

**O que uso na estratificação
de risco no mieloma
múltiplo ao diagnostico:
ISS, R-ISS, R2-ISS, FISH,
painel genético?**

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BP, A Beneficência Portuguesa de SP



Novas drogas no Mieloma Múltiplo

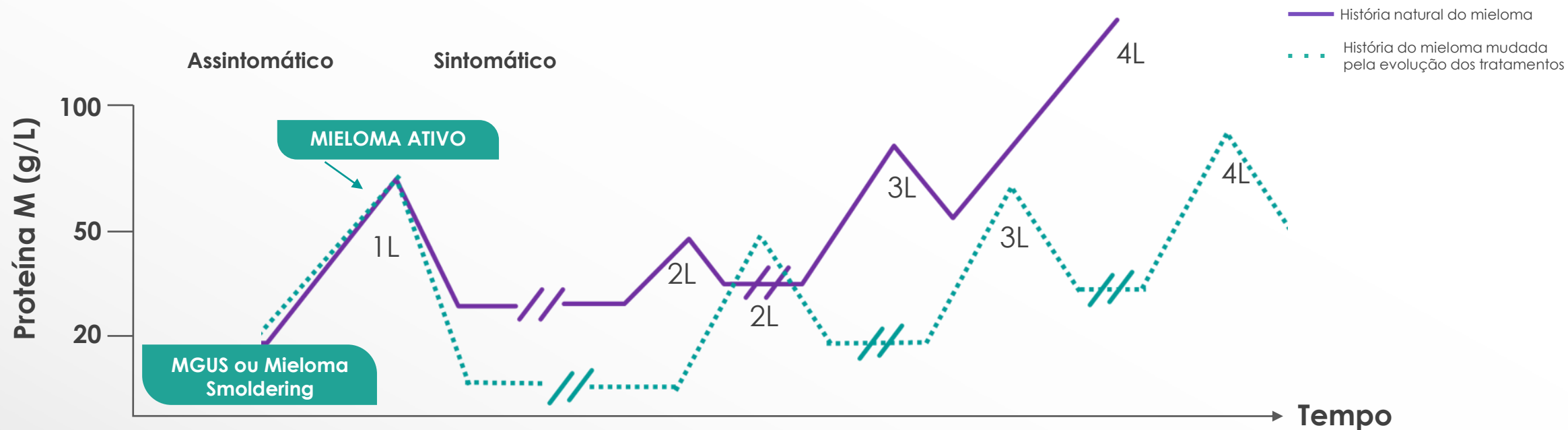


Imagem meramente ilustrativa elaborada a partir de Rodriguez-Otero et al., Cancer Treatment Reviews 100 (2021) 102284

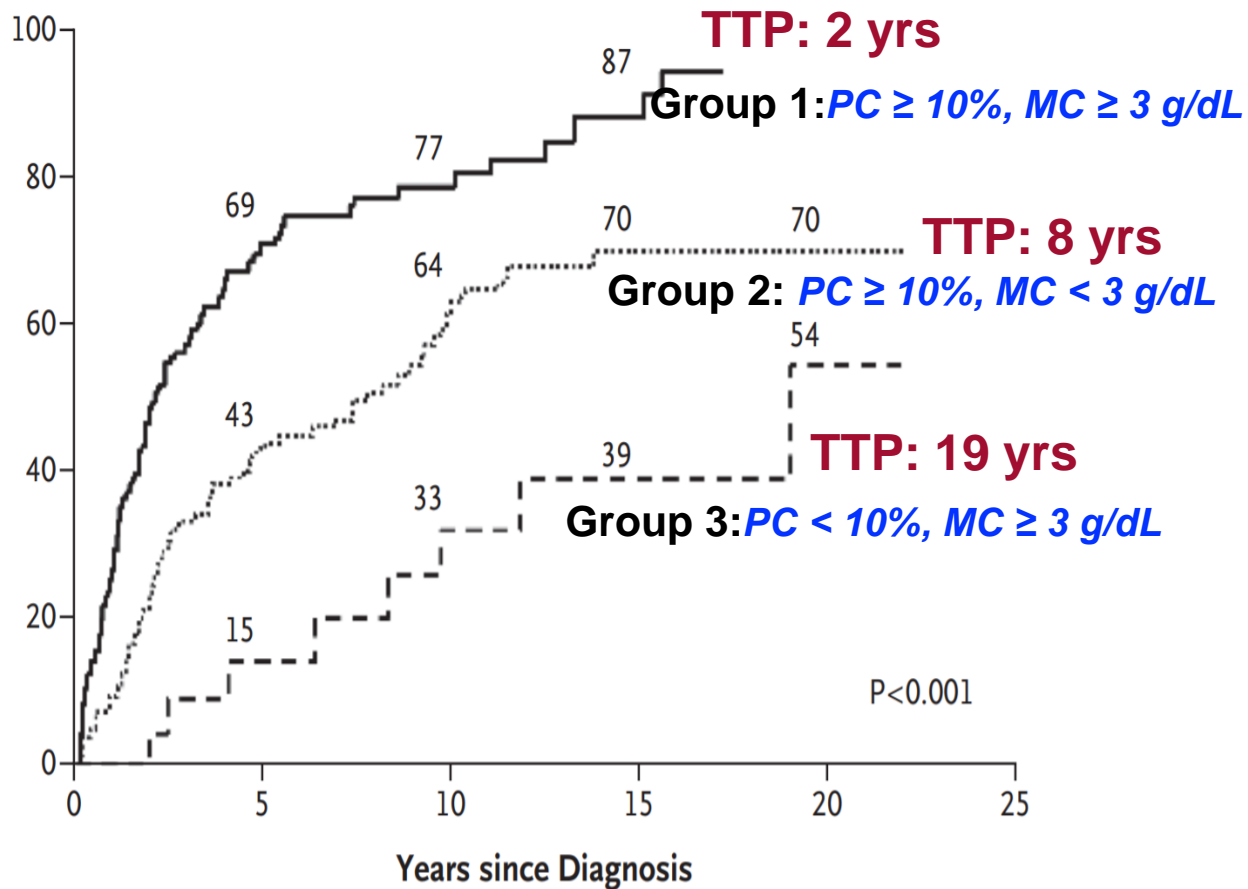
MGUS: gamopatia monoclonal de significado indeterminado

1. Kurtin, S. E. Relapsed or relapsed/refractory multiple myeloma. J Adv Pract Oncol 4. Suppl 1 (2013):5-14. 2. Rodriguez-Otero et al., Cancer Treatment Reviews 100 (2021) 102284 3. Landgren O, Iskander K. Modern multiple myeloma therapy: deep, sustained treatment response and good clinical outcomes. J Intern Med. 2017;281:365-382

