What New in Hematopoietic Stem Cell Transplantation?

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WHAT'S NEW IN HEMATOPOEITIC STEM CELL TRANSPLANTATION?

RELEVANT FINANCIAL RELATIONSHIPS IN THE PAST TWELVE MONTHS BY PRESENTER OR SPOUSE/PARTNER.

GRANT/RESEARCH SUPPORT: SPECTRUM PHARMACEUTICALS, CELGENE, GENENTECH, PHARMACYCLICS
SPEAKERS BUREAU: SEATTLE GENETICS, AMGEN, CELGENE

THE SPEAKER WILL DIRECTLY DISCLOSURE THE USE OF PRODUCTS FOR WHICH ARE NOT LABELED (E.G., OFF LABEL USE) OR IF THE PRODUCT IS STILL INVESTIGATIONAL.

Objectives

- Conditioning
  - Double vs single, ablative vs non-ablative
- Post-transplant
  - Consolidation/maintenance
- Novel treatment approaches for PTLD
  - Adoptive EBV-targeted T cell therapy

Autologous Conditioning Approaches

Abstract 401
Double Autologous Stem Cell Transplantation Significantly Prolongs Progression-Free Survival and Overall Survival in Comparison with Single Auto Transplantation in Newly Diagnosed Multiple Myeloma: An Analysis of Phase 3 EMN02/HO95 Study

Cavo M, et al. ASH 2017;session 731. Abstr 401.

Background

- Controversy: single vs. double aHCT in newly diagnosed MM
- Impact of novel new agents unknown

	EFS	OS	
IFM	25 mo vs 30 mo (P=.03)	48 mo vs 58 mo (P=.01)	Tandem favored for EFS/OS < VGPR benefit most
Bologna 96	23 mo vs 35 mo (P=.001)	65 mo vs 71 mo (P=.90)	Tandem favored for EFS
HOVON 24	21 mo vs 22 mo (P=.013)	55 mo vs 50 mo (P=0.81)	Tandem favored for EFS

- IMiDs and proteasome inhibitors also a consideration

Attal M, et al. *N Engl J Med*. 2003; 349:2495-2502.
Cavo M, et al. *J Clin Oncol*. 2007;25:2434-2441.
Sonneveld P, et al. *Haematologica*. 2007;92:928-935.

aHCT, autologous hematopoietic cell transplantation; EFS, event free survival; IMiDs, immunomodulators; OS, overall survival; VGPR, very good partial response

Background

- ASBMT
  - "...insufficient evidence to support tandem aHCT as the standard of care…"
- NCCN
  - "…a tandem transplant with or without maintenance therapy can be considered for all patients who are candidates for aHCT, and is an option for patients who do not achieve at least a VGPR after the first aHCT…"
- IMWG
  - "…double aHCT is recommended for patients with HR cytogenetics…"

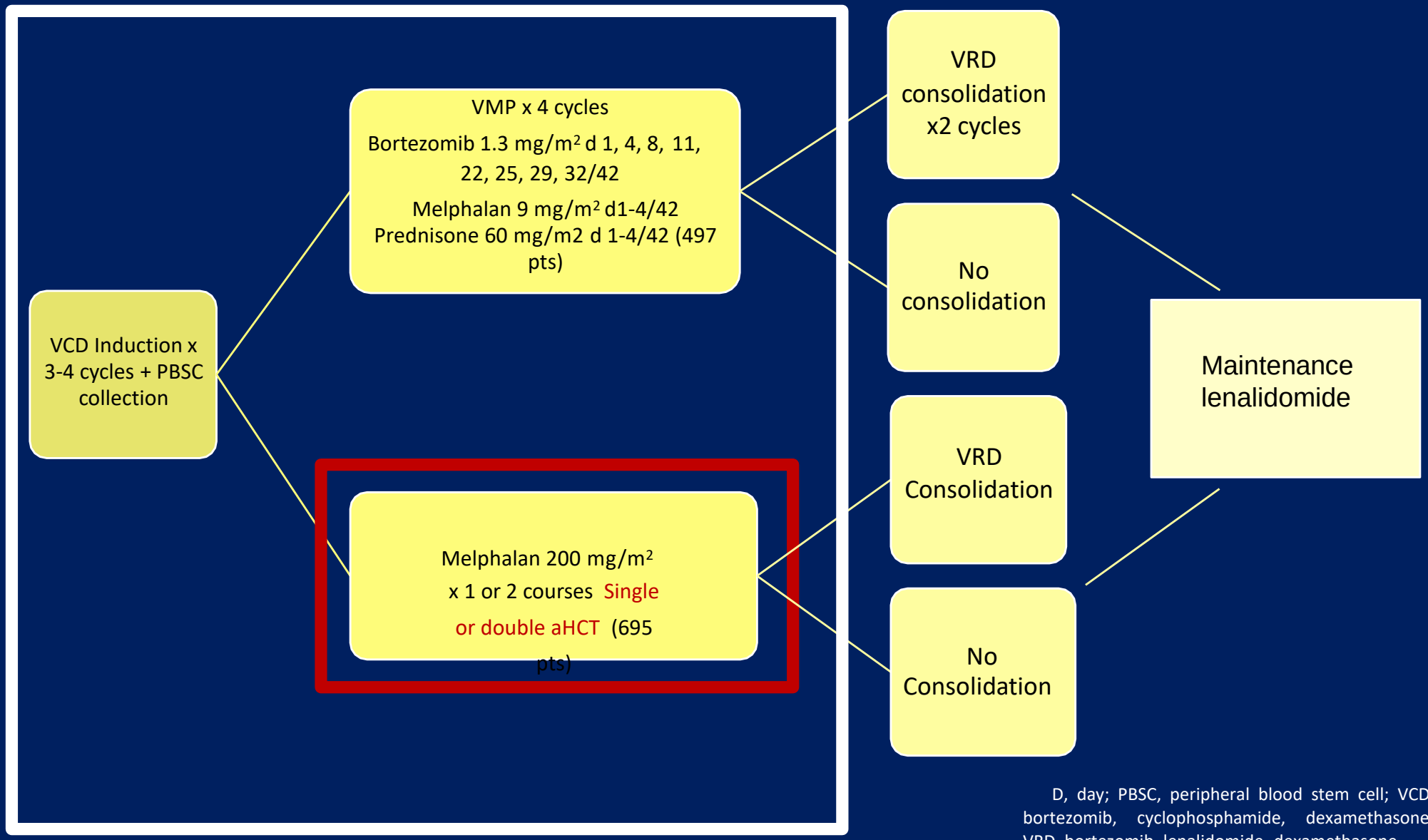
Shah N, et al. *Biol Blood Marrow Transplant*. 2015;21:115-1166.

NCCN Clinical Practice Guidelines in Oncology. MM. Version 3.2018. Available at www.nccn.org.

Sonneveld P, et al. *Blood*. 2016;127:2955-62.

ASBMT, American Society for Blood and Marrow Transplantation; HR, high risk; IMWG, International Myeloma Working Group; NCCN, National Comprehensive Cancer Network

EMN02/HO95 MM: Study Design



D, day; PBSC, peripheral blood stem cell; VCD, bortezomib, cyclophosphamide, dexamethasone; VRD, bortezomib, lenalidomide, dexamethasone

Cavo M, et al. ASH 2017;session 731. Abstr 401.

Endpoints

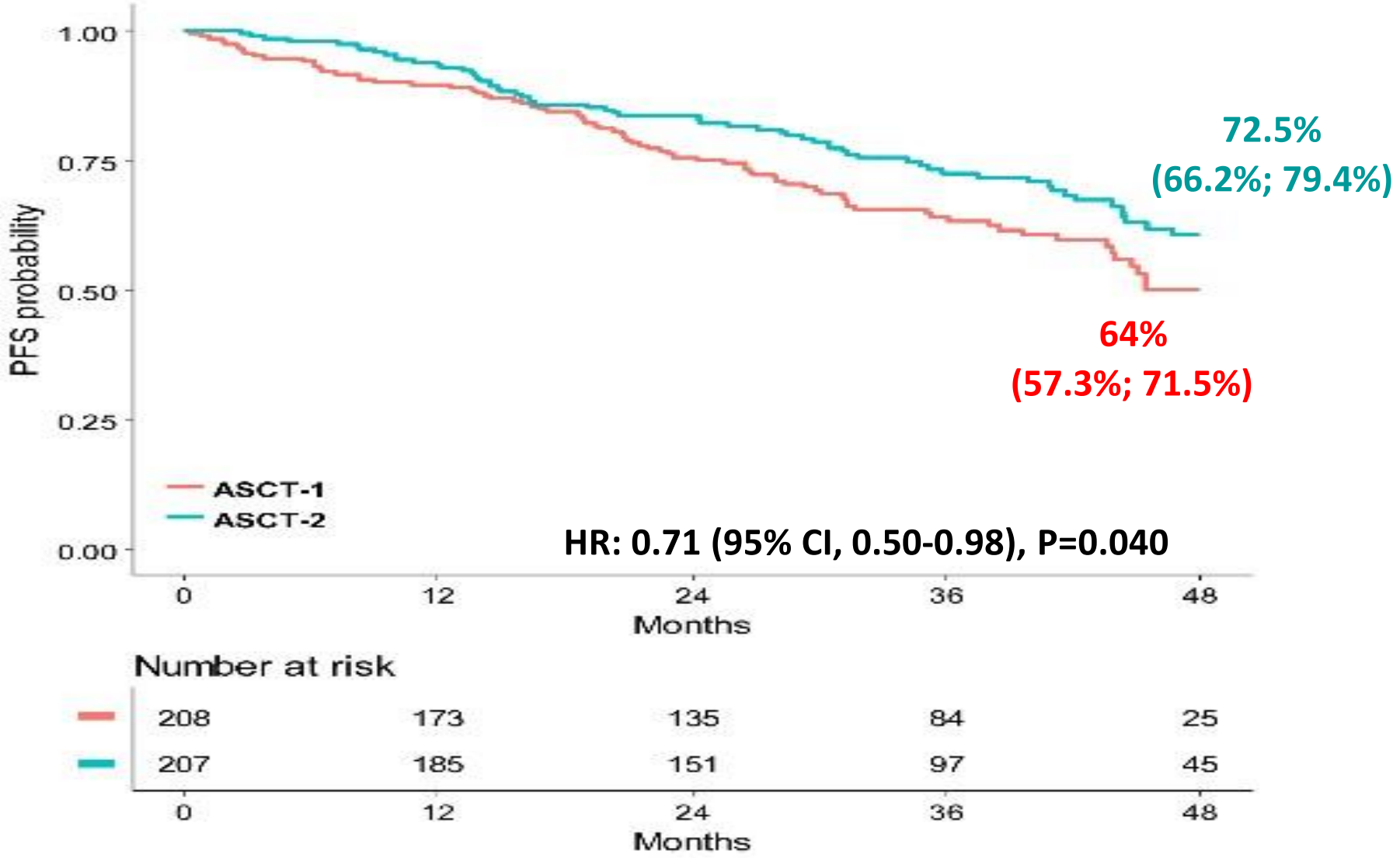
- Primary
  - PFS from R1: aHCT vs VMP
  - PFS from R2: VRD consolidation vs no consolidation

- Secondary
  - PFS from R1: high dose melphalan-1 vs high dose melphalan-2
  - Rates of response to aHCT or VMP
  - OS from R1: aHCT vs VMP
  - Toxicities with aHCT and VMP

Cavo M, et al. ASH 2017;session 731. Abstr 401.

PFS, progression free survival

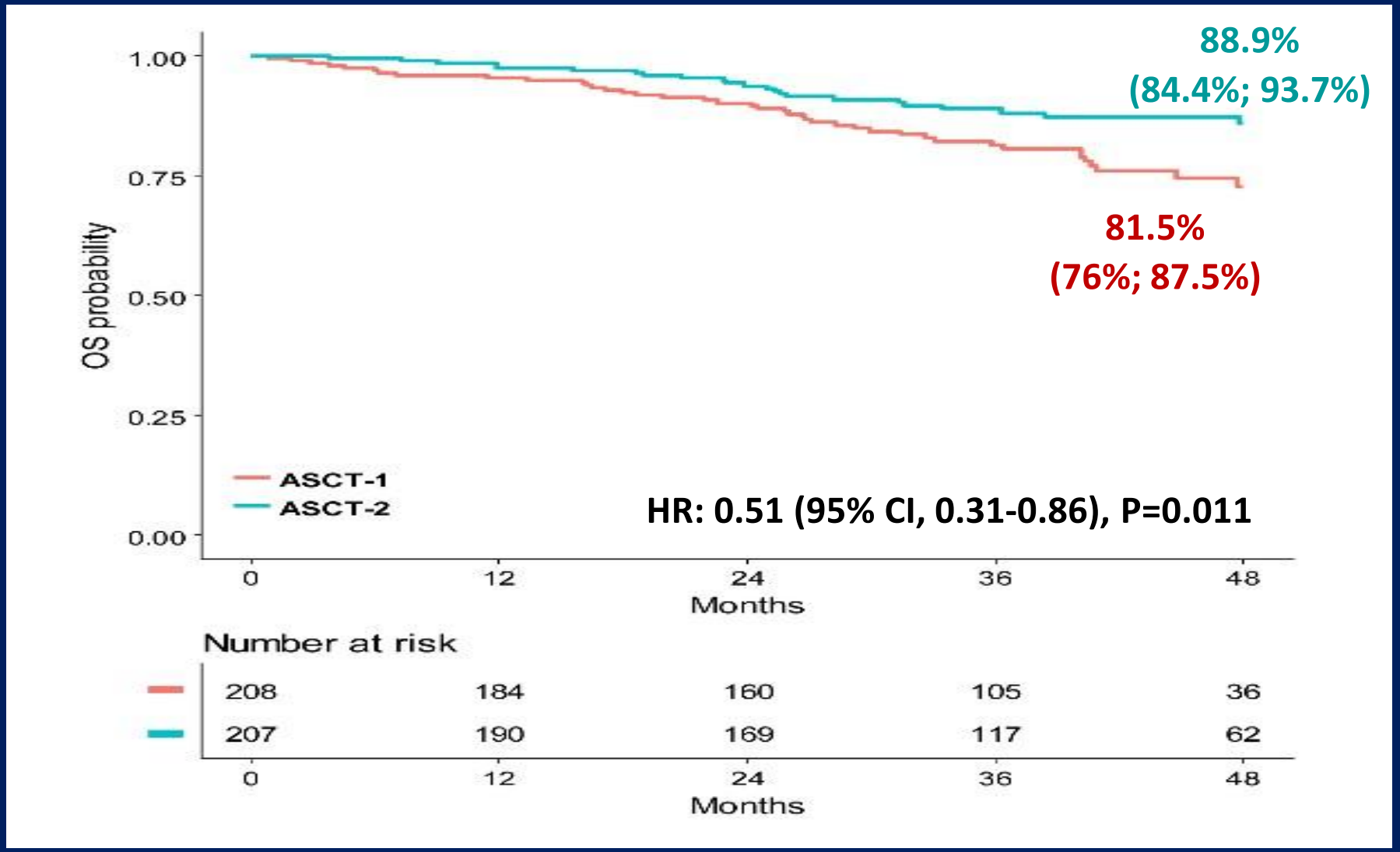
Progression-Free



Cavo M, et al. ASH 2017;session 731. Abstr 401.

