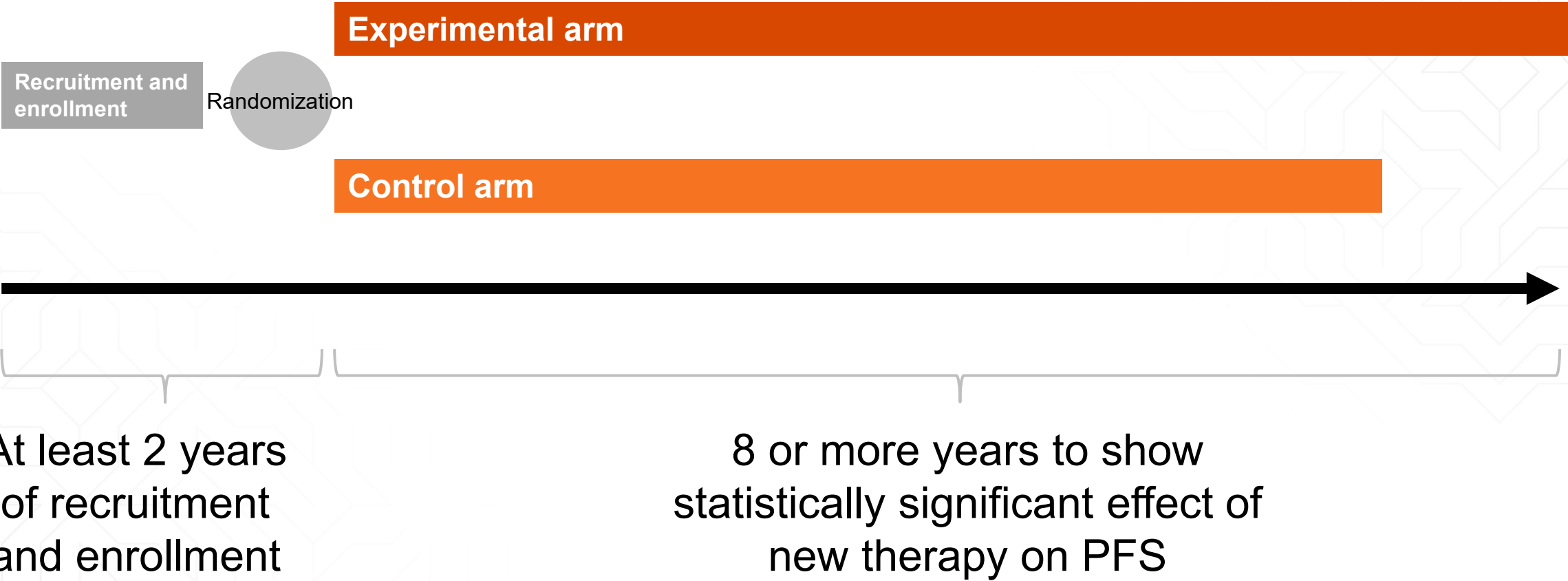
# Current Multiple Myeloma Drug Development Pathway

- Currently, clinical trials in newly diagnosed multiple myeloma use PFS as the endpoint to demonstrate clinical benefit of a new treatment regimen for full approval
- FDA decision to endorse PFS as a regulatory endpoint has facilitated the development of several new, effective multiple myeloma drugs over the past 15 years, and the success is reflected in the improvement of PFS rates and quality of life for patients over this time

# Current Multiple Myeloma Drug Development Dilemma

- Demonstrating a treatment effect on PFS entails waiting for enough PFS events to occur
- **Based on PFS results in recent clinical trials, after all patients have been enrolled, comparative studies may now require over 8 years to show a statistically significant effect of a new therapy**

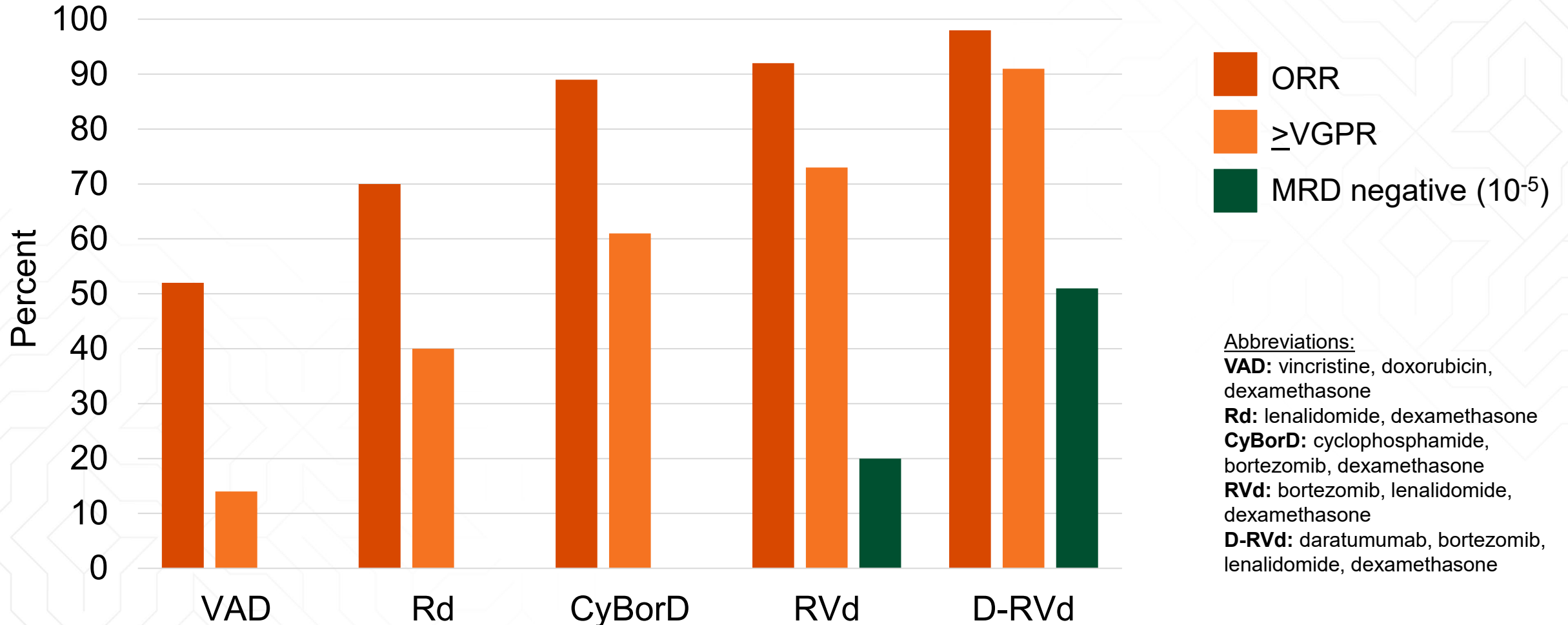
# Many Years to Show Significant Effect of New Therapy on PFS



