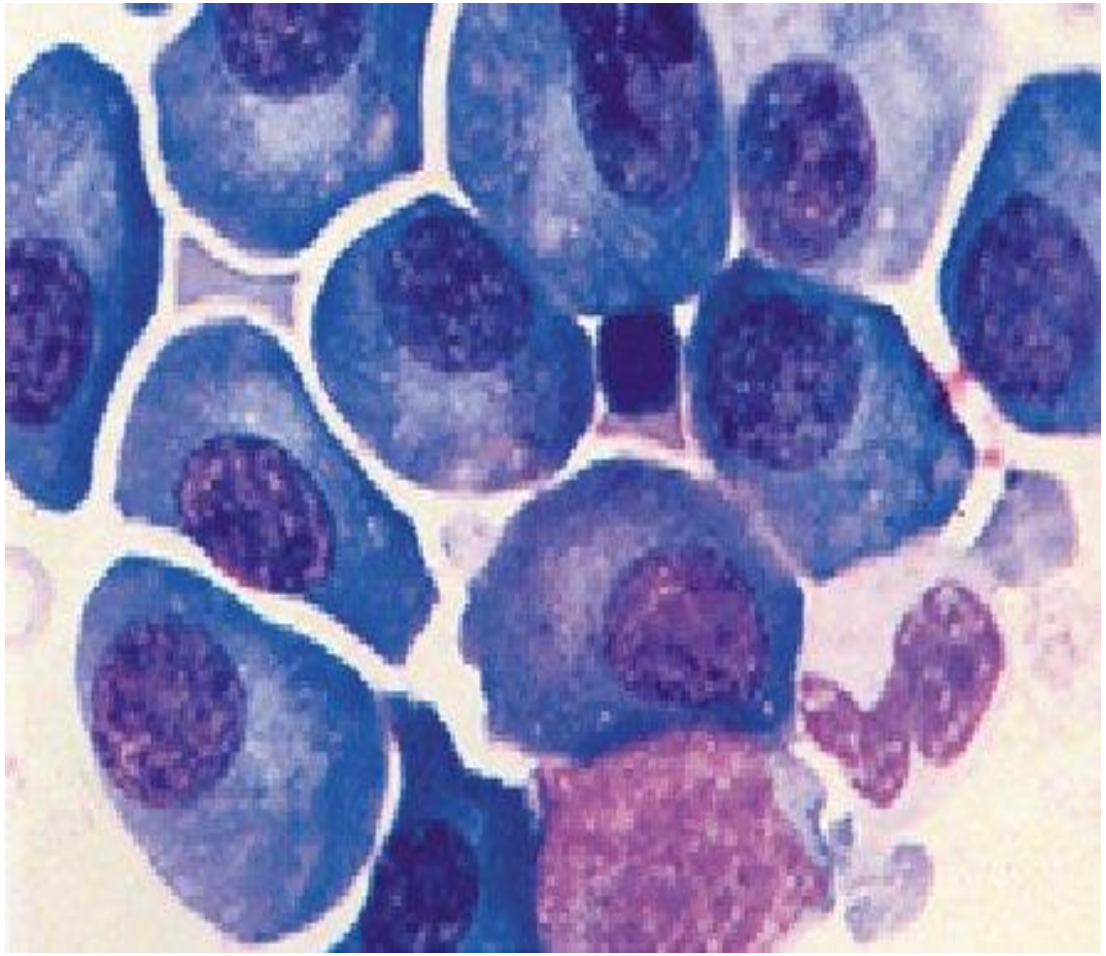
Sindromi mielodisplastiche e mieloma: evoluzioni nella diagnosi, classificazione e trattamento

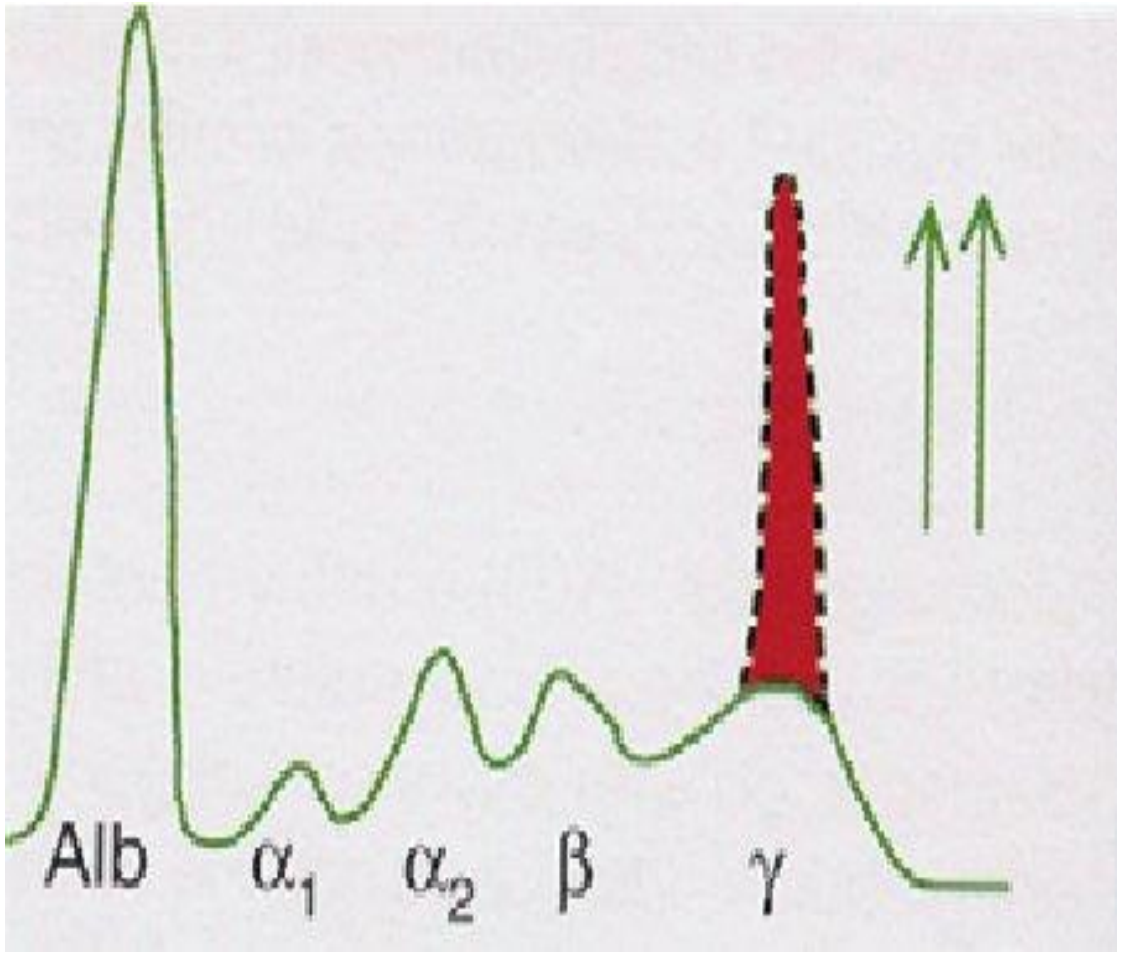
XIX Corso di aggiornamento per operatori dei registri tumori

Bari 7 Novembre 2019

Dtt. Patrizio Mazza

Le gammopatie monoclonali





DEFINIZIONE DELLE GAMMAPATIE MONOCLONALI

- **Le gammapatie monoclonali sono quadri clinico-laboratoristici caratterizzati dalla proliferazione e accumulo nel midollo osseo di un clone di linfociti B e plasmacellule sintetizzanti immunoglobuline (Ig) identiche per caratteristiche isotipiche (stessa classe di Ig) e idiotipiche (stesso sito di legame con l'antigene nella regione variabile), complete o incomplete, rilevabili nel siero e/o nelle urine.**
- **Tali Ig prendono il nome di Componente monoclonale (CM)**

CLASSIFICAZIONE DELLE GAMMAPATIE MONOCLONALI

GAMMAPATIE MONOCLONALI NEOPLASTICHE

- Mieloma multiplo
- Plasmacitoma localizzato
- Leucemia plasmacellulare
- Macroglobulinemia di Waldenstrom

GAMMAPATIA MONOCLONALE DI SIGNIFICATO NON DETERMINATO (MGUS)

IL MIELOMA MULTIPLO

- 1% di tutte le neoplasie e 10% delle neoplasie ematologiche nei bianchi
- L' incidenza aumenta con l'età e raggiunge un picco durante la settima decade di vita
- Predominanza sesso M
- Può essere associato ad esposizione a tossici:
  - radiazioni ionizzanti
  - pesticidi
  - benzene
  - altri fattori chimici
- Incrementato rischio di MM in soggetti con MGUS (16% a 10 anni)

IMWG Criteria for Diagnosis of MM

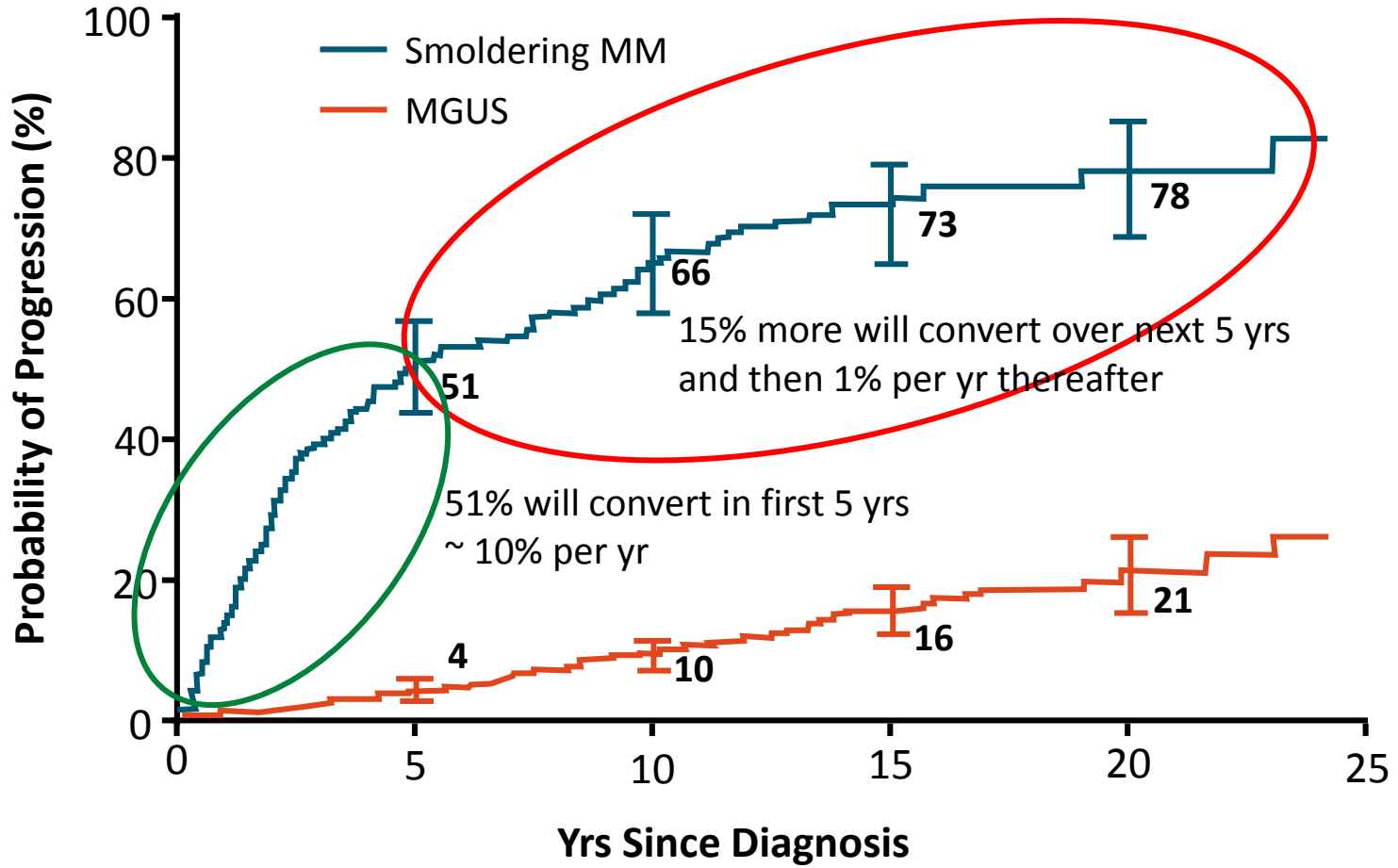
MGUS	Smoldering Myeloma	Active or Symptomatic Multiple Myeloma
▪ M protein < 3 g/dL ▪ Clonal plasma cells in BM < 10% ▪ No myeloma-defining events	▪ M protein ≥ 3 g/dL (serum) or ≥ 500 mg/24 hrs (urine) ▪ Clonal plasma cells in BM ≥ 10% to 60% ▪ No myeloma-defining events	▪ Underlying plasma cell proliferative disorder ▪ AND ≥ 1 SLiM-CRAB* feature

*S: Sixty percent clonal bone marrow plasma cells
Li: Serum free Light chain ratio ≥ 100 (involved kappa) or ≤ .01 (involved lambda)
M: MRI studies with > 1 focal lesion (> 5 mm in size)

C: Calcium elevation (> 11 mg/dL or > 1 mg/dL higher than ULN
R: Renal insufficiency (CrCl < 40 mL/min or serum creatinine > 2 mg/dL)
A: Anemia (Hb < 10 g/dL or 2 g/dL < normal)
B: Bone disease (≥ 1 lytic lesions on skeletal radiography, CT, or PET/CT)

Rajkumar. Lancet Oncol. 2014;15:e538.

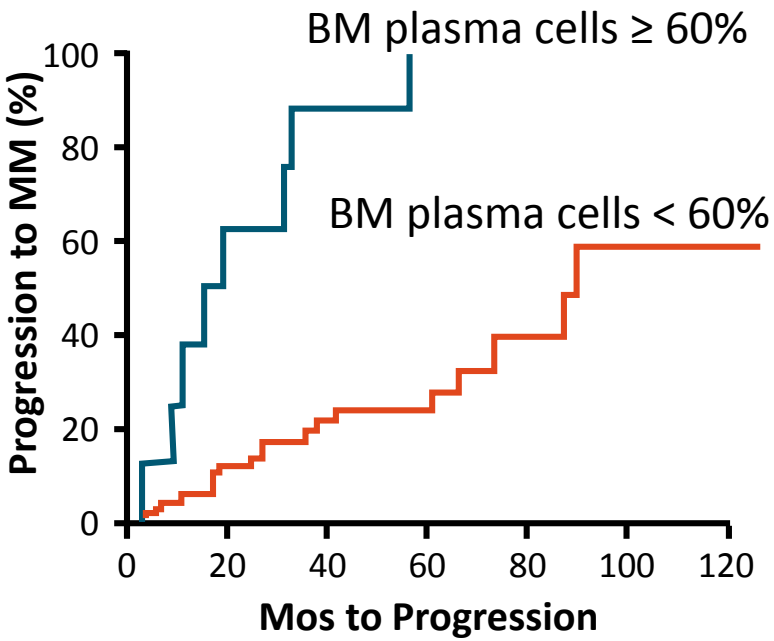
Progression to Symptomatic MM



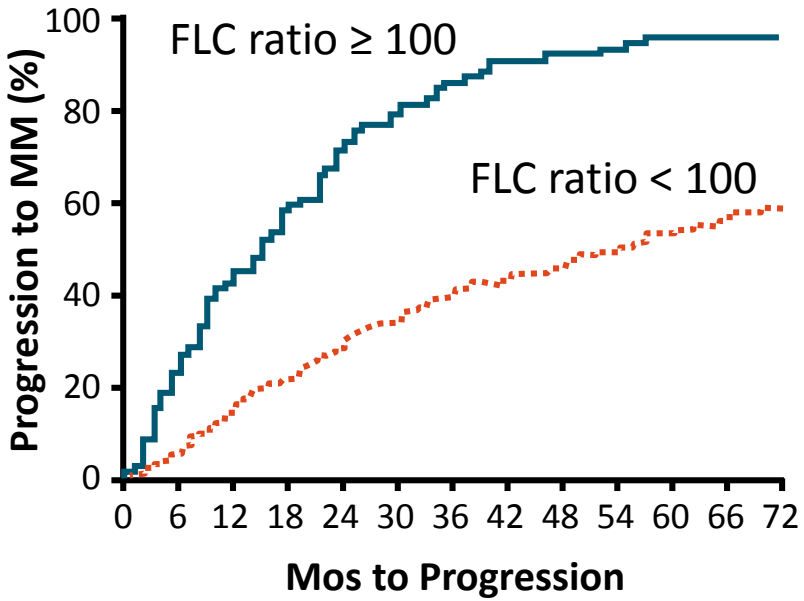
Kyle. N Engl J Med. 2007;356:2582.

Biomarkers to Predict Risk of Progression

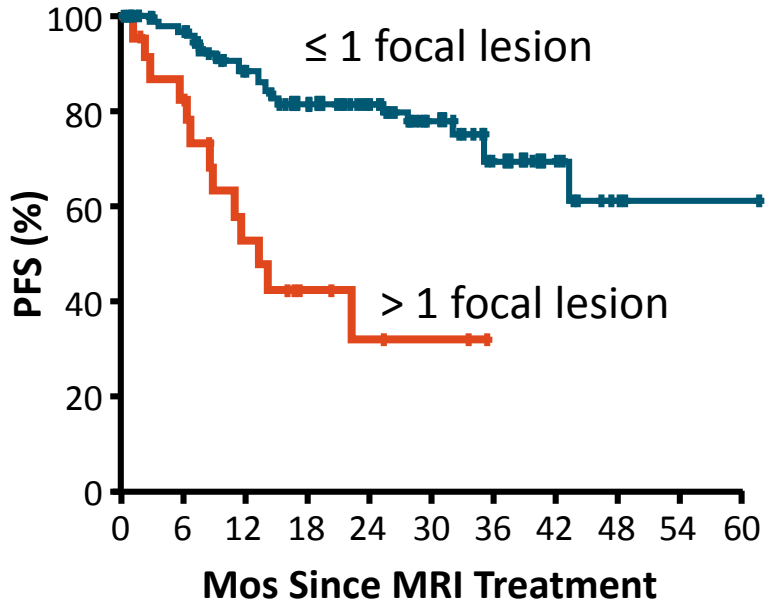
Clonal Plasma Cells in BM Predicts Risk (*P* < .001)



FLC Ratio ≥ 100 Predicts Risk (*P* < .0001)



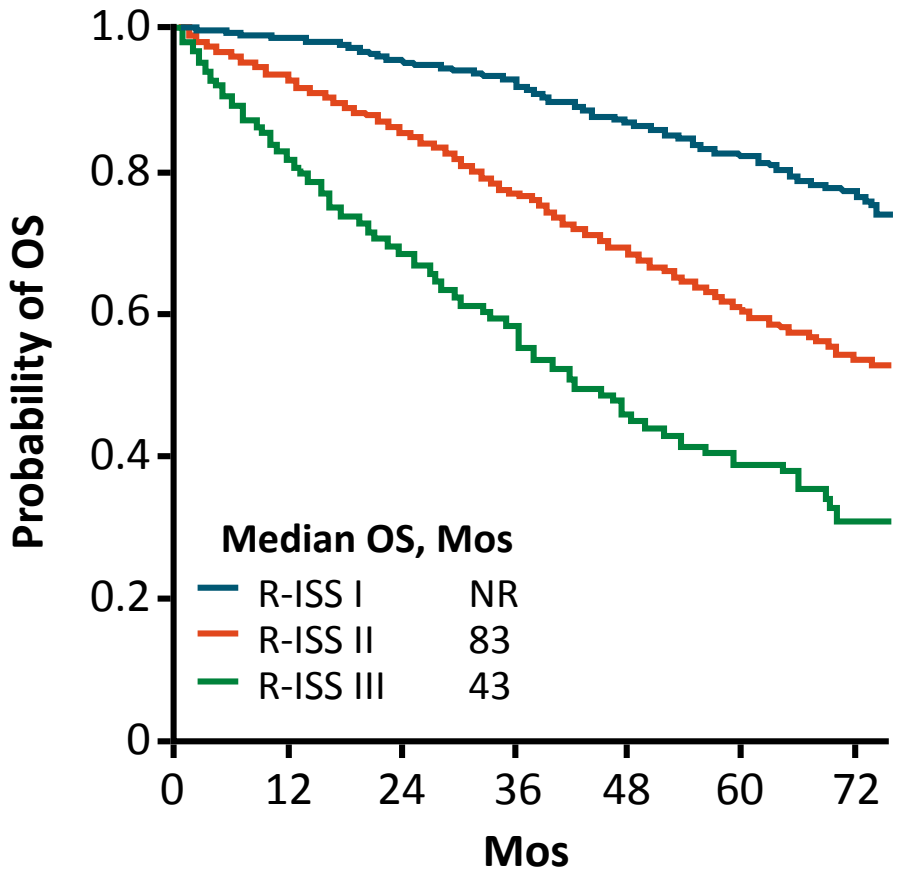
MRI Focal Lesions Predicts Risk (*P* < .001)



Larsen. Leukemia. 2013;27:941. Kastritis. Leukemia. 2013;27:947.

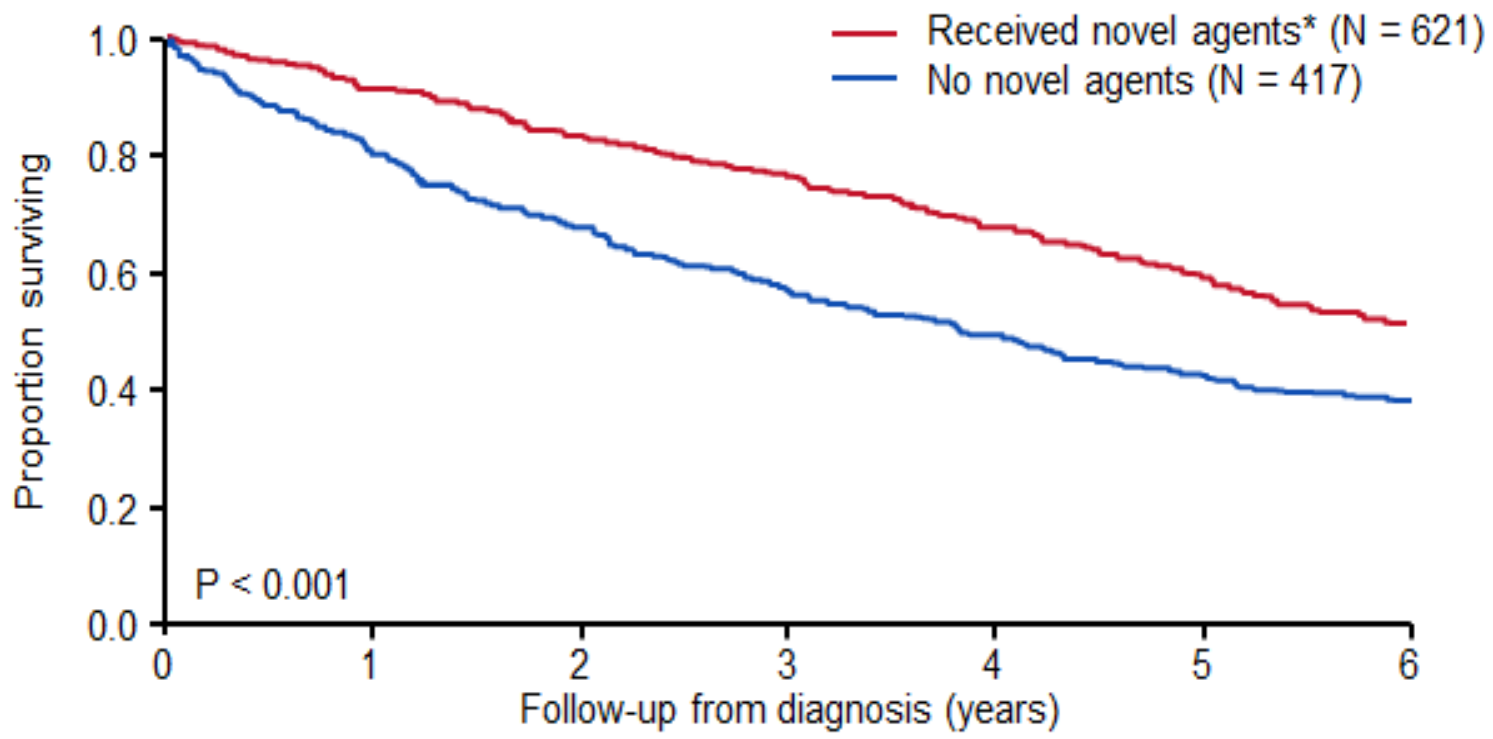
Revised ISS

ISS Definition	
I	▪ Serum albumin ≥ 3.5 g/dL *AND* ▪ β_2-M < 3.5 mg/L
II	▪ Not stage I or III
III	▪ β_2-M ≥ 5.5 mg/dL
R-ISS Definition	
I	▪ ISS stage I *AND* ▪ Normal LDH ▪ No t(4;14), t(14;16), or del(17p)
II	▪ Not stage I or III
III	▪ ISS stage III *AND* ▪ Serum LDH > ULN *OR* ▪ With t(4;14), t(14;16), or del(17p)



Palumbo. J Clin Oncol. 2015;33:2863.