CI, confidence interval; HR, hazard ratio

Overall Survival



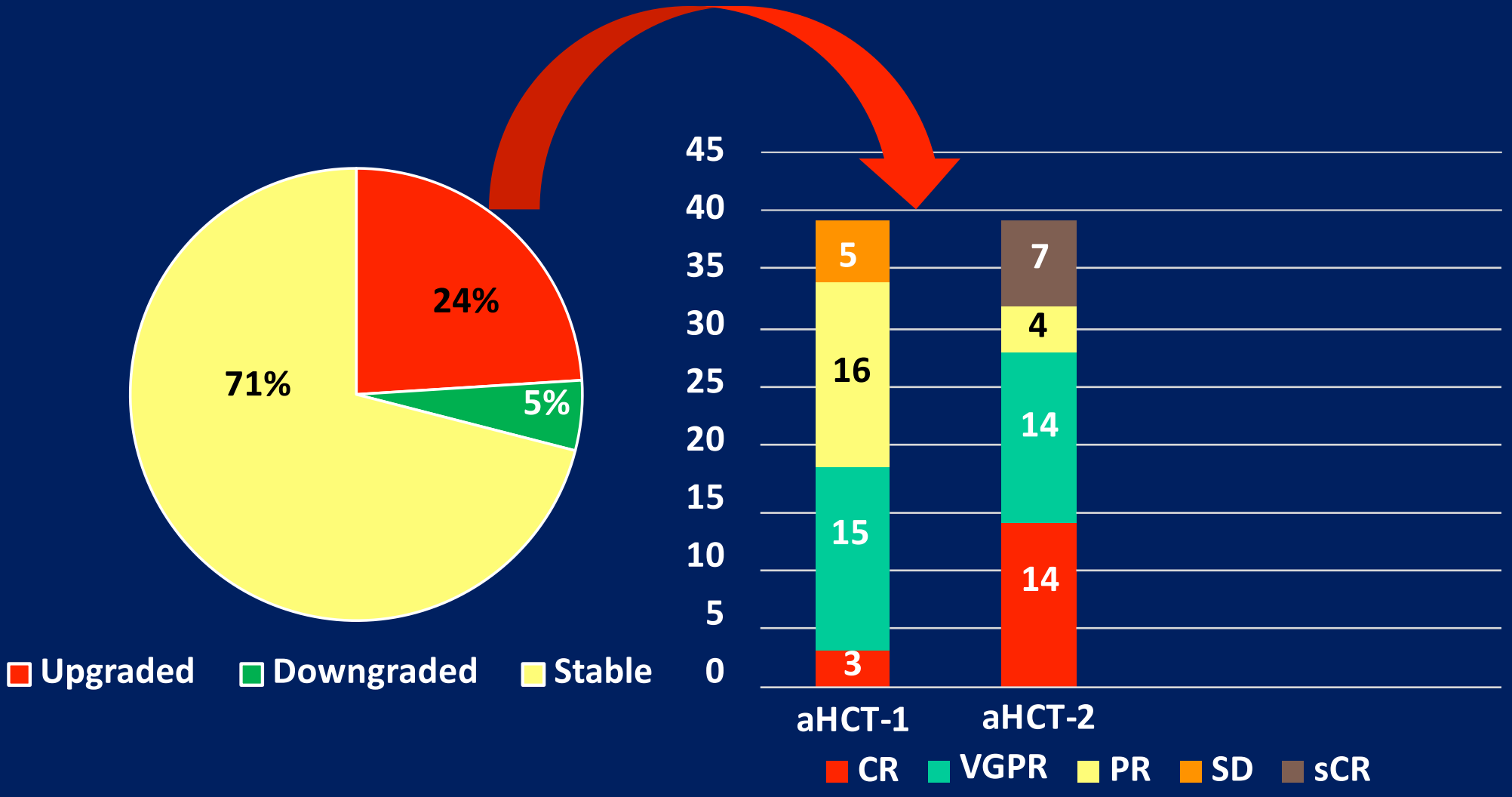
Cavo M, et al. *ASH* 2017;session 731. Abstr 401.

Results

	aHCT-2	aHCT-1	HR	95% CI	P-value
PFS by High Risk Cytogenetics	69.2% (54.7%-87.5%)	44.2% (31%-63.2%)	0.42	0.21-0.84	0.014
OS by High Risk Cytogenetics	84.9% (77.3%-93.2%)	72.8% (63.6%-83.4%)	0.52	0.28-0.98	0.042
OS by R-ISS II + III	84.9% (78.2%-92.1%)	75.2% (67.4%-84%)	0.48	0.27-0.86	0.013

Cavo M, et al. ASH 2017;session 731. Abstr 401.

Response Post aHCT-2



Cavo M, et al. ASH 2017;session 731. Abstr 401.

CR, complete response; PR, partial response; SD, stable disease; sCR, stringent CR

Conclusions

	Double ASCT	Single ASCT
Improved PFS	X	--
PFS benefit confirmed with multivariable Cox regression analysis	X	--
Overcame high risk poor prognosis	X	--
Upgraded quality of response	X	--
>50% ≥ CR	X	--

§ Results support double aHCT, especially in high risk

Cavo M, et al. ASH 2017;session 731. Abstr 401.

Autologous Conditioning Regimens: Multiple Myeloma

Bortezomib and High-Dose Melphalan vs. High-Dose Melphalan as Conditioning

Roussel M, et al. ASH 2017;session 731. Abstr 398.

Background

- High dose melphalan = standard of care in MM

- Bortezomib
  - Proteasome inhibitor
  - Synergizes with alkylating agents

- Safety and efficacy data supporting combination
  - VGPR or better: 70%
  - CR: 32%
  - No toxic deaths
  - No increased hematologic toxicity

Roussel M, et al. ASH 2017;session 731. Abstr 398.
Roussel M, et al. *Blood*. 2010;115:32-37.

Objective and Endpoints

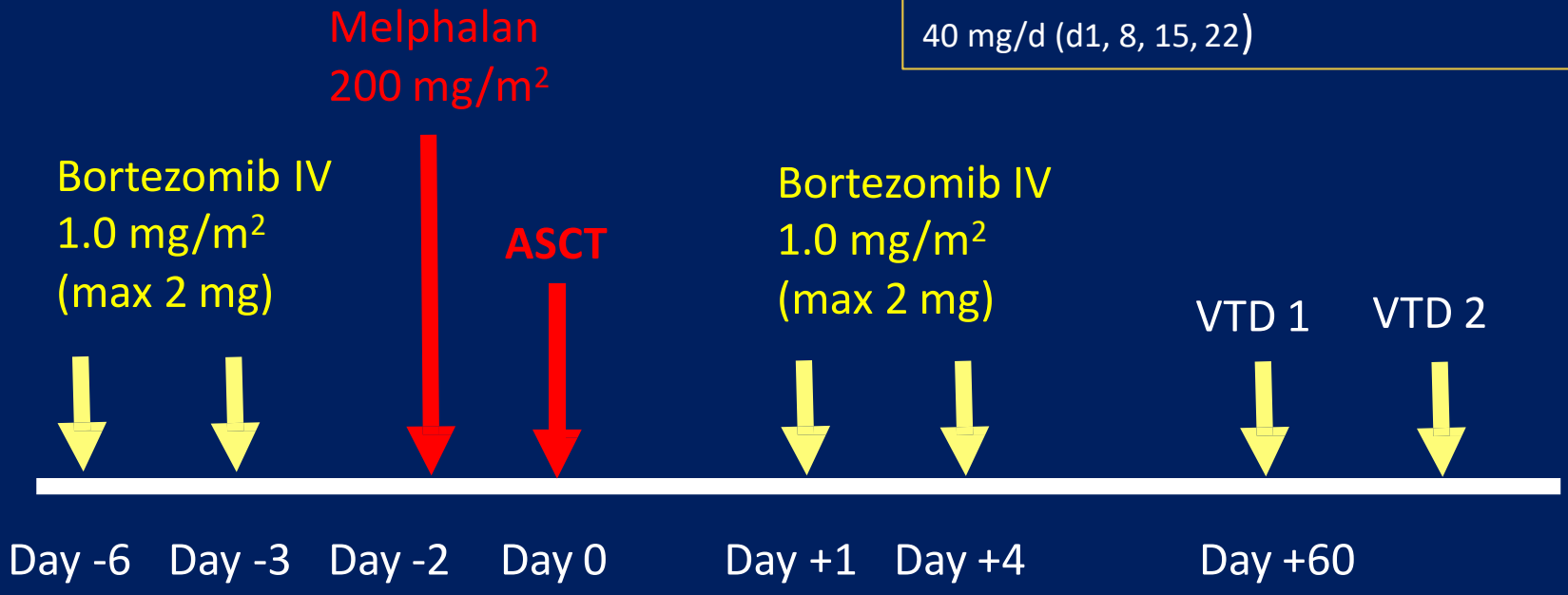
- Assess efficacy
  - Melphalan + bortezomib vs. melphalan alone
- Primary endpoint
  - CR rate at day +60 post aHCT
- Secondary endpoints
  - ORR
  - Toxicity
  - Outcomes

Roussel M, et al. ASH 2017;session 731. Abstr 398.

ORR, overall response rate

Study Design: Arm A

28-day cycle VTD
Bortezomib SC 1.0 mg/m^2 (d1, 4, 8, 11) (max 2 mg)
Thalidomide 100 mg/d continuously Dexamethasone 40 mg/d (d1, 8, 15, 22)

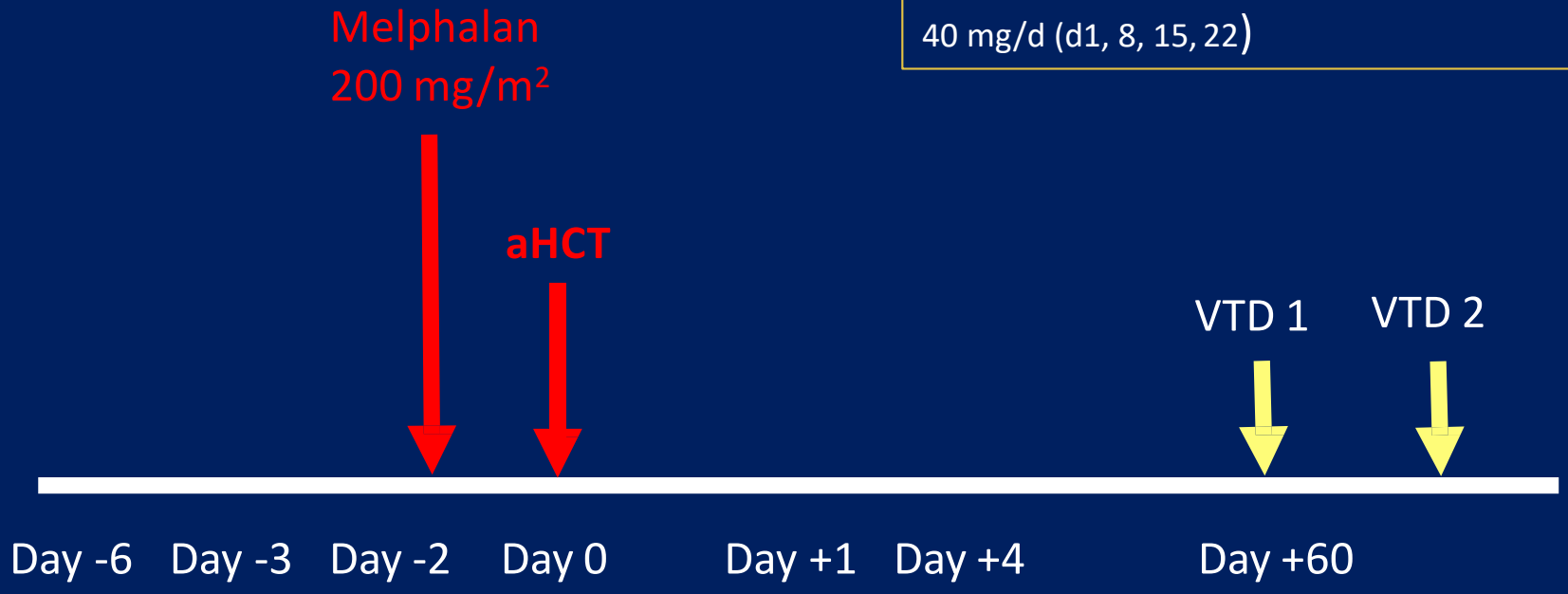


- Open-label, multicenter, phase III study in de novo MM
- Stratified by post induction response, ISS, cytogenetics

Roussel M, et al. ASH 2017;session 731. Abstr 398.

