



DEBATES IN MULTIPLE MYELOMA: EARLY VS DELAYED TRANSPLANT

DELAYED TRANSPLANT

Jonathan L. Kaufman, MD

Hematology and Medical Oncology

Winship Cancer Institute

Emory University



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COI

- Consultant/Advisory Board: Abbvie, BMS, Sanofi
- DSMC: Incyte

Role of Early Transplant in myeloma

- Deepen remission
- Prolong PFS
- Improve OS
- Increase time without treatment

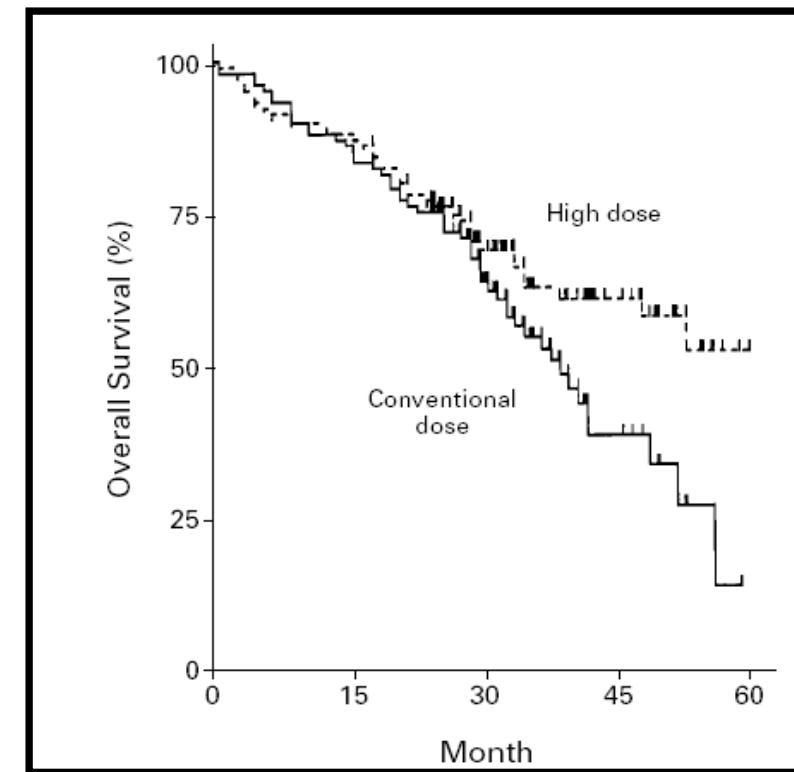
No Improvement in Therapy for Patients with Myeloma in 30 years until

A PROSPECTIVE, RANDOMIZED TRIAL OF AUTOLOGOUS BONE MARROW TRANSPLANTATION AND CHEMOTHERAPY IN MULTIPLE MYELOMA

TABLE 2. RESPONSE RATES ACCORDING TO TREATMENT GROUP.*

TYPE OF RESPONSE	CONVENTIONAL DOSE (N=100)	HIGH DOSE (N=100)
	no. of patients	
Complete	5	22
Very good partial	9	16
Partial	43	43
Minimal	18	7
Progressive disease	25	12

*P<0.001 for the comparison of the various response categories between the two groups by the chi-square test. Seventy-four patients in the high-dose group underwent autologous bone marrow transplantation.

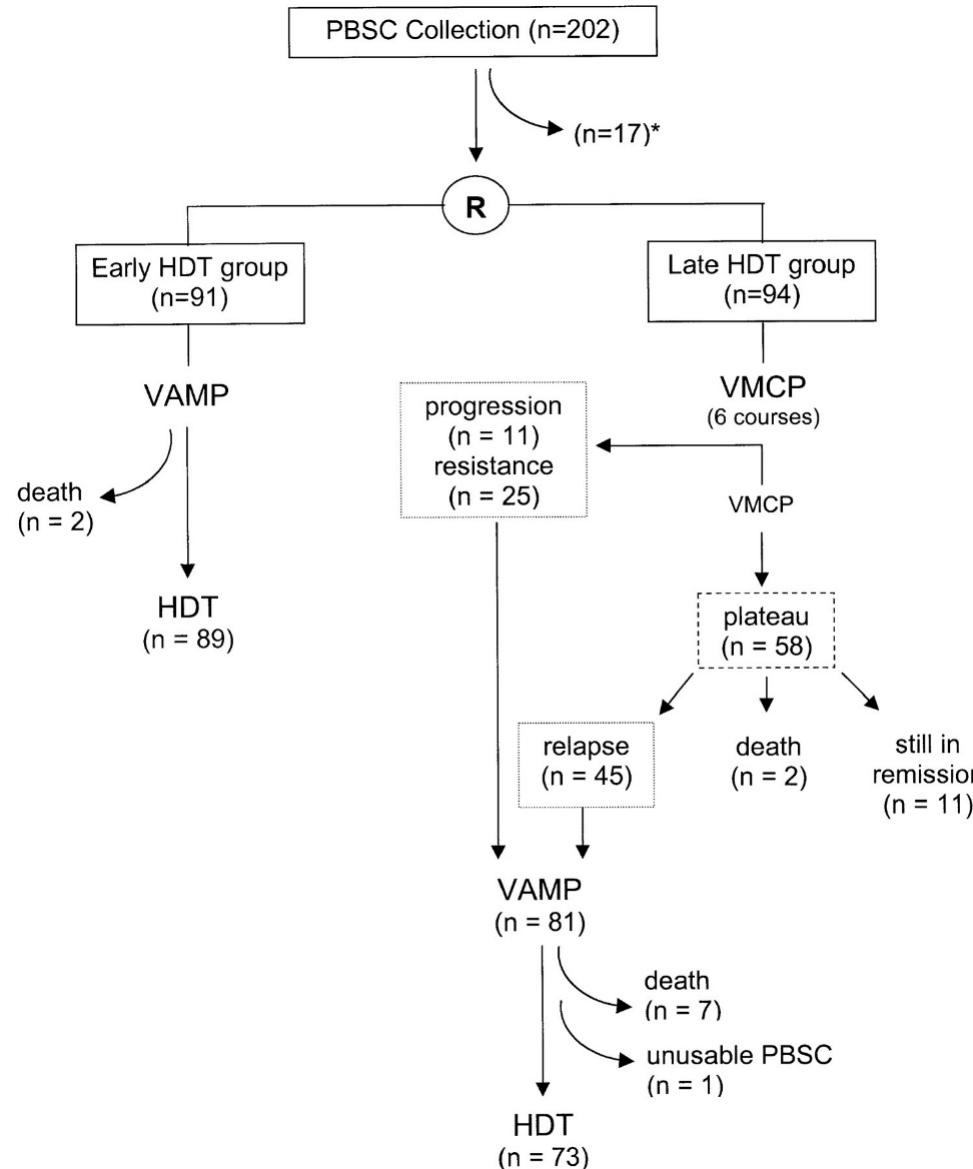


Attal H, et al. NEJM 1996

When: Now or Later.

blood

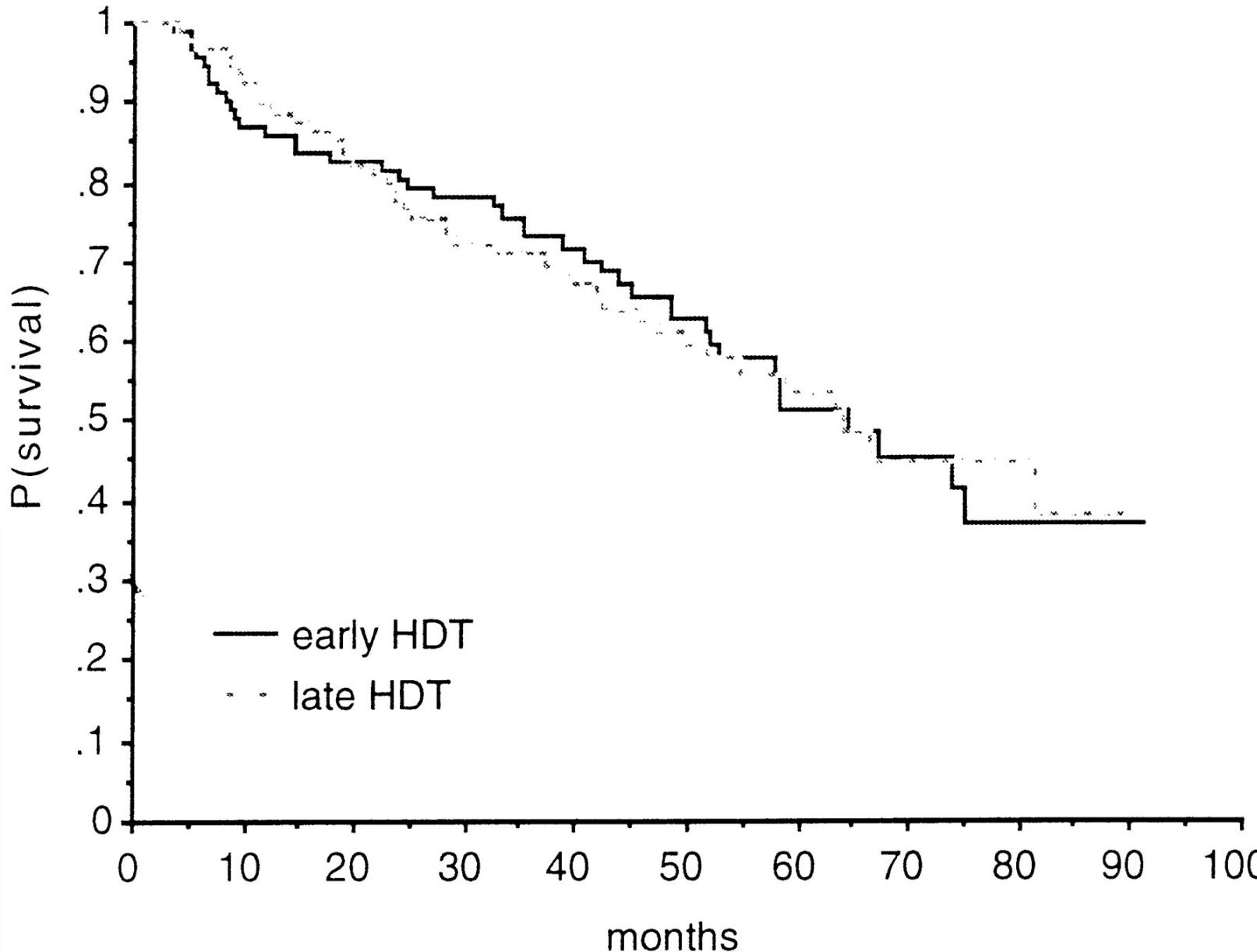
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HEMATOLOGY



