

Framework for Defining Evidentiary Standards for Biomarker Qualification: Minimal Residual Disease (MRD) in Multiple Myeloma (MM)

MRD in Multiple Myeloma Team
Biomarker Qualification Workshop
Framework for Defining Evidentiary Standards for Surrogate endpoints



Overview

- MRD in MM Case Study Framework Alignment Overview
- Problem Statement
- Need Statement
- Context of Use
- Benefit and Risk Descriptions
- Current State of Evidence
- Level of Evidentiary Standards Required
- Issues that need to be discussed
 - Universality
 - Plausibility
 - Causality
 - Proportionality
 - Specificity
- Conclusions
- Panel

Biomarker Evidentiary Framework

- Clinical outcomes take many years to develop
 - Longer, more expensive clinical trials will delay availability of active clinical agents to patients
 - Less industry interest in developing new myeloma drugs
- Urgent need for clinical monitoring of MRD in MM to track patient cancer progression and treatment response

- Benefits of the marker**
- The patients would benefit because it would allow more rapid development of therapies and more accurate tracking of treatment response. *Increased likelihood to be used.*
 - The field would be able to seek regulatory approval faster for drugs and biomarkers.
 - This biomarker will allow quantitative testing in a population.
- Risks of the marker (*magnitude of potential risks with MRD is low*)**
- Novel therapeutic approved that doesn't impact traditional clinical benefit measures, OS.
 - Early trial termination due to incorrect futility analysis if benefit not seen with MRD assessment
 - Patients may not receive treatment that improve survival
 - Achieving MRD negativity may not correlate with OS (Additional treatment may not be necessary in certain patients)
- What is the acceptable level of uncertainty?**
- *The patient population is motivated to take on more risk to help achieve beneficial therapies.*

In Drug Development

Factor likelihood and magnitude

Informs Required Stringency of EC



MRD, as assessed via bone marrow aspirate, measured using a validated assay, is a response biomarker that can be used in patients with multiple myeloma to assess response to treatment correlated with outcome

- Surrogate Endpoint Evidentiary Categories**
- Biological plausibility
 - Multiple testing methods
 - Good correlation with disease
 - Causality
 - Residual disease cells are what is being tested (*reasonably likely, but hard to prove*)
 - Universality
 - Good initial clinical data, additional clinical data needed for meta-analyses for specific COUs
 - Proportionality
 - Specific meta-analysis needed to prove this
 - Specificity
 - Residual disease cells are what is being tested (*reasonably likely, but hard to prove*)

Problem Statement

MM Cases Increasing Especially in Minorities

- MM increasing in prevalence as Americans age
- 1.77 % new cancers, 30,770 new cases est. in U.S. in 2018
- Estimated Deaths are 12,770 for 2018
- High incidence in African Americans, Pacific Islanders
- Associated with second cancers in 10% of cases

Problem Statement

Novel Therapies Have Prolonged Patient Survival and Trial Length Increasing and Patients Eligible for Enrollment Decreasing

- Optimal treatment effect in newly diagnosed population
 - Less clonal heterogeneity compared to rel/ref setting
 - Lower burden of residual side effects from previous treatments
- 22 FDA approvals of new therapies to treat MM has increased patient survival from 3-4 years to 8-10 years
 - Over last 5 years at least 6 new agents have been approved with multiple, complementary mechanisms of action
 - Promising agents with novel MOAs are under investigation
- However, the several-fold prolongation in PFS makes future clinical trials with endpoints of extending PFS by 30-50% now prohibitively long
 - Average phase 3 resources and timelines in NDMM
 - 600-800 pts in non-transplant studies, ↑ing to 800-1000 pt in transplant eligible segment
 - Minimum 4-5 year readout for primary endpoint of PFS; longer in transplant eligible studies
 - Average all-in cost for company sponsored phase 3 study \$180-200MM
- ***Simply not enough pts, time, and money to evaluate all promising agents in newly diagnosed pts via phase 3 studies***

Need Statement

- What is needed is a response biomarker that has been validated as a surrogate endpoint that:
 - Reliably correlates with and likely predicts long term patient outcomes
 - Will accelerate drug development for promising agents (especially for newly diagnosed pts)
 - Will stop development programs early that are unlikely to deliver meaningful benefits for pts so limited resources are optimized

Context of Use

(Currently Featured COU – Others Expected in Future)

■ Use Statement:

- MRD evaluated via bone marrow aspirate from multiple myeloma patients using an analytically validated assay is a biomarker that may be used as a surrogate endpoint to assess treatment response and predict benefit to PFS/OS.