Improvements in survival have been attributed to the use of novel agents

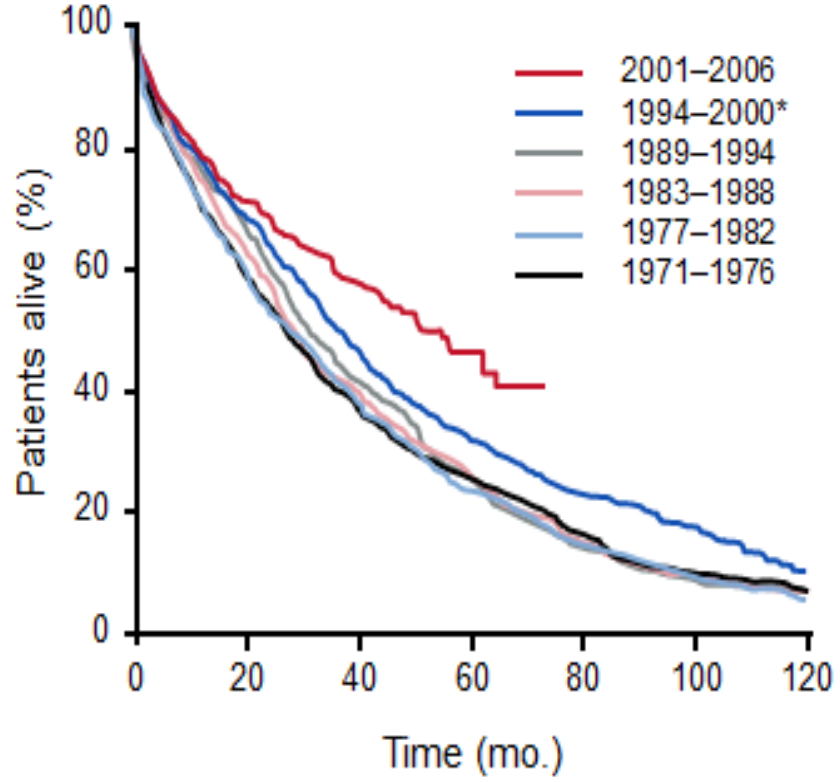


Kumar SK, et al. Leukemia 2014;28:1122–8.

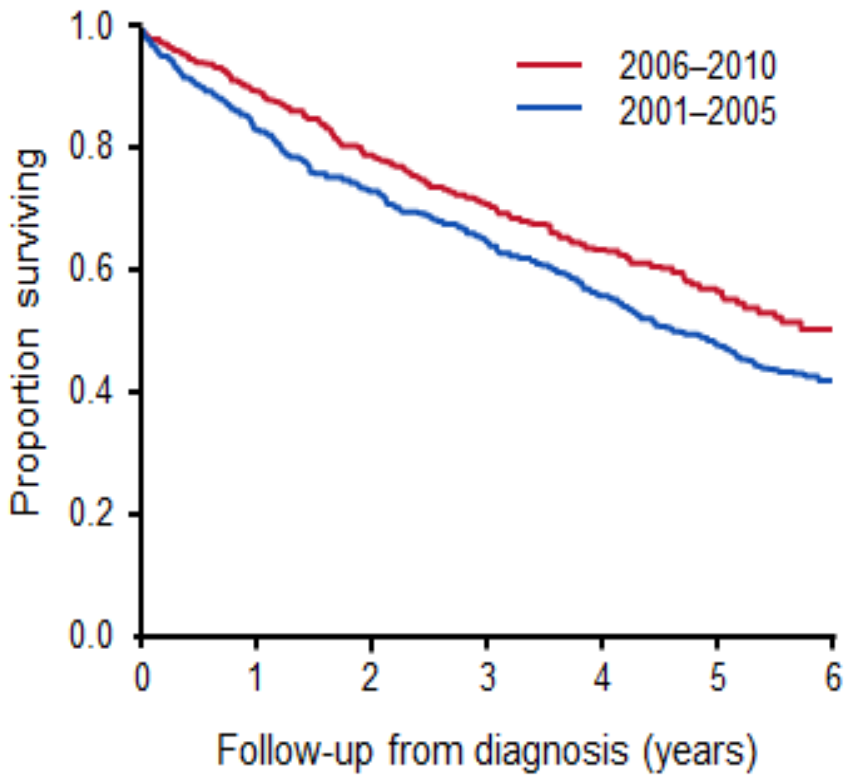
*Bortezomib, lenalidomide or thalidomide as part of initial therapy.

Overall survival (OS) in MM continues to improve vs historical estimates

OS from diagnosis between 1971 and 2006 (N = 2,981)[1]



OS from diagnosis between 2001 and 2010 (N = 1,038)[2]

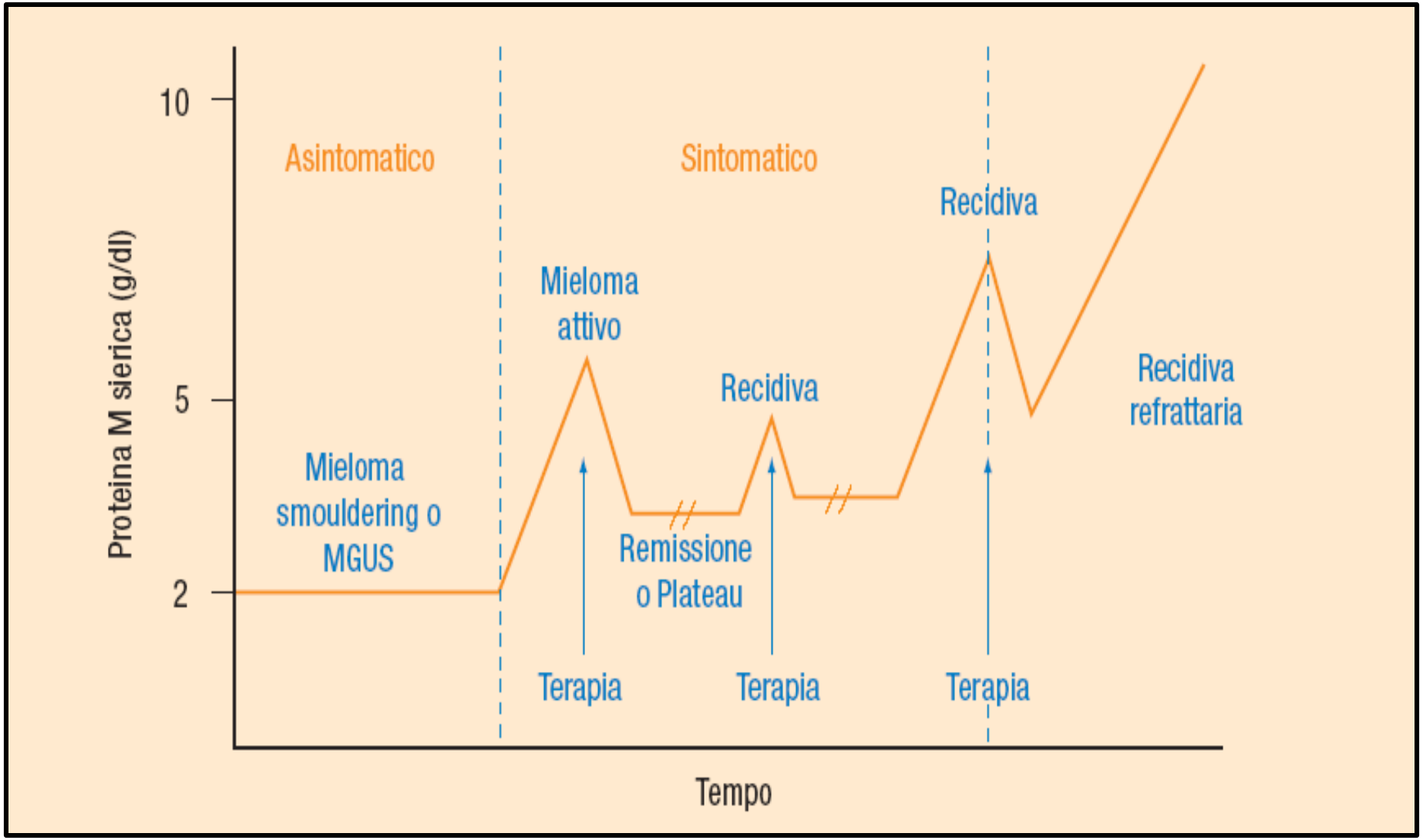


1. Kumar SK, et al. Blood 2008;111:2516–20;
2. Kumar SK, et al. Leukemia 2014;28:1122–8.

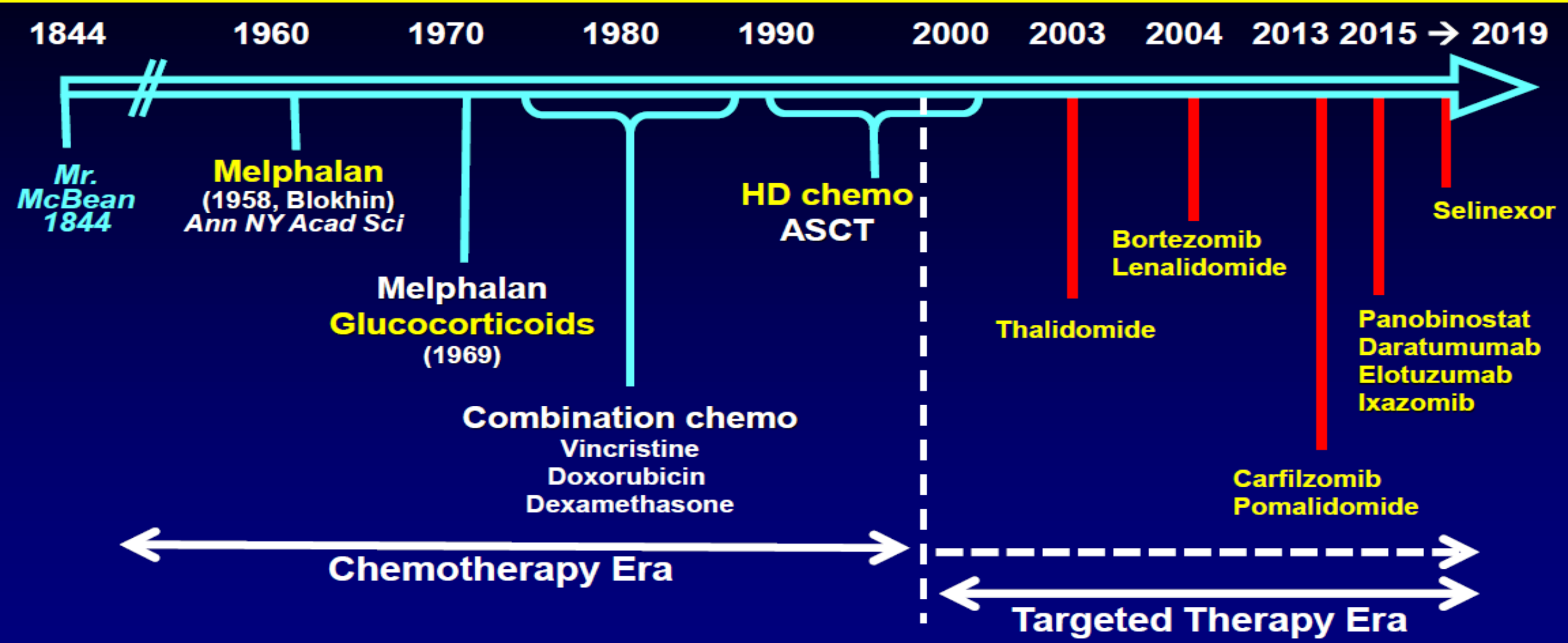
*Trend in improvement in this time period thought to be due to high-dose therapy (HDT) and supportive care.

«Oltre la seconda linea di trattamento»

- Storia Naturale del Mieloma Multiplo -

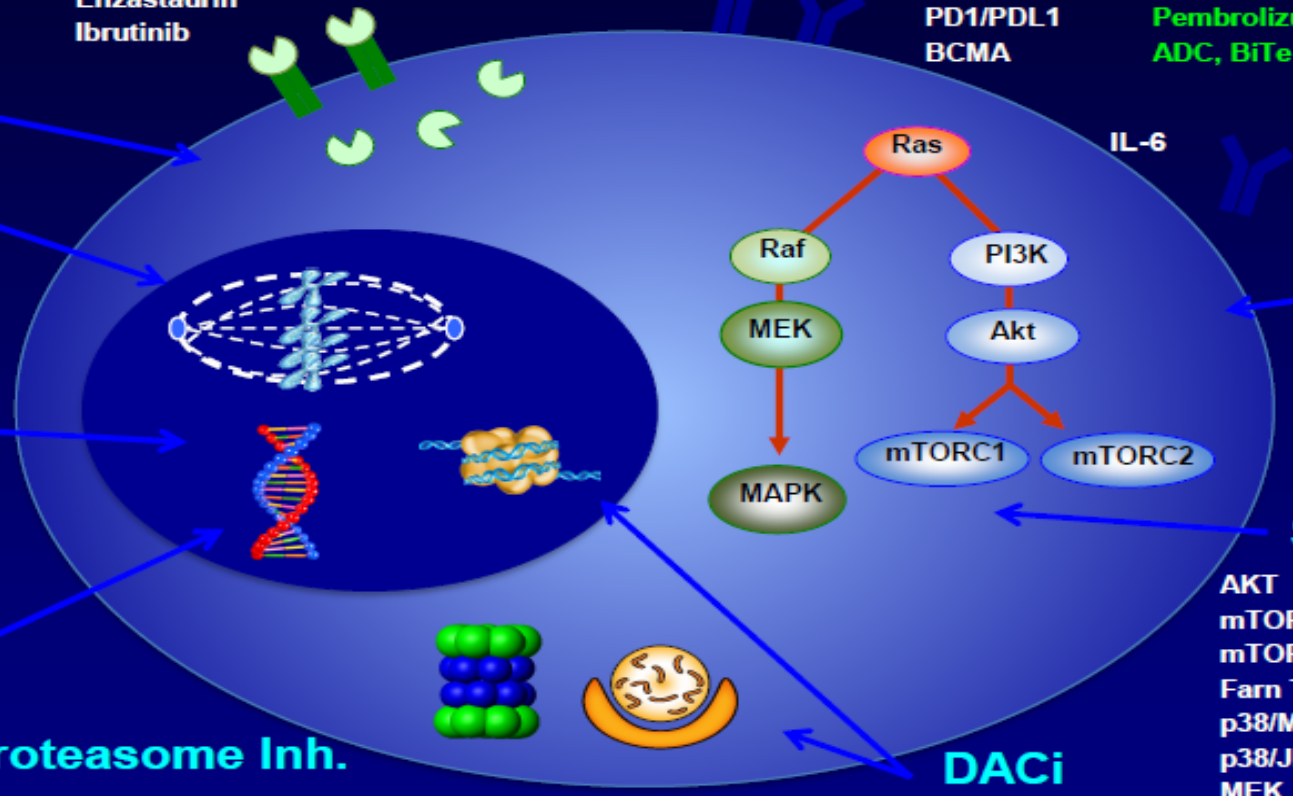


Treatment of MM



Do we need other agents with novel MoA?

New drugs and mechanisms of action in MM



Kinase Inh.

CDK 1, 2, 5, 9	Dinaciclib / TG02
FGFR3	Dovitinib / AB1010 / MFGR 1877S
cKit /PDGFR	Imatinib / Dasatinib
VEGF-R	Bevacizumab
IGF-1R	AVE1642 / CP-751, 851
EGF-R	Cetuximab
PKC	Enzastaurin
BTK	Ibrutinib

MoAb

CS-1	Elotuzumab
CD38	Daratumumab / Isatuximab
CD138	nBT062-DM4
CD56	Lorvotuzumab
CD40	Dacetuzumab / Lucatumumab
BAFF	Tabalumab
KiR	IPH2101
PD1/PDL1	Pembrolizumab / Nivolumab / Pidilumab
BCMA	ADC, BiTe

Cell cycle Inh.

KSP Inh	Filanesib
Aurora K Inh	MLN8237
CDK 4/6 Inh	Seleciclib

IL-6 — Siltuximab

Lymph.
NK cell

IMIDs

Thalidomide
Lenalidomide
Pomalidomide

Alkylators

Melphalan
Cyclophosphamide
Bendamustine
Melflufen
TH-302

Signaling Pathways

AKT	Perifosine / Afuresertib
mTORC1	Everolimus / Temsirolimus
mTOR C1/C2	MLN0128 / INK128
Farn Transf	Tipifarnib
p38/MAPK inh	SCIO-469
p38/JNK act	Aplidin
MEK	Selumetinib
Bcl-2	Venetoclax
Mcl1	MIK665; AMG176/397; AZD5991
XPO	Selinexor
PIM	PIM447

Other DNA damaging

DNA Damaging	Zalypsis
PARP Inhibitor	Veliparib

Proteasome Inh.

Bortezomib
Carfilzomib
Ixazomib
Oprozomib
Marizomib

Hsp-90 Inh.

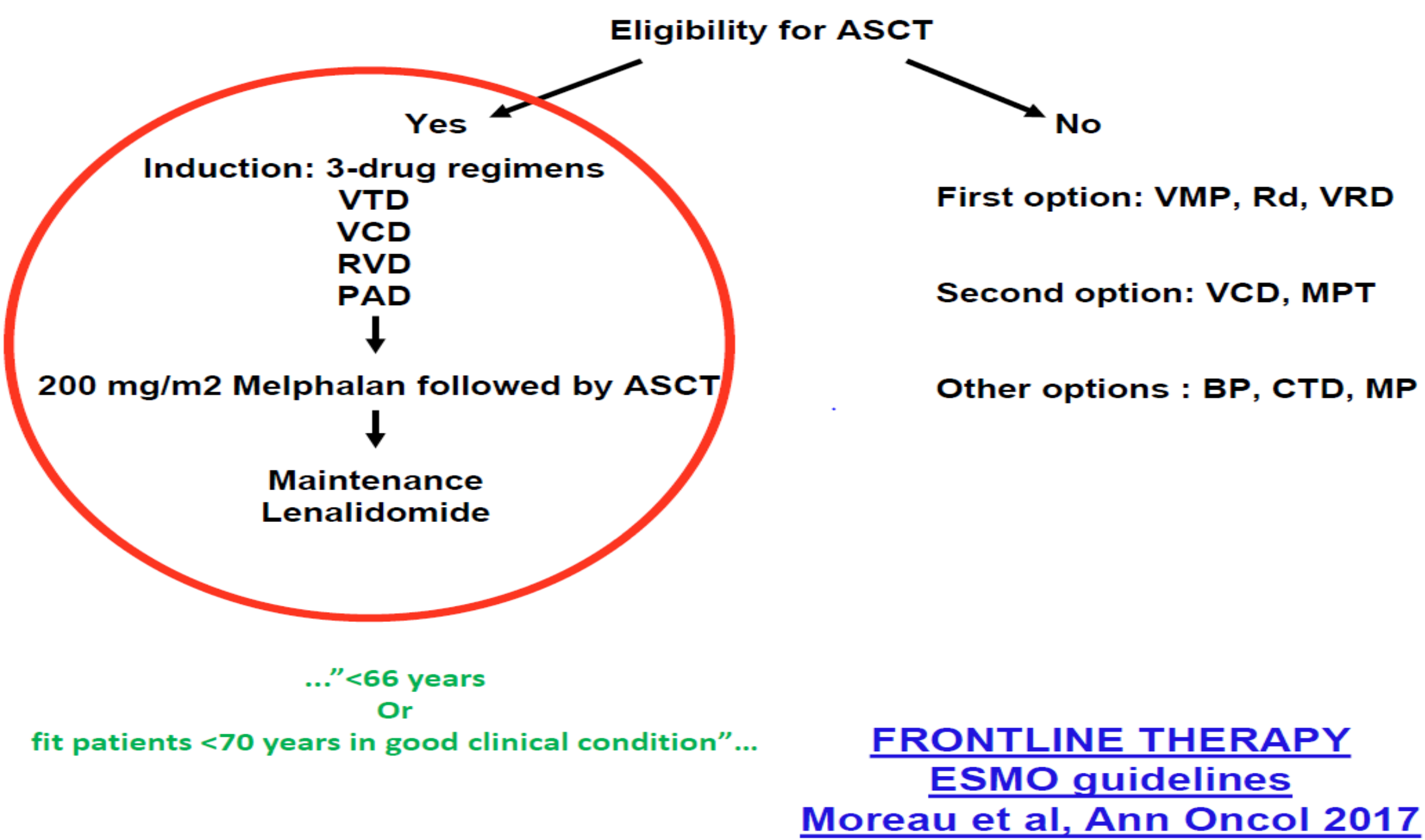
Tanespimycin
AUY922

DACi

Panobinostat
Vorinostat
Romidepsin
Givinostat
Rocilinostat

Approved

Ocio, Leukemia 2014. Updated



..."<66 years
Or
fit patients <70 years in good clinical condition"...

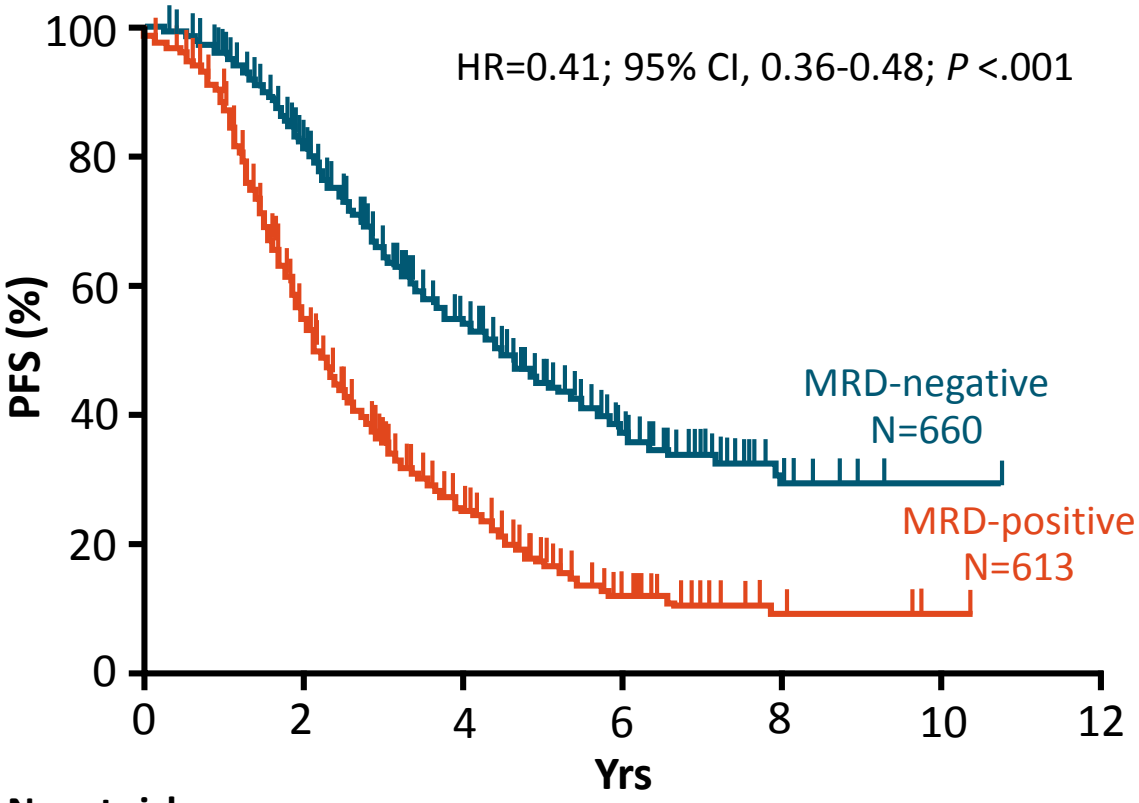
FRONTLINE THERAPY
ESMO guidelines
Moreau et al, Ann Oncol 2017

Goals of Induction Therapy

- High response rate; rapid/deep response
- Improve performance status and quality of life
- Not limit PBSC mobilization (for younger patients)
- Current issues
  - Optimal regimen
  - Optimal duration of therapy
  - Role of transplantation

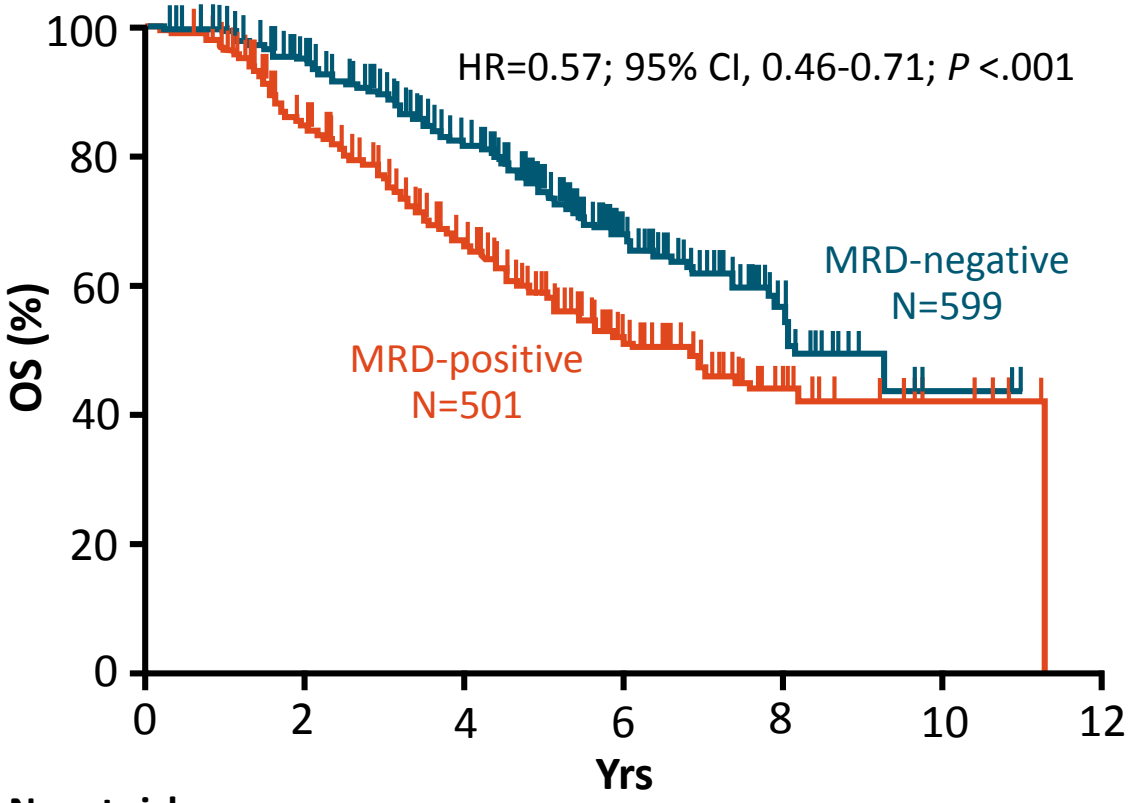
How deep of a response should we aim for?