Fermand, J.-P. et al. Blood 1998;92:3131-3136

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No Difference In Overall Survival



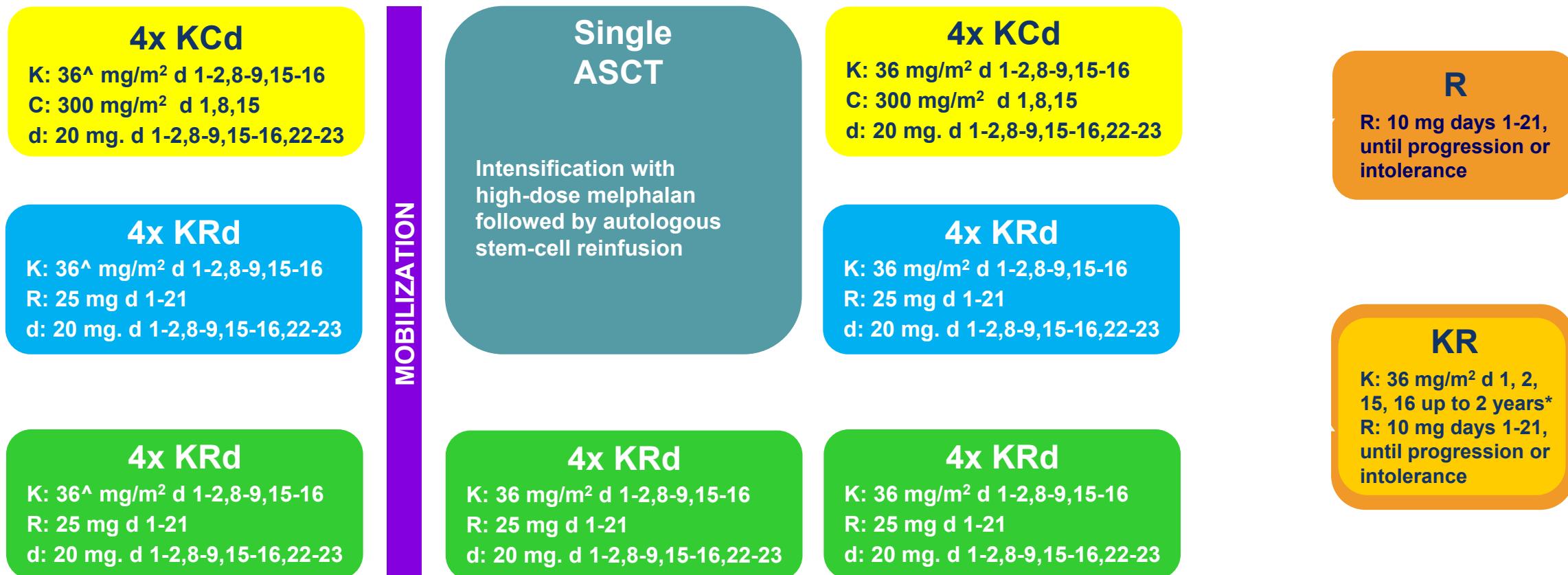
Fermand, J.-P. et al. *Blood* 1998;92:3131-3136

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Trial design

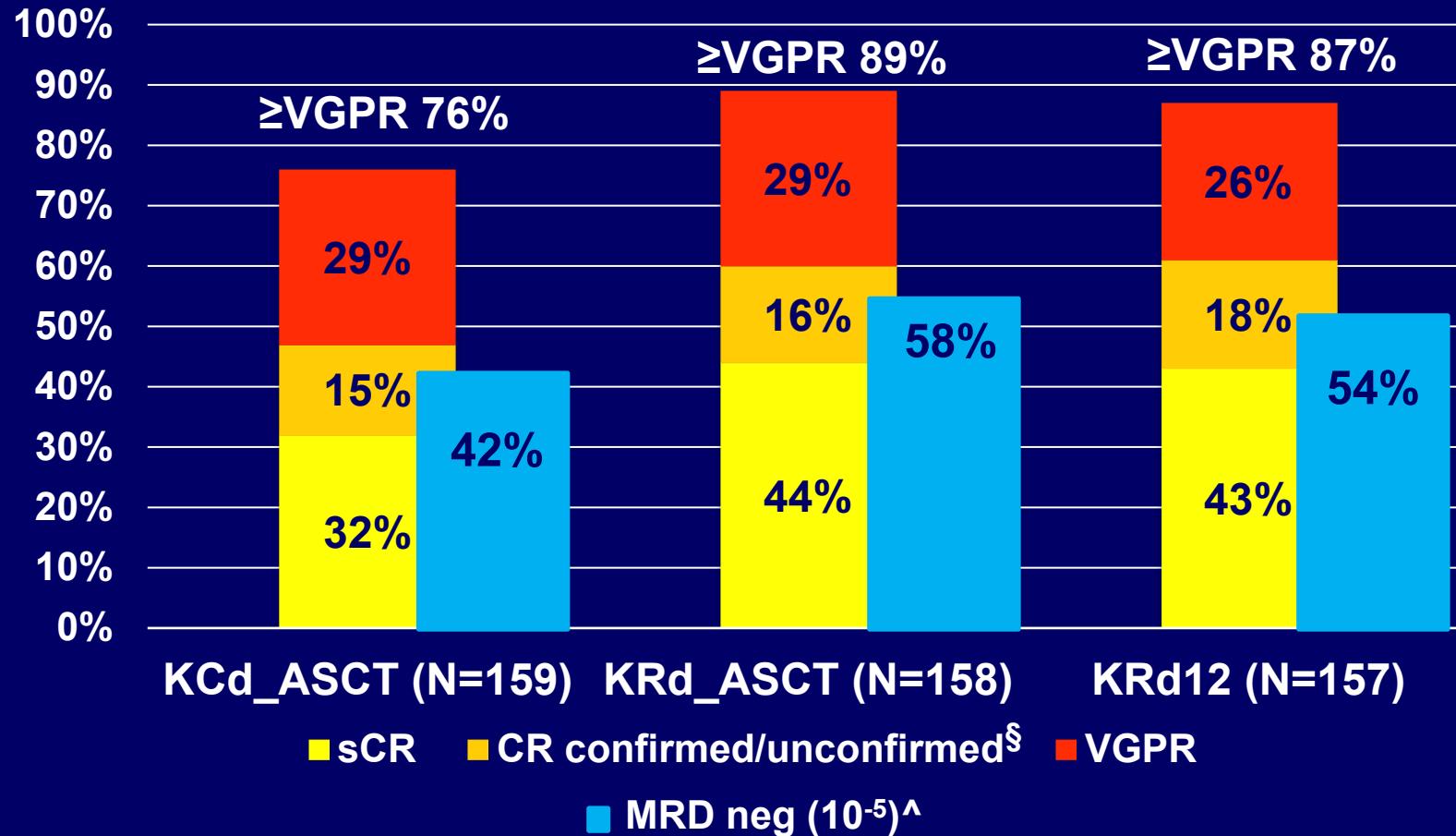
474 NDMM patients, transplant-eligible and younger than 65 years



[^]20 mg/m² on days 1-2, cycle 1 only. *Carfilzomib 70 mg/m² days 1, 15 every 28 days up to 2 years for patients that have started the maintenance treatment from 6 months before the approval of Amendment 5.0 onwards. NDMM, newly diagnosed multiple myeloma; R1, first randomization (induction/consolidation treatment); R2, second randomization (maintenance treatment); IQR, interquartile range K, carfilzomib; C, cyclophosphamide; R, lenalidomide; d, dexamethasone; d, days; ASCT, autologous stem-cell transplantation.

KRd_ASCT vs. KRd12 vs. KCd_ASCT: Efficacy

Pre-maintenance response rate and MRD negativity ITT analysis



	OR	p-value*
≥VGPR		
KRd_ASCT vs KCd_ASCT	2.53	0.004
KRd12 vs KCd_ASCT	2.11	0.015
sCR		
KRd_ASCT vs KCd_ASCT	1.65	0.035
KRd12 vs KCd_ASCT	1.60	0.048

MRD neg (10^{-5})	OR	p-value*
KRd_ASCT vs KCd_ASCT	2.02	0.009
KRd12 vs KCd_ASCT	1.73	0.042

[^]Patients whose samples were not available (~10%) were considered as positive. *Adjusted for ISS, Age, FISH, LDH.

