Does ‘cure’ have a different meaning in multiple myeloma?

Mohamad Mohty

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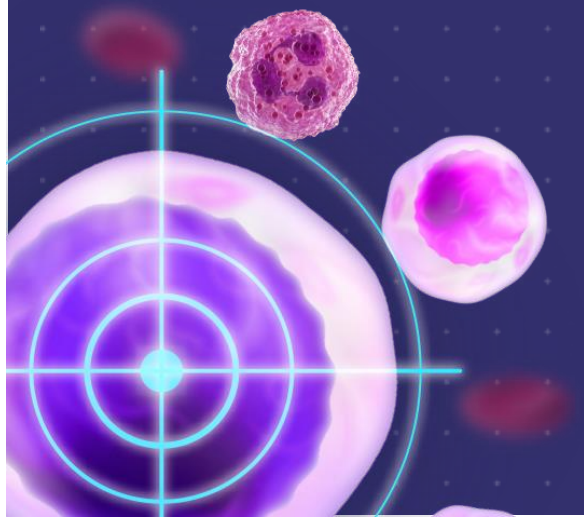

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Employee	NA
Consultant	NA
Major stakeholder	NA
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Scientific advisory board	NA

NA, not applicable

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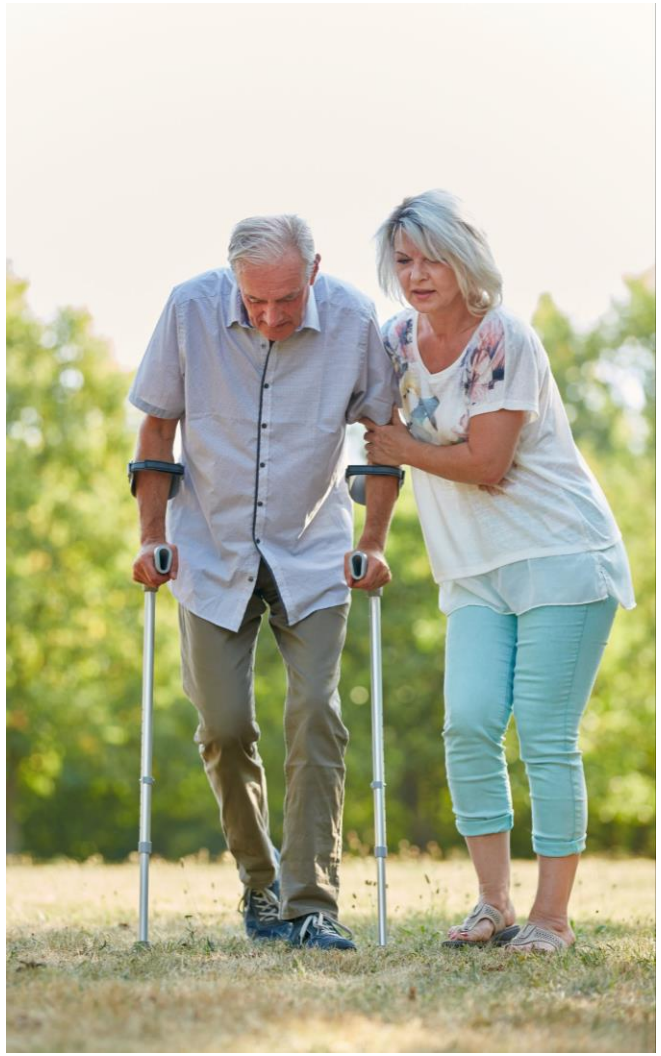
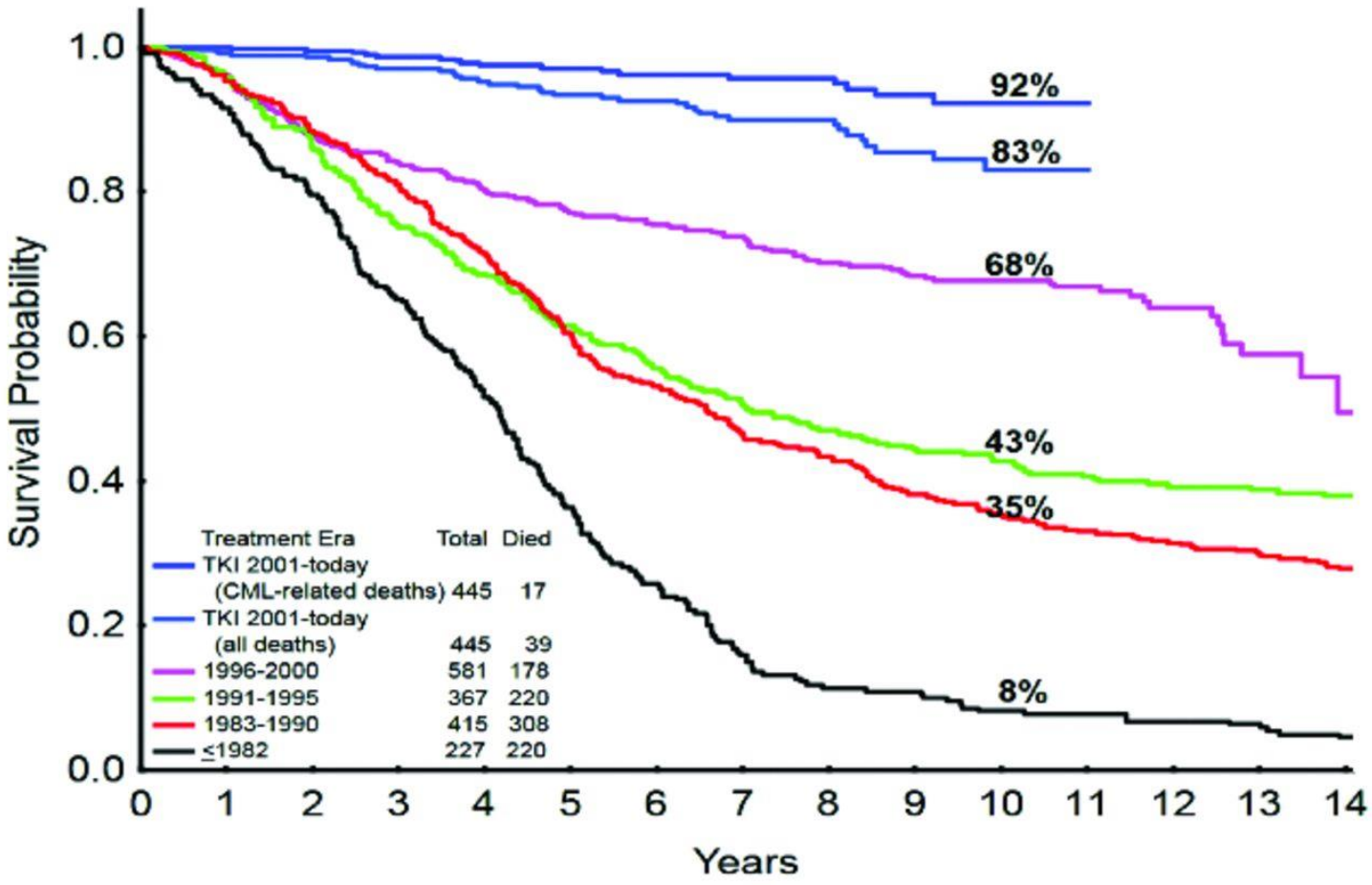


‘Cure’ in chronic myeloid leukemia



CML, chronic myeloid leukemia; TKI, tyrosine kinase inhibitor.
Mughal TI, et al. *Haematologica*. 2016;101(5):541.

Does ‘cure’ have a different meaning in multiple myeloma?

EDITORIAL

Toward a Cure for Multiple Myeloma?

Bart Barlogie, M.D.

N Engl J Med 1991 325:1304-1306

‘Cure’ can mean different things within the myeloma community

Review > Bone Marrow Transplant. 2005 Feb;35(3):215-24. doi: 10.1038/sj.bmt.1704757.

Cure of myeloma: hype or reality?

A Fassas [1], J Shaughnessy, B Barlogie

But at the same time

Review > Mayo Clin Proc. 2008 Oct;83(10):1142-5. doi: 10.4065/83.10.1142.

Treatment of myeloma: cure vs control

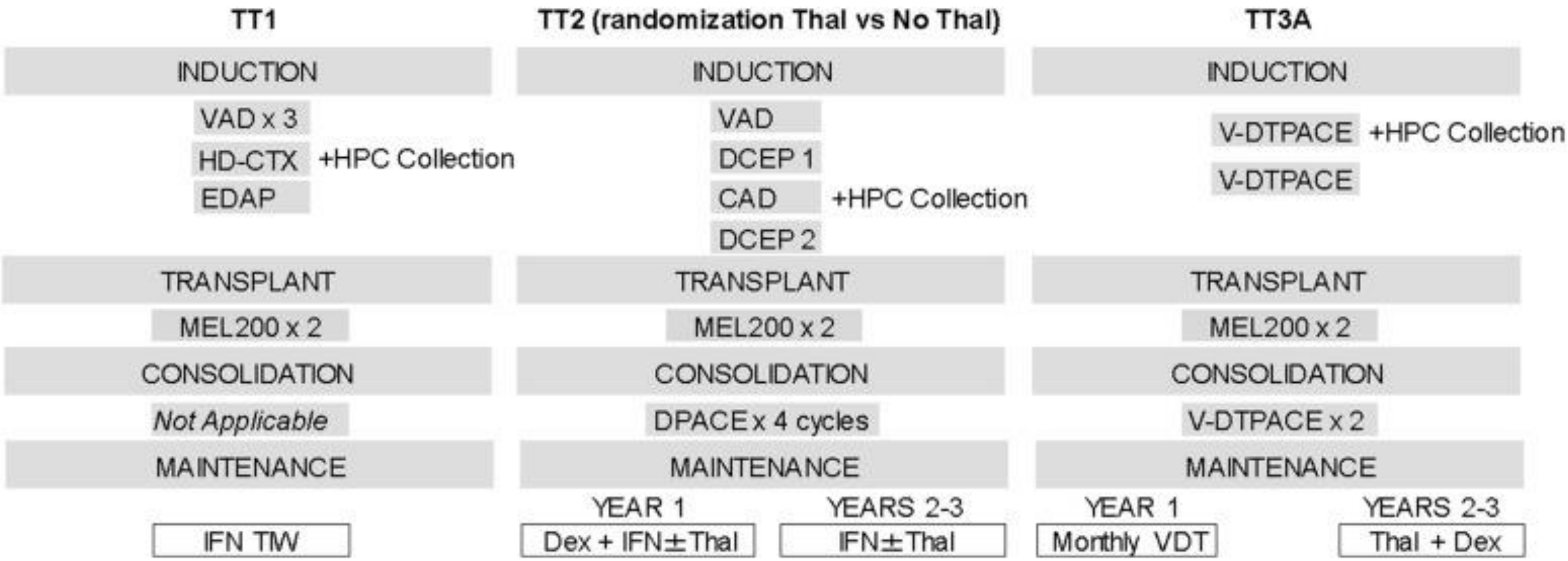
S Vincent Rajkumar [1]

> Blood. 2014 Nov 13;124(20):3043-51. doi: 10.1182/blood-2014-07-552059. Epub 2014 Oct 7.

