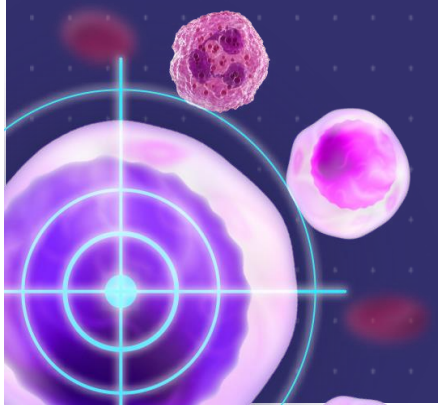
Treating elderly and frail patients with MM: Cure *versus* disease control

Vincent Rajkumar

Mayo Clinic, Rochester, US



Treating elderly and frail patients with MM: Cure versus disease control

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Scottsdale, Arizona

Rochester, Minnesota

Jacksonville, Florida

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No conflicts to disclose

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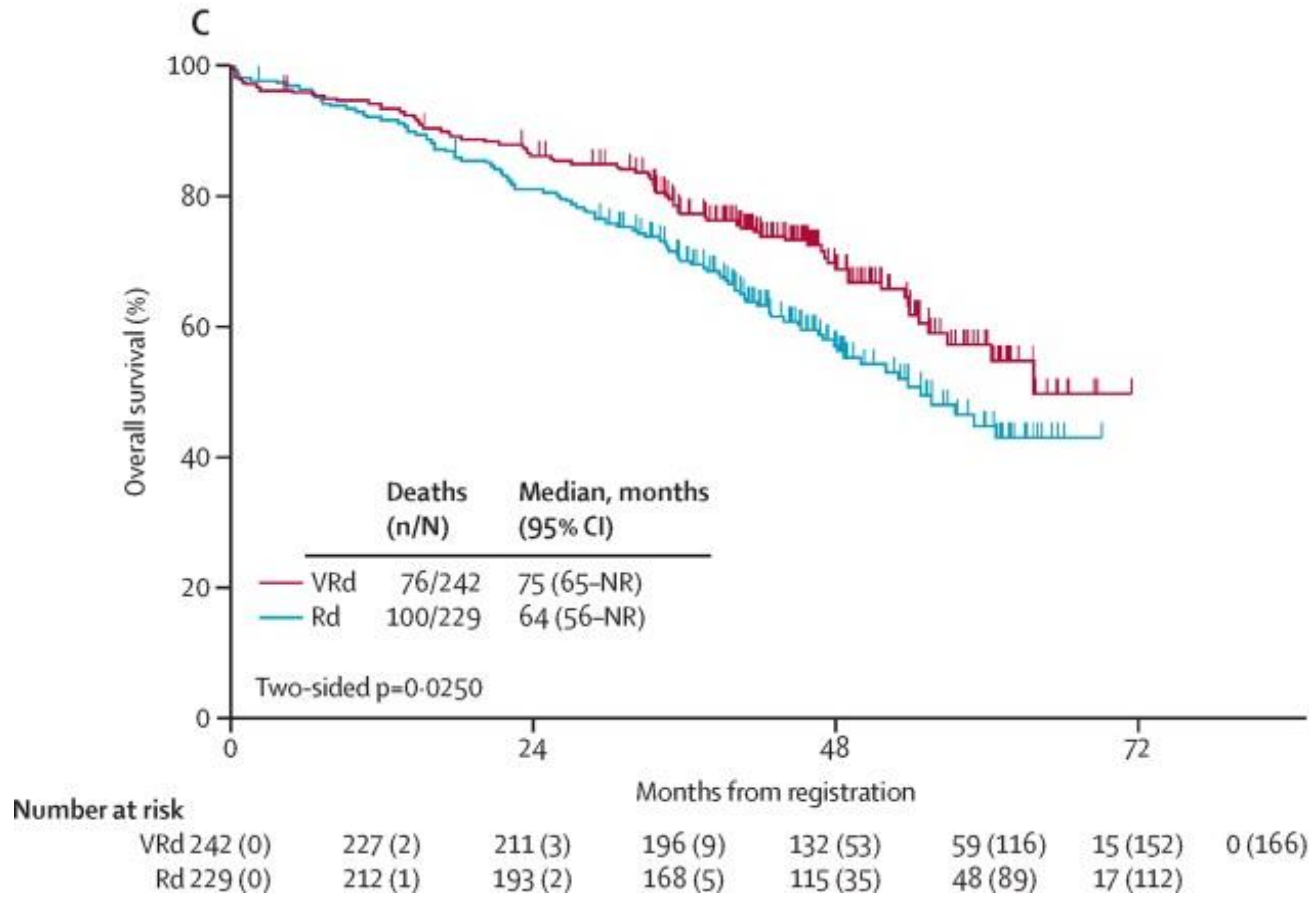
S0777 Trial: VRd vs Rd

Overall Survival



Durie et al. The Lancet 2017 389, 519-527DOI: (10.1016/S0140-6736(16)31594-X)

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Age >75

- SWOG S0777 trial VRd vs Rd
- PFS and OS Age <65, 65–75, >75 years
- VRd was superior in Age >75 years
  - Median PFS 39 *vs* 20 months
  - Median OS 63 *vs* 31 months (P<0.05)

***Durie et al. The Lancet* 2017 389, 519-527DOI: (10.1016/S0140-6736(16)31594-X)**

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Key Questions: Cure or Control

- **Can we improve on the VRd triplet?**
  - Carfilzomib based (eg., KRd)
  - Monoclonal Antibody based (eg., DRd)

- **Should we use a quadruplet?**
  - Cost
  - Toxicity

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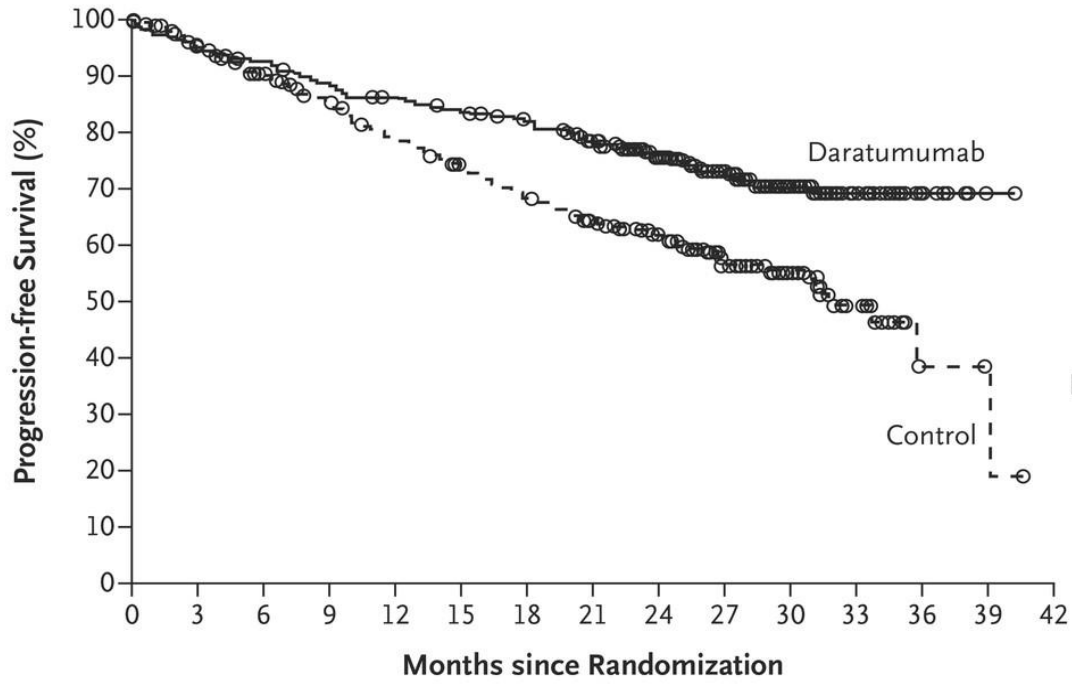
Dara-Rd vs Rd (MAIA trial)
Progression-Free Survival



	No. of Patients	Median Progression-free Survival
		mo
Daratumumab	368	Not reached
Control	369	31.9

Hazard ratio for disease progression or death, 0.56 (95% CI, 0.43–0.73)
P<0.001

No. at Risk

Daratumumab	368	347	335	320	309	300	290	271	203	146	86	35	11	1	0
Control	369	332	307	280	254	236	219	200	149	94	50	18	3	2	0

T Facon et al. N Engl J Med 2019;380:2104-2115.

The NEW ENGLAND JOURNAL of MEDICINE

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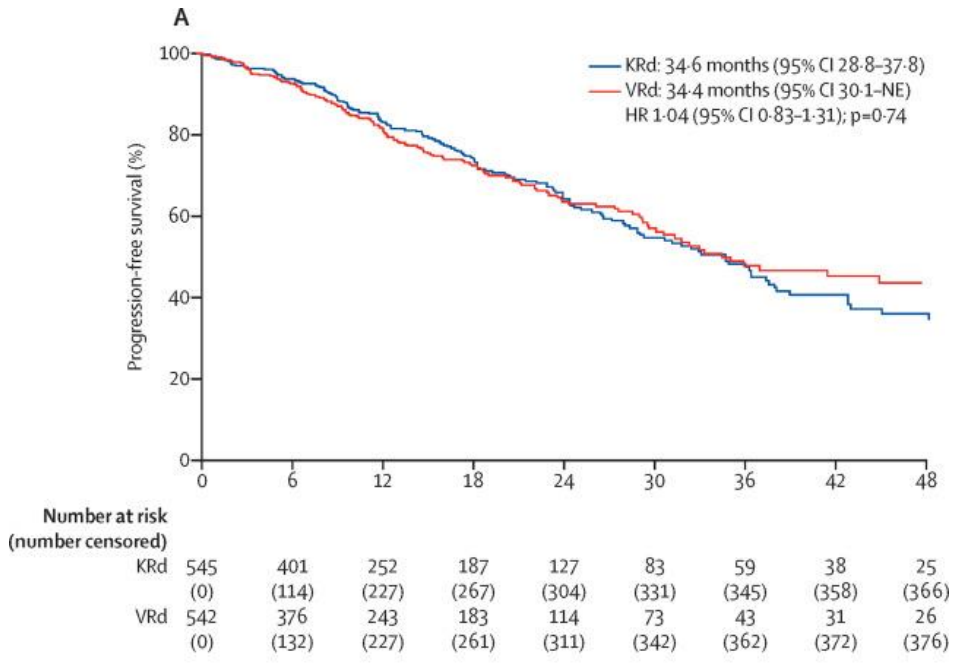
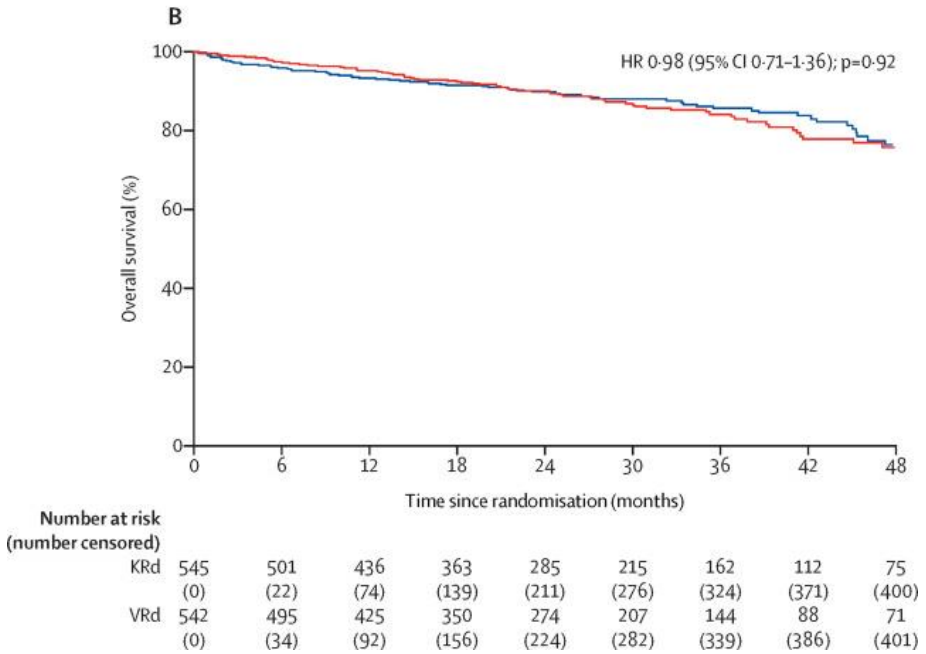
KRd vs VRd (ENDURANCE TRIAL)





