Is the treatment of high-risk SMM the way for achieving the cure?

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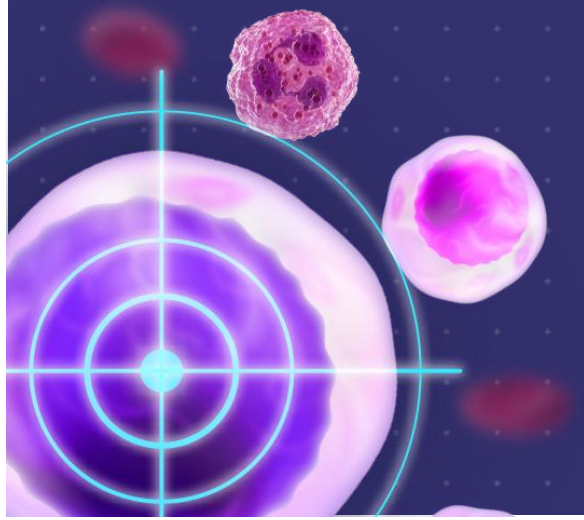


Disclosures

Research Support/P.I.	NA
Employee	NA
Consultant	NA
Major stakeholder	NA
Speakers bureau	NA
Honoraria	Takeda, Janssen, Celgene, Amgen, GSK, AbbVie, Oncopeptides, Sanofi, ONO
Scientific advisory board	Takeda, Janssen, Celgene, Amgen, GSK, AbbVie, Oncopeptides, Sanofi, ONO, Regeneron, Pfizer, Seagen

NA, not applicable.

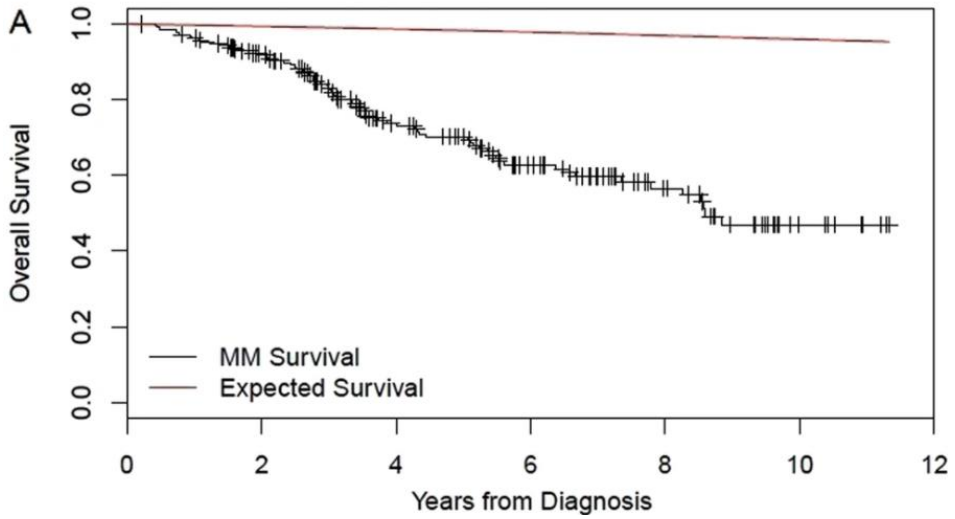
What is the definition of cure?

- **1963:** Cure should connote that in time—probably a decade or two after treatment—there remains a group of disease-free survivors whose annual death rate from all causes is similar to that of a normal population group of the same sex and age distribution.
- **1971:** Cure should be unassociated with continuing morbidity from the disease or its treatment.
- **Now:** The particular time point—typically between 1–5 years in most curable cancers—at which the plateau in disease-free survival ought to occur, although it can depend on the disease kinetics of a particular tumor.

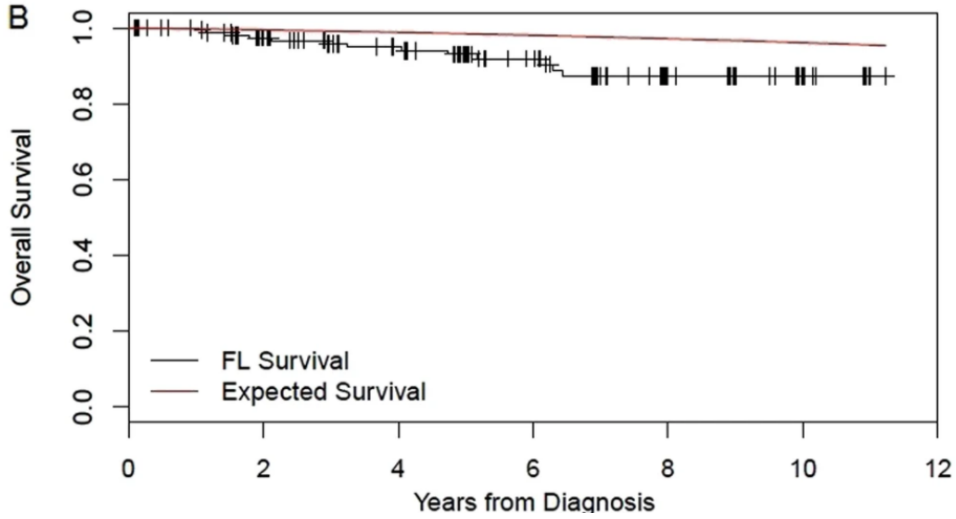
Are these concepts applicable to myeloma?

Is MM a curable disease?

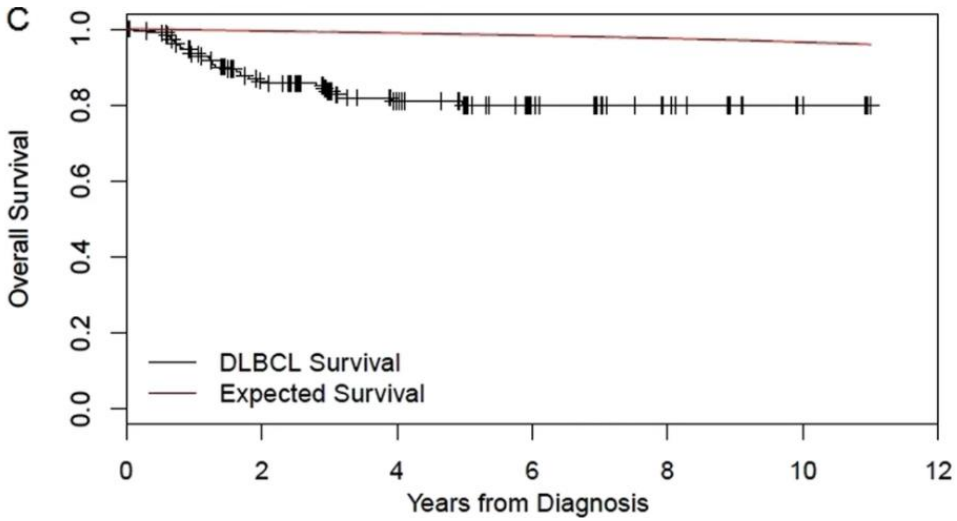
MM



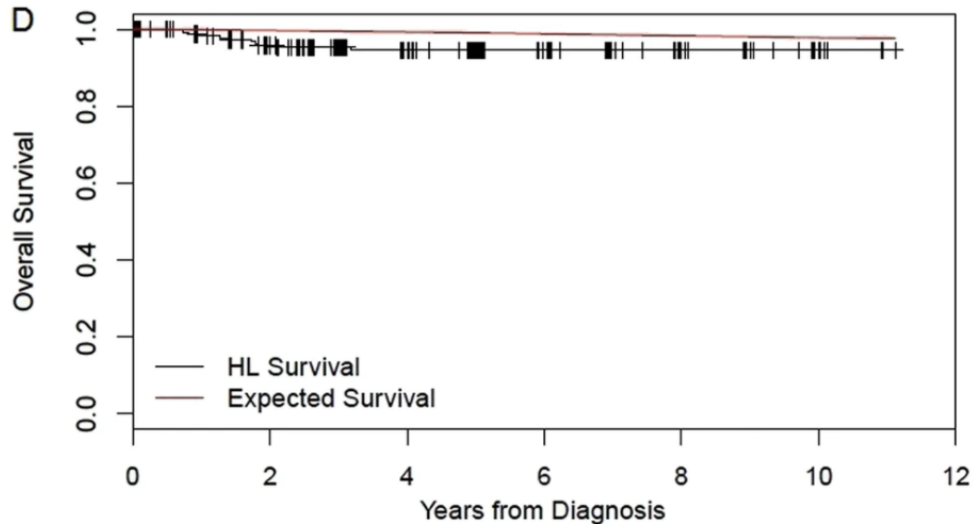
FL



DLBCL



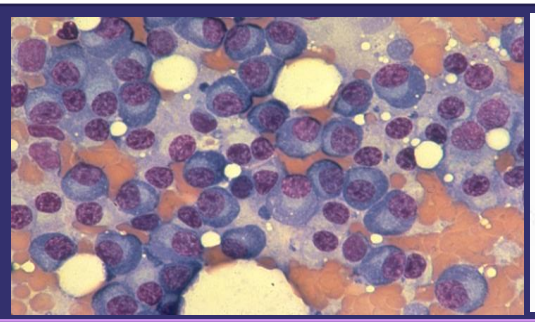
HL

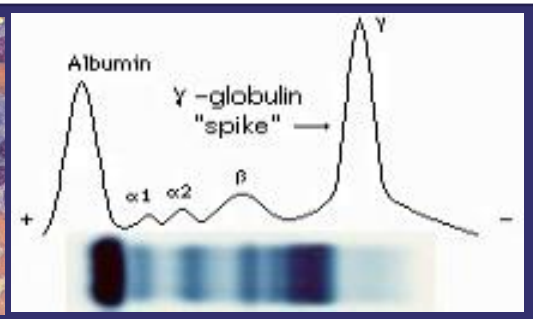


DLBCL; diffuse large B cell lymphoma; FL; follicular lymphoma; HL, Hodgkin lymphoma; MM, multiple myeloma; OS, overall survival.

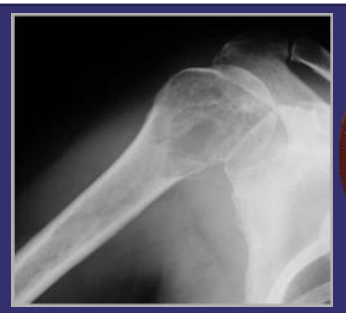
Ravi P, et al. *Blood Cancer J.* 2018;8(3):26

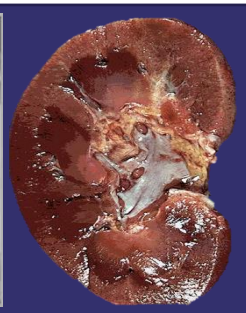
Development of myeloma



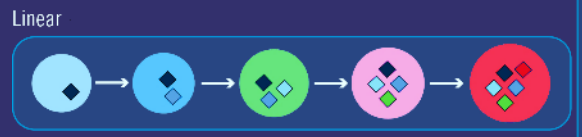


Myeloma-defining events

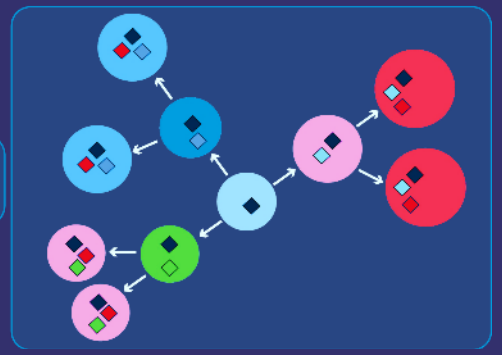




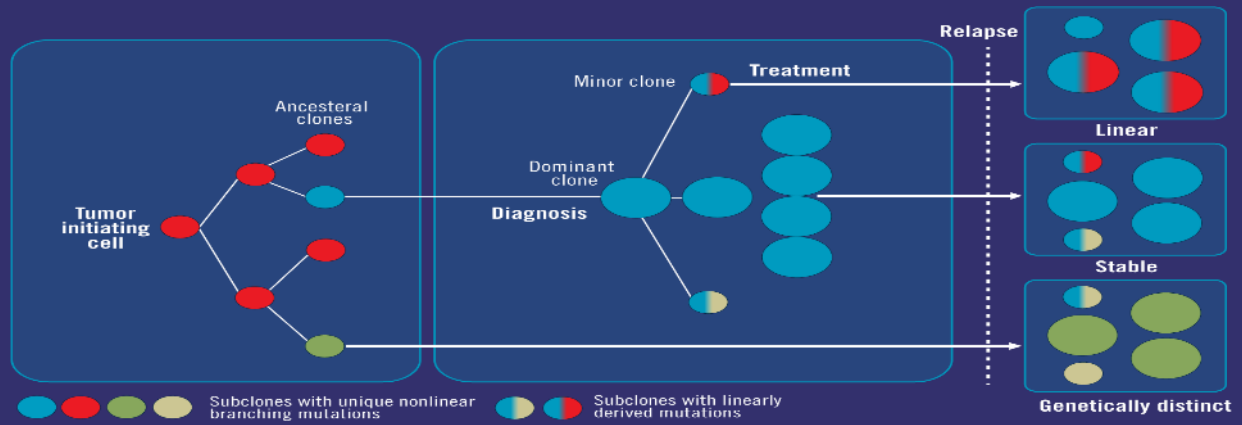
Malignant PCs may not evolve in a linear manner



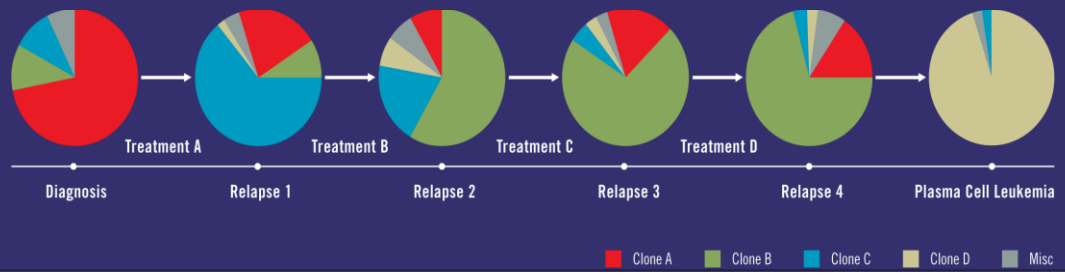
Branching model, resulting in substantial clonal diversity

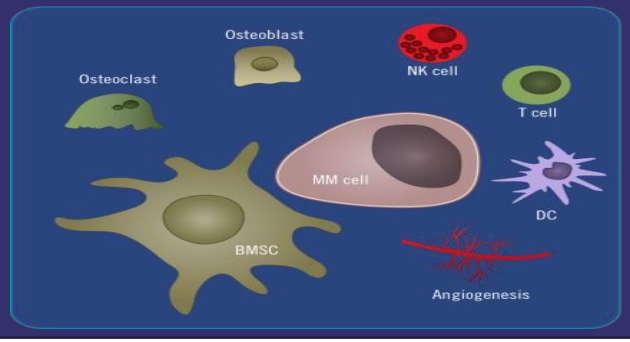


Subclonal heterogeneity is also present at all different stages of the disease



Treatment may control an indolent or sensitive clone, allowing a more aggressive clone to expand





In addition, cellular and noncellular components are important for MM pathogenesis

The roadmap to cure patients with MM

1. To eradicate all tumor cells.
2. To use high sensitivity techniques/tools to evaluate treatment efficacy.
3. **Early detection & early intervention**.
4. To use the most active treatments in patients with standard-risk disease
5. To investigate experimental therapies upfront in patients with high-risk disease

MM, multiple myeloma.