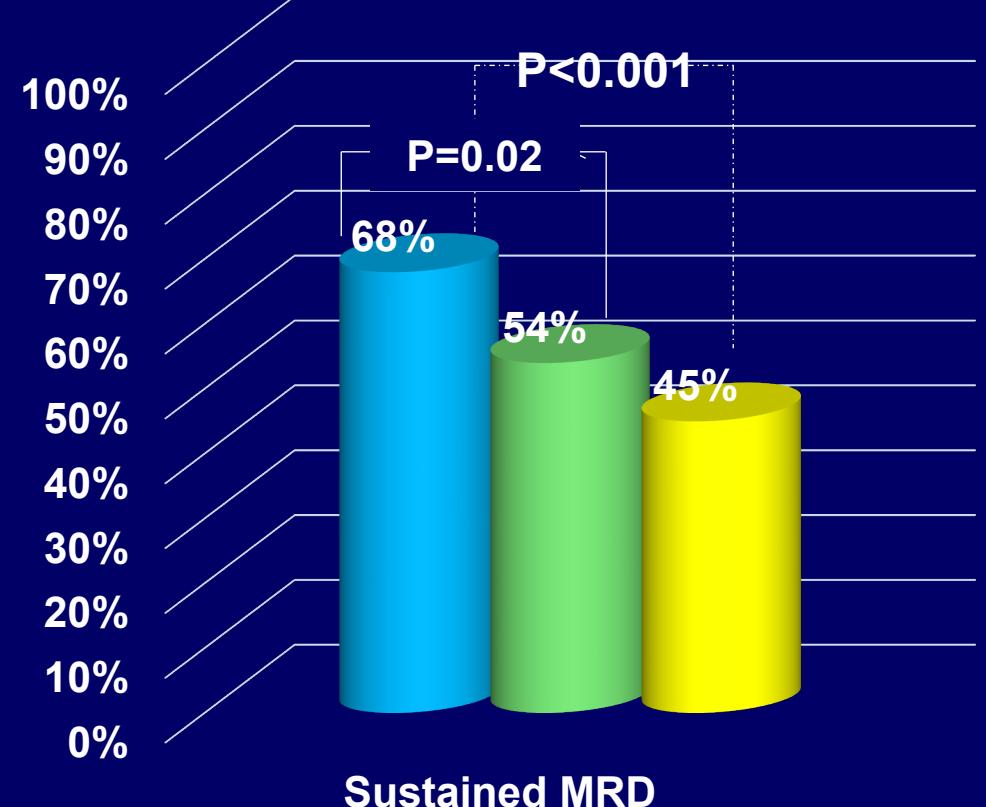
[§] Unconfirmed CR/sCR: patients missing immunofixation/sFLC analysis needed to confirm CR/sCR (6% in KCd_ASCT_KCd; 8% in KRd_ASCT_KRd; 6% KRd_12).

ASCT, autologous stem-cell transplantation; K, carfilzomib; R, lenalidomide; C, cyclophosphamide; d, dexamethasone; KCd_ASCT, KCd induction-ASCT-KCd consolidation; KRd_ASCT, KRd induction-ASCT-KRd consolidation; KRd12, 12 cycles of KRd; MRD, minimal residual disease; neg, negativity; ITT, intention to treat; SCR, stringent complete response; CR: complete response; VGPR: very good partial response; OR: odds ratio; FISH, fluorescence in situ hybridization; LDH, lactate dehydrogenase; FLC, free light chain, ISS, International Staging System.

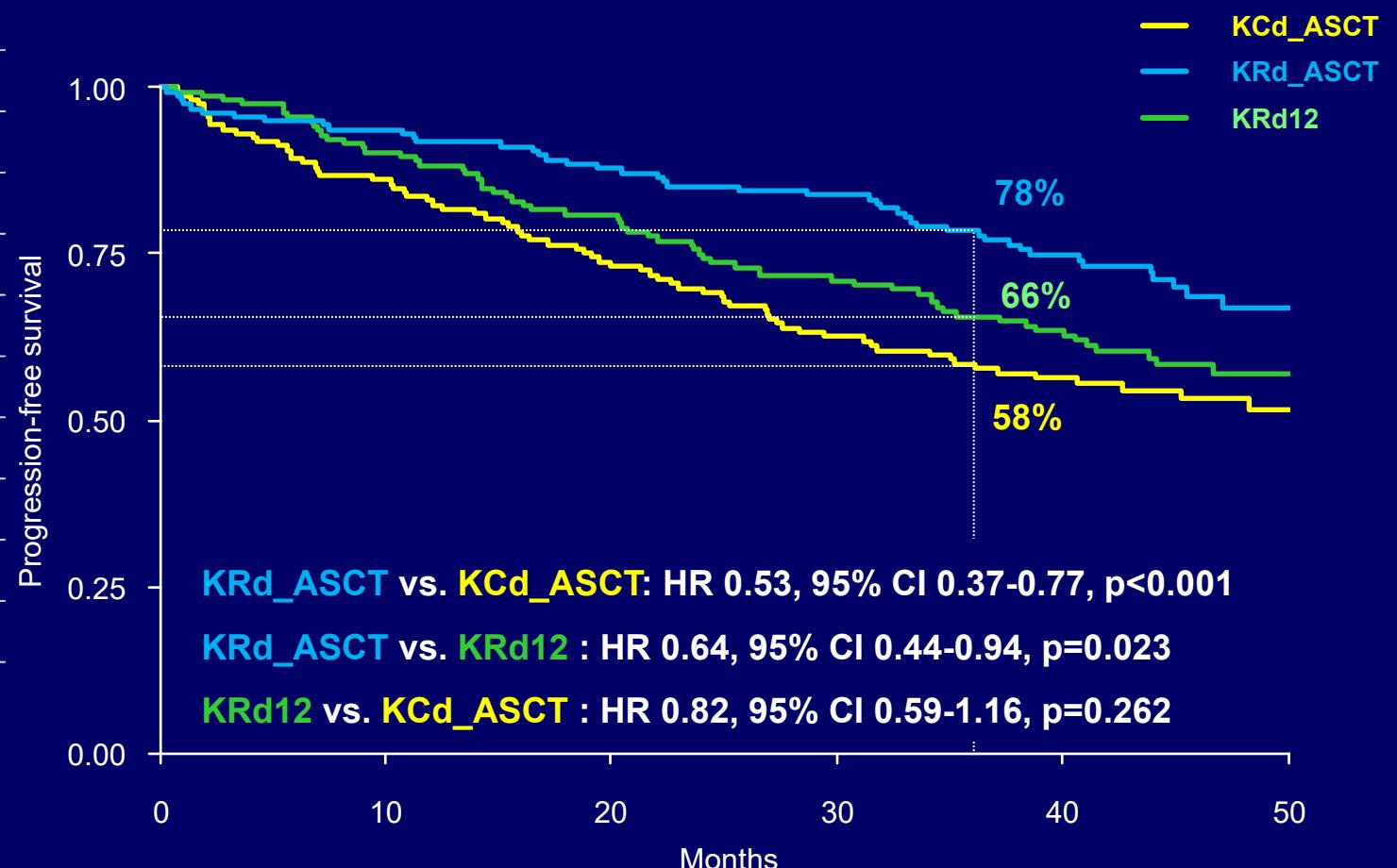
Progression-free survival: Random 1

Median follow-up from Random 1: 45 months (40-49 months)