Kumar S. Lancet Oncol 2020

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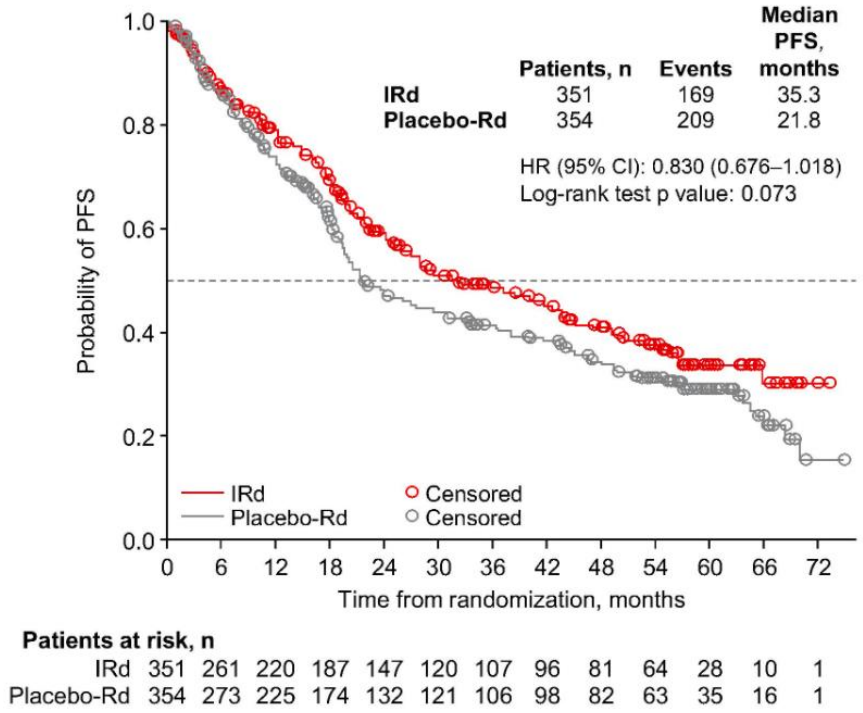
TOURMALINE-MM2 trial: Ixazomib-Rd vs placebo-Rd

- Data cutoff: Dec 2, 2019.
- Median follow-up for PFS
  - IRd: 53.3 months
  - Placebo-Rd: 55.8 months
- Median DOT: 20 cycles in each arm
  - 54% of patients in the IRd arm and 54% in the placebo-Rd arm entered Cycle 19.
  - Mean relative dose intensity for all agents was similar between arms.



CI, confidence interval; DOT, duration of treatment; HR, hazard ratio; IRd, ixazomib, lenalidomide, dexamethasone; PFS, progression-free survival; Rd, lenalidomide, dexamethasone; vs, versus.

Facon T, et al. Abstract #551. 62nd ASH Annual Meeting & Exposition; Dec 7, 2020; Virtual. NCT01850524

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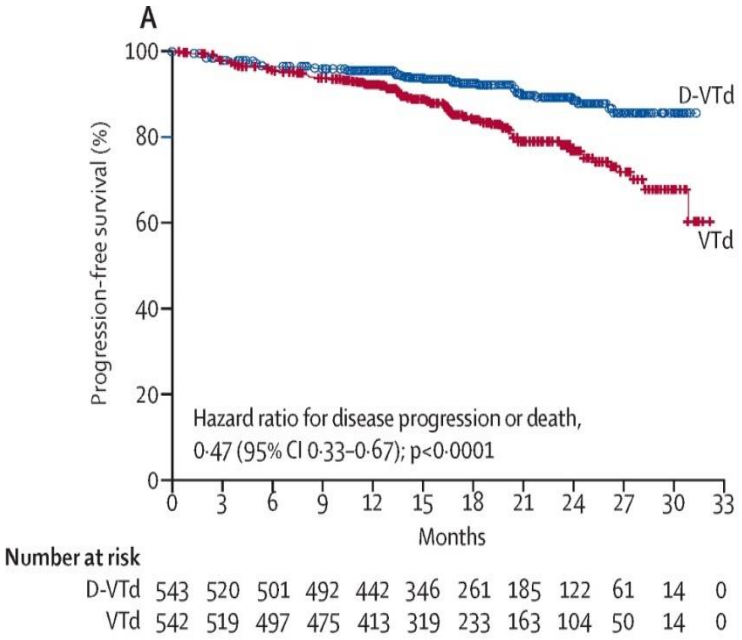
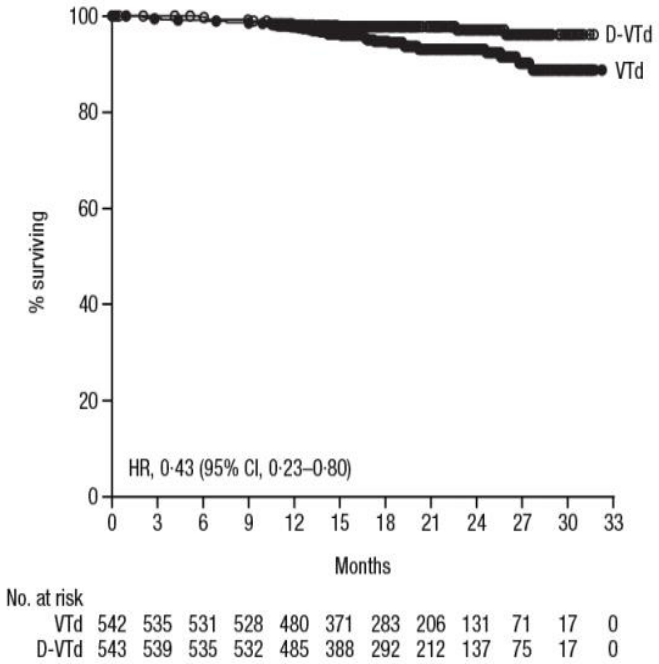
CASSIOPEIA TRIAL: Dara-VTd vs VTd Quadruplets as Initial Therapy





The Lancet 2019 394, 29-38DOI: (10.1016/S0140-6736(19)31240-1)

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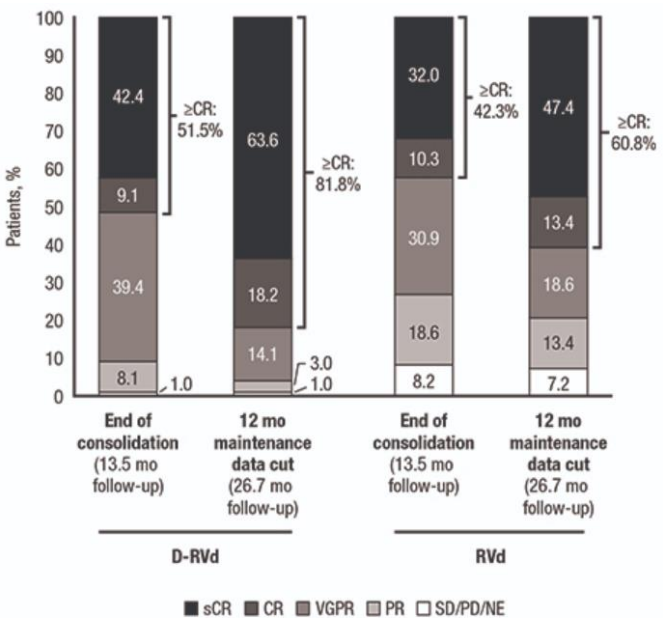
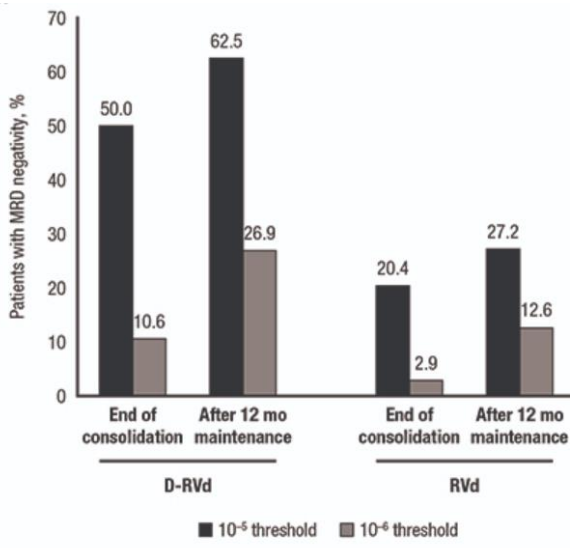
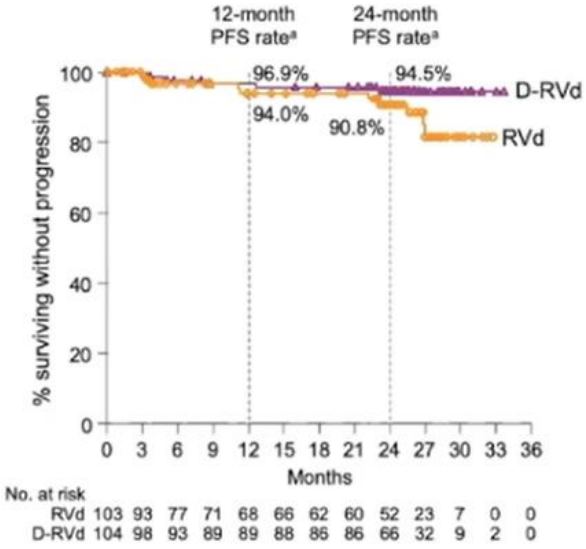
GRIFFIN trial: D-RVd *vs* RVd

D-RVd in transplant-eligible NDMM improves depth of response and MRD negativity (10^{-5}) over time.







CR, complete response; D-RVd, daratumumab, lenalidomide, bortezomib, dexamethasone; MRD, minimal residual disease; NDMM, newly diagnosed multiple myeloma; NE, not evaluated; No, number; PD, progressive disease; PR, partial response; RVd, lenalidomide, bortezomib, dexamethasone; sCR, stringent complete response; SD, stable disease; VGPR, very good partial response; *vs*, versus.

Kaufman JL, et al. Abstract #549. 62nd ASH Annual Meeting & Exposition; Dec 7, 2020; Virtual. NCT02874742

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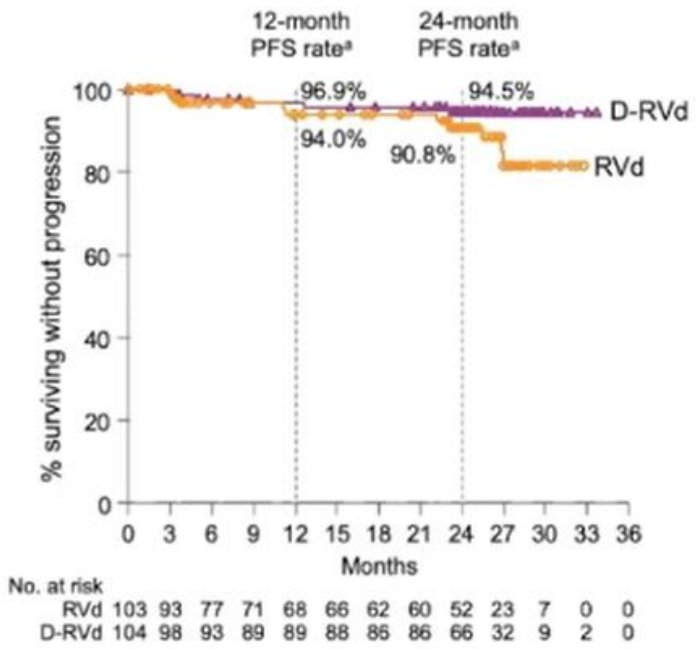
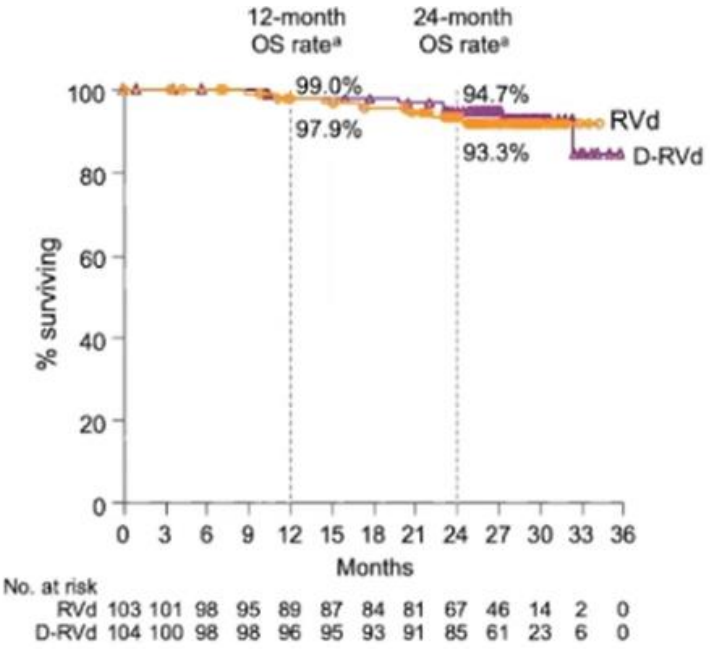
GRIFFIN trial: D-RVd *vs* RVd

With a median follow-up of 27.4 months, PFS and OS were not yet reached.