Effect of MRD Status on PFS and OS in Multiple Myeloma: A Meta-analysis



No. at risk:

MRD neg:	457	214	70	12	1
MRD pos:	308	113	28	4	1



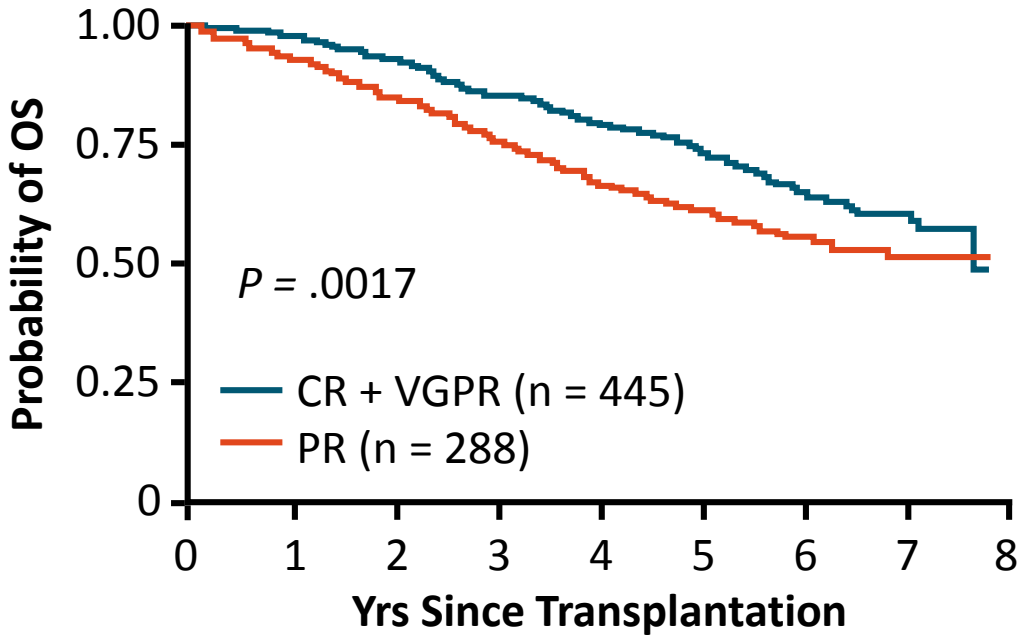
No. at risk:

MRD neg:	508	359	139	26	4
MRD pos:	390	250	105	17	5

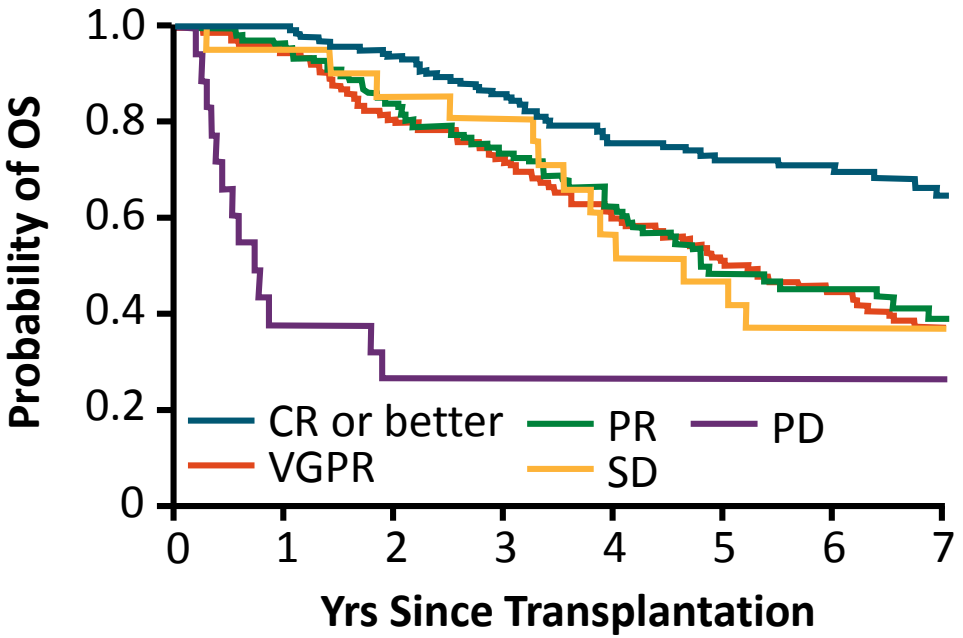
Munshi. JAMA Oncol. 2017;3:28.

Achieving ≥ VGPR or CR Should Be the Goal of Therapy

Achieving ≥ VGPR[1]



Achieving CR[2]



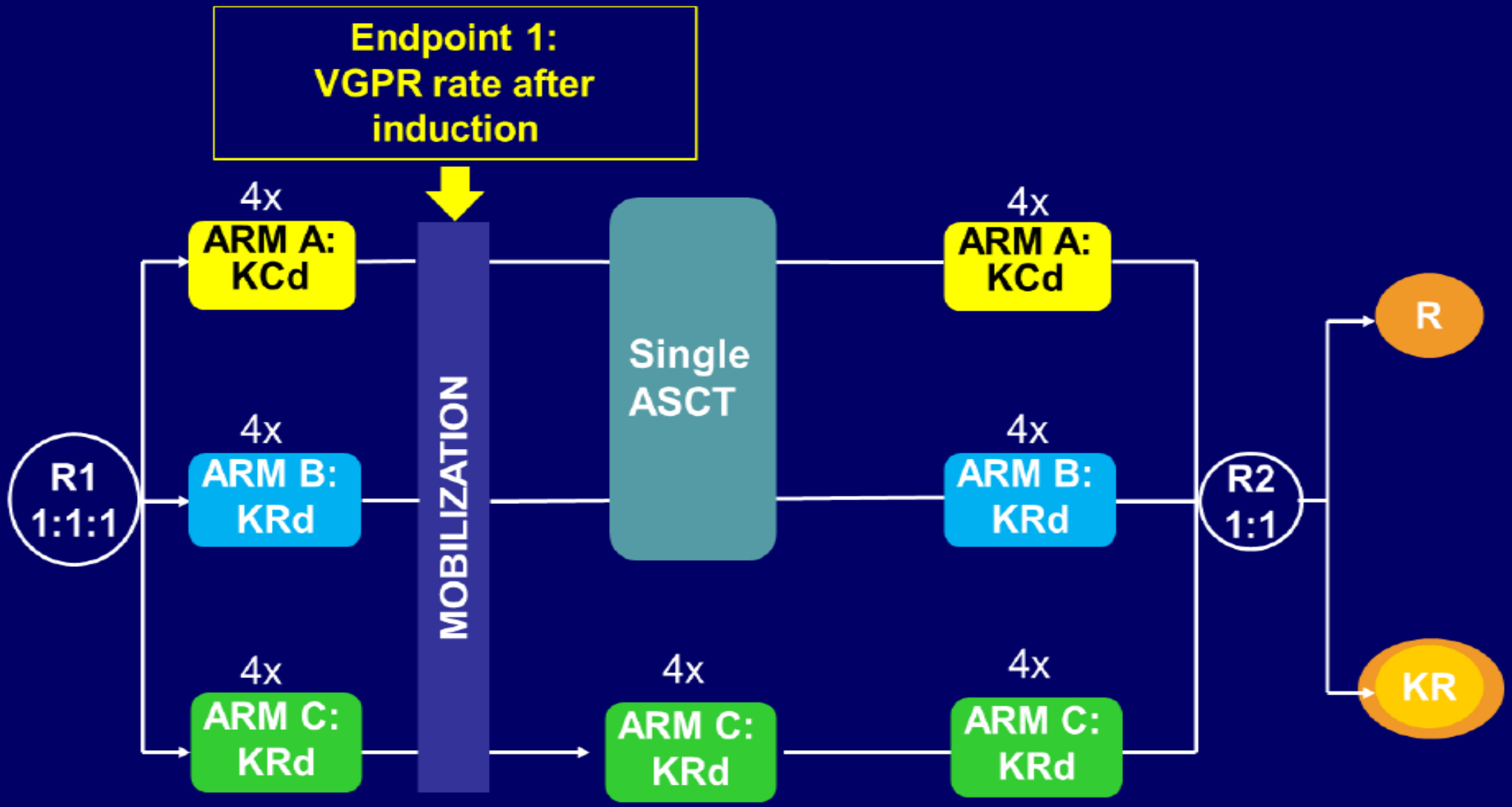
- Significantly better 5-yr OS in patients with sCR (80%) vs CR (53%) or nCR (47%) ($P < .001$)

1. Harousseau JL, et al. J Clin Oncol. 2009;27:5720-5726.
2. Kapoor P, et al. J Clin Oncol. 2013;31:4529-4535.

FORTE Trial Design

Gay et al; ASCO 2017

- NDMM patients, transplant eligible and younger than 65 years

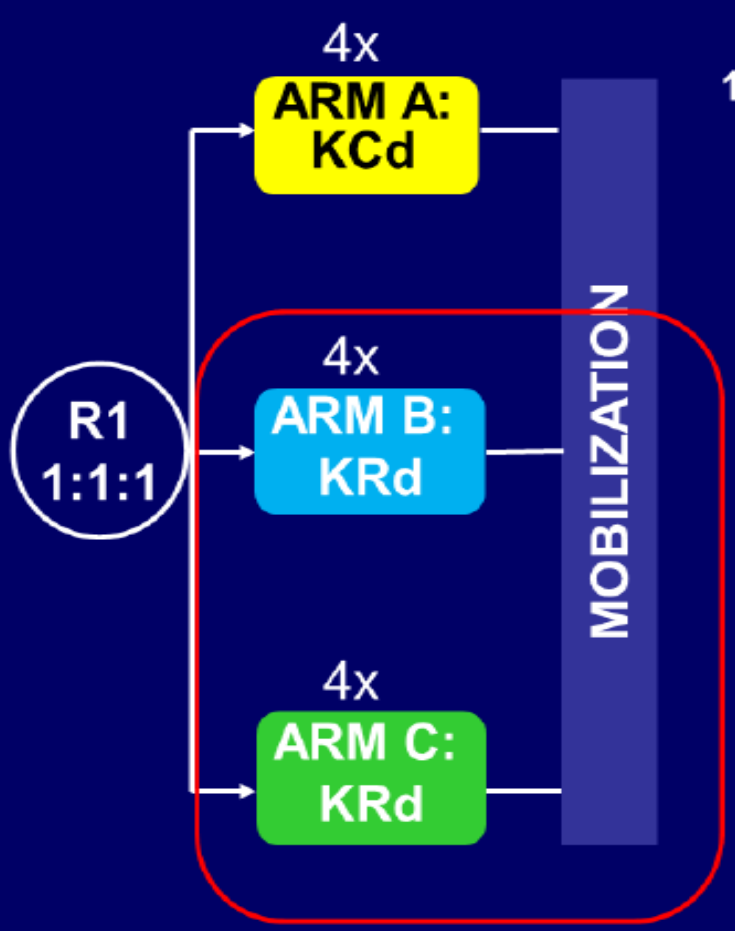


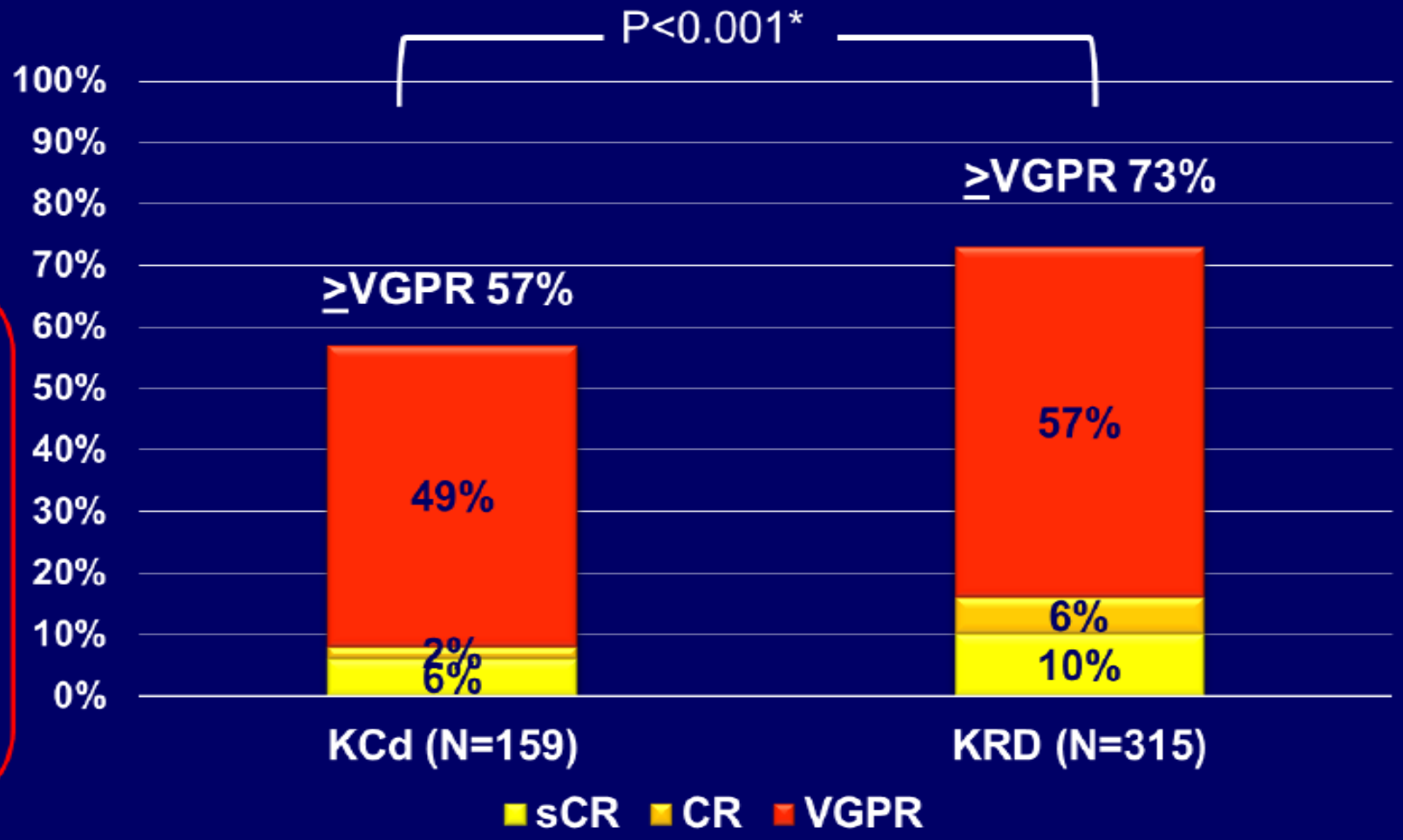
R1: randomization1; KCd: Carfilzomib, Cyclophosphamide, dexamethasone; KRd: Carfilzomib, Lenalidomide, dexamethasone; ASCT: Autologous Stem Cell Transplant; R2: randomization2; R: Lenalidomide; KR: Carfilzomib, Lenalidomide. NDMM, newly diagnosed multiple myeloma; ; VGPR: very good partial response; sCR, stringent complete response; MRD, minimal residual disease.

Gay et al; ASCO 2017

Induction Phase

Endpoint 1: VGPR rate with KRd vs KCd induction
ITT analysis

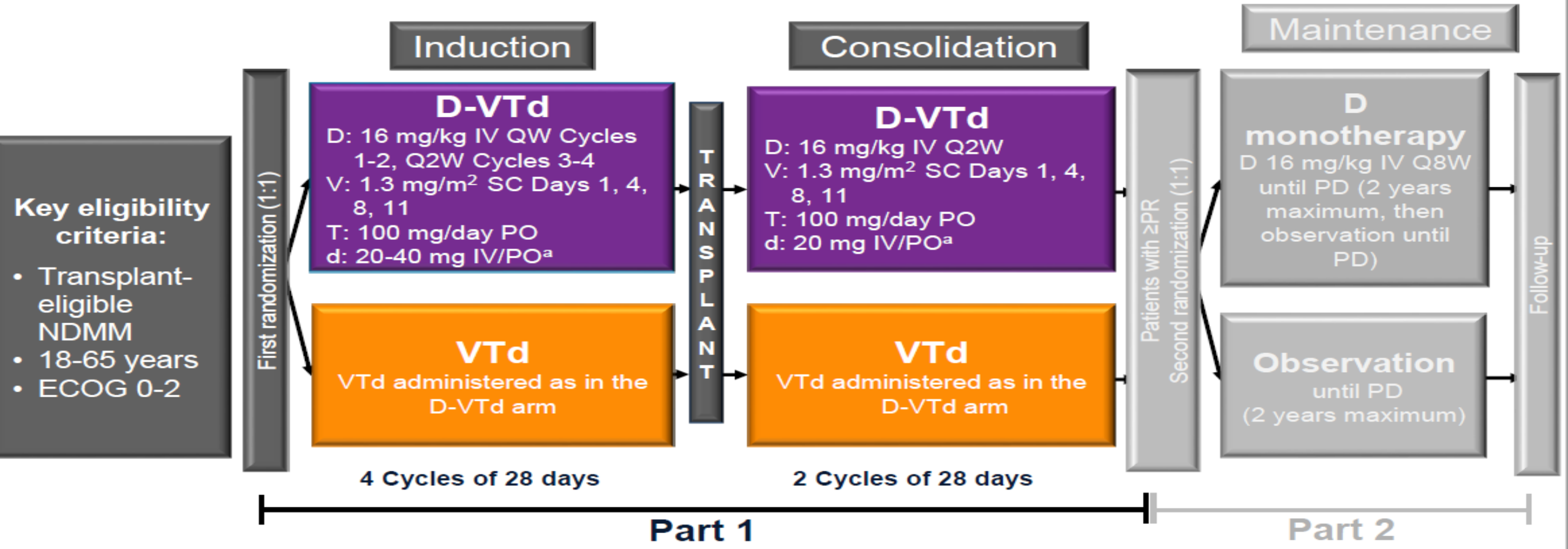




R1: randomization1; KCd: Carfilzomib, Cyclophosphamide, dexamethasone; KRd: Carfilzomib, Lenalidomide, dexamethasone; sCR: stringent complete response; CR: complete response; VGPR: very good partial response; *adjusted for International Staging System Stage, FISH analysis and age

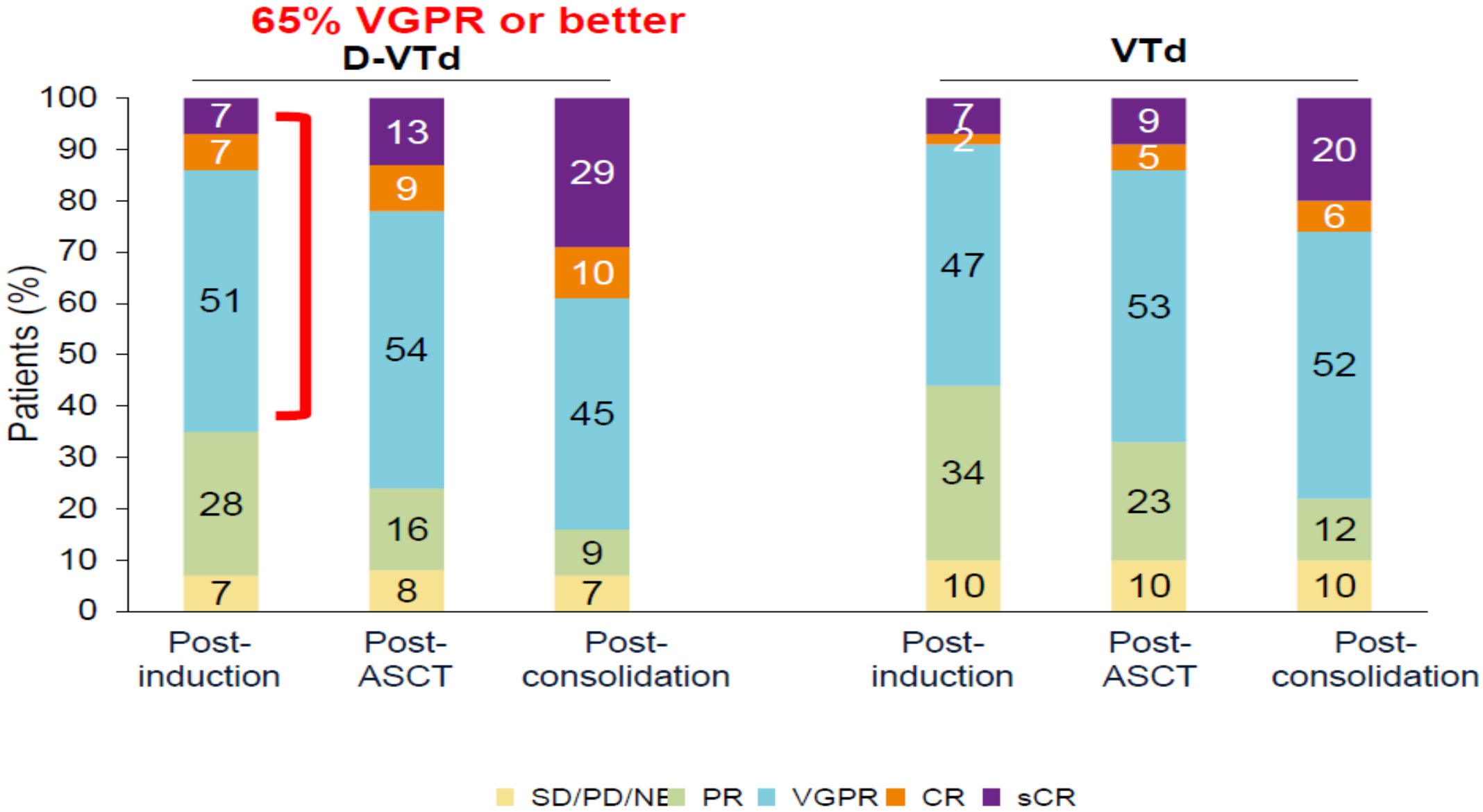
CASSIOPEIA Study Design

- Phase 3 study of D-VTd versus VTd in transplant-eligible NDMM (N = 1,085), 111 sites from 9/2015 to 8/2017