Risk of Progression: Smoldering MM to Active MM

Mayo Classification

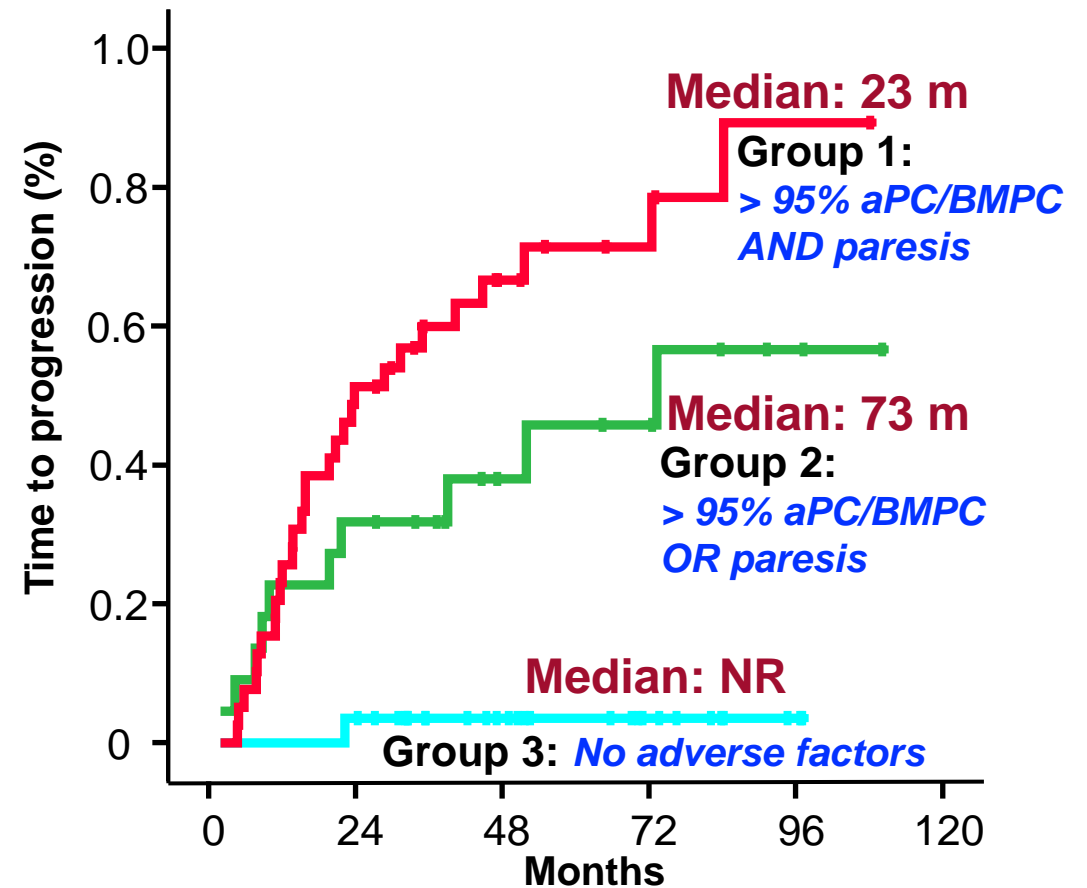
PCs BM Infiltration $\geq 10\%$ and MC $\geq 3\text{g/dL}$



Kyle R, et al. *N Engl J Med.* 2007;356:2582-2590.

Spanish Classification

BM PCs $\geq 10\%$ or MC $\geq 3\text{g/dL}$ AND $> 95\%$ aPC/BMPC + paresis



Pérez-Persona E, et al. *Blood.* 2007;110:2586-2592

IMWG 2/20/20 Risk Score to Predict Progression Risk at 2 Years

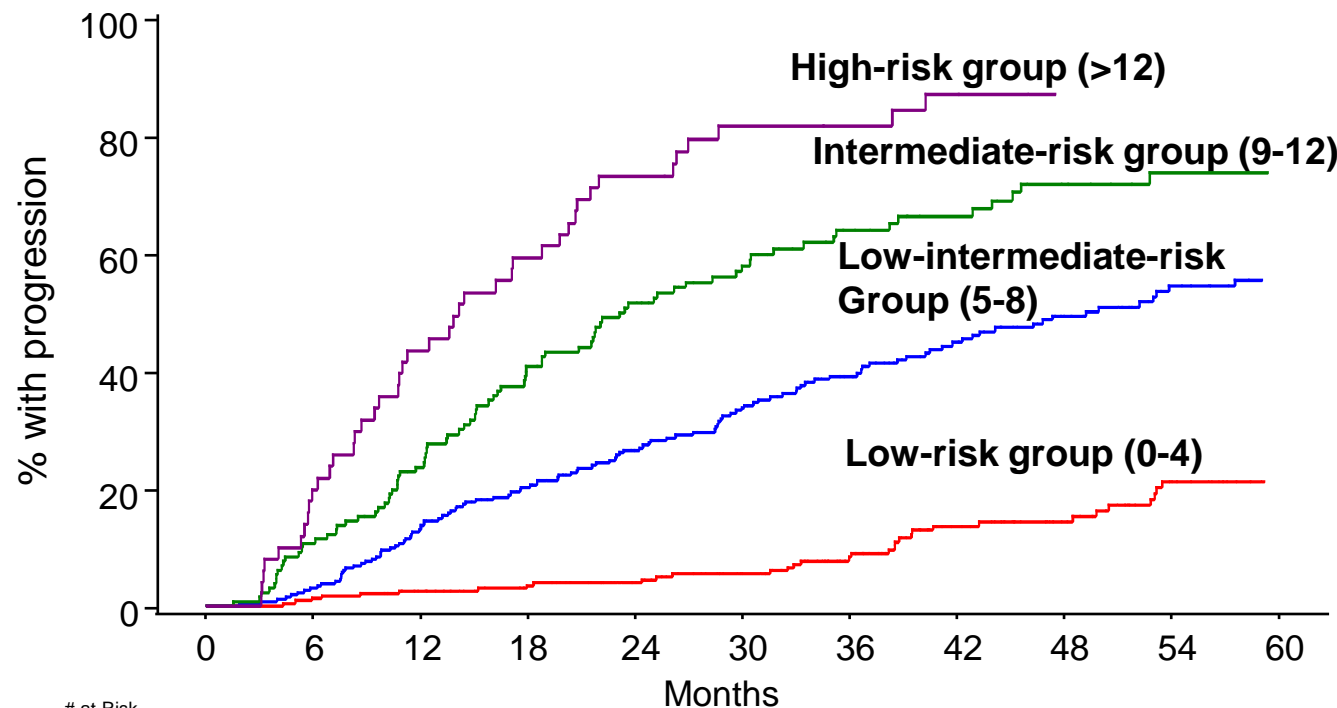
M Spike: >2 g/dL

FLC Ratio: >20

BMPC: >20%

2- 3 factors

A more precise and individualized scoring tool to classify individuals by risk of progression using the entire spectrum of values for each patient



# at Risk	0	6	12	18	24	30	36	42	48	54	60
0-4	241	238	229	213	194	175	153	117	100	76	63
5-8	264	256	229	197	174	145	118	91	73	53	44
9-12	133	119	98	73	59	47	33	26	20	14	13
>12	51	41	29	21	14	9	7	5	2	2	2

MyeRisk Calculator

Risk Factor	Coefficient	P-value	Score
FLC Ratio			
0-10 (reference)	-	-	0
>10-25	0.69	0.014	2
>25-40	0.96	0.004	3
>40	1.56	<0.0001	5
M protein (g/dL)			
0-1.5 (reference)	-	-	0
>1.5-3	0.95	0.0002	3
>3	1.30	<0.0001	4
BMPC%			
0-15 (reference)	-	-	0
>15-20	0.57	0.04	2
>20-30	1.01	0.0002	3
>30-40	1.57	<0.0001	5
>40	2.00	<0.0001	6
FiSH abnormality	0.83	<0.0001	2

Total Risk Score	2-Year Progression, n (%)
0-4	3.7%
5-8	25.4%
9-12	48.9%
> 12	72.6%