Rate of sustained MRD MCF 10^{-5}



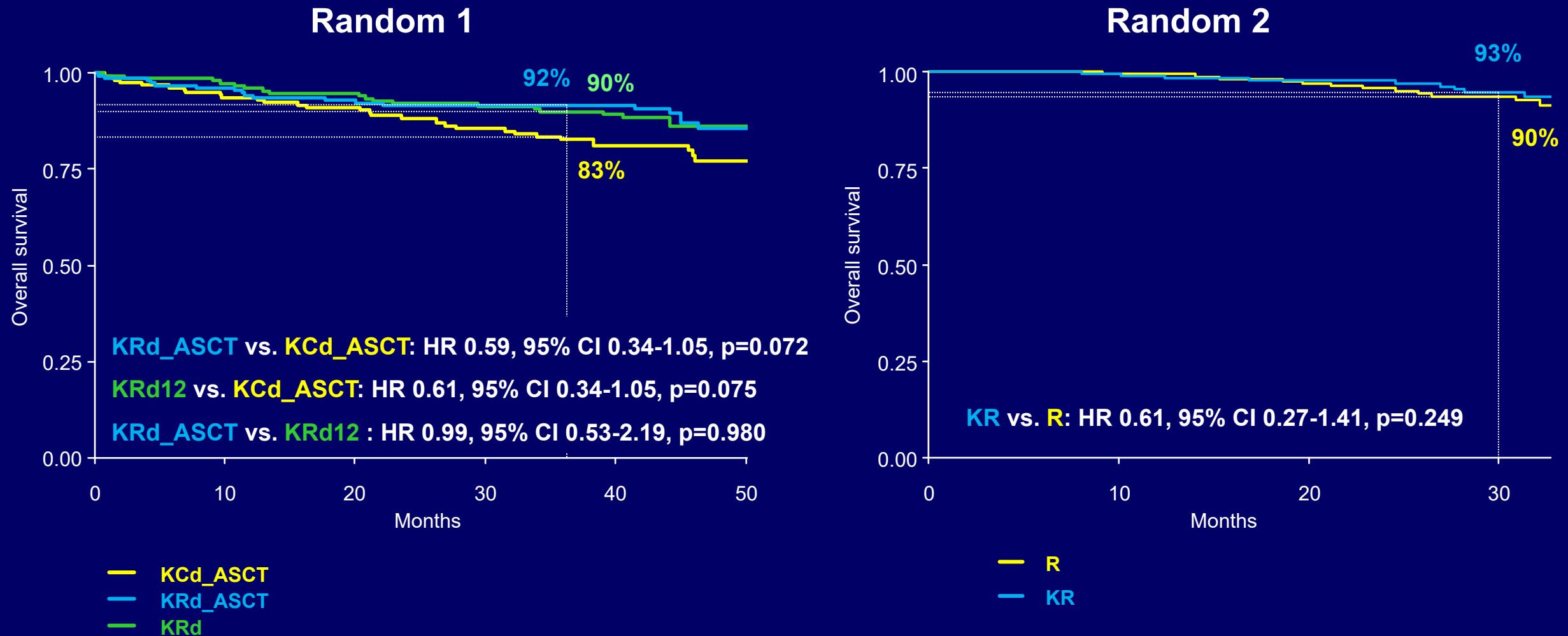
Progression-free survival



■ KRD_ASCT ■ KRd12 ■ KCd_ASCT

Random 1, first randomization (induction/consolidation treatment); ASCT, autologous stem-cell transplantation; K, carfilzomib; R, lenalidomide; C, cyclophosphamide; d, dexamethasone; KCd_ASCT, KCd induction-ASCT-KCd consolidation; KRd_ASCT, KRd induction-ASCT-KRd consolidation; KRd12, 12 cycles of KRd; p, p-value; HR, hazard ratio; CI, confidence interval; MRD, minimal residual disease; MFC, multiparameter flow cytometry; 3-year PFS reported in the figure.

Overall survival: Random 1 and Random 2



Random 1, first randomization (induction/consolidation treatment); Random 2, second randomization (maintenance treatment); OS, overall survival; ASCT, autologous stem-cell transplantation; K, carfilzomib; R, lenalidomide; C, cyclophosphamide; d, dexamethasone; KCd_ASCT, KCd induction-ASCT-KCd consolidation; KRd_ASCT, KRd induction-ASCT-KRd consolidation; KRd12, 12 cycles of KRd; p, p-value; KR, carfilzomib-lenalidomide maintenance; R, lenalidomide maintenance; HR, hazard ratio; CI, confidence interval; p, p-value. 3-year OS reported for Random1 and 30-month OS reported for Random 2 in the figures.

IFM 2009 Study design

700 patients randomized stratified on ISS and FISH

Arm A – RVD alone

3 RVD

PBSC collection (cyclophosphamide 3g/m² and GCSF 10 µg/kg/d)

5 RVD

Lenalidomide maintenance 13 cycles (10-15 mg/d)

Arm B - Transplantation

3 RVD

HD Melphalan 200 mg/m² + ASCT

2 RVD

RVd 21d cycles

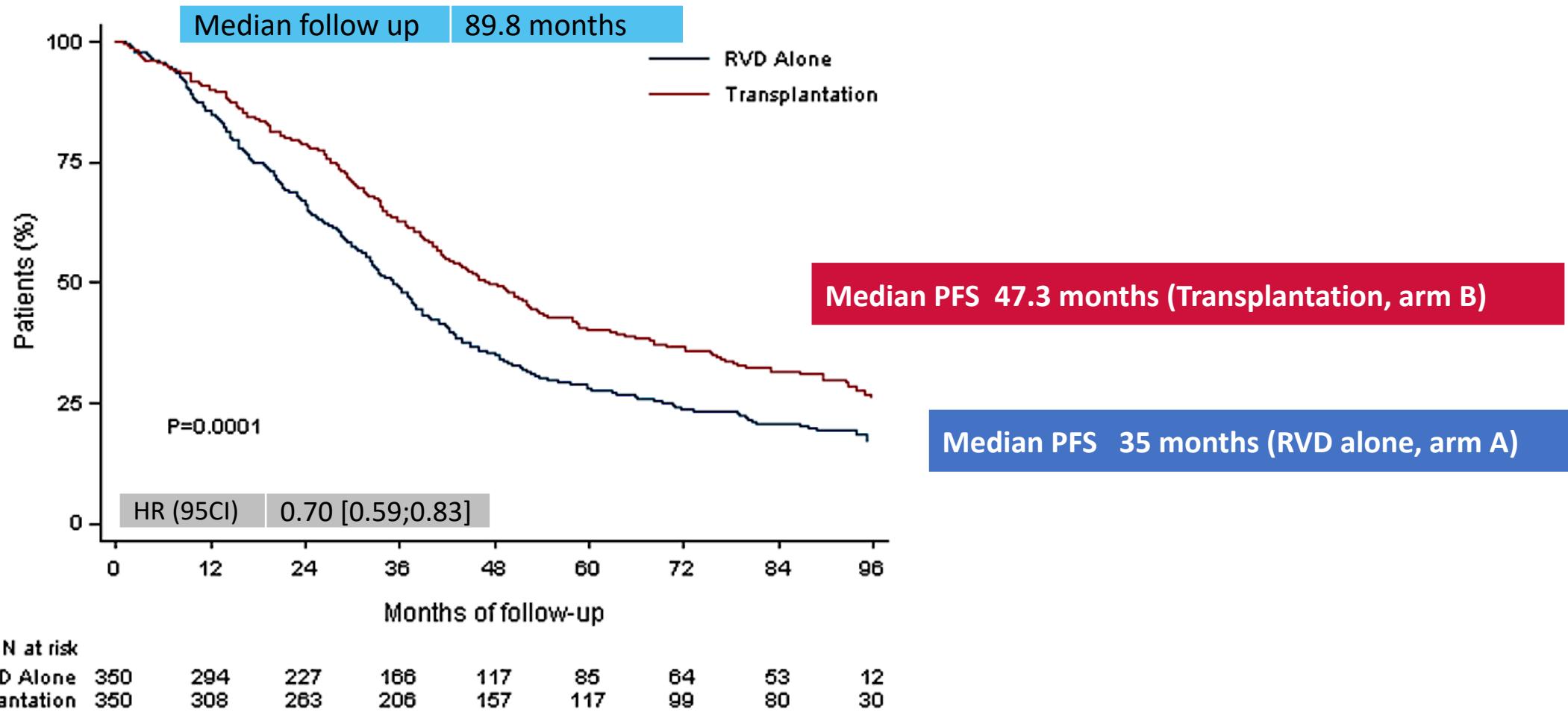
- . Lenalidomide 25 mg/d: D1-D14
- . Bortezomib 1.3 mg/m² D1, D4, D8, D11
- . Dexamethasone 20 mg/d: D1, D2, D4, D5, D8, D9, D11, D12

Primary endpoint = PFS

Secondary endpoints

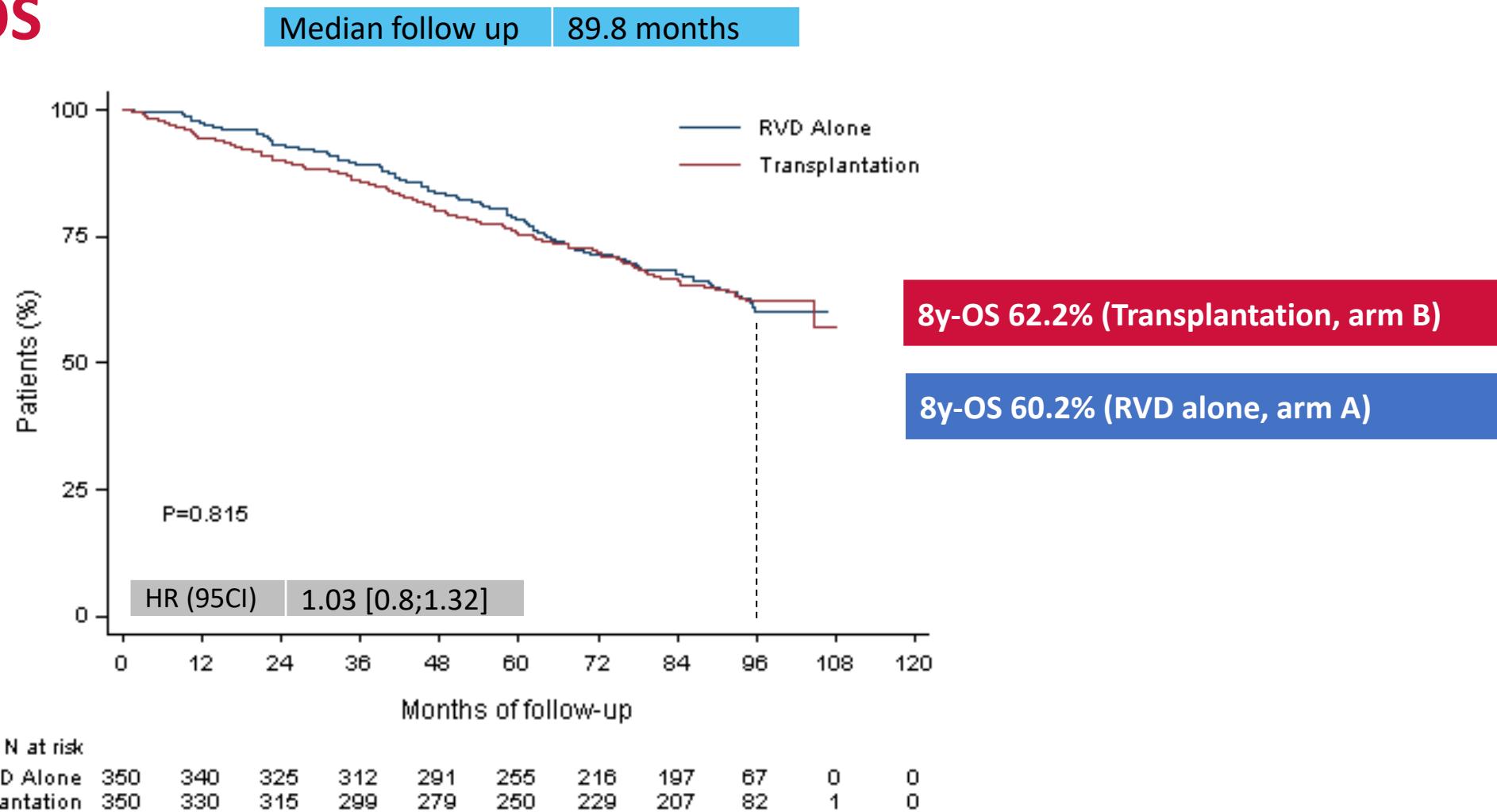
- . ORR, MRD
- . TTP
- . OS
- . Toxicity

