UCLouvain

BHS
Belgian Hematology Society

INSTITUT ROI ALBERT II
CANCÉROLOGIE ET HÉMATOLOGIE
Cliniques universitaires SAINT-LUC | UCL Bruxelles

MM 2023

1	**Diagnosis, upfront therapy – M.C. Vekemans**
2	First relapse - M.C. Vekemans
3	Second relapse and beyond - N. Kint

BHS Course

22 April 2023

Disclosures

Advisory board of BMS-Celgene, Janssens, Sanofi, Amgen, Takeda, Pfizer, GSK

Agenda

1	Generalities
2	SMM
3	MM, Principles of therapy
4	Transplant eligible patients
5	Transplant non eligible patients
6	High risk disease
7	MRD to define therapy

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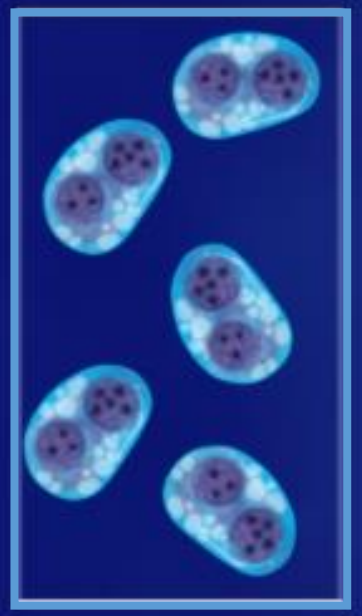
Multiple myeloma

- Clonal plasma (myeloma) cells in bone marrow
- Lytic bone lesions (holes in the bone)
- M protein in blood or urine



Clonal plasma cells

Lytic bone lesions

Myeloma (M) protein

Definition

MGUS	Smouldering Multiple Myeloma	Symptomatic Multiple Myeloma
monoclonal component (blood and/or urine)	monoclonal component (blood and/or urine)	monoclonal component (blood and/or urine)
BM PC < 10 %	BM PC ≥ 10 %	BM PC ≥ 10 %
no CRAB	no CRAB	at least 1 CRAB

Evidence of end-organ damage ("CRAB")

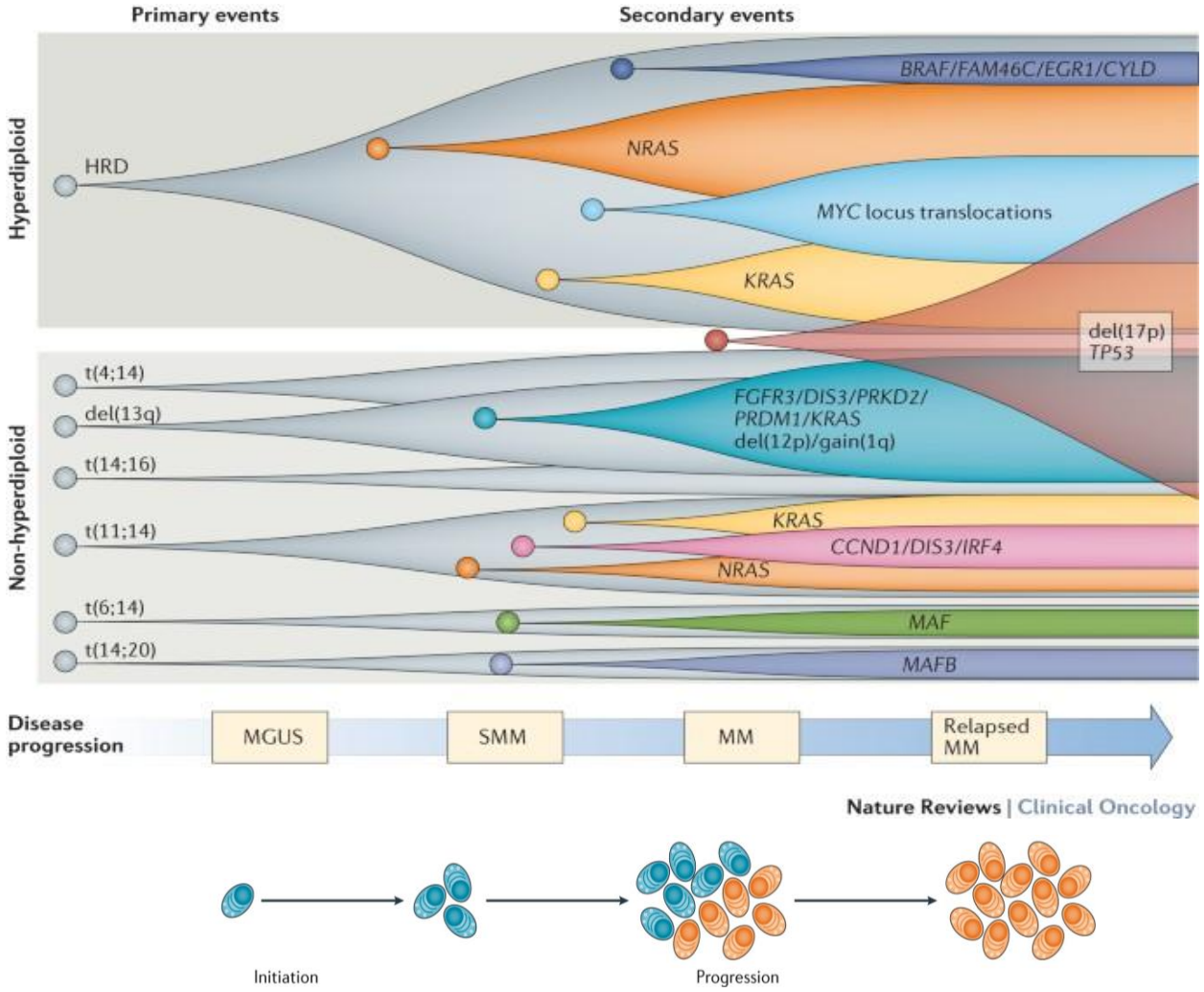
- **C**alcium level elevation
  - >11 mg/dL or >1 mg/dL higher than ULN
- **R**enal insufficiency
  - Creatinine clearance <40 mL/min or creatinine >2 mg/dL
- **A**nemia
  - Hemoglobin <10 g/dL or 2 g/dL <ULN
- **B**one lesions
  - Lytic bone lesions by skeletal survey or PET/CT

Pathophysiology

Genetic changes

BM angiogenesis

Cytokines



MGUS 1-2% per year → SMM

SMM 10% per year → MM

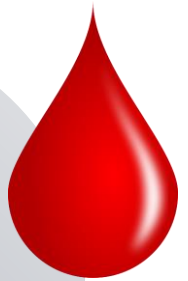
Incidence

2 %

of all cancers in Caucasians

15%

of all hematological cancers



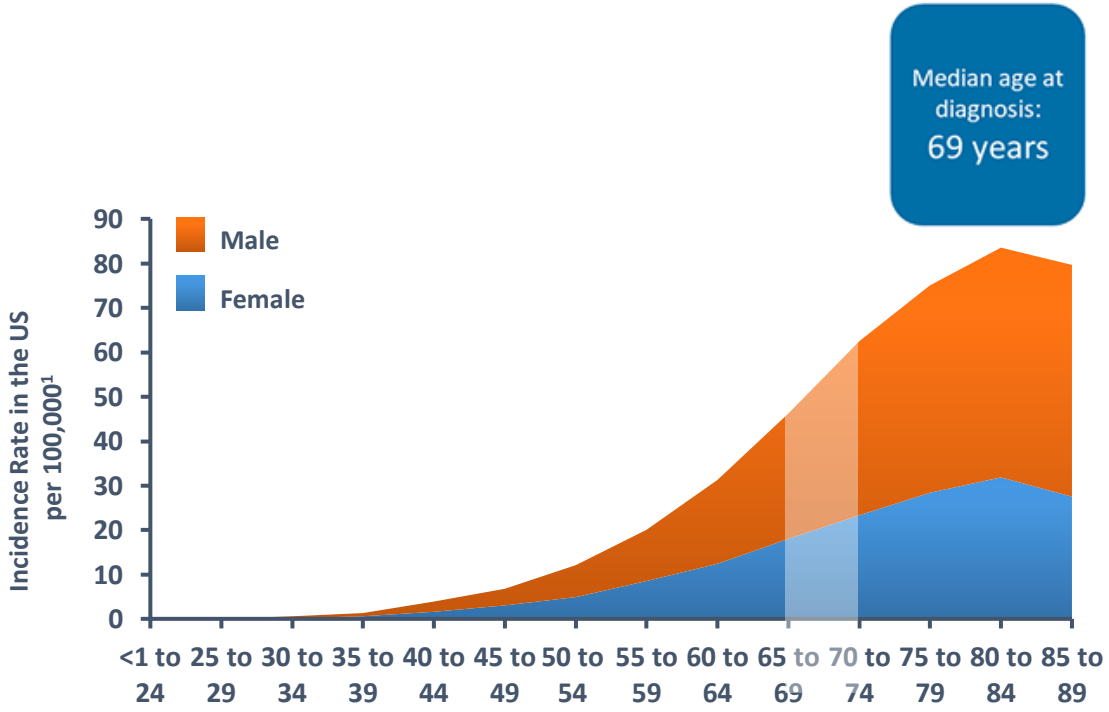
2d MOST COMMON HEMATOLOGICAL MALIGNANCY

4.5 – 6 per 100 000 per year

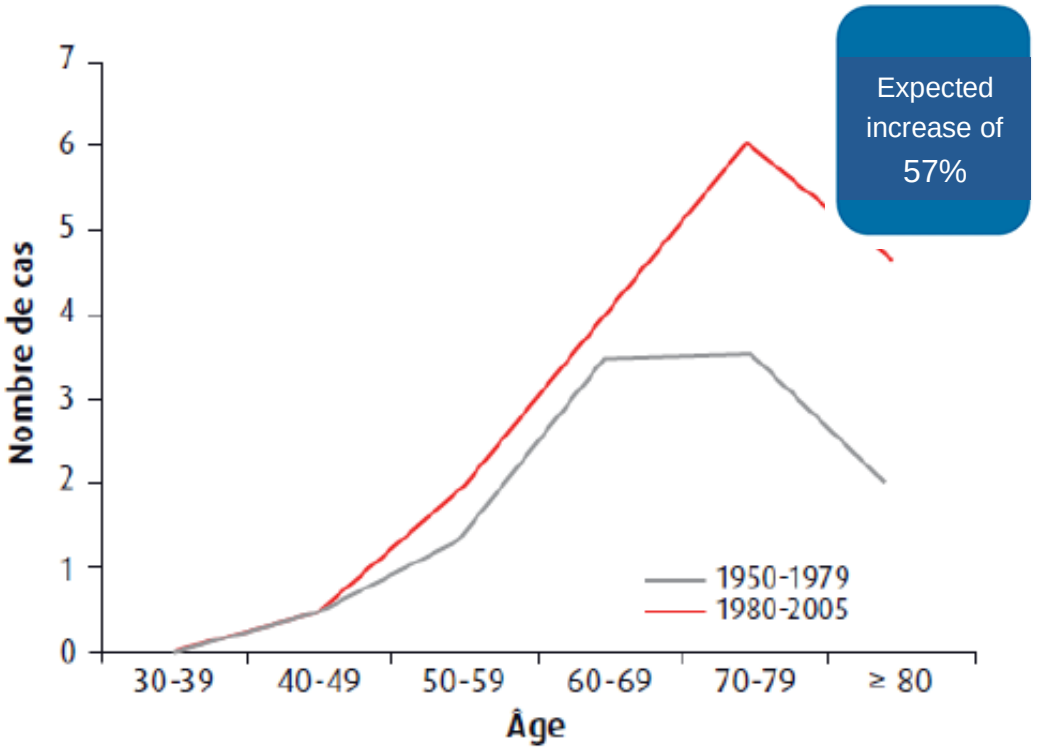
Dimopoulos MA,, Ann Oncol 2010

Epidemiology

MM is a disease of the **elderly**

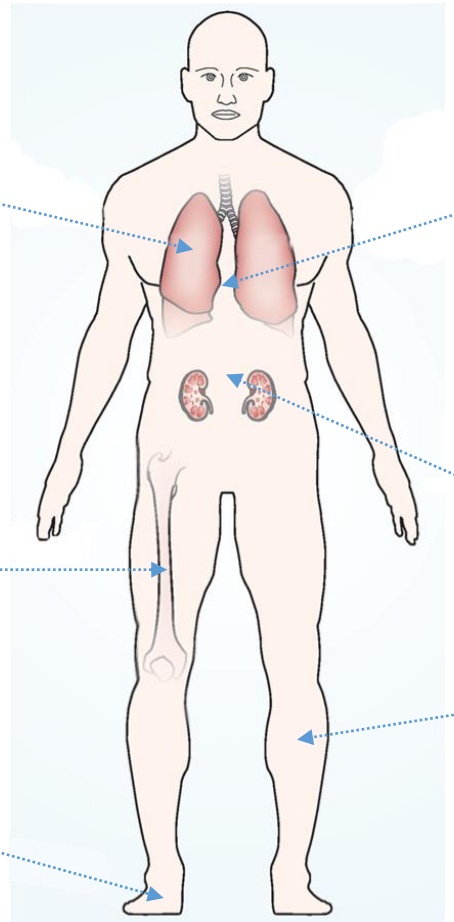


Incidence of MM is **rising over time**



Turesson, Mayo Clin Proc 2010

Clinical presentation



Infections

Anemia (73%)

Renal failure (19%)

Bone disease (79%)

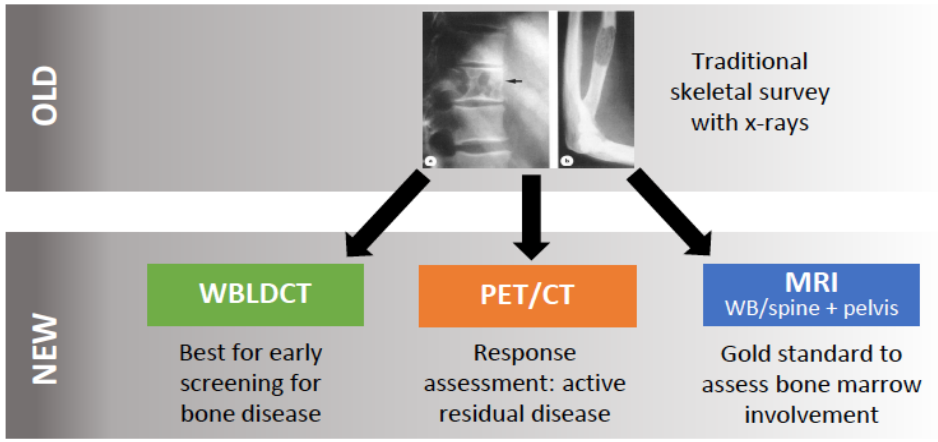
Thromboembolic event

Peripheral neuropathy

Kyle, Mayo Clin Proc 2003

Evaluation of patients suspected of having MM

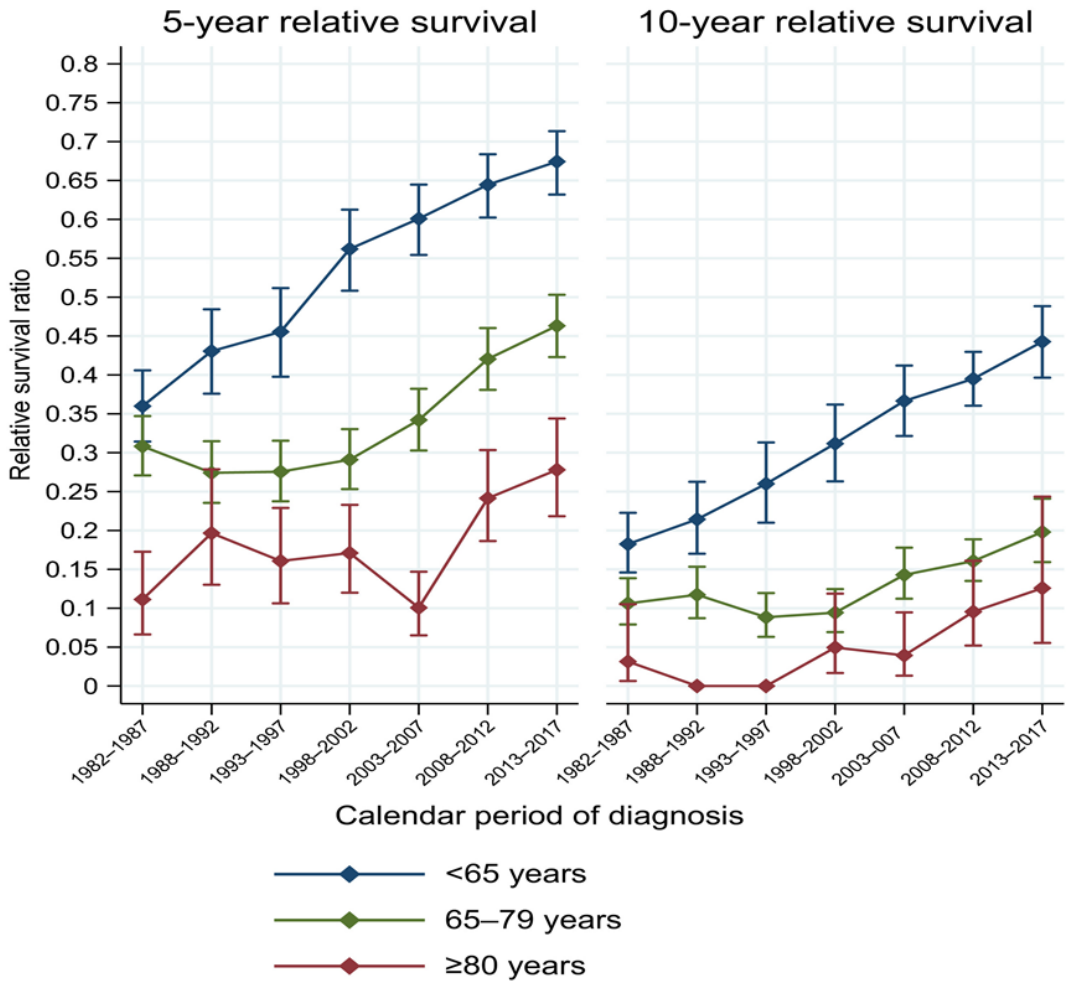
Biology	Complete blood count Creatinin, calcium β2-microglobulin, albumin, LDH, CRP
M-component	Serum/urine electrophoresis (24h urine) Quantification of IgA, IgG, IgM immunoglobulins Characterisation of heavy/light chains by IF Measurement of FLC
BM plasma cells	iFISH on sorted plasma cells t(4;14), t(14;16), del 17p, chromosome 1 abnormalities t(11;14)
Lytic bone lesions	WBLD-CT (standard) (conventional X-ray) MRI (greater details (focal lesions), cord compression) PET-CT



Note: Bone scan (DEXA) for bone density, not MM

Dimopoulos, Ann Oncol 2021

Prognosis



Langseth, Br J Haematol 2020

Staging

SD

Stage I	All of the following: • Hemoglobin > 10 g/dL • Serum calcium level normal (< 12 mg/dL) • No lytic bone lesions • Serum IgG < 5 g/dL • Serum IgA < 3 g/dL • Urine monoclonal protein < 4 g/d
Stage II	Does not fit stage I or stage III criteria
Stage III	One or more of the following: • Hemoglobin < 8.5 g/dL • Serum calcium > 12 mg/dL • Lytic bone lesions • Serum IgG > 7g/dL • Serum IgA > 5 g/dL • Urine monoclonal protein >12 g/d

stade A: créatinine < 20 mg/L; **stade B**: créatinine ≥ 20 mg/L.

ISS

Stage	Characteristics	Median Survival (mo)
I	Serum β_2-microglobulin <3.5 mcg/mL Serum albumin ≥3.5 g/dL	62
II	Not stage I or stage III	44
III	Serum β_2-microglobulin ≥5.5 mcg/mL	29

Durie, Cancer 1975; Greipp, J Clin Oncol 2005

High risk features

Table 1: A) Prognostic factors in Multiple Myeloma (MM) and B) Cytogenetic abnormalities and relationship with outcomes

A) Prognostic factors in MM

Patient-related	*Disease burden-related*	*Disease biology-related*	*Therapy-related*
Age	High B_2 microglobulin*	Cytogenetic abnormalities	Quality of response
Performance status	Low albumin*	GEP	Early relapse
Comorbidities	Renal impairment	Circulating PC	
	LDH above ULN	EMD	
		High proliferation rate	

B) Cytogenetic abnormalities and relationship with outcomes

Chromosome/region (frequency)	*Gene involved/effect*	*Prognostic implication*
14q32 (locus IGH) (45-50%)		
t(11;14) (20%)	Cycline D1 hyperexpression	Neutral
t(4;14) (10-15%)	FGFR3 and MMSET deregulated	Unfavorable (worsened by chromosome 1 alterations, improved by trisomy 5)
t(14; 16) (< 5%)	cMAF	Doubt, mainly unfavorable
t(14; 20) (< 5%)	UK	Doubt, mainly unfavorable
1q21 acquisition (30%)	CKS1B, MCL1	
Gain (2-3copies)		Partially unfavorable
Amplification (≥ 4)		Unfavorable
1p32 deletion (10%)	FAF1/ CDKN2C	Unfavorable
17p deletion (8-15% according to PCs cutoff)	TP53 and UK	
Single-hit	deletion	Unfavorable
Double-hit	Bi-allelic inactivation (deletion + mutation)	Very unfavorable

Abbreviations: EMD= extramedullary disease; GEP= gene expressing profile; ISS= International Staging System; LDH= lactate dehydrogenase; PC= plasma cells; UK= unknown; ULN= upper limit of normal. *ISS

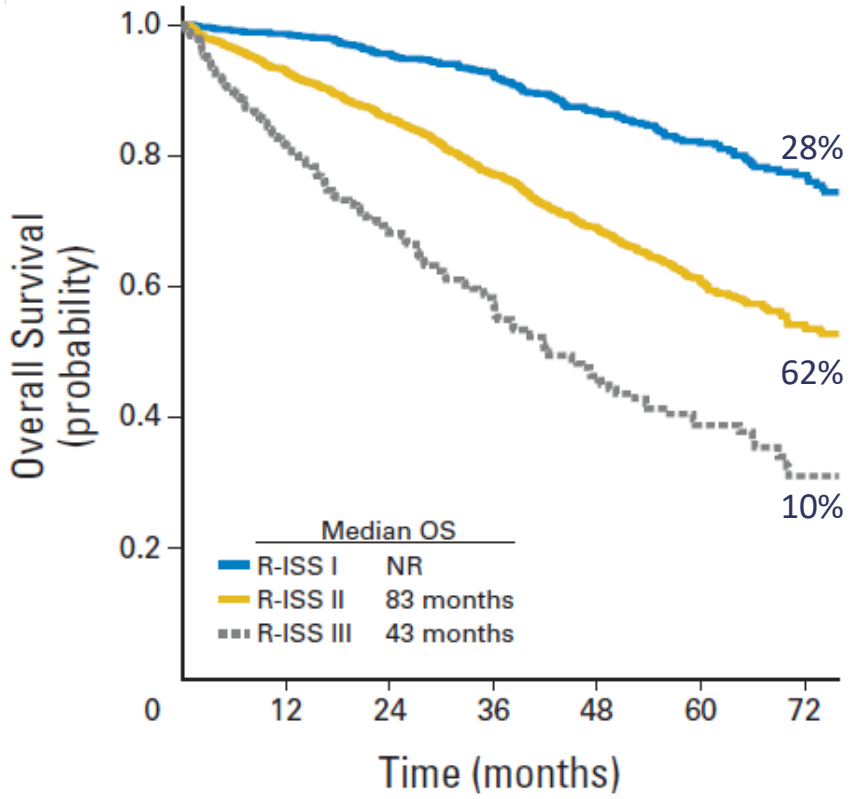
Zamagni, Blood 2021

Staging

R-ISS

Table 1. Standard Risk Factors for MM and the R-ISS

Prognostic Factor	Criteria
ISS stage	
I	Serum β_2-microglobulin < 3.5 mg/L, serum albumin ≥ 3.5 g/dL
II	Not ISS stage I or III
III	Serum β_2-microglobulin ≥ 5.5 mg/L
CA by iFISH	
High risk	Presence of del(17p) and/or translocation t(4;14) and/or translocation t(14;16)
Standard risk	No high-risk CA
LDH	
Normal	Serum LDH < the upper limit of normal
High	Serum LDH > the upper limit of normal
A new model for risk stratification for MM	
R-ISS stage	
I	ISS stage I and standard-risk CA by iFISH and normal LDH
II	Not R-ISS stage I or III
III	ISS stage III and either high-risk CA by iFISH or high LDH



Palumbo, J Clin Oncol 2015

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SMM

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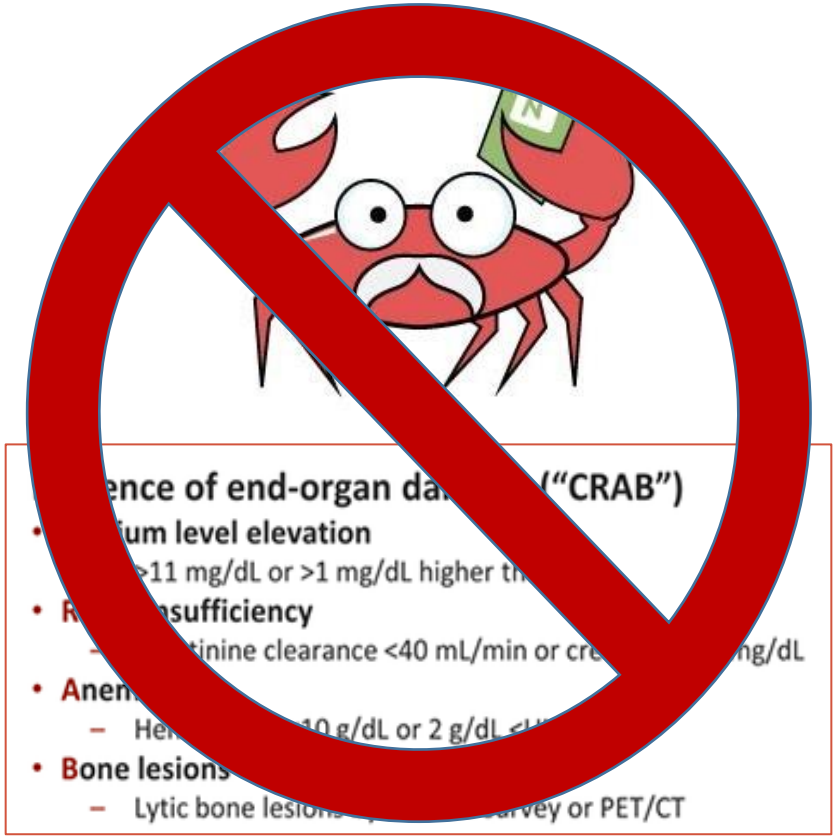
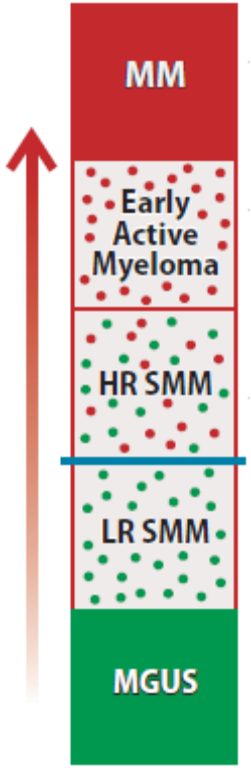


