Traitement du Myélome selon le risque jusqu'à l'espoir de guérison : à l'ère des nouveaux médicaments

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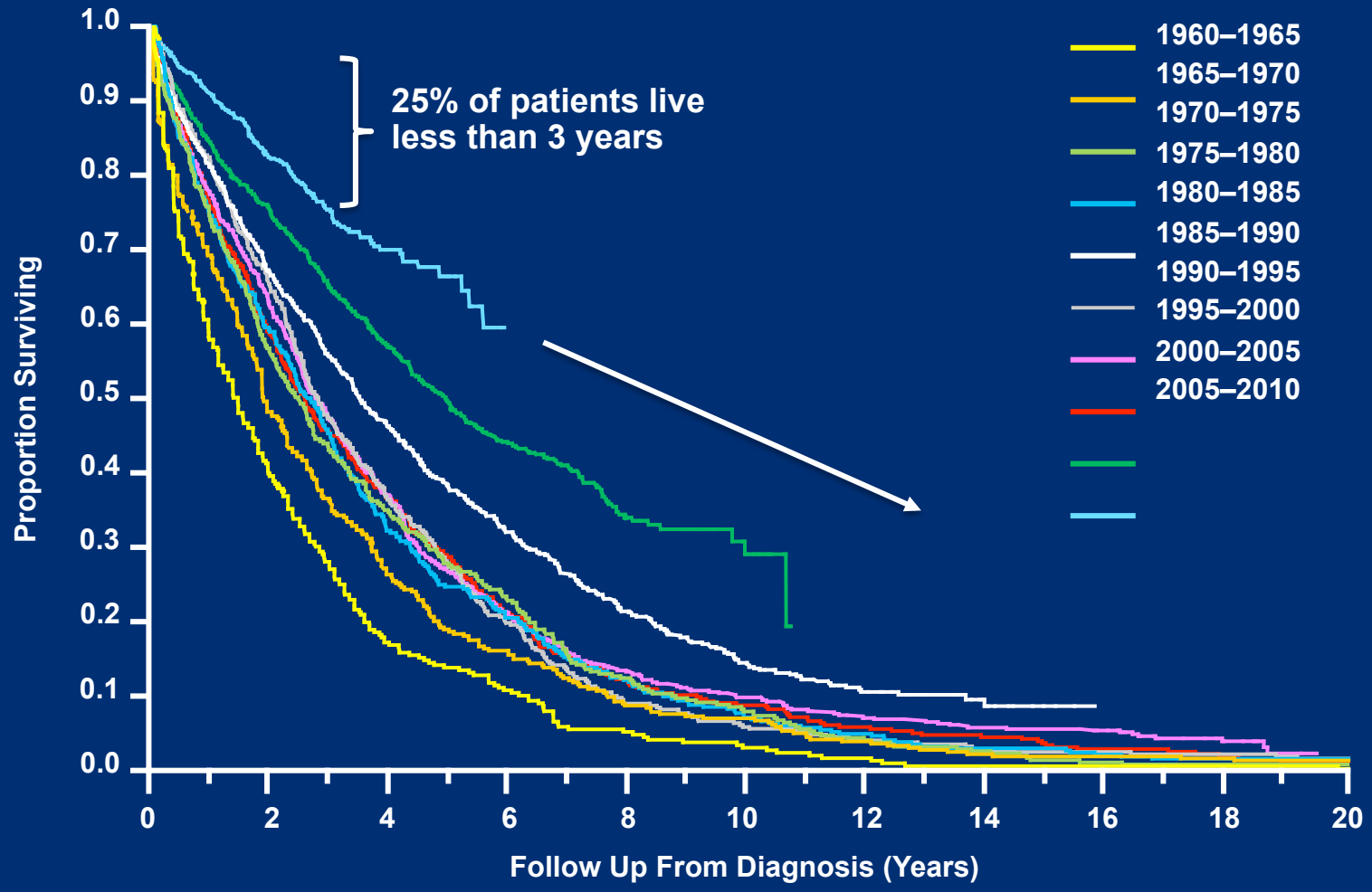
Improving Survival in MM



Adapted from Kumar SK et al. *Leukemia.* 2014;28:1122.

- What are the poor-risk factors ?

- Who is using a risk-adapted strategy ?

- A simple scoring system to predict early death from progressive disease ?

What are factors that confer a poor prognosis?

- Age
- Performance status, comorbidities, e.g. renal impairment

- High β_2 microglobulin
- Low albumin
- LDH

- Cytogenetic abnormalities / genetic changes
- Circulating plasma cells
- High proliferation rate

- Number of lesions MRI / PET-CT

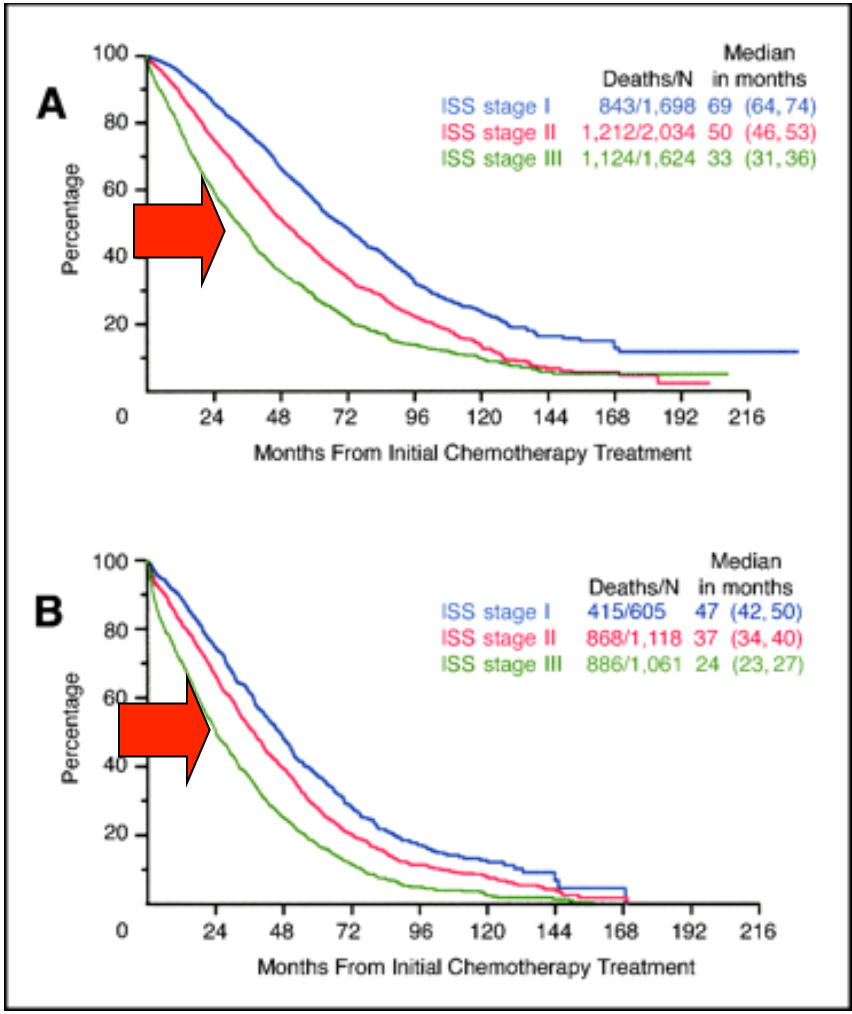
- Lack of response to induction treatment

The International Staging System (ISS)

Prognostic model based on β_2-microglobulin and albumin

Patients < 65 y

Stage	Criteria
I	β_2m < 3.5 mg/L & albumin ≥ 3.5 g/dL
II	Not stage I or III
III	β_2m ≥ 5.5 mg/L



Patients > 65 y

Greipp *et al*. J Clin Oncol **2005**;23:3412-20

Prognostic factors: leukemic presentation

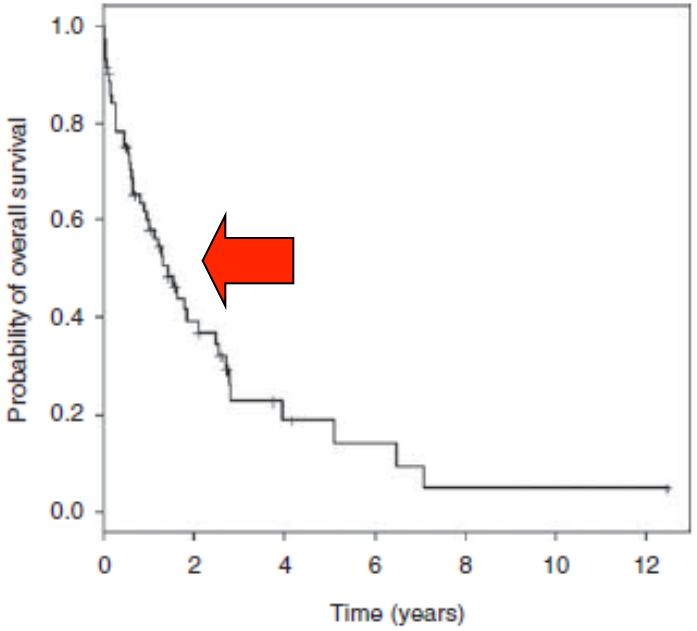


Figure 1 Overall survival of the whole cohort of patients with pPCL.

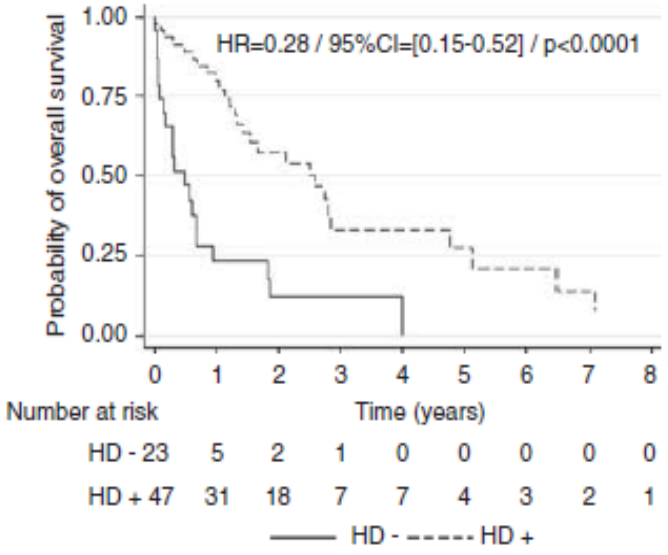
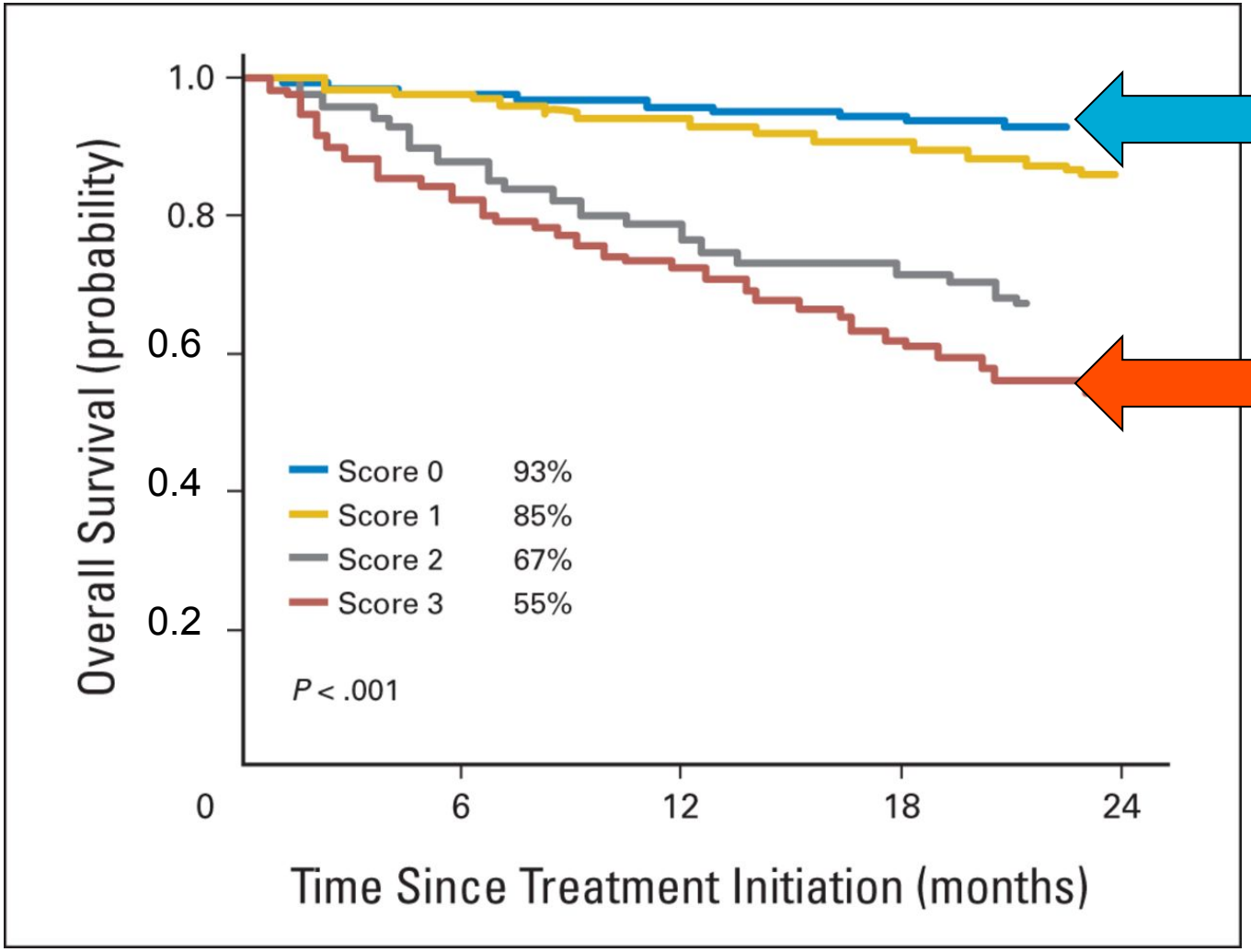


Figure 2 Overall survival of patients treated with high-dose approaches (HD+) vs a conventional approach (HD−).

Avet-Loiseau et al. Leukemia 2012

Overall survival for 1,601 patients with lactate dehydrogenase, International Staging System, and cytogenetic data available.



Prognostic Classification Consisting of 4 Categories Based on 3 Variables:

- **High LDH**

- **ISS3**

- **t(4;14) and/or del(17p)**

Moreau P et al. JCO 2014;32:2173-2180

Revised International Staging System (R-ISS) for MM

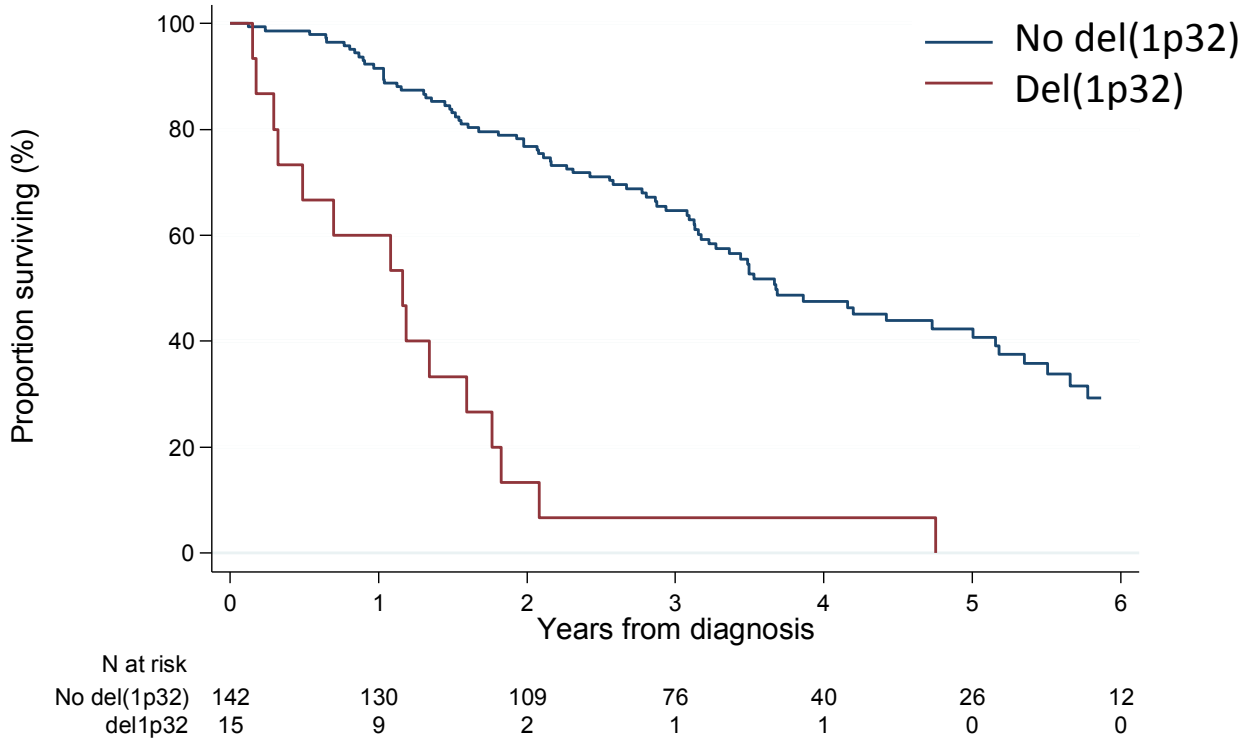
- R-ISS I (n=871)
  - Including ISS stage I (serum β2M level <3.5 mg/L and serum albumin level ≥3.5 g/dL)
  - No high-risk CA [del(17p) and/or t(4;14) and/or t(14;16)]
  - Normal LDH level (less than the upper limit of normal range)
- R-ISS III (n=295)
  - Including ISS stage III (serum β2M level >5.5 mg/L)
  - High-risk CA or high LDH level
- R-ISS II (n=1,894)
  - Including all the other possible combinations