Study Design: Arm B

28-day cycle VTD
Bortezomib SC 1.0 mg/m^2 (d1, 4, 8, 11) (max 2 mg)
Thalidomide 100 mg/d continuously Dexamethasone 40 mg/d (d1, 8, 15, 22)



- Open-label, multicenter, phase III study in de novo MM
- Stratified by post induction response, ISS, cytogenetics

Roussel M, et al. ASH 2017;session 731. Abstr 398.

Response (I)

	Arm A (n=152*) Bortezomib + Melphalan (%)	Arm B (n=146) Melphalan (%)
Response at day 60		
Response assessment		
At least CR, ITT (n=154)	23.4	20.5
sCR	10.5	13.0
CR	13.2	8.2
VGPR	55.9	53.4
PR	19.1	21.2
SD	0.7	2.7
PD	0.7	1.4
*Two patients in arm A not treated		
MRD at screening		
N/missing	116/36	117/29
Negative, %	50.9	47.0

Roussel M, et al. ASH 2017;session 731. Abstr 398.

ITT, intent-to-treat; PD, progressive disease

Response (II)

	Arm A Bortezomib + Melphalan (%)	Arm B Melphalan (%)
Response post consolidation (Arm A = n of 141, Arm B = n of 139)		
sCR CR VGPR	19.9 14.2 50.4	20.9 14.4 44.6
MRD at screening N/missing Negative, %	 112/29 64.3	 115/24 59.1
18 mo Progression Free Survival (P=0.4232)	78.5% (69.8 – 85.0)	79.9% (71.0 – 86.3)
18 mo Overall Survival (P=0.1277)	93.4 (86.2 – 96.9)	99.3 (95.0 – 99.9)

Roussel M, et al. ASH 2017;session 731, Abstr 398.

Conclusions

- Bortezomib plus melphalan is *not* superior to melphalan
- CR or better rates at day 60
  - Bortezomib plus melphalan = 23.7%
  - Melphalan = 21.2%
- MRD negativity similar regardless of time
- No increased or unexpected toxicities

Roussel M, et al. ASH 2017;session 731. Abstr 398.

What if you try something else?

Such as busulfan…

Abstract 399
A Randomized Phase III Trial of Busulfan + Melphalan Vs Melphalan Alone for Multiple Myeloma

Muzaffar H, et al. ASH 2017;session 731. Abstr 399.

Background

- High dose melphalan is standard of care in MM *…still*

- Busulfan plus melphalan = longer PFS
  - Oral Busulfan used
  - VOD ↑
  - TRM ↑

- Busulfan IV
  - NRM ↓

Lahuerta JJ, et al. *Haematologica*. 2010;95:1913-1920.
Blanes M, et al. *Leuk Lymphoma*. 2015;56:415-419.
Kebriaei P, et al. *Biol Blood Marrow Transplantation*. 2011;17:412-420.

NRM, non-relapse mortality;
TRM, transplant related mortality;
VOD, veno-occlusive disease

Objective and Endpoints

- Busulfan plus Melphalan (Bu-Mel) vs. Melphalan alone

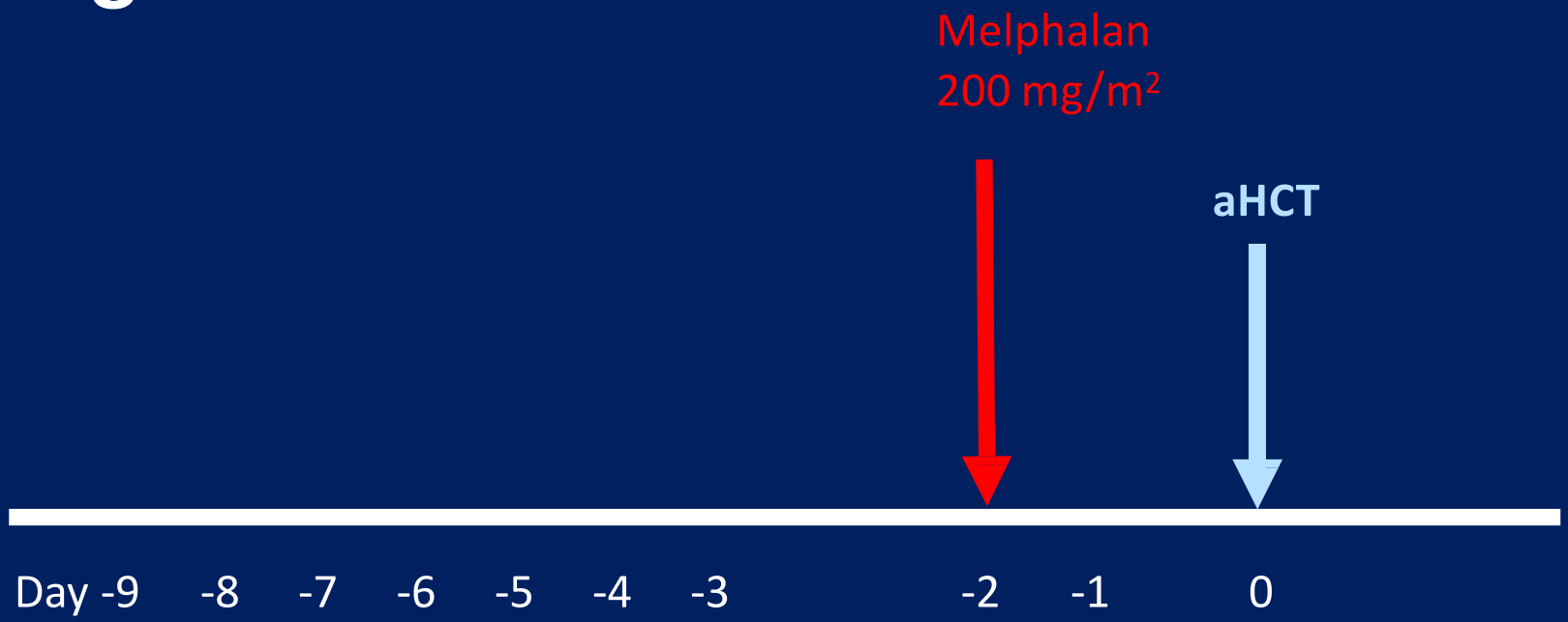
- Primary endpoint
  - CR rate at day +90 post aHCT

- Secondary endpoints
  - PFS
  - OS
  - NRM
  - Grade 3-4 AEs
  - QoL

Muzaffar H, et al. ASH 2017;session 731. Abstr 399.

QoL: quality of life

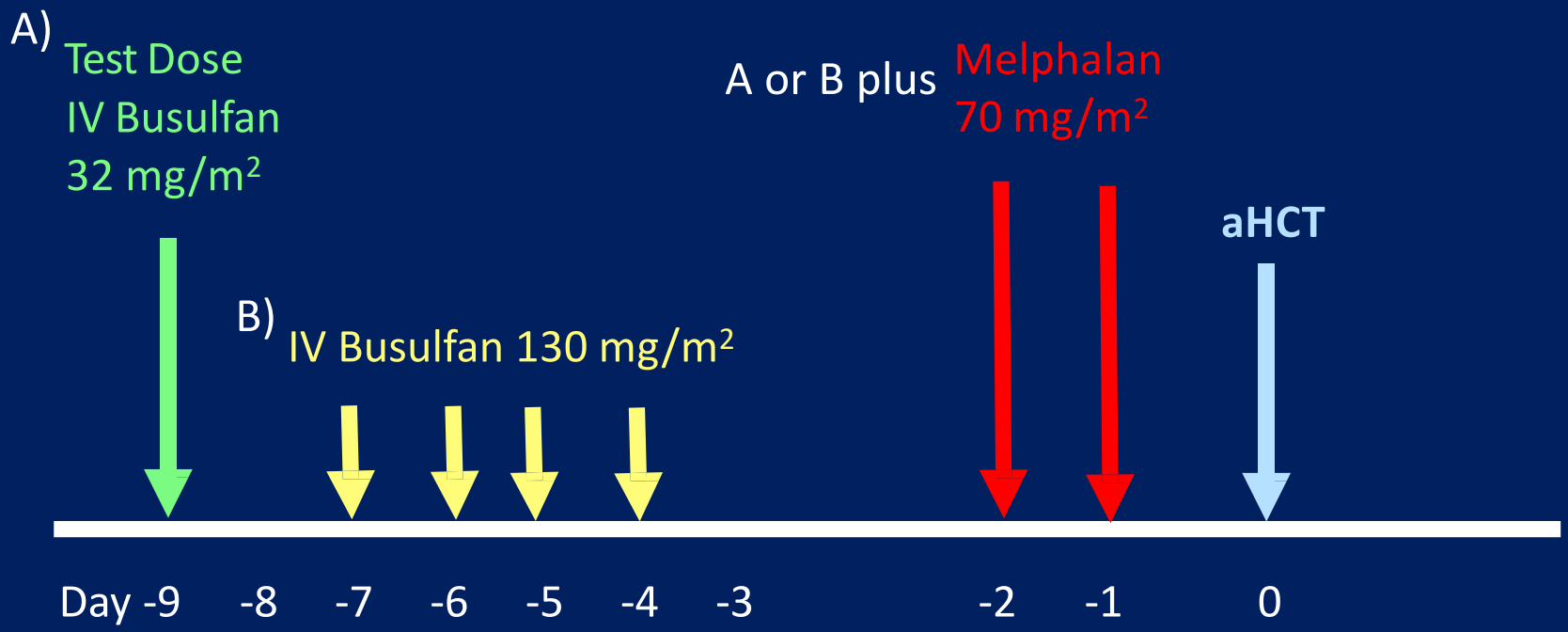
Study Design



§ Randomized phase III study

Muzaffar H, et al. ASH 2017;session 731. Abstr 399.

Study Design



- Busulfan target AUC: 5,000 µM-min ± 12% determined by test dose
- Phenytoin = seizure prophylaxis

Muzaffar H, et al. ASH 2017;session 731. Abstr 399.

AUC, area under the concentration curve

Outcomes

- Follow-up: 28.1 month

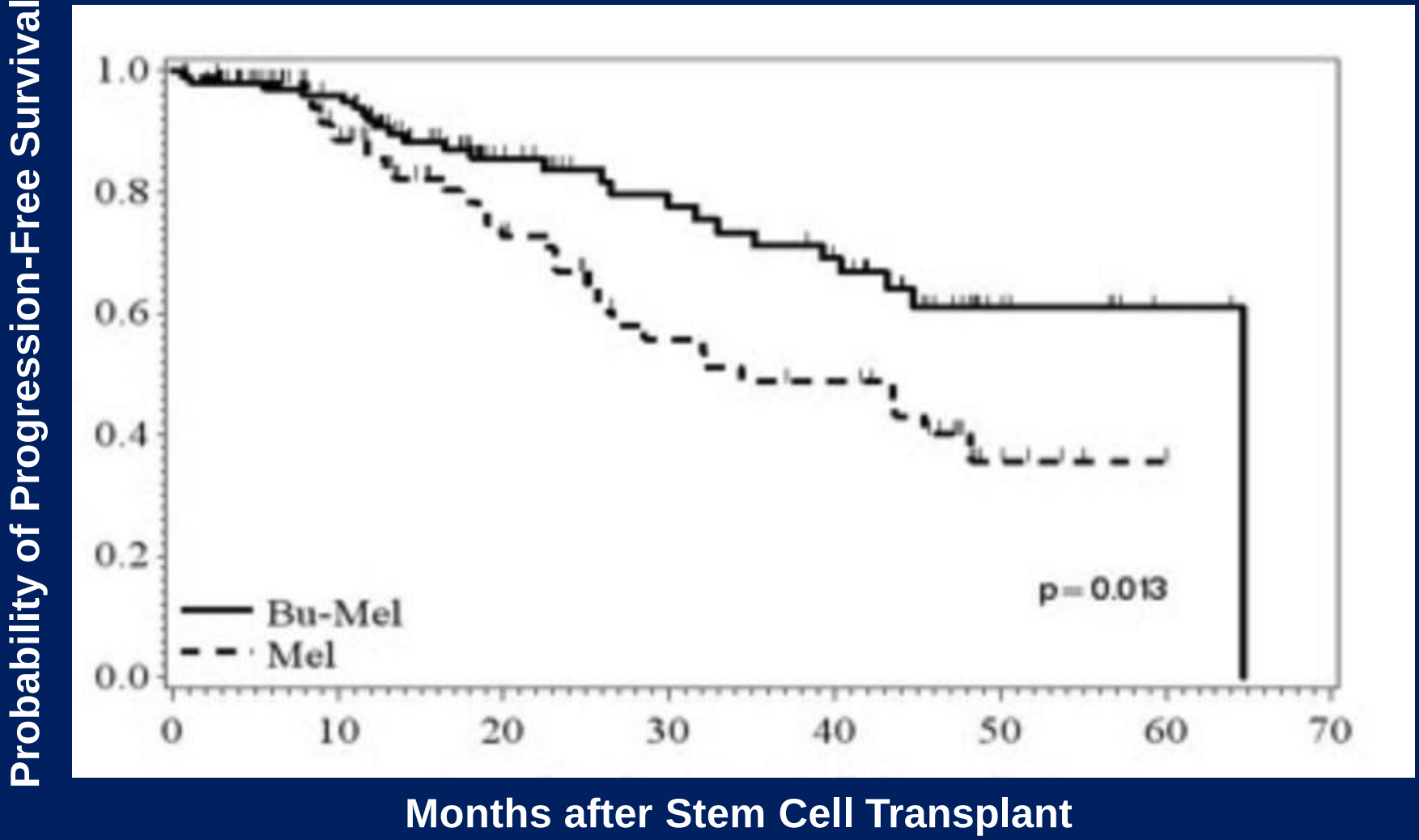
	Busulfan + Melphalan	Melphalan	P-value
CR (d 100)	27 (26)	34 (34)	0.22
MRD-/VGPR (d 100)	53/68 (78)	58/72 (81)	0.83
CR (Final)	52 (51)	54 (54)	0.57
NRM (d 100)	0	0	1.00
NRM (1-year)	2	0	0.11
SPM	2 (2)	3 (3)	0.67
PFS, median (mo)	64.7	34.4	0.013

- PFS was preserved after adjusting for maintenance therapy
- PFS was longer with Bu-Mel in high-risk patients (P=0.021)
- No difference in OS (P=0.94)

Muzaffar H, et al. ASH 2017;session 731. Abstr 399.