High Risk SMM: Factors Identifying 50% Risk of Progression at 2 Years

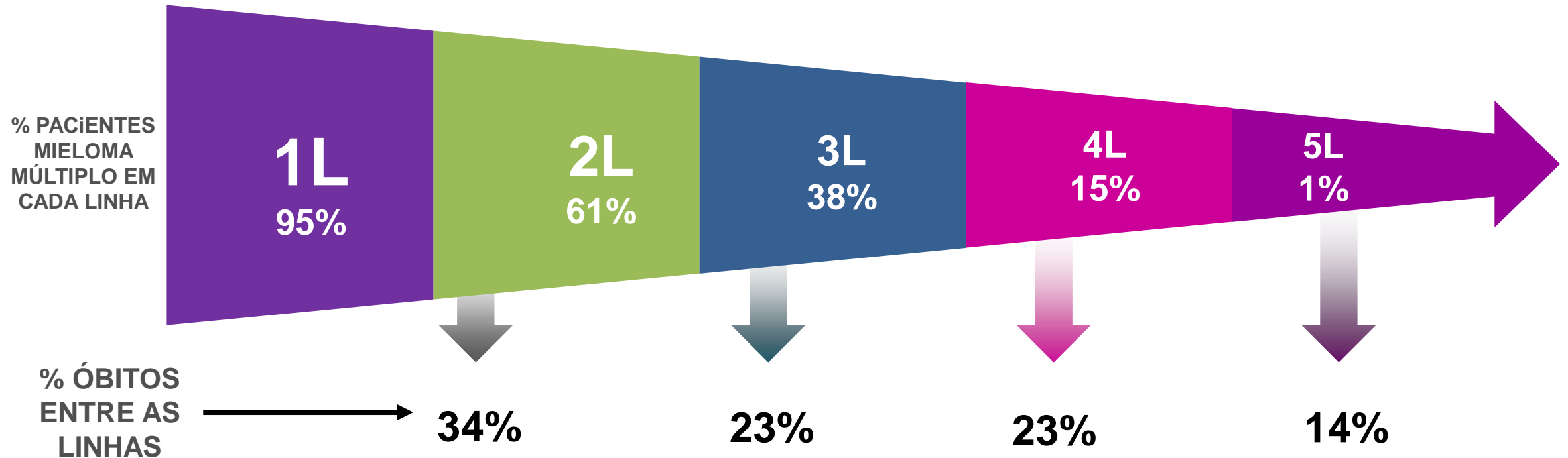
- **Evolving SMM:** For the **MC:** Increase by >25% in 2 consecutive measurements or ≥ 0.3 g/dL within 6 mo. For **Hb:** decrease of ≥ 0.5 g/dL Hb within 12m of diagnosis. For **FLCr** $\geq 50\%$ * increase or For **Risk scoring** *
- **BJ proteinuria** (if > 500 mg/24h the TTP is 13m)
- **Circulating PC** >0.02%
- **High-risk Cytogenetics:** t(4;14), del(17p), 1q, MYC structural variants and MYC-IG translocations
- **Genomic Profiling** (score > 0.26). DNA Repair, MYC, MAP Kinase mutations (*Annand et al (ASH 2021)*)
- **MRI:** New focal lesion or increase of an existing FL or progressive diffuse infiltration (repeat in 3-6m)
- **PET/CT:** Positive PET without lysis

• *Vsram et al (BCJ 2021) patients evolving to a high-risk score may benefit from early intervention therapeutic approaches.*
Pts with >20%PC+ evolving MC & Hb: 90% risk at 2y

* *Theresia Akhlaghi (Memorial Sloan K): 398 pts*

PORQUE TRATAR AS RECAÍDAS COM O MELHOR ARSENAL?

SOMENTE 1/3 DOS PACIENTES RECEBEM MAIS DE 2 LINHAS DE TRATAMENTO

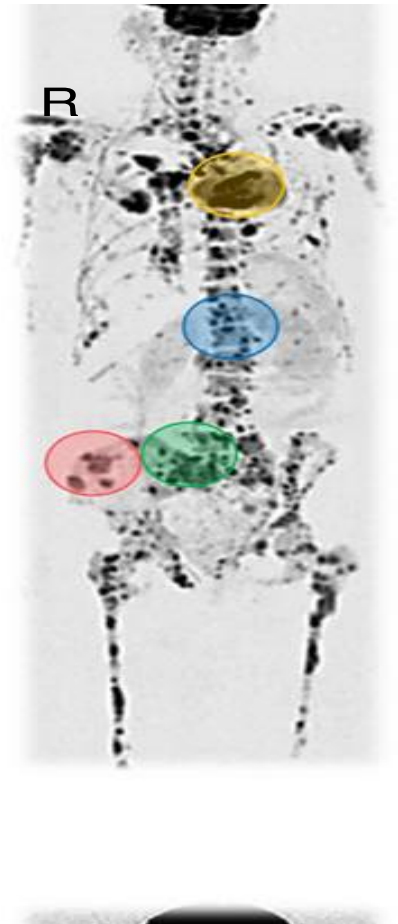
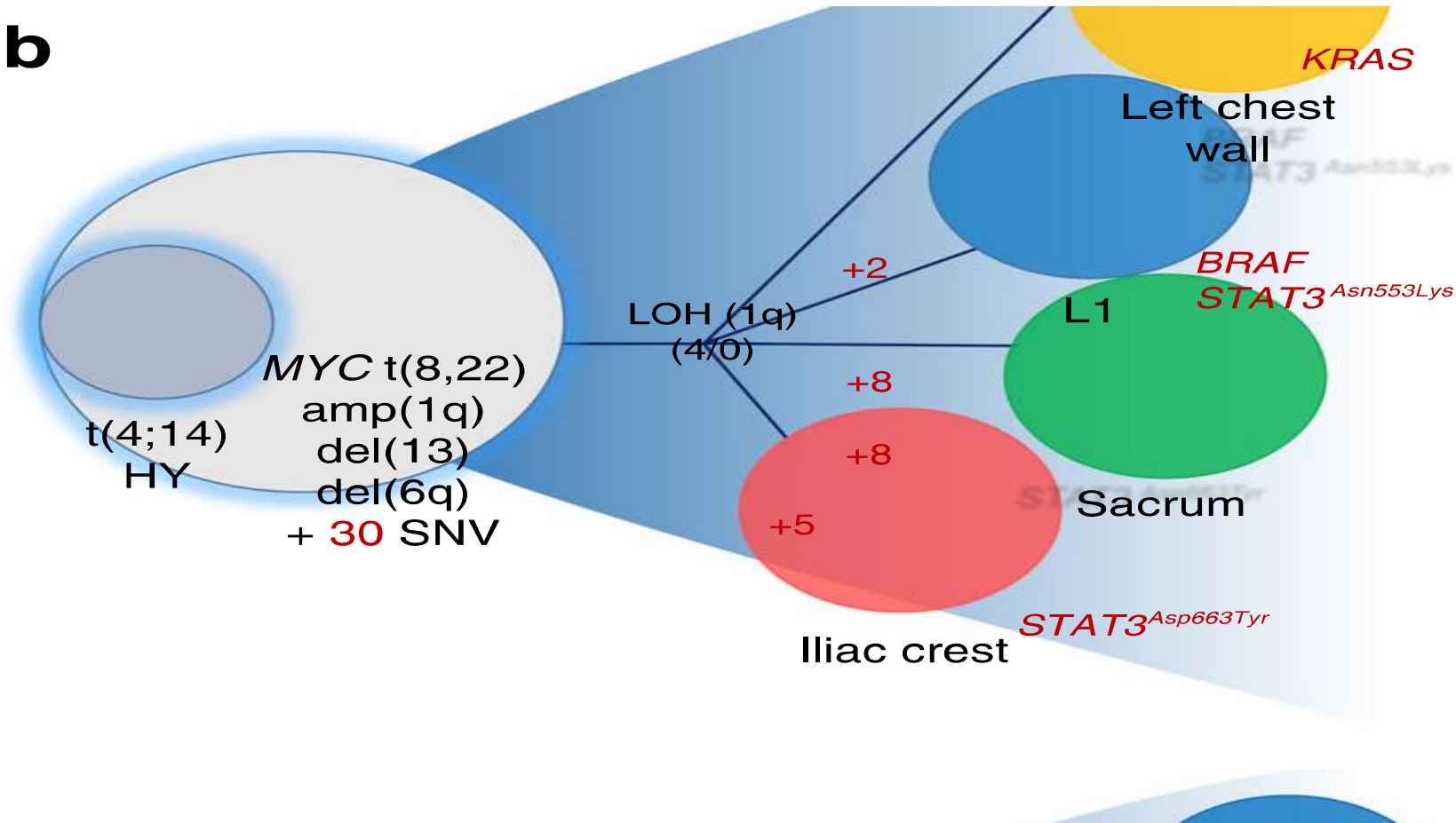


EM CADA LINHA DE TRATAMENTO, ~15-35% DOS PACIENTES VÃO A ÓBITO

Adaptado de Yong, K et al. Br J Haematology 2016;175(2):252-264.