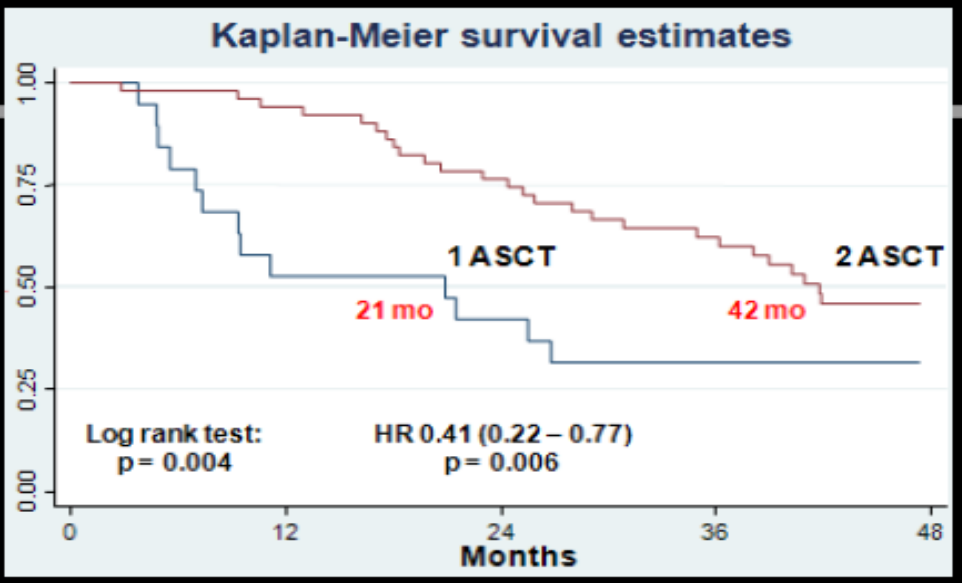


Moreau et al. The Lancet, 3 june 2019

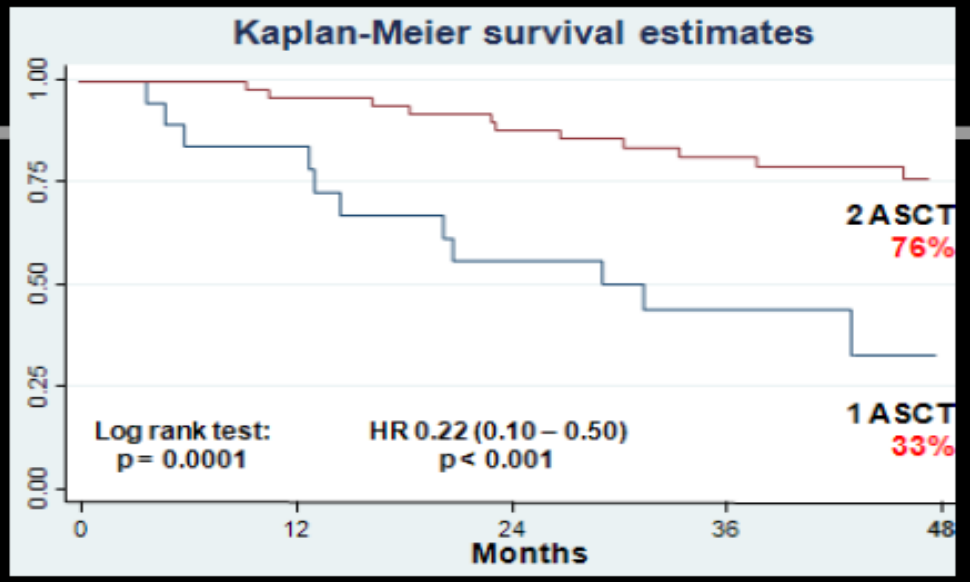
Efficacy: Response Rates Over Time

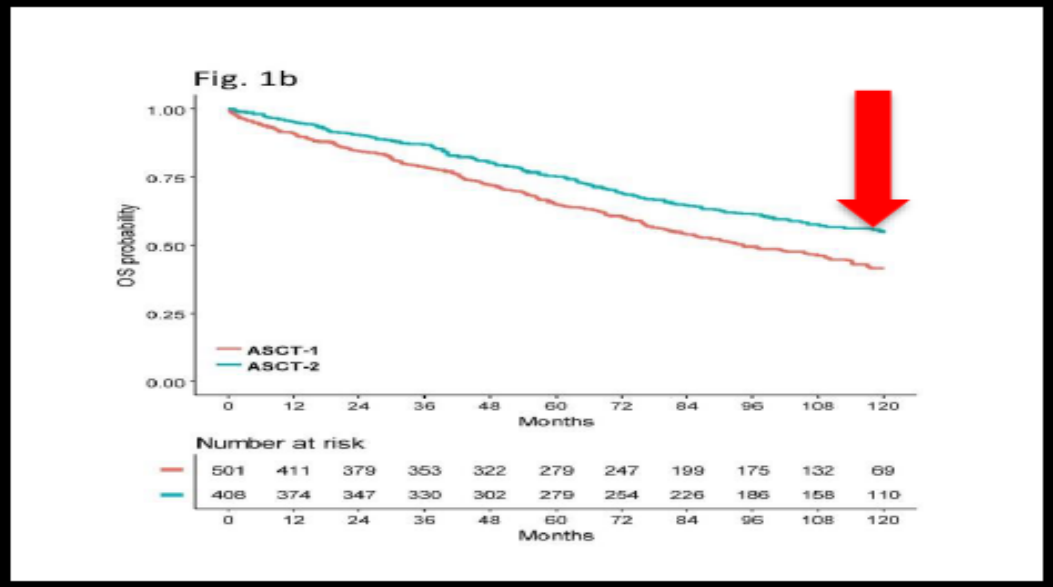


Double vs single ASCT after bortezomib-based induction



Cavo et al. ASH 2013 Abstract 767), oral presentation



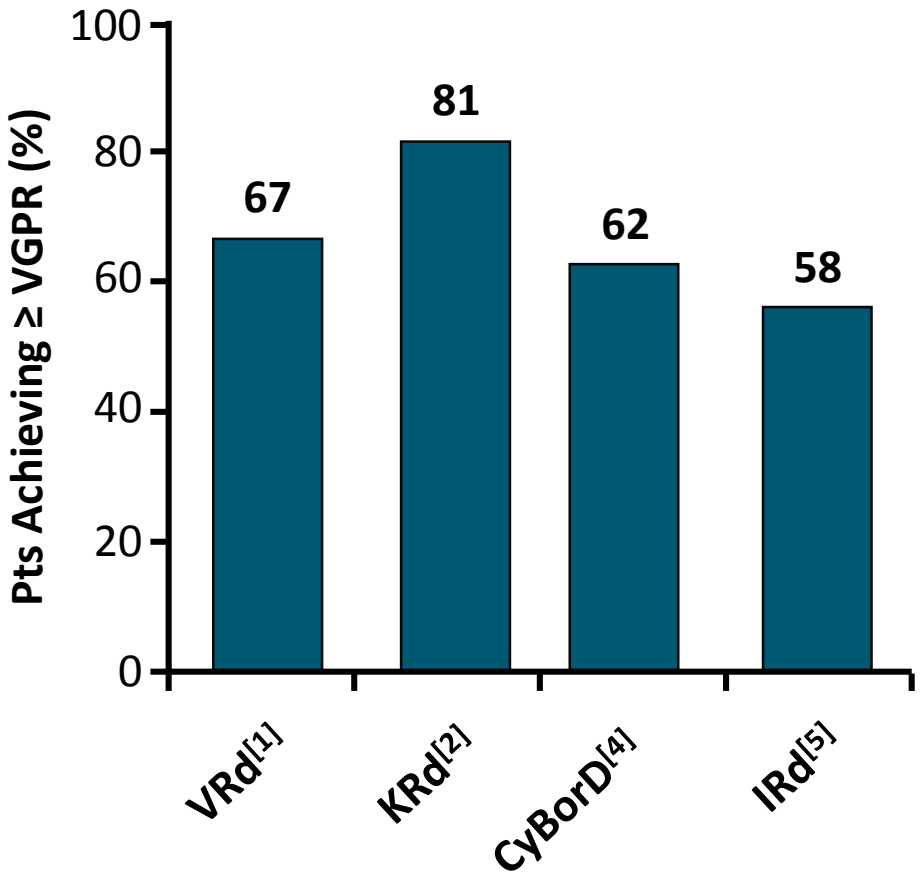


Cavo et al. ASH 2018 Abstract 124

Induction Regimens for Transplantation-Eligible Pts

Regimen	Median Total Cycles, n	Survival, %
VRd[1]	10*	18-mo PFS: 75 18-mo OS: 97
KRd[2,3]	12	12-mo PFS: 97 2-yr PFS: 92 3-yr PFS: 79 3-yr OS: 96
CyBorD[4]	4†	5-yr PFS: 42 5-yr OS: 70
IRd[5]	7	12-mo PFS: 88 12-mo OS: 94

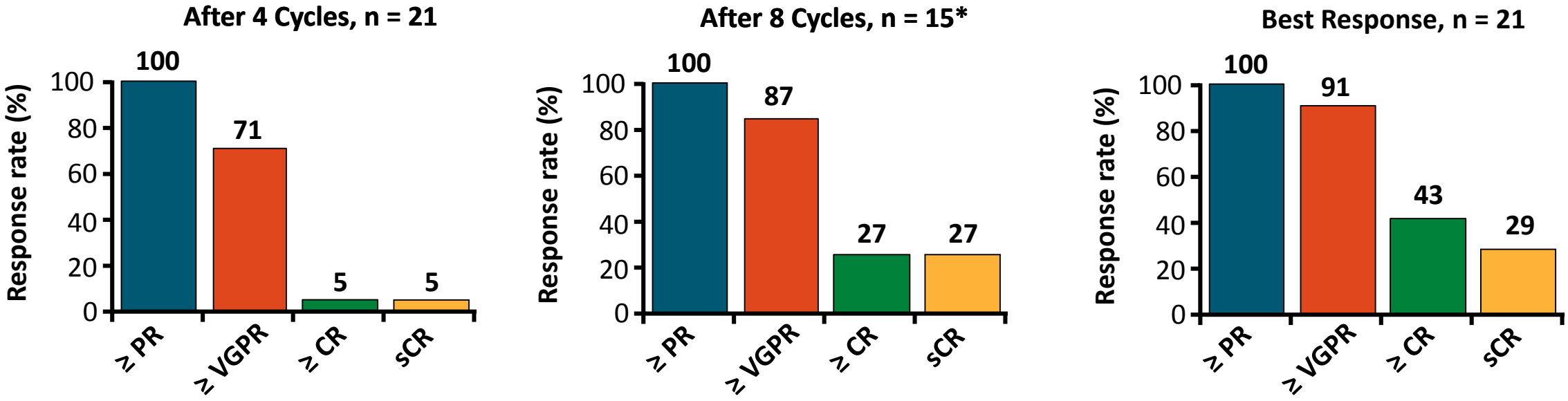
*Induction and maintenance; any drug
†Median NR; response after 4 cycles was primary study goal.



1. Richardson. Blood. 2010;116:679. 2. Jakubowiak AJ. Blood. 2012;120:1801. 3. Jasielec. ASH 2013. Abstract 3220. 4. Reeder. Br J Haematol. 2014;167: 563. 5. Kumar. Lancet Oncol. 2014;15:1503.

Daratumumab + KRd in Newly Diagnosed MM: Response

- Median number of treatment cycles: 11.5 (range: 1.0-13.0)



Depth of response improved with duration of treatment

*5 patients who proceeded to ASCT before cycle 8 and 1 patient who discontinued due to PD at cycle 7 were excluded.

- Median follow-up: 10.8 mos (range: 4.0-12.5)
- OS: 100% at follow-up

Jakubowiak. ASCO 2017. Abstract 8000.

Phase III IFM/DFCI 2009: Frontline VRd ± ASCT in Younger Pts With MM

- Previously untreated patients ≤ 65 yrs of age (N = 700)

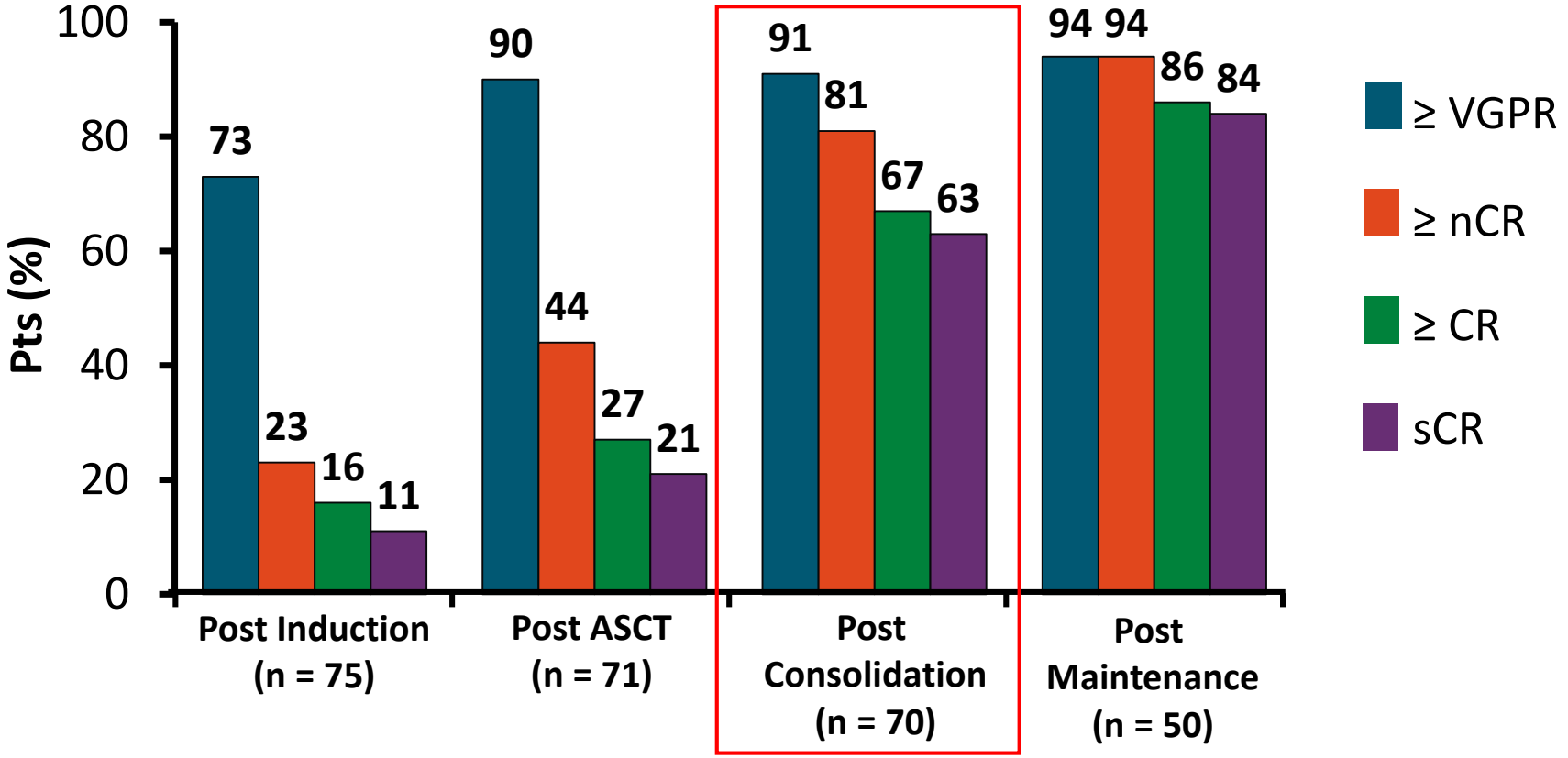
Outcome	VRd + ASCT (n = 350)	VRd Only (n = 350)	HR (95% CI)	*P* Value
Median PFS, mos	50	36	0.65 (0.53-0.80)	< .001
4-yr OS, %	81	82	1.16 (0.80-1.680	.87
≥ 1 SPM, %	7	6		
ORR, %	98	97		
≥ VGPR, %	88	77		.001

- PFS benefit in ASCT arm uniform across subgroups: age (< 60 or 60-65 yrs), sex, isotype (IgG or IgA or light chain), ISS stage (I or II or III), cytogenetics (standard or high risk)

Attal. N Engl J Med. 2017;376:1311.

Phase II MMRC Trial: Extended KRd Therapy + ASCT in Pts With Newly Diagnosed Myeloma

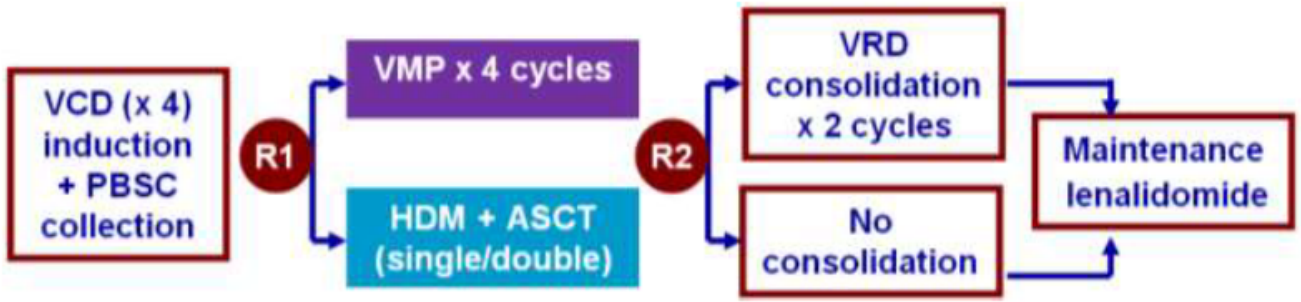
- 4 cycles of KRd induction + ASCT, 4 cycles of KRd consolidation, 10 cycles of KRd maintenance

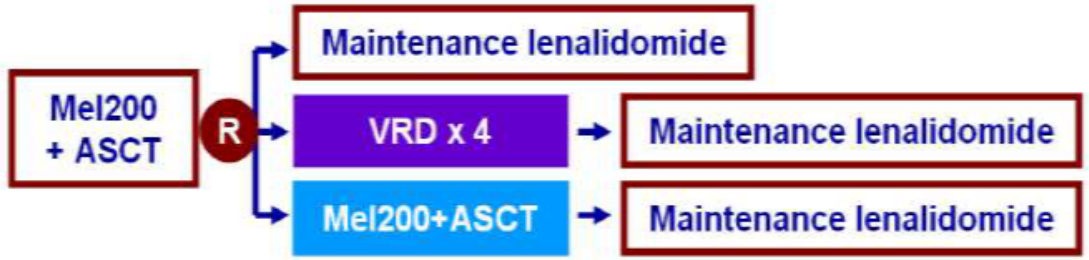


Zimmerman. ASH 2016. Abstract 675.

Consolidation therapy after ASCT: state of the art

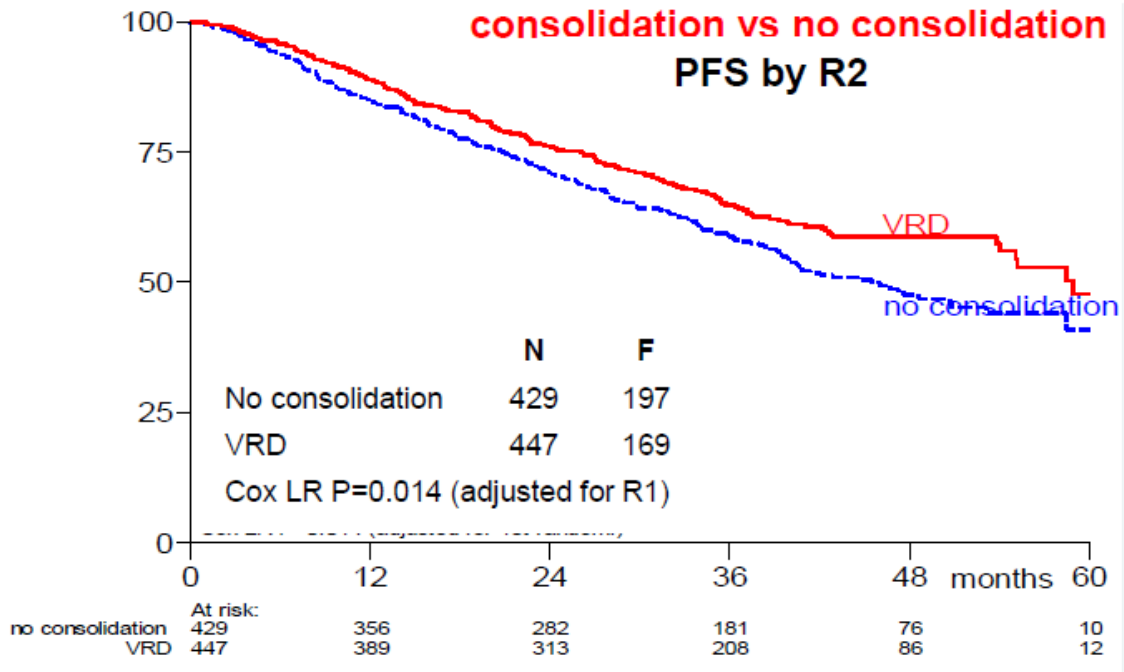
Consolidation is not yet a standard clinical practice outside of clinical trials





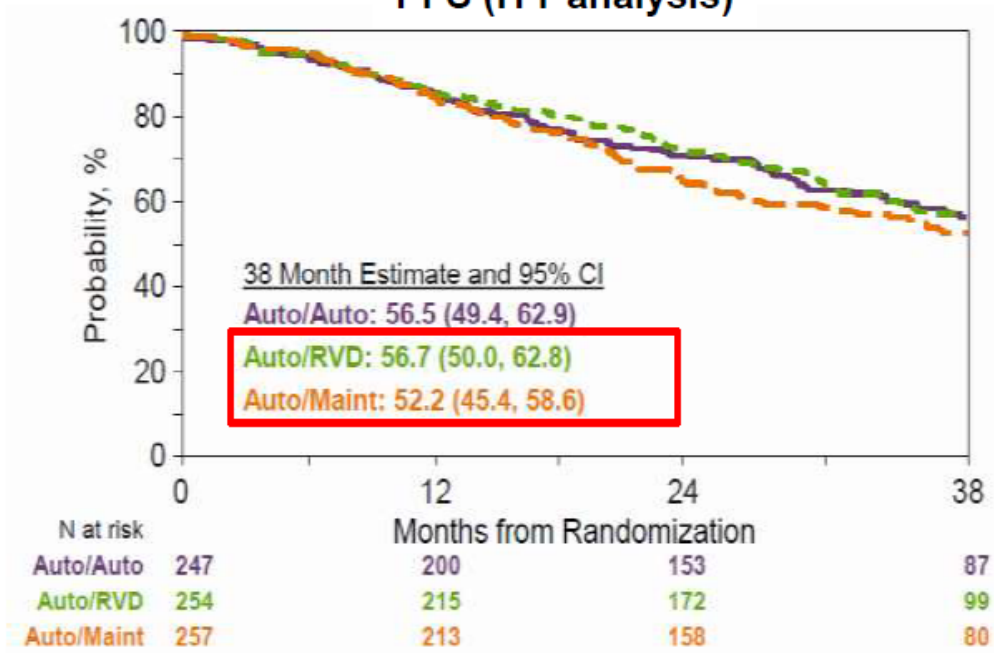
EMN02 phase 3 study of VRD consolidation vs no consolidation

PFS by R2



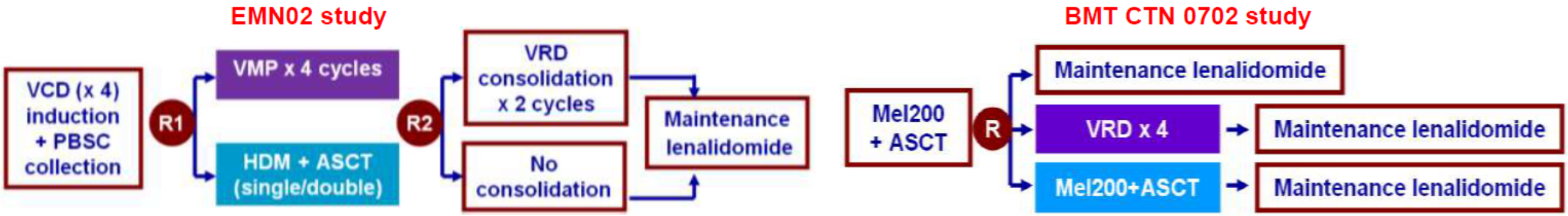
STaMINA phase 3 study of VRD consolidation vs no consolidation

PFS (ITT analysis)



Sonneveld P, et al. EHA 2018, oral presentation; Stadtmauer EA et al. J Clin Oncol 2019;37(7):589-597.