Curing myeloma at last: defining criteria and providing the evidence

Bart Barlogie [1], Alan Mitchell [2], Frits van Rhee [1], Joshua Epstein [1], Gareth J Morgan [1], John Crowley [2]

The TOTAL THERAPY concept

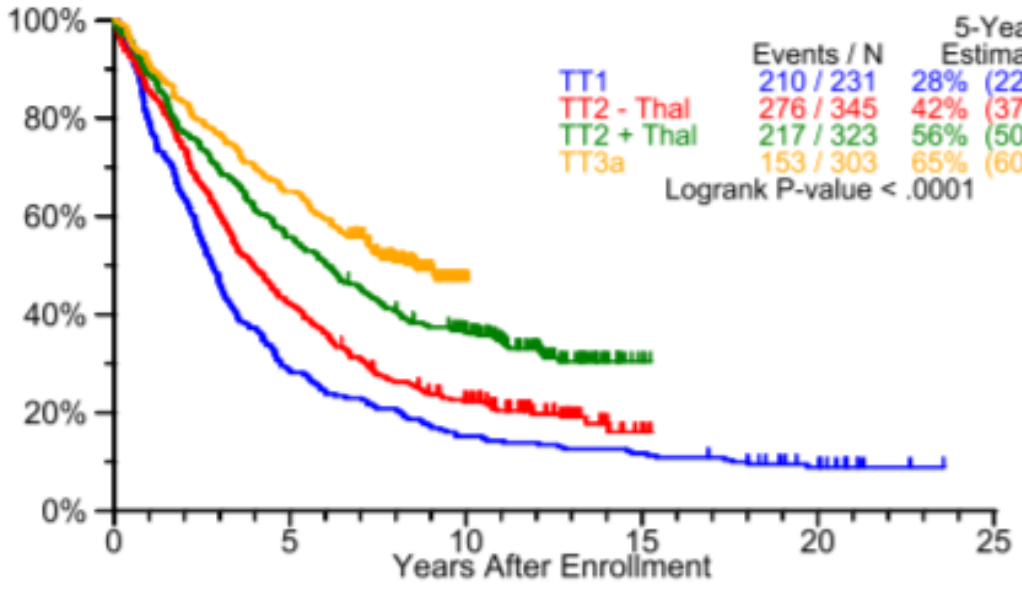


CAD, cyclophosphamide, adriamycin, dexamethasone; DCEP1, dexamethasone, cyclophosphamide, etoposide, cisplatin; Dex, dexamethasone; DPACE, dexamethasone, cisplatin, doxorubicin, cyclophosphamide, etoposide; EDAP, etoposide, dexamethasone, cytarabine, cisplatin; HD-CTX, high-dose cyclophosphamide; HPC, hematopoietic stem cell; IFN TW, interferon twice weekly; MEL200, melphalan 200 mg/m2; Thal, thalidomide; TT, total therapy; VAD, vincristine, doxorubicin, and dexamethasone; V-DTPACE; bortezomib, dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, etoposide; VTD; bortezomib, thalidomide, dexamethasone.

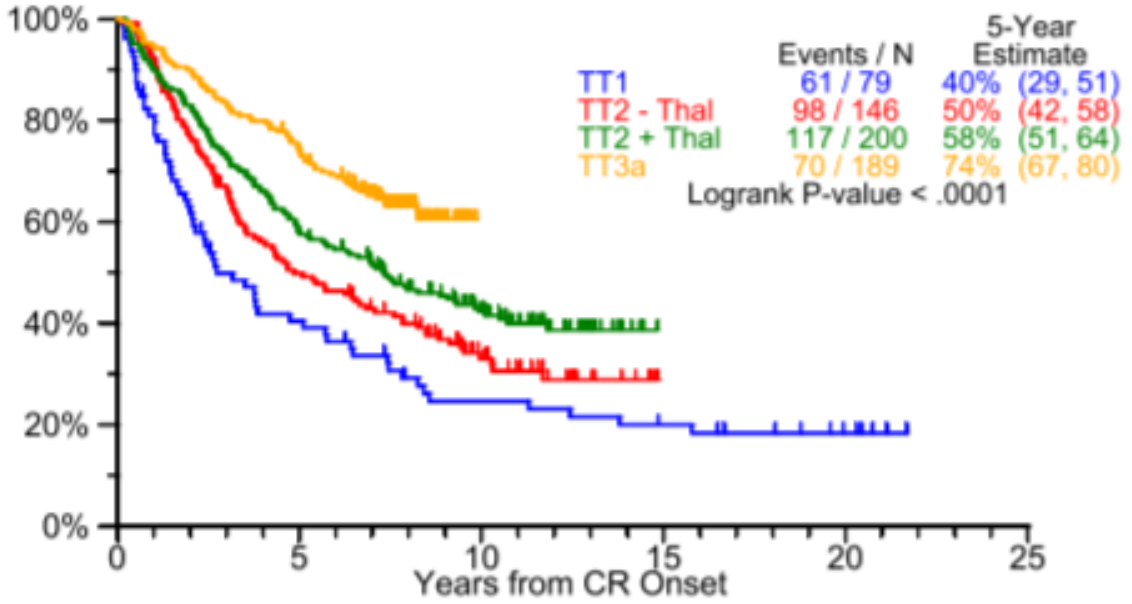
Barlogie B, et al. *Blood.* 2014;124(20):3043.

The TOTAL THERAPY concept

PFS by protocol



CR duration

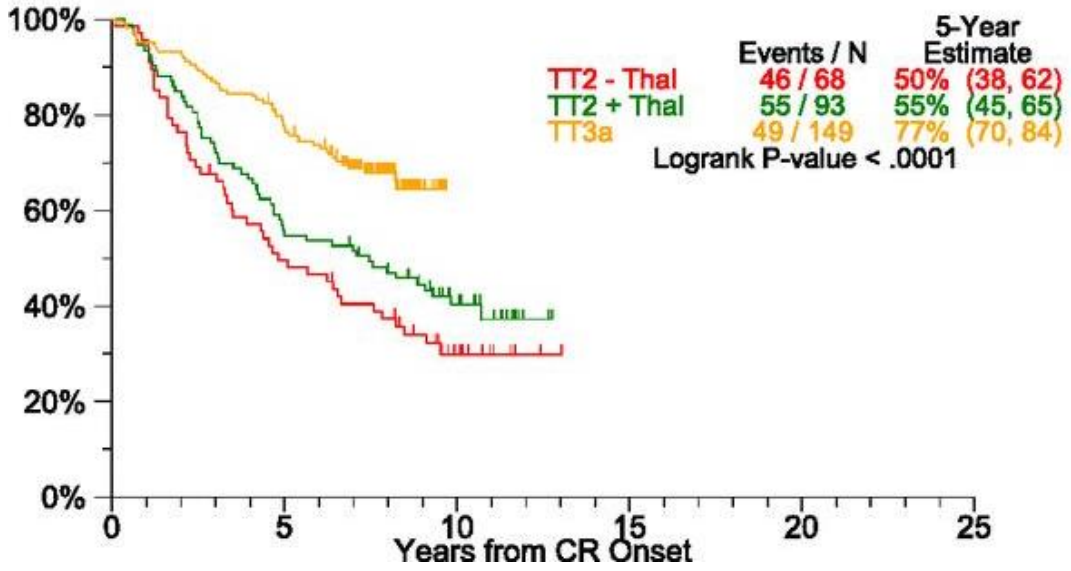


CR, complete response; PFS, progression-free survival; Thal, thalidomide; TT, total therapy.

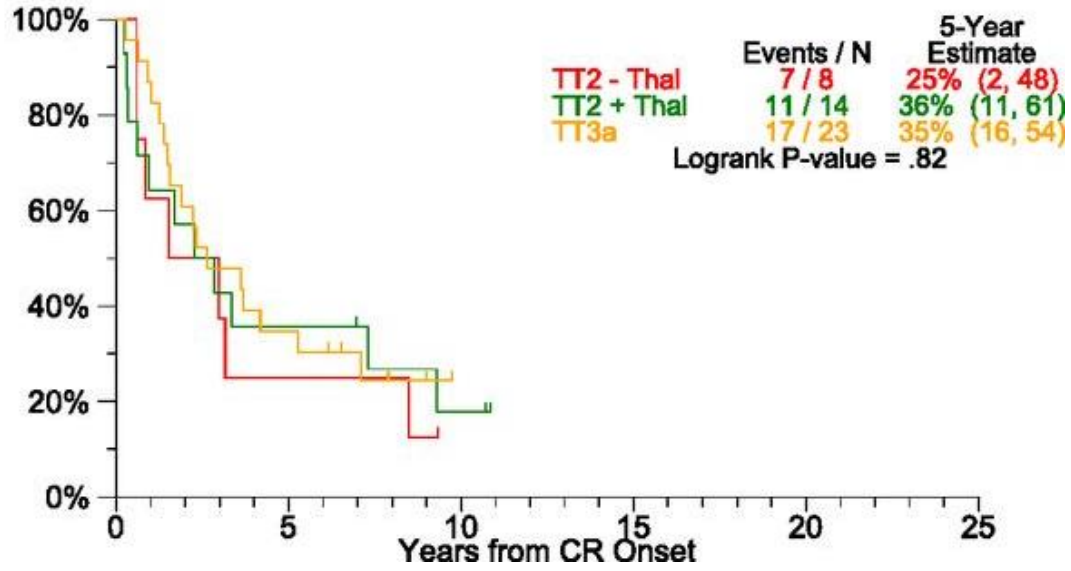
Barlogie B, et al. *Blood.* 2014;124(20):3043.

Addition of bortezomib resulted in curative gains for low-risk *vs* high-risk disease

GEP 70 low-risk



GEP 70 high-risk

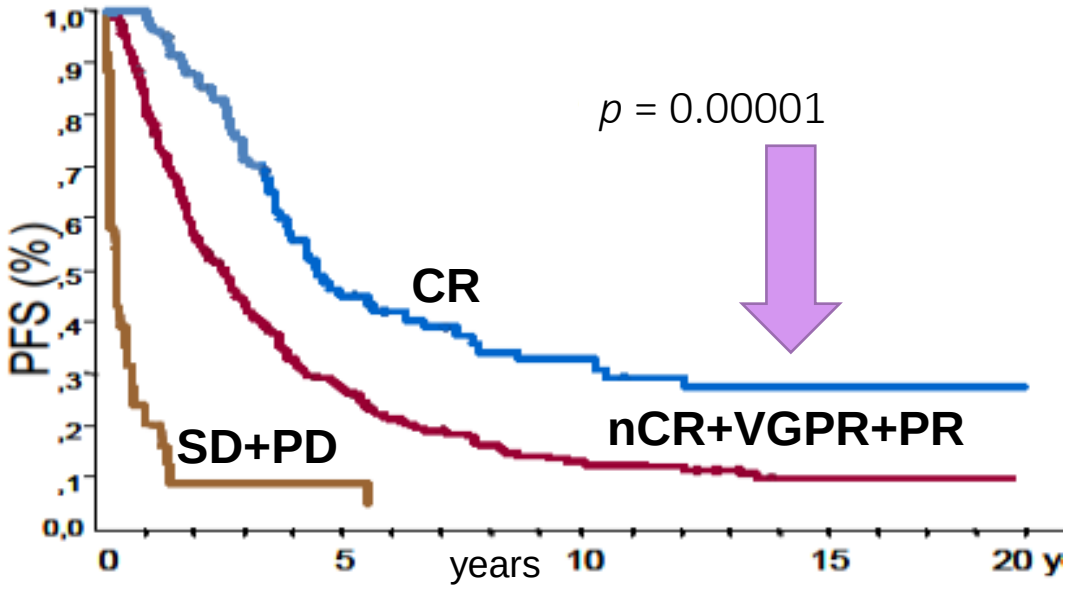


CR, complete response; GEP, gene-expression profiling; Thal, thalidomide; TT, total therapy.