D-RVd, daratumumab, lenalidomide, bortezomib, dexamethasone; No, number; OS, overall survival; PFS, progression-free survival; RVd, lenalidomide, bortezomib, dexamethasone; *vs*, versus.

Kaufman JL, et al. Abstract #549. 62nd ASH Annual Meeting & Exposition; Dec 7, 2020; Virtual. NCT02874742

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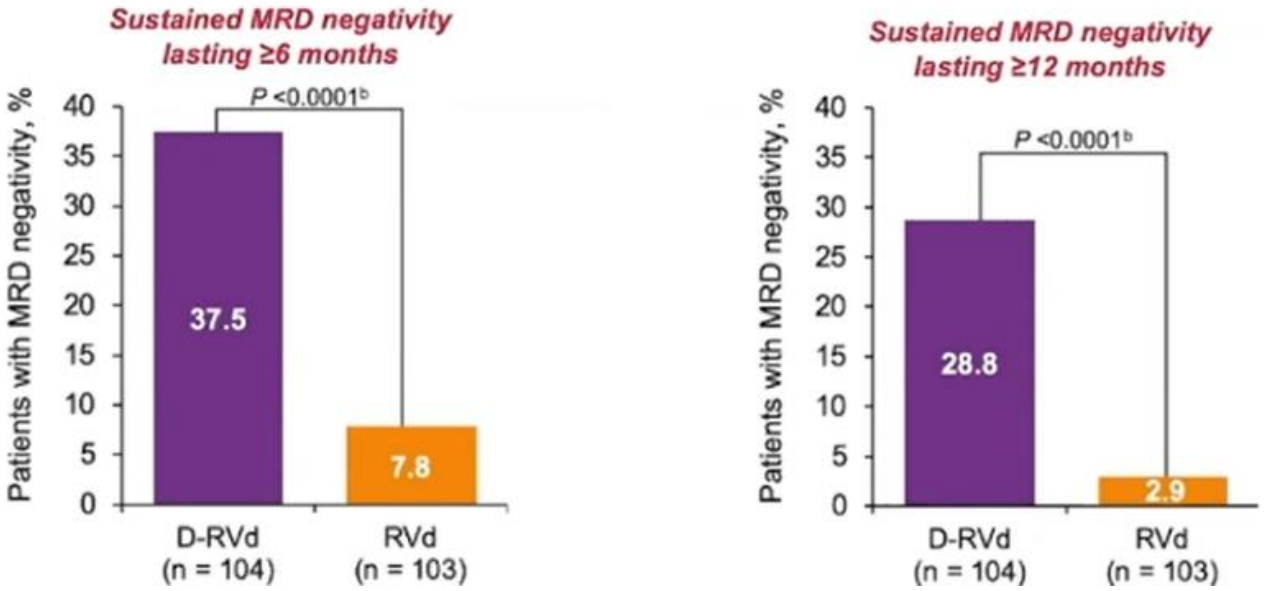
D-RVd in transplant-eligible NDMM improves MRD negativity (10^{-5}) over time.



CR, complete response; D-RVd, daratumumab, lenalidomide, bortezomib, dexamethasone; MRD, minimal residual disease; NE, not evaluated; NDMM, newly diagnosed multiple myeloma; No, number; PD, progressive disease; PR, partial response; RVd, lenalidomide, bortezomib, dexamethasone; sCR, stringent complete response; SD, stable disease; VGPR, very good partial response; *vs*, versus.

Kaufman JL, et al. Abstract #549. 62nd ASH Annual Meeting & Exposition; Dec 7, 2020; Virtual. NCT02874742

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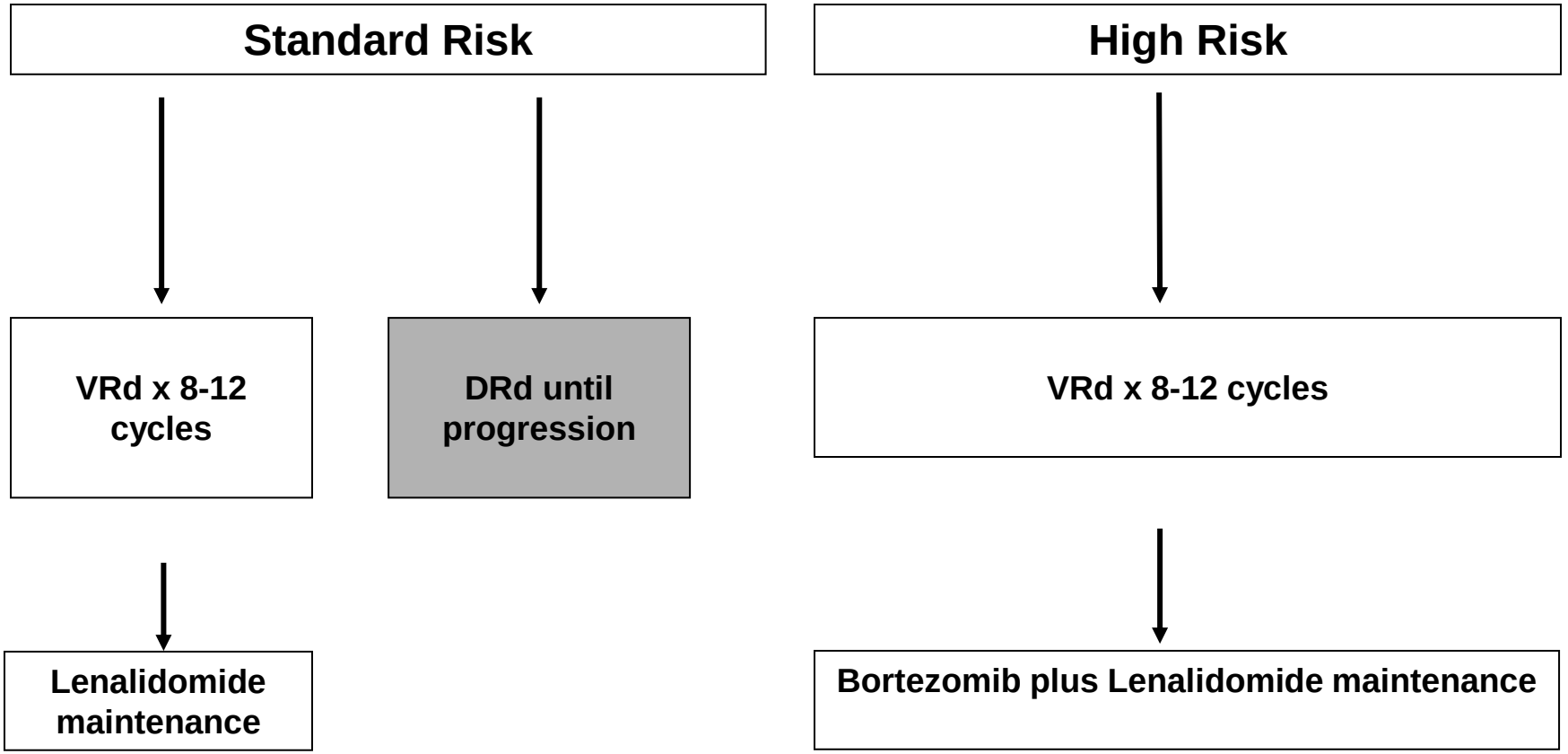
Newly Diagnosed Myeloma: Transplant Ineligible



Rajkumar SV. Blood Cancer J. 2020

Cure *versus* control

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Key considerations

- Definition of cure
- Distinguishing our desire for cure from whether we are already there
- Distinguishing our goal in clinical trials (with informed consent) versus adventurous recommendations of unproven therapy in clinical practice (based on hope)
- How can we achieve cure?
- How can we achieve good disease control?

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Mayo Clinic Proceedings

A peer-reviewed medical journal sponsored by Mayo Clinic and authored by physicians worldwide

October 2008, Volume 83, Number 10 [Table of Contents]

COMMENTARY

Treatment of Myeloma: Cure vs Control

S. Vincent Rajkumar, MD

Although not often openly acknowledged, "cure vs control" is the dominant philosophical difference behind many of the strategies, trials, and debates related to the management of myeloma. Should we treat patients with myeloma with multidrug, multitransplant combinations with the goal of potentially curing a subset of patients, recognizing that the risk of adverse events and effect on quality of life will be substantial? Or should we address myeloma as a chronic incurable condition with the goal of disease control, using the least toxic regimens, emphasizing a balance between efficacy and quality of life, and reserving more aggressive therapy for later?

when it was found to prolong survival compared with conventional chemotherapy.[5-7] Subsequently, bisphosphonates were found to be effective in decreasing the incidence of bone lesions.[8,9] In the past decade, thalidomide,[10] bortezomib,[11-13] and lenalidomide[14,15] emerged as effective agents for the treatment of myeloma, producing spectacular results in combination with other known agents in terms of response rate, CR rate, progression-free survival (PFS), and (more recently) overall survival. Numerous combinations have been developed, resulting in a veritable alphabet soup of clinical trials,[16] and drug combinations are vying with each other for the highest response rate (and promi-

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What is cure?