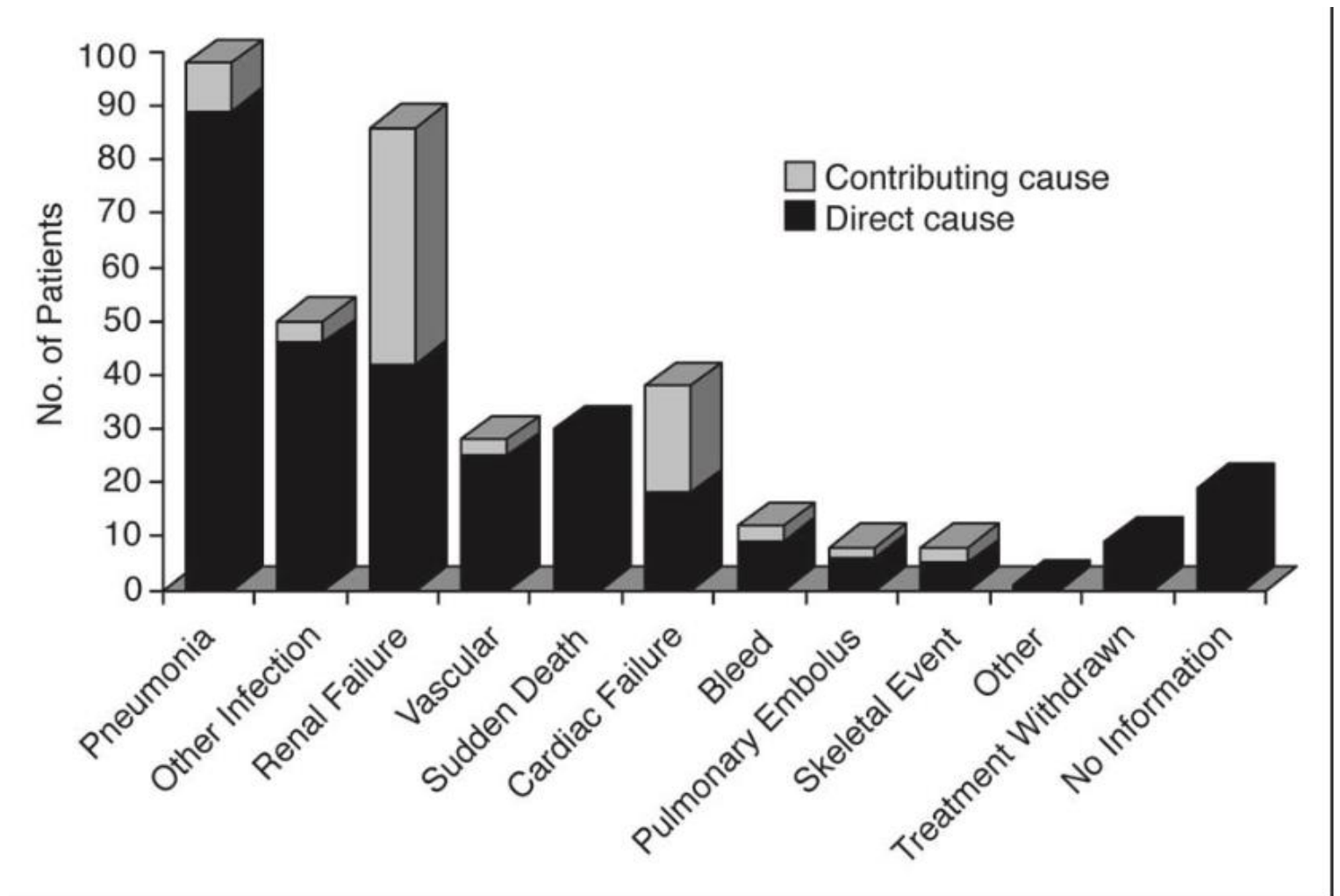
Spatial genomic heterogeneity in multiple myeloma revealed by multi-region sequencing

b



Mortalidade Precoce: 60 dias do diagnóstico de Mieloma

J Clin Oncol 23:9219-9226



- Bacterial infection directly caused 135 early deaths (45%) and contributed to death in almost 50% of cases.
- Specifically pneumonia occurred in 89 (66%) of 135 bacterial infections, generalized sepsis occurred in 31 (23%) of 135 bacterial infections

TRATAMIENTO INDIVIDUALIZADO – AVALIAÇÃO GERIÁTRICA

AVALIAÇÃO GERIÁTRICA

SCORE DE FRAGILIDADE IMWG (Edad, ADL, IADL, Índice de Comorbidiade Charlson)
R-MCI (Edad, SP Karnofsky, enf Renal e hepática, Fragilidade e Citogenética)
ÍNDICE DE FRAGILIDADE MAYO (Idade, SP ECOG, NT-ProBNP)

FIT



INTERMEDIÁRIO



FRAIL



OBJETIVO = Alta Eficácia

- 3 – 4 drogas
- 2 drogas
- Considerar ASCT

OBJETIVO = Eficácia e Segurança

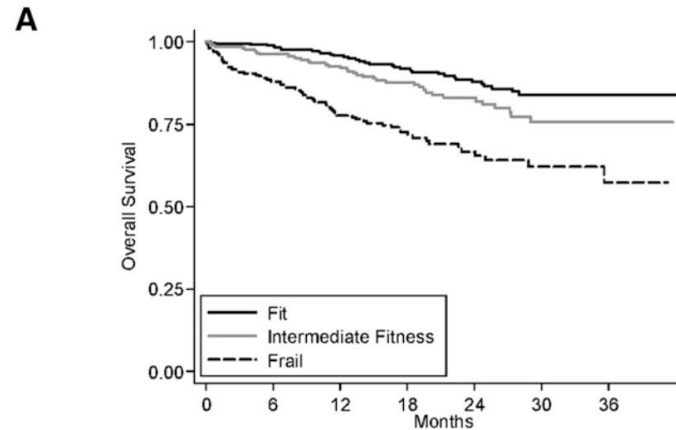
- 3 drogas em dose baixa
- 2 drogas

OBJETIVO = Baixa Toxicidade e Qualidade de Vida

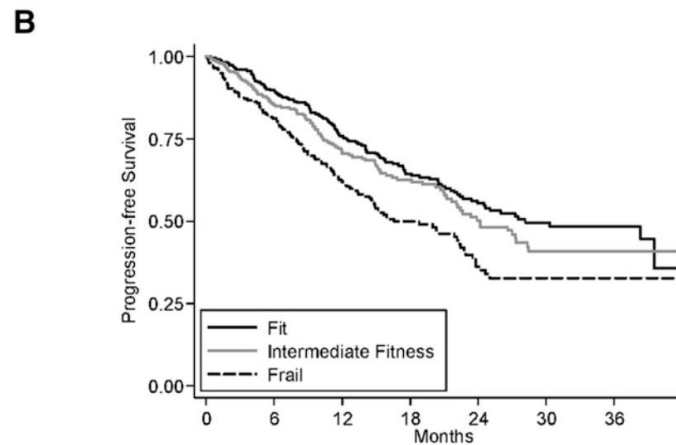
- 2 drogas em dose baixa
- Tratamento paliativo e de suporte

Geriatric assessment predicts survival and toxicities in elderly myeloma patients: an International Myeloma Working Group report

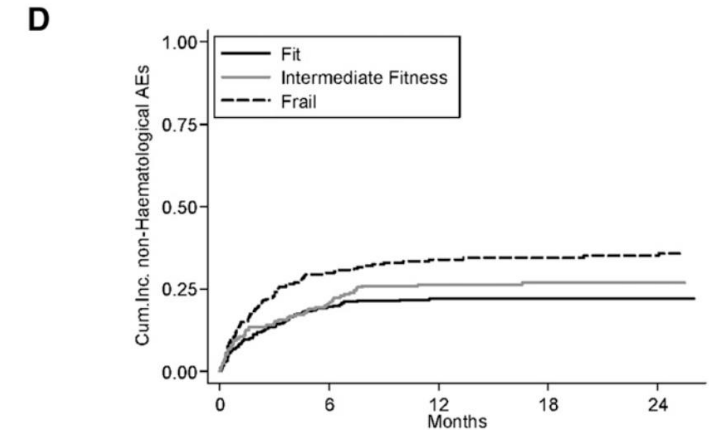
Palumbo, Blood. Mar 26; 125(13): 2068–2074.



