Oncology Endpoint Development

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Outline

1. Endpoints in Regulatory Decision-making
2. Novel Endpoint Development
3. OCE Endpoint Initiatives

- **FDA Guidance E9 Statistical Principles for Clinical Trials (1998):**
  - "There should be sufficient evidence that the primary variable (primary endpoint) can provide a valid and reliable measure of some clinically relevant and important treatment benefit…"

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Regulatory Approval Pathways

- Regular Approval
  - Approval is based on demonstration of clinical benefit or an effect on an established surrogate

- Accelerated Approval
  - Treatment of serious or life-threatening illness
  - Taking into account the condition and availability of alternative treatments, provides a meaningful benefit
  - Approval is based on a surrogate endpoint that is reasonably likely to predict clinical benefit or on a clinical endpoint other than survival or irreversible morbidity, an intermediate endpoint, that is reasonable likely to predict clinical benefit
  - May require post-approval trials to verify and describe the anticipated clinical benefit

21 CFR 314.510
FDA Guidance for Industry: Expedited Programs for Serious Conditions- Drugs and Biologics

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Types of Endpoints

- Clinical Benefit
  - Direct measure of how a patient feels, functions, or survives
- Surrogate Endpoint
  - Predicts clinical benefit, but is not a measure of clinical benefit
  - Clinical validation that the marker predicts clinical benefit
- Surrogate endpoint reasonably likely to predict clinical benefit
- Intermediate clinical endpoint
  - Therapeutic effect that can be measured earlier than morbidity or mortality, but reasonably likely to predict clinical benefit

Types of Endpoints

- Most oncology endpoints are not surrogates

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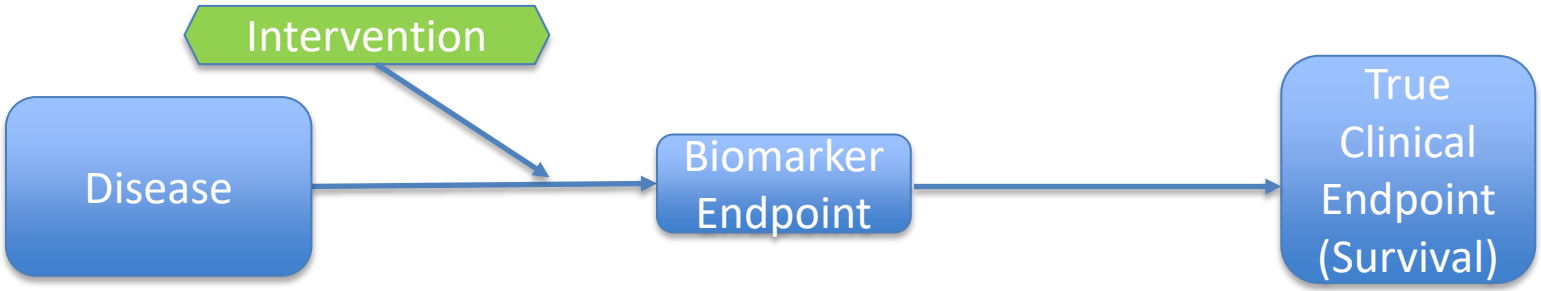

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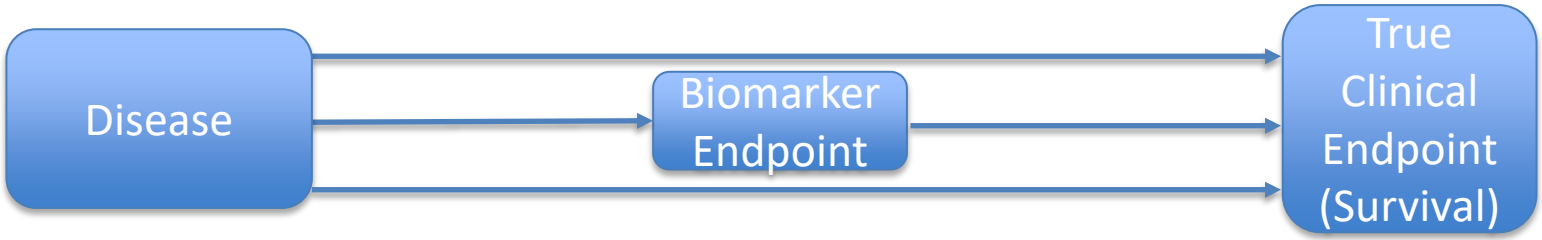

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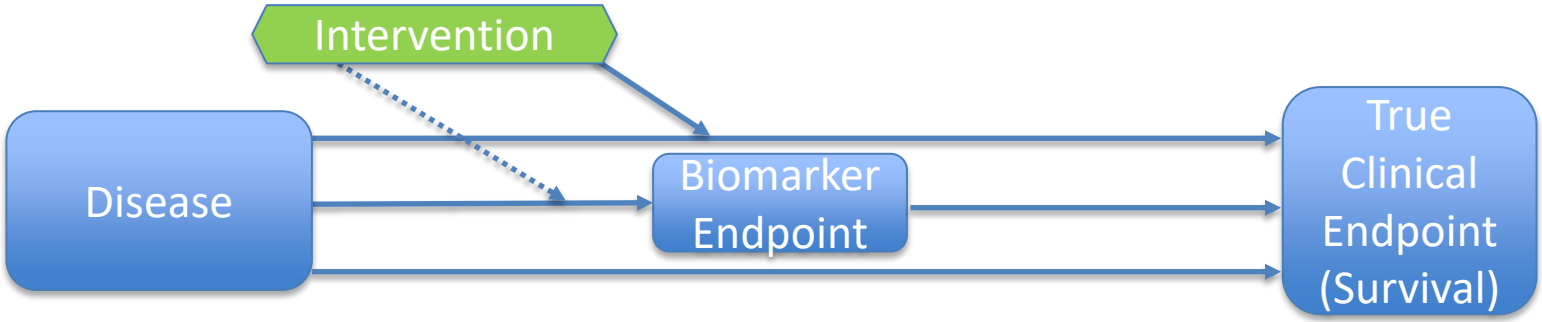

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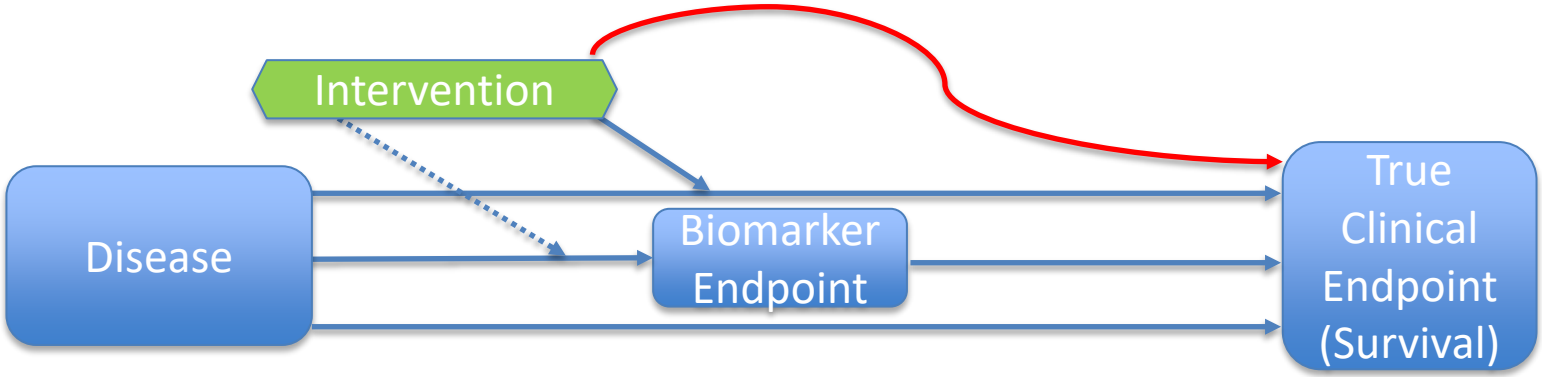

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Novel Endpoint Development: Surrogate Validation

- Prentice Criteria
  - The surrogate must be a correlate of the true clinical endpoint
  - The treatment effect on the surrogate should capture the full effect of treatment on the clinical endpoint
- Meta-analytical methods
  - Patient-level data
  - Allow for assessment of Individual Level and Trial Level Surrogacy
    - Individual Surrogacy- Correlation between candidate surrogate and true clinical endpoint on an individual level
    - Trial Level Surrogacy- Correlation between effect of treatment on the candidate surrogate and the effect of treatment on the true clinical endpoint
  - Surrogate Threshold Effect
    - Minimum treatment effect on the surrogate necessary to predict a non-zero effect on the true clinical endpoint

Novel Endpoint Development

- Meta-analysis Considerations
  - Inclusion of more trials increases the statistical rigor of the analysis and may allow for more interrogation of the data to address uncertainties.
  - Inclusion of trials with a range of treatment effects (positive and negative trials) increases the accuracy and precision of trial level surrogacy assessment.
  - When designing a meta-analysis, consideration of biomarker timing of assessment, missing data is important.
  - The trial populations and treatments included in the meta-analysis inform future applicability of the surrogate biomarker.

FDA Guidance. Hematologic Malignancies: Regulatory Considerations for use of MRD in Development of Drug and Biological Products for Treatment

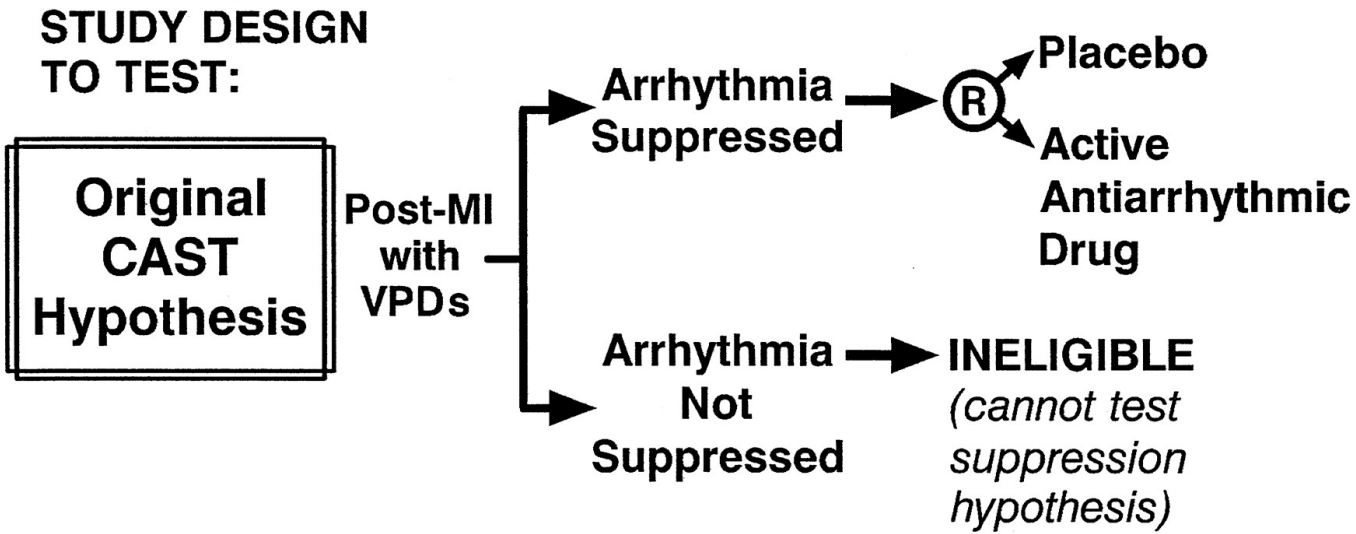
Novel Endpoint Development

- Caveats regarding use of surrogate endpoint
  - Use of surrogate may not be appropriate for subpopulations or future trial populations if there are significant differences between the population in the meta-analysis and the trial population.
  - Use of surrogate may not be appropriate for therapeutic modalities that have substantially different MOA (e.g., cytotoxic vs. immunotherapies).

Abbreviations: MOA, Mechanism of Action

FDA Guidance. Hematologic Malignancies: Regulatory Considerations for use of MRD in Development of Drug and Biological Products for Treatment

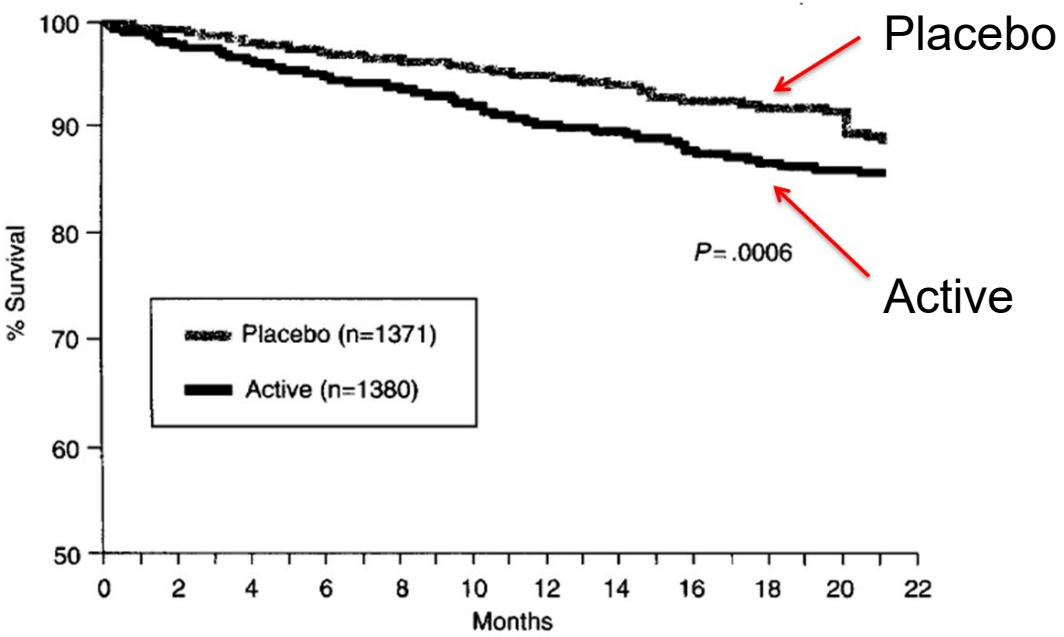
The CAST Trial



Abbreviations: VPDs, Ventricular premature depolarizations

Pratt Circulation 1995

The CAST Trial



Epstein JAMA 1993

Potential OS Detriments Demonstrated Across the PI3K Inhibitor Class

Study	Population & Treatment	PFS HR (95% CI)	OS HR (95% CI)
DUO	• Previously treated CLL/SLL • **Duvelisib** vs ofatumumab	0.52 (0.39, 0.69)	1.09 (0.79, 1.51)
312-0123	• Untreated CLL • Bendamustine and rituximab ± **idelalisib**	1.10 (0.48, 2.52)	3.34 (1.08, 10.39)
313-0124	• Previously treated indolent NHL • Rituximab ± **idelalisib**	0.50 (0.29, 0.85)	4.74 (0.6, 37.12)
313-0125	• Previously treated indolent NHL • Bendamustine and rituximab ± **idelalisib**	0.74 (0.5, 1.1)	1.51 (0.71, 3.23)
CHRONOS-3	• Previously treated indolent NHL • Rituximab ± **copanlisib**[#]	0.52 (0.39, 0.69)	0.87[#] (0.57, 1.35)
UNITY-CLL	• Untreated and previously treated CLL • **Umbralisib** + ublituximab vs GC	0.55 (0.41, 0.72)	1.23

