La terapia front-line del mieloma multiplo è la stessa per tutti i pazienti?

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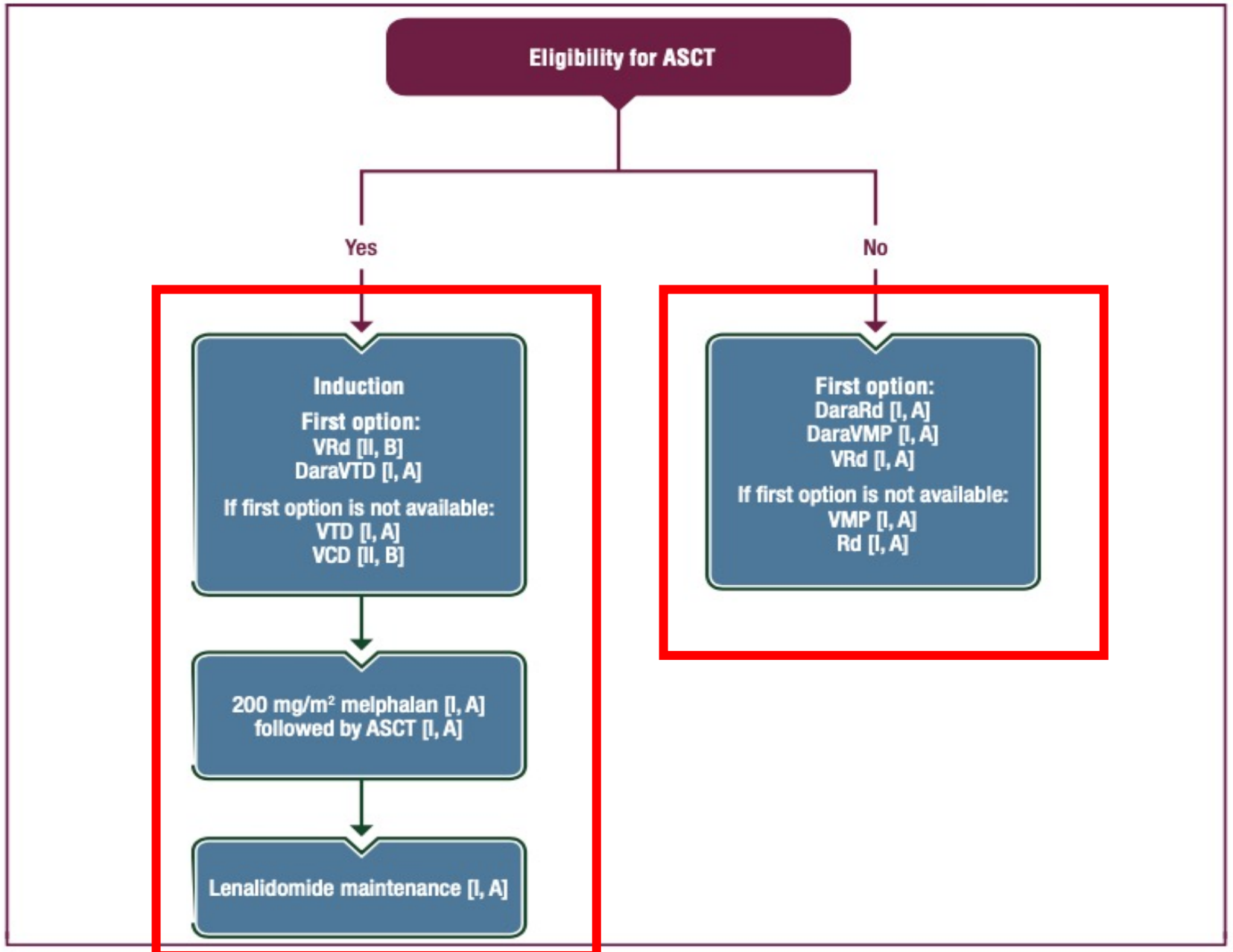
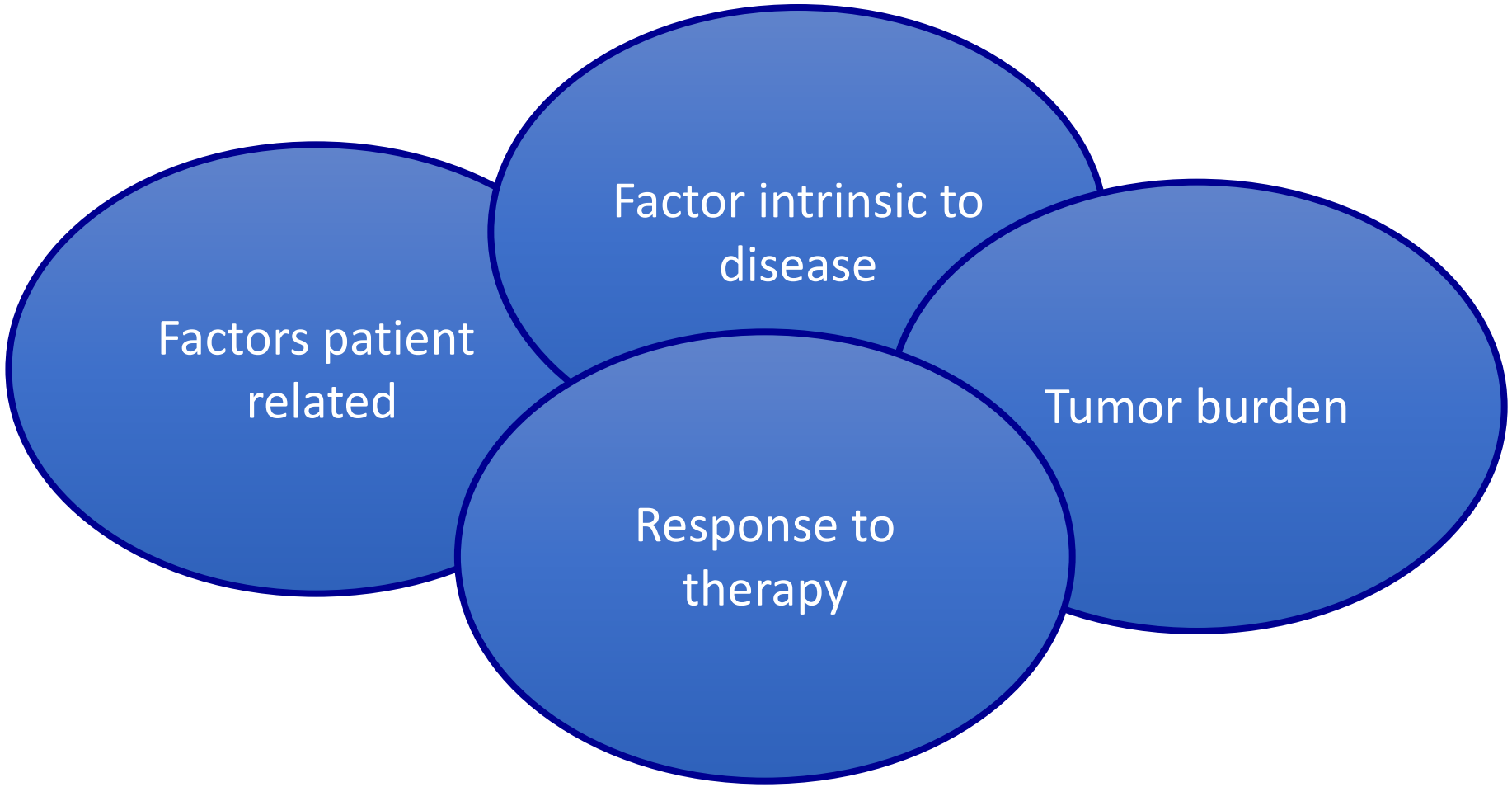
Disclosures of Name Surname

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Celgene Bristol						x	
Takeda						x	
GSK						x	
Jannsen						x	
Amgen						x	

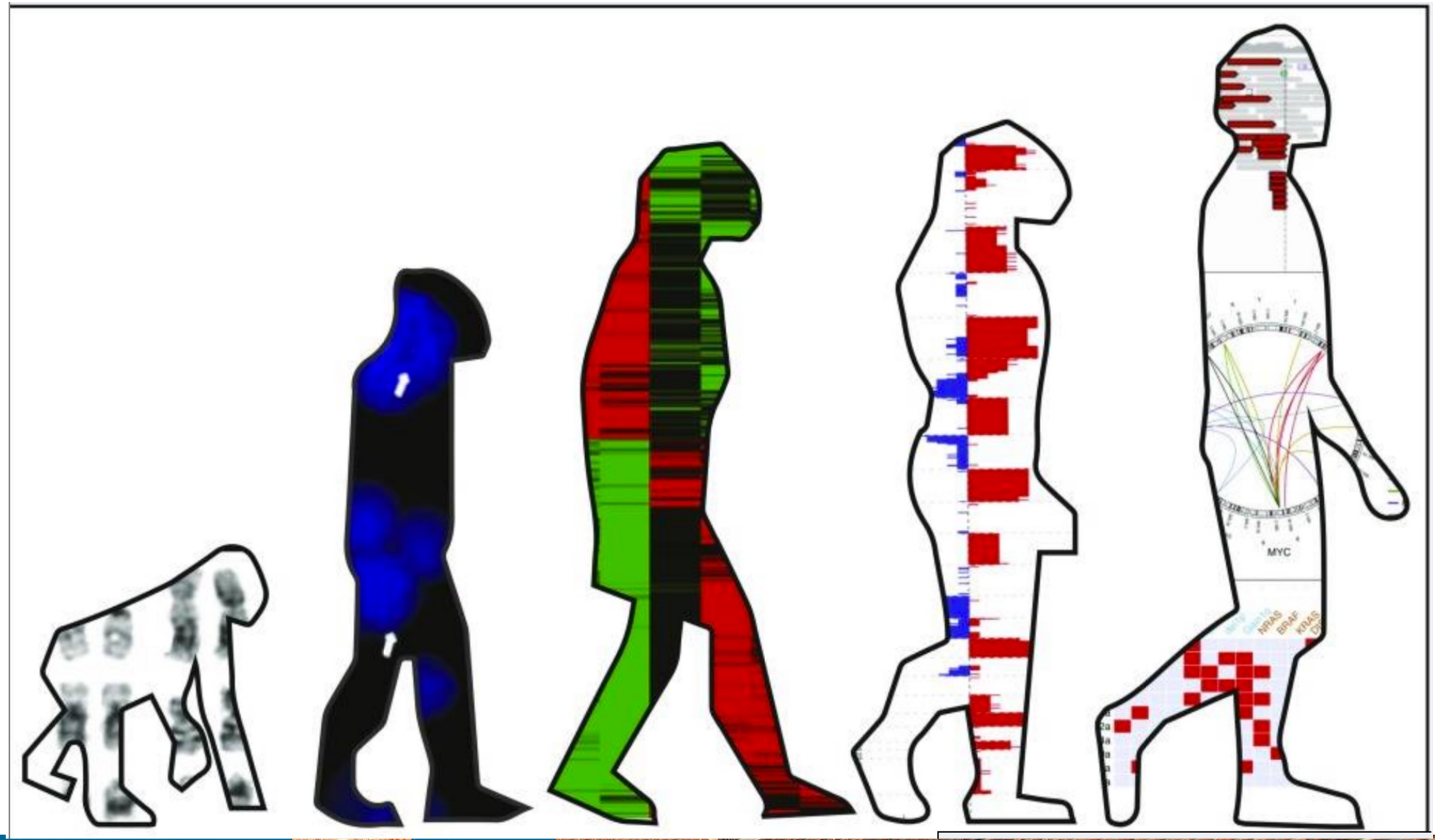


Dimopoulos et al, Annals of Oncology epub 3 February 2021

Prognostic factors in multiple myeloma

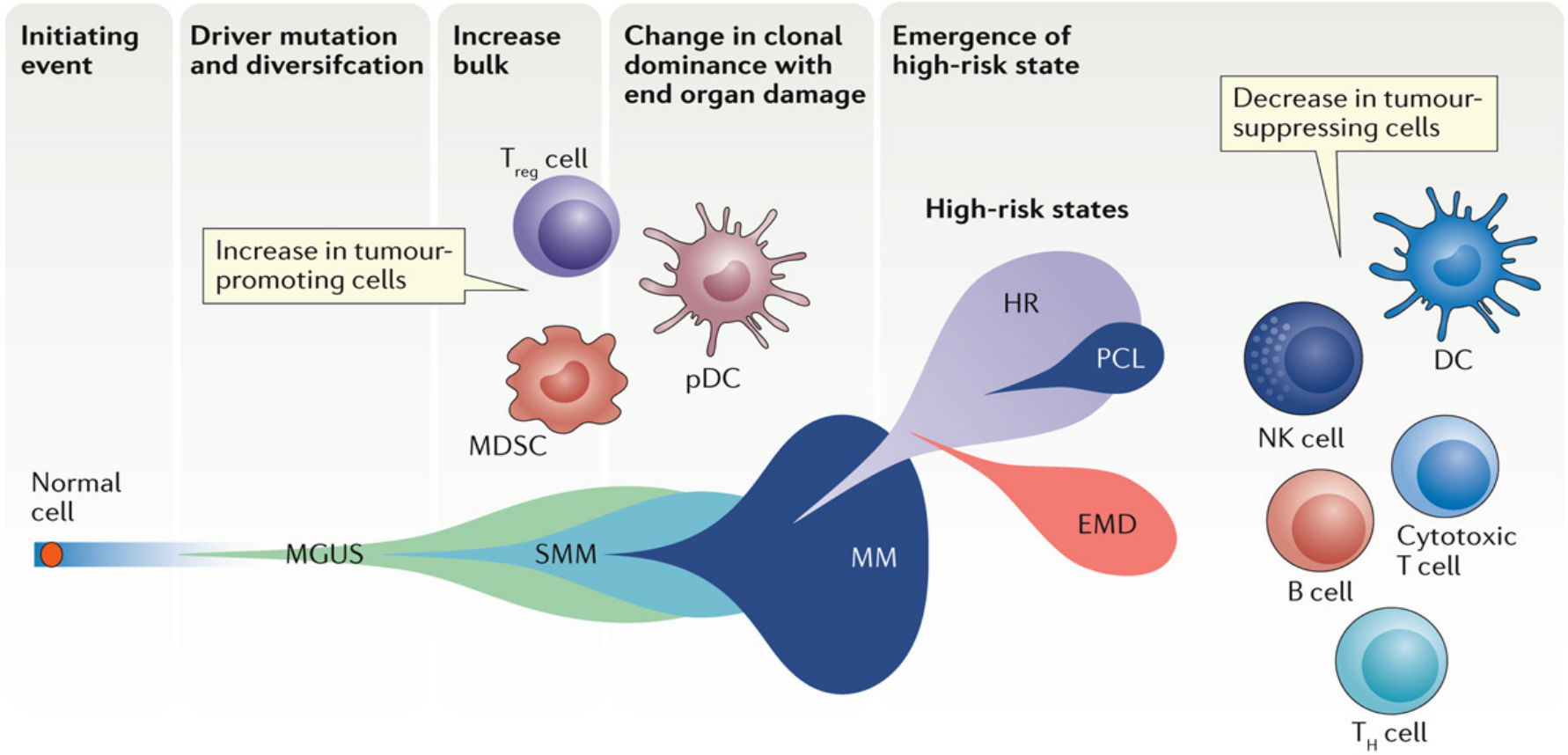


Evolution of molecular analysis techniques in myeloma.



Pawlyn C and Davies FD Blood 2019

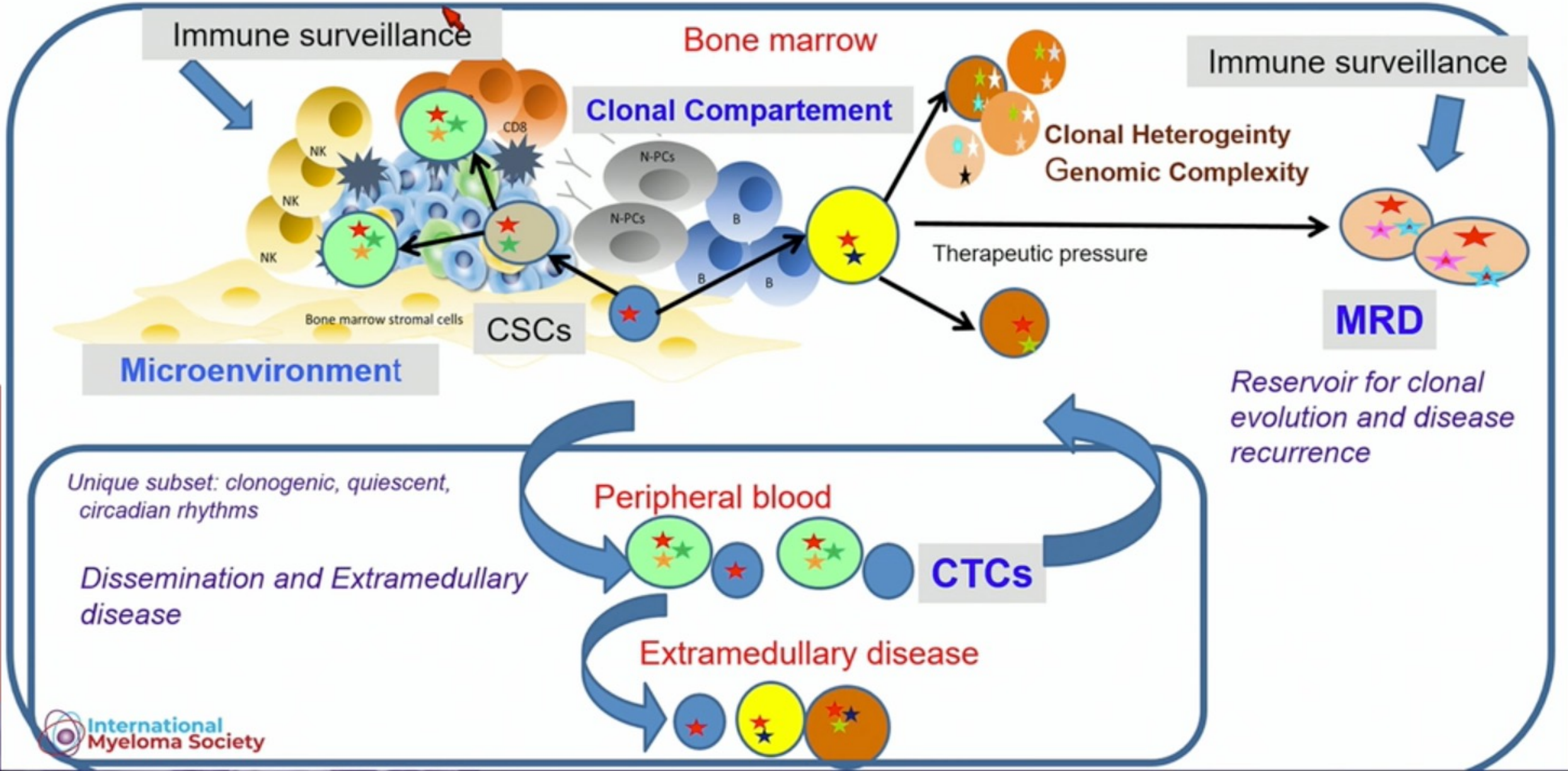
The interaction between genetic drivers and microenvironment changes drives high-risk disease states



Pawlyn C, Morgan G. Nature revievs Cancer 2017

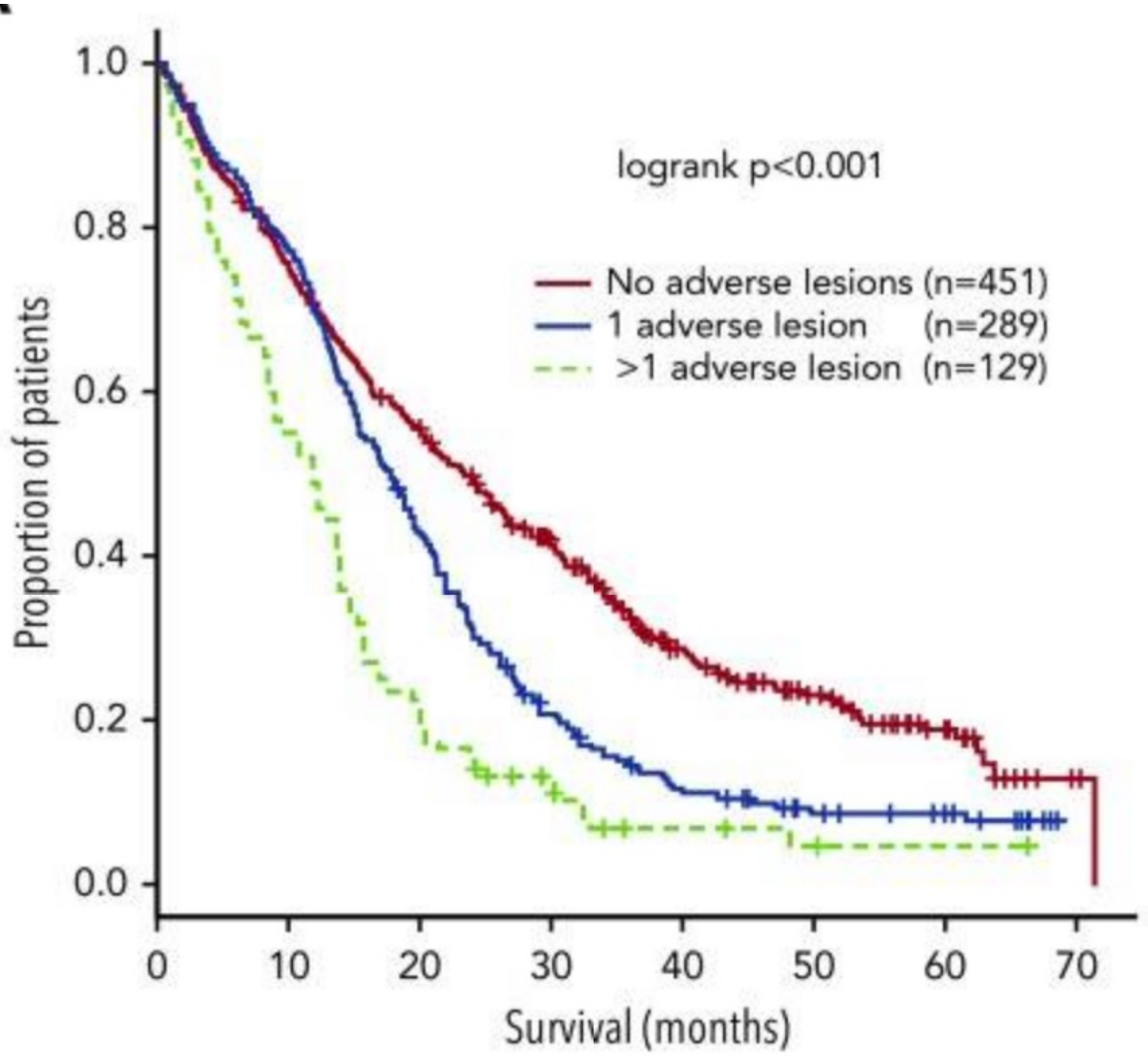
Myeloma Pathogeneis

To identify signatures of High Risk clones: **as tools for understanding disease dissemination & resistance " Achilees´heel"**



