Minimal Residual Disease

July 14, 2023

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Tech Support

1-719-234-7952

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Resources

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Submit your questions throughout the program!

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MMRF Research Initiatives

MULTIPLE MYELOMA Research Consortium

CoMMpass Study℠

CureCloud®

For more information, visit themmrf.org

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Speakers

Benjamin A. Derman, MD
University of Chicago
Chicago, Illinois

Rafael Fonseca, MD
Mayo Clinic
Phoenix, Arizona

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Principles of MRD Testing

Benjamin A. Derman, MD
University of Chicago
Chicago, Illinois

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Goals of Multiple Myeloma Therapy

- Reduce the amount of M protein (as measured by serum protein electrophoresis) or light chains (as measured via the free light chain test) to the lowest level possible.
- **Eliminate myeloma cells (as measured via minimal residual disease [MRD] testing).**
- Improve quality of life with as few treatment side effects as possible.
- Provide the longest possible period of response before first relapse.
- Prolong overall survival.

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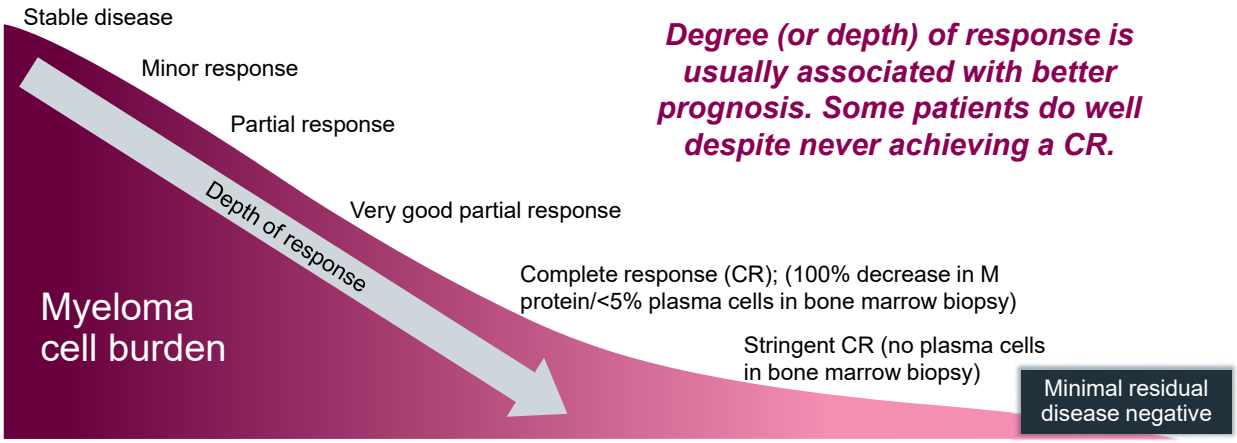
Measuring Response to Therapy



Degree (or depth) of response is usually associated with better prognosis. Some patients do well despite never achieving a CR.

ClonoSEQ is an FDA-approved next-generation sequencing (NGS) test to measure MRD in multiple myeloma patients.

Palumbo A et al. *J Clin Oncol*. 2014;32:587.
Kumar S et al. *Lancet Oncol*. 2016;17:e328.

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What is MRD?

The presence of small amounts of myeloma cells in the body after treatment

The most sensitive MRD tests can detect at least 1 myeloma cell out of 1,000,000 cells.

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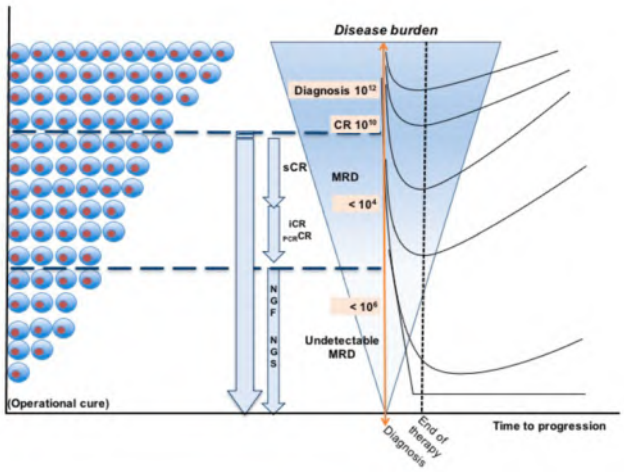
Why should we measure MRD?