	5-Year OS* (%)	5-Year PFS* (%)
R-ISS I	82	55
R-ISS II	62	36
R-ISS III	40	24

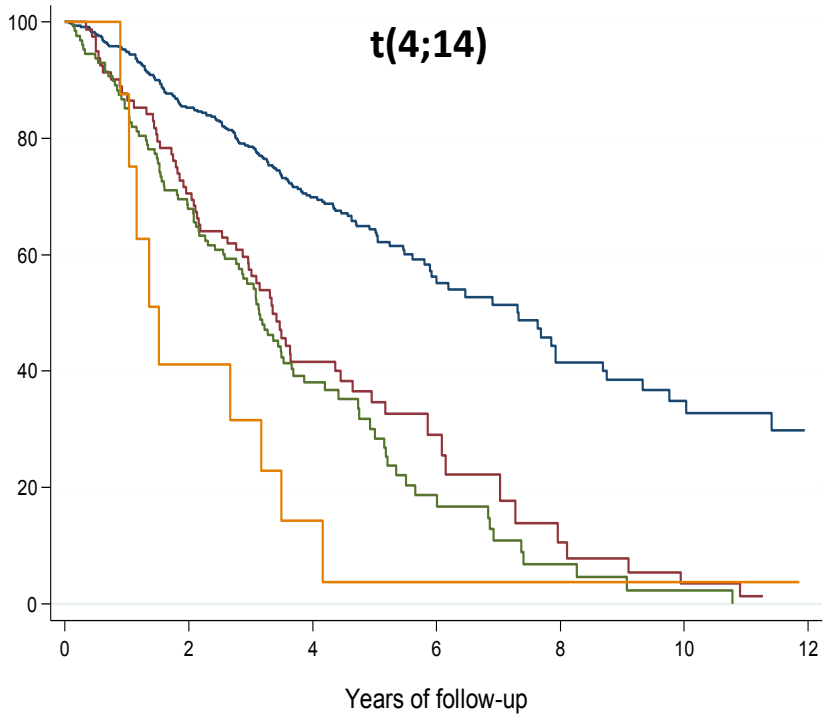
*At a median follow-up of 46 months

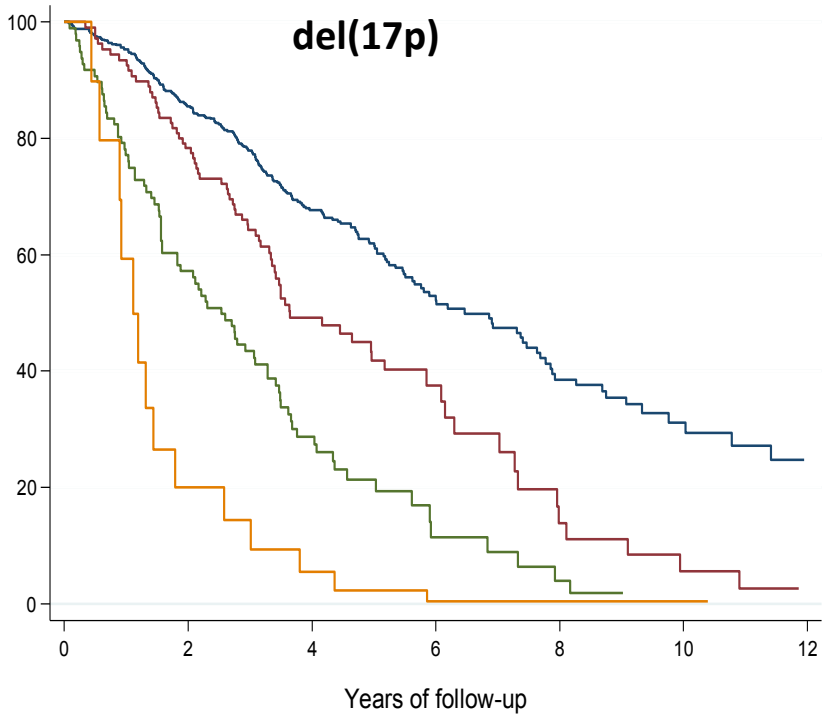
Palumbo A et al. *J Clin Oncol*. 2015;33:2863.

Overall survival of patients with t(4;14) according to del(1p32)



Overall survival* according to trisomy 21 and t(4;14) or del(17p)





No high risk, No Trisomy 21

No high risk, Trisomy 21

High risk, No Trisomy 21

High risk, Trisomy 21

***adjusted for trisomies 3 and 5**

Conclusion

- What are the chromosomal changes impacting high-risk patients survival ?

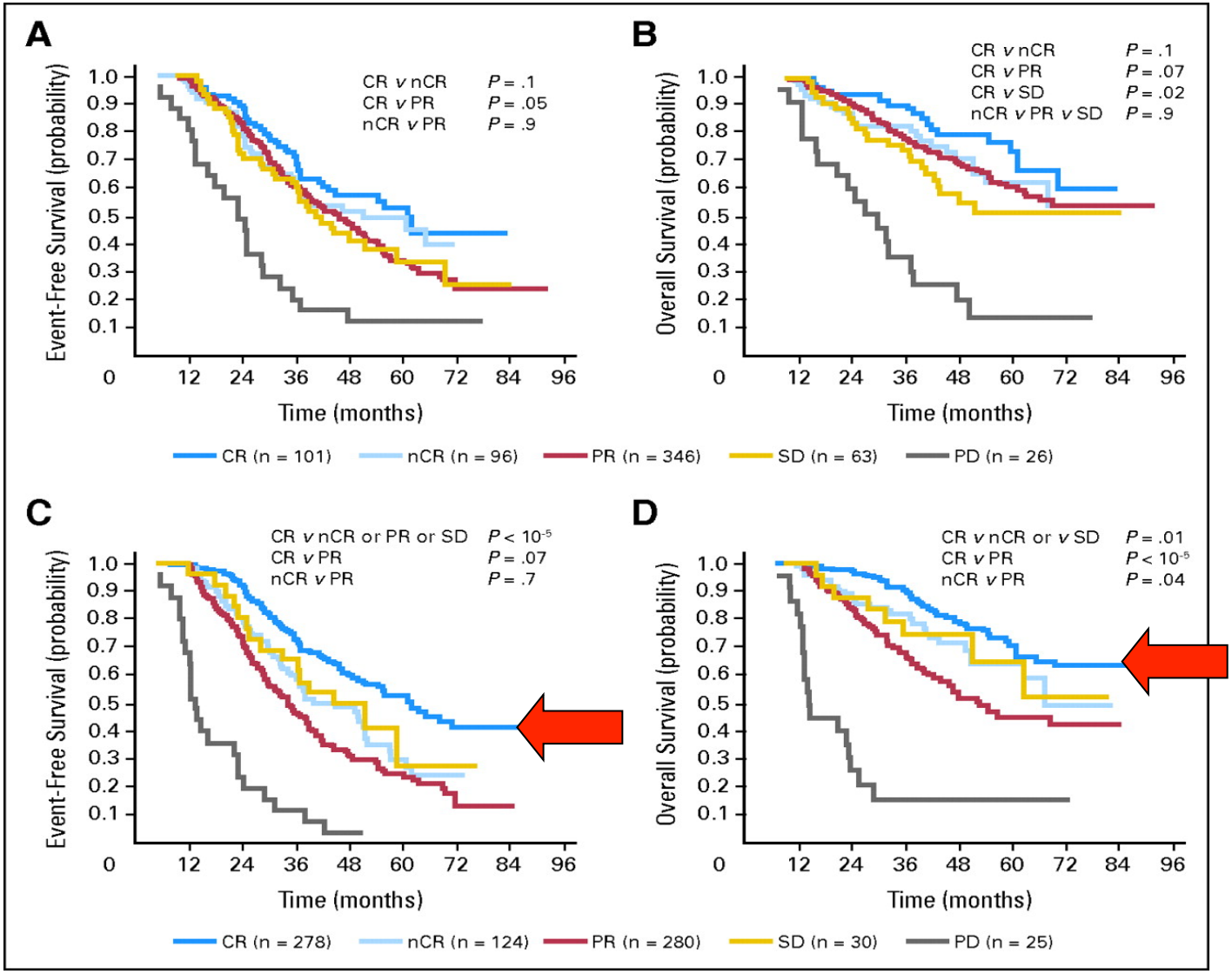
  del(1p32) and trisomy 21 

  trisomies 3 and 5 

- SNP-array allows an accurate prediction of prognosis in myeloma

- Need for larger series of high-risk patients to improve risk estimate in subgroups

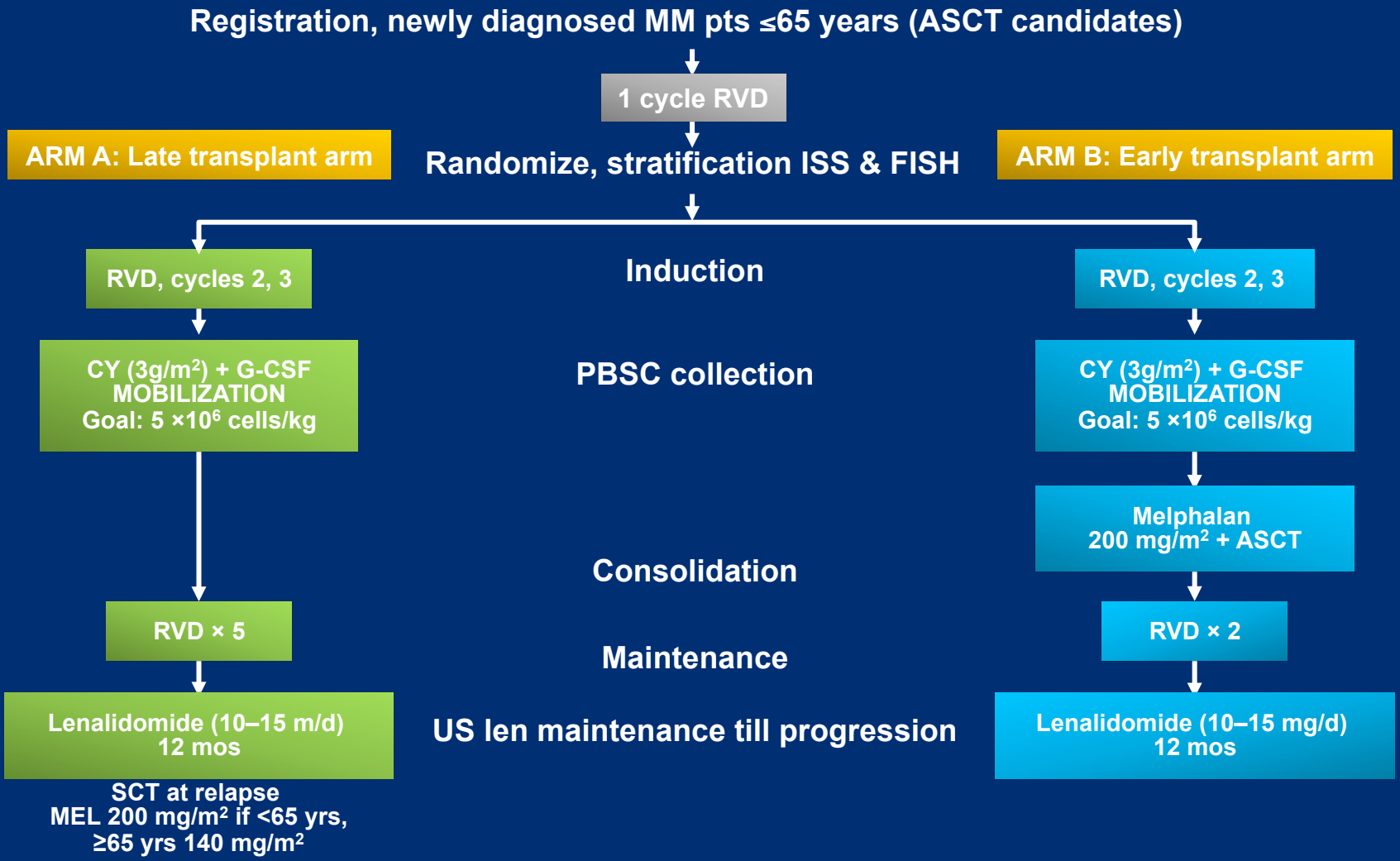
Influence of response obtained after high-dose therapy plus ASCT on (C) EFS and (D) OS



Lahuerta, J. J. et al. J Clin Oncol; 26:5775-5782 2008

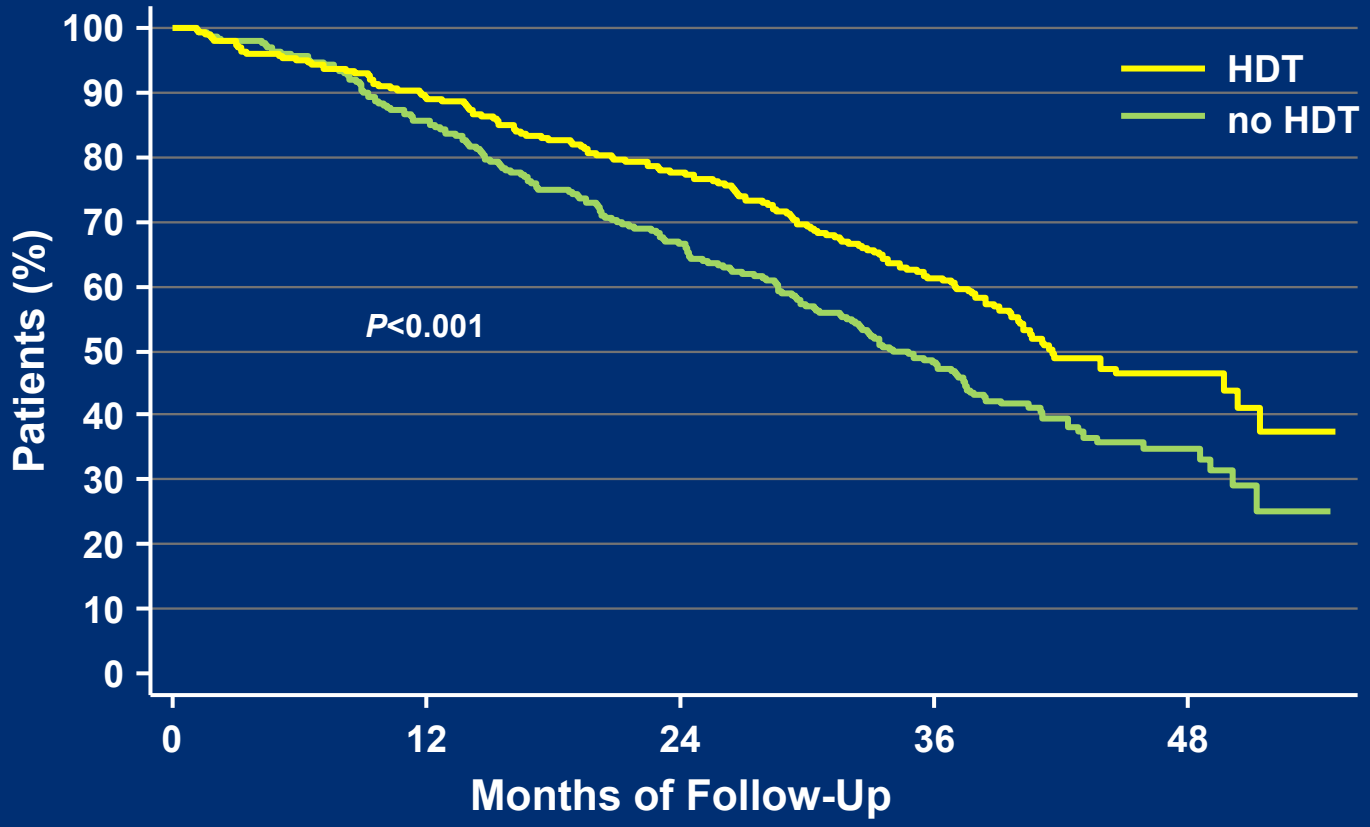
L'intensification autogreffe en première ligne est-elle toujours la règle absolue ??

IFM/DFCI 2009 Study Schema



Attal M et al. *Blood*. 2015;126: Abstract 391.

IFM 2009: PFS (9/2015)

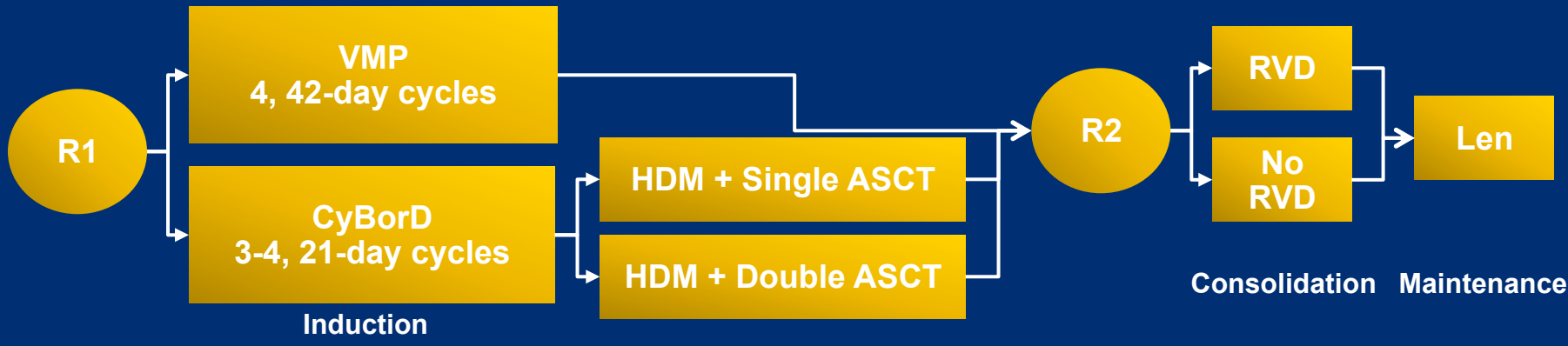


N at risk

HDT	350	309	261	153	27
no HDT	350	296	228	128	24

Attal M et al. *Blood*. 2015;126: Abstract 391.