# 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



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Adapted from: Landgren and Iskander J Intern Med. 2017;281(4):365-382 & Vorhees, et al. Blood 2020;136(8):936-945

# Multiple Myeloma Drug Development: Current Needs

- To accelerate the availability of new and effective treatments for patients with multiple myeloma, **an objective and reliably measured early endpoint that is reasonably likely to predict long-term outcomes and clinical benefit is urgently needed**
- Several studies have demonstrated that minimal residual disease (MRD) negativity is associated with improved PFS and suggest that depth of response, as demonstrated by MRD negativity, may potentially be used to reliably predict both PFS and OS in patients with multiple myeloma
- MRD is a measure of the number of multiple myeloma cells in the patient's bone marrow, and it is often used in patients with complete response (CR) to further quantify depth of response to treatment beyond CR. MRD negativity indicates that the MRD measurement is below a given threshold

# FDA Industry Guidance on Regulatory Considerations for MRD

- In January 2020, FDA published industry guidance on regulatory considerations for use of MRD in development of drug and biologic products for treatment
- **The final FDA guidance described two potential uses of MRD:** as a validated surrogate endpoint for traditional approval, or as a surrogate endpoint reasonably likely to predict clinical benefit for accelerated approval
- In both cases, the guidance explained that **the strength of evidence required for a surrogate endpoint is:**
  - A. Based on the biological plausibility of the relationship
  - B. Demonstration of the prognostic value of the surrogate endpoint for the clinical outcome, and
  - C. Evidence from clinical trials that treatment effects on the surrogate endpoint correspond to effects on the long-term clinical outcome



# Design of Meta-Analysis Based on FDA Guidance

- We were motivated to design and conduct an analysis based on FDA guidance for a meta-analysis of MRD as a clinical endpoint and potential basis for accelerated approval, with the aim to assess the prognostic value of bone marrow MRD negativity and prediction of the treatment effects for PFS and OS in clinical trials of patients with newly diagnosed multiple myeloma
- **Our results support the consideration of MRD as an early clinical endpoint reasonably likely to predict clinical benefit in multiple myeloma that may be used to support accelerated approval** and thereby expedite approval and adoption of novel therapeutic agents for treatment of patients with newly diagnosed multiple myeloma

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

**C. Ola Landgren, M.D., Ph.D<sup>1</sup> & Sean M. Devlin, Ph.D<sup>2</sup>**

and pharma companies and academia

*<sup>1</sup>University of Miami, Miami, FL; <sup>2</sup>Memorial Sloan Kettering Cancer Center, New York, NY*

# Approaches and Considerations Regarding Study Design

Variable	EVIDENCE Study (Landgren/Devlin)
Patient population	Newly diagnosed multiple myeloma
Time-point to evaluate MRD status	Driven by available datasets*
Patients in CR w/o MRD evaluation	ITT approach MRD+
Sensitivity cut-off for MRD assays	10 <sup>-5</sup> or better

*\*A pre-specified time point (window) jointly agreed upon by lead principal investigator, lead study statistician, collaborating agencies, and the FDA before the meta-analysis: 12 months with a window of ± 3 months for an MRD assessment to have taken place*

# The EVIDENCE Study: EValuating minimal residual Disease as an iNtermediate Clinical Endpoint for Multiple Myeloma

## Patient-level data from randomized, controlled clinical trials that met the following criteria:

- A. Phase 2 or 3 randomized, controlled clinical trials that enrolled patients with newly diagnosed multiple myeloma (transplant eligible or transplant-ineligible)
- B. Performed validated MRD assays by either NGS and/or MFC in accordance with guidelines from the FDA, National Cancer Institute, and IMWG, as well as institutional standards of care for the treatment of patients with multiple myeloma
  - NGS analyses were conducted using the FDA-cleared Adaptive clonoSEQ 2.0 diagnostic test
  - MFC analyses were conducted using a multicolor method, with a sensitivity of  $10^{-5}$  or better
- C. MRD negativity was specified as a primary, secondary, or exploratory endpoint in the trial protocol
- D. Had a median follow-up of at least 6 months following the end of the time chosen to be the a priori defined time point of 12 months after randomization for the assessment of MRD negativity, determined by a Kaplan-Meier estimate of the censoring distribution

# Primary Objectives of Our Study

- To evaluate whether MRD negativity while in a CR at an *a priori* defined time point\* is a reasonably likely endpoint for clinical benefit as measured by PFS in newly diagnosed, transplant-eligible patients with multiple myeloma
- To evaluate whether MRD negativity while in a CR at an *a priori* defined time point\* is a reasonably likely endpoint for clinical benefit as measured by PFS in newly diagnosed, transplant-ineligible patients with multiple myeloma

*\*Jointly agreed upon by lead principal investigator, lead study statistician, collaborating agencies, and the FDA before the meta-analysis: 12 months with a window of  $\pm$  3 months for an MRD assessment to have taken place*

# Key Secondary Objectives of Our Study

- To evaluate whether MRD negativity at an *a priori* defined time point\* is a reasonably likely endpoint for clinical benefit as measured by PFS in patients with NDMM, regardless of transplant eligibility (i.e., combined population of transplant-eligible and transplant-ineligible)
- To evaluate whether MRD negativity is reasonably likely to predict clinical benefit as measured by OS