International Myeloma Society

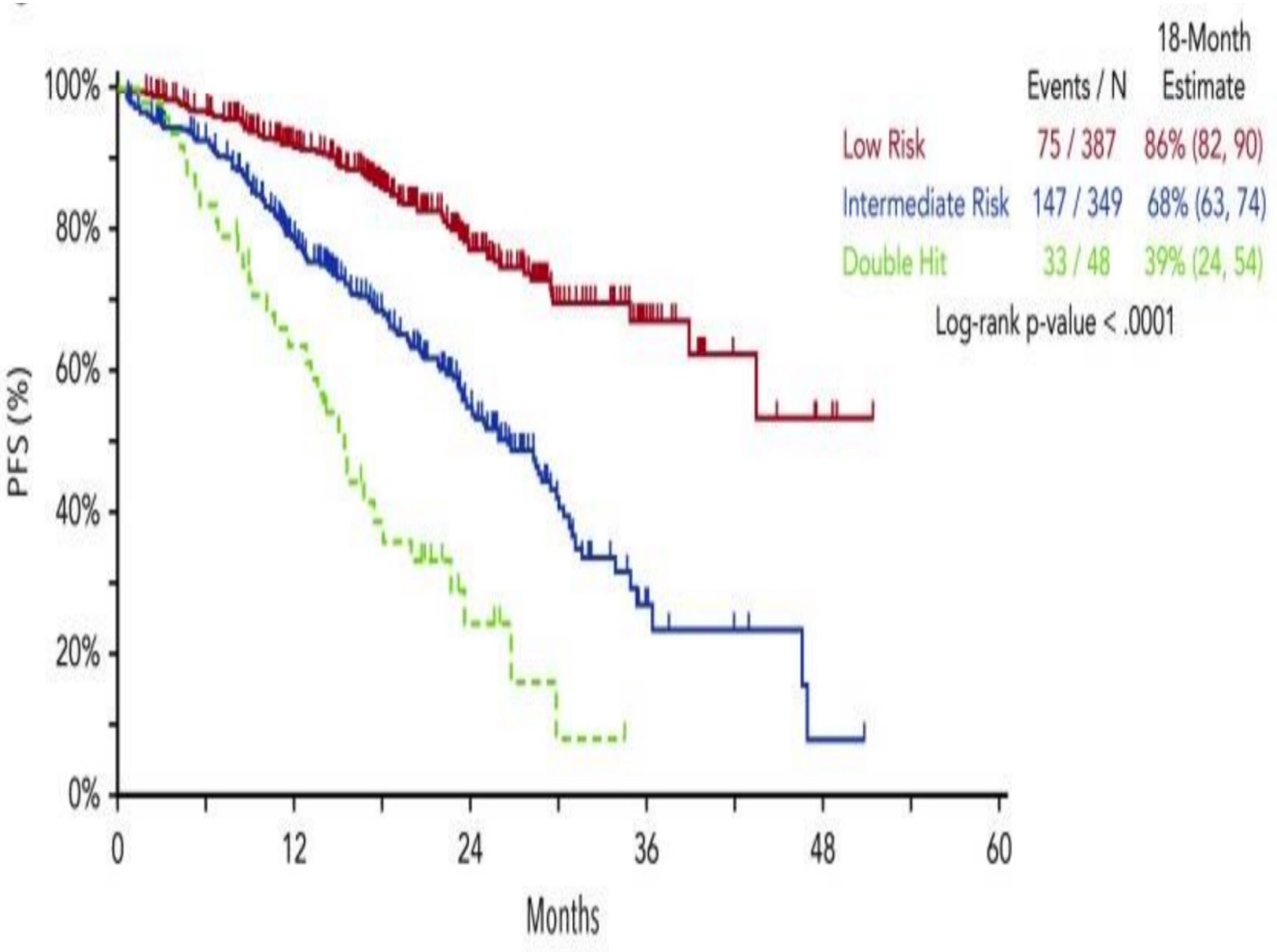
PFS as defined by the different risk stratification systems



Ultrahigh risk defined by the presence of >1 adverse lesion (t(4;14), t(14;16), t(14;20), del(17p), and gain(1q)) in the analysis of 869 cases from the MRC Myeloma IX trial

Boyd KD et al Leukemia 2012

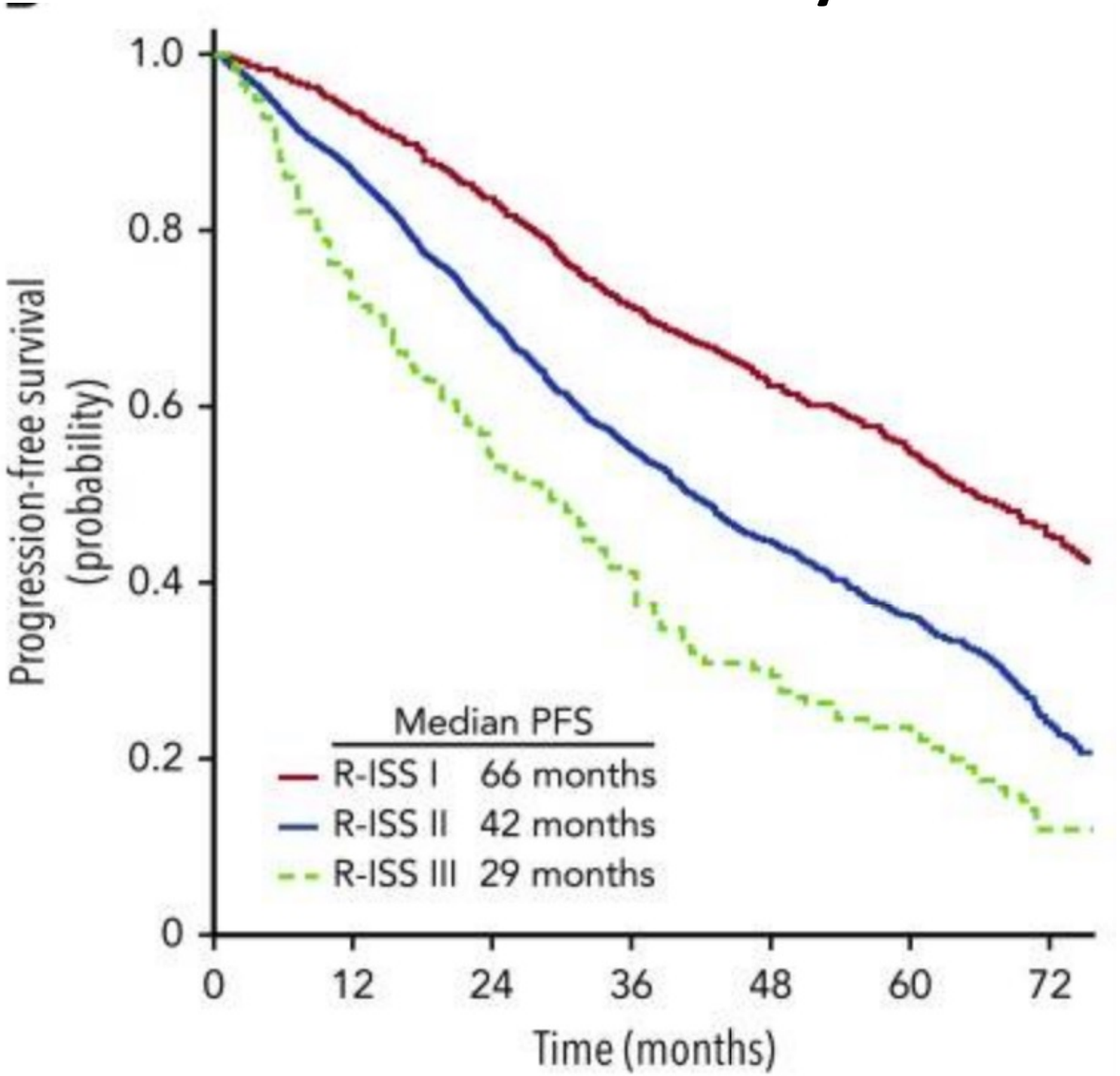
PFS as defined by the different risk stratification systems



Ultra high-risk defined as double-hit myeloma (either loss of both alleles of TP53 [by mutation, deletion or both] or with 2 extra copies of 1q, resulting in amplification rather than a single gain) by incorporating NGS data in the Myeloma Genome Project analysis of 784 patients

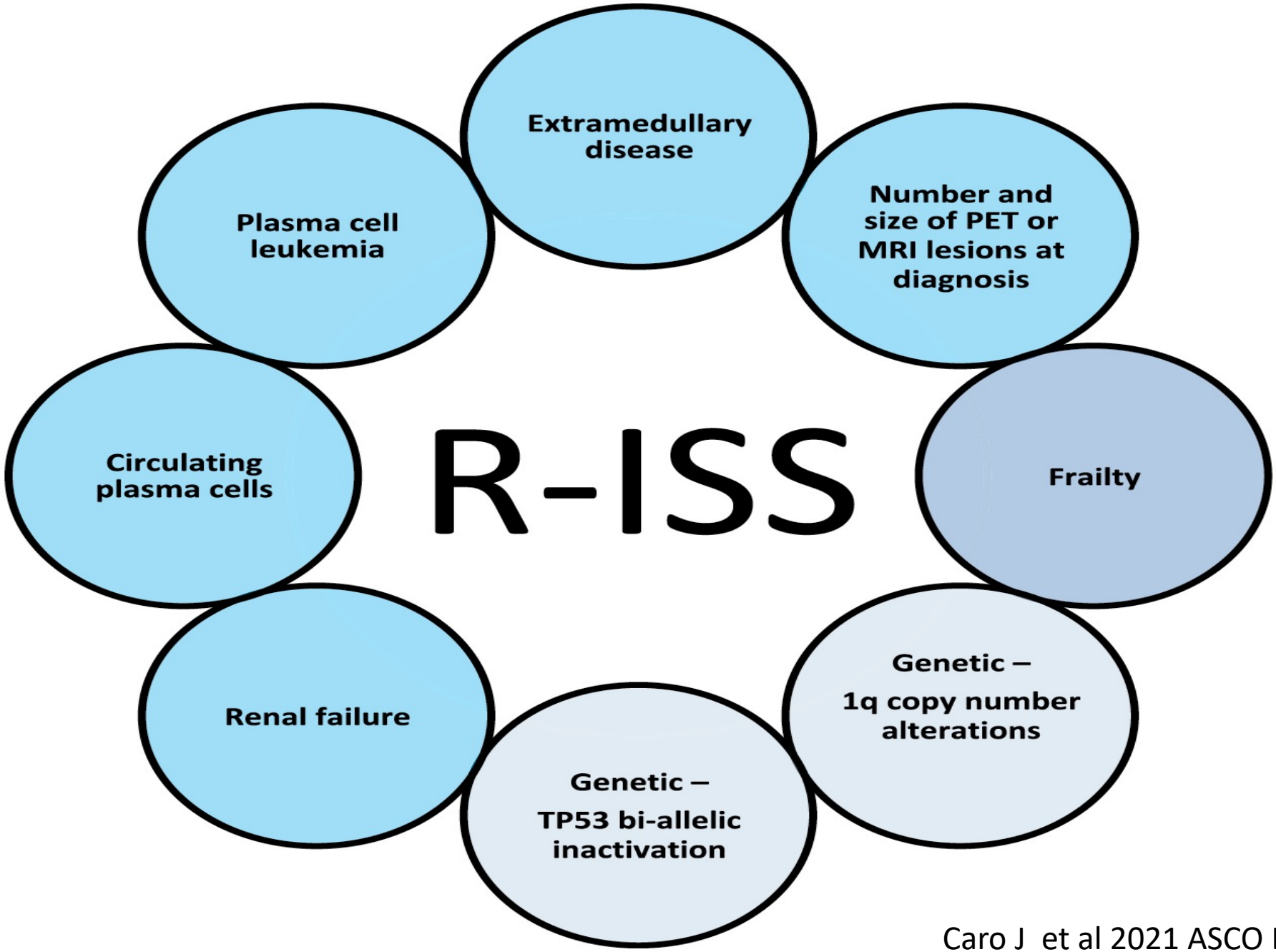
Walker BA et al Leukemia 2019

PFS as defined by the different risk stratification systems

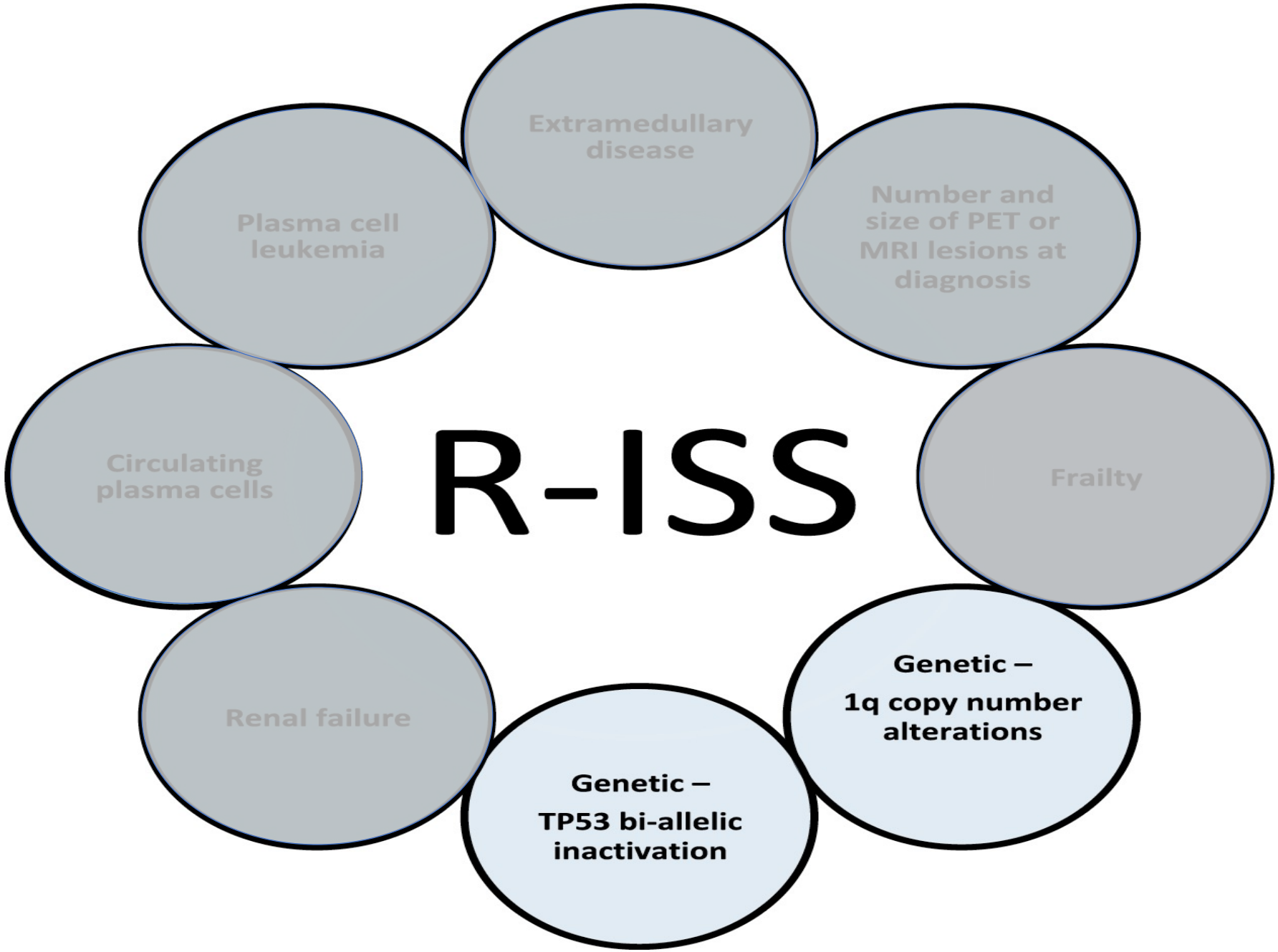


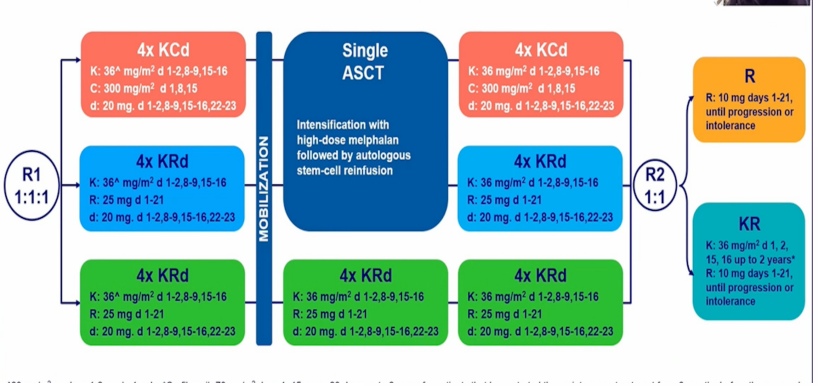
Ultrahigh risk defined by the R-ISS (low-risk R-ISS group I [ISS stage I with no high-risk CA (del(17p) and/or t(4;14 and/or 14;16)) and normal LDH level] to high-risk R-ISS group III [ISS stage III and high-risk CA or high LDH level]) in a pooled study of 4445 patients with newly diagnosed multiple myeloma from 11 clinical studies.

Palumbo A et al JCO 2015



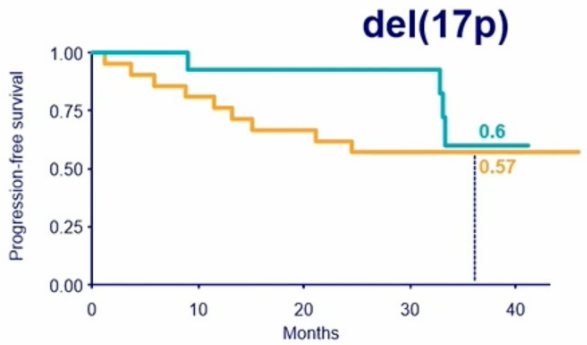
Caro J et al 2021 ASCO EDUCATIONAL BOOK


R-ISS
Extramedullary disease
Number and size of PET or MRI lesions at diagnosis
Frailty
Genetic – 1q copy number alterations
Genetic – TP53 bi-allelic inactivation
Renal failure
Circulating plasma cells
Plasma cell leukemia

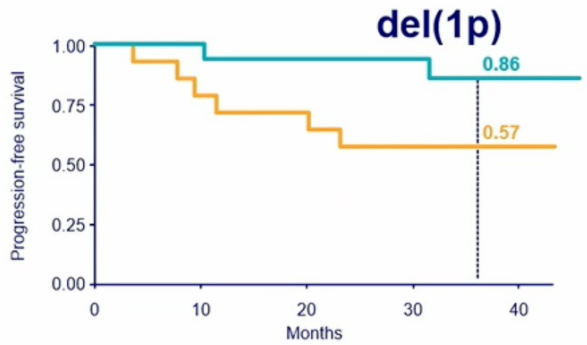


Progression-free survival: Random 2

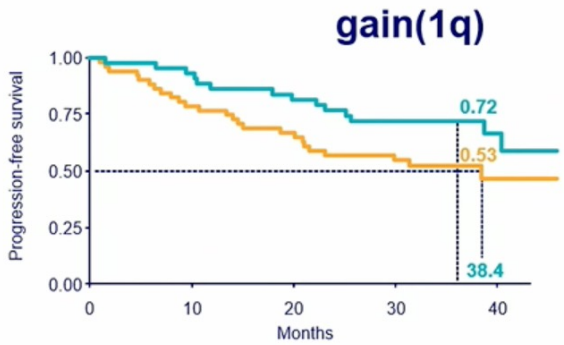
KR vs. R



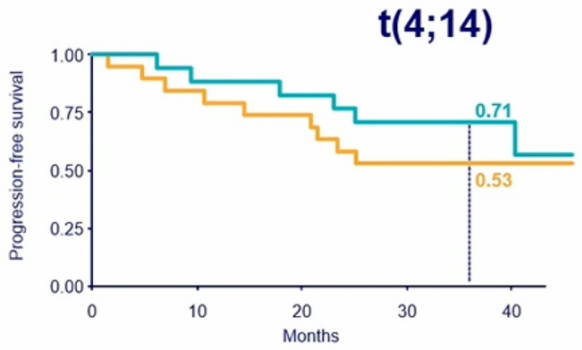
KR vs. R: HR 0.65 95% CI (0.2-2.13)



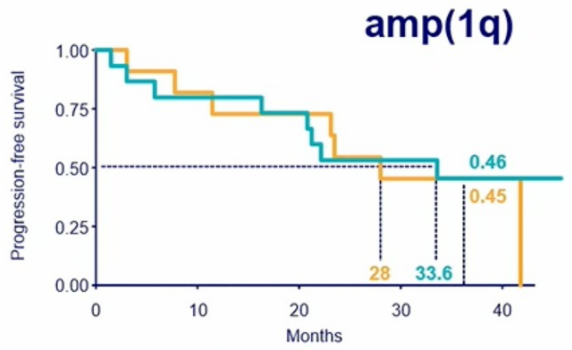
KR vs. R: HR 0.20 95% CI (0.04-0.98)



KR vs. R: HR 0.54 95% CI (0.28-1.05)



KR vs. R: HR 0.69 95% CI (0.24-1.96)

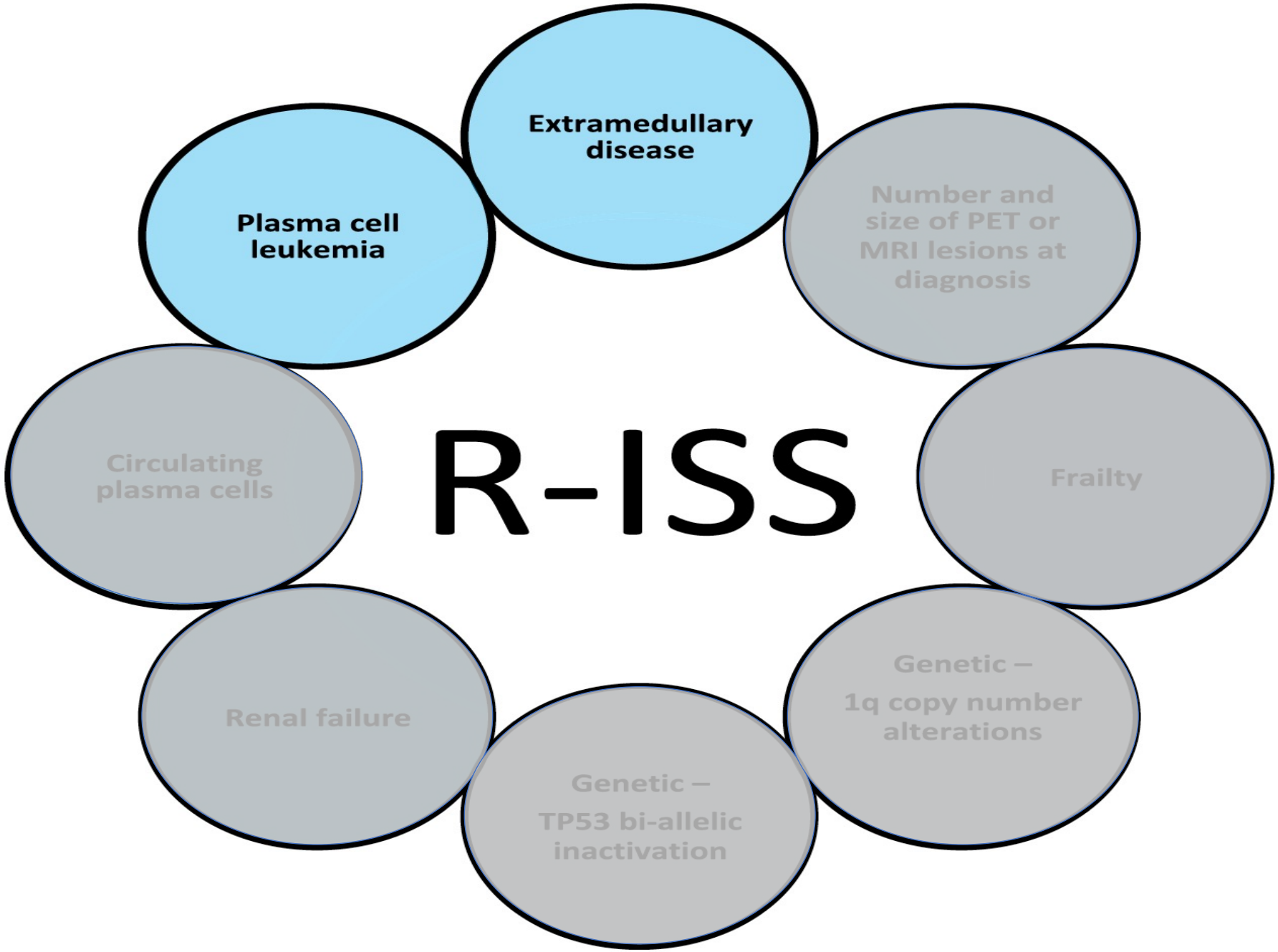


KR vs. R: HR 0.72 95% CI (0.25-2.04)

KR prolongs PFS in all CA subgroups, except… in patients with amp(1q)

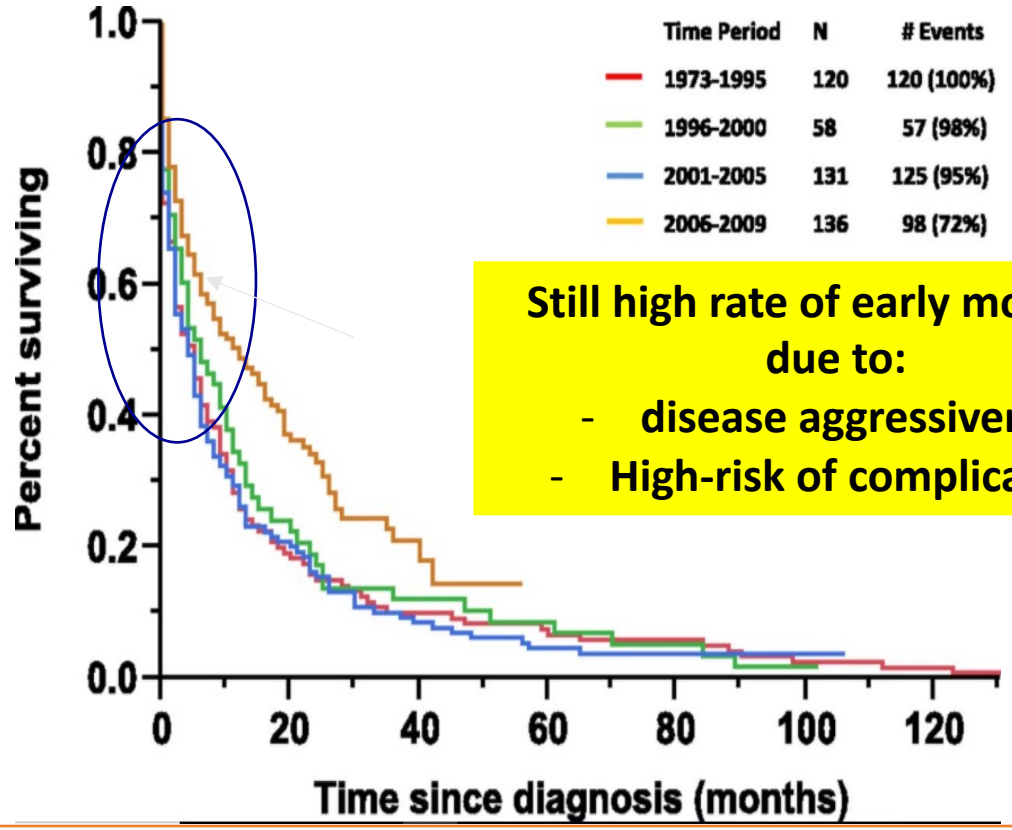
3-year PFS reported in the figure.