Intensification Therapy with Bortezomib-Melphalan-Prednisone Versus Autologous Stem Cell Transplantation for Myeloma: An Intergroup, Multicenter, Phase III Study of the European Myeloma Network (EMN02/HO95 MM Trial)

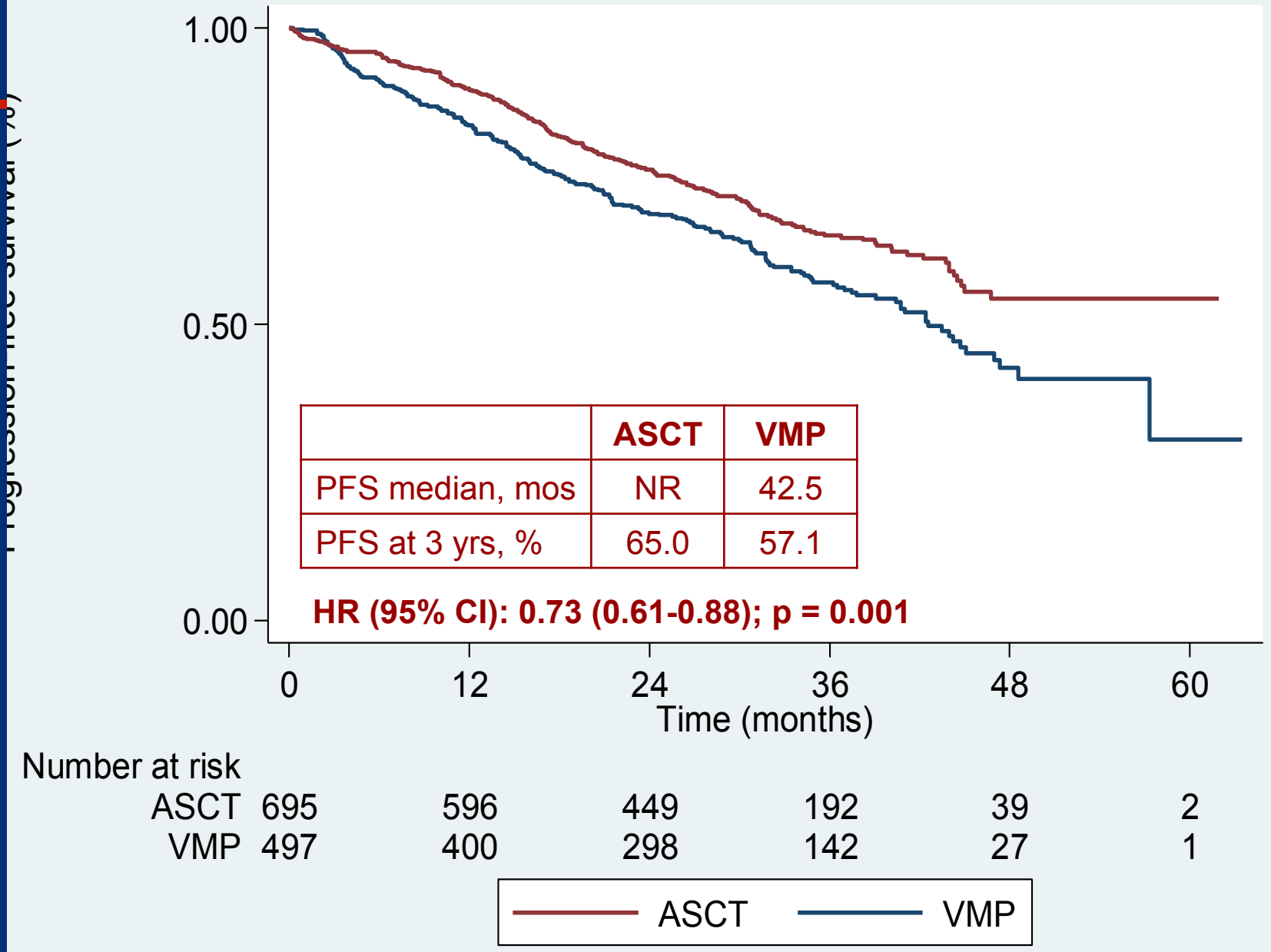


	VMP (n=497)	HDM (n=695)	HR/OD (95% CI)	*P* Value
Median PFS (mos)	44	NR	—	—
3-Yr PFS (%)	57.5	66	HR 0.73 (0.59-0.90)	0.003
Probability of achieving ≥VGPR (%)	74	85.5	OD 1.90 (1.42-2.54)	<0.001

Upfront HDM and ASCT significantly improved PFS and increased the rate of high quality responses.

Cavo M et al. *Blood.* 2016;128: Abstract 673.

PFS by randomization 1 (VMP *vs.* ASCT)



Quid du couple
Consolidation / Entretien ??

Double vs single ASCT after bortezomib-based induction:
Integrated analysis of phase European 3 studies

- Pts (n=606)
  - Bortezomib-based induction
  - Single (n=254) or double (n=352) ASCT

- Differentiation of 4 groups based on adverse prognostic variables:
  - ISS 3, high-risk cytogenetics, failure to achieve CR after induction therapy

- Group 0 (13%): ISS 1-2, lack of high-risk cytogenetics, CR after induction
- Group 1 (61%): one adverse variable
- Group 2 (23%): two adverse variables
- Group 3 (3%): all three adverse variables

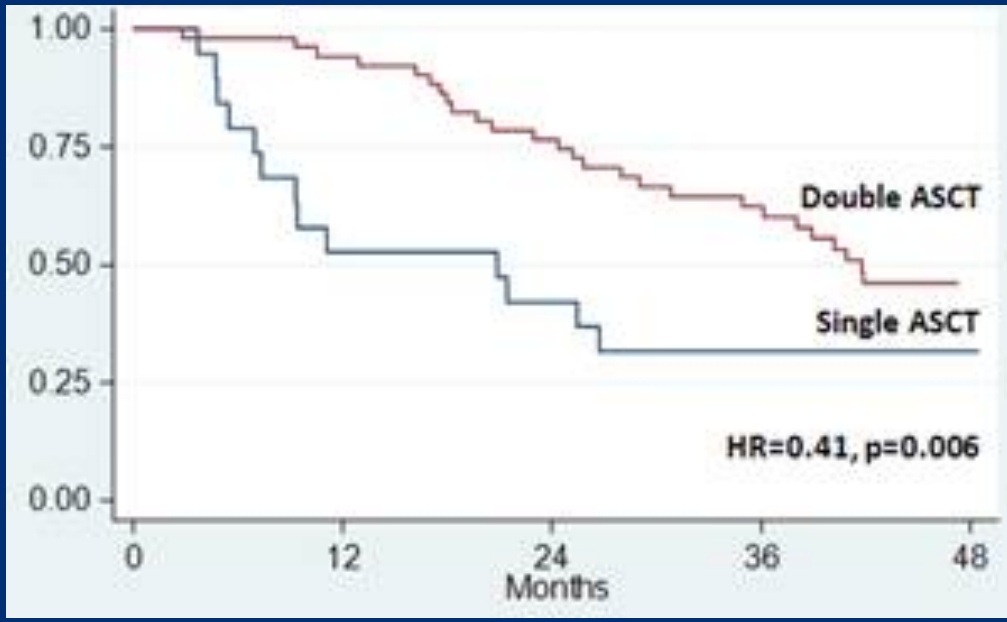
Cavo et al. ASH 2013 (Abstract 767), oral presentation

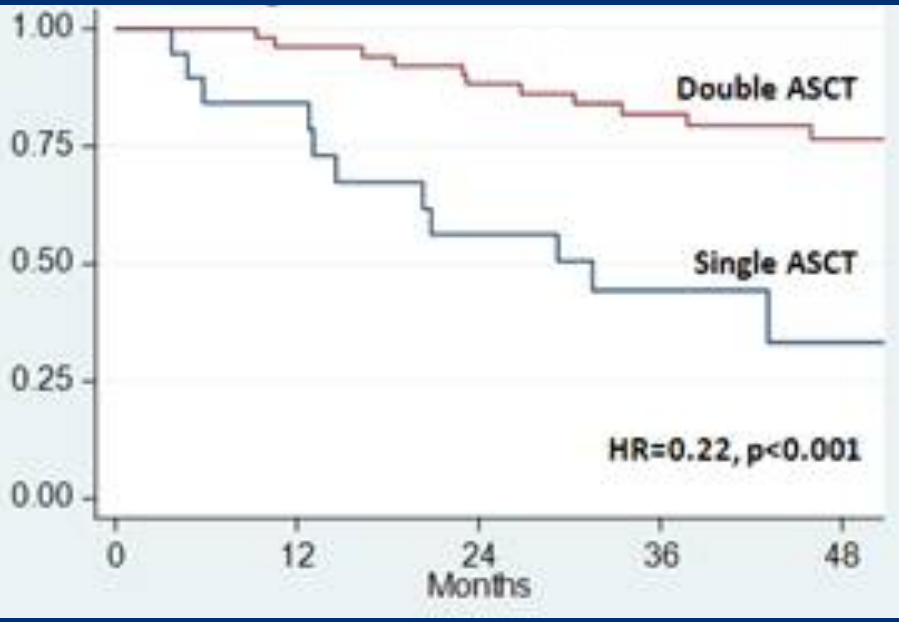
Double vs single ASCT after bortezomib-based induction

PFS and OS in pts with 2 adverse variables

	Double ASCT	Single ASCT	P
PFS	41 mos	20 mos	0.003
OS	67 mos	31.5 mos	<0.001

PFS and OS for pts with high-risk cytogenetics and who failed CR after bortezomib-based induction regimens





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

Double vs single ASCT after bortezomib-based induction:
Integrated analysis of phase European 3 studies

	Group 0 (no adverse variable)	**Group 1** (1 adverse variable)	**Group 2** (2 adverse variables)	**Group 3** (3 adverse variables)
Median PFS	61 mos	56 mos	36 mos	26 mos

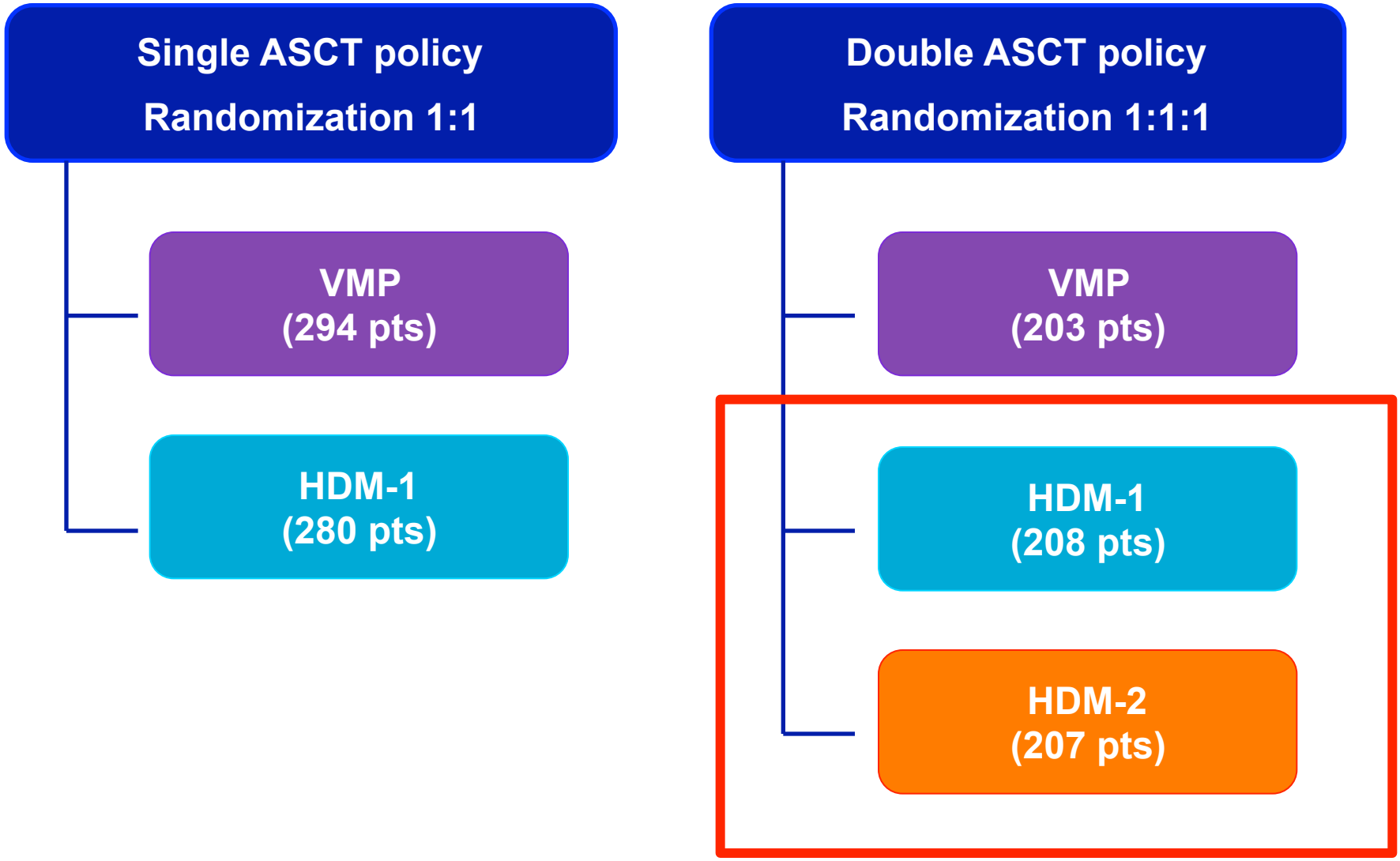
- Presence of 2 (P<0.001) or 3 (P<0.001) adverse prognostic variables associated with progressively shorter OS compared to lack of all 3 adverse variables

Adverse variables: ISS 3, high-risk cytogenetics, failure to achieve CR after induction therapy

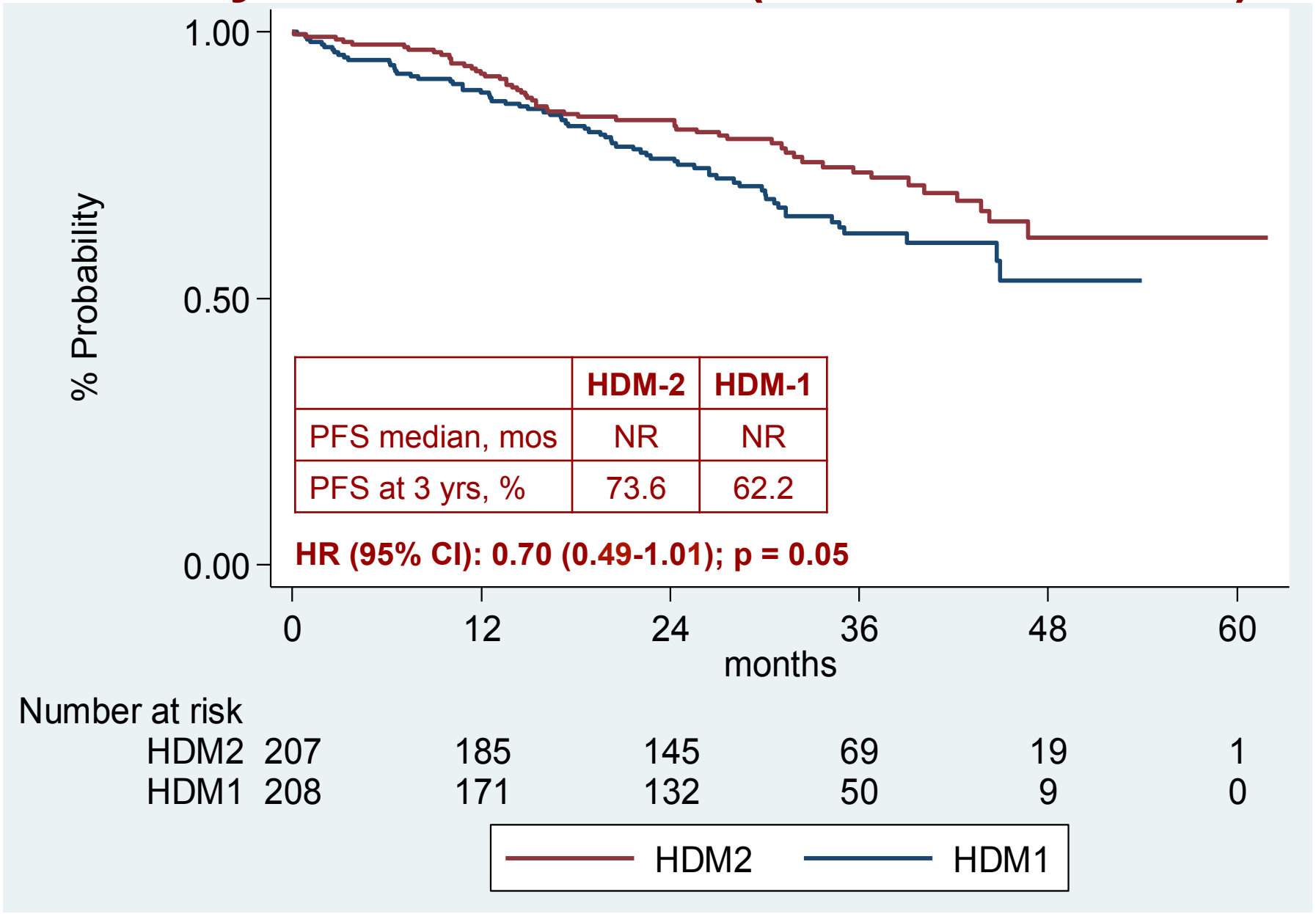
Cavo et al. ASH 2013 (Abstract 767), oral presentation