SPM, secondary primary malignancy

Progression-Free Survival



Muzaffar H, et al. ASH 2017;session 731. Abstr 399.

Conclusion

- Busulfan plus melphalan vs. melphalan alone
  - Toxicities: higher rates of
    - Grade I-III mucositis
    - ALT elevation
    - Neutropenic fever

- Outcomes
  - No difference in NRM
  - No difference in CR
  - No difference in MRD negativity rates
  - No difference in OS
  - Longer PFS (also seen in high risk)

Muzaffar H, et al. ASH 2017;session 731. Abstr 399.

Allogeneic Conditioning Regimens

"Which RIC vs. MAC?
The Never-Ending Debate"

MAC, myeloablative conditioning;
RIC, reduced intensity conditioning;

Background: RIC vs. MAC Debate

§ Conflicting data

- CTN 0901 = ↑ RFS with MAC
- Bornhauser M, et al. 2012 = No difference in relapse and OS
- RICMAC-Trial = No difference in RFS and OS

Kroger N, et al. *J Clin Oncol*. 2017;35:2157-2164.
Scott BL, et al. *J Clin Oncol*. 2017;35:1154-1161.
Bornhauser M, et al. *Lancet Oncol*. 2012;13:1035-1044.

RFS, relapse free survival

Objective

- CIBMTR
- Identify optimal regimen for AML or MDS
- Conditioning regimens
  - Bu/Cy
  - Flu/Bu 4 (Busulfan dose: IV 10-13 mg/kg)
  - Flu/Bu 2 (Busulfan dose: IV 5-6 mg/kg)
  - Flu/Mel (Mel dose: IV 130-140 mg/m2)

AML, acute myeloid leukemia; Bu/Cy, busulfan/cyclophosphamide; CIBMTR, Center for International Blood & Marrow Transplant Research; Flu/Bu, fludarabine/busulfan; Flu/Mel, fludarabine/melphalan; MDS, Myelodysplastic syndrome

Eapen M, et al. ASH 2017;session 732. Abstr 598.

Risk of Relapse and Mortality Compared to Bu/Cy

	NRM	Relapse	TF	Mortality
Bu/Cy	1.00	1.00	1.00	1.00
Flu/Bu 4	0.99	1.05	1.03	1.05
Flu/Bu 4 + ATG	1.05	1.47*	1.22*	1.28*
Flu/Bu 2	0.71*	1.66*	1.24*	1.14
Flu/Bu 2 + ATG	0.72*	2.09*	1.41*	1.21*
Flu/Mel	1.12	0.71*	0.93	0.92
Flu/Mel + ATG	1.17	0.99	1.16	1.36

* $p<0.05$

Eapen M, et al. ASH 2017;session 732. Abstr 598.

TF = treatment failure; relapse or death; inverse of relapse-free survival

Conclusions

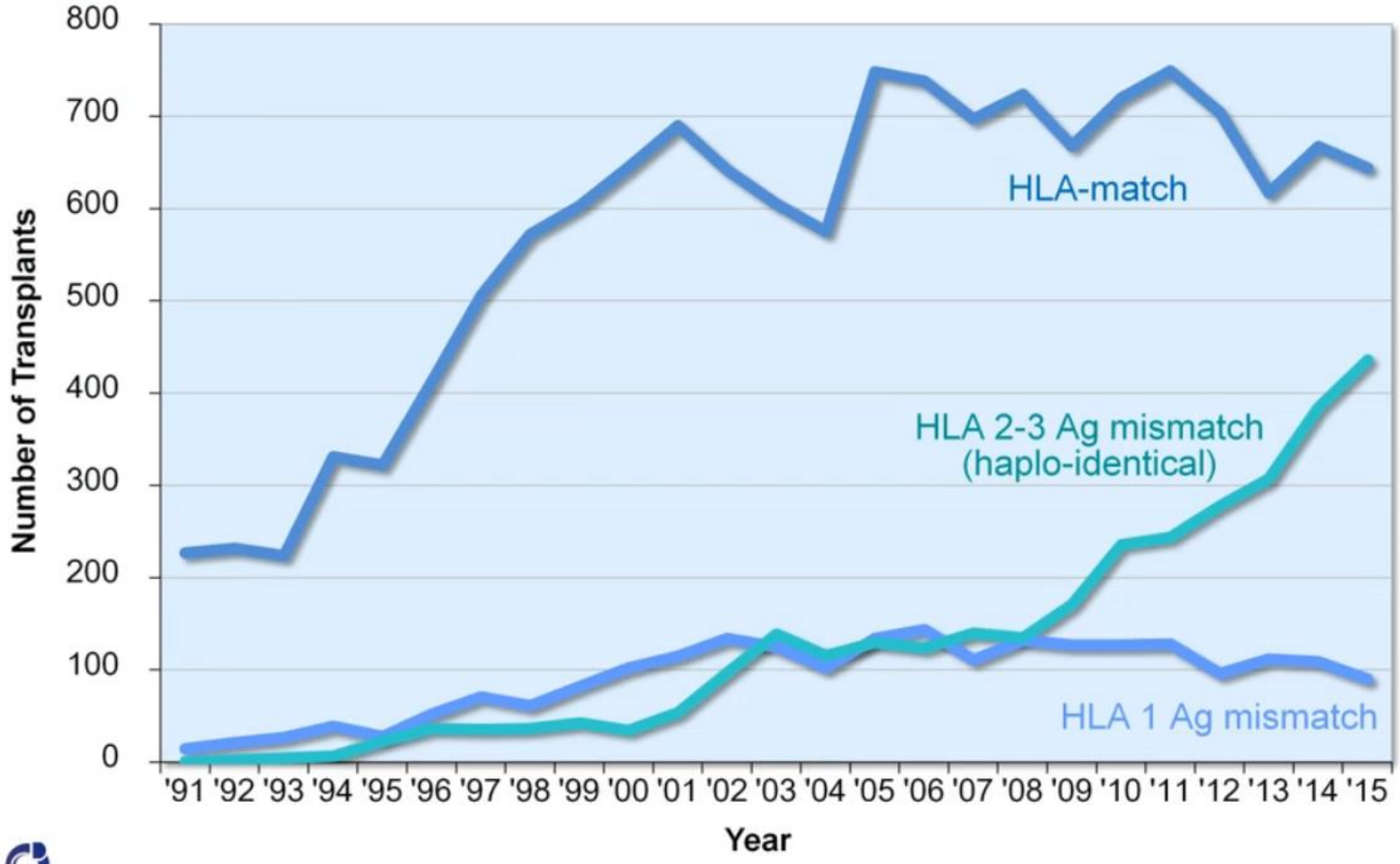
- Consider
  - Bu/Cy
  - Flu/Bu 4
  - Flu/Mel
    - Small number of patients
- Avoid Flu/Bu 2 (↑ relapse, ↓ RFS)
- Caution using ATG with
  - Flu/Bu (↑ relapse, ↓ RFS, ↓ OS)
  - Flu/Mel (↓ OS)

Eapen M, et al. ASH 2017;session 732. Abstr 598.

Myeloablative versus reduced-intensity conditioning in HLA-haploidentical peripheral blood stem cell transplantation using posttransplant cyclophosphamide

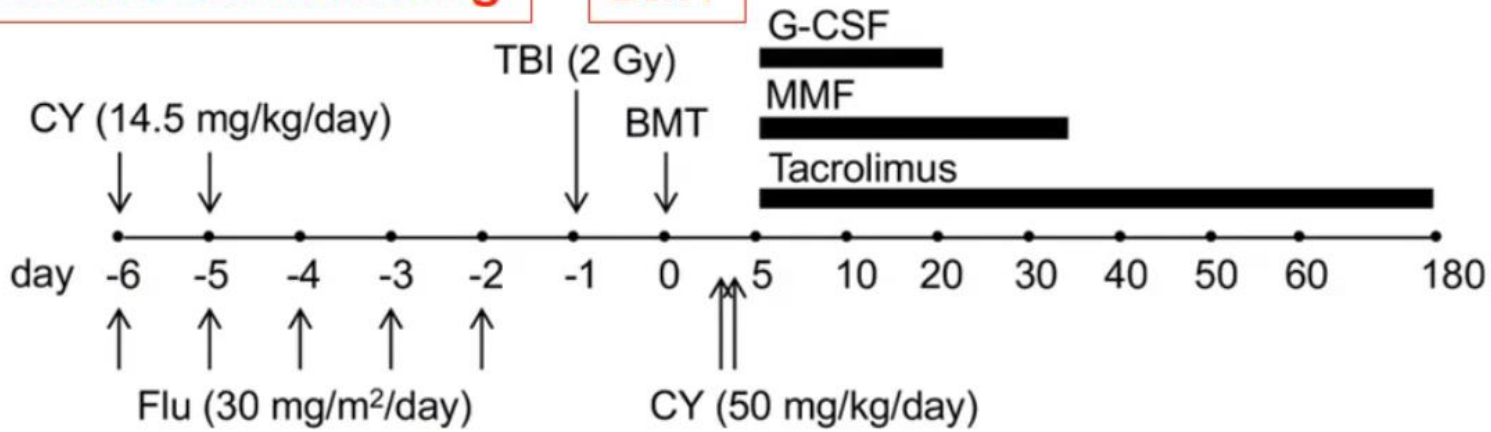
Junichi Sugita[1], Yusuke Kagaya[2], Toshihiro Miyamoto[3], Yasuhiko Shibasaki[4], Koji Nagafuji[5], Shuichi Ota[6], Tatsuo Furukawa[7], Miho Nara[8], Keitaro Matsuo[9], Koichi Akashi[3], Shuichi Taniguchi[10], Mine Harada[11], Takanori Teshima[1], **on behalf of the Japan Study Group for Cell Therapy and Transplantation (JSCT)**

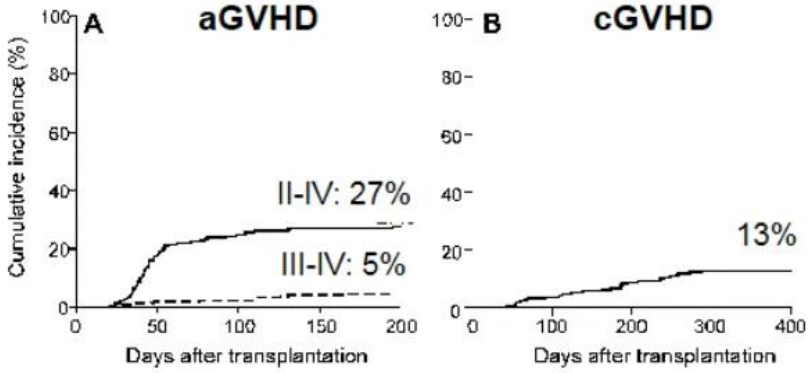
Annual Number of Allogeneic HCTs from related donors by Year and Donor Type (HLA-matched/HLA-non-id relative)