Random 2, second randomization (maintenance treatment); K, carfilzomib; R, lenalidomide; HR, hazard ratio; p, p-value; PFS, progression-free survival; CA, chromosomal abnormalities.


Extramedullary disease
Plasma cell leukemia
Number and size of PET or MRI lesions at diagnosis
Circulating plasma cells
R-ISS
Frailty
Renal failure
Genetic – 1q copy number alterations
Genetic – TP53 bi-allelic inactivation

pPCL and EMM: prognosis and overall survival (OS)

pPCL

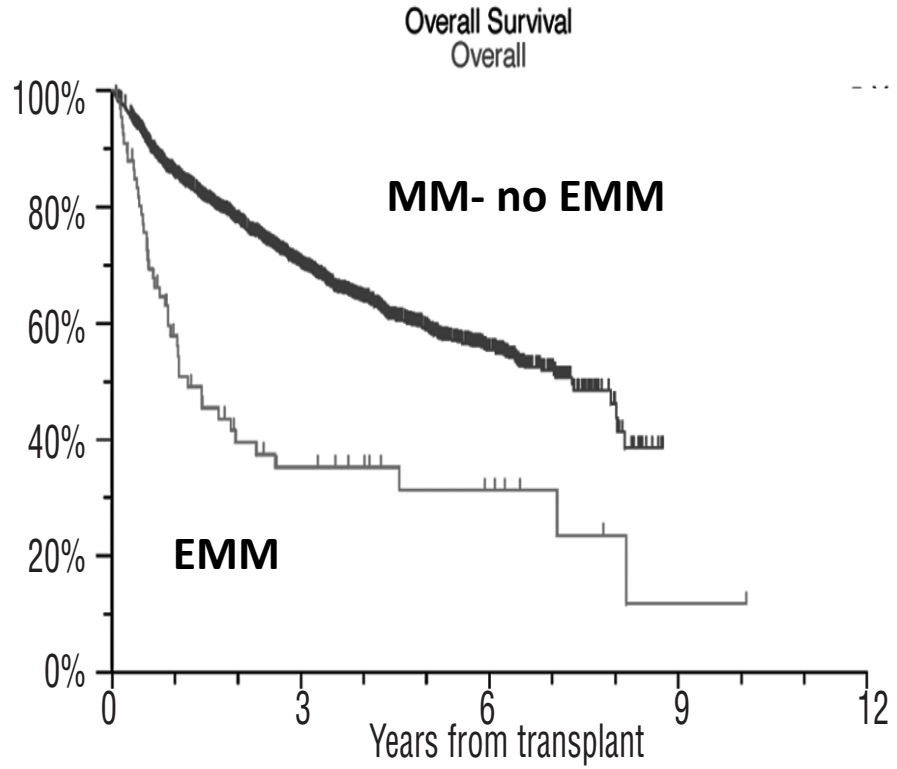


Still high rate of early mortality due to:

- **disease aggressiveness**
- **High-risk of complications**

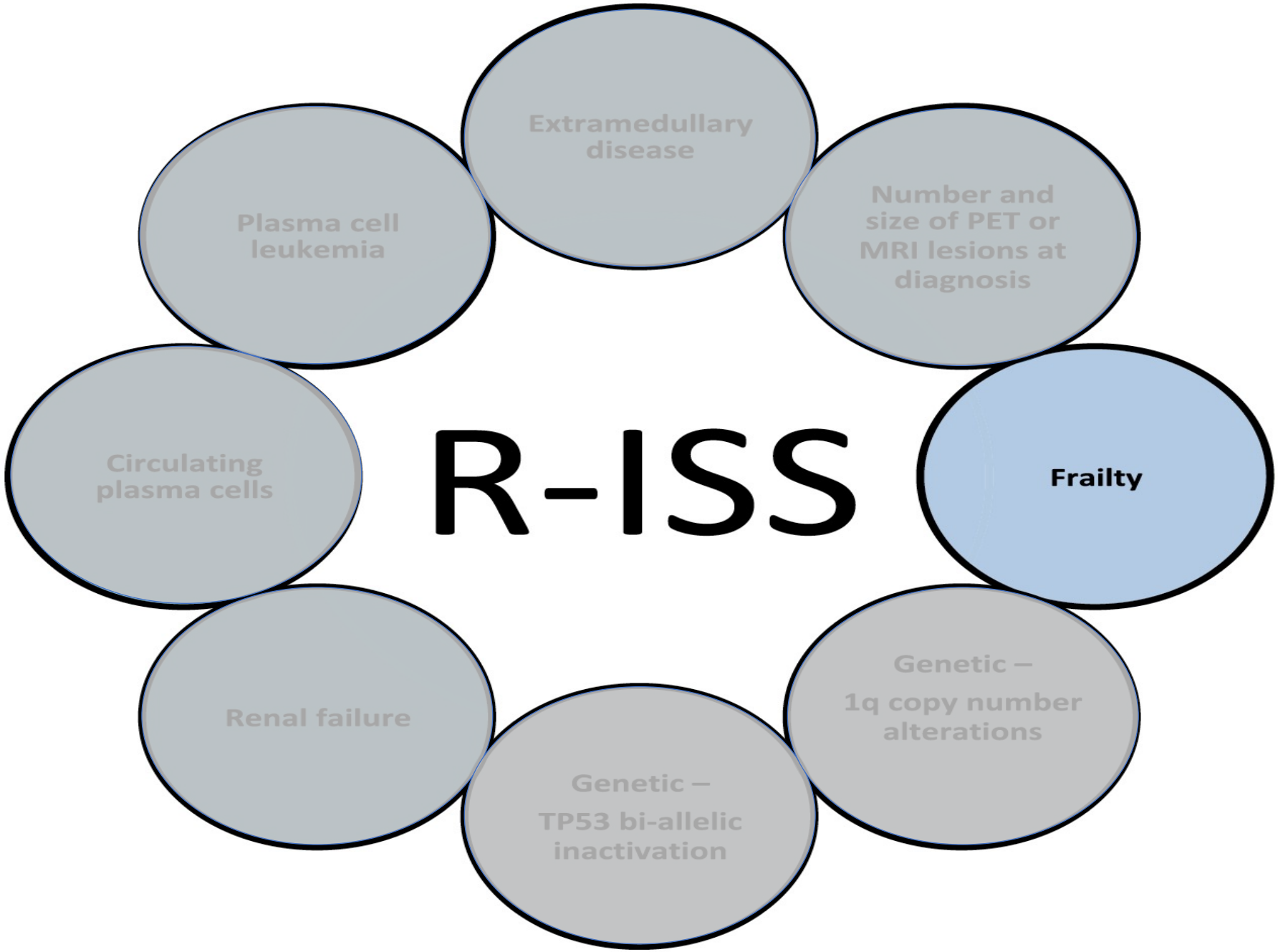
Time interval (year of diagnosis)	Median OS (months)	Early mortarlity (< 1 month)
1973-1995	5	28%
1996-2000	6	23%
2001-2005	4	27%
2006-2009	12 (p < 0.001)	15% (P=0.043)

EMM



	5 year OS
EMM	31%
MM- NO EMM	59%
P Value	< 0.0001

Gonsalves et al., Blood 2014, Usman S et al , Hematologica 2012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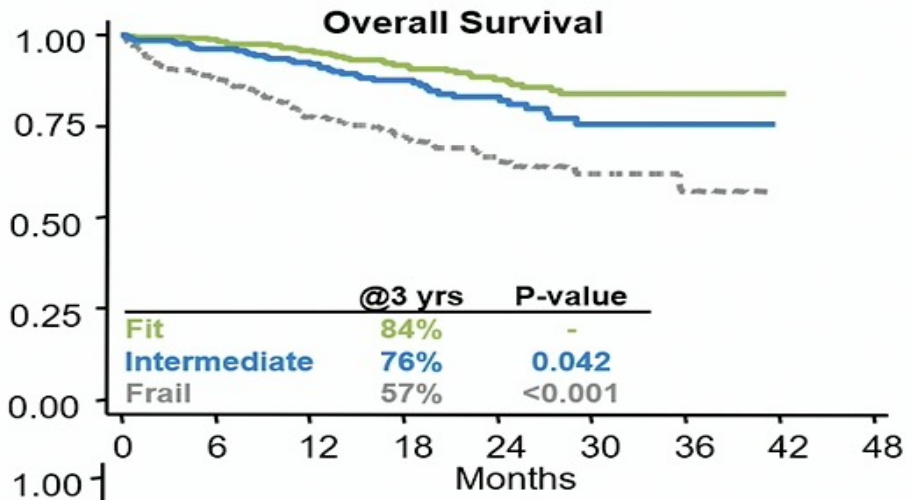
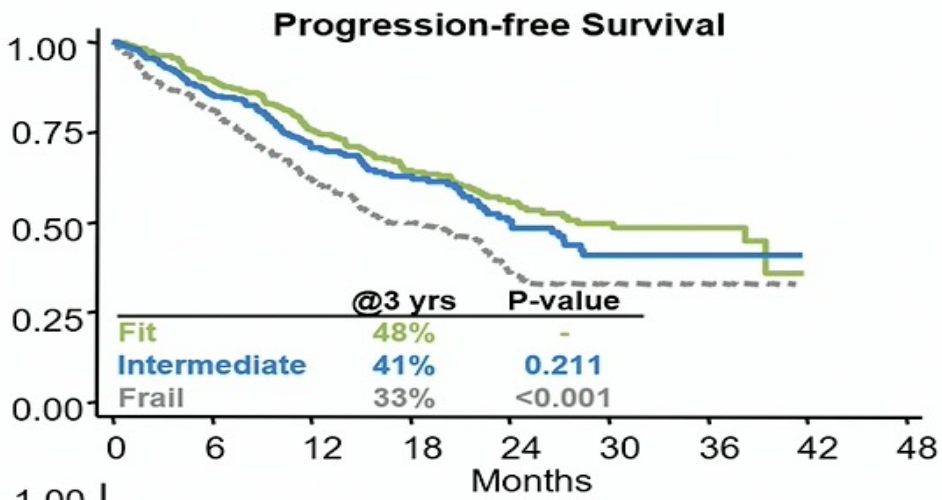
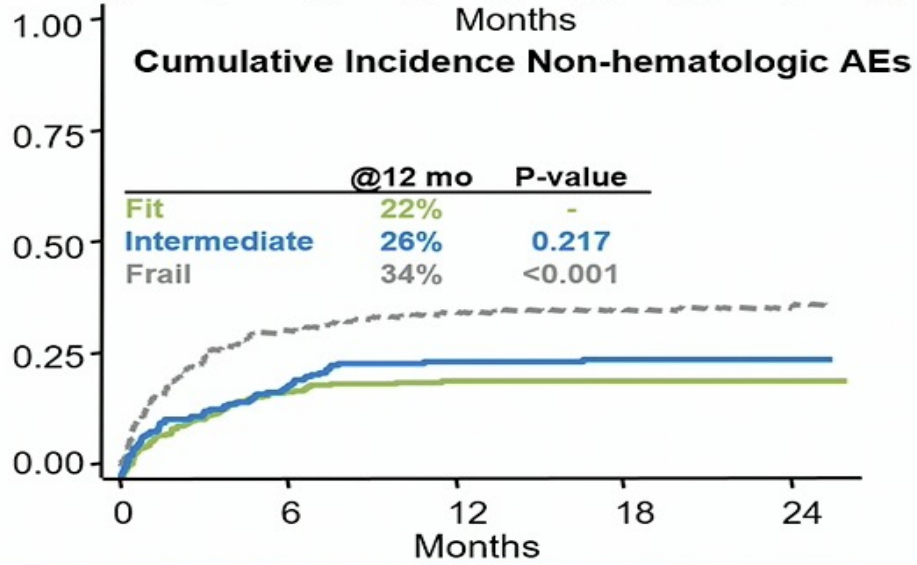
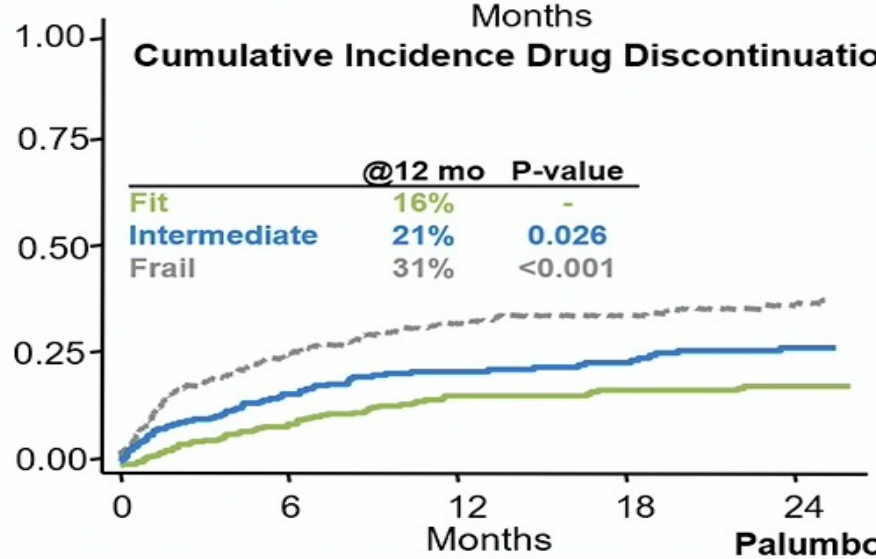
IMWG frailty score: Long-term outcome



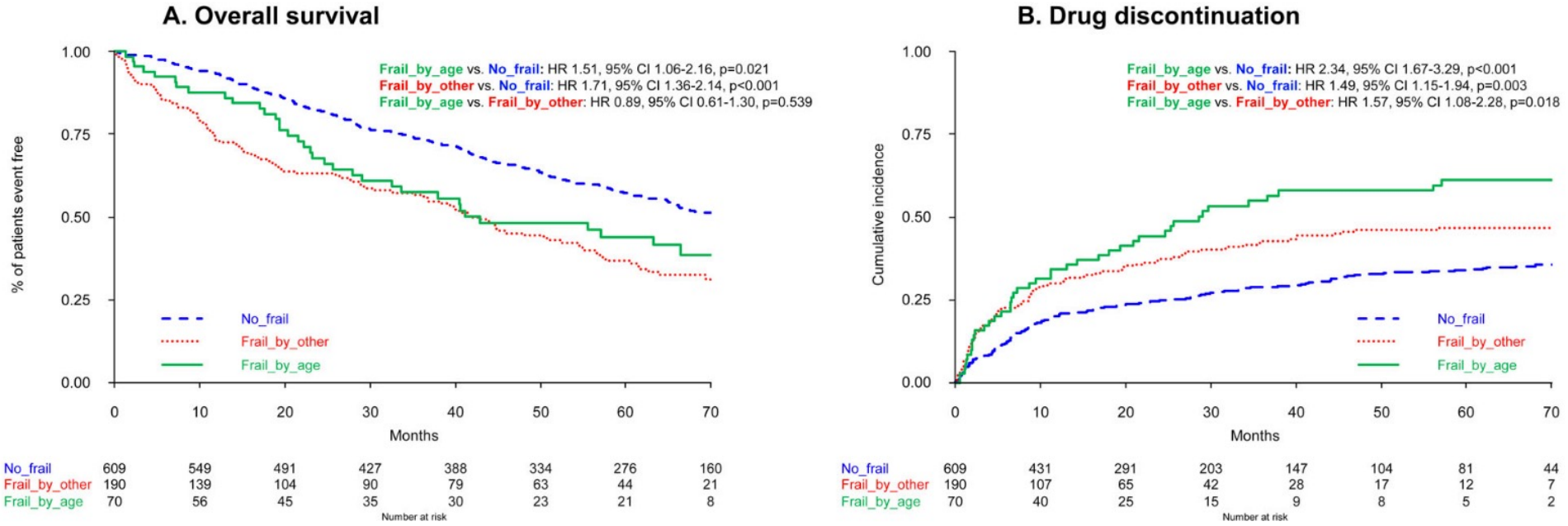




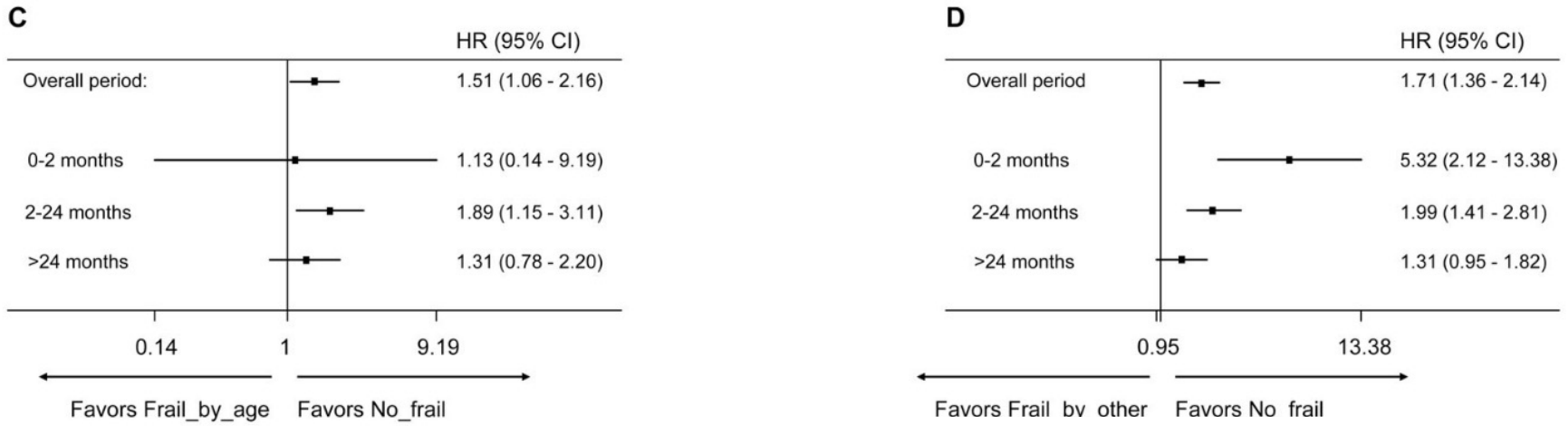


Palumbo A et al. Blood 2015;25:2068-2074.

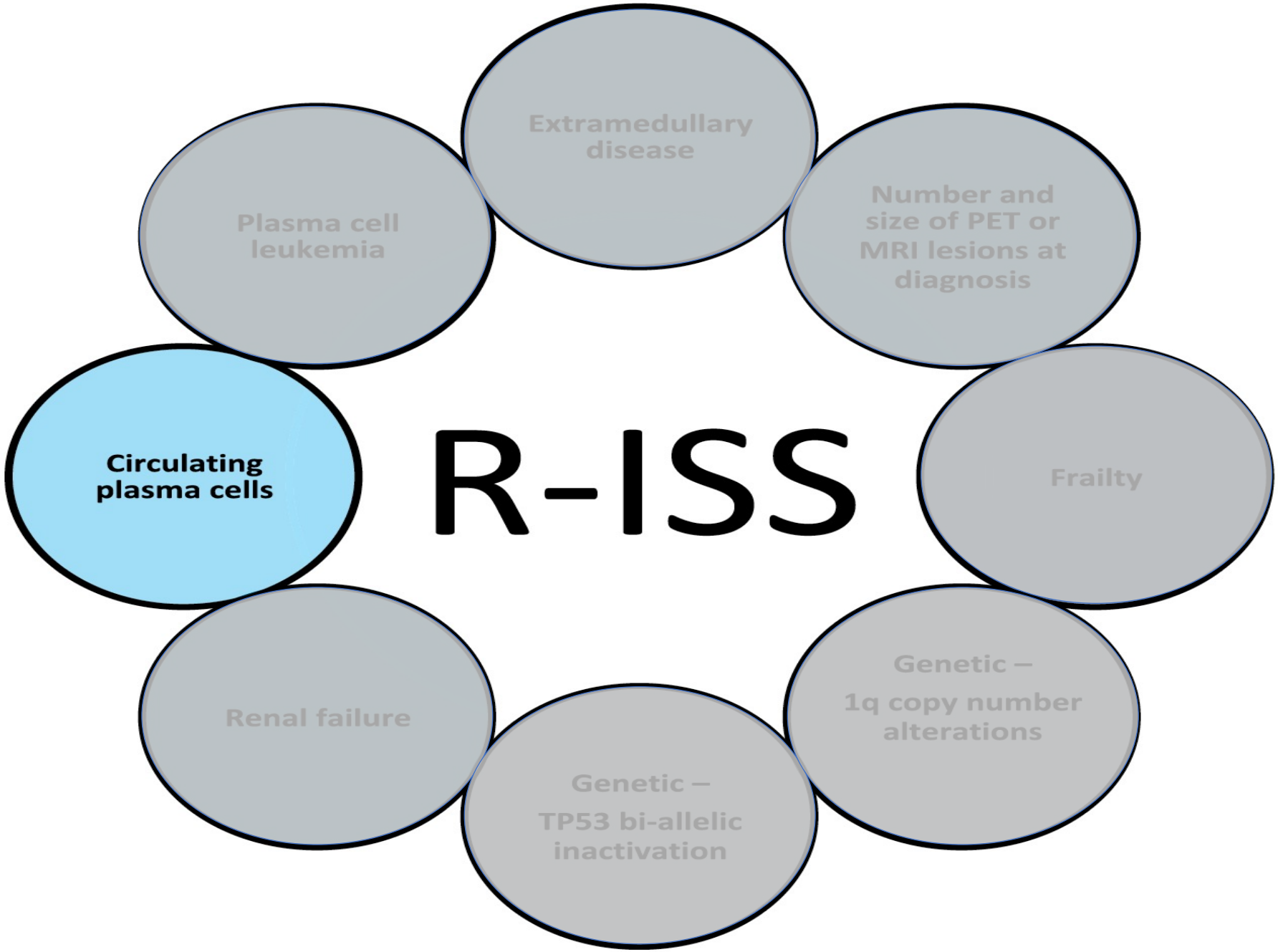
Outcomes of octogenarian newly diagnosed multiple myeloma patients according to frailty group