*\*Jointly agreed upon by lead principal investigator, lead study statistician, collaborating agencies, and the FDA before the meta-analysis: 12 months with a window of  $\pm$  3 months for an MRD assessment to have taken place*

# Data, Methodology, and Results



**Sean Devlin, Ph.D**

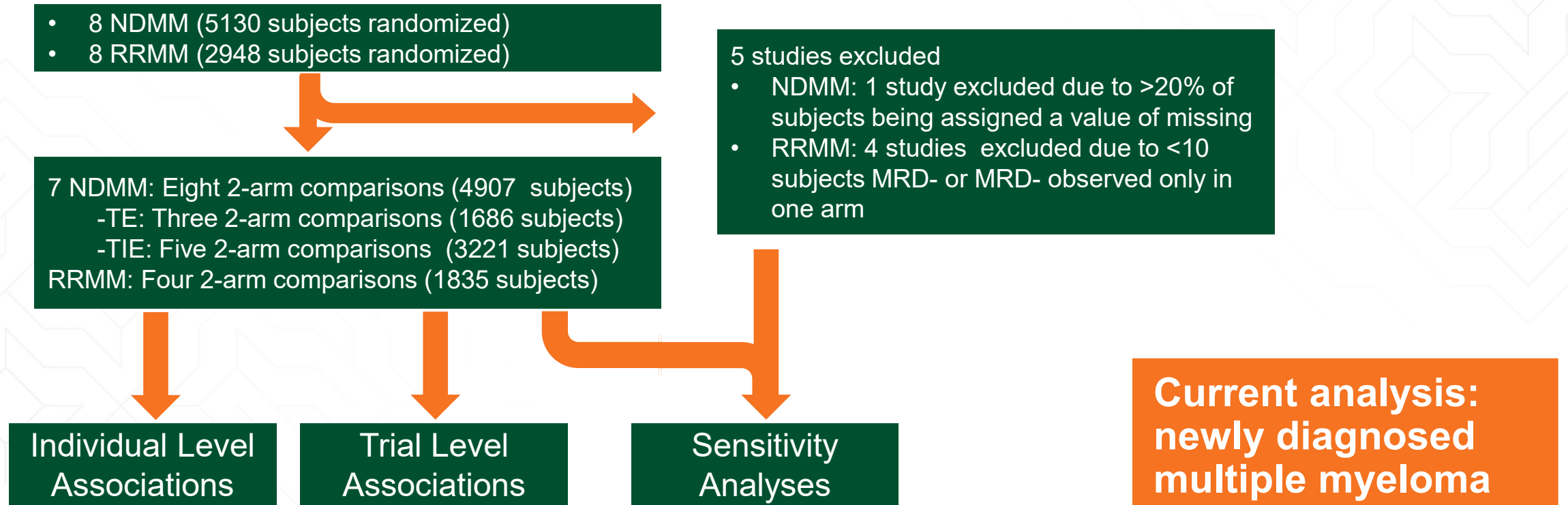
*Lead Study Statistician*

**Associate Attending, Biostatistics**

**Expertise:** Clinical Trial Design,  
Evaluation of Prognostic Models

# Data

16 high-quality datasets were identified with MRD data from assays, which were validated to a sensitivity level of at least  $10^{-5}$



*Clinical trial data was provided by Janssen, Sanofi, Amgen, Takeda, AbbVie, Heidelberg University Hospital, and Paracelsus Medical University*



# Methodology

The analytic framework for **evaluating MRD as a reasonably likely endpoint for clinical benefit** followed FDA's 2020 guidance for evaluating MRD using a meta-analysis:

## Trial-Level Association

- Across randomized trials, is the treatment effect on the MRD endpoint correlated with the treatment effect on the long-term endpoint(s)?

## Individual-Level Association

- Is the attainment of MRD negativity prognostic for the long-term endpoint(s)?

# Methodology: Trial-Level Association

1.  $R^2_{WLS}$ : separately estimate the treatment effect on the MRD and on the long-term endpoint using logistic and proportional hazard regression within each trial. Using weighted least squares, estimate the correlation between the log odds ratio and log hazard ratio across all studies. Weights are based on each study's sample size or the standard error estimates for the log odds ratio treatment effect
2.  $R^2_{Copula}$ : a bivariate Placket copula estimates the treatment effect on MRD and the long-term endpoint while accounting for patient-level correlation. The methodology was developed by Burzykowski, Molenberghs, and Buyse (2004)
  - Widely used in oncology when estimating a binary or ordinal surrogate endpoint, e.g., Burzykowski et al. (2008); Halabi et al. (2013); Shi et al. (2017); Shi et al. (2018); Blumenthal et al. (2015); Dixon et al. (2022)

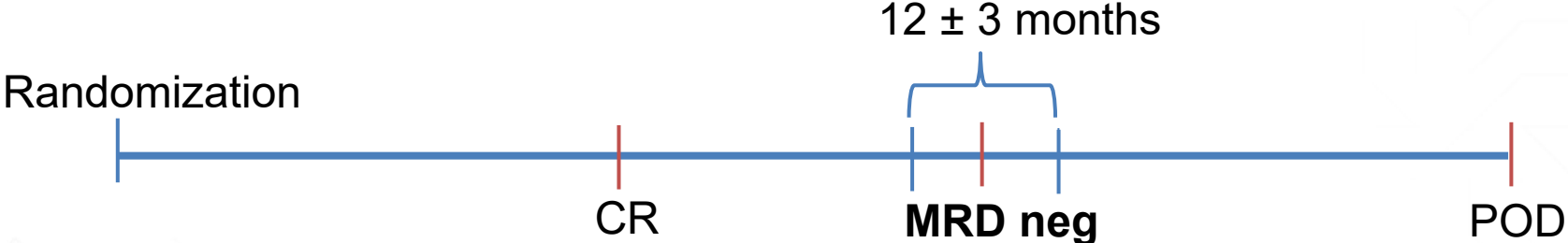
# Methodology: Individual-Level Association