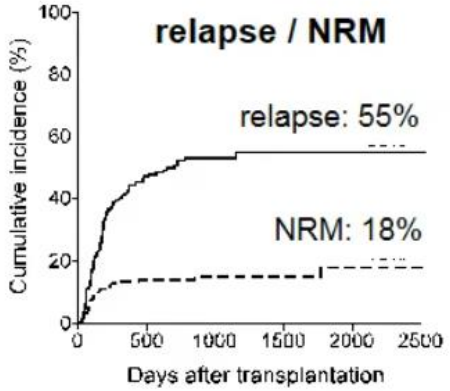


JOHNS HOPKINS, Baltimore

Non-myeloabative conditioning **BMT**

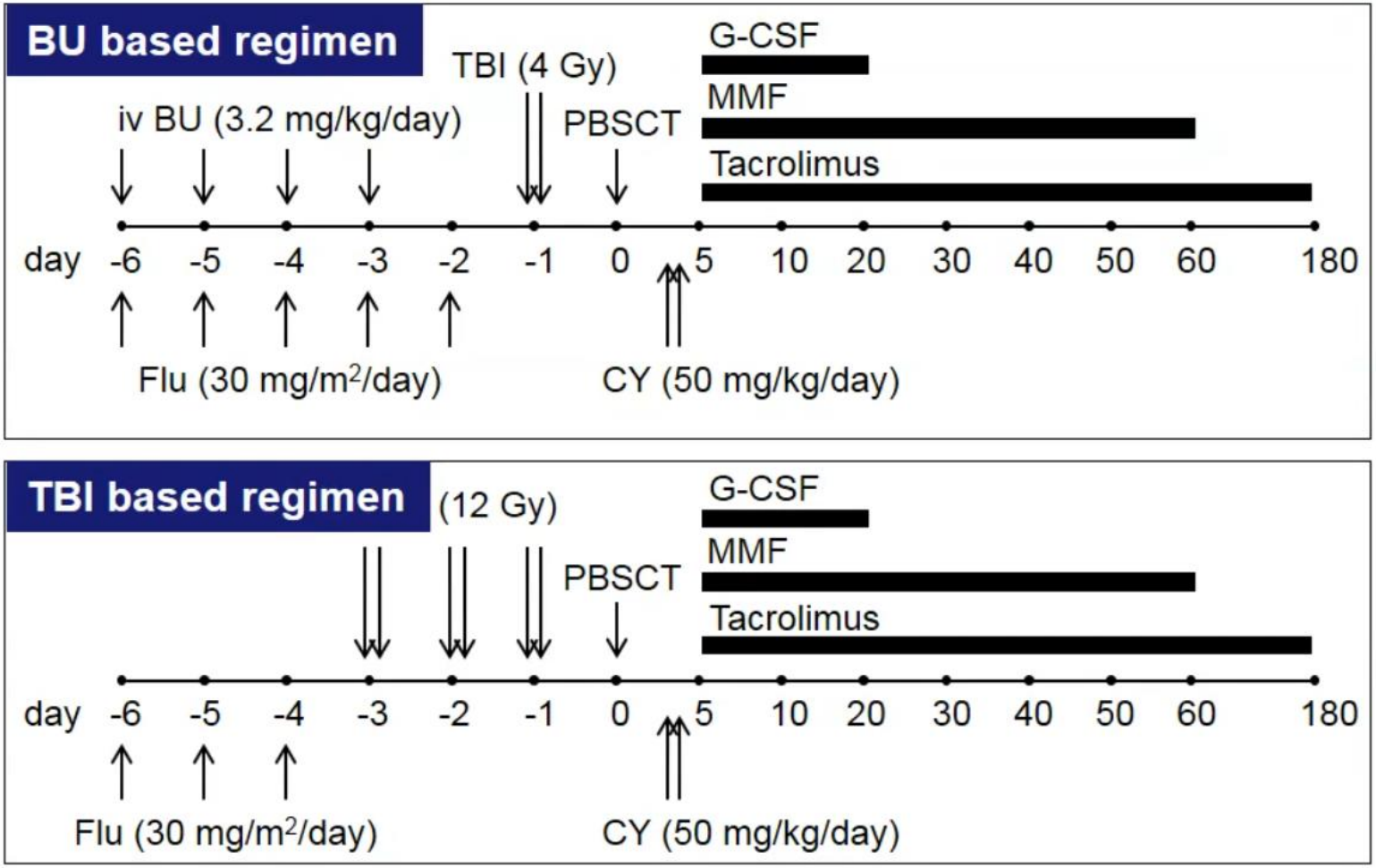




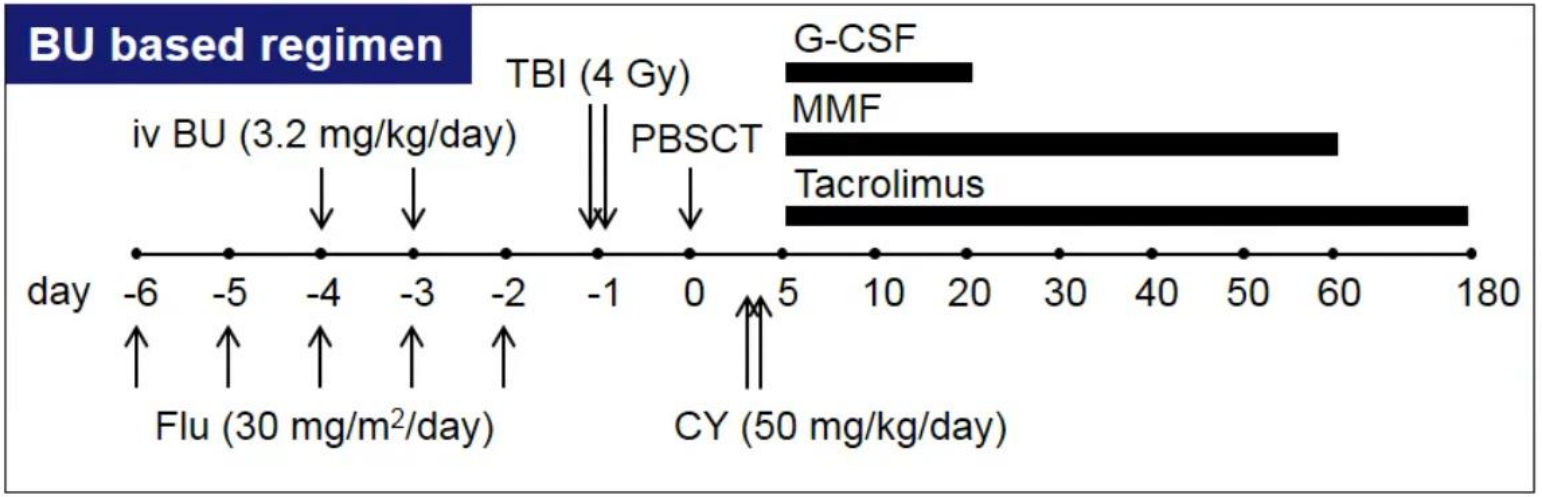


Kasamon YL, Biol. Blood Marrow Transplant. 2010.
Luznik L, et al. Biol. Blood Marrow Transplant. 2008.

Myeloablative conditioning (MAC)



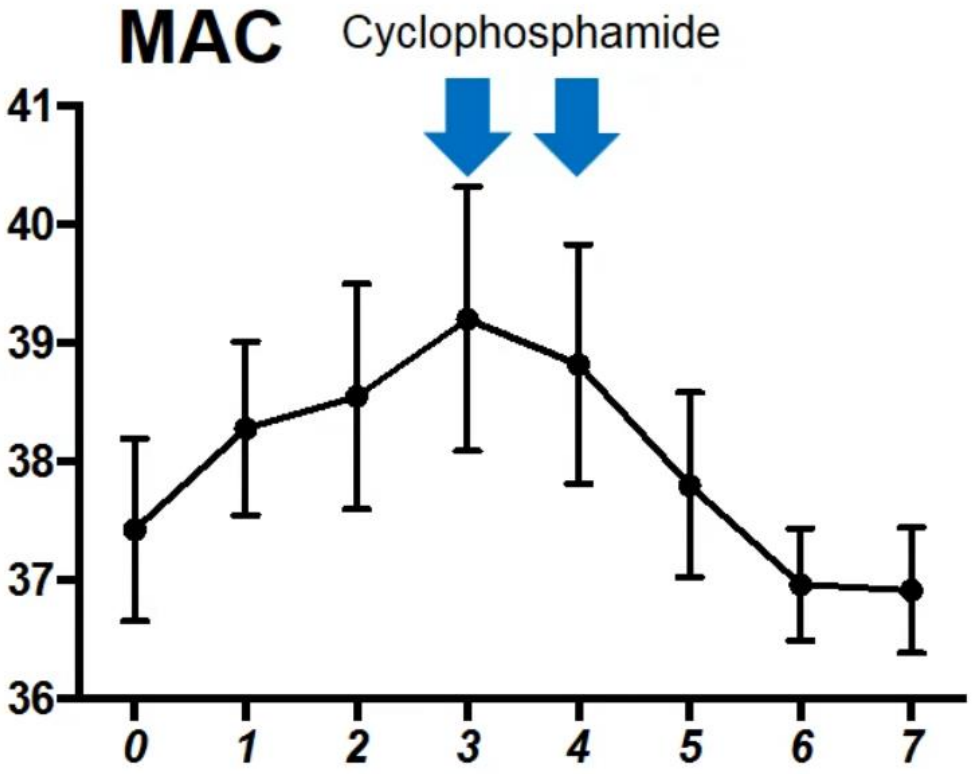
Reduced-intensity conditioning (RIC)



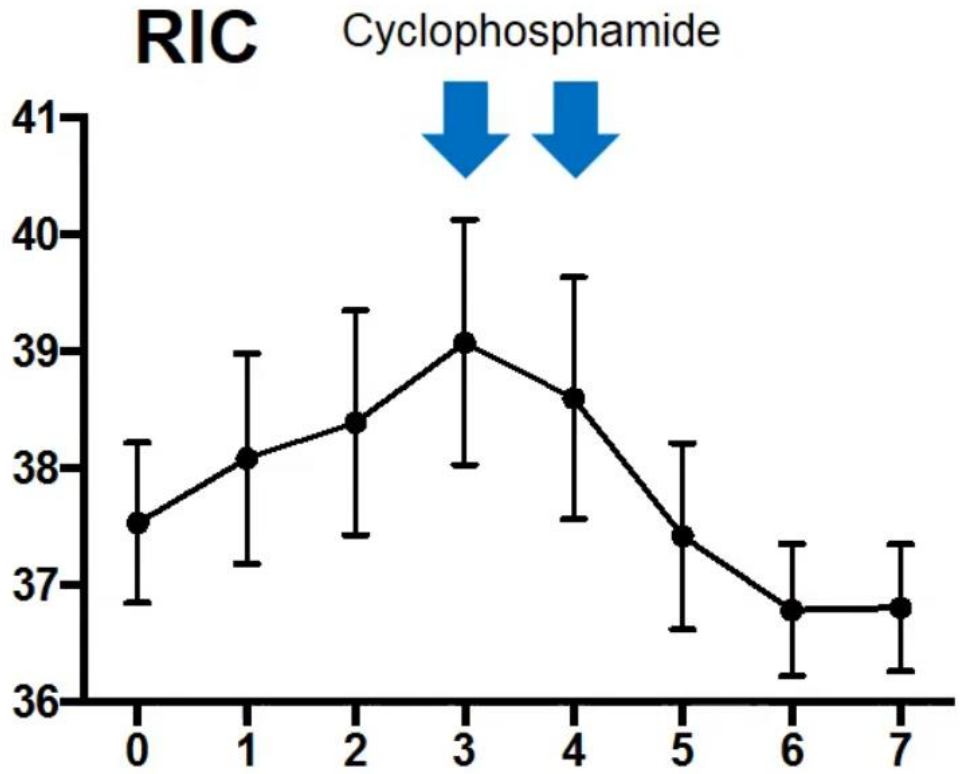
JSCT Haplo13 Flu + CY + BU + TBI (2Gy)

JSCT Haplo14 RIC Flu + ~~CY~~ + BU + **TBI (4Gy)**

Cytokine release syndrome (CRS)

