i²TEAMM Presentation to Support MRD as Accelerated Approval Endpoint

Oncologic Drugs Advisory Committee (ODAC)

April 12, 2024

Introduction

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Cedars-Sinai Outpatient Cancer Center

International Independent Team for Endpoint Approval of Myeloma Minimal Residual Disease (i²TEAMM)

Academic Sites

International Independent Team for Endpoint Approval of Myeloma Minimal Residual Disease (i²TEAMM)

Academic Sites and Industry Global Trials

Unique Time in Progress of Myeloma Therapy

19 drugs
approved in
the last 20 years

→ **Significant prolongation**
of survival outcomes

↓

Multiple new drugs and combinations
under evaluation

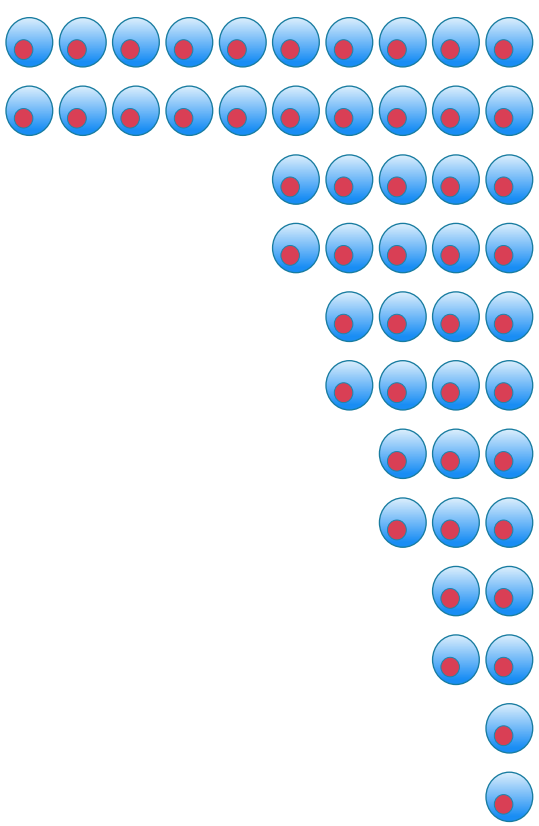
→ **Patients will have to wait for longer and longer periods**
for documented PFS benefit

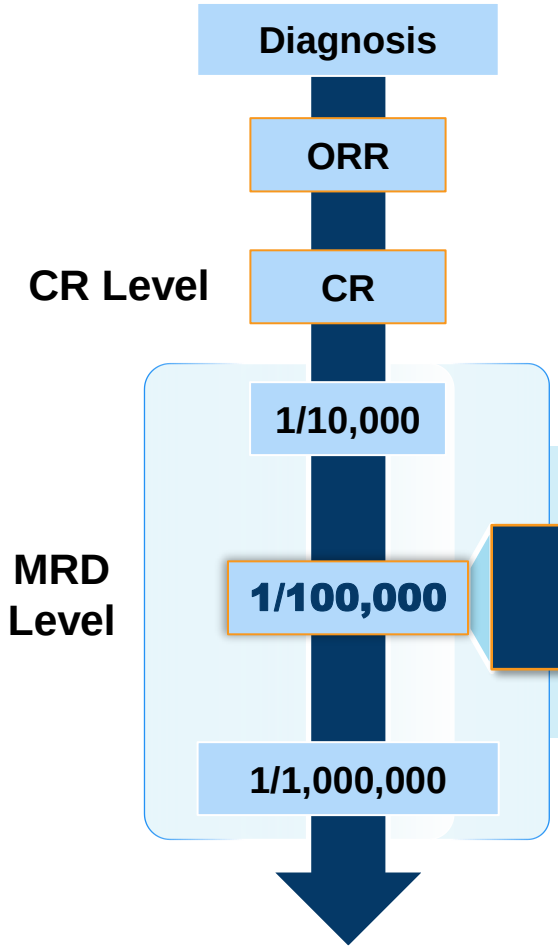
Unmet Need in 2024

- **Early endpoint that can reliably predict Progression Free Survival (PFS)**

Minimal residual disease (MRD) testing fulfills this unmet need

Depth of Response Predicts Longer PFS and OS





DEPTH OF RESPONSE

Matters

The deeper the response

the longer the PFS and OS

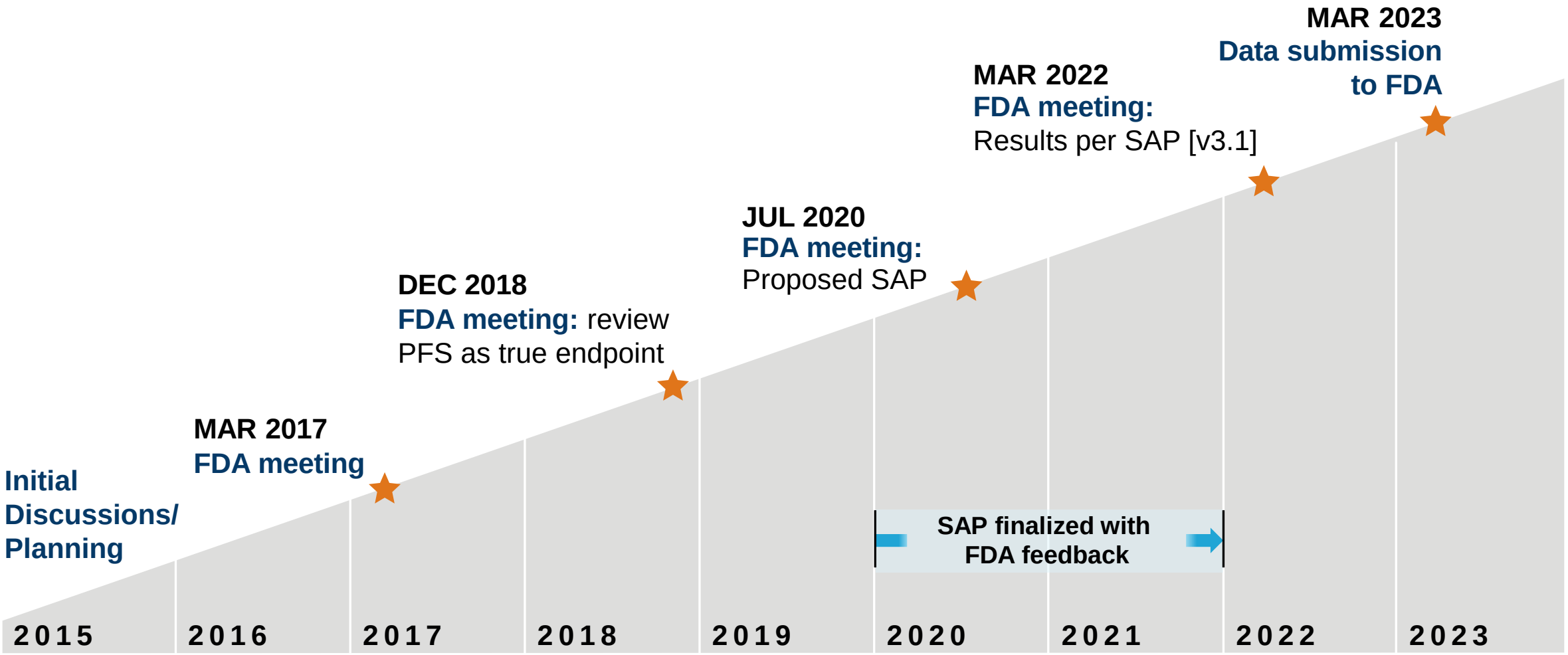
MRD significantly improves

upon use of ORR and CR alone for response assessment

Advantages of MRD as Early Endpoint

- **Earlier readouts: 9-12 months versus ≥5 years**
- **Timely approval of life saving therapies / combinations**
- **Major positive impact for patients**

In Pursuit of MRD Endpoint Approval Goal, Multiple FDA Interactions Occurred



Intent for Today's ODAC

Seeking approval for the use of MRD negative CR as an early endpoint for accelerated drug approval in multiple myeloma

Upcoming Presentation Agenda

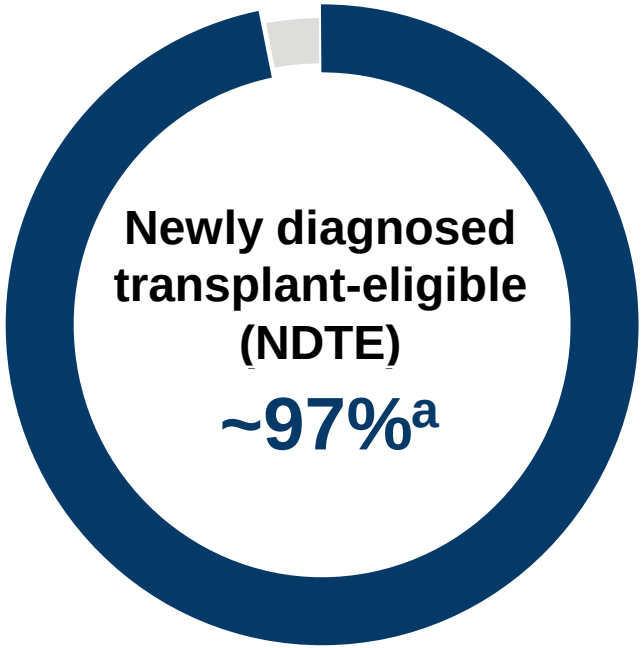
The Need for MRD Assessment	**Bruno Paiva, PhD** Director of Flow Cytometry CIMALAB Diagnostics Department of Hematology Clinica Universidad de Navarra, SPAIN
Meta-Analysis and Key Results	**Qian Shi, PhD** Professor of Biostatistics and Oncology Mayo Clinic
Conclusions	**Kenneth C. Anderson, MD** Kraft Family Professor of Medicine Dana-Farber Cancer Institute and Harvard Medical School

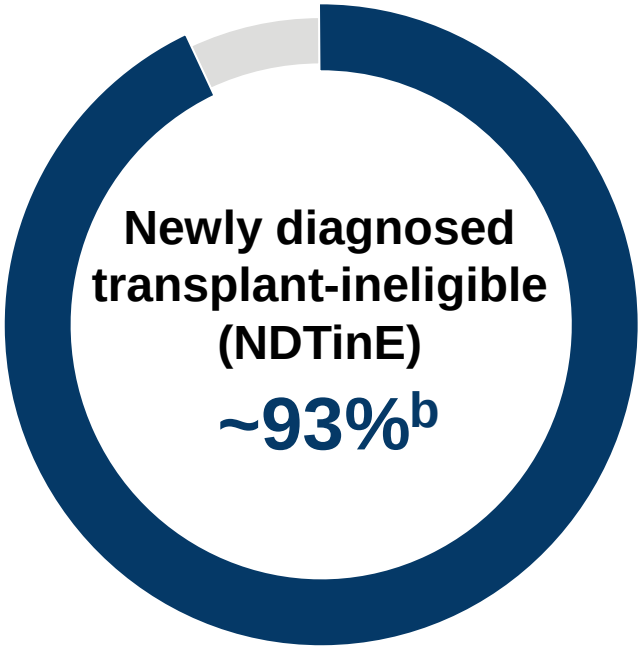
The Need for MRD Assessment

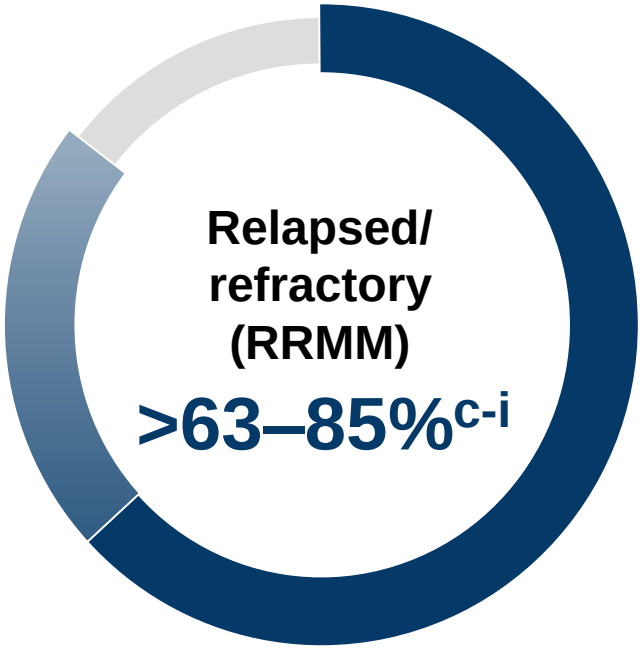
Bruno Paiva, PhD,

Director of Flow Cytometry CIMALAB Diagnostics
Department of Hematology
Clinica Universidad de Navarra, SPAIN