■ Conditions for Qualified Use:

- Assay: An analytically validated assay must be used for detection of MRD.

■ Patient Populations

- Patients enrolled on clinical trials with the clinical criteria below would be appropriate for MRD assessment:
 - Patients with newly diagnosed multiple myeloma who have attained a CR.
 - Patients with relapsed or refractory multiple myeloma who have attained a CR.

■ Future COUs will take into account forthcoming trial data

Benefit Assessment

- By qualifying minimal residual disease (MRD) measurements as a surrogate endpoint for multiple myeloma:
 - Faster patient access to more agents
 - More accurate tracking of patients for treatment response
 - More rapid identification of viable novel agents

- MRD directly measures depth of response and is being examined in myeloma to assess whether it can serve as a surrogate for:
 - Accelerated regulatory approval
 - Progression free survival/Overall Survival
 - Full regulatory approval

Risk Assessment

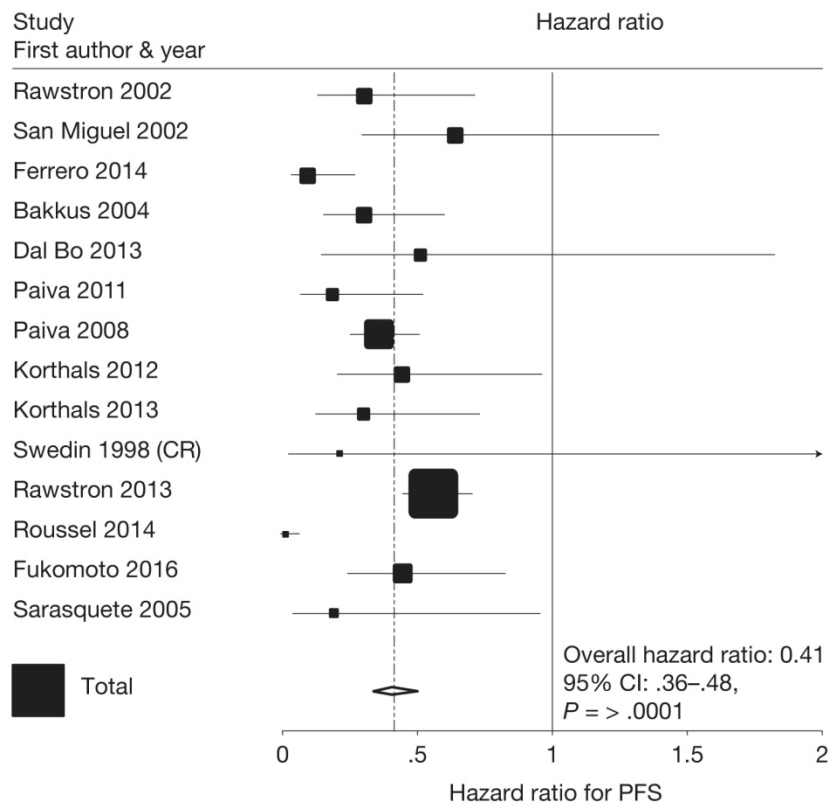
- Potential consequence or harm if MRD's performance did not meet expectations:
 - Incorrect regulatory decision:
 - Novel therapeutic could be approved that actually doesn't impact traditional clinical benefit measures, OS.
 - Investigators might terminate trials early due to incorrect futility analysis if actual benefit is not appreciated with MRD assessment.
 - Incorrect treatment decision:
 - Patients may not receive treatment that improves survival
 - Achieving MRD negativity may not correlate with OS (Additional treatment may not be necessary in certain patient populations)

- Potential Risk Mitigation
 - Regulatory risk could be mitigated by ensuring orthogonal testing and long-term data tracking and follow-up to continue validation of the marker and ensure long-term clinical benefit in confirmed
 - Patient treatment risk could be mitigated by changing to a new treatment quickly if the patient begins progressing; multiple treatments exist that can be tried
 - Given the diagnosis, most patients willing to assume additional risk versus other diseases