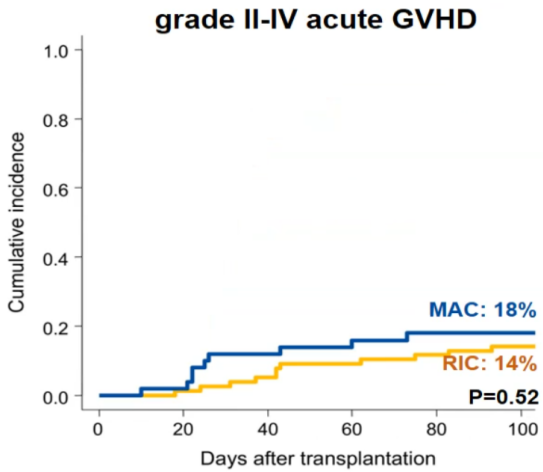


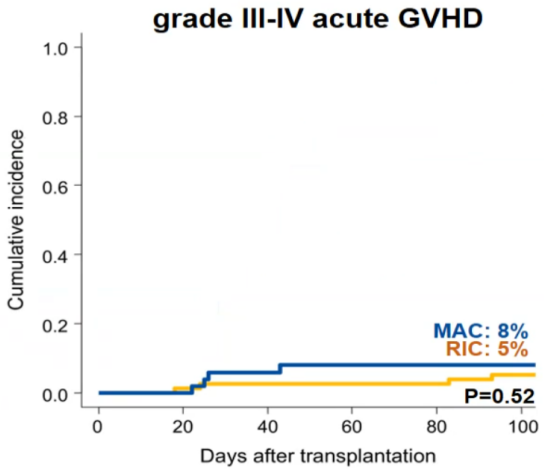
48 (96%) of 50 patiens developed CRS



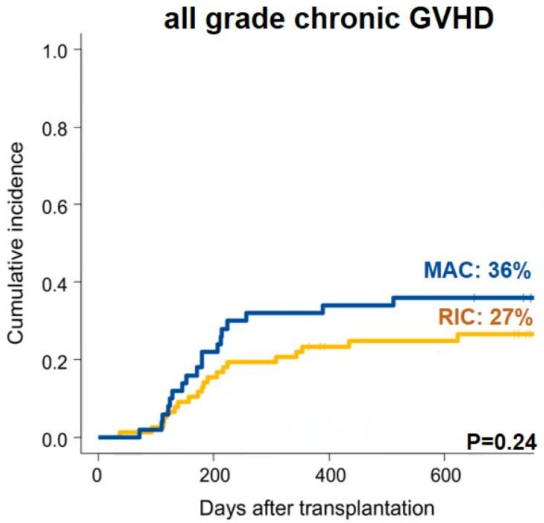
72 (94%) of 77 patiens developed CRS

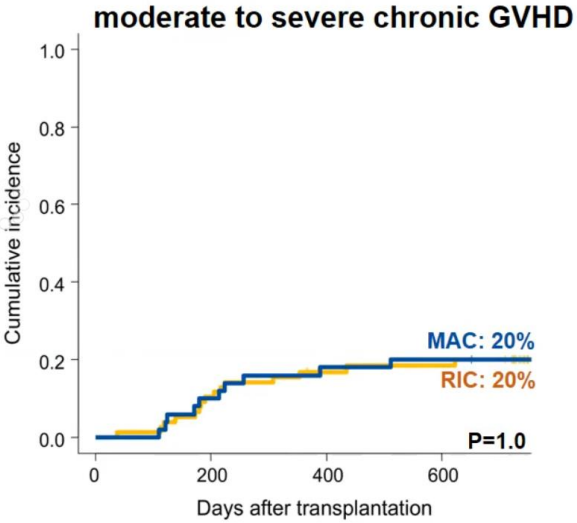
acute GVHD



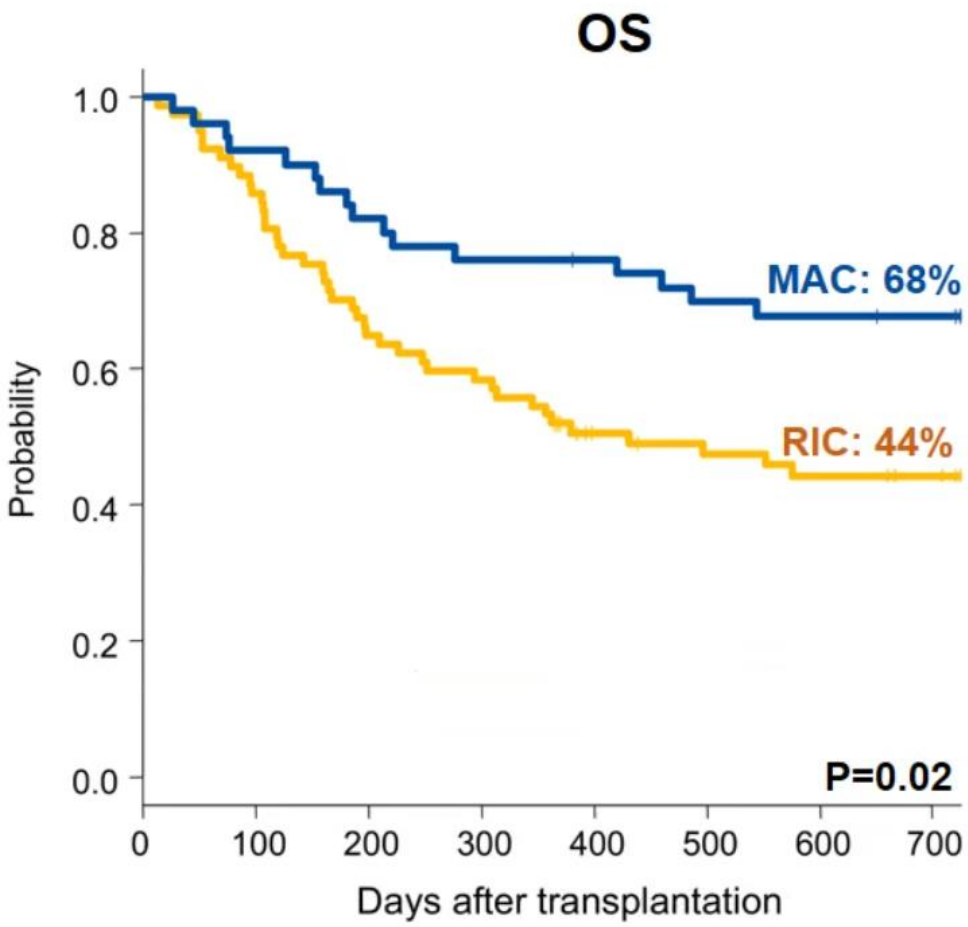


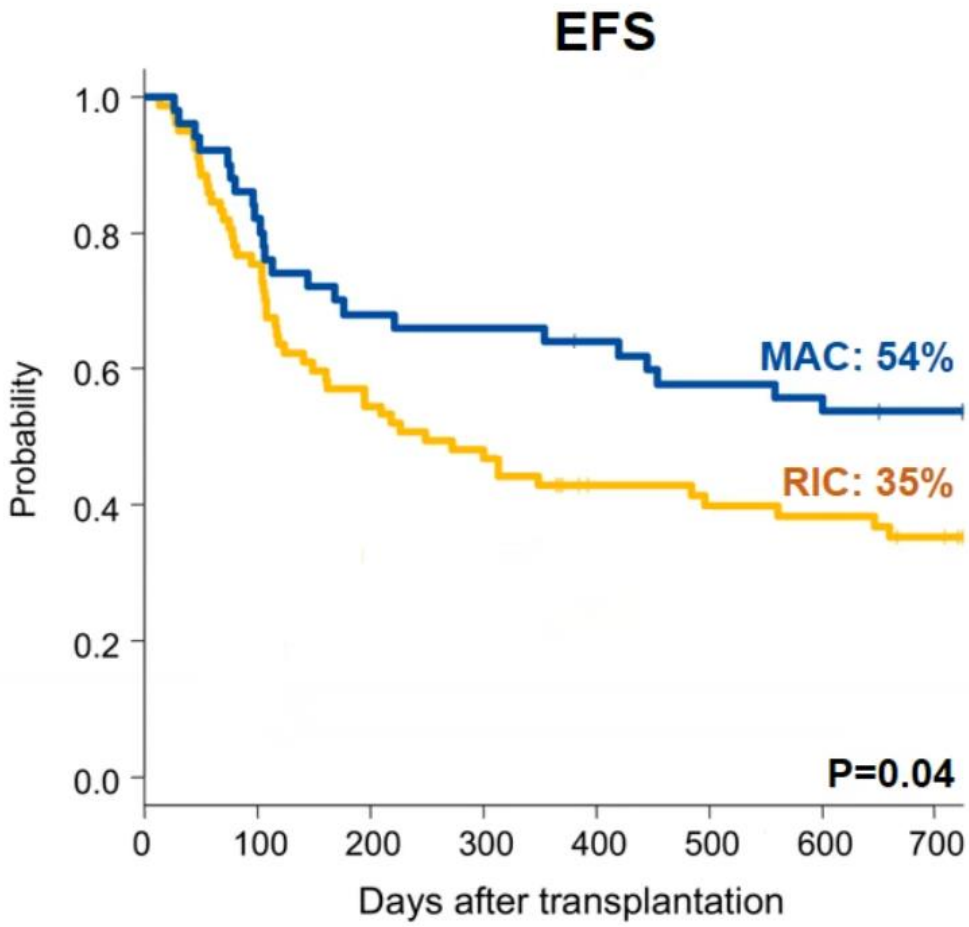
chronic GVHD





OS·EFS


OS
1.0
0.8
0.6
0.4
0.2
0.0
Probability
MAC: 68%
RIC: 44%
P=0.02
0
100
200
300
400
500
600
700
Days after transplantation


EFS
1.0
0.8
0.6
0.4
0.2
0.0
Probability
MAC: 54%
RIC: 35%
P=0.04
0
100
200
300
400
500
600
700
Days after transplantation

	Johns Hopkins[1] BM (n=210)	Haplo14 MAC PBSC (n=50)	Haplo14 RIC PBSC (n=77)
Condtioning regimen	Flu/CY/TBI	**Flu/TBI Flu/BU4/TBI**	**Flu/BU2/TBI**
GVHD prophylaxis	PTCy+Tac+MMF	**PTCy+Tac+MMF**	**PTCy+Tac+MMF**
Engraftment	87% day15 (11-42)	**98% day17 (12-39)**	**94% day18 (13-50)**
Acute GVHD			
II-IV	27%	**18%**	**14%**
III-IV	5%	**8%**	**5%**
Chronic GVHD			
all	13%	**36%**	**27%**
mod-sev	-	**20%**	**20%**
NRM	18%	**10%**	**20%**

Maintenance Therapy Strategies Post-Transplant

Approach to Relapse Prevention

- Prevention is the most effective intervention to manage relapse
- Consolidation
  - Short-term, more intensive therapy
  - Goal: To deepen response
- Maintenance
  - Long-term, less intense therapy
  - Goal: Suppress minimal residual disease (MRD), prolong response, progression-free survival (PFS), overall survival (OS)
- Increasingly sensitive methods of MRD detection
  - Allows for risk stratification
  - Goal: To prevent overt relapse

Facon T, et al. Hematology Am Soc Hematol Educ Program. 2015;2015:279-85.

Maintenance Therapy Strategies Post-Transplant for Multiple Myeloma

Lenalidomide: Randomized Controlled Trials

Study	Regimen	Median f/u	Median TTP/PFS (LEN vs PBO)	OS (LEN vs PBO)	Comments
CALGB 100104 McCarty, 2012 (n = 460)	Single aHCT à LEN 10-15mg daily until progression vs PBO	34 mo	TTP: 46 vs 27 mo (p<0.001)	3 years: 88% vs 80% (HR 0.62, CI 0.4-0.95)	Unblinded at 18 mo, 86/128 pts in PBO crossed over
IFM 2005-02 Attal, 2012 (n = 614)	Single or tandem aHCT à LEN consolidation x 2 à LEN 10-15mg daily x 2 years vs PBO	45 mo	PFS: 41 vs 23 mo (p<0.001)	4 years: 73% vs 75% (p=NS)	LEN stopped at 2 years due to SPM
GIMEMA Palumbo, 2014 (n = 135)	LEN-Dex x 6 à aHCT vs MPR consolidation à LEN 10mg on days 1-21, Q28 days until progression vs OBS	51.2 mo	PFS (from diagnosis): 54.7 vs 37.4 mo (p<0.001)	5 years: 78% vs 66.6% (p=0.14)	Data from the 135 patients randomized post aHCT

PBO: placebo, TTP: time to progression, Dex: dexamethasone, OBS: observation, SPM: second primary malignancy

McCarthy PL, et al. N Engl J Med. 2015;366:1770-1781. Attal M, et al. N Engl J Med. 2012;366:1782-1791. Palumbo A, et al. N Engl J Med. 2014;371:895-905

Lenalidomide: Second Primary Malignancies

Study	Median f/u	Treatment Arm	Invasive SPMs	Solid Cancers	Heme Cancers	Non-melanoma Skin Cancers	Incidence of Invasive SPMs
CALGB 100104 McCarty, 2012 (n = 460)	34 mo	LEN	18	10	8	4	7.8%*
		Placebo	6	5	1	3	2.6%*
IFM 2005-02 Attal, 2012 (n = 614)	45 mo	LEN	23	10	13	5	7.5%*
		Placebo	9	4	5	3	2.9%*
GIMEMA Palumbo, 2014 (n = 231, total randomized to maintenance)	51.2 mo	LEN	5	NR	NR	NR	4.3%
		Observation	5	NR	NR	NR	4.3%

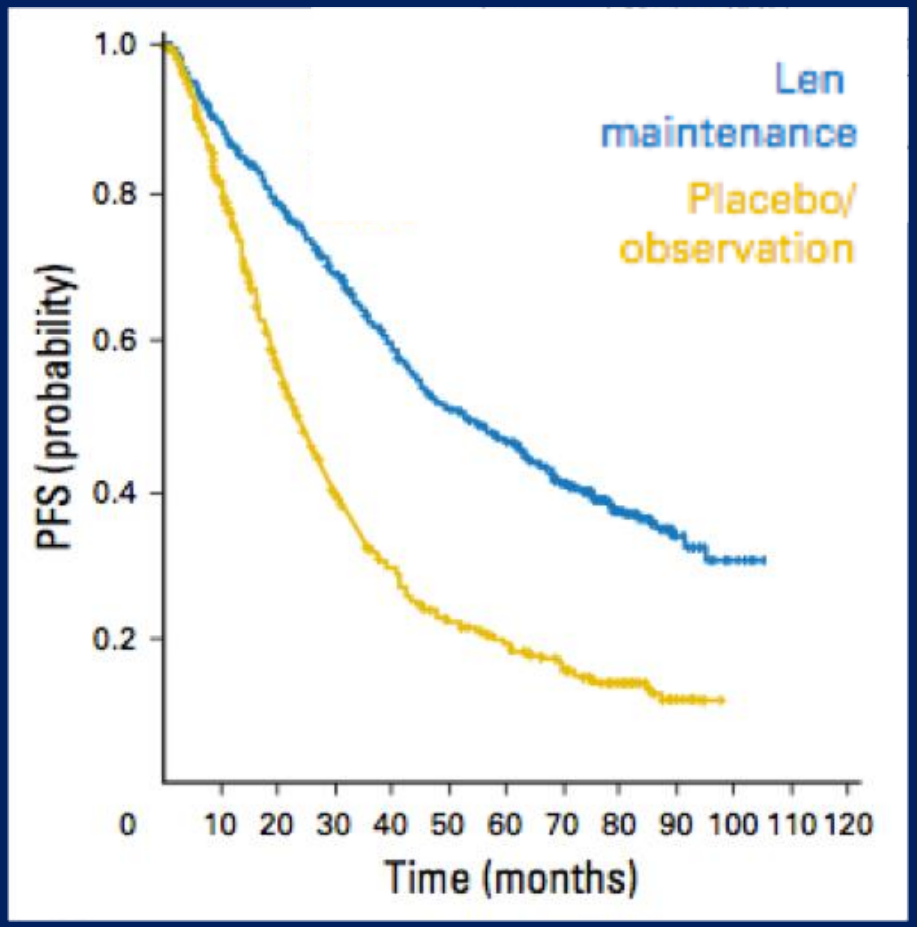
McCarthy PL, et al. N Engl J Med. 2015;366:1770-1781. Attal M, et al. N Engl J Med. 2012;366:1782-1791.
Palumbo A, et al. N Engl J Med. 2014;371:895-905. Yang J, et al. Adv Hematol. 2012;2012:801495.