[#]In the CHRONOS-3 trial, decreased overall survival was demonstrated in the first 2 years in the copanlisib arm, followed by a crossing of KM curves

Abbreviations: CI, confidence interval; CLL, chronic lymphocytic leukemia; GC, obinutuzumab plus chlorambucil; HR, Hazard Ratio; NHL, non-Hodgkin lymphoma; OS, overall survival; SLL, small lymphocytic lymphoma; PI3K, Phosphatidylinositol 3-kinase; KM, Kaplan-Meier

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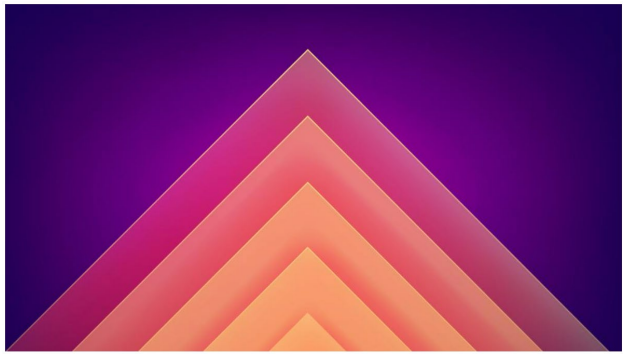
Project Endpoint

- Oncology Center of Excellence initiative to enhance development of endpoints in oncology drug development.
  - Explore potential uses for early, novel endpoints
  - Foster engagement with the broader community
  - Aims to advance use of more established late endpoints



https://www.fda.gov/about-fda/oncology-center-excellence/project-endpoint

FDA-AACR-ASA WORKSHOP: OVERALL SURVIVAL IN ONCOLOGY CLINICAL TRIALS

- To discuss best practices of trial design, analyses, and interpretation of overall survival in oncology clinical trials
- Explore approaches to address the uncertainty of OS analyses based on early or limited data and incorporate this information into the benefit-risk assessment
- Advance methods to incorporate OS when it is not the primary or secondary endpoint to evaluate for the potential for harm

Abbreviations: OS, Overall Survival

Mitigating Risk of Early Endpoints

- There are risks associated with use of early endpoints
- Risks can be mitigated by assessment of late endpoints
  - Overall survival as a safety assessment
- Regulatory authorities exist to mitigate risks associated with use of early endpoints
  - Consolidated Appropriations Act, 2023
    - Provides FDA authority to require a confirmatory trial to be underway prior to granting accelerated approval
    - Created a formal expedited withdrawal procedure for drugs approved through accelerated approval in which confirmatory study fails to verify the anticipated clinical benefit

Conclusions

- Novel endpoints have potential to expedite drug development
- Endpoints used to support regulatory decisions should provide a valid and reliable measure of a clinically meaningful and important treatment benefit
- Most endpoints in oncology are intermediate clinical endpoints
- To minimize risk associated with use of intermediate clinical endpoints or any early endpoint, later endpoints such as overall survival should also be evaluated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Multiple Myeloma

Minimal Residual Disease

Bindu Kanapuru, MD
Associate Director of Therapeutic Review
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Discussion Topics

- Discuss the adequacy of available data to support the use of MRD as an accelerated approval endpoint in MM.

- Discuss whether the available data supports the use of MRD as an endpoint in different MM disease settings.
  - Newly diagnosed MM
  - Relapsed/Refractory MM

- Discuss the acceptability of the timepoints for MRD assessment:
  - 9-months, 12-months, MRD negative CR at any time
  - Requirement for assessment of durability

MRD: Minimal Residual Disease, MM: Multiple Myeloma, CR: Complete Response

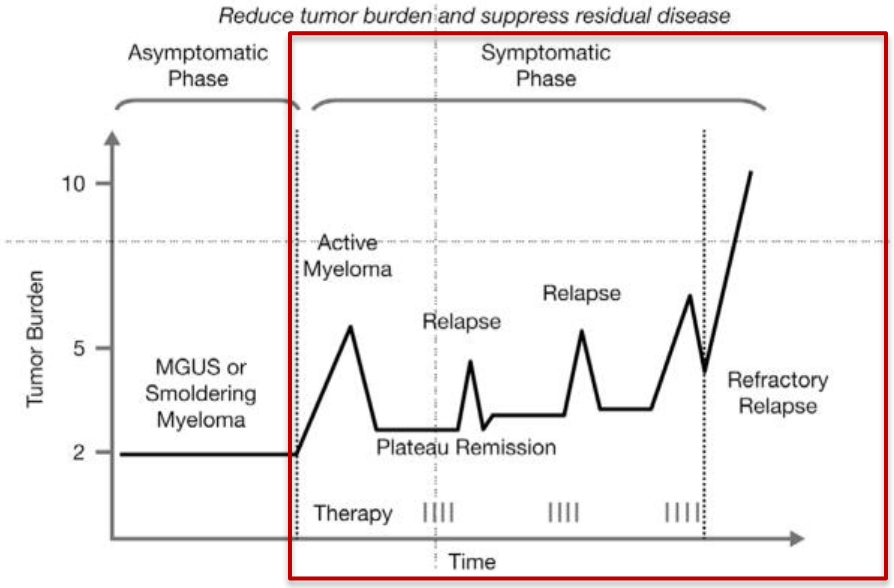
Voting Question

Does the evidence support the use of MRD as an accelerated approval endpoint in MM clinical trials?

MRD: Minimal Residual Disease, MM: Multiple Myeloma

Multiple Myeloma

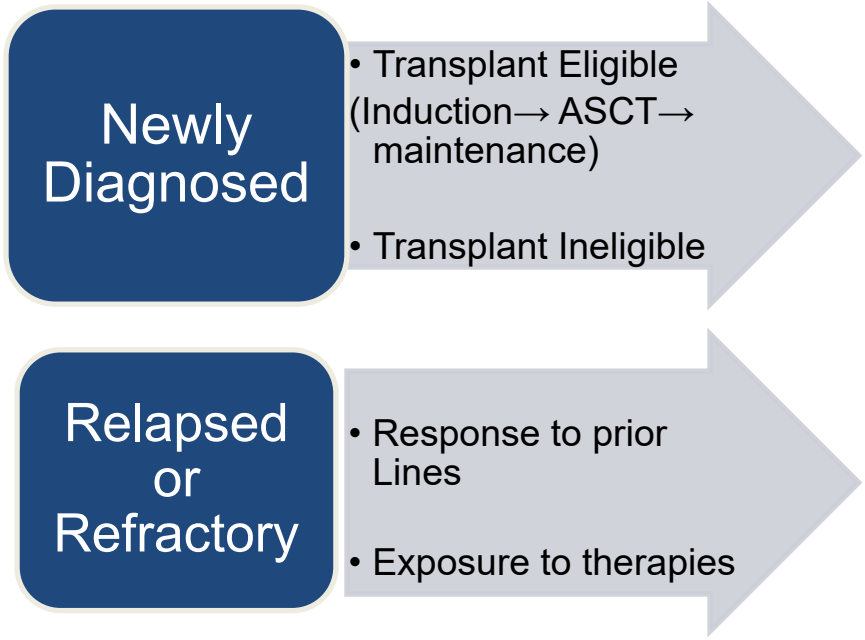
- Clonal plasma cell disorder
- Monoclonal protein in the blood or urine, and associated organ dysfunction.
- Standard criteria for diagnosis and staging of the disease.
- IMWG established criteria for response in MM
  - Serum and urine monoclonal proteins, free light chains and bone marrow assessments



Borello Leuk Res. 2012 Nov; 36(0 1): S3–12.

Rajkumar et al. Lancet Oncology 2014; Palumbo et al Journal of Clinical Oncology 2015; IMWG: International Myeloma Working Group Criteria

MM Treatment



MM: Multiple Myeloma. ASCT: Autologous Stem Cell Transplantation.

MM Treatment

Newly Diagnosed

- Transplant Eligible (Induction→ ASCT→ maintenance)
- Transplant Ineligible

Relapsed or Refractory

- Response to prior Lines
- Exposure to therapies

Approved Therapies and Combinations	
Newly Diagnosed Transplant Eligible	D-VTd, Rd, Td, VMP
Newly Diagnosed Transplant Ineligible	DRd, D-VMP, Rd, Td, VMP
Relapsed or Refractory MM	DRd, KRd, IRd, ERd, Vd, SVd, DVd EPd, IsaPd, DPd, DKd, IsaKd, Rd, Kd, Pd, V, Daratumumab, Cilta-cel, Ide-cel Teclistamab, Elranatamab, Talquetamab

Substantial improvement in survival, but remains incurable

Proteasome Inhibitors V: Velcade (bortezomib); K: Kyprolis (carfilzomib), I: Ixazomib. Immunomodulatory Agents T: Thalidomide, R-Revlimid (lenalidomide), P-Pomalidomide. CD38 monoclonal antibodies Isa: Isatuximab, D: Daratumumab. SLAMF 7 antibody E: Elotuzumab. XPO1 inhibitor S: Selinexor. Chimeric T cell antigen cilta-cel: Ciltacabtagene autoleucel, Ide-cel: idecabtagene vicleucel. Bi-specifics Talquetamab, teclistamab and elranatamab. Other MP- Melphalan and prednisone, d-Dexamethasone. MM: Multiple Myeloma. ASCT: Autologous stem Cell Transplantation.

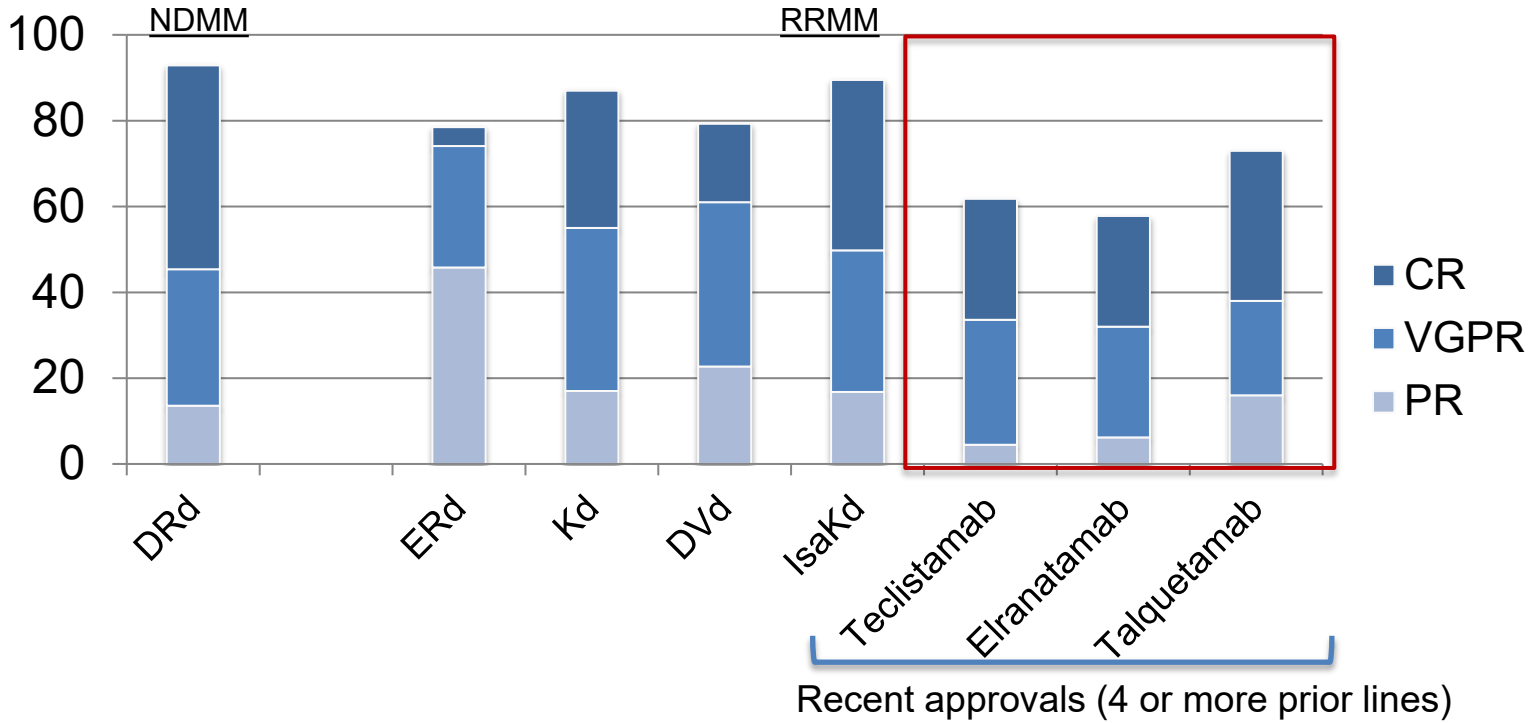
Approval Pathways and Endpoints - MM

- Regular Approval
  - PFS supported by an assessment of OS
  - Substantial improvements in PFS and OS in recent trials

- Accelerated Approval
  - ORR (sCR+CR+VGPR+PR) based on IMWG criteria with durability

ORR; Overall Response Rate, CR: Complete Response, VGPR: Very Good Partial Response, PR: Partial Response, MM: Multiple Myeloma.
PFS: Progression-Free Survival, OS: Overall Survival. FDA Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics

Response Rates - MM



CR: Complete Response includes stringent CR (sCR), VGPR: Very Good Partial Response, PR: Partial Response; R-Revlimid (lenalidomide), Isa: Isatuximab, K: kyprolis (carfilzomib), D: daratumumab, d-dexamethasone. MM: Multiple Myeloma, NDMM: Newly Diagnosed MM, RRMM: Relapsed or Refractory MM
Drugs@ FDA: FDA-Approved Drugshttps://www.accessdata.fda.gov/scripts/cder/daf/index.cfm

MRD in MM

- Sensitive cellular flow-based or molecular methods available to measure residual tumor cells
- MRD is a deeper level of response
- Flow based methods
  - Widely available
  - Specific markers to distinguish malignant plasma cells
- Sequencing based methods
  - Identify patient specific clonal rearrangements of tumor cells
  - The dominant sequence from a baseline sample can be monitored

MRD: Minimal Residual Disease, MM: Multiple Myeloma

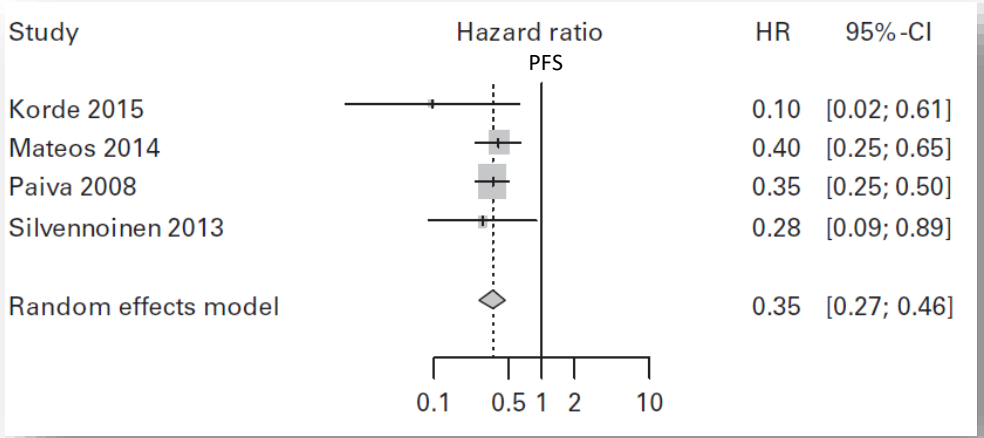
MRD in MM

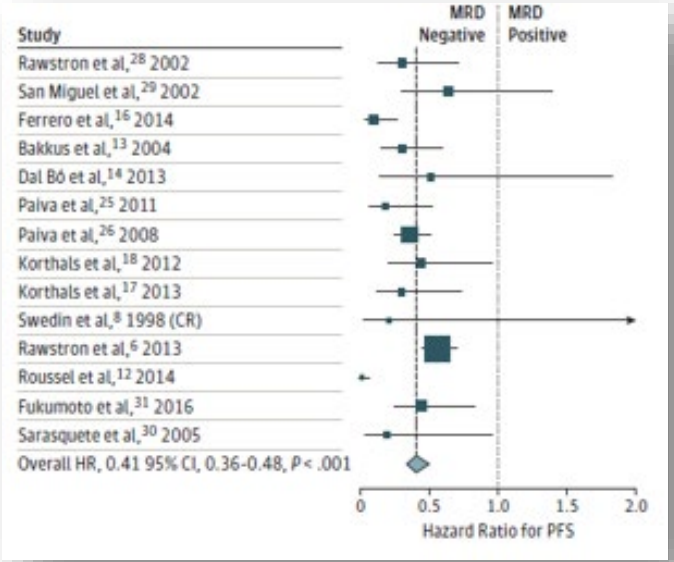
- Updated IMWG criteria for MRD response
  - Assessed in patients with CR or better
  - Flow MRD-negative and sequencing MRD-negative
  - Sensitivity of 1 nucleated tumor cell in 100,000 normal cells
  - Sustained MRD negativity

- MRD response is evaluated in MM clinical trials

MRD: Minimal Residual Disease, CR: Complete Response, IMWG: International Myeloma Working Group, MM: Multiple Myeloma

MRD in MM





Primarily Newly Diagnosed MM studies

Different assessment times

Landgren BMT 2016, Munshi Jama Oncol 2016, MRD: Minimal Residual Disease, MM: Multiple Myeloma

Regulatory Considerations
MRD in MM

Assay considerations

- Flow cytometry based or sequencing based platforms
- Agnostic to the type of assay
  - Adequate performance
  - Appropriately validated for the context of use
  - Thresholds should be within the limit of detection of the assay
  - Standardized procedures for sample collection and processing
    - Only 42% of the trials in MM had adequate MRD data
    - Multiple reasons for exclusion including analytic and test validation deficiencies, performance issues etc.