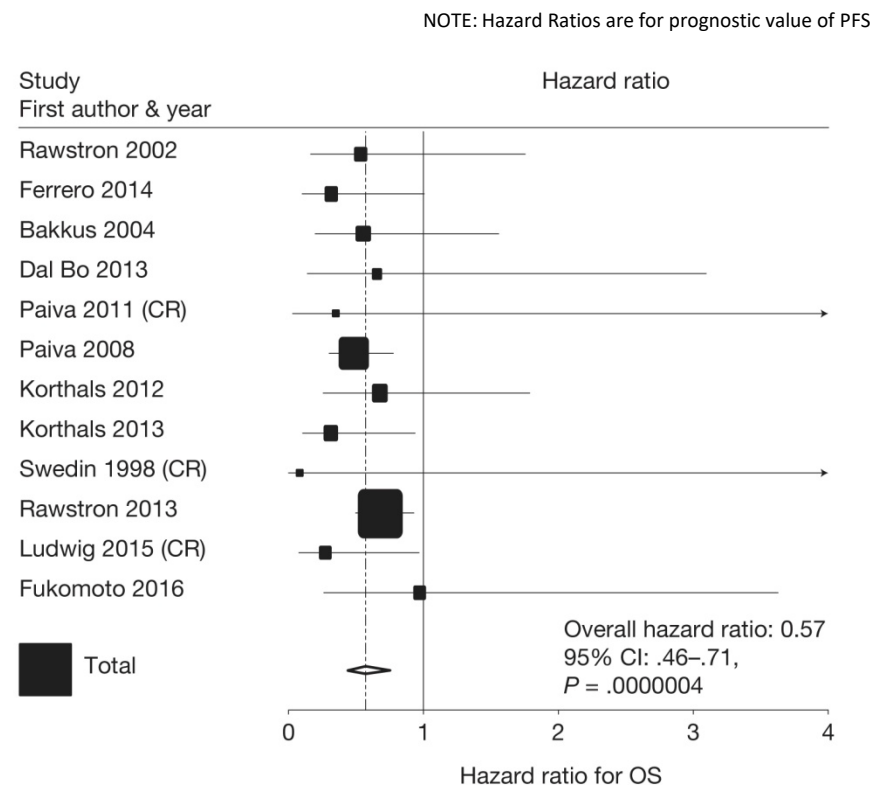
Current State of Evidence

(Current Meta-analysis Conducted)

A



B



Recent meta-analysis of trials examining MRD's prognostic capabilities suggest potential as a surrogate endpoint.

Munshi N et al., JAMA Oncol, 2017

Current State of Evidence

MM Trials with MRD Collected

- Currently there 80+ MM trials with thousands of patients that are either completed, in progress, or planned
- 51 of the trials plan on collecting MRD data

Trial Type	Phase 1		Phase 2		Phase 3		Phase 4/Not Stated	
MRD Endpoint	# of Trials	# of Pts	# of Trials	# of Pts	# of Trials	# of Pts	# of Trials	# of Pts
Secondary (PFS or OS correlation)	6	551	23	1,748	14	7,586	8	513

NOTE: These trials represent collection at different timepoints with different types of assays. They would need to be sub-grouped for each for meta-analysis.

- 16 of these trials with relevant MRD data as a secondary endpoint have been highlighted in recent publications in the last 5-7 years

Trial Type Treatment Line	Phase 2 First Line		Phase 2 Second Line and Beyond		Phase 3 First Line		Phase 3 Second Line and Beyond	
MRD Endpoint	# of Trials	# of Pts	# of Trials	# of Pts	# of Trials	# of Pts	# of Trials	# of Pts
Secondary (PFS or OS correlation)	7	852	5	144	2	1,001	2	1,067

NOTE: These trials represent collection at different timepoints with different types of assays. They would need to be sub-grouped for each for meta-analysis.

Current State of Evidence

Relationship between Biomarker and Clinical Outcome

■ Meta-analytical Methods

- Patient-level data
- Allows 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 the 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 an effect on the true clinical endpoint

Buyse, Nat Rev Onc 2010
Sargent, JCO 2015

■ 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 MRD timing of assessment and missing data is important.
- The trial population and treatments included in the meta-analysis inform future applicability of the surrogate endpoint.

Buyse, Bioment J 2016
Sargent, Clinical Trials 2013

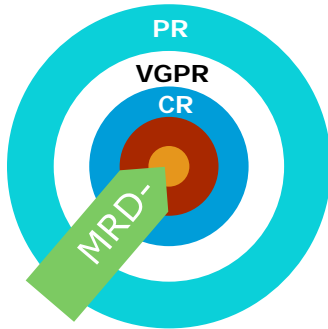
■ Multiple Myeloma Considerations

- Determination of the clinical MRD negativity threshold that best correlates with the clinical outcome of interest (10^{-4} , 10^{-5} , 10^{-6})
- Applicability of MRD as a surrogate endpoint in different disease settings (i.e., relapsed disease, newly diagnosed, smoldering)
- Role of cytogenetics
- Sensitivity and Subgroup analyses in the meta-analysis may help address the aforementioned issues
- Extra medullary disease should be accounted for when considering using MRD as a surrogate
- When possible, the MRD data would be evaluated as a continuous variable