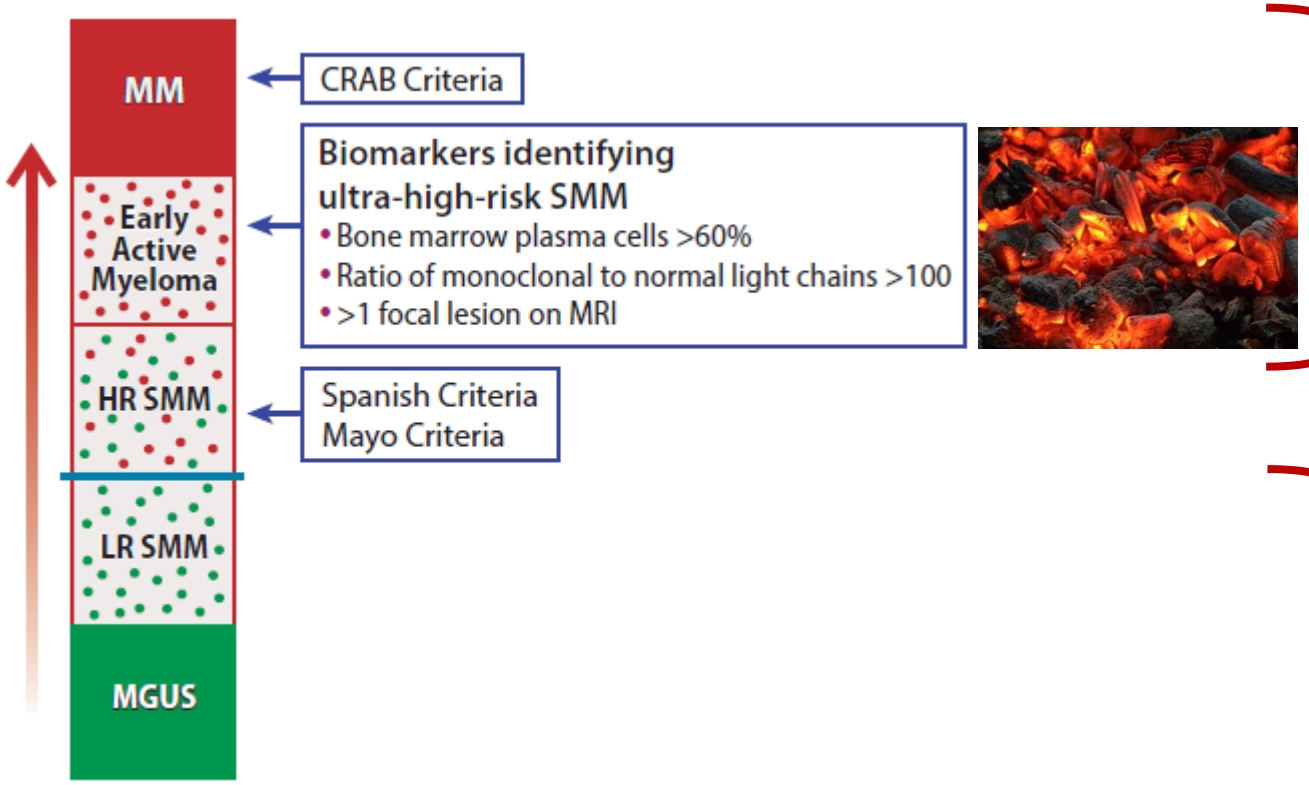
Definition



SMM - MGUS

SMM - MM

Indication of therapy in SMM



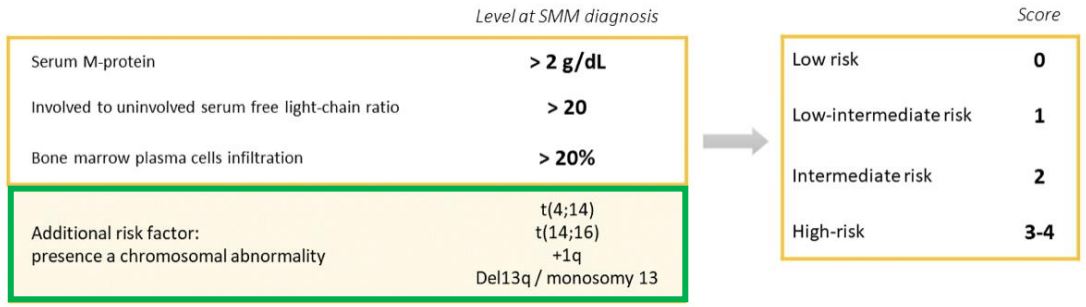
Treatment to be started

Close monitoring

every 3-6 months

SMM risk stratification 20-20-20 model

Figure 1. The IMWG 2/20/20 risk stratification model.[1]



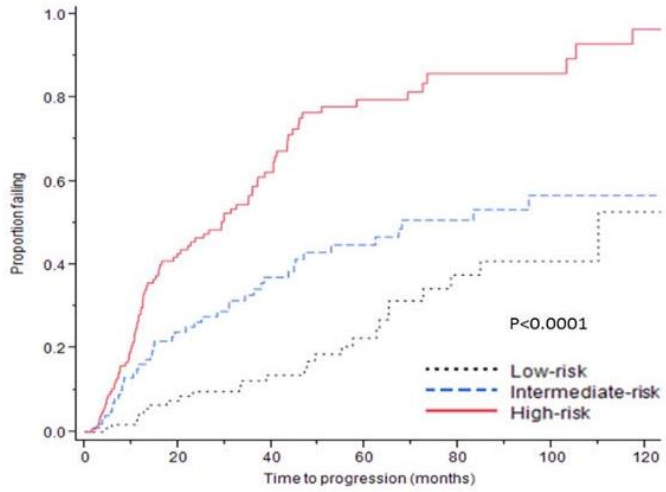


Table 2. Probability of progression from SMM to MM at 2 years according to described risk factors from IMWG 2/20/20 with three- and four-risk factor model.[1]

Risk	Number of risk factors	Hazard ratio (95% CI)	Risk of progression at 2 years, %	N (%)
		3-risk factor model (2/20/20)		
Low-risk	0	Reference	6.2	522 (38.
Intermediate-risk	1	2.99 (1.97–4.54)	17.9	445 (32.
High-risk	2–3	9.02 (6.15–13.2)	44.2	396 (29.
		4-risk factor model		
Low-risk	0	Reference	6.0	225 (32.
Low-intermediate	1	4.16 (2.26–7.67)	22.8	224 (32.
Intermediate-risk	2	9.82 (5.46–17.7)	45.5	177 (25.
High-risk	3–4	15.5 (8.23–29.0)	63.1	63 (9.1

Lakshman, Br Cancer J 2018; Mateos, Blood Cancer J 2020

Therapy in SMM

Balance regarding treatment initiation in SMM patients

- Over-treatment, toxicities and secondary malignancies or
- Undertreatment, risk of organ damage, reduced PFS/OS and poorer outcomes

Guidelines presented at ASH 2022

- Close monitoring in low- or intermediate-risk SMM

Lack of consensus regarding treatment in high-risk patients

- Two phase 3 in HR-SMM treated with Rd/R vs. observation alone : reduced risk of progression to active MM with improved OS in one of them

- Two phase 2 in HR-SMM treated with HDT with/without ASCT, followed by R/Rd vs. observation alone : high response rates and durable MRD

Mateos, ASH 2022, #781; Kumar, ASH 2022, #2022; Mateos, NEJM 2013; Lonial, J Clin Oncol 2020

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- **B**one lesions
  - Lytic bone lesions by skeletal survey or PET/CT

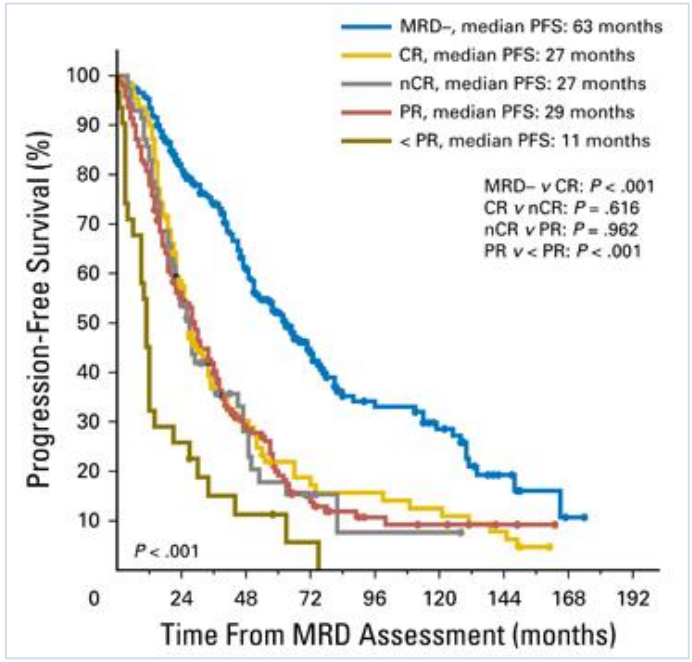
Biomarkers identifying ultra-high-risk SMM

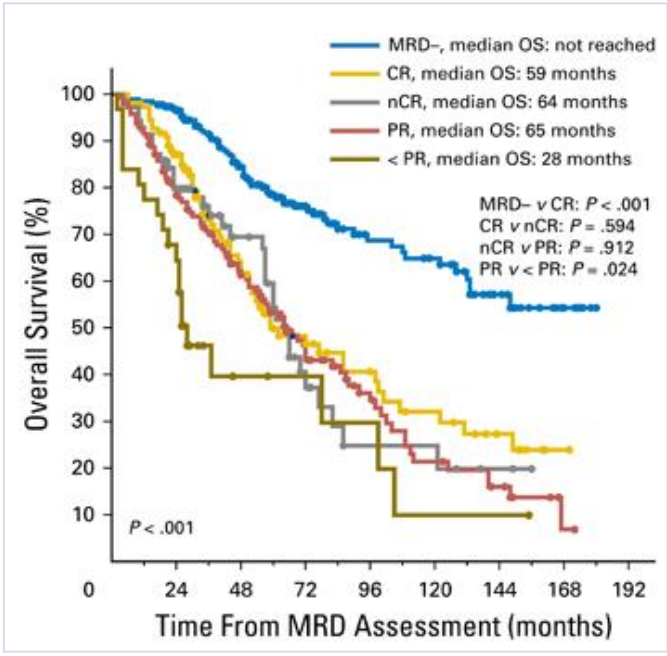
- Bone marrow plasma cells >60%
- Ratio of monoclonal to normal light chains >100
- >1 focal lesion on MRI

Goal of therapy

Outcome does not rely on CR but on MRD-

CR

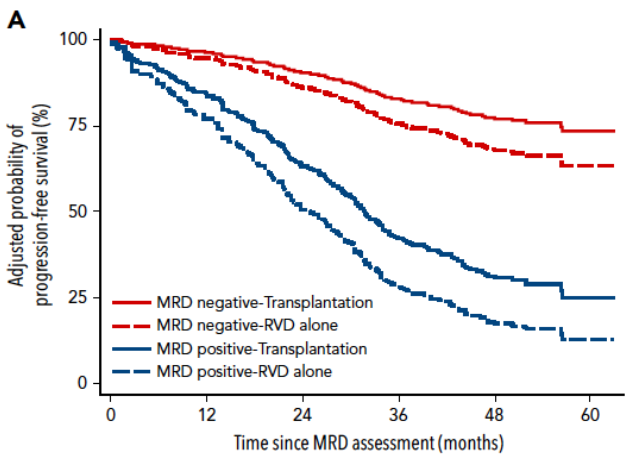


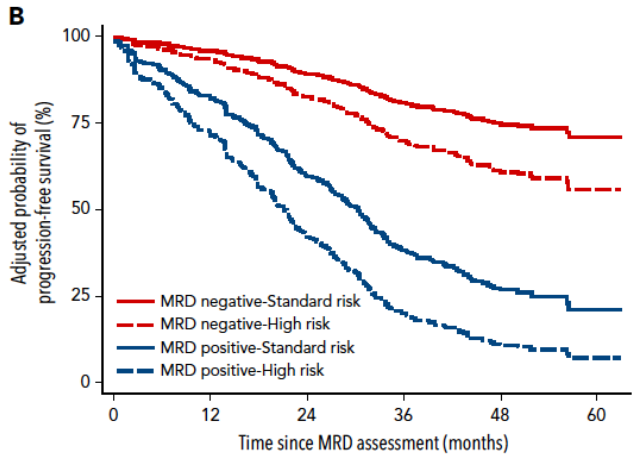


Lahuerta, J Clin Oncol 2017

Goal of therapy

Outcome depends on the depth of response





Attal, NEJM 2017; Perrot, ASH 2020

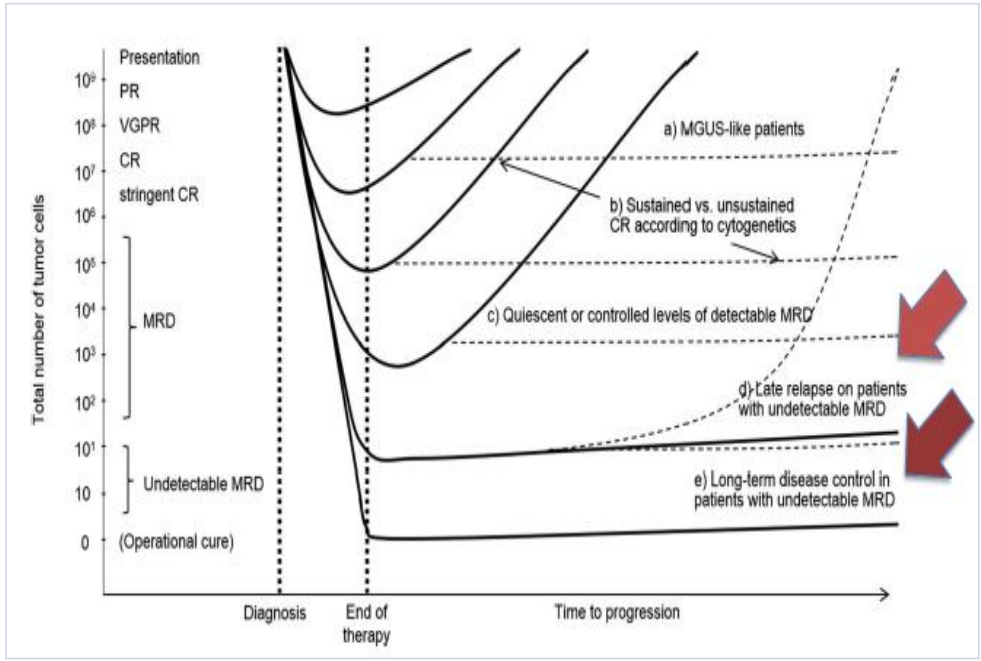
Goal of therapy

Prolonged PFS and OS associated with MRD-

Conventional techniques (electrophoresis, immunofixation, FLC)

CR

MRD



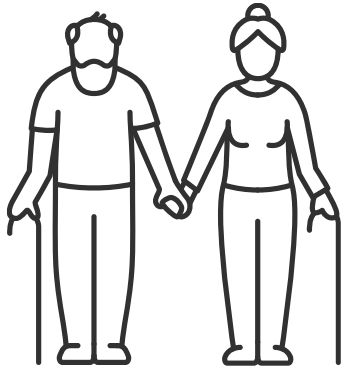
Paiva, Blood 2015

Be right from the start

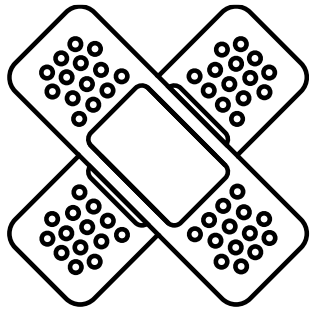
Significant patient drop out at each treatment line

N = 4997 patients charts

Factors to consider before starting therapy

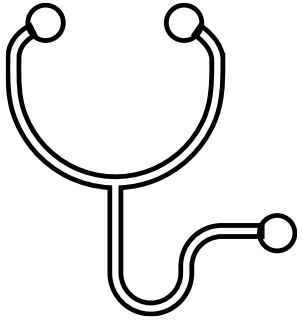


Age



Comorbidities

Frailty



Treatment efficacy

Expected toxicities

Goal of therapy

Patient preferences

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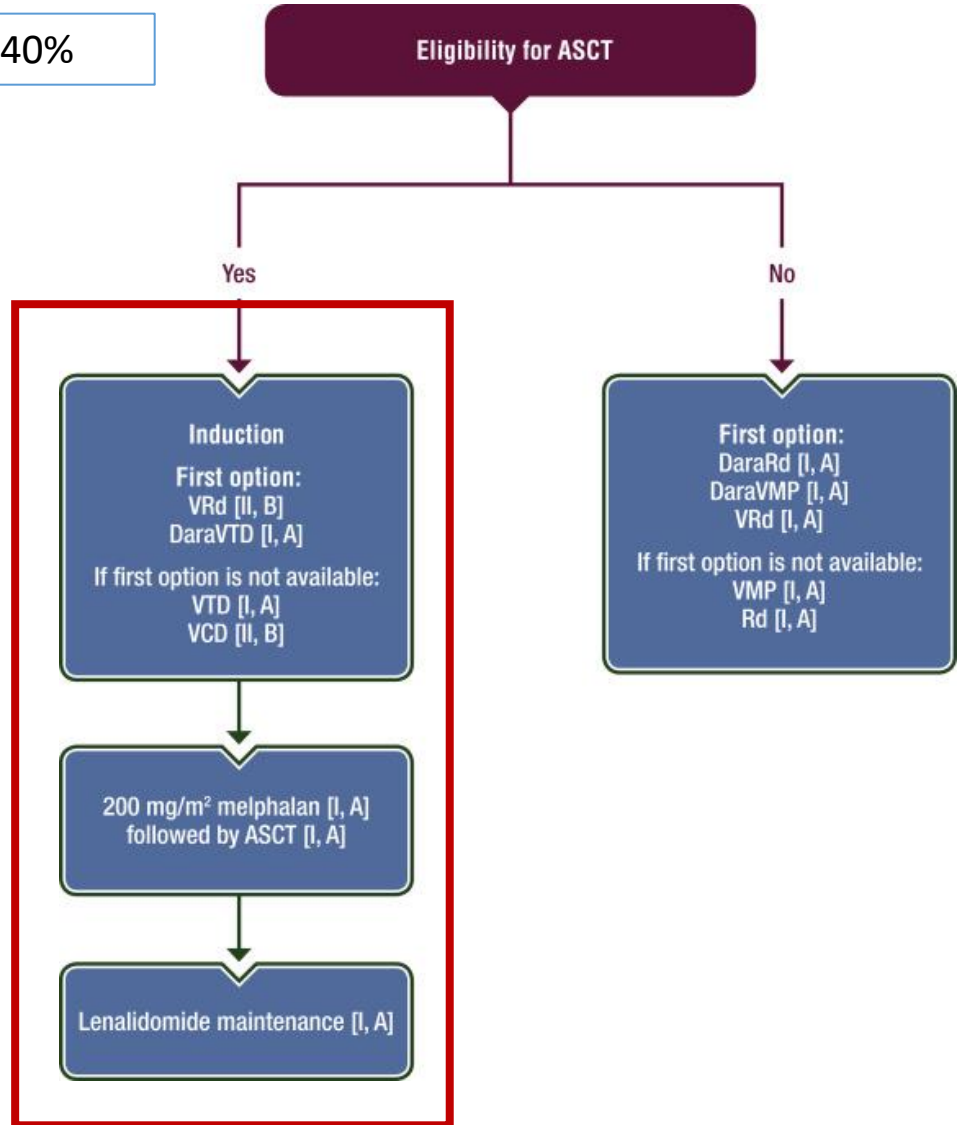
2021 ESMO guidelines – upfront therapy

ASCT

40%



3-6 months

CONSOLIDATION

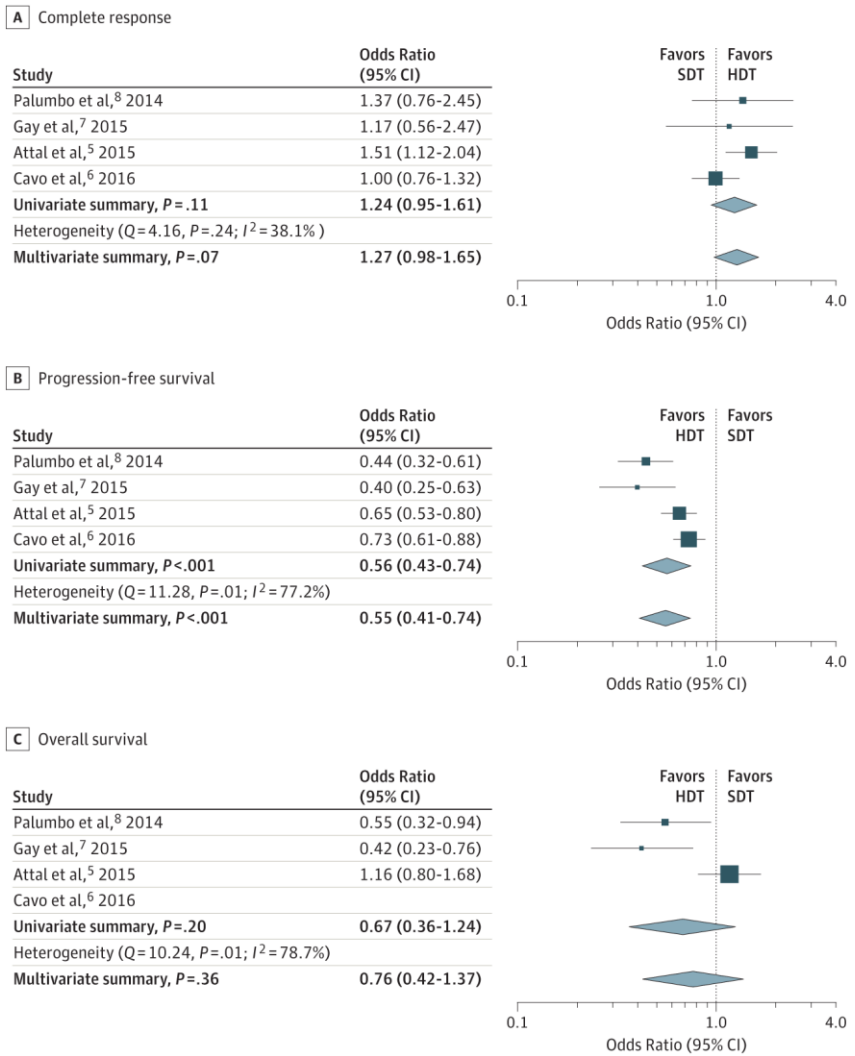
Dimopoulos, Ann Oncol 2021

ASCT upfront or delayed

RCT

Table 1. Randomized studies comparing ASCT with conventional chemotherapy as consolidation therapy.

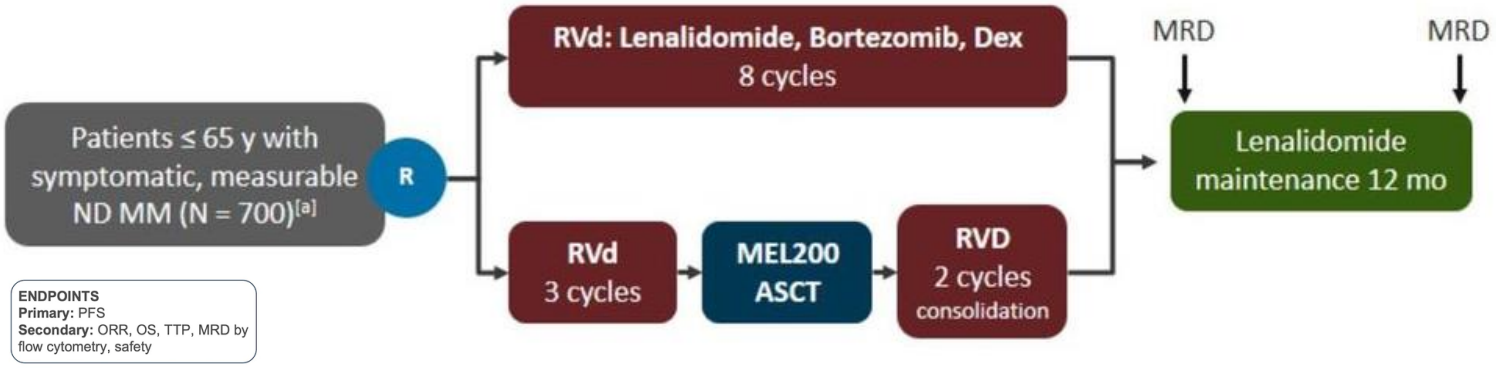
Study	Induction	ASCT/Chemo Regimen	Post-SCT Maintenance	PFS	OS
IFM 90 [6]	4–6 alternating cycles of VMCP/BVAP	Mel 140 + TBI vs. total 18 cycles of VMCP/BVAP	Interferon-alfa	Median EFS: 27 mo (ASCT) vs. 18 mo (chemo) $p = 0.01$	5-year OS: 52% (ASCT) vs. 12% (chemo) $p = 0.03$
SWOG 9321 [51]	4 cycles of VAD	Mel 140 + TBI vs. VBMCP for response reaches a plateau or progression	Interferon for 4 yrs vs. observation	7-yr EFS: 17% (ASCT) vs. 14% (chemo) $p = 0.16$	7-yr OS: 38% (ASCT) vs. 39% (Chemo) $p = 0.78$
MRC VII [52]	Intensive therapy (VCAP) vs. Standard therapy (BCAM)	Mel 200 or Mel 140+TBI vs. BCAM up to 12 cycles Stem cell mob with HD CTX	Interferon	Median PFS: 31.6 mo (ASCT) vs. 19.6 mo (chemo) $p \leq 0.001$	Median OS: 54.1 mo (ASCT) vs. 42.3 mo (Chemo) $p = 0.04$
GIMEMA RV-209 [53]	4 cycles of Rd	Tandem ASCT with Mel 200 vs. MPR × 6	Randomization to R (Len) vs. observation in each arm	Median PFS: 43 mo (ASCT) vs. 22.4 mo (chemo) $p < 0.001$	4-yr OS: 81.6% (ASCT) vs. 65.3% (chemo) $p = 0.02$
RV-MM-EMN-441 [54]	4 cycles of Rd	Single or tandem ASCT vs. CRD × 6	Randomization to R (Len) or R plus prednisone until progression in each arm	Median PFS: 43.3 mo (Mel200) vs. 28.6 mo (CRD) $p < 0.001$	4-yr OS: 86% (Mel200) vs. 73% (CRD) $p = 0.004$
IFM/DFCI 2009 [55]	3 cycles of RVd	RVd × 2 following ASCT vs. RVd × 5	Len maintenance in both arms until progression (US) or for 1 year (France)	Median PFS: 47.3 mo (ASCT) vs. 35 mo (chemo) $p < 0.001$	8-yr OS: 62.2%% (ASCT) vs. 60.2%% (chemo) $p = 0.81$
EMN02/HO95 [56]	3–4 cycles of VCd	R1: Mel 200 ASCT (single or double) vs. VMP R2: VRd × 2 or no consolidation	Len maintenance for both arms until progression	3-yr PFS: 66% (ASCT) vs. 57.5% (VMP)	NR

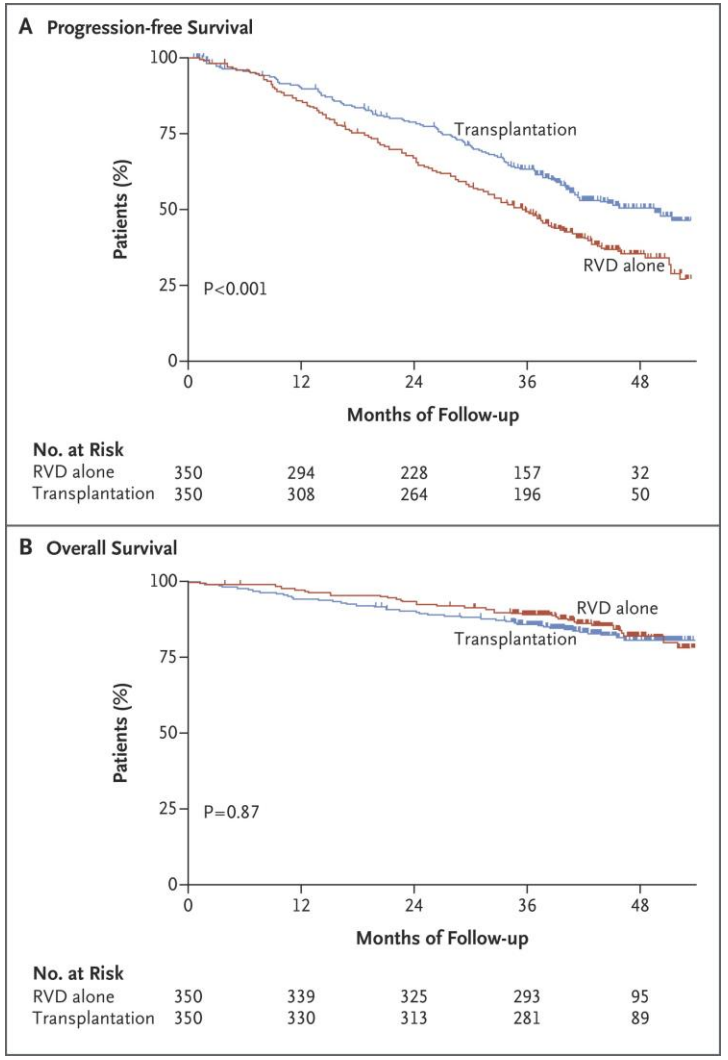


Devarankonda, Cancers 2021

ASCT upfront or delayed

IFM 2009





- ✓ No difference in terms of OS
- ✓ More toxicity in ASCT arm

BUT

- ✓ Better PFS
- ✓ Better MRD negativity rate
- ✓ 21% of the pts in the RVD group could not received ASCT at the time of relapse

Table 2. Response to Treatment.*

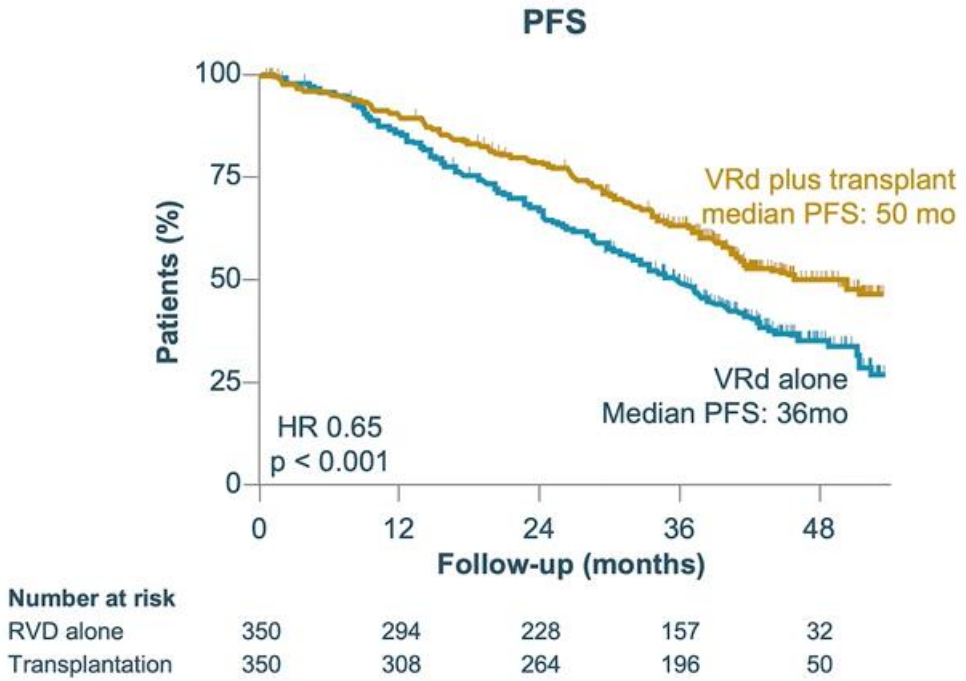
Outcome	RVD-Alone Group (N=350)	Transplantation Group (N=350)	Adjusted P Value†
Best response during the study — no. (%)			0.02
Complete response	169 (48)	205 (59)	
Very good partial response	101 (29)	102 (29)	
Partial response	70 (20)	37 (11)	
Stable disease	10 (3)	6 (2)	
Complete response — no. (%)	169 (48)	205 (59)	0.03
Complete response or very good partial response — no. (%)	270 (77)	307 (88)	0.001
Minimal residual disease not detected during the study — no./total no. with complete or very good partial response (%)‡	171/265 (65)	220/278 (79)	<0.001

* Responses were assessed according to the International Uniform Response Criteria for Multiple Myeloma. Percentages may not total 100 because of rounding.
† P values were adjusted for multiplicity with the use of the Holm procedure to control the family-wise error rate at 0.05.
‡ Minimal residual disease was detected by means of flow cytometry. As a result of decisions made by the patient or the investigator, 5 patients in the RVD-alone group and 29 patients in the transplantation group were not tested.