Survival analysis



D'Agostino et al. Blood Cancer Journal (2021) 11:73


R-ISS
Extramedullary disease
Number and size of PET or MRI lesions at diagnosis
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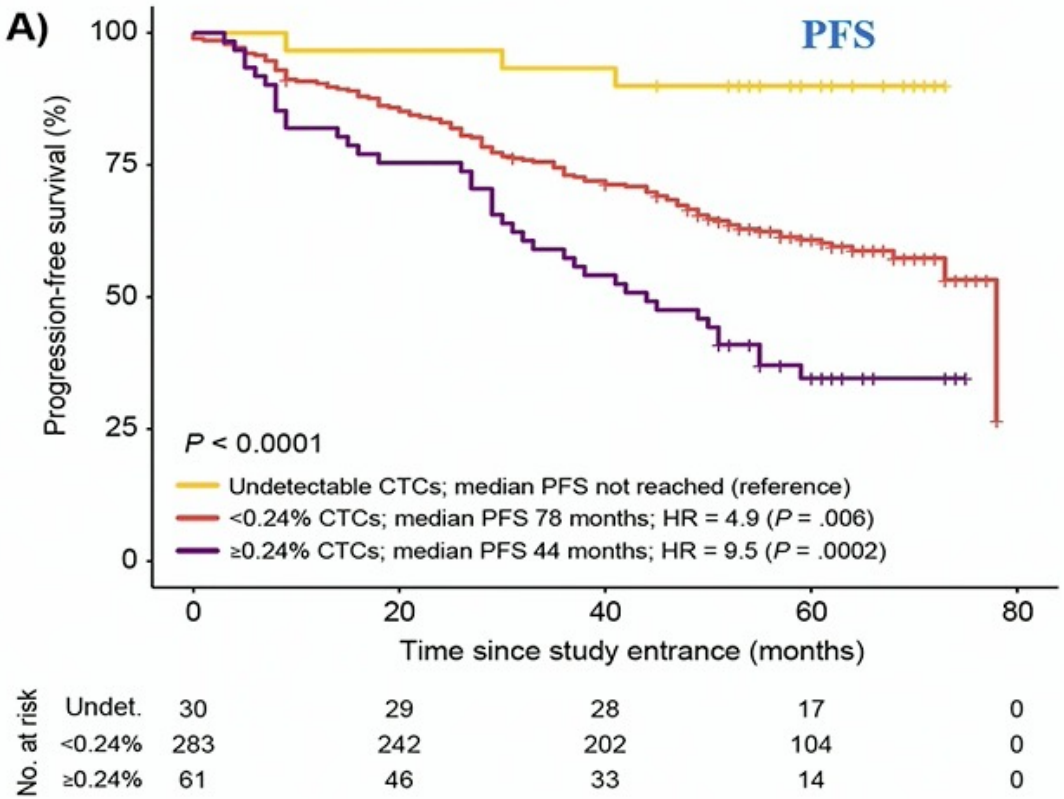
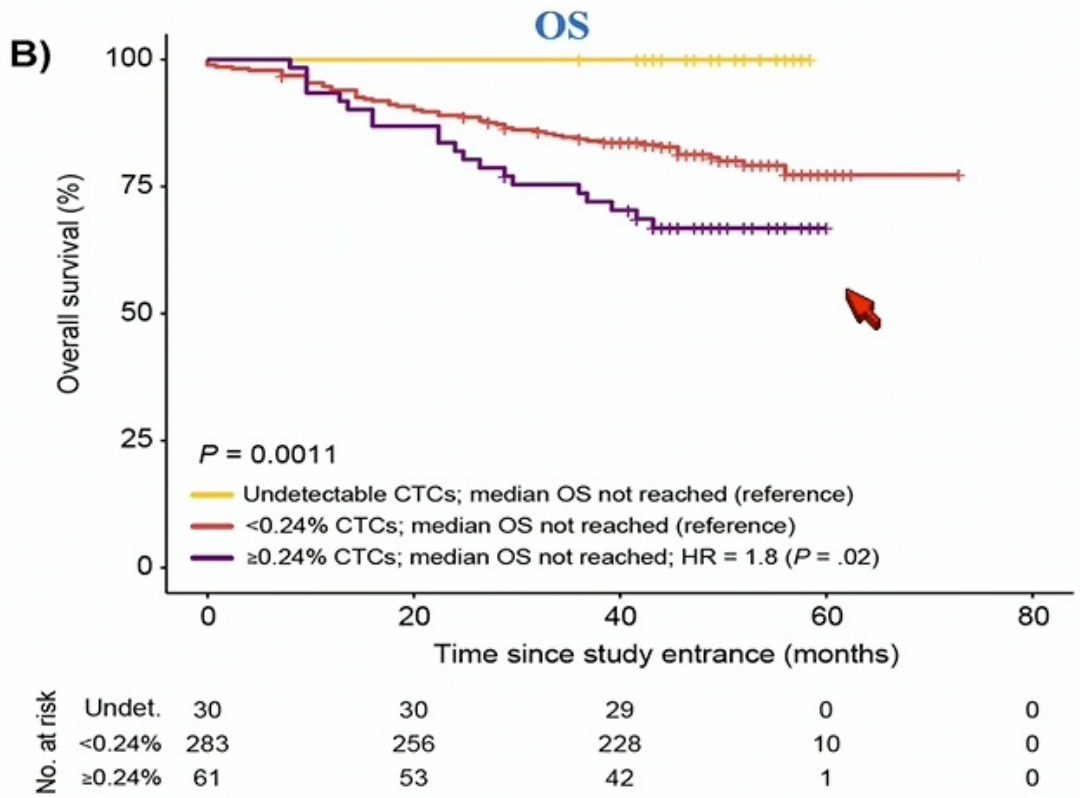
Circulating plasma cells
Plasma cell leukemia

CTCs are the most relevant diagnostic biomarker in MM (GEM12)

- ***Detected by NGF in 92% of patients.***
- ***Higher number of CTCs were observed in patients with advanced ISS, elevated LDH and high-risk genetics***

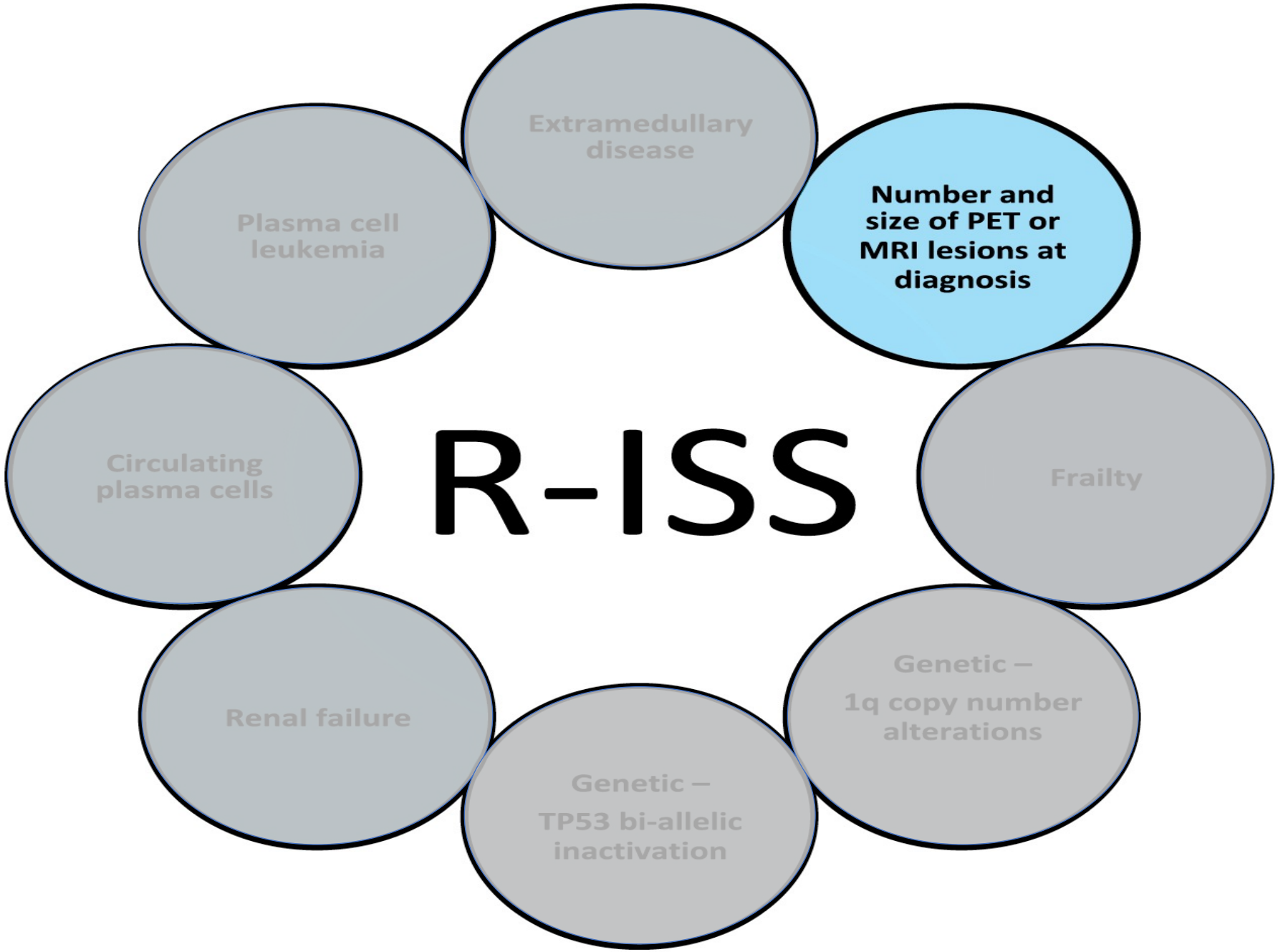




CTC levels are the most powerful independent prognostic factor at diagnosis

Model for MM dissemination: a high occupancy of hypoxic BM niches + pro-inflammatory microenvironment: force cancer cells to stop proliferating, recirculate in PB and seek other BM niches to continue growing

Garces JJ, et al. EHA 2021, Manuscript in preparation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Extramedullary disease
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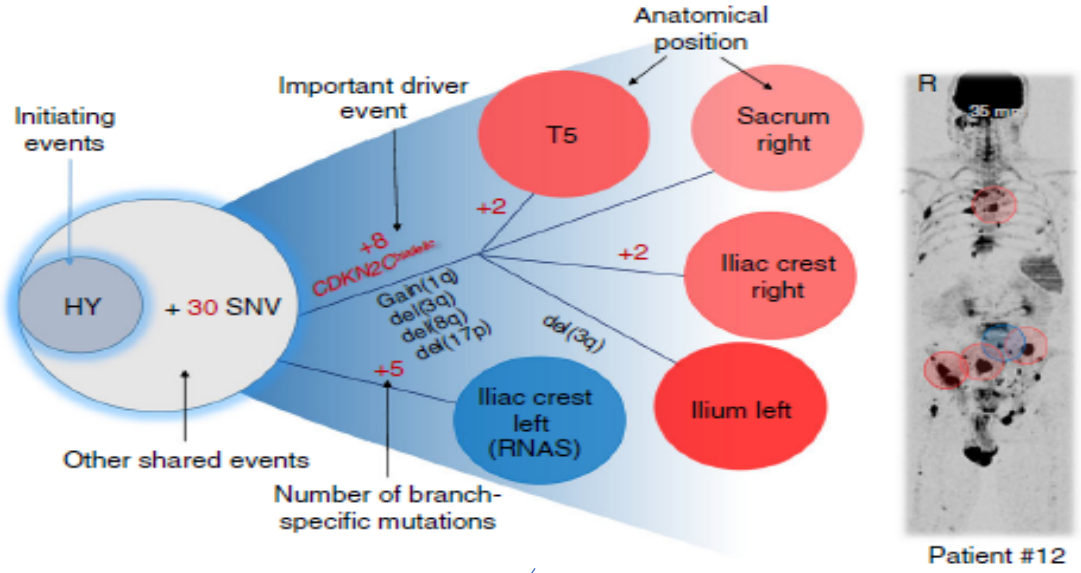
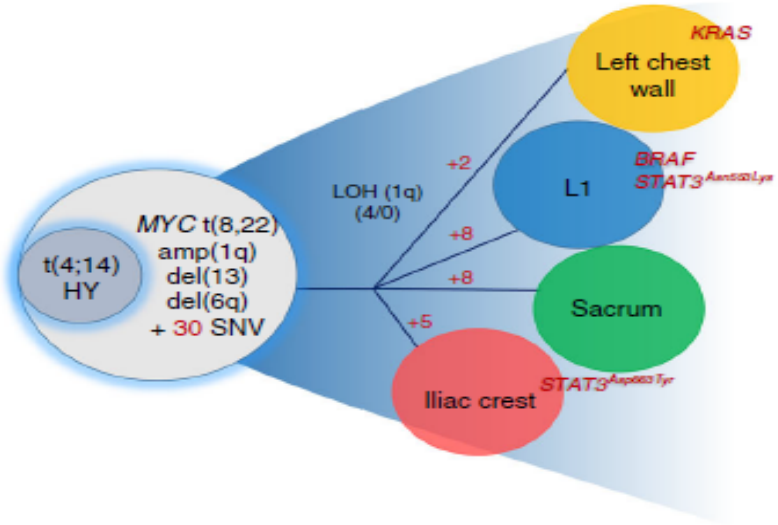
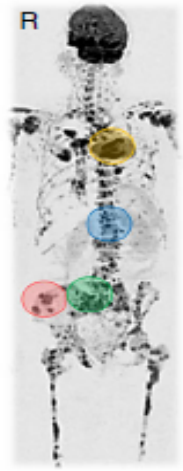
Renal failure
Circulating plasma cells
Plasma cell leukemia

Multi-regional evolutionary events underlie disease progression



Patient #12



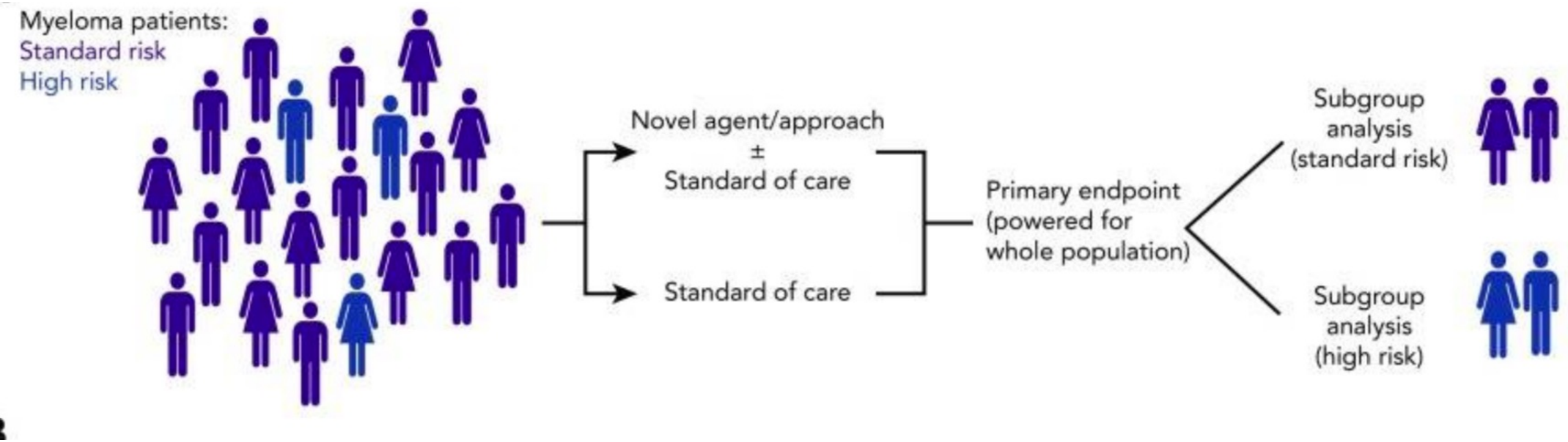


Patient #8

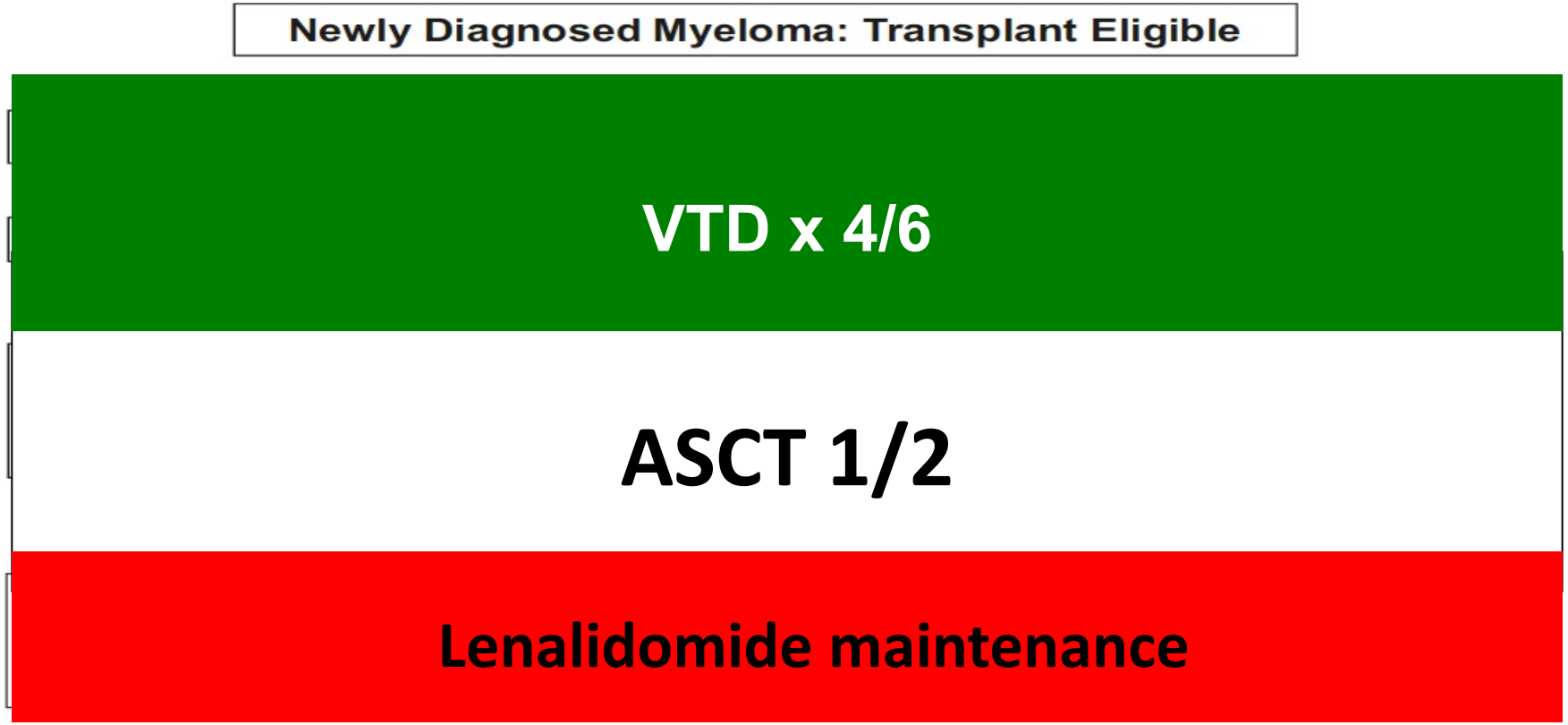
FLs have a common high-risk ancestor which disseminates in a metastatic way on a background of GEP70 low-risk disease

All sites have a common ancestor which was further changed during progression

Rasche et al, Nature Comm 2017

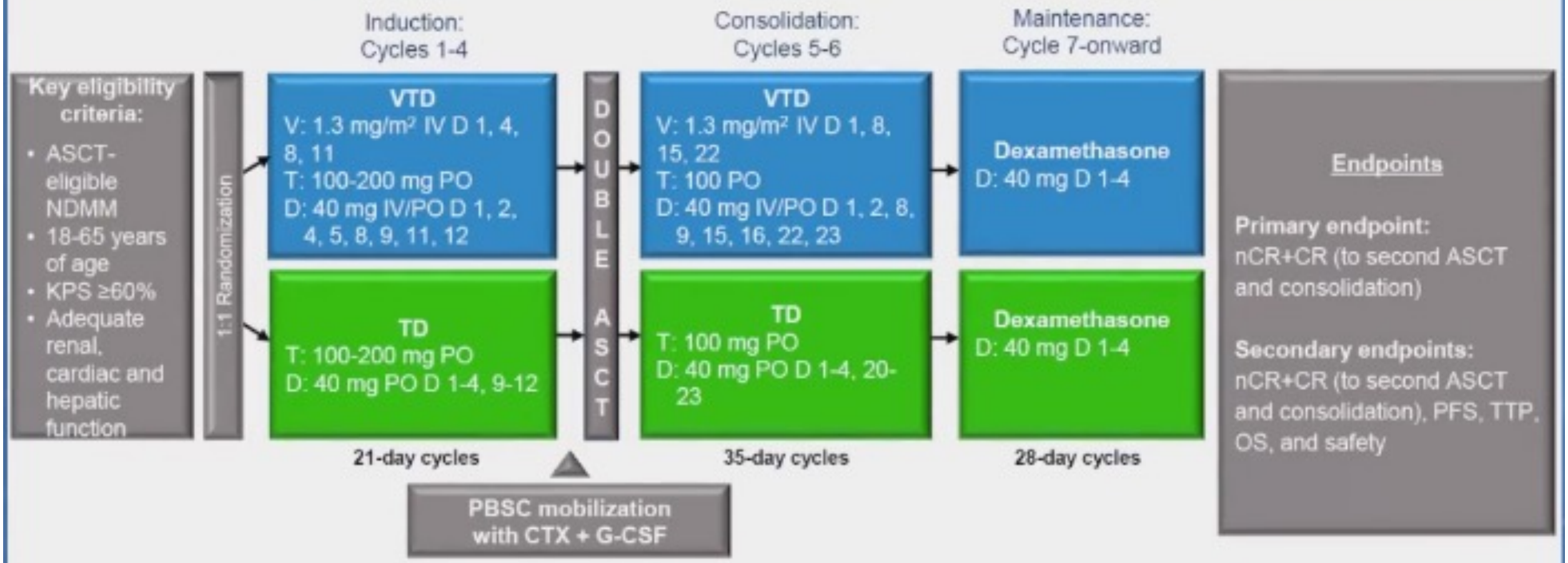

Myeloma patients:
Standard risk
High risk
Novel agent/approach
±
Standard of care
Standard of care
Primary endpoint
(powered for
whole population)
Subgroup
analysis
(standard risk)
Subgroup
analysis
(high risk)

Risk-oriented therapeutic approach for NDMM transplant eligible (Mayo-Clinic)



Rajkumar V. Blood Cancer Journal 2020

Phase 3 GIMEMA-MMY-3006 study

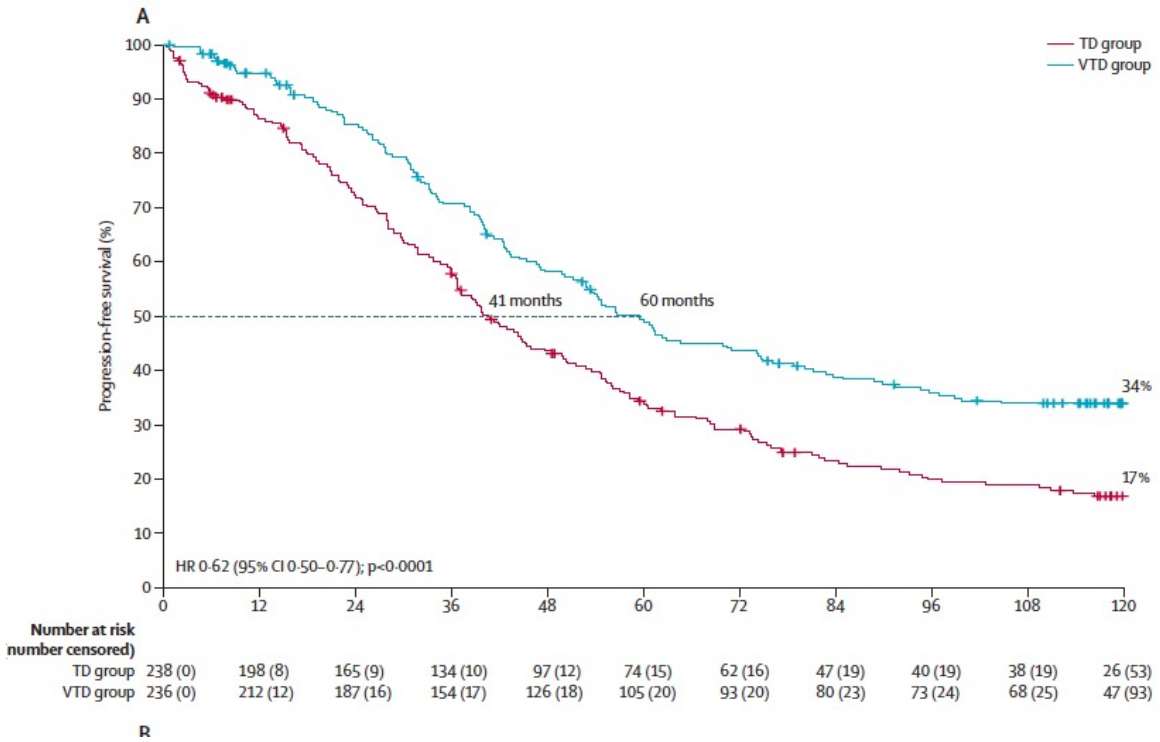


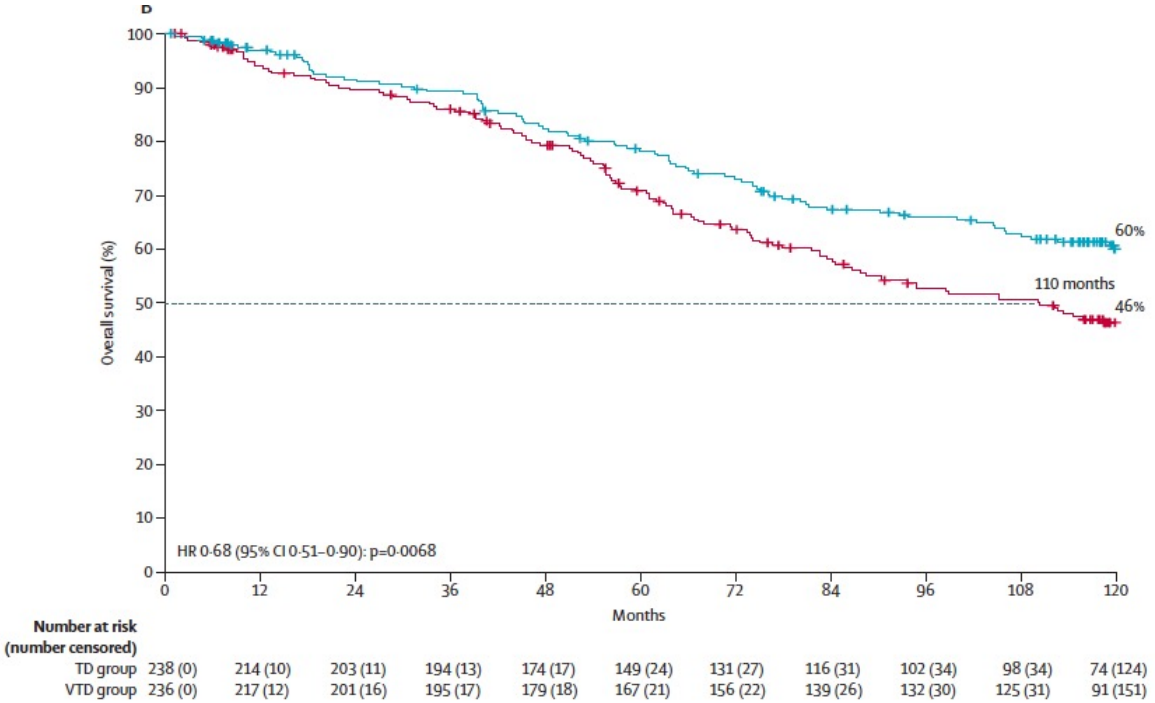
- **Enhanced rates of high-quality responses with VTD vs TD across all treatment phases, including induction and consolidation therapy, ultimately resulting in longer PFS and OS**
- **Established role of a PI- and IMiD-based triplet as a new standard-of-care for ASCT-eligible MM**