Current State of Evidence - Evidentiary Criteria

MRD Assay Considerations

- Validated Assay
- Standardized procedures for sample collection and processing
- Predetermined MRD Thresholds within limit of detection of the assay
- Standardized reporting results
- Standardized times of collection and follow up



- MRD correlates with long-term outcomes, PFS and OS (Munshi et al pooled analysis 14 trials)
 - MRD-: mPFS=54m, mOS=98m
 - MRD+: mPFS=26m, mOS=82m
 - HR for PFS=0.41; $p<0.001$; HR for OS=0.57; $p<0.001$

■ Key Milestones to Achieve Surrogacy

- Technical validation of MRD Clonoseq 2.0 NGS assay for clinical trials (510(k) submission)
- Clinical validation of MRD as a surrogate for treatment benefit (trial level data)
- Ongoing MRD Consortium collaborations: pooled meta-analysis across treatments to support prognostic value of MRD in MM

LaHuerta. *JCO*. 2017; Munshi. *Jama Oncol*. 2016; Landgren. *Bone Marrow Transplant*. 2016.

International Myeloma Working Group (IMWG) MRD Criteria Defines Current Status of Regulatory and Clinical Use of MRD

- MRD Negative: Absence of aberrant clonal plasma cells in bone marrow aspirate, ruled out by an assay with minimum sensitivity of 1×10^{-5} nucleated cells or higher. Current methods are flow cytometry or NGS.
- Sustained (Durability) MRD-negative: MRD negativity in the marrow (Flow or NGS, or both) and by imaging as defined below, confirmed minimum of 1 year apart.
- Imaging plus MRD-negative: MRD negativity as defined by Flow or NGS plus disappearance of every area of increased tracer uptake found at baseline or a preceding PET/CT or decrease to less mediastinal blood pool SUV or decrease to less than that of surrounding normal tissue

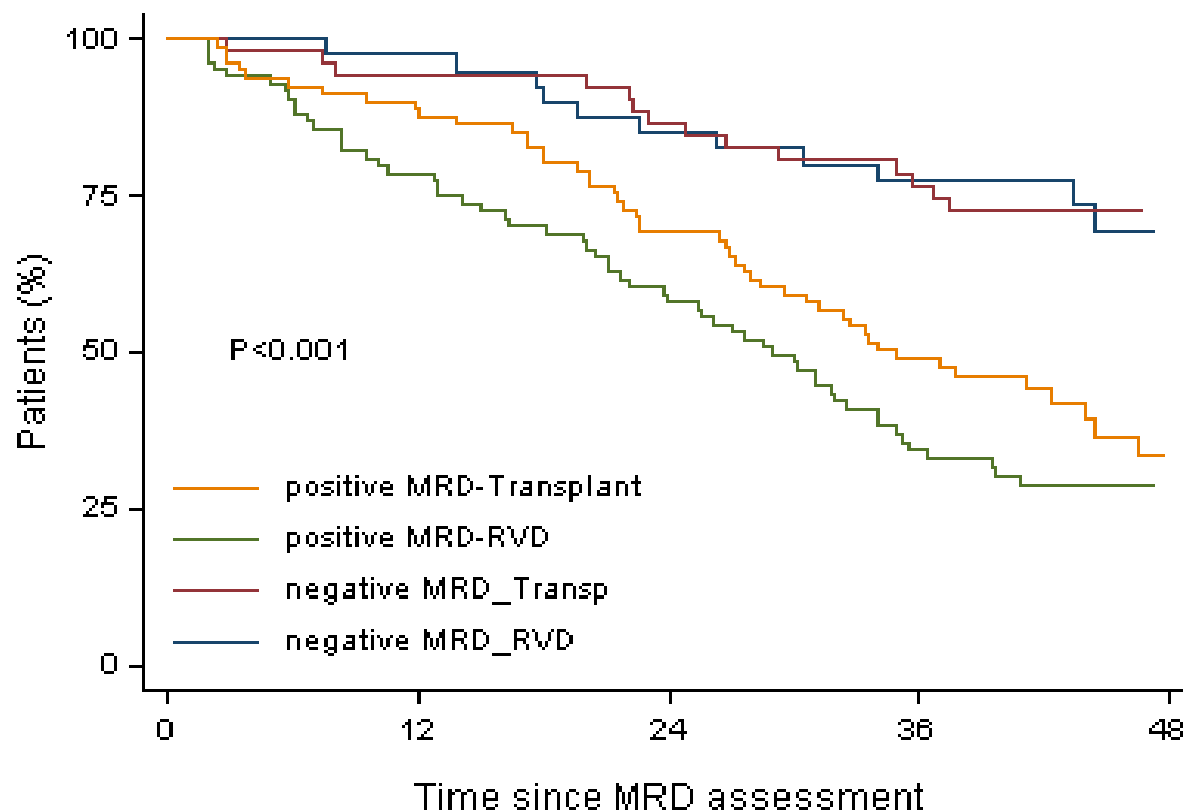
*The group understands that collecting data through these criteria alone will not be sufficient to achieve surrogacy status for MRD; however, they will make for a **good starting point for standardization of the data** to be collected.*