Overall Response Rates (ORR) Are Nearing 100% with Standards of Care

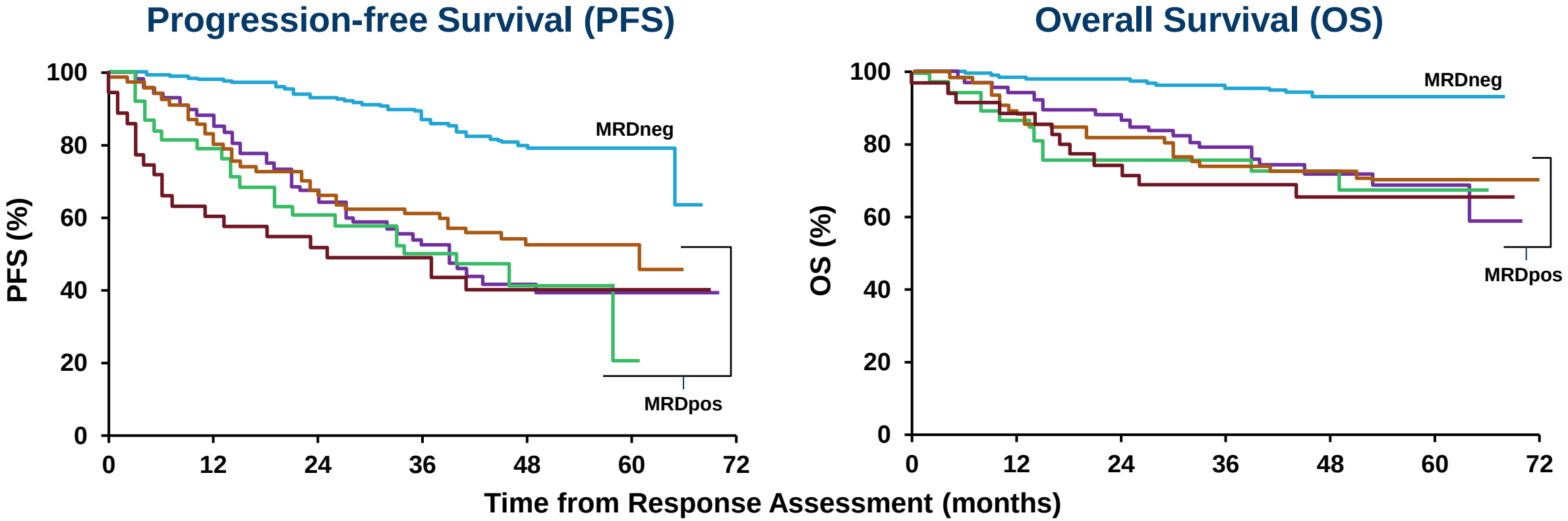






a: PERSEUS (Sonneveld, *N Engl J Med* 2023); b: MAIA (Facon, *Lancet Oncol* 2021); c: ICARIA (Moreau, *Lancet Oncol* 2021); d: CANDOR (Usmani, *Lancet Oncol* 2022); e: APOLLO (Dimopoulos, *Lancet Oncol* 2021); F: Talquetamab (Chari *N Engl J Med* 2022); g: Teclistamab (Moreau *N Engl J Med* 2022); h: KarMMa-3 (Rodriguez-Otero, *N Engl J Med* 2023); I: CARTITUDE-4 (San-Miguel, *N Engl J Med* 2023)

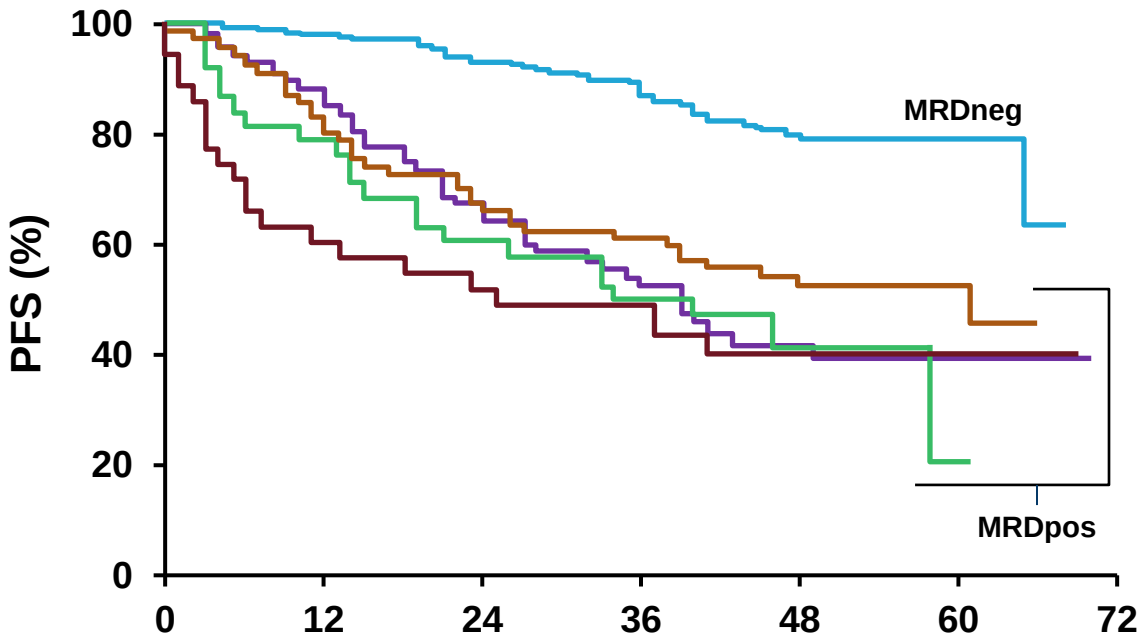
MRD is the Most Accurate Response Criterion to Measure Treatment Efficacy and Predict Longer Survival[1]



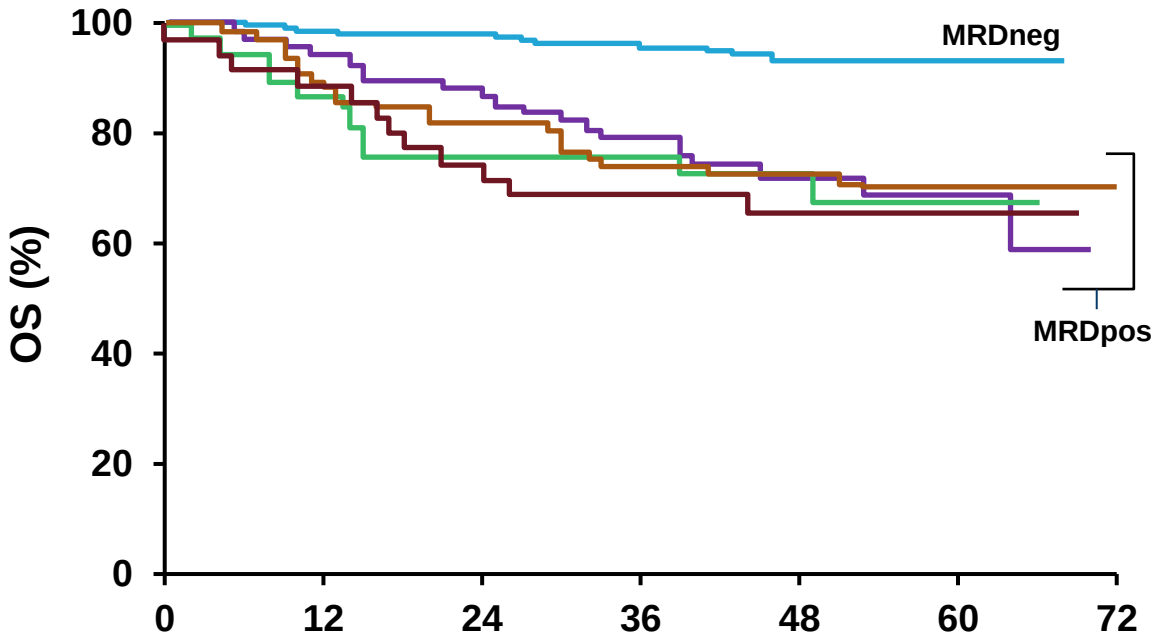
1. Jimenez-Ubieto A & Paiva B, et al. *Blood*. 2021;138(19):1901-1905.

MRD is the Most Accurate Response Criterion to Measure Treatment Efficacy and Predict Longer Survival[1]

Progression-free Survival (PFS)



Overall Survival (OS)

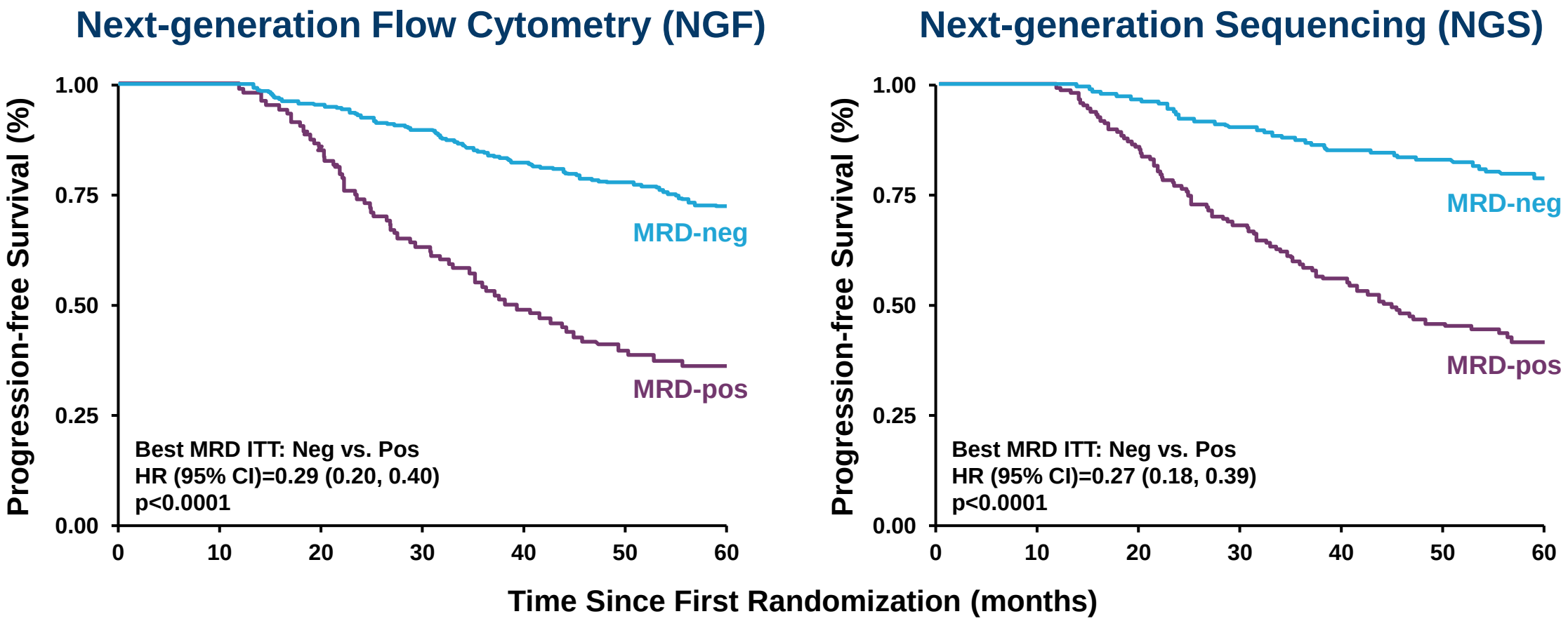


Time from Response Assessment (months)

MRD negativity is the new CR

1. Jimenez-Ubieto A & Paiva B, et al. *Blood*. 2021;138(19):1901-1905.

Two Next-Generation MRD Methods Detect MRD at 10^{-5} Threshold



Oliva S, et al. *EClinicalMedicine*. 2023 Jun 9;60:102016.

MRD Assessment is Feasible in Clinical Trials

458 NDTE Patients and 1119 Assessments

MRD DATA OBTAINED IN

99.6%

of samples

THE MEDIAN LIMIT OF DETECTION WAS

2.9×10^{-6}

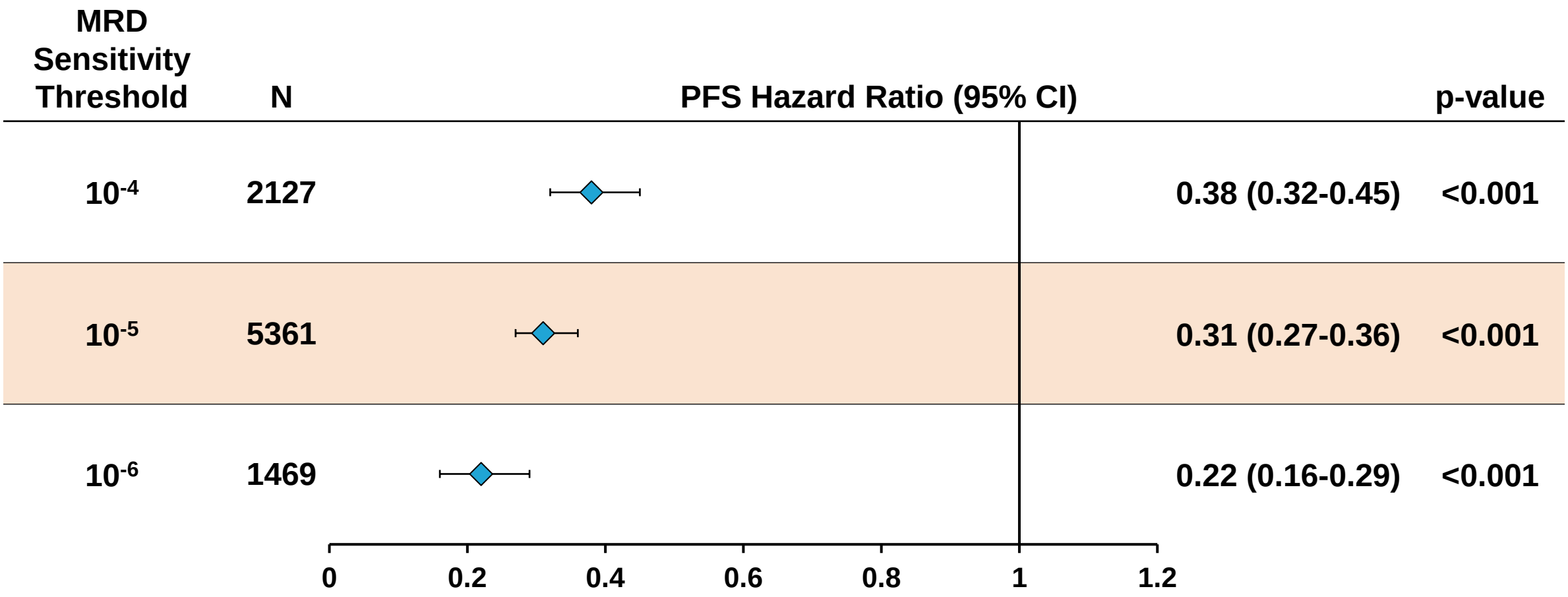
10^{-5} SENSITIVITY ACHIEVED IN

99.9%

of samples

Paiva B, et al. *J Clin Oncol*. 2020 Mar 10;38(8):784-792.

The More Sensitive the MRD Assessment, the Better the Prediction of Clinical Benefit



Munshi NC, et al. *Blood Adv.* 2020 Dec 8;4(23):5988-5999.