Cavo M et al. Lancet 2010;376:2075-85; Cavo et al. Blood 2012;120:9-19; Tacchetti P, et al. Lancet Haematol 2020;7:e861-73

GIMEMA-MMY-3006: long-term follow-up

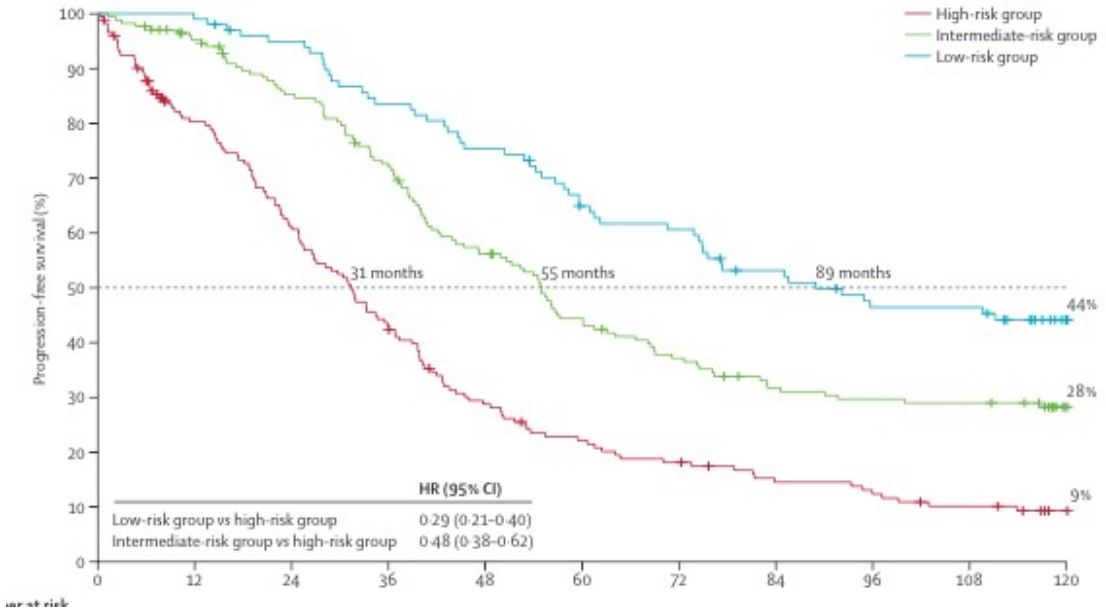
Median follow up: 10 years

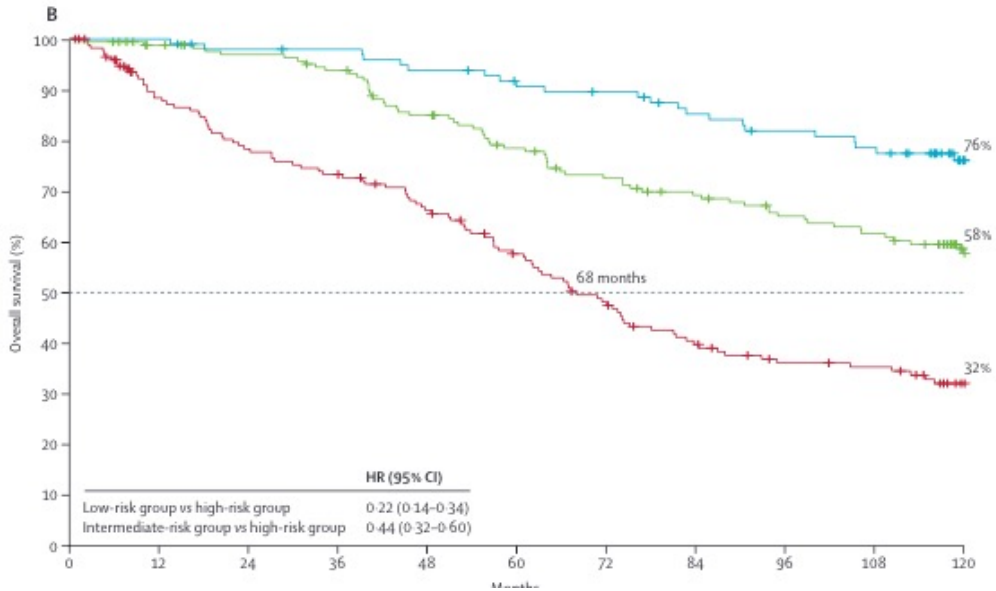




Tacchetti P. Lancet Hematol 2020

GIMEMA-MMY-3006: long-term follow-up



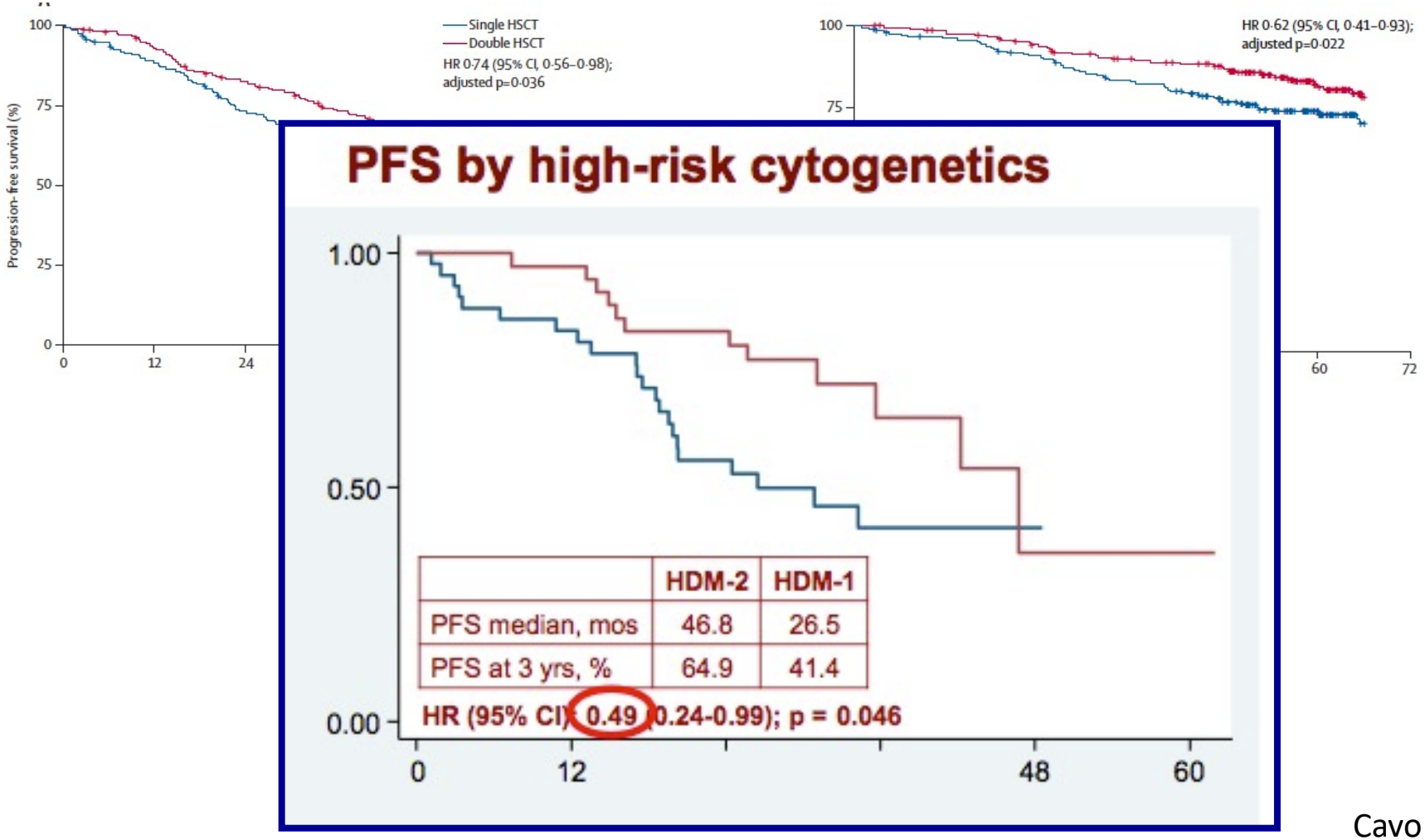


Risk factors: High risk cytogenetic (3)
ISS 2 or 3 (2)
lack of CR (3)

Low risk < 2
Intermediate 2-3
High risk > 3

Tacchetti P. Lancet Hematol 2020

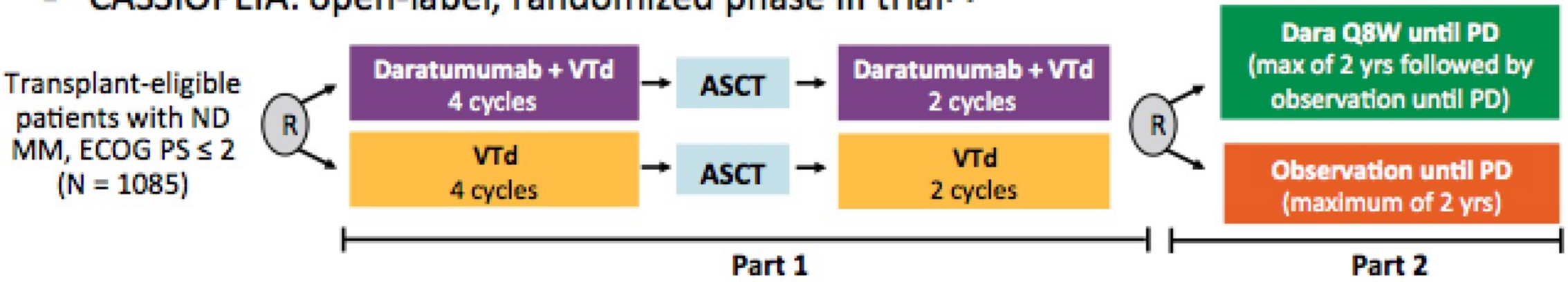
EMN02: Single vs Double ASCT



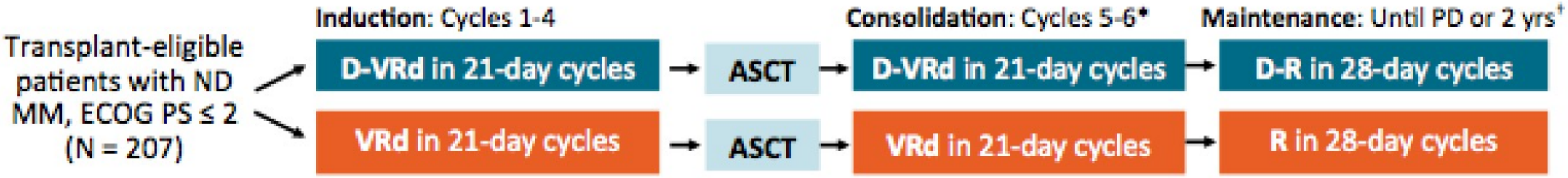
Cavo M Lancet Haematol 2020

Clinical Trials With Quad Therapy in Newly Diagnosed MM

- CASSIOPEIA: open-label, randomized phase III trial[1]



- GRIFFIN: open-label, randomized phase II trial[2]



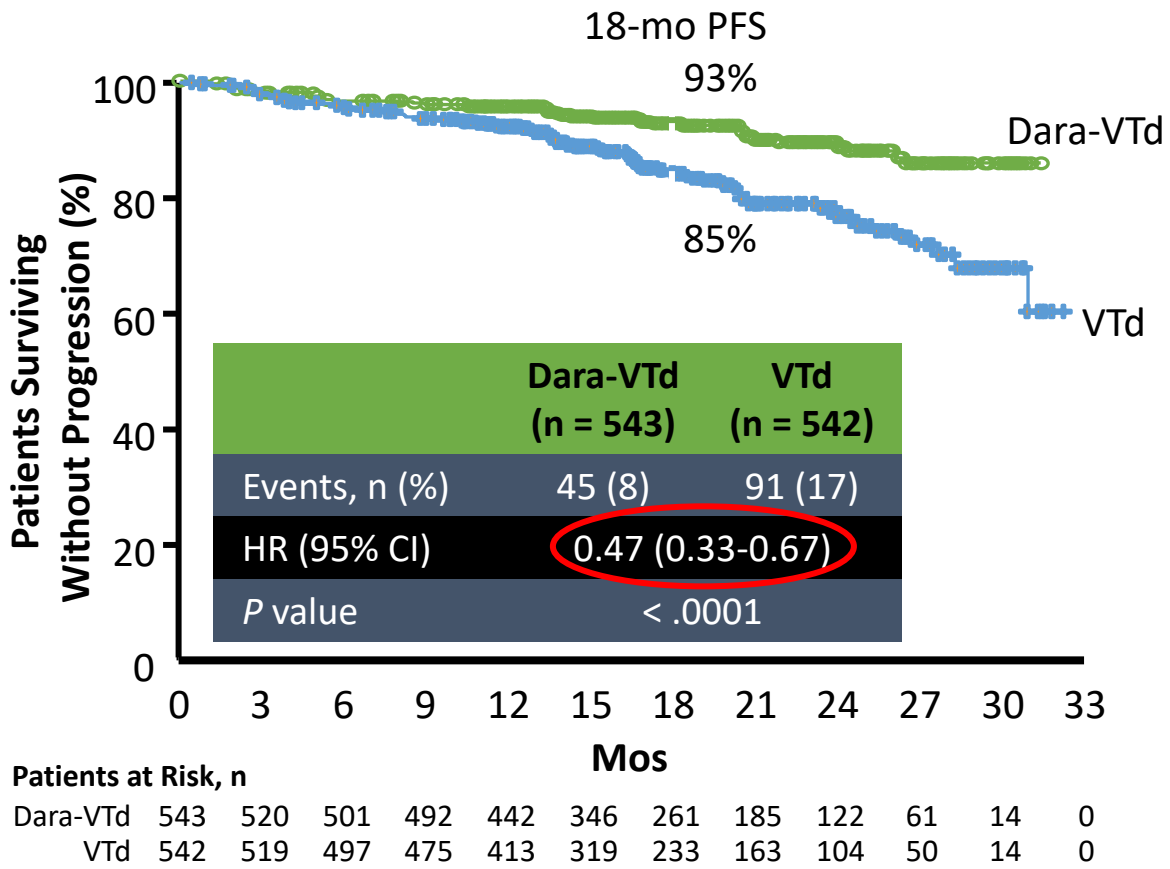
*Consolidation began 60-100 days after ASCT. †Patients completing maintenance were permitted to continue single-agent len.

1. Moreau. Lancet. 2019;394:29. 2. Voorhees. Blood. 2020;[Epub].

CASSIOPEIA: Dara-VTd vs VTd: PFS and MRD (NGF 10^{-5})

Primary end point: sCR after consolidation

Primary and final PFS analysis of Part 1

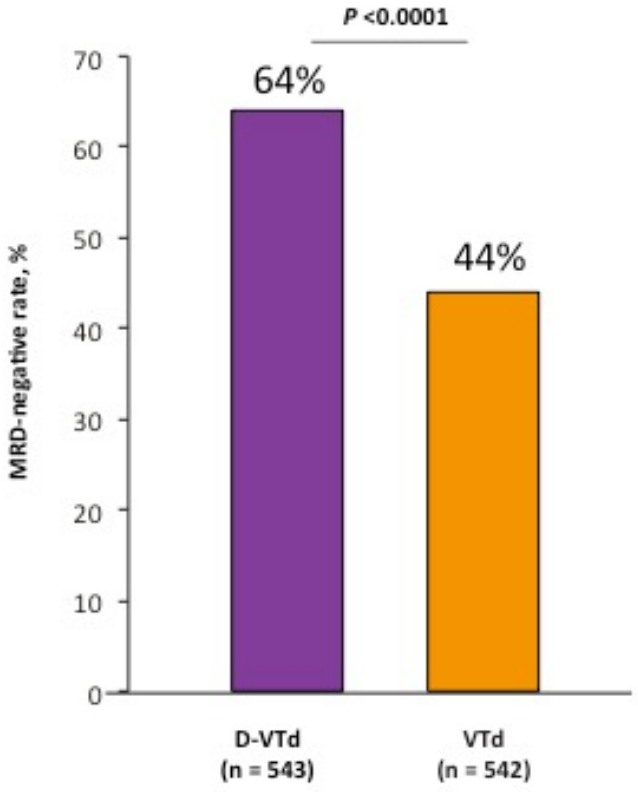


	Dara-VTd (n = 543)	VTd (n = 542)
Events, n (%)	45 (8)	91 (17)
HR (95% CI)	0.47 (0.33-0.67)	
P value	< .0001	

Patients at Risk, n

Dara-VTd	543	520	501	492	442	346	261	185	122	61	14	0
VTd	542	519	497	475	413	319	233	163	104	50	14	0

- Median follow-up: 18.8 mos (range: 0-32.2)

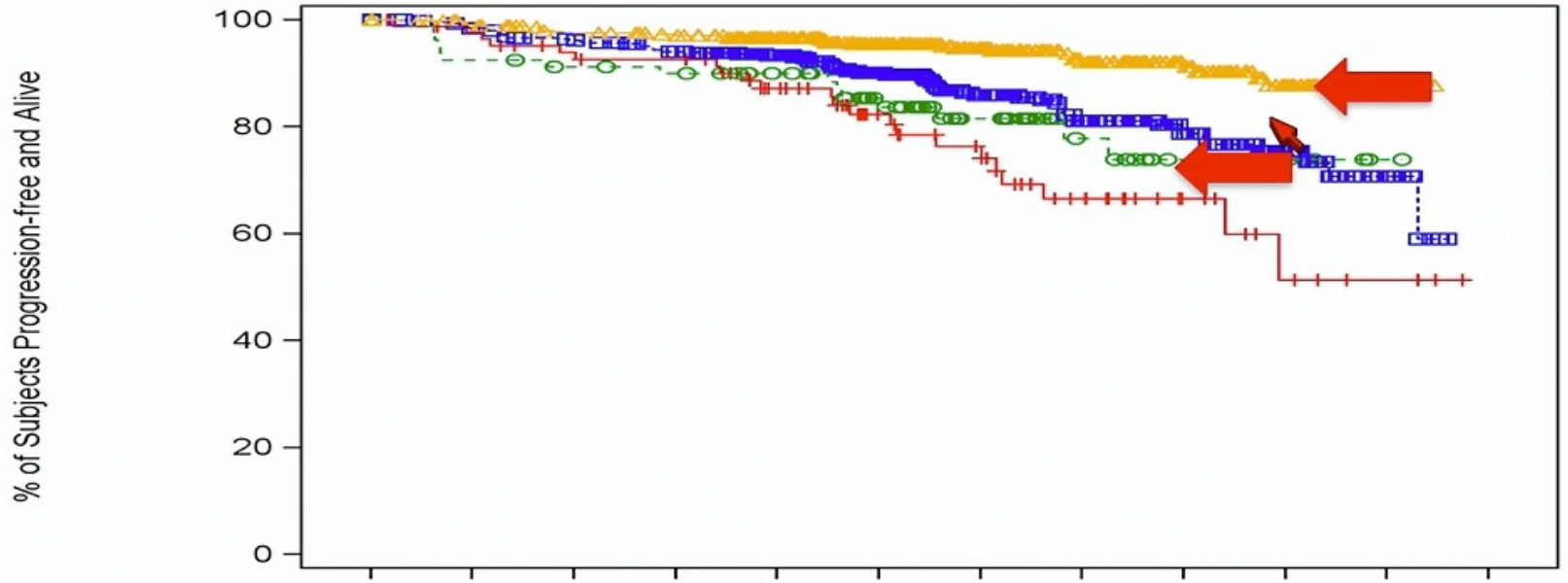


D-VTd superior across all subgroups including high-risk cytogenetics and ISS stage III

Moreau et al, Oral Presentation, ASCO 2019

Moreau, Lancet. 2019;394:29.

CASSIOPEIA: PFS According to Risk Status



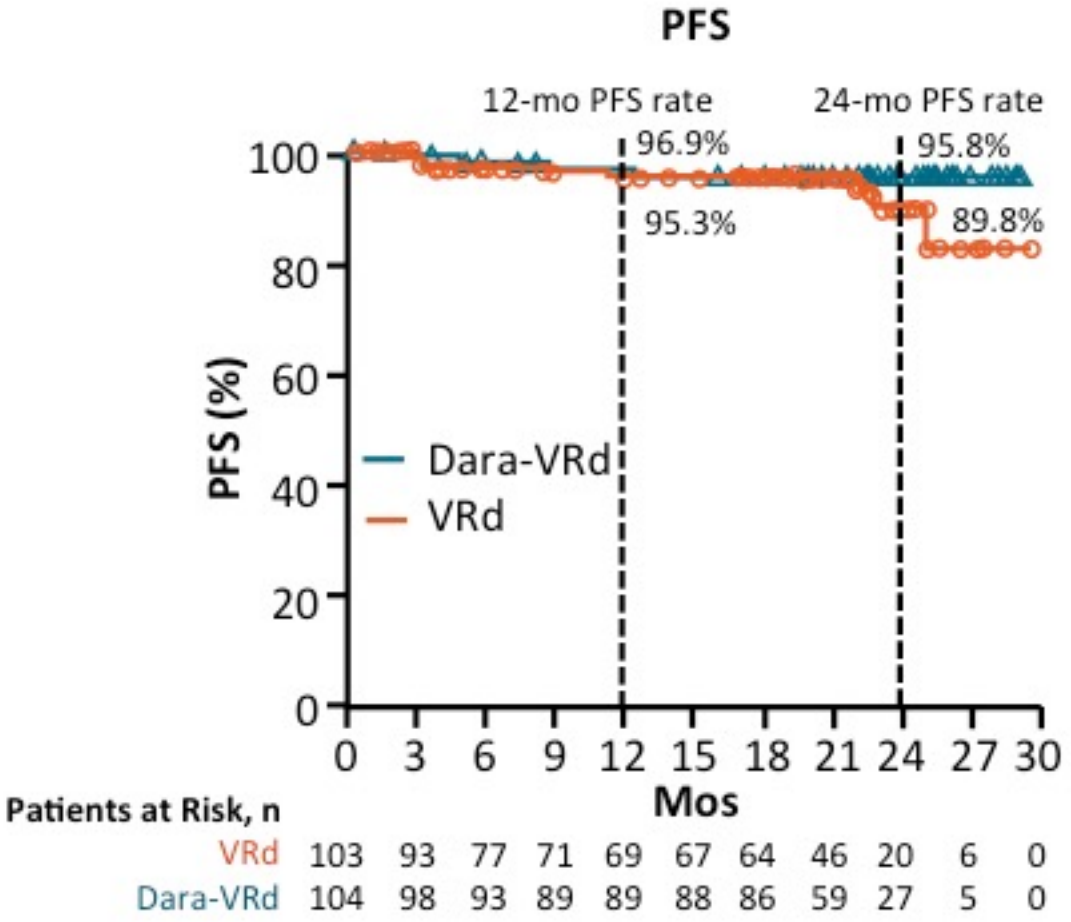
Subjects at risk												
VTd High risk	86	80	74	72	59	43	35	22	12	6	3	0
DVTd High risk	82	74	71	69	63	49	33	20	11	7	1	0
VTd Standard risk	454	437	421	401	352	274	196	139	91	44	11	0
DVTd Standard risk	460	445	429	422	378	296	227	164	111	54	13	0

Moreau, Sonneveld, Avet-Loiseau; unpublished data.