1. The association parameter for the Plackett copula corresponds to a global odds ratio, which is interpreted as the ratio of the odds of the long-term endpoint's being greater than a fixed time point (e.g., 4 years) for MRD-negative patients compared to MRD-positive patients. Example of calculation and interpretation:
  - Probability that an MRD-negative patient has PFS >4 years: 75% (odds 3:1)
  - Probability that an MRD-positive patient has PFS >4 years: 33% (odds 0.5:1)
  - Odds ratio: 6 ( $=3/0.5$ )
2. Supplementary analyses examined the association between MRD status at 12 months and subsequent PFS among the patients who were alive and progression-free at the landmark time (12-month landmark) to quantify, with the commonly used hazard ratio, the PFS in MRD-negative patients vs PFS in MRD-positive patients

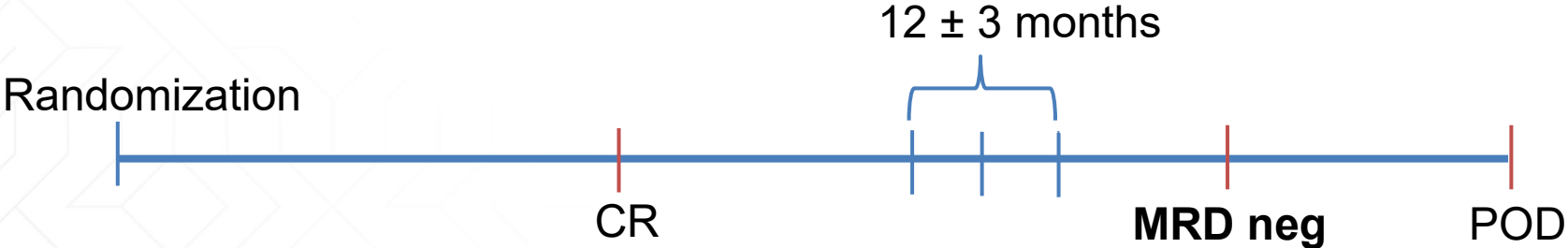
# Methodology: Approach

- The analysis followed the intent-to-treat (ITT) principle; all randomized patients were included
- Patients with missing MRD evaluations were considered as not achieving an MRD negative response (i.e., classified as MRD+)
- Primary analysis only included studies with <20% missing a 12-month ( $\pm 3$ ) MRD evaluation

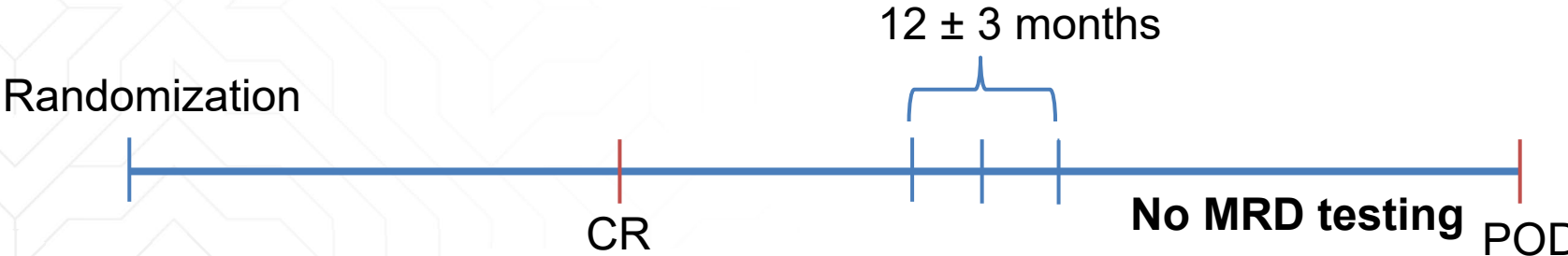
# Individual Patients' MRD Testing: Classifications of MRD



**MRD negative**

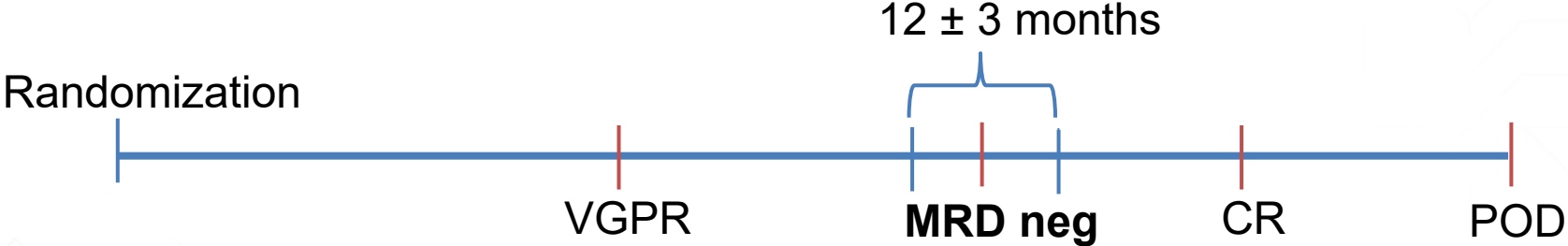


**MRD positive**

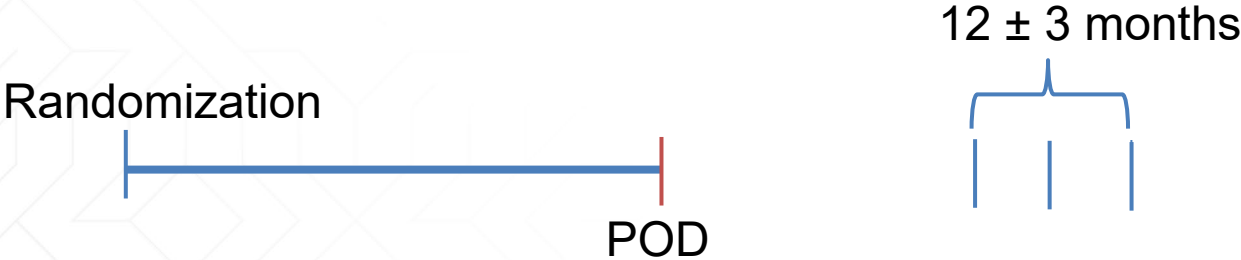


**MRD positive**

# Individual Patients' MRD Testing: Classifications of MRD (cont.)



MRD positive



MRD positive

# Results: Individual-Level Association

## Copula: MRD and progression-free survival

Population	Total Sample Size	Copula Global Odds Ratio (95% CI)
All newly diagnosed multiple myeloma patients (NDMM)	4907	4.72 (3.53-5.90)
Transplant eligible NDMM patients	1686	2.45 (1.40-3.51)
Transplant ineligible NDMM patients	3221	6.15 (4.27-8.03)