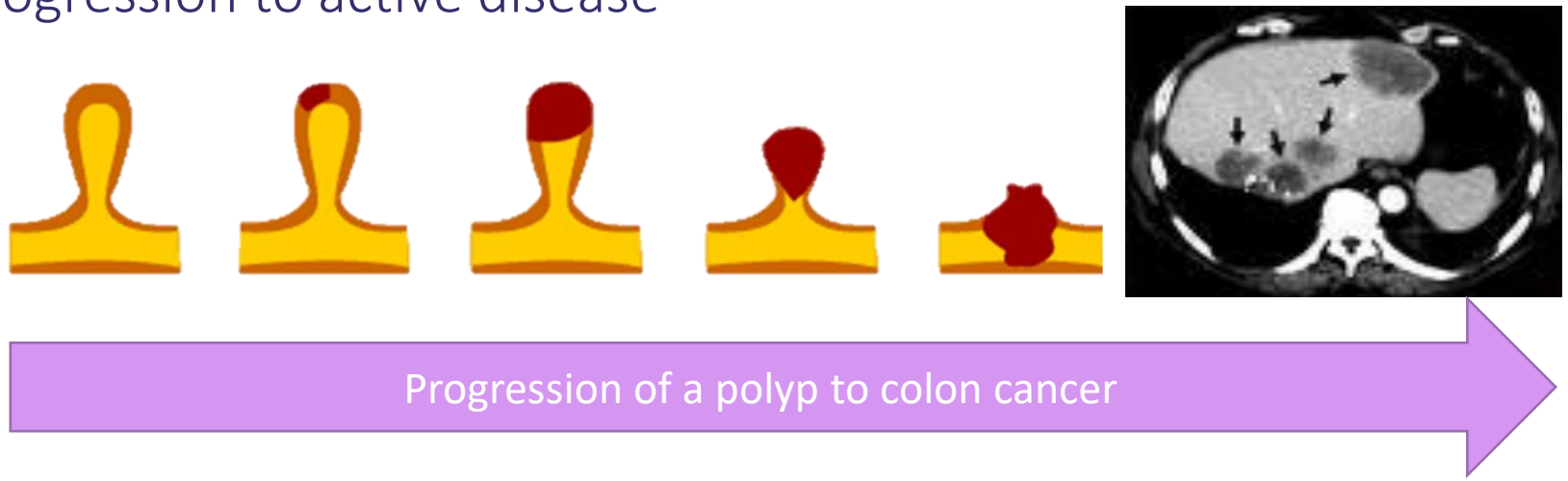
Nonhematologic malignancies: Oncology perspective

Early intervention

In almost all malignancies (breast, prostate, colon cancers, ...)

Two possible objectives:

- To cure/eradicate
- To delay progression to active disease

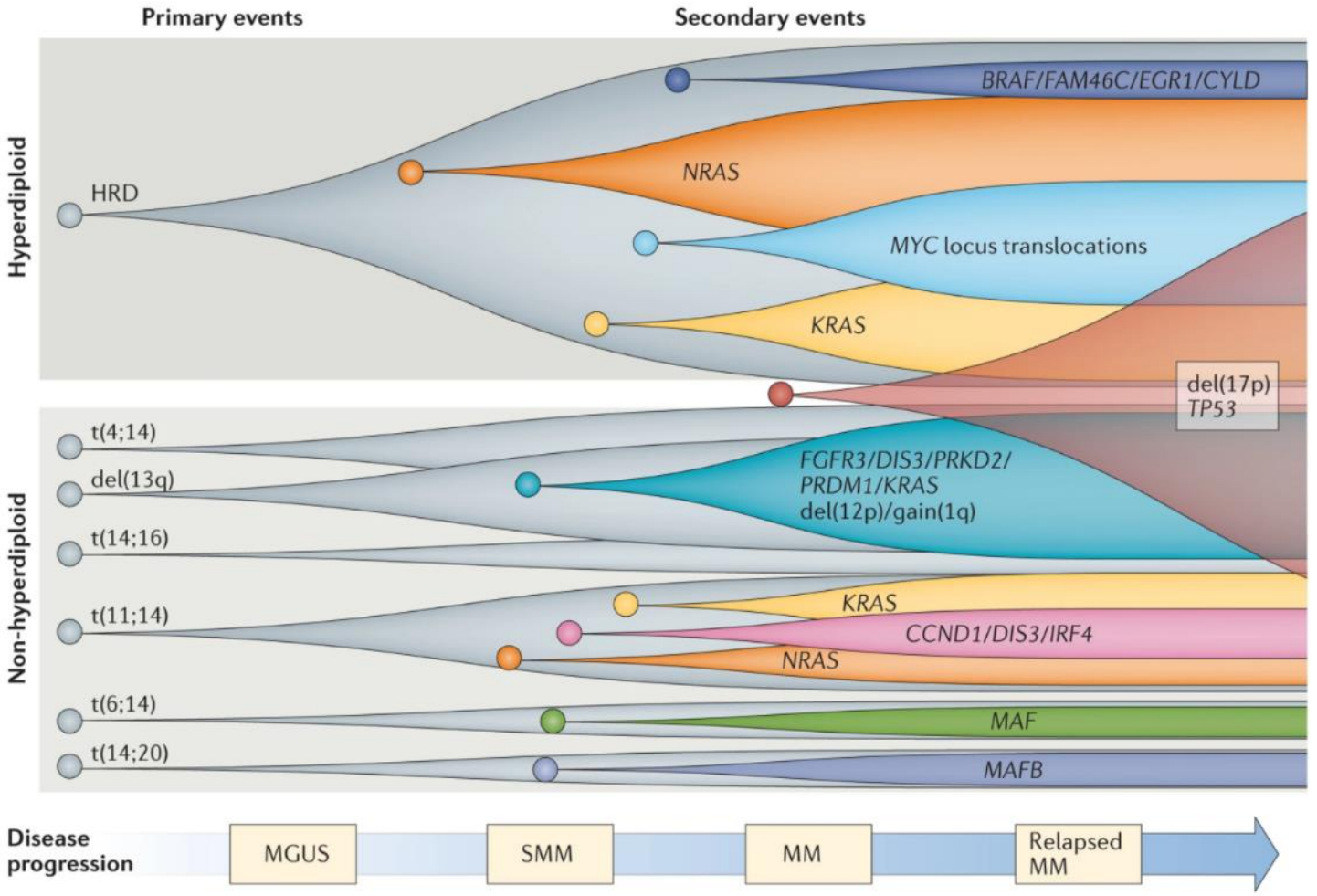


Would you consider it appropriate to wait until the colon cancer resulted in liver involvement to plan active treatment?

Model for molecular pathogenesis of SMM and MM

Initial transition to a recognizable tumor involves two mostly nonoverlapping pathways:

- primary events associated with dysregulated Cyclin D expression in SMM and MM.
- Transition from SMM to MM is associated with increased MYC expression, and sometimes with activating mutations such as K-RAS or chromosome 13 deletion.



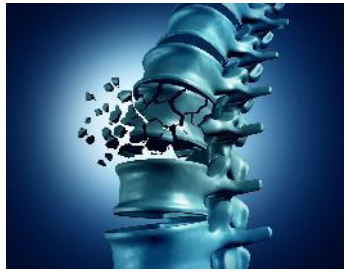
MGUS, monoclonal gammopathy of undetermined significance; MM, multiple myeloma; SMM, smoldering multiple myeloma.

Manier S, et al. *Nat Rev Clin Oncol*. 2017;14(2):100-113.

What are the signs and symptoms of MM?

- Bone pain, usually in the back and ribs

- Broken bones, usually the spine

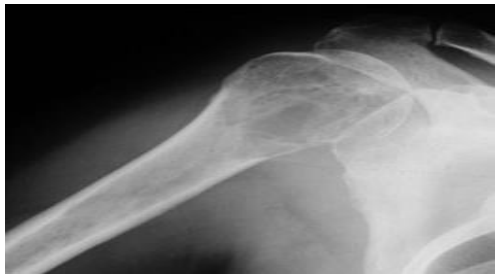


- Frequent infections and fevers

- Renal dysfunction

- Anemia

- Lytic bone lesions



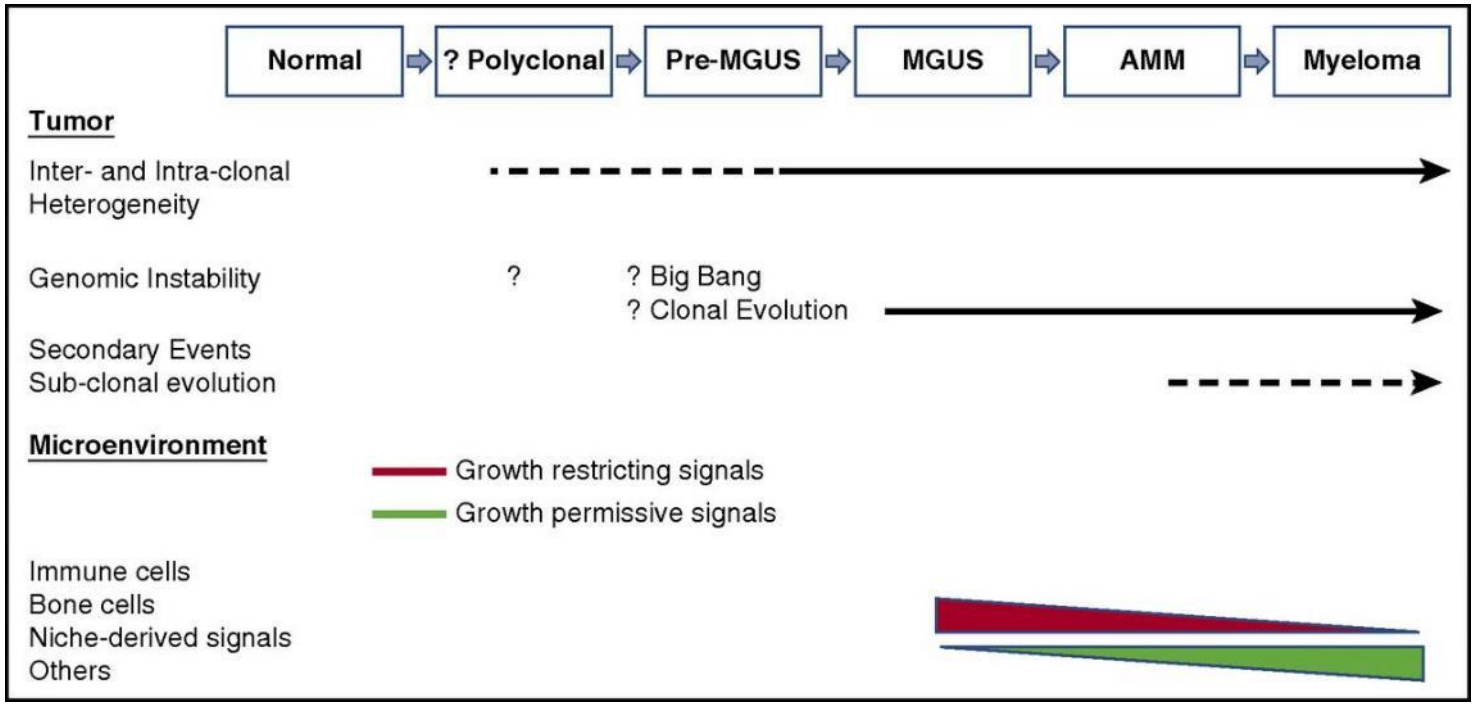
MM, multiple myeloma.

Should we treat all patients with plasma cell disorders when detected early?

Evolution of MGUS > SMM > MM

All MM clones are preceded by corresponding precursor states, but not all of them take the same road.