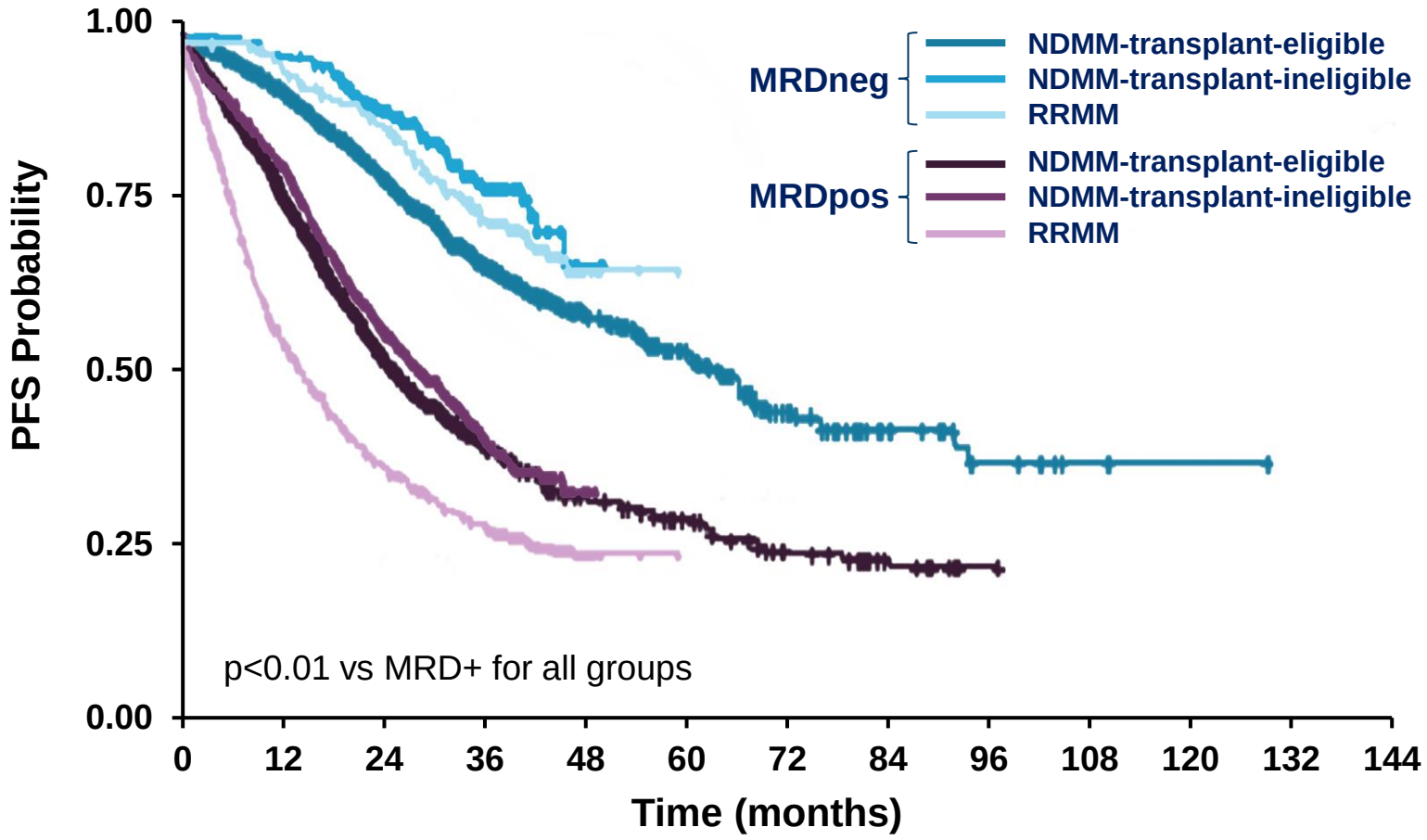
MRD is a Key Prognostic Factor in All Disease Settings

Large Meta-analysis Using Published Data

93
publications

8098
patients

Association of MRD Negativity with PFS by Disease Settings



Munshi NC, et al. *Blood Adv.* 2020 Dec 8;4(23):5988-5999.

MRD Negative Rates Predict Clinical Benefit

Phase 3 Trials Investigating Anti-CD38 Antibodies

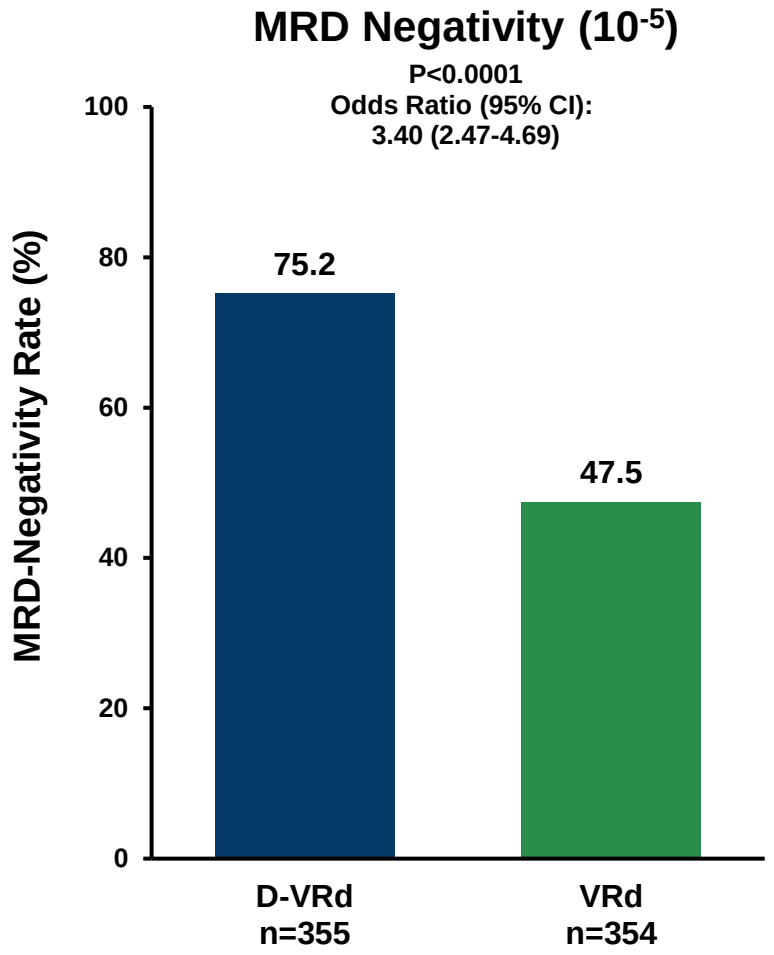
Clinical Trial	Disease Setting	Randomization	Approval
CASSIOPEIA	NDTE	D-VTD vs VTD	D-VTD
ALCYONE	NDTinE	D-VMP vs VMP	D-VMP
MAIA	NDTinE	D-Rd vs Rd	D-Rd
CASTOR	RRMM	D-Vd vs Vd	D-Vd
IKEMA	RRMM	I-Kd vs Kd	I-Kd
POLLUX	RRMM	D-Rd vs Rd	D-Rd

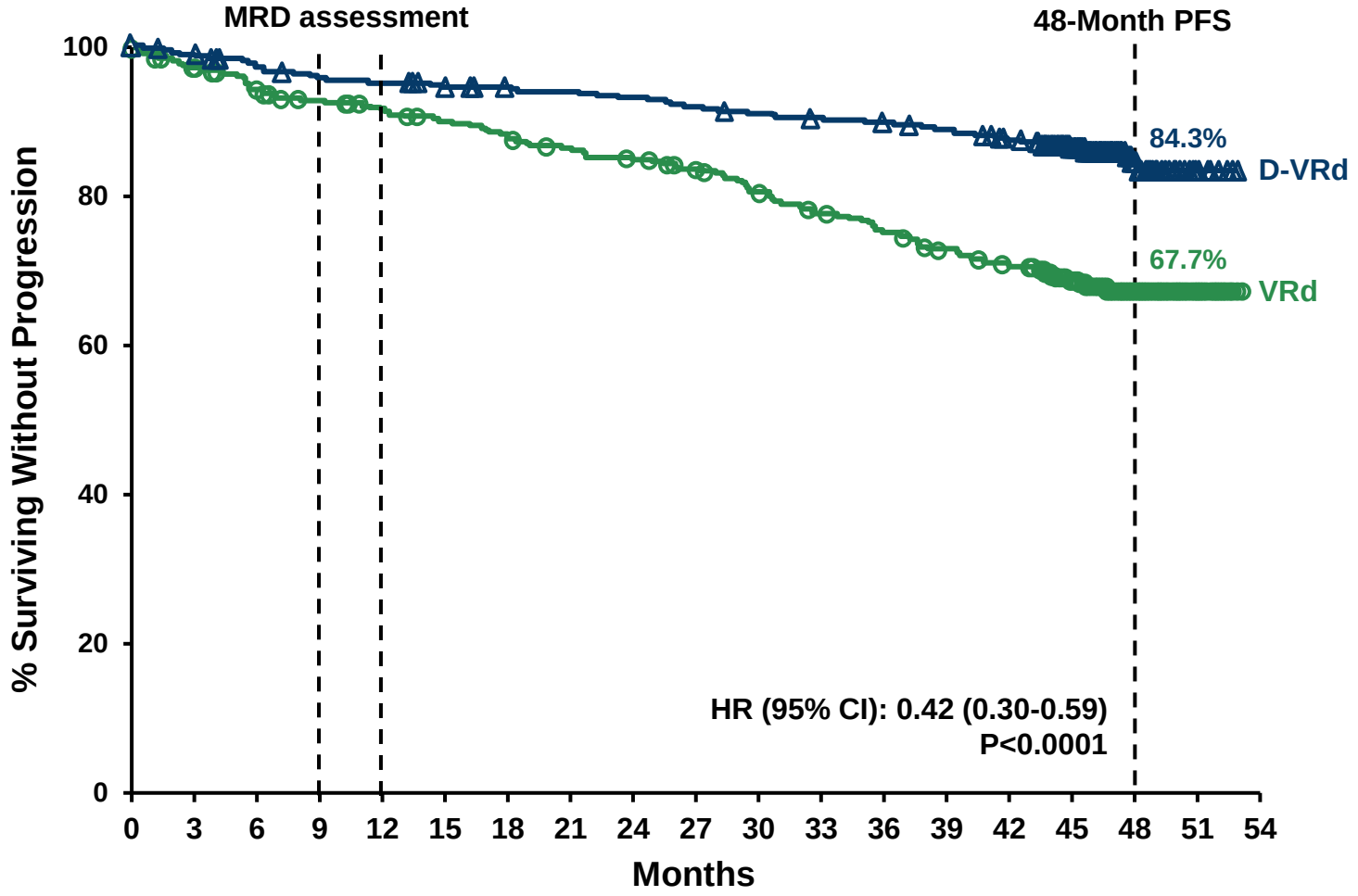
Significantly higher MRD negative rates preceded significant differences in PFS

CASSIOPEIA: Moreau, *Lancet*. 2019; ALCYIONE: Mateos, *Lancet* 2020; MAIA: Facon, *Lancet Oncol* 2021; CASTOR: Mateos, *Clin Lymphoma Myeloma Leuk* 2020; IKEMA: Moreau, *Lancet* 2021; POLLUX: Bahlis, *Leukemia* 2020

Increased Rates of MRD Negativity Are Associated With Prolonged PFS

PERSEUS Phase 3 Trial



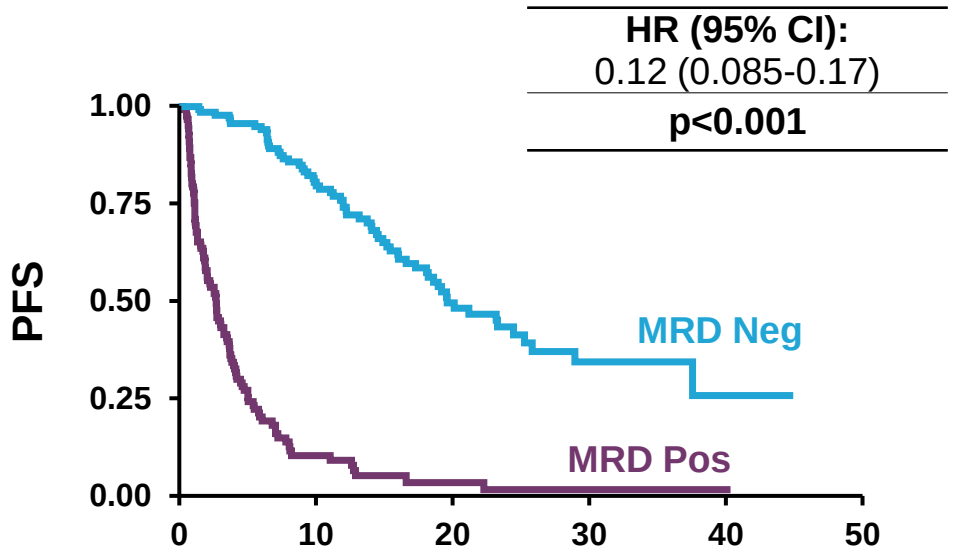


Sonneveld P, et al. *N Engl J Med*. 2024 Jan 25;390(4):301-313.

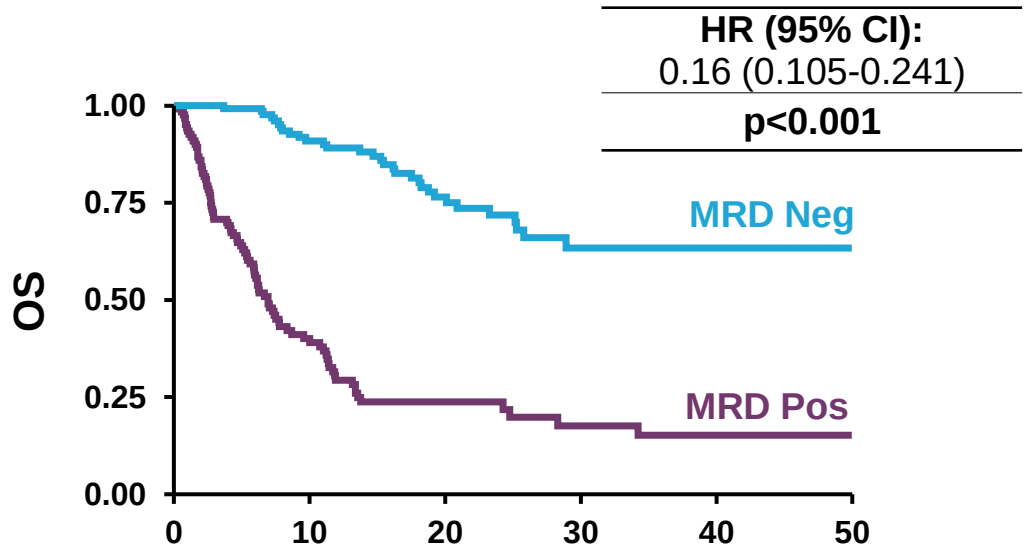
MRD Negativity is Associated with Longer PFS/OS in All Treatment Modalities Including Novel Immunotherapies

CAR T cells and TCE

Progression-Free Survival



Overall Survival



Time Since Treatment Initiation (months)

Ongoing RCT investigating CAR T cells or TCE are using MRD as co-primary endpoint

CAR T=chimeric antigen receptor; TCE=T cell engager therapies

Zabaleta A, et al. *Blood* 2023; 142 (Supplement 1): 94.

