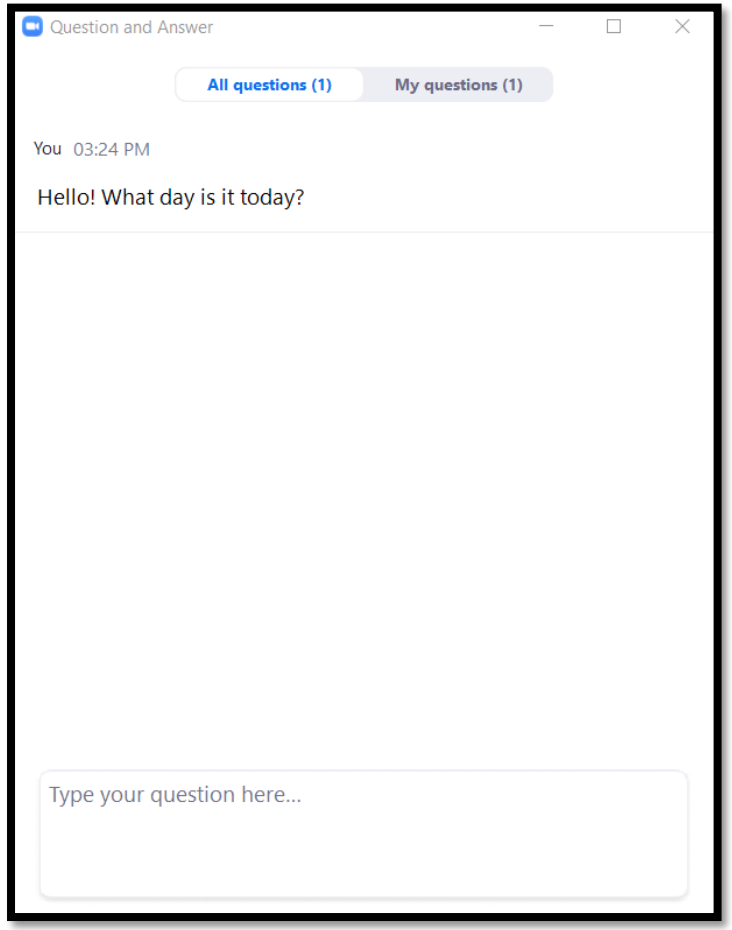
Stem Cell Transplantation for Multiple Myeloma: A Global Perspective

Organized by WBMT and ASTCT

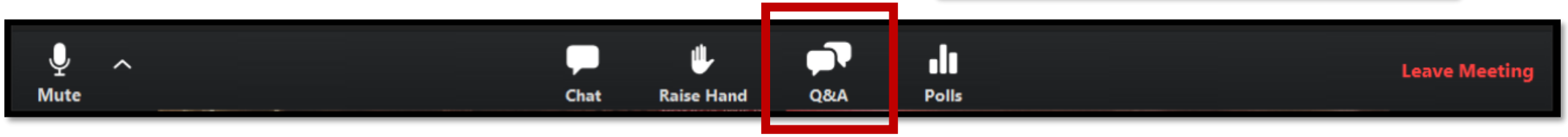
Tuesday, September 22, 14:00 – 15:00 CEST

Today's Webinar

We will have a panel discussion portion at the end of this webinar, so please **submit any thoughts, comments or questions** during this webinar in the Zoom panel at the bottom of your screen.



If you have any questions, please email info@astct.org



Welcome and Introductions

Sebastian Galeano

British Hospital, Montevideo, Uruguay

WBMT Education & Dissemination Committee Co-Chair

Damiano Rondelli

University of Illinois at Chicago, Chicago, USA

ASTCT Committee on International Affairs Chair

The Global State of Hematopoietic Cell Transplantation for Multiple Myeloma: An Analysis of the Worldwide Network of Blood and Marrow Transplantation (WBMT) and Global Burden of Disease Study

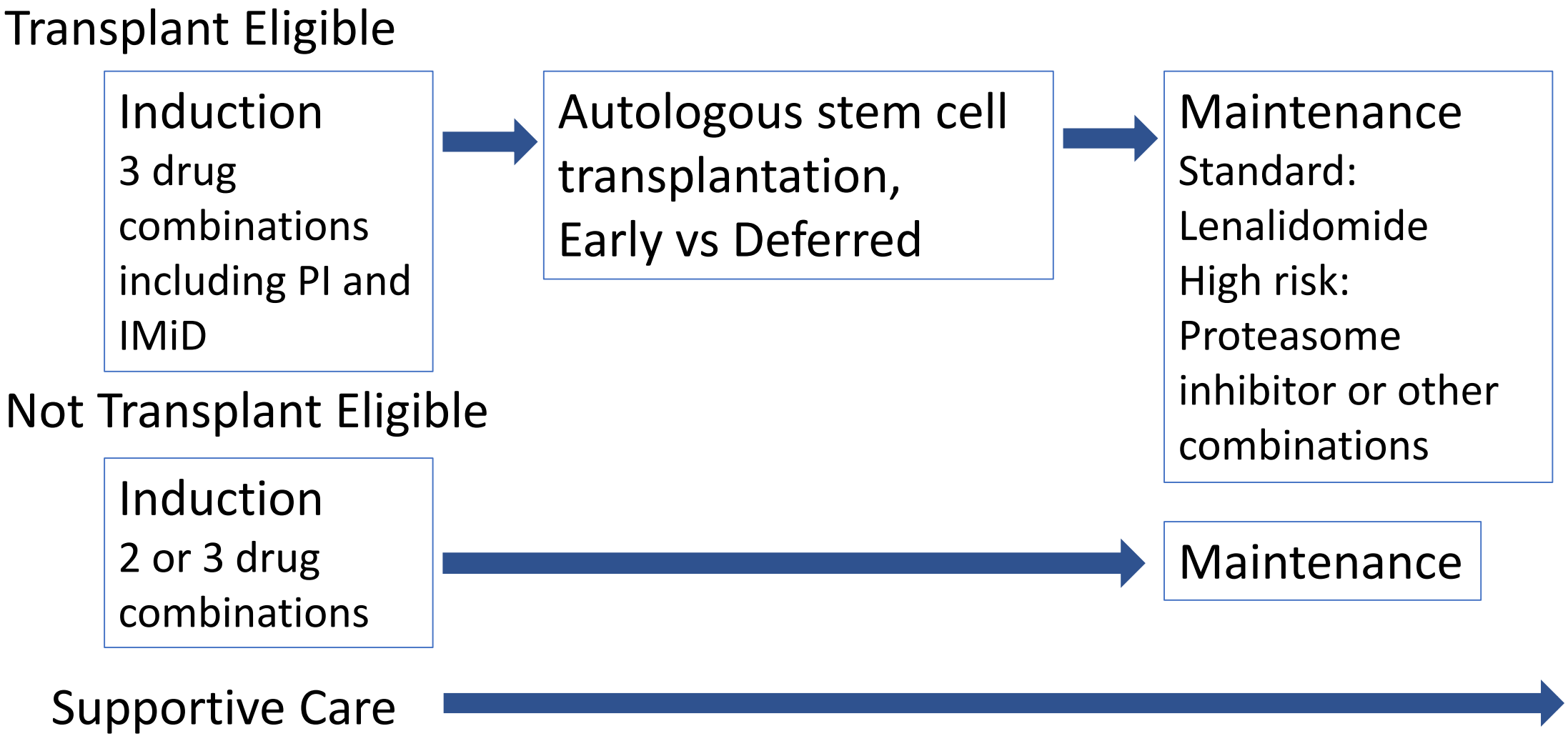
Andrew J Cowan, Helen Baldomero, Yoshiko Atsuta, Joseph Mikhael, Mahmoud Aljurf, Adriana Seber, Hildegard Greinix, Mickey Koh, Nina Worel, Edward N. Libby, Marcelo Pasquini, Sebastian Galeano, Wael Saber, Minako Iida, Gregorio Jaimovich, Juliana Martinez Rolon; Yoshihisa Kodera; Malek Benakli; Bazuaye G. Nosa; Alaa Elhaddad, Jeff Szer, Jakob Passweg, Nicolaus Kroeger, Daniel Weisdorf, Dietger Niederwieser

FRED HUTCH

WBMT
WWW.WBMT.ORG

UNIVERSITY of WASHINGTON

What are the current standards of care for treatment of multiple myeloma?

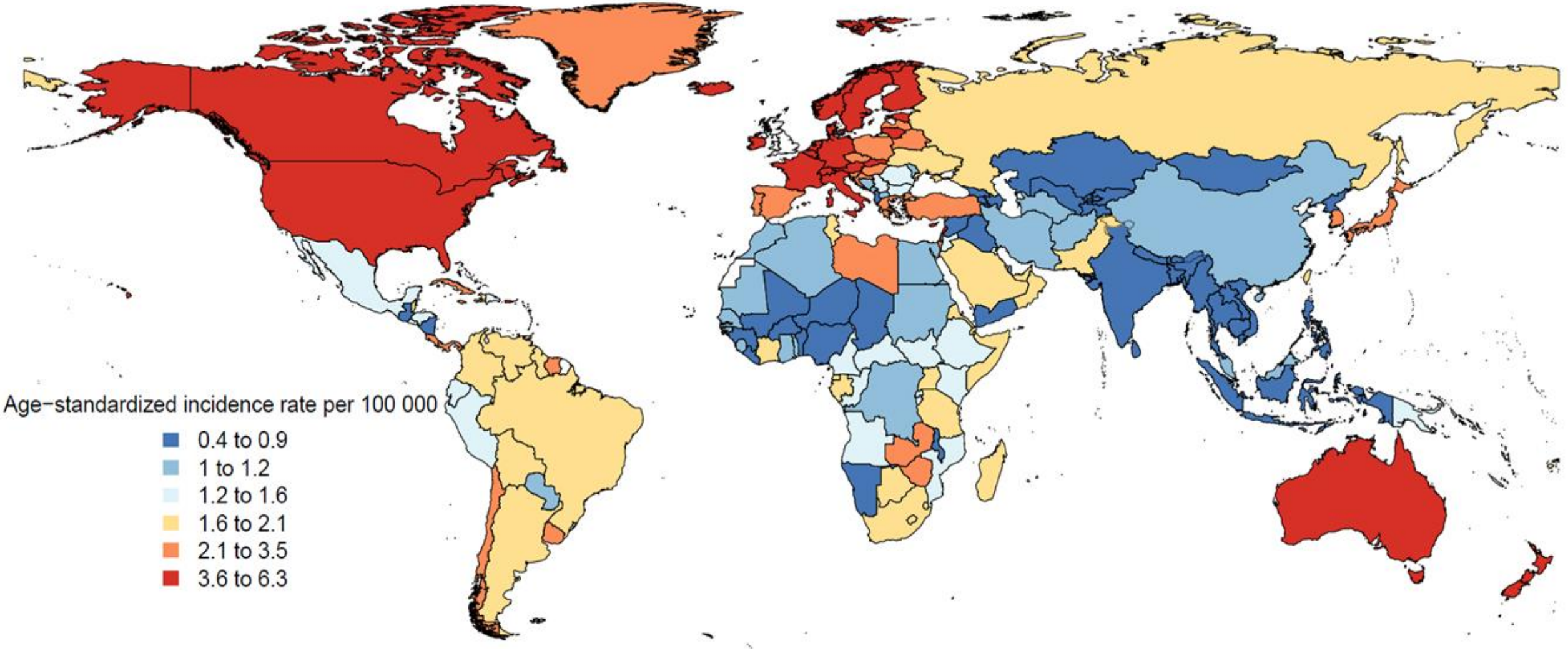


Autologous Stem Cell Transplantation for Multiple Myeloma

- Still considered a standard of care for eligible MM patients globally
- Most recent randomized trial demonstrated a benefit in PFS, but not OS[1]
- Acute toxicities are manageable
- In some countries, access to transplantation may be limited[2]

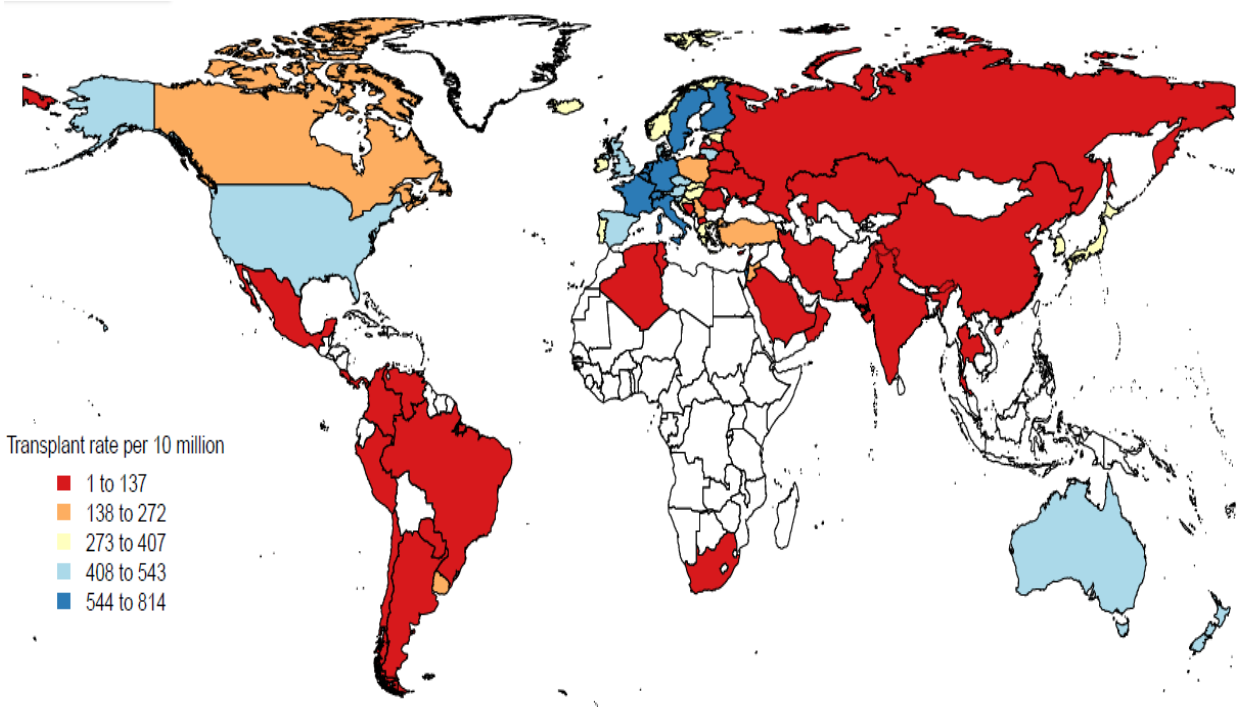
[1]Attal M et al, N Engl J Med, 376 (14), 1311-1320
[2]Cowan AJ, et al JAMA Oncol. 2018 Sep; 4(9): 1221–1227

Global Incidence Multiple Myeloma, 2016



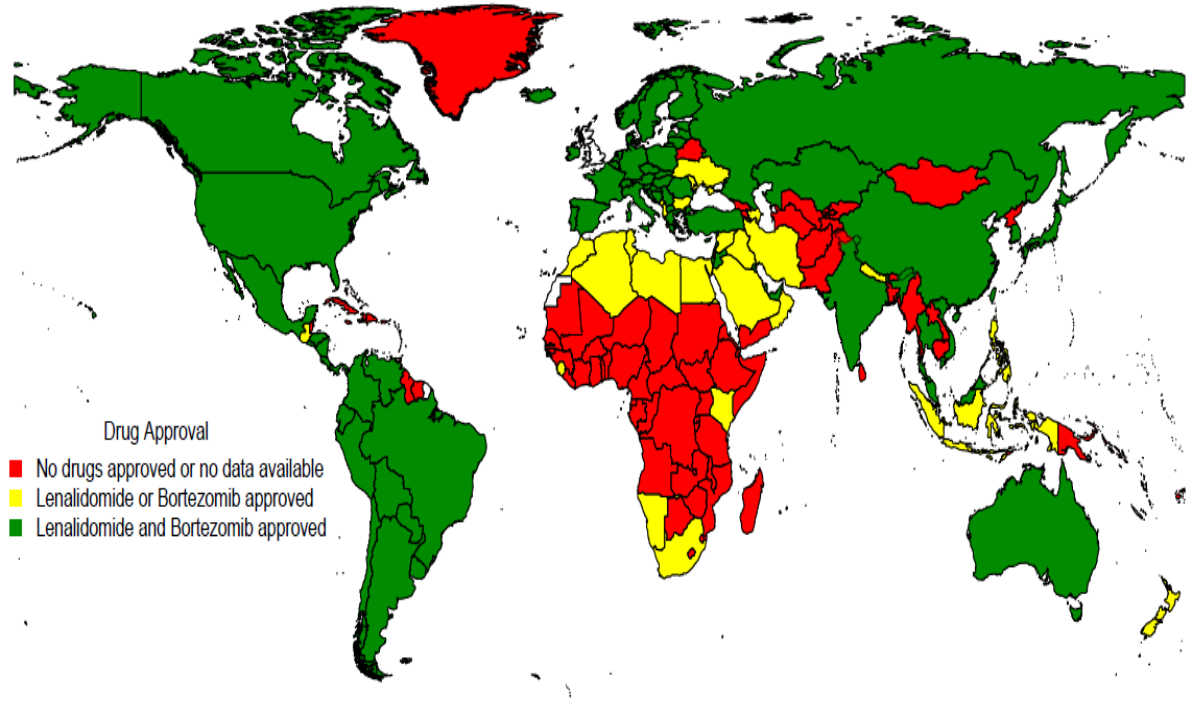
Cowan AJ, et al JAMA Oncol. 2018 Sep; 4(9): 1221–1227

Disparities in Access and Utilization of MM Therapy



Transplant Rates (Auto+Allo) per 10 Million[1]

Global Approval of Lenalidomide and Bortezomib, as of 2018[2]



[1]Cowan AJ, et al JAMA Oncol. 2018 Sep; 4(9): 1221–1227

[2]Gratwohl A, et al. Lancet Haematol. 2015 Mar;2(3):e91-100.