MRD: Minimal Residual Disease, MM: Multiple Myeloma, Baines et al Clinical Cancer Research 2022

BELLINI (Study M14-031)

A Phase 3, Multicenter, Randomized, Double Blind Study of Bortezomib and Dexamethasone in Combination With Either Venetoclax or Placebo in Subjects With Relapsed or Refractory Multiple Myeloma Who Are Sensitive or Naïve to Proteasome Inhibitors

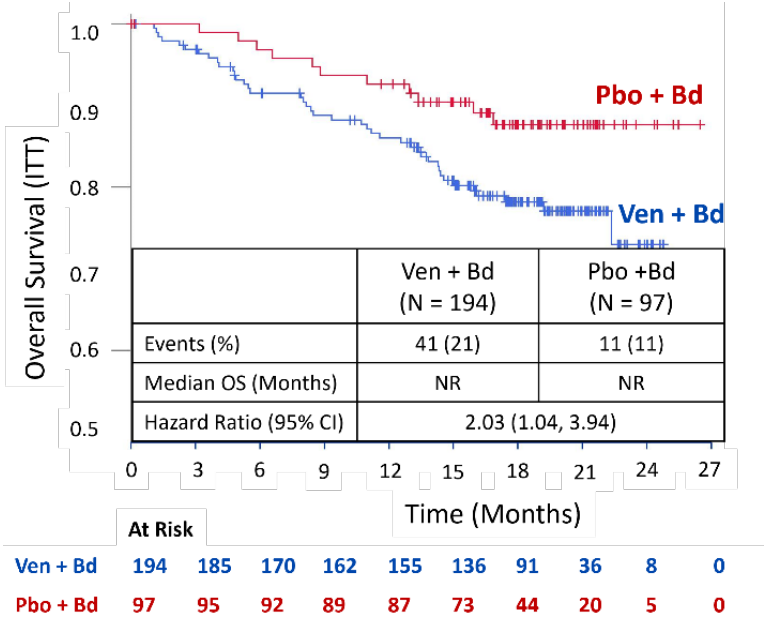
	Ven + Bd (N = 194)	Pbo + Bd (N = 97)
mPFS (95% CI)	22.4 months (15.3, NR)	11.5 months (9.6, 15)
	HR (95% CI) 0.63 (0.44, 0.90)	
ORR (95% CI)	82% (75.8, 87.1)	68% (57.8, 77.1)
MRD(-) (95% CI)	**13%** (8.9, 19)	**1%** (0, 5.6)

MRD: Minimal Residual Disease, OS: Overall Survival, PFS: Progression-Free Survival, ORR: Overall Response Rate, HR: Hazard ratio, CI; Confidence interval. Pbo: Placebo, Bd: bortezomib and dexamethasone, Ven: venetoclax

https://www.fda.gov/drugs/drug-safety-and-availability/fda-warns-about-risks-associated-investigational-use-venclexta-multiple-myeloma

BELLINI (Study M14-031)

Overall Survival



Importance of early endpoints *and* late endpoints that provide evidence of clinical benefit

MRD: Minimal Residual Disease, MM: Multiple Myeloma, Pbo: Placebo, Bd: bortezomib and dexamethasone, Ven: venetoclax, NR: Not Reached, ITT: Intention –To-Treat, OS: Overall Survival , CI: Confidence Interval.

https://www.fda.gov/drugs/drug-safety-and-availability/fda-warns-about-risks-associated-investigational-use-venclexta-multiple-myeloma

Regulatory Considerations
Accelerated Approval

- Confirmatory trials required to verify clinical benefit

- Recent legislations provides that the FDA, “may require confirmatory studies to be underway prior to approval”

- Provides expedited withdrawal for drugs that do not verify benefit from the market

Summary

- In MM, MRD has the potential to expedite drug development
- MRD is a more sensitive measure of residual tumor cells
- Specific regulatory considerations exist in the evaluation of potential new endpoints to support approval
- Meta-analysis of patient level data can generate evidence

MRD: Minimal Residual Disease, OS: Overall Survival, PFS: Progression-Free Survival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Minimal Residual Disease to Support Accelerated Approval in Multiple Myeloma

Oncologic Drugs Advisory Committee (ODAC) Meeting

April 12, 2024

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Clinical Reviewer
DHM2, OOD, OND, CDER, FDA

Jing Zhang, PhD
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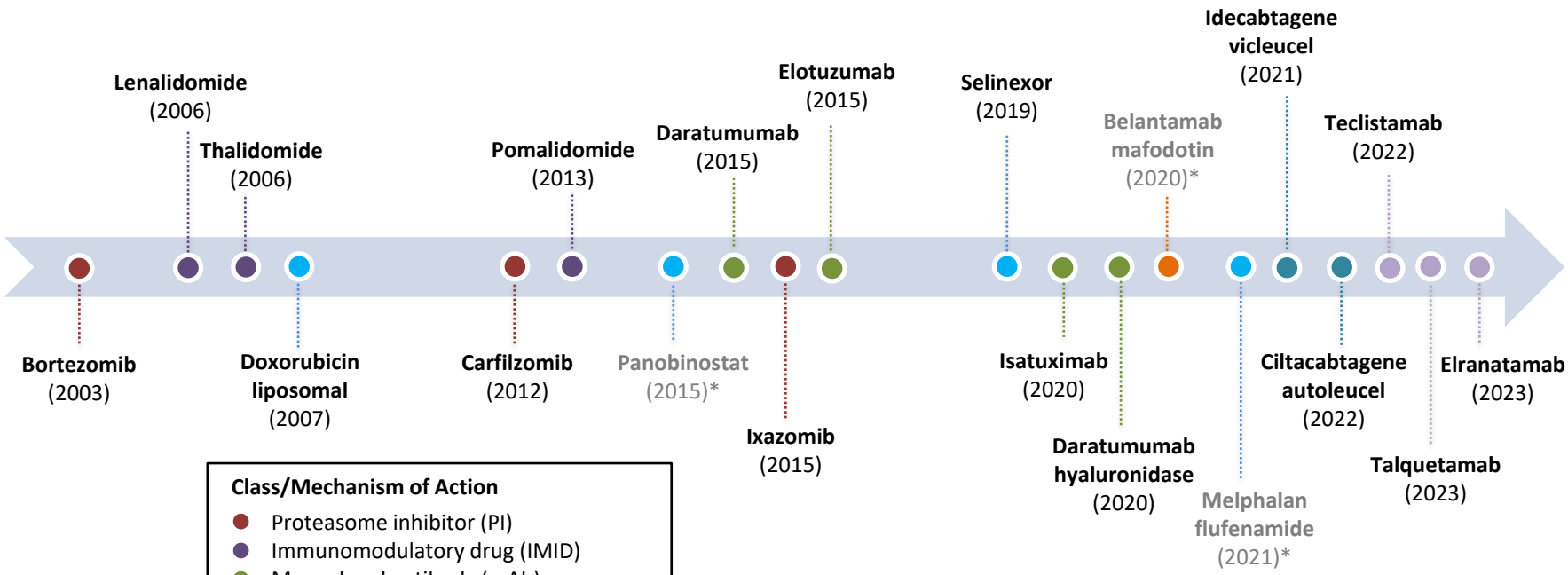
Christopher Trindade, PhD

Purpose of Meeting

- Discuss the adequacy of available data to support the use of Minimal Residual Disease (MRD) as an accelerated approval (AA) endpoint in multiple myeloma (MM)

- Discuss considerations around the use of MRD
  - Disease settings
  - Timepoints for MRD assessment

MM Treatment Landscape (2003 – 2023)



*Approval withdrawn

MM: Multiple Myeloma

Regulatory Considerations for MM Drug Development

Regular Approval:

- Demonstration of clinical benefit
  - Measure of how a patient feels, functions, or survives
- Accepted endpoints in MM:
  - Progression-free survival (PFS)
  - Overall survival (OS)

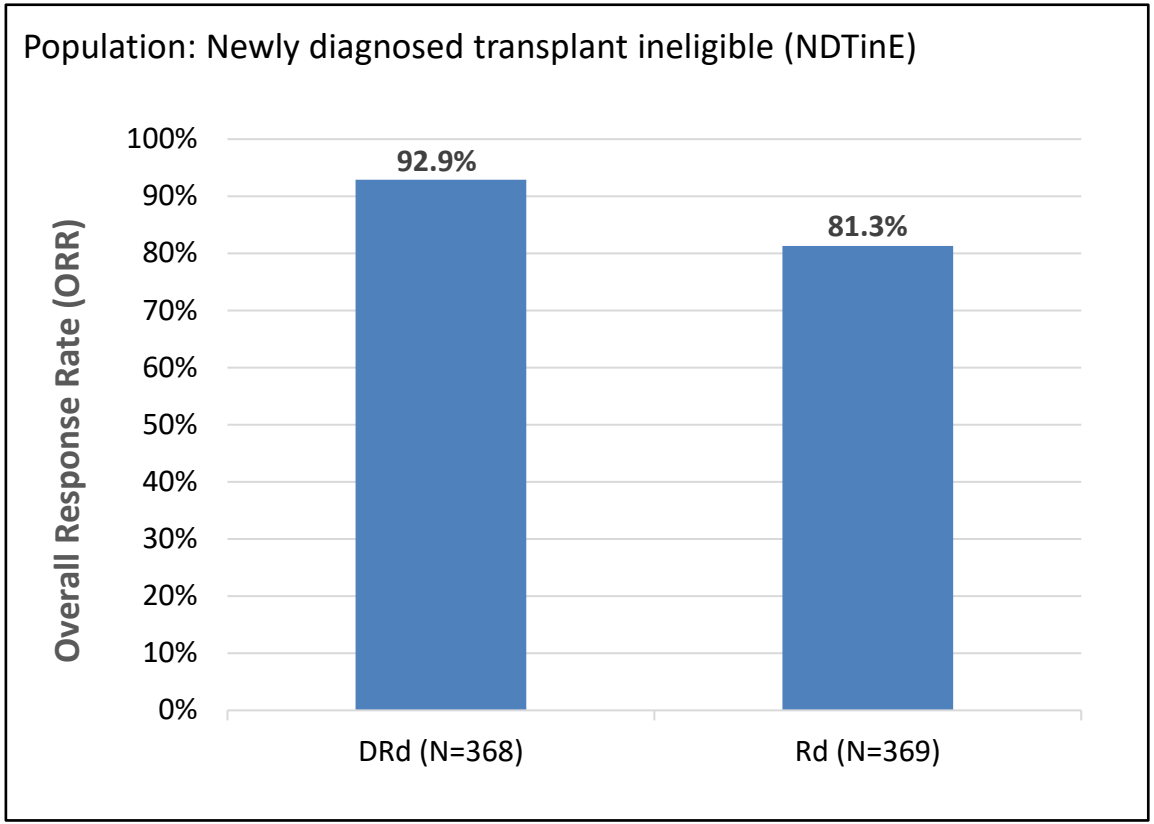
Accelerated Approval:

- Serious or life-threatening disease
- Based on an intermediate clinical endpoint or a surrogate endpoint reasonably likely to predict clinical benefit
- Meaningful benefit in the context of other available therapy
- Accepted Endpoint in MM:
  - Overall Response Rate (ORR)