# Results: Individual-Level Association

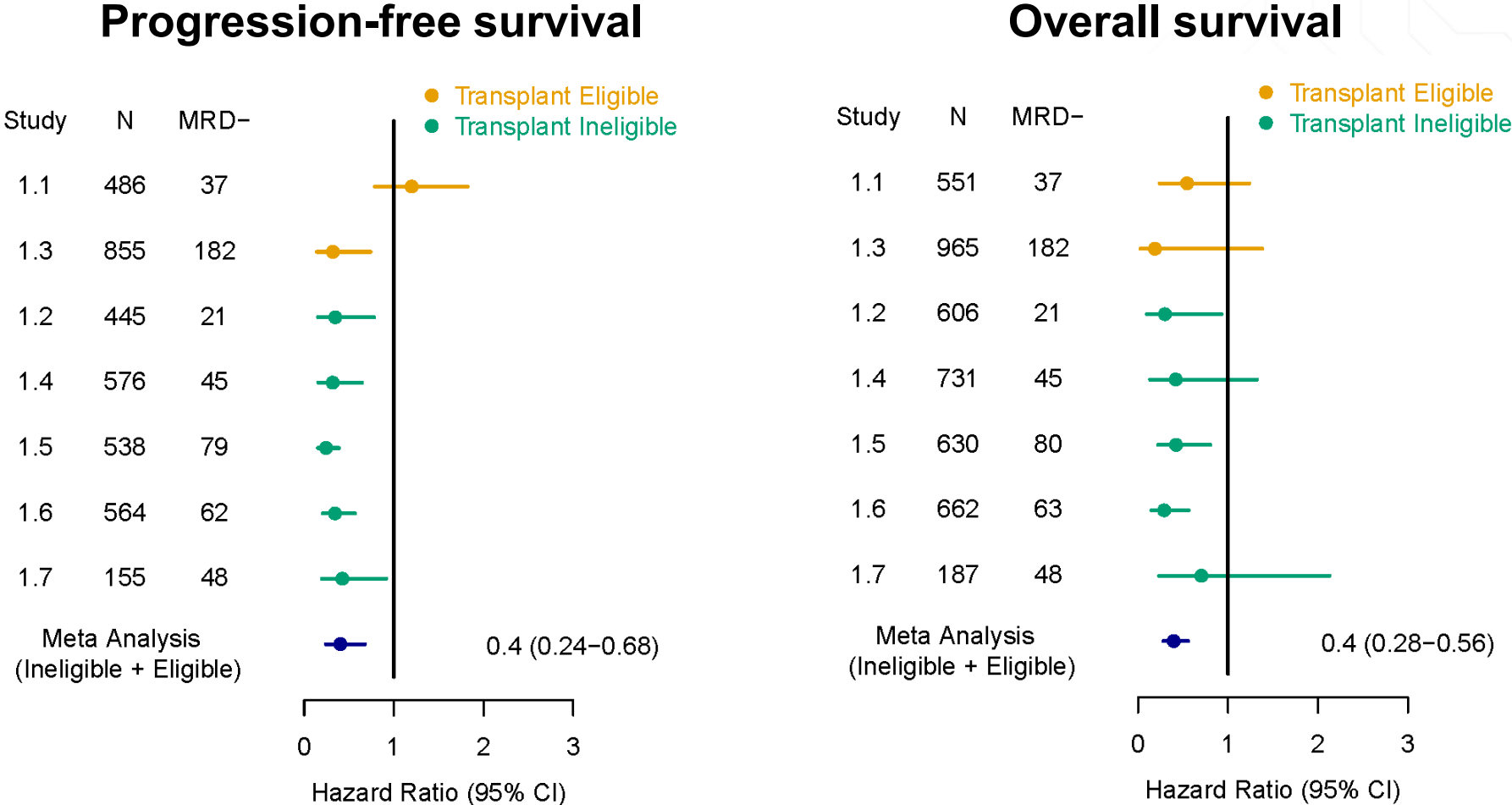
## Copula: MRD and overall survival

Population	Total Sample Size	Copula Global Odds Ratio (95% CI)
All newly diagnosed multiple myeloma patients (NDMM)	4907	4.02 (2.57-5.46)
Transplant eligible NDMM patients	1686	3.78 (0.78-6.78)
Transplant ineligible NDMM patients	3221	4.08 (2.44-5.72)