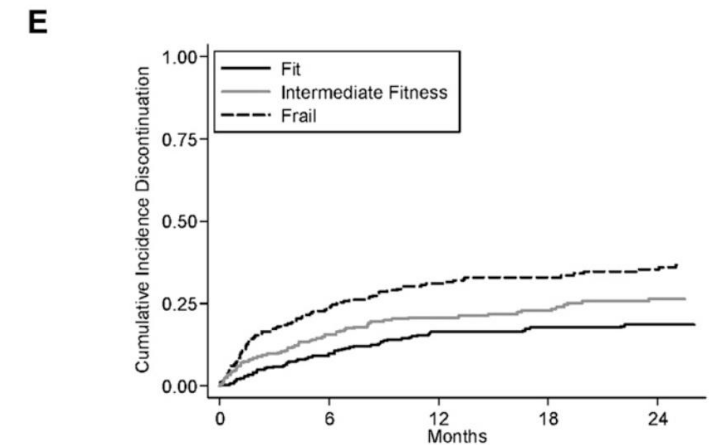
At risk:	0	6	12	18	24	30	36
Fit	340	323	248	182	133	84	43
Intermediate Fitness	269	242	183	123	83	47	15
Frail	260	209	151	91	52	27	12



At risk:	0	6	12	18	24	30	36
Fit	340	292	196	127	78	45	19
Intermediate Fitness	269	216	138	88	50	28	8
Frail	260	193	120	63	31	17	8



At risk:	0	6	12	18	24
Fit	340	248	167	110	70
Intermediate Fitness	269	182	108	67	41
Frail	260	142	79	42	19



At risk:	0	6	12	18	24
Fit	340	283	184	119	71
Intermediate Fitness	269	205	122	78	39
Frail	260	182	108	54	28

R-ISS

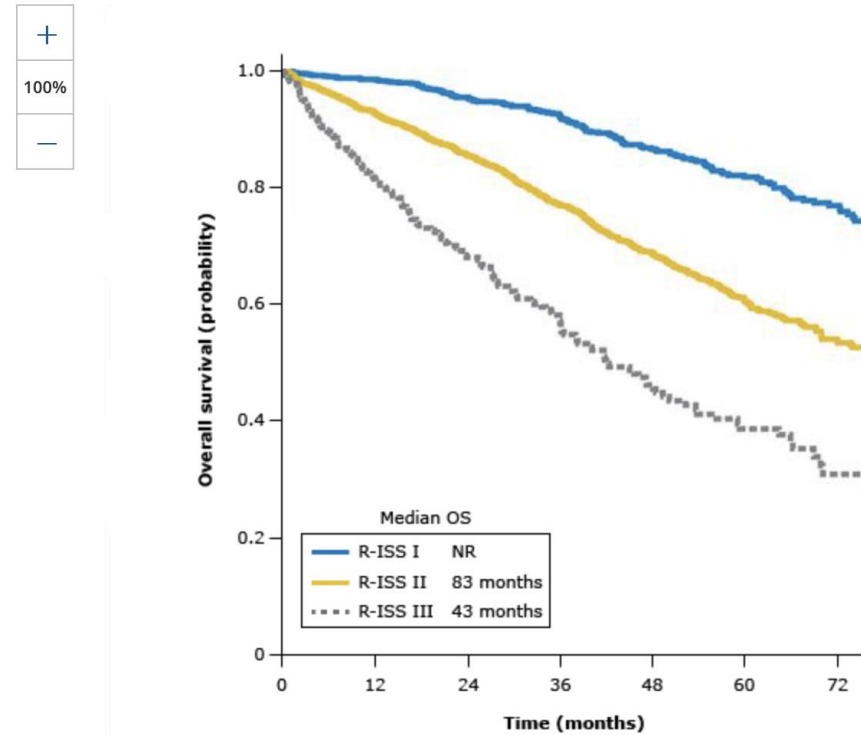
Revised International Staging System for multiple myeloma

Stage I	Stage II	Stage III
All of the following: <ul style="list-style-type: none">▪ B2M <3.5 mg/L▪ Serum albumin \geq3.5 g/dL▪ Normal LDH▪ No del(17p), t(4;14), or t(14;16) by FISH	Neither stage I nor stage III	Both of the following: <ul style="list-style-type: none">▪ B2M \geq5.5 mg/L▪ Elevated LDH and/or del(17p), t(4;14), or t(14;16) by FISH

B2M: beta-2 microglobulin; LDH: lactate dehydrogenase; FISH: fluorescence in situ hybridization.

Adapted from: Palumbo A, Avet-Loiseau H, Oliva S, et al. Revised International Staging System for Multiple Myeloma: A Report From International Myeloma Working Group. *J Clin Oncol* 2015; 33:2863.

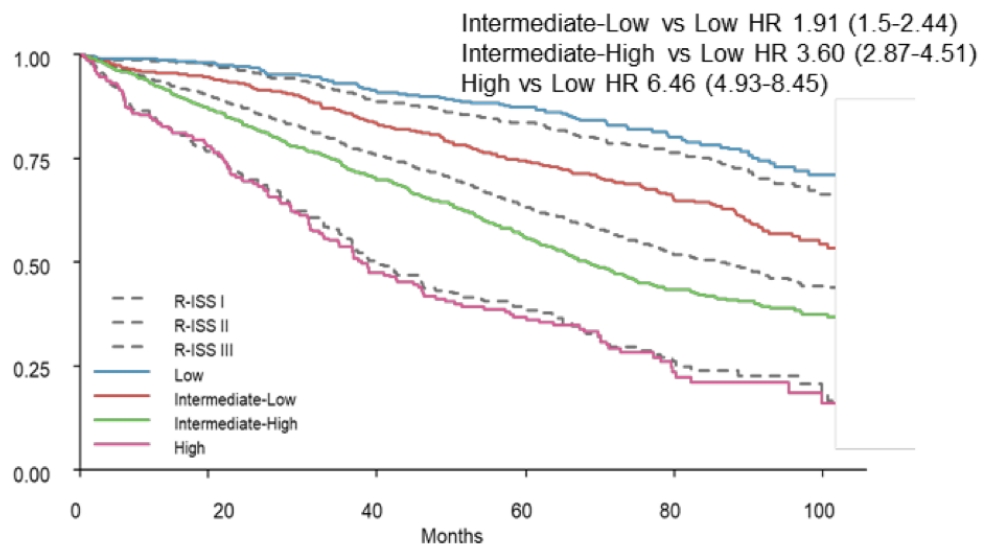
Overall survival by Revised International Staging System (R-ISS) in multiple myeloma