Summary of MRD Assessment in Multiple Myeloma

- **ORR are becoming universal in MM**
  - Treatment efficacy must be measured with higher sensitivity
- **MRD is evaluated with state-of-the-art and uniform technology**
  - Provides results and achieves 10-5 sensitivity in virtually all samples
  - More sensitive than CR criterion
- **MRD assessment has shown to be prognostic in all disease settings and treatment scenarios**
  - Confirmed in a large meta-analysis based on published data[1]
  - **Yet to be confirmed in a large meta-analysis based on individual patient data**
- **Virtually all phase 3 trials leading to drug approvals in MM have shown superior MRD negative rates in the investigational arm**
  - Confirmed in a meta-analysis based on published data[2]
  - **Yet to be confirmed in a large meta-analysis based on individual patient data**

1. Munshi NC, et al. *Blood Adv.* 2020 Dec 8;4(23):5988-5999.
2. Paiva B, et al. *Blood Adv.* 2024 Jan 9;8(1):219-223.

Meta-Analysis and Key Results

Qian Shi, PhD

Professor of Biostatistics and Oncology
Department of Quantitative Health Sciences
Mayo Clinic, Rochester MN, USA

Overview

- **Initial Objective**
  - To validate minimal residual disease (MRD) as a full surrogate endpoint of **PFS** in multiple myeloma (MM) clinical trials using individual patient data (IPD) from a large collection of randomized clinical trials
- **Revised Objective**
  - To evaluate if current available data can support MRD as an **Early Endpoint** that is reasonably likely to predict clinical benefit in future MM clinical trials
  - Two-level meta-analytic evaluation:
    - **Primary Evaluation:** Individual-patient-level correlation by **Global Odds Ratio (OR)**
    - Supplemental evaluation: Trial-level correlation by $\mathbf{R^2_{WLS}}$ and $\mathbf{R^2_{Copula}}$

Prespecified Study Selection Criteria

Inclusion Criteria

- **Multi-center, randomized clinical trial**
- **Previously untreated patients with NDTE, NDTinE or RR multiple myeloma (MM)**
- **>100 patients**
- **Published after 2006[1]**

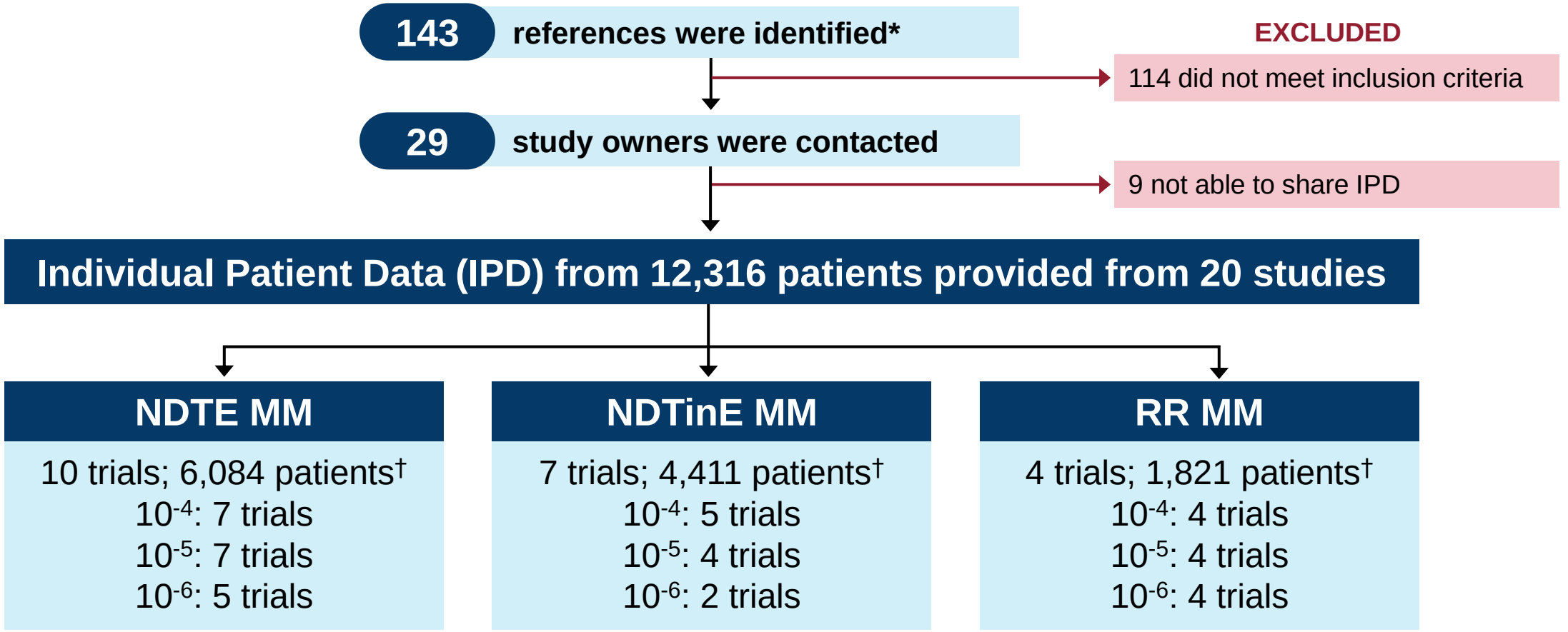
Exclusion Criteria

- **Evidence that MRD testing with 10^{-4} or higher sensitivity level was never performed**
- **Uncertain/insufficient MRD data quantity and quality**

NDTE=Newly Diagnosed Transplant-eligible
NDTinE= Newly Diagnosed Transplant-ineligible
RR=Relapsed/Refractory

1. Durie BG, Harousseau JL, Miguel JS, et al: International uniform response criteria for multiple myeloma. *Leukemia* 20:1467-73, 2006

Unprecedented Data Sharing in Multiple Myeloma



Note: one trial enrolled patients in both NDTE and NDTinE populations

*Identified March 2020, Medline database search for publications and conference abstracts using the strategy of the MeSH terms “multiple myeloma” AND “neoplasm, residual” AND the nonMeSH terms “MRD”, “myeloma”, AND “minimal residual disease”.
†Unique patients indicated in the transferred datasets who were randomized.

Primary: Individual-patient-level Correlation – Global OR

- **Measuring the correlation between MRD and PFS/OS endpoints at individual-patient level**
  - Interpretation: Ratio of odds that a patient remaining progression-free and alive beyond any timepoint for patients who achieved MRD negativity compared to those who remained MRD positive
  - Statistical Significance: 95% confidence interval (CI) excluding 1.0
  - Estimated via Bivariate Plackett Copula Model[1]
- Supplemental analysis:
  - Landmark log-rank test comparing PFS/OS between patients who achieved MRD negativity compared to those who remained MRD positive

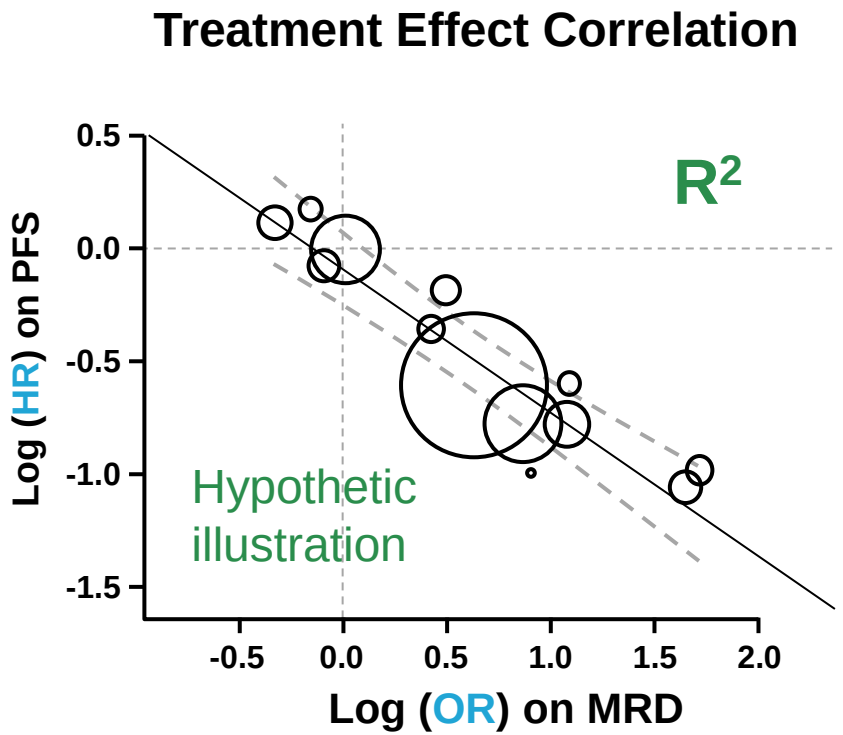
[1]Burzykowski et al. *J Royal Statist Soc.* 2004

Supplemental: Trial-level Correlation – R^2_{WLS} and R^2_{Copula}

- **Measures how precisely treatment effect on the true endpoint may be predicted based on observed treatment effect on the surrogate endpoint**
  - Interpretation: closer to 1.0, stronger the trial-level correlation
  - Estimated via two-stage models
    - **R^2_{WLS}:** Coefficient of determination of weighted linear regression[1]
      - Paired data: $\log(OR_{MRD})$ via Logistic model and $\log(HR_{PFS})$ via Cox model
    - **R^2_{Copula}:** Coefficient of determination of random effect model[2]
      - Paired data: $\log(OR_{MRD})$ & $\log(HR_{PFS})$ estimated by Bivariate Plackett Copula Model
  - **Require sufficient number of trials (2-arm comparisons) to provide robust estimations[3]**

1. Sarget et al. *JCO 2005 & 2007;* 2. Burzykowski et al. *J Royal Statist Soc.* 2004; 3. Shi et al. *CSDA* 2011

Supplemental: Trial-level Correlation – R^2_{WLS} and R^2_{Copula}



Analytic Units: Trials (2-arm comparisons)

Data Values: ORs comparing MRD, HRs comparing PFS

Inclusion of 2-arm comparison:

- **≥80%** of patients' MRDneg-CR status can be determined & **≥50** patients
- **>0%** MRDneg-CR rate in all arms

Among included 2-arm comparisons, patients with missing MRD were

- excluded (Primary)
- imputed as MRD positive (Sensitivity)

Pre-defined and endorsed by FDA

Object size is proportional to sample size

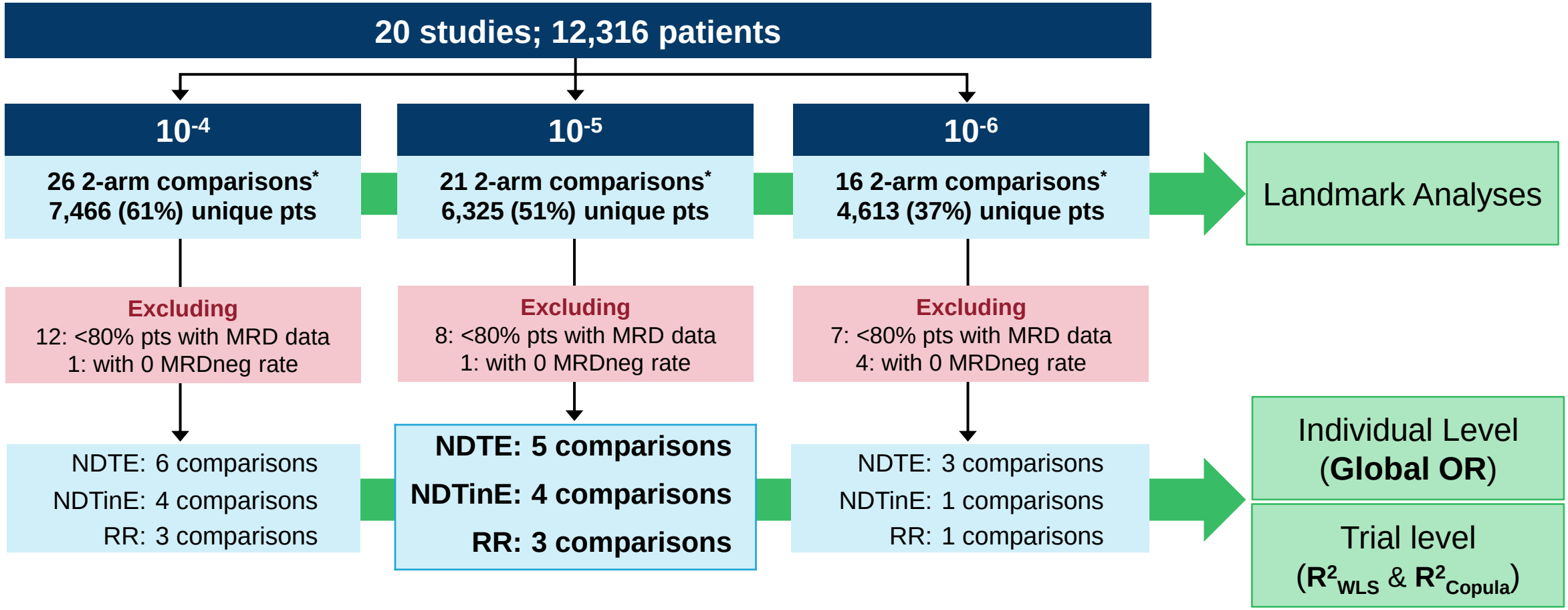
MRD Early Endpoint Candidates

- **Primary: 9 months MRDneg-CR**
  - Defined as % of patients with MRD negative status observed at 9 months (+/-3 months) after the date of randomization
- **Secondary: 12 months MRDneg-CR**
  - Defined as % of patients with MRD negative status observed at 12 months (+/-3 months) after the date of randomization
- **MRD negativity required ≥1 confirmed CR/sCR during evaluation period**
- **Pre-defined based on clinical justifications and data availabilities before formal meta-analyses and endorsed by FDA (July of 2020)**