Key Aims

- Hypothesis: Hematopoietic cell transplantation (HCT) for multiple myeloma is widely utilized in high-income countries, but less available and utilized across low-middle income countries (LMIC).

- Specific Aims:

- 1. Determine region-specific rates and numbers of autologous stem cell transplantation performed for Multiple Myeloma

- 2. Describe region specific rates and numbers of allogeneic stem cell transplantation performed for multiple myeloma

Study Design – Data Sources

1.

WBMT: Retrospective Survey of all HSCT Teams Worldwide[1]

↓

Autologous and Allogeneic Transplants for PCD (2006) and MM (2007-2015)

2.

Global Burden of Disease Study[2]

↓

Multiple myeloma incidence 2006-2015

↙ All ages

↘ Age < 70

[1]Gratwohl A, et al. Lancet Haematol. 2015 Mar;2(3):e91-100.

[2]Global Burden of Disease Collaborative Network. Global Burden of Disease Study 2017 (GBD 2017) Results Seattle, United States: Institute for Health Metrics and Evaluation (IHME), 2018.

Analyses

- Number of **first** transplants for multiple myeloma per year from 2006 – 2015, separated by donor type (auto vs allo)

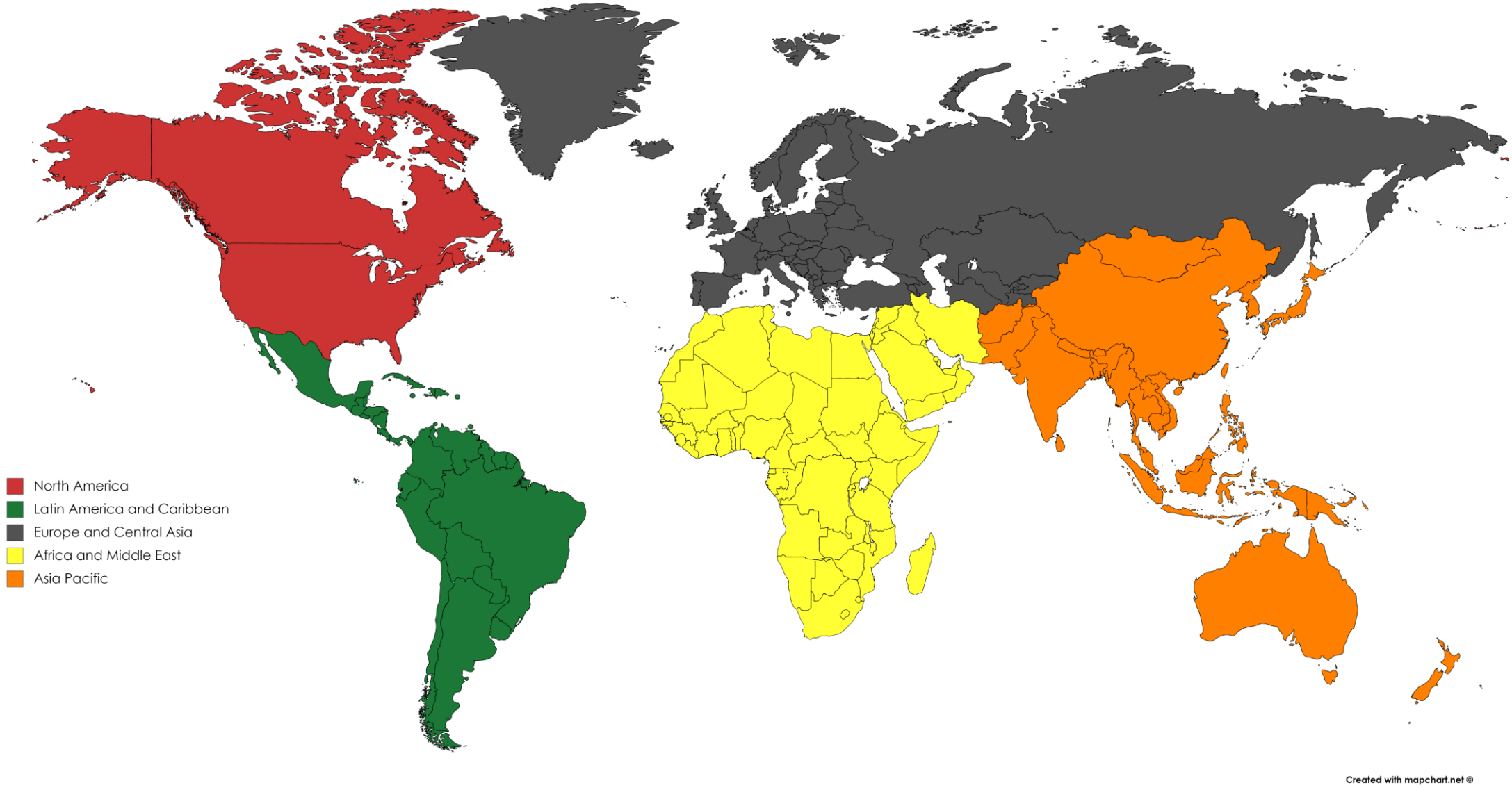
- Separated by world regions
  - N America
  - Latin America / Caribbean
  - Europe and Central Asia
  - Asia Pacific (including India)
  - Africa, Eastern Mediterranean

- Europe: first allo HCT included both tandem auto-allo and first allo HCT; all other regions reported first allo HCT only

- Transplant utilization determined by: **T / MM incidence x 100**
  - Transplants for MM in calendar year / gross annual MM incidence per region

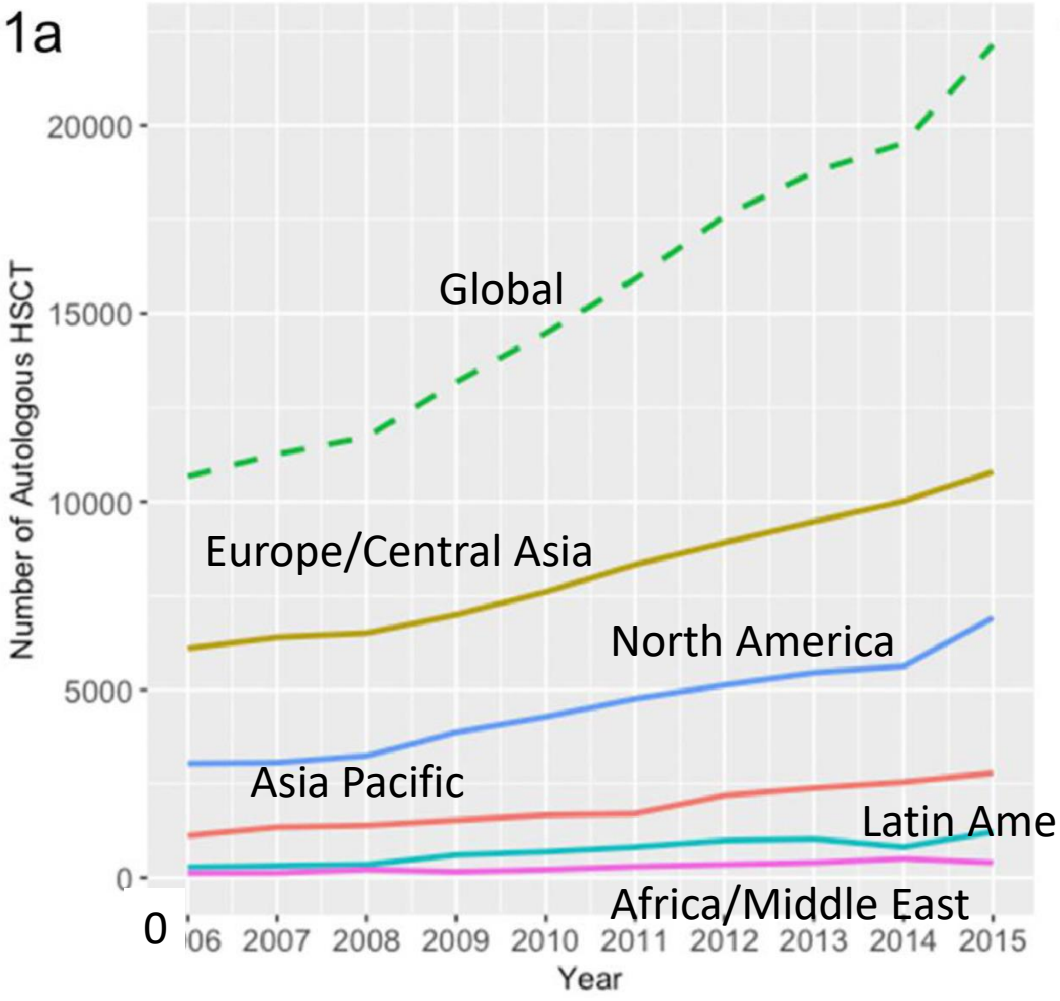
- Separate analyses for all ages, and age < 70

World Regions



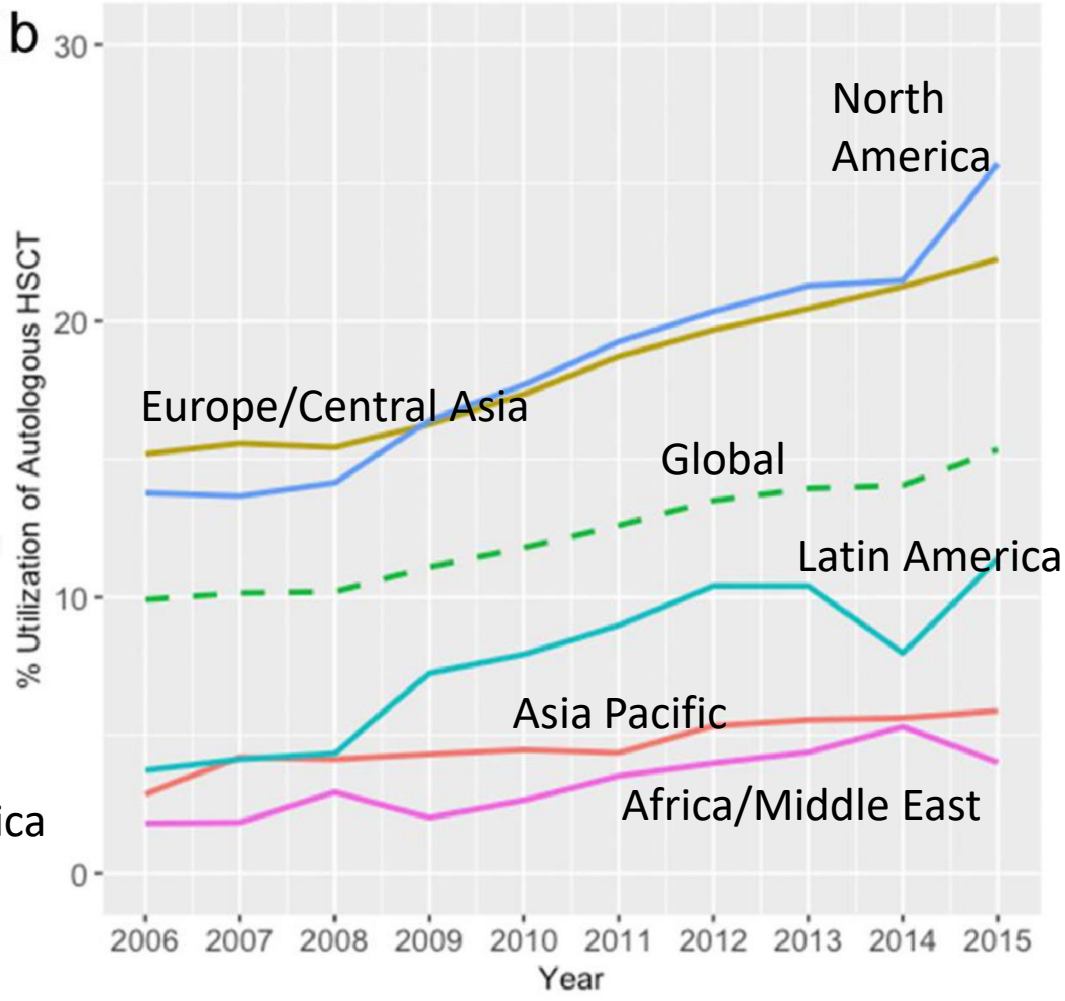
Autologous HCT for MM: Baseline Numbers and Global Utilization