Kumar et al., Lancet Oncol 2016; 17: e328-46.

Issues of Focus to Be Discussed

- **Causality**
 - is there a compelling case for it being causal so there is less of a need for evidence of universality?
- **Plausibility**
 - is the biology of the surrogate so compelling that it adds to the weight of evidence for acceptance?
- **Specificity and potential for off target effects**
- **Proportionality**
 - to what extent does the surrogate explain the disease or the change in disease?
- **Universality**
 - to what extent is there evidence across drug mechanisms or across different populations?

MRD Negative Patients Have Improved Outcome Irrespective of Therapy Used



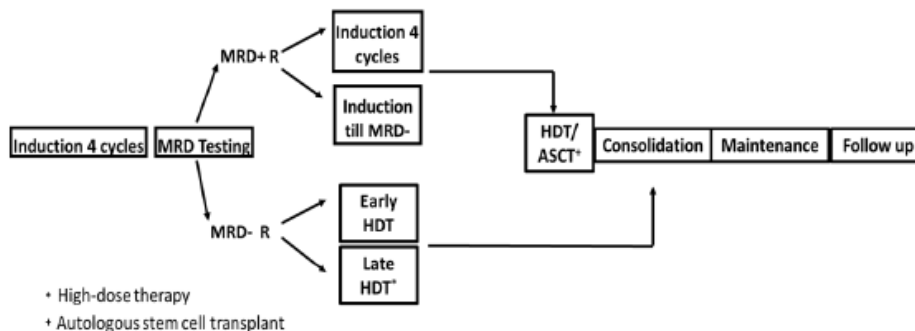
	N at risk				
positive MRD-Transplant	81	72	56	35	9
positive MRD-RVD	84	65	48	26	8
negative MRD_Transp	52	49	45	37	17
negative MRD_RVD	40	39	34	31	10

Universality

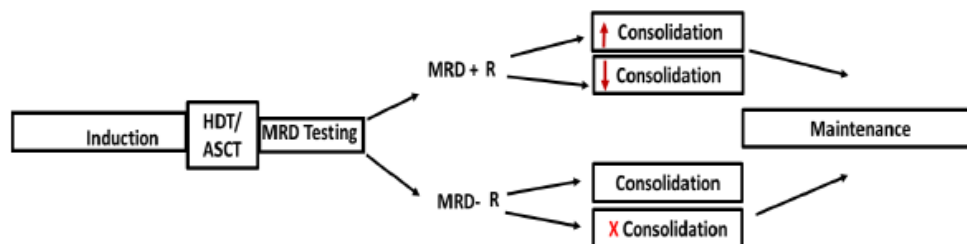


Avet-Loiseau et al, 2017

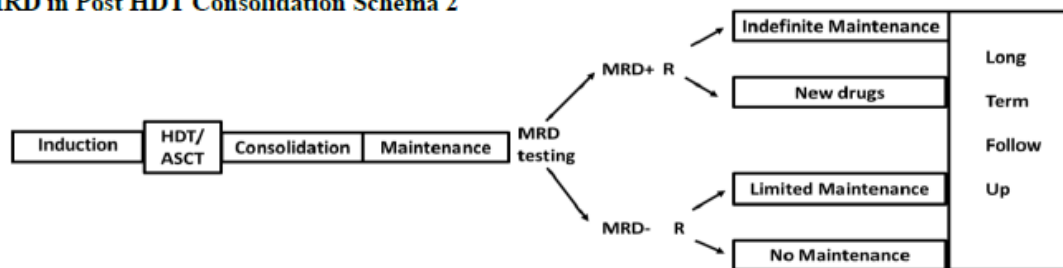
Incorporation of MRD into Novel Multiple Myeloma Trial Design Schemas Could Provide Data for Universality of the Biomarker



Role of MRD in Timing of HDT Therapy in Multiple Myeloma Schema 1



Role of MRD in Post HDT Consolidation Schema 2



Adapted from Kumar S. Clin Adv Hematol Oncol. 2014;12:133-134.