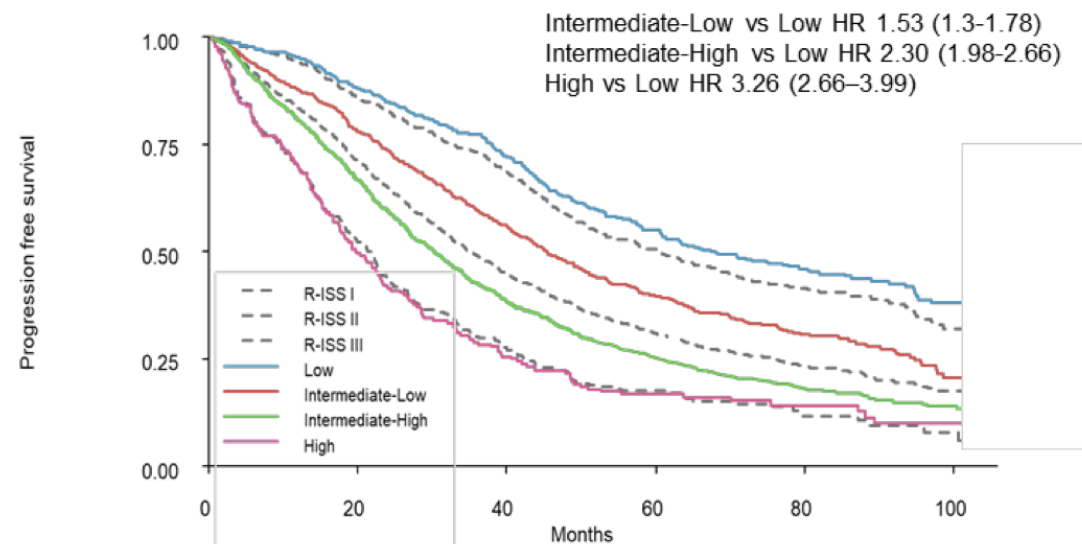
R2-ISS

Group	5-y OS	Median OS (months)	5-y PFS	Median PFS (months)
Low risk	88%	Not reached	55%	68
Intermediate-low risk	75%	109.2	40%	45.5
Intermediate-high risk	56%	68.5	25%	30.2
High risk	37%	37.9	17%	19.9

OS



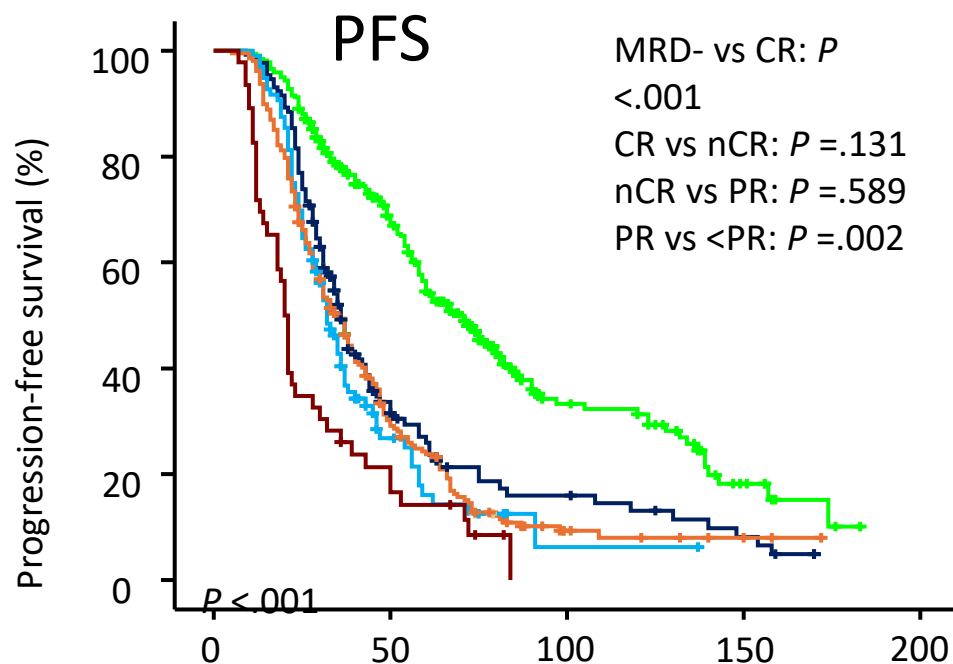
PFS



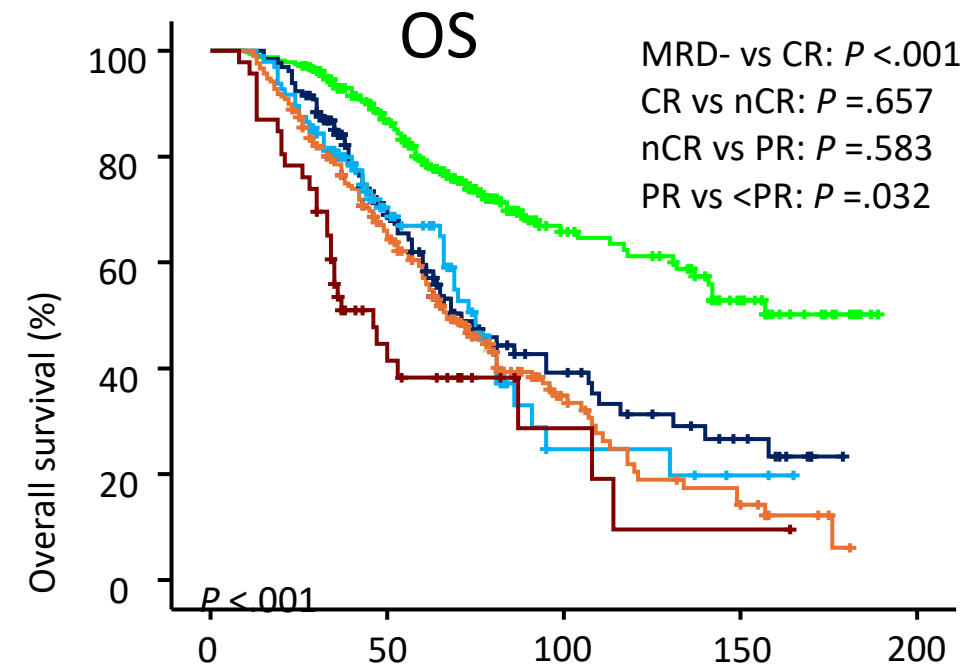
R2-ISS: Revision 2 of the International Staging System; R-ISS: Revised International Staging System; HR: hazard ratio; OS: Overall Survival; PFS: Progression-free Survival

Depth of Response correlate with Survival

MRD is the best biomarker to predict outcomes



- MRD- (n=318) median PFS: 70 months
- CR (n=130) median PFS: 36 months
- nCR (n=96) median PFS: 32 months
- PR (n=207) median PFS: 35 months
- <PR (46) median PFS: 20 months

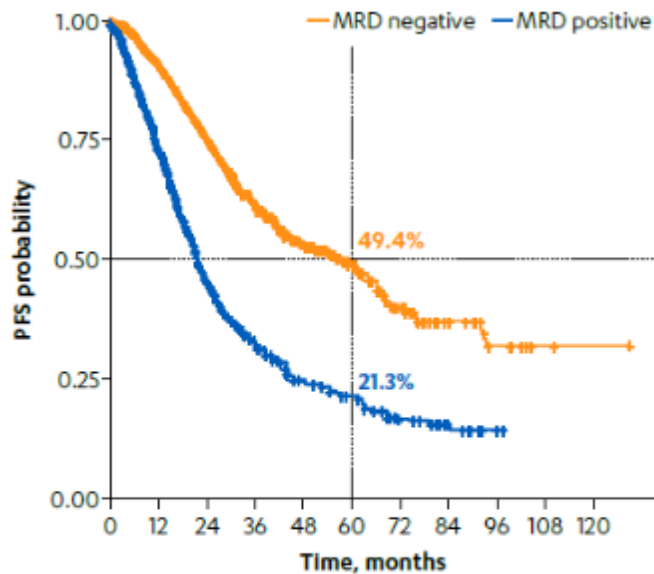


- MRD- (n=318) median OS: Not reached
- CR (n=130) median OS: 71 months
- nCR (n=96) median OS: 75 months
- PR (n=207) median OS: 67 months
- <PR (46) median OS: 46 months