Gross Numbers, Auto HSCT



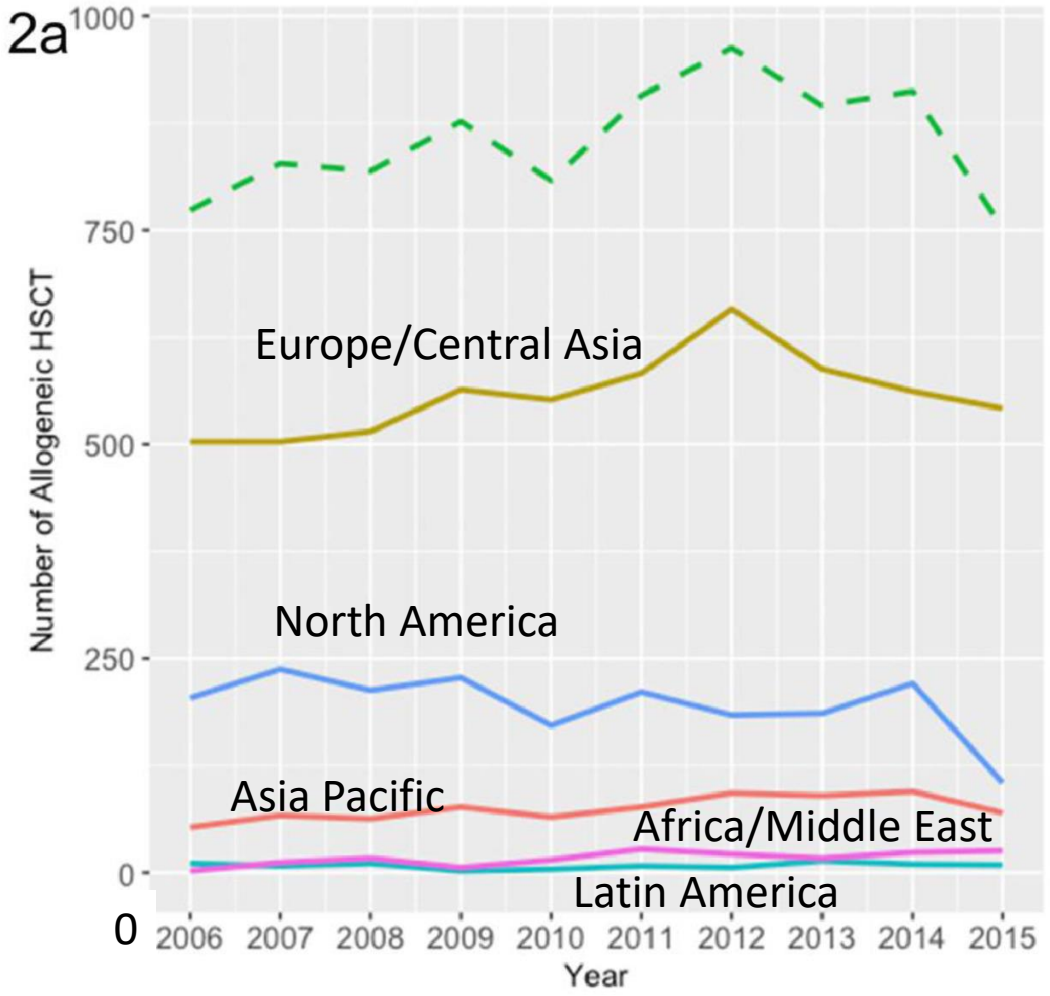
30%

Utilization, Auto HSCT

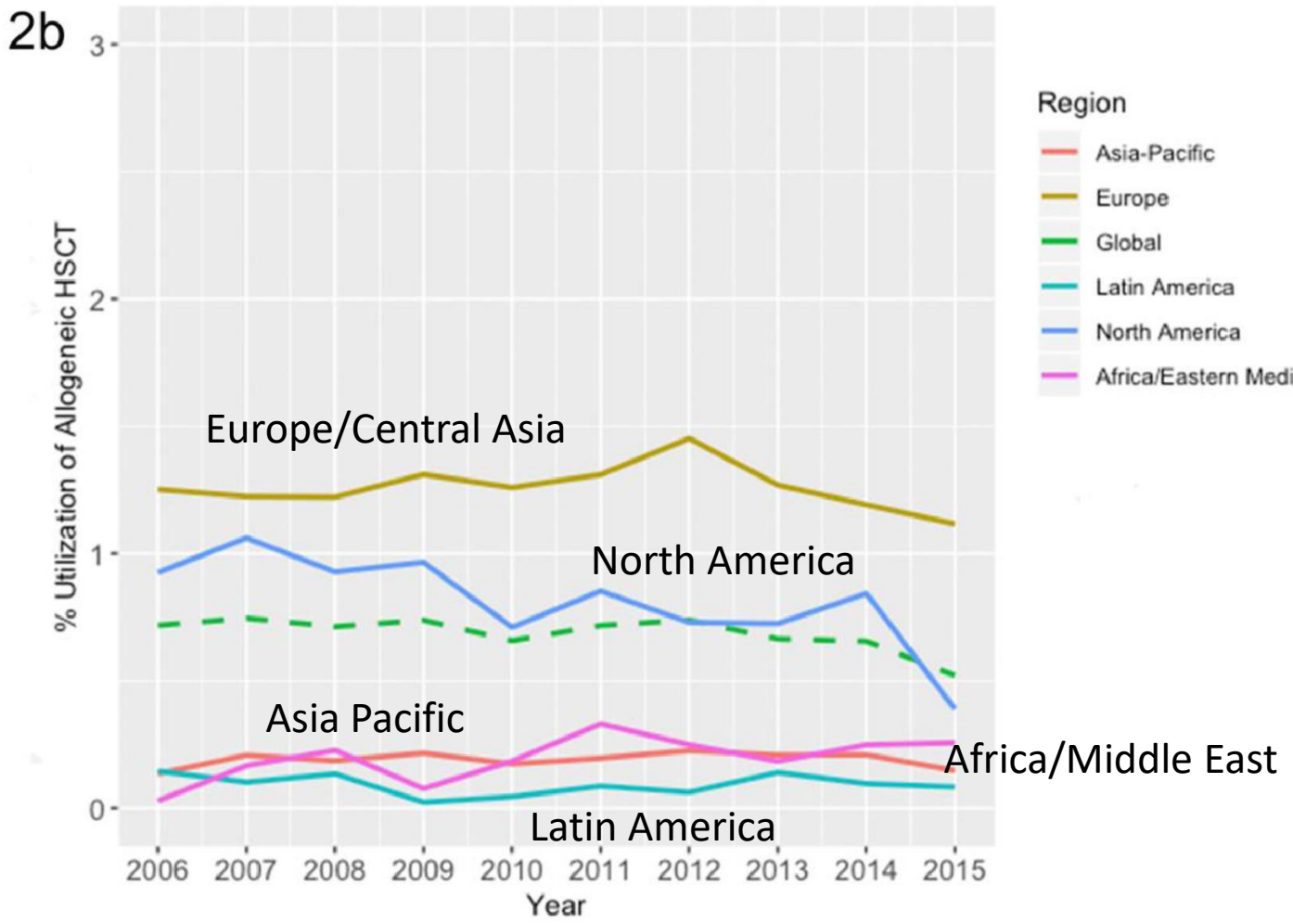


Allogeneic HCT for MM, Baseline Numbers and Global Utilization

Gross Numbers, Allo HSCT

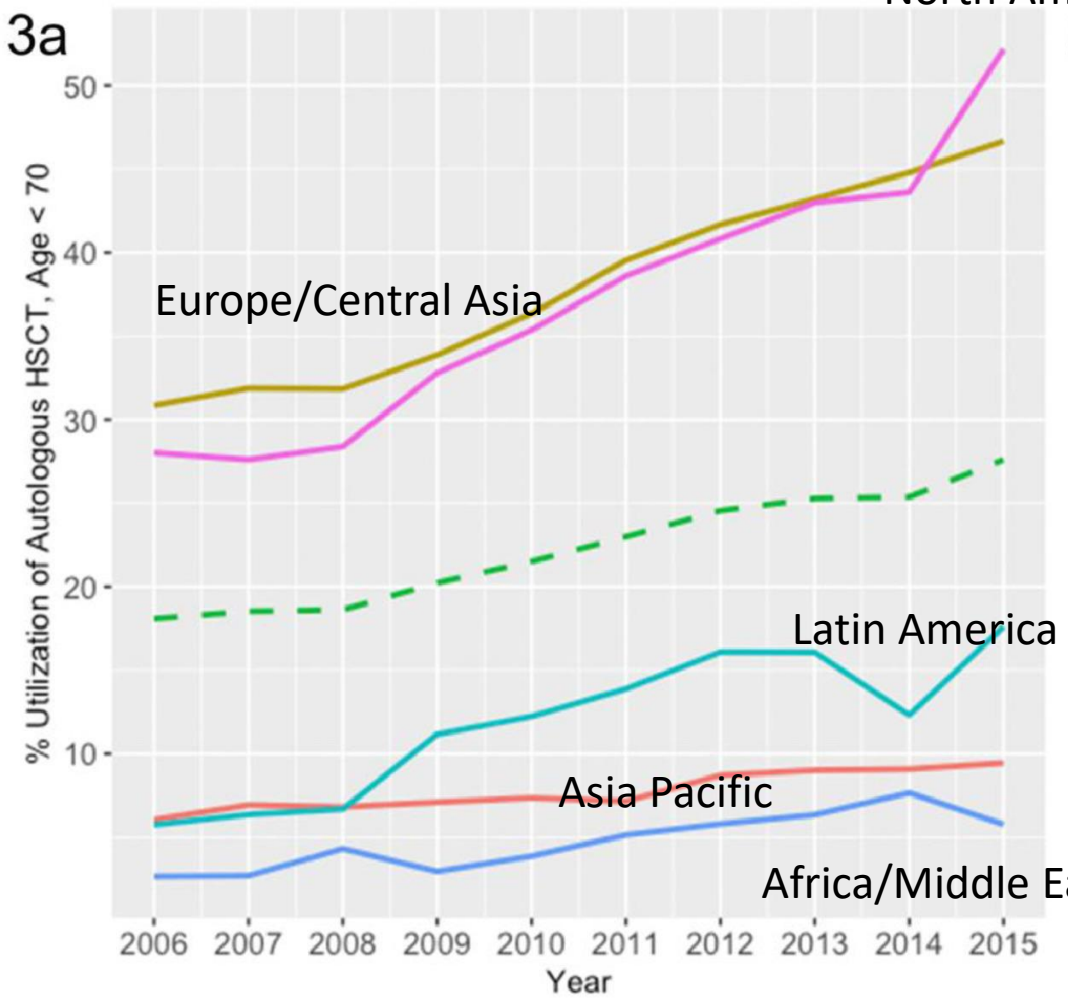


Utilization, Allo HSCT



Utilization of HCT, Age < 70

Autologous HSCT



North America

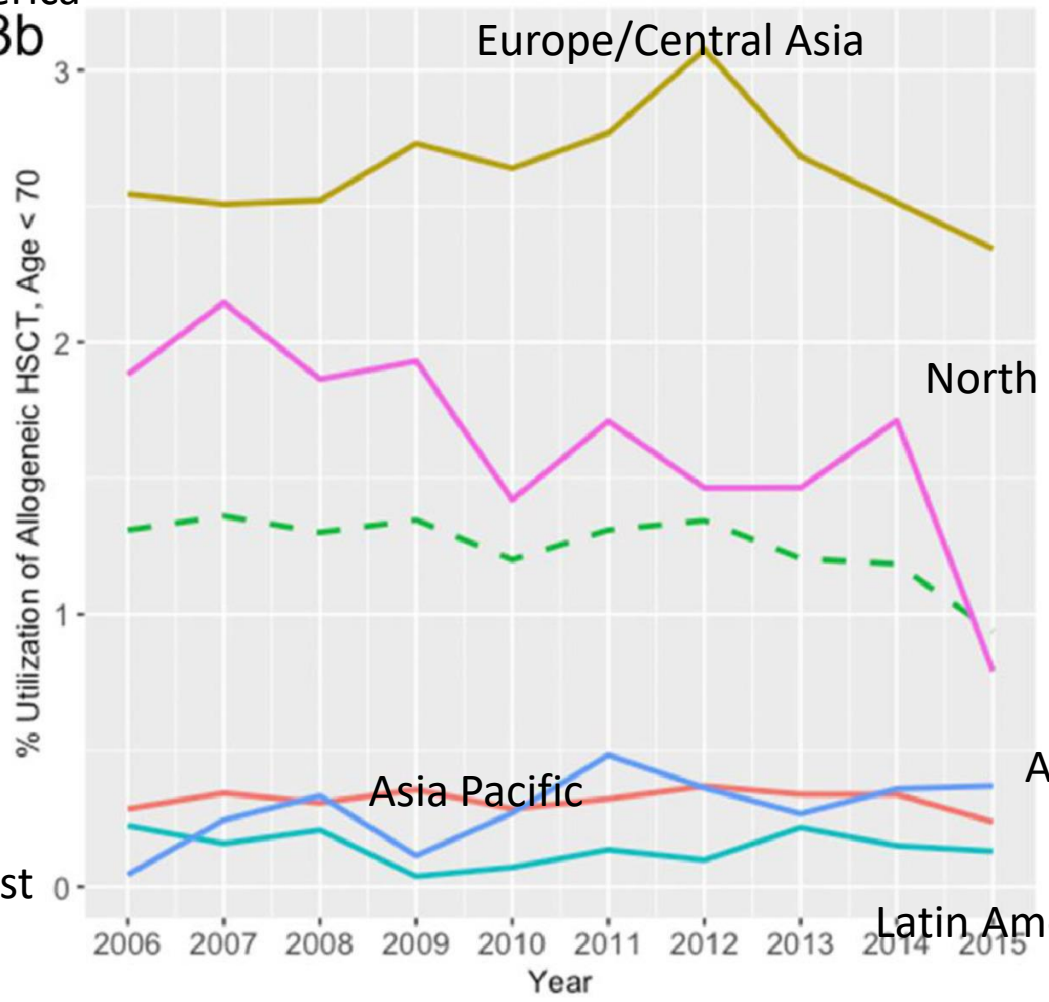
Europe/Central Asia

Latin America

Asia Pacific

Africa/Middle East

Allogeneic HSCT



Europe/Central Asia

North America

Africa/Middle East

Asia Pacific

Latin America

Conclusions

- Some world regions have dramatically increased utilization of ASCT over the 9 year period, particularly Latin America
- There is a disparity in transplant utilization amongst high income sociodemographic index regions compared with lower middle income (LMIC) regions
- Conflicting clinical trial data may have led to declines in first allogeneic HSCT utilization
- More work is needed to improve access to HCT for MM patients globally
- Important limitation: incidence data from GBD were used, and some data are likely limited due to under ascertainment or diagnostic limitations

Thank you and Acknowledgements

- WBMT
  - Dietger Niederwieser, MD
  - Helen Baldomero
  - Daniel Weisdorf, MD
  - Mahmoud Aljurf, MD
  - Hildegard Grenix, MD
  - Adriana Seber, MD
  - Jeff Szer, MD
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- Alaa Elhaddad MD
- Jakob Passweg, MD
- Nicolaus Kroeger, MD
- **Global Burden of Disease Study**
  - Christina Fitzmaurice MD MPH
- **Institute for Health Metrics and Evaluation**
- University of Washington
- Fred Hutchinson Cancer Research Center
- Seattle Cancer Care Alliance

Autologous Transplant in Multiple Myeloma Without Cryopreservation

Amado J Karduss U
Bone Marrow Transplantation Program
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Instituto de Cancerología Las Américas

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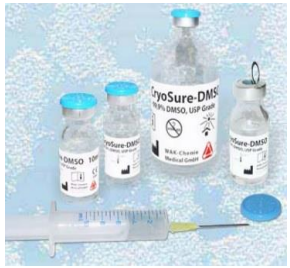
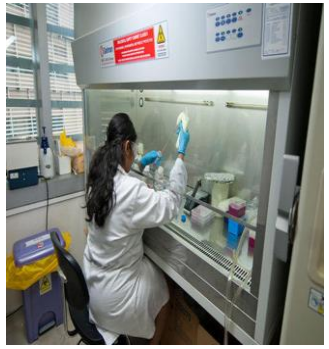
Disclosure

- I do not have any conflict of interest to declare

Hematopoietic Stem Cell Storage

Cryopreservation – disavantages





- Expensive
- Time Consuming
- Needs lots of resources
- Labor intensive
- DMSO Potentially dangerous

Hematopoietic Stem Cell Storage

Refrigeration Blood Bank Freezer

1. HSC storage at 4°C, for 6 days, keeps enough clonogenic capacity to restore hematopoises after myeloablative chemotherapy

1. This interval, 6 days, allow for the use of the most common conditioning for trasplanting myeloma, but, also lymphoma

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Lab Data

Ann Hematol (1996) 72:303–306

ORIGINAL ARTICLE

G. Hechler · R. Weide · J. Heymanns ·
H. Köppler · K. Havemann

Storage of noncryopreserved periphered blood stem cells for transplantation

Samples from fourteen patients who underwent APBSCT were stored at 4ºC for 8 days -In vitro analysis

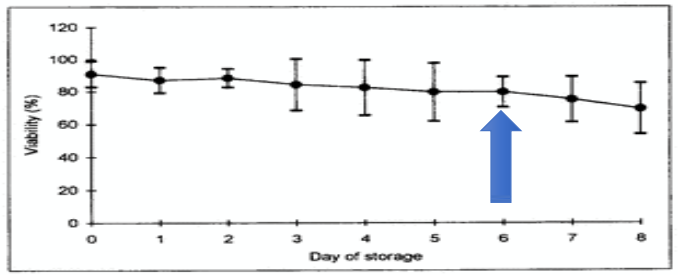


Fig. 1 Change of viability of nucleated cells over a storage period of 8 days using the trypan-blue exclusion test

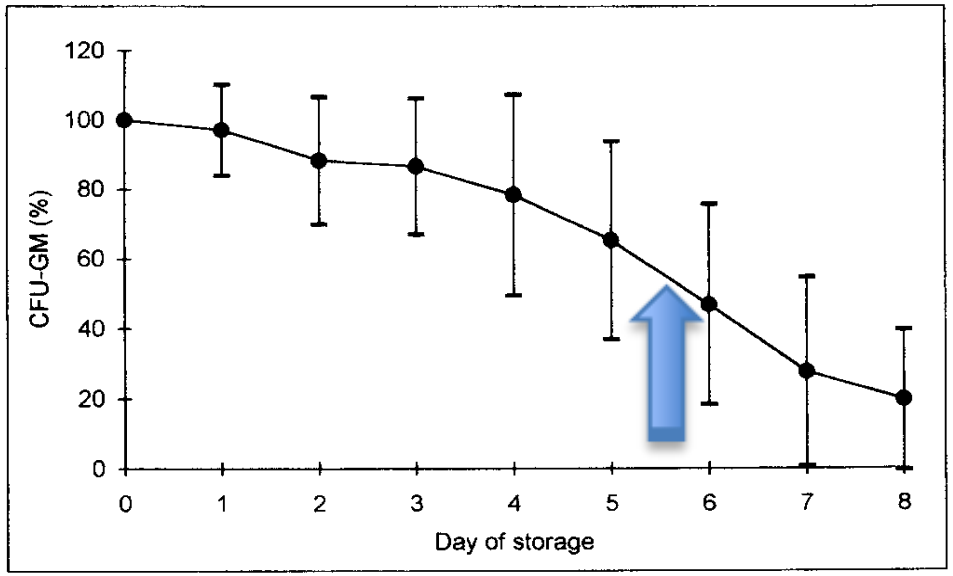


Fig. 2 Change of CFU-GM during the period of storage

Viability at 6th day: 80%

Clonogenic capacity at 5^{th} -6^{th} day: 50%

Hematologic Reconstitution Following High-Dose and Supralethal Chemoradiotherapy Using Stored, Noncryopreserved Autologous Hematopoietic Stem Cells