- With increasingly effective treatments, more patients can achieve a CR/sCR (no myeloma proteins in the blood or bone marrow by conventional tests)…
- …but low levels of myeloma cells may remain and may be responsible for disease progression



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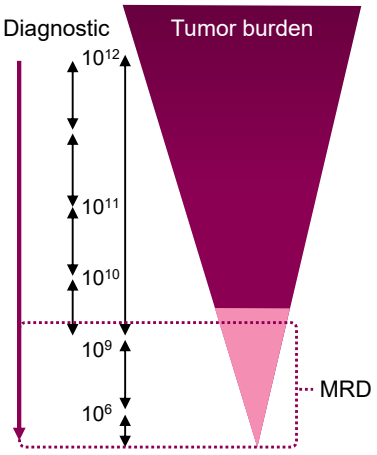
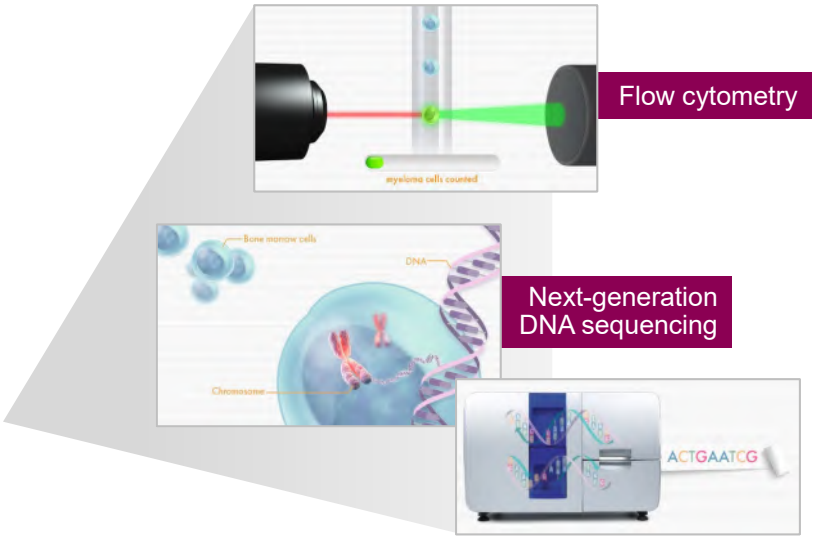
How is MRD measured?





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Techniques Available to Measure MRD in Multiple Myeloma

	Next-generation flow (NGF)	Next-generation sequencing (NGS)
Availability	Variable	Variable
Diagnostic sample	Helpful but not mandatory	Mandatory
Applicability	Universal (~100%)	High (~90%)
Turnaround time	2 hours	7 days
Cost	~250 USD	~700 USD
Sensitivity	With ~10 million cells	With around 2+ million cells
Quantitative	Yes	Yes
Fresh sample	Needed	Not needed
Patchy sample	Impacts	Impacts
Global cell characterisation	Yes	No
Standardisation	Ongoing (EuroFlow)	Yes (Adaptive)

Adapted from Paiva B et al. *Blood*. 2015;125:3059.

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Key Terms for MRD

MRD positive or MRD positivity (MRD+)

- Myeloma cells are still detectable

MRD negative or MRD negativity (MRD-)

- Myeloma cells are not detected

Sustained MRD-

- Two measurements of MRD negativity performed at least 12 months apart

Level of sensitivity can be different depending on methodology used (flow cytometry or NGS) and the number of cells analyzed

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Comprehensive Response Assessment

Right now, measurement of MRD depends on counting cells or DNA sequences in bone marrow samples

What if myeloma is present outside of the bone marrow?

Imaging (PET/CT or DW-MRI) may detect MRD outside the bone marrow.

Peripheral blood tests are also under investigation.

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Patients Who Achieve MRD Negativity Following Treatment Live Longer Than Those Who Are MRD Positive

Key points from 44 studies analyzed

- MRD negativity is associated with longer progression-free and overall survival.
- This association stands regardless of disease risk, MRD assay used, sensitivity threshold, disease setting, and conventional disease response.

Munshi NC et al. *Blood Adv*. 2020;4:5988.

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Where is the MRD field going?