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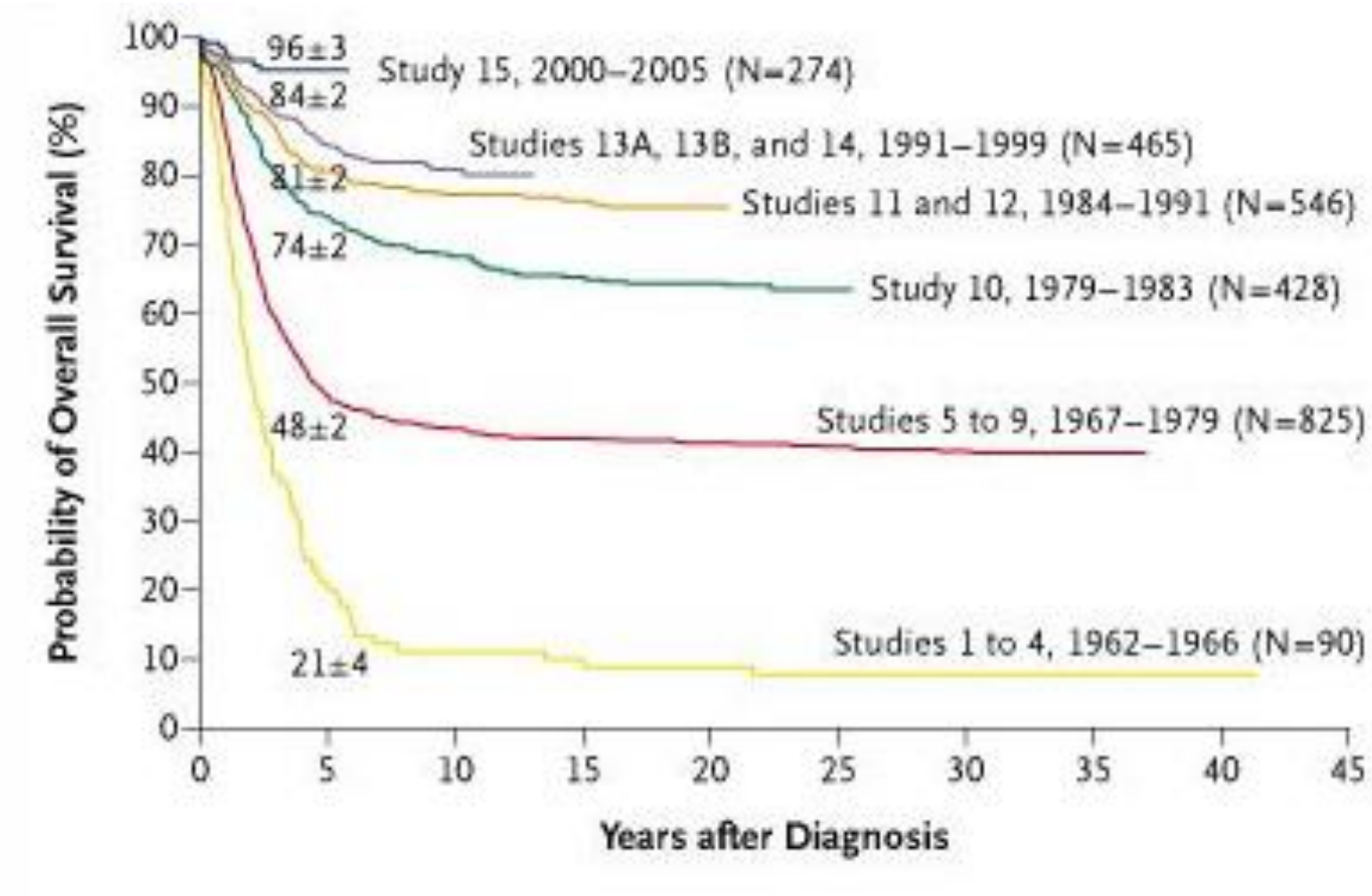
ALL



Pui et al. N Engl J Med 2006; 354:166-178

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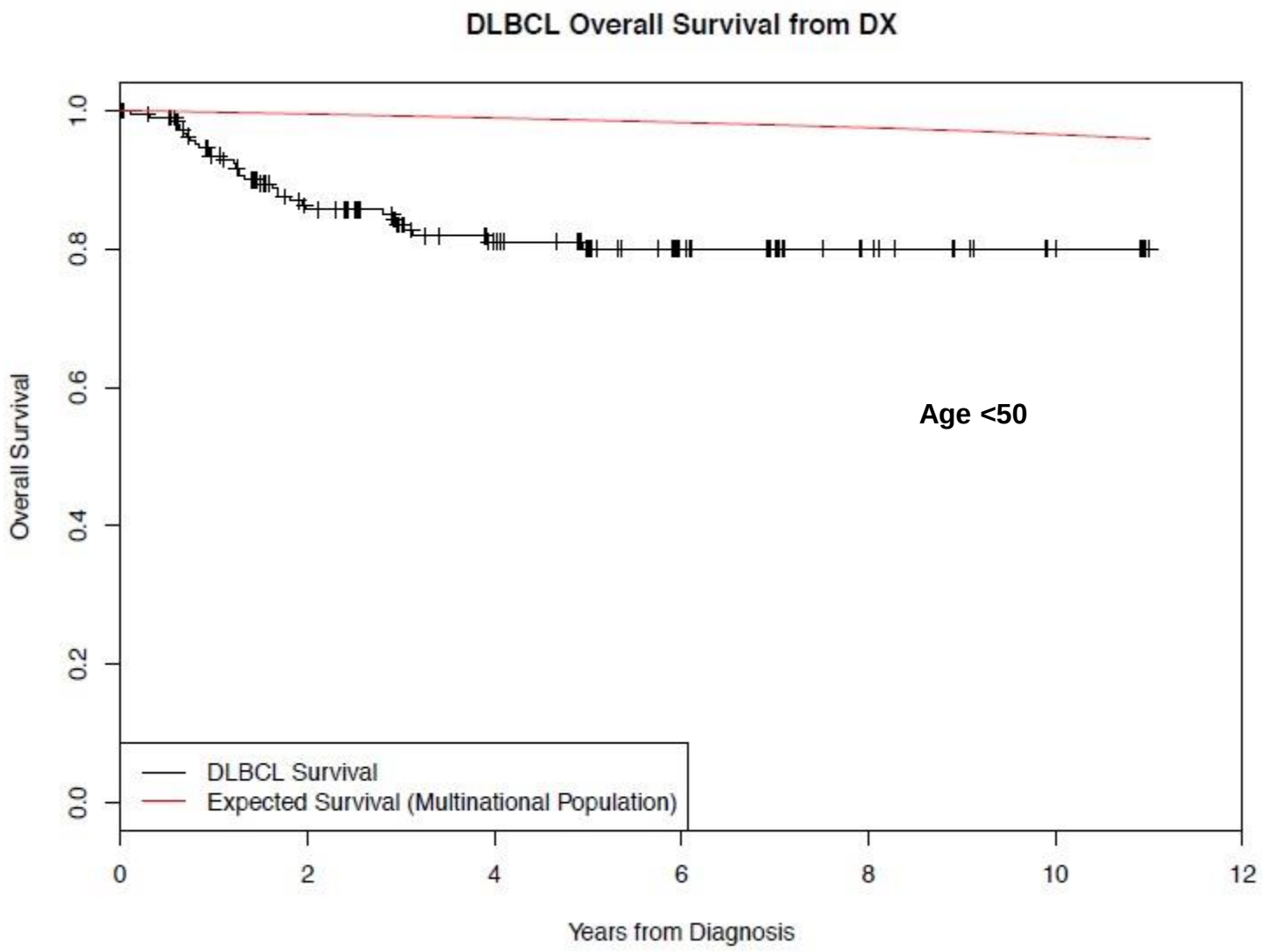

Ravi P…..Rajkumar SV. Blood Cancer J 2018 Feb 28;8(3):26

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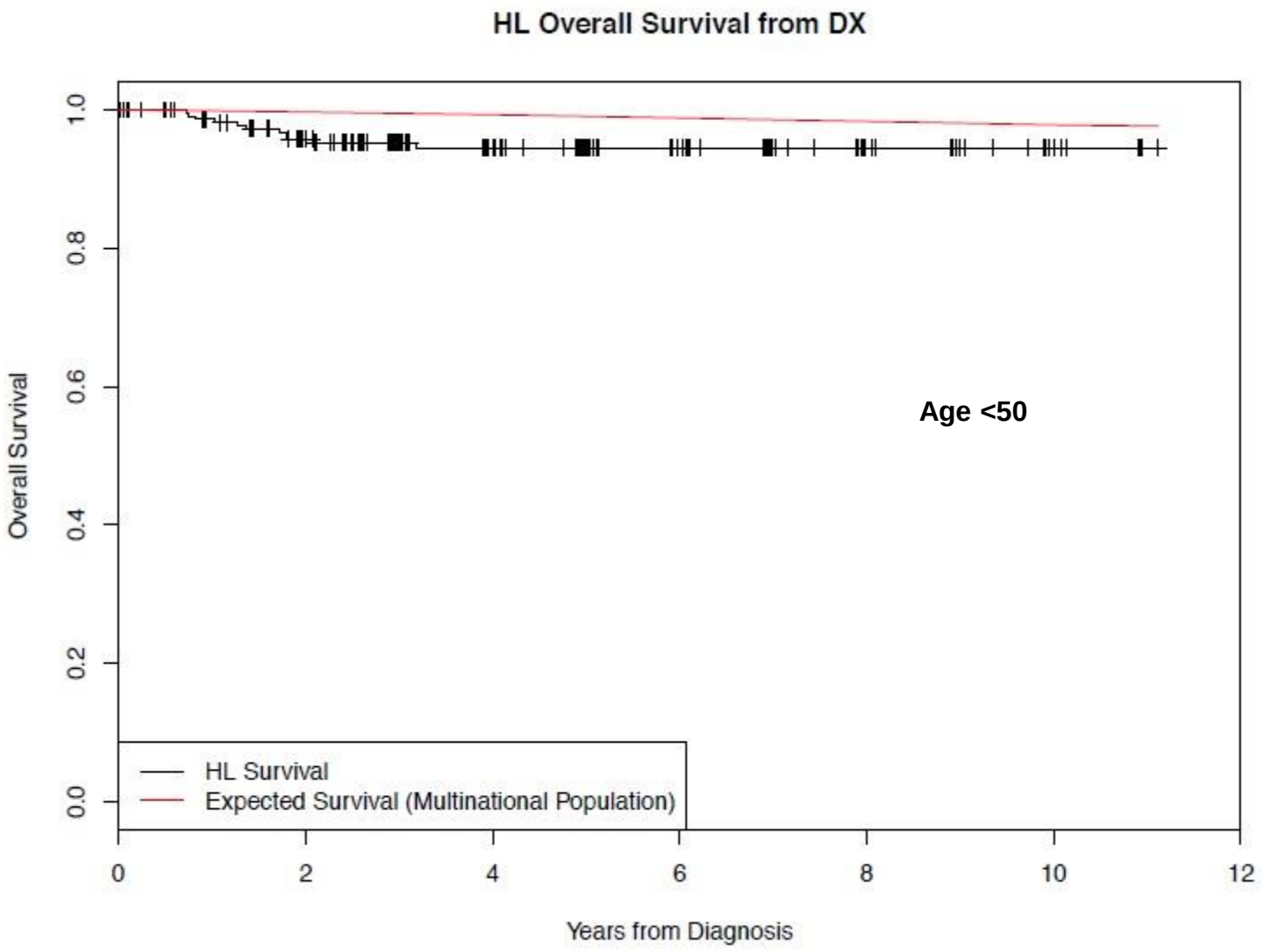

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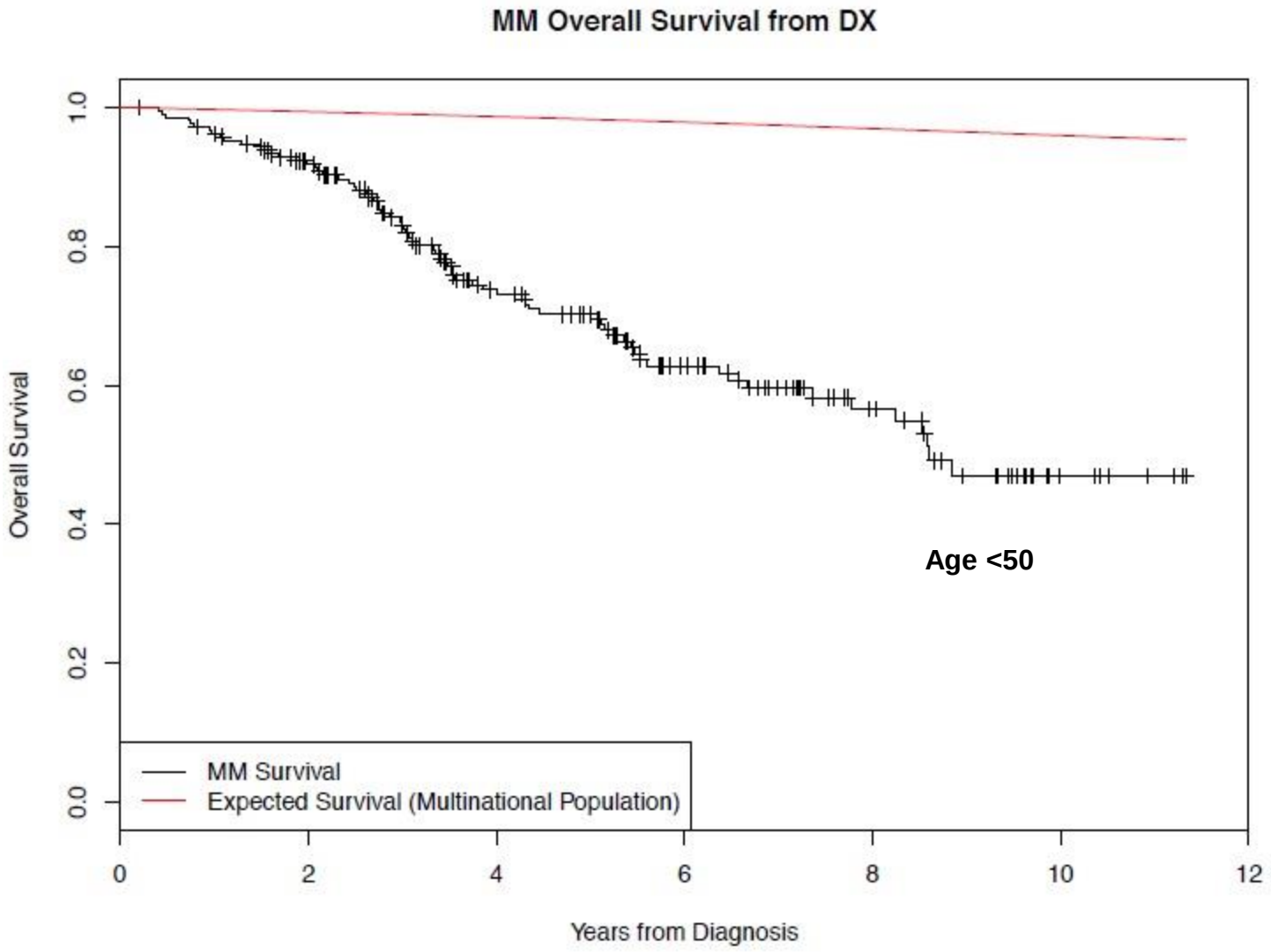