9 Months MRDneg-CR Rate

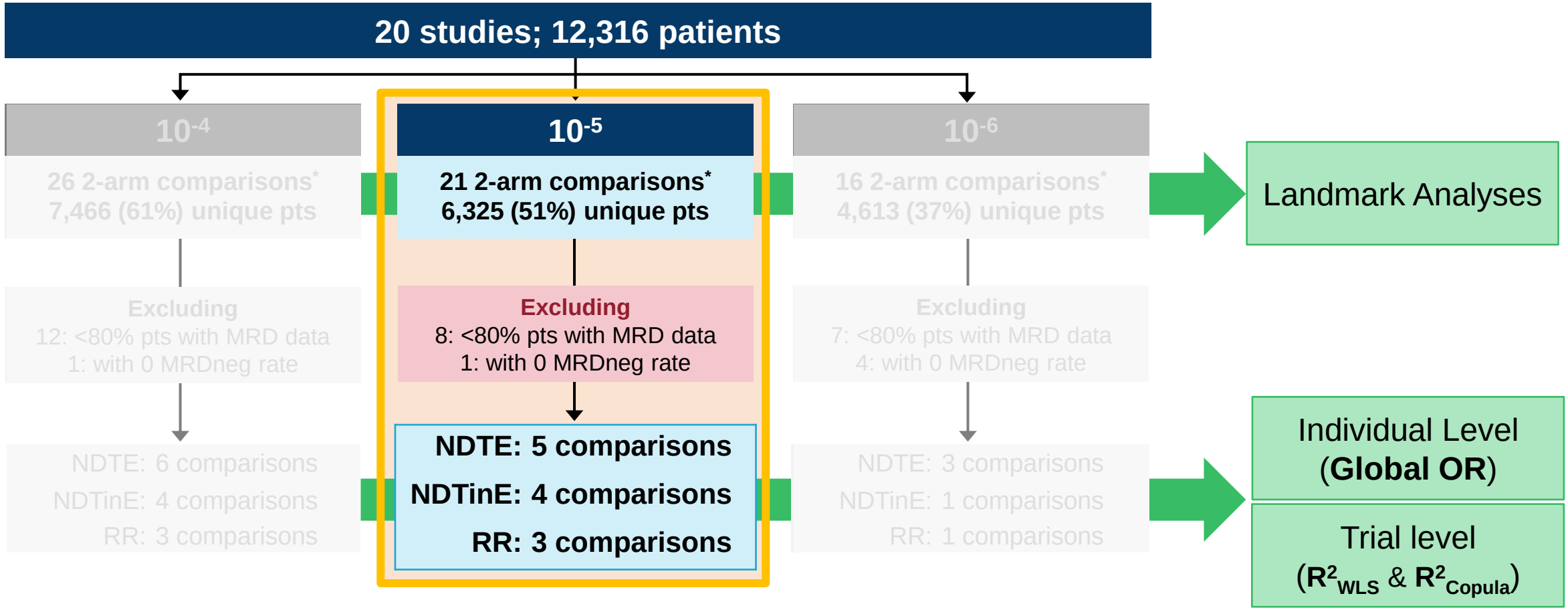
Primary surrogate endpoint candidate for **PFS and OS**

Data Availability for 9 Months MRDneg-CR Status



*Multiple 2-arm comparisons were formed for trials with either 1) > 1 experimental arms or 2) > 1 randomization;
NDTE, newly diagnosed transplant eligible; MM, multiple myeloma; NDTinE, newly diagnosed transplant ineligible; RR, relapsed or refractory

Data Availability for 9 Months MRDneg-CR Status



*Multiple 2-arm comparisons were formed for trials with either 1) > 1 experimental arms or 2) > 1 randomization;
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Strong Individual-Patient-Level Correlation by Population

9 months MRDneg-CR Status, Classified at 10^{-5} Threshold

Clinical Endpoint: Progression-Free Survival

Disease Population	Excluded Patients with Missing MRD		Imputed Missing MRD as Positive	
	N Comp. (N Pts)	Global OR (95% CI)	N Comp. (N Pts)	Global OR (95% CI)
NDTE	5 (1,430)	3.06 (2.09-4.03)	5 (1,622)	2.74 (1.88-3.61)
NDTinE	4 (2,235)	9.80 (5.14-14.46)	4 (2,605)	8.17 (4.29-12.05)
RR	3 (1,378)	8.24 (4.41-12.07)	3 (1,514)	6.70 (3.61-9.78)

Strong Individual-Patient-Level Correlation by Population

9 months MRDneg-CR Status, Classified at 10^{-5} Threshold

Clinical Endpoint: Overall Survival

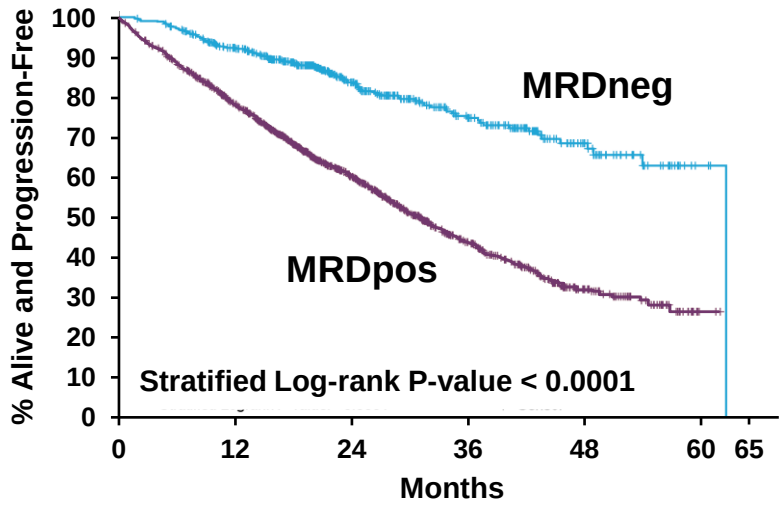
Disease Population	Excluded Patients with Missing MRD		Imputed Missing MRD as Positive	
	N Comp. (N Pts)	Global OR (95% CI)	N Comp. (N Pts)	Global OR (95% CI)
NDTE	5 (1,430)	2.81 (1.54-4.08)	5 (1,622)	2.57 (1.41-3.73)
NDTinE	4 (2,235)	10.34 (0.97-19.72)	4 (2,605)	9.25 (0.86-17.63)
RR	3 (1,378)	6.60 (2.36-10.85)	3 (1,514)	5.63 (2.02-9.23)

MRD Negativity Strongly Associated with Longer PFS in all 3 Populations

9 months MRDneg-CR Status, Classified at 10^{-5} Threshold

Clinical Endpoint: Progression-Free Survival

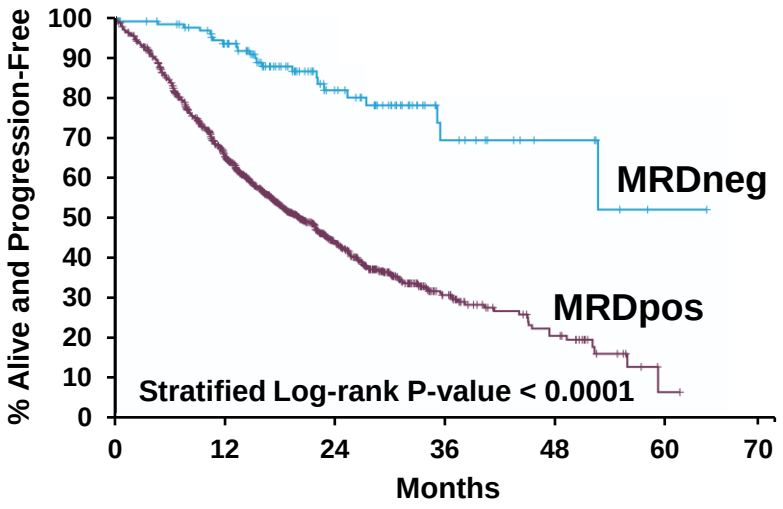
NDTE MM



Patients at Risk							
MRDneg	533	456	246	130	49	3	
MRDpos	1412	1036	576	221	62	2	

HR=0.29 (0.24-0.37)

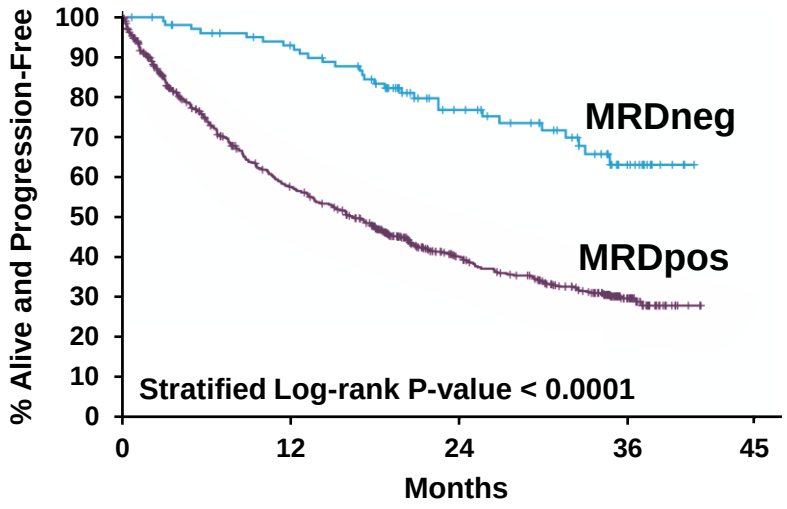
NDTinE MM



Patients at Risk							
MRDneg	133	110	47	16	7	1	0
MRDpos	1585	910	265	61	23	1	0

HR=0.24 (0.16-0.36)

RR MM



Patients at Risk				
MRDneg	104	89	51	17
MRDpos	845	426	200	49

HR=0.31 (0.20-0.46)

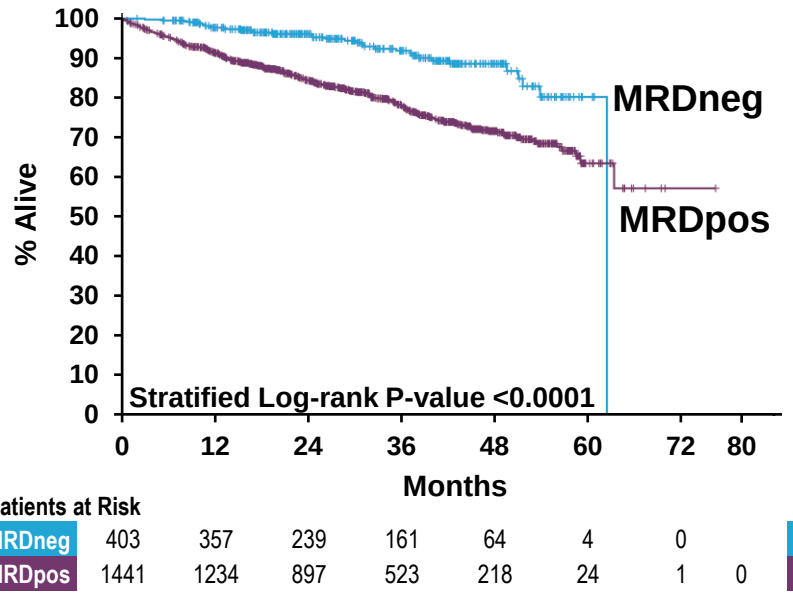
Stratified by studies

MRD Negativity Strongly Associated with Longer OS in all 3 Populations

9 months MRDneg-CR Status, Classified at 10^{-5} Threshold

Clinical Endpoint: Overall Survival

NDTE MM

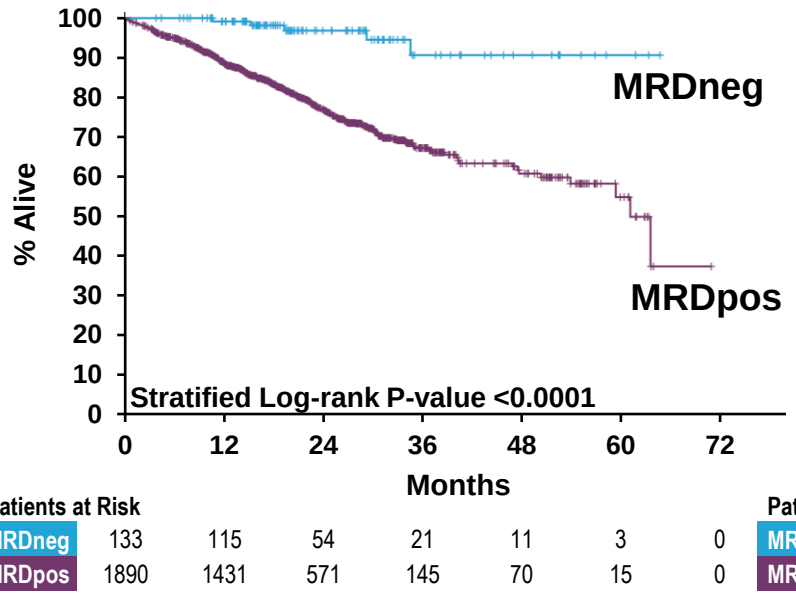


Patients at Risk

MRDneg	403	357	239	161	64	4	0	
MRDpos	1441	1234	897	523	218	24	1	0

HR=0.38 (0.27-0.56)