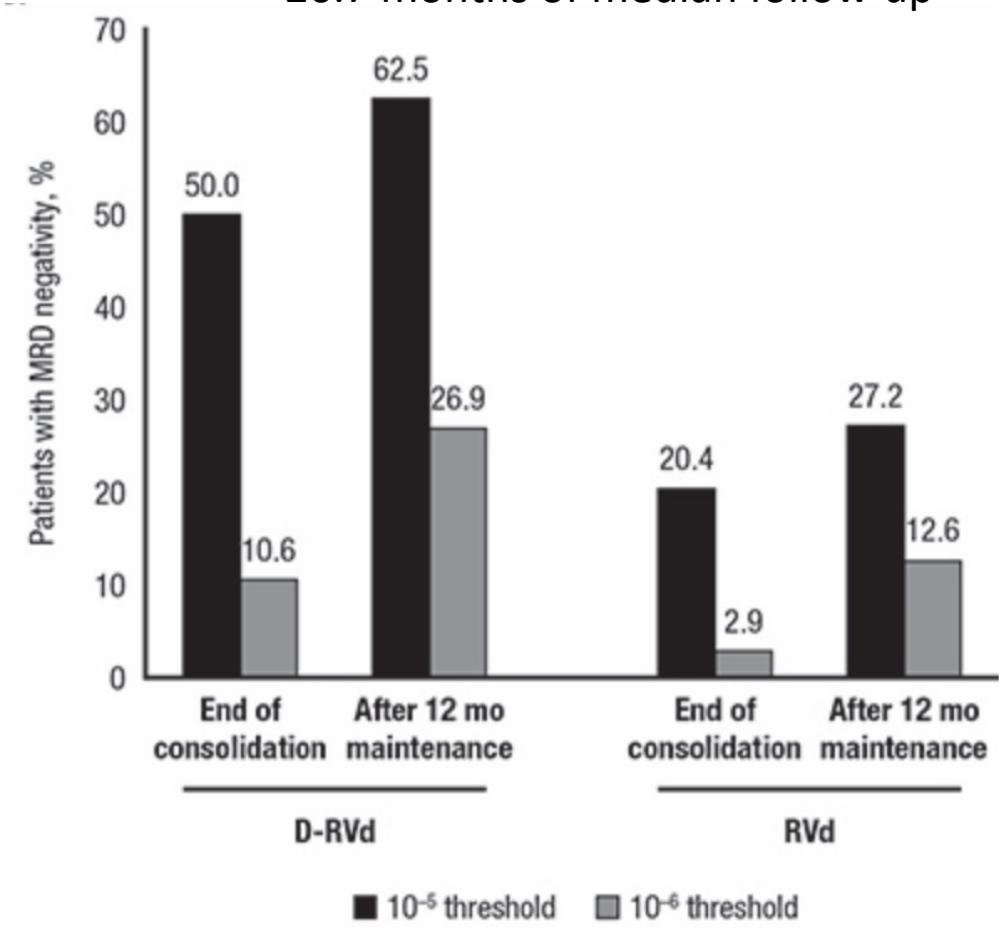
GRIFFIN: Randomized Phase 2

Phase 2 study of D-RVd versus RVd in transplant-eligible NDMM, primary endpoint sCR after consolidation

22.1 months of median follow-up



26.7 months of median follow-up

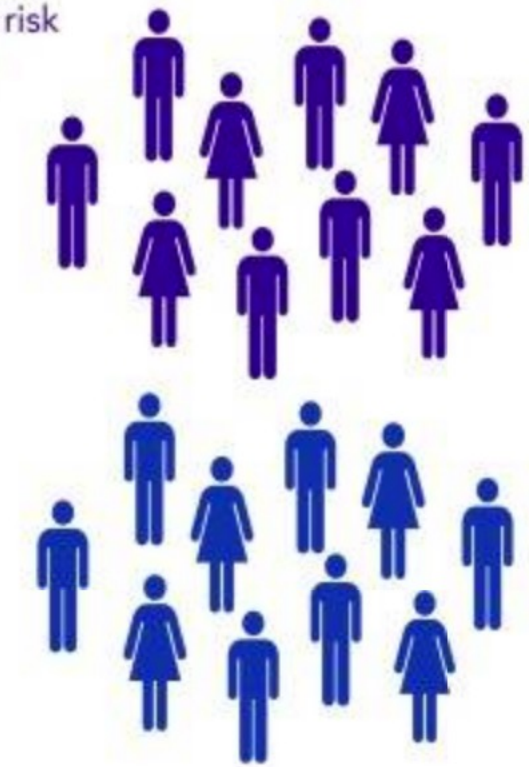


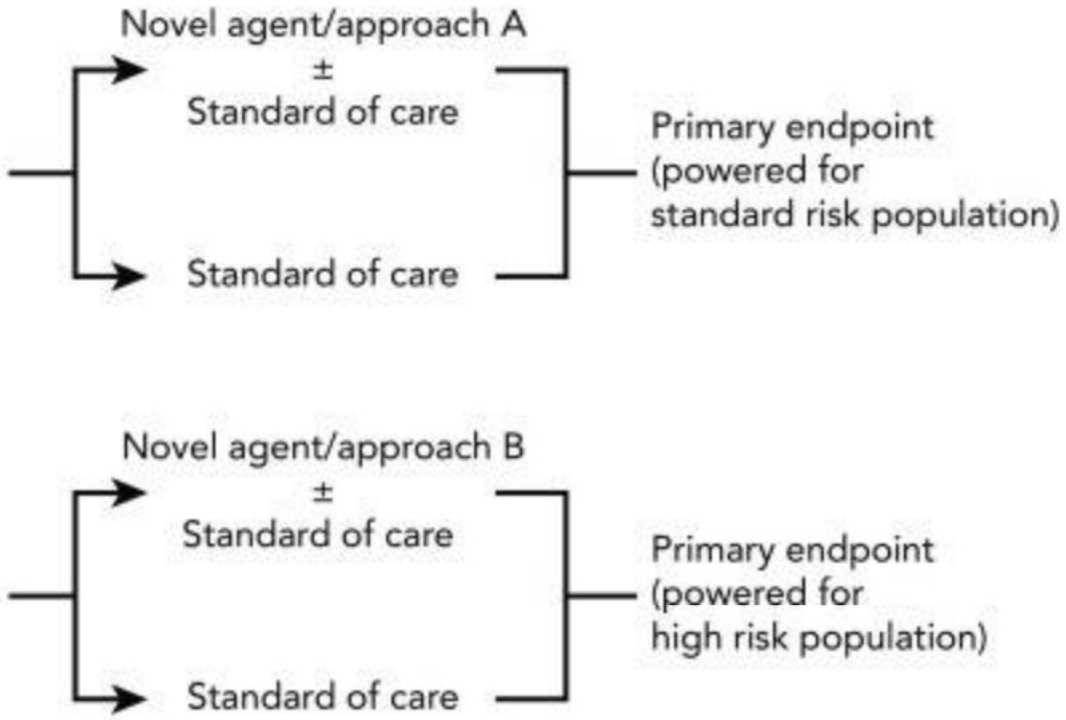
D-RVd improved sCR and MRD-negativity rates across most subgroups

Voorhees. Blood 2020; 136:936.

Kaufman. ASH 2020. Abstr 549.

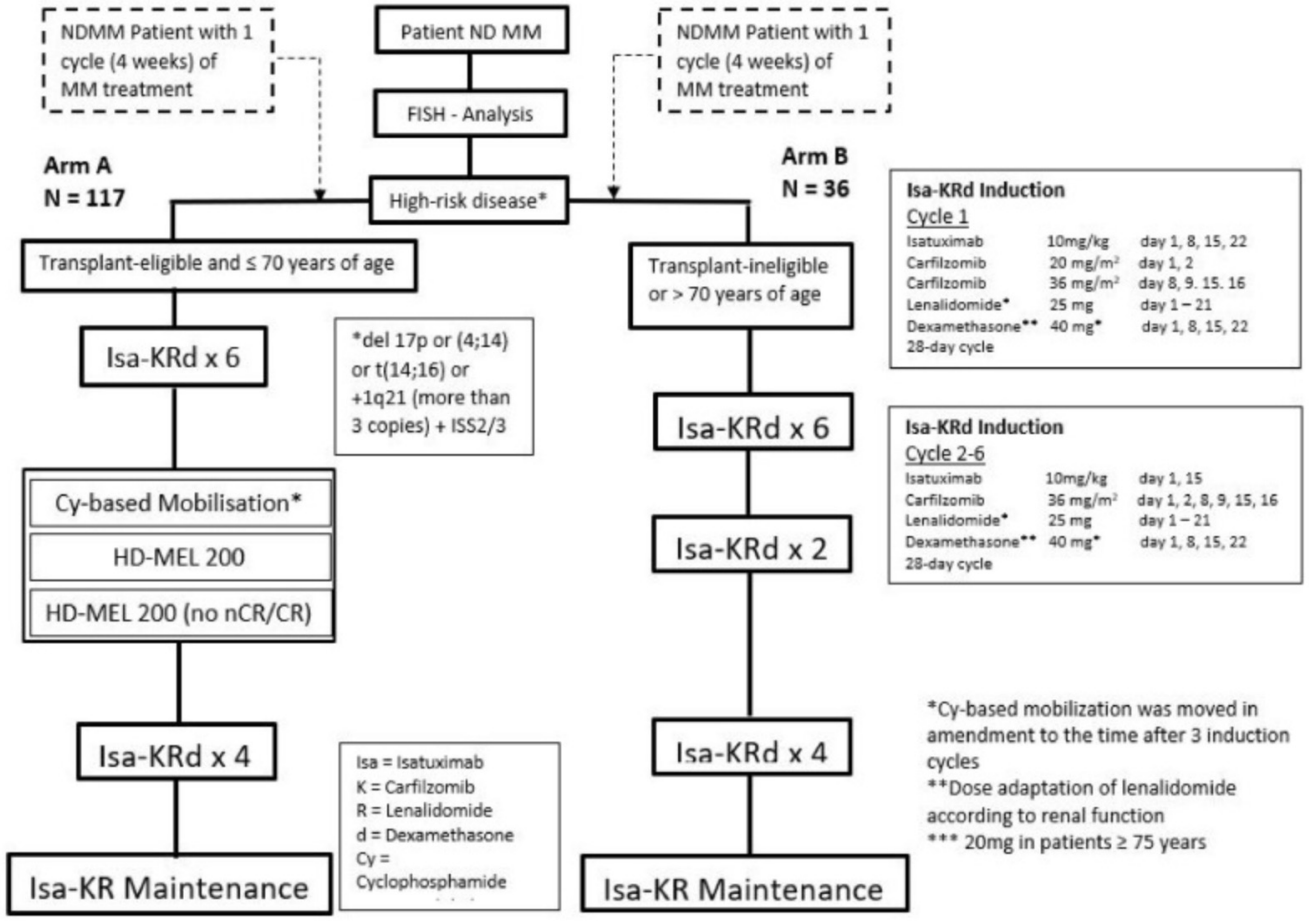
Myeloma patients:
Standard risk
High risk



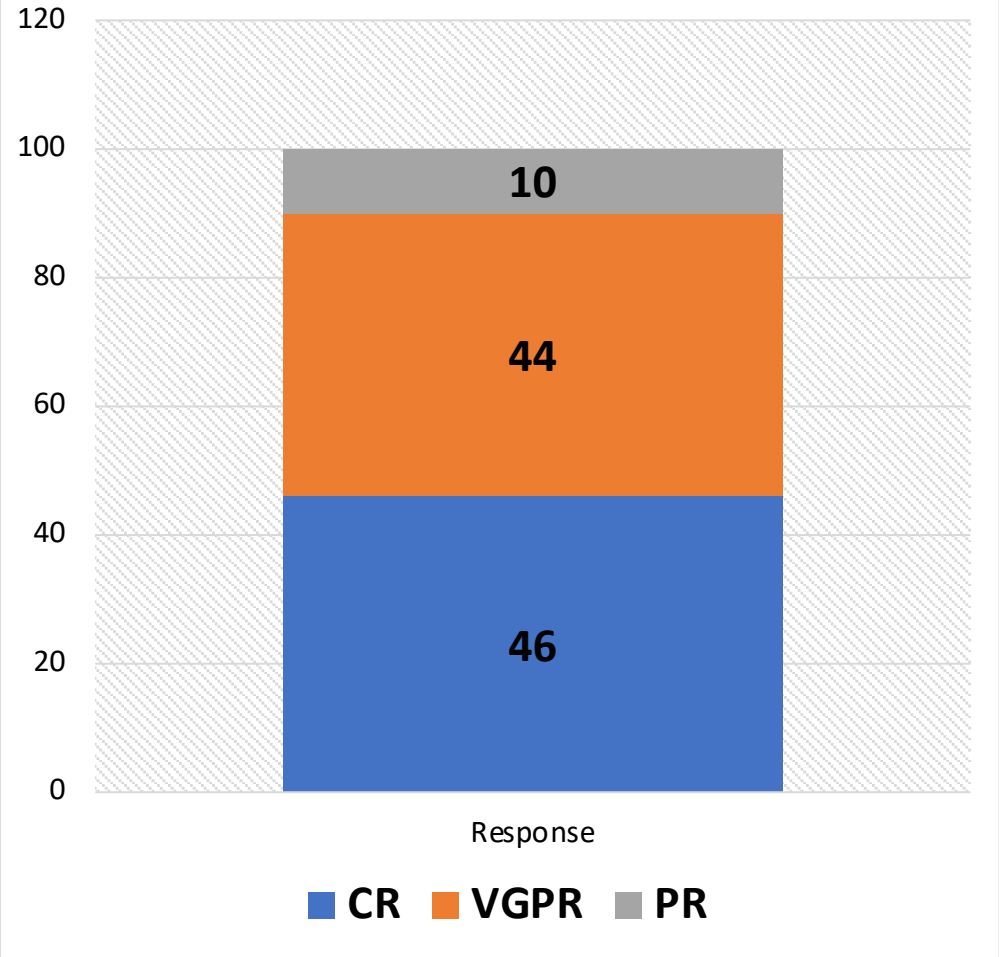


GMMG-Concept: ISATUXIMAB-KRD

Phase 2 for transplant and non-transplant eligible pts for HR MM.
Primary endpoint: MRD negativity measured by NGF after consolidation



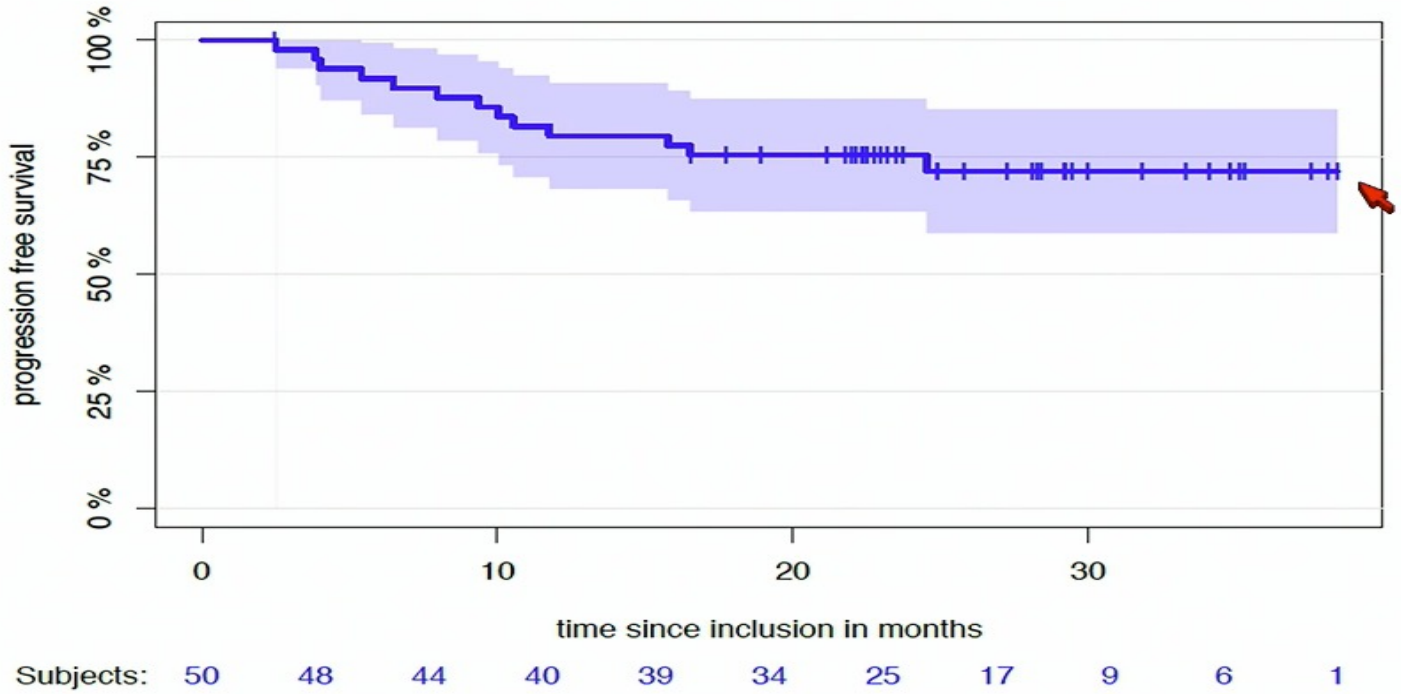
Response after induction in the first 50 patients of the GMMG CONCEPT study



MRD assessment in 33 patients, 20 negative

Weisel K et al, JCO 2020

Progression-free Survival



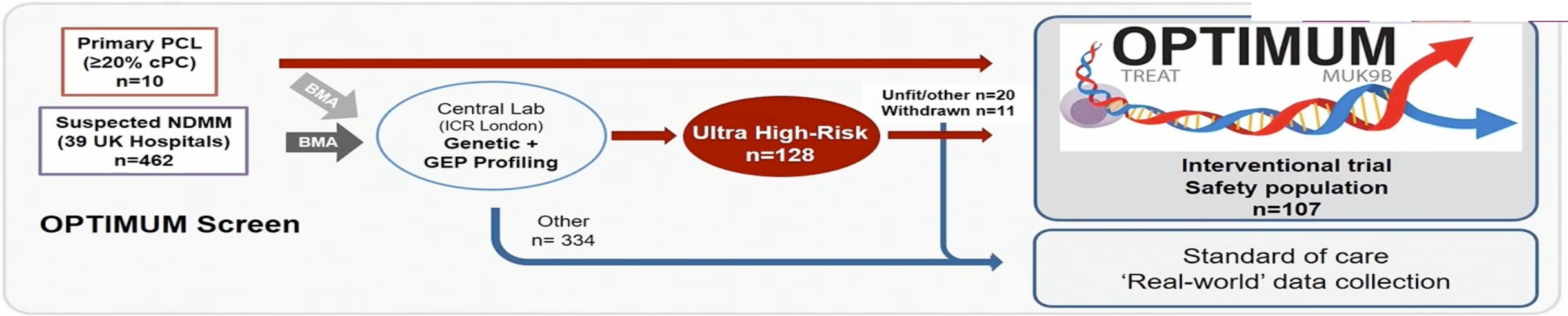
Median follow-up: 24.9 months

- 12-month PFS: 79.6% (68.3%; 90.9%)
- 24-month PFS: 75.5% (63.5%; 87.6%)

Data cut-off: Jan. 26, 2021
(95%-confidence level)

40/50 patients were relapse-free after 1 year

OPTIMUM design



Patient population (Screen)

- Patients with (suspected) newly diagnosed myeloma (NDMM) or pPCL fit for intensive therapy

Trial objectives (Treat)

- Evaluate efficacy of Dara-CVRd combination therapy + ASCT in Ultra High-Risk MM and pPCL
  - Response and MRD after induction and ASCT
  - Progression free survival – compared to matched Ultra High-Risk control group from Myeloma XI
- Determine safety and toxicity of Dara-CVRd in Ultra High-Risk MM and pPCL

Brown S, et al., BMJ Open 2021

Presented by: **Martin Kaiser, MD, FRCP, FRCPath**
@MyMKaiser

Trial therapy

Bridging
Max
2 cycles

SOC
(VTD
CVD)

Induction
Max 6 cycles
(incl bridging)

Dara-CVRd

Daratumumab iv 16 mg/kg
Cycle 1&2: Days 1, 8, 15
Cycle 3+: Day 1
Cyclophosphamide po 500 mg
Days 1, 8
Bortezomib sc 1.3 mg/m^2
Days 1, 4, 8, 11*
Lenalidomide po 25 mg
Days 1-14
Dexamethasone po 40 mg†
Days 1, 4, 8, 11

21d cycles

Stem Cell Mobilisation

V-HD-MEL +ASCT

Melphalan iv 200 mg/m^2
Day -1
Autologous Stem Cell Translantation
Day 0

Bortezomib 1.3 mg/m^2
Days -1, +5, +14,*
Weekly after haematopoietic recovery

Consolidation 1
6 Cycles
Start 100-120d post ASCT

Dara-VRd

Daratumumab sc
1800 mg Day 1
Bortezomib sc 1.3 mg/m^2
Days 1, 8, 15, 22*
Lenalidomide po 25 mg
Days 1-21
Dexamethasone po 40 mg †
Day 1, 8, 15, 22

28d cycles

Consolidation 2
12 Cycles

Dara-VR

Daratumumab sc
1800 mg Day 1
Bortezomib sc 1.3 mg/m^2
Days 1, 8, 15*
Lenalidomide po 25 mg
Days 1-21

28d cycles

Maintenance
Until progression

Dara-R

Daratumumab sc
1800 mg Day 1
Lenalidomide po 25 mg
Days 1-21

28d cycles

Central Response, Birmingham University (HydraShift)

*Permissive bortezomib dose reduction schedule
†20mg for elderly/frailer

Day 100-120 post-ASCT

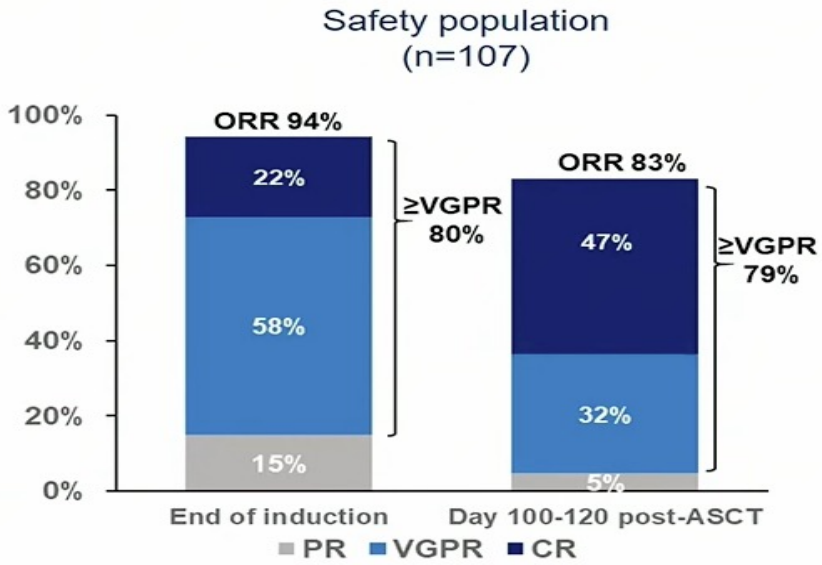
Central MRD, HMDS Leeds (Flow cytometry, 10^{-5} sensitivity)

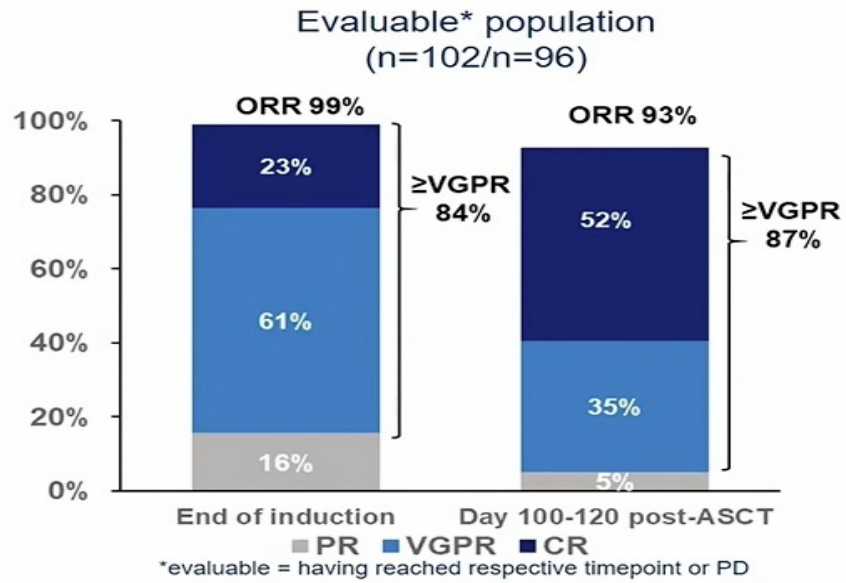
Brown S, et al., BMJ Open 2021

Presented by: **Martin Kaiser, MD, FRCP, FRCPath**
@MyMKaiser

Central response results

Response Safety Population (n=107)	End of induction	100-120 days post-ASCT
CR	23 (21.5%)	50 (46.7%)
VGPR	62 (57.9%)	34 (31.8%)
PR	16 (15.0%)	5 (4.7%)
PD	1 (0.9%)	7 (6.5%)
Timepoint not reached	5 (4.7%)	11 (10.3%)





pPCL (evaluable D100-120; n=8)

- CR: 2 (25%)
- VGPR: 2 (25%)
- PR: 2 (25%)
- PD: 2 (25%)

Primary analysis of the randomized phase II trial of bortezomib, lenalidomide, dexamthasone with/without elotuzumab for newly diagnosed, high-risk multiple myeloma (SWOG-1211).