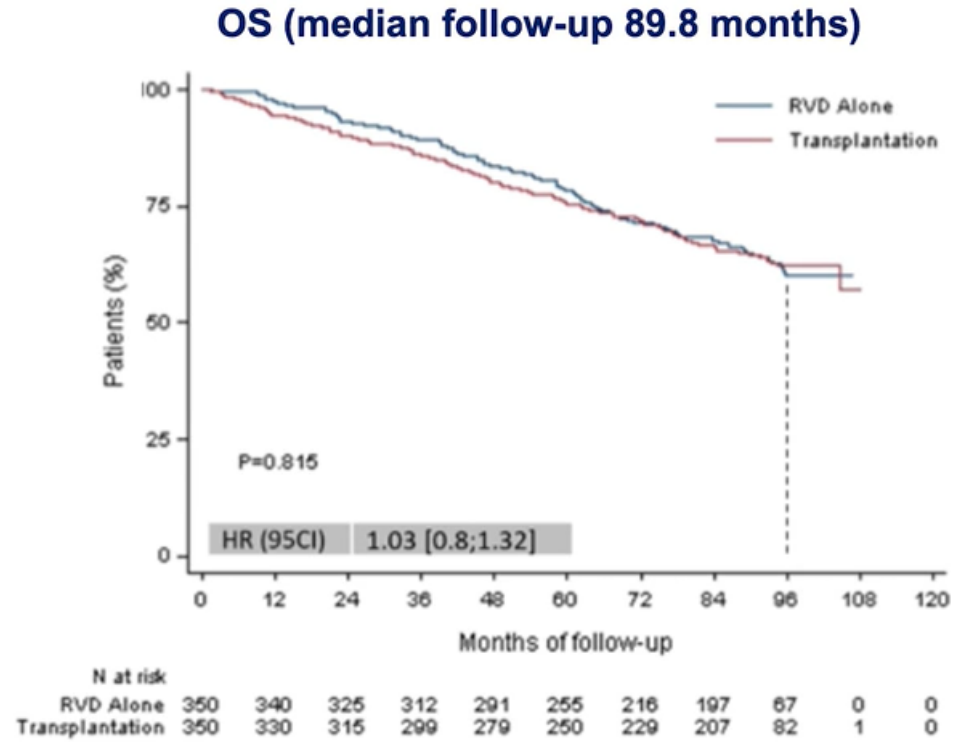
Attal, NEJM 2017; Perrot, ASH 2020

ASCT upfront or delayed

IFM 2009



Better PFS with VRD + ASCT compared to VRD alone

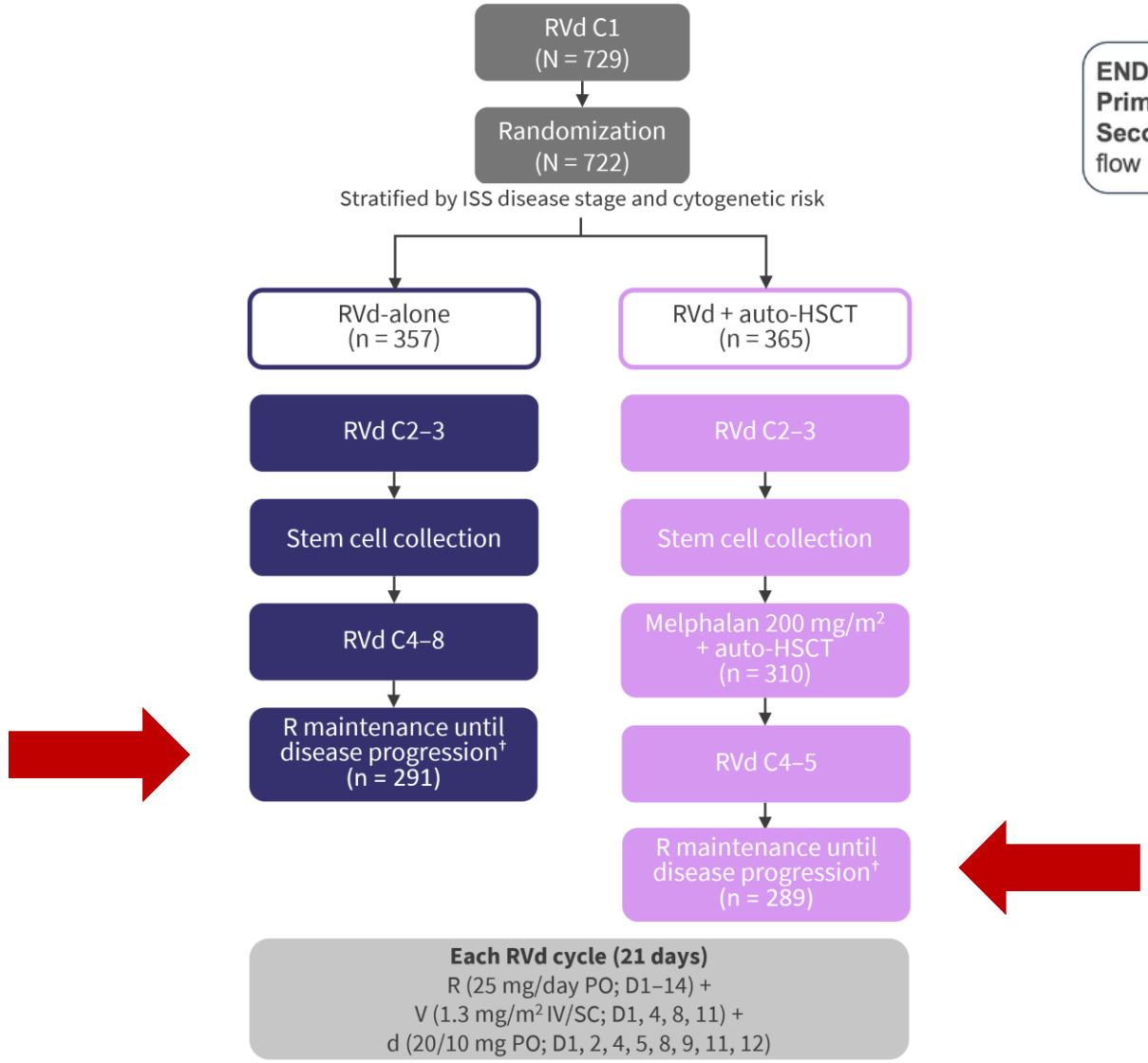


60.2% (RVD) vs 62.2% (ASCT) of patients are alive after 8 years of follow-up

Attal, NEJM 2017; Perrot, ASH 2020, #143

ASCT upfront or delayed

DETERMINATION



ENDPOINTS
Primary: PFS
Secondary: ORR, OS, TTP, MRD by flow cytometry, safety

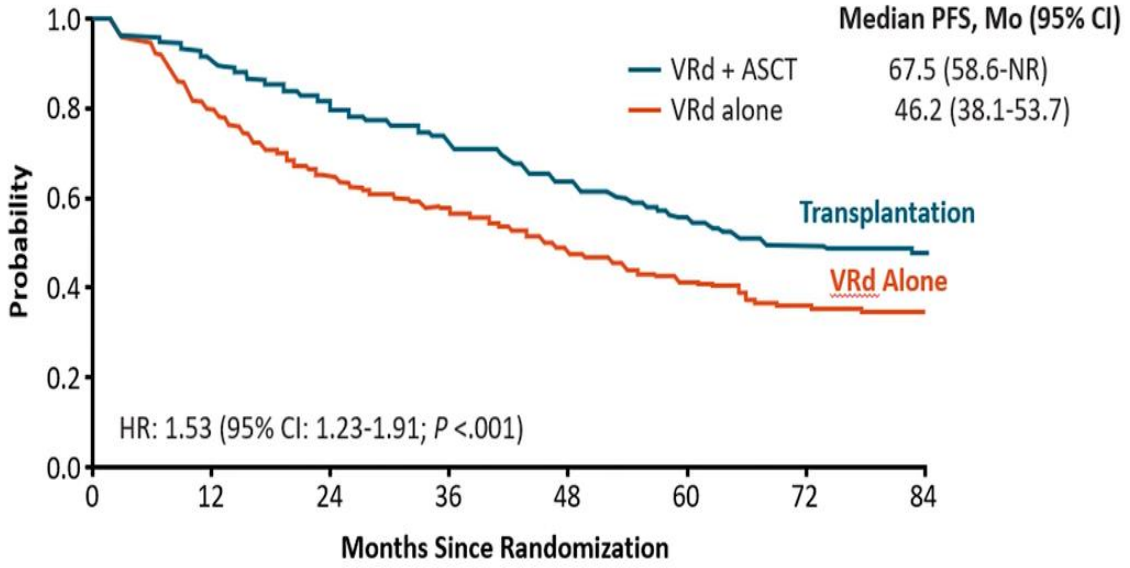
Richardson, NEJM 2022

ASCT upfront or delayed

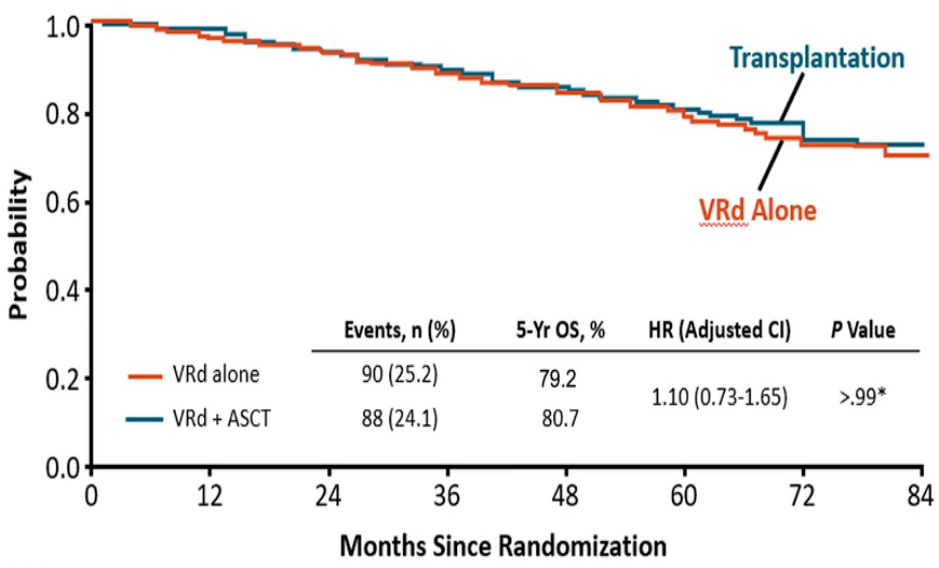
DETERMINATION

mFU, 76 months

PFS



OS



VRD + ASCT prolongs PFS compared to VRD alone

67.5 vs. 46.5 months
53% higher risk of progression/death with VRD

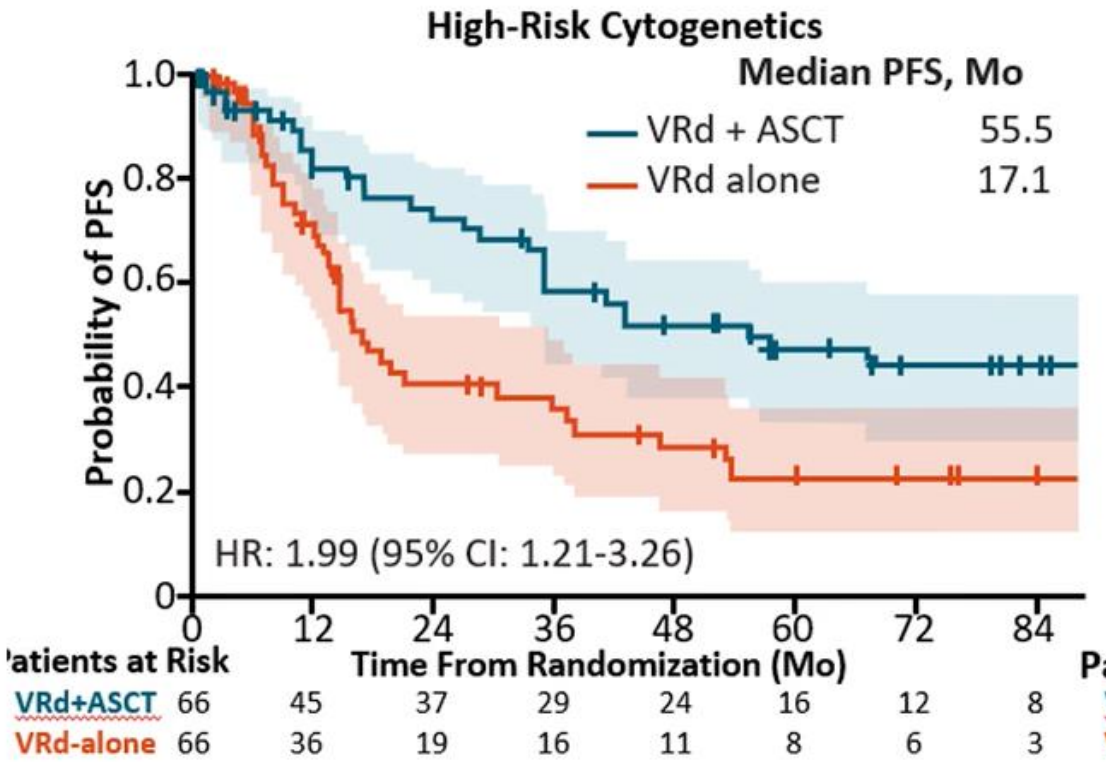
No OS benefit

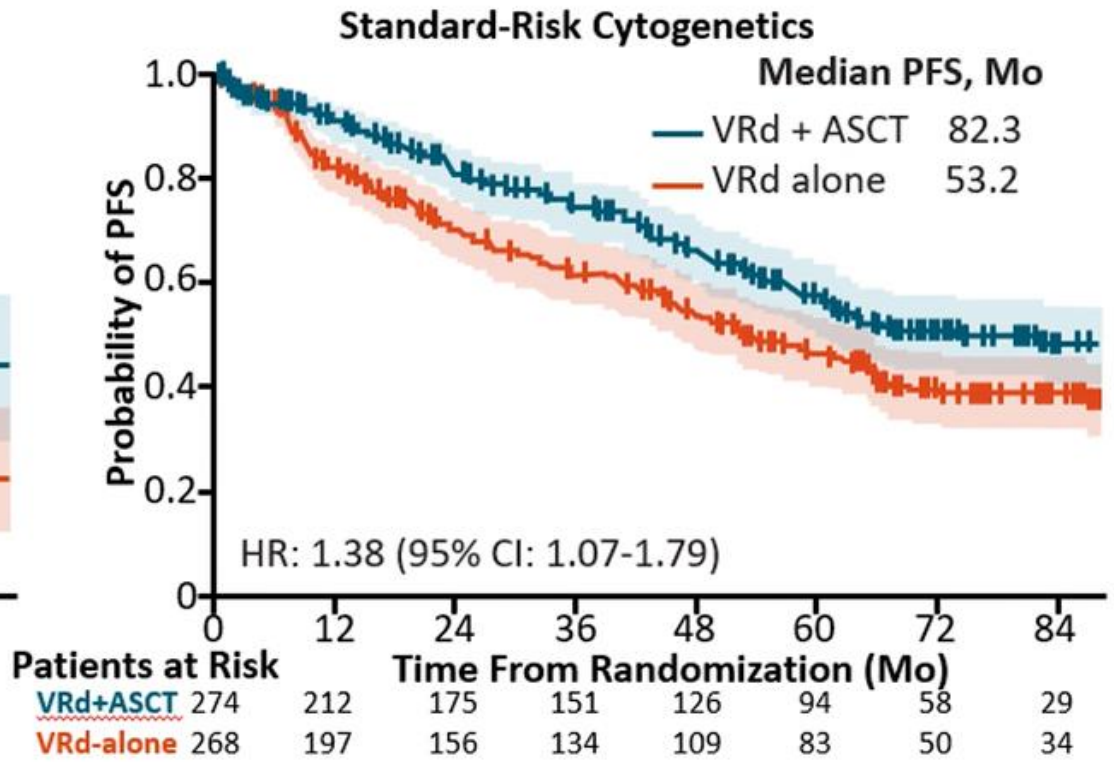
Richardson, NEJM 2022; EHA 2022; ASCO 2022

ASCT upfront or delayed

DETERMINATION

PFS by cytogenetic risk

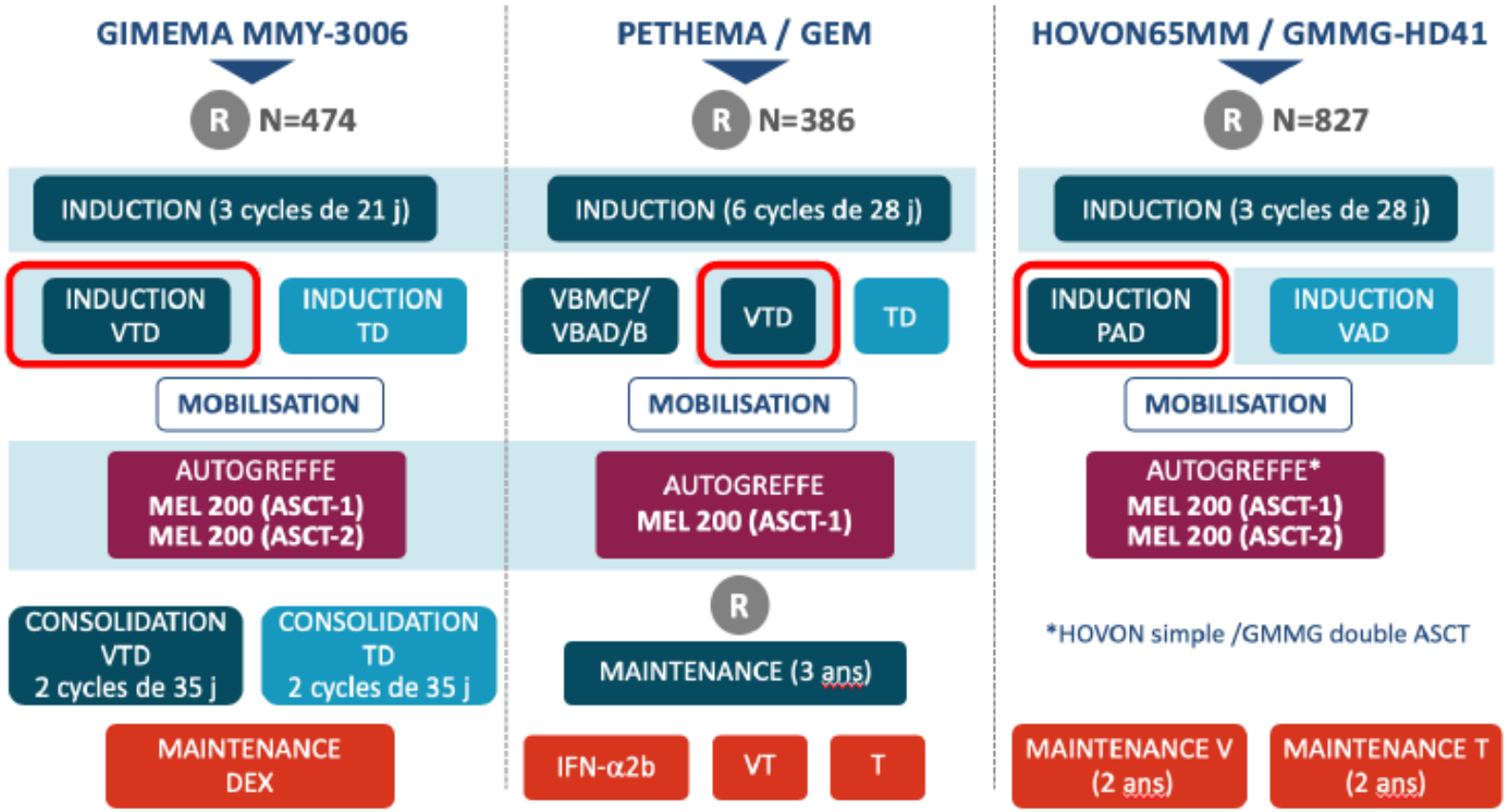




Richardson, NEJM 2022; EHA 2022; ASCO 2022

ASCT single or double

META-ANALYSIS



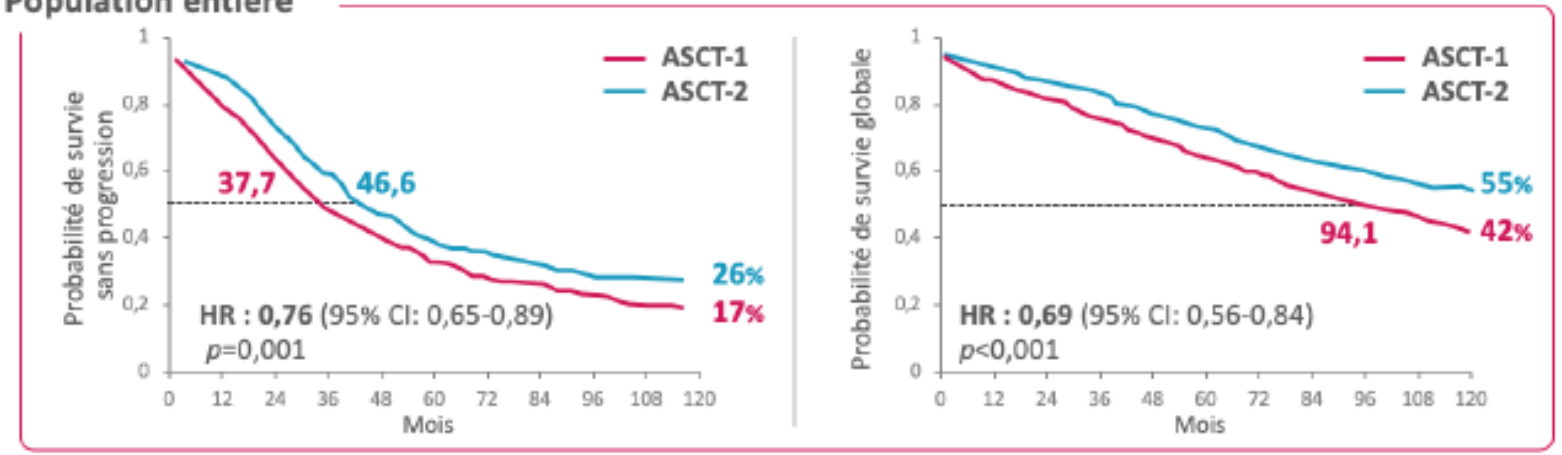
Cavo, ASH 2018

ASCT single or double

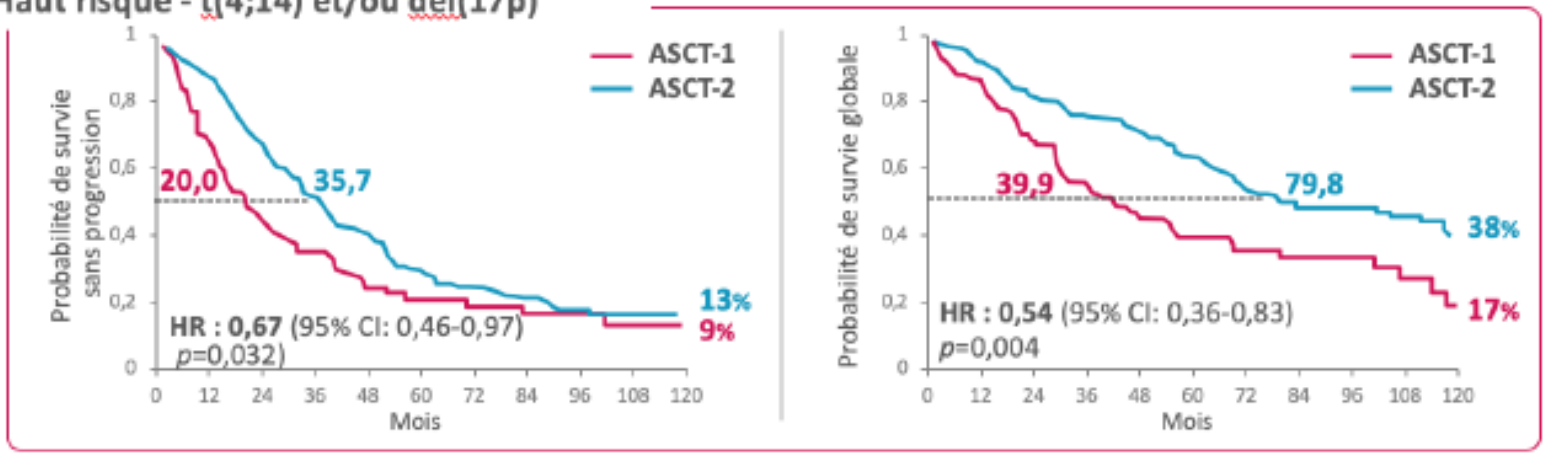
EMN02-HO95

n = 909

Population entière



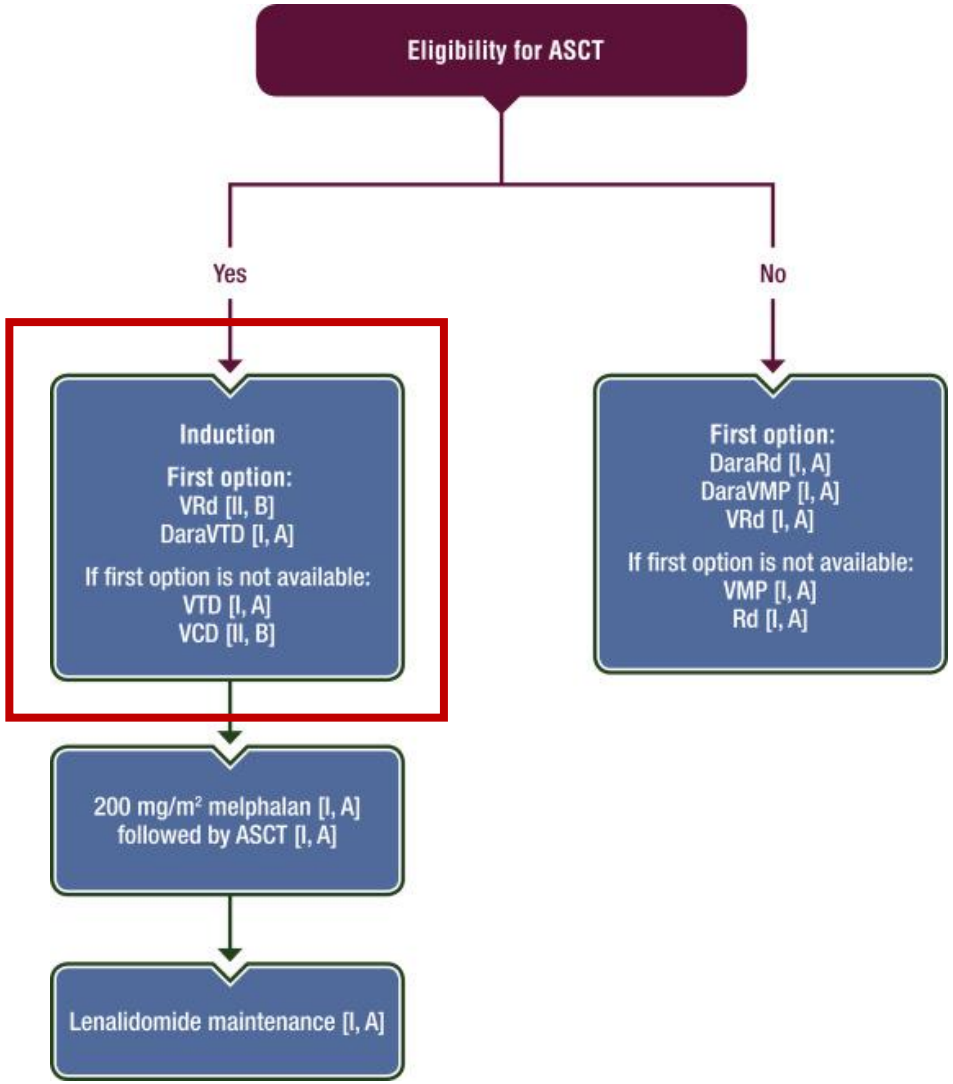
Haut risque - t(4;14) et/ou del(17p)