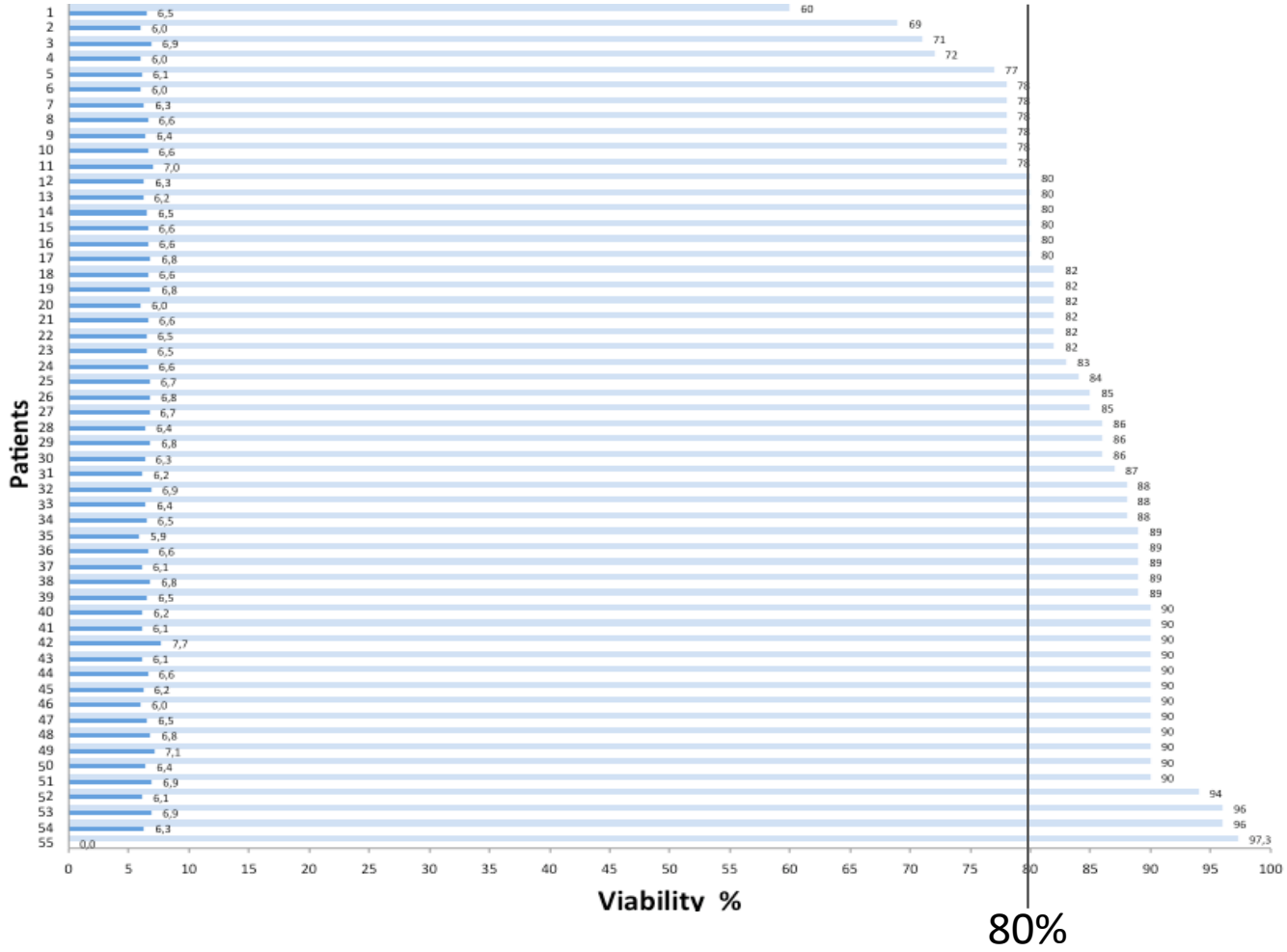
F. Cuellar-Ambrosi, U.A. Karduss, W.R. Gómez, M.C. Mondragón, M. Velasquez-Lopera, and S. Calle

Transplantation Proceedings, 36, 1704–1705 (2004)

- 47 patients - hematological malignancies - APBST
- APBSC kept **at 4ºC for 6 days**
- 17 patients: determination of CFU-GM at collection and 6th day
- CFU-GM at collection ……X:262x10(4)/kg
- CFU-GM recovery at preinfusion, 6th day……X:136x10(4)/kg **(50%)**
- Viability (trypan blue)……80%

Engraftment of patients alive after day +30…….100%
Neutrophyl engraftment …….. D+11(9-15)
Platelets engraftment …….. D+16(11-44)

Viability after 6 days of refrigeration - 55 patients



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Recovery of CFU GM and Viability After Thawing of Cryopreserved PBSC

Table 1. Cryopreservation Cell Concentrations and Cell Recoveries After Thawing

	Mean ± SD	Range
Cryopreserved*		
Nucleated cell count (× 10^{10})	4.8 ± 3.4	0.6-14.9
Volume frozen (mL)	127 ± 45	34-300
Nucleated cell concentration (× 10^8/mL)	3.7 ± 1.9	0.4-8.0
Platelet concentration (× 10^9/mL)	2.9 ± 2.1	0.4-10.9
Hematocrit (%)	12.9 ± 7.2	2.8-44.7
Proportion mononuclear cells (%)	52.9 ± 27.2	10.5-100.0
Proportion viable cells (%)	97.9 ± 1.4	91.2-99.2
No. viable CD34+ cells (× 10^7)	9.3 ± 8.1	0.2-28.6
No. CFU-GM (× 10^7)	1.2 ± 1.2	0.0-7.2
No. BFU-E (× 10^7)	2.6 ± 2.3	0.2-28.6
Thawed*		
Recovery of nucleated cells (%)	75.4 ± 13.0	43.2-102.8
Proportion viable cells (%)		
All cells	63.6 ± 15.2	31.2-85.0
Mononuclear cells	84.4 ± 5.5	73.8-95.2
Recovery of viable CD34+ cells (%)	71.4 ± 51.9	8.9-226.5
Recovery of CFU-GM (%)	45.3 ± 45.9	0.0-217.8
Recovery of BFU-E (%)	48.8 ± 33.9	0.0-170.7

From the Clinical Research Division, Fred Hutchinson Cancer Center Blood, Vol 83, No 9 (May l), 1994 pp 2731-2736

TABLE 1. Comparison of the characteristics of PBSCs that were cryopreserved using two different protocols (Protocol A = 1 × 10^8 cells/mL [n = 280] and Protocol B = 2 × 10^8 cells/mL [n = 139])

Variable	Protocol	Mean	SD	Median	Range	p value*
Before cryopreservation						
Nucleated cells (×10^8)	A	360.7	202.6	309.6	8.7-1,049.1	<0.01
	B	515.8	216.4	480	150-1,527.2	
Viability (%)	A	99.5	1.10	100	90.5-100.0	<0.01
	B	98.9	1.43	99.4	88.7-100.0	
MNCs (%)	A	74.5	15.6	78	11-9	<0.01
	B	80	16.9	85	21-100	
CD34+ cells (×10^6)	A	274.9	334.4	168.4	5.8-3,577.5	0.04
	B	370.6	555.7	205.2	1.1-4,689.9	
CFU-GM cells (×10^4)	A	1,342.8	2272.6	668.7	2.7-21,635.7	0.24
	B	1,365	2453.3	672	22.2-23,752	
After cryopreservation						
Number of bags	A	5.0	2.6	4.0	1-20	<0.01
	B	3.7	1.6	4.0	1-11	
Volume of bags from apheresis (mL)	A	348.8	190	300	60-975	<0.01
	B	259.8	107.6	240	75-745	
Viability (%)	A	86.4	8.2	87.6	59-100	0.53
	B	85.3	8.8	87.3	47.1-98.6	
CFU-GM cells (×10^4)	A	596.9	1097.3	252.0	1.5-11,572.9	<0.01
	B	869.4	1503.1	372.6	14.1-12,260	
Viability recovery	A	86.9	8.2	88.1	59.1-100	0.92
	B	86.5	8.8	87.9	47.5-100	
CFU-GM recovery	A	45.9	32.0	41.2	1.2-254.5	<0.01
	B	66.7	44.0	57.3	4.0-229.4	

* Mann-Whitney test.

TRANSFUSION 2010;50:2402-2412.

Clinical Results

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Hematopoietic Autologous Stem Cell Transplant Without Cryopreservation. LATAM experience in patients with Myeloma and Lymphoma

- ✓ Submyeloablative chemotherapy support with stem cells in whole blood without cryopreservation. Procc. Am. Socc.Clin. Oncol. 15: 343, 1996
- ✓ Non-Cryopreserved Peripheral Blood Stem Cells Autotransplants for Hematological Malignancies Can Be Performed Entirely on an Outpatient Basis. American Journal of Hematology 58:161–164 (1998)
- ✓ Non Cryopreserved peripheral stem cells stimulated with filgrastim: A simple, efficient and inexpensive procedure for autotransplantation. Results in 15 cases. Blood 1999;94 sppl #1: 337b. Abstract 4730
- ✓ Hematologic reconstitution following high-dose and supralethal chemoradiotherapy using stored, non cryopreserved autologous hematopoietic stem cells. Transplant Proc 2004; 36: 1704–1705.
- ✓ Results of an autologous noncryopreserved, unmanipulated peripheral blood hematopoietic stem cell transplant program: a single-institution, 10-year experience. Acta Haematol 2003; 110: 179–
- ✓ A simplified method for stem cell autografting in multiple myeloma: a single institution experience. Bone Marrow Transplantation (2009) 00, 1–5
- ✓ Autologous Peripheral Blood Stem Cell Transplant Using BEAM or CBV without Cryopreservation. 82 procedures in patients with relapsed Hodgkin and non- Hodgkin´s lymphoma. Biology of Blood and Marrow Transplantation Vol. 20, Number 2, Supplement 1, Page S113. 2014

review

Annals of Oncology 18: 623–632, 2007
doi:10.1093/annonc/mdm069
Published online 12 March 2007

Feasibility and safety of autotransplants with noncryopreserved marrow or peripheral blood stem cells: a systematic review

L. Wannesson[1]*, T. Panzarella[2], J. Mikhael[1] & A. Keating[1]

	Author	Year	Country of origin	Source	Peer-reviewed source (Y/N)	Type of article
1	Kingston et al. [38]	1984	UK	British Journal of Haematology	Y	Retrospective review of a multicentric case series
2	Carella et al. [42]	1985	Italy	European Journal of Cancer and Clinical Oncology	Y	Retrospective review of a multicentric case series
3	Russell et al. [41]	1989	Canada/UK	Bone Marrow Transplantation	Y	Phase II, multicentric
4	Ahmed et al. [28]	1991	USA	Acta Haematologica	Y	Retrospective, single-center cohort comparison
5	Carey et al. [37]	1991	UK	Blood	Y	Retrospective review of a single-center case series
6	Köppler et al. [43]	1991	Germany	Bone Marrow Transplantation	Y	Phase II, single center
7	Sierra et al. [40]	1993	Spain	Annals of Hematology	Y	Retrospective, multicentric cohort comparison
8	Taylor et al. [44]	1993	UK	British Journal of Cancer	Y	Retrospective review of a single-center case series
9	Ager et al. [45]	1995	UK	Bone Marrow Transplantation	Y	Retrospective review of a single-center case series published as correspondence
10	Jones et al. [39]	1996	UK	European Journal of Cancer	Y	Retrospective review of a single-center case series
11	Papadimitriou et al. [29]	1999	Greece	Transplantation Proceedings	Y	Retrospective review of a single-center case series
12	Holowiecki et al. [36]	2002	Poland	Transplantation Proceedings	Y	Retrospective review of a single-center case series
13	Holowiecki et al. [46]	2002	Poland	Blood, abstract from 2002 ASH meeting	Y	Retrospective review of a single-center case series
14	Ruiz-Argüelles et al. [33]	2003	Mexico	Acta Haematologica	Y	Retrospective review of a single-center case series
15	Cuellar-Ambrosi et al. [32]	2004	Colombia	Journal of Clinical Apheresis	Y	Retrospective review of a single-center case series
16	Mabed and Al-Kgodary [47]	2006	Egypt	Bone Marrow Transplantation	Y	Retrospective review of a single-center case series

- 16 studies, **560** patients.
- Engraftment rate 99.5%
- Heterogeneous diseases - Heterogeneous preparative regimens
- Heterogeneous time of storage

Recent Information
Homogeneous Diseases
Homogeneous Conditioning

Freezing the graft is not necessary for autotransplants for plasma cell myeloma and lymphomas

Amado Kardduss-Urueta[1] · Robert Peter Gale[2] · César H. Gutierrez-Aguirre[3] · Miguel Angel Herrera-Rojas[3] · Iván Murrieta-Álvarez[4,5] · Rosendo Perez-Fontalvo[1] · Guillermo J. Ruiz-Delgado[4,5] · Giovanni Ruiz-Rojas[1] · Gregorio Jaimovich[6] · Leonardo Feldman[7] · Nancy Labastida-Mercado[4] · Alicia Endara[7] · Martín Castro[6] · Samantha Galindo-Becerra[4] · María Angélica Cardona-Molina[1] · David Gomez-Almaguer[3] · Guillermo J. Ruiz-Argüelles[4,5]

Retrospective analysis

Five centers; Mexico: 2, Argentina: 2, Colombia: 1

Consecutive patients with myeloma or lymphoma
Transplanted without cryopreservation

2002 to 2016

359 patients

Bone Marrow Transplantation (2018) 53:457–460

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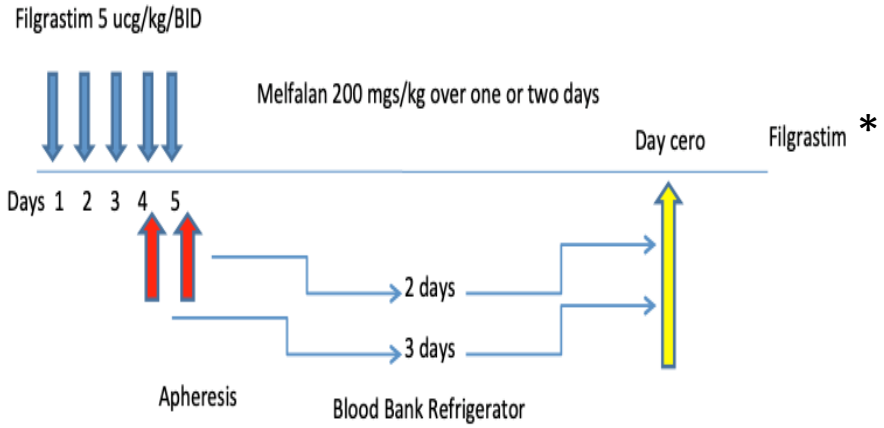
Freezing the graft is not necessary for autotransplants for plasma cell myeloma and lymphomas

Amado Kardduss-Urueta[1] · Robert Peter Gale[2] · César H. Gutierrez-Aguirre[3] · Miguel Angel Herrera-Rojas[3] · Iván Murrieta-Álvarez[4,5] · Rosendo Perez-Fontalvo[1] · Guillermo J. Ruiz-Delgado[4,5] · Giovanni Ruiz-Rojas[1] · Gregorio Jaimovich[6] · Leonardo Feldman[7] · Nancy Labastida-Mercado[4] · Alicia Endara[7] · Martín Castro[6] · Samantha Galindo-Becerra[4] · María Angélica Cardona-Molina[1] · David Gomez-Almaguer[3] · Guillermo J. Ruiz-Argüelles[4,5]

Scheme – Myeloma



Myeloma

N: 216

Melphalan 200 mgs/m2: 211

Melphalan 140 mgs/m2: 05

CD34 collected: 3.6 millions/kg

Viability, trypan blue: 90 % (IQR 7%)

*One center, during one period, did not use filgrastim after transplant

Bone Marrow Transplantation (2018) 53:457–460

Freezing the graft is not necessary for autotransplants for plasma cell myeloma and lymphomas

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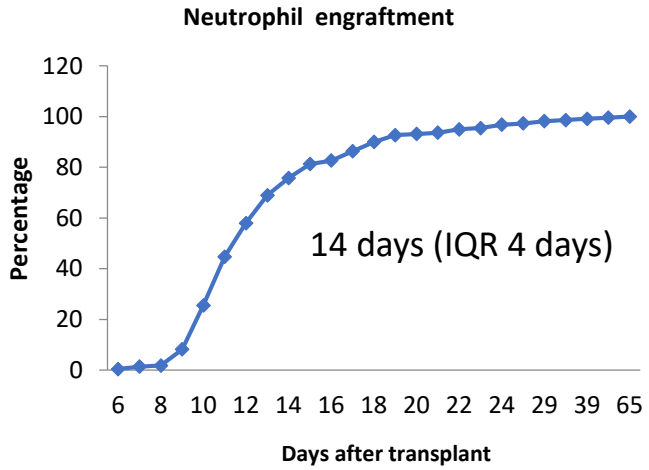
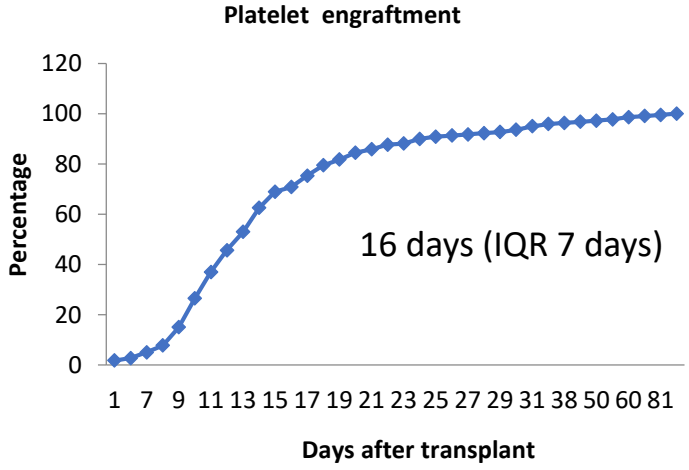
N: 216

Hematopoiesis recovery: 100%
Neutrophil 500 or more: 14 days (IQR 4 days)
Platelets 20,000 or more: 16 days (IQR 7 days)

TRM @ day + 100: 1.8%*
Overall survival at 5 years: 50%*





*Data not shown in the publication

Bone Marrow Transplantation (2018) 53:457–460

Use of Non-Cryopreserved Peripheral Blood Stem Cells Is Associated with Adequate Engraftment in Patients with Multiple Myeloma Undergoing an Autologous Transplant

Uday Kulkarni, Anup J. Devasia, Anu Korula, NA Fouzia, PN Nisham, Yasir J. Samoon, Kavitha M. Lakshmi, Aby Abraham, Alok Srivastava, Vikram Mathews, Biju George*

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Data on Engraftment from Studies Using Cryopreserved Grafts versus Those Using Non-Cryopreserved Grafts in Multiple Myeloma

	Non-cryopreserved grafts				
	Present study	Kayal et al. [2]	Naithani et al. [9]	Kardduss-Urueta et al. [4]	Sarmiento et al. [18]
No. of patients	224	92	59	216	29
Mobilization strategy	G	G	G, n = 38 C, n = 8 P + G, n = 8 C + P, n = 3 Chemo, n = 2	G, n = 189 C, n = 16 P, n = 11	G ± P
Median CD34 dose, $\times 10^6$/kg	4.87	2.9	2.8	3.6	5.1
Graft failure	1/224	0/92	1/59	0/216	0/29
Median day of neutrophil engraftment (range)	12 (9-22)	10 (8-27)	11 (9-14)	14 (9-39)	8 (8-11)
Median day of platelet engraftment (range)	17 (10-44)	14 (9-38)	11 (9-32)	16 (7-83)	10 (8-11)
TRM, %	3.1	3.2	1.7	1.4	0

G indicates G-CSF; C, cyclophosphamide; P, plerixafor; Chemo, chemotherapy; NR, not reported; TRM, transplant-related mortality.