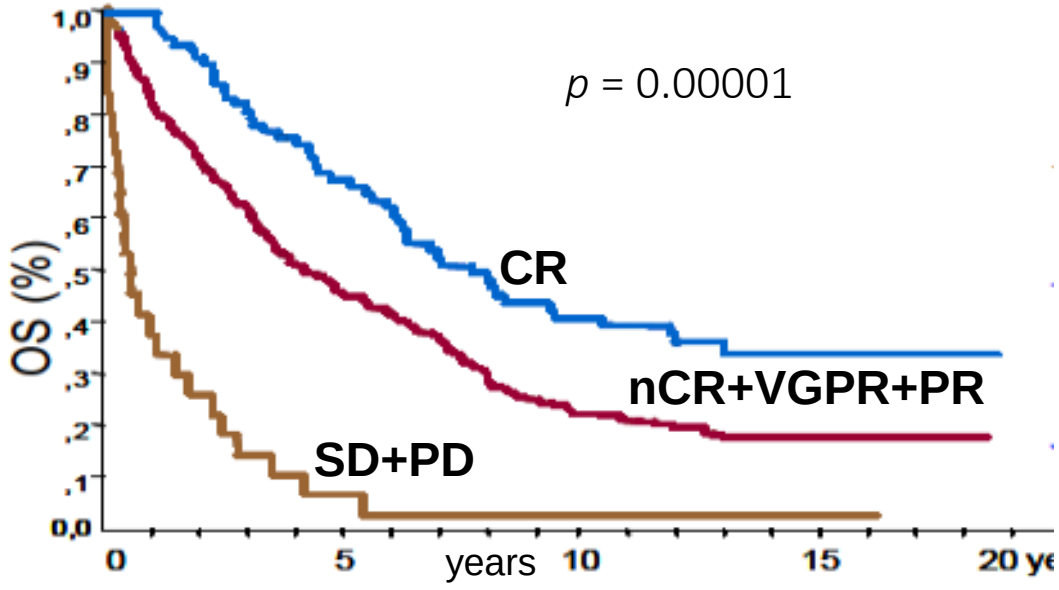
Barlogie B, et al. *Blood.* 2014;124(20):3043.

Prognostic impact of CR *vs* nCR/VGPR/PR *vs* SD/PD after high-dose therapy plus ASCT (n = 344)

PFS



OS



ASCT, autologous stem cell transplant; CR, complete response; nCR, near complete response; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; VGPR, very good partial response.

Martinez-Lopez J, et al. *Blood*. 2011;118(3):529.

The concept of ‘operational cure’ in myeloma

First time this term was used: Ray Powles[1] (ASH abstract)

Continued first complete remission in multiple myeloma for over 10 years: a series of ‘operationally cured’ patients[1]

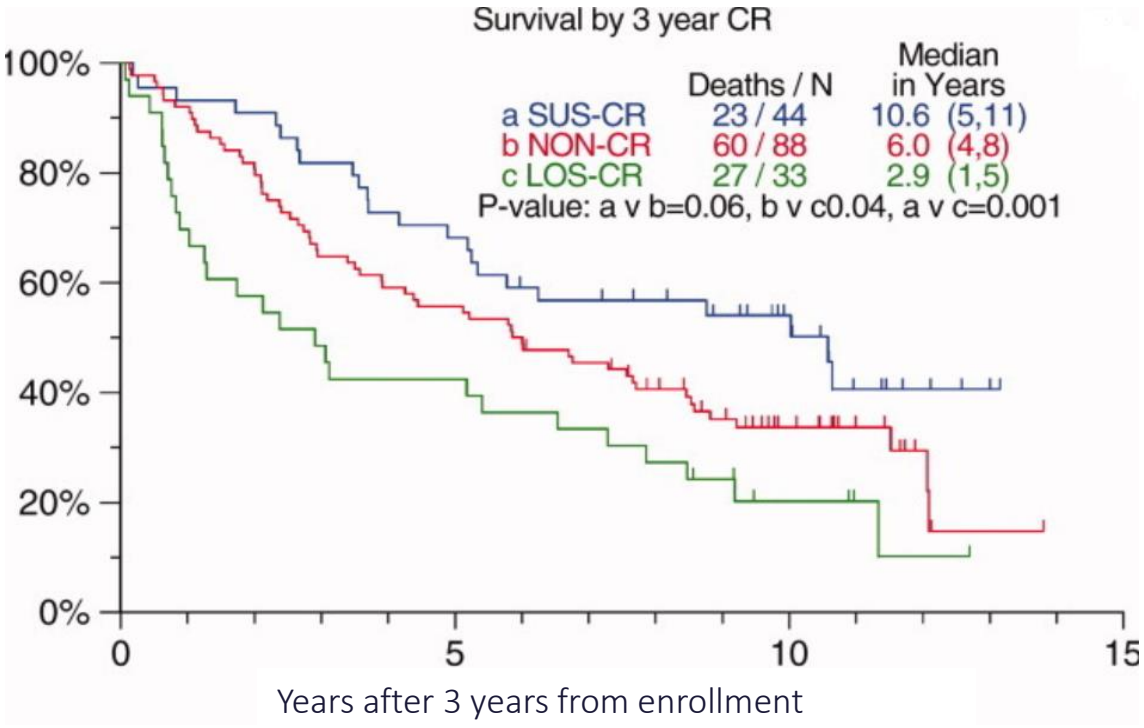
Current accepted definition: Patients who remain in CR for more than 10 years[2]

10 years ago, CR achievement was the requirement for operational cure!

ASH, American Society of Hematology; CR, complete response.

1. Powles R, et al. *Blood*. 2000;96(Suppl. 1):515a; **2.** San-Miguel JF & Mateos MV. *Haematologica.* 2011;96(9):1246.

CR achievement is not sufficient



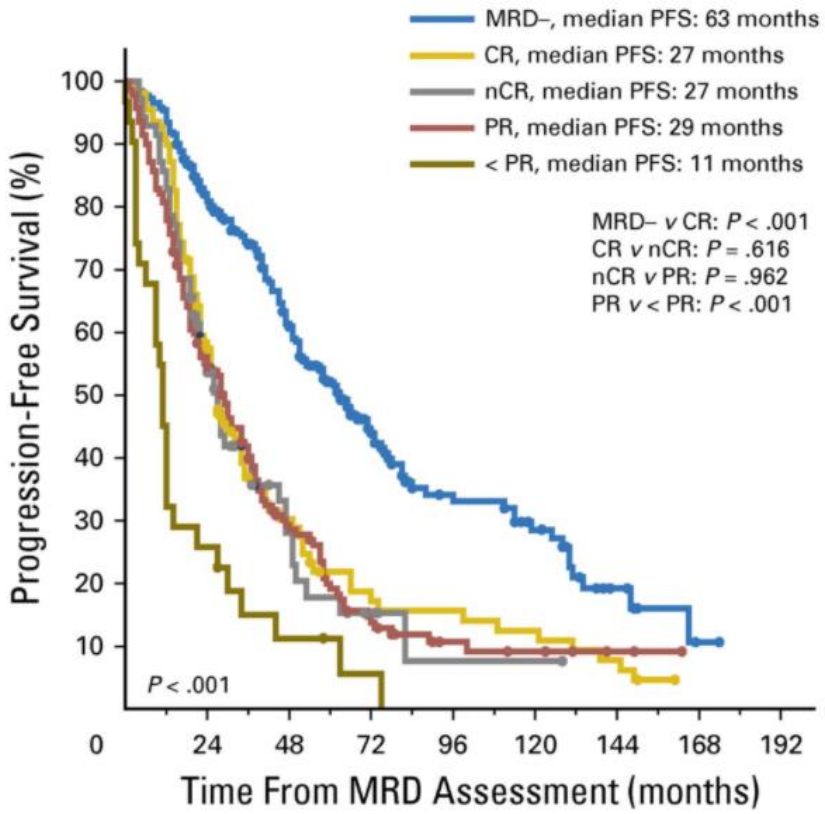
Sustained CR (3-year landmark analysis) was associated with the highest probability of 10-year OS.

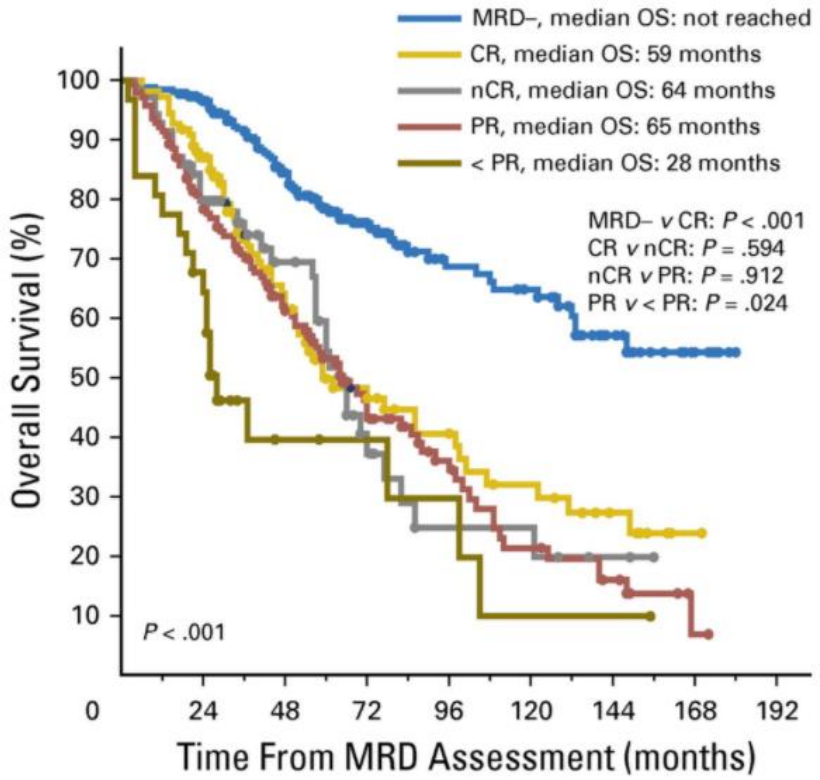
CR, complete response; LOS-CR, lost CR status; NON-CR, never achieved-CR status; OS, overall survival; SUS-CR, achieved and sustained CR status.
Barlogie B, et al. *Cancer*. 2008;113(2):355.