# Results: Individual-Level Association

## Association between MRD at 12 months and long-term endpoints



### Landmark analysis at 12 months

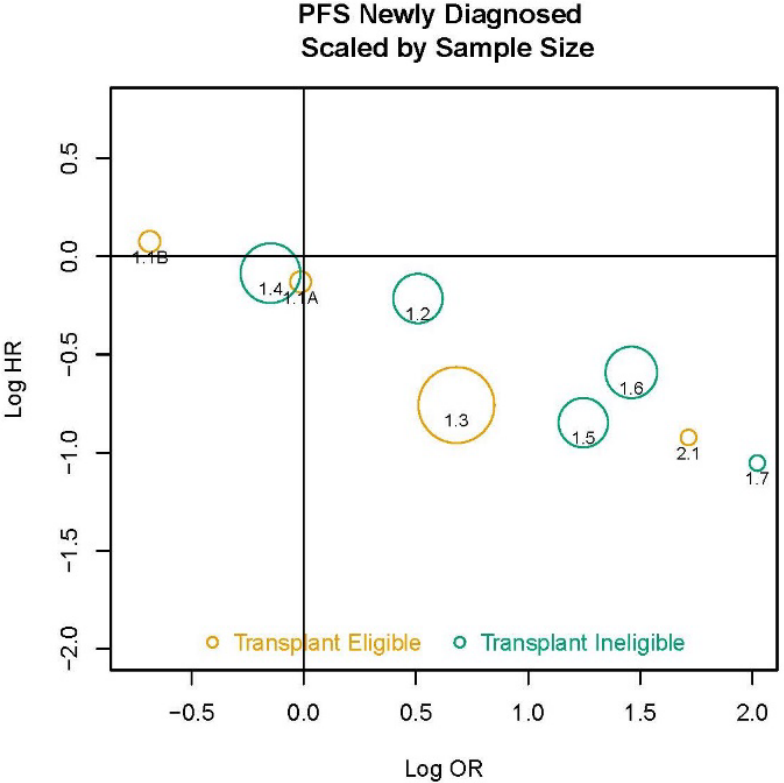
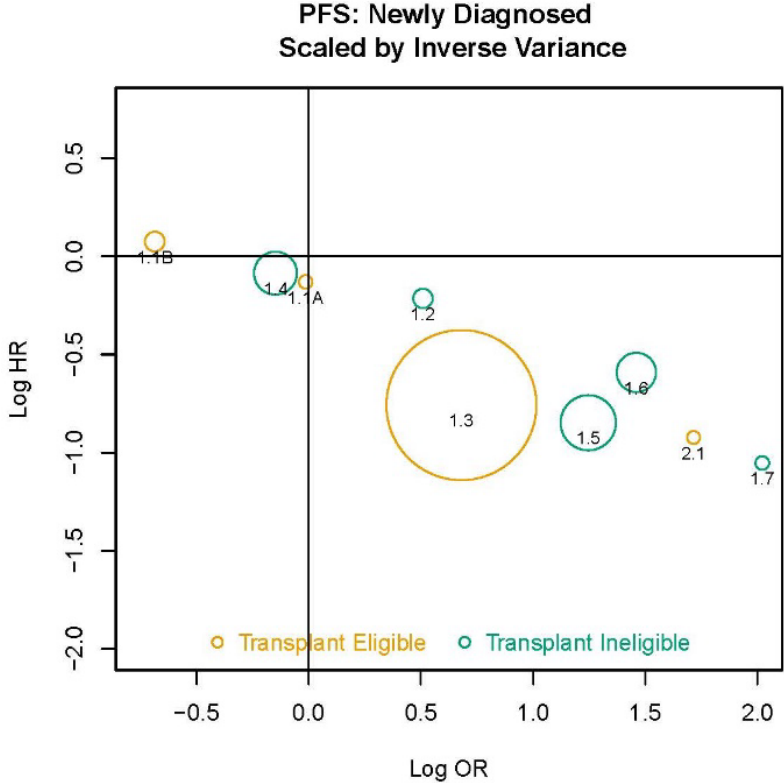
# Results: Trial-Level Association for Progression-Free Survival

Newly diagnosed multiple myeloma, **all patients**

$R^2_{WLS}$  (Inv.-Variance)  
0.67 (95% CI: 0.43-0.91)

$R^2_{WLS}$  (Sample Size)  
0.72 (95% CI: 0.51-0.93)

$R^2_{Copula}$   
0.84 (95% CI: 0.64-0.99)



Study 2.1 is included as a sensitivity analysis

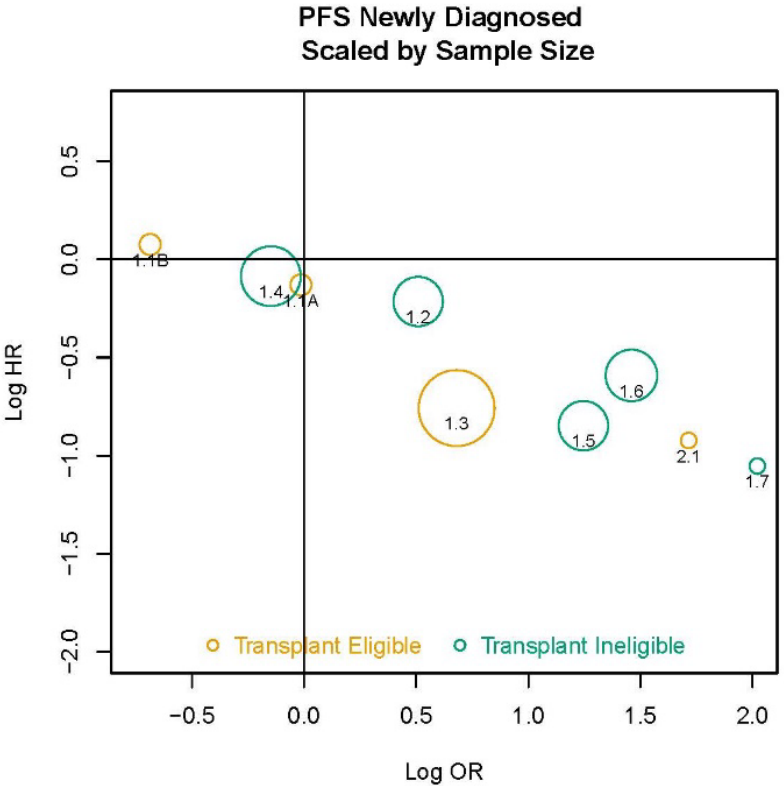
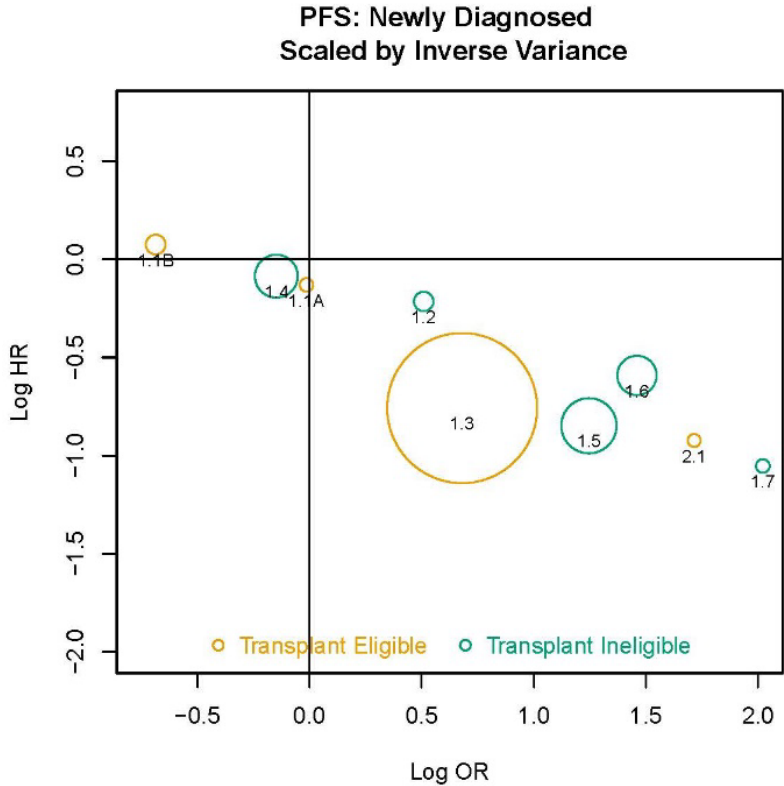
# Results: Trial-Level Association for Progression-Free Survival