NDTinE MM

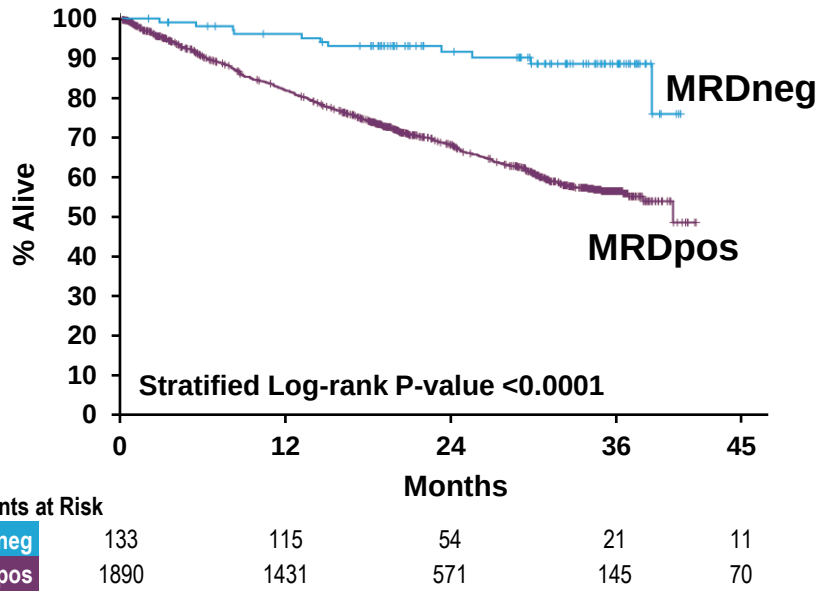


Patients at Risk

MRDneg	133	115	54	21	11	3	0
MRDpos	1890	1431	571	145	70	15	0

HR=0.16 (0.07-0.38)

RR MM



Patients at Risk

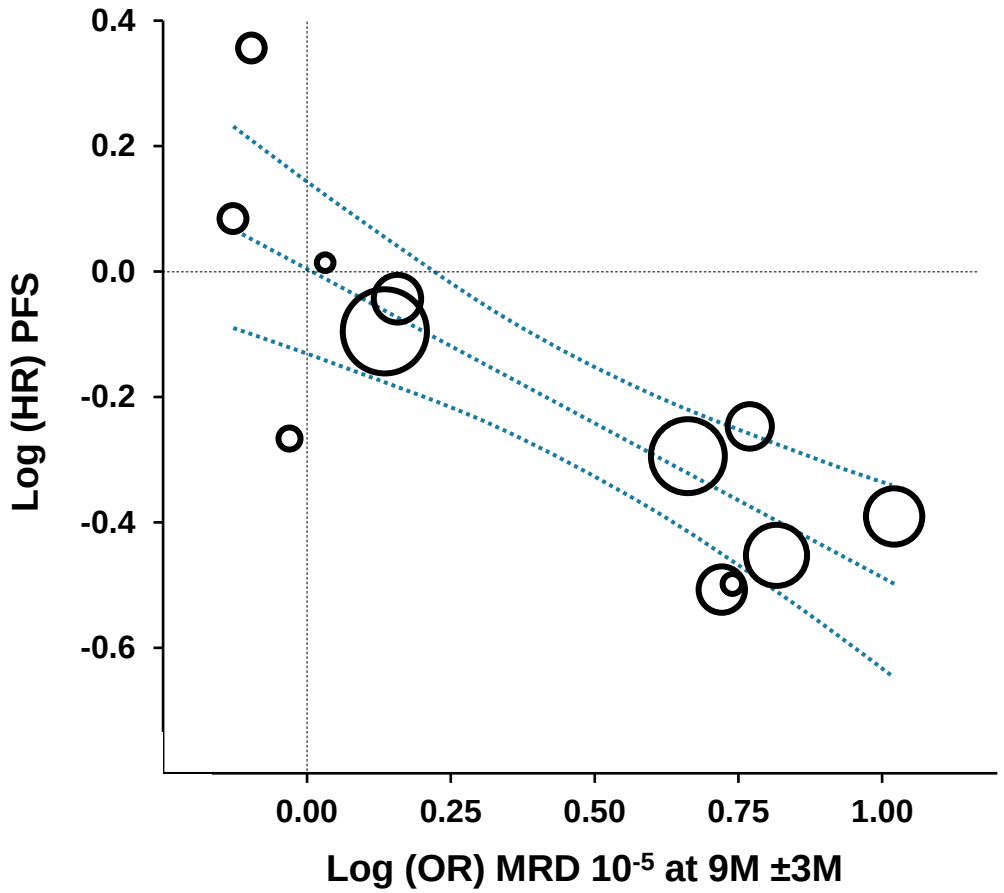
MRDneg	133	115	54	21	11
MRDpos	1890	1431	571	145	70

HR=0.25 (0.14-0.46)

Stratified by studies

Trial-Level Correlation Between 9 Months MRDneg-CR Rate and PFS – Pooling 3 Populations

Clinical Endpoint: Progression-Free Survival



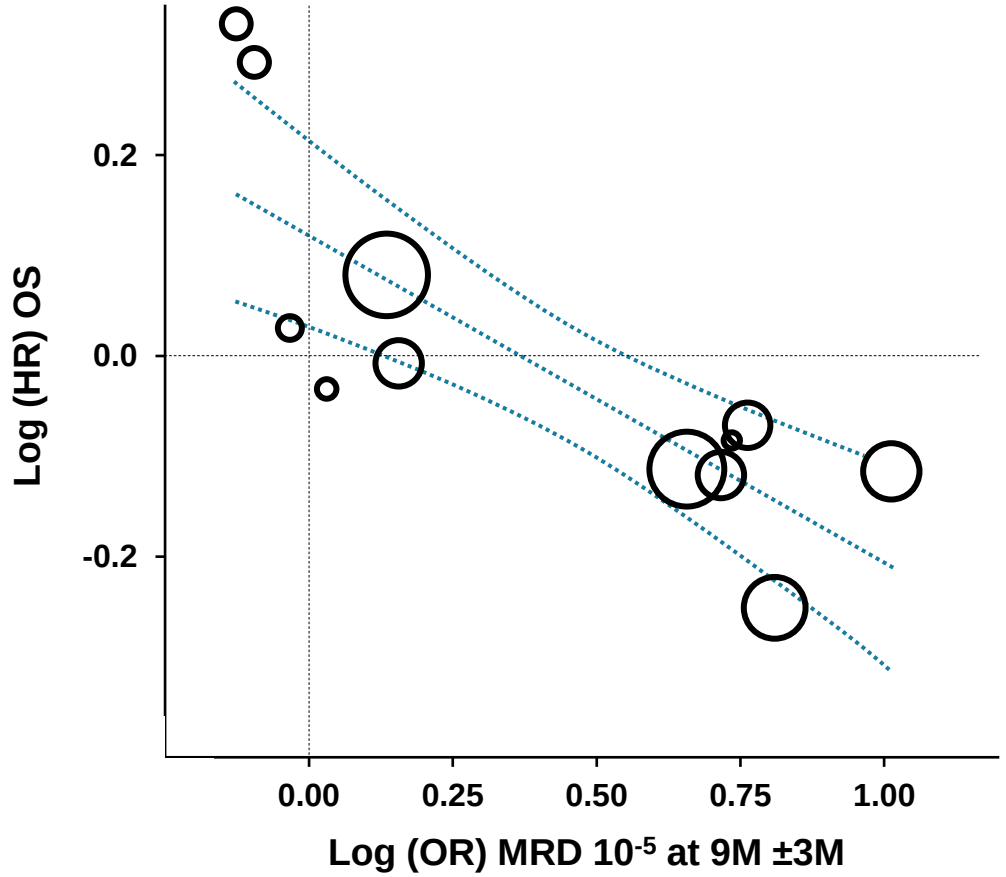
Excluding pts with missing MRD status	
12 comparisons; 5,043 patients	
R^2_{WLS} (95% CI)	R^2_{Copula} (95% CI)
0.70 (0.47, 0.92)	**0.66 (0.36, 0.97)**

Imputing missing MRD status as MRD+	
12 comparisons; 5,741 patients	
R^2_{WLS} (95% CI)	R^2_{Copula} (95% CI)
0.73 (0.53, 0.93)	**0.71 (0.43, 0.99)**

Note: size of dot is proportional to sample size

Trial-Level Correlation Between 9 Months MRDneg-CR Rate and OS – Pooling 3 Populations

Clinical Endpoint: Overall Survival



Excluding pts with missing MRD status	
12 comparisons; 5,043 patients	
R^2_{WLS} (95% CI)	R^2_{Copula} (95% CI)
0.69 (0.51, 0.87)	**0.64 (0.31, 0.96)**

Imputing missing MRD status as MRD+	
12 comparisons; 5,741 patients	
R^2_{WLS} (95% CI)	R^2_{Copula} (95% CI)
0.71 (0.50, 0.93)	**0.64 (0.31, 0.97)**

Note: size of dot is proportional to sample size

Trial-Level Correlation Between 9 Months MRDneg-CR Rate and PFS/OS – Pooling NDTE and NDTinE Populations

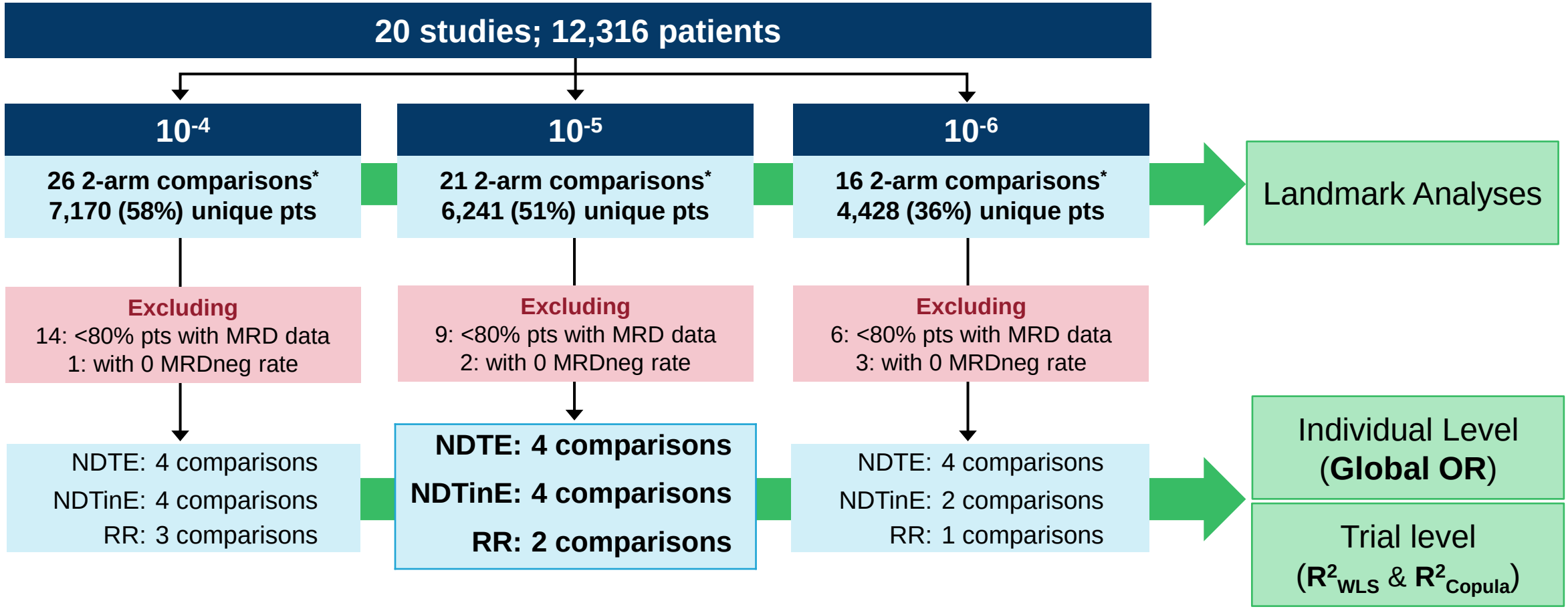
Corresponding to U. of Miami Analysis

Missing MRD	N Comp. (N Pts)	Progression-Free Survival		Overall Survival	
		R^2_{WLS} (95% CI)	R^2_{Copula} (95% CI)	R^2_{WLS} (95% CI)	R^2_{Copula} (95% CI)
Excluded	9 (3,665)	0.73 (0.39, 1.00)	0.67 (0.31, 1.00)	0.78 (0.51, 1.00)	0.67 (0.32, 1.00)
Imputed as MRD Positive	9 (4,227)	0.77 (0.49, 1.00)	0.73 (0.42, 1.00)	0.79 (0.49, 1.00)	0.67 (0.31, 1.00)

12 Months MRDneg-CR Rate

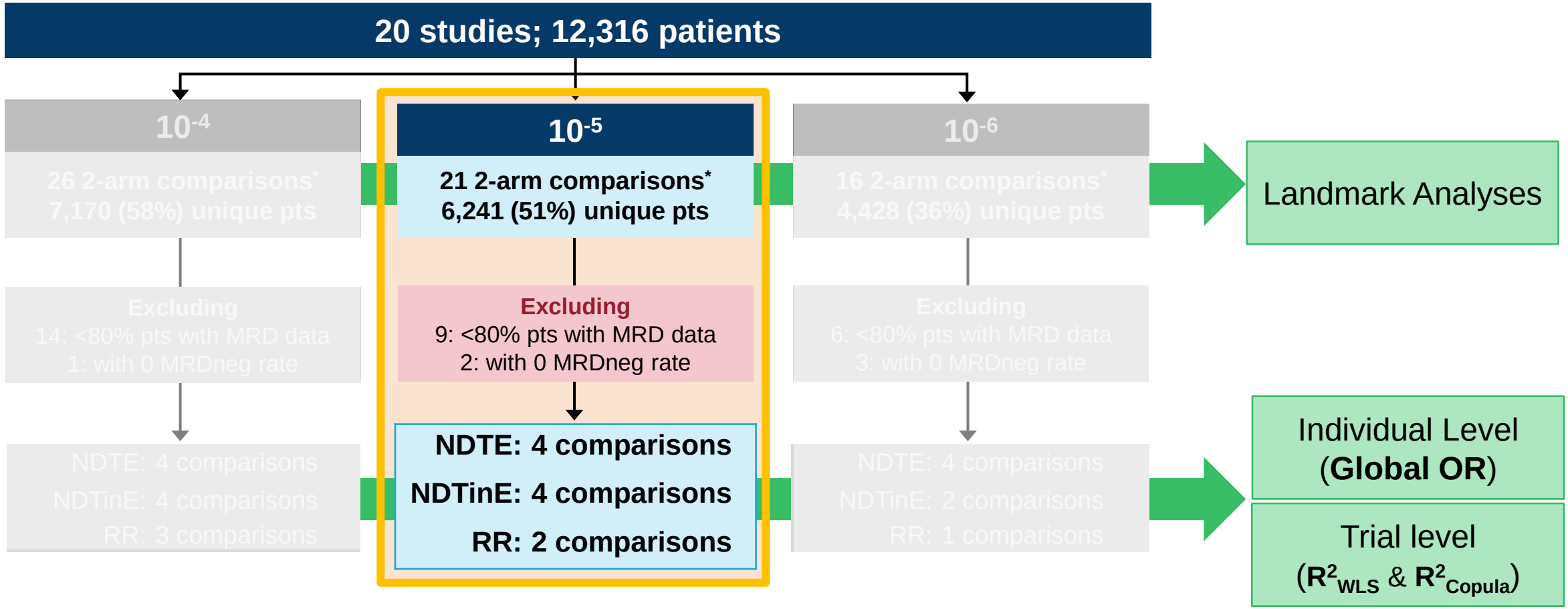
Secondary surrogate endpoint candidate for **PFS and OS**