Randomization 1

1192 pts were eligible for randomization 1



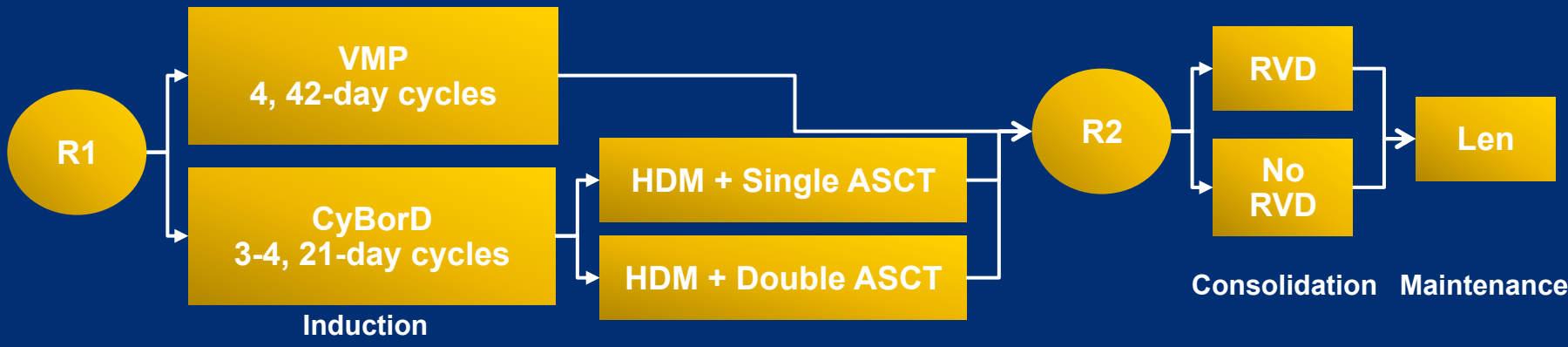
PFS by randomization 1 (HDM-1 *vs* HDM-2)



Median follow-up: 32 months (IQR 26-41)

Prolong Response: Consolidation

EMN02/HO95

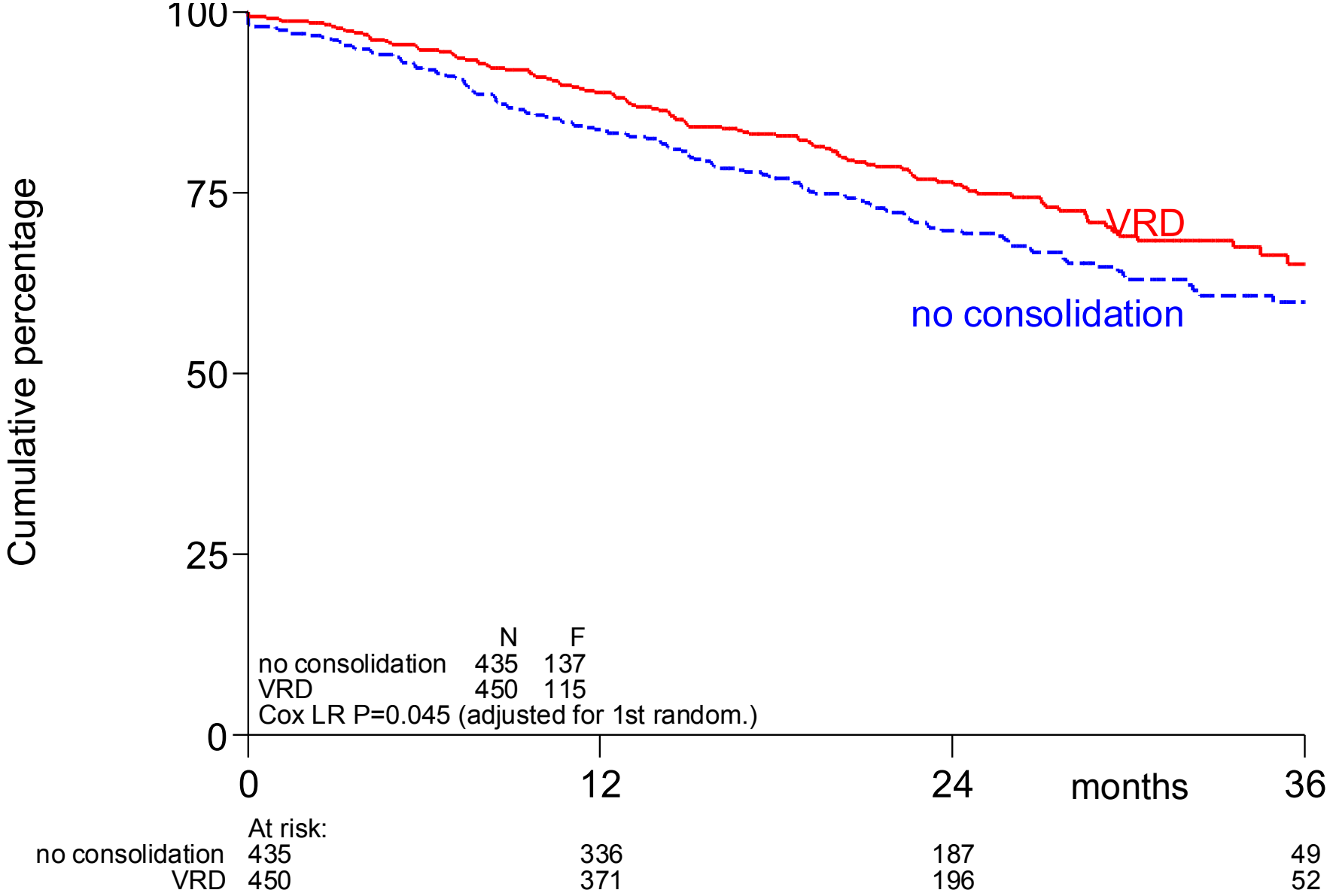


	Consolidation	No Consolidation	*P* Value
3-year PFS (%)	65	60	0.045

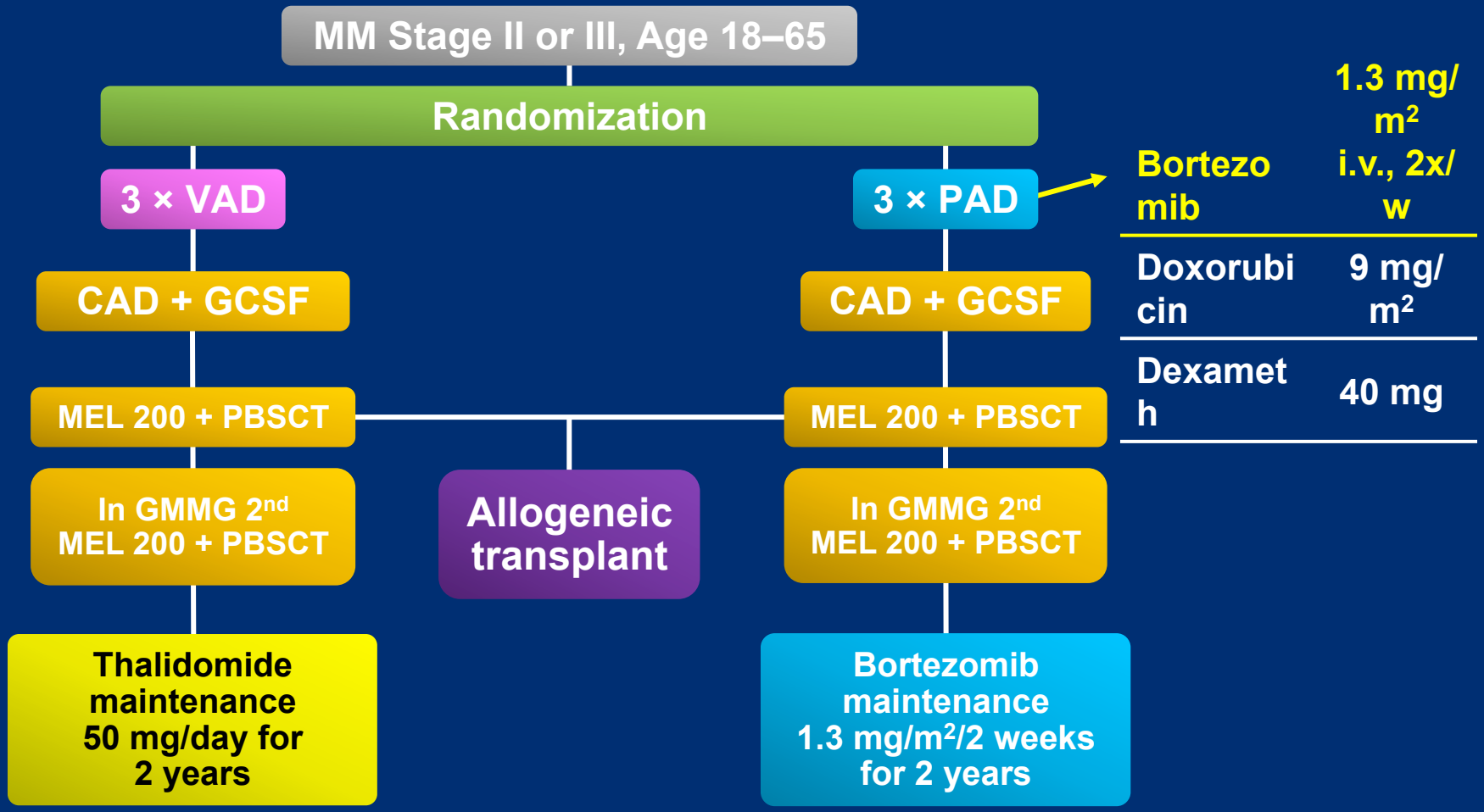
Not retained in high risk cytogenetics (0.91)

Sonneveld P et al. *Blood*. 2016;128: Abstract 242.

Progression-free survival



HOVON Study Schema



Sonneveld P et al. *J Clin Oncol*, 2012;30:2946.

Prolong Response: Consolidation

BMT CTN 0702

Register and Randomize → **MEL 200mg/m²**

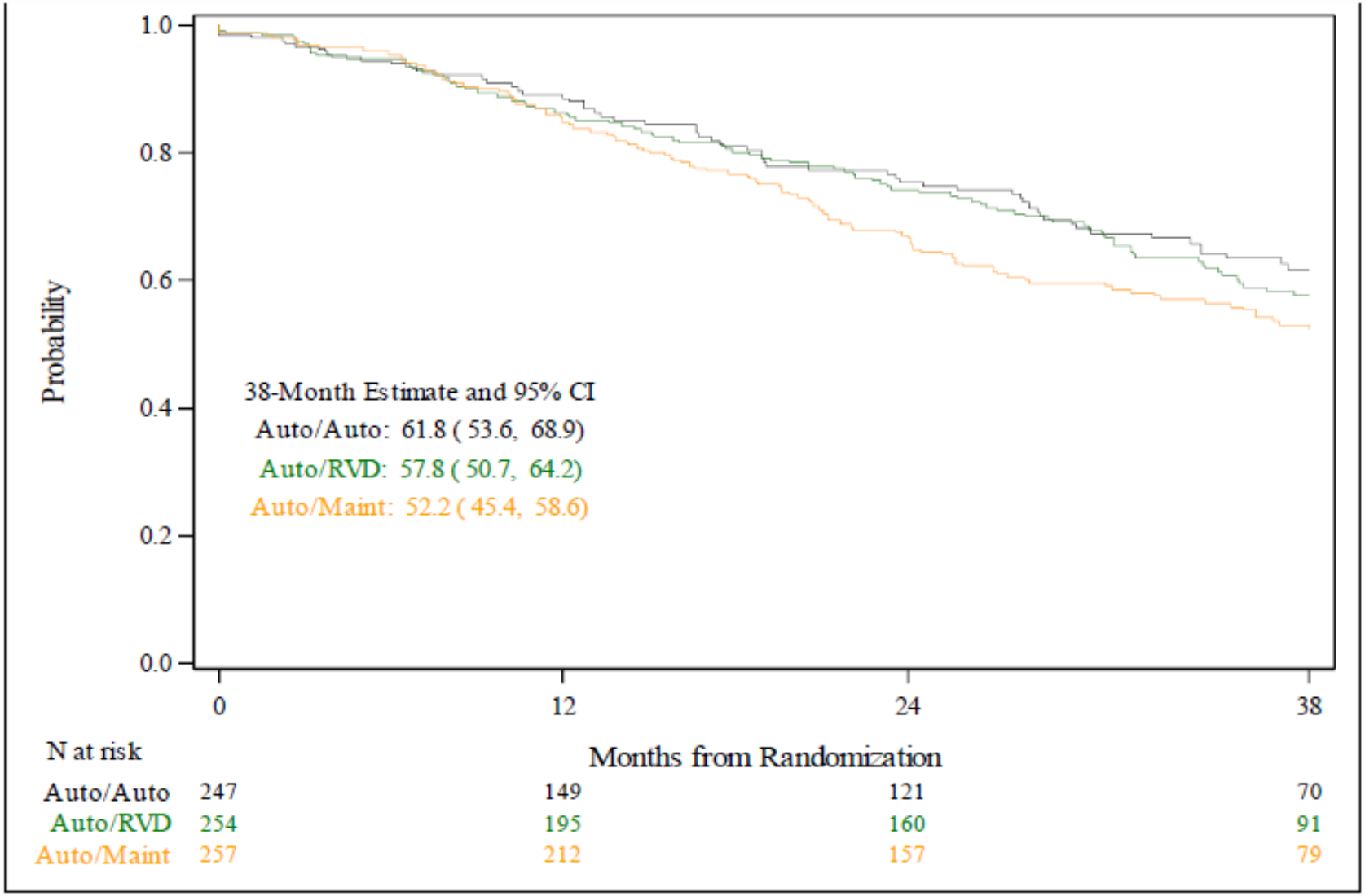
N=750 pts (250 in each arm)

- **Lenalidomide Maintenance** — AM
- **VRD x 4** → **Lenalidomide Maintenance** — ACM
- **MEL 200mg/m²** → **Lenalidomide Maintenance** — TAM

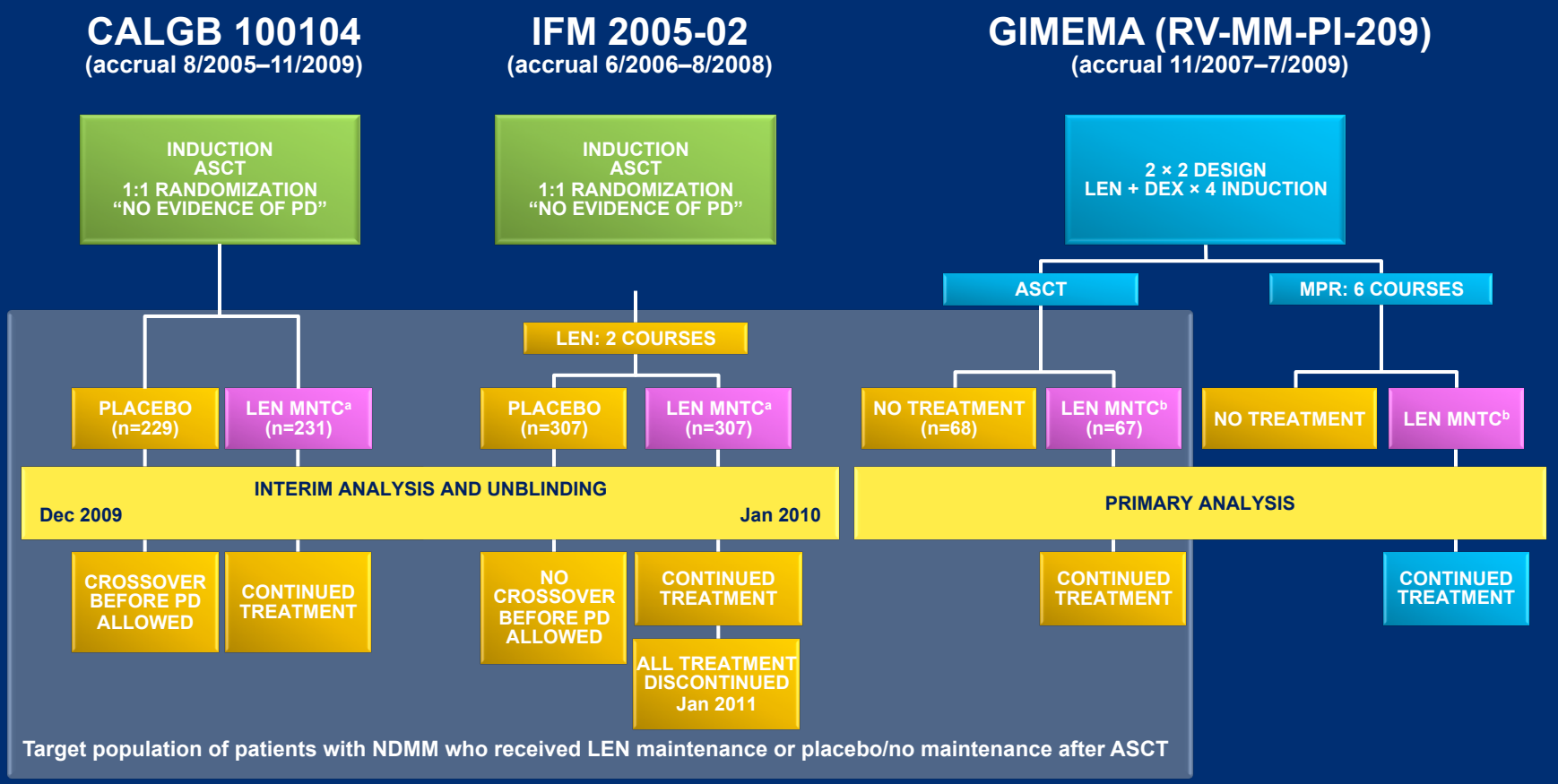
	ASCT with Len Maintenance (AM)	Consolidation with Len Maintenance (ACM)	Tandem ASCT with Len Maintenance (TAM)
N	257	254	247
38-mo PFS (%)	52	57	56

Stadtmauer EA et al. *Blood*. 2016;128: Abstract LBA-1.