Ravi P…..Rajkumar SV. Blood Cancer J 2018 Feb 28;8(3):26

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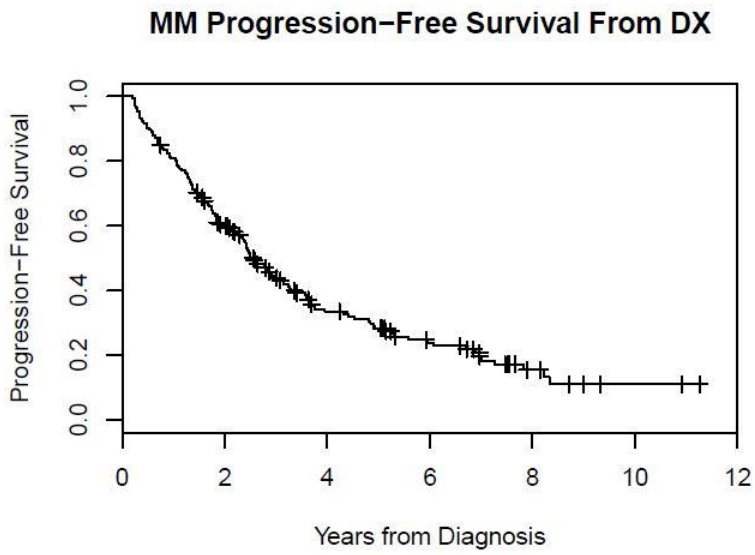
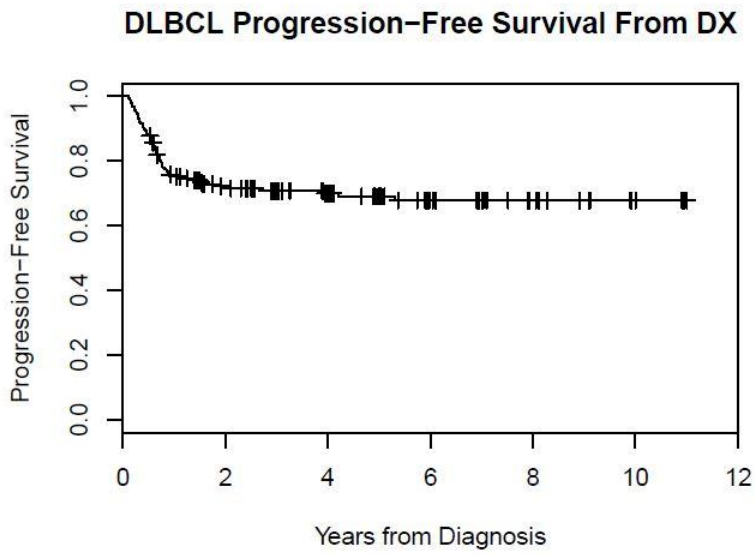
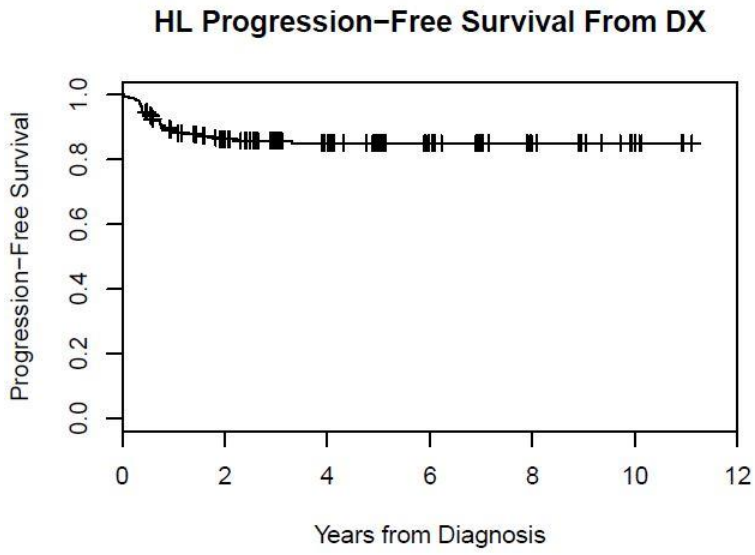
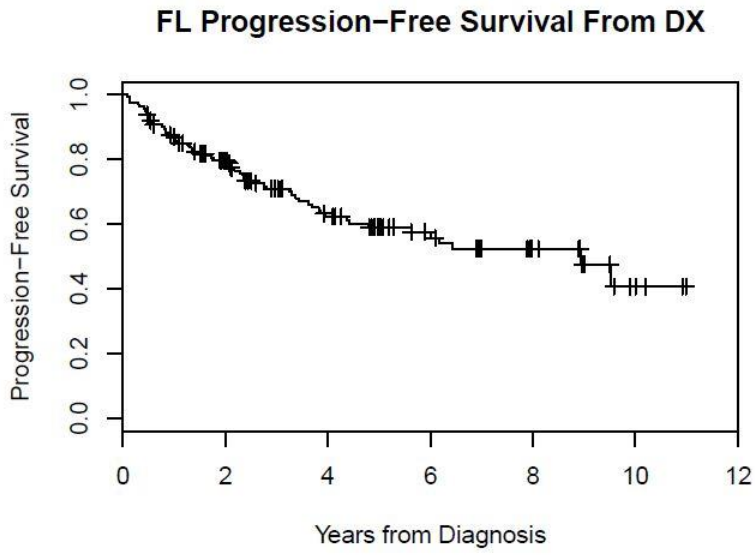
Age <50









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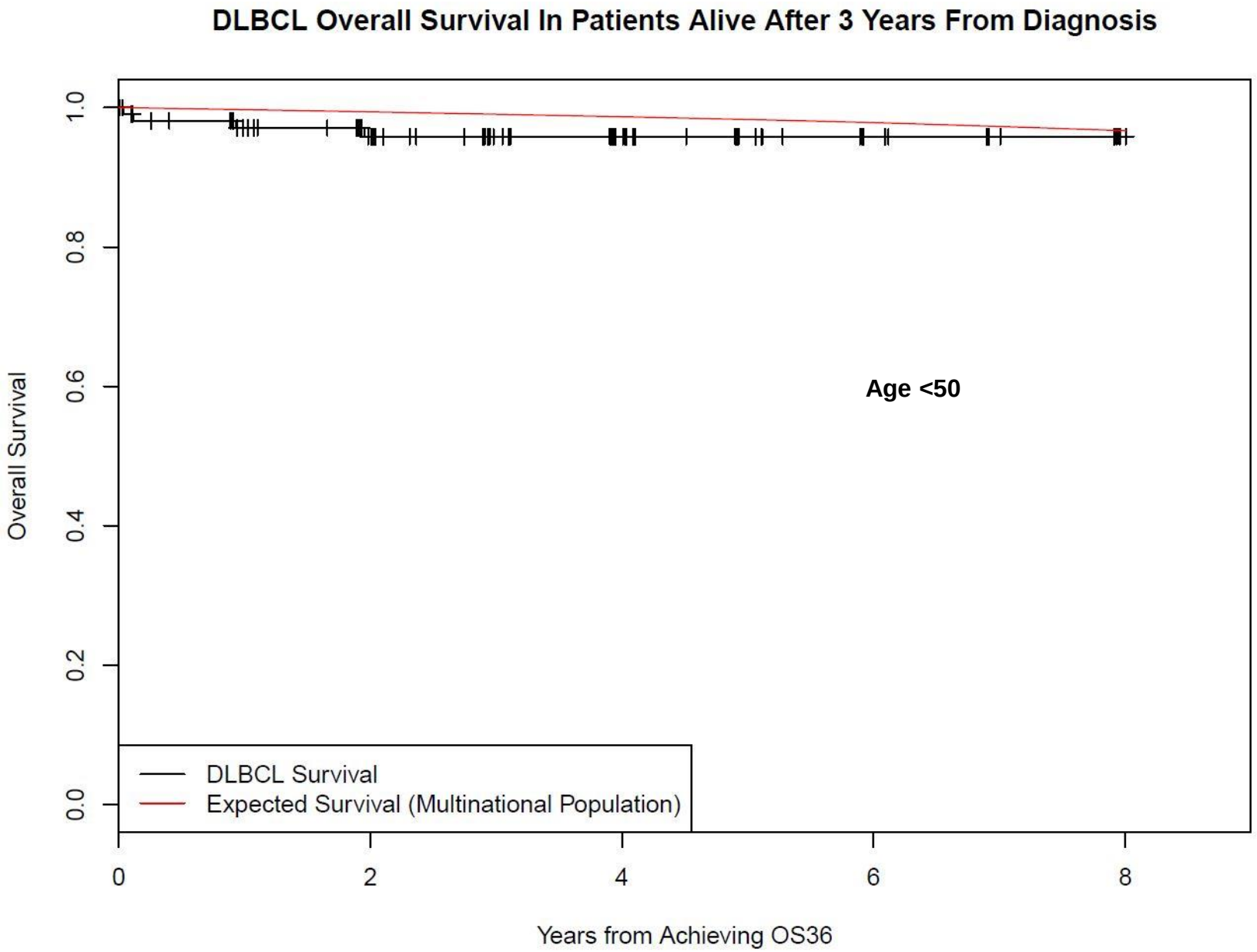