MRD-driven therapy

New MRD assays that do not depend on bone marrow samples

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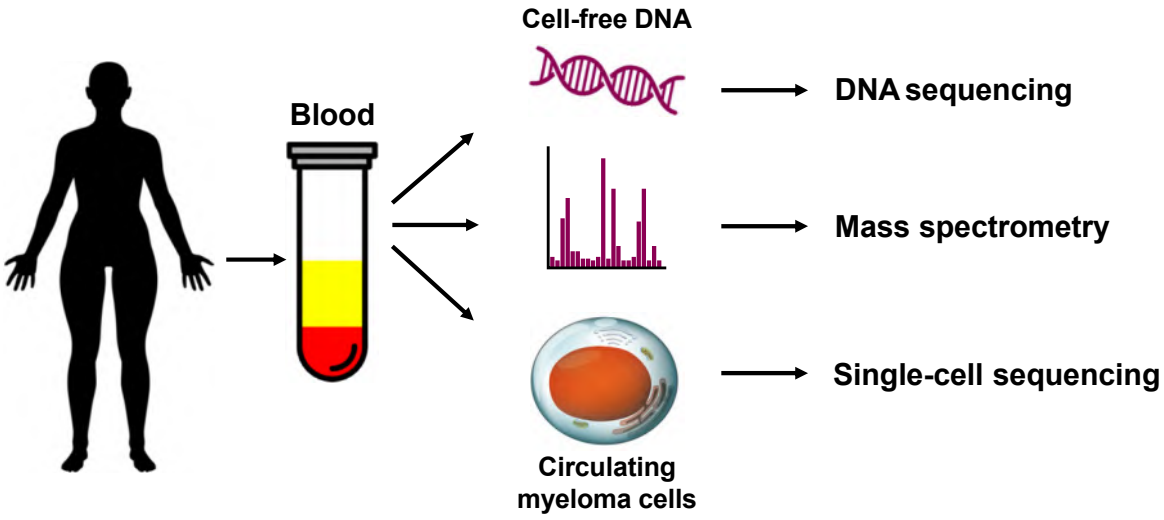
Three Types of MRD Blood Tests



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Blood-Based MRD Testing: Mass Spectrometry

Induction: KRd × 4 → Melphalan 200 mg/m^2 + ASCT → Consolidation: KRd × 14 → MRD → Maintenance: lenalidomide → MRD

Zajec M et al. *Clin Chem.* 2020;66:421.

Mass spectrometry (MS) is being evaluated as a method to detect free light chains (FLCs) in the blood as a potentially more sensitive test to detect MRD in patients after therapy. There are several different methods to do this.

A study was performed in patients with newly diagnosed myeloma who had both bone marrow (NGS) and blood (MS) MRD samples drawn at the same time.

In some cases, MS from the blood was able to detect disease when bone marrow testing was not—AND this identified patients who would later have disease progression.

MS may provide a useful alternative to bone marrow testing to detect MRD in patients and may even help identify patients at increased risk of early relapse if they are MRD negative but MS positive during maintenance therapy.

Derman BA et al. *Blood Cancer J.* 2021;11:19.

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Summary

- MRD is the deepest response after myeloma treatment, including bone marrow MRD and imaging MRD. Flow cytometry and NGS are the two most commonly used marrow MRD tests. Blood-based MRD is under investigation.
- MRD has been associated with longer progression-free and overall survival to predict lower risk of progression.
- MRD response–directed therapy is being assessed in clinical studies to explore how to guide treatment decisions in myeloma.
- MRD status is under investigation as an end point in clinical studies helping to expedite new drug approval in myeloma.

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Achieving MRD Negativity

Rafael Fonseca, MD
Mayo Clinic
Phoenix, Arizona

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MRD Negativity Achieved in Patients With NDMM by Various Regimens

	Combination therapy	ASCT	MR -negativity
Triplet regimen[1,2]	KRd 8 cycles	Yes	58%
	KRd 12 cycles	No	54%
	VRd ×6 cycles	Yes	20%
Quadruplet regimens[2,3]	VRd-daratumumab ×6 cycles	Yes	51%
	KRd-daratumumab ×8 cycles	No	71%

1. Gay F et al. *J Clin Oncol*. 2019;37: Abstract 8002. **2.** Voorhees PM et al. *Blood*. 2020;136:936. **3.** Landgren O et al. *JAMA Oncol*. 2021;7:862