EMN02 and BMT CTN 0702: study inconsistencies

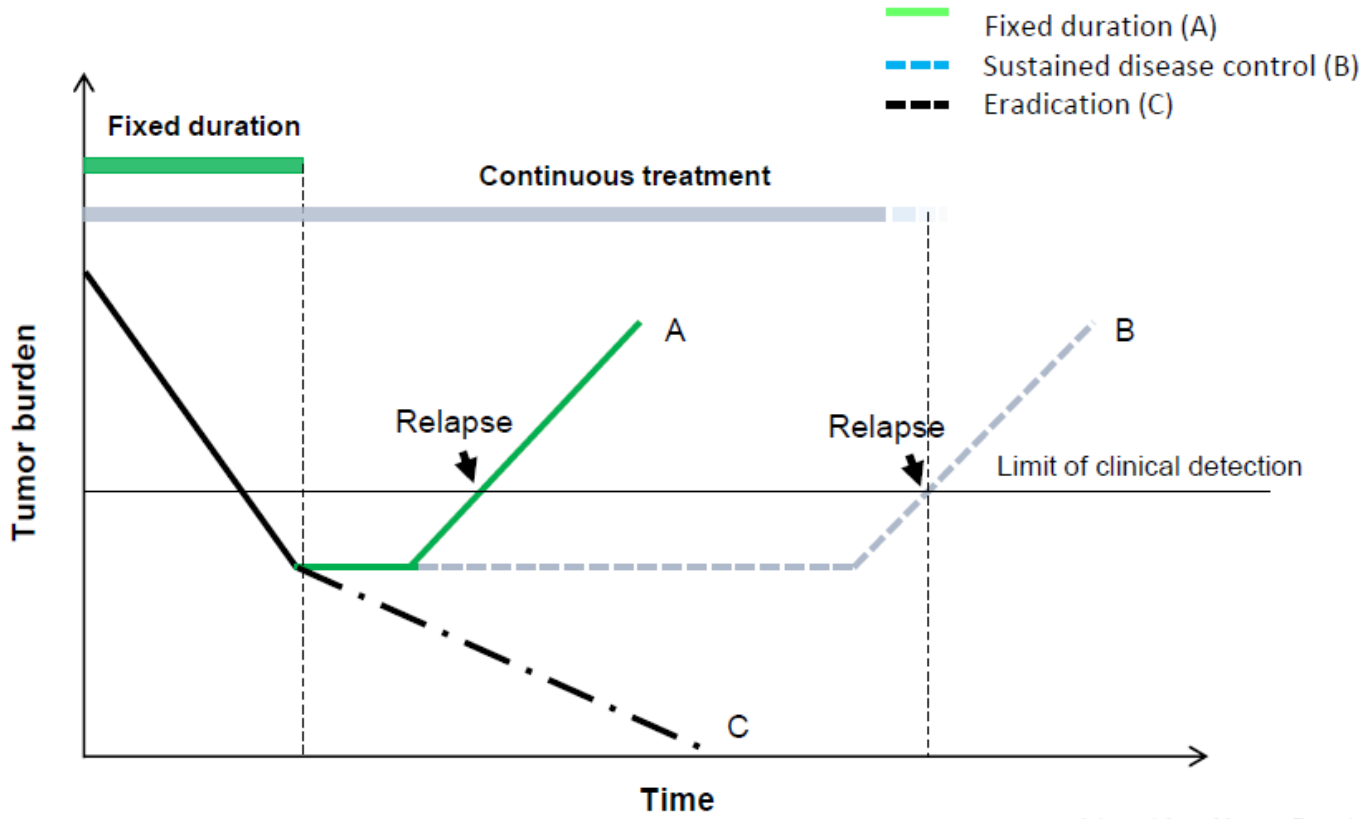


	EMN02	STAMINA
Newly diagnosed (%)	100	85
Induction regimen (%)	VCD (100)	VCD (14) VRD (55)
Length of induction therapy (months)	2-3	2-14
Failure to receive double ASCT (%)	19.8	32
Consolidation therapy (%)	Yes (50)	NO (100)
Maintenance therapy	Len (10 mg)	Len (10-15) mg
PFS at 36-38 mos (%) - All patients - High-risk patients*	 73.6 64.9	 56.5 42.2

*Different criteria

Cavo M, et al. ASH 2017 (Abstract 401), Oral presentation; Stadtmauer EA et al. J Clin Oncol 2019;37(7):589-597.

Maintenance or continuous treatment: rationale and objectives



Adapted from Moreau P et al. *Leuk Res.* 2012;36 (suppl 1):S13-S8.

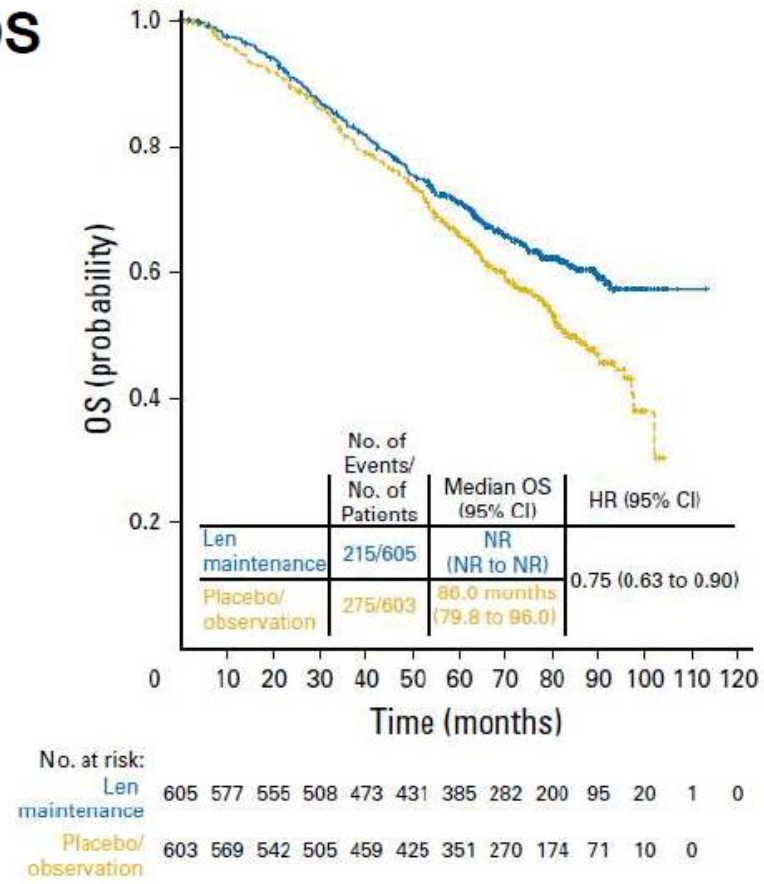
- ***Effective maintenance/continuous therapy should be convenient for the patient***, *extend remission*, and ultimately *OS*, while keeping *toxicity minimal*[1,2]

1.McCarthy PL, Holstein SA: Hematology (Am Soc Hematol Educ Program) 2016:504-511, 2016

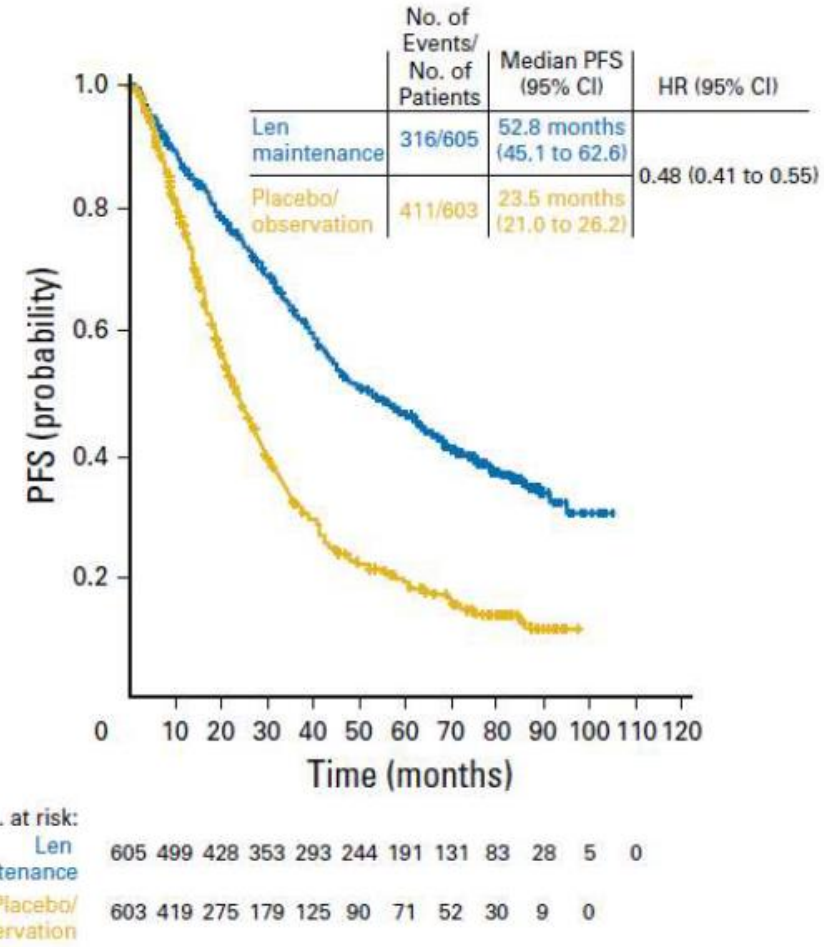
Maintenance therapy: state of the art

ESMO Guidelines 2017
Lenalidomide at 10-15 mg daily is the standard EMA-approved maintenace therapy after ASCT

OS



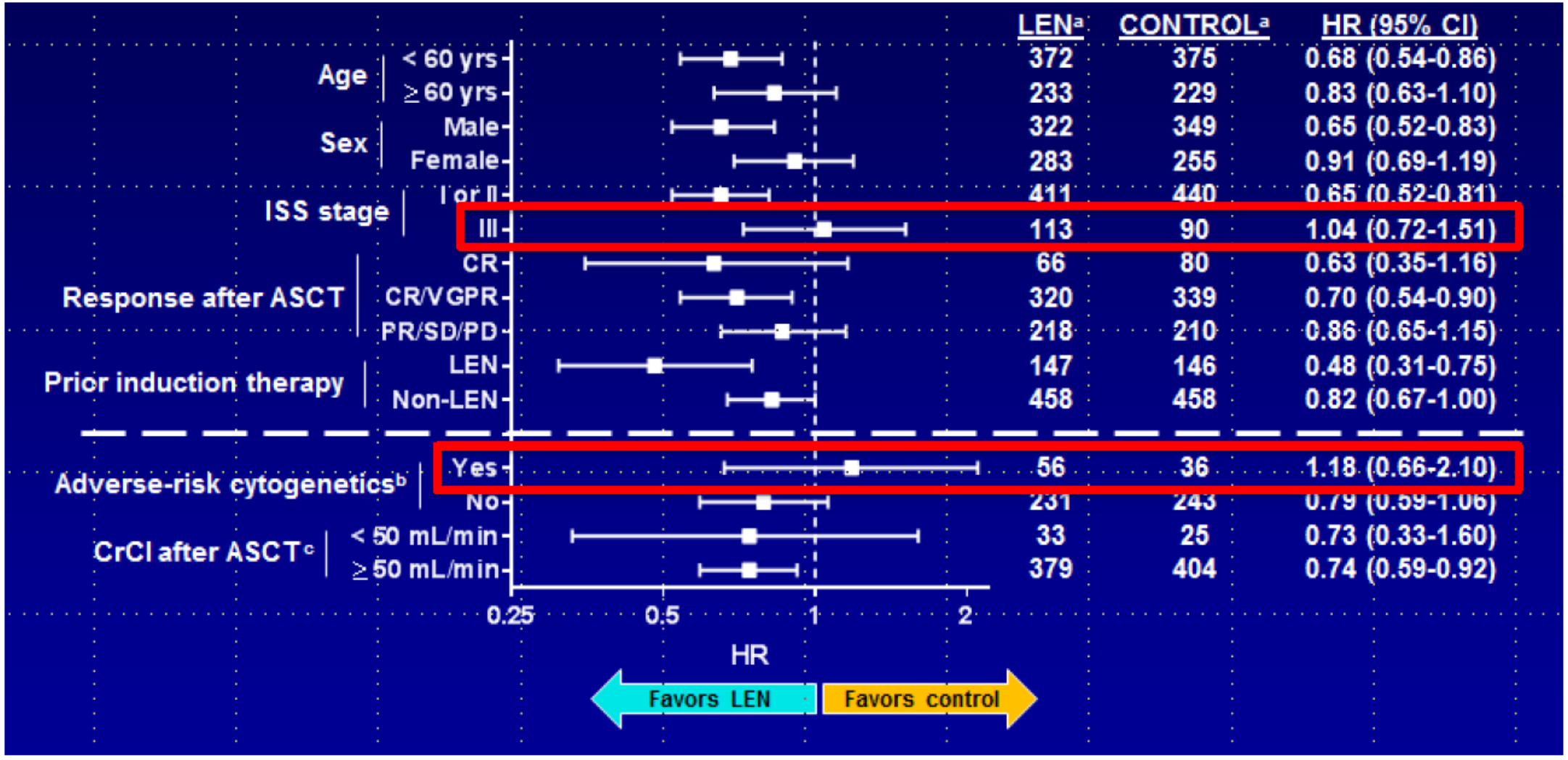
PFS



- **Median follow-up 80 months**

McCarthy PL, et al. J Clin Oncol. 2017;35(29):3279-3289.

Lenalidomide maintenance: OS subgroup analysis



a Number of patients. b Cytogenetic data were available only for the IFM and GIMEMA studies. c CrCl post-ASCT data were available only for the CALGB and IFM studies. ASCT, autologous stem cell transplant; CR, complete response; CrCl, creatinine clearance; HR, hazard ratio; ISS, International Staging System; LEN, lenalidomide; OS, overall survival; PD, progressive disease; PR, partial response; SD, stable disease; VGPR, very good partial response.

Attal M, et al. ASCO 2016, abstract 8001, oral presentation

Bortezomib maintenance therapy

- **Lack of studies designed to compare bortezomib maintenance vs placebo/observation or lenalidomide, and to isolate the contribution of bortezomib as maintenance therapy.**

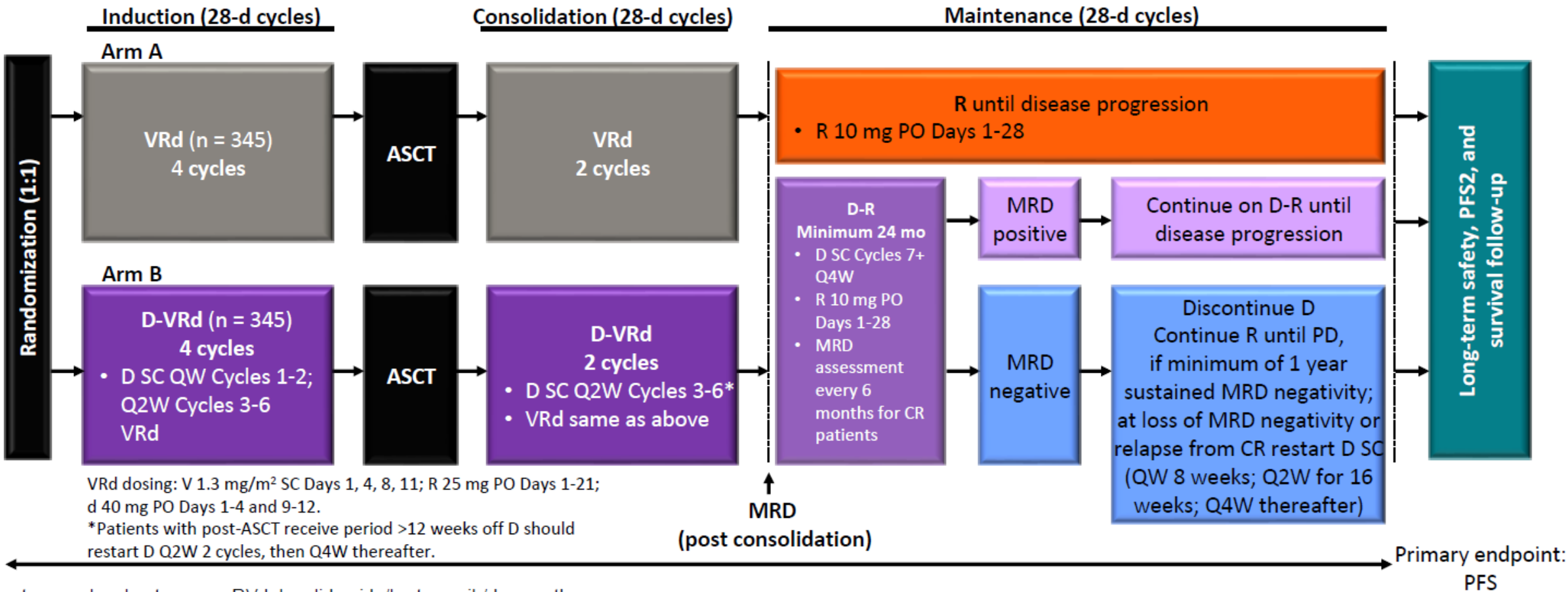
Study details	n	Treatment	Outcome	
			PFS	OS
HOVON 65 MM/ GMMG-HD4[1,2]	413	PAD x 3 → HDM → bortezomib every 2 weeks for 2 years	34 mo	91 mo
Median follow-up: 96 months	414	VAD x 3 → HDM → thalidomide daily for 2 years	28 mo p <0.001	82 mo
PETHEMA/GEM[3]	89	VT (1 cycle bortezomib† every 3 months, thalidomide daily) for 3 years	50.6 mo	OS not significantly different between arms
Median follow-up: 58.6 months	87	Thalidomide (daily for 3 years)	40.3 mo	
	90	Interferon-α2b (3 x per week for 3 years)	32.5 mo p < 0.003	

*Bortezomib administered at 1.3mg/m^2 IV in both studies †Bortezomib administered on Days 1,4,8, and 11

1. Goldschmidt, H. et al. Leukemia 2018;32(2):383-390; 2. Sonneveld et al. ASH 2015 (Abstract 27), oral presentation; 3. Rosiñol et al. Leukemia. 2017;31(9):1922-1927.

Daratumumab-VRd vs VRd Study Design
PERSEUS phase 3 trial

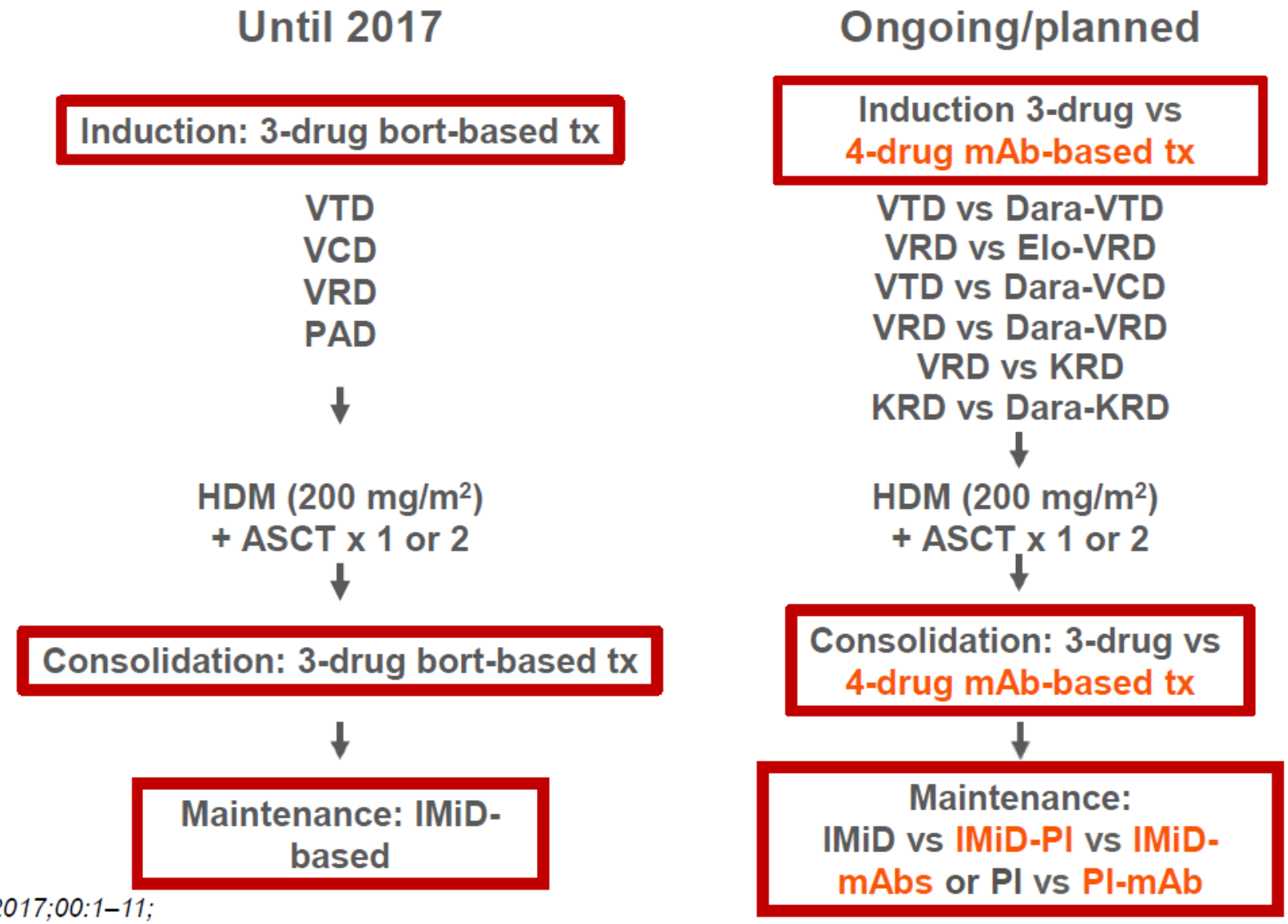
- Collaborative study with European Myeloma Network (EMN)
- Phase 3 study of DARA in combination with VRd versus VRd for newly diagnosed transplant-eligible patients; N ≈ 690



DSC, daratumumab subcutaneous; RVd, lenalidomide/bortezomib/dexamethasone; ASCT, autologous stem cell transplant; QW, weekly; Q2W, every 2 weeks; Q4W, every 4 weeks; MRD, minimal residual disease; PO, by mouth; PFS2, progression-free survival on next line of therapy.
Protocol EMN17/54767414MMY3014.

www.clinicaltrials.gov identifier: NCT03710603, accessed March 2019

Summary current and future treatment algorithm for transplant-eligible MM patients



Moreau P, et al. Ann Oncol 2017;00:1–11;

Cavo, personal communication; clinicaltrials.gov identifiers: NCT02874742; NCT02541383; NCT02495922; NCT01863550

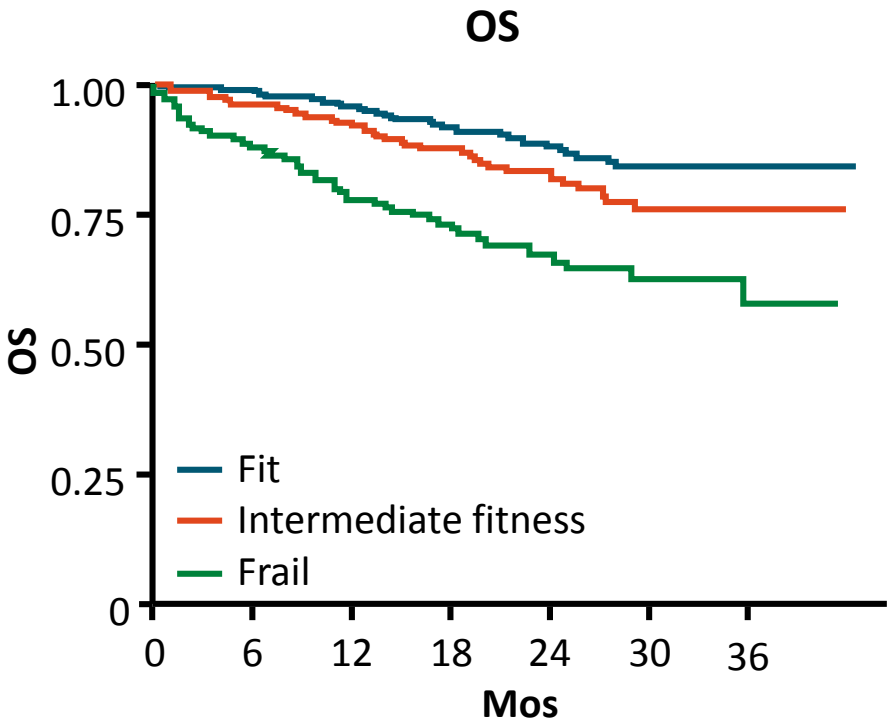
Myeloma in the Elderly: Considerations

- Is the disease different?
  - Comorbidities raise risk of toxicity
  - Frailty score (from 0-5)—based on age, comorbidities, and cognitive and physical conditions—can predict mortality, risk of toxicity[1]
- What are the goals of therapy?
  - 3-drug vs 2-drug induction
  - Duration of response to therapy important even in elderly

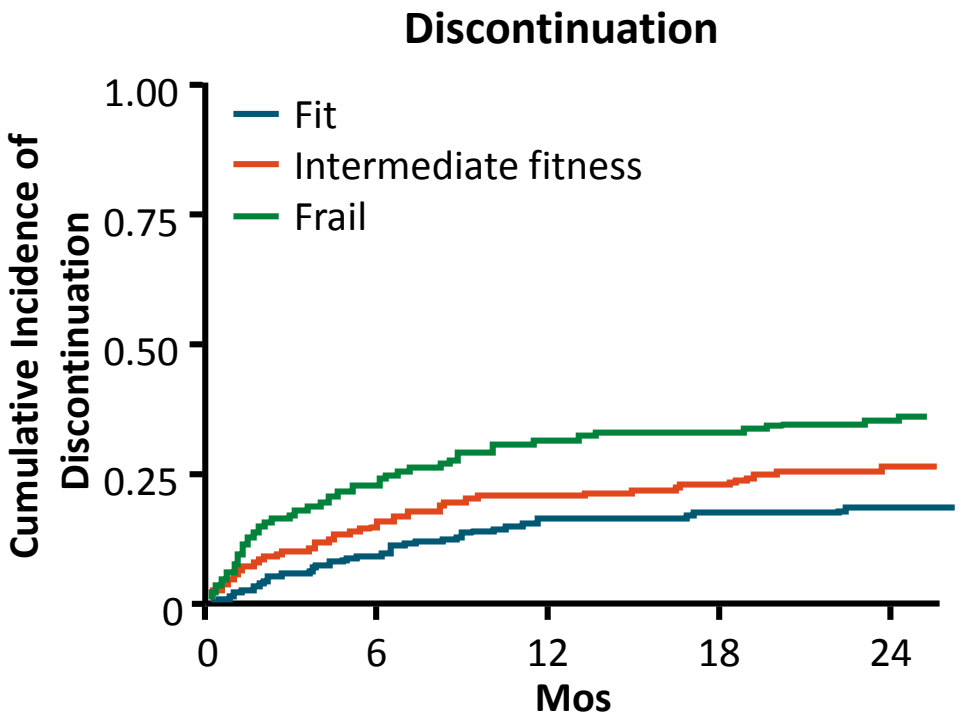
Palumbo. Blood. 2015;125:2068.