Progression-Free Survival – as treated/per protocol Analysis



Studies Included in Meta-Analysis

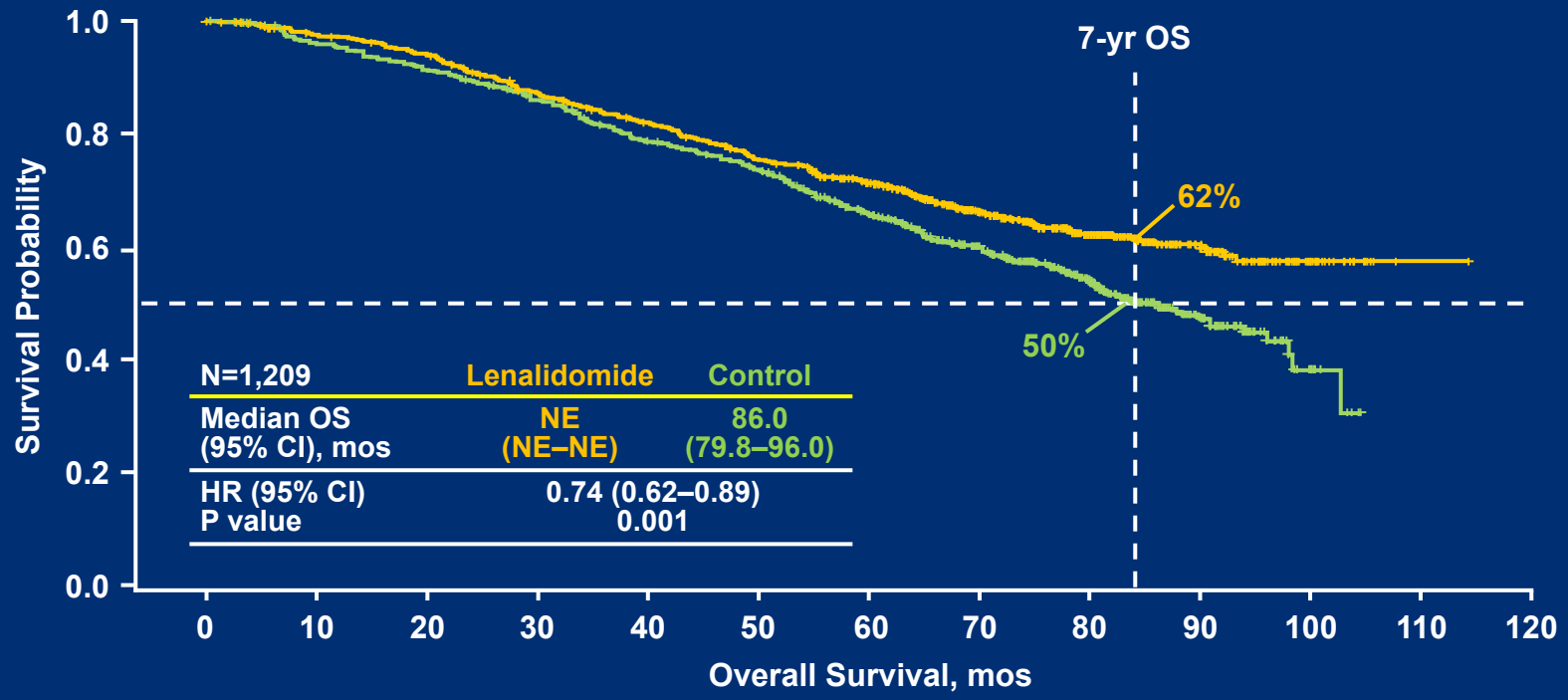


[a] Starting dose of 10 mg/day on days 1–28/28 was increased to 15 mg/day if tolerated and continued until PD.
[b] Patients received maintenance 10 mg/day on days 1–21/28 until PD.

Attal M et al. *J Clin Oncol*. 2016;34: Abstract 8001.

Overall Survival: Median Follow-Up of 80 Months

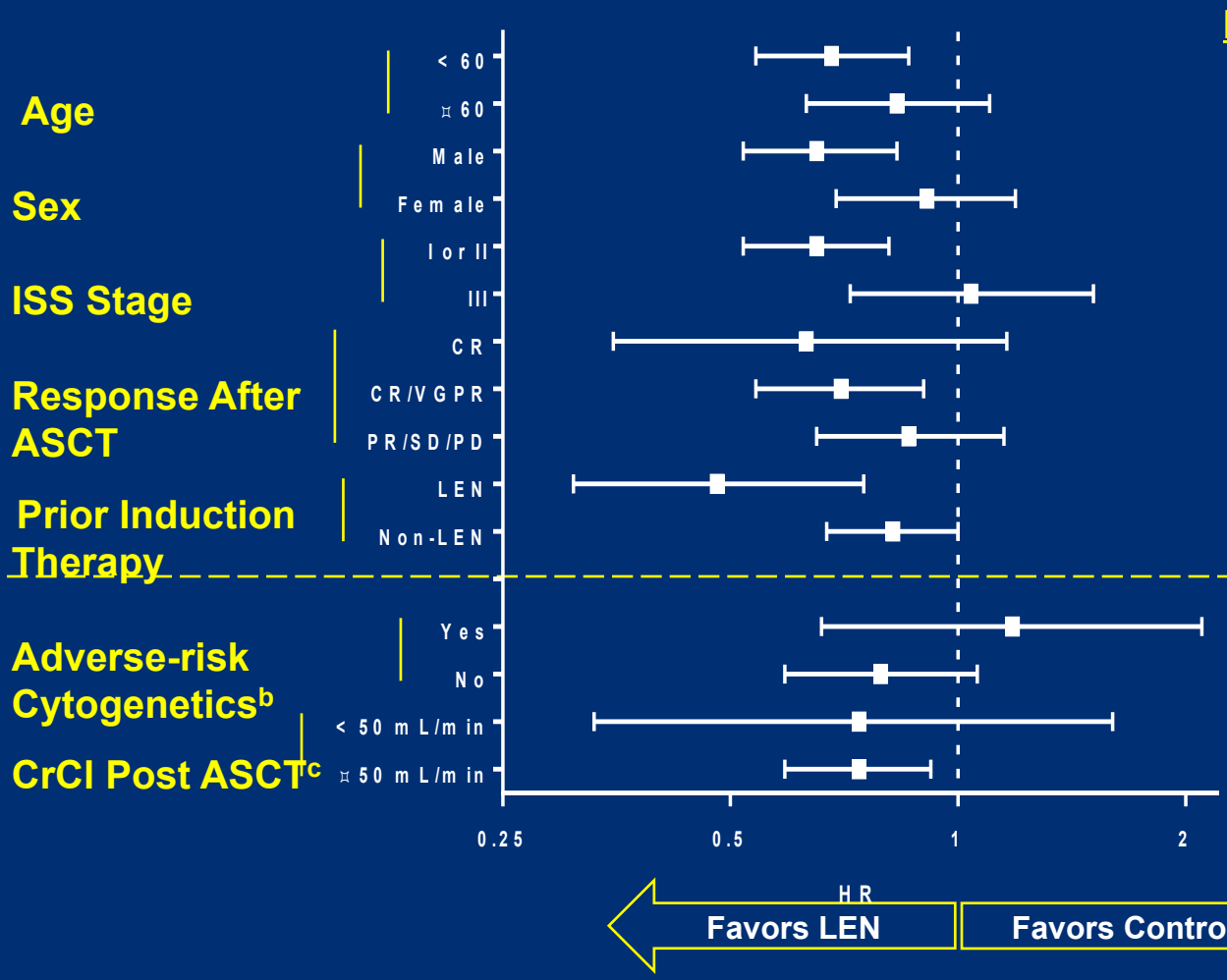
There is a 26% reduction in risk of death, representing an estimated 2.5-year increase in median survival.[a]



[a] Median for lenalidomide treatment arm was extrapolated to be 116 months based on median of the control arm and HR (median, 86 months; HR = 0.74).

Attal M et al. *J Clin Oncol*. 2016;34: Abstract 8001.

Overall Survival: Subgroups



	LEN	CONTROL	HR (95% CI)
Age			
< 60	372	375	0.68 (0.54-0.86)
≥ 60	233	229	0.83 (0.63-1.10)
Sex			
Male	322	349	0.65 (0.52-0.83)
Female	283	255	0.91 (0.69-1.19)
ISS Stage			
I or II	411	440	0.65 (0.52-0.81)
III	113	90	1.04 (0.72-1.51)
Response After ASCT			
CR	66	80	0.63 (0.35-1.16)
CR/VGPR	320	339	0.70 (0.54-0.90)
PR/SD/PD	218	210	0.86 (0.65-1.15)
Prior Induction Therapy			
LEN	147	146	0.48 (0.31-0.75)
Non-LEN	458	458	0.82 (0.67-1.00)
Adverse-risk Cytogenetics[b]			
Yes	56	36	1.18 (0.66-2.10)
No	231	243	0.79 (0.59-1.06)
CrCl Post ASCT[c]			
< 50 mL/min	33	25	0.73 (0.33-1.60)
≥ 50 mL/min	379	404	0.74 (0.59-0.92)

[a] Number of patients. [b] Cytogenetic data were only available for the IFM and GIMEMA studies. [c] CrCl post-ASCT data were only available 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.

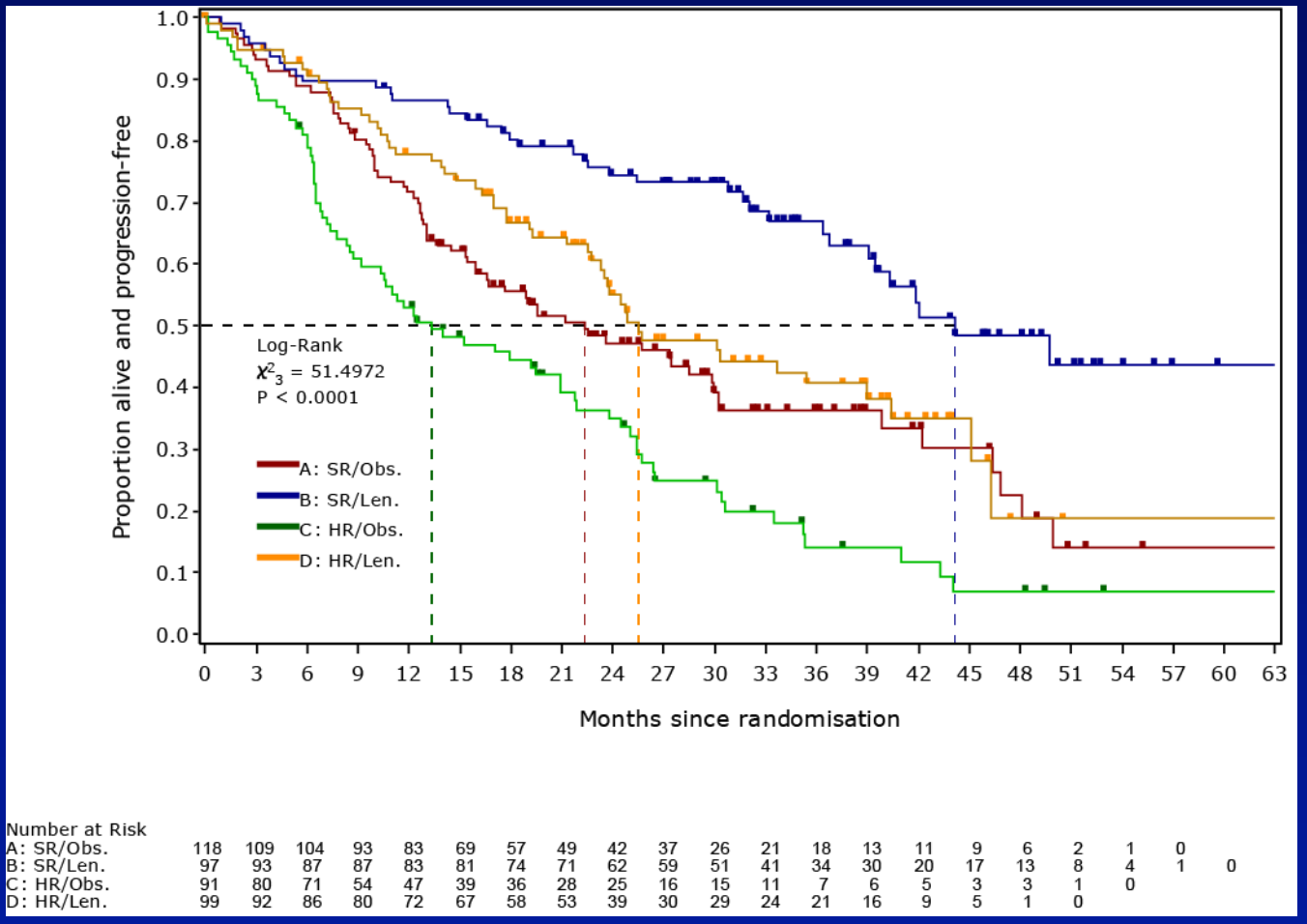
Lenalidomide is Highly Effective Maintenance Therapy in MM: Phase 3 Myeloma XI study

- Lenalidomide continued to disease progression versus no therapy in both newly diagnosed transplant eligible (TE) and transplant non-eligible (TNE) populations

	TE (n=828)		TNE (n=722)		
	Maint	No Maint	Maint	No Maint	*P* Value
Median PFS (mos)	60	28	26	12	<0.0001

Jackson G et al. *Blood.* 2016;128: Abstract 1143.

Impact of maintenance by cytogenetic risk status



Outcome of HR subgroup is clearly improved by the use of maintenance lenalidomide

Conclusions

- Treatment with lenalidomide until progression results in a highly significant improvement in PFS for NDMM patients of all ages
- Effective irrespective of risk status or response status at time of entry
- Increases responses over time
- No evidence of increased DNA instability at mutational or structural level
- OS results will be presented when the number of events reaches 458

Maintenance Therapy Post SCT: What Is Known

- Bortezomib maintenance; HOVON[1]
- Lenalidomide maintenance after ASCT reduces the risk of progression or death by approximately 50%[2-5]
- All phase 3 studies had progression-free survival as the primary end point

1. Sonneveld P et al. *J Clin Oncol*, 2012;30:2946.
2. Palumbo A et al. *N Engl J Med*. 2014;371:895.
3. McCarthy PL et al. *N Engl J Med*. 2012;366:1770.
4. Attal M et al. *N Engl J Med*. 2012;366:1782.
5. Palumbo A et al. *N Engl J Med*. 2012;366:1759.