21 CFR 314.510
FDA Guidance for Industry: Expedited Programs for Serious Conditions- Drugs and Biologics

MM: Multiple Myeloma

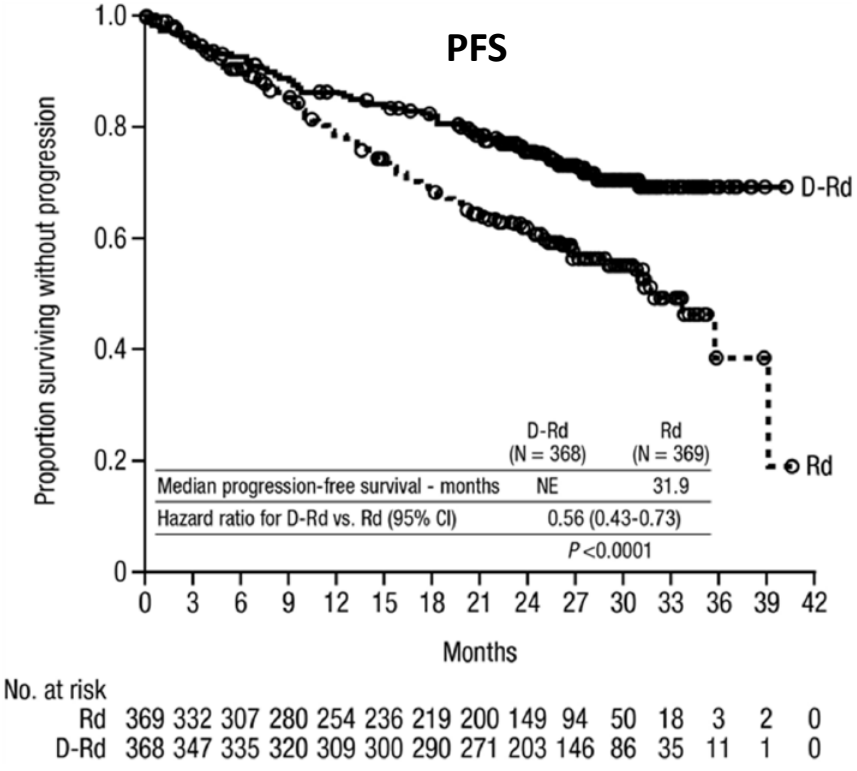
Current Endpoints in MM: MAIA Trial



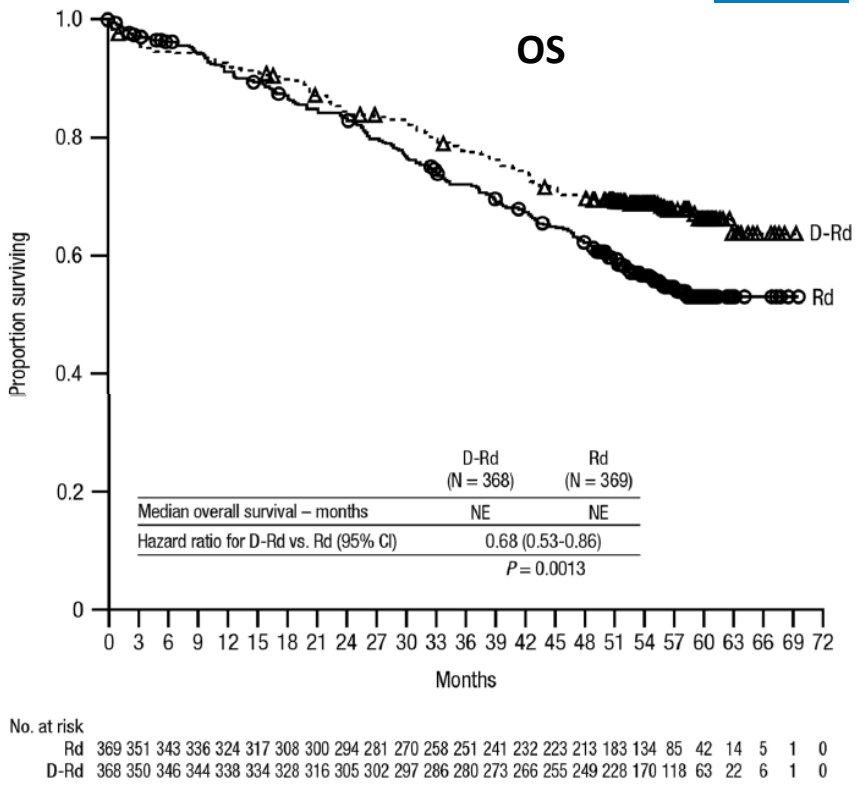
Source: FDA Analysis

MM: Multiple Myeloma; DRd: daratumumab, lenalidomide, dexamethasone; Rd: lenalidomide, dexamethasone

Current Endpoints in MM: MAIA Trial



PFS median follow-up: 28 months

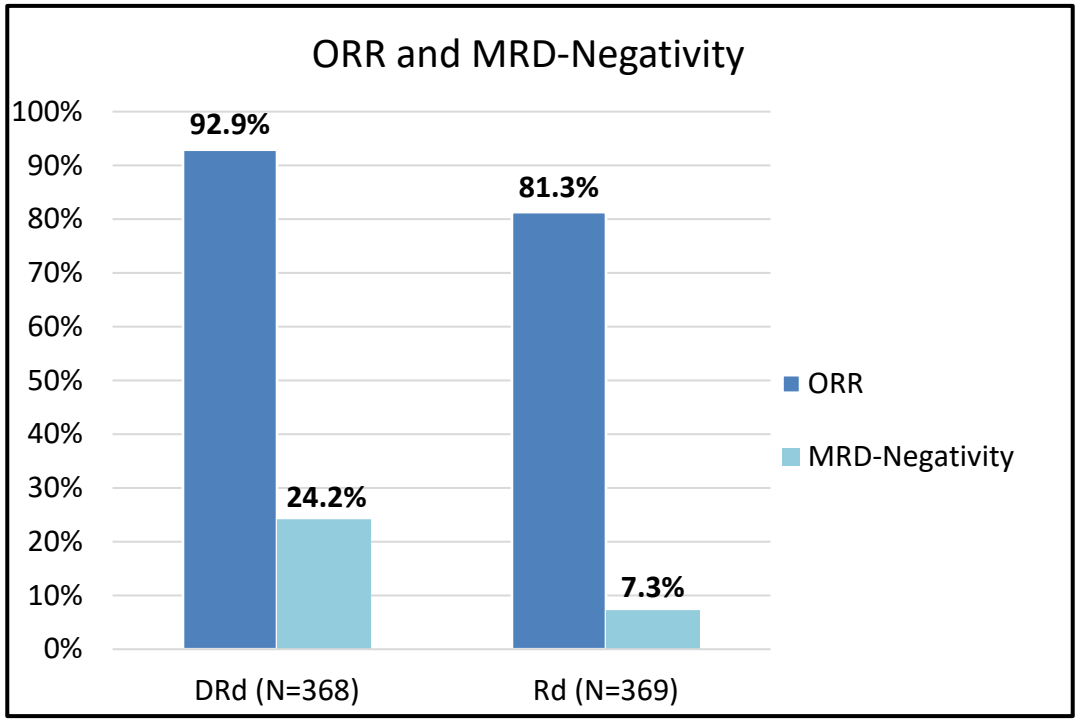


OS median follow-up: 56 months

Source: FDA Analysis; daratumumab USPI

MM: Multiple Myeloma; PFS: Progression-Free Survival; OS: Overall Survival; DRd: daratumumab, lenalidomide, dexamethasone; Rd: lenalidomide, dexamethasone; NE: Not Estimable

Current Endpoints in MM: MAIA Trial

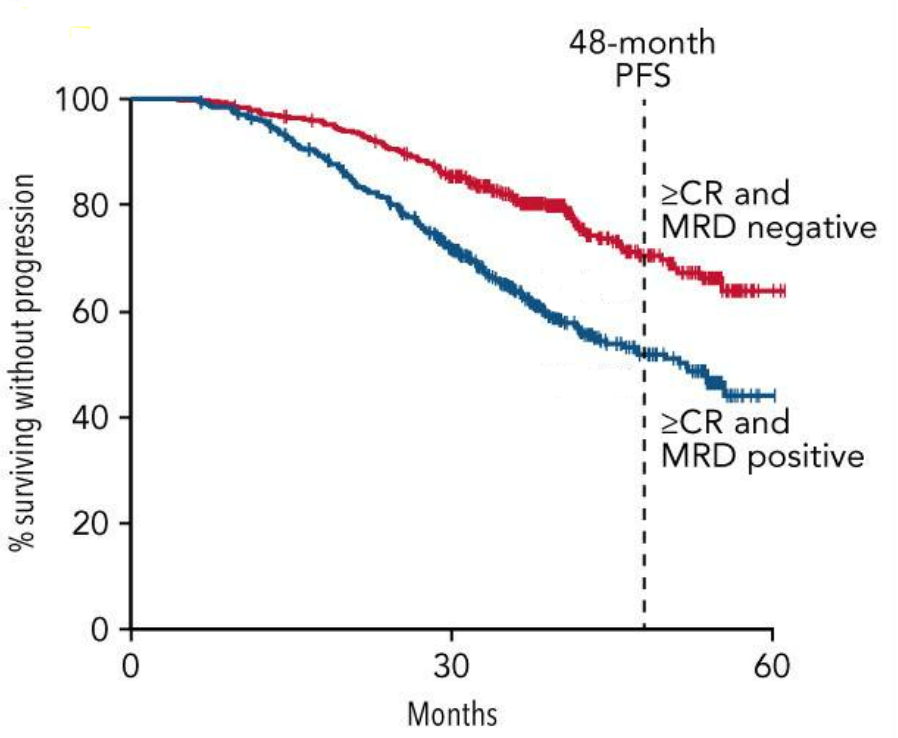


Source: FDA Analysis

MM: Multiple Myeloma; ORR: Overall Response Rate; MRD: Minimal Residual Disease;
DRd: daratumumab, lenalidomide, dexamethasone; Rd: lenalidomide, dexamethasone

MRD in Multiple Myeloma

- Measure of tumor burden in the bone marrow
- Prognostic in MM



Cavo, M. et al. *Blood*. 2022 Feb 10;139(6):835-844

MRD: Minimal Residual Disease; MM: Multiple Myeloma;
CR: Complete Response; PFS: Progression-Free Survival

Development of New Regulatory Endpoints

Regular Approval:

- Clinical benefit
- Validated surrogate endpoint

Accelerated Approval:

- Intermediate clinical endpoint or surrogate endpoint reasonably likely to predict clinical benefit
- Most common endpoint in MM:
  - Overall Response Rate (ORR)

MM: Multiple Myeloma

Methodology for Assessment of Surrogacy: Meta-Analysis

- **Individual-level Association**
  - Strength of the association between the **candidate surrogate endpoint** (MRD) and the **true clinical endpoint** (PFS/OS)
  - "Is MRD-Negative CR prognostic for PFS/OS?"

- **Trial-level Association**
  - Strength of the association between the **treatment effect on the surrogate** (MRD) and the **treatment effect on the true endpoint** (PFS/OS)
  - "If a treatment improves MRD-Negative CR over the control arm, will a similar improvement be observed in PFS/OS?"

Hematologic Malignancies: Regulatory Considerations for Use of Minimal Residual Disease in Development of Drug and Biological Products for Treatment Guidance for Industry

MRD: Minimal Residual Disease; PFS: Progression-Free Survival; OS: Overall Survival;
MRD-Negative CR: MRD negativity with Complete Response

Results of Trial-Level Association

- Strong trial-level association → Validated surrogate endpoint → May support regular approval
  - Very few oncology endpoints have met this standard
  - Most endpoints that support AA have not been assessed for trial level surrogacy or have weak trial-level associations

AA: Accelerated Approval

Statistical Methods in Applicants' Meta-Analyses

- **Individual-Level Assessment (Prognostic Assessment)**
  - Measure: Global odds ratio based on a bivariate copula model[1].
- **Trial-Level Assessment (Treatment Effect)**
  - Measures: R^2_{wls} and R^2_{Copula}
  - i2TEAMM pre-specified a decision rule for "validated surrogate"
  - No formal criteria exist within FDA
- **Surrogate Threshold Effect (STE):**
  - The minimum treatment effect on the surrogate necessary to predict a positive effect on the established endpoint for clinical benefit with 95% confidence

[1]Burzykowski T et al.: The validation of surrogate endpoints by using data from randomized clinical trials: a case-study in advanced colorectal cancer. J R Stat Soc A. 2004;167(Part 1):103- 124. R^2_{wls}: R-squared based on weighted least square regression. R^2_{Copula}: R-squared based on the bivariate Placket copula model

Summary of I2TEAMM and University of Miami Analyses

- Conclusions:
  - Strong individual-level association for both PFS and OS
  - Trial-level associations are weak to moderate in disease subpopulations for PFS (NDTE, NDTinE, RR)
    - Stronger results observed in the NDTinE population
  - Associations in pooled populations moderate for PFS (NDTE+NDTinE, NDTE+NDTinE+RR, NDTinE+RR)
  - Trial-level associations generally weaker for OS

- FDA agrees with general approaches and interpretation of results

PFS: Progression-Free Survival; OS: Overall Survival; NDTE: Newly diagnosed transplant eligible; NDTinE: Newly diagnosed transplant ineligible; RR: Relapsed/Refractory

Strengths and Limitations of The Meta-Analyses

Strengths	Limitations
Broad experience across multiple settings and randomized trials	Heterogeneity in trial designs, conduct, and patient populations
All assays NGS or FC; majority have sensitivity of 10^{-5} or better	Variation in MRD assays used
Individual-level patient data available for all trials analyzed	Limited number of trials
Analysis methods and approach pre-specified in SAP and discussed with FDA	Unknown impact of disease setting

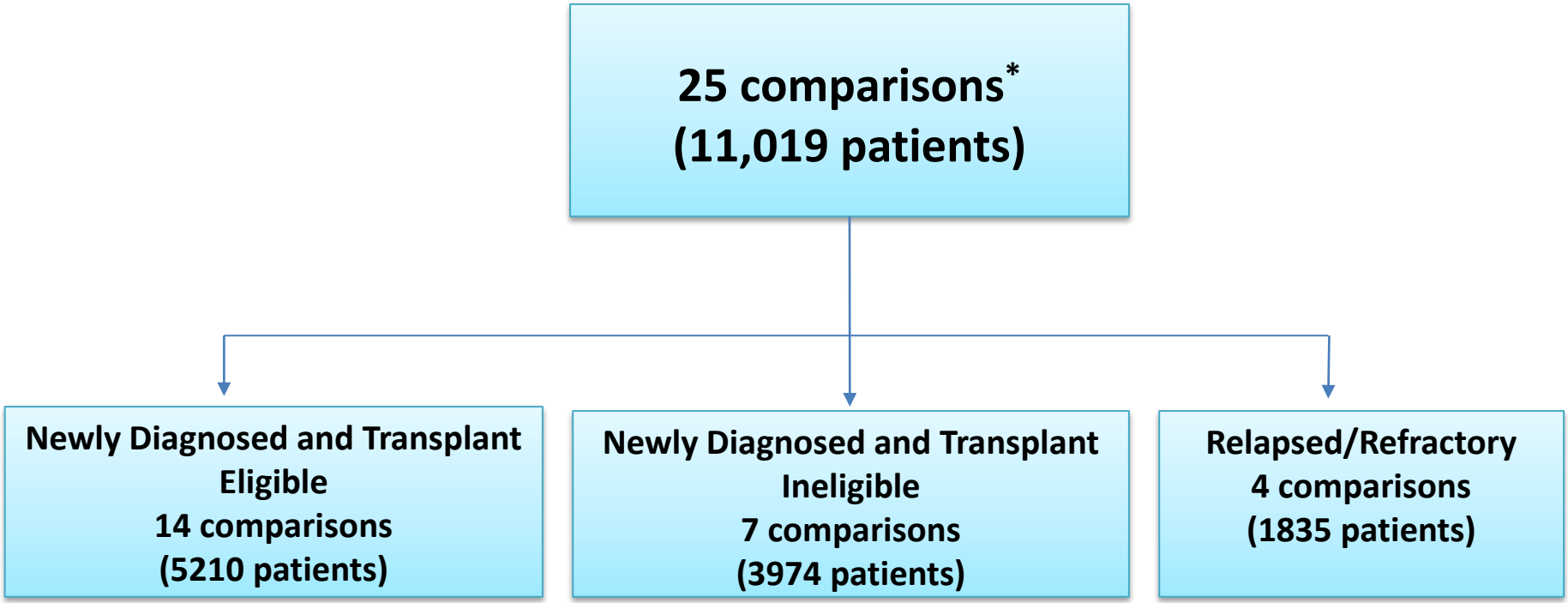
NGS: Next Generation Sequencing; FC: Flow Cytometry; MRD: Minimal Residual Disease; SAP: Statistical Analysis Plan

FDA's Meta-Analysis

- FDA conducted additional meta-analyses based on all data submitted by either Applicant
  - **Purpose**: to determine whether utilization of all available data would impact the results or conclusions
    - Analysis was based on the ITT population
    - Missing MRD status were imputed as non-responders
    - 18 trials resulting in 25 two-arm comparisons
- "MRD-Negative CR at any time" in the RR setting was also explored using data submitted to the FDA