Effect of Patient Fitness on Myeloma Treatment Outcomes

- Pooled analysis of newly diagnosed elderly patients from 3 trials (N = 869)



3-yr OS: fit 84%, intermediate 76% (HR: 1.61; *P* = .042), frail 57% (HR: 3.57; *P* < .001)



D/c at 12 mos: fit 17%, intermediate 21% (HR: 1.41; *P* = .052), frail 31% (HR: 2.21; *P* < .001)

Palumbo. Blood. 2015;125:2068.

Myeloma in Octogenarians: The Era of Modern Myeloma Therapy

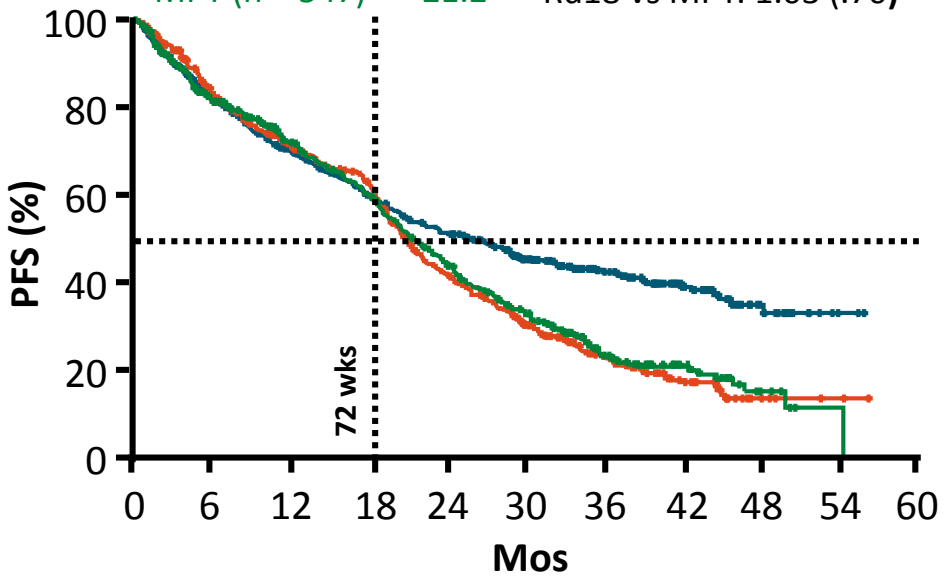
- More moderate to severe renal impairment
- Worsening PS (≥ 2)
- More frequent ISS 3 disease
- Cytogenetics different; less frequently del(17p) and t(4;14)
- Efficacy comparisons between those < 65 vs ≥ 80 yrs of age

Outcome	Pts < 65 Yrs of Age	Pts ≥ 80 Yrs of Age
Response to therapy, %	85	63
Median PFS, mos	31	11
OS	66% at 5 yrs	Median 19.5 mos
Early mortality at 2 mos, %	3	14

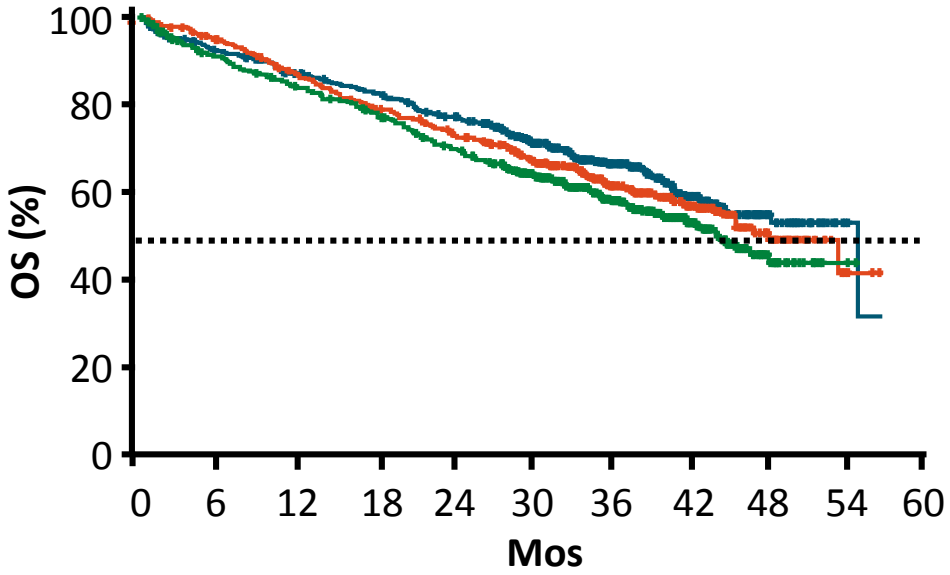
Dimopoulos. ASH 2014. Abstract 4738.

FIRST Trial: Efficacy Analysis of Len/Dex vs MPT in SCT-Ineligible Pts With MM

	Median PFS, Mos	HR (*P* Value)
Rd (n = 535)	25.5	Rd vs MPT: 0.72 (< .001)
Rd18 (n = 541)	20.7	Rd vs Rd18: 0.70 (< .001)
MPT (n = 547)	21.2	Rd18 vs MPT: 1.03 (.70)



	4-Yr OS, %	HR (*P* Value)
Rd (n = 535)	59	Rd vs MPT: 0.78 (.02)
Rd18 (n = 541)	56	Rd vs Rd18: 0.90 (.31)
MPT (n = 547)	51	Rd18 vs MPT: 0.88 (.18)



- Overall response (continuous Rd vs MPT): 75% vs 62% (*P* < .001)
- Similar, tolerable safety profiles between treatment groups
- Invasive SPM: 3% with continuous Rd vs 6% with Rd18 vs 5% with MPT

Benboubke. N Engl J Med. 2014;371:906. Delforge. ASCO 2014. Abstract 8516.

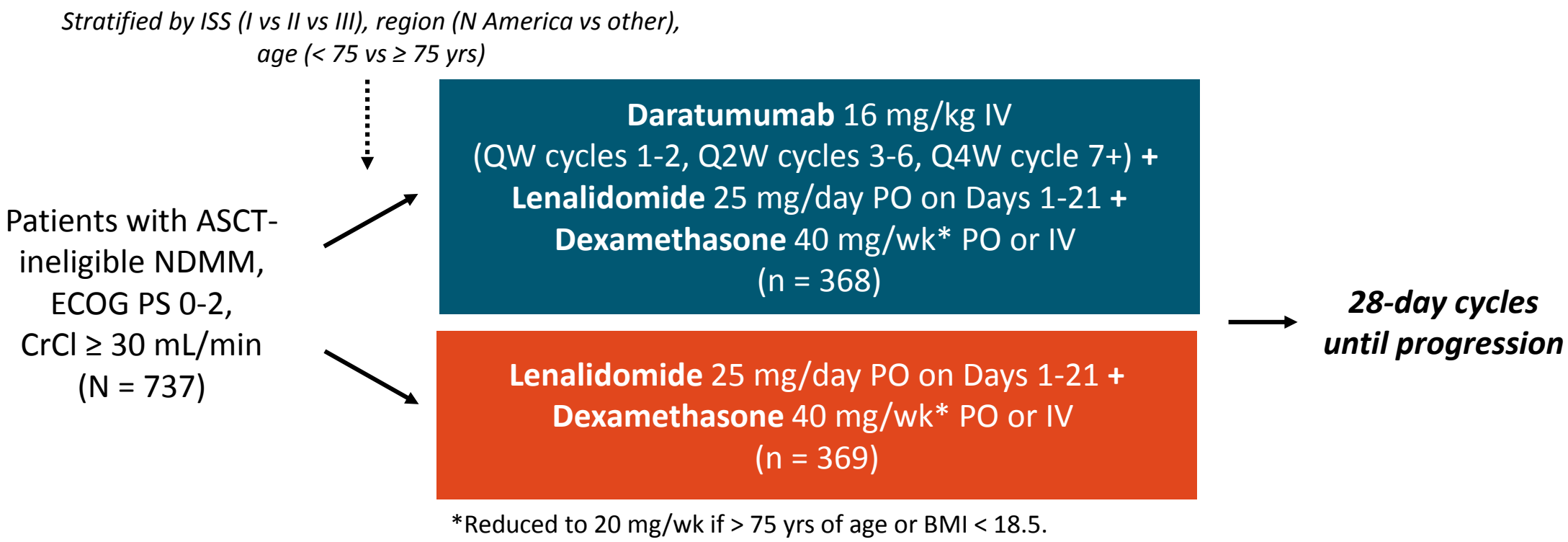
Modified Lenalidomide/Bortezomib/Dexamethasone in ASCT-Ineligible Pts

- Phase II trial exploring utility of modified VRd (VRd lite); N = 53
  - Lenalidomide: single daily PO dose of 15 mg on Days 1-21
  - Bortezomib: 1.3 mg/m2 SC once weekly on Days 1, 8, 15, 22
  - Dexamethasone: 20 mg 2x weekly if ≤ 75 yrs or 1x weekly if > 75 yrs
- VRd lite resulted in 90% ORR (≥ PR), ≥ VGPR: 60%
  - 5 patients d/c after < 4 cycles: worsening adrenal insufficiency (n = 1), len-based rash (n = 1), investigator discretion (n = 1), travel distance (n = 2)
- AEs manageable and well tolerated in an older population
  - Grade ≥ 3 AEs: hypophosphatemia (31%), rash (10%)

O'Donnell. Br J Hematol. 2018;182:222.

Phase III MAIA: Lenalidomide/Dexamethasone ± Daratumumab in Patients With ASCT-Ineligible NDMM

- Randomized phase III trial

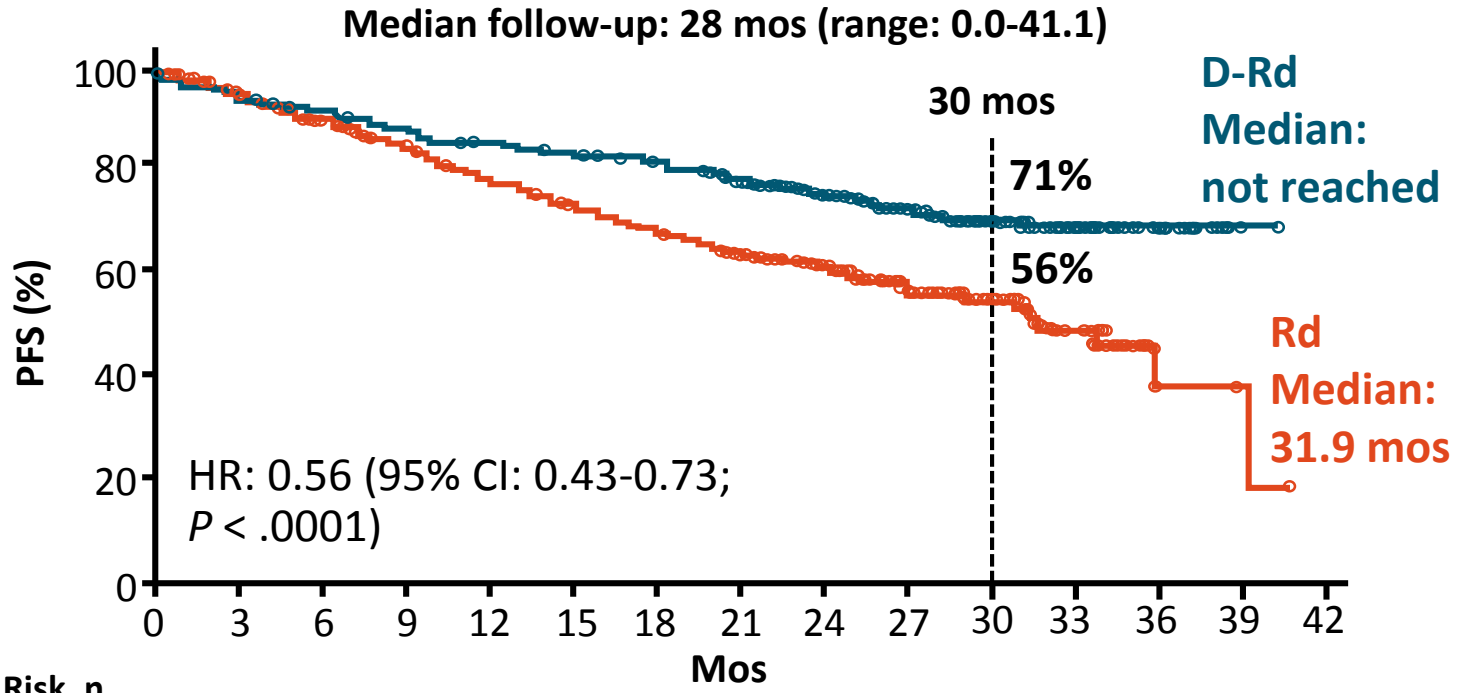


*Reduced to 20 mg/wk if > 75 yrs of age or BMI < 18.5.

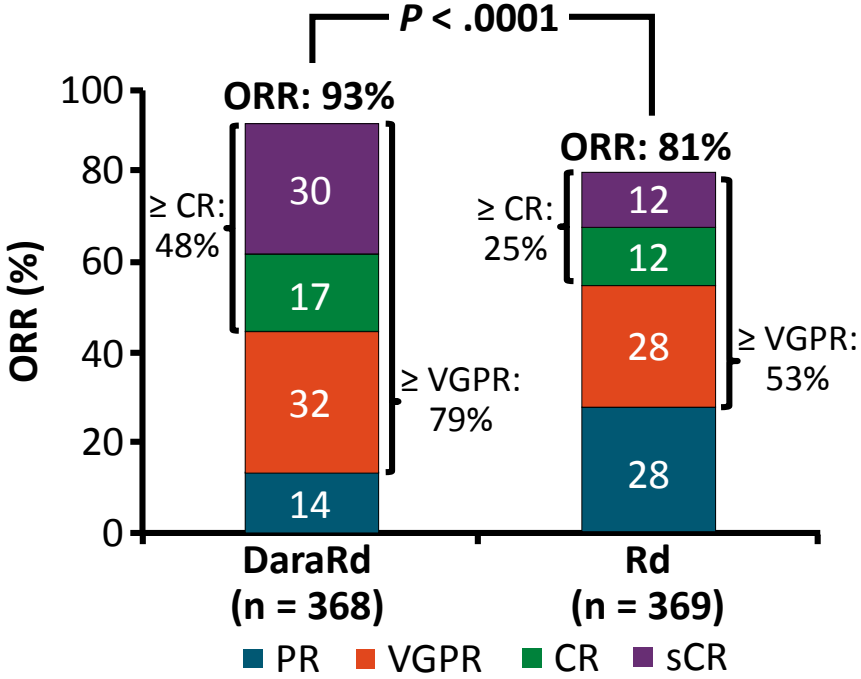
- Primary endpoint: PFS
- Secondary endpoints : ≥ CR rate, ≥ VGPR rate, MRD negativity, ORR, OS, safety

Facon. ASH 2018. Abstr LBA-2.

Phase III MAIA Trial: Survival With DaraRd vs Rd in Older or ASCT-Ineligible Patients



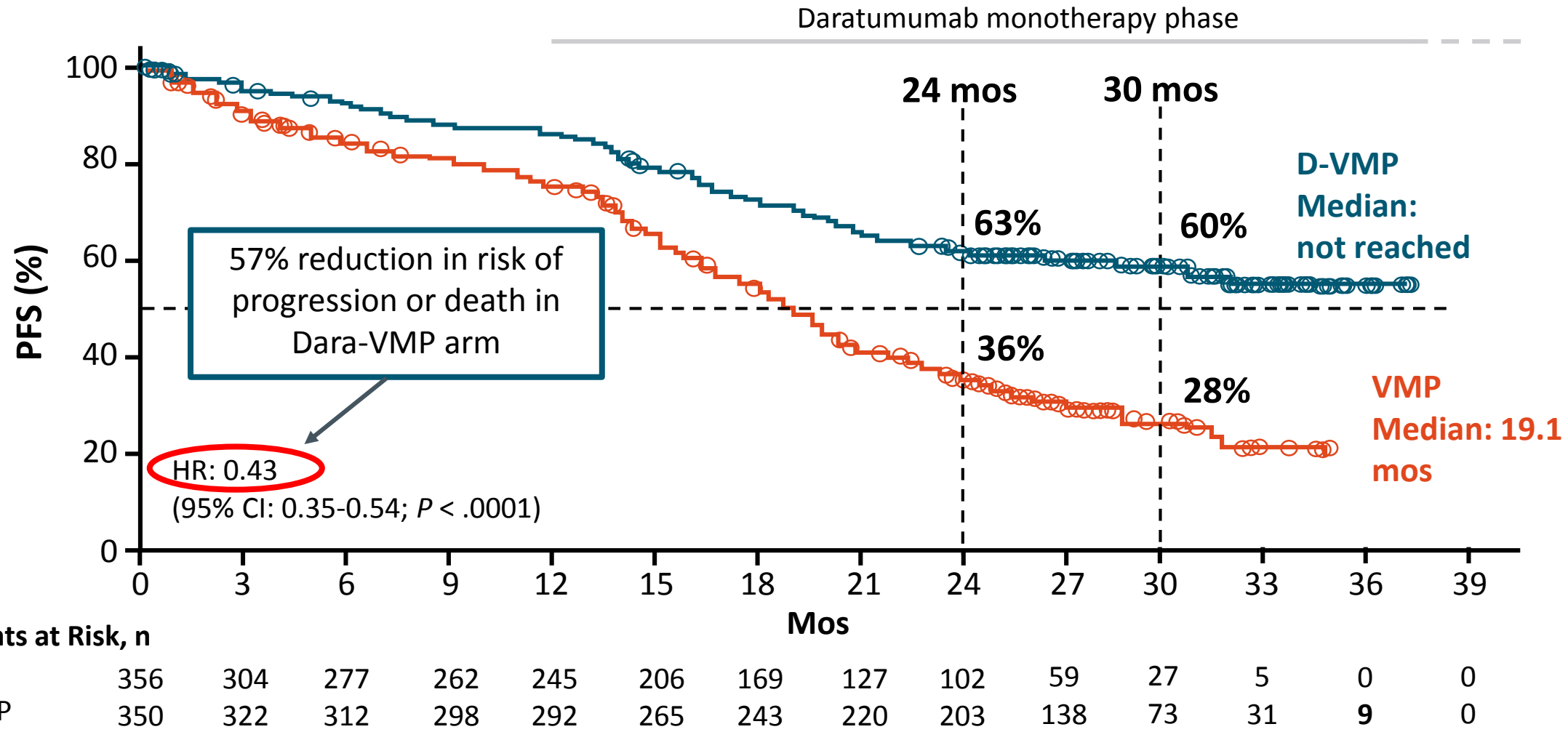
Pts Risk, n															
Rd	369	332	307	280	254	236	219	200	149	94	50	18	3	2	0
DaraRd	**368**	**347**	**335**	**320**	**309**	**300**	**290**	**271**	**203**	**146**	**86**	**35**	**11**	**1**	**0**



- Daratumumab treatment favored in most subgroups analyzed, including age, race, ISS stages, ECOG PS scores
- Reduced risk of progression or death with MRD negativity in both arms
- MRD negativity increased with addition of daratumumab
  - **DaraRD: 24% MRD negative**
  - Rd: 7% MRD negative

Facon. ASH 2018. Abstr LBA-2.

Phase III ALCYONE Trial: VMP ± Daratumumab in ASCT-Ineligible Patients With Newly Diagnosed Myeloma



Patients at Risk, n

VMP	356	304	277	262	245	206	169	127	102	59	27	5	0	0
D-VMP	350	322	312	298	292	265	243	220	203	138	73	31	**9**	0

Dimopoulos. ASH 2018. Abstr 156.

Treatment Considerations: Special Populations

Patient Population	Considerations
Frail, elderly patients	Use standard 3-drug regimens with available dose reductions to improve tolerability Some would consider doublet therapy with Rd or melphalan-based regimen VMP
Renal dysfunction	Consider RVd, with lenalidomide dose adjusted based on CrCl Consider VD (with high-dose dexamethasone) or VMP as other options
Cardiac dysfunction	Avoid carfilzomib Use thromboprophylaxis with lenalidomide-based therapy
Peripheral neuropathy	Administer bortezomib SQ and use weekly dosing Consider induction with carfilzomib/len/dex (KRd) or ixazomib/len/dex (IRd)
Aggressive, high-risk disease	Consider induction with carfilzomib/len/dex (KRd)
Extramedullary disease and plasma cell leukemia	Associated with shorter survival rates, and considered as high-risk Consider VTD-PACE and ASCT

Summary of Currently Available Treatment Options for Newly Diagnosed Myeloma

ASCT Eligible

- Induction triplet regimens
  - VRd (preferred)
  - Carfilzomib/Len/Dex (for high-risk patients)
  - Bortezomib/Cyclo/Dex
  - Promising new data with quad regimens
- ASCT consult recommended for all patients
- Maintenance
  - Lenalidomide approved following ASCT
  - Consider IMiD/PI-based maintenance for high-risk patients

ASCT Ineligible

- Induction regimens
  - VRd or VRd-lite (preferred)
  - Dara-Rd (preferred)
  - Carfilzomib/Len/Dex
  - Len/Cyclo/Dex
  - Bortezomib/Cyclo/Dex
  - Dara-VMP
  - Len/Dex
- Continuous therapy until progression

Definition of Relapsed and Refractory Myeloma

- Relapsed/refractory myeloma[1,2]
  - Meets IMWG criteria for PD[3]
  - RR MM: progression on therapy in patients who obtain ≥ minor response or progress within 60 days of most recent therapy
  - Primary refractory MM: progression on therapy without having achieved at least minor response
  - Relapsed MM: meets IMWG criteria for PD but does not fit definition of RR or primary refractory MM

IMWG Criteria for PD[3]

≥ 25% increase from nadir in:

- Serum or urine M-protein (absolute increase ≥ 0.5 g/dL* and ≥ 200 mg/24 hrs, respectively), *or*
- Difference between involved and uninvolved FLC levels† (absolute increase > 100 mg/L), *or*
- Bone marrow plasma cells‡ (absolute increase ≥ 10%), *or*
- New lesions (≥ 50% increase in SPD of > 1 lesion or longest diameter of previous lesion > 1 cm in short axis), *or*
- Circulating plasma cells (≥ 50% increase [minimum 200 cells/μL] if only measure of disease)

*If lowest M component ≥ 5 g/dL, increase must be ≥ 1 g/dL.
†In patients without measurable serum/urine M-protein.
‡In patients without measurable serum/urine M-protein or involved FLC.

1. Nooka. Blood. 2015;125:3085. 2. Rajkumar. Blood. 2011;117:4691. 3. Kumar. Lancet Oncol. 2016;17:e328.

Most Recent Approved Agents and Regimens for Relapsed/Refractory Myeloma

Treatment	Previous Lines of Therapy
Carfilzomib (IV proteasome inhibitor) monotherapy	≥ 1
Carfilzomib (IV proteasome inhibitor) + dexamethasone ± lenalidomide	1-3
Daratumumab (IV CD38-targeted antibody) monotherapy	≥ 3
Daratumumab (IV CD38-targeted antibody) + dexamethasone + lenalidomide or bortezomib	≥ 1
Daratumumab (IV CD38-targeted antibody) + pomalidomide + dexamethasone	≥ 2
Elotuzumab (IV SLAMF7-targeted antibody) + lenalidomide + dexamethasone	1-3
Elotuzumab (IV SLAMF7-targeted antibody) + pomalidomide + dexamethasone	≥ 2
Ixazomib (PO proteasome inhibitor) + lenalidomide + dexamethasone	≥ 1
Panobinostat (PO HDAC inhibitor) + bortezomib + dexamethasone	≥ 2

Carfilzomib [PI]. Daratumumab [PI]. Elotuzumab [PI]. Ixazomib [PI]. Panobinostat [PI].

Phase III Lenalidomide-Based Therapy for R/R Myeloma

Trial	ORR, %	≥ CR, %	≥ VGPR, %	Median PFS, Mos	Median OS, Mos	Median F/u (OS), Mos
ASPIRE: KRd vs Rd[1]	87 vs 67	32 vs 9	70 vs 40	26.3 vs 16.6 HR: 0.69	48.3 vs 40.4 HR: 0.79	67.0
TOURMALINE-MM1: IxaRd vs Rd[2]	78 vs 72	14 vs 7	48 vs 39	20.6 vs 14.7 HR: 0.74	NR	23.0
POLLUX: DRd vs Rd[3-5]	93 vs 76	57 vs 23	80 vs 49	44.5 vs 17.5 HR: 0.44	NR vs NR HR: 0.63	36.0
ELOQUENT-2: ERd vs Rd[6,7]	79 vs 66	5 vs 9	36 vs 30	19.4 vs 14.9 HR: 0.73	48.3 vs 39.6 HR: 0.78	60.5

1. Stewart. ASH 2017. Abstr 743. 2. Moreau. NEJM. 2016;374:1621. 3. Dimopoulos. NEJM. 2016;375:1319.
4. Dimopoulos. ASH 2017. Abstr 739. 5. Bahlis. ASH 2018. Abstr 1996. 6. Dimopoulos. EHA 2017. Abstr S456.
7. Lonial. ASCO 2018. Abstr 8040.