Recommandations ESMO
ESMO guidelines, Moreau et al. Ann Oncol 2017

Eligibility for ASCT

Yes

Induction: 3-drug regimens
VTD
VCD
RVD
PAD
↓

200 mg/m2 Melphalan
followed by ASCT

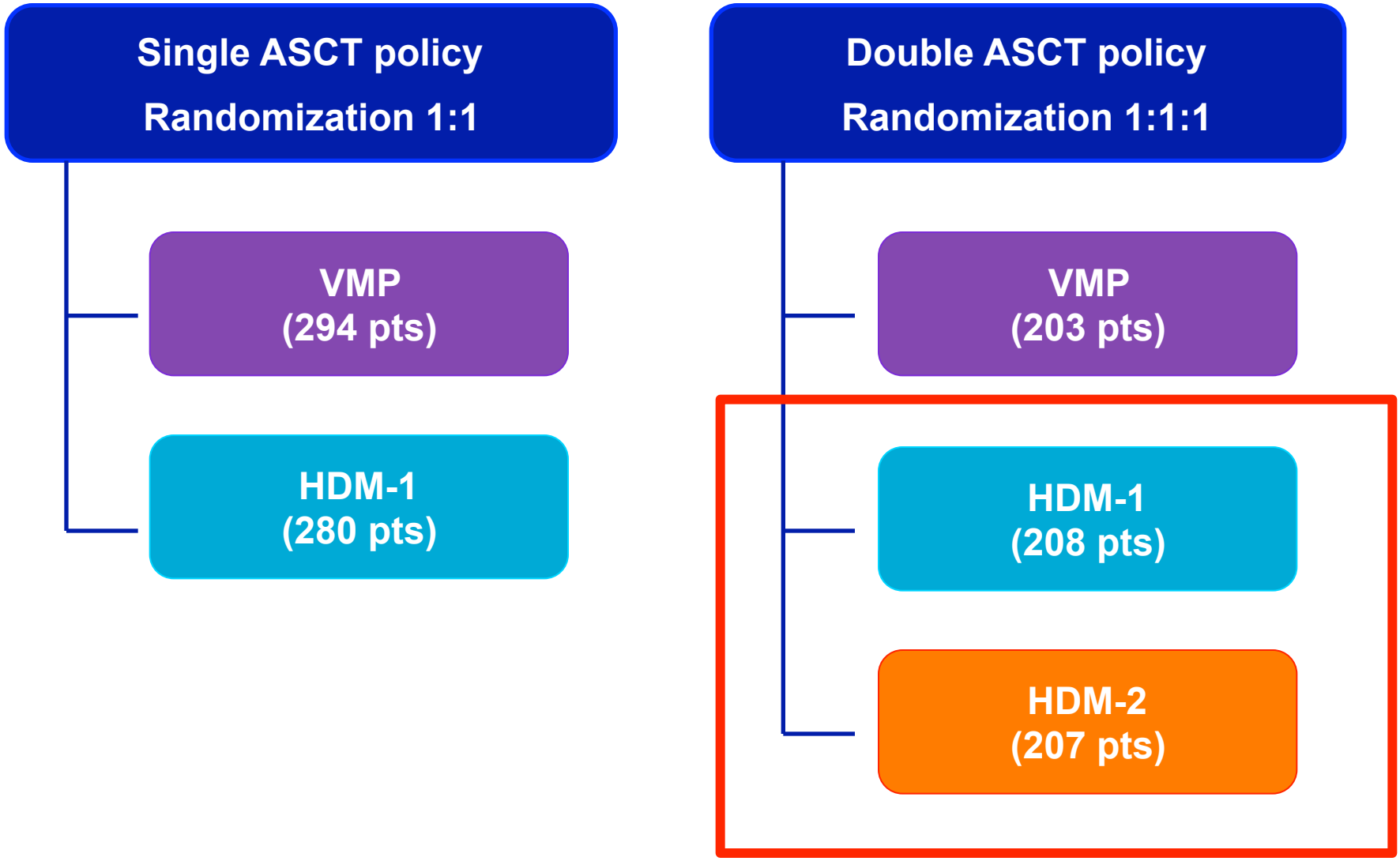
↓

Maintenance
Lenalidomide

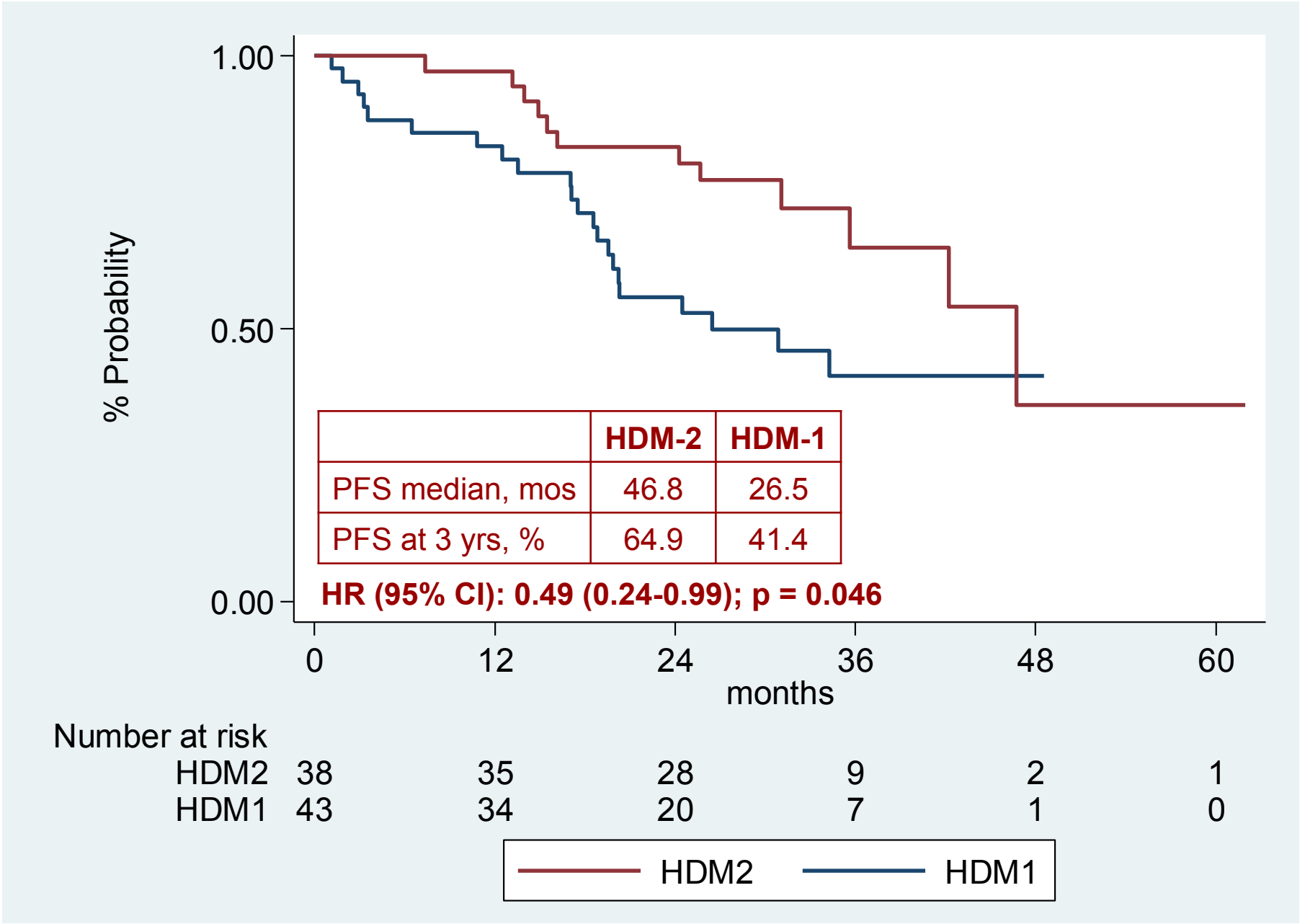
Doit-on, Peut-on proposer une attitude spécifique aux patients considérés de haut risque ?

Randomization 1

1192 pts were eligible for randomization 1



PFS by high-risk cytogenetics



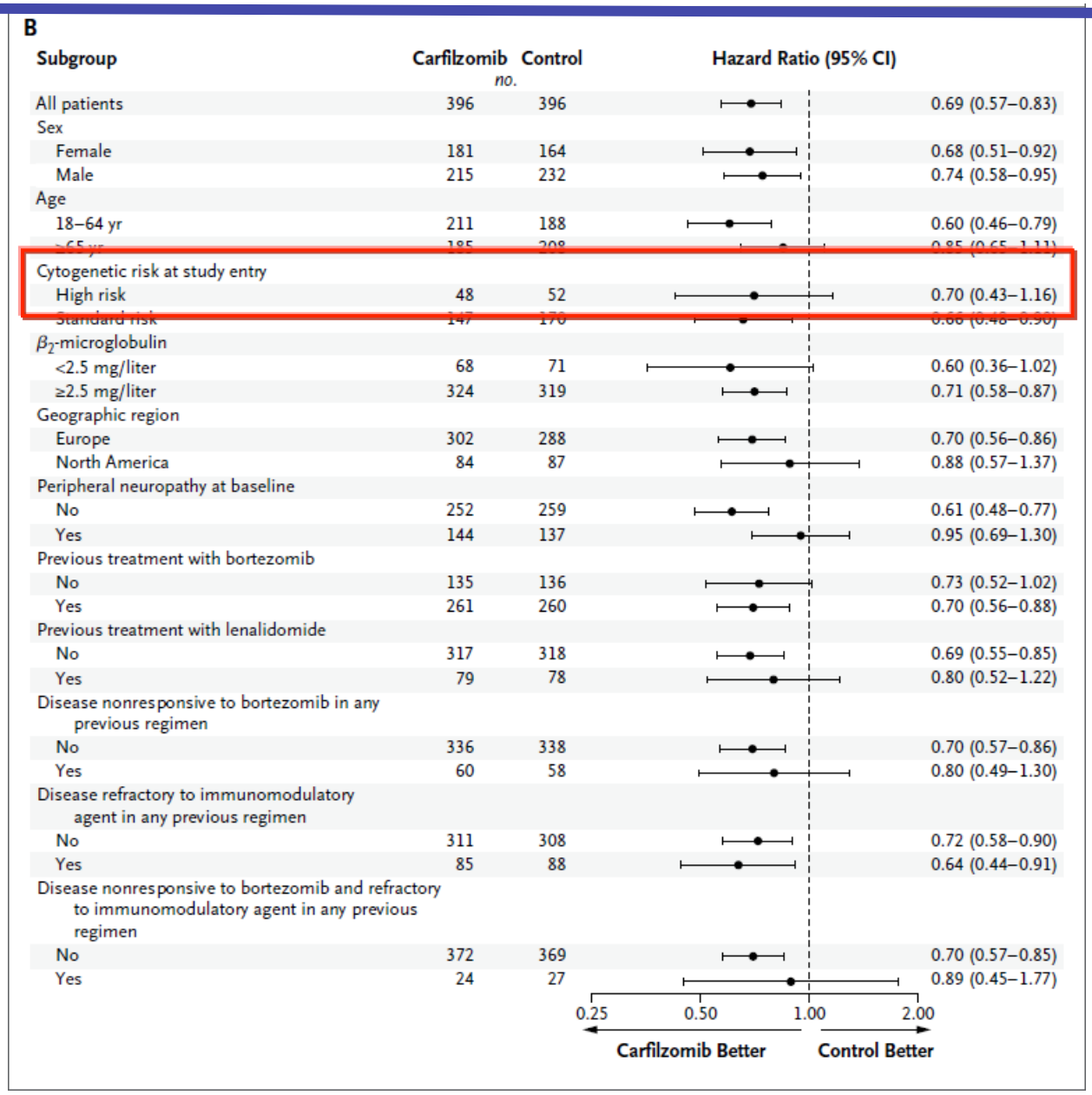
	HDM-2	HDM-1
PFS median, mos	46.8	26.5
PFS at 3 yrs, %	64.9	41.4

Pomalidomide-Dex in cytogenetically-defined high risk MM

Agent	PFS	OS
Pomalidomide-Dex (MM-003)[1]		
Low Risk		14 mos
High Risk		9.9 mos
del(17p)		12.6 mos
t(4;14)		7.5 mos
Pomalidomide-Dex[2]		
del(17p)	7.3 mos	12 mos
t(4;14)	2.8 mos	9.2 mos

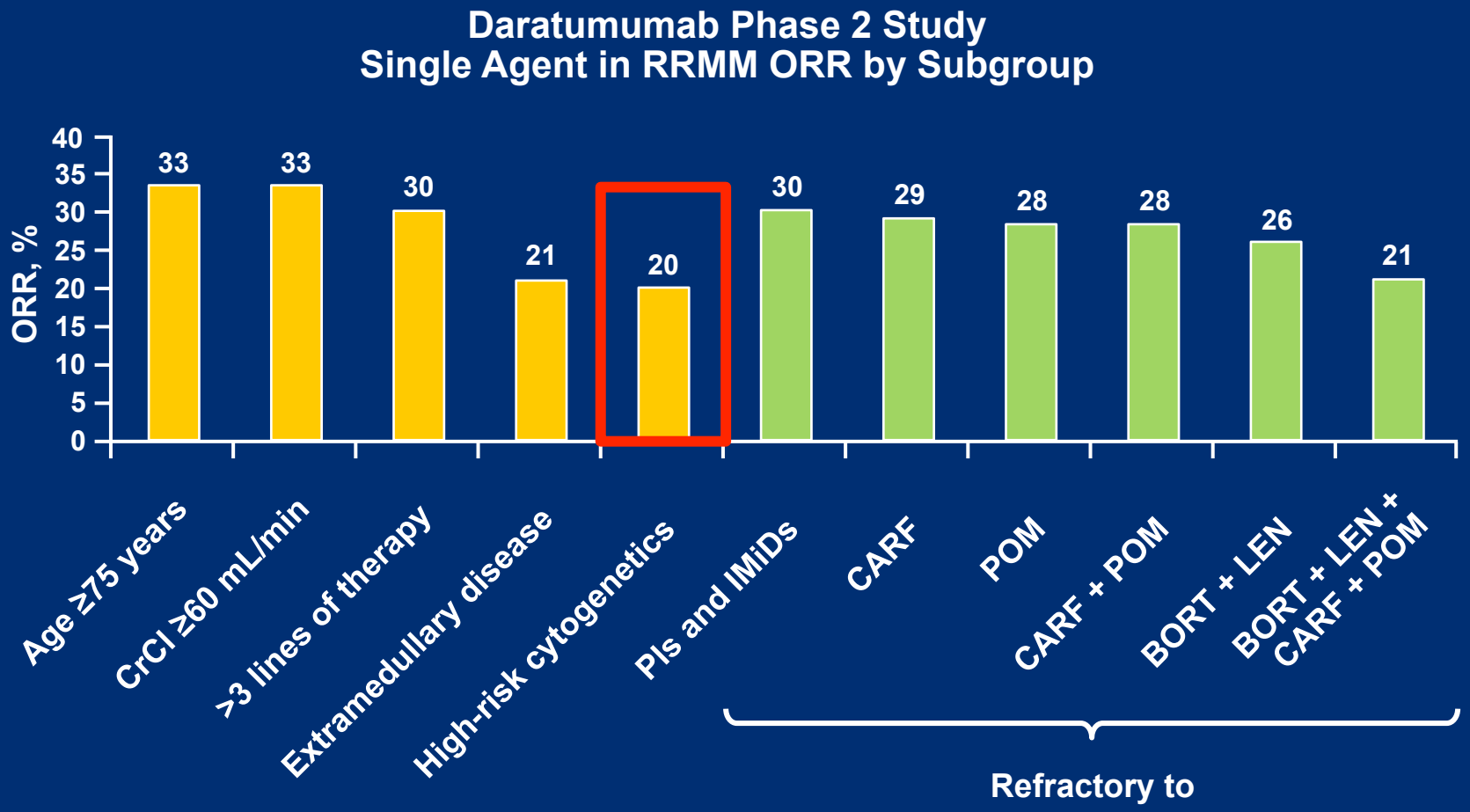
[1] Dimopoulos MA et al. *ASH 2013*
[2] Leleu et al. *Blood 2015*

Carfilzomib-Len-Dex in cytogenetically-defined high-risk MM



Stewart AK et al. *New Engl.J. Med 2015*

Daratumumab in High-Risk Patients

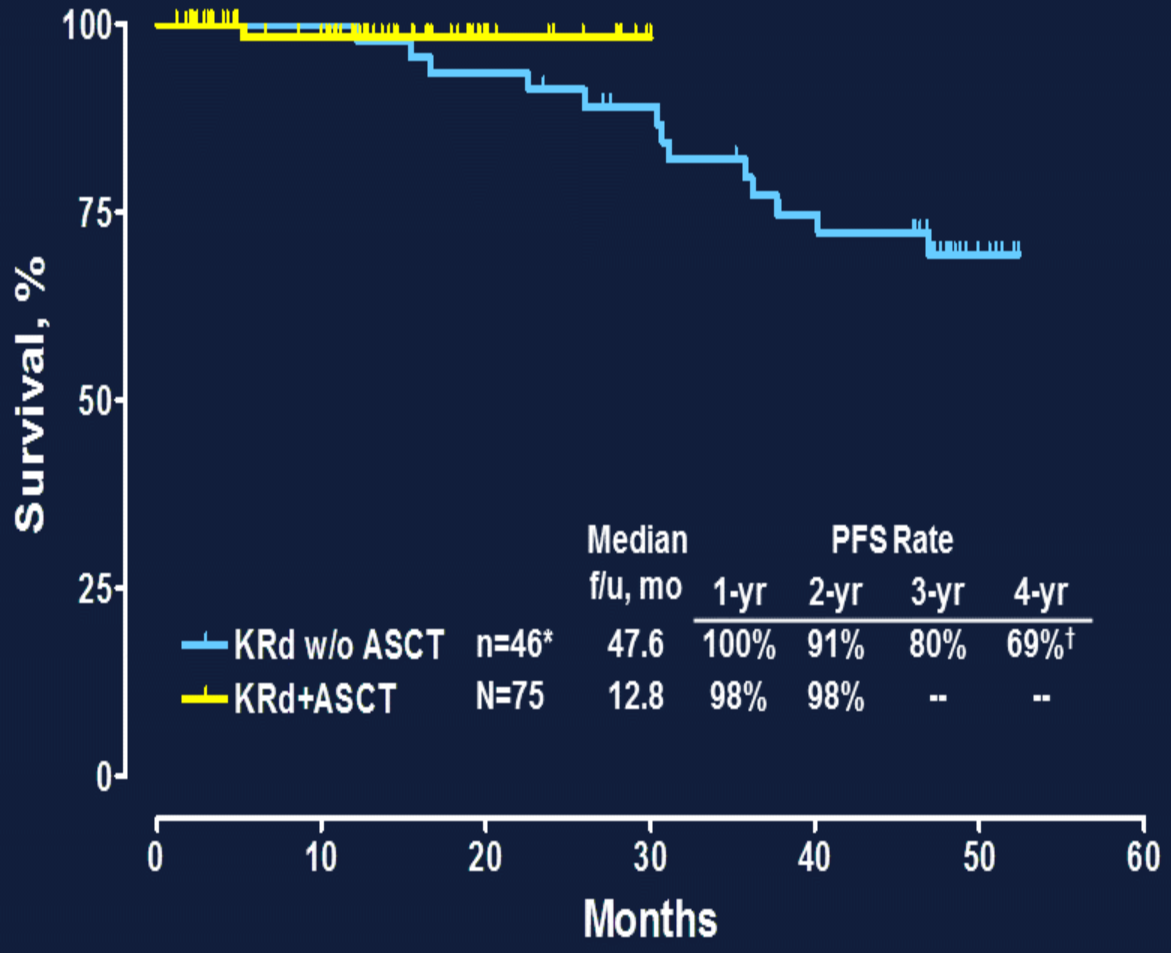


Lonial S et al. *J Clin Oncol*. 2015;33. Abstract LBA 8512.