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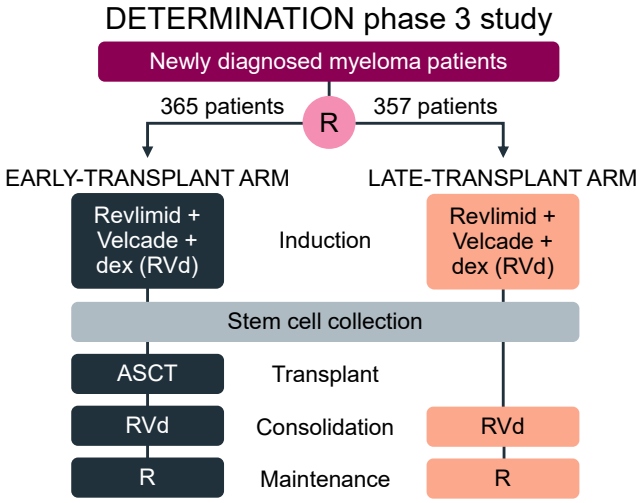
MRD Negativity Achieved in Patients With NDMM by Various Regimens



Richardson PG et al. *N Engl J Med*. 2022;387:132.

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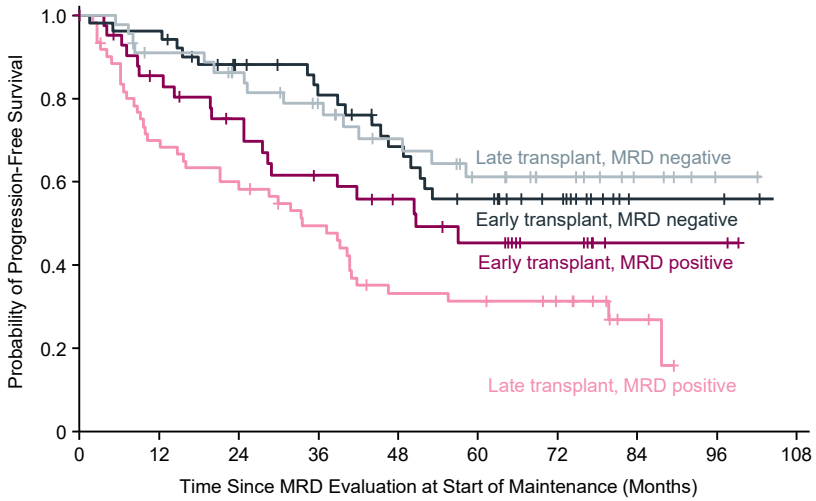
MRD Negativity Achieved in Patients With NDMM by Various Regimens

Patients who achieve MRD negativity following treatment experience longer remission than those who are still MRD positive after treatment.



MRD by next-generation sequencing (sensitivity 1×10^{-5})
Determination Study. Richardson PG et al. *N Engl J Med*. 2022;387:132.

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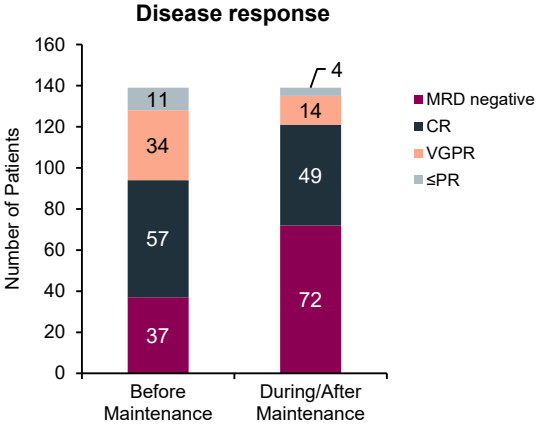
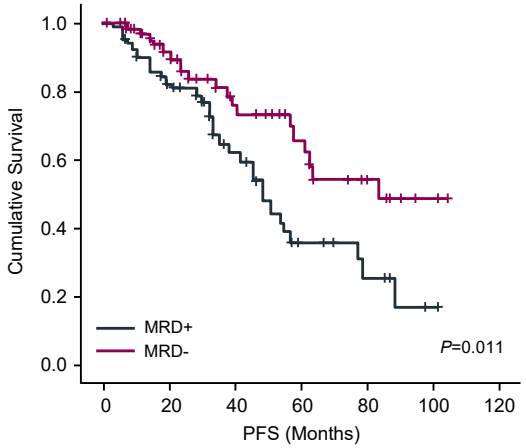
Revlimid Maintenance Therapy: Improves Depth of Response





At maximal response during or after maintenance treatment with Revlimid

Alonso R et al. *Blood Adv*. 2020;4:2163.