Only achieving MRD-negativity prolongs survival

The value of CR relies on MRD status, and CR w/o MRD is no better than PR.

N = 609*



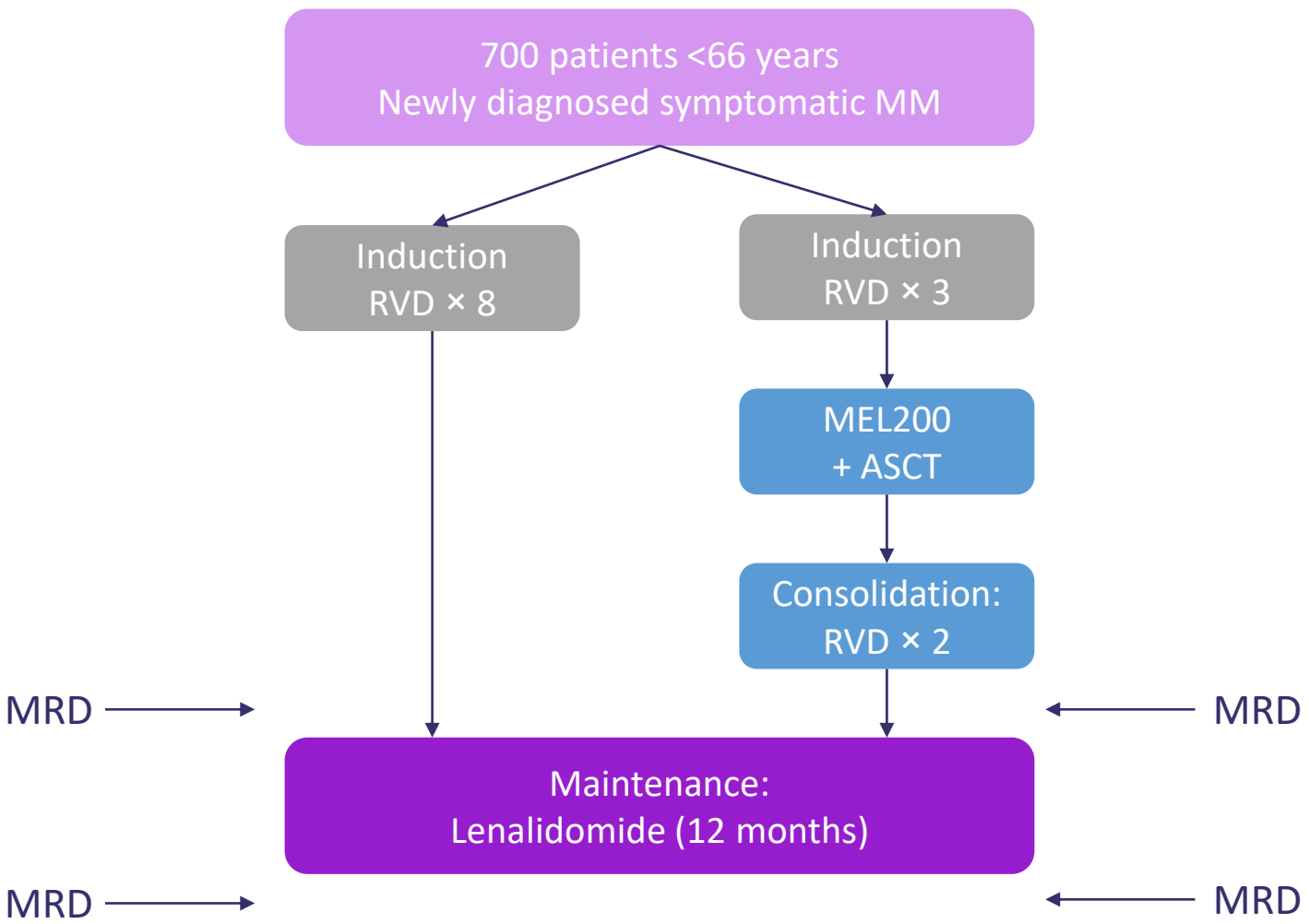


CR, complete response; MRD, minimal residual disease; nCR, near-CR; PFS, progression-free survival; PR, partial response; *v*, versus; w/o, without.

*Patients enrolled in GEM 2000, and GEM2005MENOS65 trials for transplant-eligible MM, and GEM2010MAS65 trial for elderly patients with MM, who had MRD assessments 9 months after enrollment; median follow-up: 71 months.

Lahuerta JJ, et al. *J Clin Oncol*. 2017;35(25):2900.

MRD assessment by NGS in IFM/DFCI 2009 trial

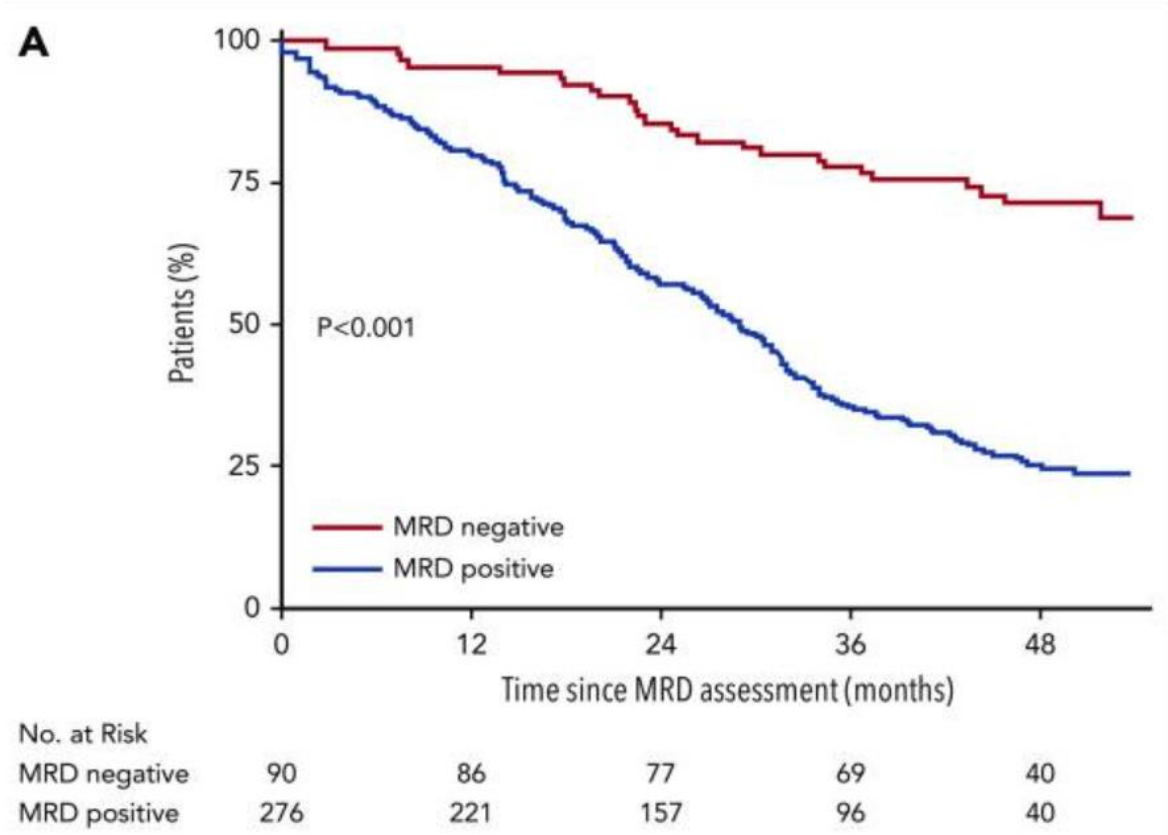


ASCT, autologous stem cell transplantation; IFM/DFCI, Intergroupe Francophone du Myélome/Dana-Farber Cancer Institute; MEL200, melphalan 200 mg/m^2; MM, multiple myeloma; MRD, minimal residual disease; NGS, next-generation sequencing; RVD, lenalidomide, bortezomib, dexamethasone.

Perrot A, et al. *Blood.* 2018;132(23):2456. NCT01191060

MRD assessment by NGS in IFM/DFCI 2009 trial

Progression-free survival according to MRD status at the start of maintenance



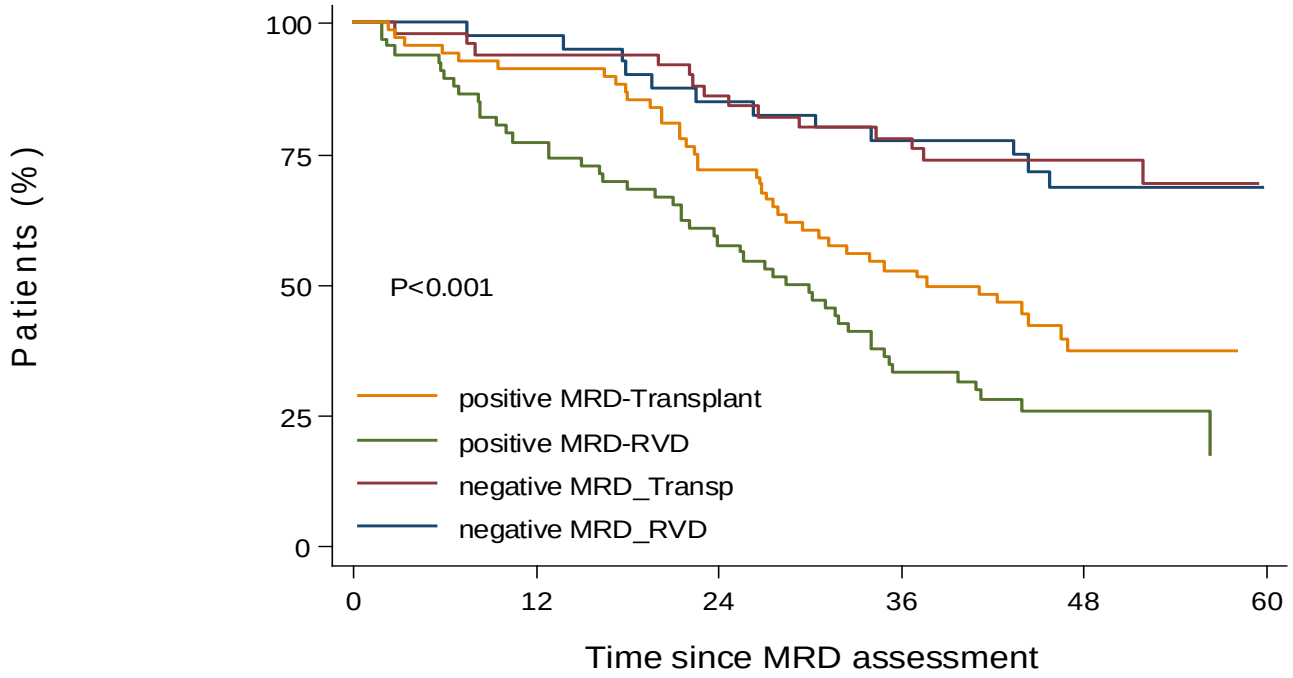
< 10^{-6}

> 10^{-6}

IFM/DFCI, Intergroupe Francophone du Myélome/Dana-Farber Cancer Institute; MRD, minimal residual disease; NGS, next-generation sequencing; No, number.
Perrot A, et al. *Blood.* 2018;132(23):2456. NCT01191060