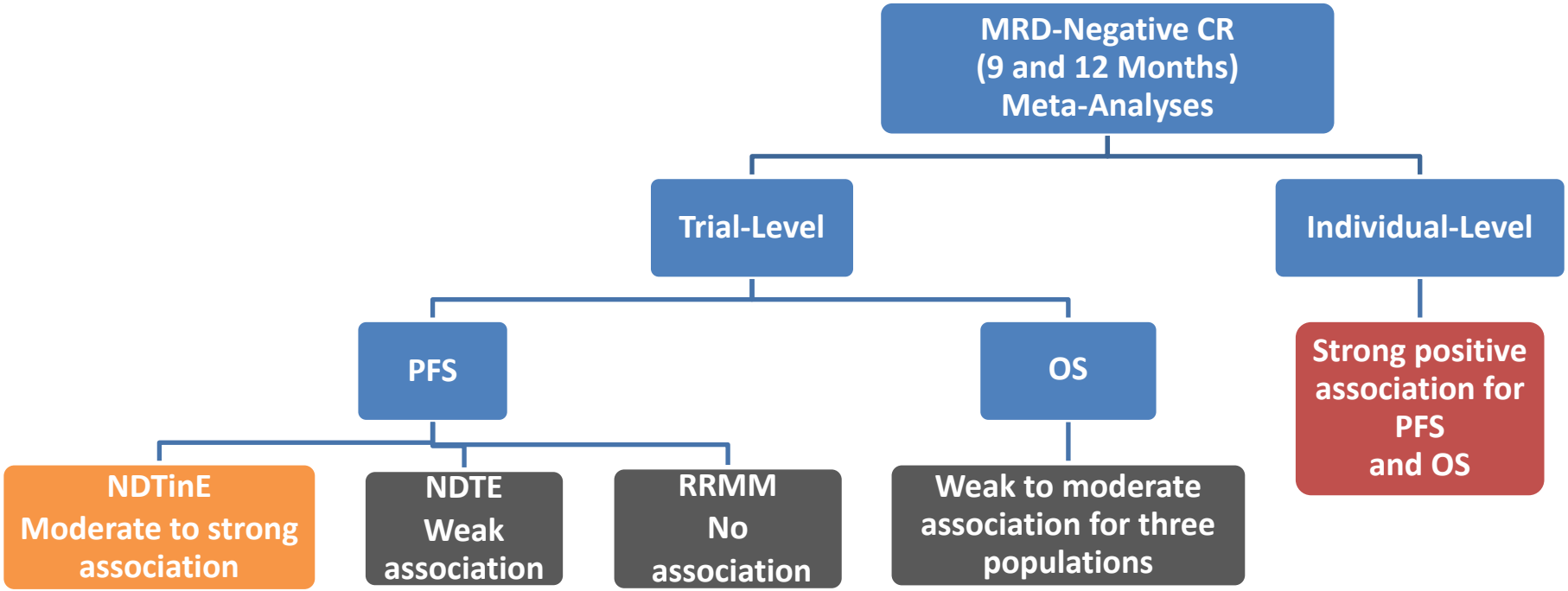
ITT: Intention-To-Treat; MRD: Minimal Residual Disease; CR: Complete Response; RR: Relapsed/Refractory

Study Flowchart by Population



*Two-arm comparisons; the number of patients are based on the two-arm comparisons included in each subpopulation.

Scope of the Results



MRD: Minimal Residual Disease; CR: Complete Response; PFS: Progression-Free Survival; OS: Overall Survival
NDTE: Newly diagnosed transplant eligible; NDTinE: Newly diagnosed transplant ineligible; RRMM: Relapsed Refractory Multiple Myeloma

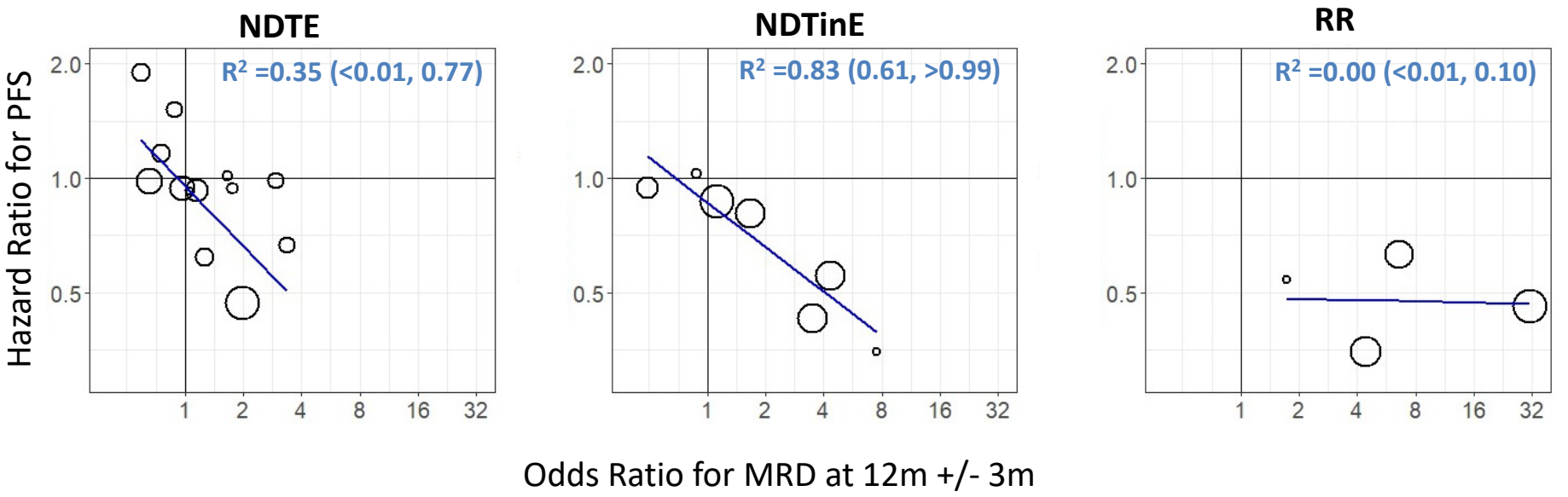
Individual-level Association : MRD-Negative CR vs PFS and OS

	Population	N Comparisons (N Patients)	Individual-Level Association Odds Ratio[1] (95% CI)
9 months MRD-CR vs PFS	NDTE	12 (4820)	2.85 (2.37, 3.34)
	NDTinE	7 (3974)	6.55 (4.48, 8.63)
	RR	4 (1835)	7.40 (4.17, 10.62)
12 months MRD-CR vs PFS	NDTE	13 (4993)	3.39 (2.87, 3.92)
	NDTinE	7 (3974)	7.30 (5.21, 9.38)
	RR	4 (1835)	7.67 (4.24, 11.1)
9 months MRD-CR vs OS	NDTE	12 (4820)	2.77 (2.15, 3.38)
	NDTinE	7 (3974)	5.02 (2.82, 7.21)
	RR	4 (1835)	6.46 (2.54, 10.38)
12 months MRD-CR vs OS	NDTE	13 (4993)	3.83 (3.00, 4.67)
	NDTinE	7 (3974)	4.75 (2.91, 6.58)
	RR	4 (1835)	6.03 (2.48, 9.59)

Individual-level Association: Higher global odds ratio indicates a higher prognostic value of MRD

[1]Global odds ratio computed using Plackett copula model
MRD-Negative CR: MRD negativity with Complete Response [10^{-4}, 10^{-5}, and 10^{-6}; 10^{-5} prioritized]
PFS: Progression-Free Survival; OS: Overall Survival; NDTE: Newly diagnosed transplant eligible;
NDTinE: Newly diagnosed transplant ineligible; RR: Relapsed/Refractory

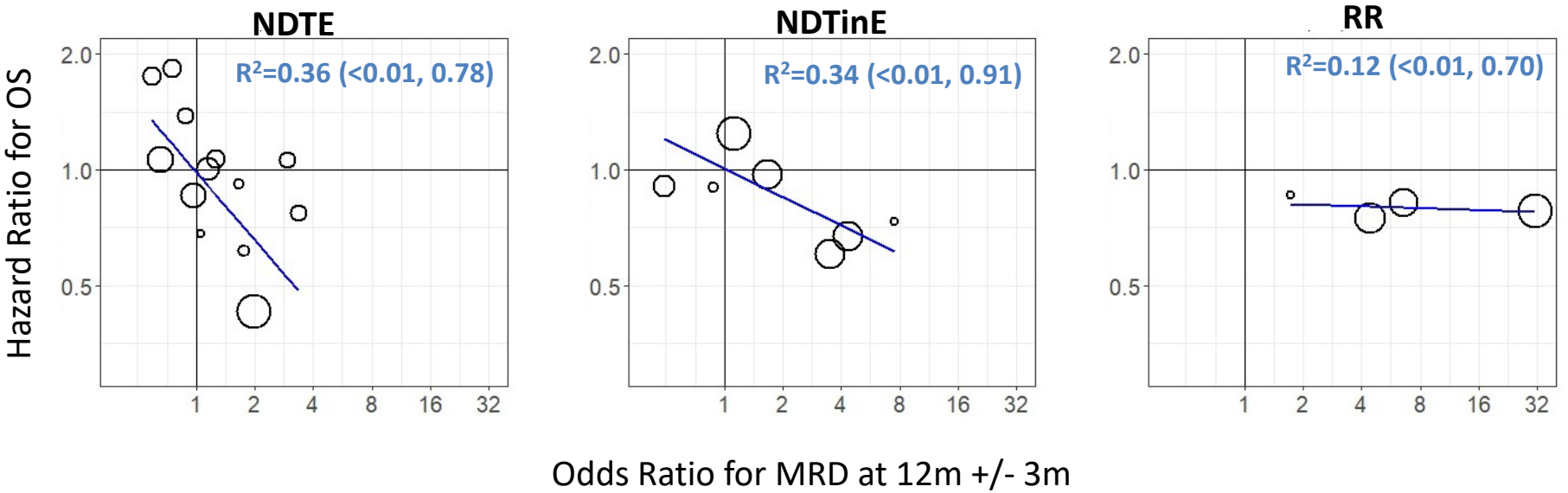
Trial-level Association: MRD-Negative CR vs PFS



Numerically higher correlation was observed between MRD-Negative CR and PFS in the NDTinE population

MRD-Negative CR: MRD negativity with Complete Response [10^{-4}, 10^{-5}, and 10^{-6}; 10^{-5} prioritized]
PFS: Progression-Free Survival; NDTE: Newly diagnosed transplant eligible; NDTinE: Newly diagnosed transplant ineligible;
RR: Relapsed/Refractory; MRD: Minimal Residual Disease; m: months; R^2 is calculated using the bivariate Placket copula model

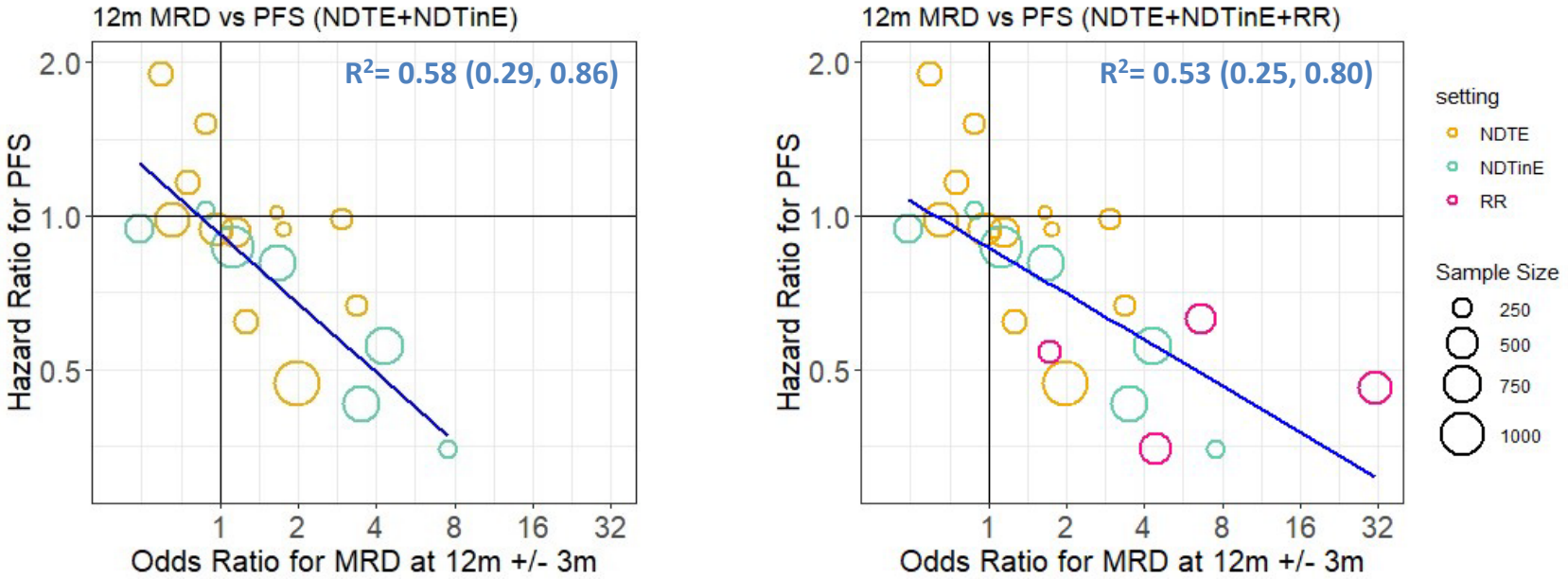
Trial-level Association: MRD-Negative CR vs OS



Weak to moderate association was found between MRD-Negative CR and OS in the trial-level analysis for all three populations

MRD-Negative CR: MRD negativity with Complete Response [10^{-4}, 10^{-5}, and 10^{-6}; 10^{-5} prioritized]
OS: Overall Survival; NDTE: Newly diagnosed transplant eligible; NDTinE: Newly diagnosed transplant ineligible;
RR: Relapsed/Refractory; MRD: Minimal Residual Disease; m: months; R^2 is calculated using the bivariate Placket copula model

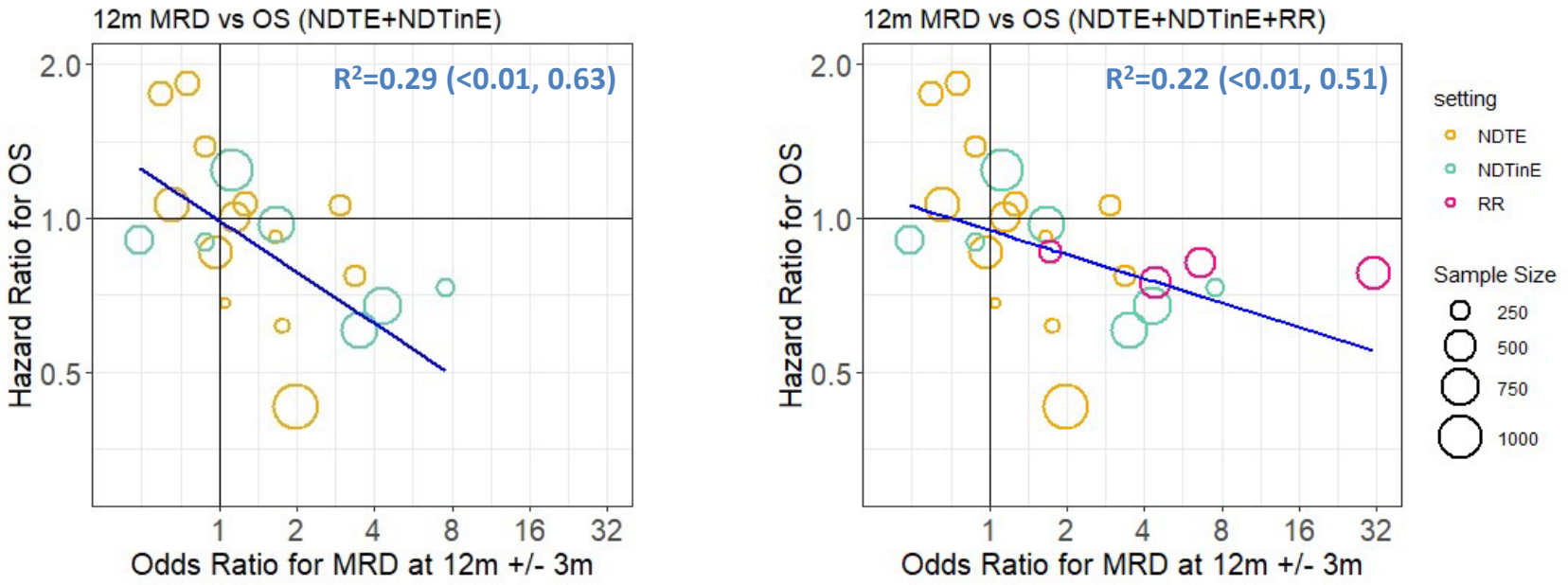
Trial-Level Association: MRD-Negative CR vs PFS Pooled Populations