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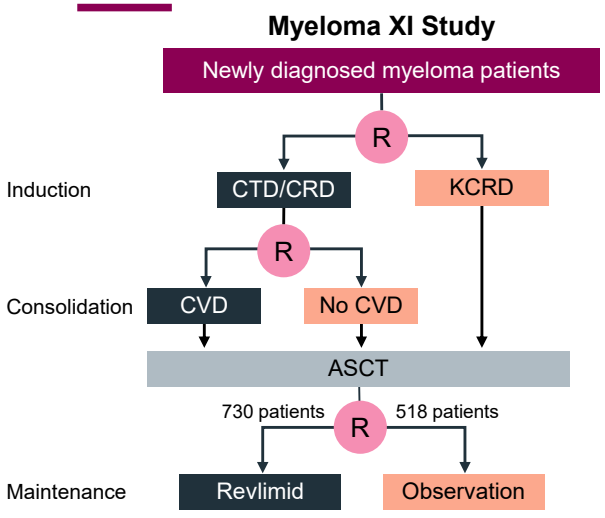
Maintenance Duration



PFS, progression-free survival

Pawlyn C et al. *Blood*. 2022;140. Abstract 570.

Median PFS (mos)	At time of randomization to maintenance therapy (median follow up 44.7 mos)
	All patients*
Revlimid	64
Observation	32
Hazard ratio	0.52
P Value	<0.001

*PFS benefit across all patient subgroups on Revlimid maintenance therapy: standard risk; molecular high risk, which included the presence of del(17p), gain(1q), t(4;14), t(14;16), or t(14;20); MRD positive; and MRD negative.

More evidence for the benefit of longer duration of Revlimid maintenance in patients who are MRD positive than MRD negative. And evidence of ongoing benefit beyond 2–3 years for patients with both standard- and high-risk disease.

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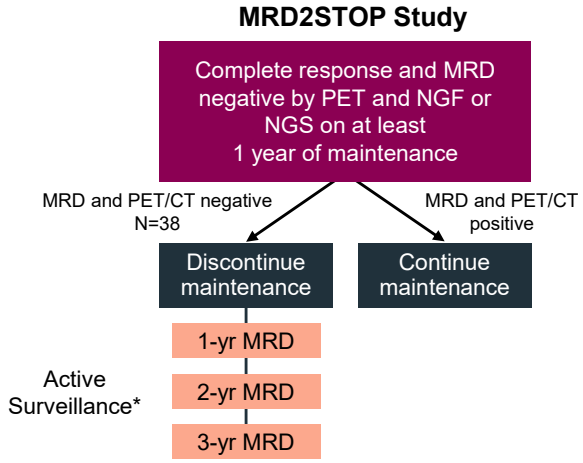
Using MRD Negativity to Guide Discontinuation of Maintenance Therapy



*MRD assessment performed with PET, flow cytometry (10^{-5}), NGS (10^{-6}), and CD138-selected NGS (10^{-7})

Derman BA et al. *Blood*. 2022;140. Abstract 870.

- After median follow-up of 14 months, 89% remain on study (5% with PD, 6% withdrew).
- MRD resurgence occurred in 13% of patients (2 patients had resurgence of M protein and disease progression).
- MRD negativity (at 10^{-6} and 10^{-7}) is sustained even after discontinuation of maintenance therapy.

MRD-guided discontinuation of maintenance may carry significant cost savings.

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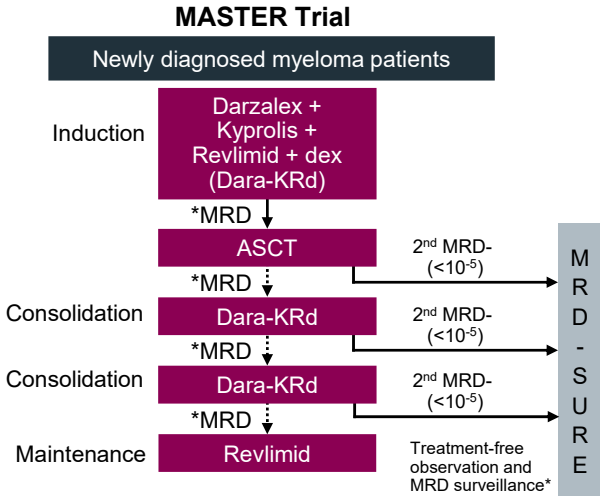
MRD Response-Adapted Consolidation and Treatment Cessation



*24 and 72 weeks after completion of therapy (by NGS)

Costa LJ et al. *Blood*. 2021;138. Abstract 481. Costa LJ et al. *J Clin Oncol*. 2021 Dec 13 [epub ahead of print].