* Platelet count above 50×10^9/L.

N:	620
CD34	3.8 Mill/kg
Graft Failure	2 /620 (0.32%)
X neutro recov	11 days
X platel recov	13.6 days
TRM %	0- 3,2%

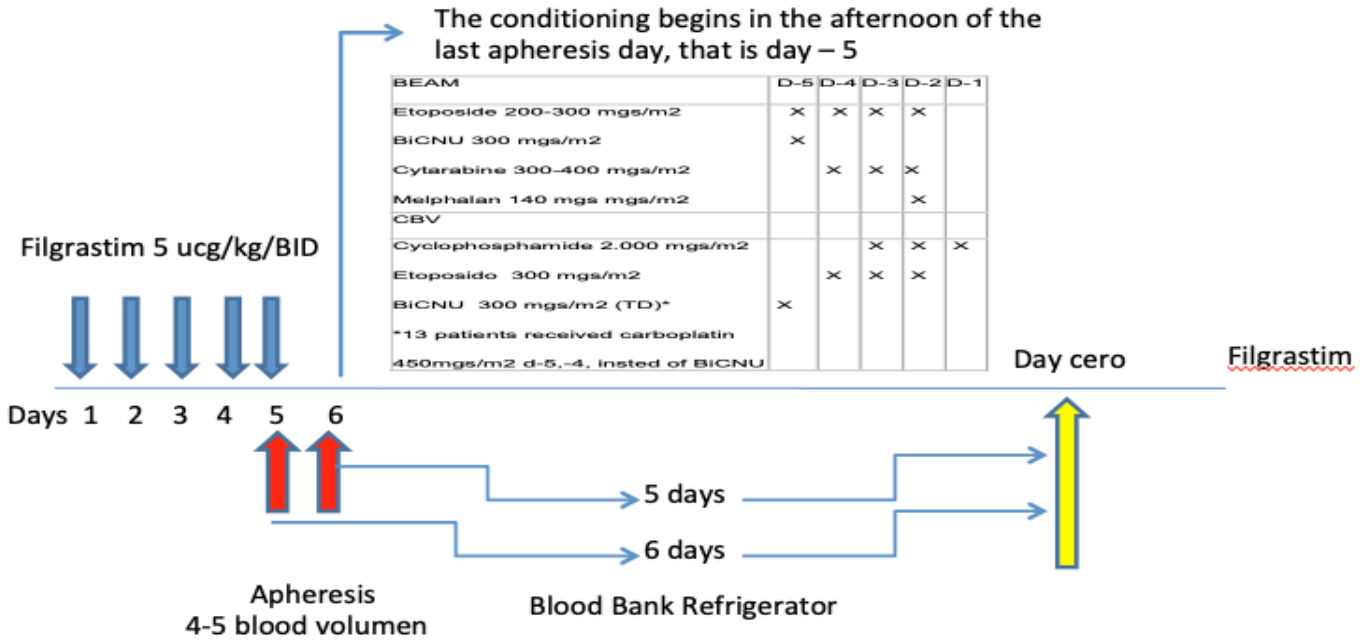
U. Kulkarni et al. / Biol Blood Marrow Transplant 24 (2018) e31e35

Myeloma- Conclusion

Data from more than 600 patients support the use of refrigerated PBSC for transplanting myeloma.

It is safe and produces the same results that what are obtained with the use of cryopreserved cells

Is possible to perform APBS transplant in lymphoma without cryopreservation



BEAM	D-5	D-4	D-3	D-2	D-1
Etoposide 200-300 mgs/m2	X	X	X	X	
BiCNU 300 mgs/m2	X				
Cytarabine 300-400 mgs/m2		X	X	X	
Melphalan 140 mgs mgs/m2				X	
CBV					
Cyclophosphamide 2.000 mgs/m2			X	X	X
Etoposido 300 mgs/m2		X	X	X	
BiCNU 300 mgs/m2 (TD)*	X				
*13 patients received carboplatin 450mgs/m2 d-5,-4, insted of BiCNU					

- With small modifications, both regimens, BEAM and CBV, can be administered in full dose, split in 5 days, without increasing the toxicity

- The stem cell can be stored for 6 days at 4oC with preservation of enough clonogenic capacity to restore the hematopoiesis

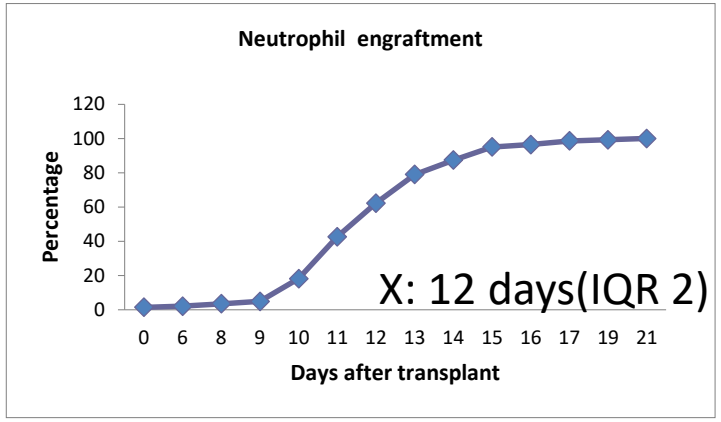
Instituto de Cancerología Las Américas
auna

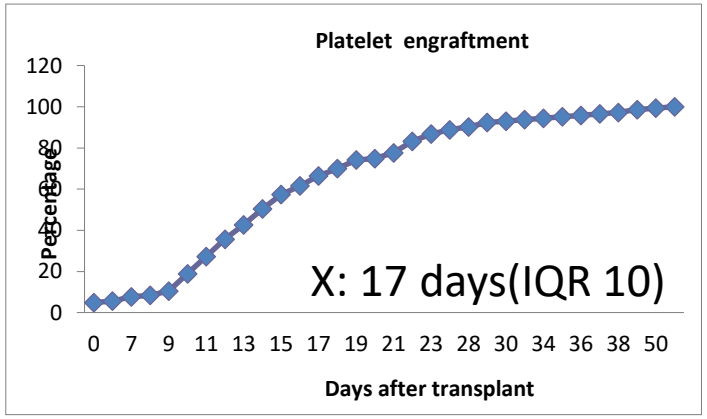
Freezing the graft is not necessary for autotransplants for plasma cell myeloma and lymphomas

Bone Marrow Transplantation (2018) 53:457–460

Non Hodgkin and Hodgkin Lymphoma patients: 140
Hematological recovery : 99%, 139 out of 140 evaluable
Neutrophil 500 or more: 12 days (IQR 2 days))
Platelets 20,000 or more: 17 days (IQR 10 days)

TRM @ day + 100: 2.8%
Overall survival at 5 years
Hodgkin…….59%
NHL……..42%





There was no significant correlation between days of refrigeration (3 vs. 6) and interval to recovery neutrophils (*r* : -0.054, p: 0.52), or platelets (*r* : 0116; p:0.14)

Hematopoietic Autologous Stem Cell Transplant Without Cryopreservation

Conclusion:

Autologous transplant with PBSC storage at 4ºC,
is feasible, safe, and produces a reliable engraftment

Advantages:

Simplicity
Low cost
<u>It can be used with the more common conditioning regimens</u>
Avoid the DMSO toxicity
It can be used in areas with limited resources
It can be the first step to implement a PBSC transplant program

Disadvantages

It requires an efficient coordination of stem cell mobilization, apheresis, administration of conditioning, and re-infusion of cells
It cannot be used with conditioning that lasts more than 6 days, neither for more than one transplant
The harvest would be lost if the transplant is stopped for some reason

Acknowledgment

Guillermo Ruiz-Arguelles
Puebla- México

David Gómez-Almaguer
Monterrey- México

Francisco Cuéllar Ambrosi
Medellín- Colombia

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“Latest data on treatment approaches for transplant-eligible patients in frontline myeloma”

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Disclosures (relevant to this talk)

I have the following relationships to disclose:

1. Employment/leadership position/advisory role: *No*
2. Stock ownership or options: No
3. Patent royalties/licensing fees: No
4. Honoraria: *Adaptive Biotechnologies, Amgen, BMS, Celgene, Janssen, Takeda, Novartis, Sanofi*
5. Manuscript fees: No
6. Research funding: *Celgene, Janssen, Sanofi*
7. Subsidies or donations: No
8. Endowed departments by commercial entities: No
9. Gifts and others: No
10. Off-label use: This presentation may include discussion of off-label use of some drugs.

Frontline Therapy
Transplant-eligible patients

Induction: 3-drug regimens

VTD

VCD

VRD

PAD

↓

200 mg/m^2 Melphalan followed by ASCT

↓

Maintenance

Lenalidomide

PAD, bortezomib, doxorubicin, dexamethasone; VTC, bortezomib/cyclophosphamide, dexamethasone; VRD, bortezomib, lenalidomide, dexamethasone; VTD, bortezomib/thalidomide/dexamethasone

Moreau P, et al. Ann Oncol 2017;28(suppl_4):iv52-iv61

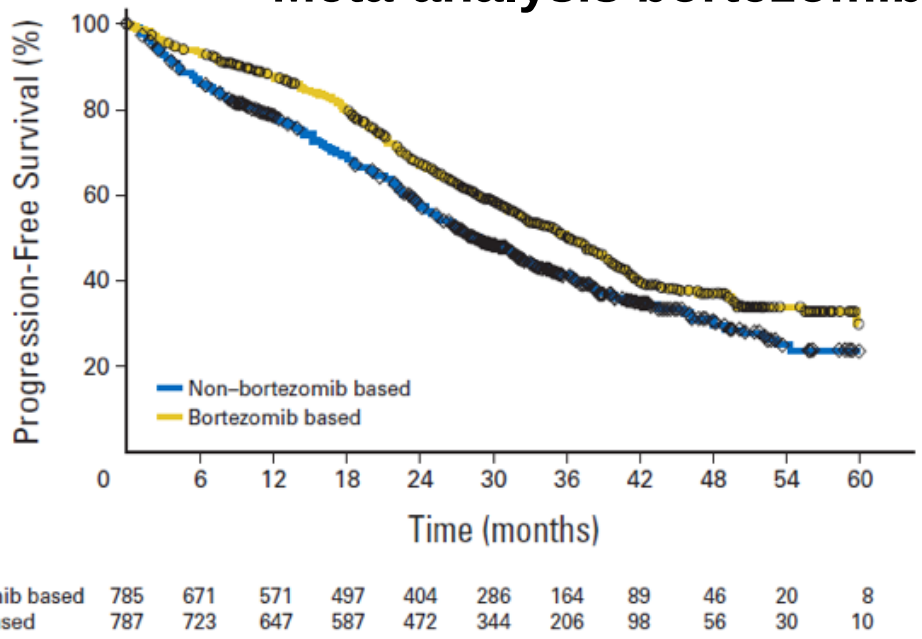
What we know today for transplant-eligible patients with MM: Induction

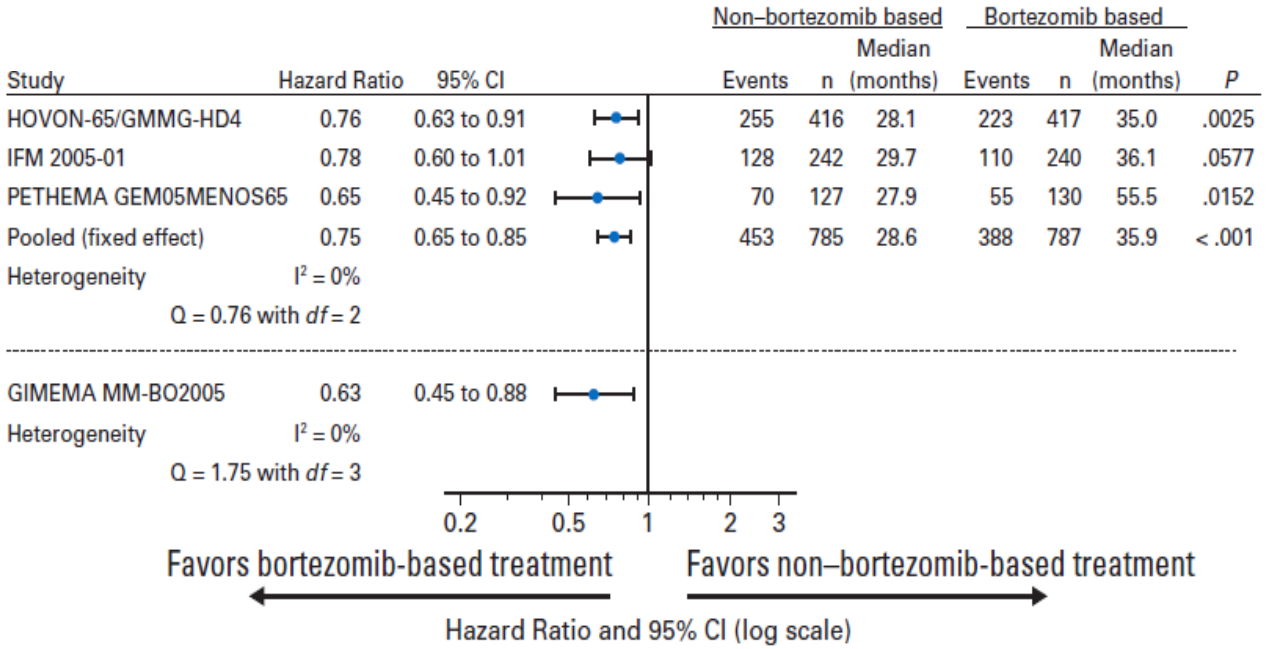
Induction therapy

ESMO Guidelines 2017[1]
3-drug VD-based combinations are the current standard of care for induction therapy
4–6 courses of induction are recommended prior to peripheral blood stem cell collection

VTD
VCD
VRD
PAD

Meta-analysis bortezomib-based induction vs non bortezomib[2]



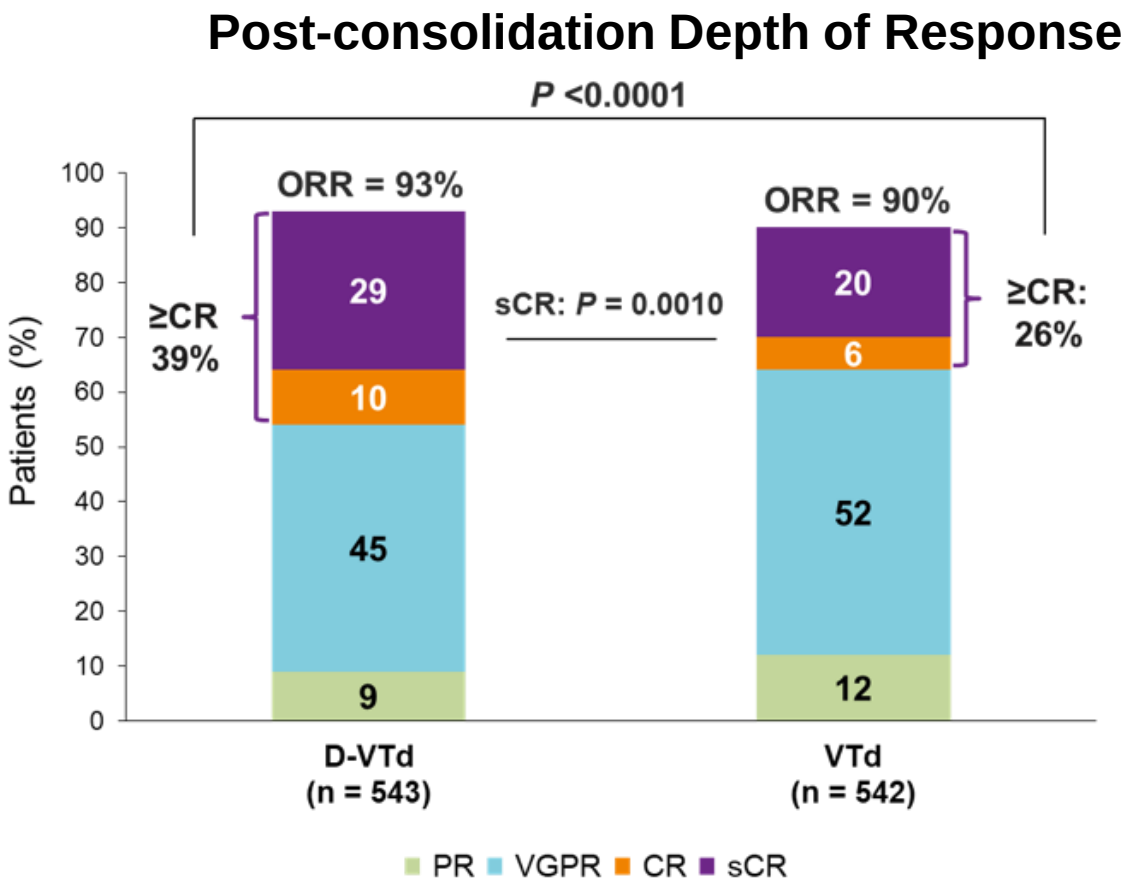


VCD, bortezomib-cyclophosphamide-dexamethasone; VRD, bortezomib-lenalidomide-dexamethasone; VTD, bortezomib-thalidomide-dexamethasone; PAD, bortezomib-doxorubicin-dexamethasone.