Data Availability for 12 Months MRDneg-CR Status



*Multiple 2-arm comparisons were formed for trials with either 1) > 1 experimental arms or 2) > 1 randomization;
NDTE, newly diagnosed transplant eligible; MM, multiple myeloma; NDTinE, newly diagnosed transplant ineligible; RR, relapsed or refractory

Data Availability for 12 Months MRDneg-CR Status



*Multiple 2-arm comparisons were formed for trials with either 1) > 1 experimental arms or 2) > 1 randomization;
NDTE, newly diagnosed transplant eligible; MM, multiple myeloma; NDTinE, newly diagnosed transplant ineligible; RR, relapsed or refractory

Strong Individual-Patient-Level Correlation by Population

12 months MRDneg-CR Status, Classified at 10^{-5} Threshold

Clinical Endpoint: Progression-Free Survival

Disease Population	Excluded Patients with Missing MRD		Imputed Missing MRD as Positive	
	N Comp. (N Pts)	Global OR (95% CI)	N Comp. (N Pts)	Global OR (95% CI)
NDTE	4 (1,285)	4.45 (3.19-5.70)	4 (1,405)	3.86 (2.79-4.93)
NDTinE	4 (2,281)	11.95 (7.32-16.58)	4 (2,605)	10.01 (6.15-13.87)
RR	2 (863)	16.24 (5.77-26.71)	2 (950)	12.09 (4.36-19.83)

Strong Individual-Patient-Level Correlation by Population

12 months MRDneg-CR Status, Classified at 10^{-5} Threshold

Clinical Endpoint: Overall Survival

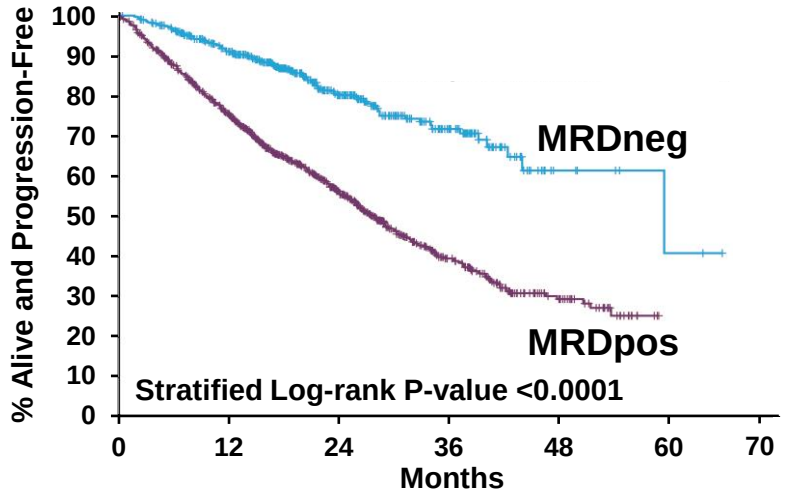
Disease Population	Excluded Patients with Missing MRD		Imputed Missing MRD as Positive	
	N Comp. (N Pts)	Global OR (95% CI)	N Comp. (N Pts)	Global OR (95% CI)
NDTE	4 (1,285)	5.16 (2.80-7.53)	4 (1,405)	4.81 (2.62-7.00)
NDTinE	4 (2,281)	7.08 (2.84-11.31)	4 (2,605)	6.45 (2.60-10.31)
RR	N/A	N/A	N/A	N/A

MRD Negativity Strongly Associated with Longer PFS in all 3 Populations

12 months MRDneg-CR Status, Classified at 10^{-5} Threshold

Clinical Endpoint: Progression-Free Survival

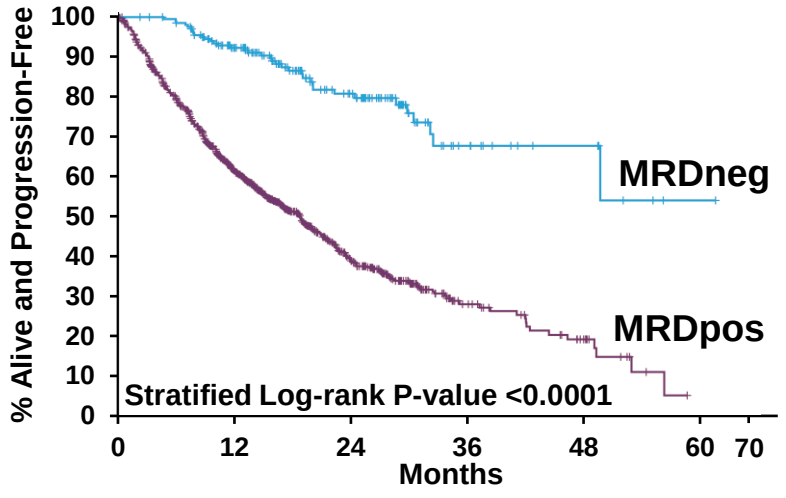
NDTE MM



Patients at Risk							
MRDneg	531	414	188	69	7	2	0
MRDpos	1120	775	406	131	39	2	

HR=0.37 (0.29-0.47)

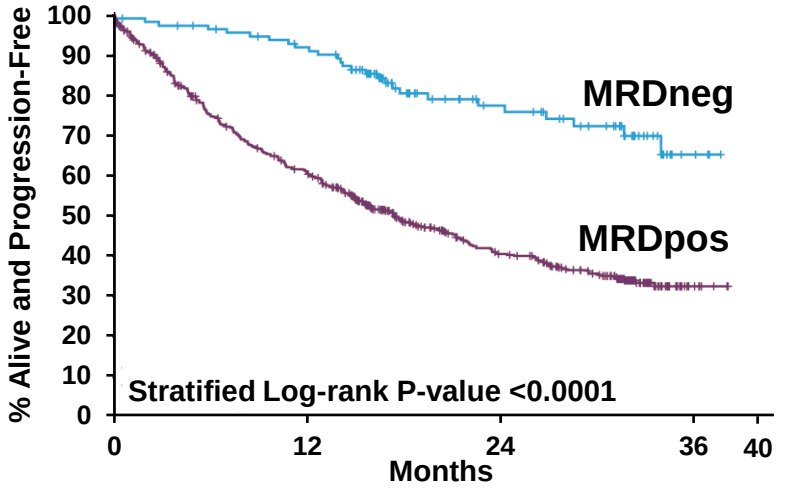
NDTinE MM



Patients at Risk							
MRDneg	208	160	76	17	8	1	
MRDpos	1428	657	187	37	13	0	

HR=0.22 (0.16-0.31)

RR MM



Patients at Risk				
MRDneg	115	100	48	4
MRDpos	654	366	163	8

HR=0.30 (0.20-0.45)

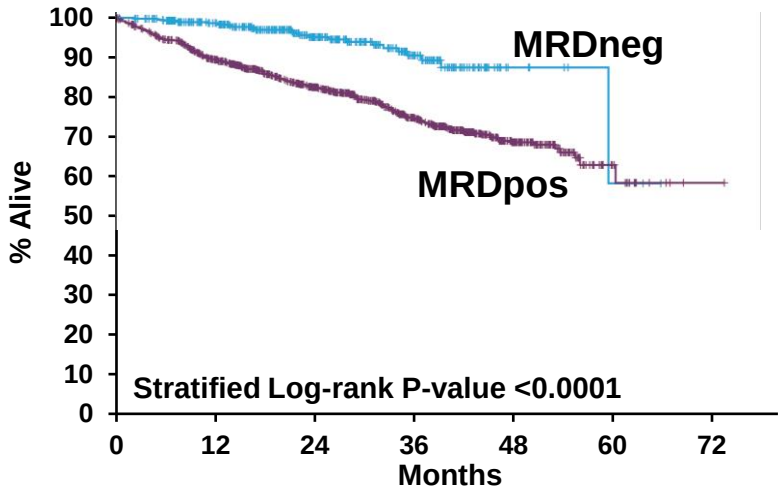
Stratified by studies

MRD Negativity Strongly Associated with Longer OS in all 3 Populations

12 months MRDneg-CR Status, Classified at 10^{-5} Threshold

Clinical Endpoint: Overall Survival

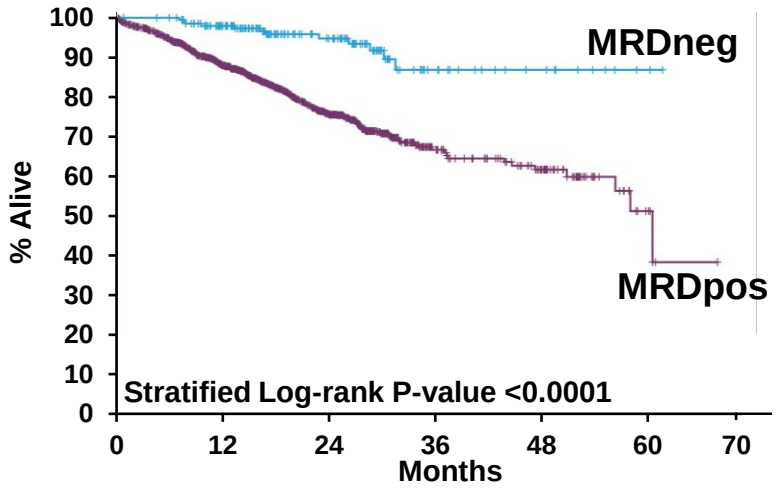
NDTE MM



Patients at Risk							
MRDneg	394	320	191	82	7	2	0
MRDpos	1224	1004	749	398	151	16	1

HR=0.34 (0.22-0.54)

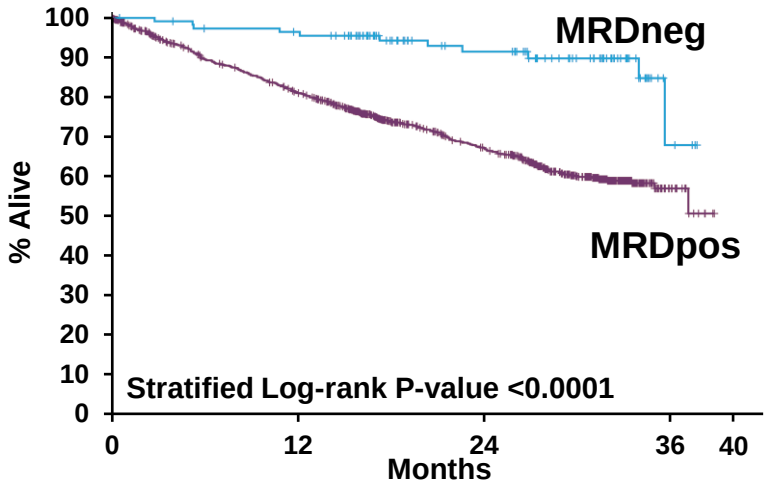
NDTinE MM



Patients at Risk							
MRDneg	208	172	88	22	11	2	0
MRDpos	1799	1162	465	98	49	6	0

HR=0.26 (0.14-0.46)

RR MM



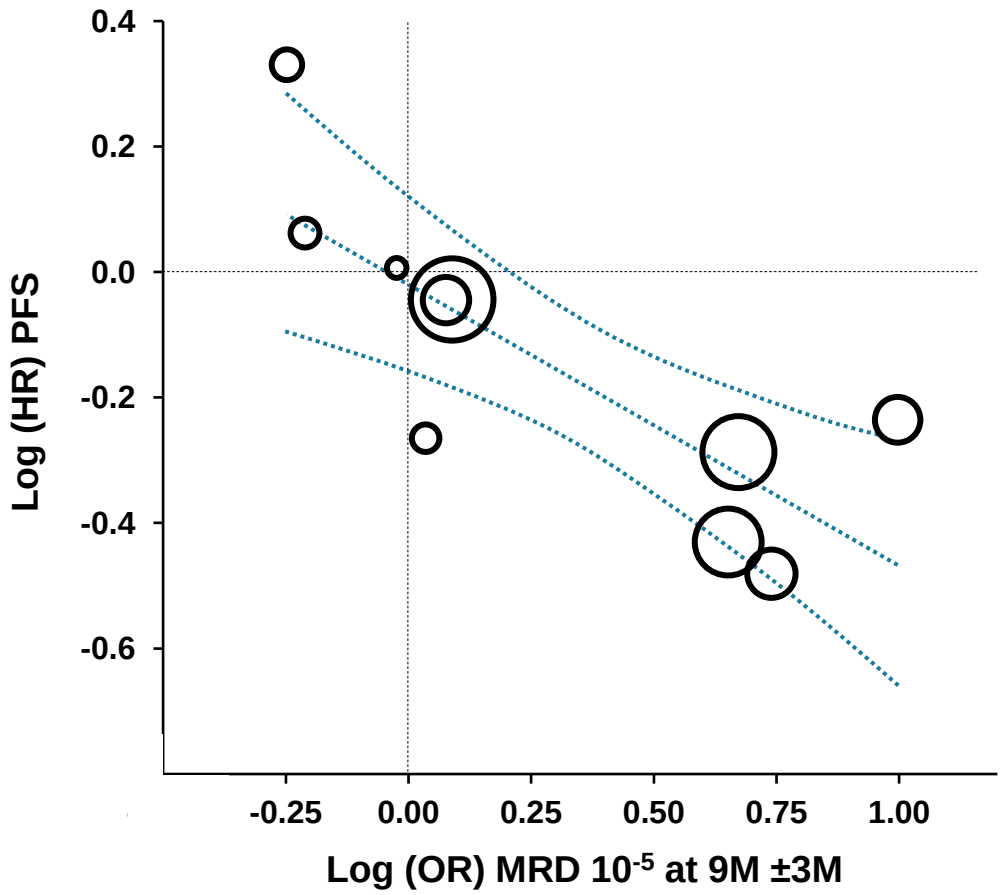
Patients at Risk				
MRDneg	115	107	63	4
MRDpos	1108	813	480	21