- 80% of patients achieved MRD negativity (at <1 × 10^{-5}) and 66% achieved MRD negativity at <1 × 10^{-6}.
- 86% of patients achieved a CR or better.
- Responses deepened with each phase of treatment—and were similar in patients with zero, one, or two or more high-risk genetic abnormalities.
- ASCT increased the rates of MRD negativity following induction therapy, benefitting patients with highest-risk disease features.

Nearly all patients with no or only one high-risk genetic abnormality and confirmed MRD negativity had no disease progression or MRD resurgence since stopping treatment.

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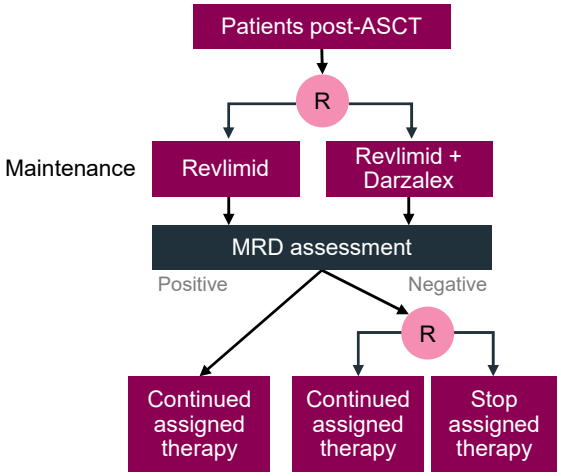
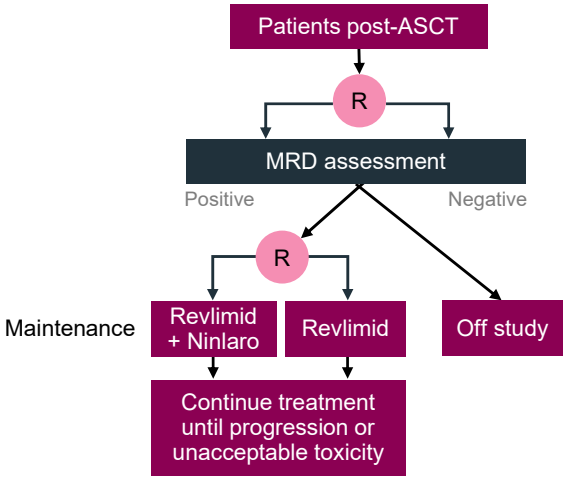
Ongoing Studies Using MRD Results to Direct Therapy

Phase 3 DRAMMATIC Study[1]



Phase 3 OPTIMUM Study[2]



1. https://clinicaltrials.gov/ct2/show/NCT04071457. **2.** https://clinicaltrials.gov/ct2/show/NCT03941860.

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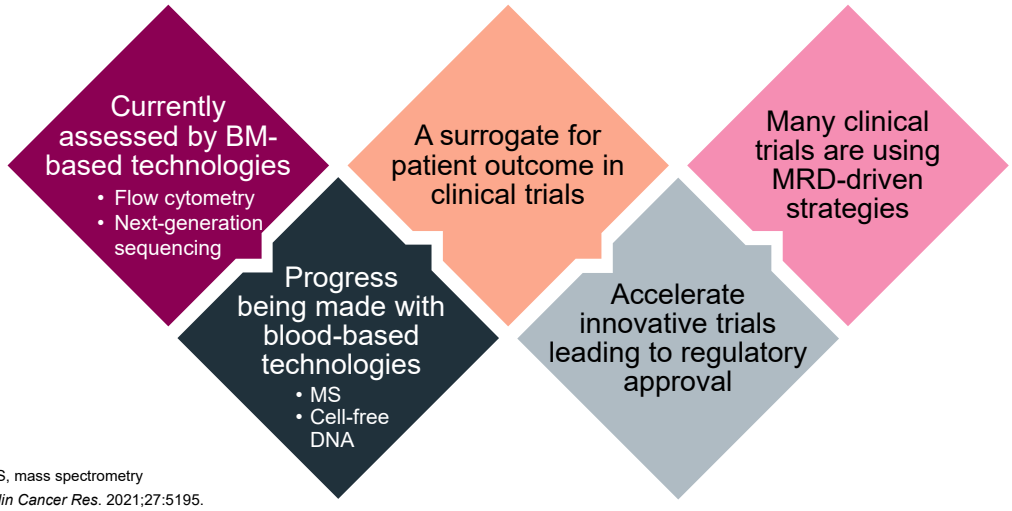
MRD Is Important for Clinical Care and New Drug Registration