Moderate associations for MRD-negative CR vs. PFS observed in pooled populations

MRD-Negative CR: MRD negativity with Complete Response [10^{-4}, 10^{-5}, and 10^{-6}; 10^{-5} prioritized]
PFS: Progression-Free Survival; NDTE: Newly diagnosed transplant eligible; NDTinE: Newly diagnosed transplant ineligible;
RR: Relapsed/Refractory; MRD: Minimal Residual Disease; m: months; R^2 is calculated using the bivariate Placket copula model

Trial-Level Association: MRD-Negative CR vs OS Pooled Populations



Weak associations for MRD-negative CR vs. OS observed in pooled populations

MRD-Negative CR: MRD negativity with Complete Response [10^{-4}, 10^{-5}, and 10^{-6}; 10^{-5} prioritized]
OS: Overall Survival; NDTE: Newly diagnosed transplant eligible; NDTinE: Newly diagnosed transplant ineligible;
RR: Relapsed/Refractory; MRD: Minimal Residual Disease; m: months; R^2 is calculated using the bivariate Placket copula model

Surrogate Threshold Effect (STE) for PFS and OS

MRD-Negative CR at 12 Months

	N comparison (N Patients)	STE odds ratio (PFS)	STE odds ratio (OS)
NDTE	13 (4993)	4.95	5.81
NDTinE	7 (3974)	2.12	12.30
RR	4 (1835)	NA	NA

MRD-Negative CR: MRD negativity with Complete Response [10^{-4}, 10^{-5}, and 10^{-6}; 10^{-5} prioritized]
PFS: Progression-Free Survival; OS: Overall Survival; NDTE: Newly diagnosed transplant eligible;
NDTinE: Newly diagnosed transplant ineligible; RR: Relapsed/Refractory; NA: Not Applicable

Surrogate Threshold Effect (STE) for PFS and OS

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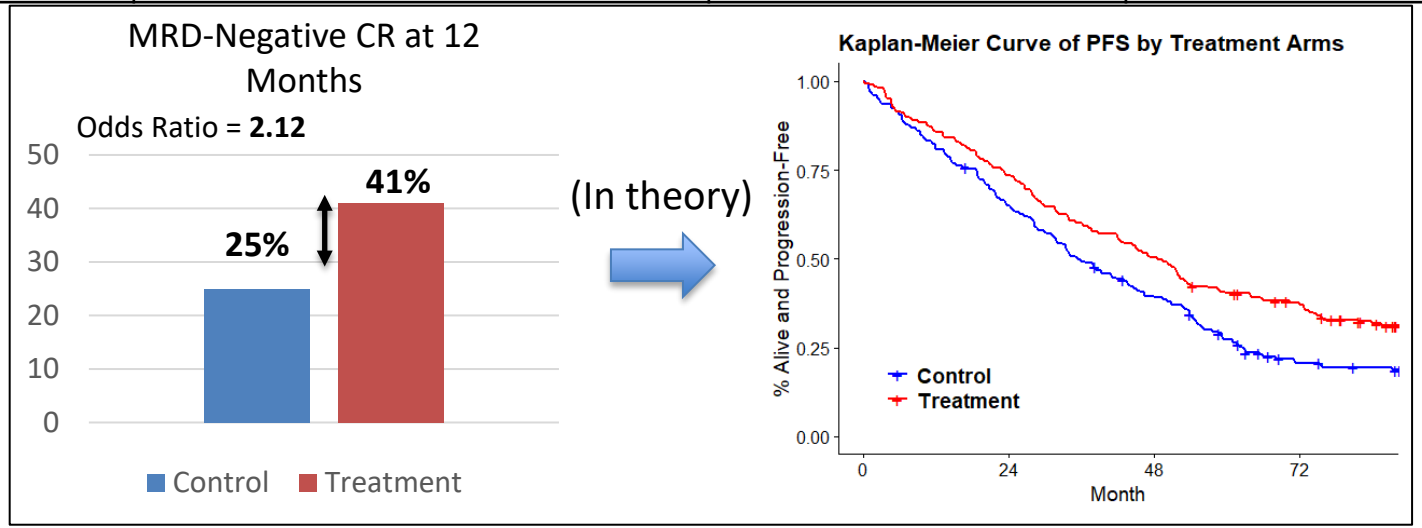
NDTE	13 (4993)	4.95	5.81
NDTinE	7 (3974)	**2.12**	12.30
RR	4 (1835)	NA	NA

Example:



MRD-Negative CR: MRD Negativity with Complete Response [10^{-4}, 10^{-5}, and 10^{-6}; 10^{-5} prioritized]; PFS: Progression-Free Survival; OS: Overall Survival; NDTE: Newly diagnosed transplant eligible; NDTinE: Newly diagnosed transplant ineligible; RR: Relapsed/Refractory

Surrogate Threshold Effect (STE) for PFS and OS

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NDTE	13 (4993)	4.95	5.81
NDTinE	7 (3974)	2.12	12.30
RR	4 (1835)	**NA**	**NA**

In general, STE can be calculated when there is sufficiently strong trial-level association

STE cannot be calculated for RR due to small sample size

MRD-Negative CR: MRD negativity with Complete Response [10^{-4}, 10^{-5}, and 10^{-6}; 10^{-5} prioritized]
PFS: Progression-Free Survival; OS: Overall Survival; NDTE: Newly diagnosed transplant eligible; NDTinE: Newly diagnosed transplant ineligible; RR: Relapsed/Refractory; NA: Not Applicable

Meta-Analysis: MRD-Negative CR at Any Time (RR population)

- Results are similar to those for the MRD-Negative CR at 9 months and 12 months
  - Data includes all trials submitted to FDA under NDA, BLA, or IND

- Individual-level association
  - Strong association was demonstrated for MRD-Negative CR at any time in RR population for both OS and PFS
  - Odds ratio: 8.70 (95% CI: 4.84-12.55)

- Trial-level Association
  - Weak association was found in the trial-level analysis
  - R^2_{wls} : 0.10 (95% CI: <0.01-0.35); R^2_{copula} : 0.11 (95% CI: <0.01-0.62)

MRD-Negative CR: MRD negativity with Complete Response [10^{-4}, 10^{-5}, and 10^{-6}; 10^{-5} prioritized]; NDA: New Drug Application; BLA: Biologics License Application; IND: Investigational New Drug; RR: Relapsed/Refractory; PFS: Progression-Free Survival; OS: Overall Survival

Statistical Conclusions

- **Strong individual-level associations** have been observed across all patient populations for MRD-Negative CR at 9 month and 12 months

- Generally, **weak to moderate trial-level associations** were observed for PFS in most disease subpopulations. These associations were weaker for OS.
  - Higher trial-level correlation was observed in the NDTinE subpopulation
  - Moderate associations were observed for PFS in the pooled populations

- The results for MRD-Negative CR at any time in the RR setting are similar to the results for MRD-Negative CR at 9 or 12 months in this setting

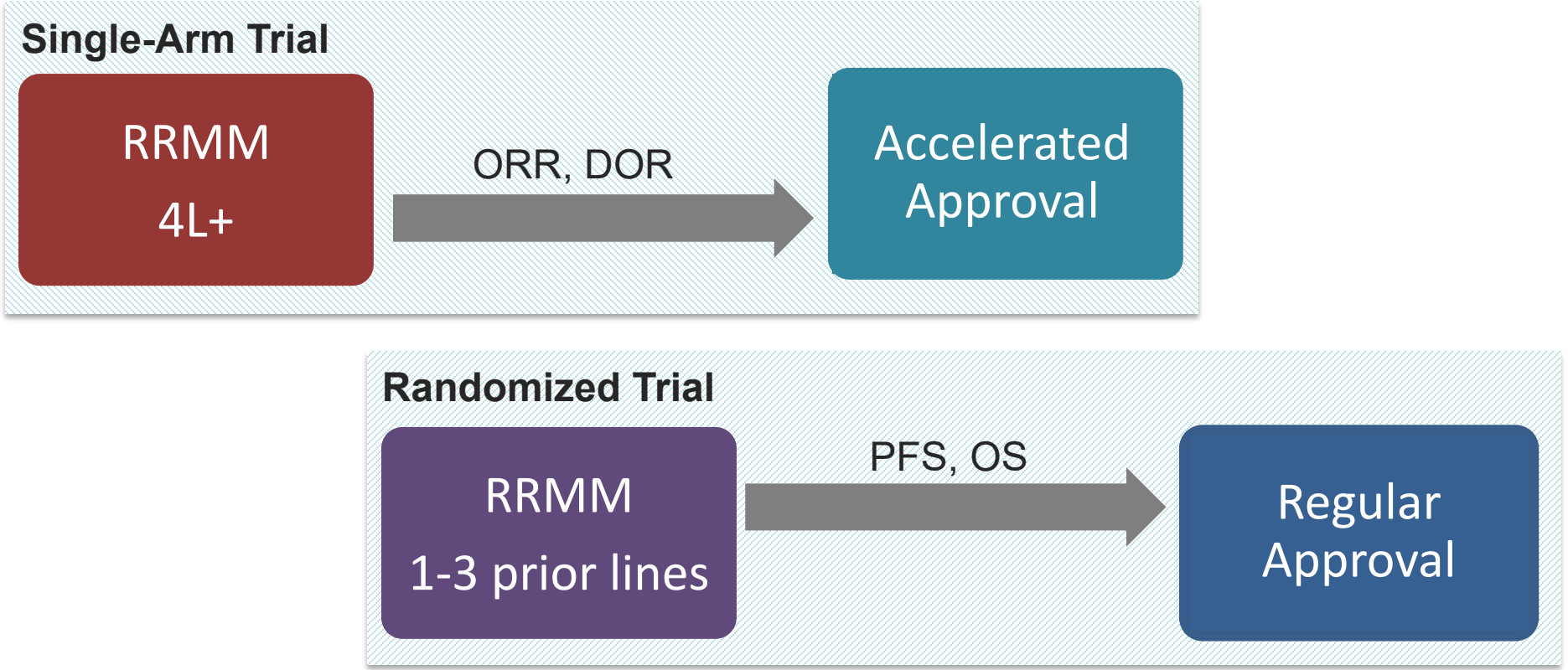
MRD-Negative CR: MRD negativity with Complete Response [10^{-4}, 10^{-5}, and 10^{-6}; 10^{-5} prioritized]; PFS: Progression-Free Survival; OS: Overall Survival; NDTinE: Newly diagnosed transplant ineligible; RR: Relapsed/Refractory

Where Does this Leave Us?

- Lack of strong trial-level association for MRD and PFS/OS
  - ➢ MRD is not a validated surrogate endpoint
- Strong individual-level association for MRD and PFS/OS
  - ➢ MRD is prognostic
- Analysis results provided:
  - Robust data regarding the prognostic value of MRD
  - Data regarding potential timepoints for MRD assessment
  - Information to support future trials using MRD as an AA endpoint as part of a comprehensive development program

MRD: Minimal Residual Disease; PFS: Progression-Free Survival; OS: Overall Survival; AA: Accelerated Approval

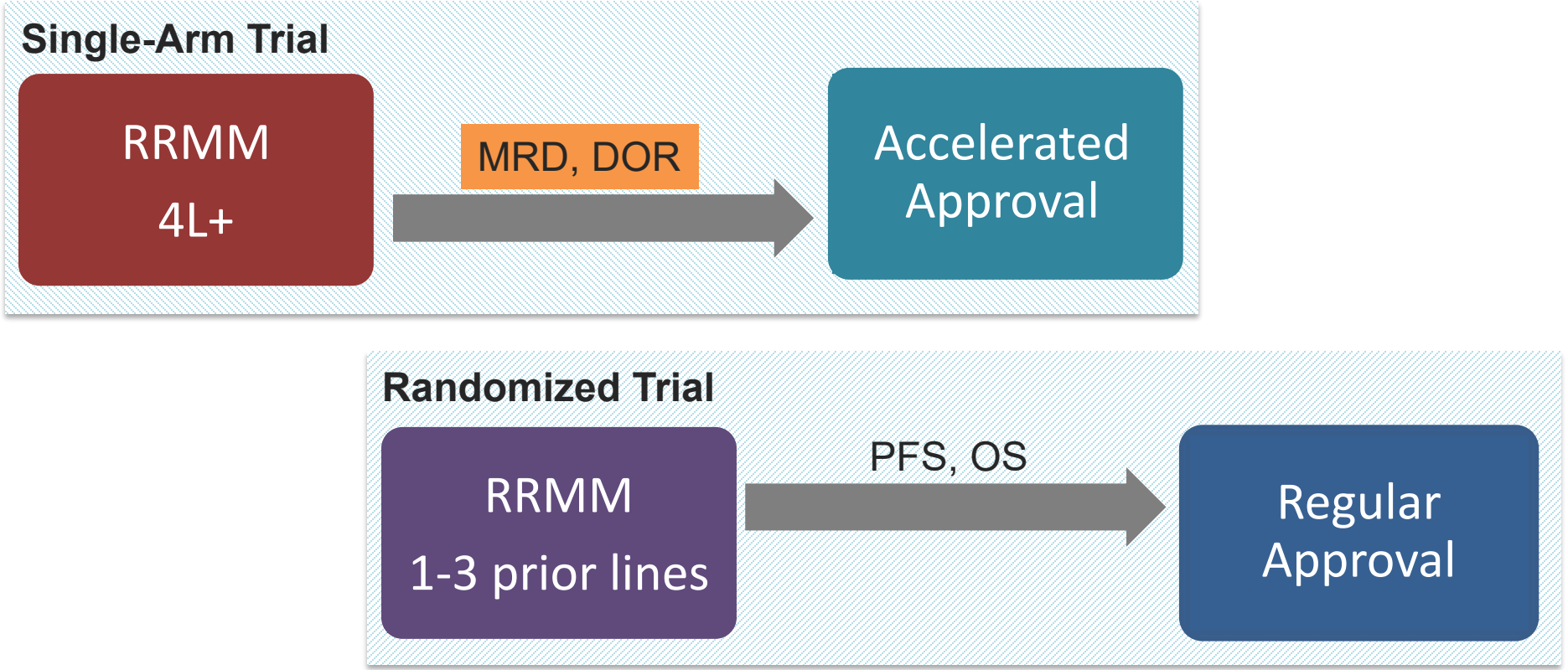
Clinical Trial Design: The Traditional Two-Trial Approach



RRMM: Relapsed/Refractory Multiple Myeloma; ORR: Overall Response Rate; DOR: Duration of Response; PFS: Progression-Free Survival; OS: Overall Survival