Role of MRD in Maintenance Therapy in Multiple Myeloma Schema 3

Universality



Meta-Analysis Suggested Significant Impact of MRD Status on Survival Outcomes In MM Patients with Complete Response

- A total of 405 published articles with MRD
 - 25 recently published articles
- Of these, 21 reported overall survival (OS) or progression-free survival (PFS) results, as well as MRD status
- Overall, 2,208 pts were evaluated for MRD
- Nine publications reported conventional complete response (CR) at the time of MRD measurement. Six represented unique data sets.

Universality

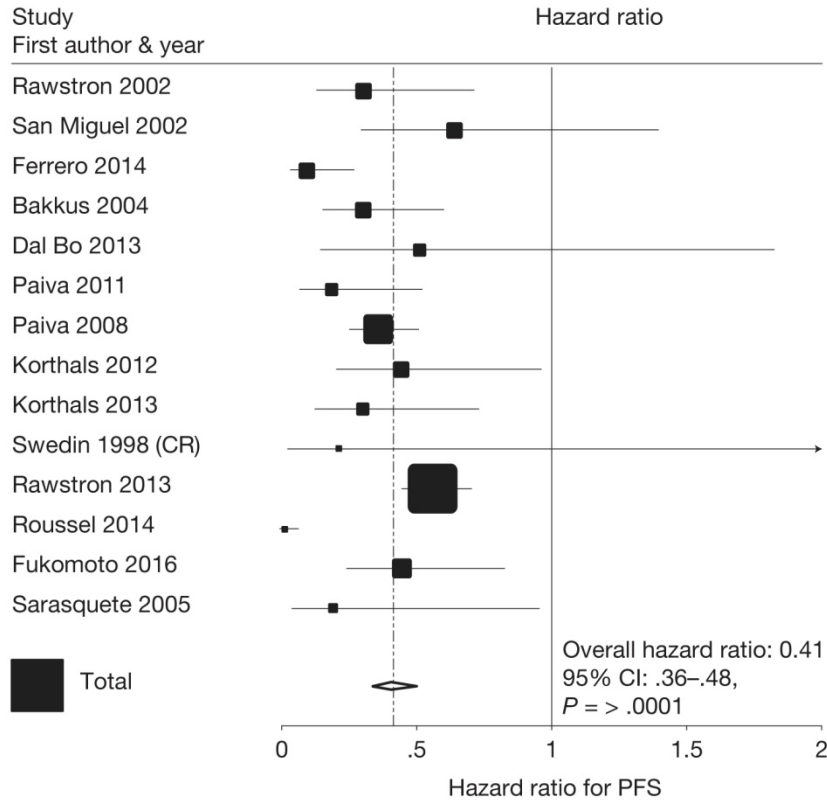
Munshi N et al., JAMA Oncol 2017



The Effect of MRD Status on PFS and OS

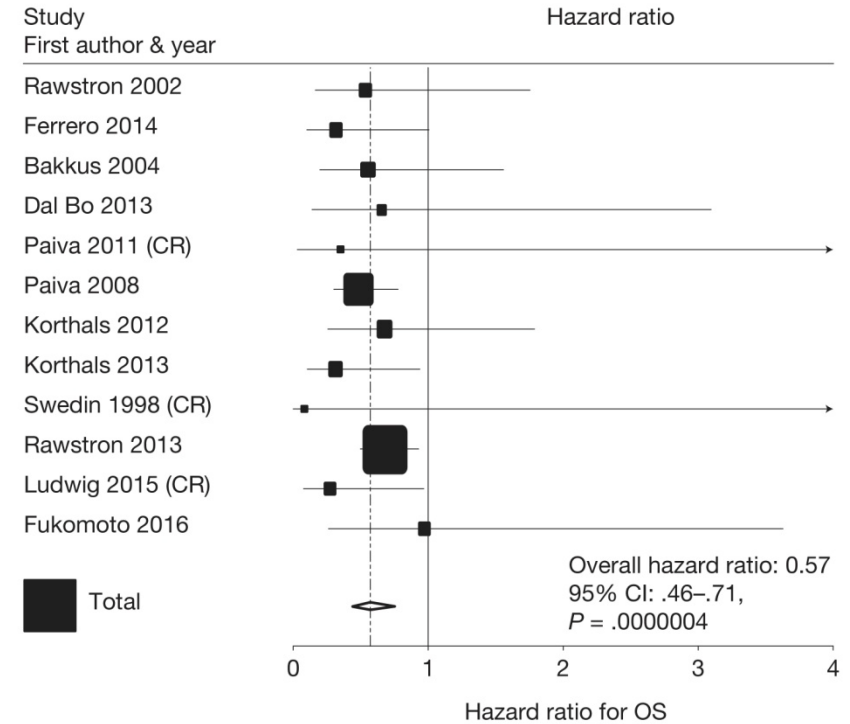
(All patients)