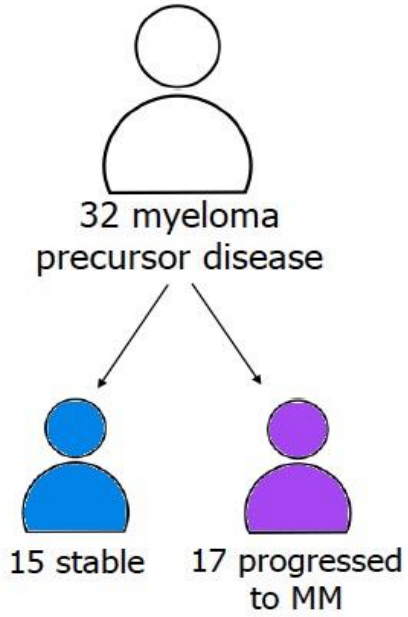
- Most genomic complexity is already established by MGUS stage
- Transition from MGUS > SMM > MM is driven by interactions with the tumor microenvironment, immune cells, bone cells, etc.
- Transition is not uniform; some patients with MGUS/SMM will never develop MM

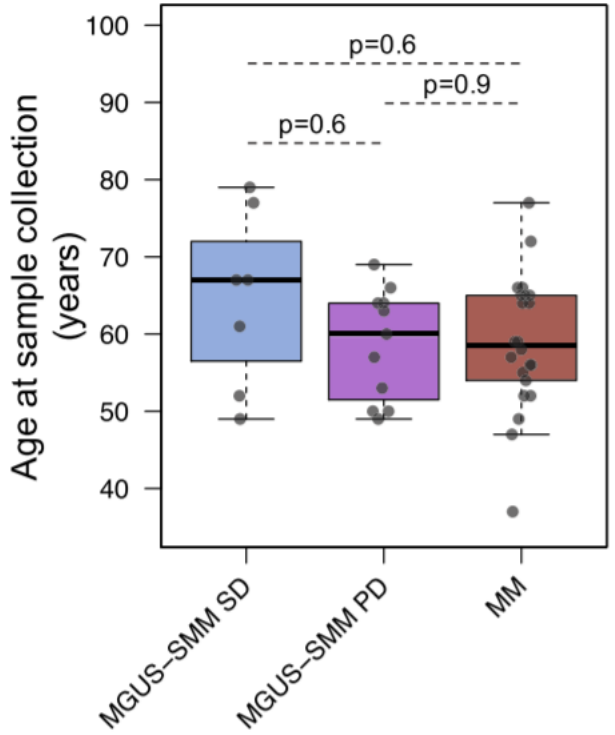


AMM, asymptomatic multiple myeloma; MGUS, monoclonal gammopathy of undetermined significance; MM, multiple myeloma; SMM, smoldering multiple myeloma.
Dhodapkar MV. *Blood*. 2016;128(23):2599-2606.

WGS reveals evidence of two biologically and clinically different entities: progressive *vs* stable precursor disease

Stable precursors present different genomic landscape *vs* progressive precursors and MM



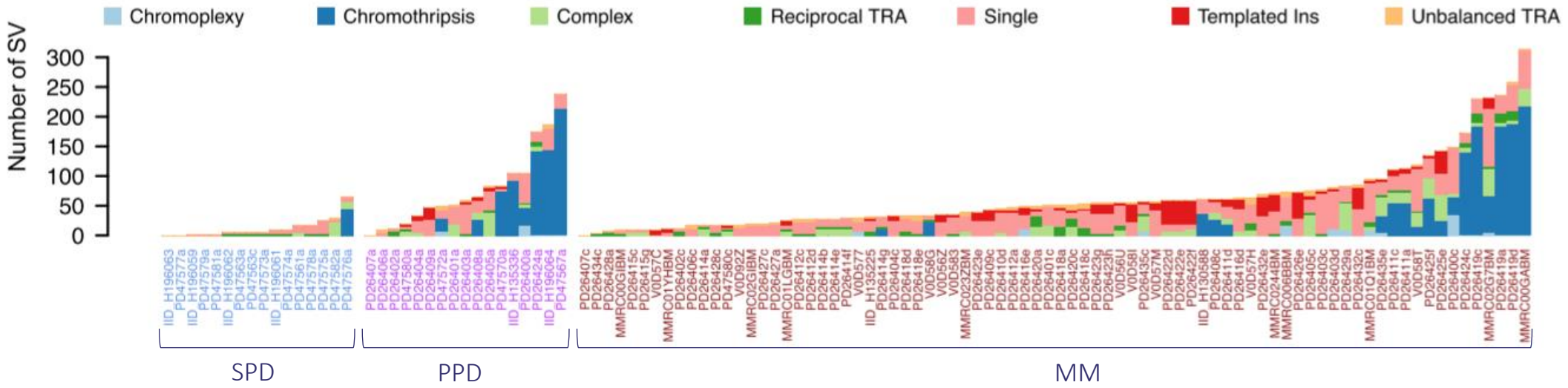


MGUS, monoclonal gammopathy of undetermined significance; MM, multiple myeloma; PD, progressive precursor disease; SD, stable precursor disease; SMM, smoldering multiple myeloma; WGS, whole-genome sequencing; *vs*, versus.

Oben B et al. *Nature Commun*. 2021;12(1):1861.

WGS reveals evidence of two biologically and clinically different entities: progressive *vs* stable precursor disease

- Patients with SD had a lower burden of structural variants and complex events, compared to those with PD and MM.
- Chromothripsis and templated insertions were absent among those with SD
- Landscape structural variants of progressors were similar to those with MM



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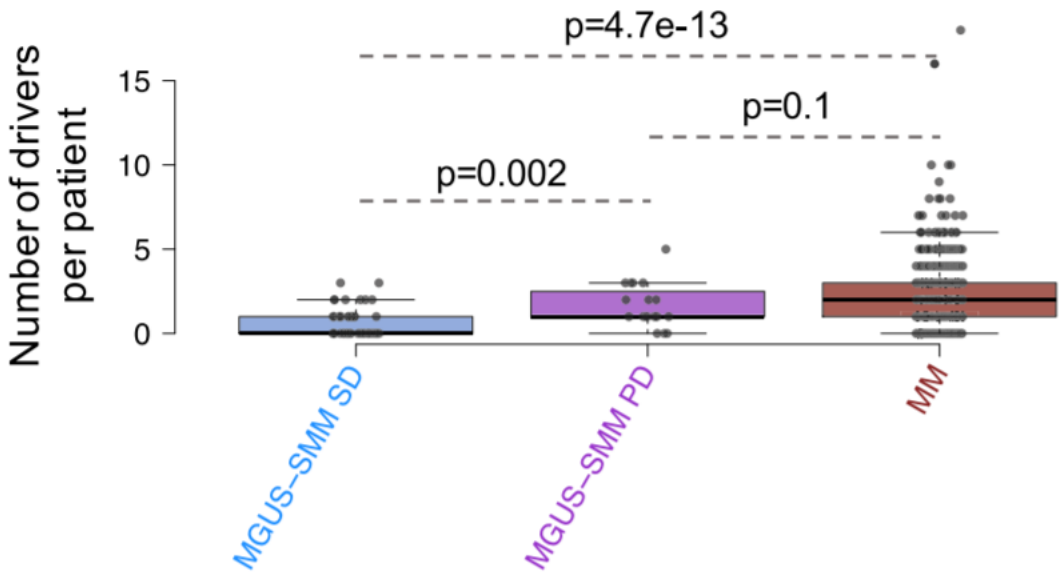
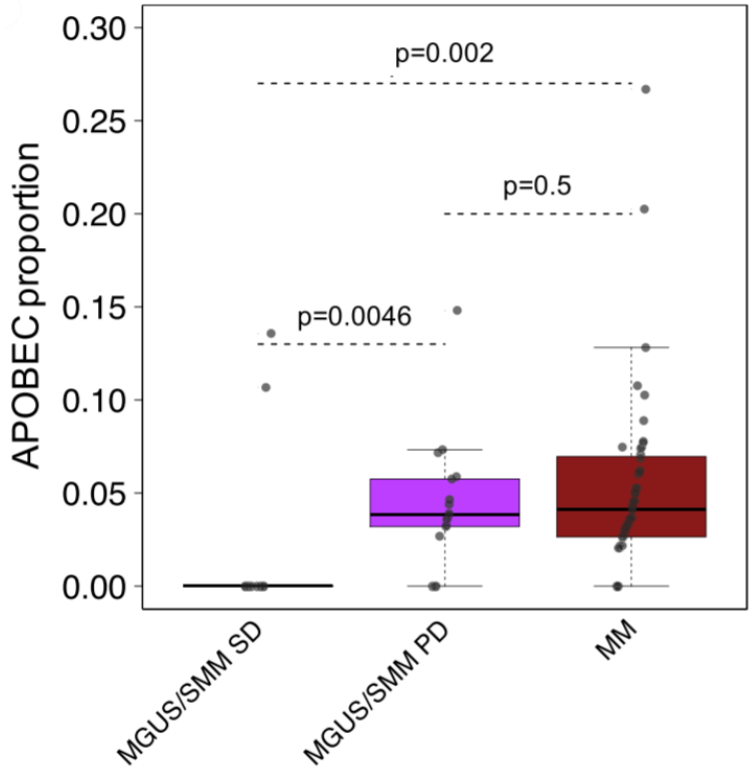
Adapted from Oben B et al. *Nature Commun*. 2021;12(1):1861.

WGS reveals evidence of two biologically and clinically different entities: progressive *vs* stable precursor disease

- Patients with SD have a lower mutational burden compared to those with PD or MM.
- Absence of canonical APOBEC mutation signature in patients with SD





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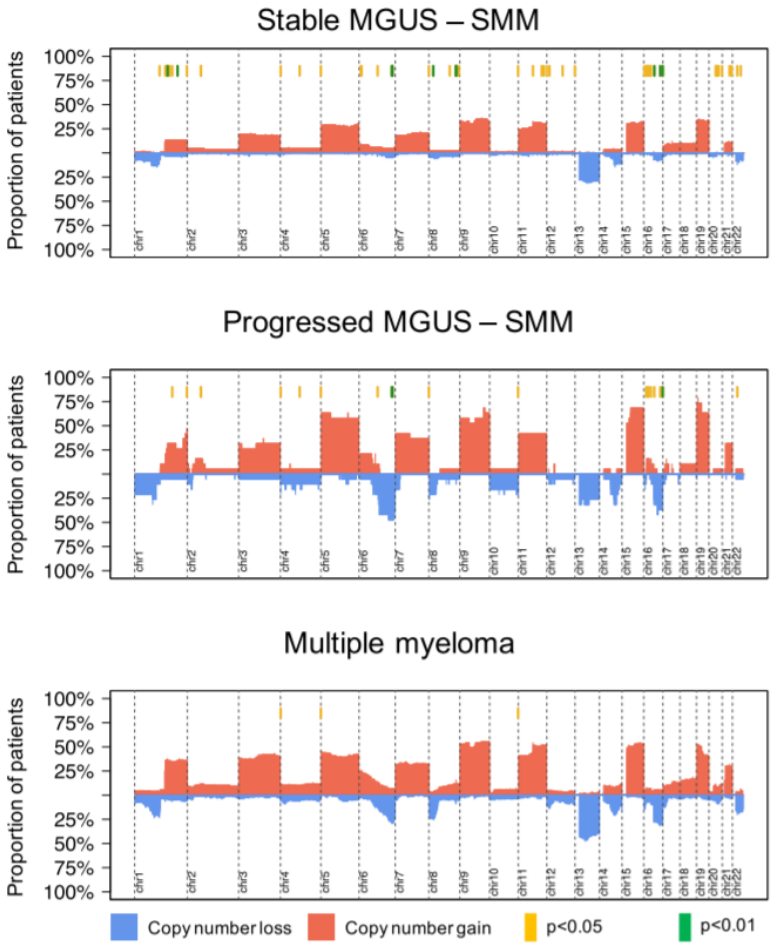
Oben B et al. *Nature Commun*. 2021;12(1):1861.

WGS reveals evidence of two biologically and clinically different entities: progressive *vs* stable precursor disease

- Patients with SD have a lower prevalence of known recurrent MM aneuploidies.
- No difference in the cytogenetic landscape of patients with PD and MM.



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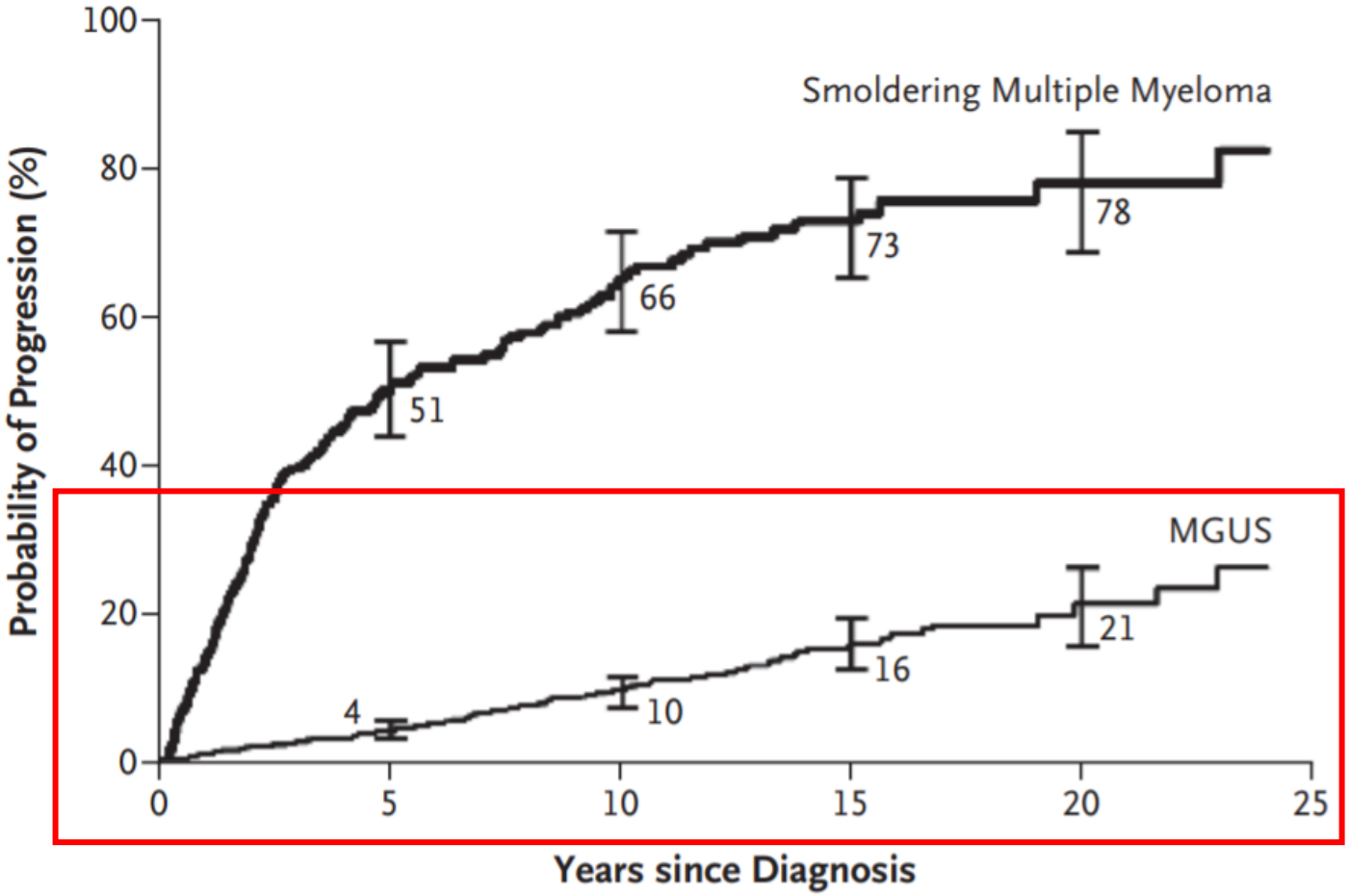
Oben B et al. *Nature Commun*. 2021;12(1):1861.