1. Moreau P, et al. Ann Oncol 2017;28(suppl_4):iv52-iv61;
2. Sonneveld P, et al. J Clin Oncol 2013;31:3279-3287.

New findings in transplant-eligible MM:
Daratumumab-VTD vs VTD

CASSIOPEIA phase 3 study: Daratumumab-VTD vs VTD (4 cycles induction and 2 cycles consolidation; maintenance – daratumumab vs observation)



- Median follow-up: 18.8 months
- Primary endpoint
  - Post-consolidation sCR
    - 29% D-VTd vs 20% VTd
    - Odds ratio, 1.60; 95% CI, 1.21-2.12; *P* = 0.0010
- sCR definition per IMWG
  - All required:
    - SIFE negative
    - UIFE negative
    - <5% plasma cells in the BM
    - Four-color flow negativity
    - Normal FLC ratio
    - Disappearance of all plasmacytomas
    - Confirmation at next visit required

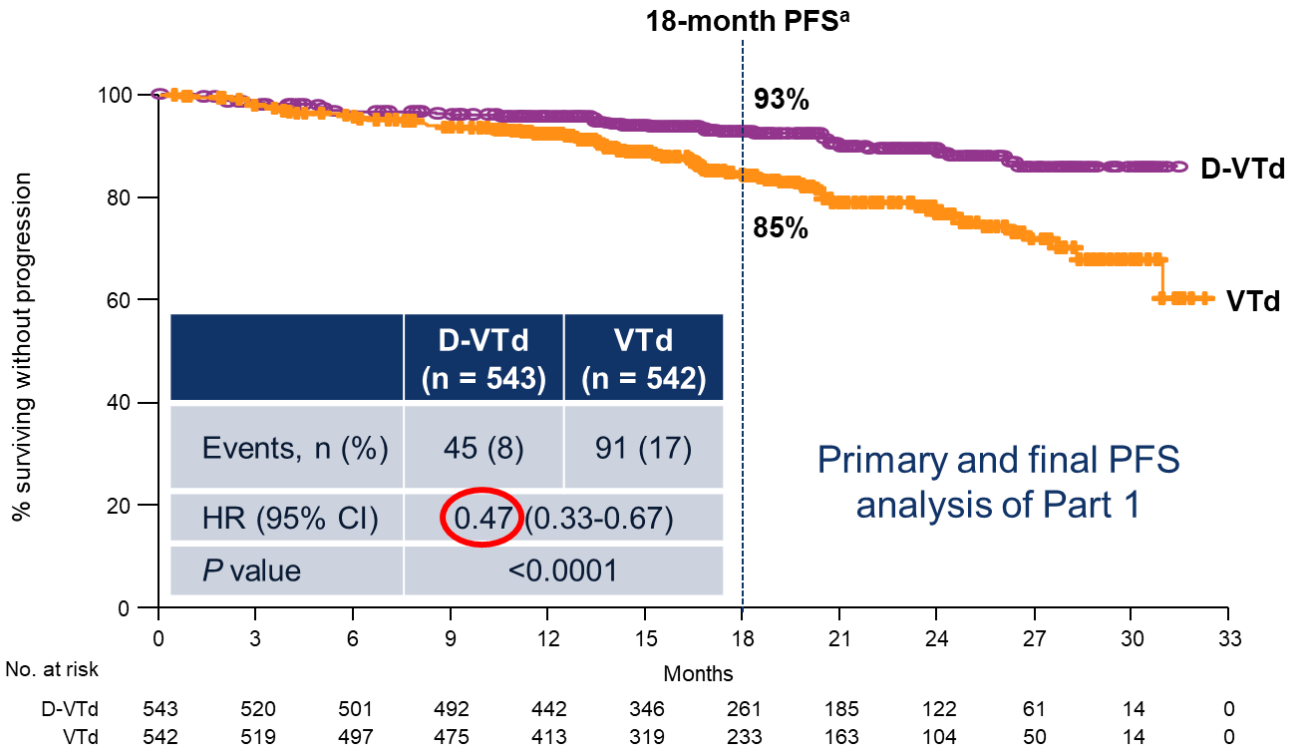
The addition of daratumumab to VTd improved depth of response

D-VTd, daratumumab/bortezomib/thalidomide/dexamethasone; VTd, bortezomib/thalidomide/dexamethasone;ORR, overall response rate; VGPR, very good partial response; CI, confidence interval; PR, partial response; sCR, stringent complete response; CR, complete response; VGPR, very good partial response; SIFE, serum immunofixation; UIFE, urine immunofixation; BM, bone marrow; FLC, free light chain.

Moreau P, et al. Lancet 2019;394:29–38

New findings in transplant-eligible MM:
Daratumumab-VTD vs VTD

PFS From First Randomization

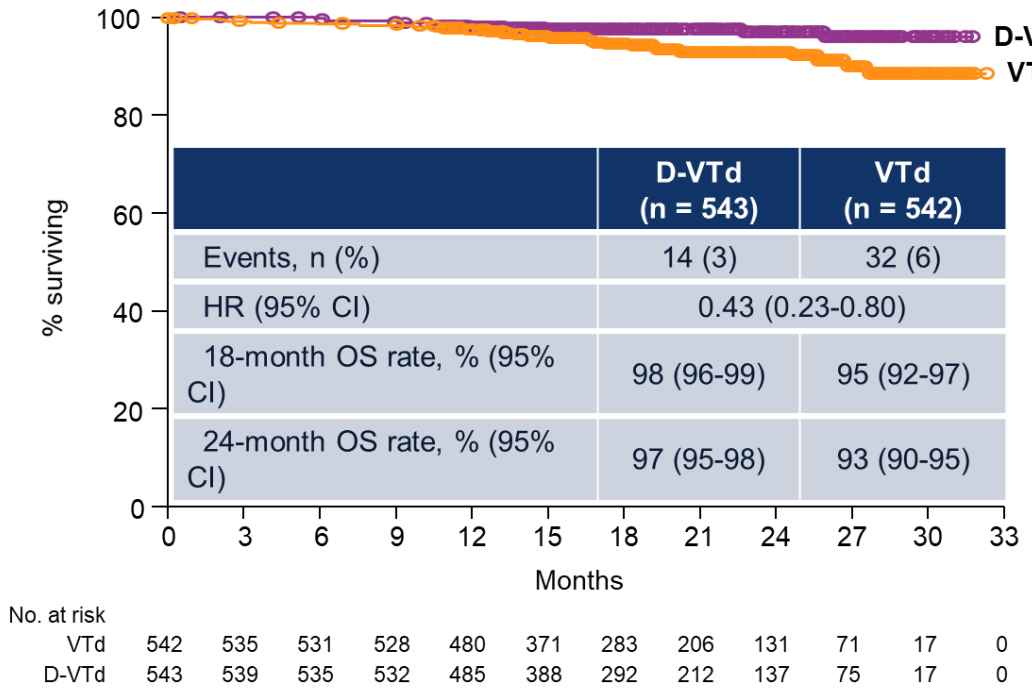


	D-VTd (n = 543)	VTd (n = 542)
Events, n (%)	45 (8)	91 (17)
HR (95% CI)	0.47 (0.33-0.67)	
P value	<0.0001	

Primary and final PFS analysis of Part 1

53% reduction in the risk of progression or death in the D-VTd arm

OS



	D-VTd (n = 543)	VTd (n = 542)
Events, n (%)	14 (3)	32 (6)
HR (95% CI)	0.43 (0.23-0.80)	
18-month OS rate, % (95% CI)	98 (96-99)	95 (92-97)
24-month OS rate, % (95% CI)	97 (95-98)	93 (90-95)

OS data are immature after median follow-up of 18.8 months

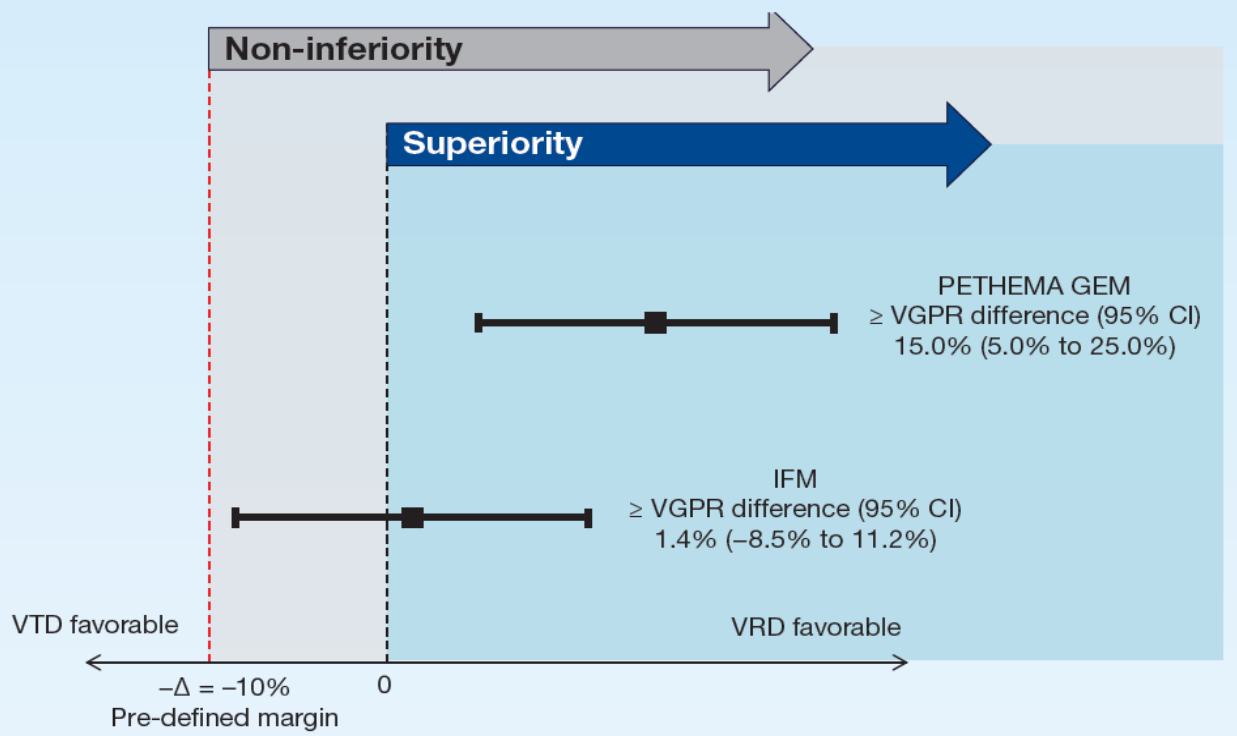
HR, hazard ratio; OS, overall survival; PFS, progression-free survival.
[a]Kaplan-Meier estimate.

Moreau P, et al. Lancet 2019;394:29–38 and suppl.

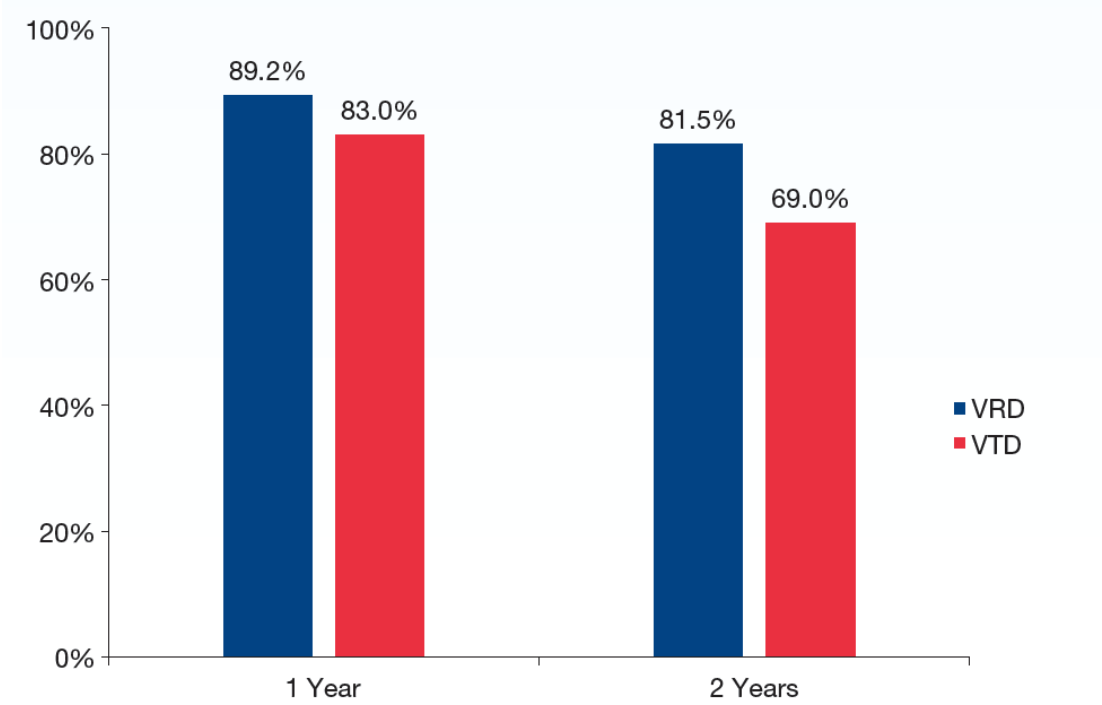
New findings in transplant-eligible MM:
VRD vs VTD induction integrated analysis

Four studies included: GEM2005 and GEM2012 (main studies); IFM 2009 and IFM 2013-04 (supportive)

Primary Endpoint was met
Non-inferiority of ≥ VGPR rate following induction



Event-free PFS in GEM studies



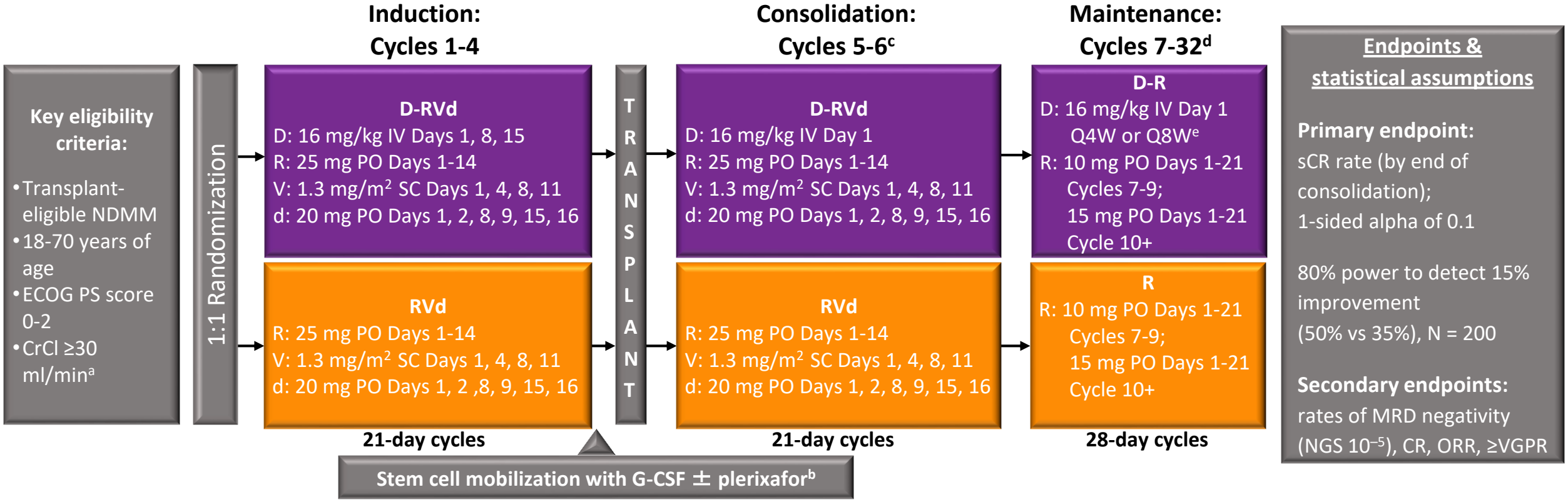
Data support favorable benefit-risk profile of VRD vs VTD induction in transplant-eligible NDMM

PFS, progression-free survival; VGPR, very good partial response; VRD, bortezomib-lenalidomide-dexamethasone; VTD, bortezomib-thalidomide-dexamethasone.