Lenalidomide: Meta-Analysis

- Requested by the US Food and Drug Administration
- Primary endpoint: Overall survival
- Inclusion criteria:
  - LEN maintenance arm vs a control arm post aHCT
  - Database lock for primary efficacy analysis
  - Primary source patient-level data
- Three RCTs identified:
  - CALGB 100104
  - IFM 2005-02
  - GIMEMA
- Median follow-up: 79.5 months

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

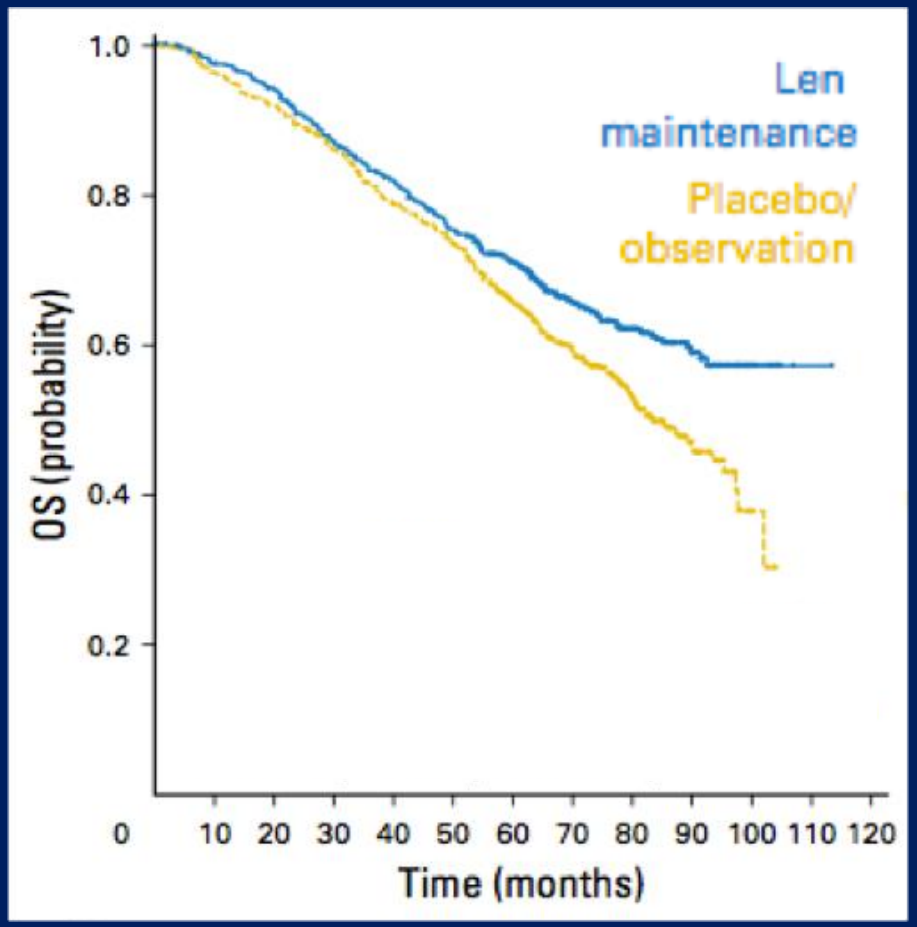
Lenalidomide: Meta-Analysis PFS



- Median PFS: 52.8 mo LEN vs
  23.5 mo control
  (HR = 0.48; 95% CI 0.41-0.55)
- Median PFS2 (PFS after next therapy): 73.3 mo LEN vs 56.7 mo control
  (HR = 0.72; 95% CI 0.62-0.84)

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

Lenalidomide: Meta-Analysis OS

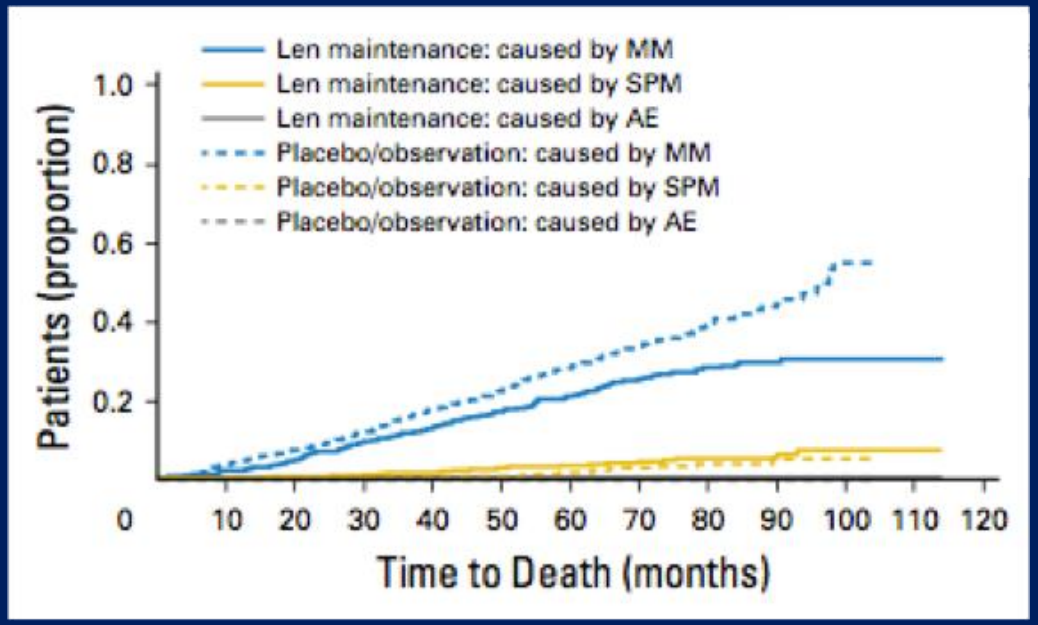


- Median OS: not reached LEN vs 86 mo control (HR = 0.75; 95% CI 0.63-0.9)
- 7 year survival rate: 62% LEN vs 50% control
- At median follow-up of 79.5 mo, 64% LEN vs 54% control alive

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

Lenalidomide: Meta-Analysis SPMs

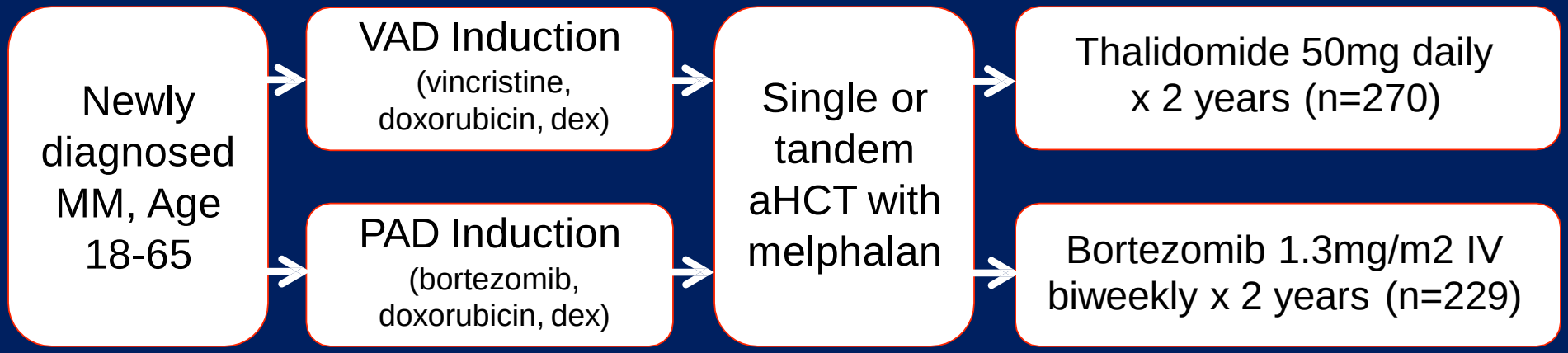
- Heme SPMs: 7.3% LEN vs 4.2% control
- Solid SPMs: 6.1% LEN vs 2.8% control
- Time to invasive SPM occurring before progressive disease (PD) was shorter in LEN vs control [HR 2.67 (95% CI 1.54-4.62; p<0.001)]
- Time to PD was longer with LEN vs control [HR 0.51 (95% CI 0.45-0.59; p<0.001)]
- Time to death as a result of MM was longer with LEN vs control [HR 0.66 (95% CI, 0.53-0.81; p<0.001)]
- No difference in time to death as a result of SPMs between groups



McCarthy PL, et al. J Clin Oncol. 2017;35:3279-3289.
Supplement to: McCarthy PL, et al. J Clin Oncol. 2017;35:3279-3289.

Bortezomib: HOVON-65/GMMG-HD4

Phase III, randomized, open label



- Median f/u: 41 months
- ≥VGPR post aHCT: 62% PAD vs 36% VAD
- Median PFS: 35 mo PAD vs 28 mo VAD (p=0.002)
- 5 year OS: 61% PAD vs 55% VAD (p=0.07)
- Grade 2-4 neuropathy 40% PAD vs 18% VAD (p=0.001)
- Discontinuation due to ADRs: 11% PAD vs 30% VAD

Sonneveld P, et al. J Clin Oncol. 2012;30:2946-2955.

Bortezomib: HOVON-65/GMMG-HD4

Subgroup	PFS			OS		
	Median, mo (PAD vs VAD)	HR (95% CI)	p	(PAD vs VAD)	HR (95% CI)	p
SCr > 2	30 vs 13	0.45 (0.26-0.78)	0.004	Median, mo: 54 vs 21	0.33 (0.16-0.65)	<0.001
del(17p13)	26.2 vs 12	0.41 (0.19-0.91)	0.024	3 yr, %: 69 vs 17	0.37 (0.14-0.93)	0.028
t(4;14)	25.3 vs 21.7	0.6 (0.32-1.15)	0.12	3 yr, %: 66 vs 44	0.68 (0.29-1.59)	0.37

- Potential role for bortezomib in patients with increased SCr or del(17p13)
- No PFS or OS advantage was seen in the LEN meta-analysis in patients with CrCl <50 mL/min or poor risk cytogenetics

Sonneveld P, et al. J Clin Oncol. 2012;30:2946-2955.
Neben K, et al. Blood. 2012;119:940-948.

Minimal residual disease negativity and Lenalidomide maintenance therapy are associated with superior survival outcomes in multiple myeloma

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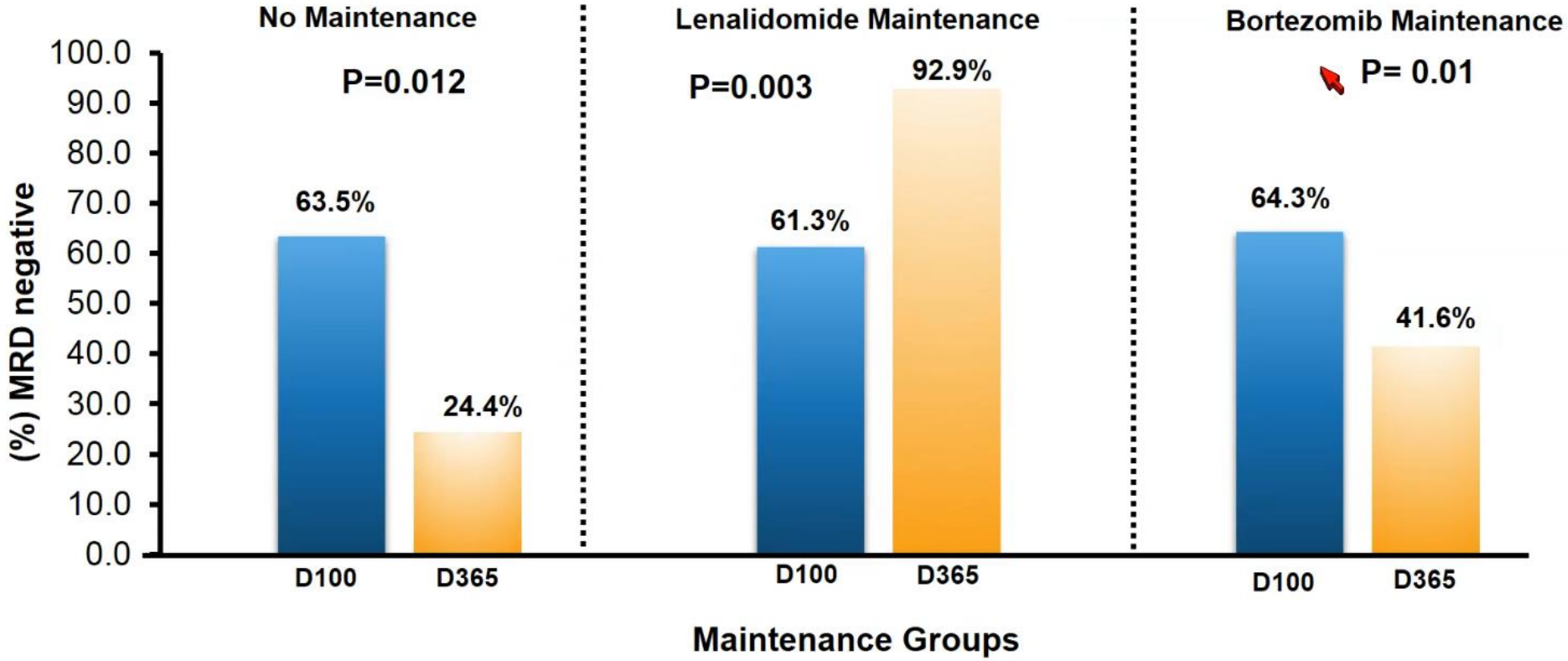
Lenalidomide maintenance increases MRD negativity at 1 year post ASCT compared to Bortezomib and no maintenance therapy