MGUS: Risk of progression to MM

Patients with MGUS should not be treated

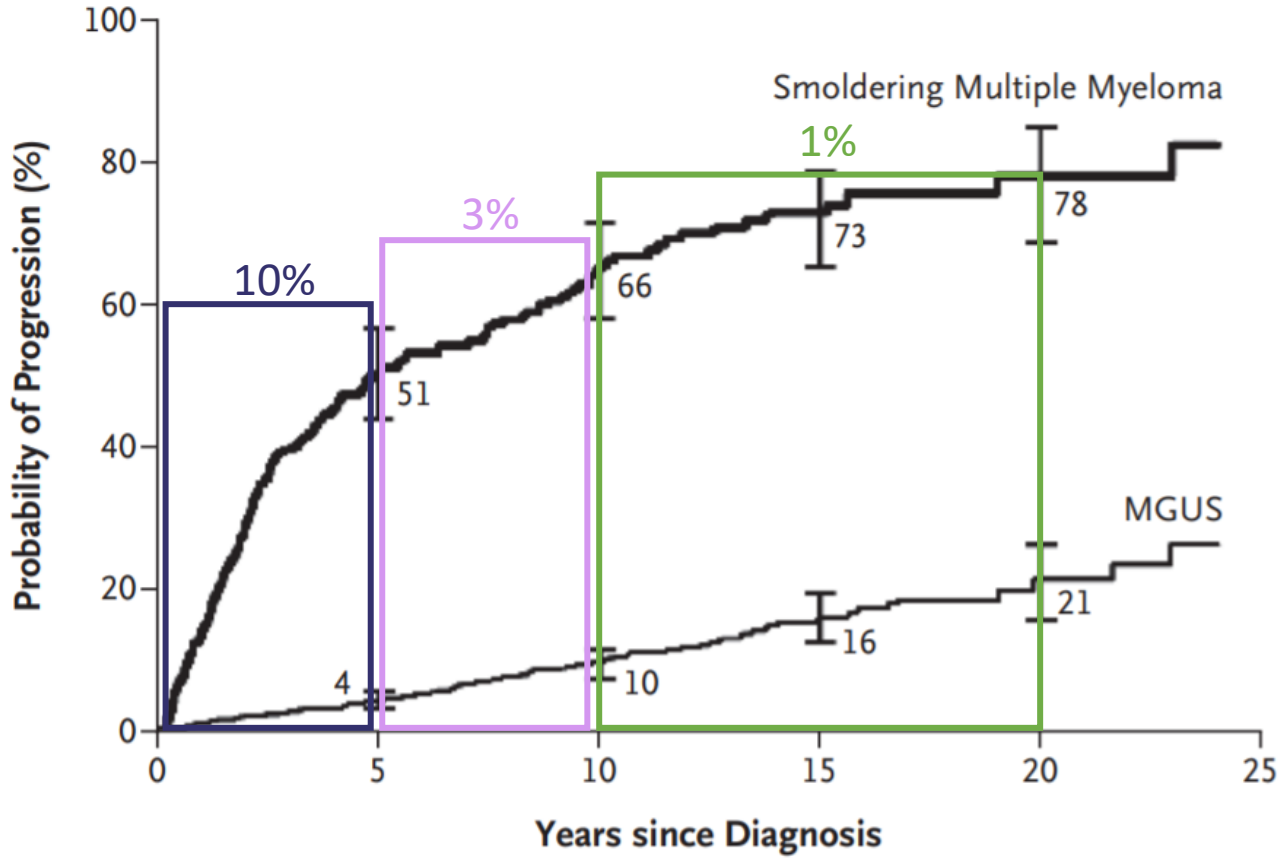


MGUS, monoclonal gammopathy of undetermined significance; MM, multiple myeloma.

Kyle RA, et al. *N Engl J Med*. 2007;356(25):2582-2590.

SMM: Risk of progression to active disease

According to the heterogeneity in the risk of progression to MM, we must identify the individual risk for each new patient with SMM.

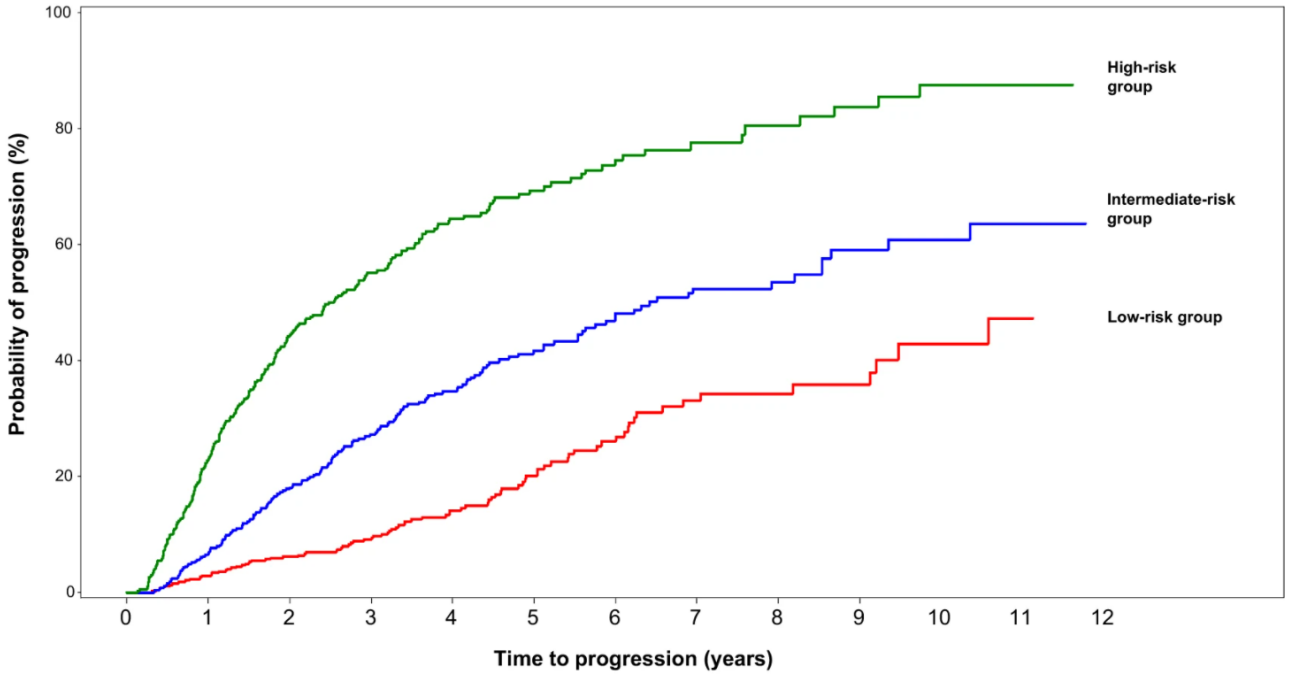


MM, multiple myeloma; SMM, smoldering multiple myeloma.
Adapted from Kyle RA, et al. *N Engl J Med*. 2007;356(25):2582-2590.

Updated risk stratification model SMM incorporating the revised IMWG diagnostic criteria (n > 1000)

2/20/20 risk stratification model:

- Serum M spike: >2 g/dL
- FLC ratio: >20
- BMPC: >20%



Risk stratification groups	Number of risk factors	HR (95% CI) *vs* low-risk group	Risk of progression at 2 years	Number of patients
Low-risk	0	Reference	**6.2%**	**522 (38.3%)**
Intermediate-risk	1	2.99 (1.97–4.54)	**17.9%**	**445 (32.7%)**
High-risk	2–3	9.02 (6.15–13.2)	**44.2%**	**396 (29.1%)**

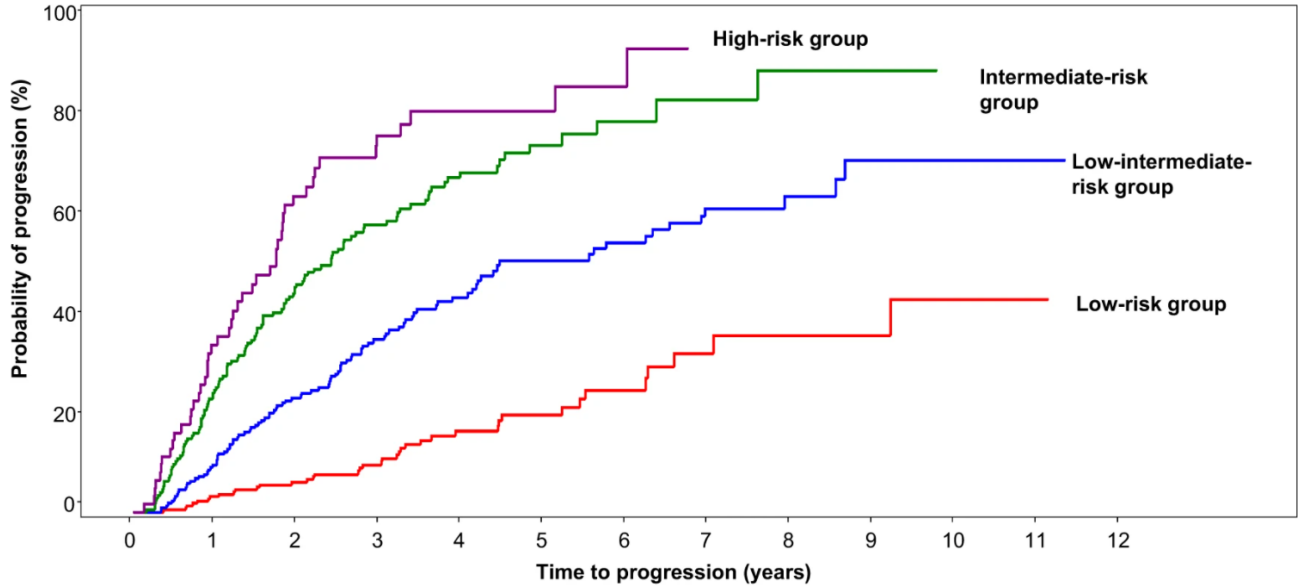
BMPC, bone marrow plasma cell; CI, confidence interval; FLC, free light-chain; HR, hazard ratio; IMWG, International Myeloma Working Group; SMM, smoldering multiple myeloma; *vs*, versus.

Adapted from Mateos MV, et al. *Blood Cancer J.* 2020;10(10):102.

Updated risk stratification model SMM incorporating the revised IMWG diagnostic criteria (n > 1000)

2/20/20 risk stratification model:

- Serum M spike: >2 g/dL
- FLC ratio: >20
- BMPC: >20%
- Plus ≥1 CA: t(4;14), t(14;16), +1q, and/or del13q/monosomy 13



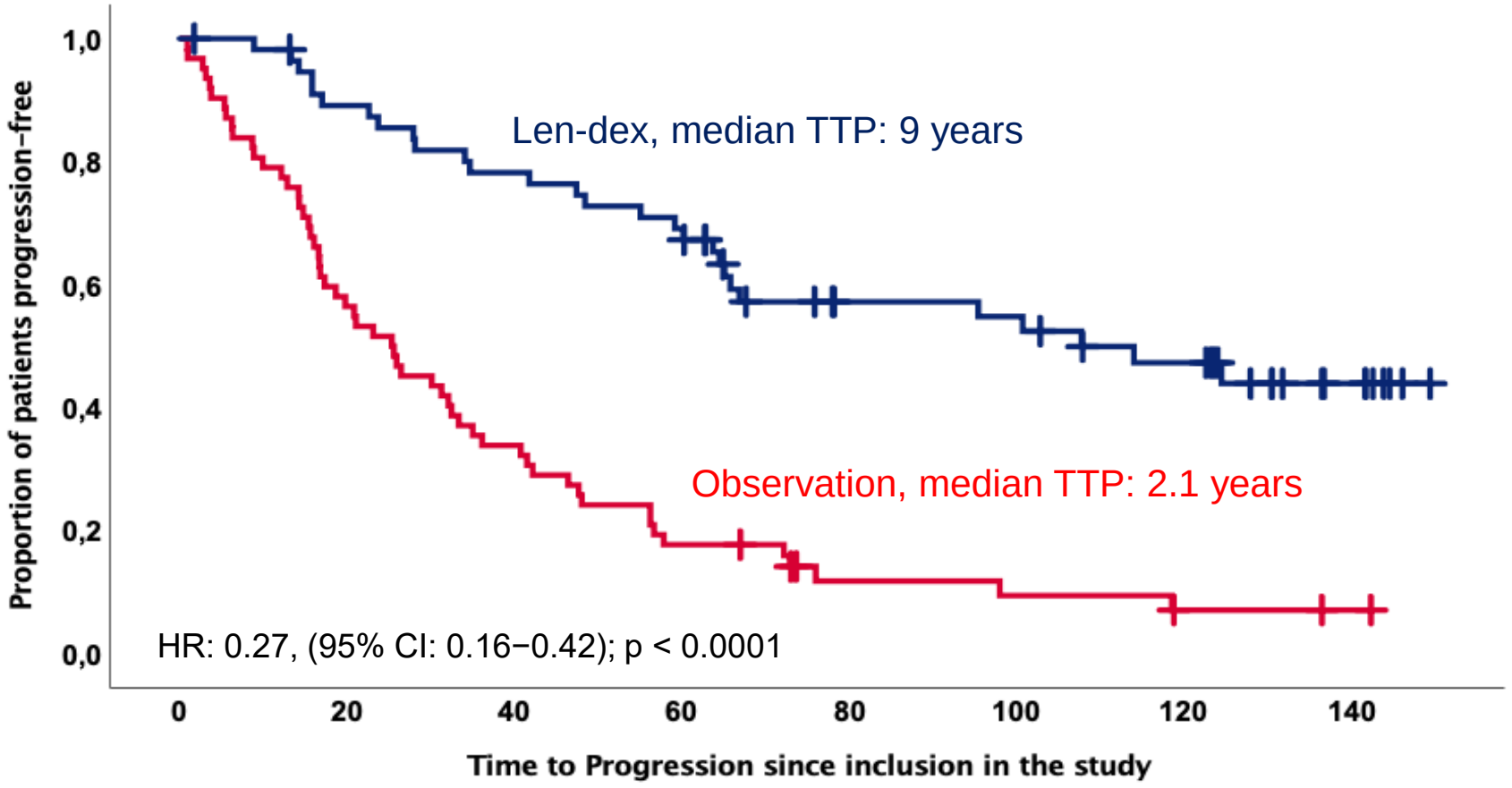
Risk stratification groups	Number of risk factors	HR (95% CI) *vs* low-risk group	Risk of progression at 2 years	Number of patients
Low-risk	0	Reference	**6.0%**	225 (32.7%)
Low-intermediate-risk	1	4.16 (2.26–7.67)	**22.8%**	224 (32.5%)
Intermediate-risk	2	9.82 (5.46–17.7)	**45.5%**	177 (25.7%)
High-risk	≥3	15.5 (8.23–29.0)	**63.1%**	63 (9.1%)