How to Make the Best Choice for Therapy

PD While Not on Lenalidomide Maintenance	*PD On Lenalidomide Maintenance (Len-Refractory)*
Triplets (with Rd as backbone)	**Triplets (with other backbones)**
Daratumumab + Rd	**Daratumumab + Vd**
Carfilzomib + Rd	**Daratumumab + PomD**
Ixazomib + Rd	**Daratumumab + KD**
Elotuzumab + Rd	**Carfilzomib + PomD**
	Ixazomib + PomD
	Elotuzumab + PomD

Other options: Kd, PomD, clinical trial (!)

Continue with triplet combinations with ≥ 1 new agent at each relapse

Future of Myeloma Therapy

- New drugs with different mechanisms of action
- Heterogeneous disease: have to match the mechanism with the biologic abnormality
- Combination regimens may provide possible cure
  - For example, agent generally effective against myeloma with targeted agent for specific subtype
- Effective combinations have to move to upfront setting
- Early intervention may be the key for cure

LE SINDROMI MIELODISPLASTICHE (SMD) (ANEMIE REFRATTERIE)

DISORDINI ACQUISITI CLONALI DELLE CELLULE STAMINALI EMOPOIETICHE CARATTERIZZATI DA:

- EMOPOIESI INEFFICACE

  (MIDOLLO IPERCELLULARE)

- ANEMIA e/o NEUTROPENIA e/o PIASTRINOPENIA
- EVOLUZIONE IN LEUCEMIA ACUTA (L.A. SECONDARIE)
- FREQUENZA CRESCENTE CON L'ETA'

ANEMIA:	II GRUPPO; ERITROPOIESI INEFFICACE, IPERPLASTICA E DISPLASTICA; RIDOTTA FORMAZIONE ERITROCITI; POCHI RETICOLOCITI
NEUTROPENIA:	GRANULOCITOPOIESI INEFFICACE, DISPLASTICA; MATURAZIONE INCOMPLETA, DIFETTIVA
PIASTRINOPENIA:	PIASTRINOPOIESI INEFFICACE, MEGA-CARIOCITI DISPLASTICI, IPODIPLOIDI

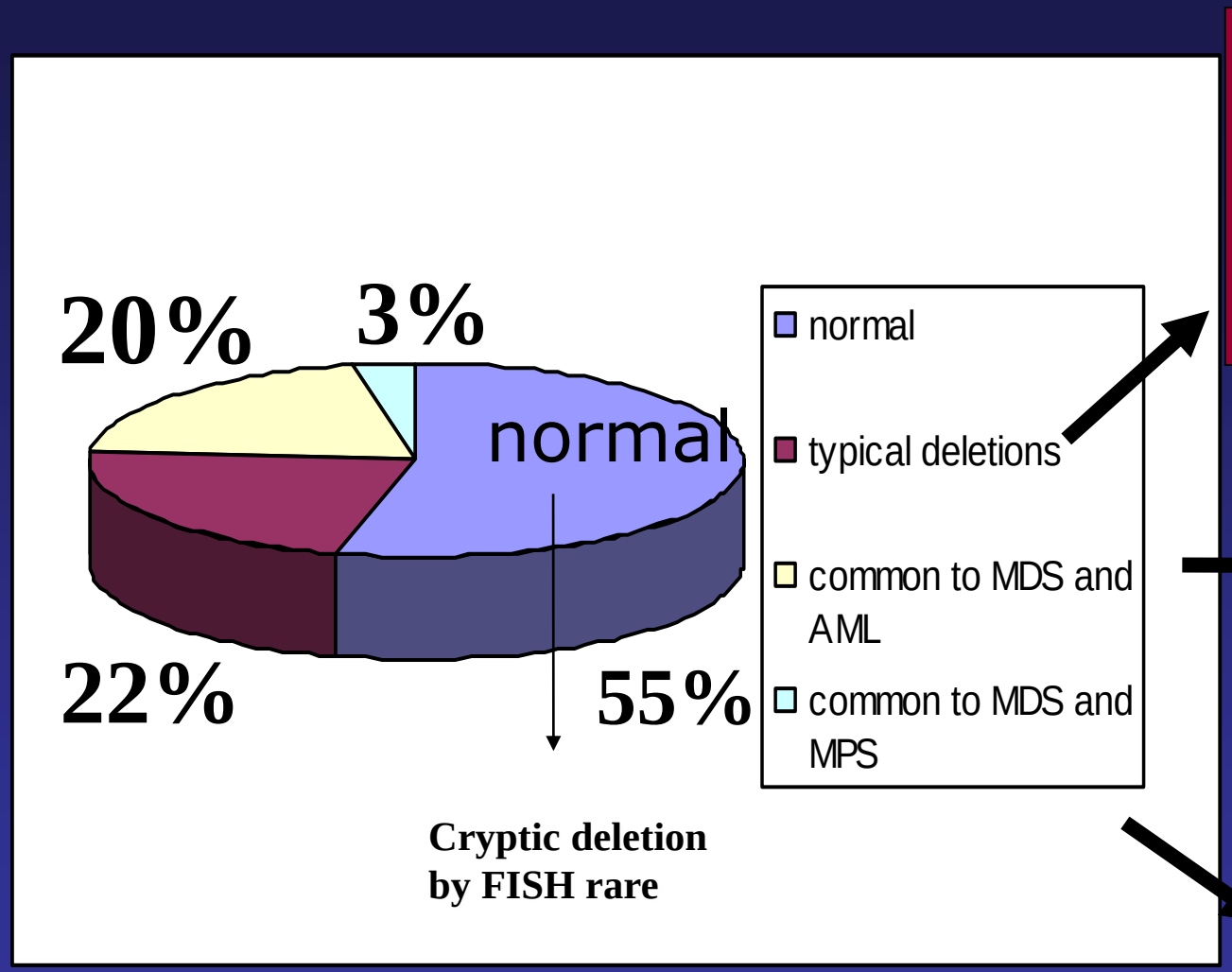
COME SI STUDIANO LE SMD

- ESAME EMOCROMOCITOMETRICO E MORFOLOGICO DEL SANGUE (Hb, CONTA GLOBULI ROSSI, RETICOLOCITI, LEUCOCITI E PIASTRINE, FORMULA LEUCOCITARIA)
- ASPIRATO MIDOLLARE / BIOPSIA OSSEA (CELLULARITA', DISERITROPOIESI, DISGRANULOPOIESI, DISPLASIA MKC, PERCENTUALE DI BLASTI, SIDEROBLASTI AD ANELLO)
- "IMMUNOFENOTIPO": CELLULE CD34+, FENOTIPI ABERRANTI
- CITOGENETICA: CARIOTIPO: BANDEGGIO E FISH (FLUORESCENCE-IN-SITU-HYBRIDIZATION)

SINDROMI MIELODISPLASTICHE

LE PRINCIPALI ANOMALIE CROMOSOMICHE	
- 5 o del (5q)	- Identifica una particolare SMD (quando è un'anomalia isolata)
- 7 o del (7q)	- Significato prognostico negativo, sia isolata che associata ad altre anomalie
- +8	- Significato incerto

Importanza dell'analisi del cariotipo nelle MDS



SINDROMI MIELODISPLASTICHE

LA “VECCHIA” CLASSIFICAZIONE F.A.B. (FRENCH – AMERICAN – BRITISH)

ANEMIA REFRATTARIA
ANEMIA REFRATTARIA CON SIDEROBLASTI AD ANELLO
ANEMIA REFRATTARIA CON ECCESSO DI BLASTI
(BLASTI 5- 20%)

ANEMIA REFRATTARIA CON ECCESSO DI BLASTI, IN TRASFORMAZIONE (BLASTI 20-30%)

LEUCEMIA MIELOMONOCITICA CRONICA

LA CLASSIFICAZIONE E’ BASATA SULLA PERCENTUALE DEI BLASTI NEL MIDOLLO

SINDROMI MIELODISPLASTICHE

LA "NUOVA" CLASSIFICAZIONE WHO (WORD HEALTH ORGANIZATION)

1. CITOPENIA REFRATTARIA CON DISPLASIA UNILINEARE	ANEMIA O NEUTROPENIA, O PIASTRINOPENIA
2. ANEMIA REFRATTARIA CON SIDEROBLASTI AD ANELLO	ANEMIA, SIDEROBLASTI AD ANELLO
3. CITOPENIA REFRATTARIA CON DISPLASIA MULTILINEARE	ANEMIA e/o NEUTROPENIA e/o PIASTRINOPENIA (almeno due citopenie)
4. ANEMIA REFRATTARIA CON ECCESSO DI BLASTI – I	CITOPENIA UNI o MULTILINEARE, CON BLASTI MIDOLLARI 5-9%
5. ANEMIA REFRATTARIA CON ECCESSO DI BLASTI – II	CITOPENIA UNI o MULTILINEARE, CON BLASTI MIDOLLARI 10-19%
6. SMD CON Del (5q) ISOLATA	ANEMIA, del(5q)

LA CLASSIFICAZIONE E' BASATA SUL TIPO E SUL NUMERO DI CITOPENIE E SULLA PERCENTUALE DEI BLASTI NEL MIDOLLO

CITOPENIA REFRATTARIA CON DISPLASIA UNILINEARE

ANEMIA, o NEUTROPENIA, o PIASTRINOPENIA

SOPRAVVIVENZA MEDIANA > 5 ANNI

EVOLUZIONE LEUCEMICA < 20%

ANEMIA REFRATTARIA CON SIDEROBLASTI AD ANELLO

ANEMIA

SOPRAVVIVENZA MEDIANA > 5 ANNI

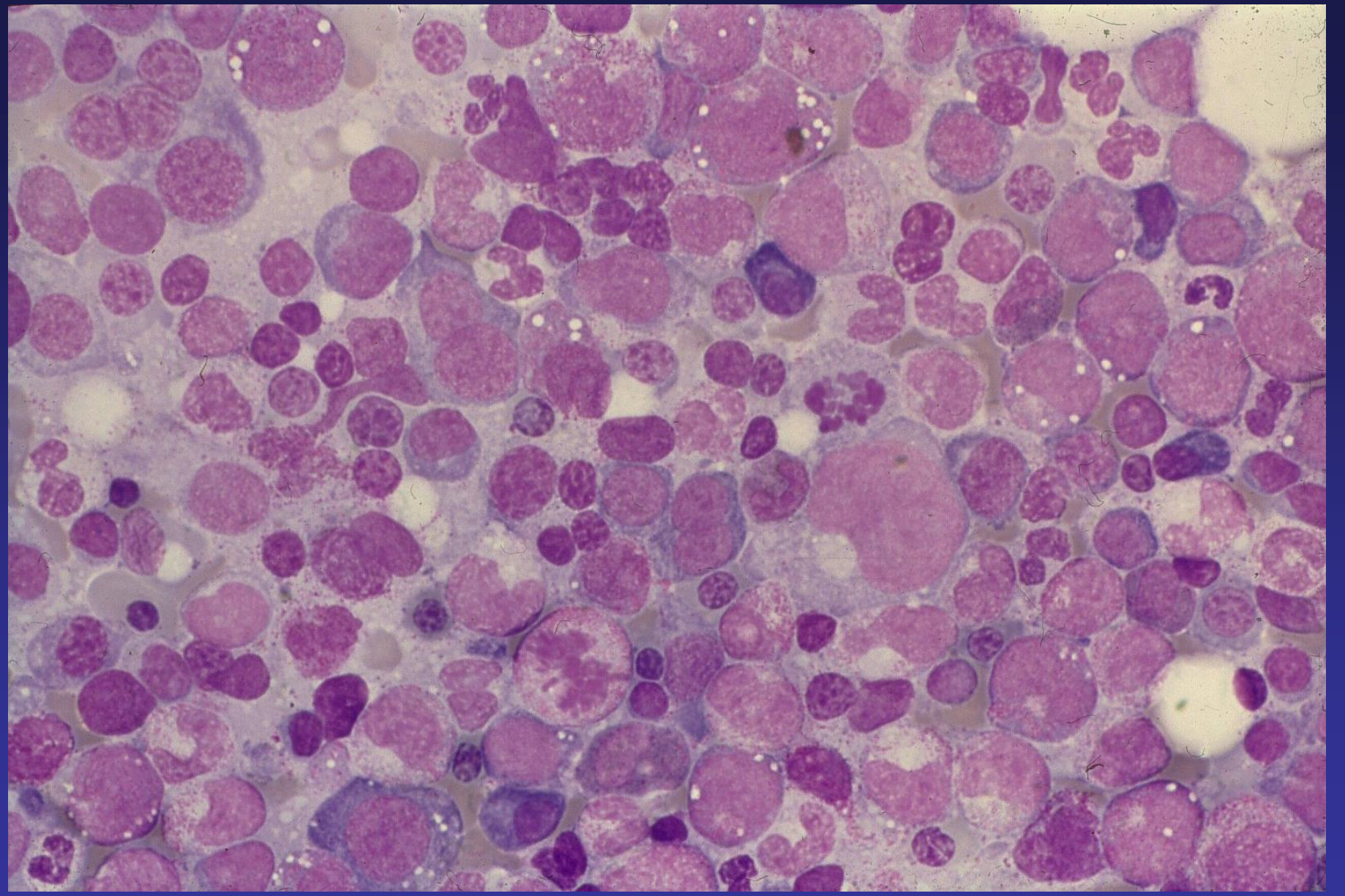
EVOLUZIONE LEUCEMICA < 10%

CITOPENIA REFRATTARIA CON DISPLASIA MULTILINEARE

ANEMIA ± NEUTROPENIA ± PIASTRINOPENIA

SOPRAVVIVENZA MEDIANA < 5 ANNI

EVOLUZIONE LEUCEMICA > 20%



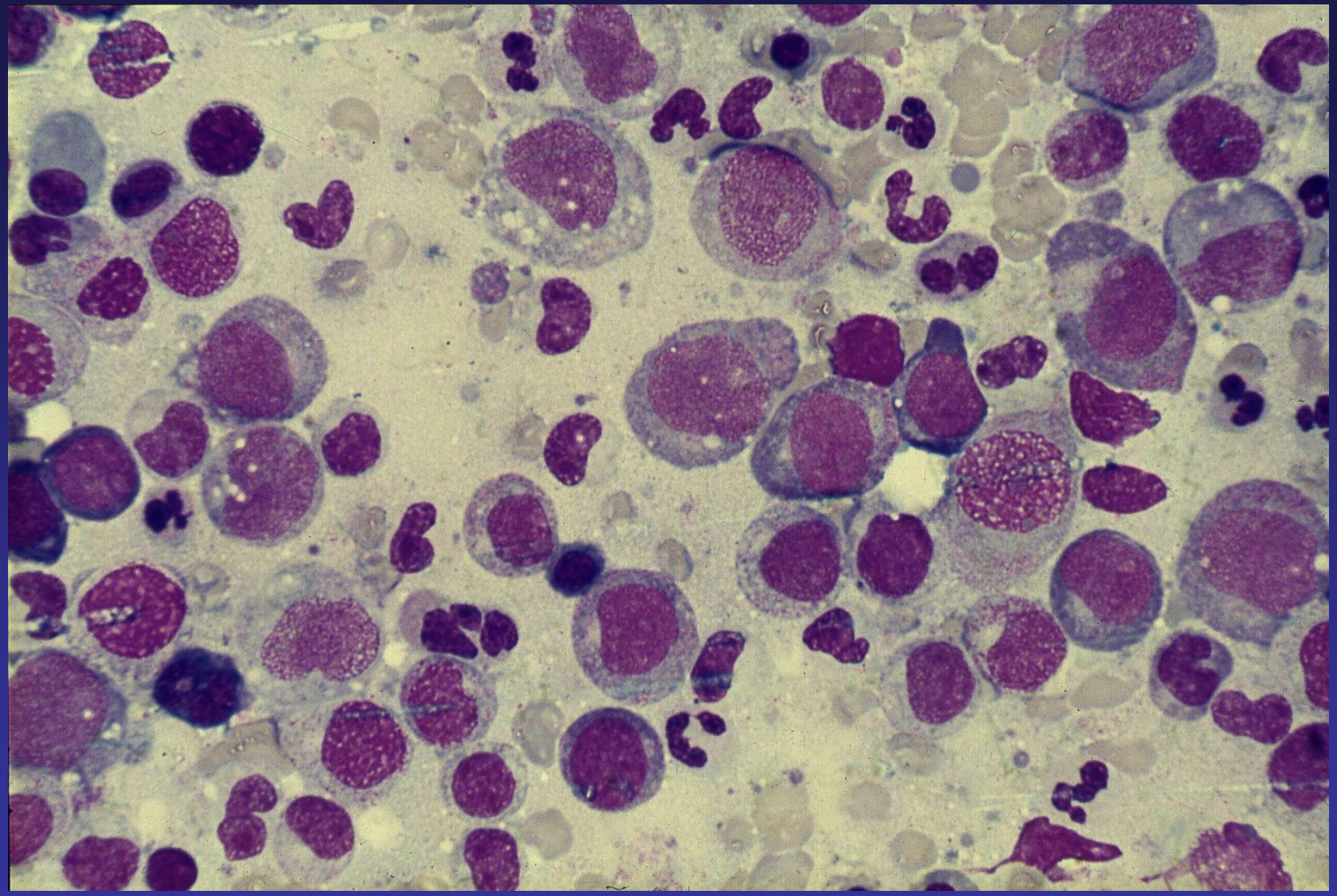
ANEMIA REFRATTARIA CON ECCESSO DI BLASTI

CITOPENIA UNI o MULTILINEARE CON BLASTI MIDOLLARI

5-9%	I
10-09%	II

SOPRAVVIVENZA MEDIANA < 2 ANNI

EVOLUZIONE LEUCEMICA > 50%



SINDROME MIELODISPLASTICA CON Del (5q-)

ANEMIA ± TROMBOCITOSI ± NEUTROPENIA

SOPRAVVIVENZA MEDIANA > 5 ANNI

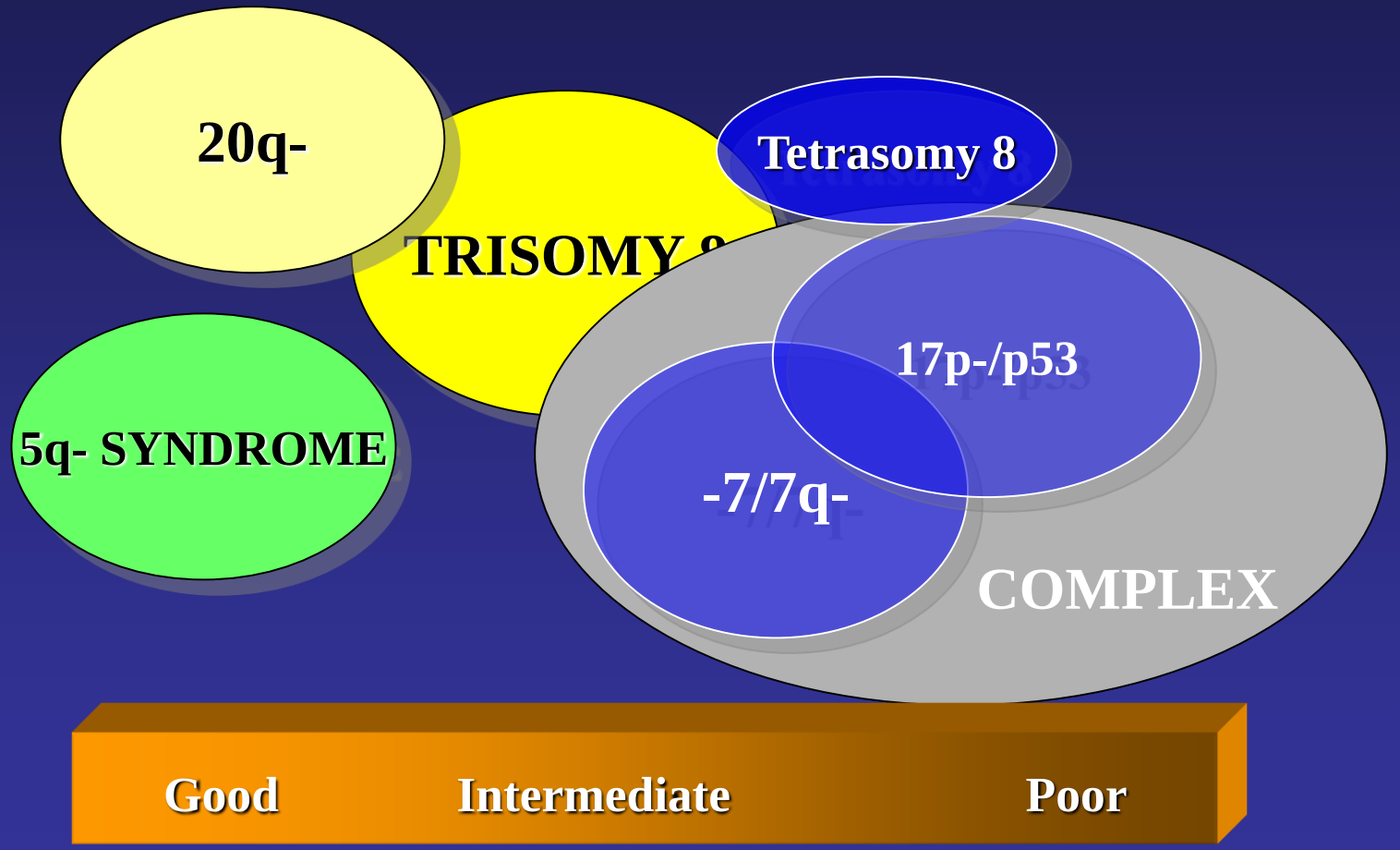
EVOLUZIONE LEUCEMICA > 20%

	SOPRAVVIVENZA MEDIANA	EVOLUZIONE LEUCEMICA
1. CITOPERNIA REFRATTARIA CON DISPLASIA UNILINEARE	> 5 anni	< 20%
2. ANEMIA REFRATTARIA CON SIDEROBLASTI AD ANELLO	> 5 anni	< 10%
3. CITOPENIA REFRATTARIA CON DISPLASIA MULTILINEARE	< 5 anni	> 20%
4/5. ANEMIA REFRATTARIA CON ECCESSO DI BLASTI	< 2 anni	> 50%
6. SMD CON Del(5q) ISOLATA	> 5 anni	> 20%

INTERNATIONAL PROGNOSTIC SCORING SYSTEM (IPSS – GREENBERG 1997)

- NUMERO DI CITOPENIE (ANEMIA, NEUTROPENIA, PIASTRINOPENIA)
- ALTERAZIONI CITOGENETICHE
  - CARIOTIPO “FAVOREVOLE”: NORMALE, -y, 5q-, 20q-
  - CARIOTIPO “SFAVOREVOLE”: COMPLESSO, -7
- PERCENTUALE DI BLASTI NEL MIDOLLO

Alterazioni citogenetiche specifiche nelle SMD



IPSS	*score*
Percentuale blasti midollo:	
<5%	0
5-10%	0.5
11-19%	1.5
20-30%	2.0
Citopenia:	
0-1	0
2-3	0.5
Cariotipo:	
favorevole (-y; 5q-; 20q-; normale)	0
tutti gli altri	0.5
sfavorevole (anomalie cr.7; anomalie complesse)	1
Grado di rischio	***Score totale***
Basso	0
Intermedio-basso	0.5-1.0
Intermedio-alto	1.5-2.0
Alto	>2.5

IPSS: prognosi

Basso rischio:
sopravvivenza mediana 5.7 anni
25% progressione leucemica 9.4 anni

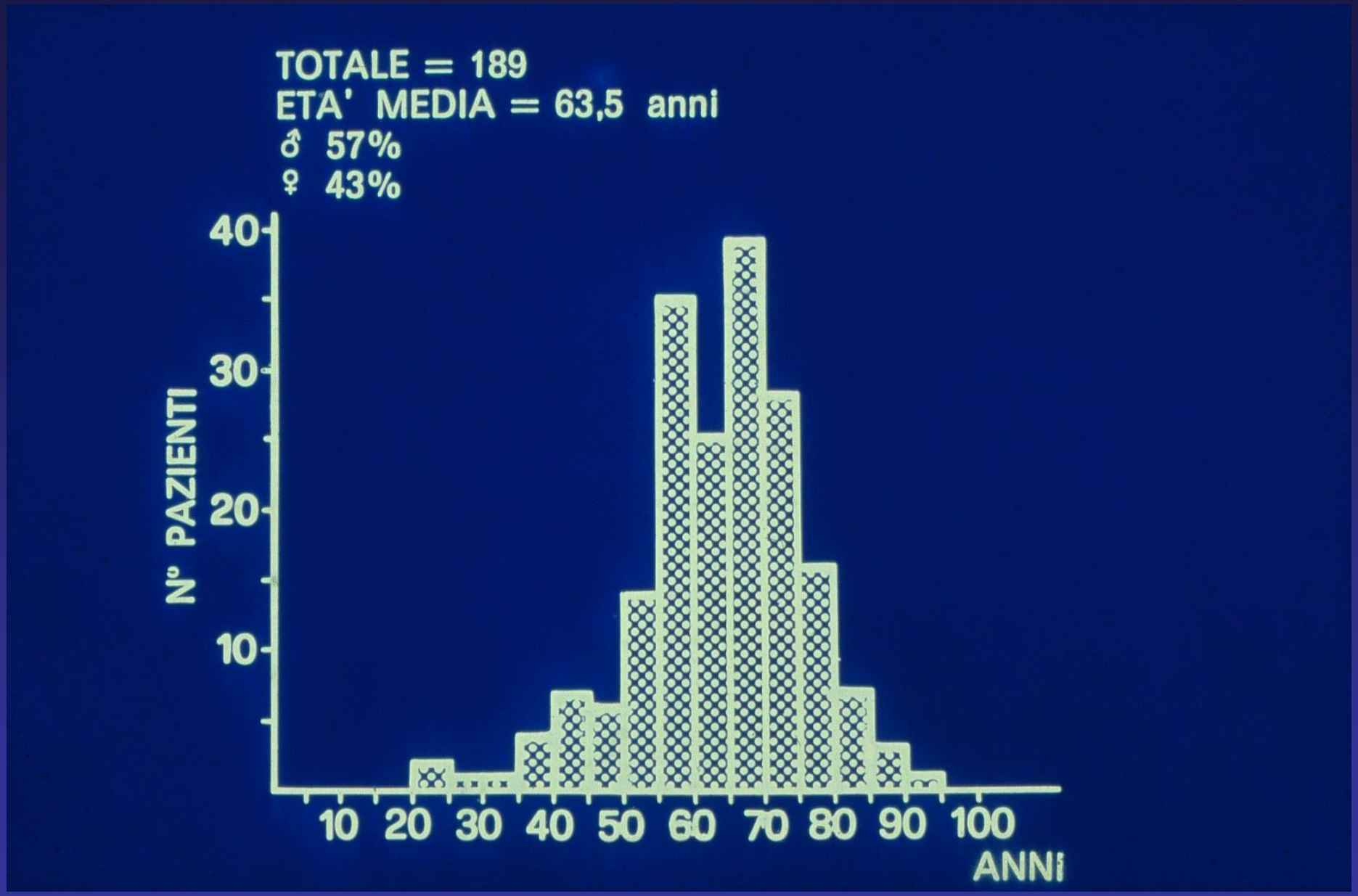
Rischio intermedio -1
sopravvivenza mediana 3.5 anni
25% di progressione leucemica 3.3 anni

ANNI

Rischio intermedio-2
sopravvivenza mediana 12 mesi
25% di progressione leucemica 12 mesi

Rischio alto
sopravvivenza mediana 4.5 mesi
25% di progressione leucemica 4.5 mesi

MESI


TOTALE = 189
ETA' MEDIA = 63,5 anni
♂ 57%
♀ 43%
N° PAZIENTI
40
30
20
10
10 20 30 40 50 60 70 80 90 100
ANNI

SINDROMI MIELODISPLASTICHE

CLINICA

- ANEMIA CRONICA
- infezioni (neutropenia)
- emorragie (piastrinopenia)

L'ANAMNESI E L'ESAME OBIETTIVO

- L'ANAMNESI PATOLOGICA "RECENTE" E' SCARSAMENTE RILEVANTE PER LA DIAGNOSI: MESI o ANNI DI ASTENIA, FACILE AFFATICAMENTO, DISPNEA DA SFORZO, CARDIOPALMO…
- L'ANAMNESI PATOLOGICA "REMOTA" E' MOLTO IMPORTANTE PER UNA CORRETTA E COMPLETA GESTIONE CLINICA CHE DEVE TENERE CONTO DELLE COMORBIDITA': CARDIOPATIE, IPERTENSIONE ARTERIOSA, DIABETE MELLITO, MALATTIE INFIAMMATORIE CRONICHE, MALATTIE DEGENERATIVE, (ETA')
- L'ESAME OBIETTIVO DEVE ESSERE NEGATIVO (SEGNI DI ANEMIA A PARTE)

COME SI FA' LA DIAGNOSI ?