BM, bone marrow; MS, mass spectrometry

Anderson KC et al. *Clin Cancer Res*. 2021;27:5195.
Costa LJ et al. *Leukemia*. 2021;35:18.

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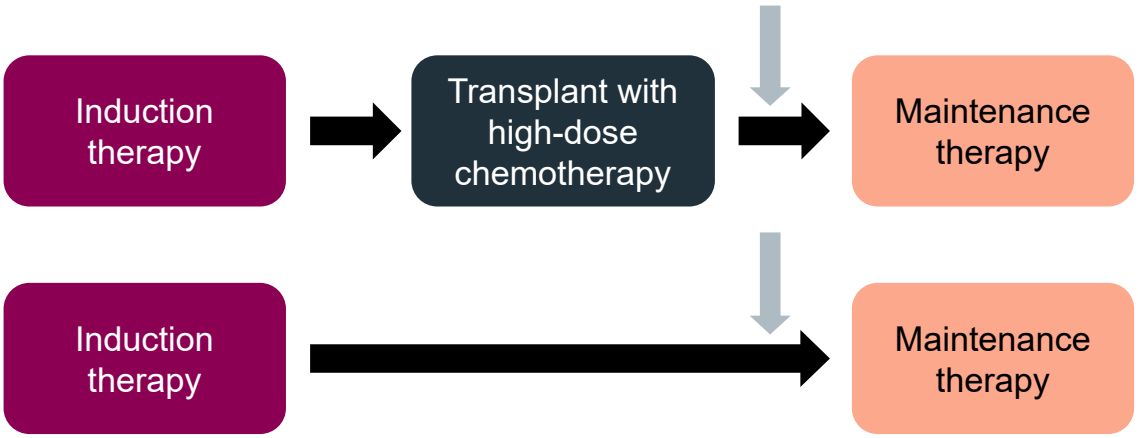
Optimal Timing of MRD Testing for Newly Diagnosed Multiple Myeloma



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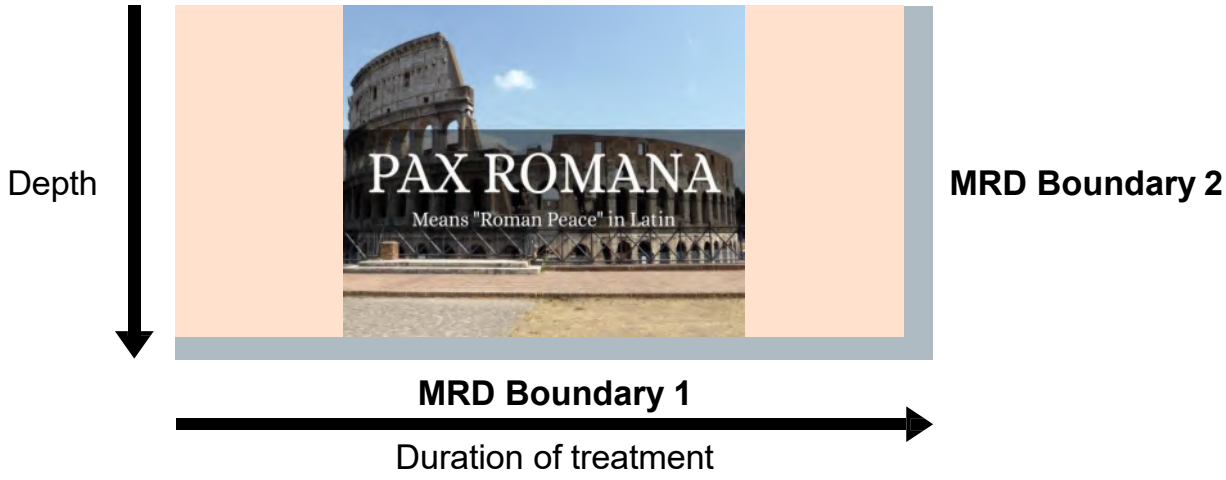
MRD Isn't Everything; It's the Only Thing!