BMPC, bone marrow plasma cell; CA, cytogenetic abnormality; CI, confidence interval; FLC, free light-chain; HR, hazard ratio; IMWG, International Myeloma Working Group; SMM, smoldering multiple myeloma; *vs*, versus.

Adapted from Mateos MV, et al. *Blood Cancer J.* 2020;10(10):102.

QuiRedex phase III study: Early treatment of high-risk SMM with Len-dex led to sustained benefit in TTP compared with observation

Median follow-up 10.8 years (n = 119)



CI, confidence interval; HR, hazard ratio; Len-dex, lenalidomide, dexamethasone; SMM, smoldering multiple myeloma; TTP, time to progression.
Adapted from Mateos MV, et al. Abstract #294867 (e-Poster #EP950). 25th EHA Annual Meeting; Jun 11–21, 2020; Virtual. NCT00480363.

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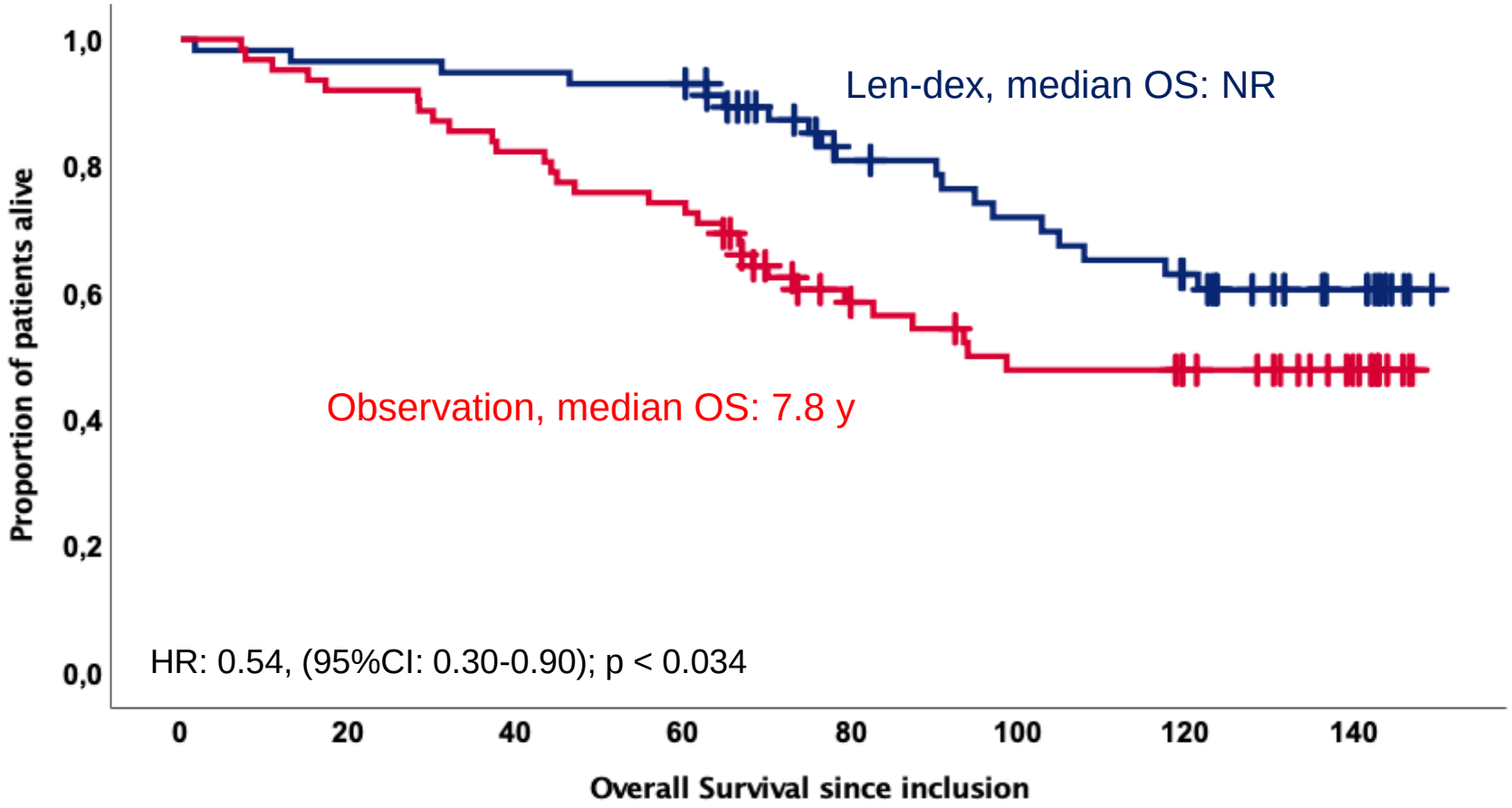
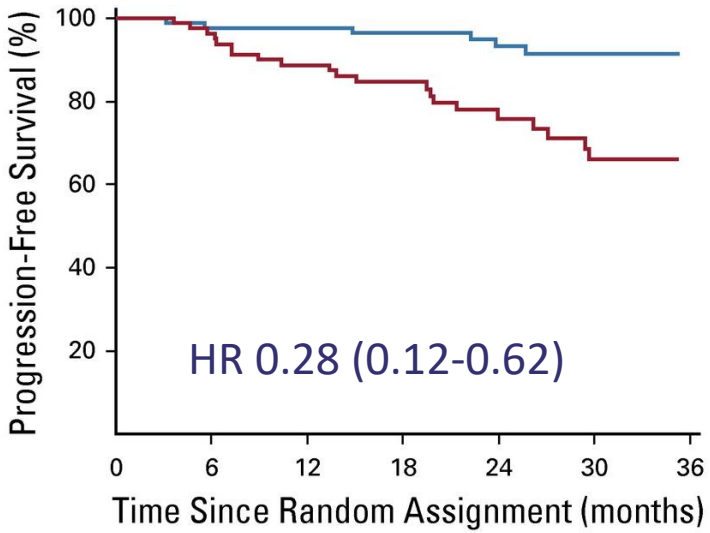


CI, confidence interval; HR, hazard ratio; Len-dex, lenalidomide, dexamethasone; NR; not reached; OS, overall survival; SMM, smoldering multiple myeloma; y, years.
Adapted from Mateos MV, et al. Abstract #294867 (e-Poster #EP950). 25th EHA Annual Meeting; Jun 11–21, 2020; Virtual. NCT00480363.

E3A06: Len *vs* observation in patients with asymptomatic SMM (n = 182)

Early treatment with Len significantly prevented progression to MM especially in the high-risk subgroup

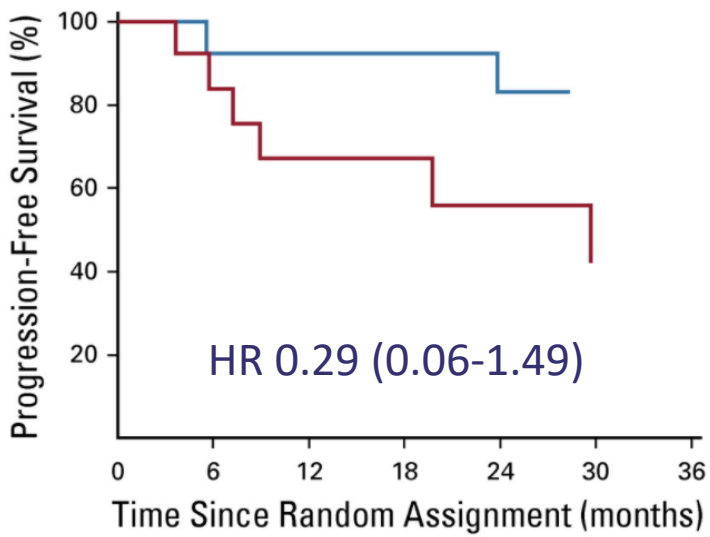
PFS in all patients



No. at risk:

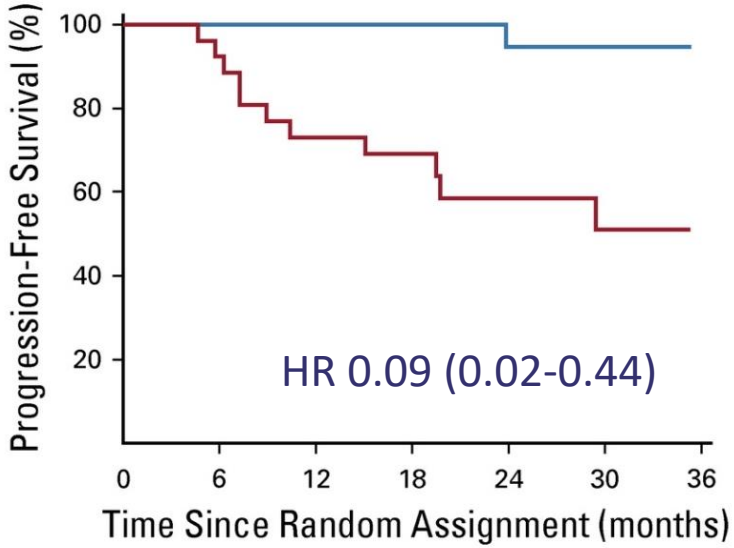
Lenalidomide	90	83	81	72	55	42	35
Observation	92	77	67	56	34	26	19

PFS with Mayo 2008 high-risk



	14	12	11	11	8	6	6
	15	10	8	7	4	3	3

PFS with Mayo 2018 high-risk



	25	25	23	22	18	15	13
	31	24	19	14	8	7	5

Mayo 2008: BMPC ≥ 10% + MC ≥ 3 g/dl; Mayo 2018: 2/20/20

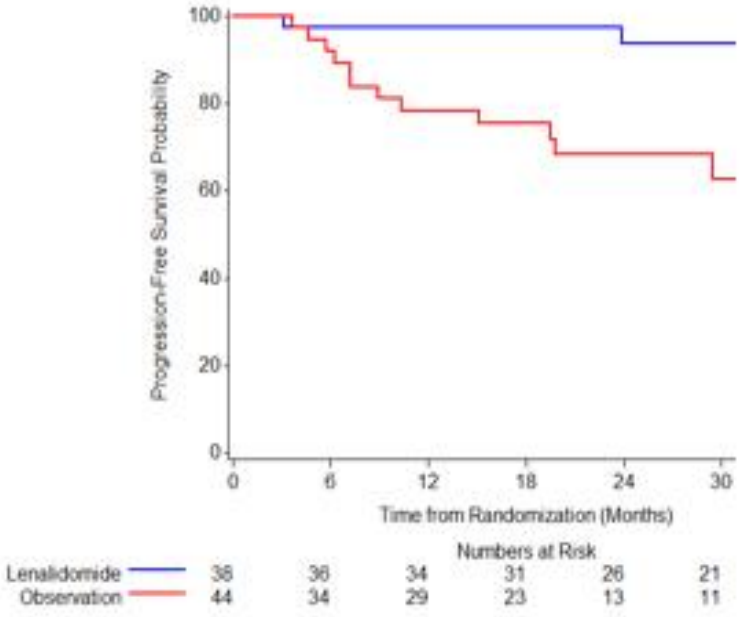
BMPC, bone marrow plasma cell; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; sFLC, serum free light-chain; HR, hazard ratio; Len, lenalidomide; No. number; PS, performance status; SMM, smoldering multiple myeloma; *vs*, versus.