Rosiñol L, et al. EHA 2019, abstract PF594, poster presentation.

GRIFFIN: Randomized Phase 2 study

- Phase 2 study of D-RVd vs RVd in transplant-eligible NDMM, 35 sites in US with enrollment from 12/2016 and 4/2018

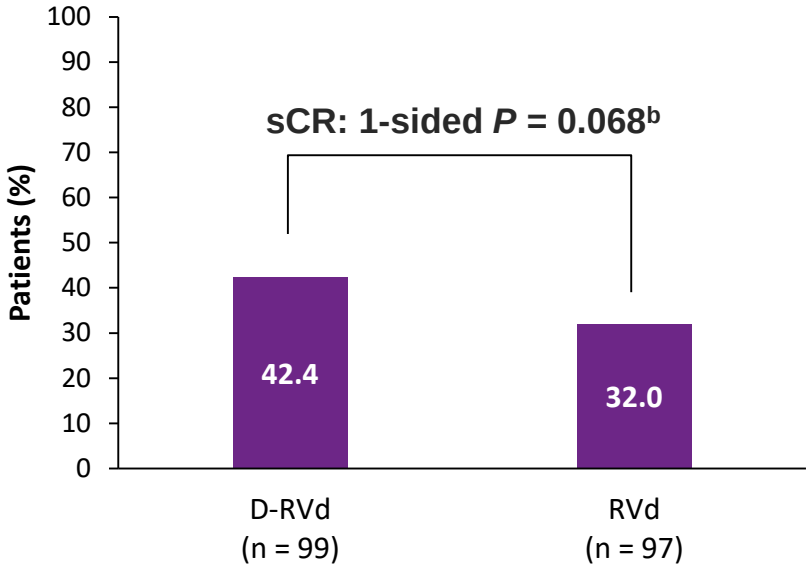


D-RVd, daratumumab plus lenalidomide/bortezomib/dexamethasone; RVd, lenalidomide/bortezomib/dexamethasone; NDMM, newly diagnosed multiple myeloma; US, United States; ECOG PS, Eastern Cooperative Oncology Group performance status; CrCl, creatinine clearance; IV, intravenously; PO, orally; SC, subcutaneously; G-CSF, granulocyte colony-stimulating factor; D-R, daratumumab-lenalidomide; Q4W, every 4 weeks; Q8W, every 8 weeks; NGS, next-generation sequencing; ORR, overall response rate; VGPR, very good partial response.
[a]Lenalidomide dose adjustments were made for patients with CrCl ≤50 mL/min. [b]Cyclophosphamide-based mobilization was permitted if unsuccessful. [c]Consolidation was initiated 60-100 days post transplant.
[d]Patients who complete maintenance cycles 7-32 may continue single-agent lenalidomide thereafter. [e]Protocol Amendment 2 allowed for the option to dose daratumumab Q4W, based on pharmacokinetic results from study SMM2001 (NCT02316106).

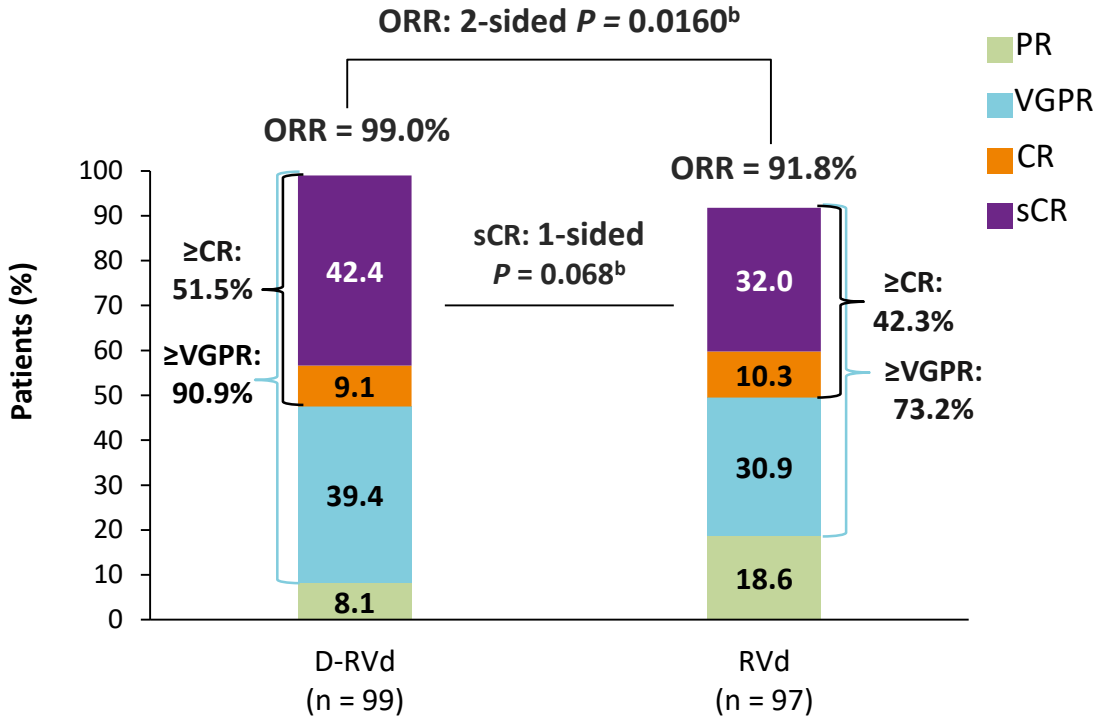
Voorhees PM, et al. ASH 2019; abstract 691;
Voorhees PN, et al. Blood 2020 [online ahead of print]

GRIFFIN phase 2 study: primary endpoint sCR by the end of consolidation[a]

- **Primary endpoint met at pre-set 1-sided alpha of 0.1**
  - sCR by end of consolidation
    - 42.4% D-RVd vs 32.0% RVd
    - Odds ratio, 1.57; 95% CI, 0.87-2.82; 1-sided *P* = 0.068[b]



Post-consolidation depth of response[a]

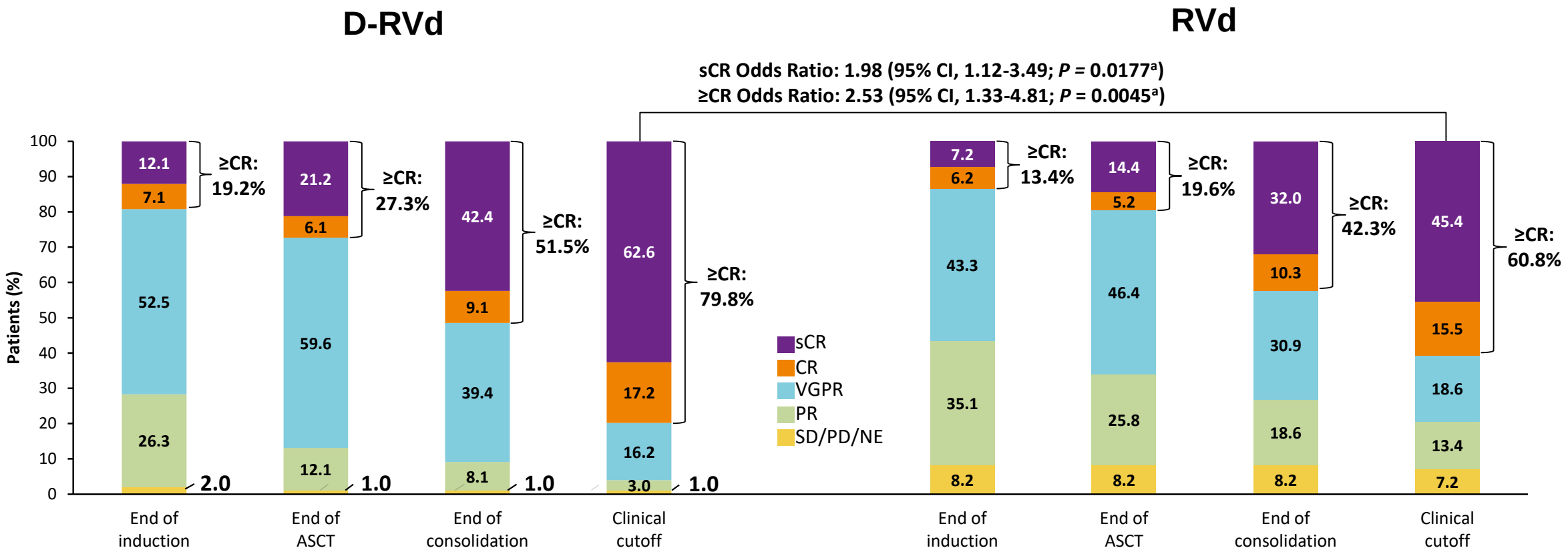


- **Median follow-up: 13.5 months**
- **Response rates and depths were greater for D-RVd at all time points**
- **Median PFS and OS not reached for D-RVd and RVd at median follow-up of 22.1 months**

[a]Results from primary analysis cutoff date (median follow-up, 13.5 months). Included patients in response-evaluable population (all randomized patients with confirmed MM diagnoses, measurable disease at baseline, received ≥1 dose of study treatment, and had ≥1 post-baseline disease assessment). [b]*P* values calculated using Cochran–Mantel–Haenszel chi-square test. A 1-sided *P* value is reported for sCR; for all other responses, 2-sided *P* values not adjusted for multiplicity are reported.

Voorhees PM, et al. ASH 2019; abstract 691;
Voorhees PN, et al. Blood 2020 [online ahead of print]

GRIFFIN: responses deepened over time



- Median follow up at primary analysis (end of consolidation) was 13.5 months; median follow up at clinical cutoff was 22.1 months

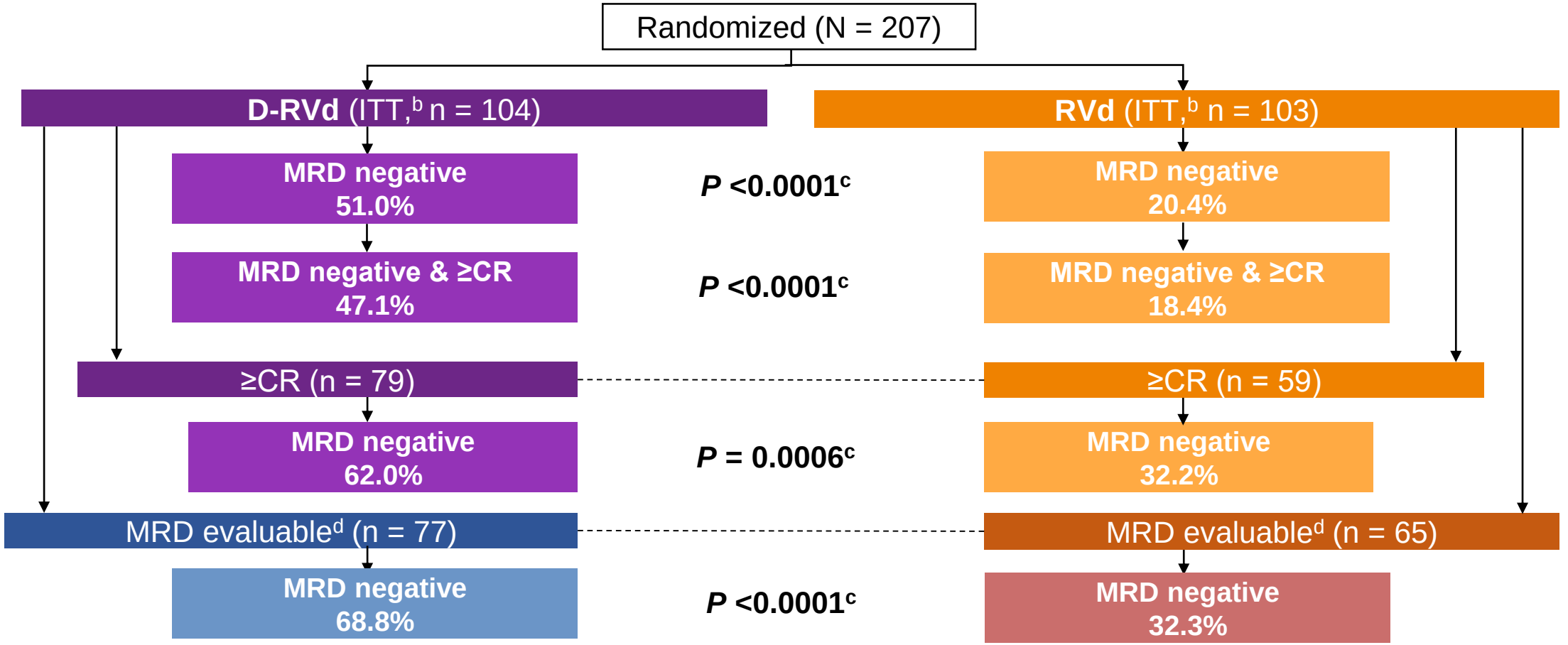
Response rates and depths were greater for D-RVd at all time points

D-RVd also shows continued improvement of MRD-negativity rates beyond post-ASCT consolidation

[a]*P* values (2-sided) calculated using Cochran–Mantel–Haenszel chi-square test.

Voorhees PM, et al. ASH 2019; abstract 691;
Voorhees PN, et al. Blood 2020 [online ahead of print]

GRIFFIN: MRD (10^{-5}) Negativity[a] at Clinical Cutoff



MRD assessments will be updated at 12 and 24 months of maintenance

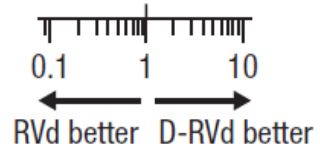
[a]The threshold of MRD negativity was defined as 1 tumor cell per 10^5 white cells. MRD status is based on assessment of bone marrow aspirates by next-generation sequencing in accordance with International Myeloma Working Group criteria. Median follow-up was 22.1 months. [b]For the ITT population, patients with a missing or inconclusive assessment were considered MRD positive. [c]*P*-values were calculated from the Fisher's exact test. [d]The MRD-evaluable population includes patients who had both baseline (with clone identified/calibrated) and post-baseline MRD (with negative, positive, or indeterminate result) samples taken.