HR=0.25 (0.13-0.45)

Stratified by studies

Trial-Level Correlation Between 12 Months MRDneg-CR Rate and PFS – Pooling 3 Populations

Clinical Endpoint: Progression-Free Survival



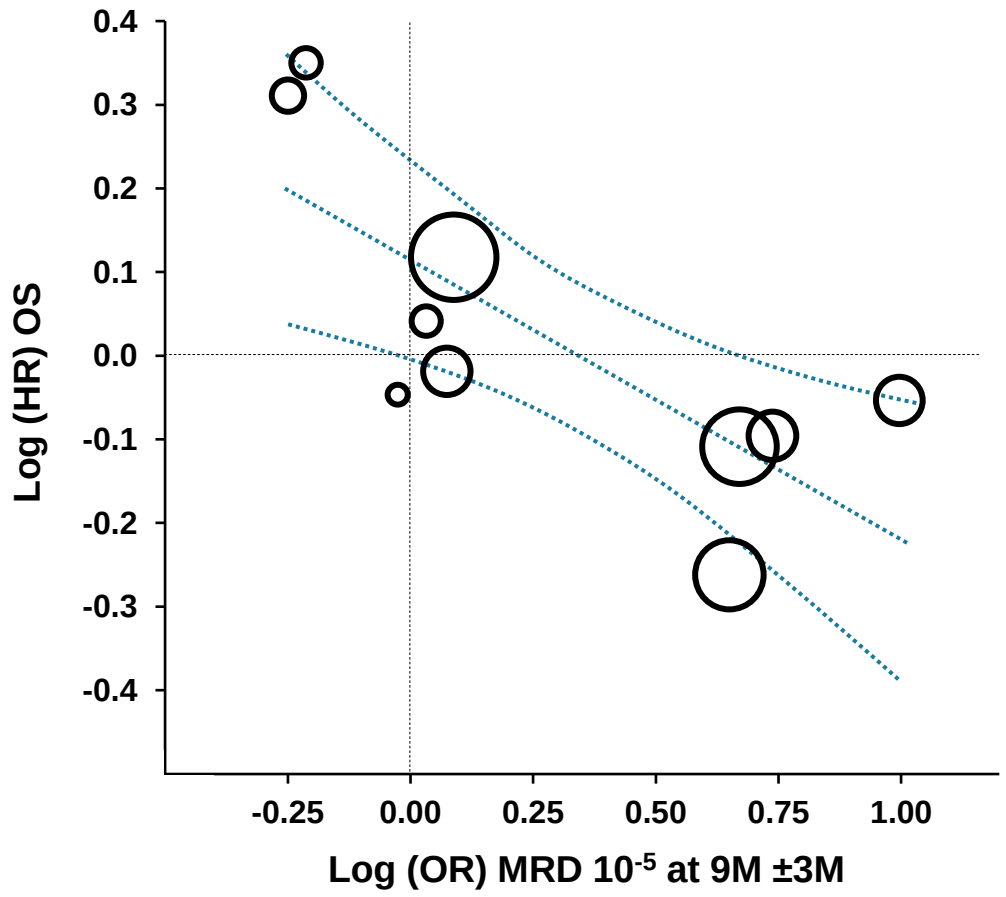
Excluding pts with missing MRD status	
10 comparisons; 4,429 patients	
R^2_{WLS} (95% CI)	R^2_{Copula} (95% CI)
0.66 (0.34, 0.98)	**0.61 (0.23, 0.99)**

Imputing missing MRD status as MRD+	
10 comparisons; 4,960 patients	
R^2_{WLS} (95% CI)	R^2_{Copula} (95% CI)
0.72 (0.46, 0.99)	**0.69 (0.38, 1.00)**

Note: size of dot is proportional to sample size

Trial-Level Correlation Between 12 Months MRDneg-CR Rate and OS – Pooling 3 Populations

Clinical Endpoint: Overall Survival



Excluding pts with missing MRD status	
10 comparisons; 4,429 patients	
R^2_{WLS} (95% CI)	R^2_{Copula} (95% CI)
0.60 (0.29, 0.92)	**0.54 (0.12, 0.96)**

Imputing missing MRD status as MRD+	
10 comparisons; 4,960 patients	
R^2_{WLS} (95% CI)	R^2_{Copula} (95% CI)
0.69 (0.45, 0.94)	**0.61 (0.23, 0.99)**

Note: size of dot is proportional to sample size

Trial-Level Correlation Between 12 Months MRDneg-CR Rate and PFS/OS – Pooling NDTE and NDTinE Populations

Corresponding to U. of Miami Analysis

Missing MRD	N Comp. (N Pts)	Progression-Free Survival		Overall Survival	
		R^2_{WLS} (95% CI)	R^2_{Copula} (95% CI)	R^2_{WLS} (95% CI)	R^2_{Copula} (95% CI)
Excluded	8 (3,566)	0.78 (0.49, 1.00)	0.71 (0.36, 1.00)	0.78 (0.53, 1.00)	0.69 (0.34, 1.00)
Imputed as MRD Positive	8 (4,010)	0.85 (0.70, 1.00)	0.82 (0.60, 1.00)	0.80 (0.52, 1.00)	0.68 (0.32, 1.00)

High Individual-Patient-Level Correlation Supports Consideration of Early Endpoint For Accelerated Approval

- **Consistent high individual-patient-level correlations provide strong evidence that 9 months MRDneg-CR rate at 10^{-5} threshold reasonably likely predicts clinical benefit of PFS in NDTE, NDTinE and RR MM populations**
  - Promising trial-level correlations pooling 3 populations provide supportive evidence
  - Similar results were seen for 12 months MRDneg-CR rate at 10^{-5} threshold
  - Similar results were seen for OS, except in the scenarios with low events

MRDneg-CR rate classified at 10^{-5} threshold at 9 and 12 months IS reasonably likely to predict clinical benefit in NDTE, NDTinE, and RR MM settings

Summary and Conclusions

Kenneth C. Anderson, MD

Kraft Family Professor of Medicine
Harvard Medical School

Clear Rationale to Seek Endpoint Measuring Earlier Response

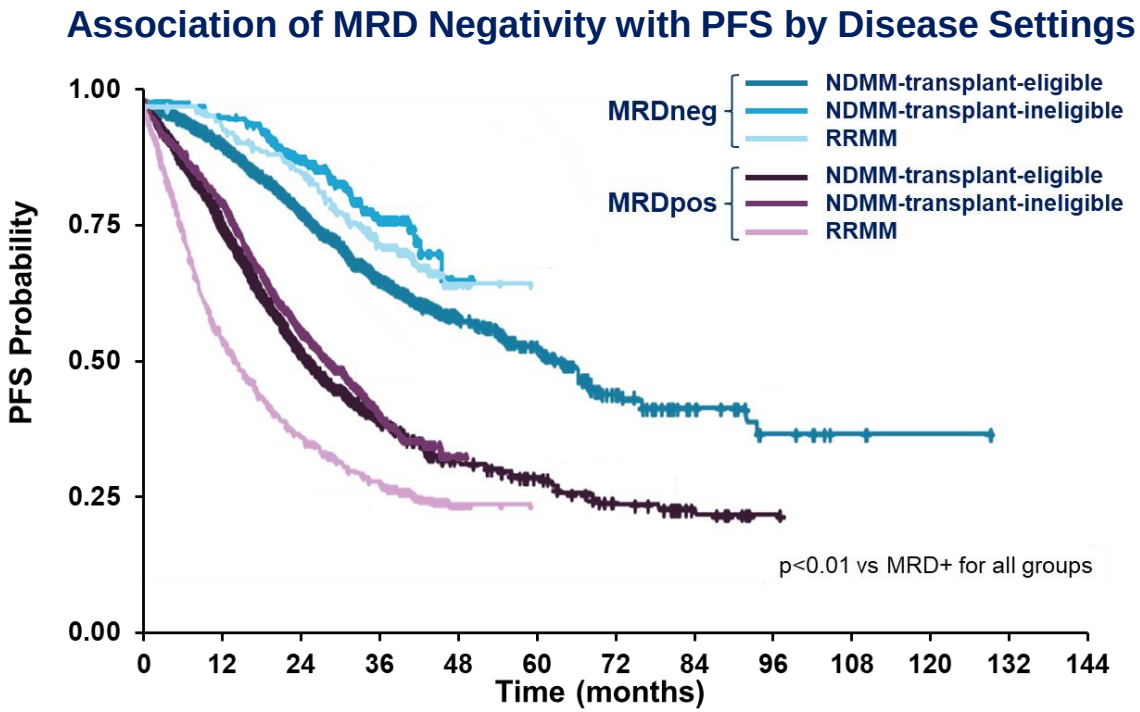
- **Therapeutic landscape in myeloma has greatly expanded**
  - ORR near 100% and CR >70%
  - Median PFS >6 years and median OS >10 years
- **Urgent need to develop alternative endpoints that provide sensitive earlier read out allowing patients timely access to newer treatment options**

MRD Determination Provides for Reproducible Assessment of Residual Disease and Predicts Outcome

- **Technological advances allow reproducible assessment of MRD**
- **Large number of studies have confirmed significant impact of MRD on PFS and OS**
- **Trial-level analyses correlating an MRD sensitivity 10^{-5} or better with PFS and OS**

93 publications

8098 patients



Munshi N et al., *Blood Adv.* 2020; 4: 5988-5999.

i²TEAMM Study: Heterogeneity is a Strength

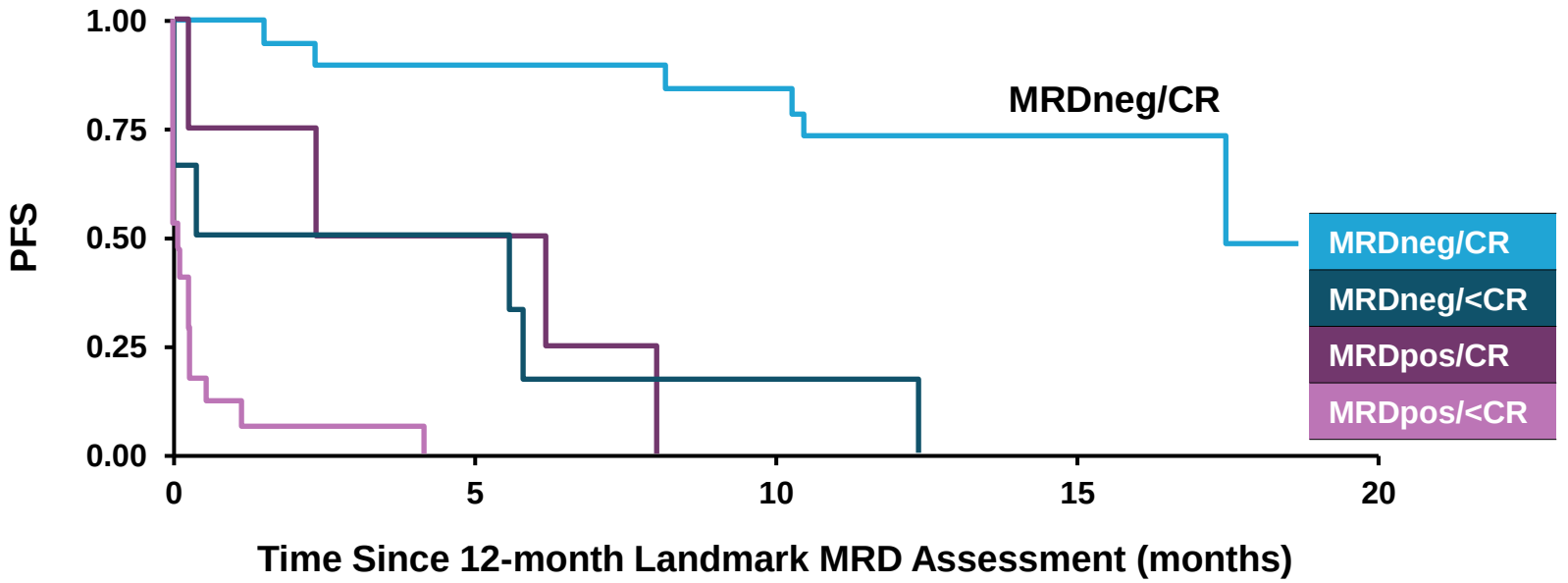
- **Trial-level meta-analysis of 20 robust, randomized, controlled Phase 3 clinical trials with mature PFS data and large sample sizes**
- **Enrolled patients from US, Europe, Middle East, Africa, and Asia**
- **Varied in design, lines of therapy, treatment strategies, MRD testing methods, timing and/or number of assessments, and sensitivity levels**

Results are largely representative of a wide spectrum of treatment options and clinical practice

i²TEAMM Study: Methods

- **Although chimeric antigen receptor (CAR) T cell therapy and T cell engager therapies are not represented, MRD is correlated with PFS after CAR T cell therapy**

12-month Analysis of PFS and MRDneg CR after idecabtagene vicleucel (ide-cel)



Paiva B et al *Blood Cancer Discovery* 2023; 4: 365-73.

Strength of Results: Consistent in 2 Independent Studies

- **Two independent analyses with differences in methodologies, but overlapping studies**
- **BOTH show a similar strong association between MRD negative CR and PFS at individual-patient-level**
- **Re-analysis by i^{2}TEAMM using similar inclusion criteria (e.g. missingness of data) shows consistent results**

i²TEAMM Study: Consistent Results of Trial and Patient Level Analyses

Trial-level association

- **MRD negative CR and PFS is promising at 10^{-5} MRD sensitivity level**

Individual patient level

- **Bivariate association analysis and landmark analysis showed strong association between MRD negative CR (at 9 and 12 months) and PFS**

Conclusion

- **Combined results of individual patient-level and trial-level surrogacy support the use of MRD negative CR as an early endpoint reasonably likely to predict clinical benefit**

Results support the use of MRD negative CR as an early endpoint for accelerated drug approval in multiple myeloma

i²TEAMM Presentation to Support MRD as Accelerated Approval Endpoint

Oncologic Drugs Advisory Committee (ODAC)

April 12, 2024