Lonial S, et al. *J Clin Oncol.* 2020;38(11):1126-1137. NCT01169337

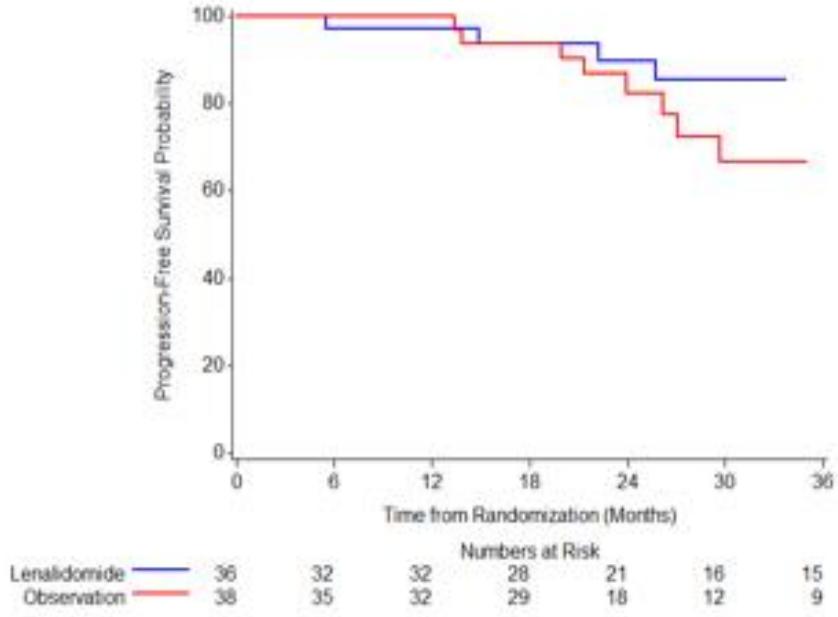
E3A06 (Len *vs* observation): Patients with high-risk SMM benefit the most from treatment

IMWG 2019 model: 2/20/20

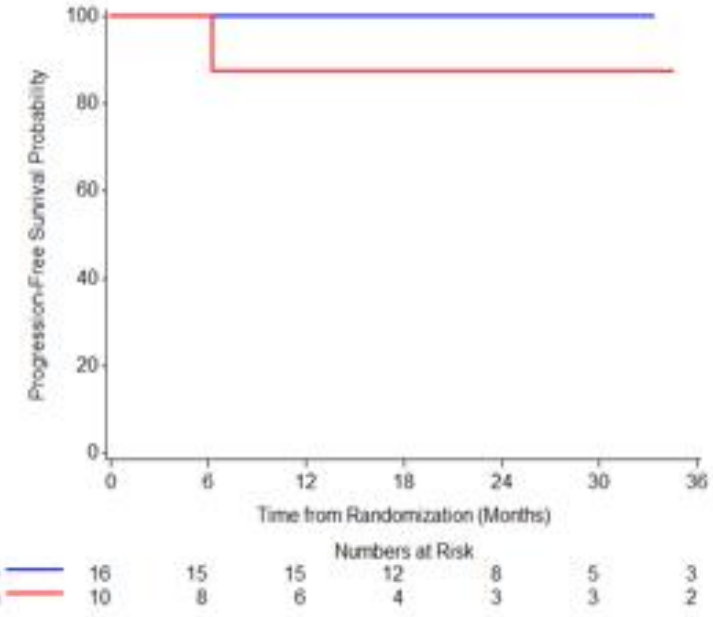
High-risk



Intermediate-risk



Low-risk

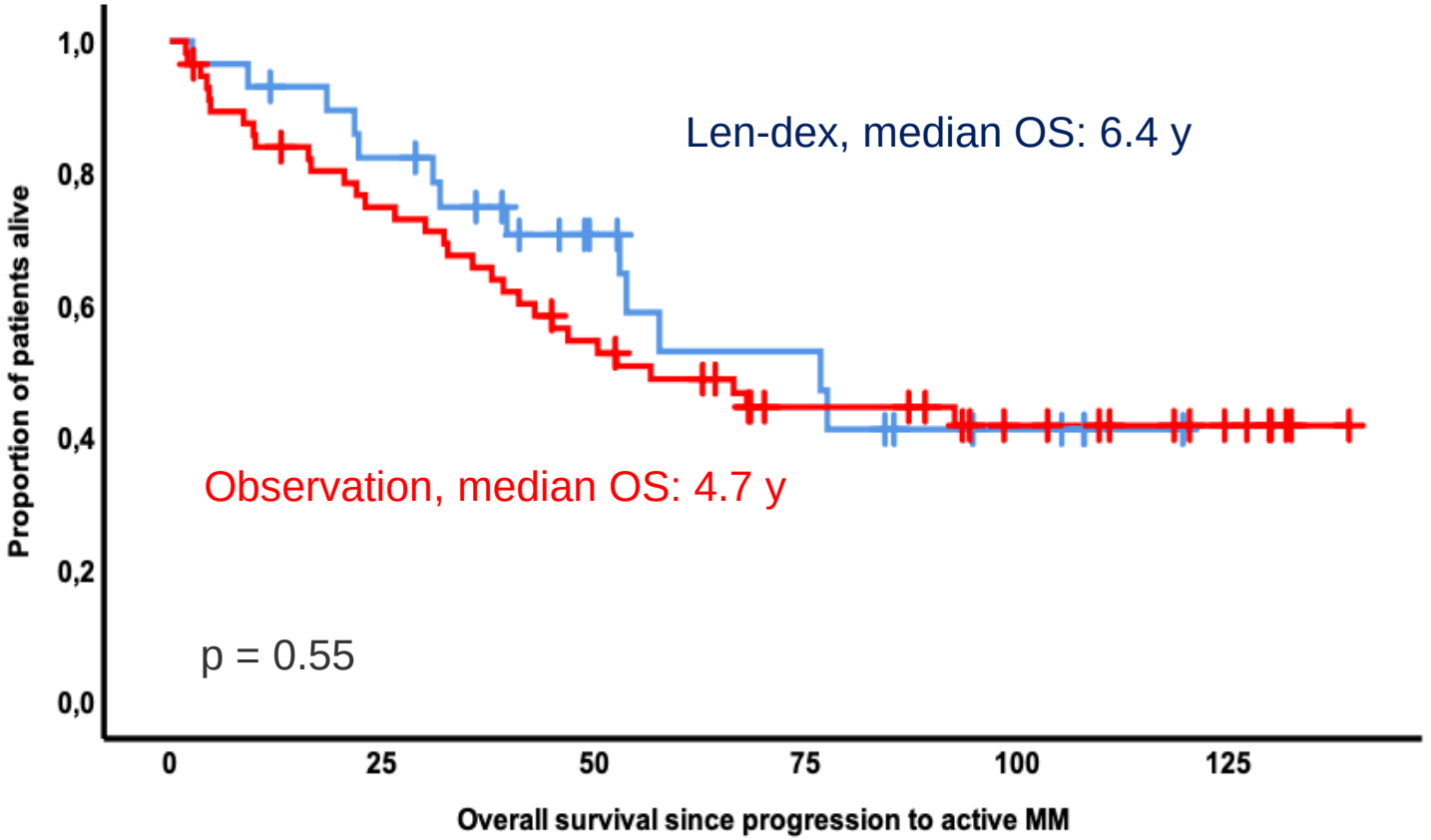


IMWG, International Myeloma Working Group; Len, lenalidomide; SMM, smoldering multiple myeloma; *vs*, versus.

Lonial S. Abstract #8001. 2019 ASCO Annual Meeting; May 30–Jun 4, 2019; Chicago, US. NCT01169337.

QuiRedex phase III study: Len-dex *vs* observation OS from progression to active disease (n = 119)*

Early treatment does not induce more resistant relapses



Len-dex, lenalidomide, dexamethasone; MM, multiple myeloma; OS; overall survival; y, years.
*Median follow-up 10.8 years.
Adapted from Mateos MV, et al. Abstract #294867 (e-Poster #EP950). 25th EHA Annual Meeting; Jun 11–21, 2020; Virtual. NCT00480363;

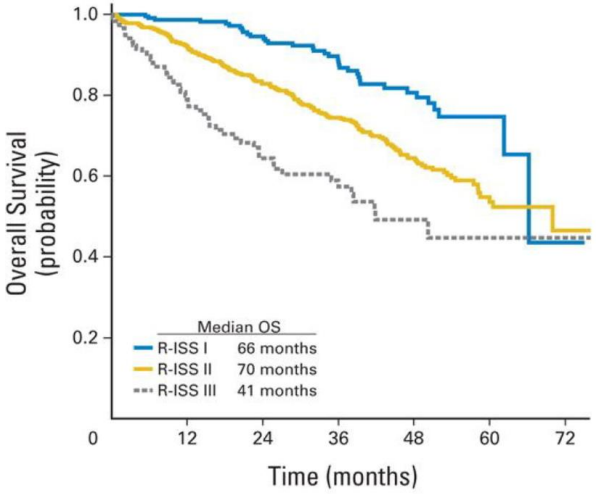
What other MM information can we utilize to plan a cure in high-risk SMM?

Revised International Staging System for MM

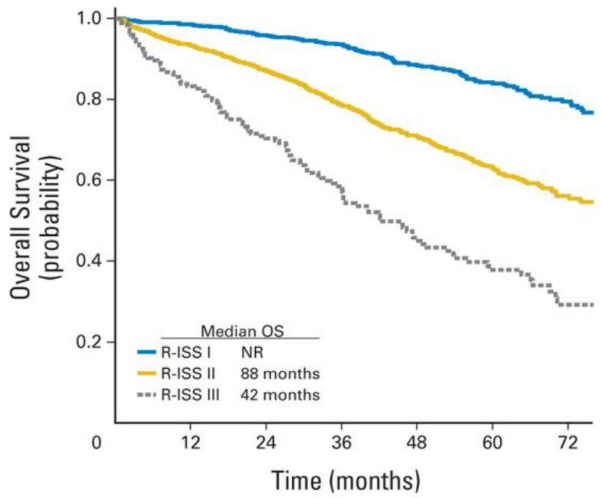
The lower the R-ISS the better the OS

Stage	Factor	% of pts	5 y PFS, %	5 y OS, %
I	Absence of adverse factors (no high LDH, ISS 2 or 3, t(4;14) t(14;16) or del(17p))	28	55	82
II	Not R-ISS I or III	62	36	62
III	ISS 3 and either high-risk CA by iFISH or high LDH	10	24	40

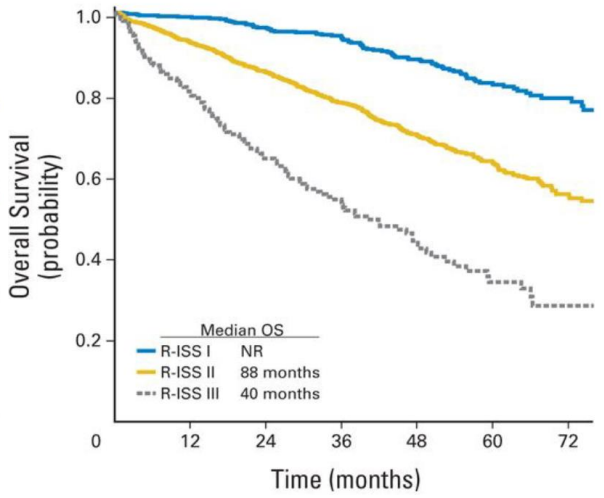
Nontransplantation-based regimens



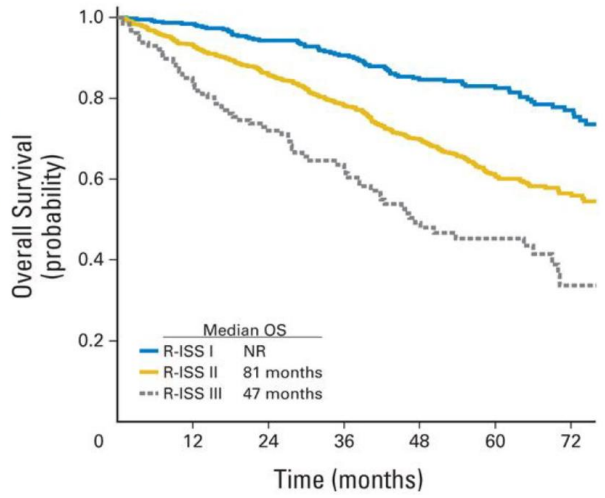
Transplantation-based regimens



Immunomodulatory-based regimens



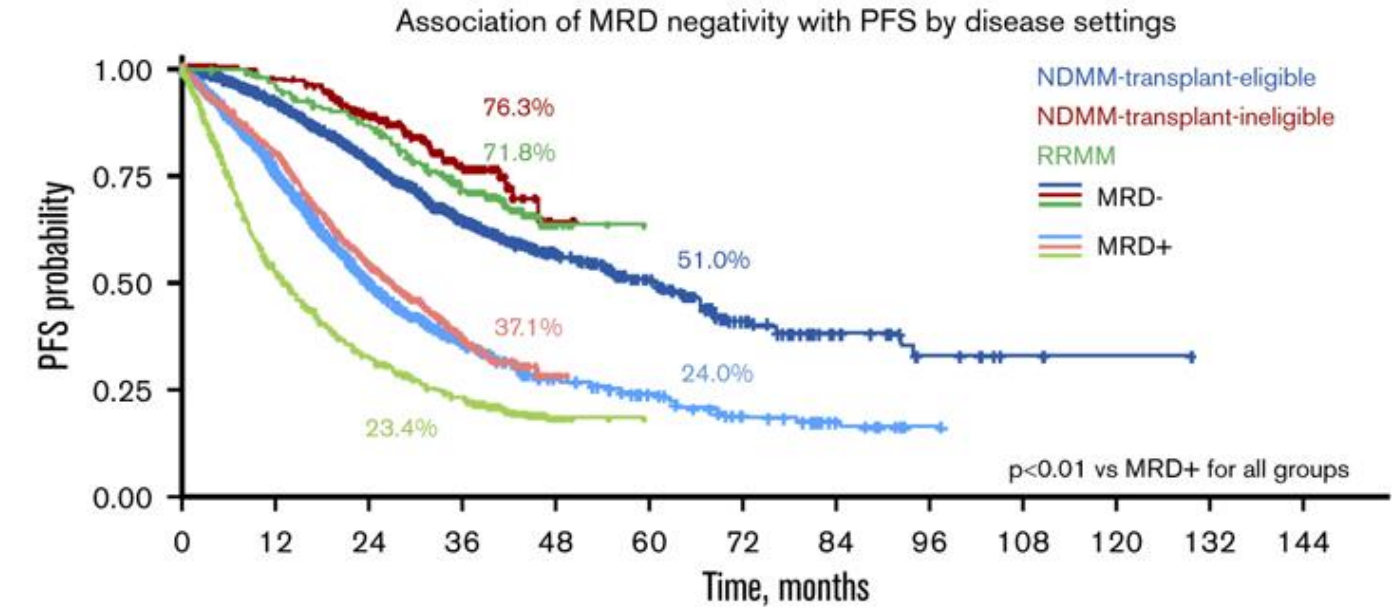
Proteasome inhibitor-based regimens



CA, cytogenetic abnormality; del, deletion; iFISH, interphase fluorescent *in situ* hybridization; ISS, International Staging System; LDH, lactate dehydrogenase; MM, multiple myeloma; NR, not reached; OS, overall survival; PFS, progression-free survival; pts, patients; R-ISS, revised International Staging System; y, years.