MRD assessment by NGS in IFM/DFCI 2009 trial

Role of treatment



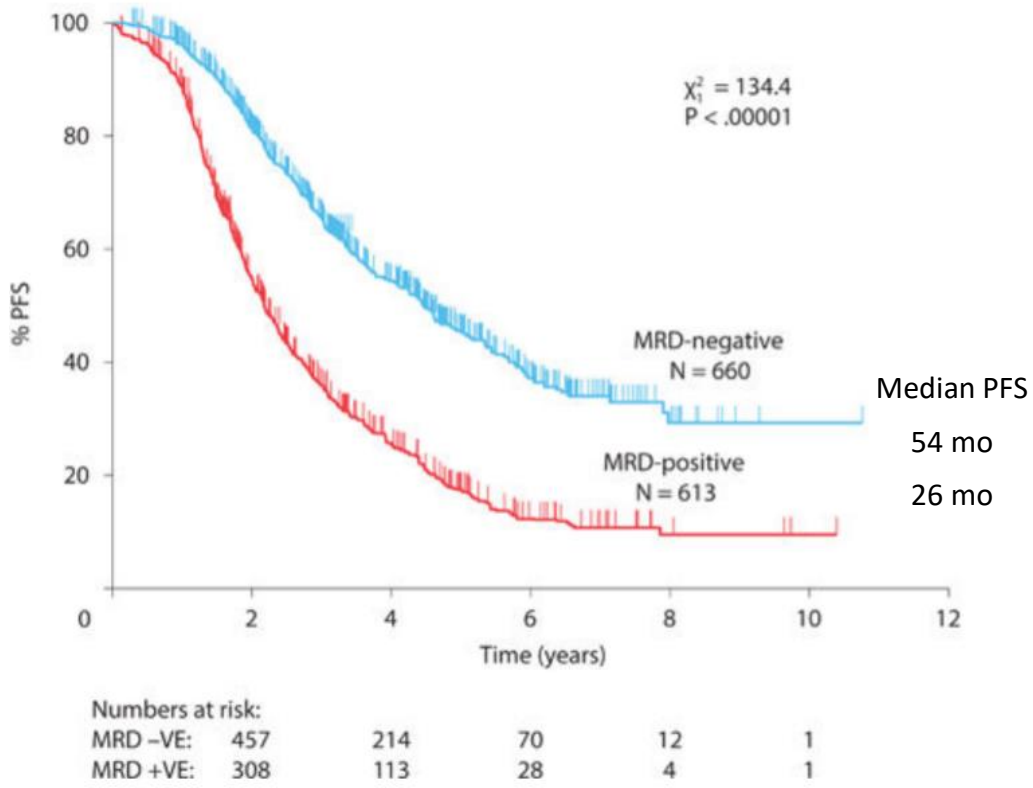
N at risk						
positive MRD-Transplant	68	62	49	35	15	1
positive MRD-RVD	66	51	38	21	11	2
negative MRD_Transp	50	47	43	38	23	4
negative MRD_RVD	40	39	34	31	17	1

IFM/DFCI, Intergroupe Francophone du Myélome/Dana-Farber Cancer Institute; MRD, minimal residual disease; N, number; NGS, next-generation sequencing; RVD, lenalidomide, bortezomib, dexamethasone.

Adapted from Perrot A, et al. *Blood.* 2018;132(23):2456. NCT01191060

Impact of MRD negativity on PFS

Meta-analysis of 14 studies (n = 1,273)

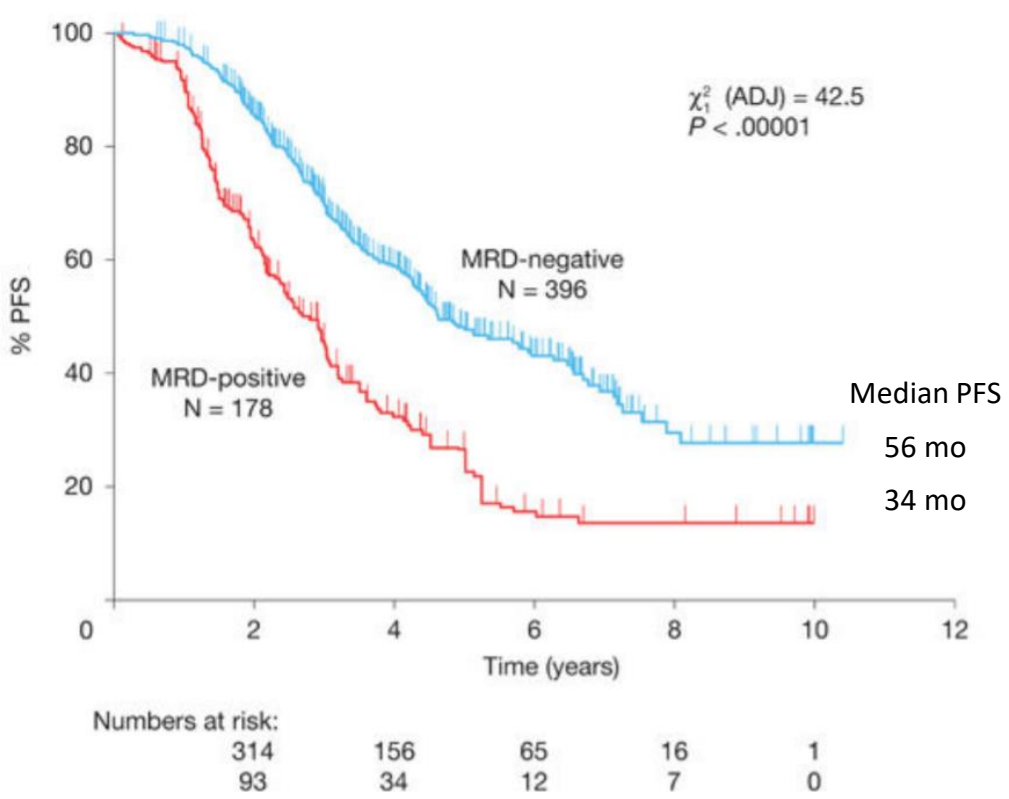


Median PFS

54 mo

26 mo

5 studies (n = 574) specifically in patients who achieved a CR



Median PFS

56 mo

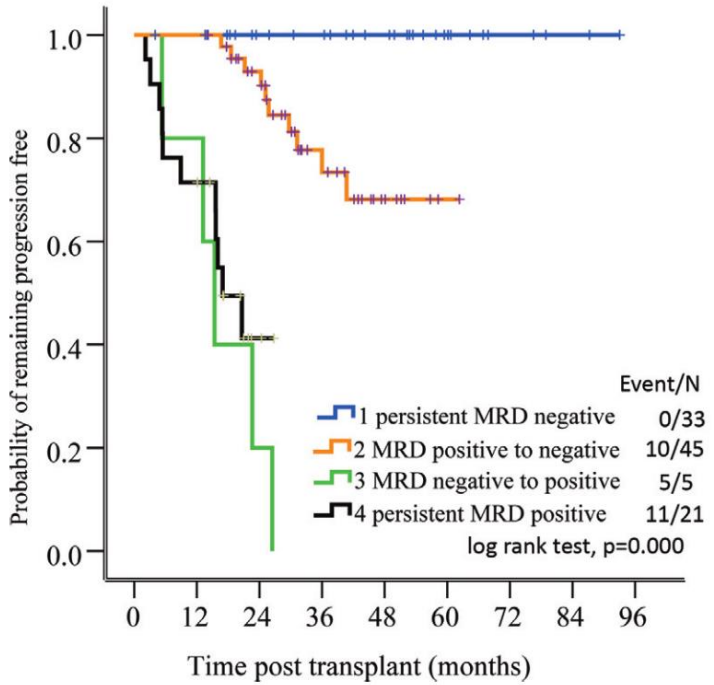
34 mo

CR, complete response; mo, months; MRD, minimal residual disease; PFS, progression-free survival.

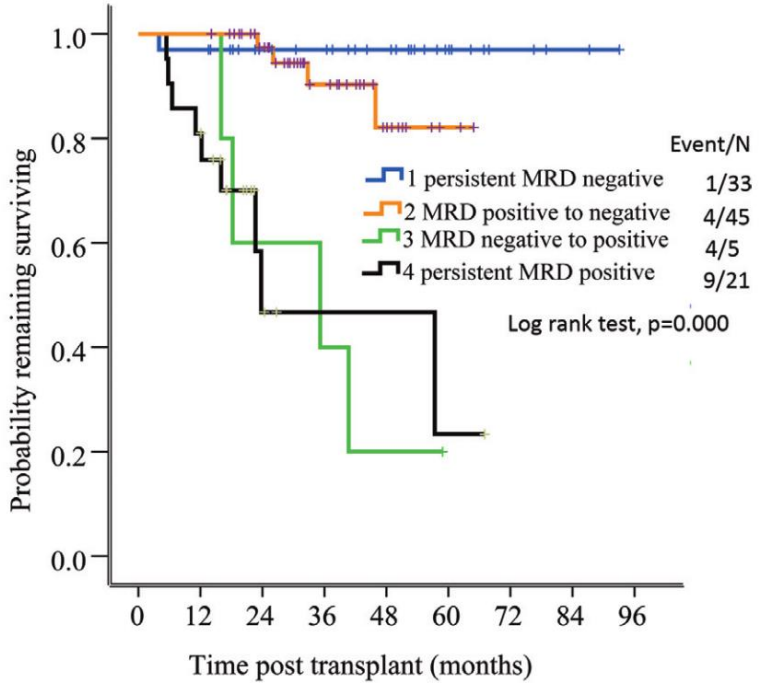
Munshi N, et al. *JAMA Oncol.* 2017;3(1):28.

24 months of sustained MRD negativity identifies patients with very low risk of disease progression

Flow MRD was monitored in 104 consecutive patients with MM after induction and every 3 months posttransplant for 24 months. Four MRD-evolution patterns were revealed.



TTP for MRD evolution patterns 1–4 were NR, NR, 15.4 ± 2.4 months, and 16.9 ± 3.0 months, respectively.