Source: FDA

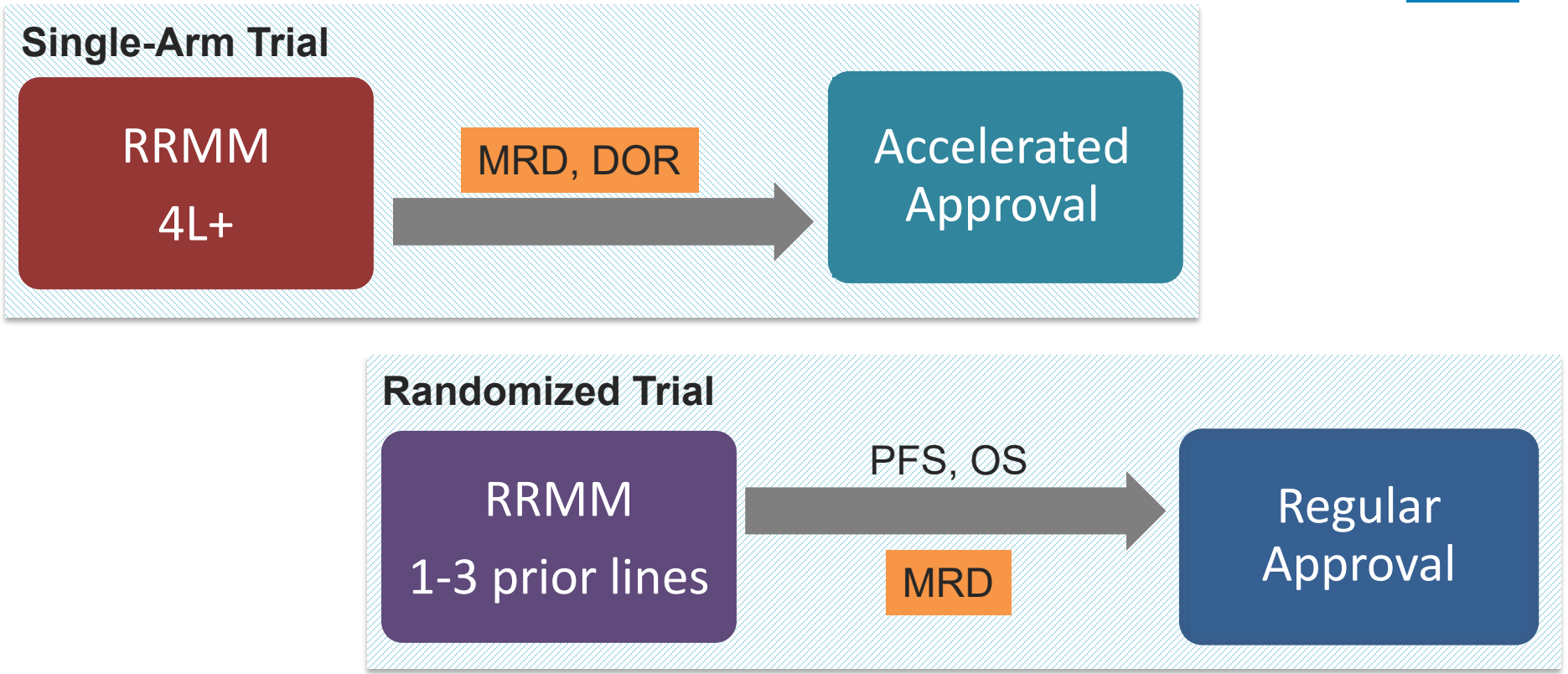
Clinical Trial Design: The Traditional Two-Trial Approach



RRMM: Relapsed/Refractory Multiple Myeloma; MRD: Minimal Residual Disease; DOR: Duration of Response; PFS: Progression-Free Survival; OS: Overall Survival

Source: FDA

Clinical Trial Design: The Traditional Two-Trial Approach



RRMM: Relapsed/Refractory Multiple Myeloma; MRD: Minimal Residual Disease; DOR: Duration of Response; PFS: Progression-Free Survival; OS: Overall Survival

Source: FDA

Clinical Trial Design: Single Trial Model

Source: FDA

RRMM: Relapsed/Refractory Multiple Myeloma; MRD: Minimal Residual Disease; DOR: Duration of Response; PFS: Progression-Free Survival; OS: Overall Survival

MRD Timepoint Assessment Considerations

- Individual level associations were consistent across 9-month,12-month time points and MRD-Negative CR at any time
  - MRD assessment at these timepoints may be reasonable
- Disease setting considerations: NDMM vs. RRMM
- Assessment of Durability
- MRD-Negative CR, supported by durability of MRD negativity may also be considered

MRD-Negative CR: MRD negativity with Complete Response; MRD: Minimal Residual Disease; NDMM: Newly Diagnosed Multiple Myeloma; RRMM: Relapsed/Refractory Multiple Myeloma

MRD Assay Considerations

- Multiparametric flow cytometry (MPFC), Next generation sequencing (NGS)
- Analytically validated
- Sensitive to detect prespecified MRD negativity threshold

MRD: Minimal Residual Disease

Considerations for the Use of MRD as an Endpoint for AA in MM

Use of MRD as an Endpoint in MM

- Strong individual-level association of MRD with PFS/OS
  - Indicates MRD is prognostic
- Weak to moderate trial-level association
- MRD could serve as an intermediate clinical endpoint (similar to ORR)
  - Deeper level of response (reduced tumor burden)
  - Can be measured earlier
  - Support expedited drug development

Residual Uncertainties

- Lack of strong trial-level association
  - MRD is not a validated surrogate endpoint
  - Most endpoints used to support AA have weak to moderate trial-level association with PFS/OS
- Uncertain impact of different disease settings and treatment types
- Magnitude of benefit is unknown
- Potential safety considerations

MRD: Minimal Residual Disease; AA: Accelerated Approval; MM: Multiple Myeloma; PFS: Progression-Free Survival; OS: Overall Survival; ORR: Overall Response Rate

Regulatory Considerations for AA

- For accelerated approval, FDA may require confirmation of benefit
- FDORA legislation provides that the FDA, “may require, as appropriate, a study or studies to be underway prior to approval”
- FDORA legislation provides expedited withdrawal process if the study fails to verify benefit

AA: Accelerated Approval; FDORA: Food and Drug Omnibus Reform Act

FDA Summary

- MM remains incurable and there is a need for alternative endpoints other than ORR and PFS/OS
- The analyses presented today suggest that MRD negativity is prognostic in MM
  - Supported by biologic plausibility
- AA intended to facilitate expedited approval of novel therapies based on an intermediate endpoint of clinical relevance reasonably likely to predict clinical benefit

MM: Multiple Myeloma; ORR: Overall Response Rate; PFS: Progression-Free Survival; OS: Overall Survival; AA: Accelerated Approval; MRD: Minimal Residual Disease

Discussion Topics

- Discuss the adequacy of available data to support the use of MRD as an accelerated approval endpoint in MM
- Discuss whether the available data supports the use of MRD as an endpoint in the different MM disease settings
  - Newly diagnosed MM
  - Relapsed/Refractory MM
- Discuss the acceptability of the timepoints for MRD assessment:
  - 9-months, 12-months, MRD-Negative CR at any time
  - Requirement for assessment of durability

MRD: Minimal Residual Disease; MM: Multiple Myeloma; MRD-Negative CR: MRD negativity with Complete Response

Voting Question

Does the evidence support the use of MRD as an accelerated approval endpoint in MM clinical trials?

MRD: Minimal Residual Disease; MM: Multiple Myeloma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ADMINISTRATION

Backup Slides Shown

Individual- vs. Trial-Level Association

- **Individual-level association**: responders live longer than non-responders

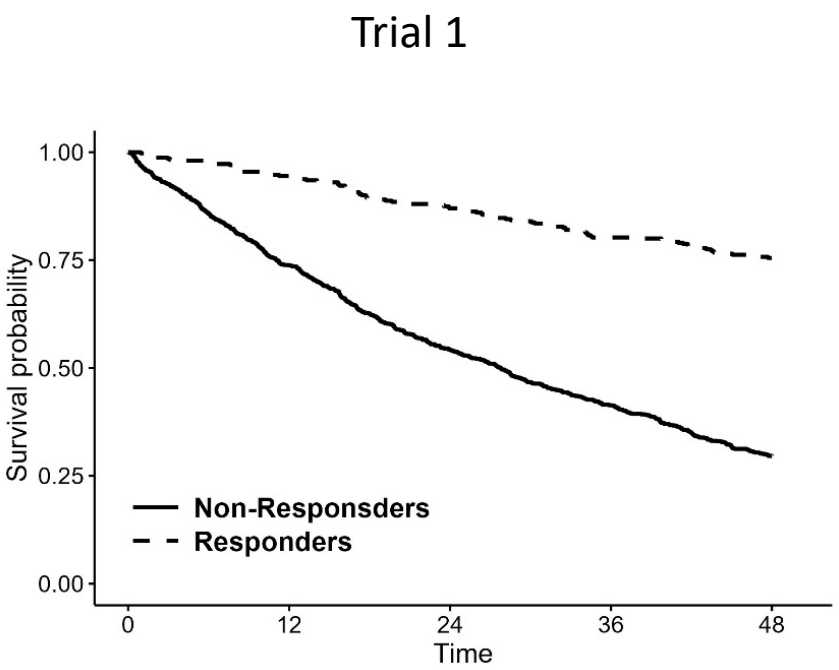
- **Trial-level association**: products that increase ORR also yield better HRs for PFS/OS
  - Also: products that do not increase ORR produce HRs=1 for PFS/OS

- Both are used for evaluating a potential surrogate endpoint

Individual-Level Association

Individual-level association means **patients who respond have better long-term outcomes than those who do not**.

- Can be observed in a single trial

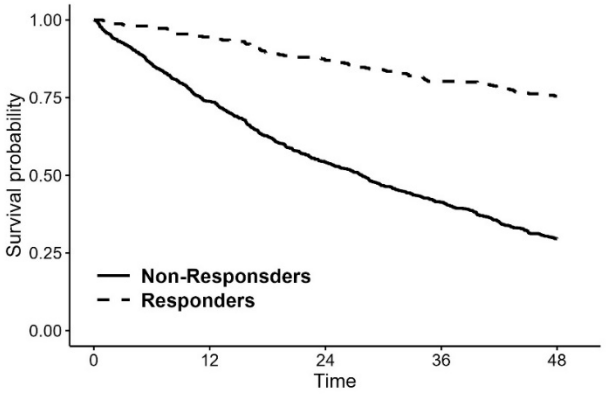


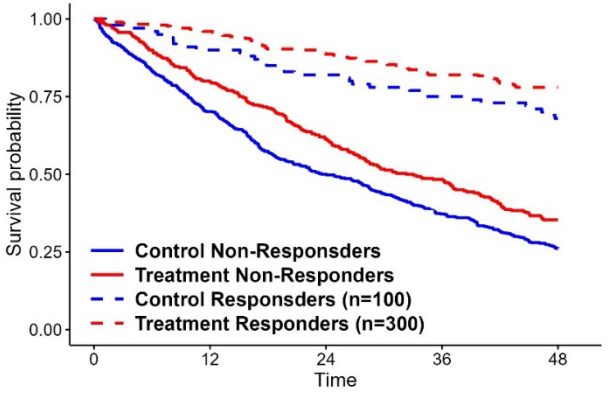
Individual-Level Association

Individual-level association means **patients who respond have better long-term outcomes than those who do not**.

- Can be observed in a single trial
- May vary by arm

Trial 1

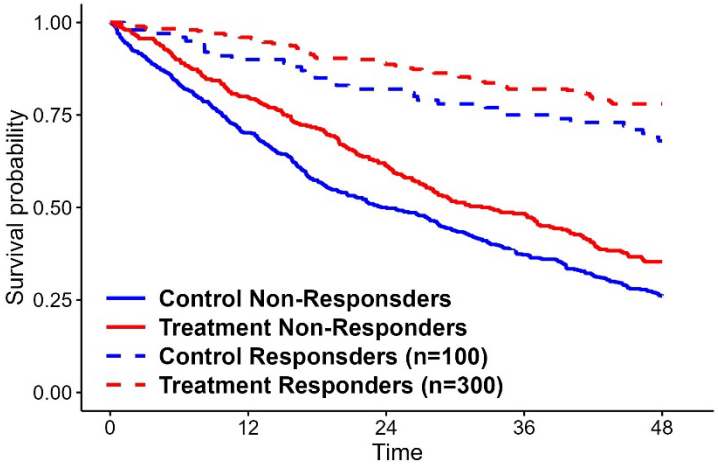




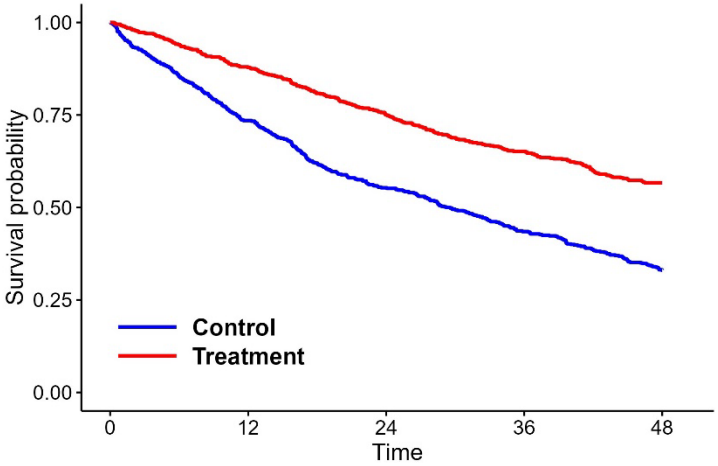
Individual-Level Association

For treatments that improve response rate, individual-level association may translate to a treatment effect on the long-term outcome.

Trial 1



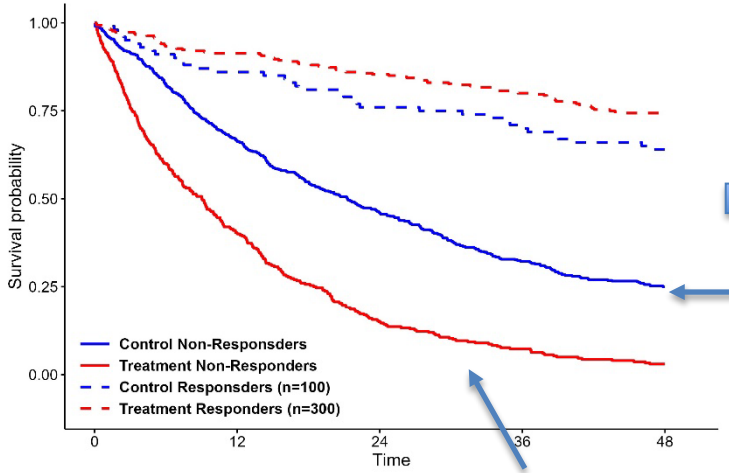
Trial 1



Individual-Level Association

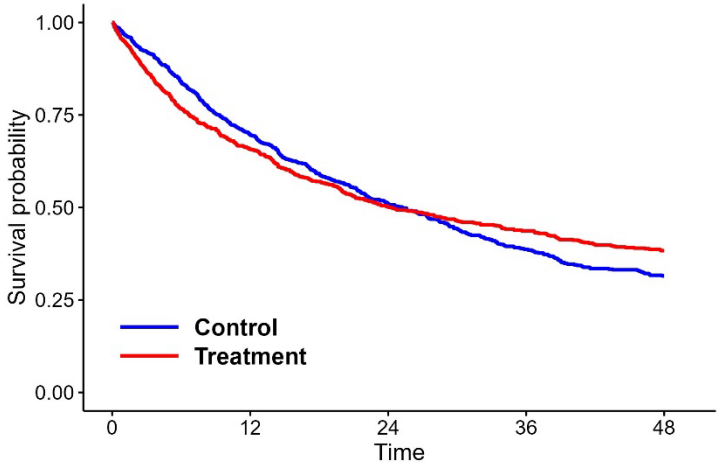
However, individual-level association does not guarantee a positive treatment effect on ORR will translate to a positive treatment effect on PFS.