Palumbo A, et al. *J Clin Oncol.* 2015;33(26):2863-2869.

MRD negativity is a strong prognostic tool associated with favorable outcomes in various MM settings

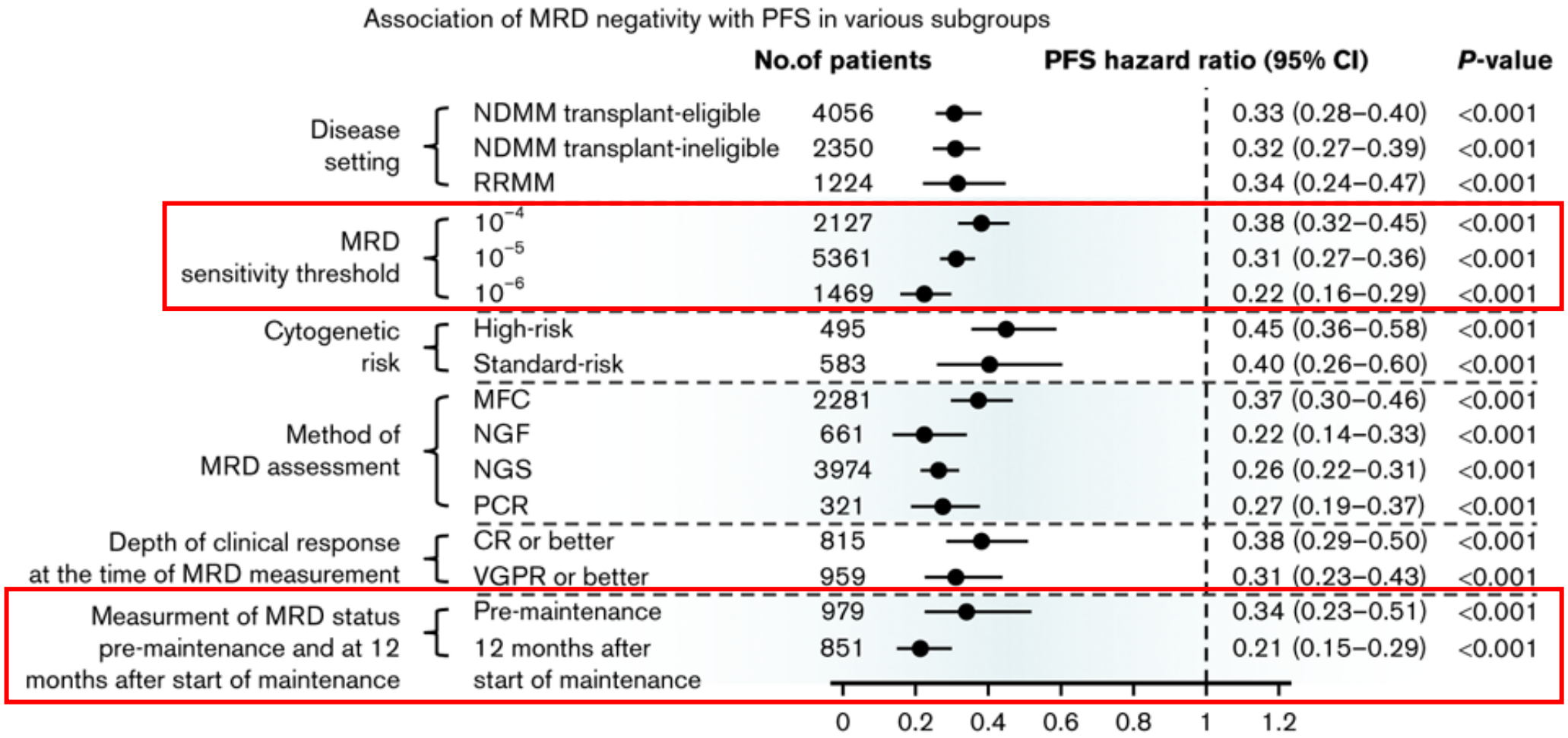


Number at risk

MRD-	1515	1055	589	332	164	95	47	22	10	3	1	0	0
MRD+	1180	719	317	153	72	50	30	13	2	0	0	0	0
MRD-	291	283	217	93	4	0							
MRD+	1328	983	516	133	5	0							
MRD-	164	155	135	97	10	0							
MRD+	960	456	269	179	11	0							

MRD, minimal residual disease; NDMM, newly diagnosed multiple myeloma; PFS, progression-free survival; RRMM, relapsed/refractory multiple myeloma.
Munshi NC, et al. *Blood Adv.* 2020;4(23):5988-5999.

MRD negativity is a strong prognostic tool associated with favorable outcomes in various MM settings



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

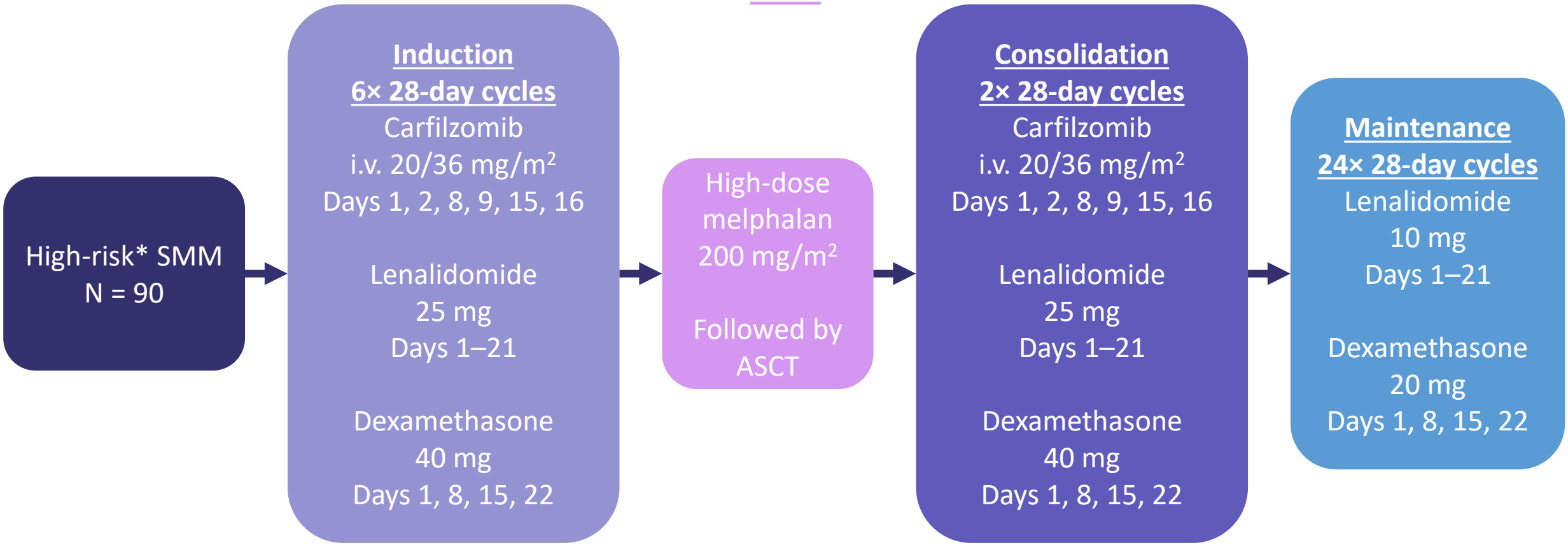
Munshi NC, et al. *Blood Adv.* 2020;4(23):5988-5999.

Road map to cure through early intervention of high-risk SMM

1. Early detection of SMM at high risk of progression to MM, optimizing the clinical models with genomic/molecular markers
2. Trying to achieve MRD negativity and sustained MRD over time as a potential surrogate measure for survival
3. Using the therapeutic combinations resulting in the highest MRD negative rates

MM, multiple myeloma; MRD, minimal residual disease; SMM, smoldering multiple myeloma.

GEM-CESAR, an open label, multicenter, phase II trial: Study design



*High-risk defined according to Mayo and/or Spanish models

- Patients with ≥1 biomarker predicting imminent risk of progression to MM were allowed to be included but…
- New imaging assessments were mandatory at screening. If bone disease was detected by CT or PET-CT, patients were excluded

ASCT, allogeneic stem cell transplant; CT, computer tomography; i.v., intravenous; MM, multiple myeloma; PET, Positron emission tomography; SMM, smoldering multiple myeloma NCT02415413

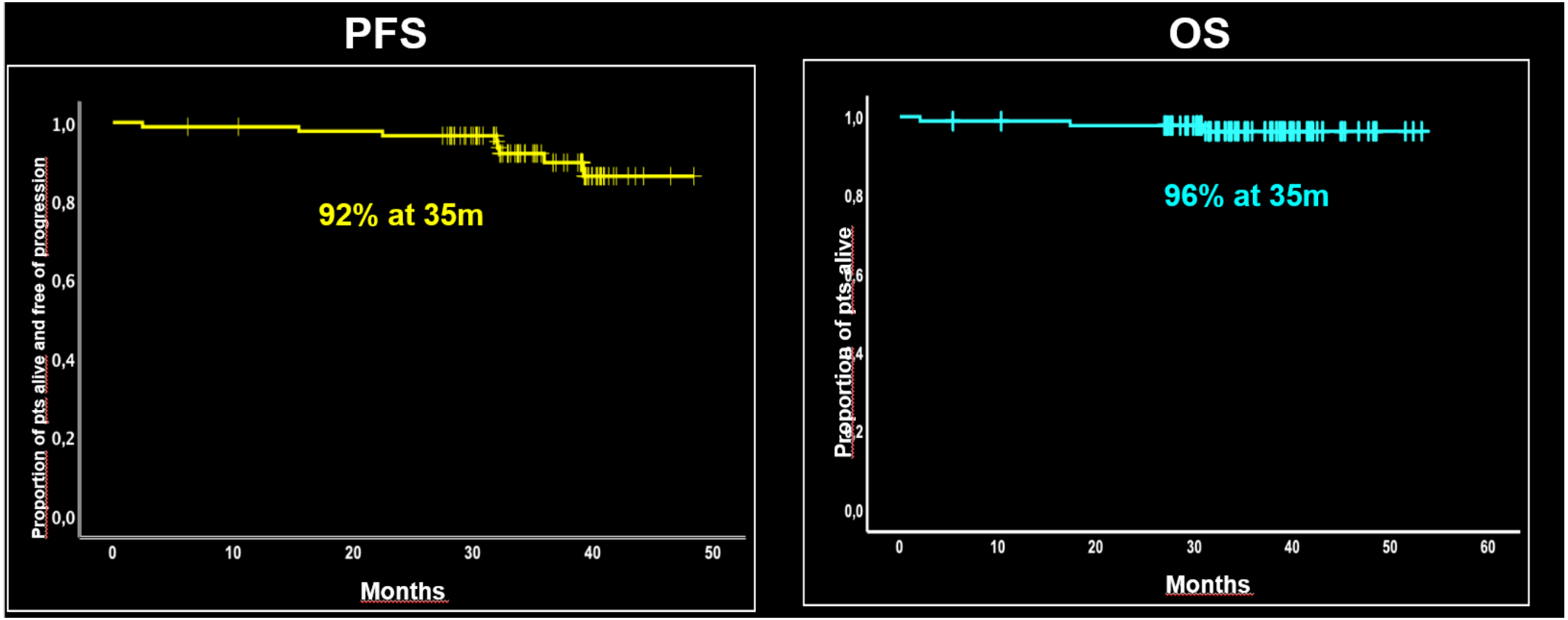
GEM-CESAR: Improvement of quality of response over treatment

N = 77 completed induction, HDT-ASCT, consolidation and 1 year of maintenance

Response	Induction (KRd × 6)	HDT/ASCT	Consolidation (KRd × 2)	Maintenance (Rd × 1 y)
≥CR	43%	63%	75%	81%
VGPR	43%	24%	18%	13%
PR	13%	13%	7%	5%
PD	—	—	—	1%*
MRD-neg	33%	49%	62%	62%

ASCT, allogeneic stem cell transplantation; CR, complete response; HDT, high-dose therapy; KRd, carfilzomib, lenalidomide, dexamethasone; MRD-neg, minimal residual disease negativity; PD, progressive disease; PR, partial response; Rd, lenalidomide, dexamethasone; VGPR, very good partial response; y, year.
*PD was biological at the end of maintenance and the MRD was positive.
Mateos MV. Abstract#781. 61st ASH Annual Meeting & Exposition Dec 7–10, 2019; Orlando US. NCT02415413