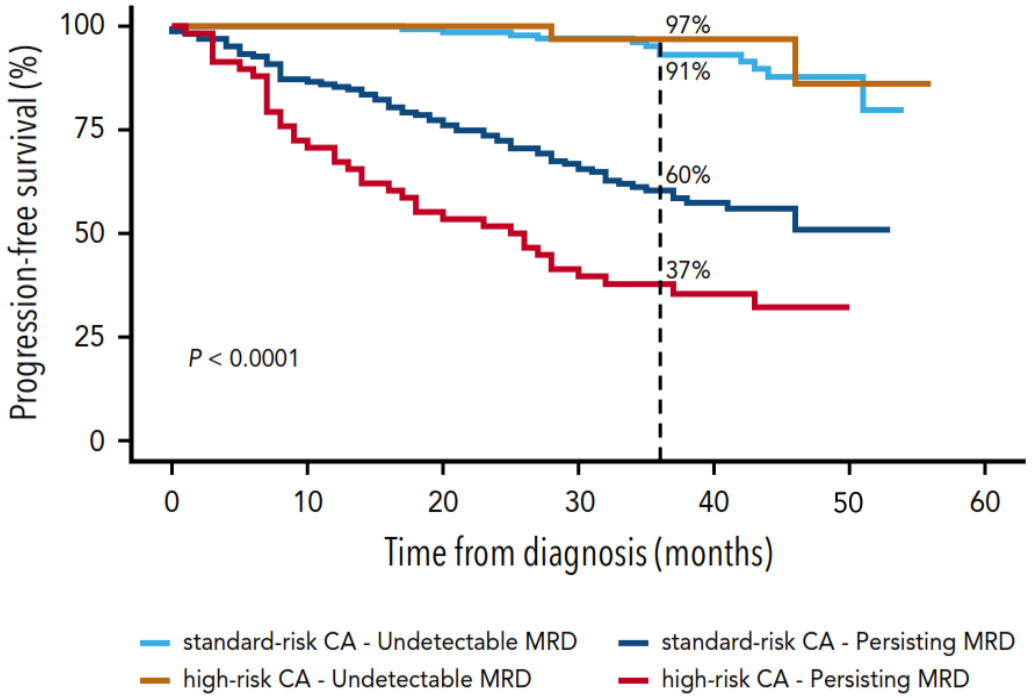
OS for MRD evolution patterns 1–4 were NR, NR, 35.2 ± 18.6 months, and 23.8 ± 15.0 months, respectively.

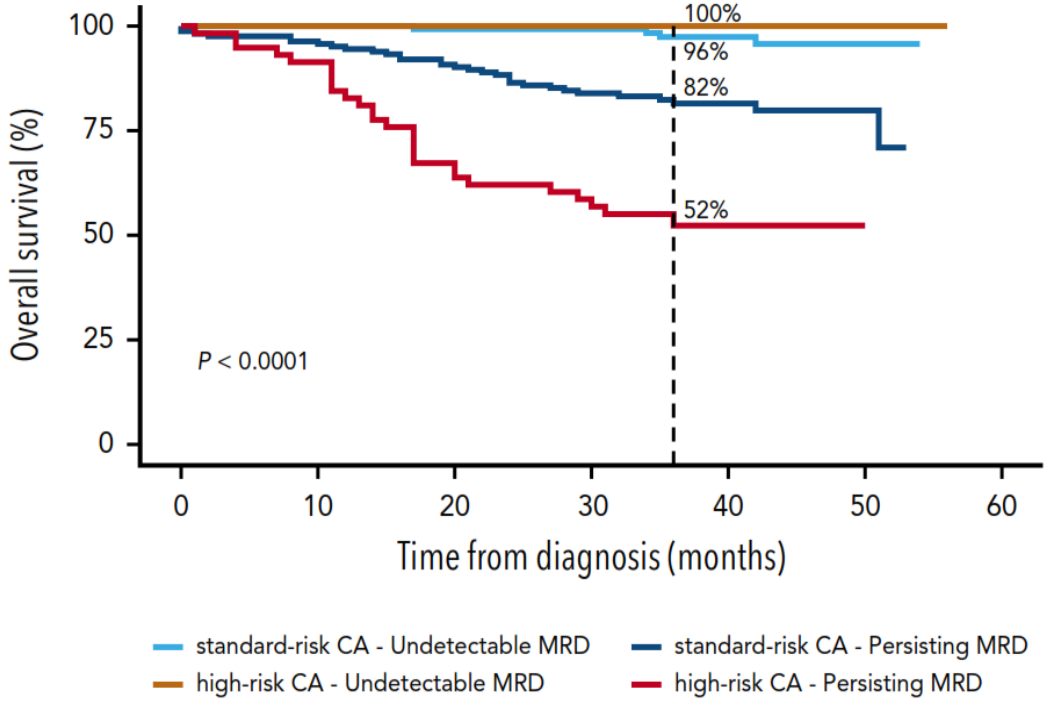
MRD, minimal residual disease; NR, not reached; OS, overall survival; TTP, time to progression.

Gu J, et al. *Biol Blood Marrow Transplant*. 2018;24(12):2568.

Achieving undetectable MRD overcomes the dismal prognosis of transplant-eligible patients with high-risk cytogenetics

NGF cytometry was used to evaluate MRD in patients with standard-risk (n = 300) *vs* high-risk (n = 90) CAs enrolled in the PETHEMA/GEM2012MENOS65* trial.



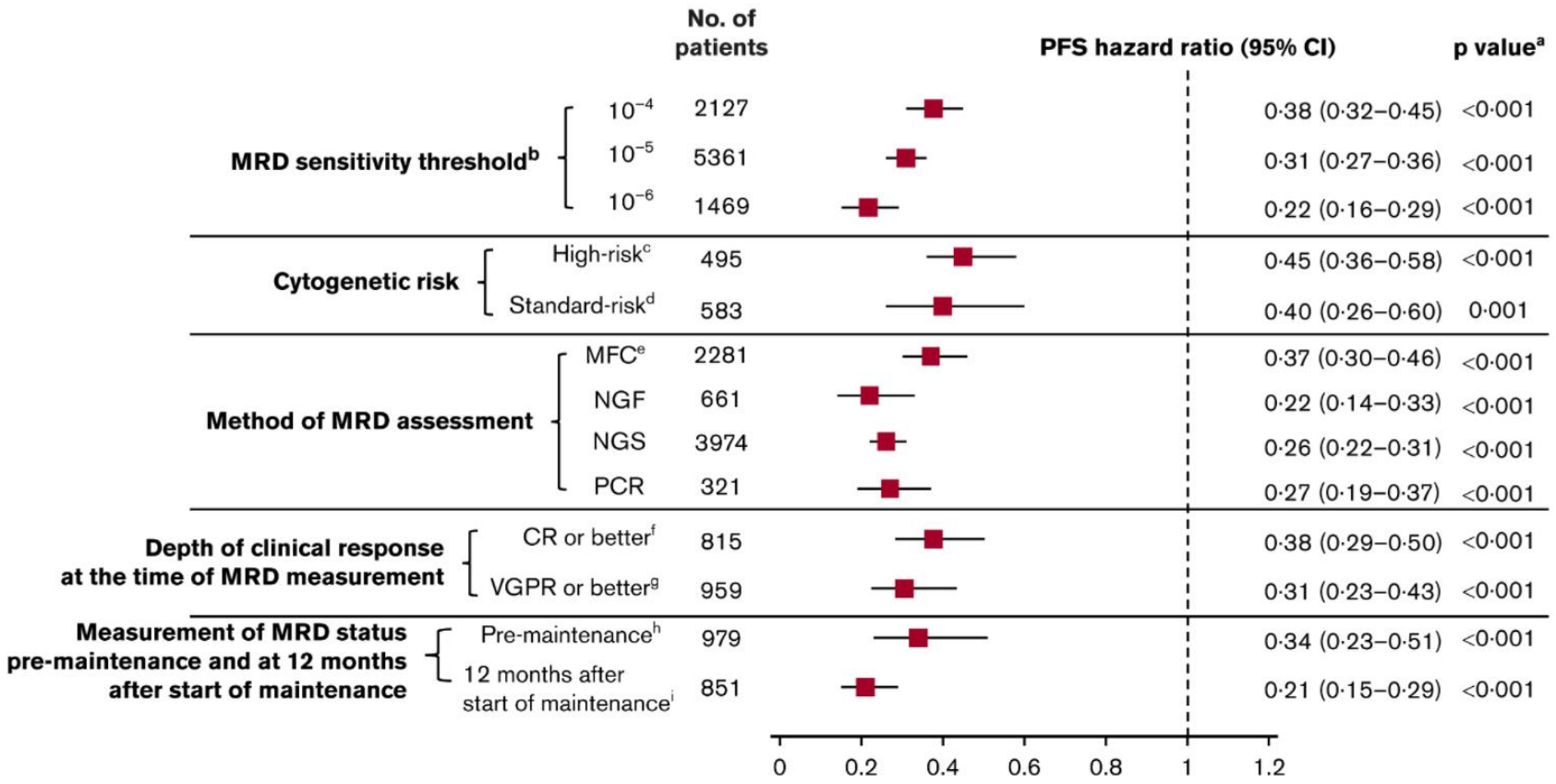


ASCT, autologous stem cell transplantation; CA, cytogenetic abnormality; MRD, minimal residual disease; NGF; next-generation flow; VRD, bortezomib, lenalidomide, dexamethasone.

*Open-label, phase III study (n = 458) patients who received 6 induction cycles of VRD; underwent ASCT conditioned with busulfan-melphalan or melphalan-200; and received 2 consolidation cycles of VRD.

Goicoechea I, et al. *Blood*. 2021;137(1):49. NCT01916252

Association of MRD negativity and PFS in different subgroups of patients: meta-analysis of 44 studies (n = 8,908)



Factors that impact PFS:

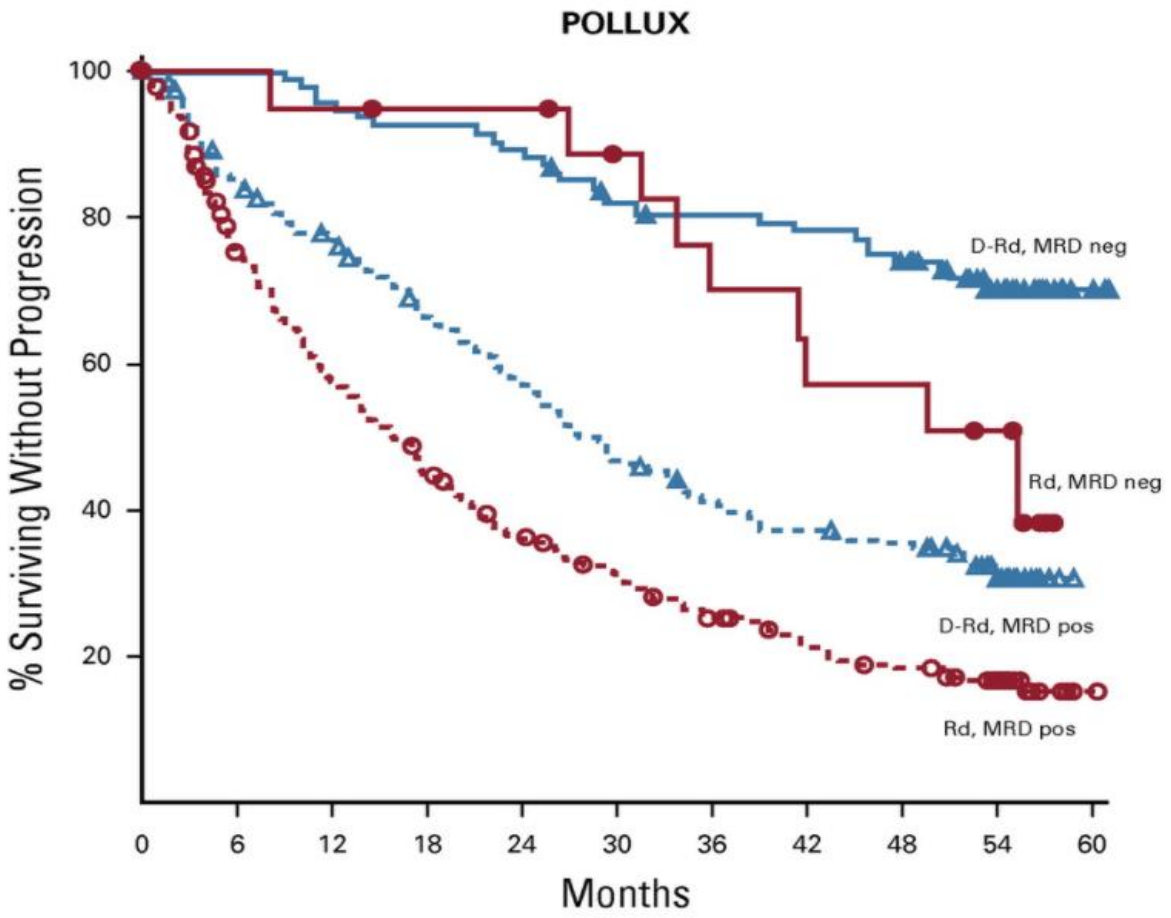
1. Sensitivity level (method used and duration of therapy)
2. Type of treatment
3. Prognostic factors (cytogenetics)
4. Age

CI, confidence interval; CR, complete response; MFC, multiparameter flow cytometry; MRD, minimal residual disease; NGF, next-generation flow; NGS, next-generation sequencing; No, number; PCR, polymerase-chain reaction; PFS, progression-free survival; VGPR, very good partial response.

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

Impact of sustained MRD negativity in the relapsed setting

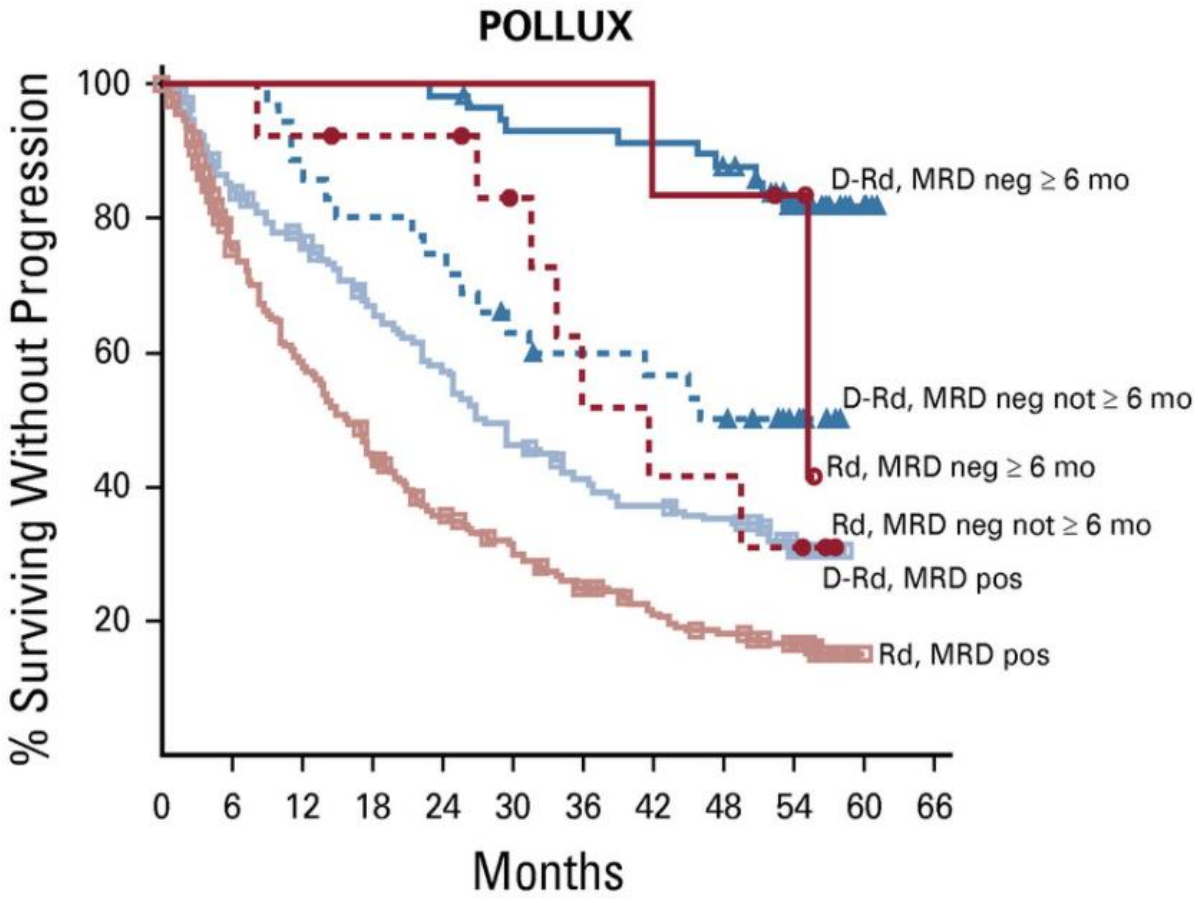
Achievement of MRD 10^{-5}



D-Rd, daratumumab, lenalidomide, dexamethasone; mo, months; MRD, minimal residual disease; neg, negative; pos, positive; Rd, lenalidomide, dexamethasone.
Avet-Loiseau H, et al. *J Clin Oncol*. 2021;39(10):1139. NCT02076009

Impact of sustained MRD negativity in the relapsed setting

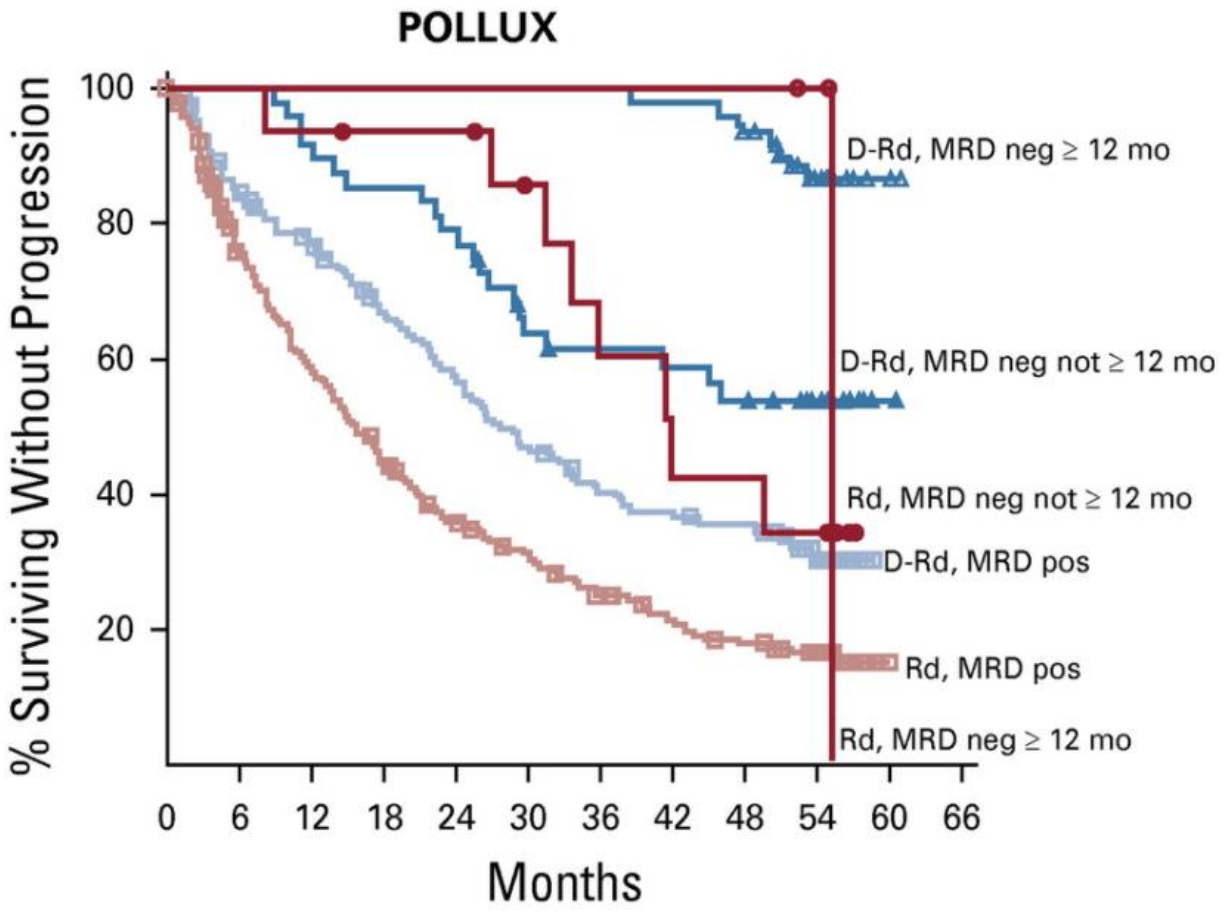
MRD negativity sustained ≥6 mo



D-Rd, daratumumab, lenalidomide, dexamethasone; mo, months; MRD, minimal residual disease; neg, negative; pos, positive; Rd, lenalidomide, dexamethasone.
Avet-Loiseau H, et al. *J Clin Oncol*. 2021;39(10):1139. NCT02076009

Impact of sustained MRD negativity in the relapsed setting

MRD negativity sustained ≥12 mo



D-Rd, daratumumab, lenalidomide, dexamethasone; mo, months; MRD, minimal residual disease; neg, negative; pos, positive; Rd, lenalidomide, dexamethasone.
Avet-Loiseau H, et al. *J Clin Oncol*. 2021;39(10):1139. NCT02076009

How can we increase the proportion of patients who can achieve operational cure?