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ALL-Like Myeloma and FL-Like Myeloma

High-risk MM

Test Results

Minimal Residual Disease (MRD) Status	Estimated Myeloma Molecules per Million Cells
NEGATIVE	0.0

Interpretation

The sample is NEGATIVE for the presence of myeloma gene rearrangements. Myeloma gene rearrangements were previously identified in an ID sample (December 24, 2015, Accession No. 205825). The previously identified myeloma gene rearrangements are NOT present in the current MRD sample, which is consistent with the sample being NEGATIVE for myeloma cells. The results of this test should be interpreted in the complete clinical context, including the patient's clinical presentation and current treatment regimen.

Hyperdiploid

Test Results

Minimal Residual Disease (MRD) Status	Estimated Myeloma Molecules per Million Cells
POSITIVE	174

Interpretation

The sample is POSITIVE for the presence of myeloma gene rearrangements. Myeloma gene rearrangements were previously identified in an ID sample (November 11, 2016, Accession No. 210889). The presence of myeloma gene rearrangements is consistent with the sample being POSITIVE for myeloma cells. The results of this test should be interpreted in the complete clinical context, including the patient's clinical presentation and current treatment regimen.

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Key Points

- Modern combination therapies result in increasingly higher MRD negativity rates, which are associated with better clinical outcomes (progression-free survival).
- To determine MRD status, patients need easy access to sensitive, reliable MRD assays that can be used in the standard-of-care setting.
- In the future, treatment strategies may be driven by increased access to modern combination therapies paired with novel FDA-approved MRD assays.
- Sustained MRD negativity could become the central definition of a cure for multiple myeloma in the future.

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MULTIPLE MYELOMA Research Foundation | 25th ANNIVERSARY

Questions & Answers

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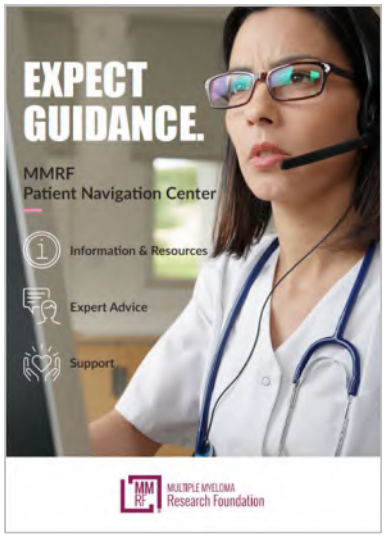
MMRF Patient Resources



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Myeloma Mentors®

Myeloma Mentors® allows patients and caregivers the opportunity to connect with trained mentors. This is a phone-based program offering an opportunity for a patient and/or caregiver to connect one-on-one with a trained patient and/or caregiver mentor to share his or her patient journeys and experiences.

No matter what your disease state—smoldering, newly diagnosed, or relapsed/refractory—our mentors have insights and information that can be beneficial to both patients and their caregivers.

Contact the Patient Navigation Center at 888-841-6673 to be connected to a Myeloma Mentor or to learn more.

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To **Learn More** & **Find Your Event today**!
www.theMMRF.org/Events

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Upcoming Patient Education Events
Save the Date

Topic	Date and Time (ET)	Speakers
Minimal Residual Disease FAQs Livestream	Friday, August 4 1:00 – 2:00 PM	Luciano J. Costa, MD, PhD
Learn Your Labs FAQs Livestream	Friday, August 9 2:00 – 3:00 PM	Hans C. Lee, MD Rebecca Lu, NP

For more information or to register,
visit **themmrf.org/resources/education-program**

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Resources

- Resource tab includes
  - Speaker bios
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Need help with travel to a clinical study?

- The MMRF has partnered with the Lazarex Cancer Foundation to help provide more equitable access to clinical studies for multiple myeloma patients
- This partnership is one facet of the MMRF's commitment to improve diversity and representation in myeloma clinical studies
- MMRF has provided $100,000 over 2 years to Lazarex to fund travel, lodging, and food for patients (and a travel companion) so that they can participate in clinical studies that are appropriate for them
- Patients are funded according to income guidelines and will be reimbursed for allowed expenses
- For more information on this program and to be connected with Lazarex, call our Patient Navigation Center at 1-888-841-6673

It's About Living
Lazarex
CANCER FOUNDATION

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Thank you!

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