A



B

NOTE: Hazard Ratios are for prognostic value of PFS



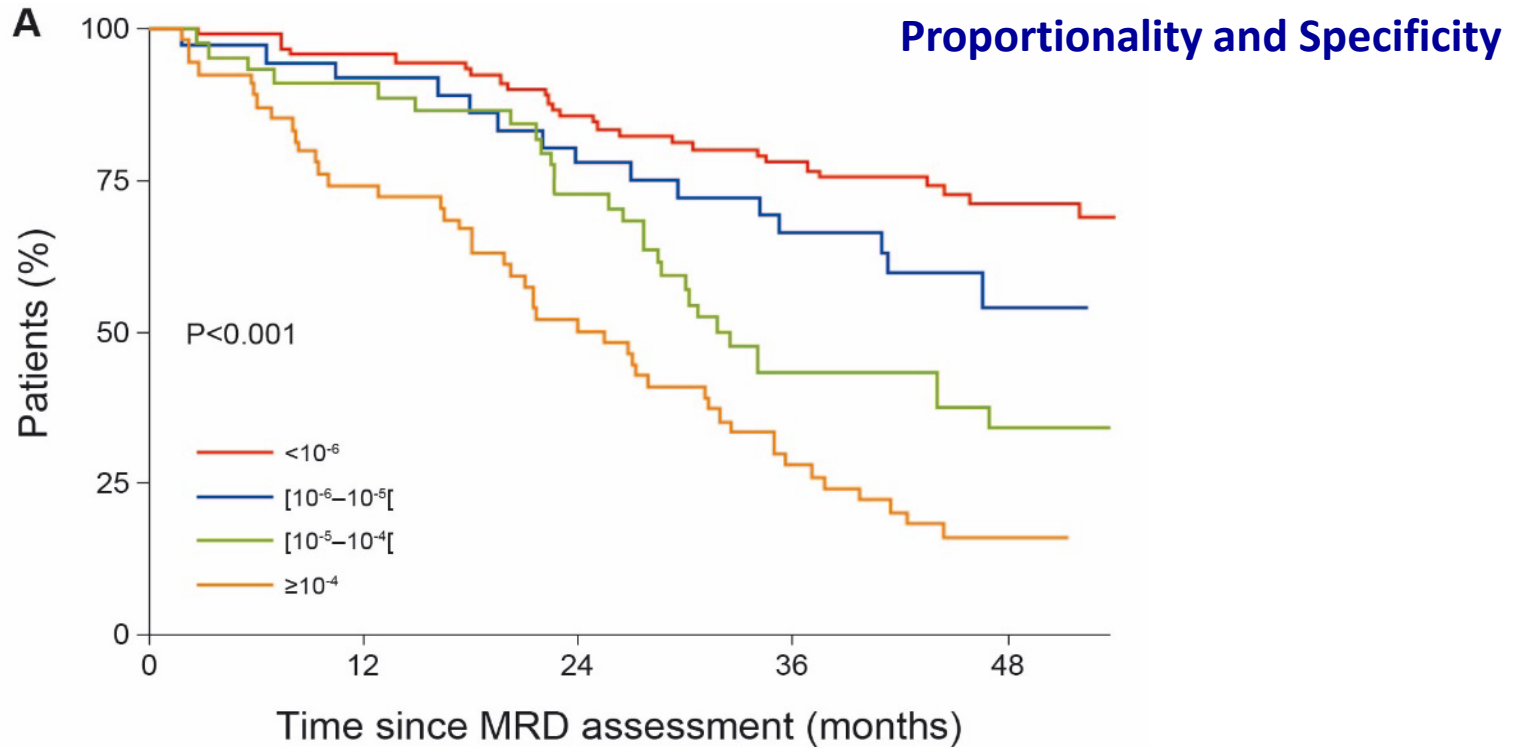
This analysis speaks to the plausibility of MRD as a surrogate endpoint.