GEM-CESAR: Outcomes with a median follow-up of 35.2 months



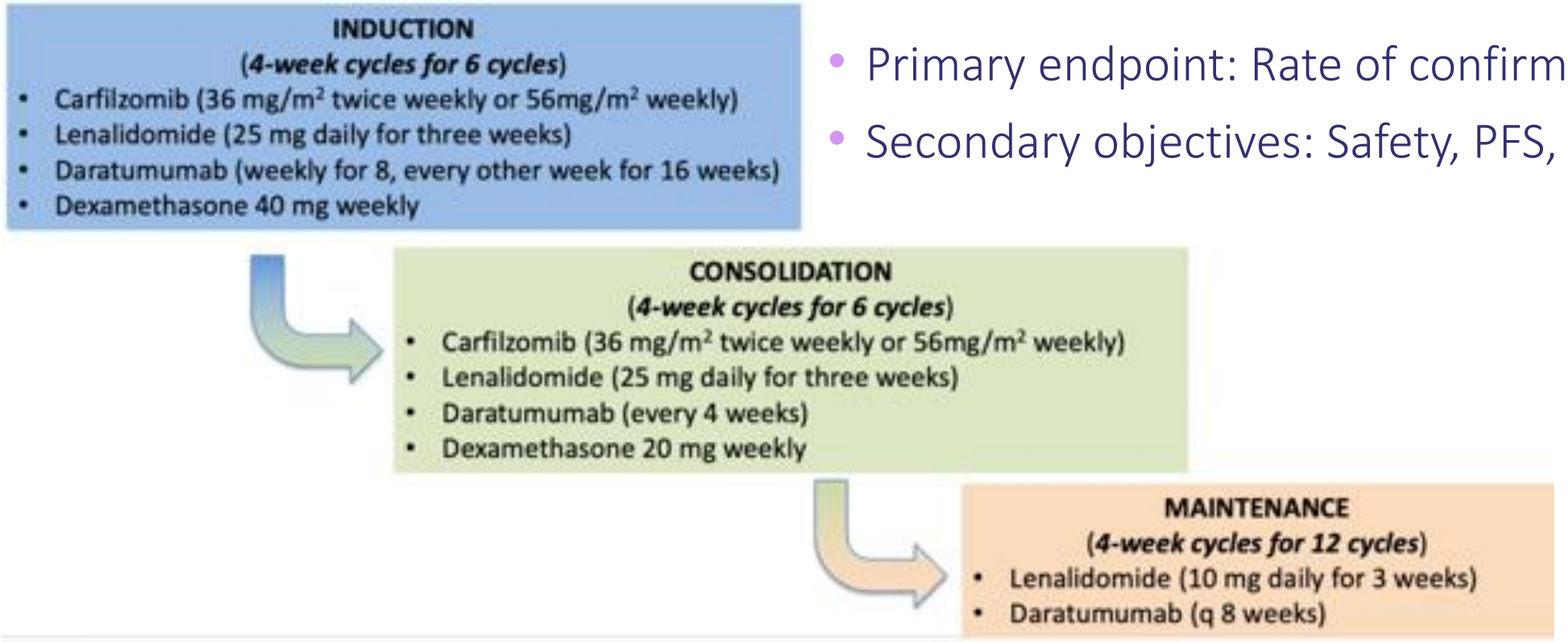
- 6 pts progressed
- 5 pts PD was biological
- 4 pts were at ultra high-risk

- 3 pts died and only one was treatment-related

OS, overall survival; PD, progressive disease; PFS, progression-free survival; pts, patients.
Mateos MV. Abstract#781. 61st ASH Annual Meeting & Exposition Dec 7–10, 2019; Orlando US. NCT02415413

ASCENT: KRd-D is well tolerated in high-risk SMM

Study design



- Primary endpoint: Rate of confirmed sCR
- Secondary objectives: Safety, PFS, OS, MRD-negativity

KRd-D, carfilzomib, lenalidomide, dexamethasone, daratumumab; MRD, minimal residual disease; OS, overall survival; PFS, progression-free survival; sCR, stringent complete response; SMM smoldering multiple myeloma.
Adapted from Kumar SK, et al. Abstract #2285. 62nd ASH Annual Meeting & Exhibition; Dec 6, 2020; Virtual. NCT03289299.

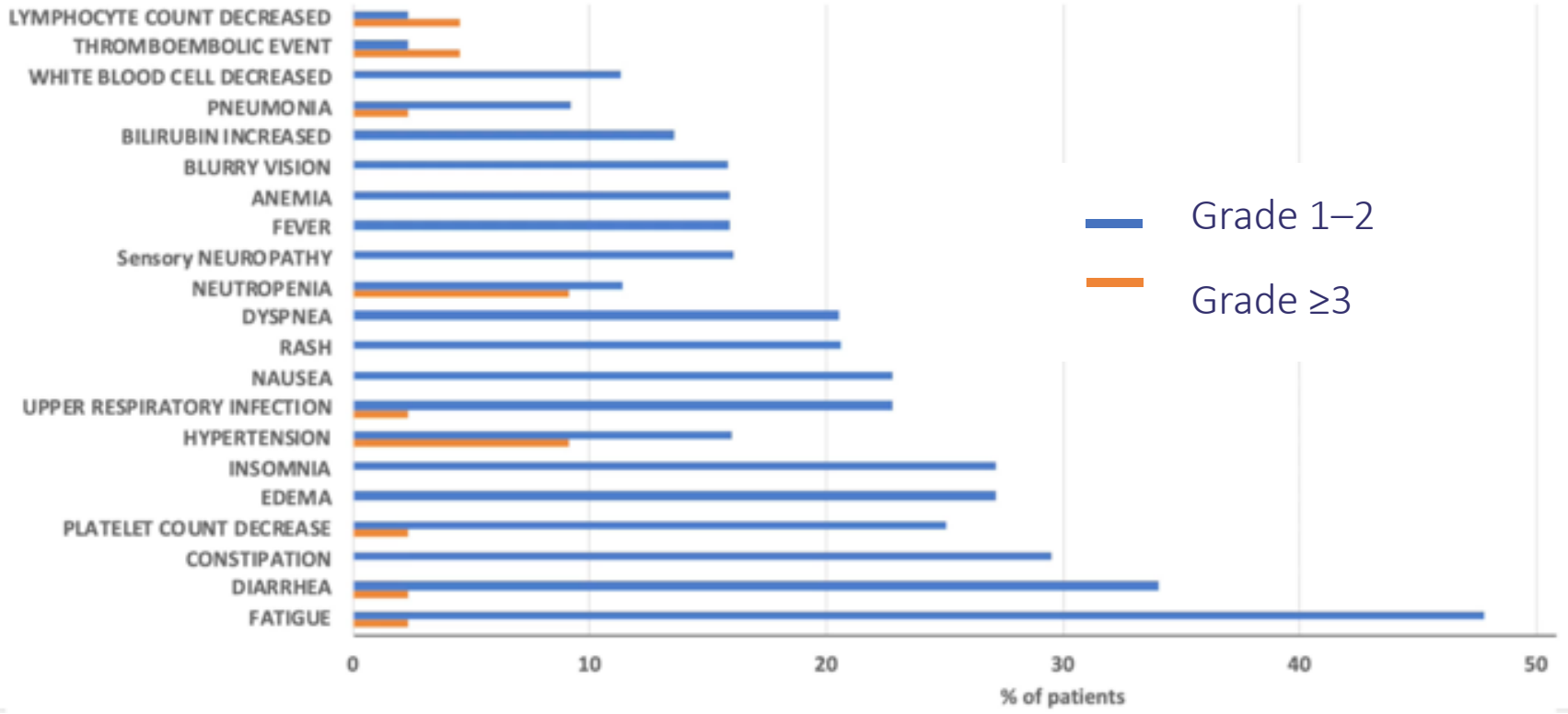
ASCENT: KRd-D is well tolerated in high-risk SMM

Results to date:

- N = 54
- Median age: 63 years
- 6% have completed maintenance, 56% consolidation, 80% induction, and 17% in induction phase

- ≥1 patient needed a dose modification
- ≥ Grade 3 AE seen in 43%

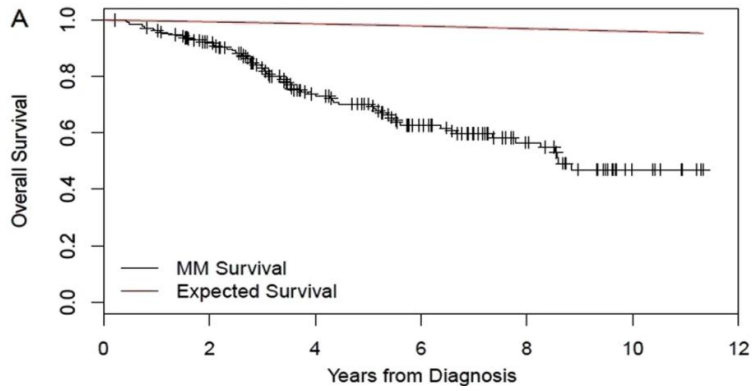
Toxicity profile

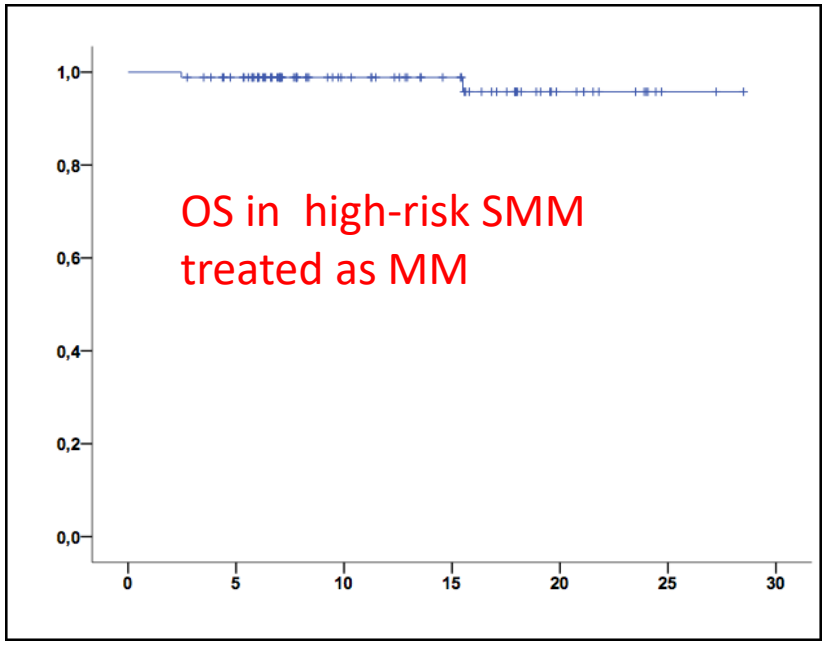


AE, adverse event; KRd-D, carfilzomib, lenalidomide, dexamethasone, daratumumab; MRD, minimal residual disease; OS, overall survival; PFS, progression-free survival; sCR, stringent complete response; SMM smoldering multiple myeloma.

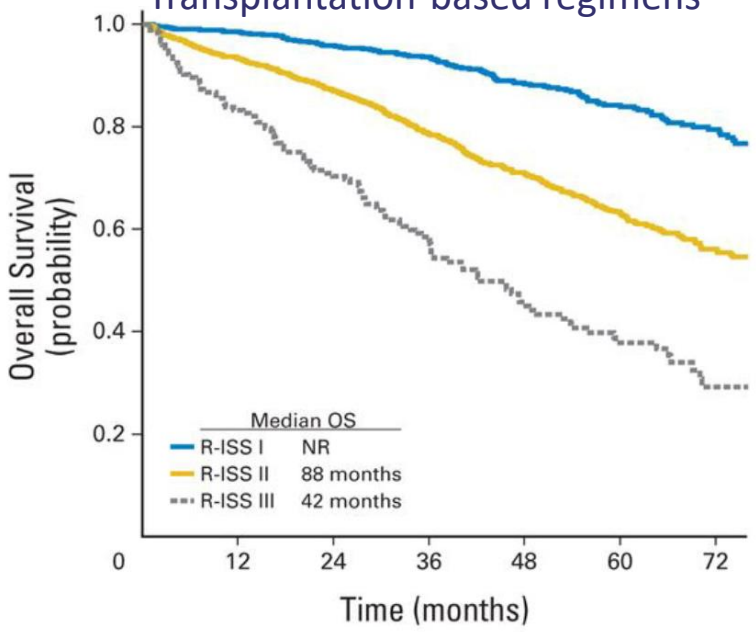
Adapted from Kumar SK, et al. Abstract #2285. 62nd ASH Annual Meeting & Exhibition; Dec 6, 2020; Virtual. NCT03289299.

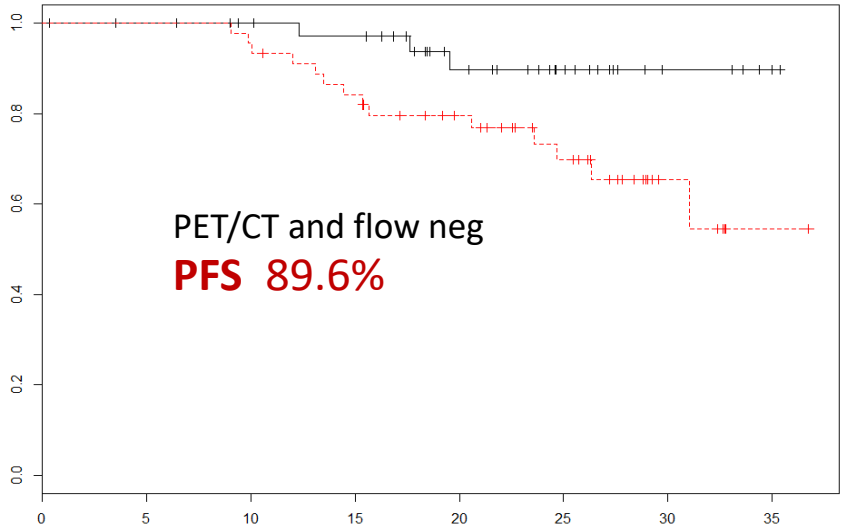
Can we dream of curing MM by treating high-risk SMM?





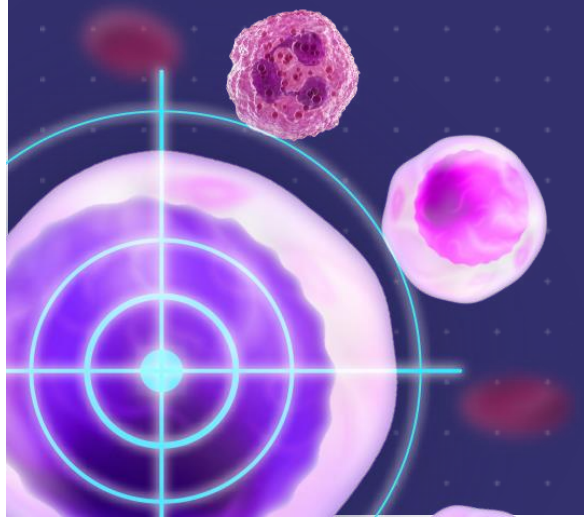
Transplantation-based regimens





MultipleMyelomaHub

Thank you



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