Updated PFS (primary endpoint)



30% reduction in the risk of progression or death in patients receiving transplant

OS



More than 60% of the patients in the two arms are alive after 8 years of follow-up

Tolerability

- **Second primary malignancies SPM (8y FU)**

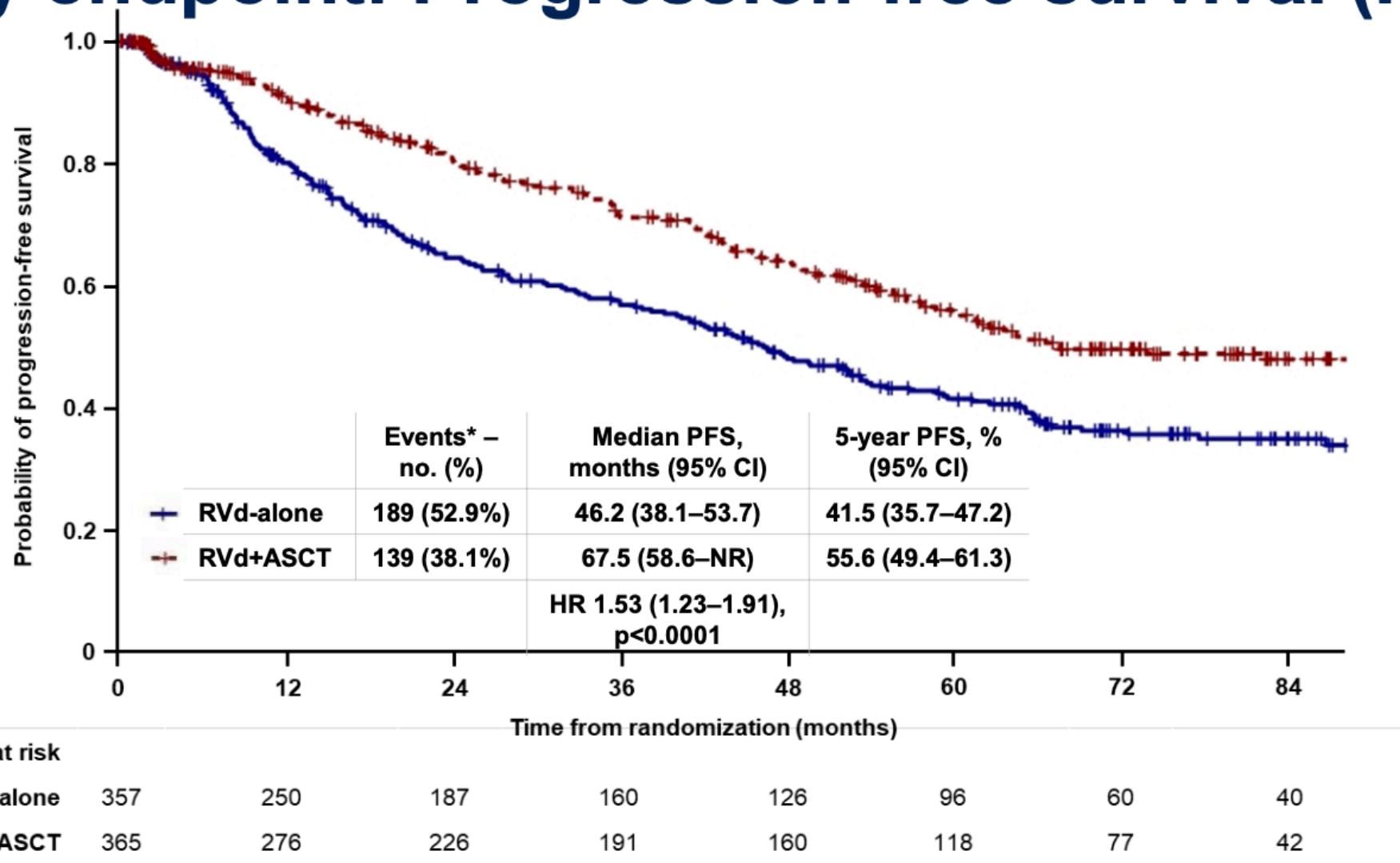
	RVd alone N=350	Transplant N=350
Patients with at least one invasive SPM (%)	7.7	9.7
MDS / AML (%)	0.9	1.7
Breast cancer (%)	0.9	1.1
Colon cancer (%)	0.9	1.1
Lung neoplasm (%)	0.9	0.6
Prostate cancer (%)	0.9	0.9
Malignant melanoma (%)	0.9	0

ORIGINAL ARTICLE

Triplet Therapy, Transplantation, and Maintenance until Progression in Myeloma

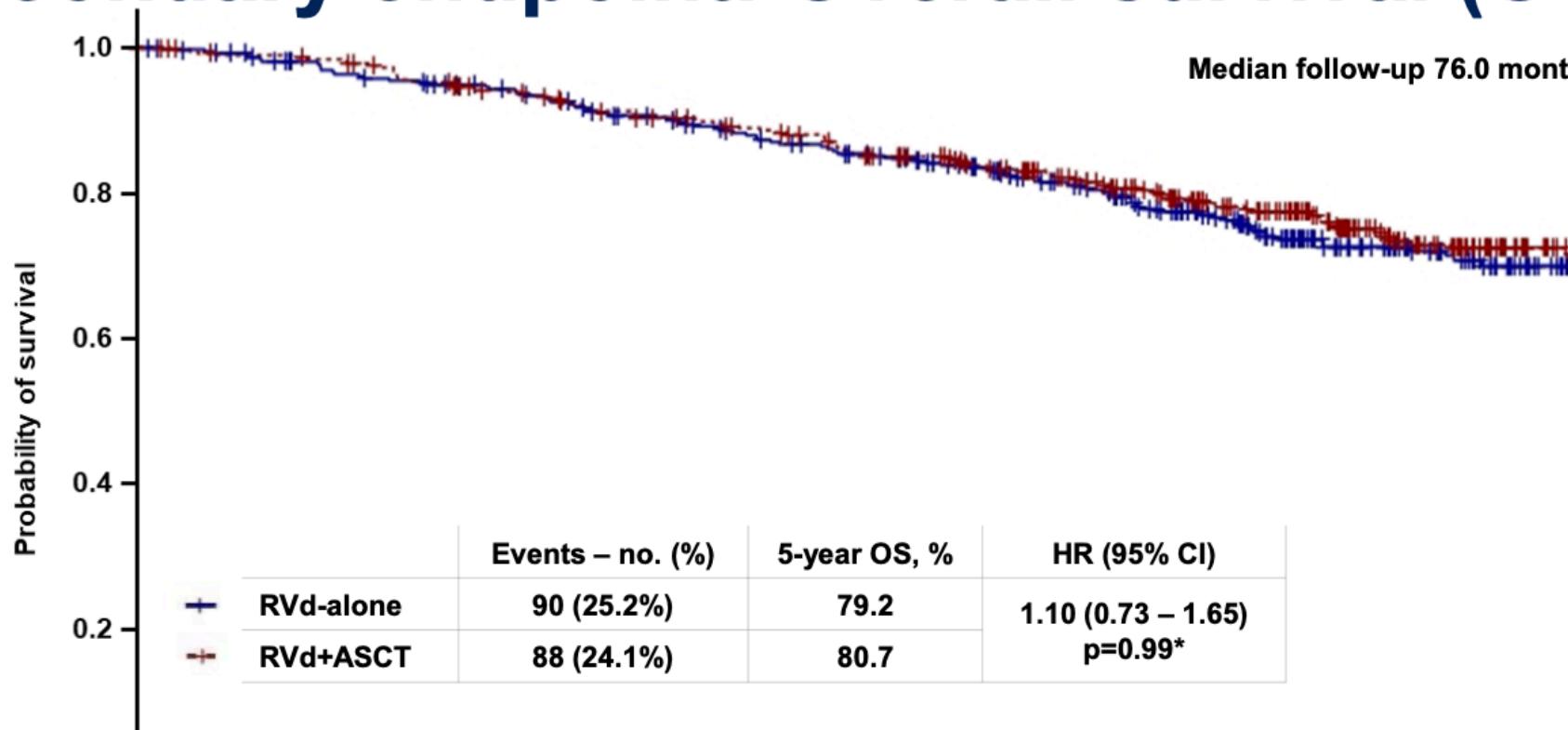
P.G. Richardson, S.J. Jacobus, E.A. Weller, H. Hassoun, S. Lonial, N.S. Raje,
E. Medvedova, P.L. McCarthy, E.N. Libby, P.M. Voorhees, R.Z. Orlowski,
L.D. Anderson, Jr., J.A. Zonder, C.P. Milner, C. Gasparetto, M.E. Agha, A.M. Khan,
D.D. Hurd, K. Gowin, R.T. Kamble, S. Jagannath, N. Nathwani, M. Alsina,
R.F. Cornell, H. Hashmi, E.L. Campagnaro, A.C. Andreeescu, T. Gentile,
M. Liedtke, K.N. Godby, A.D. Cohen, T.H. Openshaw, M.C. Pasquini, S.A. Giralt,
J.L. Kaufman, A.J. Yee, E. Scott, P. Torka, A. Foley, M. Fulciniti, K. Hebert,
M.K. Samur, K. Masone, M.E. Maglio, A.A. Zeytoonjian, O. Nadeem,
R.L. Schlossman, J.P. Laubach, C. Paba-Prada, I.M. Ghobrial, A. Perrot,
P. Moreau, H. Avet-Loiseau, M. Attal, K.C. Anderson, and N.C. Munshi,
for the DETERMINATION Investigators*