Ravi P…..Rajkumar SV. Blood Cancer J 2018 Feb 28;8(3):26

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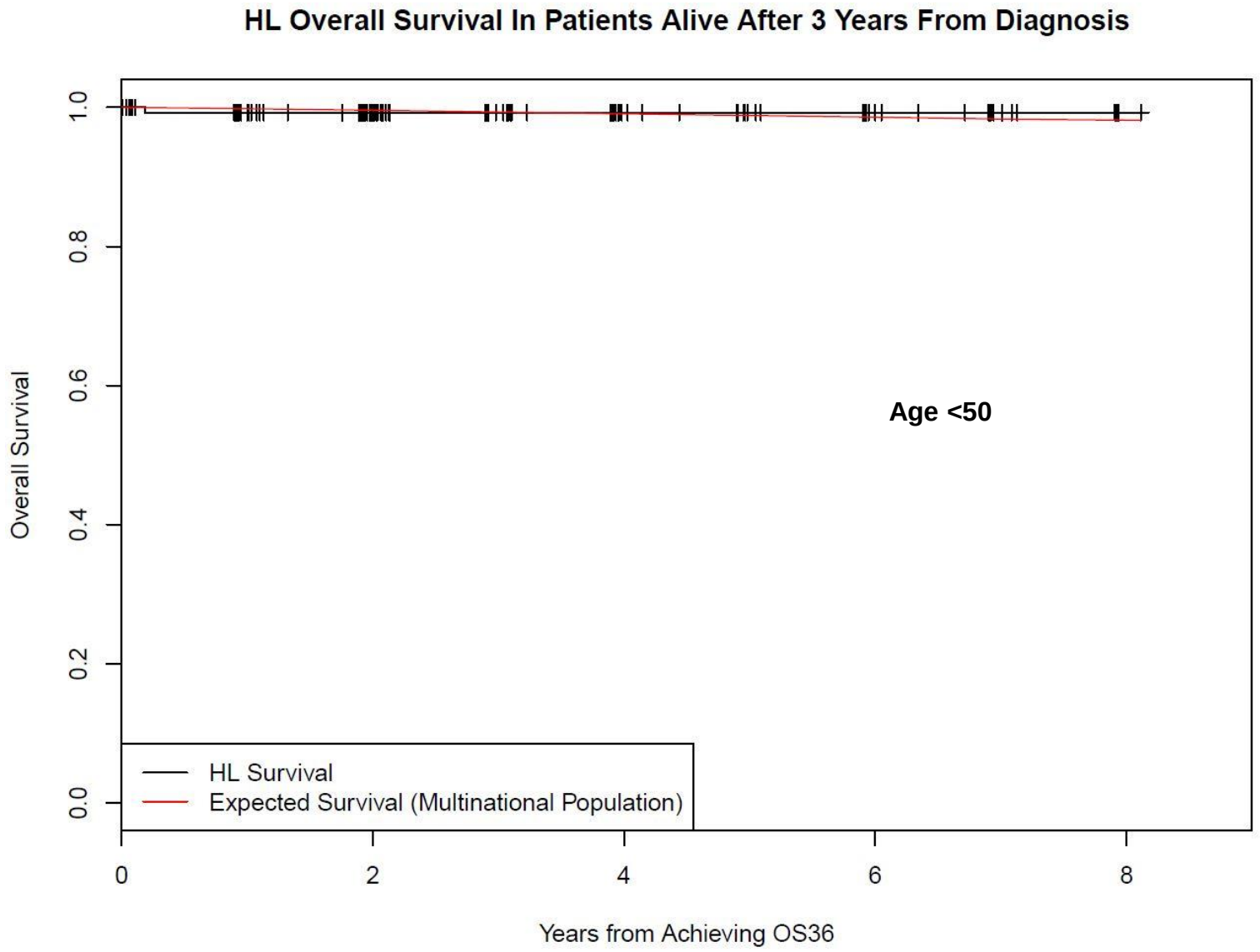

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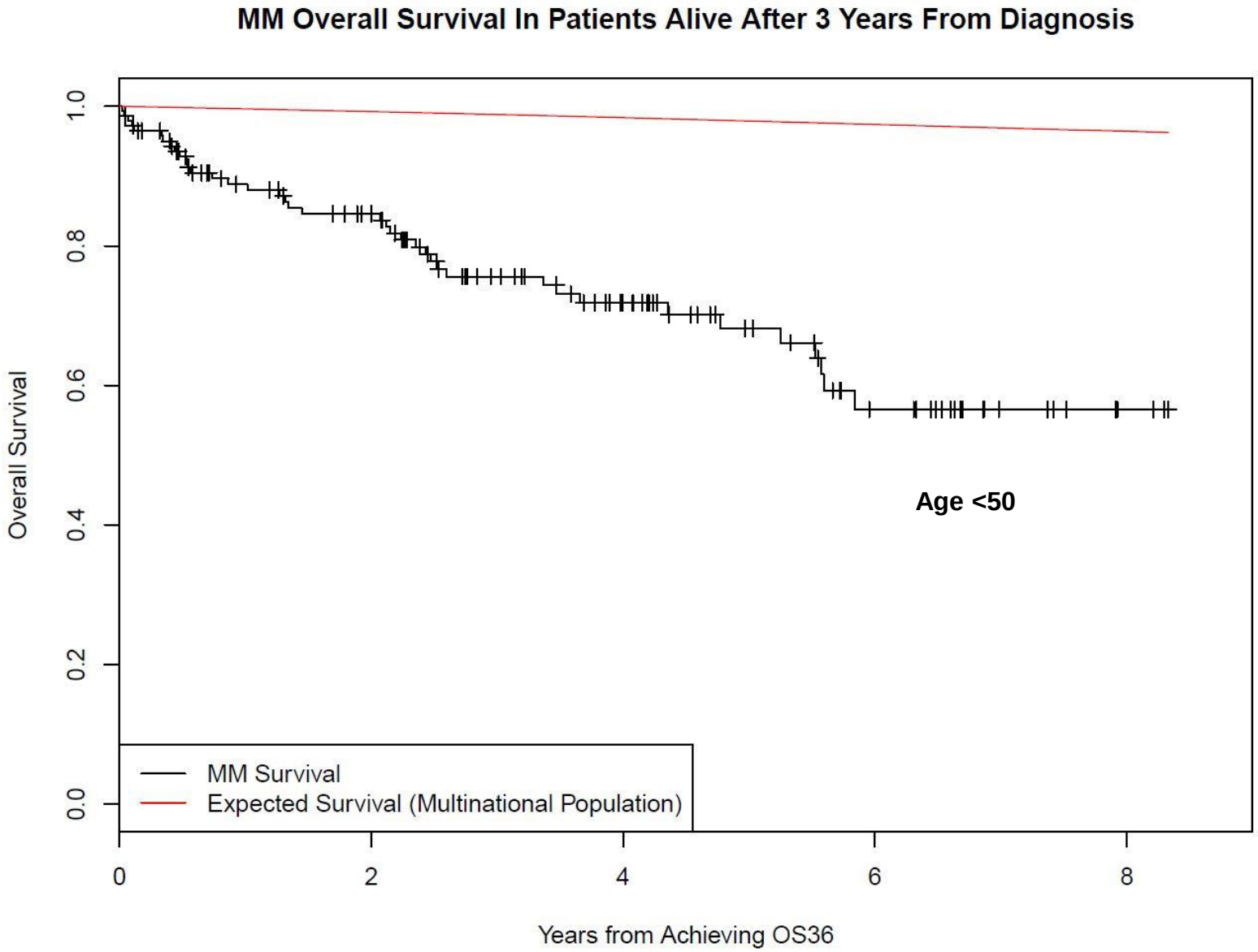

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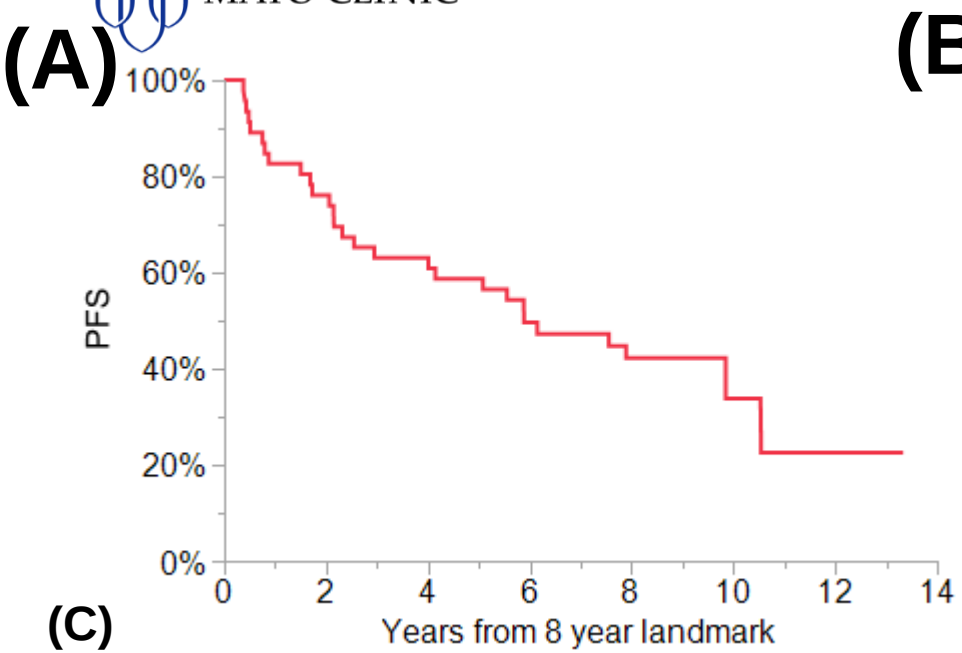

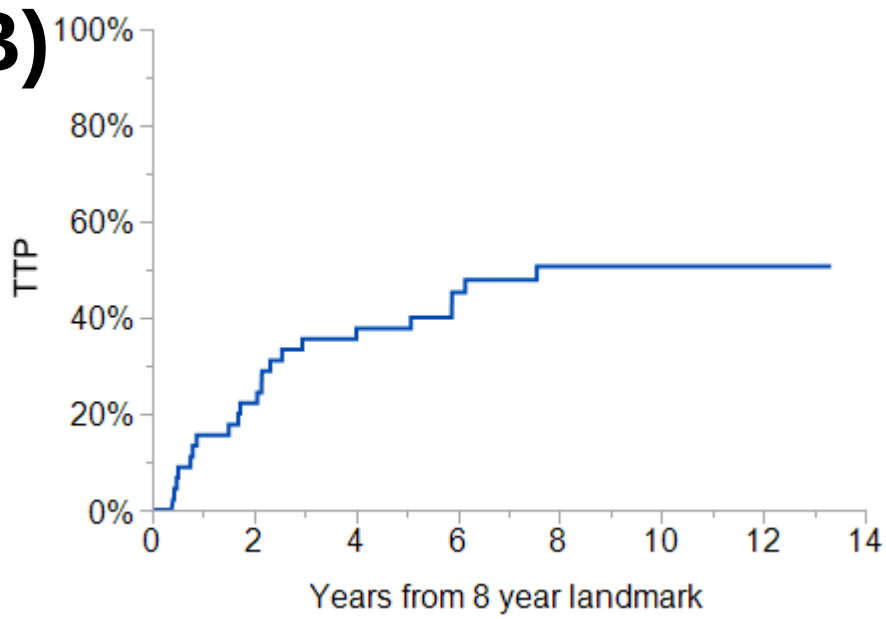

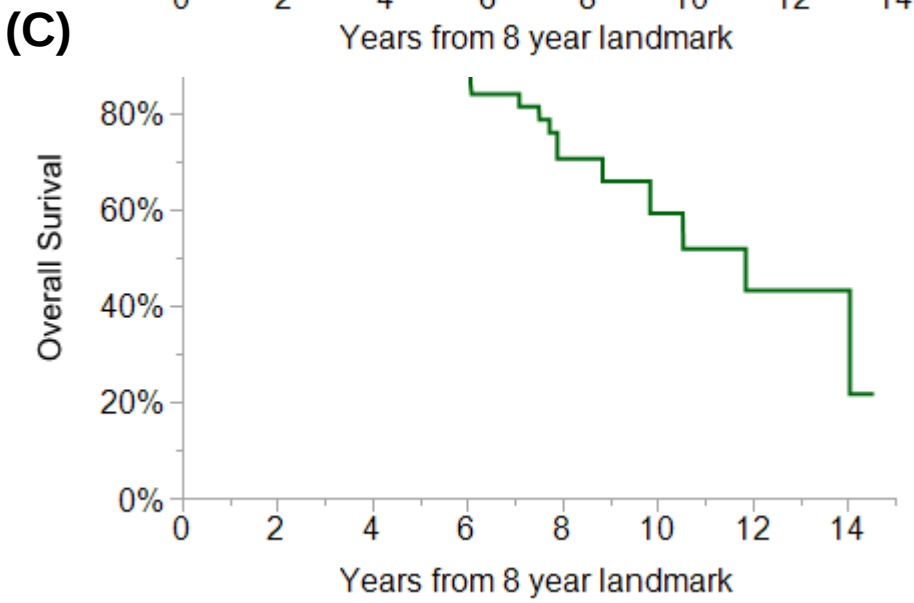

Paquin A.…Rajkumar SV. Blood Cancer J. 2020

Landmark analysis at 8 years after diagnosis of multiple myeloma showing the PFS (A), TTP (B), and OS (C) of exceptional responders to stem cell transplant

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How do we achieve cure or control?