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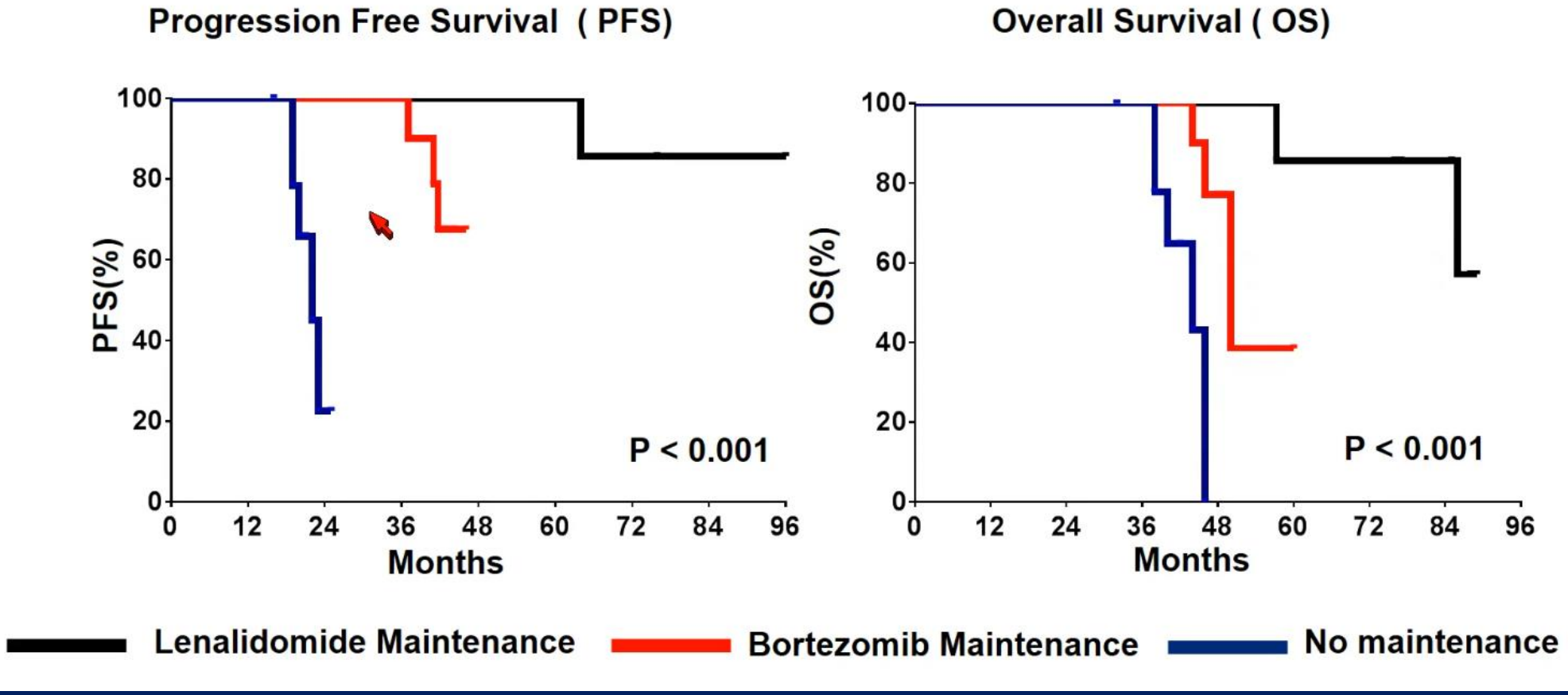
Irrespective of cytogenetic risk, lenalidomide maintenance improves PFS and OS compared to Bortezomib and no maintenance therapy



Maintenance in Myeloma: Conclusions

- Lenalidomide maintenance prolongs PFS and OS post aHCT
  - The risk of developing progressive disease and dying from MM is greater than the risk of developing a SPM
  - ASBMT Guidelines: LEN maintenance unless contraindicated (grade A)
  - NCCN Guidelines: Category 1 preferred regimen
  - FDA and European Commission granted approval for maintenance post aHCT in 2017
- Bortezomib offers an alternative for patients with high-risk cytogenetics, renal insufficiency, an inability to tolerate LEN, or previous history of another cancer
  - ASBMT Guidelines: Bortezomib may be considered in patients with renal failure or adverse chromosome changes (grade D)
  - NCCN Guidelines: Other recommended regimen

Shah N, et al. Biol Blood Marrow Transplant. 2015;21:1155-1166.
NCCN Guidelines. Multiple Myeloma. Version 3.2018. nccn.org. Accessed December 1, 2017

Maintenance Therapy Strategies Post-Transplant for MDS and AML

MDS and AML Relapse Post alloHCT

- Disease relapse is the most common cause of death post alloHCT
- Relapse rates may be rising due to increased availability of HCT to older patients with reduced intensity conditioning (RIC)
- The majority of relapses occur within 12 months
  - Maintenance therapy may control disease burden prior to a robust graft-versus-malignancy (GVM) effect
  - Toxicity profile is critical
- Role of MRD monitoring for patient selection
- Pre-emptive treatment (will not be reviewed today)
  - MRD monitoring - CD34+ donor chimerism

Hourigan CS, et al. Biol Blood Marrow Transplant. 2014;20:154-163.

Maintenance Agents Studied

- Hypomethylating agents: Azacitidine (AZA) & Decitabine
  - Direct apoptosis of cancer cells
  - Upregulation of cancer testis antigens
  - Expansion of T-regulatory cells
- Histone deacetylase inhibitor: Panobinostat
  - Moderately active against leukemia
  - Immunomodulatory effects
  - Phase I/II trial (n=42): 2 year OS 81% and RFS 75%
- FLT3 Inhibitors
  - FLT3-ITD mutations associated with high relapse rates and short remission duration
  - FLT3-TKD mutations have unclear prognostic value

Kroger N, et al. Biol Blood Marrow Transplant. 2014;20:168-172.
Bug G, et al. Leukemia. 2017;31:2523-2525.

De Lima Trial: Azacitidine

Objective	To determine a safe dose and schedule of AZA for relapse prevention following alloHCT with reduced intensity conditioning
Study Design	Phase I, dose escalation
Patients	• Age 18-75 years • AML or high-risk MDS (IPSS INT-2 or high-risk) • Not candidates for myeloablative conditioning • In CR at day +30 following alloHCT
Intervention	• AZA 8-40mg/m^2 SubQ x 5 days, Q30 days for 1-4 cycles • AZA must be initiated by day +90 • Eligibility: ANC > 1000, PLT > 15, no uncontrolled infection, no grade III/IV aGVHD

de Lima M, et al. Cancer. 2010;116:5420-5431.

De Lima Trial: Azacitidine

Results	<u>Patient Characteristics</u> • 37 patients with AML and 8 patients with MDS • Median age 60.6 years • 67% not in CR at the time of transplant • 40% had poor-risk cytogenetics <u>Outcomes</u> • Median follow-up 20.5 months, 42% died, 53% relapsed • 20% of patients completed 4 cycles • AZA 40 mg/m2 associated with thrombocytopenia • **Longer OS associated with fewer blasts, chemotherapy cycles pre-HCT, comorbidities, and more AZA cycles** • **cGVHD decreased with more AZA cycles**
Conclusions	• AZA 32 mg/m2 x 5 days for 4 cycles is safe following alloHCT • Phase 3 trial at MD Anderson Cancer Center with 1 year of maintenance is ongoing

de Lima M, et al. Cancer. 2010;116:5420-5431. NCT00887068. clinicaltrials.gov. Accessed December 1, 2017.

Oral AZA (CC-486): Phase I/II Study

Primary Outcome	Maximum tolerated dose (MTD)
Study Design	Phase I/II, dose-finding • 200mg-300mg daily x 7 days, Q 28 days x 12 cycles • 150-200mg daily x 14 days, Q 28 days x 12 cycles
Patients	• Age ≥ 18 years • AML or MDS diagnosis • Myeloablative or reduced intensity conditioning • In CR following alloHCT
Results (n = 30)	• MTD was not reached à 200mg daily x 14-day arm expanded • Median f/u: 19 months • 10/19 patients in expanded arm completed 12 cycles • **8/30 patients (27%) relapsed or had PD** • **3 patients (10%) developed grade 3 aGVHD, 8 patients developed cGVHD (2 severe cases)** • **CC-486 200mg 14-day dosing regimen will be further studied**

De
NCT01835587. clinicaltrials.gov. Accessed December 1, 2017.

AML & MDS Maintenance Post alloHCT: Ongoing Trials

Hypomethylating Agents:

Agent	Design	Duration	Patient	Primary Endpoint	Reference
AZA	Phase III	1 year	Age 18-75	RFS	NCT00887068
AZA	Phase II	1 year	Age 1-75, T-cell depleted HCT	Relapse	NCT01995578
AZA + Valproic Acid	Phase II	4 months	Age $\geq$ 2	OS	NCT02124174
AZA + GM-CSF	Phase II	1 year	All ages	RFS	NCT01700673

Rashidi A, et al. Blood. 2016;128:763-773.
clinicaltrials.gov. Accessed December 1, 2017.

Sorafenib in FLT3-ITD

- Retrospective analysis
- Patients:
  - FLT3-ITD AML diagnosed between 2008-2014
  - Received alloHCT in CR1
- Sorafenib:
  - 200mg daily to 400mg BID
  - Median time to initiation = 68 days

Outcome	Sorafenib (n=26)	Control (n=43)	P-value
2-year OS	81%	62%	0.029
2-year PFS	82%	53%	0.0081
2-year relapse	8.2%	37.7%	0.0077
2-year NRM	9.8%	9.3%	0.82
1-year cGVHD	55.5%	37.2%	0.28

Brunner AM, et al. Br J Haematol. 2016;175:496-504

AML & MDS Maintenance Post alloHCT: Ongoing Trials

FLT3 Inhibitors:

Agent	Design	Duration	Patient	Primary Endpoint	Reference
Gilteritinib	Phase III	2 years	Age ≥18, FLT3-ITD+	RFS	NCT02997202 (BMT-CTN)
Crenolanib	Phase II	2 years	Age ≥ 18, FLT3 mutated	PFS	NCT02400255
Sorafenib	Phase II	2 years	Age ≥19, FLT3-ITD+	DLT	NCT01578109
Midostaurin	Phase II	1 year	Age ≥ 60, FLT3 mutated	EFS/OS	NCT02723435
	Phase II	1 year	Age 18-60, FLT3-ITD+	RFS	NCT01883362
Quizartinib	Phase III	1 year	Age ≥19, FLT3-ITD+	EFS	NCT02668653

Rashidi A, et al. Blood. 2016;128:763-773. clinicaltrials.gov. Accessed December 1, 2017.

Phase I Trial of Post Allogeneic Stem Cell Transplant Maintenance Lenalidomide in Patients with High Risk AML or MDS

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[2] Veterans Administration Northern California Health Care System

ASBMT 2018

Objectives

- **Patients aged 18-65 with High-risk AML or MDS (defined by residual disease, poor-risk cytogenetics, secondary AML or R-IPSS >3) s/p allogeneic stem cell transplant were enrolled**
- **Regimen: Lenalidomide for 21 of 28 day cycle for up to 6 cycles**
- **Primary objective = Determine maximum tolerated dose (MTD) of Lenalidomide post transplant**
- **Secondary objective = 1-year relapse rate, 1-year disease-free survival (DFS) and 1-year Graft-versus-Host Disease (GvHD) rate**

Patient Characteristics and Efficacy

Patient #	Age/Sex	Diagnosis	# Prior therapies	Cycles completed	Transplant	Current Status as of 2/2018
001	63 F	AML - %	3	6	MUD allo	Relapsed 1 year after trial and passed 3 years later
002	62 M	AML - $	1	4	MRD allo	Alive and remains in CR
003	64 F	AML - $	5	21 days	MUD allo	Alive and remains in CR
004	36 M	AML - +	3	6	MRD allo x2	Alive and remains in CR
005	58 M	AML - +	4	6	MUD allo	Alive and remains in CR
006	56 M	AML - */#	2	6	9/10 MUD	Alive and remains in CR
007	34 M	AML - $	1	6	MUD allo	Alive and remains in CR
008	41 F	AML - %/+	3	2	MUD allo/DLI	Alive and remains in CR
009	47 M	AML - $/%	3	3	MUD allo	Alive and remains in CR
010	44 M	AML - */+	2	6	8/10 MUD allo	Alive and remains in CR
011	54 M	MDS - @	1	21 days	MUD allo	Alive and remains in CR
012	63 M	MDS - @	1	1	MUD allo	Alive and remains in CR
013	53 M	MDS - %/$	1	6	MUD allo	Alive and remains in CR

%Complex Cytogenetics $Transformed from MDS #t-AML +Relapsed/Refractory *FLT3 mutated @R-IPSS>3

Krishnan R et al ASBMT 2018

Conclusions

- Lenalidomide use as maintenance in the post-allogeneic period appears to be safe and well tolerated
- There was no increase in the incidence of acute or chronic GvHD
- Continued remissions were seen in 12 of 13 patients regardless of risk
- Further investigation to find the MTD and a larger Phase II study is warranted to determine efficacy among high risk AML and MDS

Maintenance in AML & MDS: Conclusions

- Data is preliminary and non-comparative
- Prospective, randomized trials are needed and anticipated
- Azacitidine
  - Encouraging preliminary results
  - Acceptable safety profile following reduced intensity conditioning
- FLT3 Inhibitors
  - Patients should be enrolled in clinical trials, consider sorafinib in HR Flt3 + patients
- Application of MRD monitoring will further guide relapse prevention strategies-? Ready for prime time
- Lenalidomide post allo transplant for AML appears promising. Larger trials are needed

Overall Conclusions

- Multiple Myeloma-Mel 200 remains the SOC –for now
  - Consider Double auto or Bu-Mel for high risk?
- Allo transplant
  - MAC vs RIC debate unresolved, but MAC likely better for HR patients
- Maintenance therapy
  - Myeloma-Len SOC, +/- bortez for HR (?)
  - AML-FLT3+ Sorafenib vs more targeted FLT3 inhibitors
  - MDS/AML - 5-Aza for HR
  - MCL-Rituxan post-Auto PSCT SOC
- PTLD
  - EBV-direct adoptive T cell therapy very promising
  - Always consider enrolment on clinical trials


Questions?