Quelles sont les perspectives de modifications de traitement à court ou moyen terme ?

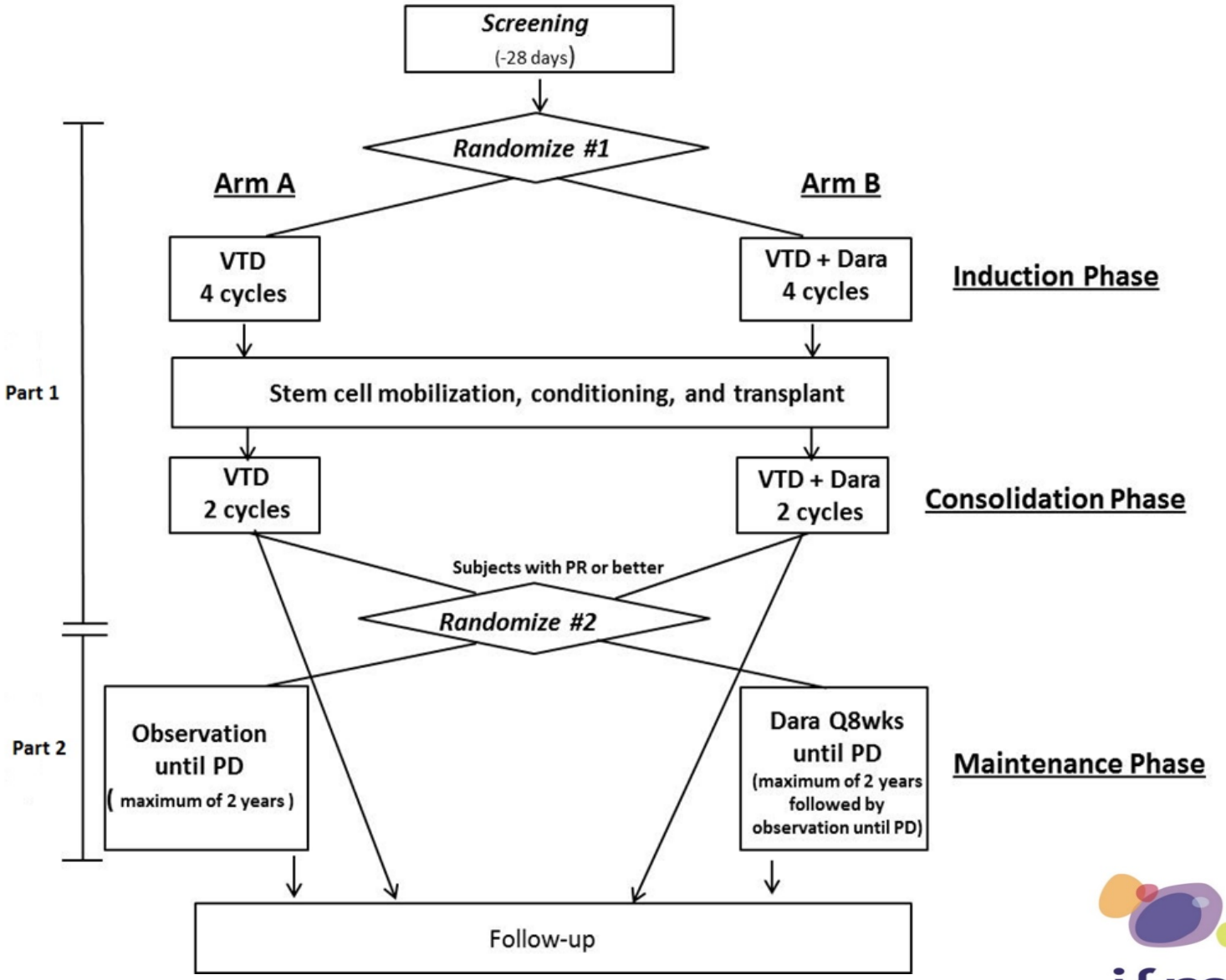
Treatment Outcomes – PFS

Courtesy Dr Jakubowiak
EHA 2016



*Excludes 7 pts who discontinued to pursue ASCT
†Intent-to-treat (N=53), 4-year PFS 64%

Study Design: Cassiopeia IFM/Hovon



IFM 2014 trial (300 patients)

VTD or VCD X 4
Randomisation

ARM A:

Mel 200 + CSP

VTD X 2

ARM B:

Vel-Mel 200 + CSP

VTD X 2

Primary end point: CR before consolidation

IFM 2017-18 version 1

	MRD1		MRD2	
Standard Risk I+RD-Dara X 6	↗ - R ↘	HDT1 + IRD-Dara X 4 IRD-Dara X 7	↗ - R ↘	REV Maint REV + DARA Maint
	+	HDT1 + KPD-Dara X 6	+	HDT 2 REV Maint REV + Dara Maint
			↗ - R ↘	REV Maint REV + DARA Maint
High Risk I+RD-Dara X 6		HDT 1 + KPD-DARA X 6	→	HDT 2 + REV + Dara Maint

Quels sont les schémas de traitement standard à ce jour en situation de première ligne pour un patient non éligible à une intensification ?

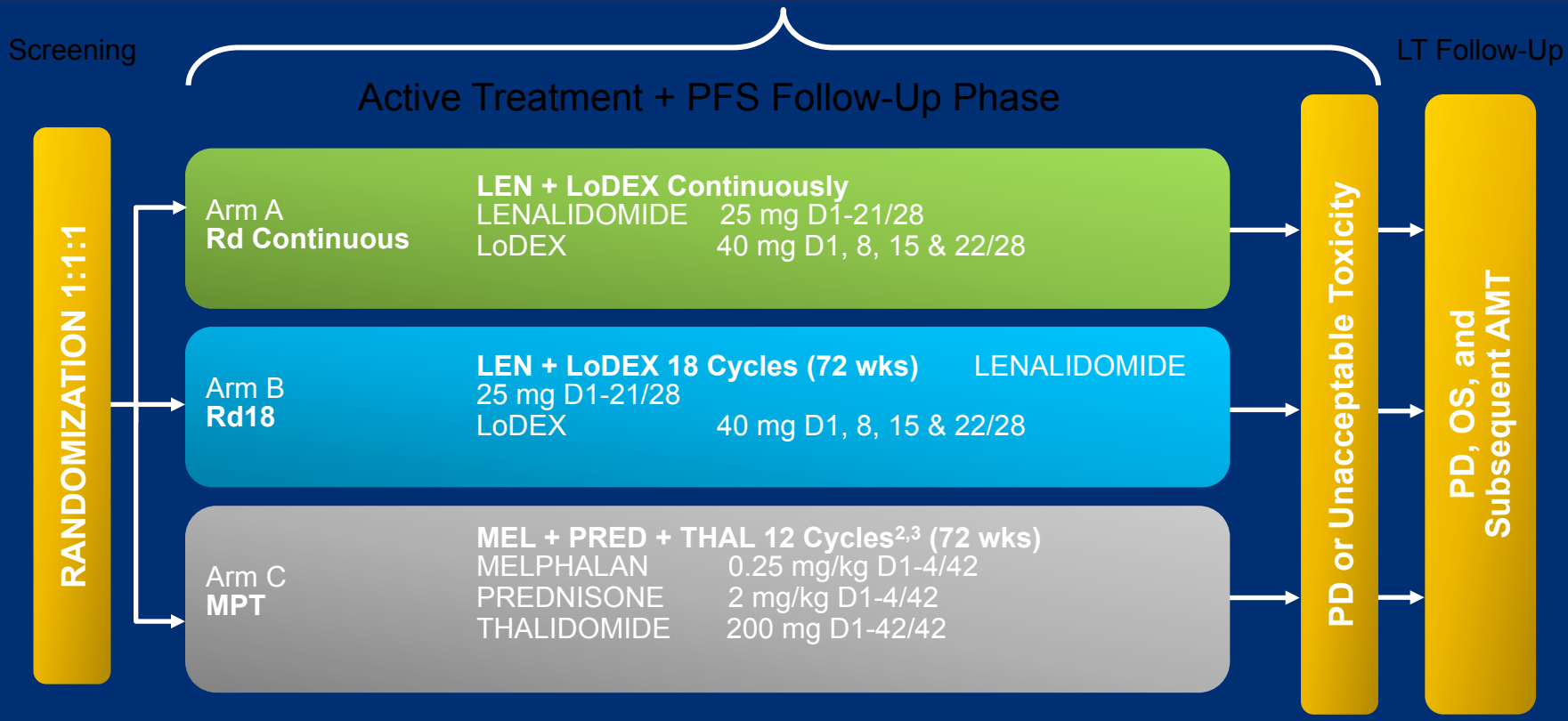
MPT et MPV
évolution via expérience clinique

- MPT: relativement stable
  - thalidomide 100 (or 200 mg/j)
- MPV: evolution importante au cours du temps
  - D'un schéma 2 fois/sem à 1 fois/sem[1,2] (2010)
  - De l'i.v. vers l'administration s.c.[3] (2012)
  - L'administration SC hebdomadaire fait partie dorénavant du schéma standard du traitement par MPV ou autre schéma à base de Velcade chez le sujet âgé

1. Palumbo A, et al. J Clin Oncol. 2010;28:5101-9.
2. Mateos MV, et al. Lancet Oncol. 2010;11:934-41.
3. Moreau P, et al. Lancet Oncol. 2011;12:431-40.

Et dès demain ?

FIRST (IFM2007-01/MM-020): Study Design



Pts aged >75 yrs: LoDEX 20 mg D1, 8, 15 & 22/28; MEL 0.2 mg/kg D1–4; THAL 100 mg D1–42/42.
All pts received thromboprophylaxis.

- Stratification: age, country, and ISS stage

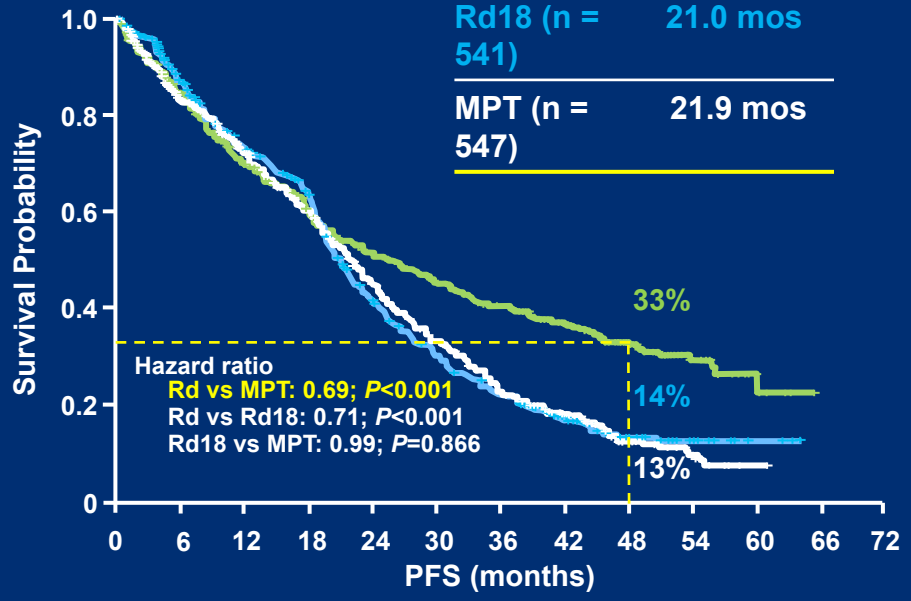
1. Benboubker L et al. *N Engl J Med.* 2014;371:906.
2. Facon T et al. *Lancet.* 2007;370:1209.
3. Hulin C et al. *J Clin Oncol.* 2009;27:3664.
Avet-Loiseau H et al. *Blood*. 2015;126: Abstract 730.

IFM 2007-01 FIRST Trial: PFS and OS

PFS as per investigator assessment[1]

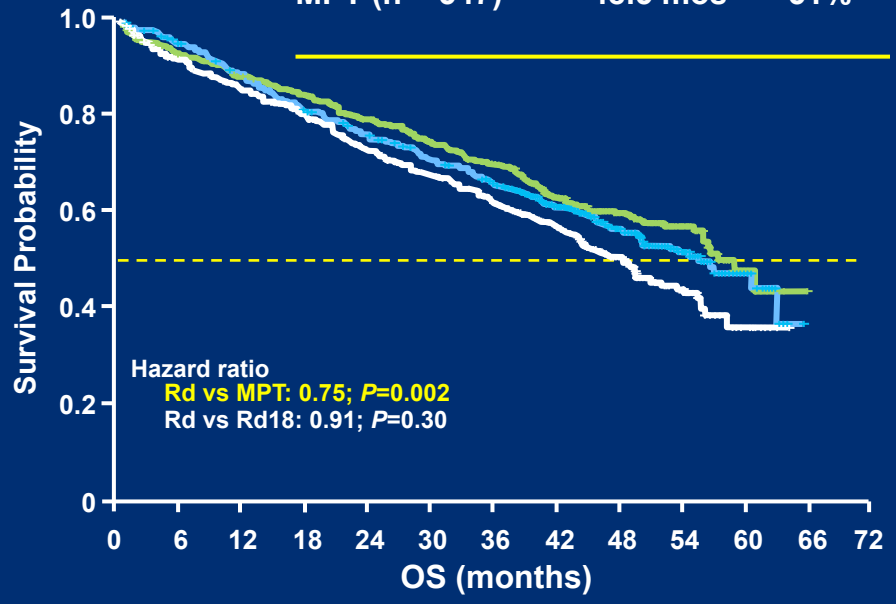
Data cut-off: 3 March 2014
Median follow-up: 45.5 mos
697 deaths (43% of ITT)

	Median PFS
Rd (n = 535)	26.0 mos
Rd18 (n = 541)	21.0 mos
MPT (n = 547)	21.9 mos



OS[2]

	Median OS	4-year OS
Rd (n = 535)	58.9 mos	60%
Rd18 (n = 541)	56.7 mos	57%
MPT (n = 547)	48.5 mos	51%



1. Lenalidomide European Public Assessment Report. March 2015.
2. Facon T et al. *J Clin Oncol*. 2015;33: Abstract 8524.

CLARION: Trial design

Newly Diagnosed MM (Target N = 882)

- Transplant-ineligible

Stratification:

- ISS stage (1 vs. 2 or 3)
- Planned BTZ route of administration (IV or SC)
- Region (North America, Europe, Asia, or other)
- Age (< 75 yrs vs. ≥ 75 yrs)

1:1

54 Weeks of Treatment as 9 x 6-week cycles

KMP

Carfilzomib: 20/36 mg/m^2 IV D1, 2, 8, 9, 22, 23, 29, 30

Melphalan 9 mg/m^2 D1-4; **Prednisone** 60 mg/m^2 D1-4

VMP

Bortezomib: 1.3 mg/m^2 D1, 4, 8, 11, 22, 25, 29, 32 Cycles 1-4

then D1, 8, 22, 29 Cycles 5-9

Melphalan: 9 mg/m^2 D1-4; **Prednisone** 60 mg/m^2 D1-4

Primary endpoint: PFS

Secondary endpoints: OS, ORR (≥PR), CRR, Neuropathy events, HR-QOL, Safety

ClinicalTrials.gov. Phase 3 Study of Carfilzomib, Melphalan, Prednisone vs Bortezomib, Melphalan, Prednisone in Newly Diagnosed Multiple Myeloma (CLARION). https://clinicaltrials.gov/ct2/show/NCT01818752?term=clarion&rank=1.