Benefit more prominent for HR diseases

Cavo, Lancet Oncol 2020

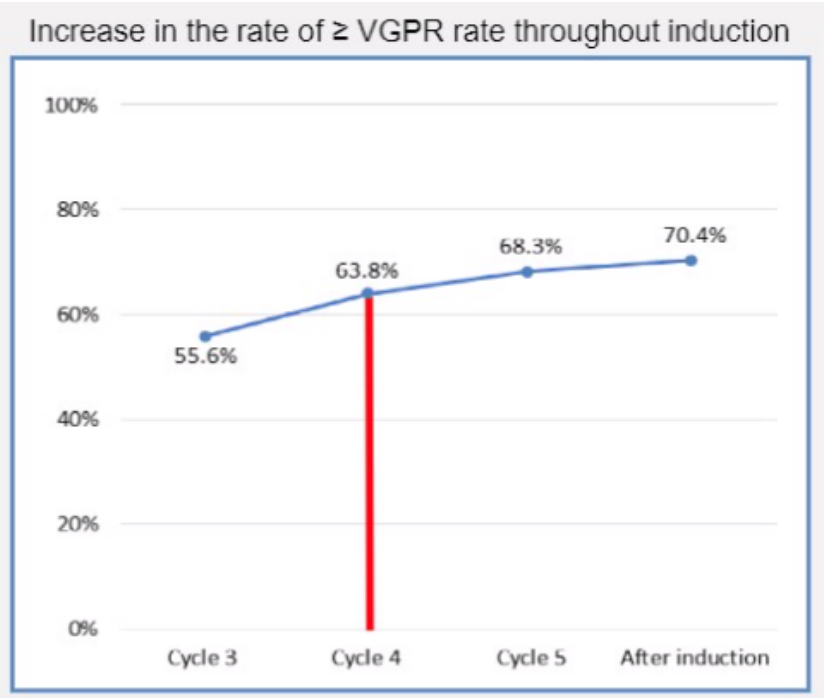
2021 ESMO guidelines – upfront therapy



Dimopoulos, Ann Oncol 2021

Induction | VRD vs. VTD | PETHEMA

		≥ VGPR	≥ CR	MRD neg (10^{-5})
VTD 3 cycles	*GIMEMA MMY3006* *M Cavo, Lancet 2010*	62 %	31 %	
VTD 4 cycles	IFM 2013-04 *P Moreau, Blood 2016*	66 %	13 %	
VTD 6 cycles	PETHEMA-GEM *L Rosinol, Blood 2012*	60 %	35 %	
VRD_{21} 3 cycles	IFM 2008 *M Roussel, JCO 2014*	58 %	23 %	16 %
VRD_{28} 6 cycles	GEM12MENOS65 *L Rosinol, ASH 2017*	68 %	39 %	34 %

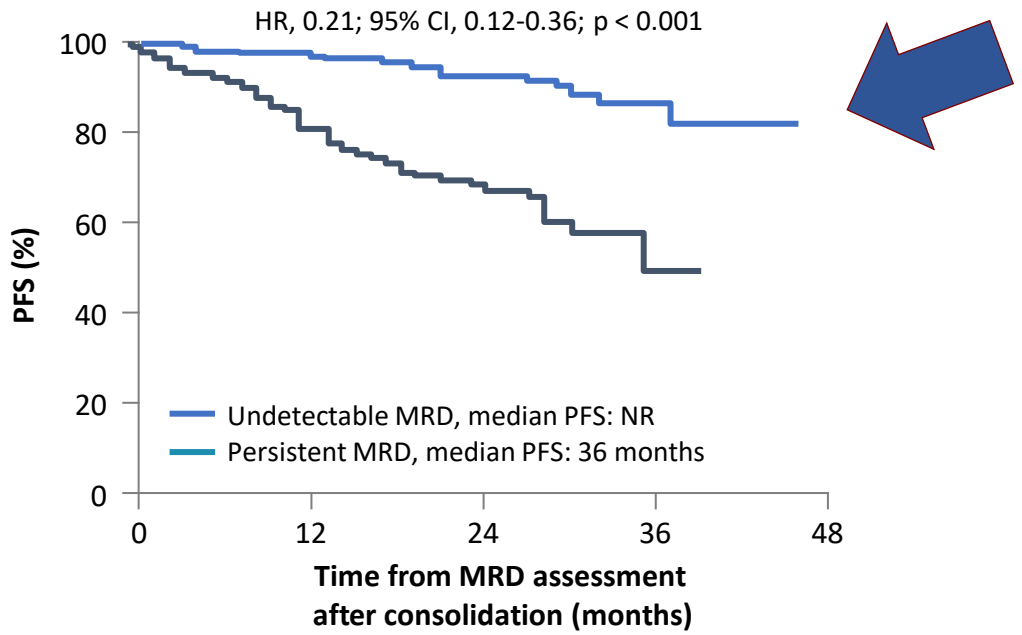


No head-to-head comparison between VTD and VRD

Rosinol, Blood 2019

Induction | VRD vs. VTD | PETHEMA

PFS according to MRD status

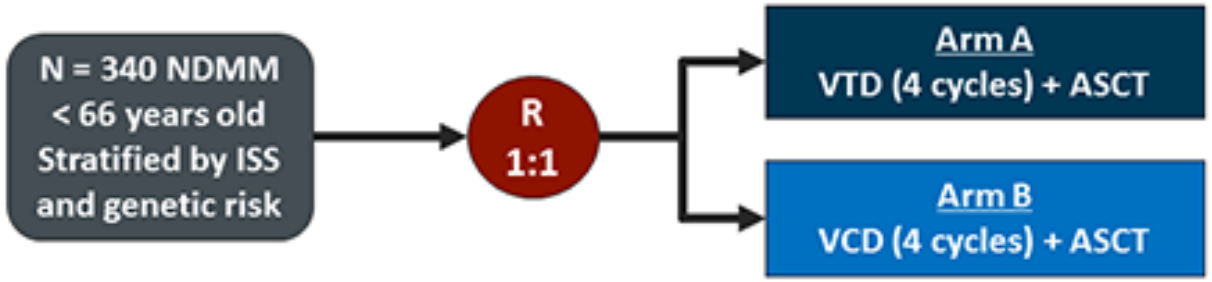


Number at risk					
Persistent MRD	152	128	64	7	0
Undetectable MRD	205	198	111	19	0

VRD is an attractive regimen

Rosinol, Blood 2019

Induction | VTD vs. VCD | IFM 2013-04



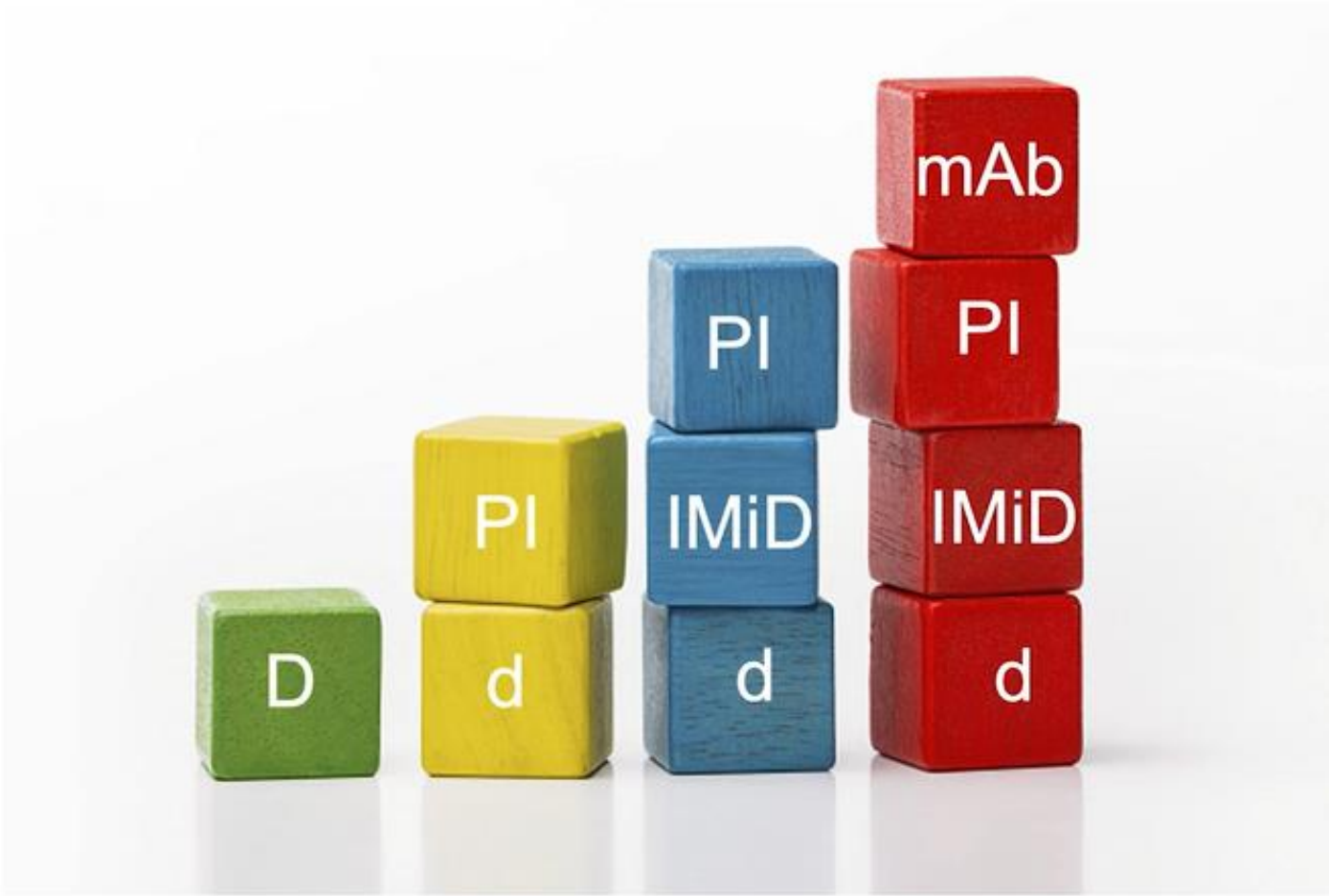
Efficacy, %	VTD + ASCT	VCD + ASCT
ORR	92.3	84
CR rate	10.7	9.5
VGPR	66.7	56.2

Safety (≥ Grade 3), %		
Peripheral neuropathy	4	2.2
Neutropenia	11.9	22.5

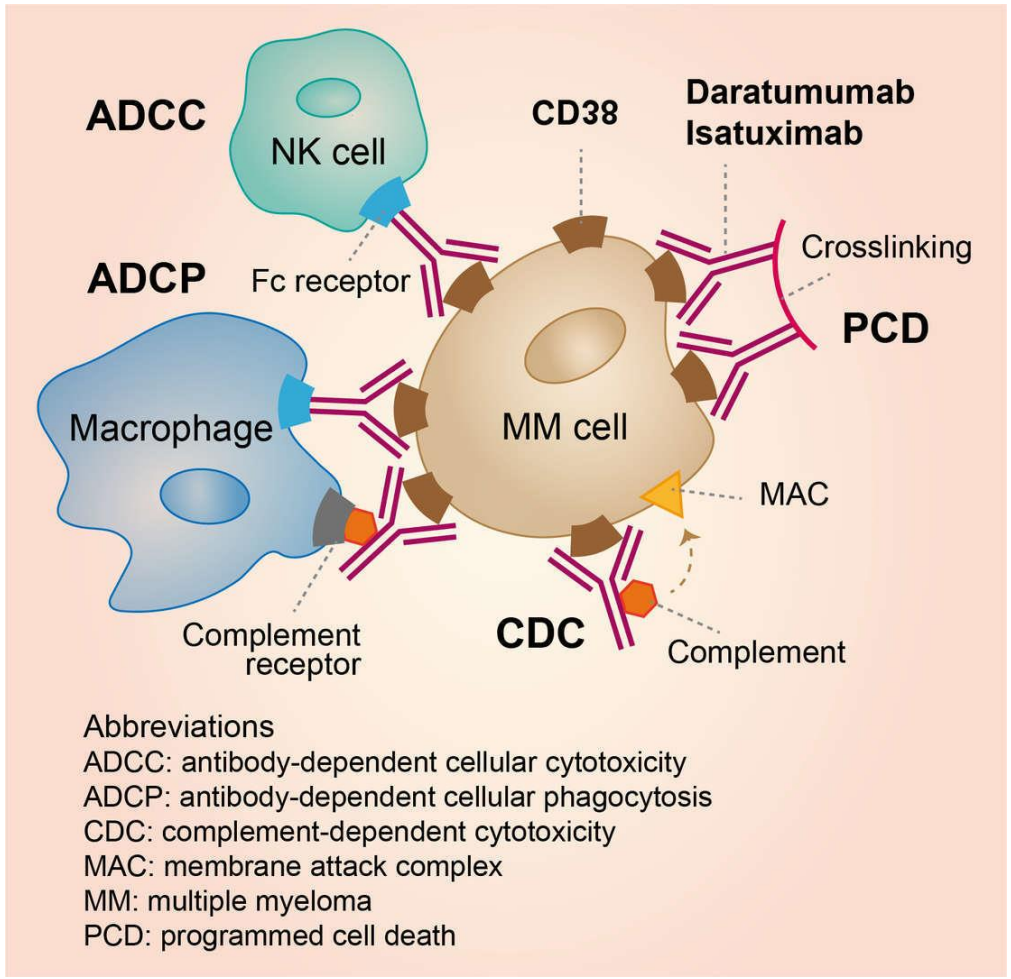
VTD is better than VCD

Moreau, Blood 2016

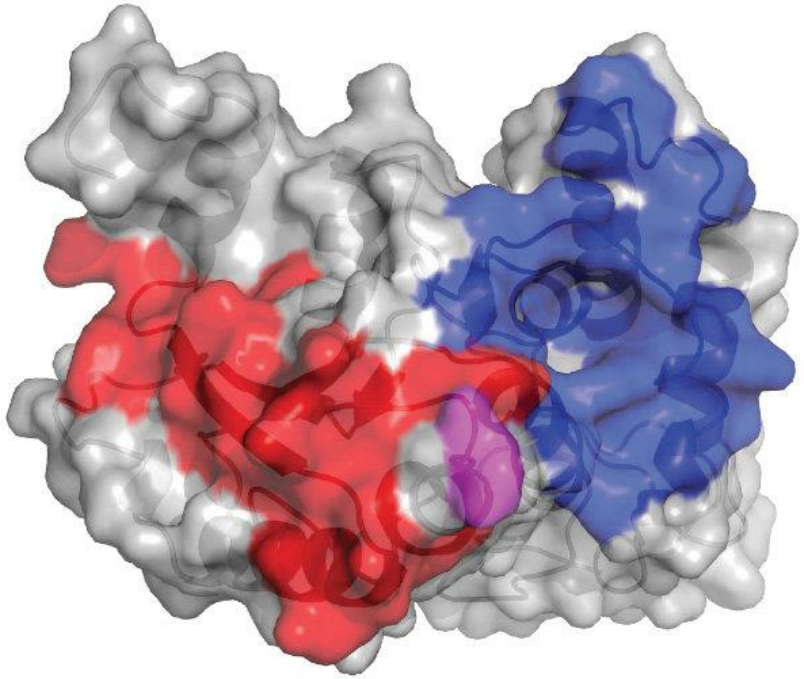
Quadruplets induction regimens



Anti-CD38 monoclonal antibodies



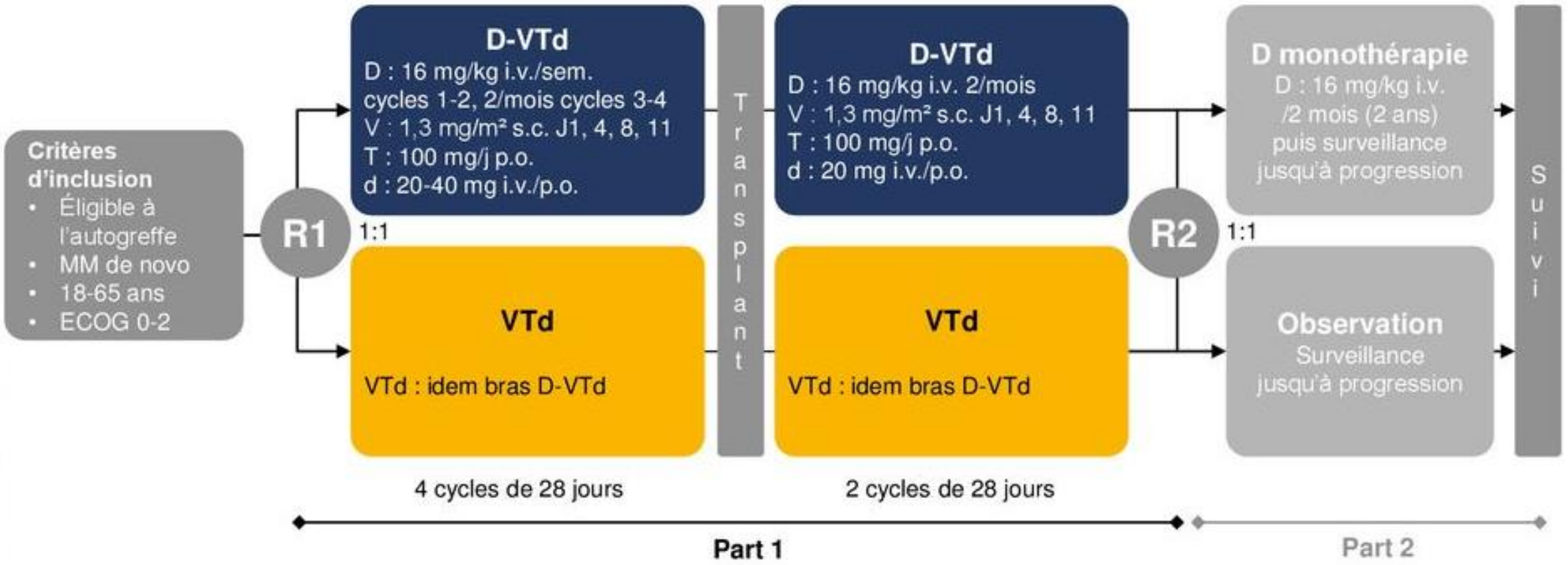
Abbreviations
ADCC: antibody-dependent cellular cytotoxicity
ADCP: antibody-dependent cellular phagocytosis
CDC: complement-dependent cytotoxicity
MAC: membrane attack complex
MM: multiple myeloma
PCD: programmed cell death



daratumumab - isatuximab

CASSIOPEIA

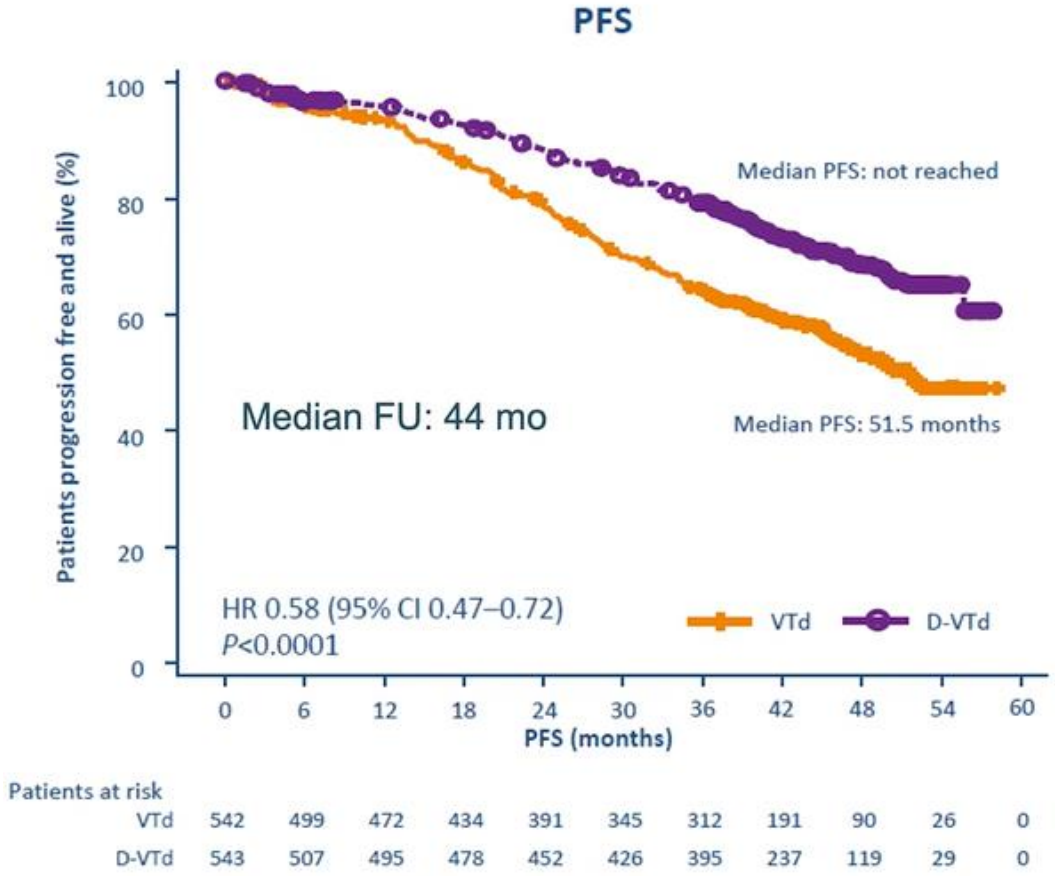
Dara-VTD in induction/maintenance

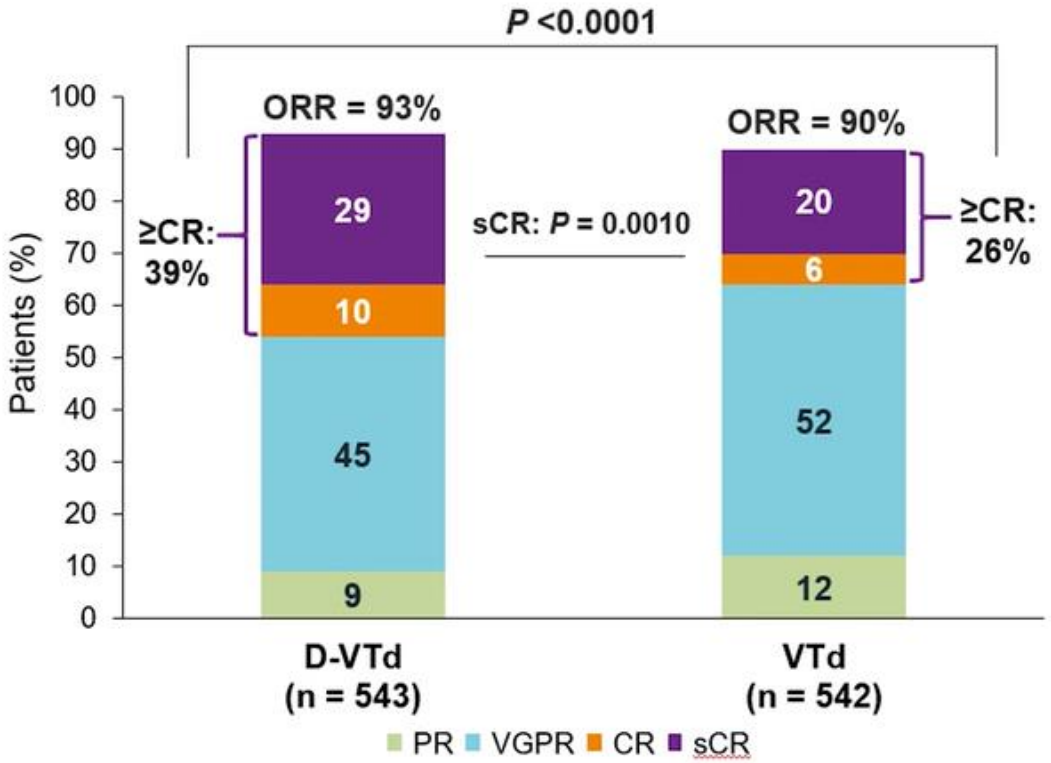


Moreau, Lancet Oncol 2019; Moreau, Lancet Oncol 2021

CASSIOPEIA

Dara-VTD vs. VTD in induction

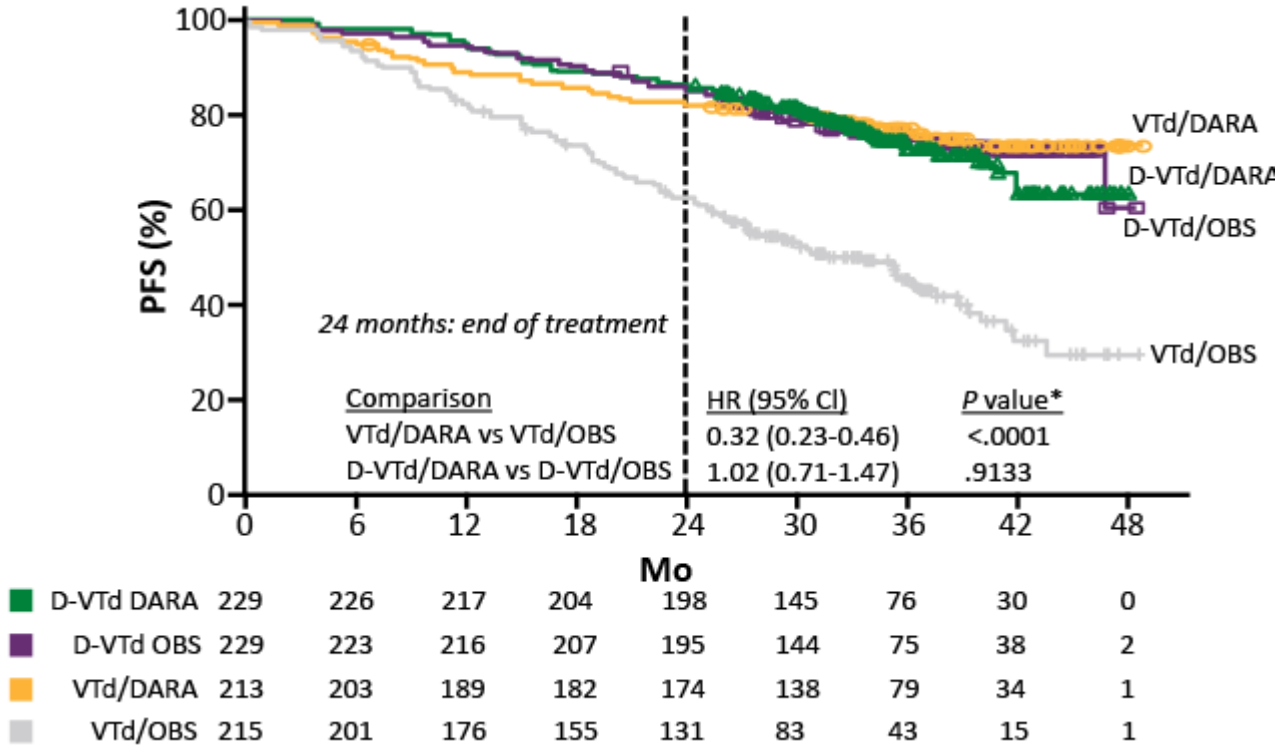




Moreau, Lancet Oncol 2019

CASSIOPEIA

Dara-VTD in induction/maintenance



- ✓ **Significant interaction between maintenance and consolidation prespecified analysis**
- ✓ **PFS benefit for VTS/dara vs. VTD/observation**
- ✓ **Comparable PFS for dara-VTD vs. dara-VTD/observation**