Newly diagnosed multiple myeloma, **transplant ineligible**

$R^2_{WLS}$  (Inv.-Variance)  
0.83 (95% CI: 0.71-0.96)

$R^2_{WLS}$  (Sample Size)  
0.84 (95% CI: 0.72-0.97)

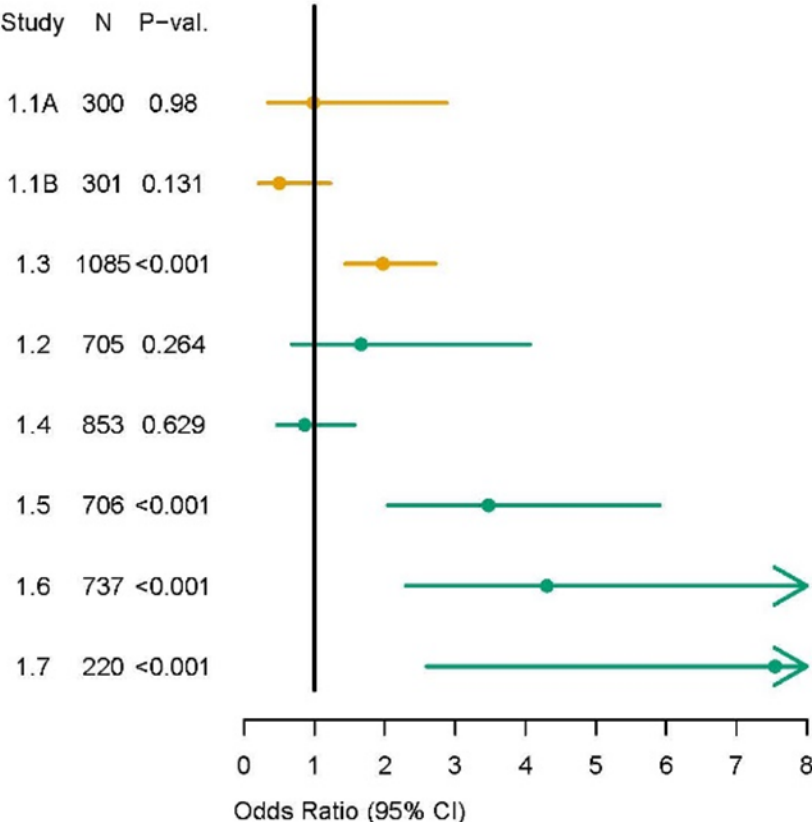
$R^2_{Copula}$   
0.85 (95% CI: 0.62-0.99)



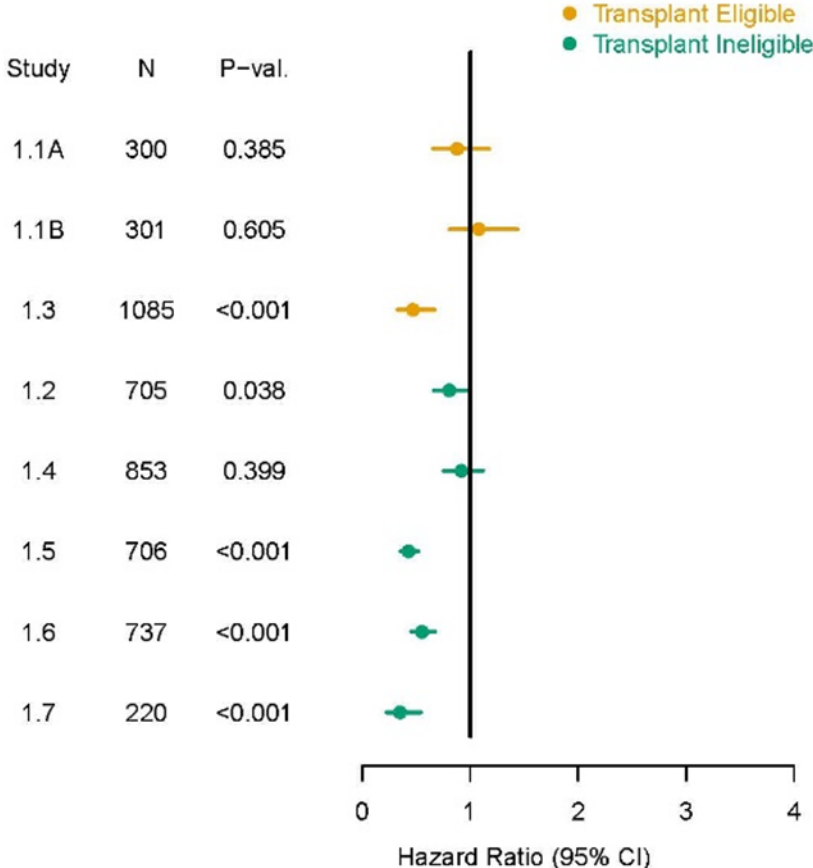
# Results: Trial-level Association for Progression-Free Survival