A large meta-analysis establishes the role of MRD negativity in long-term survival outcomes in patients with multiple myeloma

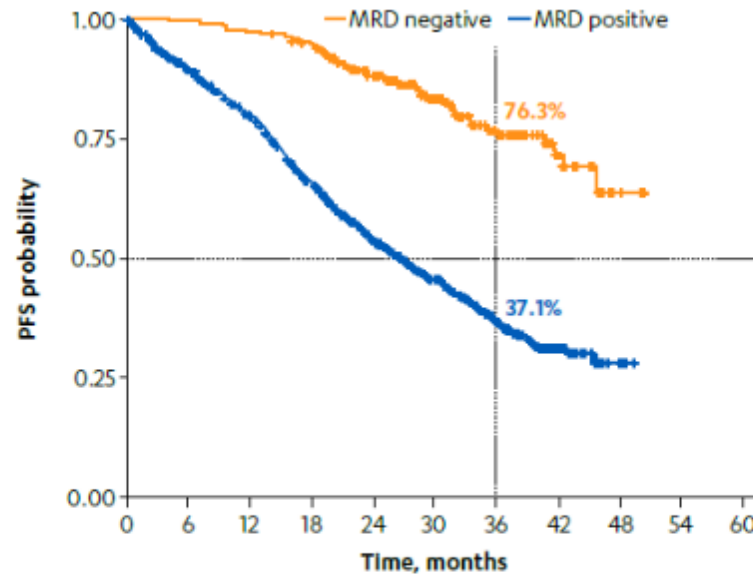
Results from an expanded meta-analysis (8,114 patients)

NDMM (transplant-eligible)



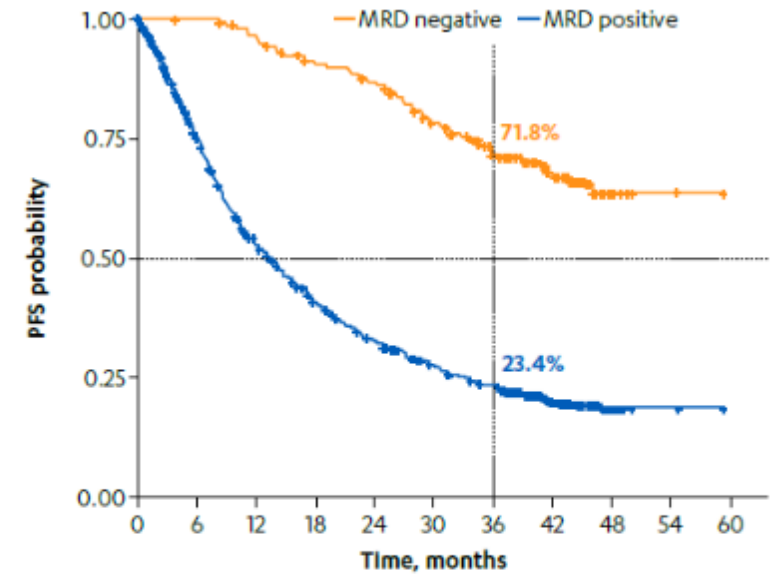
Number at risk	
MRD-	1254 803 431 287 147 95 47 22 10 3 1
MRD+	986 549 229 134 66 50 30 13 2 0 0

NDMM (transplant-ineligible)



Number at risk	
MRD-	291 290 283 274 217 139 93 30 4 0 0
MRD+	1328 1126 983 782 516 268 133 48 5 0 0

RR MM

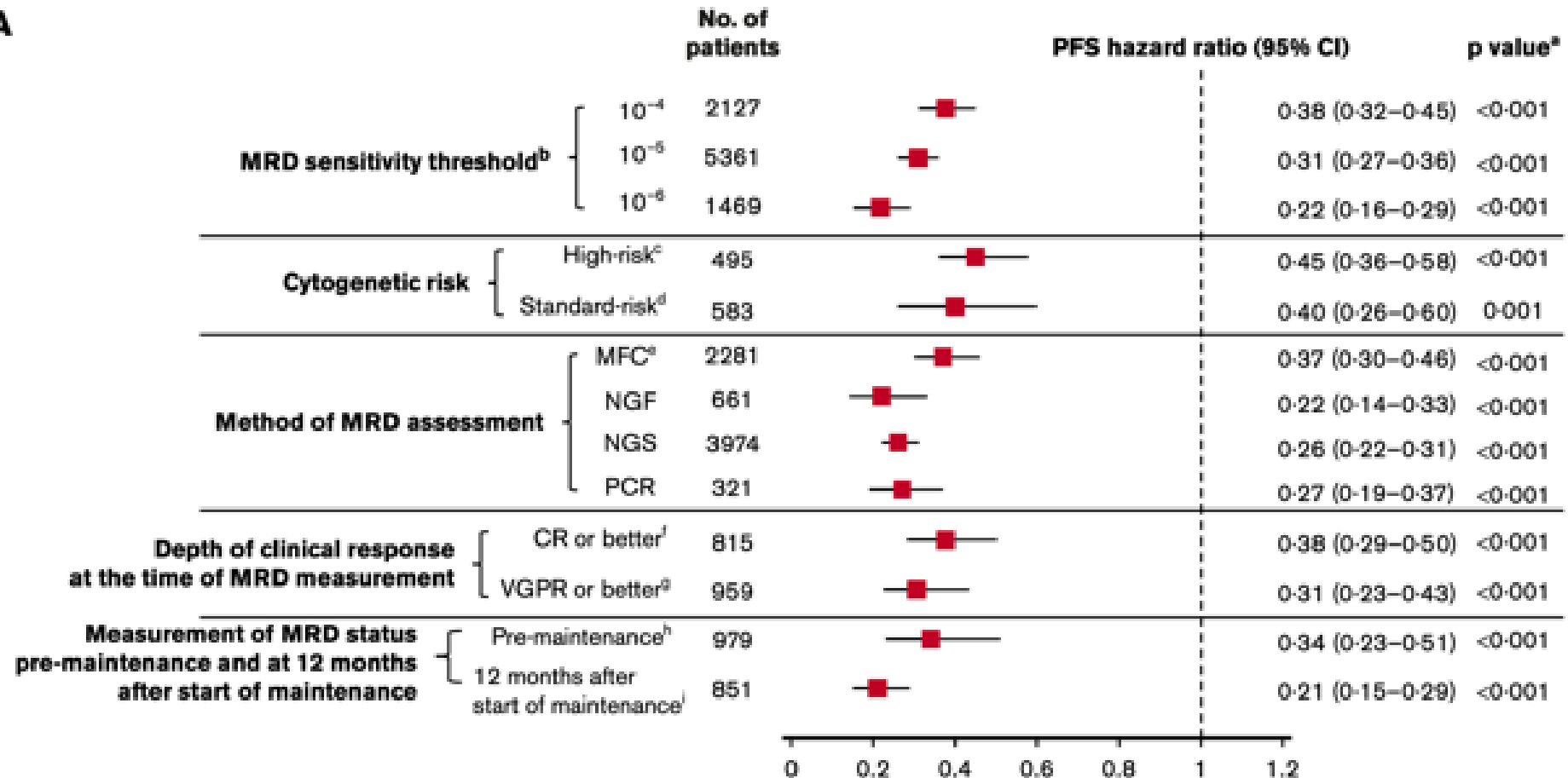


Number at risk	
MRD-	164 163 155 142 135 114 97 74 10 4 0
MRD+	960 672 456 343 269 214 179 131 11 2 0