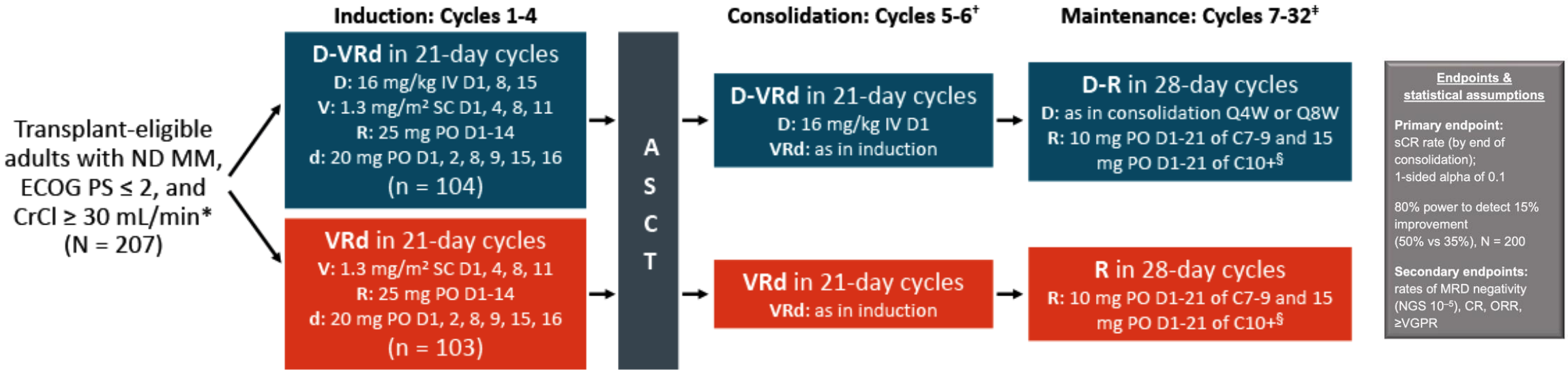
Dara significantly improves PFS

Moreau, Lancet Oncol 2021

GRIFFIN

Dara-VRD in induction/maintenance

Phase II



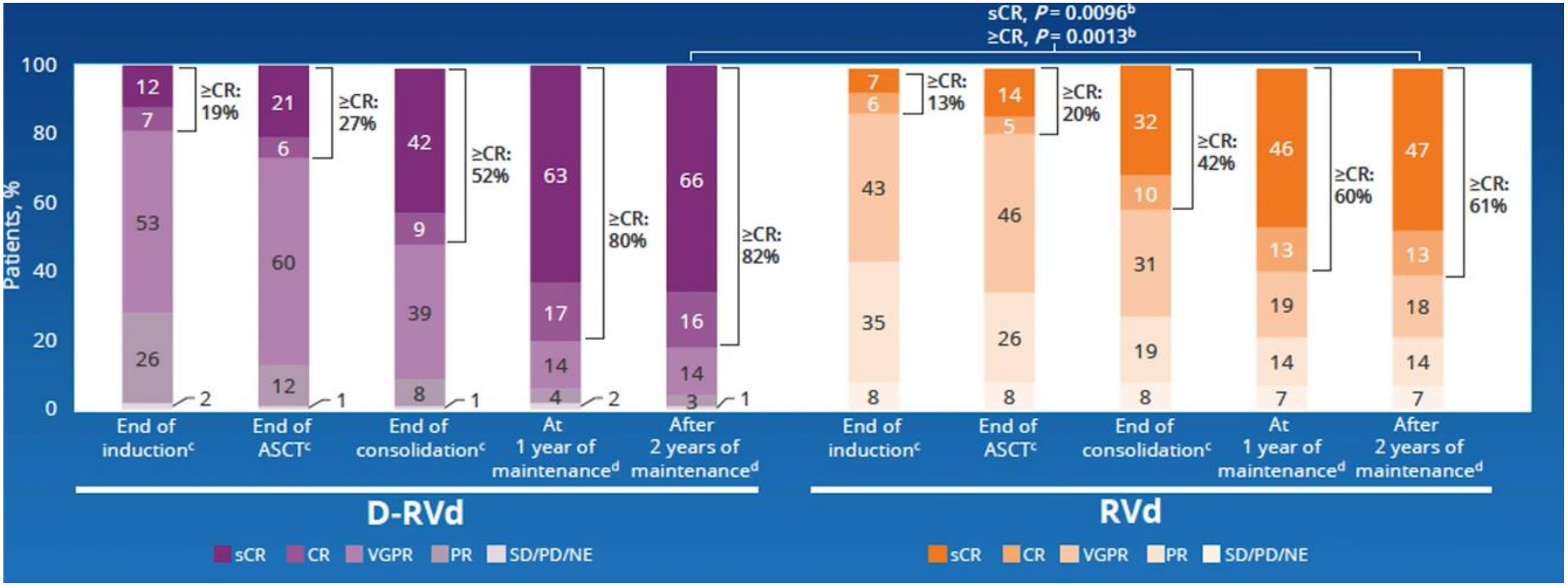
*Lenalidomide dose was adjusted in patients with CrCl ≤ 50 mL/min. †Consolidation began 60-100 days after transplantation. ‡Patients completing maintenance phase were permitted to continue single-agent lenalidomide. §15 mg administered only If tolerable.

Voorhees, Blood 2020; Laubach, ASH 2021, #79

GRIFFIN

Dara-VRD in induction/maintenance

RR after 24 months maintenance

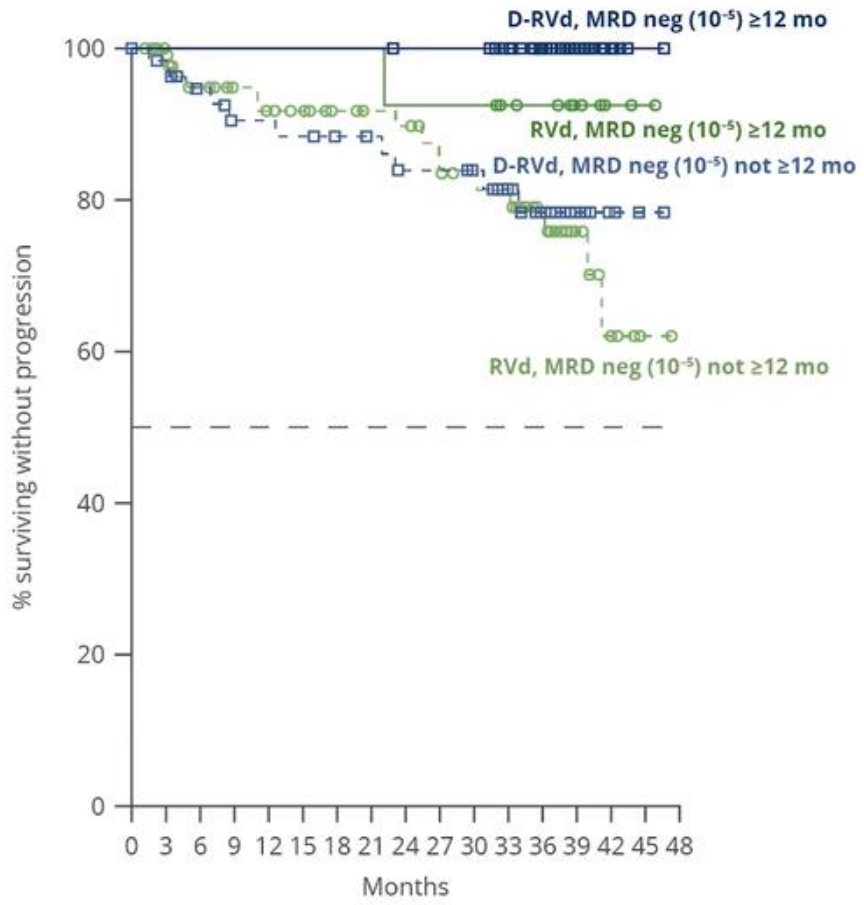


GRIFFIN

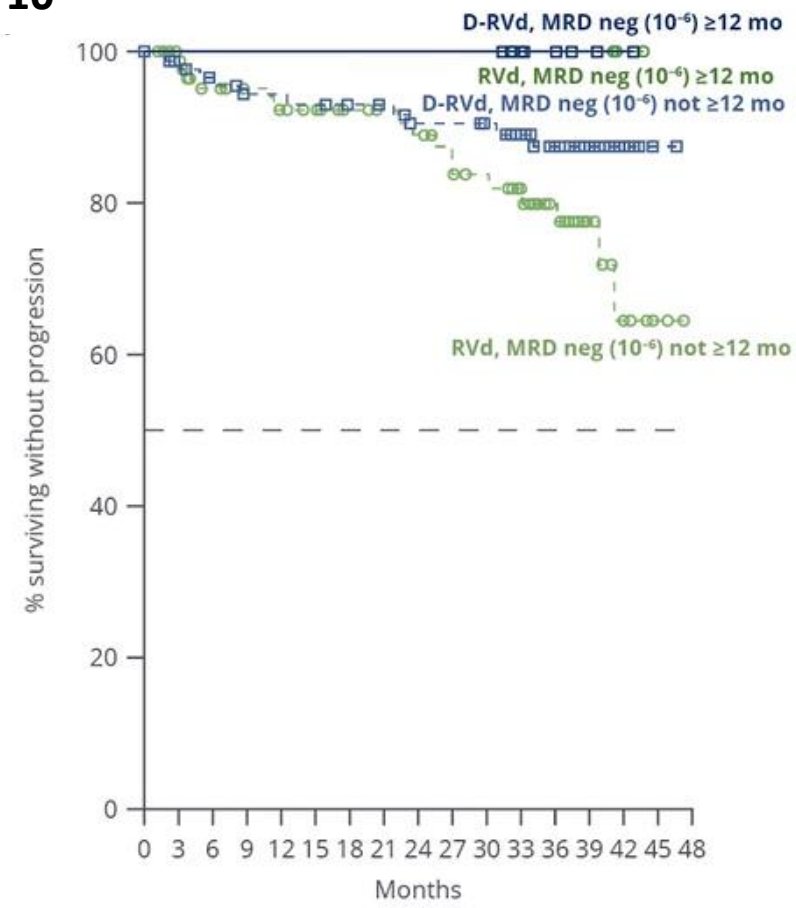
Dara-VRD in induction/maintenance

PFS by durable MRD-lasting > 12 months

10^{-5}



10^{-6}

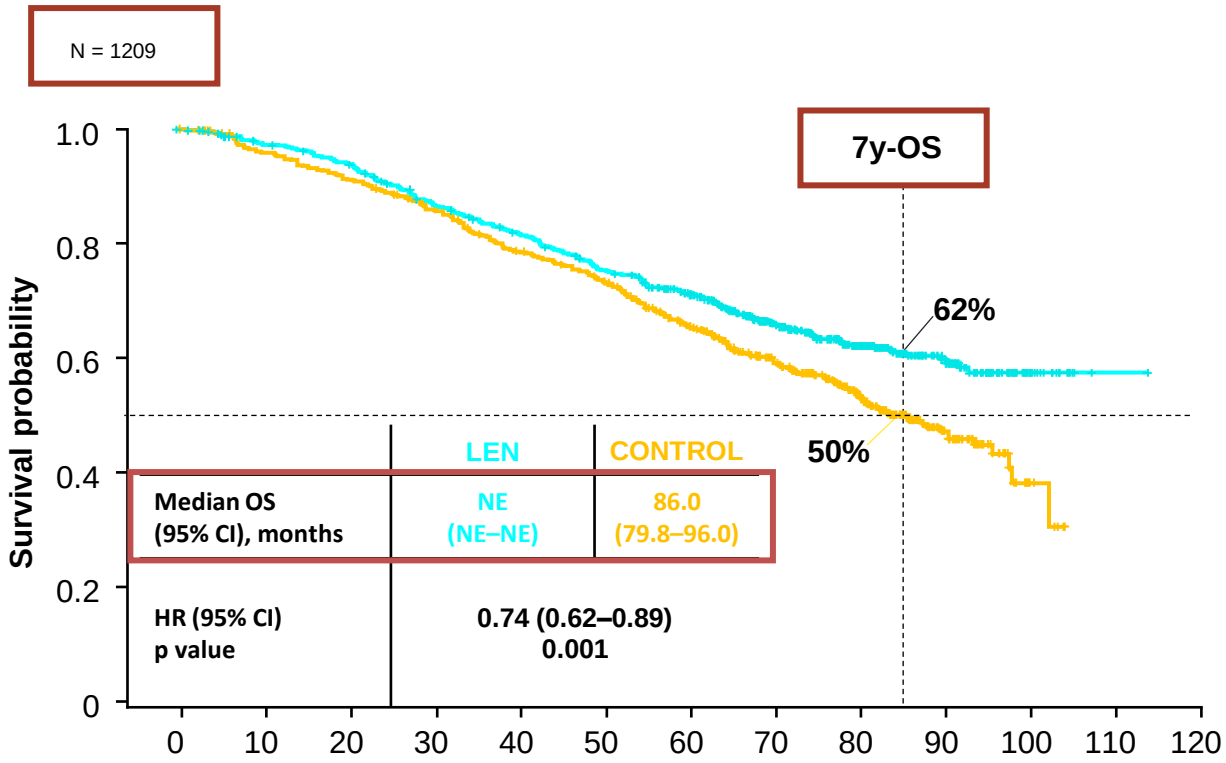


Rodrigues, ASCO 2022, #8011

Maintenance

Long term of less intensive treatment given in order to prolong response duration, PFS and OS and suppress MRD

Maintenance | Lenalidomide | Meta-analysis



26% reduction in risk of death, estimated 2.5y increase in mOS

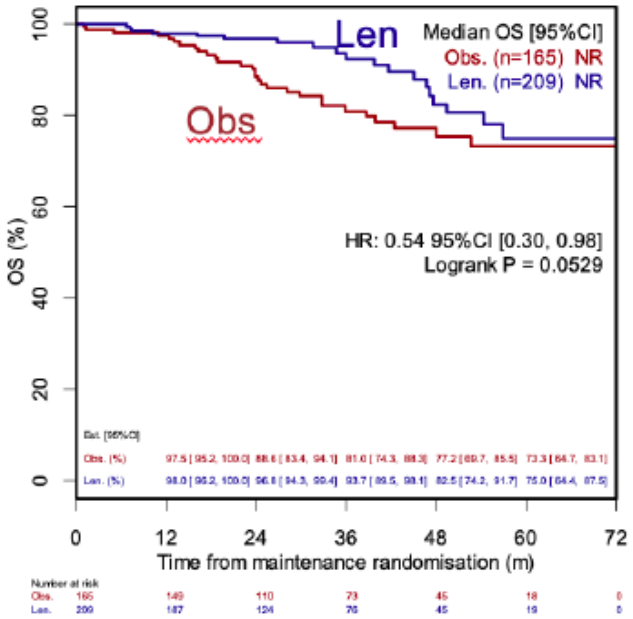
No benefit in patients with ISS 3 or HR cytogenetics

McCarthy, JCO 2017

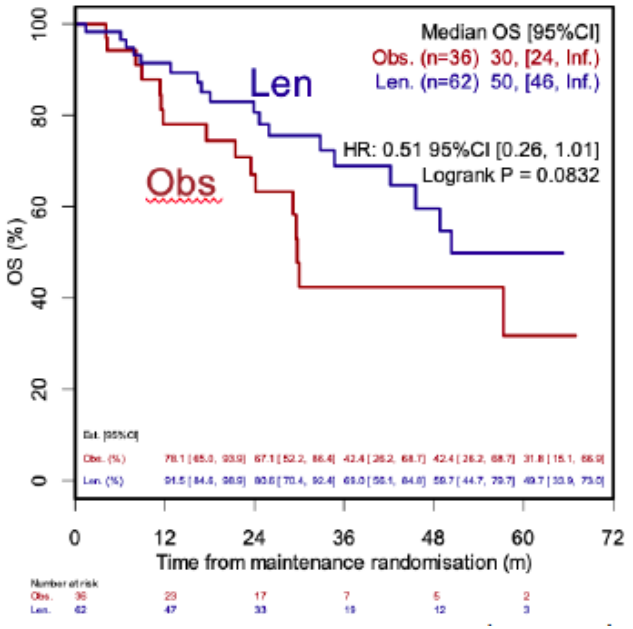
Maintenance	Lenalidomide	MMIX

Median FU, 30.6 m
n = 1.970, 1247 TE

t(4;14) and/or del(17p) absent: HR 0.54



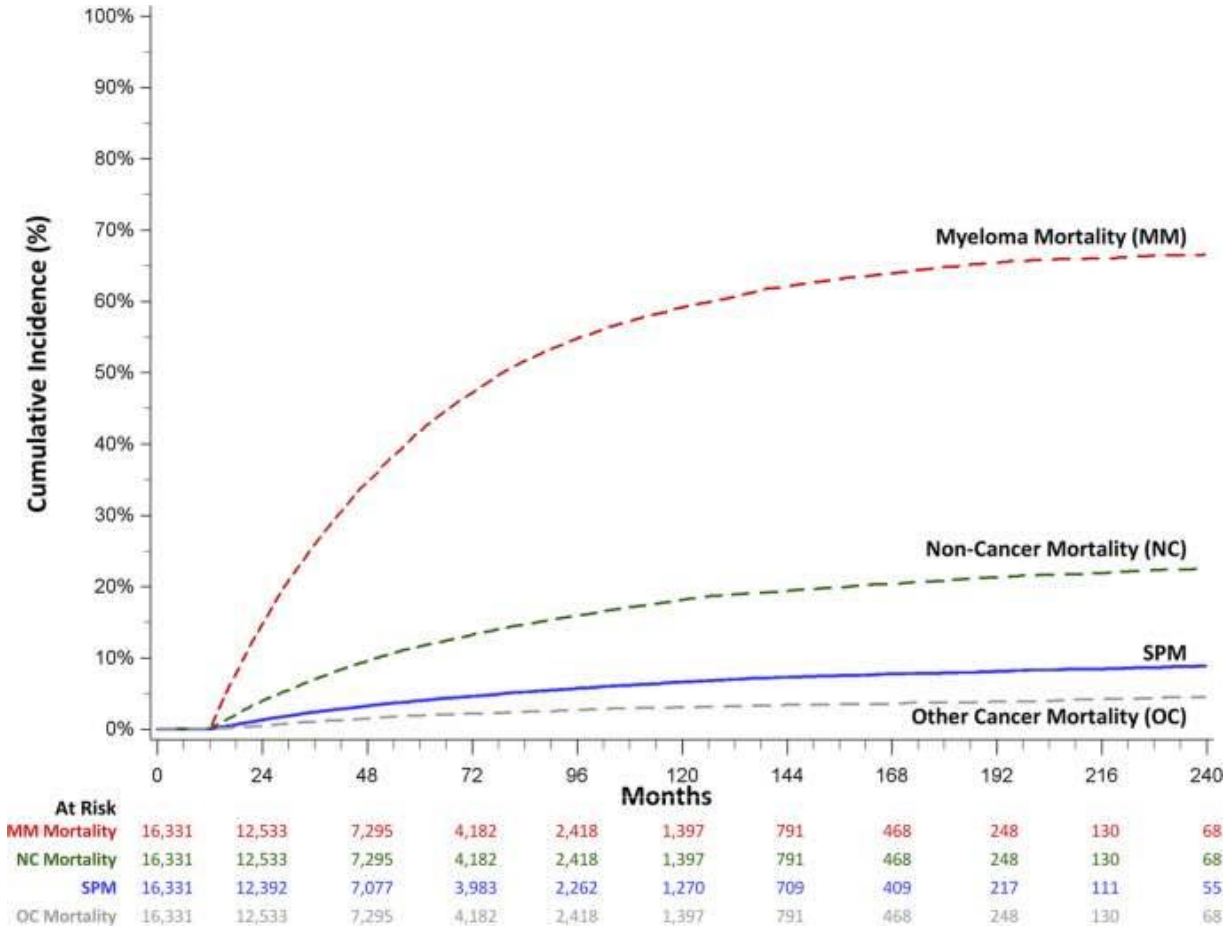
t(4;14) and/or del(17p) present: HR 0.51



Upgrade of response rates and PFS (30 to 50 months)
Benefit in OS irrespective of cytogenetic risk