## Treatment effect on each endpoint

### MRD negativity



### Progression-free survival



# Results: Trial-Level Association for Overall Survival

Newly diagnosed multiple myeloma, **all patients**

Newly diagnosed multiple myeloma, **transplant ineligible**

**$R^2_{WLS}$  (Inv.-Variance)**  
 0.21 (95% CI: <0.01-0.53)

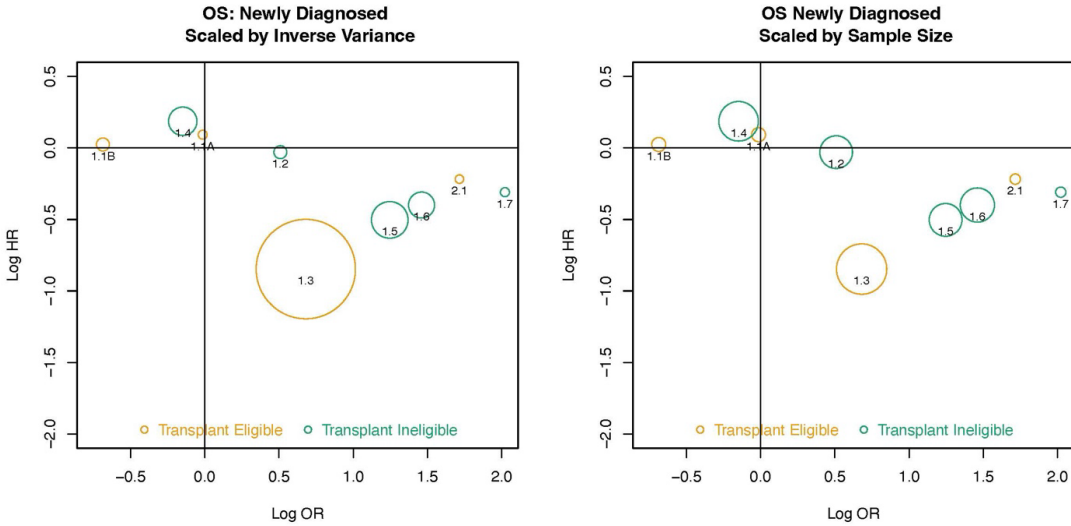
**$R^2_{WLS}$  (Sample Size)**  
 0.33 (95% CI: <0.01-0.67)

**$R^2_{Copula}$**   
 0.32 (95% CI: <0.01-0.86)

**$R^2_{WLS}$  (Inv.-Variance)**  
 0.79 (95% CI: 0.63-0.95)

**$R^2_{WLS}$  (Sample Size)**  
 0.83 (95% CI: 0.69-0.96)

**$R^2_{Copula}$**   
 0.63 (95% CI: 0.12-0.99)



Study 2.1 is included as a sensitivity analysis

# Results: Concordance of Significance

Study	Treatment Effect on MRD (2-sided test) p-value	Treatment Effect on PFS (2-sided test) p-value	Treatment Effect on OS (2-sided test) p-value
<i>Transplant <b>eligible</b> newly diagnosed multiple myeloma</i>			
1.1A	0.98	0.385	0.686
1.1B	0.131	0.605	0.901
1.3	<0.001	<0.001	0.008
<i>Transplant <b>ineligible</b> newly diagnosed multiple myeloma</i>			
1.4	0.629	0.399	0.232
1.2	0.264	0.038	0.806
1.5	<0.001	<0.001	<0.001
1.6	<0.001	<0.001	<0.001
1.7	<0.001	<0.001	0.377



# Summary and Clinical Conclusion



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Assays

# Summary

- The most effective treatment is in the first line
- With current endpoints, it takes over 10 years to show statistically significant effect of a new therapy on PFS in the newly diagnosed multiple myeloma patient population
- This delays timely drug approval and availability of new highly efficacious treatments for patients diagnosed with multiple myeloma

**Our results support the consideration of MRD as an early clinical endpoint reasonably likely to predict clinical benefit in multiple myeloma that may be used to support accelerated approval**



# Approaches and Considerations Regarding Study Designs

Variable	EVIDENCE Study (Landgren/Devlin)	I <sup>2</sup> Study (IMF/Mayo)
Patient population	Newly diagnosed multiple myeloma	Newly diagnosed and relapsed/refractory multiple myeloma
Time-point to evaluate MRD status	Driven by available datasets*	Data driven
Patients in CR w/o MRD evaluation	ITT approach MRD+	Removed from Analysis
Sensitivity cut-off for MRD assays	10 <sup>-5</sup> or better	Any sensitivity

*\*A pre-specified time point (window) jointly agreed upon by lead principal investigator, lead study statistician, collaborating agencies, and the FDA before the meta-analysis: 12 months with a window of ± 3 months for an MRD assessment to have taken place*

# Clinical Conclusion

“Palliative era”

Few options

1950s-

“Chemotherapy era”

First high-dose melphalan chemotherapy, followed by autologous stem cell transplant

1983

“Immunotherapy era”

Transplant eligible (fit patients) vs Transplant ineligible (frail/older patients)

1990

2000

2010

2020

2030

Modern chemotherapy-free therapies with potential to offer (some) patients the same life span as general population

**MRD is an objective and reliably measured early endpoint that is reasonably likely to predict long-term outcomes and clinical benefit in multiple myeloma. Approval of this endpoint will accelerate the availability of new and effective treatments for patients**

# *Thank you for your attention!*

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