Primary endpoint: Progression-free survival (PFS)



CI, confidence interval; HR, hazard ratio; Data cut off: 12/12/21. *PFS events: disease progression or death.

Key secondary endpoint: Overall survival (OS)

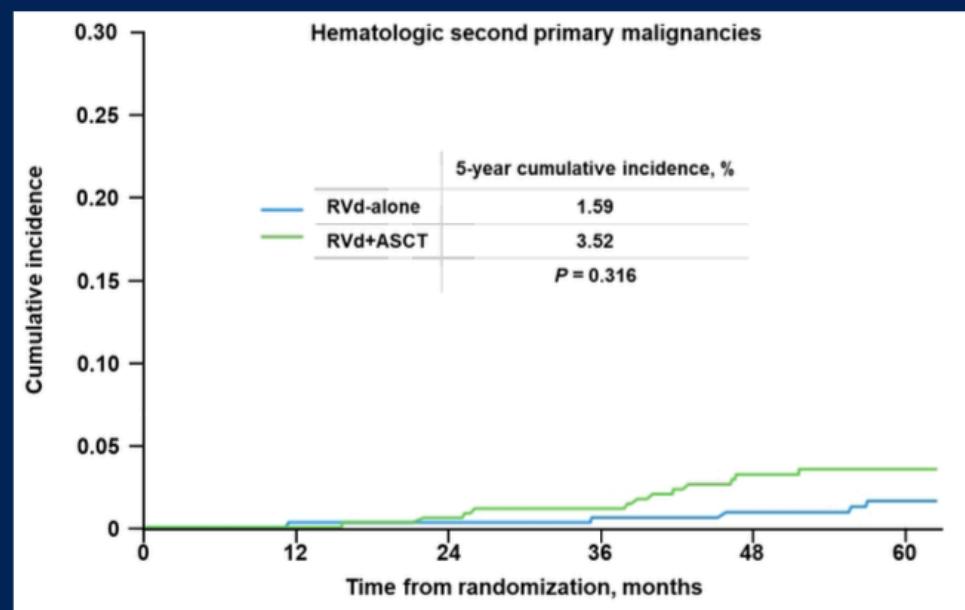


Patients at risk									[*] p-value adjusted using Bonferroni's correction to control overall family-wise error rate for secondary outcomes
	0	12	24	36	48	60	72	84	
RVd-alone	357	332	313	285	258	214	143	88	
RVd+ASCT	365	353	324	300	275	228	165	95	

Data cut off: 12/12/21

Second primary malignancies

- **5-year cumulative incidence of SPMs (RVd-alone vs RVd+ASCT):**
 - All : 9.7% vs 10.8%
 - Invasive: 4.9% vs 6.5%
 - Hematologic: 1.59% vs 3.52%



SPMs, %	RVd-alone (N=357)	RVd+ASCT (N=365)
Any	10.4	10.7
Any invasive SPM	5.3	6.8
Any hematologic SPM	2.5	3.6
ALL, n	7	3
AML/MDS, n	0*	10*
CLL/CML, n	2	0
Any solid tumor SPM	3.4	3.3
Any non-invasive solid tumor SPM	0	0.5
Any non-melanoma skin cancer	5.9	4.1

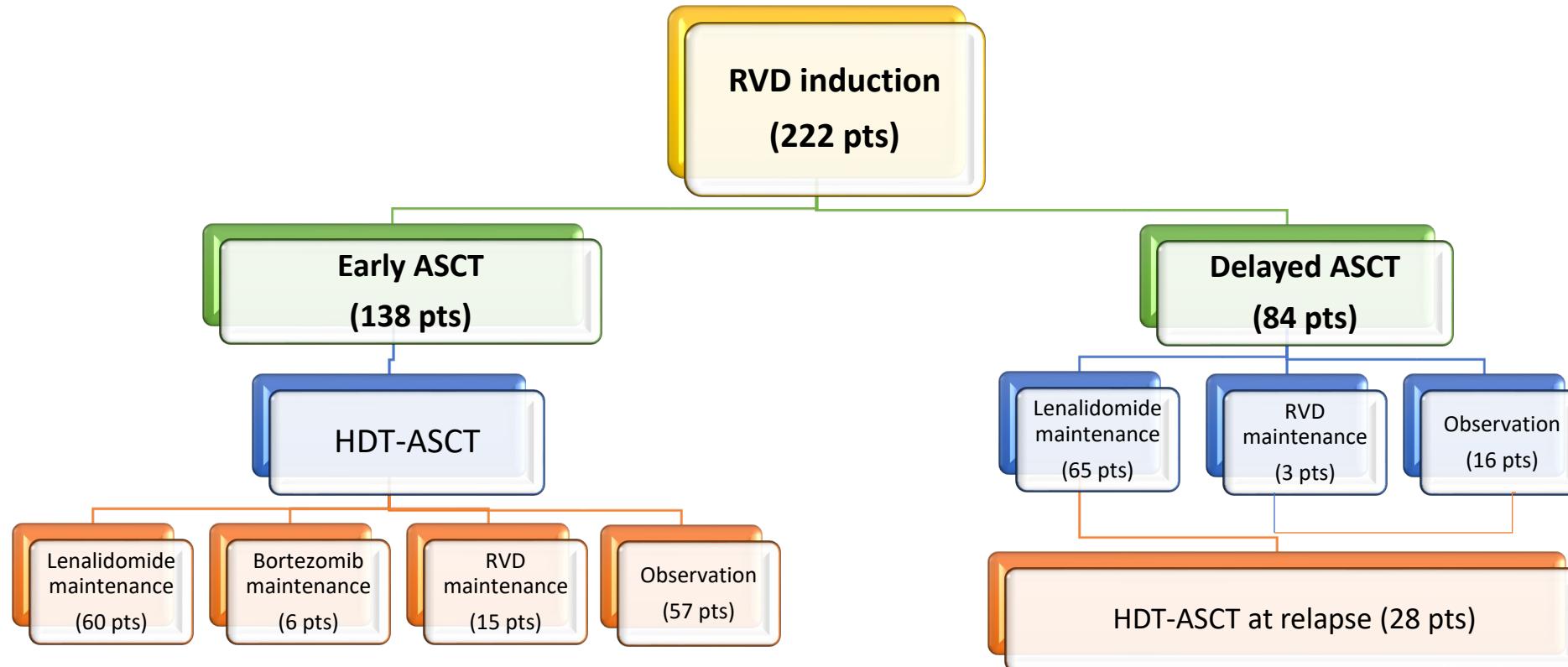
* p=0.002

Early versus delayed autologous stem cell transplant in patients receiving induction therapy with lenalidomide, bortezomib, and dexamethasone (RVD) for newly diagnosed multiple myeloma

Ajay K. Nooka, Amelia A. Langston, Edmund K. Waller, Leonard T. Heffner, Charise Gleason, Samatha Muppidi, Melanie Watson, Daniela Casbourne, Lawrence Boise, Jonathan L. Kaufman, Sagar Lonial