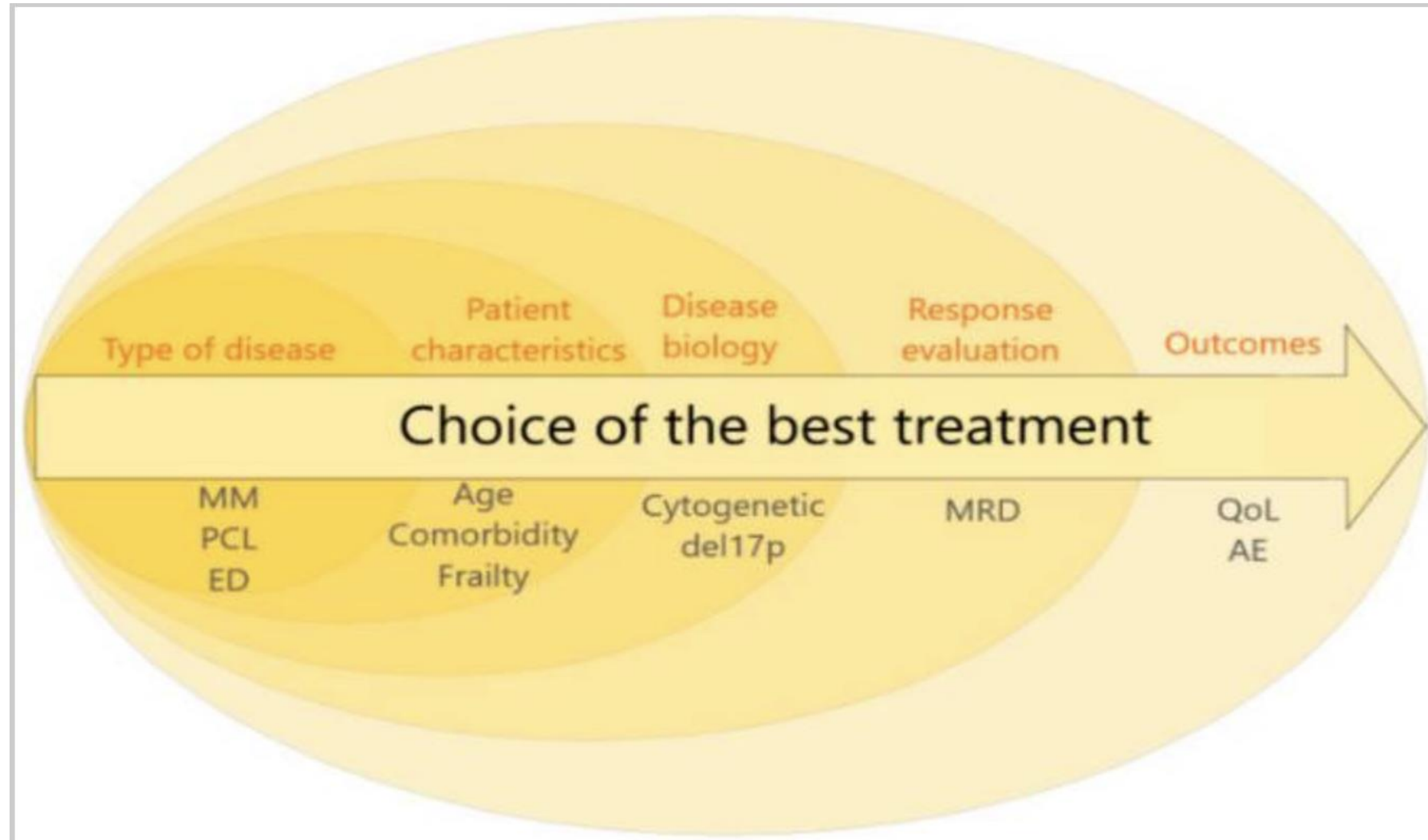
Positive vs Negative MRD: Two Different Myelomas

A large meta-analysis establishes the role of MRD negativity in long-term survival outcomes in patients with multiple myeloma

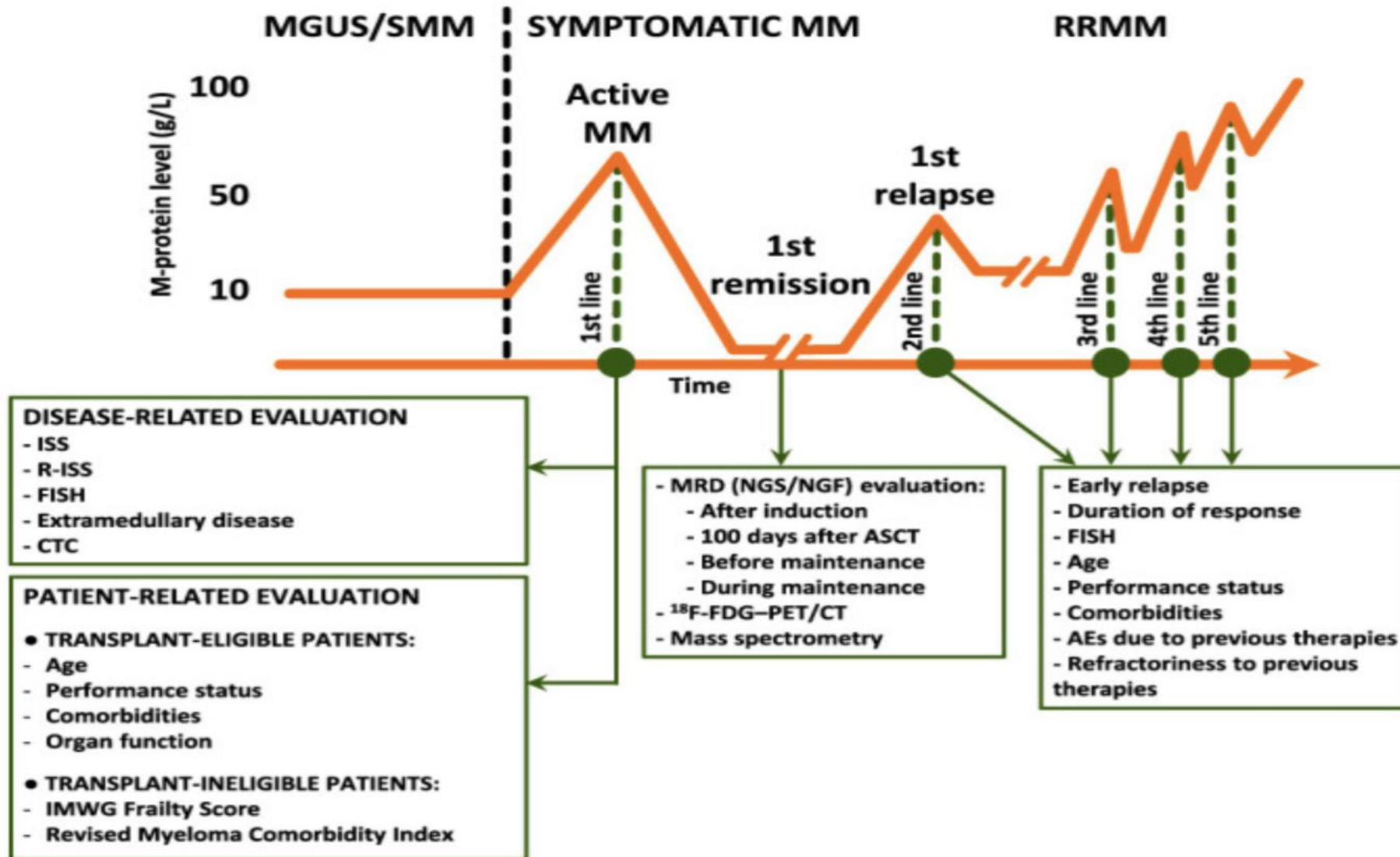
A



O que uso na estratificação de risco no mieloma múltiplo ao diagnóstico: ISS, R-ISS, R2-ISS, FISH, painel genético?



O que uso na estratificação de risco no mieloma múltiplo ao diagnóstico: ISS, R-ISS, R2-ISS, FISH, painel genético?



Obrigado pela atenção !

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