CURRENTLY >50% of patients with MRD <0 (10^{-6}) remain free of progression at 8 years with:

- Triplet induction (VTD/VRD; 3–6 cycles)
- HDM/ASCT (1/2)
- Maintenance: lenalidomide[1]

***BUT**, upfront daratumumab increases the MRD <0 rate*[2]

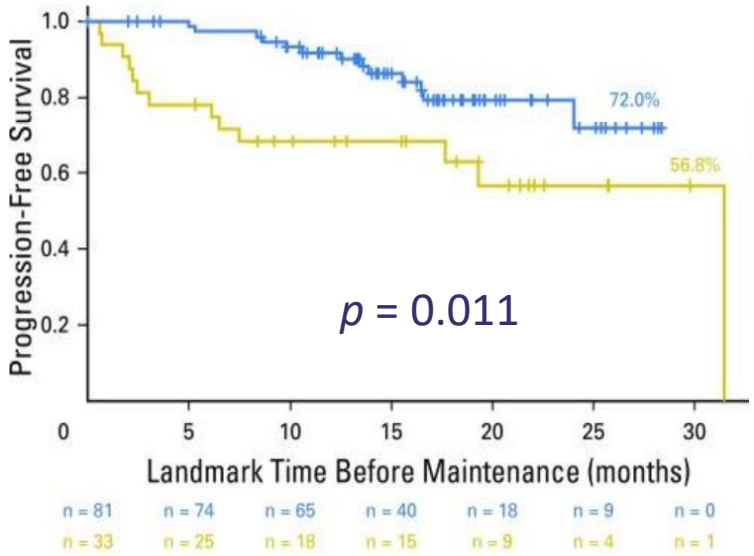
Updated analysis of the GRIFFIN trial[2]

MRD level	End of consolidation Dara-RVD	End of consolidation RVD	After 12m maintenance Dara-RVD	After 12m maintenance Dara-RVD
10^{-5}	50%	20.4%	62.5%	27.2%
10^{-6}	10.6%	2.9%	26.9%	12.6%

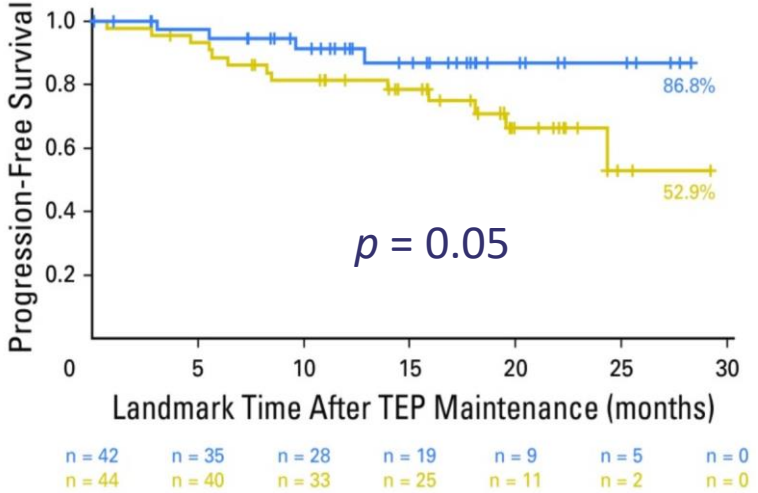
ASCT, autologous stem cell transplant; dara, daratumamab; HDM, high-dose melphalan; m, months; MRD, minimal residual disease; VRD, bortezomib, lenalidomide, dexamethasone; VTD, botezumab, thalidomide, dexamethasone; y, years.

1. Perrot A, et al. Abstract #143. 2020 ASH Meeting. **2.** Kaufman JL, et al. Abstract #549. 2020 ASH Meeting. NCT02874742

The role of PET-CT for MRD evaluation



Post-treatment <0 PET-CT has a prognostic impact IFM 2009 trial analysis



Improved PFS in patients who are both MRD <0 and PET–CT <0

Challenges of regular MRD that can be solved with PET-CT:

- Extra-medullary disease
- Bone marrow MRD can be falsely negative
- Patchy involvement
- Diluted sample

IFM, Intergroupe Francophone du Myélome; MRD, minimal residual disease; PET-CT, positron emission tomography-computed tomography; PFS, progression-free survival.

Moreau P, et al. *J Clin Oncol.* 2017;35(25):2911. NCT01309334

New definition for MRD negativity

IMWG MRD criteria (requires a complete response as defined below)	
Sustained MRD-negative	MRD negativity in the marrow (NGF or NGS, or both) and by imaging as defined below, confirmed minimum of 1 year apart. Subsequent evaluations can be used to further specify the duration of negativity (eg, MRD-negative at 5 years)†
Flow MRD-negative	Absence of phenotypically aberrant clonal plasma cells by NGF‡ on bone marrow aspirates using the EuroFlow standard operation procedure for MRD detection in multiple myeloma (or validated equivalent method) with a minimum sensitivity of 1 in 10^5 nucleated cells or higher
Sequencing MRD-negative	Absence of clonal plasma cells by NGS on bone marrow aspirate in which presence of a clone is defined as less than two identical sequencing reads obtained after DNA sequencing of bone marrow aspirates using the LymphoSIGHT platform (or validated equivalent method) with a minimum sensitivity of 1 in 10^5 nucleated cells§ or higher
Imaging plus MRD-negative	MRD negativity as defined by NGF 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¶

MRD negativity at the level of 10^{-5}

A

MRD-negative by NGF

or

+

C

Imaging plus cellular MRD-negative

B

MRD-negative by NGS

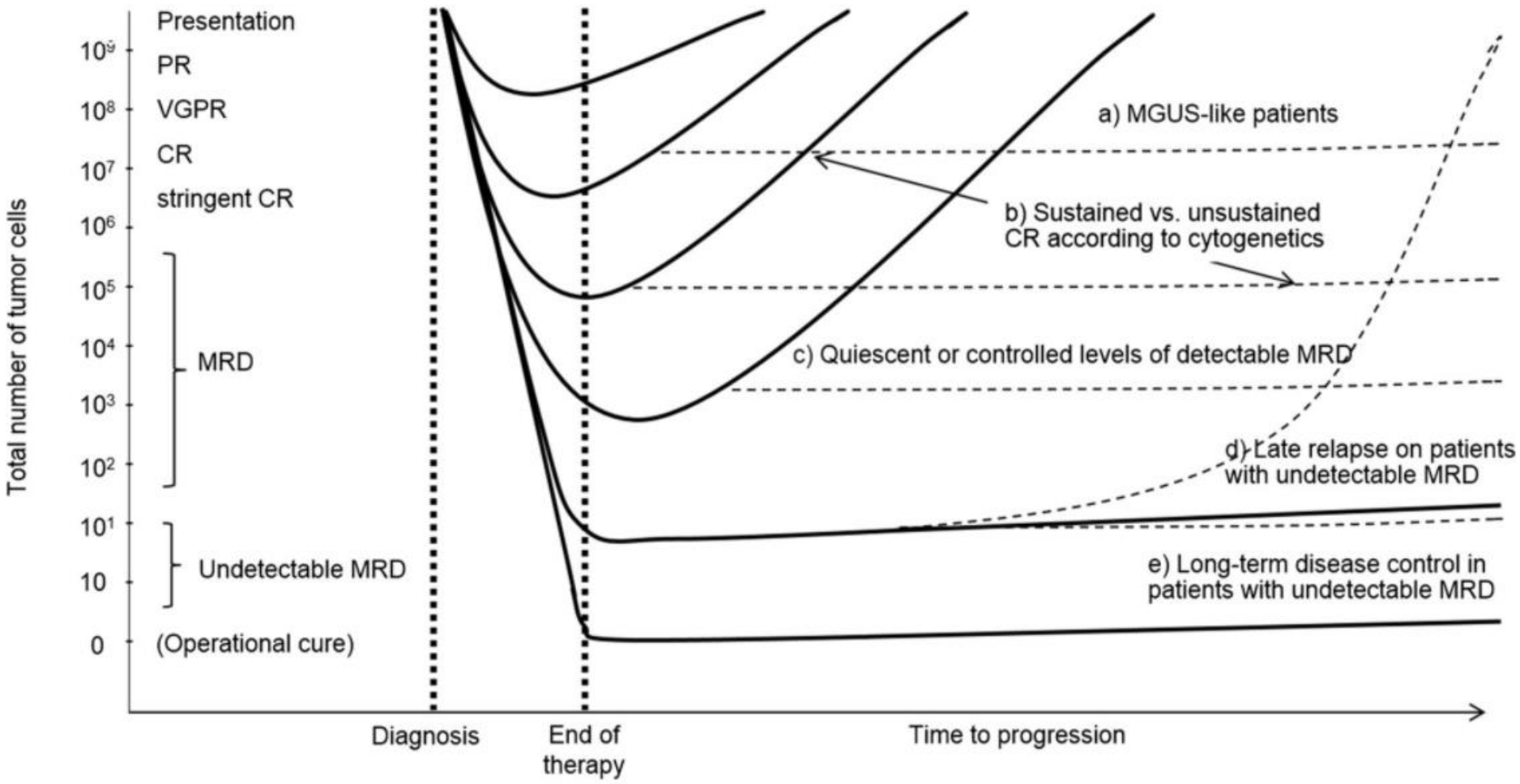
MRD, minimal residual disease; NGF, next-generation flow; NGS, next-generation sequencing.
Kumar S, et al. *Lancet Oncol*. 2016;17(8):e328.

Conclusions

- The requirement for long-term (10-year) CR is about MRD negativity (at least 10^{-5}), but the highest probability of long-term PFS is at the level of 10^{-6}!
- MRD negativity should be sustained for at least 1 year.
- MRD negativity is less frequent in high-risk myeloma but can be associated with longer PFS.
- PET–CT scan negativity is likely an important requirement.
- There is a high probability of ‘operational cure’ in young patients with myeloma receiving a ‘rejuvenated’ total therapy package (induction with PIs, IMiDs, anti-CD38, ASCT, and maintenance).
- Some elderly patients can also expect ‘operational cure.’

ASCT, autologous stem cell transplant; CR, complete response; IMiD, immunomodulatory agent; MRD, minimal residual disease; PET-CT, positron emission tomography-computed tomography; PFS, progression free survival; PI, proteosome inhibitor.

Goals of therapy in myeloma: the search for a *cure*



MRD by

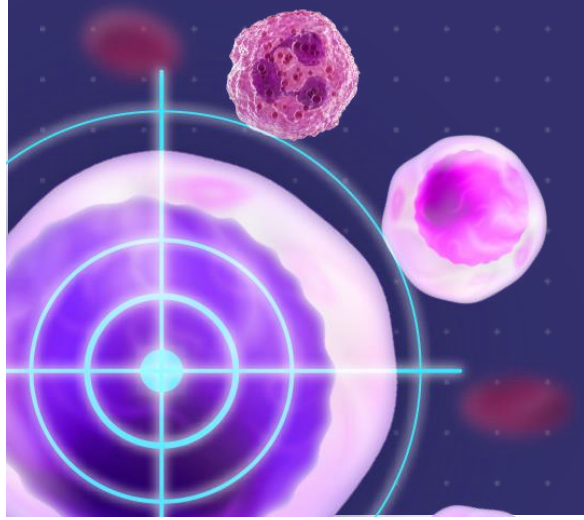
- Flow (NGF)
- Sequencing (NGS)
- Imaging (PET)

CR, compete response; MGUS, monoclonal gammopathy of undetermined significance; MRD, minimal residual disease; NGF, next-generation flow, NGS, next-generation sequencing; PET, positron-emission tomography; PR, partial response; VGPR, very good partial response.

Paiva B, et al. *Blood*. 2015;125(20):3059.

MultipleMyelomaHub

Thank you



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