Saad Zafar Usmani, Sikander Ailawadhi, Rachael Sexton, Antje Hoering, Brea Lipe, Sandi Hita, Brian G. Durie, Jeffrey A. Zonder, Madhav V. Dhodapkar, Natalie Scott Callander, S. Vincent Rajkumar, Peter Michael Voorhees, Paul G. Richardson, Robert Z. Orlowski

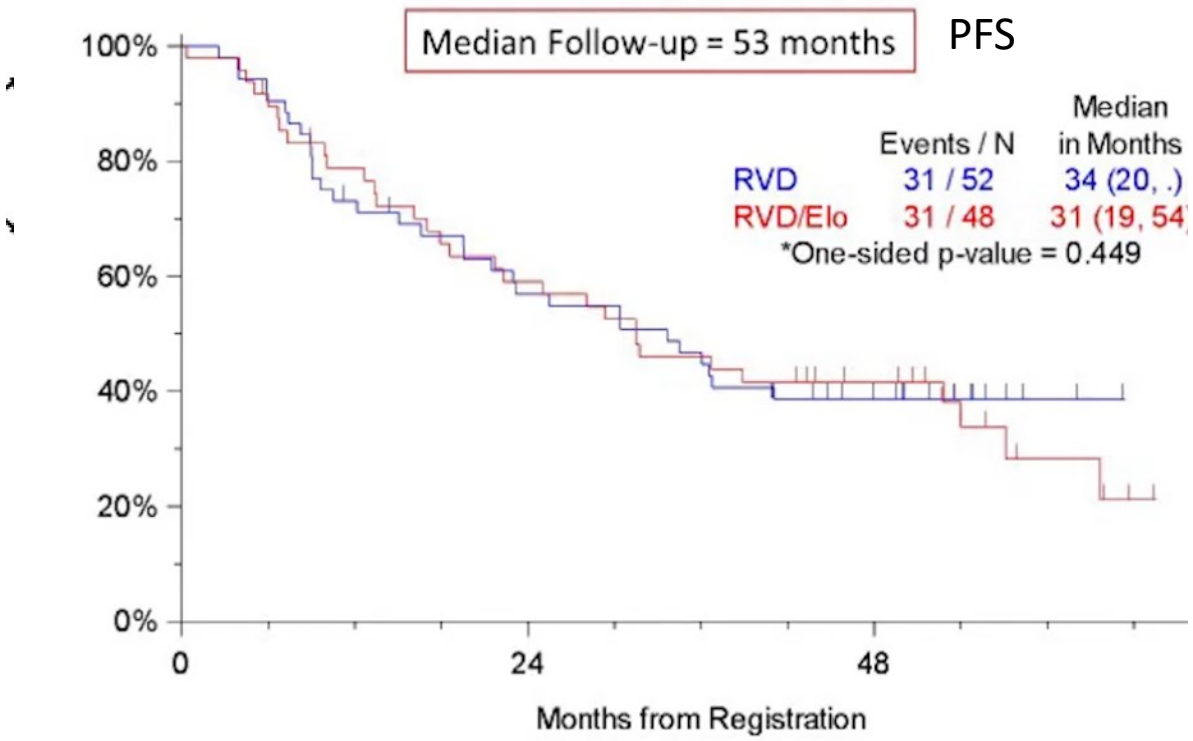
Randomization

Induction: Eight 21-day cycles

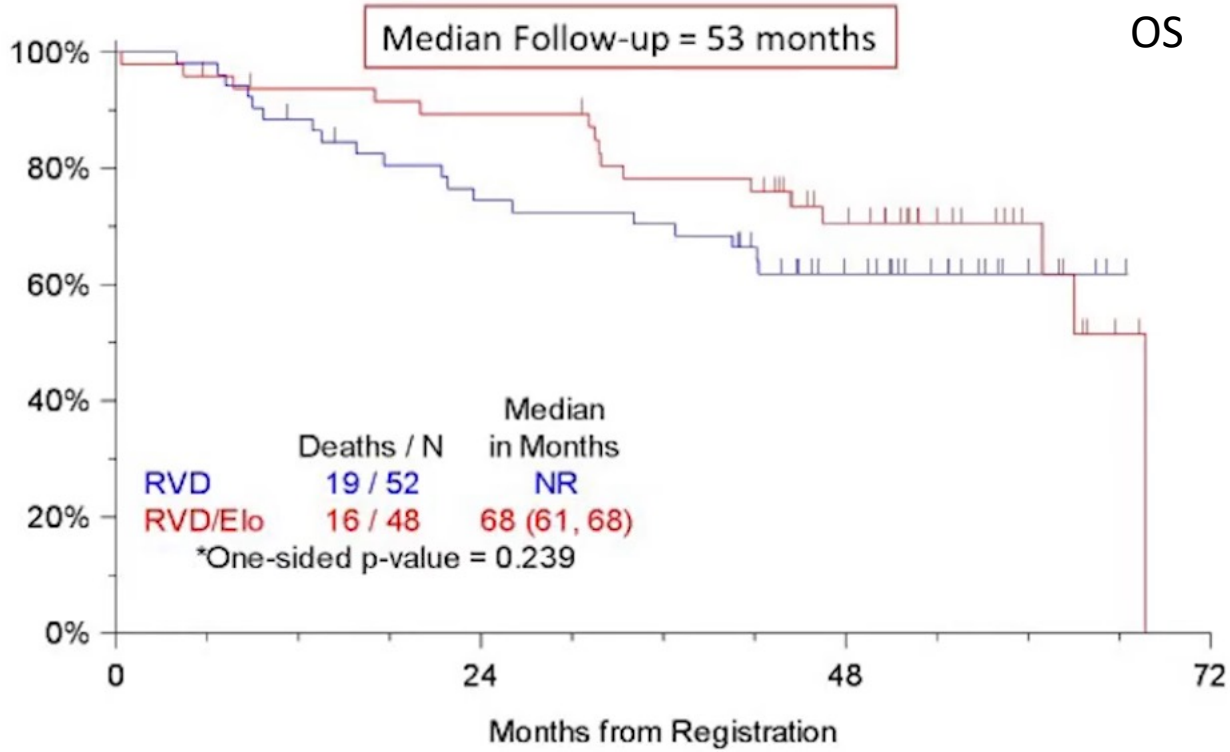
Maintenance: 28-day cycles

Highlights of the study

PFS



OS



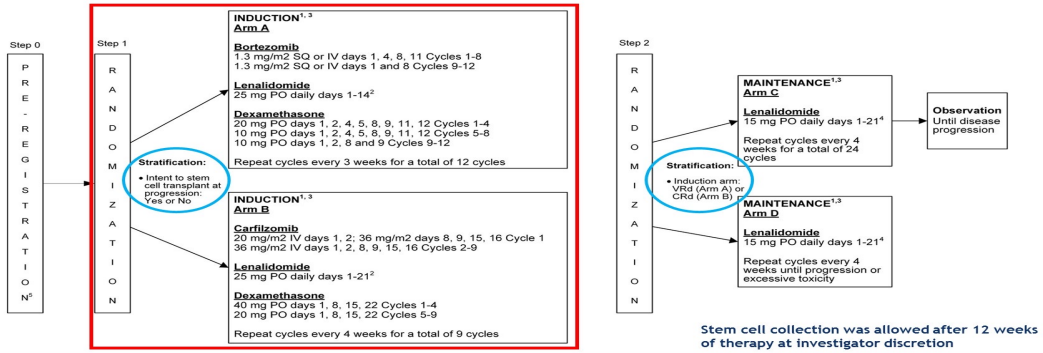
Conclusions

The addition of Elotuzumab to RVd induction and maintenance did not improve patient outcomes.

Carfilzomib, lenalidomide, and dexamethasone (KRd) versus bortezomib, lenalidomide, and dexamethasone (VRd) for initial therapy of newly diagnosed multiple myeloma (NDMM): Results of ENDURANCE (E1A11) phase III trial.

Shaji Kumar, Susanna J. Jacobus, Adam D. Cohen, Matthias Weiss, Natalie Scott Callander, Avina A. Singh, Terri L. Parker, Alex R. Menter, Xuezhong Yang, Benjamin Marshall Parsons, Pankaj Kumar, Prashant Kapoor, Aaron Seth Rosenberg, Jeffrey A. Zonder, Edward Anthony Faber, Sagar Lonial, Paul G. Richardson, Robert Z. Orlowski, Lynne I. Wagner, S. Vincent Rajkumar

Patient Randomization and Treatment Schedule



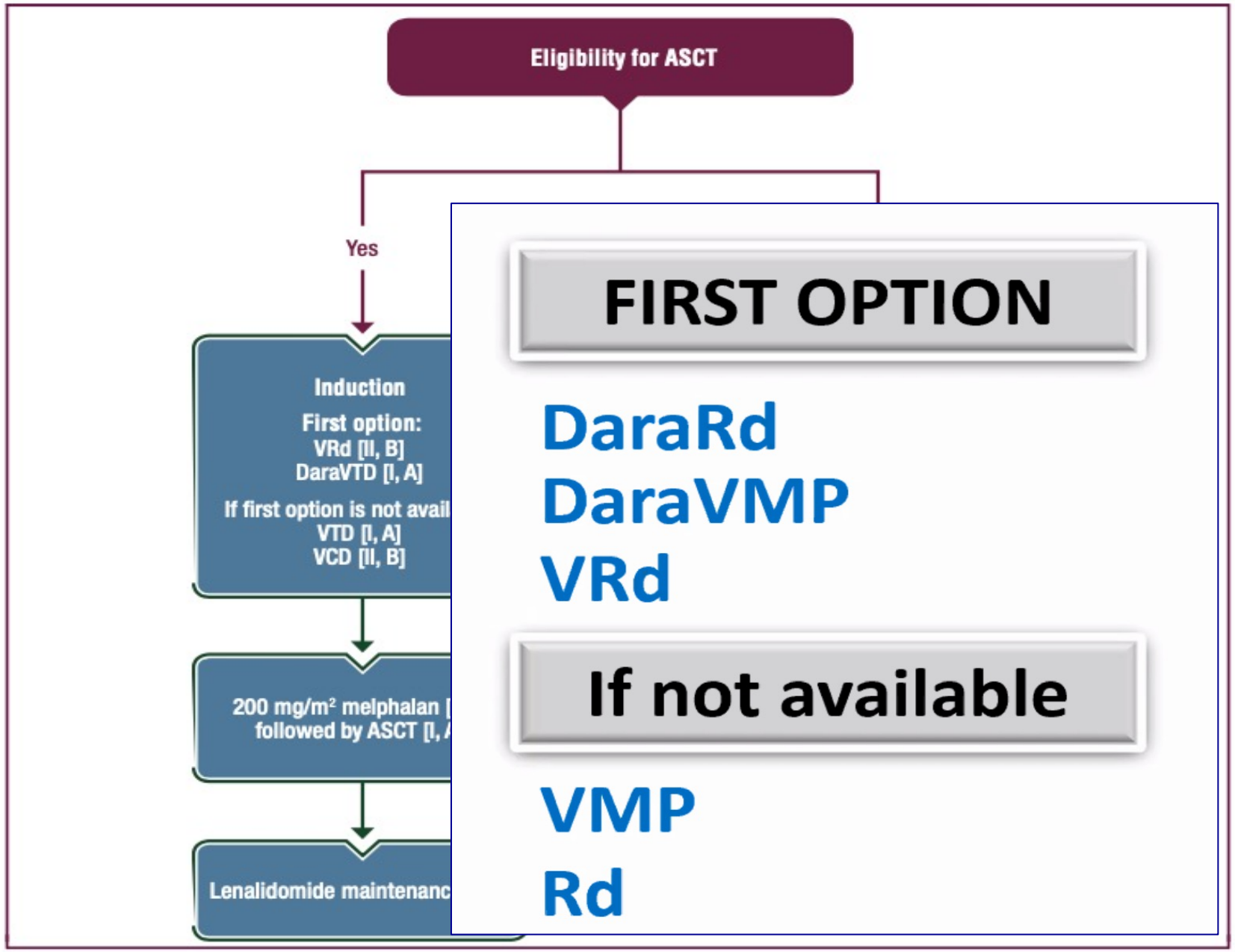
Trial Highlights
1087 patients were enrolled between December 2013 and February 2019 at 272 centers in the US
The median age was 65 years
The trial did not include High Risk Multiple Myeloma patients, defined by any of the following: deletion 17p, translocations 14;16 or 14;20, high-risk GEP70 (Gene Expression Profile), an LDH level >2xULN (upper limit of normal) or plasma cell leukemia
Patients with the 4;14 translocation were included despite its current classification as a high risk cytogenetic
Patients in the study were not planning on an upfront autologous stem cell transplant or were transplant ineligible

As of the second of three planned interim analysis, data cut-off January 7, 2020 the results were as follows:

	KRd	VRd
Median Progression Free Survival	34.6 months	34.4 months
Overall Survival (with 95% confidence interval)	86%	84%

	VRd	KRd
Over Grade 3 toxicity rates	41%	48%
Peripheral neuropathy	8%	1%
Combined cardio, pulmonary and renal	5%	16%
Patients taken off trial to use other MM therapies	18%	14%
Patients taken off trial because of severity of side effects	17%	9%
Patients taken off trial because of disease progression	6%	4%
Patients who withdrew from the trial	7%	4%

Dr. Shaji Kumar concluded that these results prove that VRd should remain the standard of care and that VRd should be the backbone upon which quadruplet therapies should be designed.

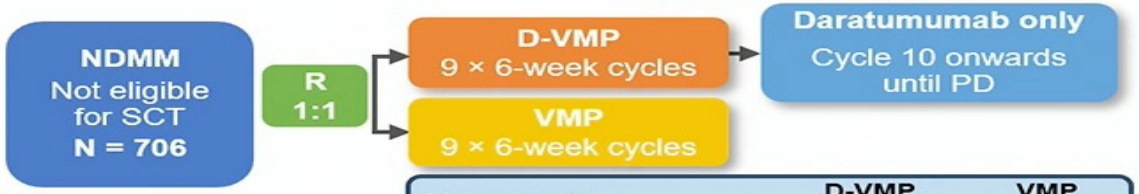


Dimopoulos et al, Annals of Oncology epub 3 February 2021

Paradigma di terapia nel paziente con MM di nuova diagnosi non candidabile alle alte dosi

Key study designs in non stem-cell transplantation NDMM

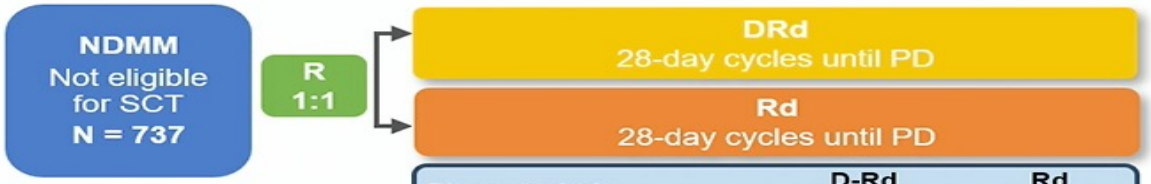
ALCYONE[1]



Primary endpoint: PFS

Characteristic	D-VMP (n = 350)	VMP (n = 356)
Median age (range), years	71 (40–93)	71 (50–91)
Age ≥ 75 years, %	30	30
ECOG PS 0/1/2, %	22/52/26	28/49/24
High-risk cytogenetics, %	17	15

MAIA[2]



Primary endpoint: PFS

Characteristic	D-Rd (n = 368)	Rd (n = 369)
Median age (range), years	73 (50–90)	74 (45–89)
Age ≥ 75 years, %	44	44
ECOG PS 0/1/2, %	35/48/17	33/51/16
High-risk cytogenetics, %	15	14

SWOG S0777[3]

Primary endpoint: PFS

Characteristic	RVd (n = 264)	Rd (n = 261)
Median age (range), years	63 (-)	63 (-)
Age ≥ 65 years, %	38	48
ECOG PS > 1, %	12	16
High-risk cytogenetics, %	-	-

RVd-lite[4,a]

Primary endpoint: ORR

Characteristic	ITT (n = 50)
Median age (range), years	73 (65–91)
Age ≥ 75 years, %	-
ECOG PS 0/1/2, %	50/36/14
High-risk cytogenetics, %	12

These charts are provided for ease of viewing information from multiple trials.
Direct comparison between trials is not intended and should not be inferred.
[a] RVd lite is phase II, others phase III.
DRd, daratumumab, lenalidomide, low-dose dexamethasone; D-VMP; daratumumab, bortezomib, melphalan, prednisone; R, randomized; SCT, stem-cell transplantation.

1. Mateos MV et al. N Engl J Med 2018;378:518–28. 2. Facon T et al. N Engl J Med 2019;380:2104–15. 3. Durie BGM et al. Lancet 2017;389:519–27. 4. O'Donnell EK, et al. Br J Haematol 2018;182:222–30.

SWOG 0777: PFS with RVd versus Rd[a]

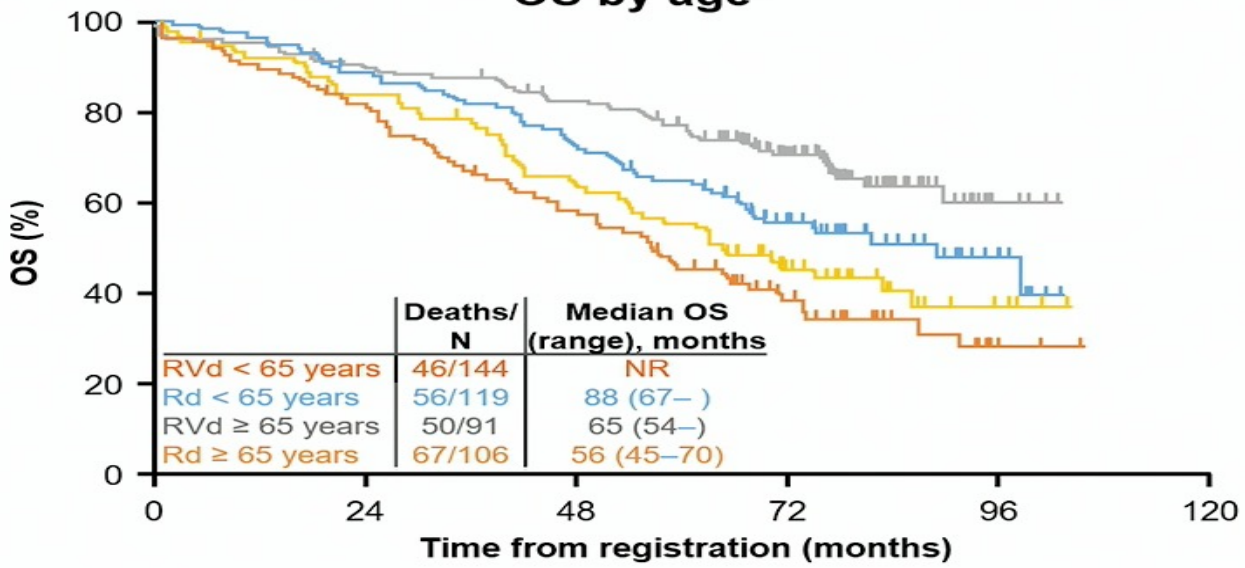
Regardless of age, treatment with RVd resulted in better responses compared with Rd

Median PFS (months)[1]

Age (years)	RVd	Rd
< 65	48	34
≥ 65	34	24
> 75	34	17

Long term FU[2]
OS in pts ≥ 65 years: HR 0.769, p 0.168

OS by age[1]



[a] For all analyses, both SWOG and IRC assessments have been conducted using the fully updated datasets with current data lock in May 2018.
D, dexamethasone; IRC, Independent Review Committee; OS overall survival; PFS, progression-free survival; R, lenalidomide, V bortezomib.

1. Durie B et al. Blood 2018;132:1992;
2. Durie B et al. Blood Cancer J 2020;10:53

Modified RVd (RVd-lite) in transplant-ineligible NDMM

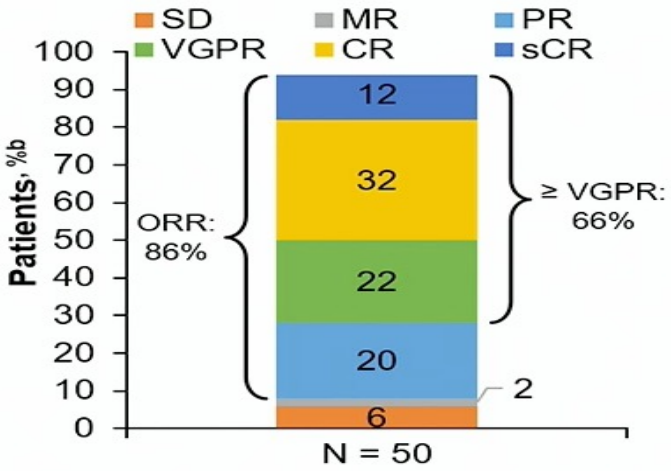
Induction (cycles 1-9)
Repeat q35 days × 9 cycles

Lenalidomide 15 mg po days 1-21
Bortezomib 1.3 mg/m^2 sc* days 1, 8, 15, 22
Dexamethasone 20 mg po days 1, 2, 8, 9, 15, 16, 22, 23 (patients ≤75 years)
Dexamethasone 20 mg po days 1, 8, 15, 22 (patients >75 years old)

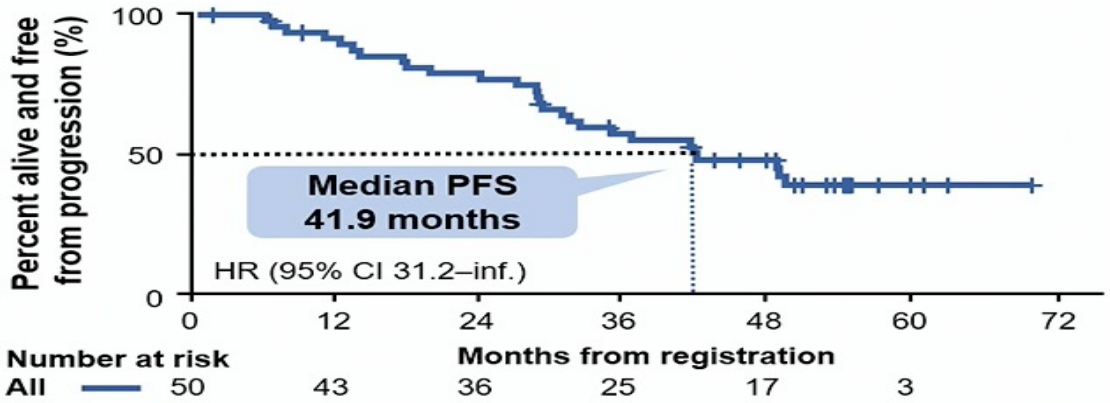
Consolidation (cycles 10-15)
Repeat q28 days × 6 cycles

Lenalidomide 15 po days 1-21 (or last tolerated dose as of cycle 9)
Bortezomib 1.3 mg/m^2 sc days 1, 15 (or last tolerated dose as of cycle 9)

Response rate



PFS



≥ CR was 44% (ITT population; N = 50)
ORR was 86%; ≥ VGPR was 66% for patients evaluable for response[a] after 4 cycles (n = 46)
Median TTR was 1.1 months

Grade 3 or 4 AEs of interest:
- Peripheral neuropathy (2%), neutropenia (14%)

RVd-lite is Investigational only, not approved.
[a] The first 10 patients received bortezomib i.v. for cycle 1 only followed by s.c. administration; subsequent patients received bortezomib s.c.; [b] 6% of patients received < 4 cycles of therapy and were therefore not evaluable.
AE, adverse event; CR, complete response; d, dexamethasone; ECOG PS, Eastern Cooperative Oncology Group Performance status; ISS, International Staging System; MR, minimal response; ORR, overall response rate; PFS, progression-free survival; R, lenalidomide; sCR, stringent complete response; TTR, time to response; V, bortezomib; VGPR, very good partial response

O'Donnell EK et al. Br J Haematol 2018;182:222-30.
O'Donnell EK et al. ASH 2019; abstract 3178.