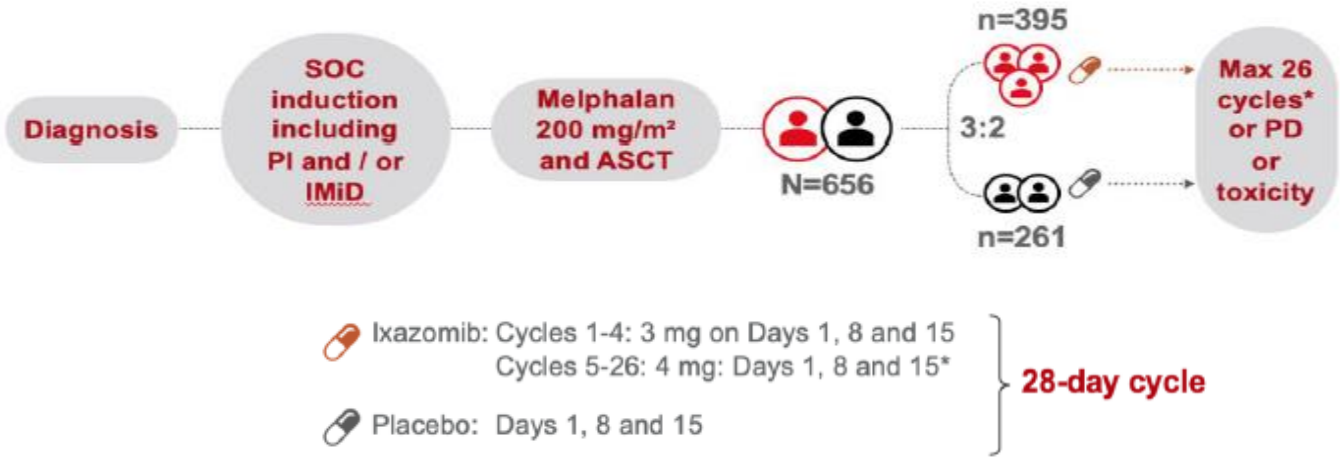
Jackson, ASH 2017, # 436

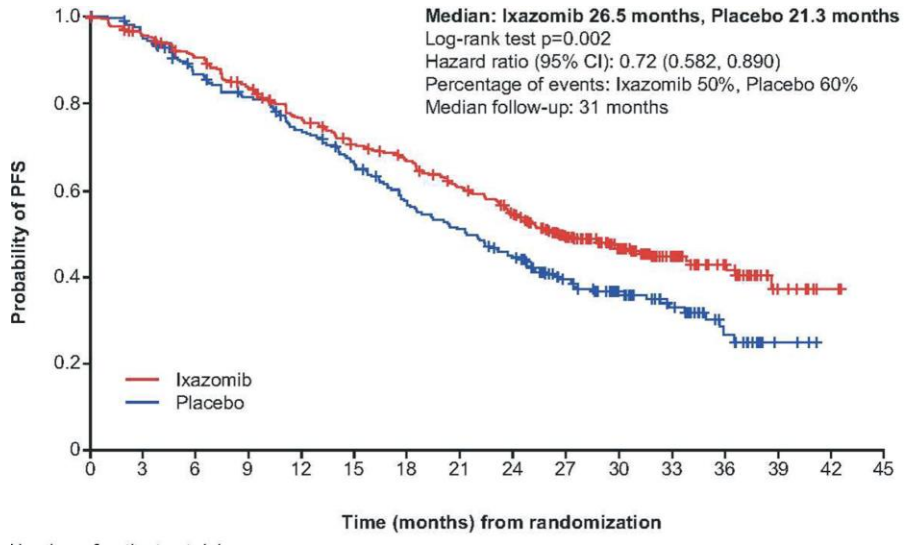
Maintenance	Lenalidomide	**SPM**



Rosenberg, Blood Cancer J 2021

Maintenance | Ixazomib | TOURMALINE 3





Ixazomib associated to 5 months increase in mPFS

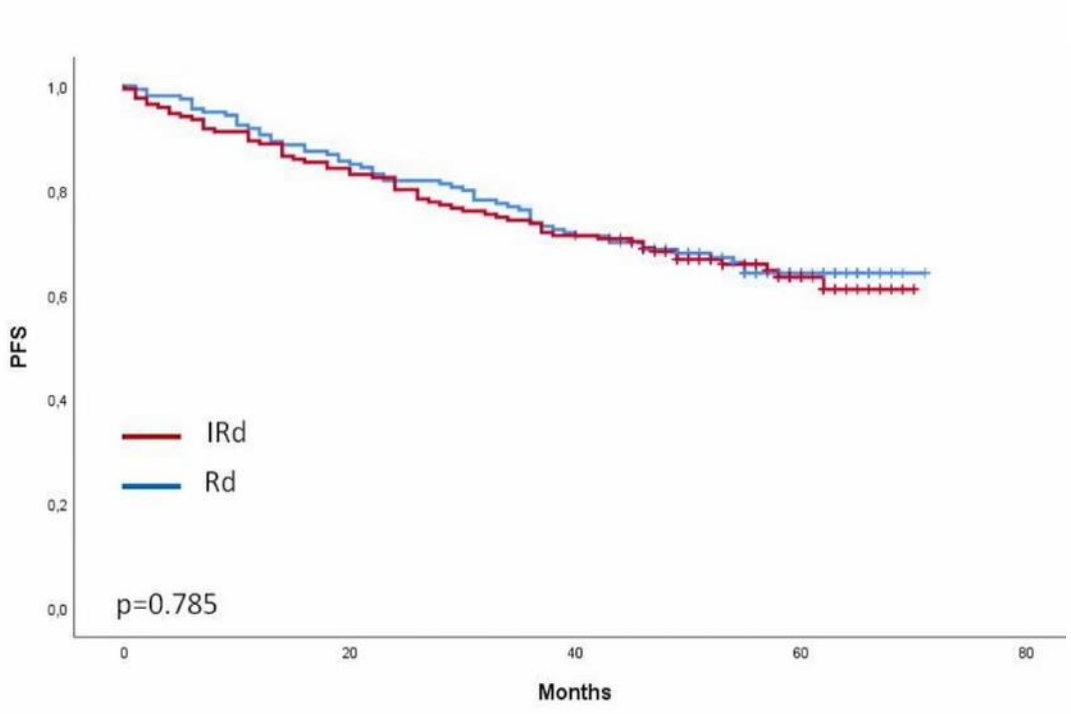
Dimopoulos, Lancet 2019

Maintenance

Combination of PI and LEN

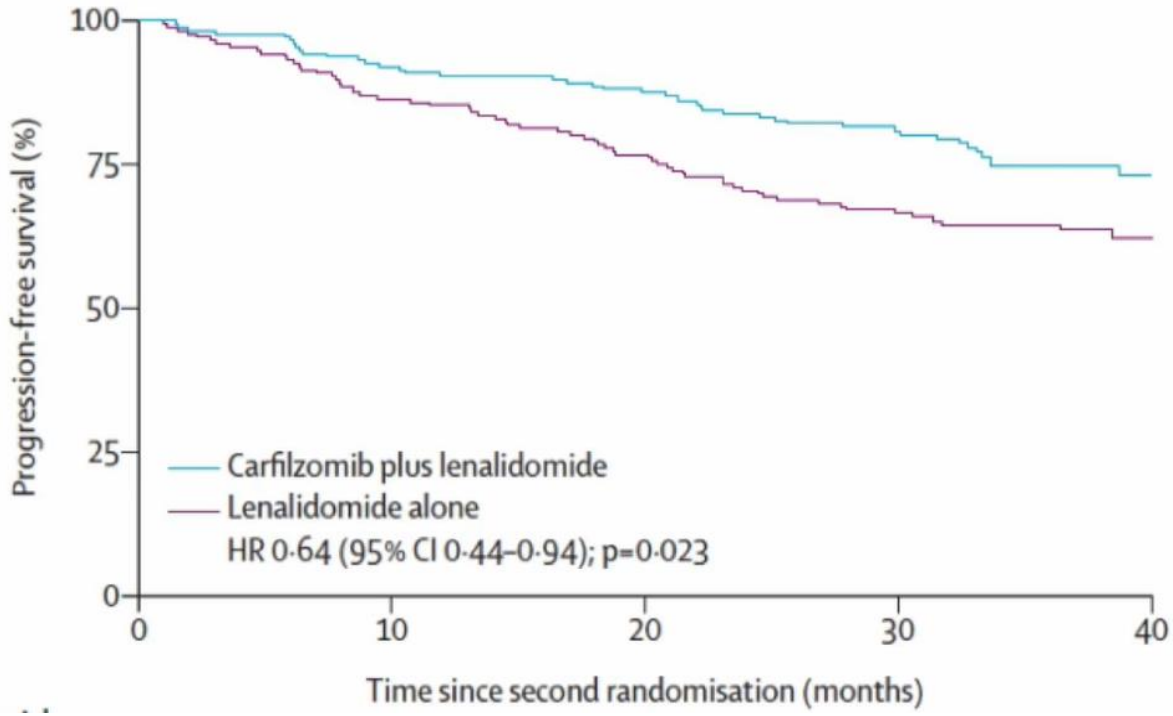
GEM2014MAIN

IRd vs. Rd



FORTE

KR vs. R

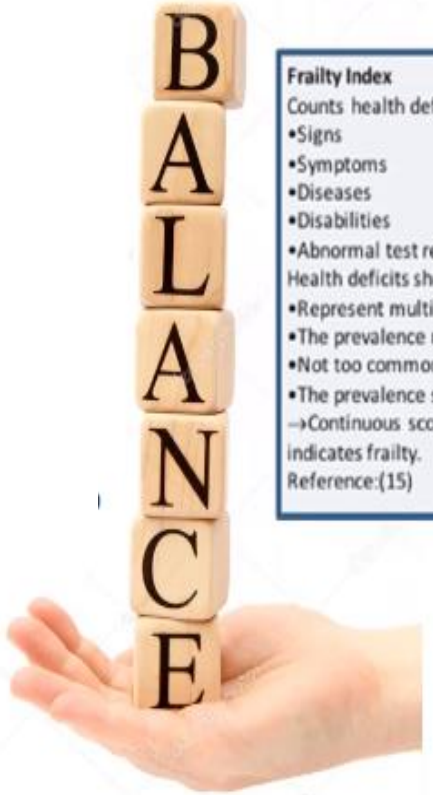


Rosinol, ASH 2021, #466; Gay, Lancet Oncol 2021

Agenda

1	Generalities
2	SMM
3	Principles of therapy
4	Transplant eligible patients
5	Transplant non eligible patients
6	High risk disease
7	MRD to define therapy

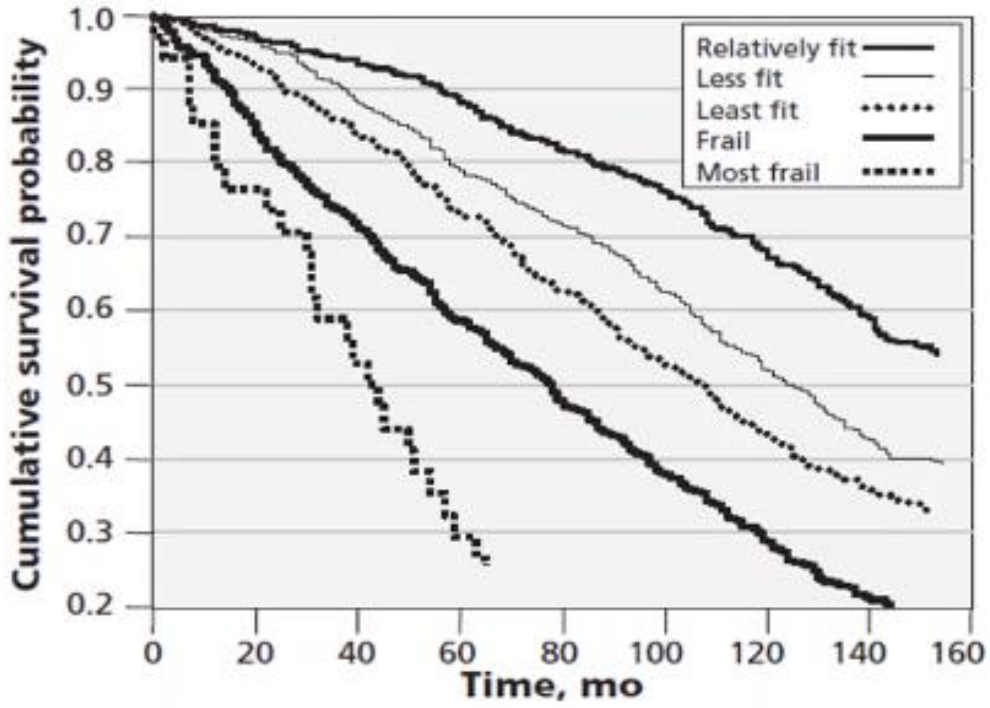
Transplant non eligible MM patients



Frailty Index
Counts health deficits (at least 30):
- Signs
- Symptoms
- Diseases
- Disabilities
- Abnormal test results

Health deficits should meet these criteria:
- Represent multiple domains of functioning or multiple organ systems
- The prevalence must increase with age
- Not too common before the age of 65 years
- The prevalence should not be lowers than 1%

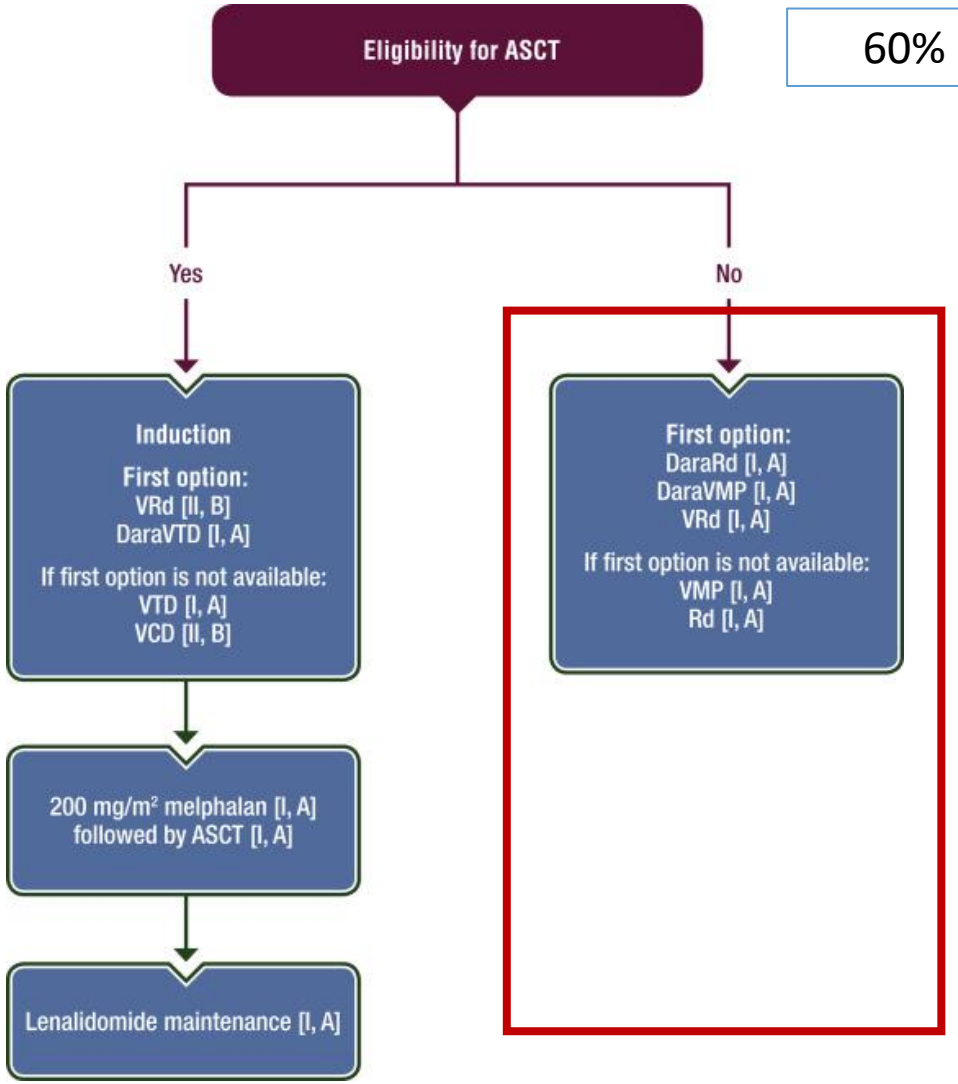
→Continuous score between 0 and 1, higher scores indicate higher degree of frailty and a cut off of 0.25 indicates frailty.
Reference:(15)



Geriatric assessment

Fried, J Gerontol 2004; Cook, Leukemia 2020; Young, Br J Hematol 2016

2021 ESMO guidelines – upfront therapy



60%

No ASCT

UNTIL PROGRESSION

Dimopoulos, Ann Oncol 2021

MAIA

DRd, the current SOC for NTE patients

Key eligibility criteria

- TIE NDMM
- ECOG PS score 0-2
- CrCl ≥30 mL/min

1:1 Randomization

D-Rd (n = 369)

Daratumumab: 16 mg/kg IV
QW Cycles 1-2, Q2W Cycles 3-6, then Q4W thereafter until PD
Lenalidomide: 25 mg PO
Days 1-21 until PD
Dexamethasone[a,b]: 40 mg PO or IV
Days 1, 8, 15, 22 until PD

Rd (n = 368)

Lenalidomide: 25 mg PO Days 1-21 until PD
Dexamethasone[b]: 40 mg PO
Days 1, 8, 15, 22 until PD

Primary endpoint

- PFS

Key secondary endpoints

- ORR
- ≥CR rate
- MRD (NGS; 10^{-5})
- OS

Cycle: 28 days

Stratification factors

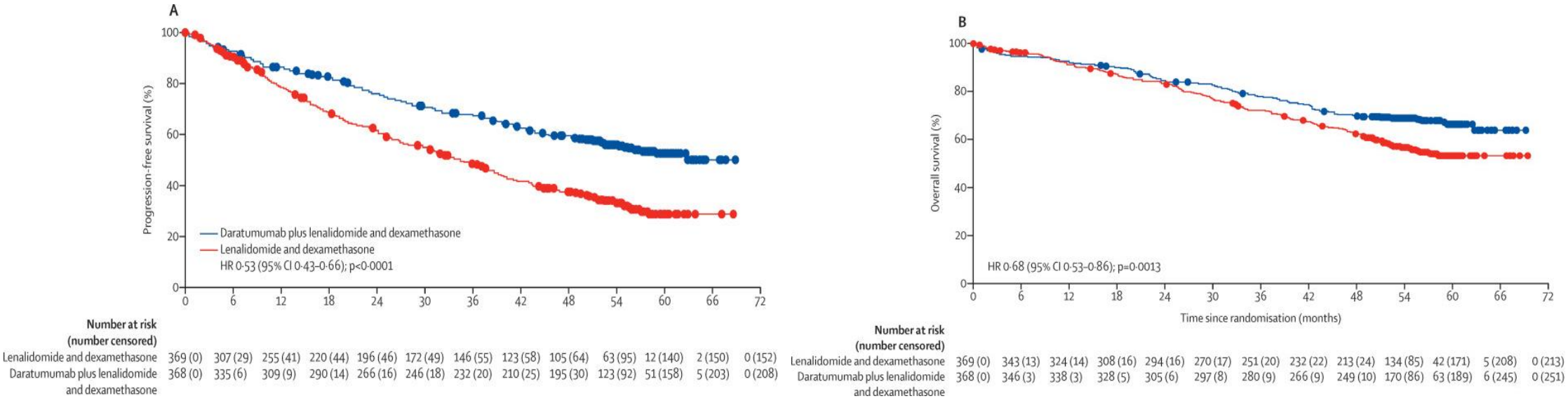
- ISS (I vs II vs III)
- Region (NA vs other)
- Age (<75 vs ≥75 years)

Facon, Lancet Oncol 2021

MAIA

Dara-Rd vs. Rd

5 years follow-up



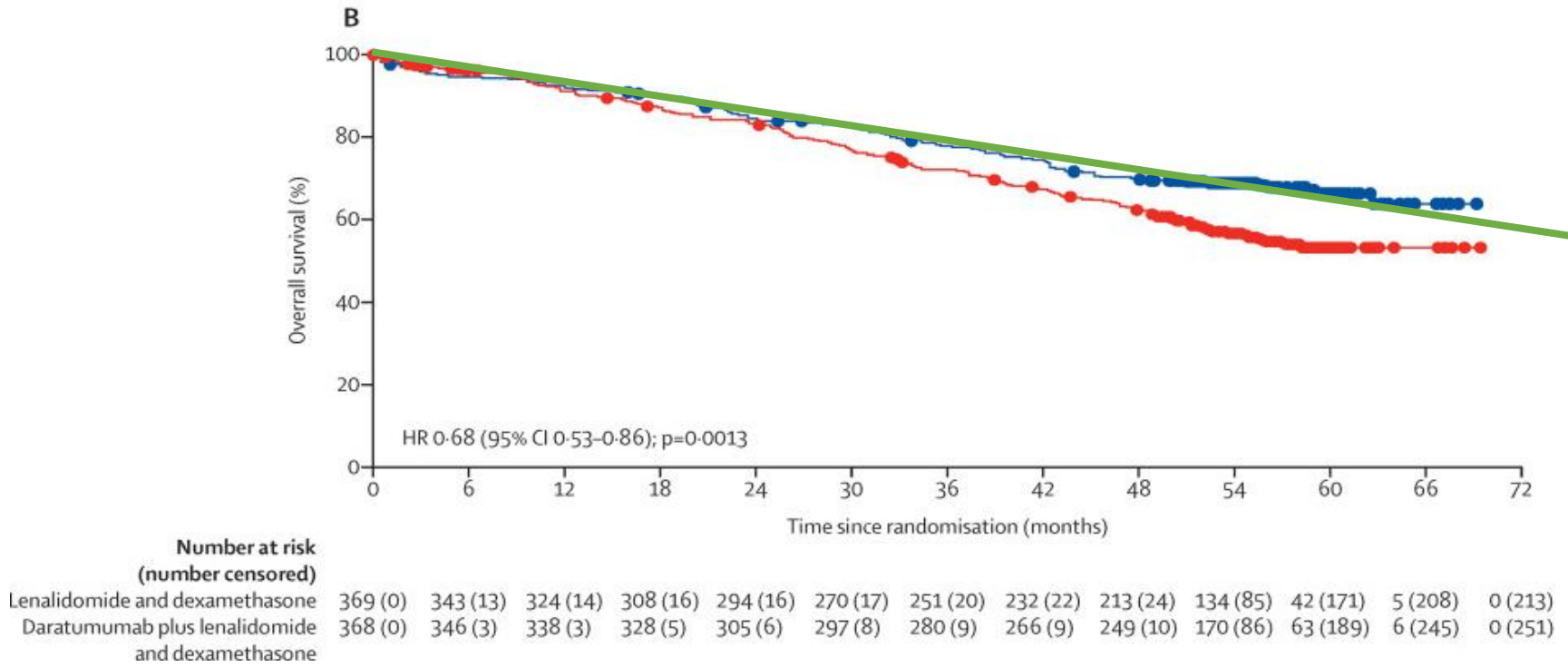
47% reduction in the risk of progression, with a mPFS not reached

32% reduction in the risk of death

Facon, Lancet Oncol 2021

MAIA

Dara-Rd vs. Rd



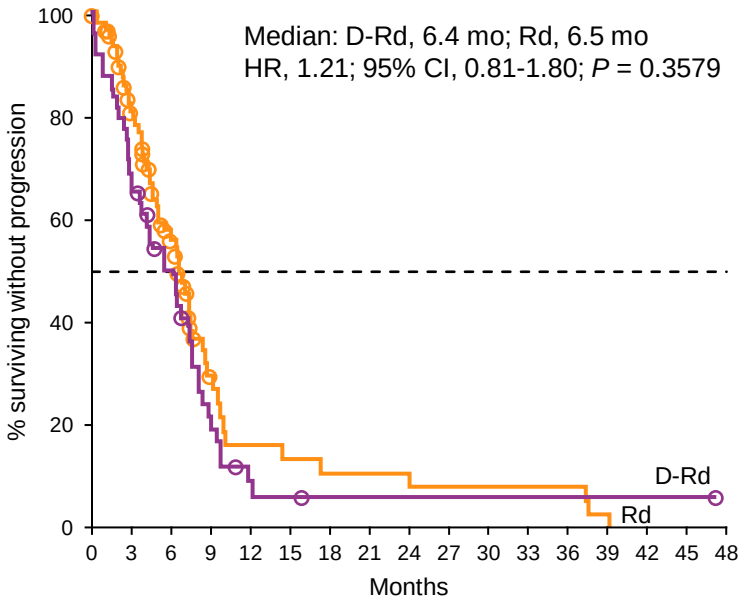
Median OS, 8 years ?

Facon, Lancet Oncol 2021

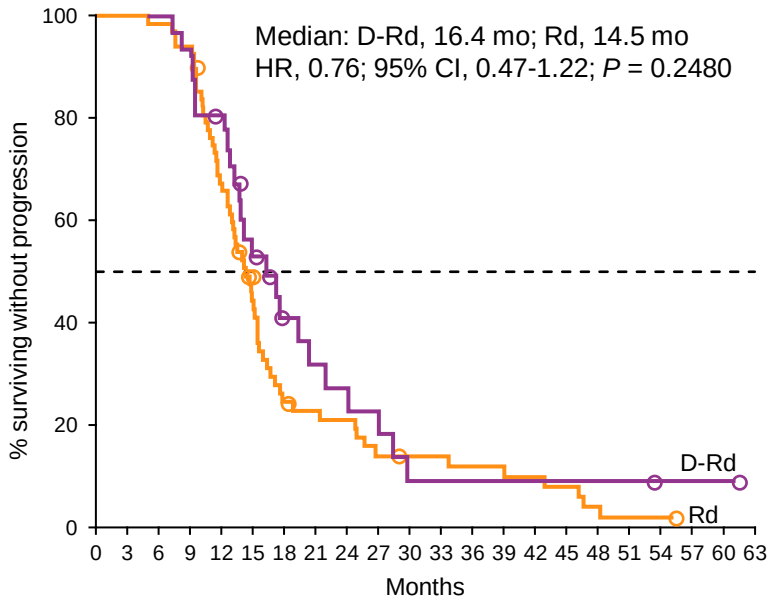
MAIA

Dara-Rd, continuous or fixed duration

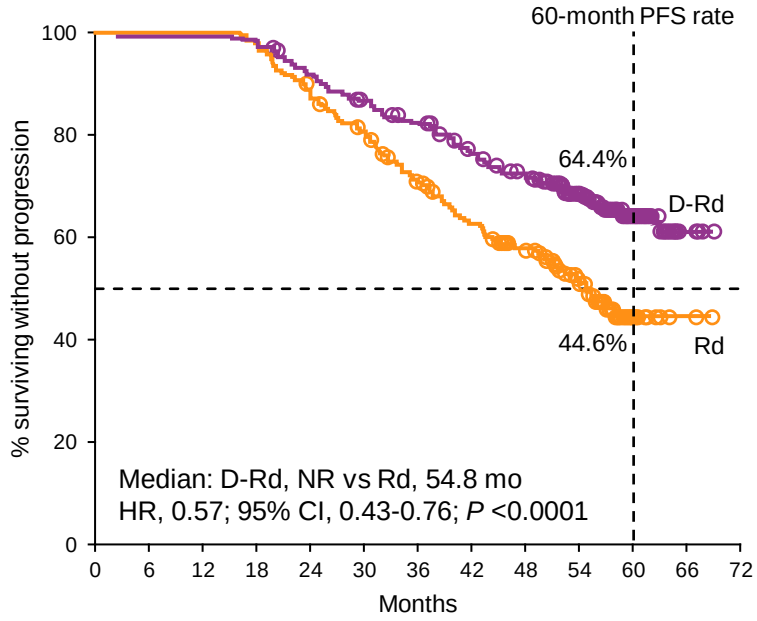
Patients who received <9 months of treatment



Patients who received ≥9<18 months of treatment



Patients who received ≥18 months of treatment

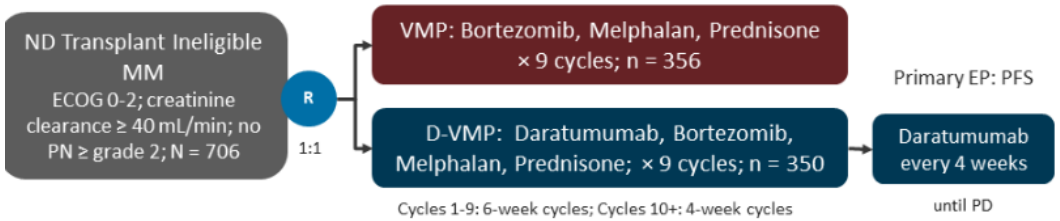


Improvement of PFS in patients treated >18 months
43% reduction in risk of progression/death

Facon, Lancet Oncol 2021

ALCYONE

Dara-VMP vs. VMP

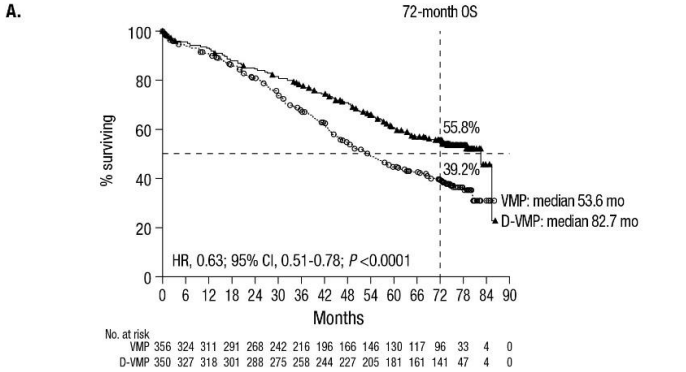


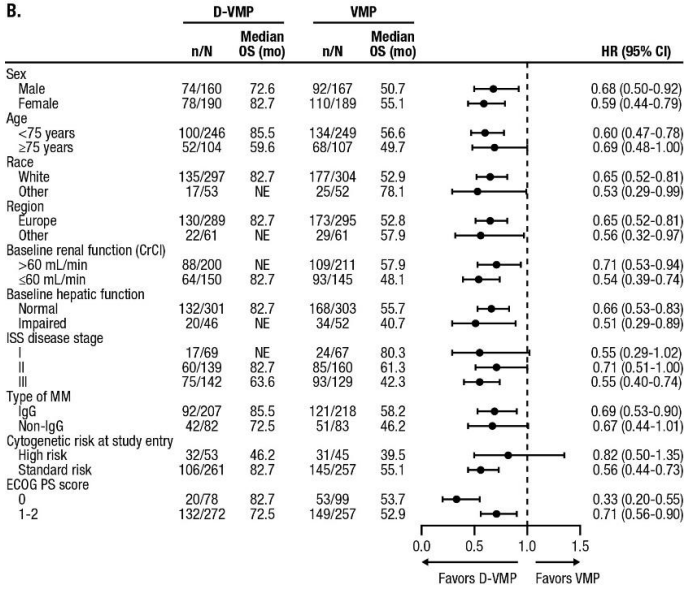
Bortezomib: 1.3 mg/m² SC (Cycle 1: twice weekly; Cycle 2-9: once weekly); melphalan: 9 mg/m² PO, d 1-4; prednisone: 60 mg/m² PO d 1-4; daratumumab: 16 mg/kg IV (cycle 1: once weekly; cycle 2-9: q 3 wk; 10+, q 4wk)

	D-VMP		VMP	
	< 75 years n = 246	≥ 75 years n = 104	< 75 years n = 249	≥ 75 years n = 107
MRD Negative (10^{-5}), %	22	24	6	8
Toxicity	Similar			

- **Dara-VMP prolong OS** versus VMP alone in TNE NDMM
- Median OS reached in both arms for the first time after a mFU of >6 years
- Dara-VMP 4-fold higher MRD-negativity rate and a **5-fold higher ≥12-month sustained MRD-negativity** rate versus VMP alone

Figure: Overall survival (A) and subgroup analysis of overall survival (B) with D-VMP and VMP in the intent-to-treat population.