Winship Cancer Institute, Emory University, Atlanta, GA

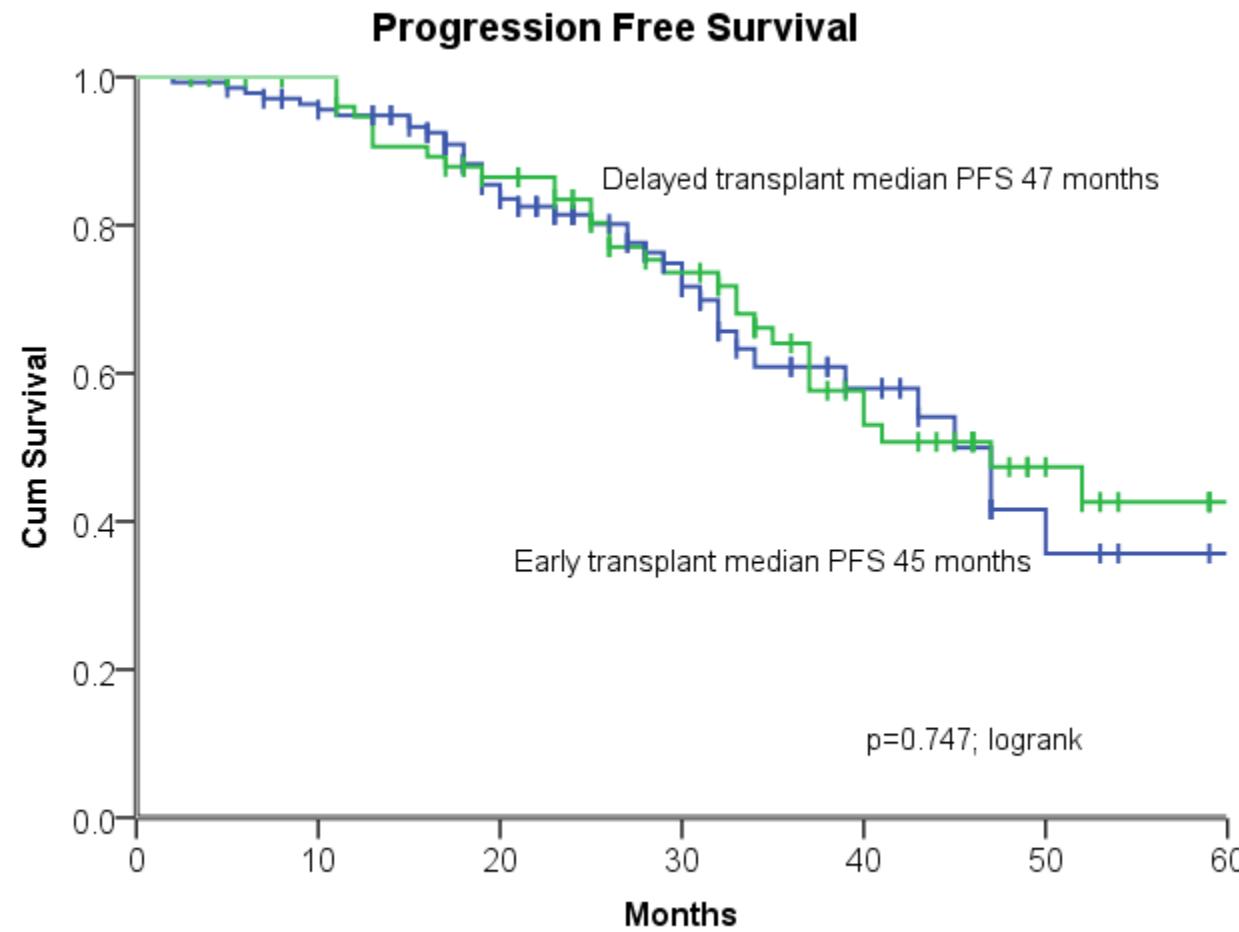
Flowchart for patients



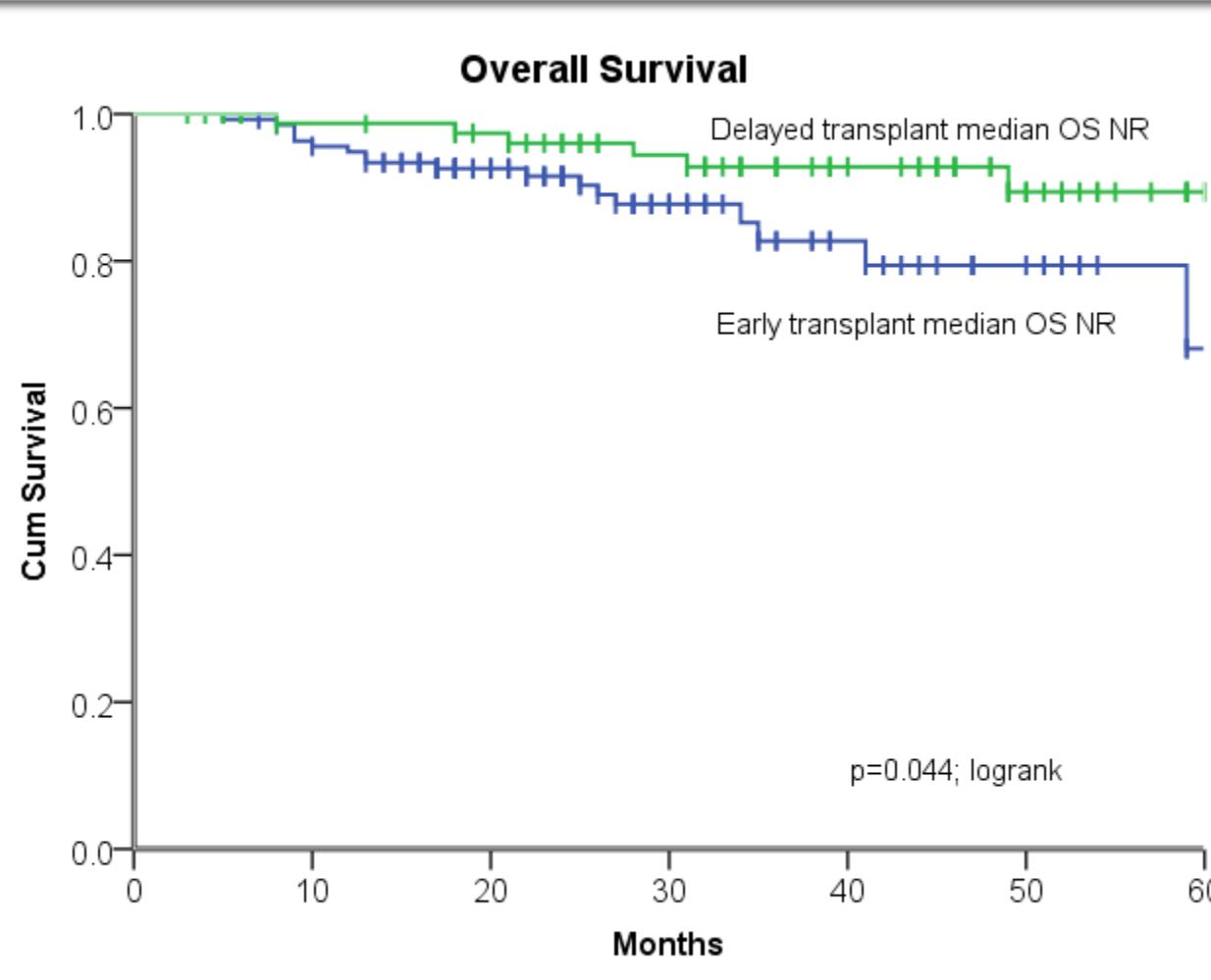
Patient Characteristics at baseline

Patient Characteristics	Early HDT-ASCT (N=138)	%	Delayed HDT-ASCT (N=84)	%
Sex (Male/female)	78/60	56.5/43.5	45/39	54/46
Race (Caucasian/AA/Hispanic/Asian)	88/45/4/1	63.5/32.5/3/1	56/21/3/5	67/25/3/5
Isotype (IgG/IgA/FLC/IgM)	83/28/27/0	60/20/20/0	53/14/16/1	63/16/19/1
ISS Stage (I/II/III/unknown)	27/31/26/54	20/22/19/38	21/32/6/25	25/38/7/30
Risk del 17/t (4;14)/t (14;16)	6/7/2	4.5/5/1.5	3/3/0	3.5/3.5/0
Median Age at dx, years (Range)	60.5 (32-77)		60 (22-73)	
Median Age at HDT-ASCT, years (Range)	61 (33-78)		63 (43-72)*	
Median no of RVD induction cycles (Range)	4 (2-9)		6.5 (2-8)	
Median β-2 microglobulin (Range)	3.8 (0.94-17.10)		2.57 (0.80-21.3)	
Median Albumin (Range)	3.6 (1.3-4.9)		3.7 (2.6-5.3)	
Median Hemoglobin (Range)	10.6 (5.0-15.60)		11.2 (7.0-16.0)	
Median Creatinine (Range)	1.10 (0.50-16.1)		1.05 (0.40-6.0)	
Median Calcium (Range)	9.1 (7.6-16.1)		9.2 (8.3-19.2)	
Median LDH (range)	150 (70-363)		142 (79-146)	
Median plasma cells in BM (range)	40 (1-100)		33 (1-100)	
Median KPS (range)	80 (40-100)		90 (60-90)	
Median time from diagnosis to therapy, months (Range)	1 (0-9)		0 (0-7)	
Median time from diagnosis to HDT-ASCT, months (Range)	7 (3-17)		26.5 (14-42)*	
Median time from therapy to HDT-ASCT, months (Range)	5 (3-12)		26 (13-41)*	
*in patients that underwent HDT-ASCT				