- ESAME OBIETTIVO "NEGATIVO" (ANEMIA A PARTE)
- EMOCROMO (ANEMIA, MCV, NORMALE / AUMENTATO, POCHI RETICOLOCITI, NEUTROPENIA, BLASTI)
- SIDEREMIA ALTA, TRANSFERRINA BASSA, FERRITINA ALTA
- MIDOLLO IPERCELLULARE, DISPLASTICO, PARZIALMENTE BLASTICO
- CARIOTIPO ALTERATO

SINDROMI MIELODISPLASTICHE

IL SOVRACCARICO DI FERRO

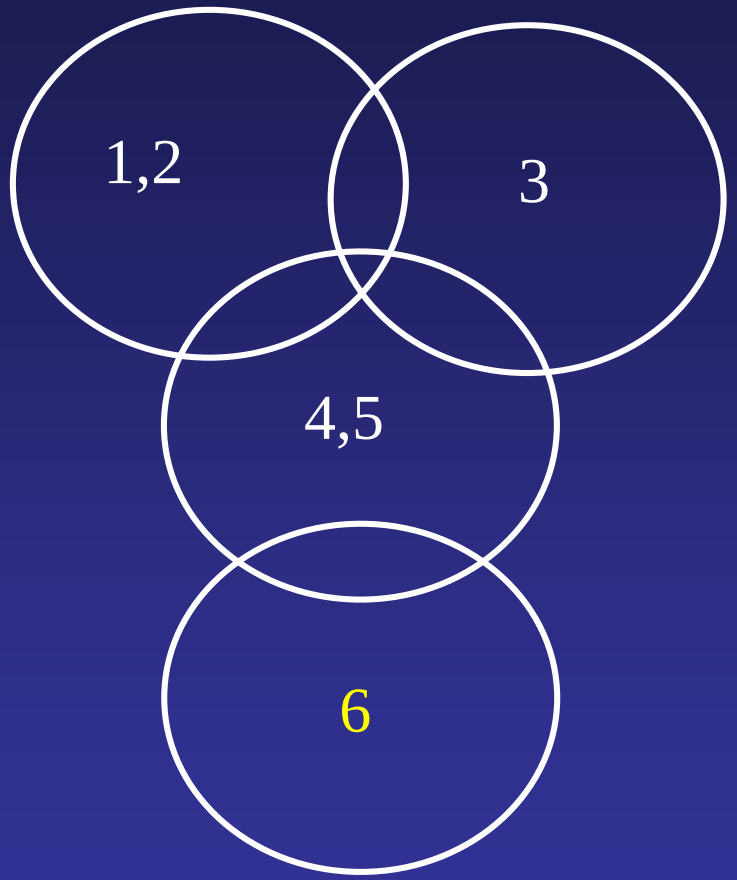
- AUMENTO ASSORBIMENTO
- CARICO TRASFUSIONALE: 1 U. DI SANGUE = 180 mg DI FERRO – 2 U. AL MESE = 24 U. DI SANGUE ALL'ANNO = 4320 mg DI FERRO ALL' ANNO
- DANNI D'ORGANO: MIOCARDIO (DEPOSITO DI FERRO, RIDOTTO APPORTO DI O_2)
- TERAPIA FERROCHELANTE (NEI PAZIENTI A RISCHIO BASSO o INTERMEDIO)

SINDROMI MIELODISPLASTICHE
TERAPIA

- NESSUNA: OSSERVAZIONE
- “SUPPORTO”: TERAPIA TRASFUSIONALE (GRC) ERITROPOIETINA, DILIGENTE CONTROLLO DELLE INFEZIONI, FATTORI DI CRESCITA GRANULOCITARI, FATTORI DI CRESCITA PIASTRINICI
- “CORRETTIVA”: 5-AZACITIDINA, DECITABINA, LENALIDOMIDE,……
- “CITOTOSSICA”: COME NELLE LEUCEMIE ACUTE MIELOBLASTICHE
- “RISOLUTIVA”: TRAPIANTO DI CELLULE STAMINALI EMOPOIETICHE ALLOGENICHE

LA TERAPIA VA MODULATA SECONDO ETA’, COMORBIDITA’ e RISCHIO

SINDROMI MIELODISPLASTICHE E LEUCEMIE ACUTE



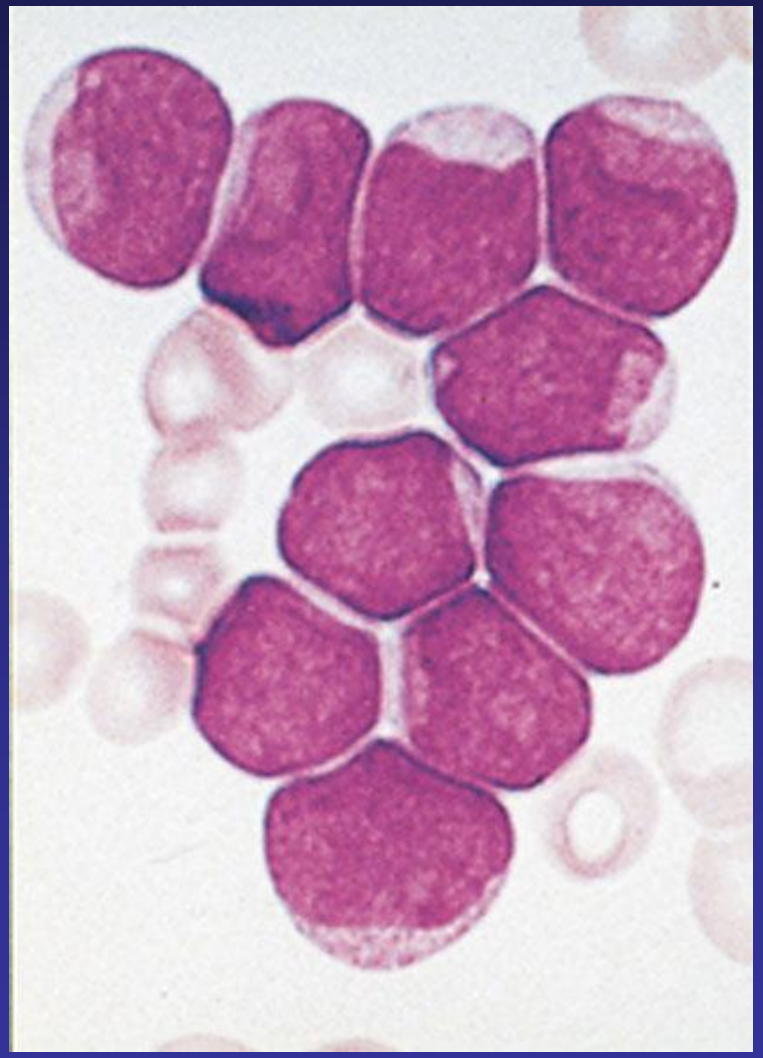
1,2 CITOPENIA REFRATTARIA CON DISPLASIA UNILINEARE (± SIDEROBLASTI ANELLO)

3 CITOPENIA REFRATTARIA CON DISPLASIA MULTILINEARE

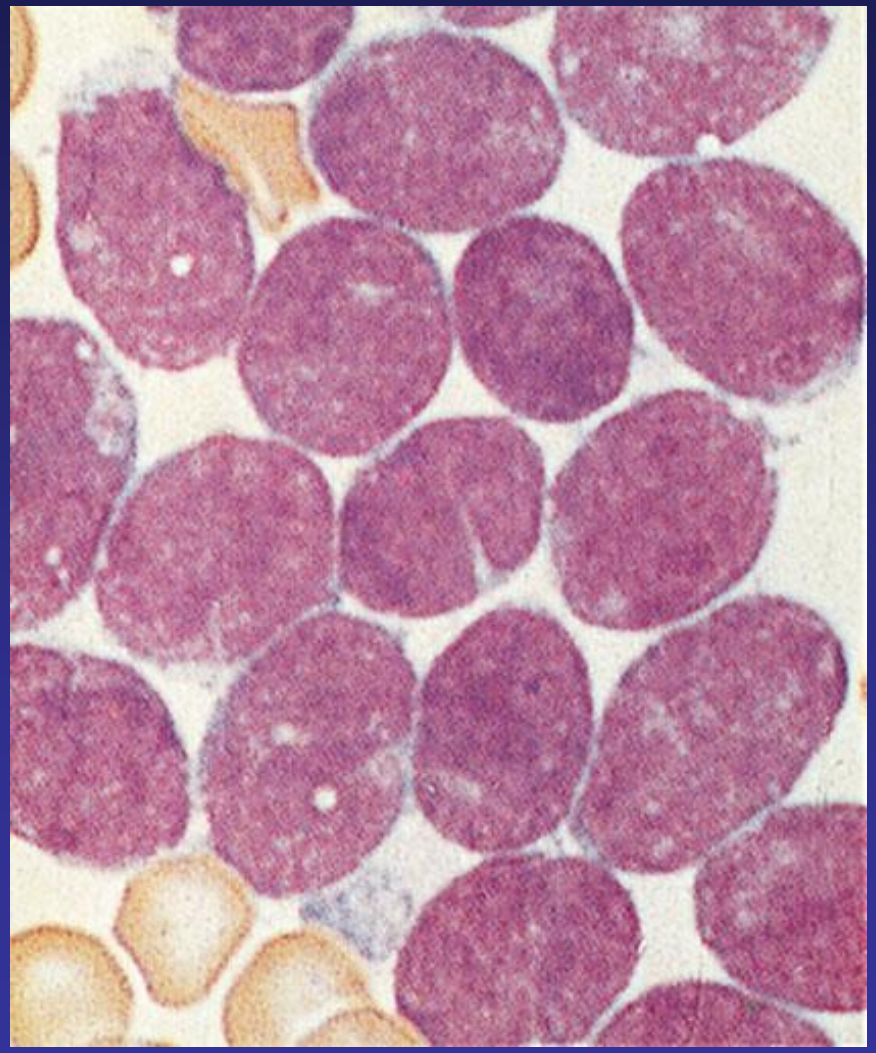
4,5 ANEMIA REFRATTARIA CON ECCESSO DI BLASTI

6 LEUCEMIE ACUTE MIELO-BLASTICHE (SECONDARIE)

LEUCEMIA ACUTA MIELOIDE



LEUCEMIA ACUTA LINFOIDE



QUALI TERAPIE

QUALI PAZIENTI

TERAPIA DI SUPPORTO NELLE SMD

Hb ≤ 8 g/dl
(≤ 9 g/dl in pazienti cardiopatici e/o broncopneumopatici)

→ **Concentrati eritrocitari**
(obiettivo → qualità di vita buona)
+
Terapia ferrochelante
(attualmente anche per os → Exjade)

PMN ≤ 0.5 x 10^9/l

→ **Profilassi antibiotica** → **NO (selezione germi resistenti)**

→ **Terapia antibiotica** → **antibiotici e.v. (beta-lattamico + chinolonico)**
(TC ≥ 38°)

→ **G-CSF** → **solo se infezioni gravi in atto (sepsi, febbre resistente)**

PLTS ≤ 30 x 10^9/l

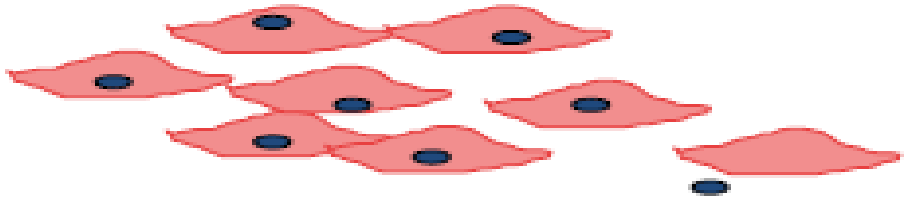
→ **Profilassi e/o emorragie minori** → **Antifibrinolitici**
Basse dosi di steroidi

→ **Emorragie mucose gravi** → **Concentrati piastrinici (mai profilassi → immunizzazione)**

PERCHE' UTILIZZARE GLI ESA NELLE SMD

Emopoiesi clonale

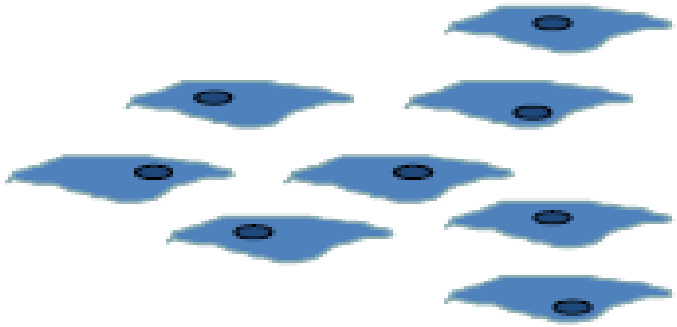
+

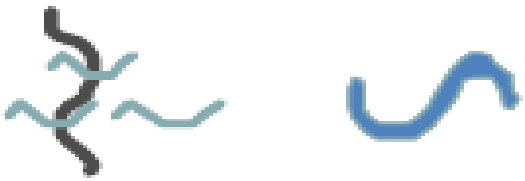


r-Hu EPO

Emopoiesi normale

++





↑ TNF IL-1

–

Fondamentale fattore
di sopravvivenza cellulare

PER MIGLIORARE I RISULTATI BISOGNA SELEZIONARE BENE I PAZIENTI!

15% di risposte

Pazienti SMD non selezionati

- Tutti i sottotipi WHO/FAB

>60% di risposte

Pazienti SMD selezionati per

- Diagnosi recente
- Trasfusione-indipendenza
- EPO sierica <200 U/l (<500 U/l)
- Citogenetica normale
- IPSS Low-risk, Int-1

Prolungare il periodo di trattamento a 24 settimane/Aggiungere G-CSF

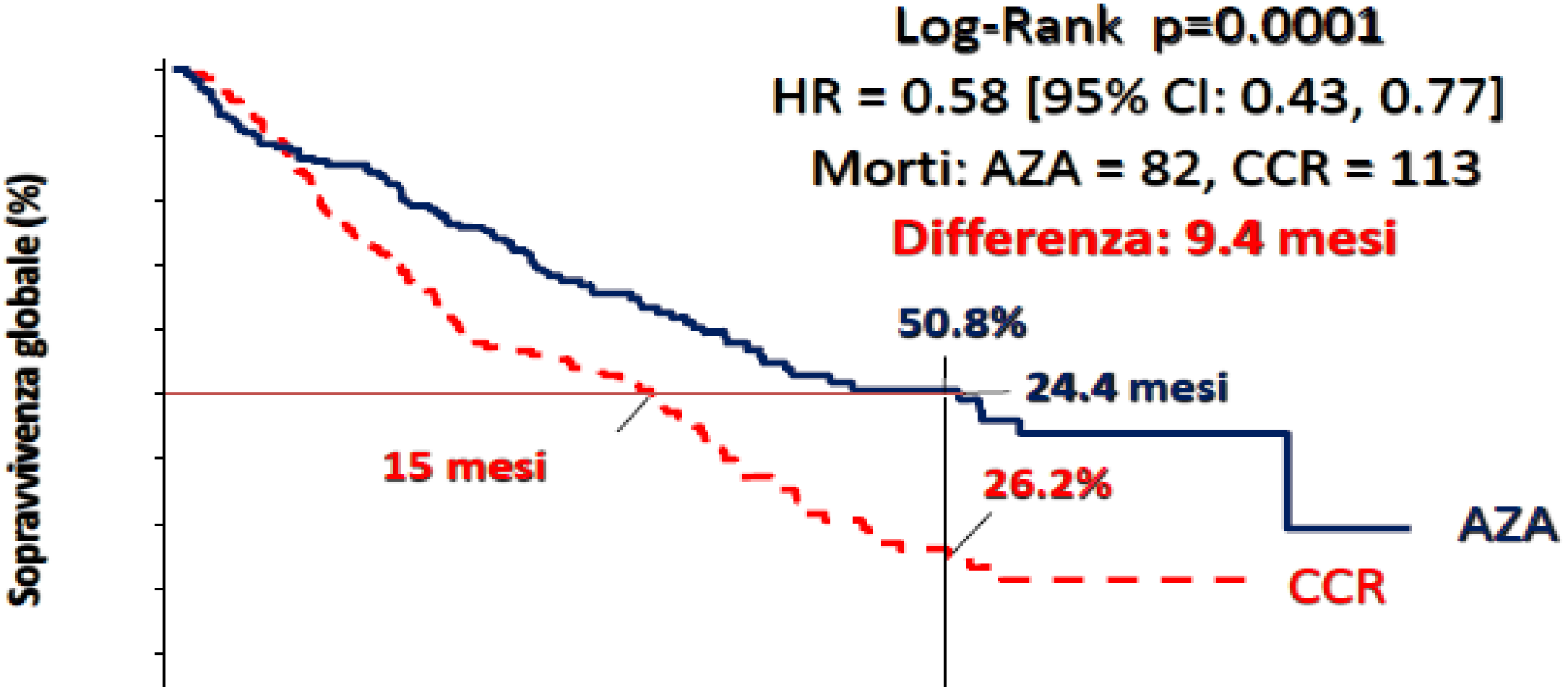
5 – AZACITIDINA NELLE SMD

PAZIENTI ELEGIBILI →
- **SMD a basso rischio resistenti all'EPO**
- **SMD ad alto rischio**

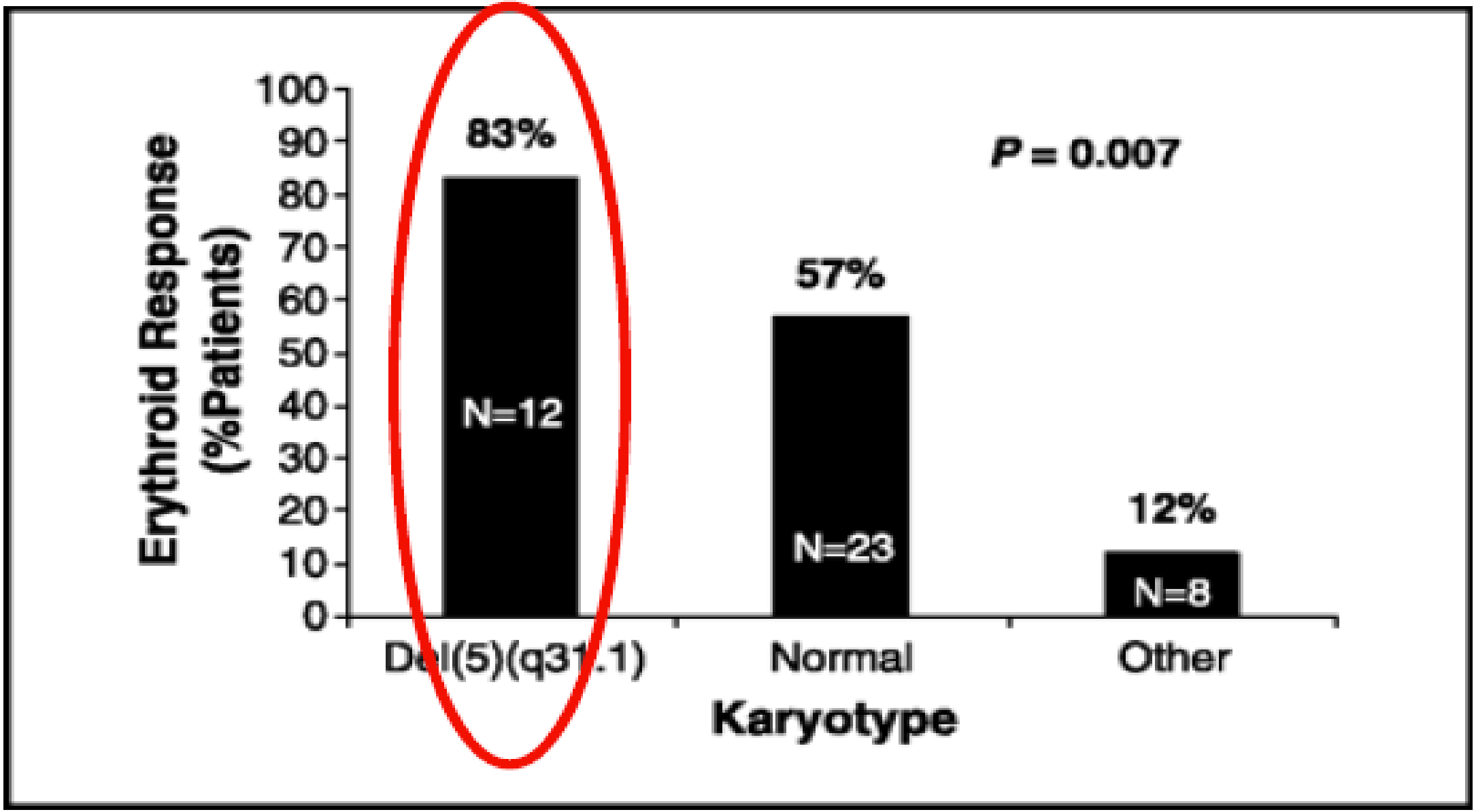
DOSAGGIO → **75 mg/m² per 5 – 7 giorni (cicli mensili)**

RISULTATI →
- **Risposte globali ~ 55 – 60% (RC 10% RP10% HI 35-40%)**
- **Miglioramento significativo S V (primo farmaco nelle SMD)**

LA TERAPIA DEMETILANTE PROLUNGA LA SOPRAVVIVENZA GLOBALE



RISULTATI DEL PROTOCOLLO MDS-001



List A, et al. N Engl J Med 2005;352:549–57

IL FUTURO DELLE SINDROMI MIELODISPLASTICHE

SINDROMI MIELODISPLASTICHE
(patologie eterogenee sotto tutti i punti di vista)

↓

MALATTIE MIELODISPLASTICHE
(ognuna caratterizzata da ezio-patogenesi, sintomatologia, terapia specifiche)

↙ ↓ ↘

SINDROME del5q | **SMD CON SIDEROBLASTI AD ANELLO** | **?**