Plausibility

Munshi N et al., JAMA Oncol, 2017



Patients Demonstrate Superior PFS with Decreasing MRD Due to Deeper Treatment Response



No. at Risk	0	12	24	36	48
$< 10^{-6}$	90	86	77	69	49
$[10^{-6} - 10^{-5}[$	36	33	28	22	9
$[10^{-5} - 10^{-4}[$	44	40	32	19	10
$\geq 10^{-4}$	54	40	27	15	7

Avet-Loiseau et al, 2017

The link between the decrease in MRD in multiple myeloma patients suggest that MRD could have the required proportionality of a surrogate endpoint.

Summary of MRD in MM Addressing Evidentiary Requirements

- Biological plausibility
 - Multiple testing methods
 - Good correlation with disease
- Causality
 - Residual disease cells are what is being tested (reasonably likely, but hard to prove)
- Universality
 - Good initial clinical data available, but likely additional clinical data needed to do specific meta-analyses for specific COUs
- Proportionality
 - Specific meta-analysis needed to prove this
- Specificity
 - Residual disease cells are what is being tested (reasonably likely, but hard to prove)

Conclusions

- Incorporation of novel agents has transformed treatment outcomes for MM
- This creates high barriers for assessing promising investigational agents with novel MOAs especially in the frontline setting
- Given that time and costs are limited resources in drug development, we need a response biomarker that is likely to predict clinical benefit and could be a surrogate for accelerated approval
- MRD accurately quantifies post-treatment residual MM cells with high sensitivity so there is intuitive biologic plausibility for MRD as a prognostic marker, but further evidence would likely be needed to extend this to surrogacy
- Prognostic value of MRD has been established across several meta-analyses
- Specific assessment gaps regarding how and when to measure MRD to ensure MRD- is a trial level surrogate likely to predict clinical benefit across different treatments are addressable by applying a uniform statistical analysis plan to trial datasets in collaboration with FDA

Issues with Case Study in Testing the Surrogate Evidentiary Framework

- Patient risk tolerance
- Specificity of the biomarker seems to be inherent due to what is being measured
- Causality related to the outcome is difficult to test
 - We are measuring the disease with MRD, but the evidence to prove that MRD is on the causal pathway to the clinical outcome of the disease has yet been established

SLIDES FOR PANEL QUESTIONS



Open Questions Regarding Validity of MRD as a Surrogate are Addressable

- Can the MRD log reduction threshold data be used to prove proportionality (10^{-4} , 10^{-5} , or 10^{-6})?
 - Can easily be analyzed from pooled trial level data
- Are the main methodologies for assessing MRD (Flow and NGS) comparable?
 - Each needs to be validated separately with trial level data
 - NGS methodology is standardized from commercial vendor facilitating technical validation
- Are the results from newly diagnosed, transplant-eligible studies extrapolatable to non-transplant-eligible pts?
 - These are discreet patient segments with different outcomes and thus should be analyzed separately
- Does between-arm differences in MRD status predict for between arm differences in PFS/OS?
- What is the appropriate timing for MRD assessment?
 - For transplant patients, a landmark analysis of MRD- rate for CR pts at day 100 post transplant consolidation will minimize ascertainment bias
 - Prolonged paraprotein half-life may lead to false positive IF at day 100, reducing the CR pool to be assessed for MRD

Open Questions Regarding Validity of MRD as a Surrogate are Addressable

- Is a snapshot assessment at one time point reliable, or does MRD- status need to be confirmed with a 2nd assessment at least 6 months later?
 - Need to compare pts with only one MRD- assessment with those whose MRD- status is sustained at least 6-12 months
- What is the optimal frequency of MRD surveillance and will it always precede a fast clinical relapse?
 - Can easily be analyzed from large pooled clinical trial data sets
 - MRD- can still be a useful surrogate for long term outcomes even if MRD status is not a useful surveillance marker for rapid relapse
- What about focal lesions or plasmacytomas detected on functional imaging in pts who are MRD- in the bone marrow?
 - Bone marrow involvement can be heterogeneous leading to the possibility of a false-negative assessment.
 - Rates of extramedullary detection increasing with sensitive imaging (e.g. ¹⁸F-FDG PET) and improved survival
 - Assessment of the extramedullary compartment must be conducted for those who are MRD- in the BM to ensure eradication of minimal residual disease