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Optimal use of Active Drugs in Multiple Myeloma

- Alkylators
- Steroids
- Anthracyclines

IMiDs
- Thalidomide
- Lenalidomide
- Pomalidomide

Proteasome Inhibitors
- Bortezomib
- Carfilzomib
- Ixazomib

Anti-SLAMF7 moAb
- Elotuzumab

Anti-CD38 moAbs
- Daratumumab
- Isatuximab
- Felzartamab (MOR202)
- TAK 079
- SAR 442085

Anti-BCMA antibody drug conjugate
- Belantamab

- Panobinostat (histone deacetylase inhibitor)
- Selinexor (XPO1 inhibitor)
- Venetoclax (BCL-2 inhibitor)
- Melflufen (peptidase enhanced cytotoxic)

Anti-BCMA CAR-T
- Cilta-cel
- Ide-cel
- JCARH125

Anti-BCMA bispecifics
- Teclistamab
- AMG 701
- CC93269

Novel bispecifics
- Talquetamab (GPRC5D/CD3)
- Cevostamab (FcRH5/CD3)

CELMoDs
- Iberdomide
- CC-92480

moAB: monoclonal antibody

Rajkumar SV. 2020

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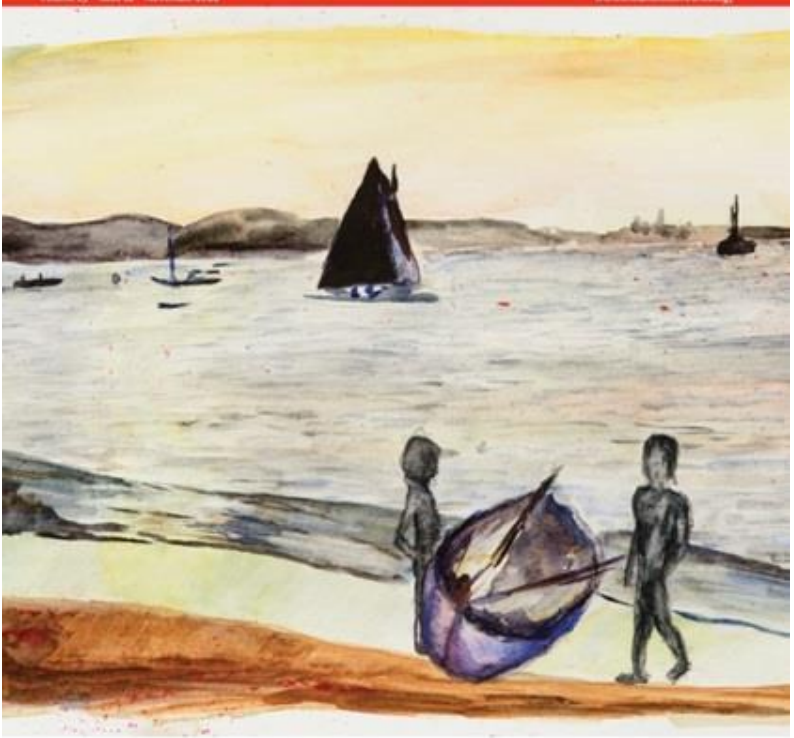
How do we achieve cure?

THE LANCET Oncology

Volume 15 · Issue 12 · November 2014 www.thelancet.com/oncology



Review

International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma

S Vincent Rajkumar, Meletios A Dimopoulos, Antonio Palumbo, Joan Blade, Giampaolo Merlini, María-Victoria Mateos, Shaji Kumar, Jens Hillengass, Efstathios Kastritis, Paul Richardson, Ola Landgren, Bruno Paiva, Angela Dispenzieri, Brendan Weiss, Xavier LeLeu, Sonja Zweegman, Sagar Lonial, Laura Rosinol, Elena Zamagni, Sundar Jagannath, Orhan Sezer, Sigurdur Y Kristinsson, Jo Caers, Saad Z Usmani, Juan José Lahuerta, Hans Erik Johnsen, Meral Beksac, Michele Cavo, Hartmut Goldschmidt, Evangelos Terpos, Robert A Kyle, Kenneth C Anderson, Brian G M Durie, Jesus F San Miguel

This International Myeloma Working Group consensus updates the disease definition of multiple myeloma to include validated biomarkers in addition to existing requirements of attributable CRAB features (hypercalcaemia, renal failure, anaemia, and bone lesions). These changes are based on the identification of biomarkers associated with near inevitable development of CRAB features in patients who would otherwise be regarded as having smouldering multiple myeloma. A delay in application of the label of multiple myeloma and postponement of therapy could be

Lancet Oncol 2014; 15: e538–48

See Online for a podcast interview with S Vincent Rajkumar

Division of Hematology, Mayo

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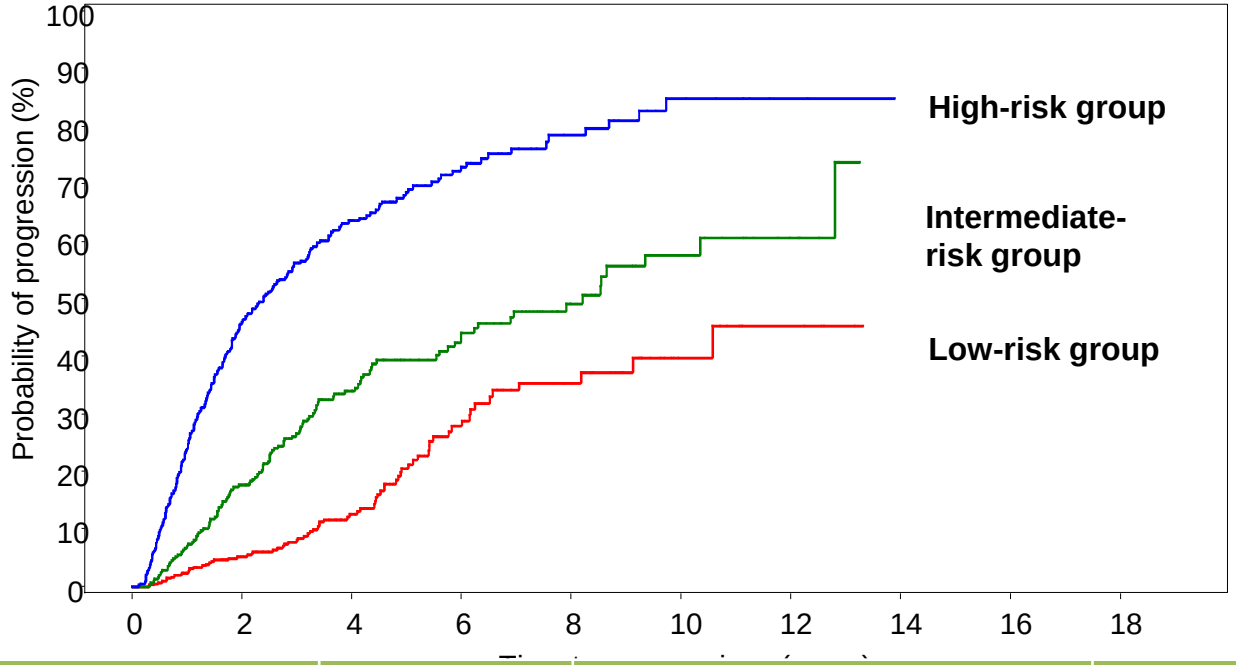
IMWG 2019 Risk Stratification of SMM (n=1151)



M Spike: >2g/dL
FLC Ratio: > 20
BMPC: > 20%

Risk Stratification Groups	Number of risk factors	Hazard Ratio (95% CI) Versus Low-risk group	Risk of Progression at 2 years	Number of patients
Low-risk group	0	Reference	5%	424 (37%)
Intermediate-risk group	1	2.25 (1.68 to 3.01)	17%	312 (27%)
High-risk group	2-3	5.63 (4.34 to 7.29)	46%	415 (36%)

San Miguel. ASCO 2019. Abstr 8000. Mateos Blood Cancer J. 2020;10:102.

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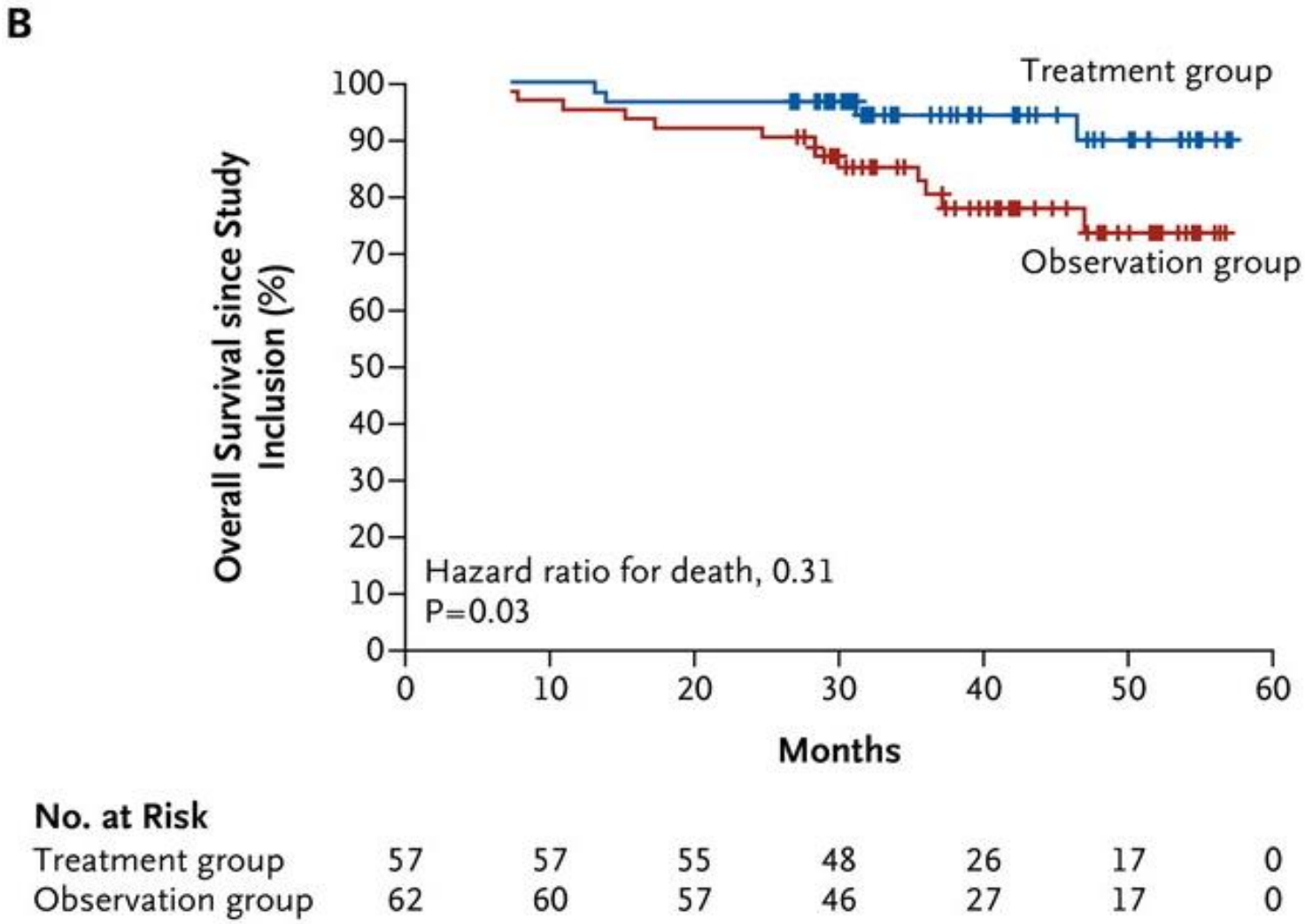
Len/Dex versus Observation in High Risk SMM: OS



Mateos M et al. N Engl J Med 2013;369:438-447.