Top-line results from Ph 3 CLARION study in newly diagnosed multiple myeloma patients

EFFICACY

CLARION did not meet the primary endpoint of superiority in PFS

- ***"The trial did not meet the primary endpoint of superiority in PFS"***
  - HR = 0.91 (95% CI, 0.75 - 1.10)
  - Median PFS: 22.3 months for KMP vs 22.1 months for VMP
- ***"The data for overall survival, a secondary endpoint, are not yet mature"***
  - Observed HR: 1.21 (95% CI, 0.90 - 1.64)
- ***"Neither result was statistically significant"***

SAFETY

Adverse events in the KMP arm were consistent with the known safety profile of Kyprolis

- **Incidence of Gr≥3 AEs**: 74.7% in KMP vs 76.2% in VMP
- **Fatal treatment-emergent AEs**: 6.5% in KMP vs 4.3% in VMP
- **Incidence of Gr≥2 peripheral neuropathy**: 2.5% in KMP vs 35.1% in VMP (secondary endpoint)

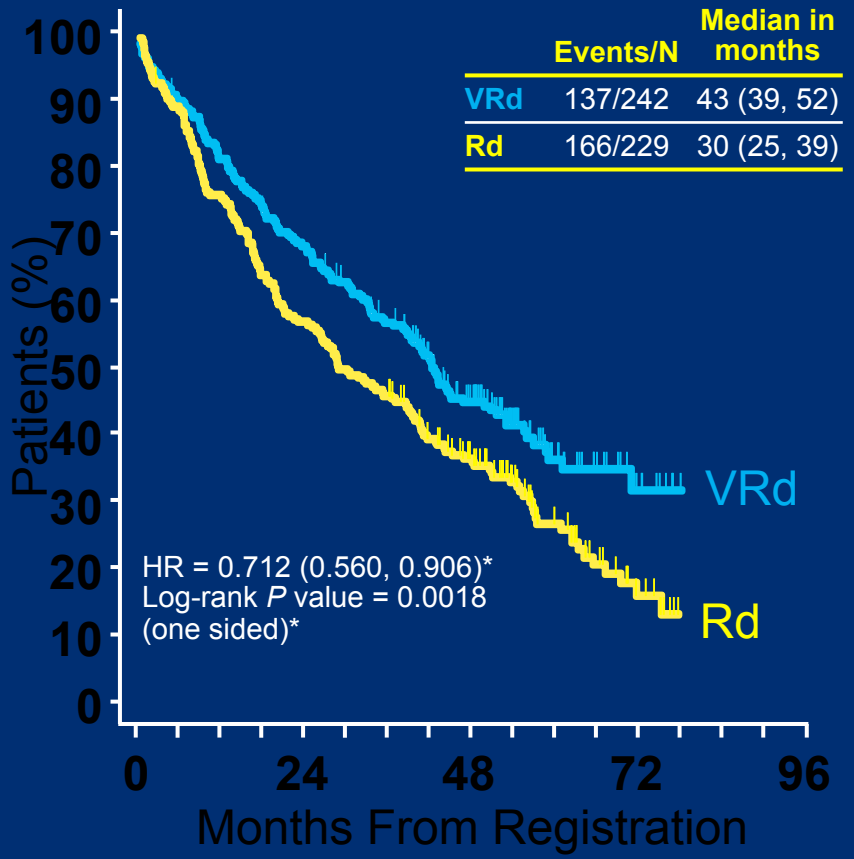
VMP: Velcade, melphalan, prednison; KMP: Kyprolis, melphalan, prednison.

http://wwwext.amgen.com/media/news-releases/2016/09/amgen-announces-topline-results-from-phase-3-kyprolis-carfilzomib-clarion-study-in-newly-diagnosed-multiple-myeloma-patients.

SWOG S0777: PFS and OS by Assigned Treatment Arm

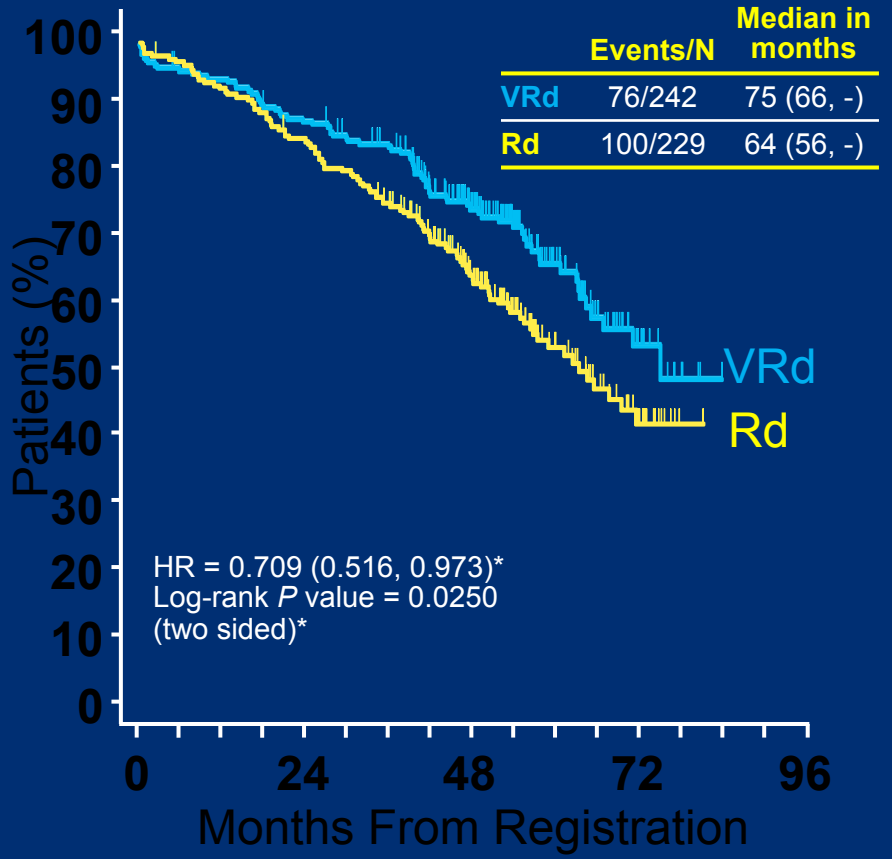
NCI National Clinical Trials Network
a National Cancer Institute program

PFS by assigned treatment arm



	Events/N	Median in months
VRd	137/242	43 (39, 52)
Rd	166/229	30 (25, 39)

OS by assigned treatment arm



	Events/N	Median in months
VRd	76/242	75 (66, -)
Rd	100/229	64 (56, -)

* Stratified

Durie B et al. *Blood*. 2015;126: Abstract 25.

FRONTLINE THERAPY
ESMO guidelines, Moreau et al. Ann Oncol 2017, in press

Eligibility for ASCT

No

First option: VMP, Rd, VRD

Second option: VCD, MPT

Other options : BP, CTD, MP

Comment s'orienter entre le jeune retraité actif et l'octogénaire fragile ?

Frailty score

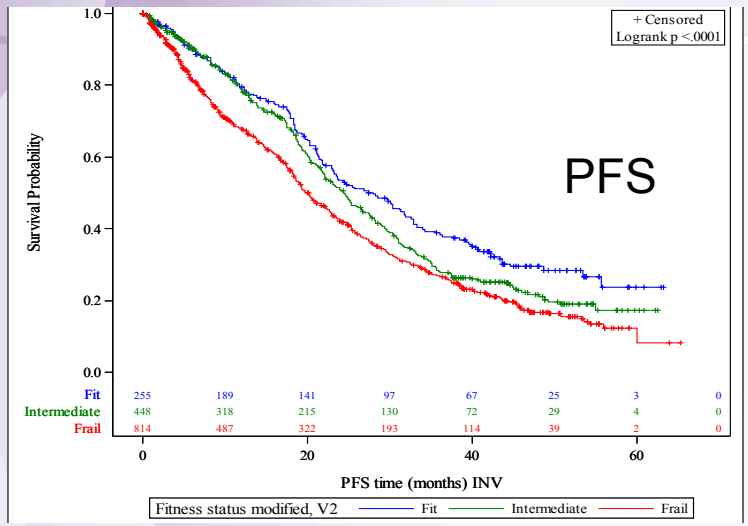
Variable		HR (CI 95%)	P	SCORE
AGE	Age <75 years	1	-	0
	Age 75-80 years	1.37 (0.93-2.03)	0.114	1
	Age >80 years	2.75 (1.81-4.18)	<0.001	2
CHARLSON INDEX	Charlson ≤1	1	-	0
	Charlson ≥2	1.6 (1.07-2.39)	0.021	1
ADL SCORE	ADL >4	1	-	0
	ADL≤4	1.76 (1.14-2.71)	0.01	1
IADL SCORE	IADL >5	1	-	0
	IADL≤5	1.53 (1.03-2.27)	0.036	1

1. Charlson M, et al. J Chronic Dis.1987; 40:373-83
2. Katz S, et al. JAMA 1963;185:914-9.
3. Lawton MP, et al. Gerontologist. 1969;9:179-86.

ADDITIVE TOTAL SCORE	PATIENT STATUS
0	FIT
1	UNFIT
≥2	FRAIL

Essai FIRST

Analyse selon facteur fragilité
EHA 2016



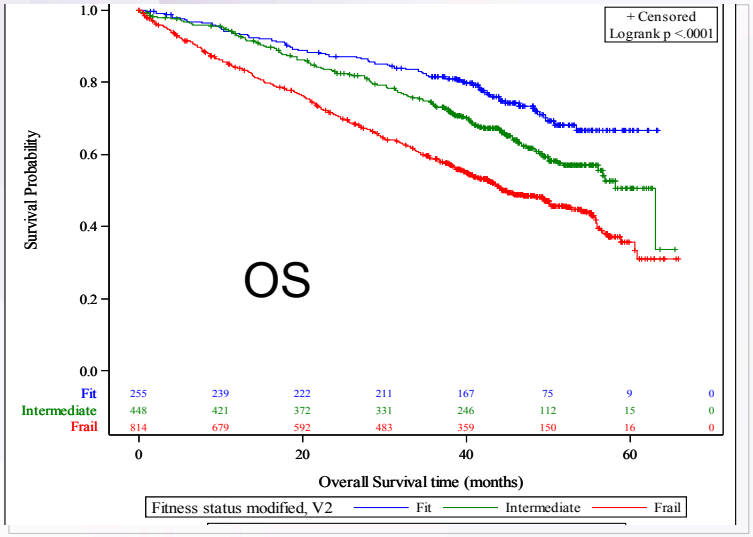
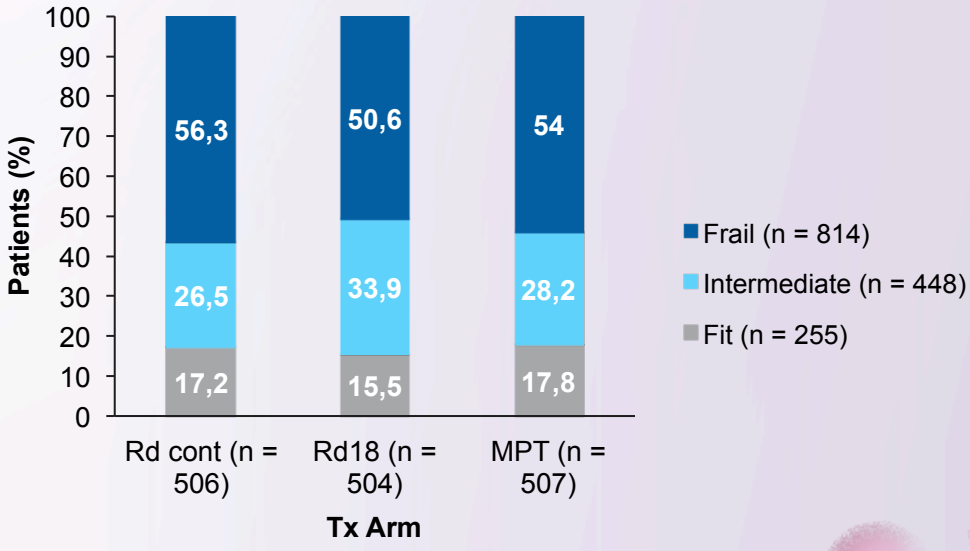


Table 1. Frailty Algorithm

Category	Score
Age	
≤ 75 yrs	0
76-80 yrs	1
> 80 yrs	2
Charlson Comorbidity Index score	
≤ 1	0
≥ 2	1
Katz Activity of Daily Living score	
> 4 *(Self Care EQ-5D = 1)*	0
≤ 4 *(Self Care EQ-5D = 2,3)*	1
Lawton Instrumental Activity of Daily Living score	
> 5 *(Usual Activities EQ-5D = 1)*	0
≤ 5 *(Usual Activities EQ-5D = 2,3)*	1
	Total
	0: Fit
	1: Intermediate
	≥ 2: Frail

EQ-5D, EuroQol five dimensions questionnaire.



FIT + ISS 1 : PFS médiane 34 mois, OS médiane non atteinte

Application clinique : frailty score

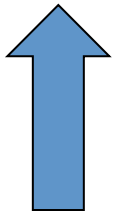
FRAIL **FIT**

LA ZONE GRISE
UNFIT

Que signifie véritablement éligible à une intensification?

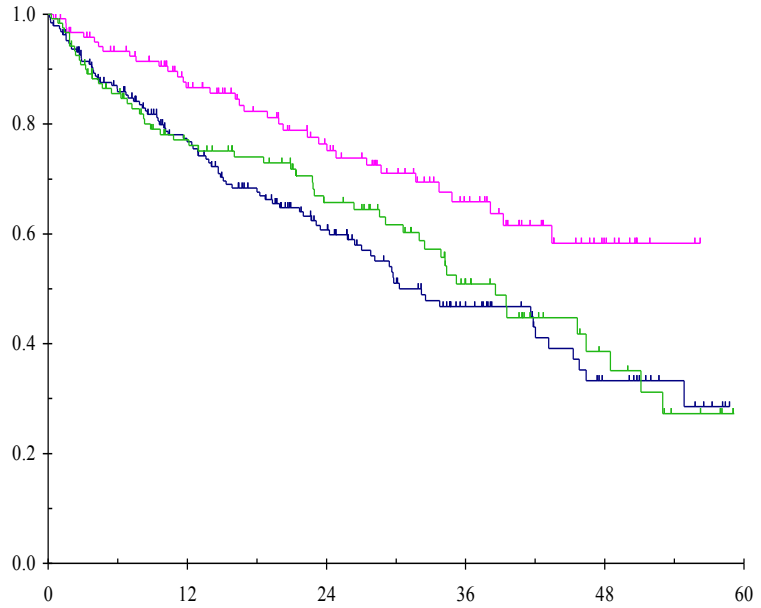
Autologous stem cell transplantation for multiple myeloma
EBMT data – *Auner et al*, BMT 2014

	Age group (years)												
	<40		40-49		50-59		60-64		65-69		≥70		
Characteristic	*No.*	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*	*p*
Patients undergoing 1st AHCT													<.001
1991-1995	172	6.7	743	29.0	1185	46.3	383	15.0	75	2.9	2	0.1	
1996-2000	396	4.3	1839	20.2	4238	46.4	1835	20.1	718	7.9	100	1.1	
2001-2005	547	3.1	2632	15.0	7115	40.6	4253	24.3	2478	14.1	497	2.8	
2006-2010	614	2.5	3482	14.2	9253	37.8	6518	26.6	3860	15.8	740	3.0	



Essai IFM 99/06

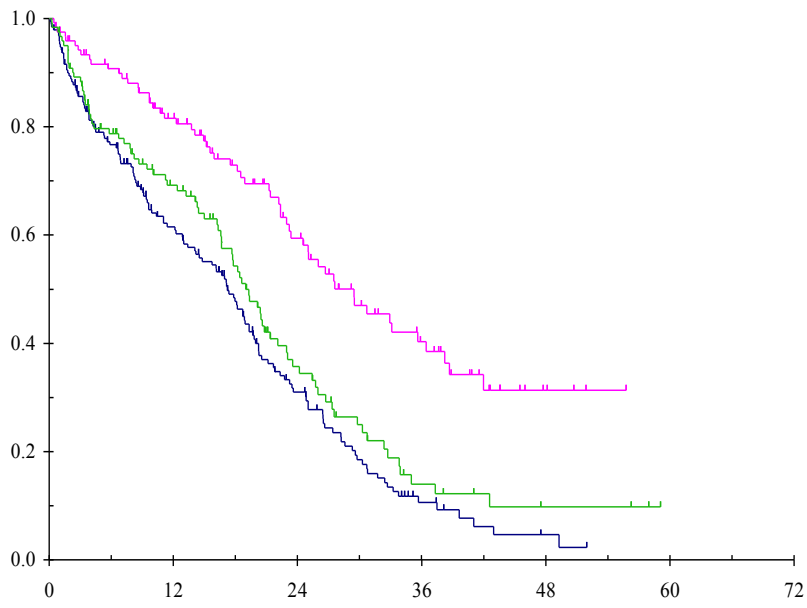
Survie globale



Temps depuis inclusion (mois)

	O/N	Survie médiane ± se (mois)
MP	86/191	30.3 ± 5.8
MP+Thal	34/124	Not reached at 56
Intensification	54/121	38.6 ± 3.0

Survie sans progression



Temps depuis inclusion (mois)

	O/N	Survie médiane ± se (mois)
MP	141/191	17.2 ± 1.5
MP+Thal	57/124	29.5 ± 3.6
Intensification	82/121	19.0 ± 1.3

Facon T, Mary JY, Hulin C, et al. Lancet 2007;370:1209-18.

L'association Lenalidomide + DXM constitue-t-elle la nouvelle plateforme systématique d'avenir ?

Phase 3 Rd-based continuous studies for elderly patients

NCT01335399

Elotuzumab

Rd

R: 25 mg PO ; D1–21

DEX: 40 mg PO ; D1, 8, 15 & 22

28-d cycles until PD

ELO-Rd

ELO: 10 mg/kg; D1, 8, 15 & 22 (cycles 1–2); D1 & 15 (cycles 3–18); 20 mg/kg on D1 (cycles ≥ 19)

R: 25 mg, D1–21

DEX: 40 mg D1, 8, 15 & 22 (cycles 1–2); D1 & 15 (cycles 3–18); D1 (cycles ≥ 19)

28-d cycles, until PD

NCT01850524

Ixazomib

Rd

R: 25 mg PO ; D1–21

DEX: 40 mg PO ; D1, 8, 15 & 22

28-d cycles/18 mos

DEX Discontinued

Placebo + R

R 10 mg

Until PD

Ixazomib-Rd

Ixazomib: 4 mg

R: 25 mg

DEX: 40 mg; D1, 8, 15 & 22

28-d cycles/18 mos

DEX Discontinued

Ixazomib+ R

Ixazomib: 3 mg

R: 10 mg

Until PD

NCT02252172

Daratumumab

Rd

R: 25 mg PO ; D1–21

DEX: 40 mg PO ; D1, 8, 15 & 22

28-d cycles until PD

DARA-Rd

DARA: 16 mg/kg q1wk for 8 wks; q2wk for 16 wks; q4wk thereafter

R: 25 mg PO d; D1–21

DEX: 40 mg PO d; D1, 8, 15 & 22

28-d cycles; Rd for up to 2 years; DARA until PD

- Primary endpoint for all studies is PFS

1. NCT01335399. 2. NCT01850524. 3. NCT02252172.

EQUIPE ACTUELLE

ANCIENNE EQUIPE