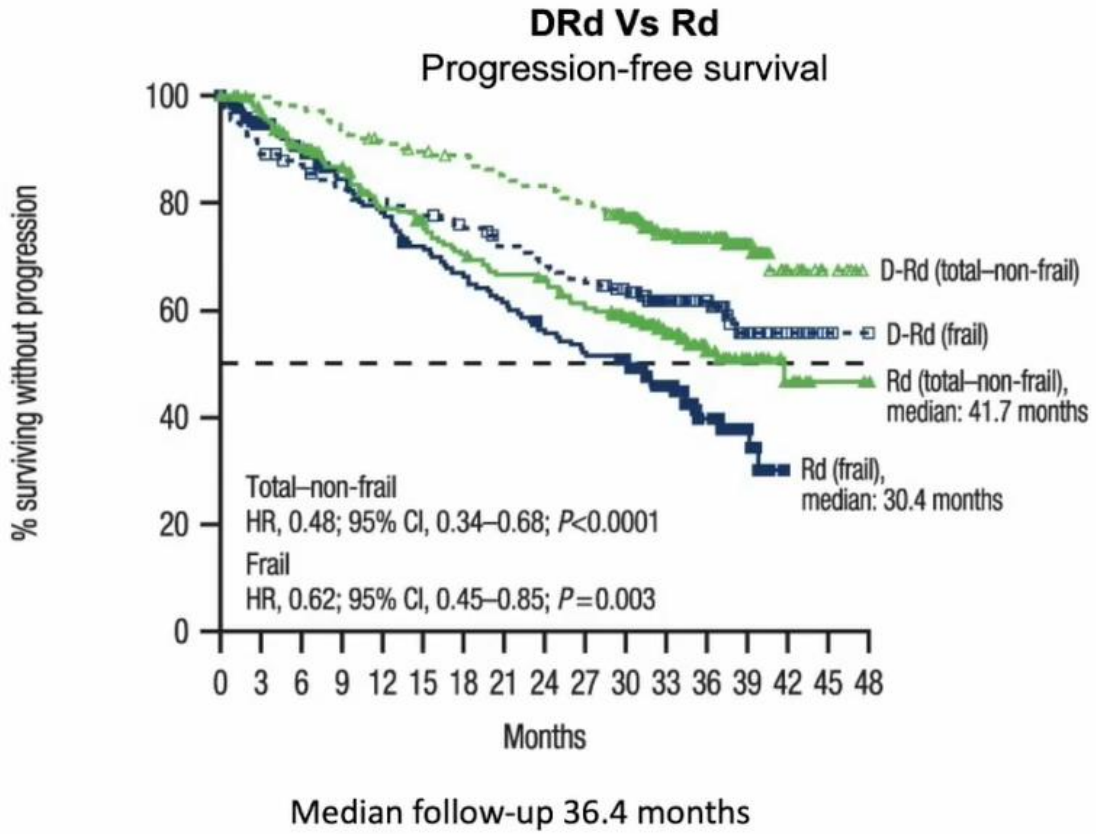


D-VMP, daratumumab plus bortezomib/melphalan/prednisone; VMP, bortezomib/melphalan/prednisone; OS, overall survival; HR, hazard ratio; CI, confidence interval; NE, not estimable; CrCl, creatinine clearance; ISS, International Staging System; MM, multiple myeloma; ECOG PS, Eastern Cooperative Oncology Group performance status.

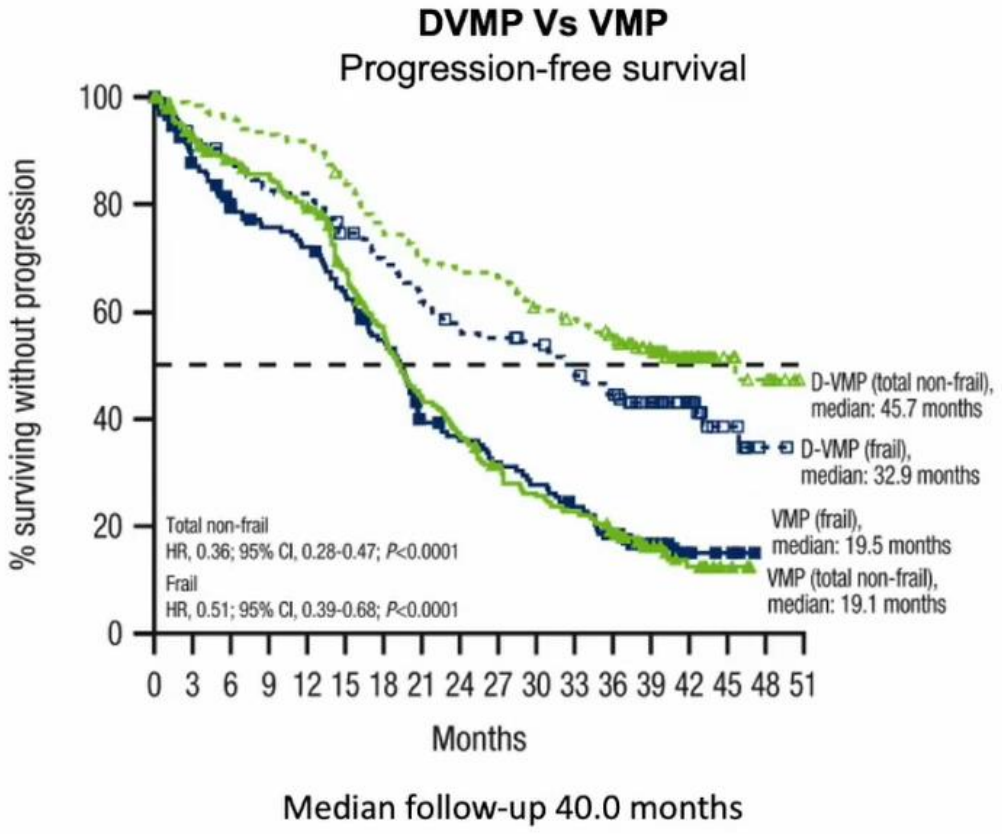
Mateos, ASH 2022, #4561

PFS by FRAILTY

Dara-Rd or Dara-VMP



Median follow-up 36.4 months



Median follow-up 40.0 months

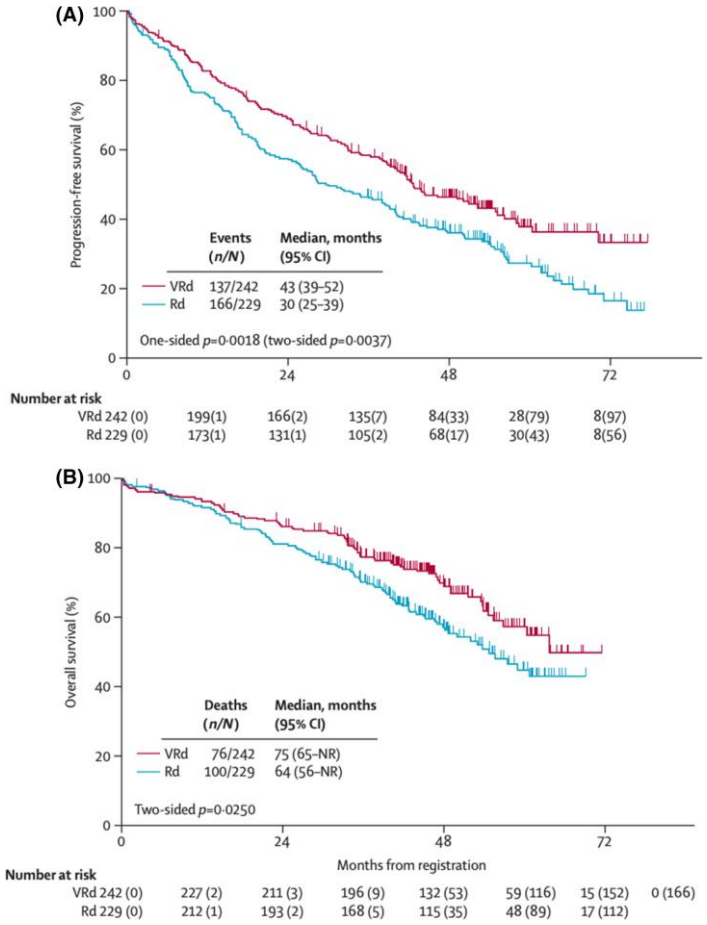
Facon, Lancet Oncol 2021; Mateos, Clin Lymph Myeloma Leuk 2021

NTE patients

Other options

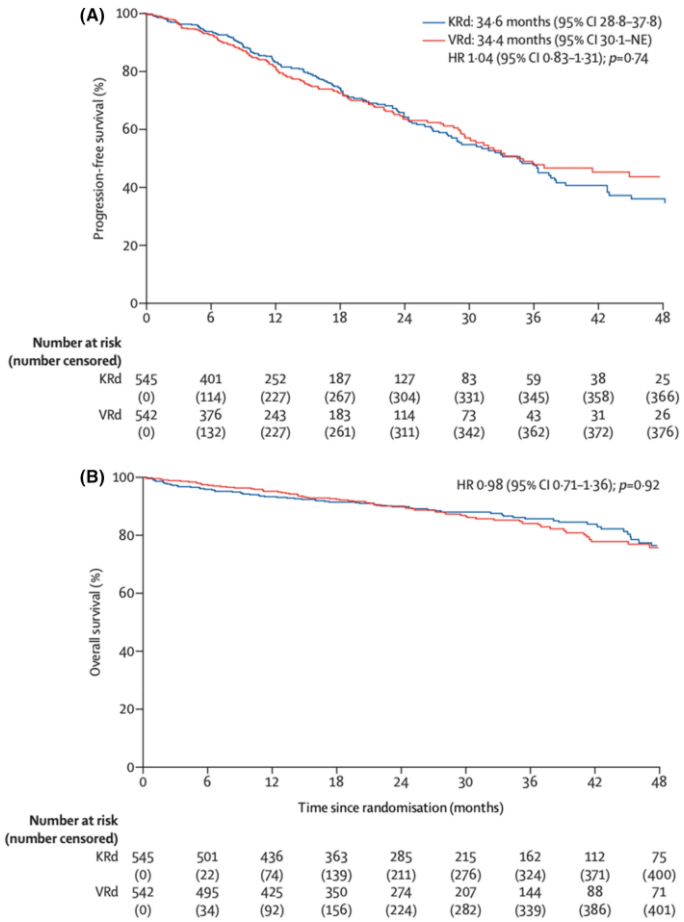
SWOG 0777

VRd vs. Rd



ENDURANCE

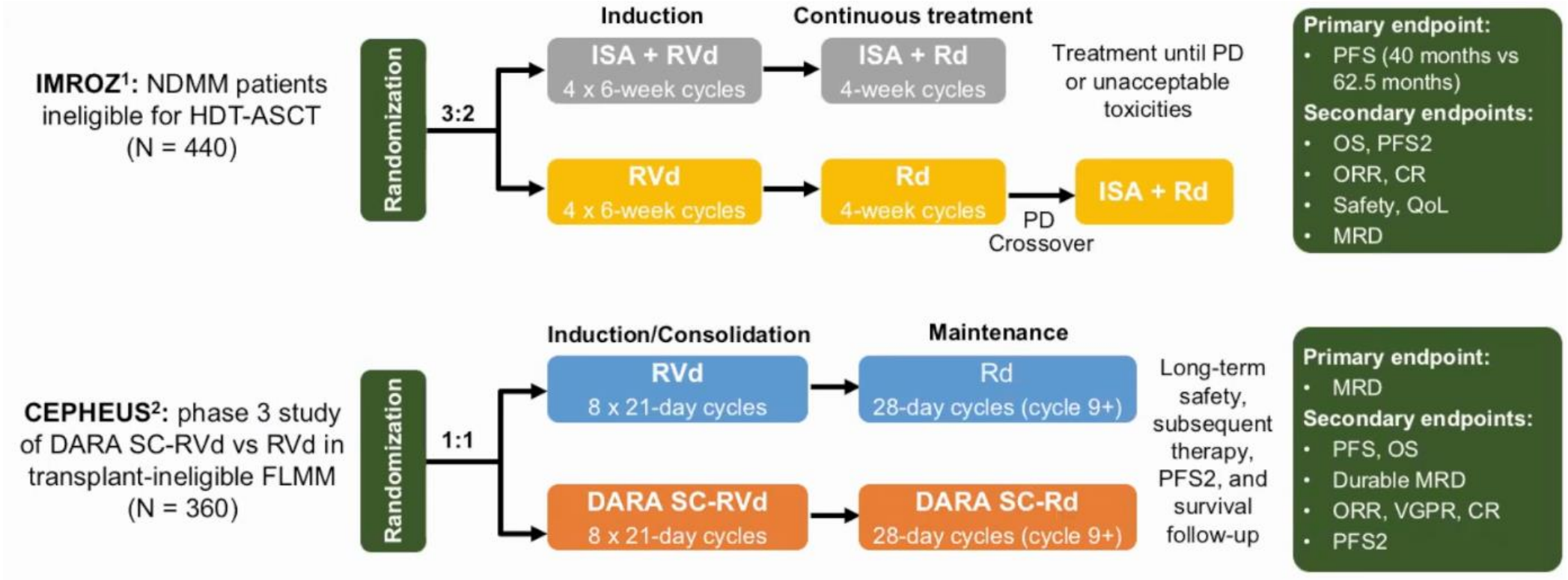
KRd vs. VRd



Durie, Lancet Oncol 2017; Kumar, Lancet Oncol 2020

IMROZ and CEPHEUS

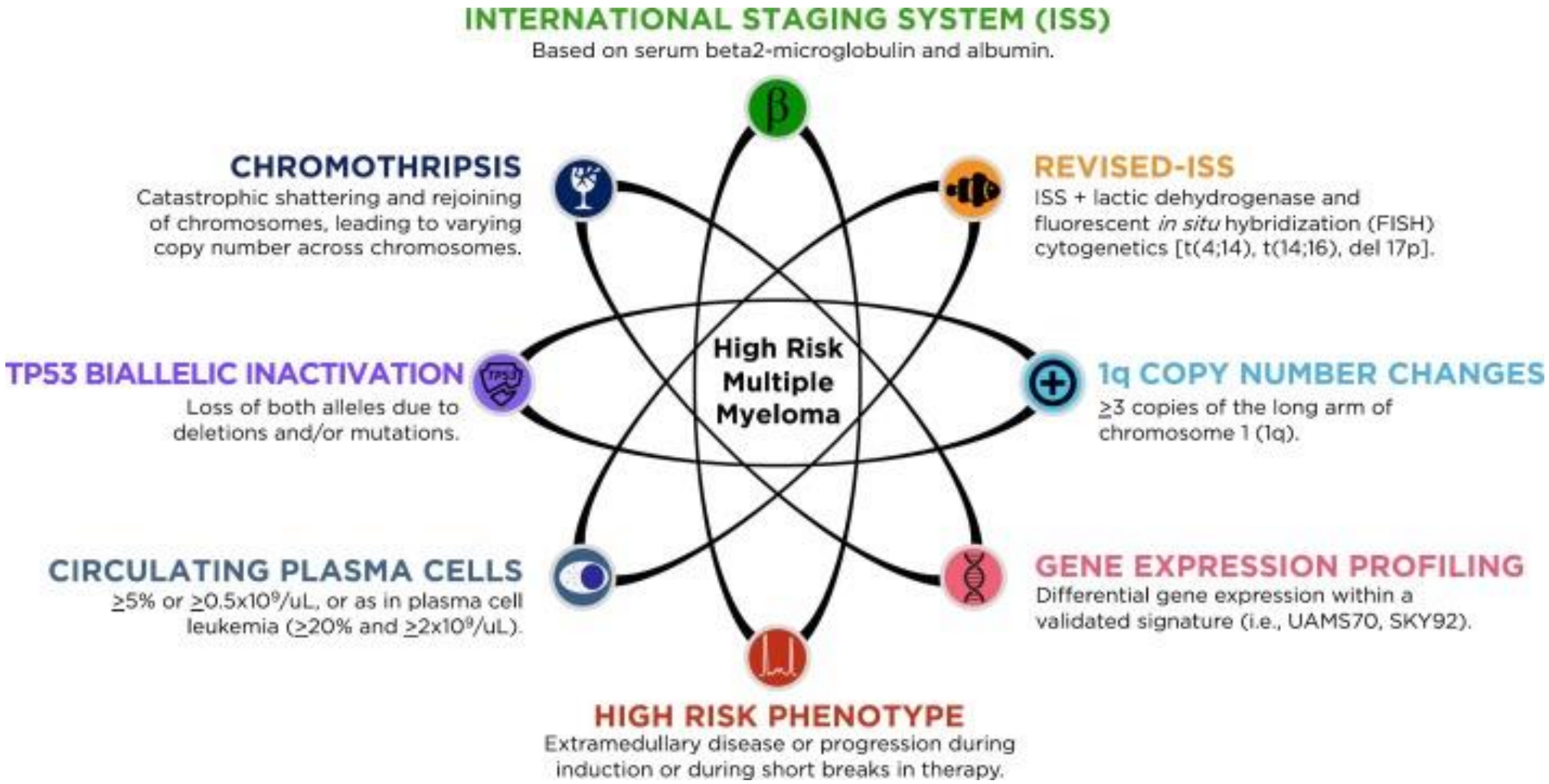
Better than Dara-Rd?



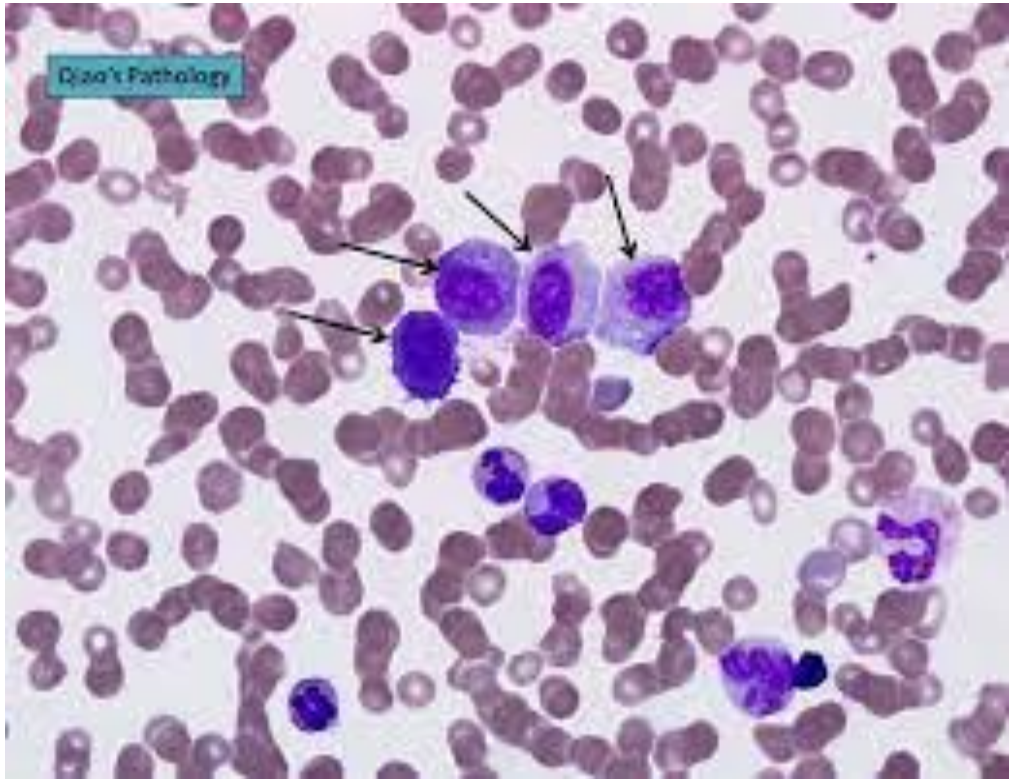
Agenda

1	Generalities
2	SMM
3	MM, Principles of therapy
4	Transplant eligible patients
5	Transplant non eligible patients
6	High risk disease
7	MRD to define therapy

High risk MM features



Plasma cell leukemia



- Terminal stage and most aggressive form of PC dyscrasia

- 2-4% off all PC malignancies

- PRIMARY (pPCL) in pts without prior history of PC dyscresia
- SECONDARY (sPCL) in pts with a history of MM

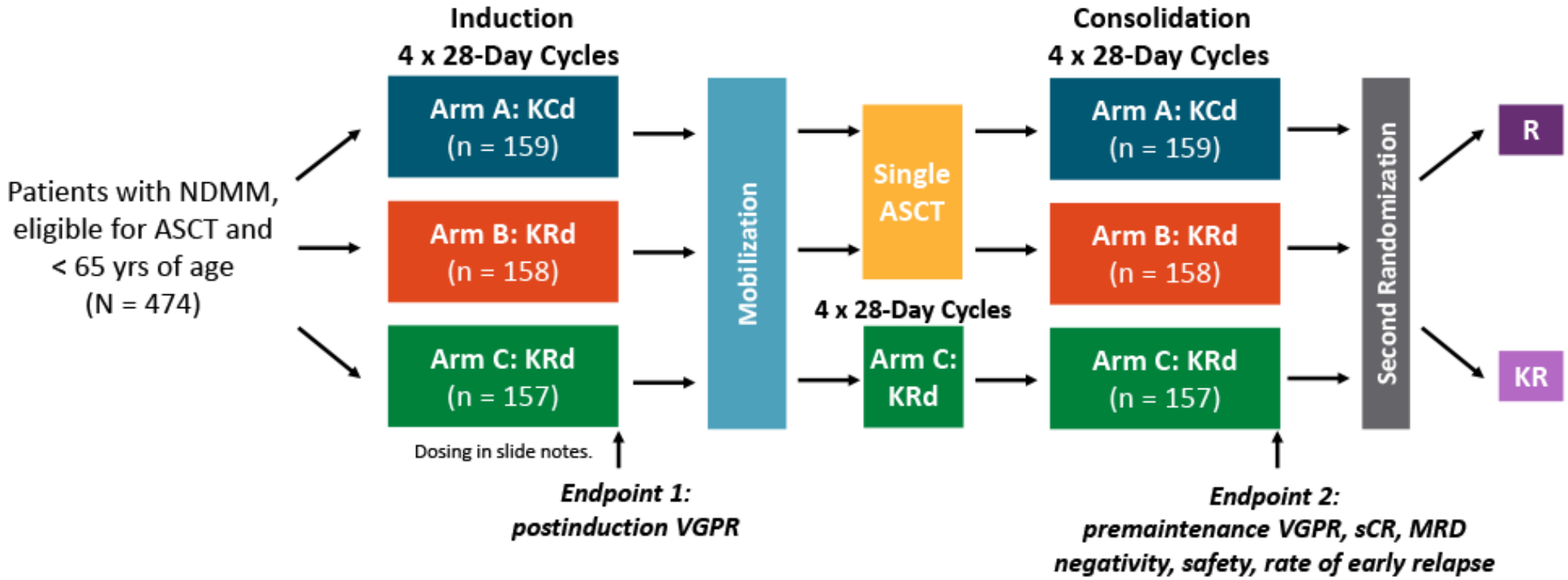
- Adverse prognosis whatever the treatment
- Particularly for sPCL with a median survival of 2-6 months

- Diagnosis following IWMG, **5%** circulating PC

FORTE

KRD vs. KCD with/without ASCT

Phase II



Gay, Lancet Oncol 2021

FORTE

KRD in HR patients

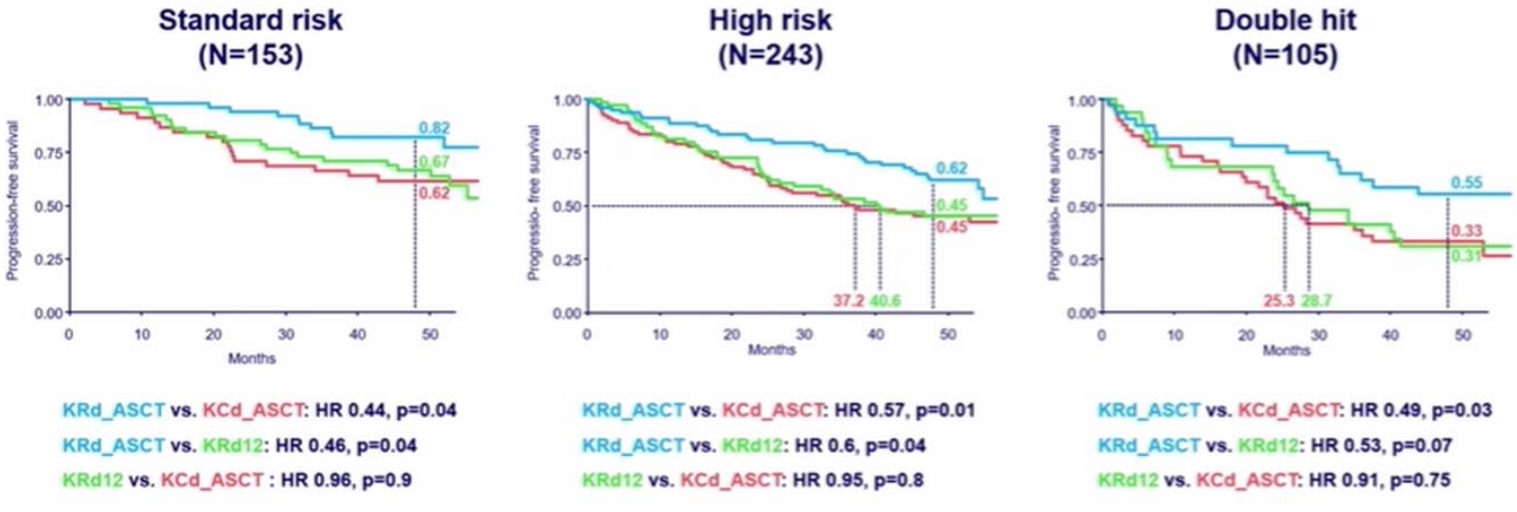
Subgroup analyses according to FISH:
del17p, t(4;14), t(14;16), del1p and 1q gain (3 copies) or amp1q (≥4 copies)

- **SR** Absence of any chromosomal abnormalities
- **HR** ≥1 chromosomal abnormalities
- **DH** ≥2 Chromosomal abnormalities

Progression-free survival: Random 1

KCd_ASCT vs. KRd_ASCT vs. KRd12

Median follow-up from Random 1: 51 months (IQR 46-55)



KRd_ASCT vs. KCd_ASCT: HR 0.44, p=0.04
KRd_ASCT vs. KRd12: HR 0.46, p=0.04
KRd12 vs. KCd_ASCT : HR 0.96, p=0.9

KRd_ASCT vs. KCd_ASCT: HR 0.57, p=0.01
KRd_ASCT vs. KRd12: HR 0.6, p=0.04
KRd12 vs. KCd_ASCT: HR 0.95, p=0.8

KRd_ASCT vs. KCd_ASCT: HR 0.49, p=0.03
KRd_ASCT vs. KRd12: HR 0.53, p=0.07
KRd12 vs. KCd_ASCT: HR 0.91, p=0.75

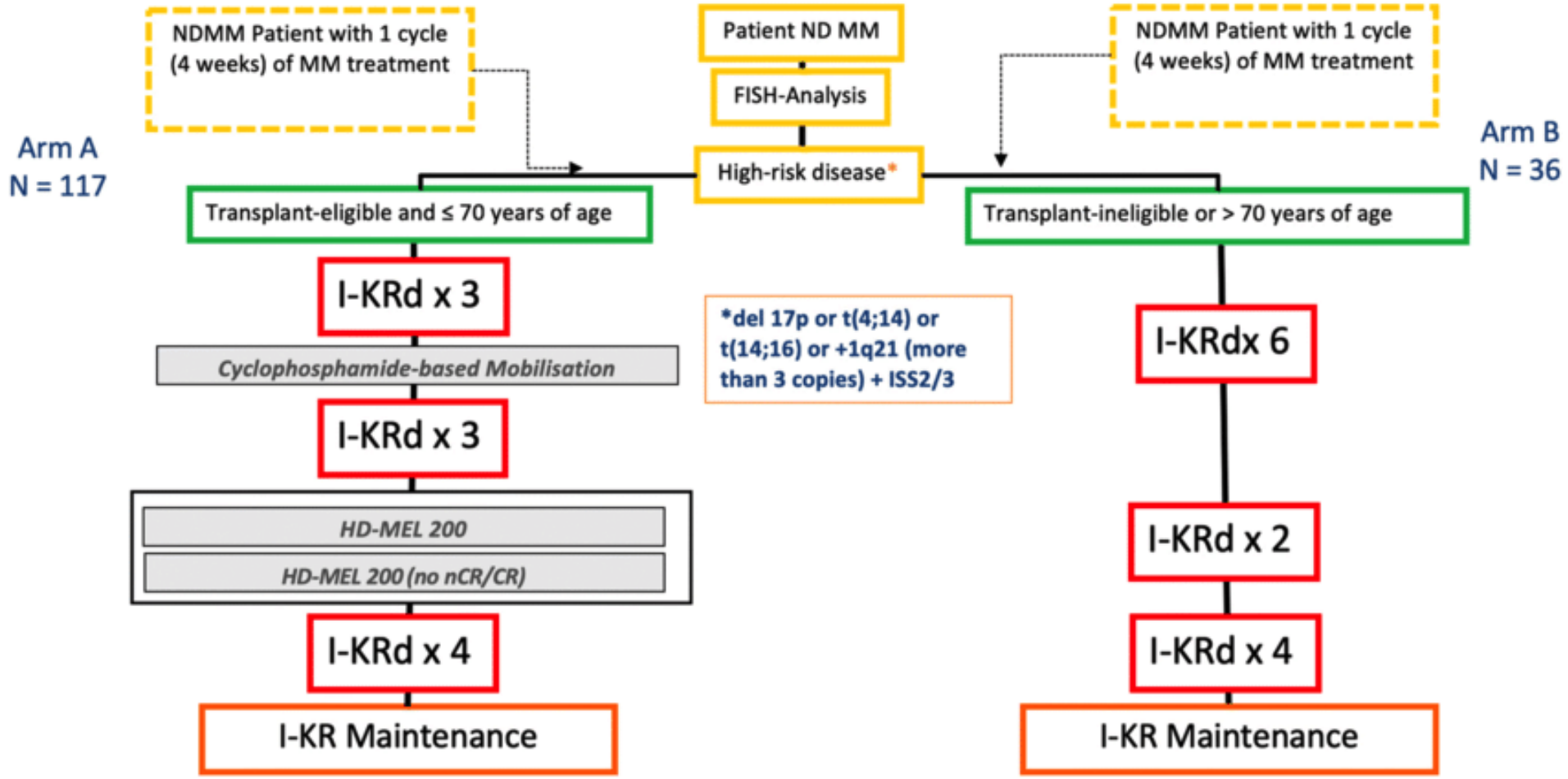
Benefit of KRD - ASCT - KR consolidation observed in all subgroups:
del17p, t(4;14), del1p, 1q gain except amp1q (≥4 copies)