Progression Free Survival – entire cohort

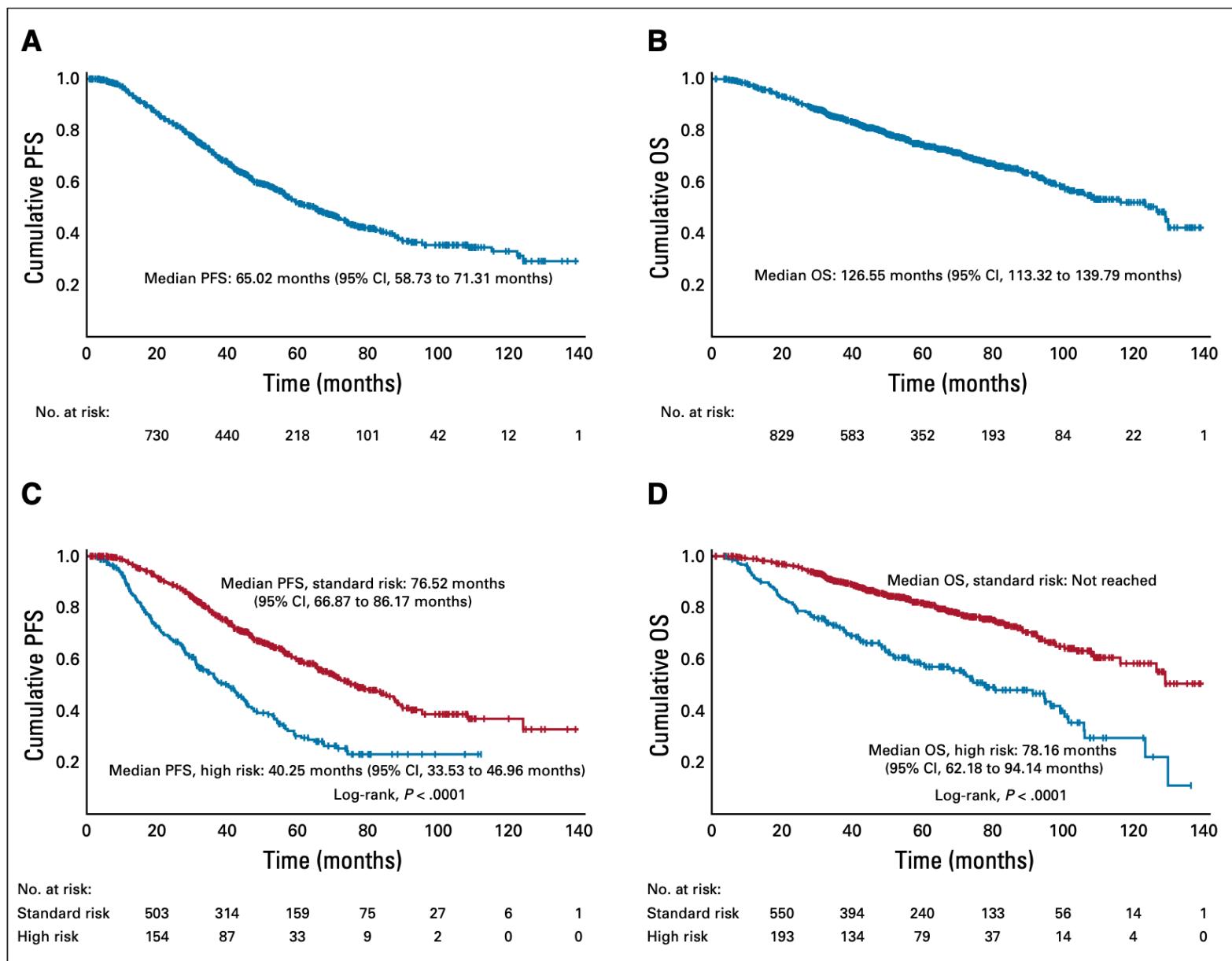


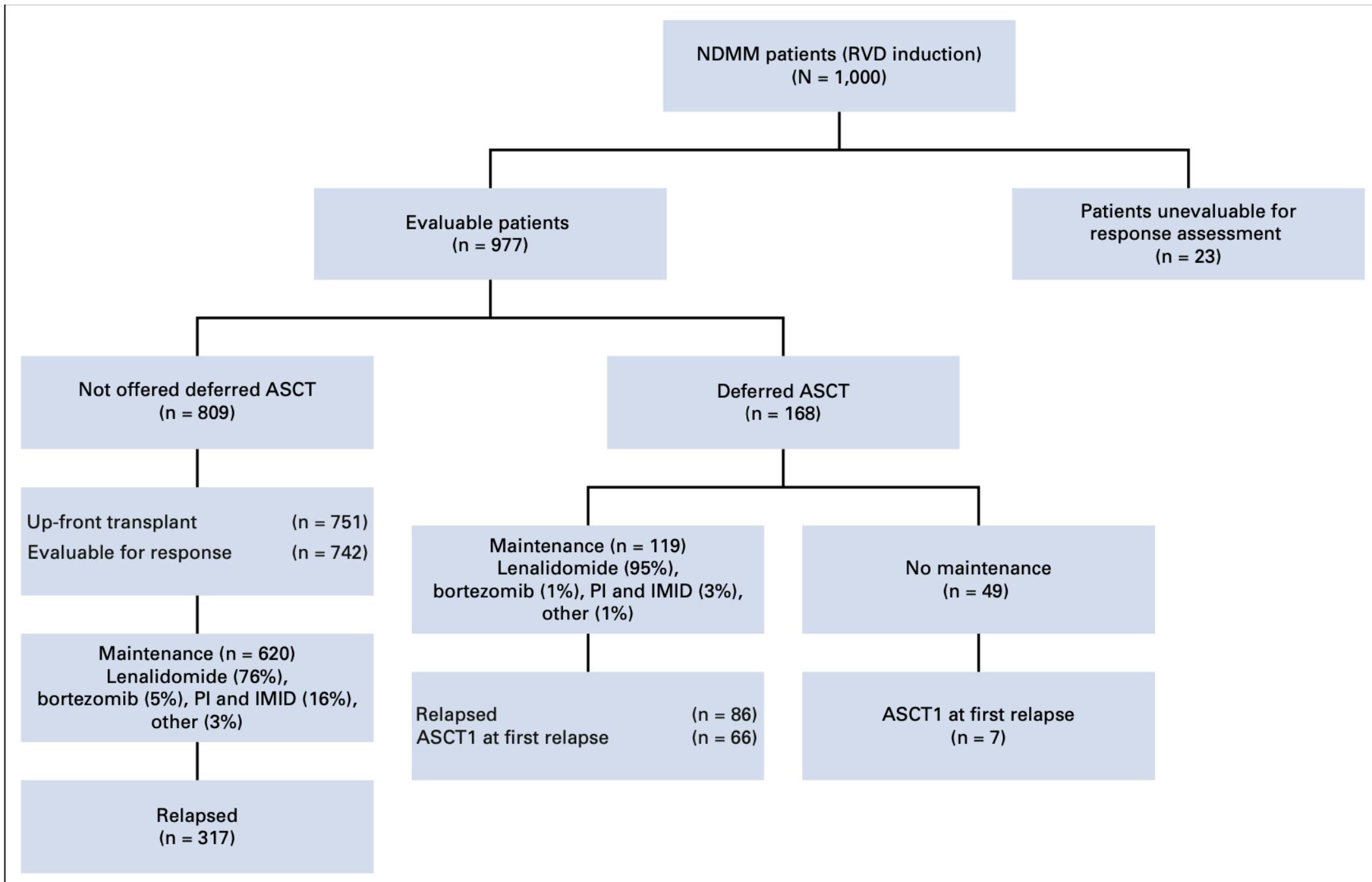
Overall Survival – entire cohort



Long-Term Follow-Up Results of Lenalidomide, Bortezomib, and Dexamethasone Induction Therapy and Risk-Adapted Maintenance Approach in Newly Diagnosed Multiple Myeloma

Nisha S. Joseph, MD¹; Jonathan L. Kaufman, MD¹; Madhav V. Dhodapkar, MD¹; Craig C. Hofmeister, MD, MPH¹; Dhwani K. Almaula, MBBS, MPH¹; Leonard T. Heffner, MD¹; Vikas A. Gupta, MD, PhD¹; Lawrence H. Boise, PhD¹; Sagar Lonial, MD¹; and Ajay K. Nooka, MD, MPH¹





Rvd1000: Delayed transplant without PFS decrease

RVD Induction Therapy in Myeloma

TABLE 2. Univariable Analysis: PFS and OS (continued)

Variable	PFS			OS			P
	Median PFS (months)	Hazards Ratio (95% CI)	P	Median OS (months)	Hazards Ratio (95% CI)	P	
Transplantation ^a				< .0001			< .0001
Yes	65.45	1		123.37	1		
No	29.01	3.03 (2.09 to 4.39)		42.55	4.05 (2.91 to 5.65)		
Deferred transplantation				.728			
Yes	74.28	1		NR	1		
No	63.01	1.04 (0.82 to 1.33)		123.37	1.5 (1.10 to 2.06)		
Maintenance				.005	< .0001		
Yes	65.45	1		129.84	1		
No	47.02	1.38 (1.10 to 1.72)		81.15	2.48 (1.94 to 3.15)		

Role of Early Transplant in myeloma

- Deepen remission - yes
- Prolong PFS – yes (mostly)
- Improve OS - no
- Increase time without treatment – no
- Increase SPM - yes