The NEW ENGLAND JOURNAL of MEDICINE

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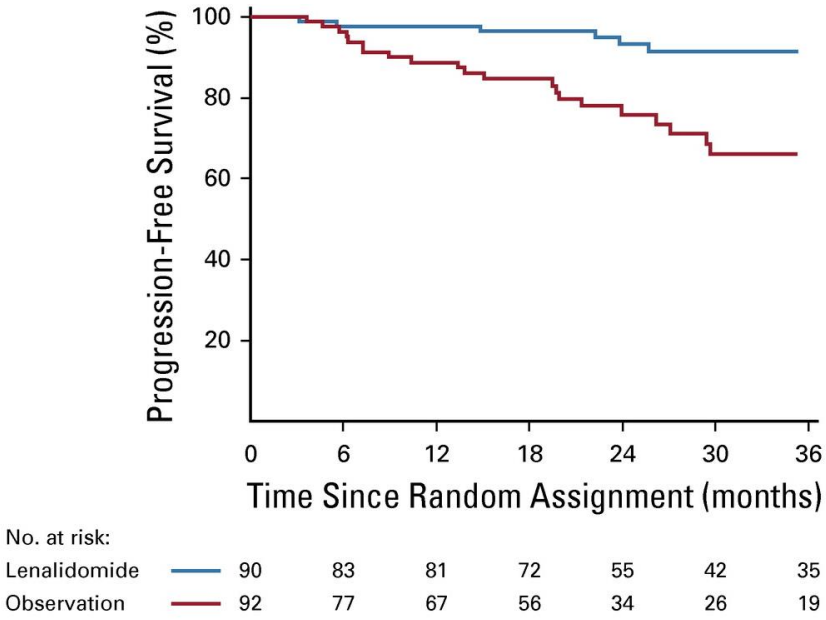
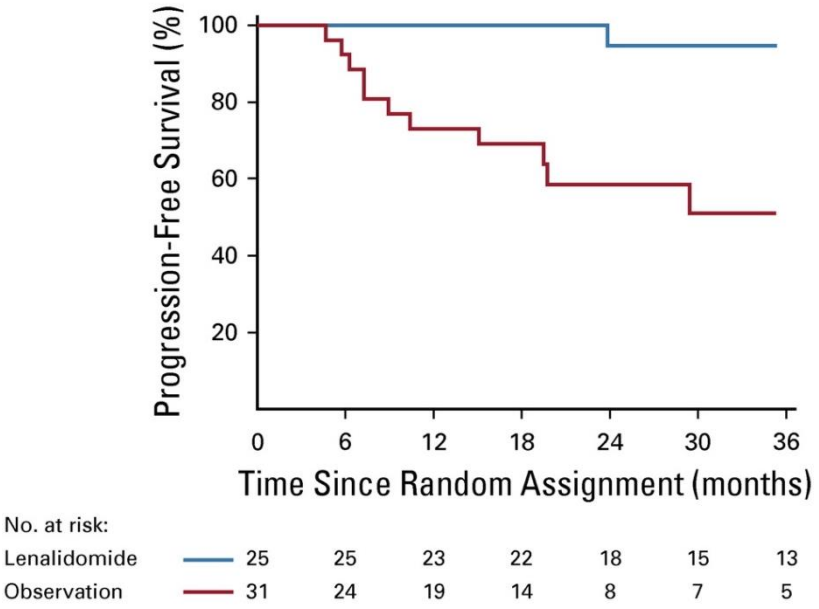
Lenalidomide vs Observation: ECOG E3A06

PFS in all patients



PFS in Mayo 2018 High Risk SMM



Published in: Sagar Lonial; Susanna Jacobus; Rafael Fonseca; Matthias Weiss; Shaji Kumar; Robert Z. Orlowski; Jonathan L. Kaufman; Abdulraheem M. Yacoub; Francis K. Buadi; Timothy O'Brien; Jeffrey V. Matous; Daniel M. Anderson; Robert V. Emmons; Anuj Mahindra; Lynne I. Wagner; Madhav V. Dhodapkar; S. Vincent Rajkumar; Journal of Clinical Oncology 2020 381126-1137.
DOI: 10.1200/JCO.19.01740

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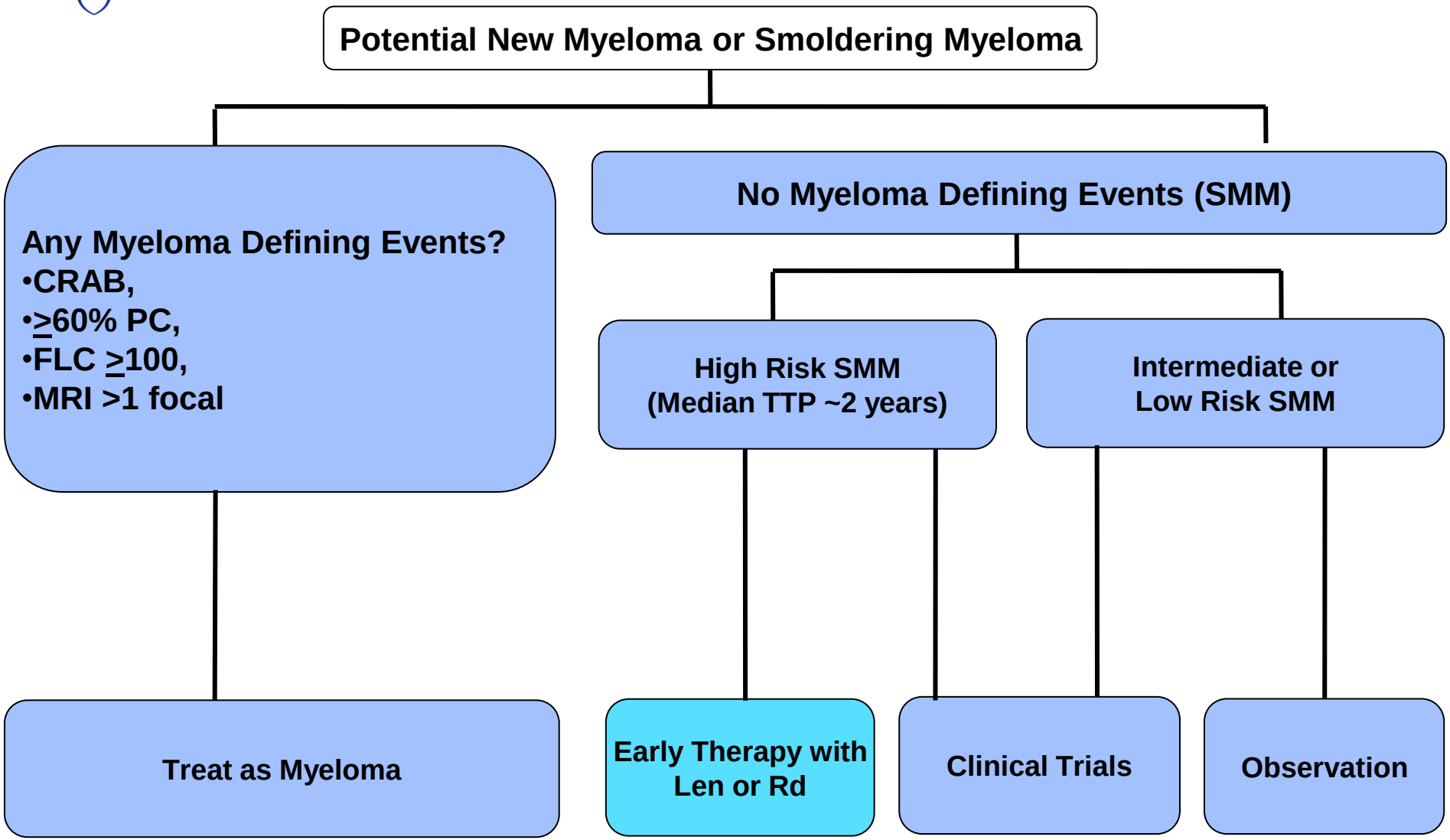
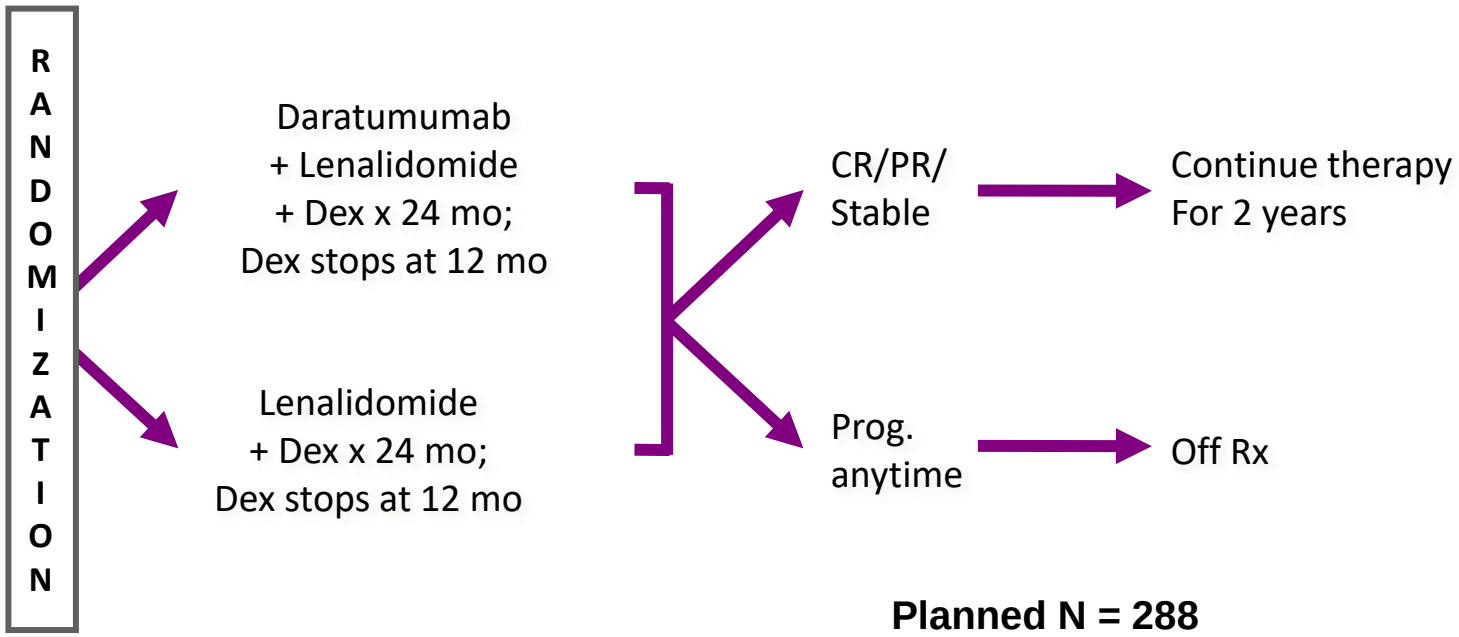


Phase III EAA173: Daratumumab to Enhance Therapeutic Effectiveness of Lenalidomide in Smoldering Myeloma (DETER-SMM)



Planned N = 288

NCT03937635.

MAYO CLINIC

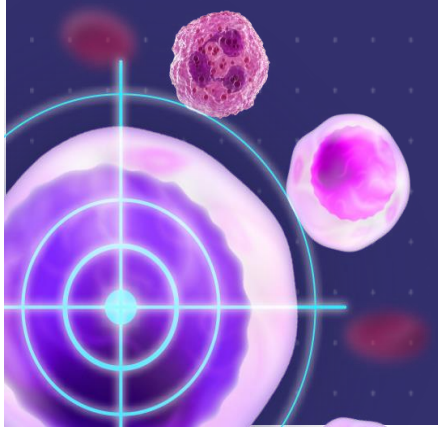
MAYO CLINIC

Recommendations

- Design trials for cure using well tolerated regimens – Time limited
- Design trials for cure using well tolerated regimens early in the disease course (high risk smoldering myeloma)
- Design trials for control using well tolerated regimens and maintenance therapy that is easy and feasible
- In clinical practice, use well tolerated regimens that have been established in clinical trials to achieve the best disease control.

MultipleMyelomaHub

Thank you



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