Daratumumab Study designs

ALCYONE

Key eligibility criteria:
- Transplant-ineligible NDMM
- ECOG PS score 0–2
- CrCl ≥ 40 mL/min
- No grade ≥ 2 PN or grade ≥ 2 neuropathic pain

1:1 Randomization (N = 706)

VMP × 9 cycles (n = 356)
V: 1.3 mg/m² SC
Cycle 1: twice weekly; Cycles 2–9: once weekly
M: 9 mg/m² PO days 1–4
P: 60 mg/m² PO days 1–4

D-VMP × 9 cycles (n = 350)
D: 16 mg/kg IV
Cycle 1: once weekly; Cycles 2–9: every 3 weeks
+
Same VMP schedule

D: cycles 10+
16 mg/kg IV Q4W, until PD

Follow-up for PD and survival

Primary endpoint:
- PFS

Secondary endpoints:
- ORR
- ≥ VGPR rate
- ≥ CR rate
- MRD (NGS; 10^{-5})
- OS
- Safety

Stratification factors
- ISS stage (I vs II vs III)
- Region (EU vs other)
- Age (< 75 vs ≥ 75 years)

- Cycles 1-9: 6-week cycles
- Cycles 10+: 4-week cycles

Statistical analyses
360 PFS events: 85% power for 8-month PFS improvement[a]

CR, complete response; CrCl, creatinine clearance; D, daratumumab; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EU, European Union; M, melphalan; MRD, minimal residual disease; ORR, overall response rate; OS, overall survival; P, prednisone; PD, progressive disease; PN, peripheral neuropathy; V, bortezomib; VGPR, very good partial response.
[a] 8-month PFS improvement over 21-month median PFS of VMP.

Mateos MV, et al. *N Engl J Med*. 2018;378(6):518-528.

MAIA

Key eligibility criteria:
- Transplant-ineligible NDMM
- ECOG PS score 0–2
- CrCl ≥ 30 mL/min

1:1 Randomization

D-Rd (n = 368)
D: 16 mg/kg IV[a]
Cycles 1, 2: QW; Cycles 3–6: Q2W; Cycles 7+: Q4W until PD
R: 25 mg PO daily days 1–21 until PD
d: 40 mg[b] PO or IV weekly until PD

Rd (n = 369)
R: 25 mg PO daily, days 1–21 until PD
d: 40 mg[b] PO or IV weekly until PD

Primary endpoint:
- PFS

Key secondary endpoints[c]:
- ≥ CR rate
- ≥ VGPR rate
- MRD-negative rate (NGS; 10^{-5})
- ORR
- OS
- Safety

Stratification factors
- ISS stage (I vs II vs III)
- Region (NA vs other)
- Age (< 75 vs ≥ 75 years)

28-day cycles

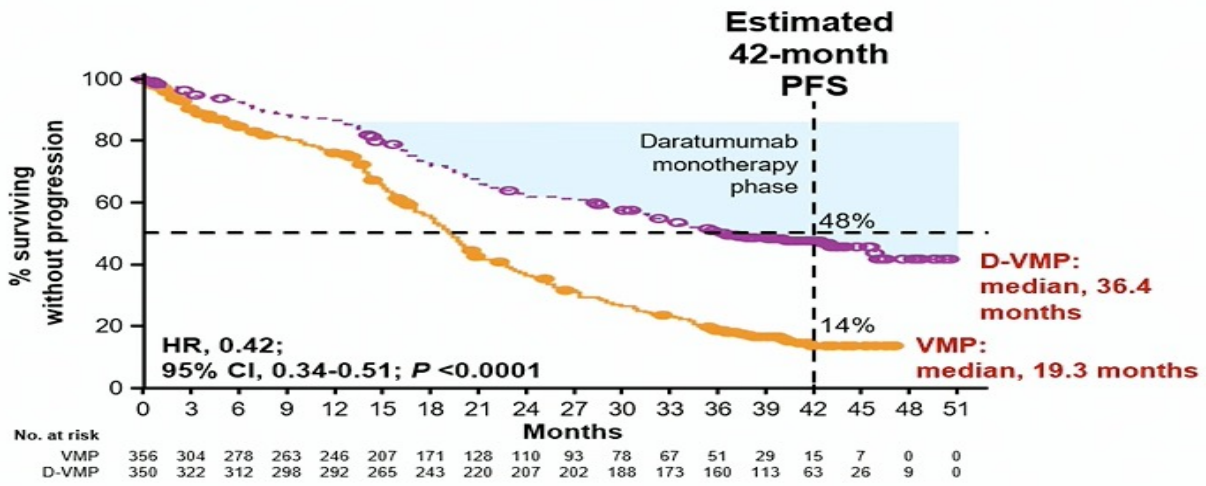
BMI, body mass index; D-Rd, daratumumab, lenalidomide, and dexamethasone; NA, North America.
[a] On days when DARA was administered, DEX was administered to patients in the D-Rd arm and served as the treatment dose of steroid for that day, as well as the required pre-infusion medication; [b] For patients > 75 years of age or with BMI < 18.5, DEX was administered at a dose of 20 mg weekly; [c] Efficacy endpoints were sequentially tested in the order shown.

Facon T et al. *Blood* 2019;132:LBA-2; Facon T et al. *N Engl J Med* 2019;380:2104-15.

PFS

ALCYONE

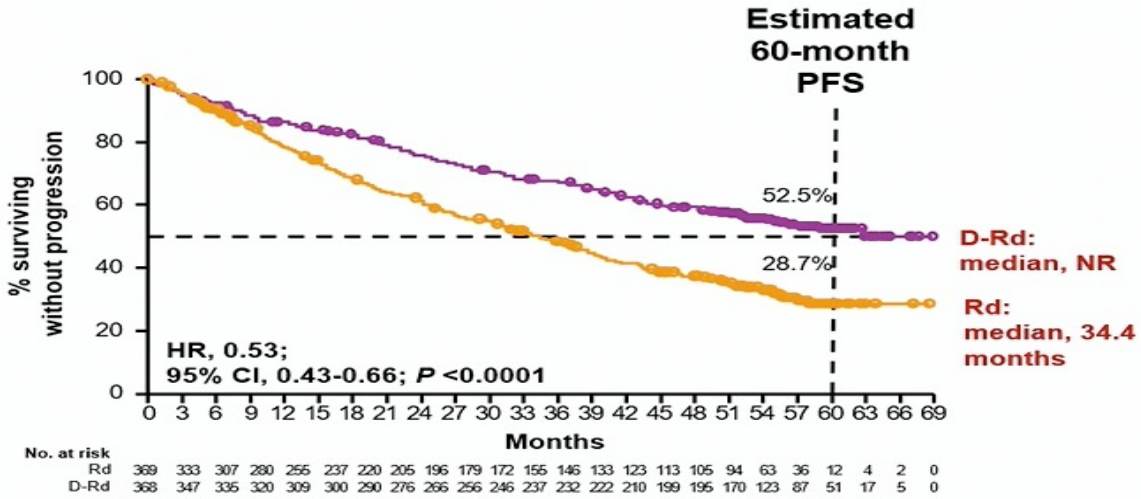
Median (range) follow-up: 40.1 (0-52.1) months



D-VMP continued to demonstrate a significant PFS benefit with extended follow up

MAIA

Median follow-up: 56.2 months



- **D-Rd continued to demonstrate a significant PFS benefit, with median PFS not reached with D-Rd**
- **These data provide a new PFS benchmark in patients with NDMM who are transplant ineligible**

D, daratumumab; PFS, progression-free survival; VMP, bortezomib, melphalan, prednisone; Rd, lenalidomide and dexamethasone; HR, hazard ratio; CI, confidence interval; NR, not reached; NDMM, newly diagnosed multiple myeloma.

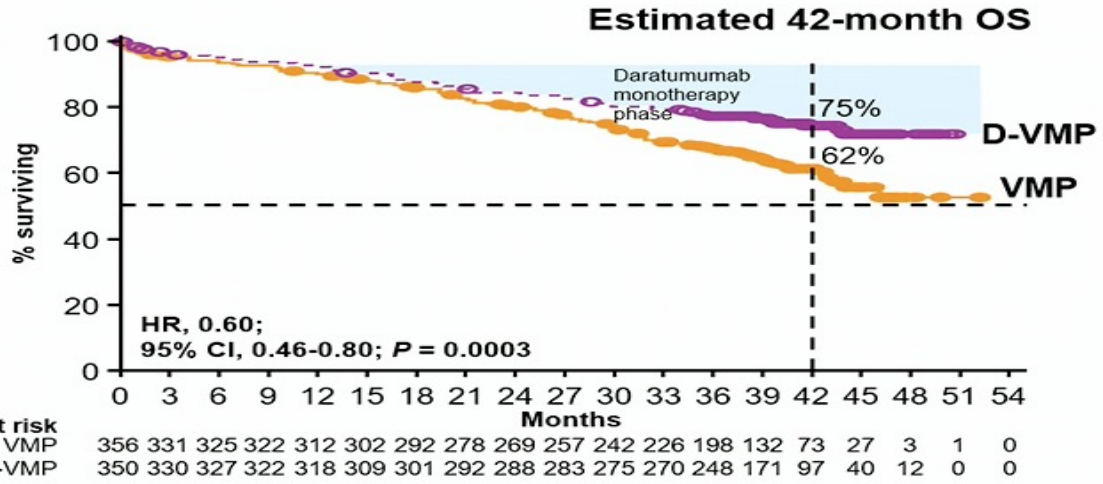
Mateos MVM et al. *Lancet*. 2019;395(10218):132-141.

Facon T et al. EHA 2021. LB1901.

OS

ALCYONE

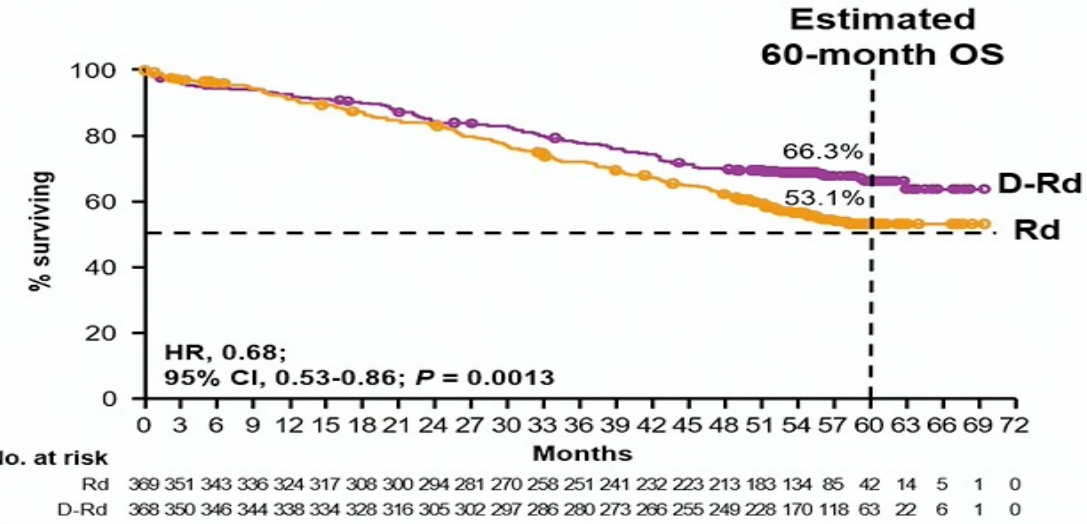
Median (range) follow-up: 40.1 (0-52.1) months
Pre-specified analysis triggered after 209 deaths were observed



40% reduction in the risk of death in patients receiving D-VMP

MAIA

Median follow-up: 56.2 months



D-Rd demonstrated a significant benefit in OS, with a 32% reduction in the risk of death, in patients with NDMM who are transplant ineligible

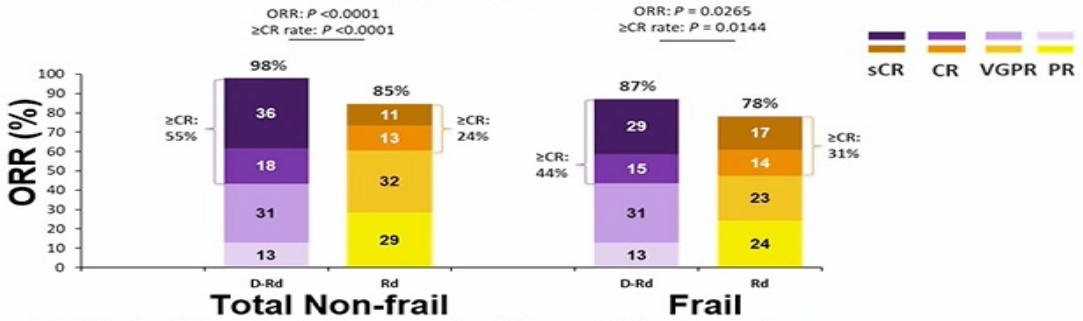
D, daratumumab; OS, overall survival; VMP, bortezomib, melphalan, prednisone; Rd, lenalidomide and dexamethasone; HR, hazard ratio; CI, confidence interval; NDMM, newly diagnosed multiple myeloma.

Mateos MVM et al. *Lancet*. 2019;395(10218):132-141.

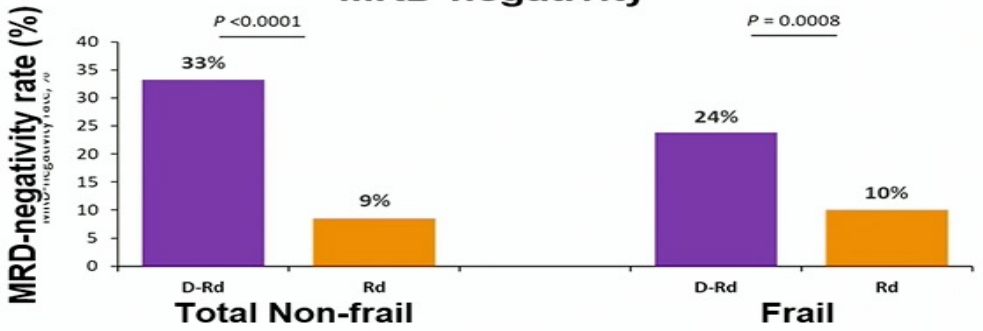
Facon T et al. EHA 2021. LB1901.

Daratumumab plus lenalidomide and dexamethasone (D-Rd) vs lenalidomide and dexamethasone (Rd) in transplant-ineligible newly diagnosed multiple myeloma (NDMM): frailty subgroup analysis of MAIA

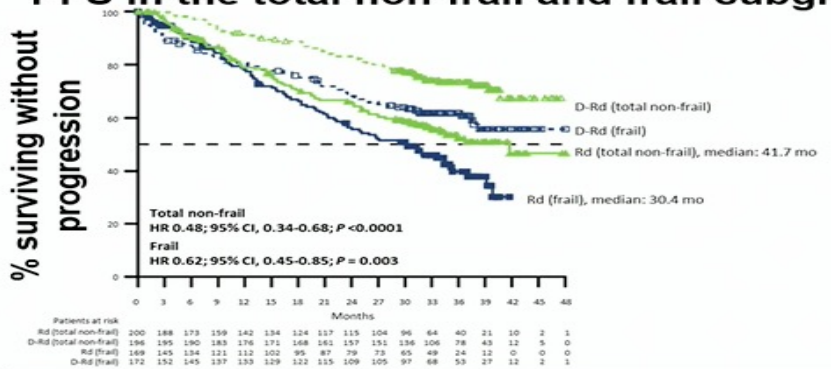
ORR and ≥CR rate



MRD-negativity



PFS in the total non-frail and frail subgroups



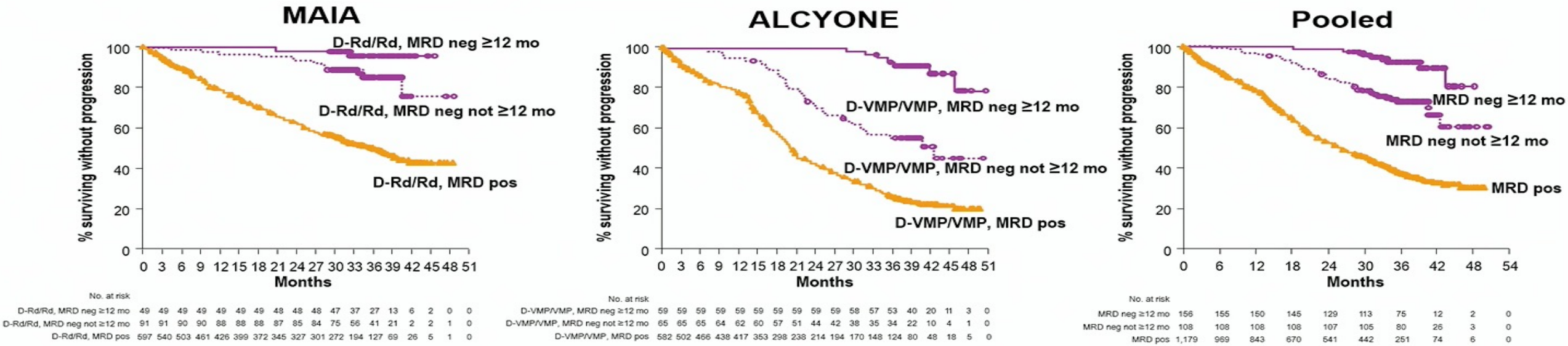
Safety

	Total Non-frail (n=395)		Frail (n=334)	
n (%)	D-Rd (n=196)	Rd (n=199)	D-Rd (n=168)	Rd (n=166)
Patients with a TEAE with outcome of death	7 (4)	7 (4)	20 (12)	20 (12)
Patients with a serious TEAE	123 (63)	126 (63)	125 (74)	121 (73)
Treatment discontinuations due to TEAEs	13 (7)	31 (16)	17 (10)	32 (19)
Deaths	26 (13)	46 (23)	57 (34)	57 (34)

Our findings, although based on a retrospective assessment of frailty, support the clinical benefit of D-Rd in patients with transplant-ineligible NDMM enrolled in MAIA, regardless of frailty status

Courtesy of S Zweegman, EMN 2021

PFS based on sustained MRD negativity (NGS, 10^{-5}) lasting ≥12 months in MAIA, ALCYONE and in both studies pooled

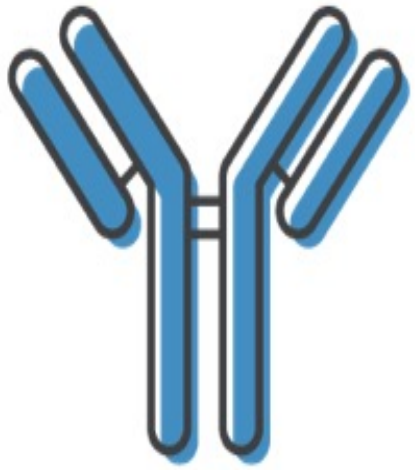


Durable MRD negativity lasting ≥12 months improved PFS compared with MRD-negative patients who did not maintain MRD negativity for ≥12 months

PFS, progression-free survival; MRD, minimal residual disease; D-Rd, daratumumab plus lenalidomide/dexamethasone; Rd, lenalidomide/dexamethasone; D-VMP, daratumumab plus bortezomib/melphalan/prednisone; VMP, bortezomib/melphalan/prednisone.

San Miguel J et al. ASH 2020; abstract 2317

Paradigma di terapia nel paziente con MM di nuova diagnosi non candidabile alle alte dosi



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- ✓ Come stabilire il protocollo di terapia per il paziente?
- ✓ I risultati degli studi clinici sono trasferiti in real life?
- ✓ Va adattata la terapia e come?
- ✓ Volontà del paziente tra indipendenza e QoL vs durata di vita?

The risks in treating older patients

- **Undertreatment**: making choice based on chronological age only
- **Overtreatment**: making choice considering only response

CAN STUDY RESULTS BE TRANSLATED TO OLDER PATIENTS IN REAL LIFE? NO

FIRST TRIAL REGISTRATION STUDY EXPERIMENTAL ARM RD	MAIA TRIAL REGISTRATION STUDY STANDARD ARM RD	LAROCCA UNFIT TRIAL REAL LIFE POPULATION STANDARD ARM RD
MPT versus Rd	Rd versus Dara-Rd ↑	Rd versus Rd-R ↓
Median PFS Rd: 25.5	34.4	20.2

EXPERIENCE

BIAS STUDY PATIENTS

Benboubker et al. N Engl J Med 2014;371:906-17, Bahlis et al. ASH 2019; abstract 1875, Larocca et al. ASH 2018

Come adattare la terapia al livello di Fragilità?

HOVON 143 study
Concept of 'non-toxic for frail' drugs

+EMN trial with ISATUXIMAB!

Induction

9 cycles, q 4 weeks

Ixazomib citrate 4 mg
days 1, 8, 15

Dexamethasone 20 mg
days 1, 8, 15, 22, cycle 1
Dexamethasone 10 mg
days 1, 8, 15, 22, cycles 2-9

Daratumumab 16 mg/kg
days 1, 8, 15, 22, cycles 1-2
days 1, 15, cycles 3-6
day 1, cycles 7-9

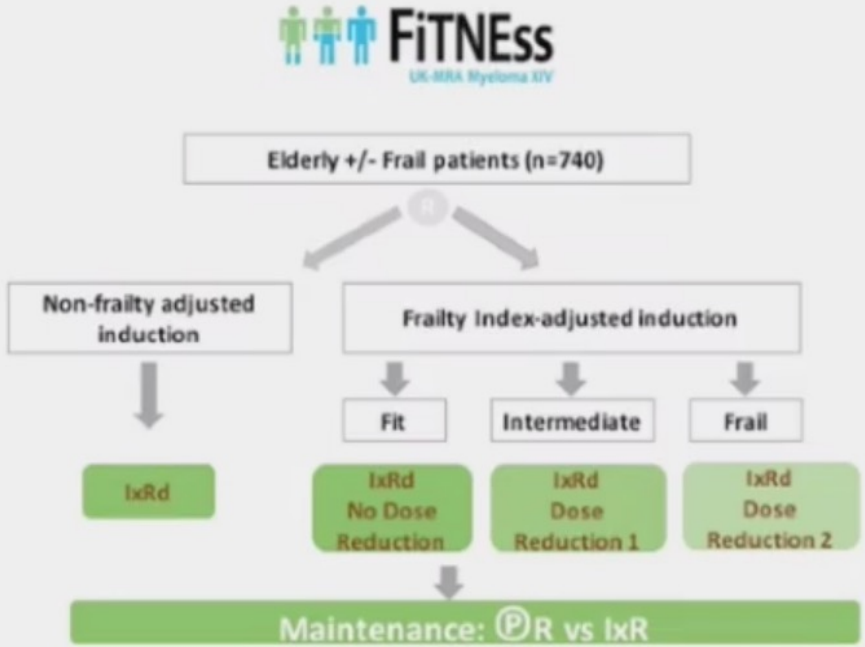
Maintenance

Maximum 2 years until PD
q8 weeks

Ixazomib citrate 4 mg
days 1, 8, 15, 29, 36, 43

Daratumumab 16 mg/kg
day 1

UK-MRA FitNEss trial
Concept of frailty-adjusted dosing



HOVON 143 - EudraCT 2016-002600-90
Fitness trial - NCT03720041

Treatment goals based on fraility score

PATIENT STATUS ASSESSMENT

Age (score 0 – 1 – 2) Charlson (score 0 – 1)

ADL (score 0 – 1) IADL (score 0 – 1)

FIT	INTERMEDIATE	FRAIL

Co-morbidities, organ function

Life expectancy

Impaired functional status

		
Goal	**Deep remission**	**Balance efficacy/safety**	**Do not harm**
Priority	CR/MRD-negativity Efficacy	Good response Combination of efficacy/safety	QoL Low toxicity

Conclusions

- *In addition to cytogenetic factors, high-risk multiple myeloma may be defined by clinical features, such as plasma cell leukemia, extramedullary disease, circulating plasma cells, renal failure, and, more recently, frailty*
- *Although most risk stratification systems assess risk at time of diagnosis, high-risk features may develop later in the disease course at the time of relapse. Although high risk cytogenetics, defined as del(17p) or t(4;14), were more common in patients with early relapse (33%), a substantial proportion of early-relapsing disease (67%) had standard risk cytogenetics.*
- *Recent data suggest that more dynamic assessment could be considered, including response to therapy, resolution of imaging findings, and the presence of MRD.*

Grazie per l’attenzione