Mina, EHA 2021, #S182

CONCEPT

Isa-KRD in HR patients

Phase II

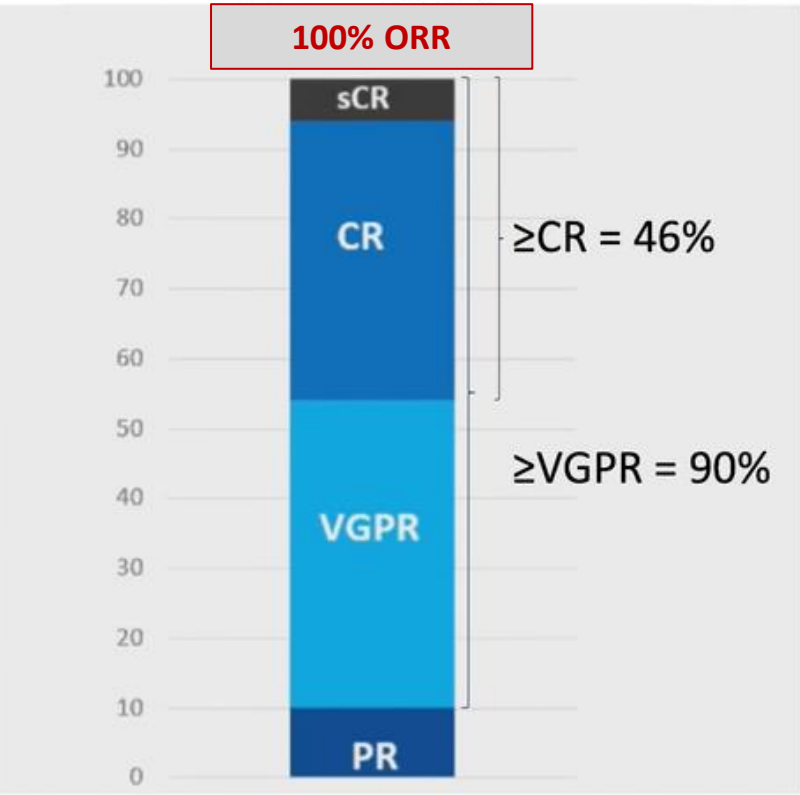


Leypold, Leukemia 2022

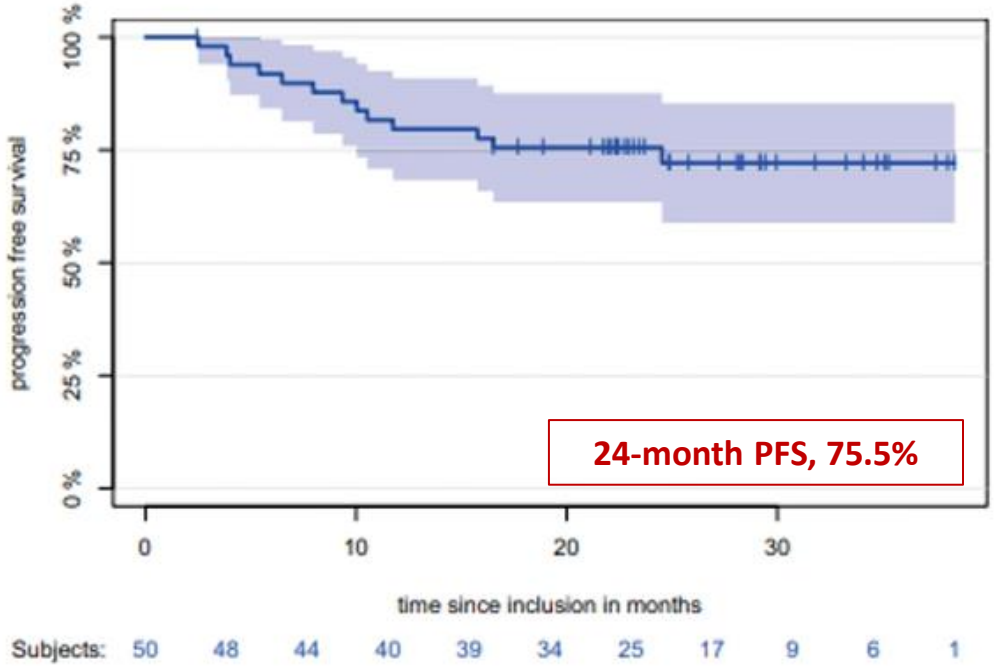
CONCEPT

Isa-KRD in HR patients

Best Response during induction (6 cycles)



n=50 (Arm A=46; Arm B=4)

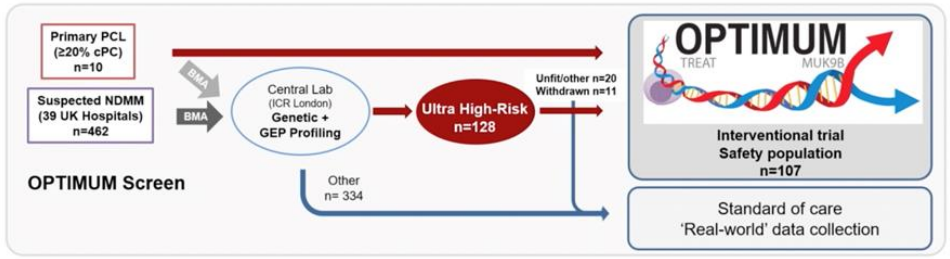


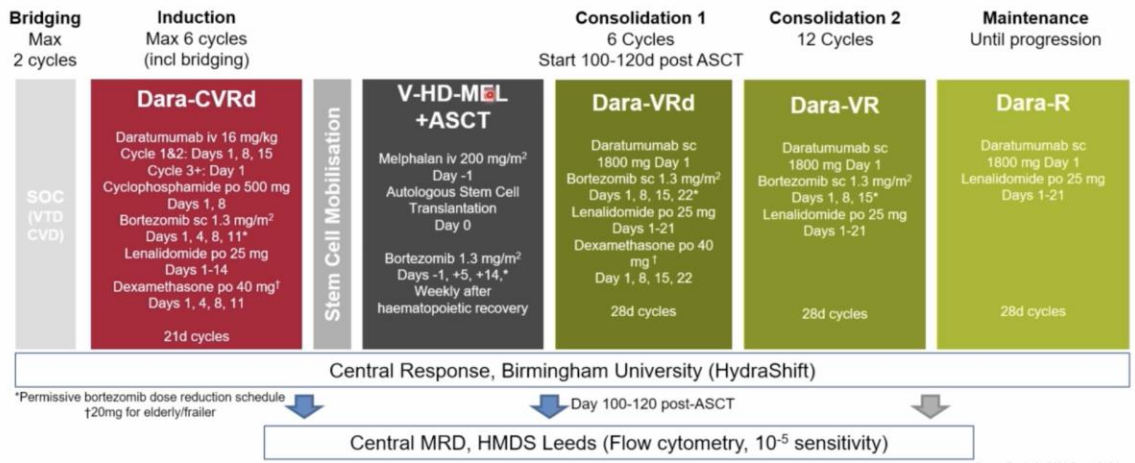
High risk: del (17p); t(4;14); t(14;16) or >3 copies 1q21 AND ISS stage 2 or 3

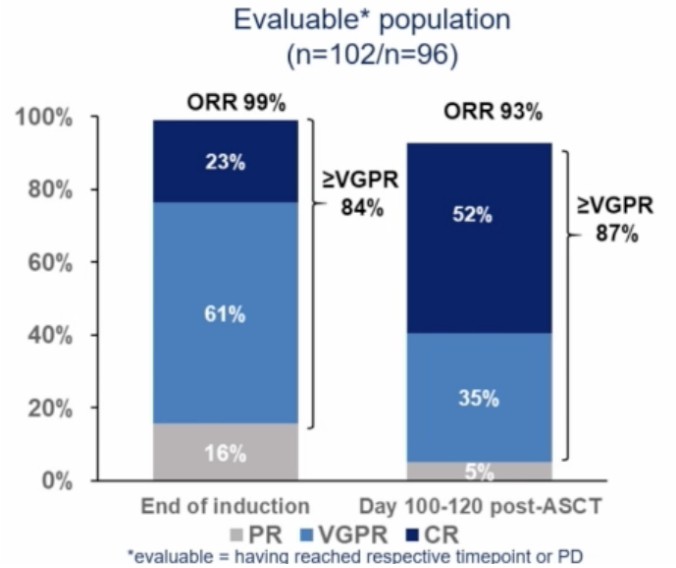
Leypold, Leukemia 2022

OPTIMUM

Dara-CVRD

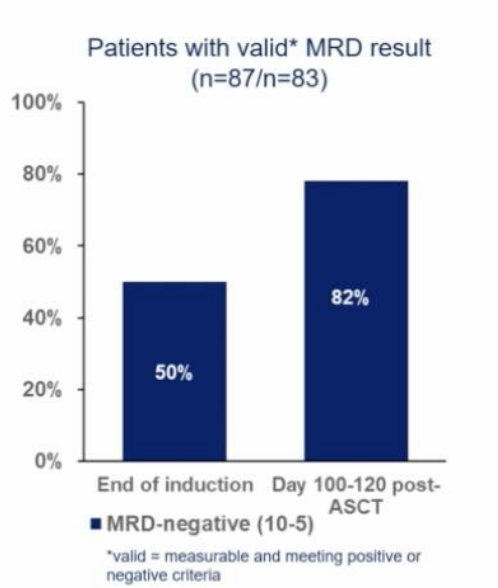






pPCL (evaluable D100-120; n=8)

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

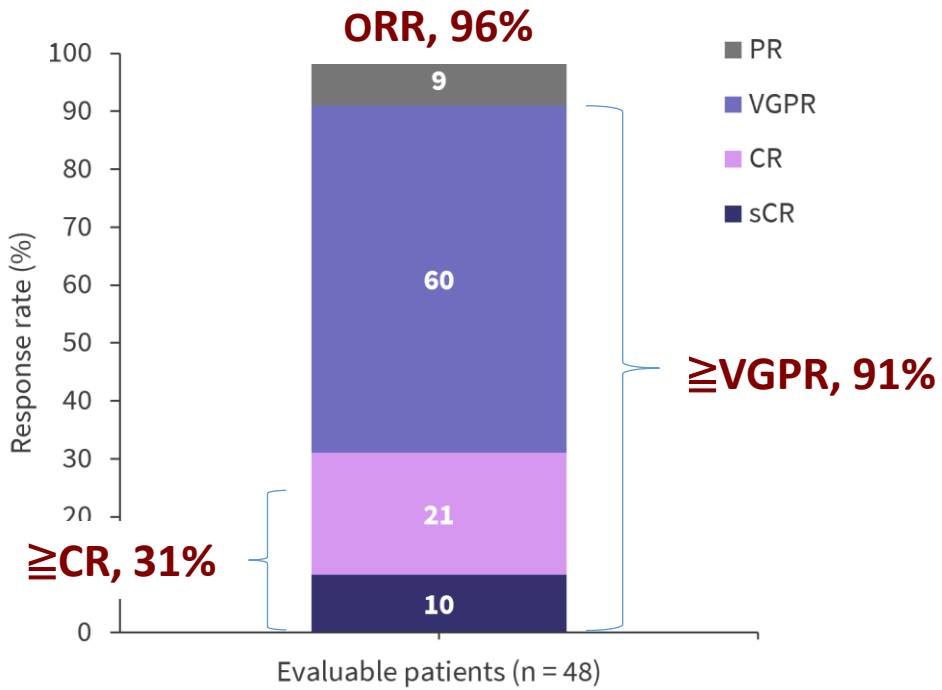


Brown, EHA 2021, #S181

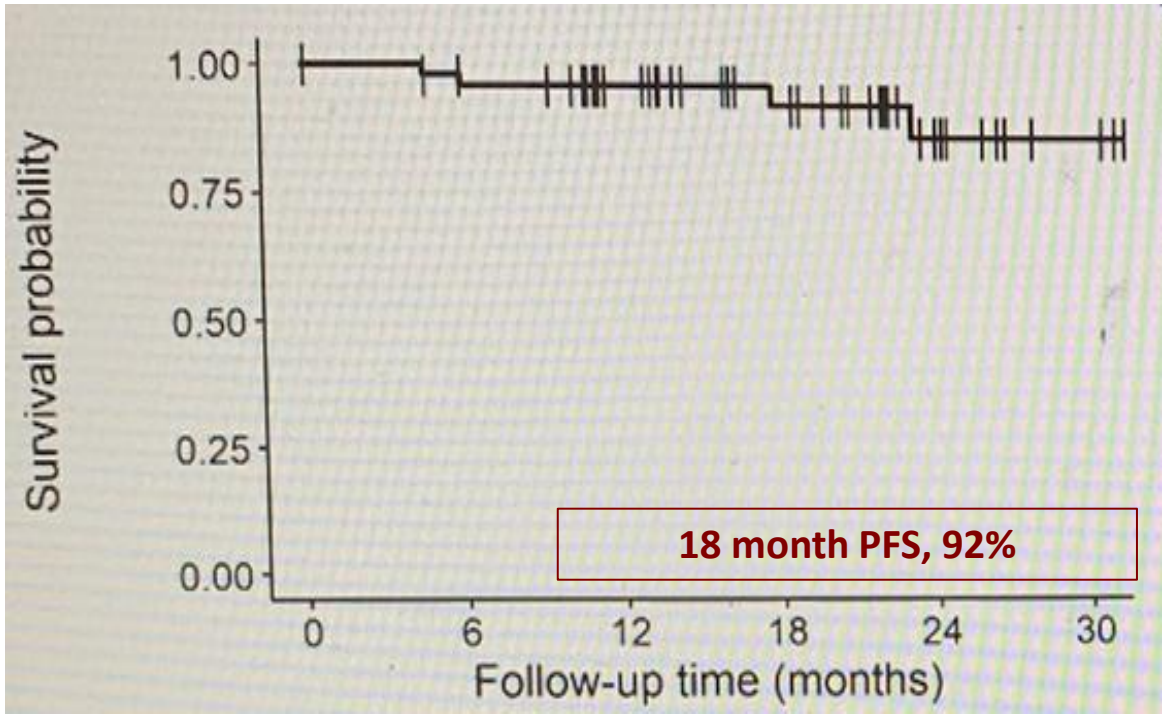
IFM 2018-04

Dara-KRD and tandem ASCT

High-risk cytogenetics	N = 50
17 p deletion	40%
t(4;14)	52%
t(14;16)	20%
1q gain	*50%*
2 HR cytogenetics abnl.	68%



MRD- 10^{-5} (NGS), 62%



Touzeau, EHA 2022, #S176

Agenda

1	Generalities
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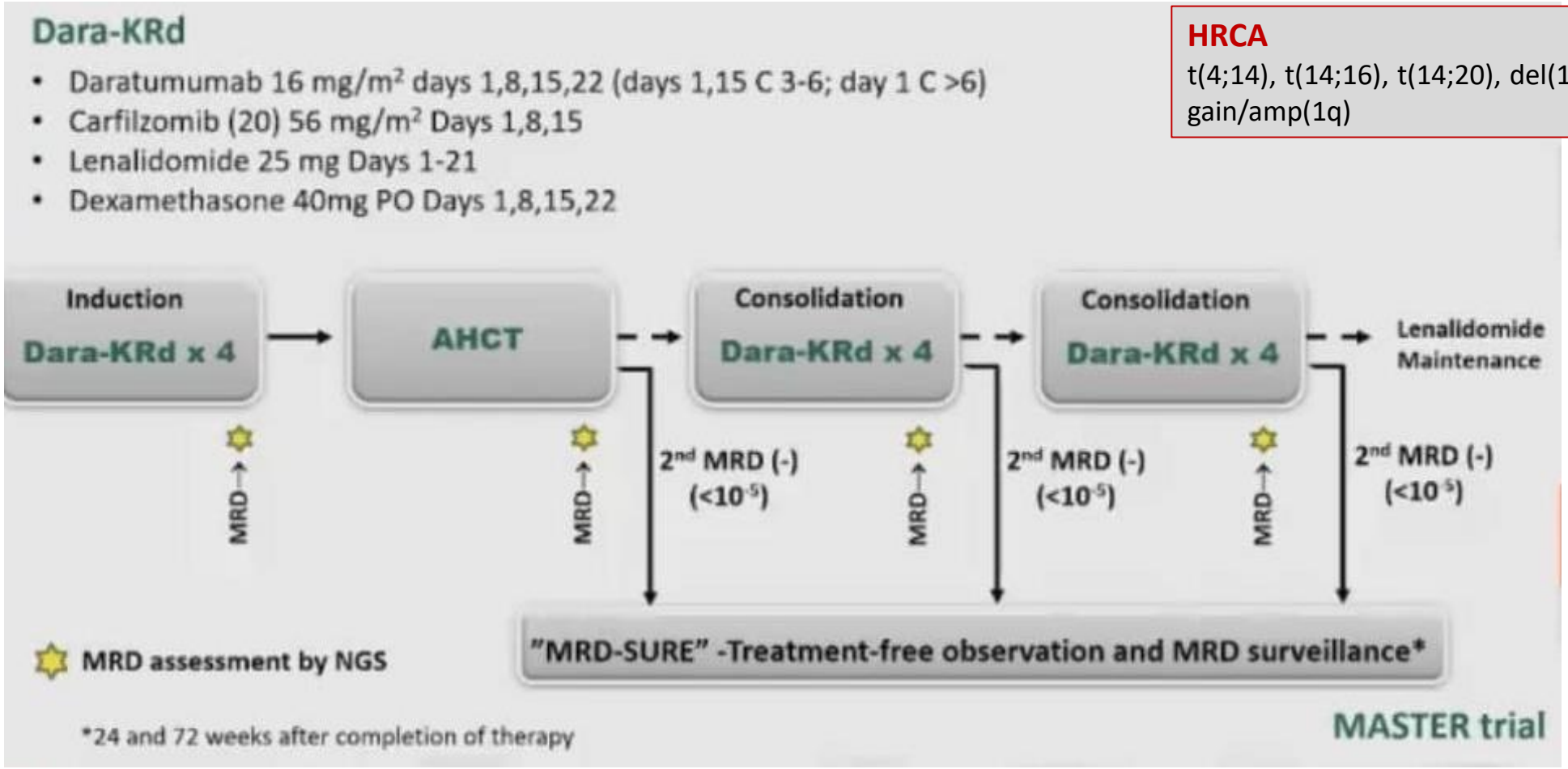
MASTER

Dara-KRD for de-escalation

Phase II

HRCA
t(4;14), t(14;16), t(14;20), del(17p), gain/amp(1q)



Costa, JCO 2021

MASTER

Dara-KRD for de-escalation

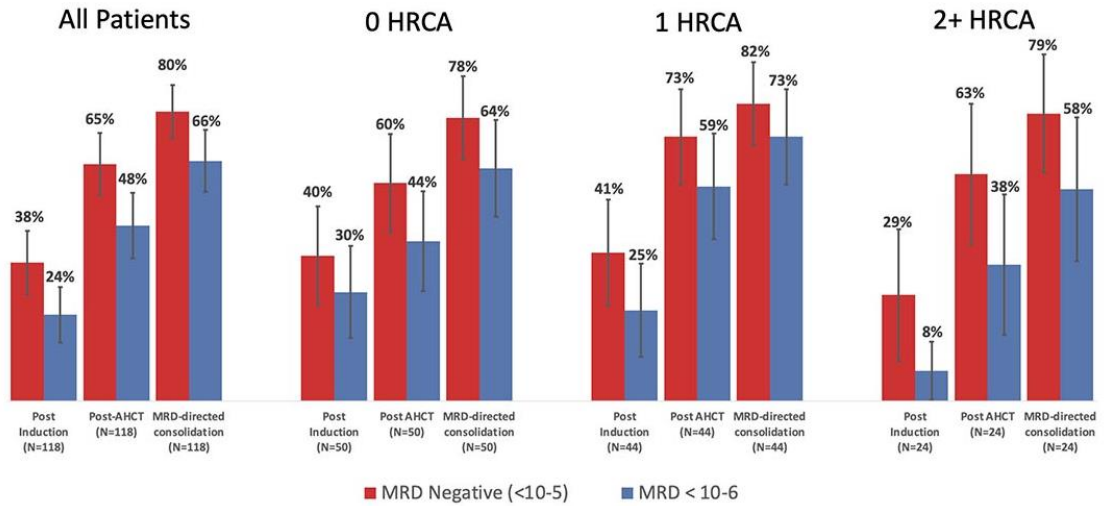


Figure 1 - Achievement of MRD negativity by intent-to-treat according to phase of therapy and number of high-risk cytogenetic abnormalities

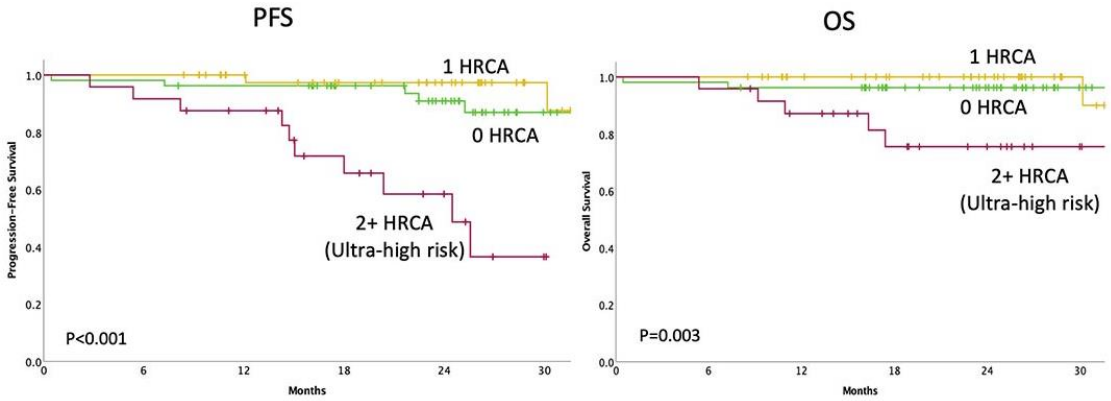


Figure 2 - PFS and OS according to number of high-risk cytogenetic abnormalities

HRCA = High-risk cytogenetic abnormalities [gain1q, t(4;14), t(14;16), t(14;20), del(17p)]

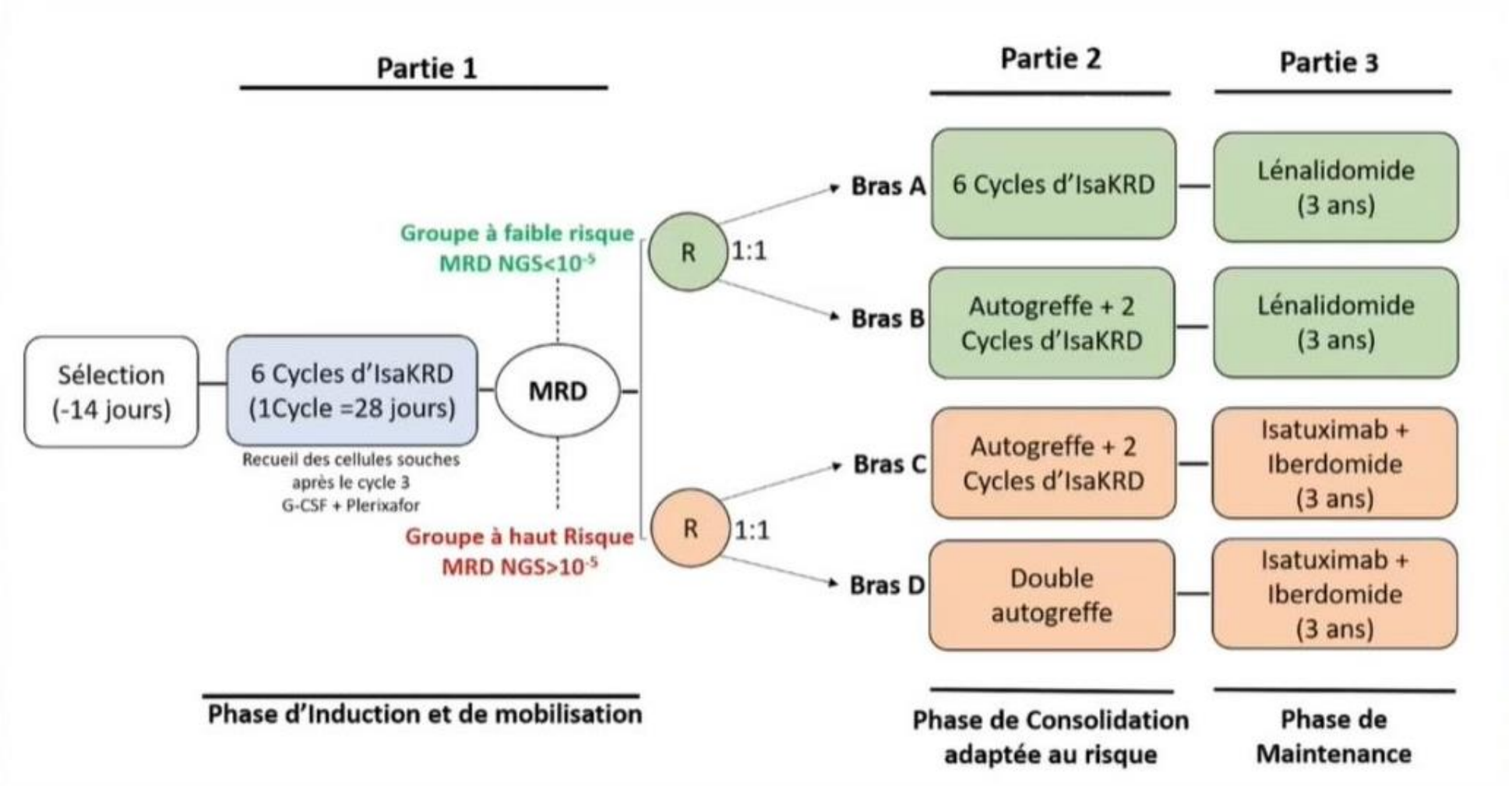
- MRD- in 80% (78%, 82%, 79% in 0, 1, 2+ HRCA)
- MRD 10^{-6} in 66%
- **MRD- 2x consecutively in 71%**

- 2y-PFS, 87% (**91%, 97%, 58%** in **0, 1, 2+ HRCA)**
- Cumulative incidence of **MRD** resurgence or progression 12 months after cessation of therapy (**4%, 0%, 27% 0, 1, 2+ HRCA**)

Costa, ASH 2022, #3237

MIDAS

Isa-KRD for escalation



Conclusions

- ✓ First-line treatment is the **most important treatment** line in the management of multiple myeloma
- ✓ The activitiy of ‘triplets’ based on a PI, IMiD and dexa can be reinforced by an **anti-CD38 monoclonal antibody**
- ✓ The discrepancy in the difference between **transplant- and non transplant**-eligible patients is gradually fading
- ✓ Whereas **depth of response** is the primary aim in fit patients, **disease control** is a more realistic target in non-fit patients
- ✓ Future challenges are optimization of treatment duration and the treatment tailoring according to disease and patient characteristics