Trial 2



Treatment non-responders progress much more quickly than **control non-responders**.

Trial 2



Trial-Level Associations

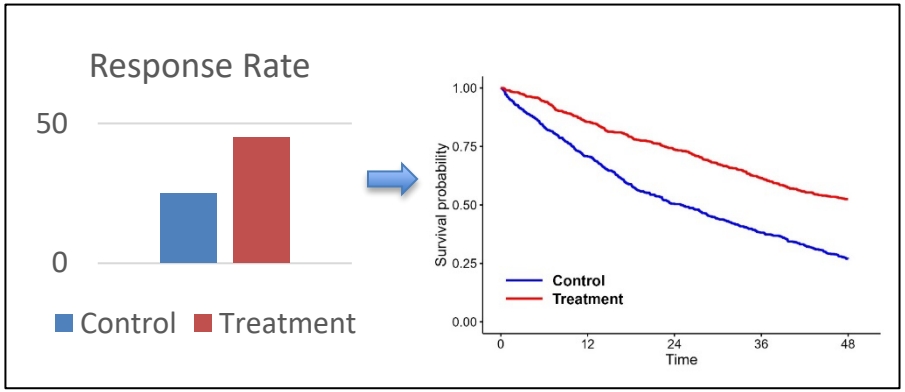
- One trial is typically not sufficient to estimate surrogacy

- Usual surrogacy analyses utilize meta-analysis of multiple trials
  - Goal is to show:
    - Positive treatment effect on ORR -> Positive treatment effect on PFS
    - No treatment effect on ORR -> No treatment effect on PFS
    - Negative treatment effect on ORR -> Negative treatment effect on PFS

ORR: Overall Response Rate; PFS: Progression-Free Survival

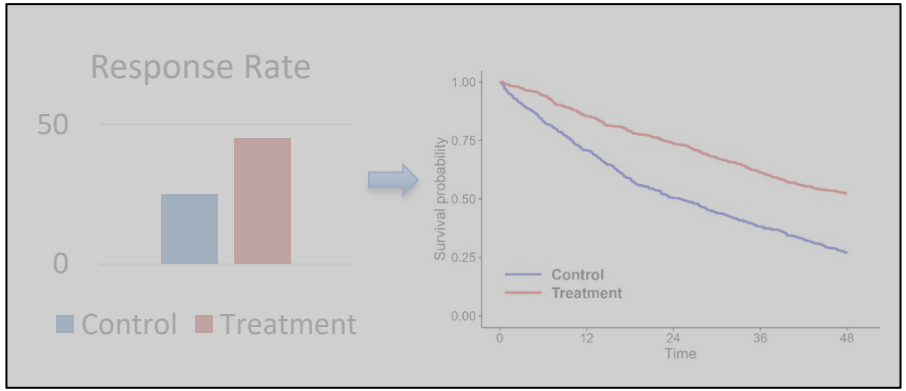
Trial-Level Associations

Trial 1

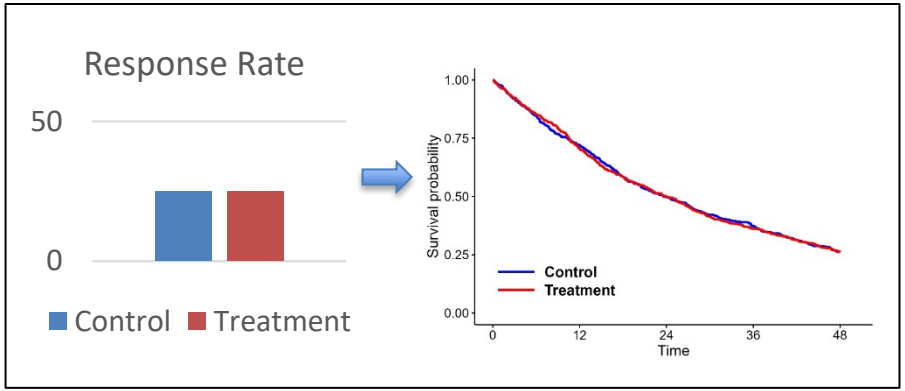


Trial-Level Associations

Trial 1

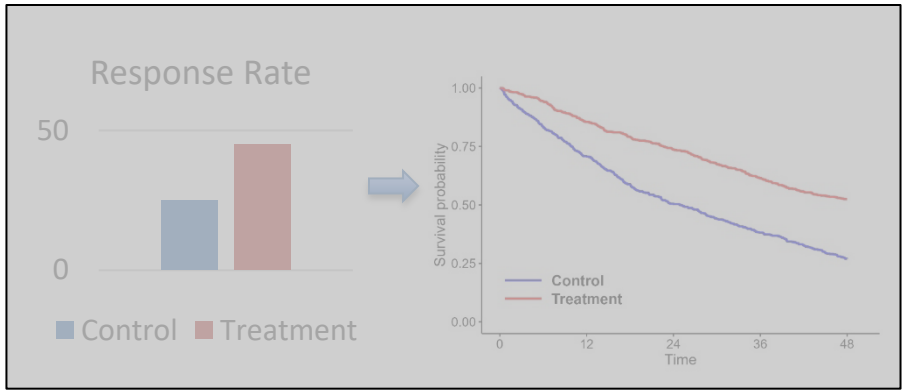


Trial 2

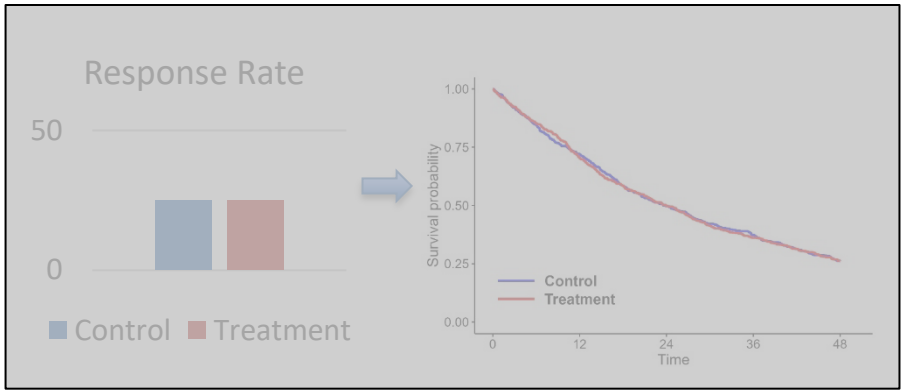


Trial-Level Associations

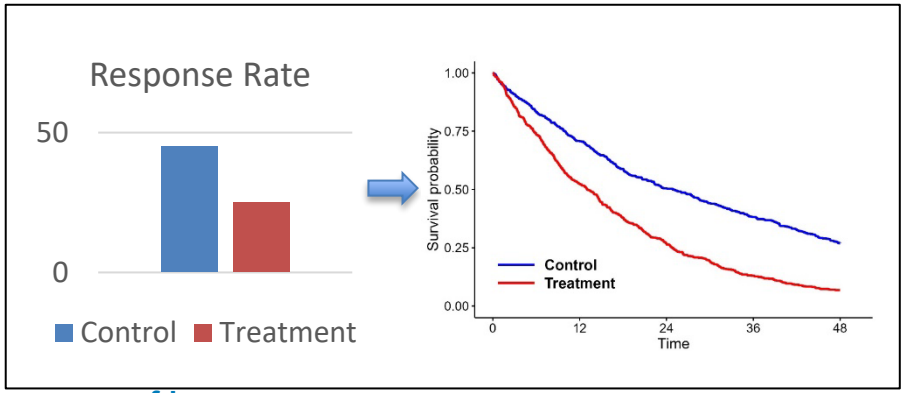
Trial 1



Trial 2

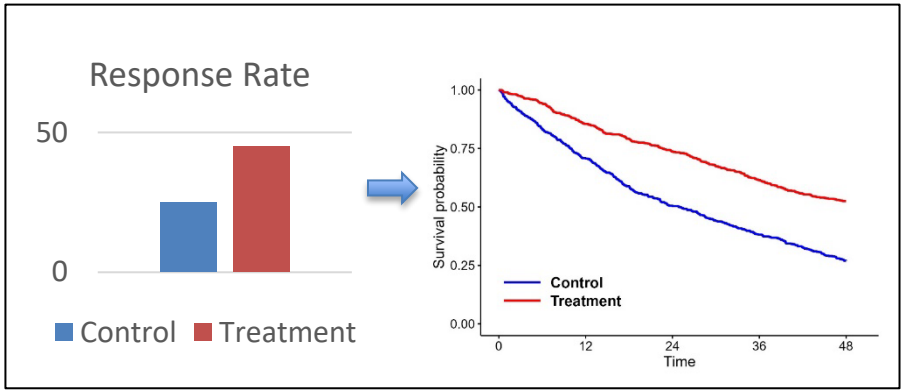


Trial 3

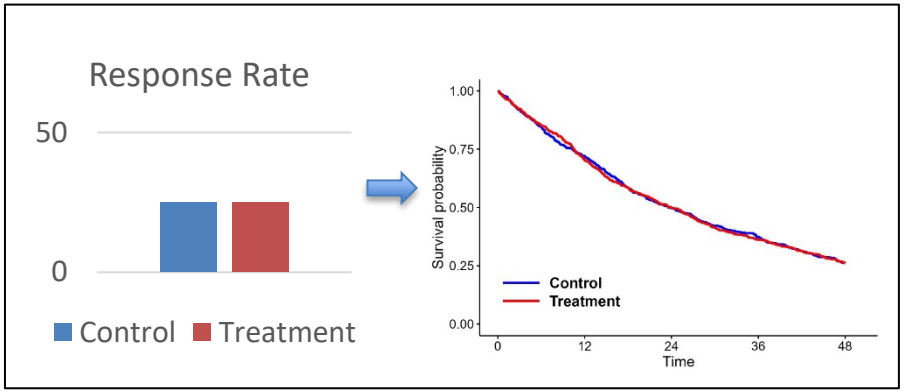


Trial-Level Associations

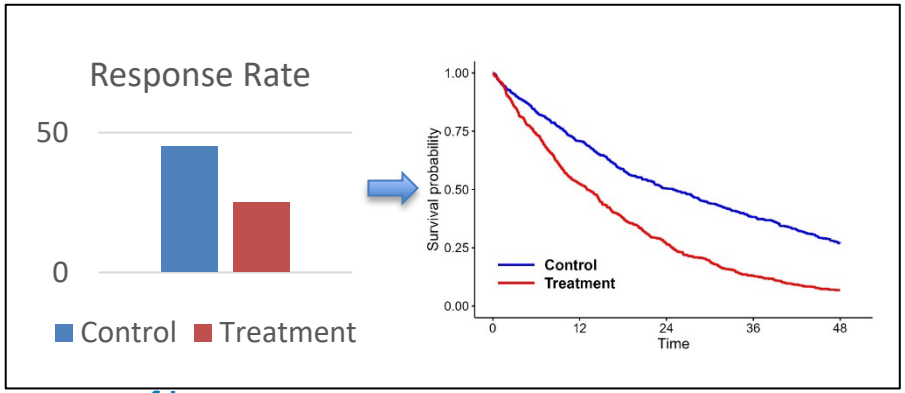
Trial 1



Trial 2



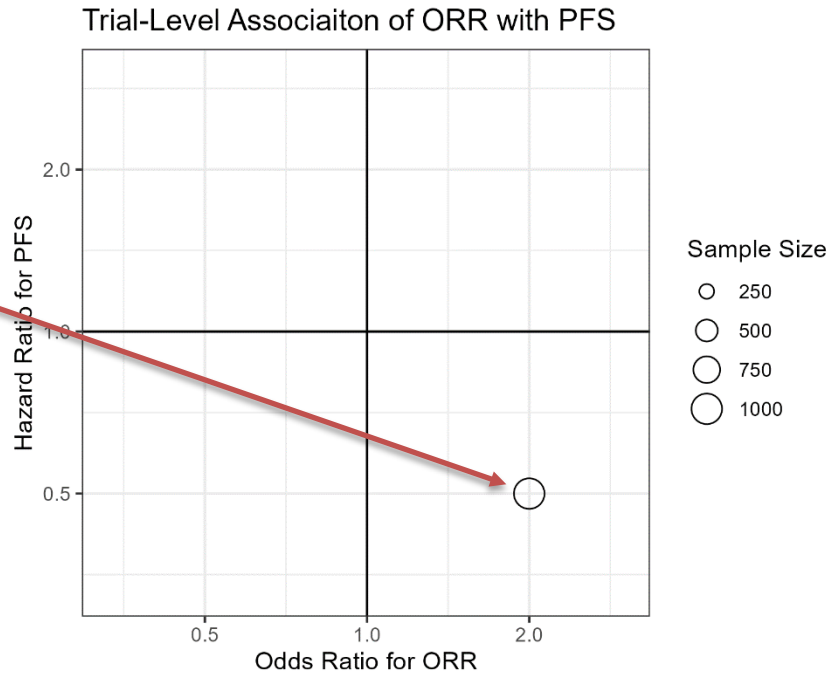
Trial 3



Trial	Odds Ratio	Hazard Ratio for PFS
Trial 1	2	0.5
Trial 2	1	1
Trial 3	0.5	2

Trial-Level Associations

Trial	N	Odds Ratio	Hazard Ratio for PFS
Trial 1	500	2	0.5
Trial 2	200	1	1
Trial 3	300	0.5	2
…		…	…
Trial 20	250	0.6	0.93



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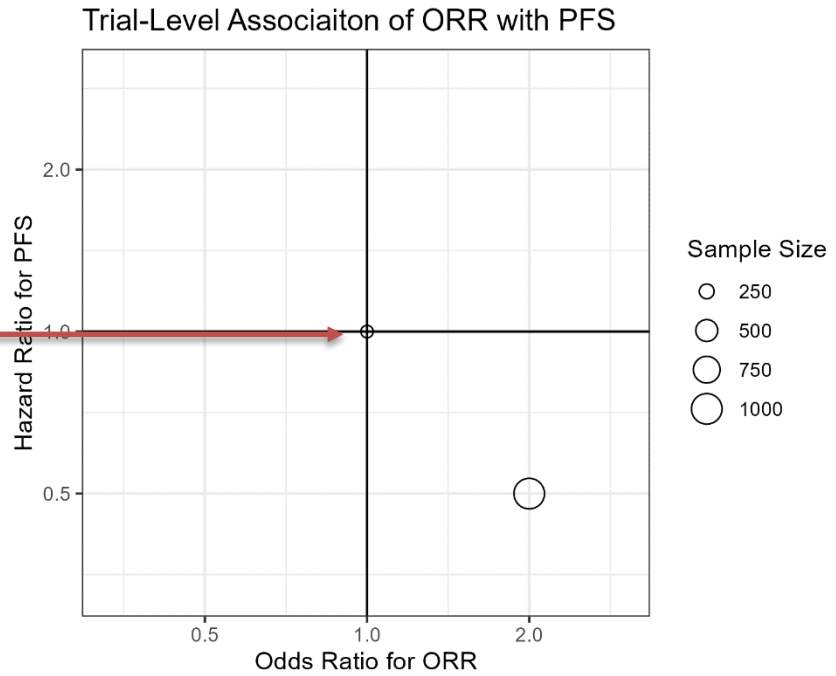

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