Voorhees PM, et al. ASH 2019; abstract 691;
Voorhees PN, et al. Blood 2020 [online ahead of print]

GRIFFIN: Subgroup analysis of sCR by the end of post-ASCT consolidation and subgroup analysis of MRD negativity

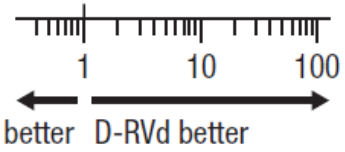
Stringent complete response by the end of post-ASCT consolidation (primary endpoint; median follow-up, 13.5 months)

Subgroup	RVd *stringent complete response, n (%)*	D-RVd *stringent complete response, n (%)*	Odds Ratio (95% CI)
Sex			
Male	18/55 (32.7)	21/55 (38.2)	1.27 (0.58-2.78)
Female	13/42 (31.0)	21/44 (47.7)	2.04 (0.84-4.92)
Age			
<65 yr	22/70 (31.4)	30/72 (41.7)	1.56 (0.78-3.10)
≥65 yr	9/27 (33.3)	12/27 (44.4)	1.60 (0.53-4.82)
ISS disease stage			
I	11/48 (22.9)	19/48 (39.6)	2.20 (0.91-5.35)
II	12/35 (34.3)	17/37 (45.9)	1.63 (0.63-4.22)
III	7/13 (53.8)	6/14 (42.9)	0.64 (0.14-2.94)
Type of multiple myeloma			
IgG	8/51 (15.7)	15/51 (29.4)	2.24 (0.85-5.88)
Non-IgG	23/46 (50.0)	25/45 (55.6)	1.25 (0.55-2.85)
Cytogenetic risk			
High risk	4/13 (30.8)	3/16 (18.8)	0.52 (0.09-2.90)
Standard risk	26/80 (32.5)	39/79 (49.4)	2.03 (1.06-3.85)
ECOG PS score			
0	13/39 (33.3)	16/38 (42.1)	1.45 (0.58-3.67)
1 or 2	18/58 (31.0)	25/60 (41.7)	1.59 (0.74-3.38)



Minimal residual disease negativity by last follow-up (median follow-up, 22.1 months)

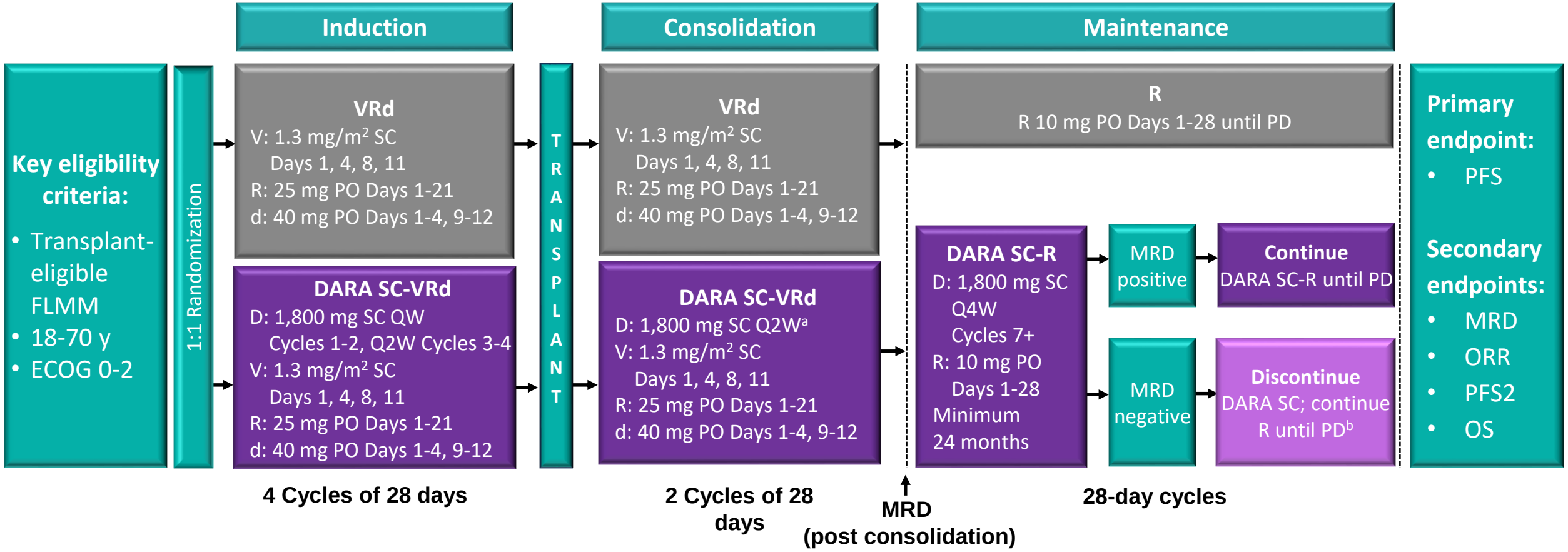
Subgroup	RVd *minimal residual disease negative, n (%)*	D-RVd *minimal residual disease negative, n (%)*	Odds Ratio (95% CI)
Sex			
Male	10/60 (16.7)	26/58 (44.8)	4.06 (1.73-9.54)
Female	11/43 (25.6)	27/46 (58.7)	4.13 (1.68-10.19)
Age			
<65 yr	16/75 (21.3)	38/76 (50.0)	3.69 (1.81-7.52)
≥65 yr	5/28 (17.9)	15/28 (53.6)	5.31 (1.57-17.97)
ISS disease stage			
I	6/50 (12.0)	25/49 (51.0)	7.64 (2.75-21.19)
II	10/37 (27.0)	20/40 (50.0)	2.70 (1.04-7.01)
III	5/14 (35.7)	8/14 (57.1)	2.40 (0.52-10.99)
Type of multiple myeloma			
IgG	11/52 (21.2)	29/55 (52.7)	4.16 (1.78-9.73)
Non-IgG	10/51 (19.6)	22/46 (47.8)	3.76 (1.53-9.26)
Cytogenetic risk			
High risk	4/14 (28.6)	6/16 (37.5)	1.50 (0.32-6.99)
Standard risk	17/83 (20.5)	45/82 (54.9)	4.72 (2.37-9.40)
ECOG PS score			
0	5/40 (12.5)	21/39 (53.8)	8.17 (2.64-25.25)
1 or 2	16/62 (25.8)	32/62 (51.6)	3.07 (1.44-6.53)



Voorhees PM, et al. ASH 2019; abstract 691; Voorhees PM, et al. Blood 2020 [online ahead of print]

PERSEUS (MMY3014; [EMN17]): Study Design

- Phase 3 study of DARA SC-VRd versus VRd in transplant-eligible NDMM (N ≈ 690)



EMN, European Myeloma Network; DARA SC-VRd, daratumumab and recombinant human hyaluronidase for subcutaneous injection-bortezomib/lenalidomide/dexamethasone; VRd, bortezomib/lenalidomide/dexamethasone; NDMM, newly diagnosed multiple myeloma; ECOG, Eastern Cooperative Oncology Group; SC, subcutaneous; PO, oral; QW, weekly; Q2W, every 2 weeks; MRD, minimal residual disease; R, lenalidomide; PD, progressive disease; DARA SC-R, daratumumab subcutaneous-lenalidomide; Q4W, every 4 weeks; PFS, progression-free survival; ORR, overall response rate; PFS2, progression-free survival on next line of therapy; OS, overall survival; ASCT, autologous stem cell transplantation; CR, complete response.

[a]Patients with post-ASCT recovery period >12 weeks off DARA SC should restart DARA SC Q2W for 2 cycles, then Q4W thereafter.

[b]If minimum of 1 year sustained MRD negativity; restart DARA SC (QW for 8 weeks, Q2W for 16 weeks, Q4W thereafter) at loss of MRD negativity or relapse from CR.

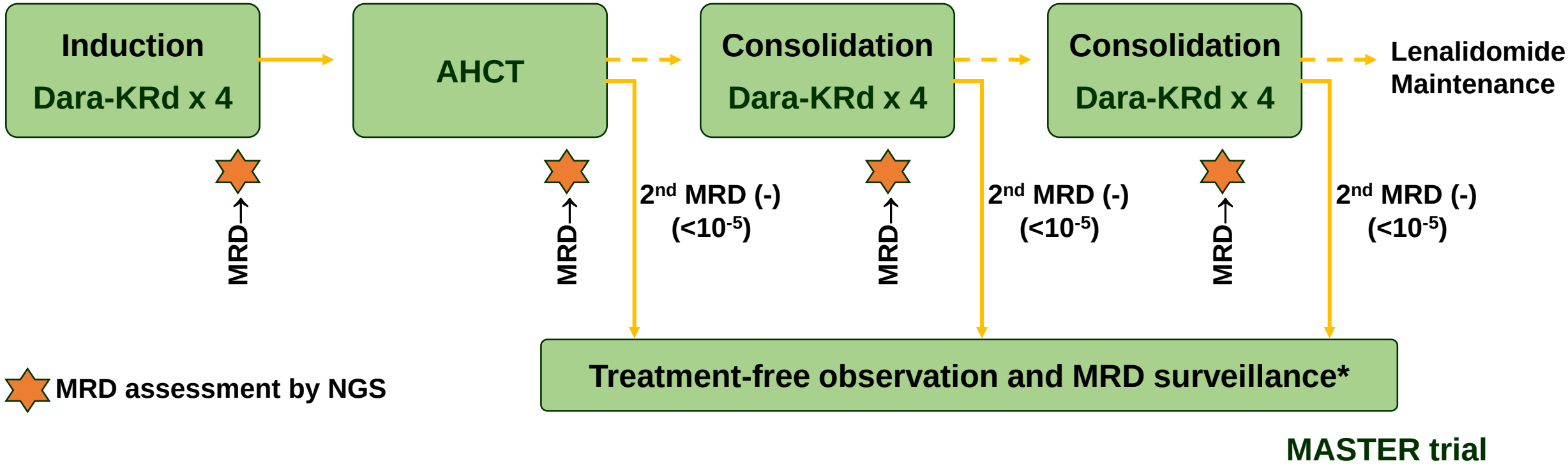
ClinicalTrials.gov Identifier: NCT03710603. Accessed 8 November 2018.

Sonneveld P, et al. ASCO 2019, abstract TPS8055

MASTER Phase 2 study: design

Dara-KRd

- Daratumumab 16 mg/m^2 Days 1,8,15,22 (days 1,15 C 3-6; day 1 C >6)
- Carfilzomib (20) 56 mg/m^2 Days 1,8,15
- Lenalidomide 25 mg Days 1-21
- Dexamethasone 40 mg PO Days 1,8,15,22



MASTER trial

- Median age 61 years

*24 and 72 weeks after completion of therapy

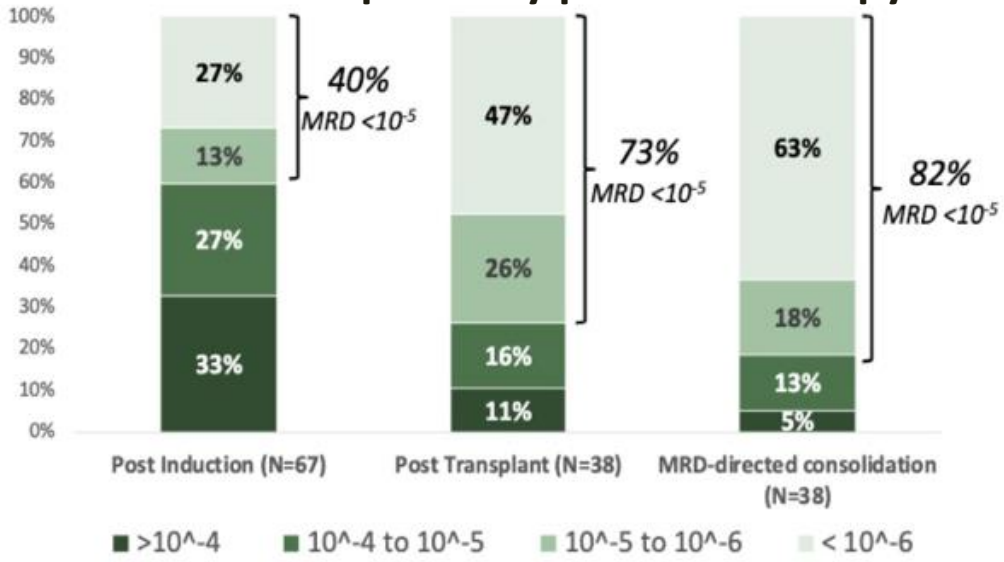
Costa L, et al. ASH 2019; abstract 860

MASTER Phase 2 study: results

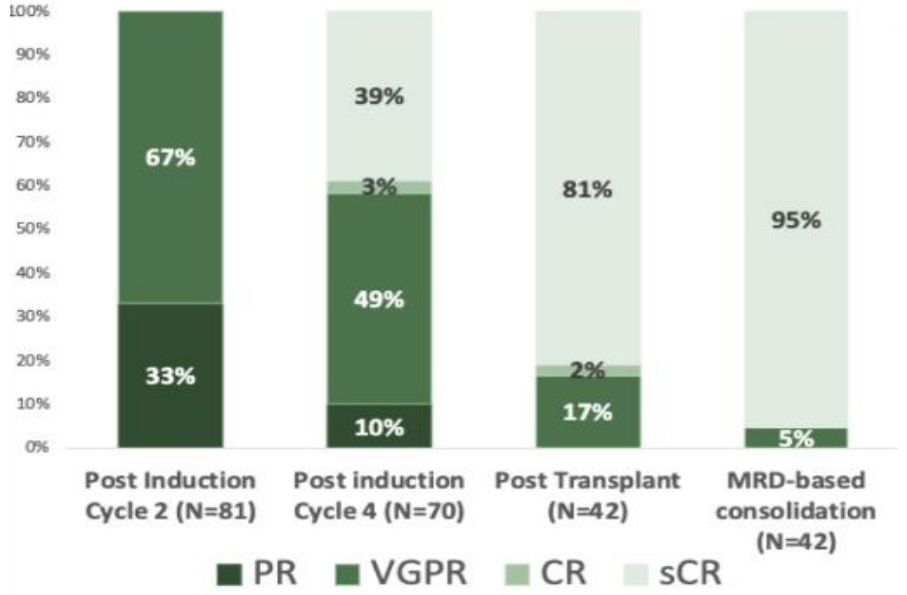
- Median follow-up 7.4 months

Most Common Treatment-Emergent AEs*		
	All grades	Grade ≥3
Hematologic		
Lymphopenia	31 (38%)	19 (23%)
Neutropenia	28 (35%)	20 (25%)
Thrombocytopenia	16 (20%)	4 (5%)
Anemia	15 (19%)	9 (11%)
Nonhematologic		
Musculoskeletal pain	50 (62%)	0 (0%)
Infections	47 (58%)	10 (12%)
Fatigue	45 (56%)	1 (1%)
Rash/cutaneous AE	45 (56%)	3 (4%)
Nausea/vomiting	41 (51%)	0 (0%)
Infusion-related reaction	31 (38%)	2 (2%)
Constipation	26 (32%)	0 (0%)
Peripheral neuropathy	23 (28%)	2 (2%)
Dyspnea	19 (23%)	1 (1%)
Hypertension	16 (20%)	3 (4%)
Venous thromboembolism	7 (9%)	1 (1%)

Best MRD response by phase of therapy



Best IMWG response by phase of therapy



Costa L, et al. ASH 2019; abstract 860

Response to induction with or without daratumumab

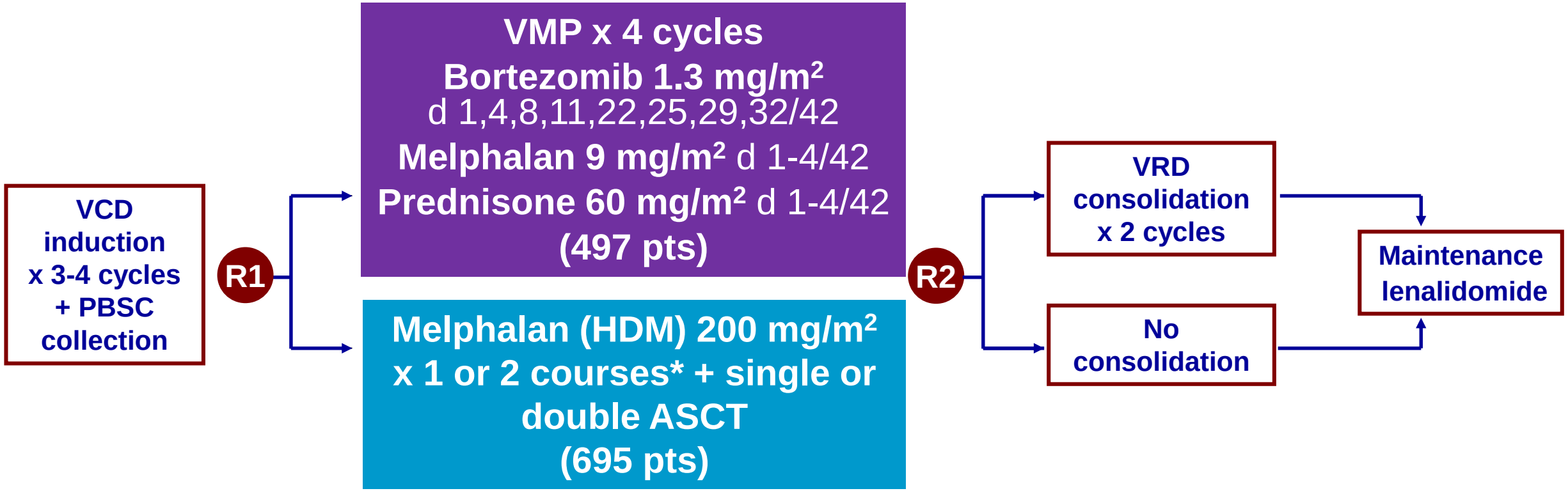
	VTd 28 d Cassiopeia trial	D-VTd 28 d Cassiopeia trial	RVd 21 d IFM2009 trial	RVd 28 d GEM2012 trial	RVd 21d	Dara-VRd 21d
N° of cycles of induction	4	4	3	6	4	4
N° of patients	542	543	350	458	102	99
Response Post-induction						
≥ VGPR	56.1	65	47	67	57	72
≥ CR	8.9	14		33	13	19
s-CR	6.5	7			7	12

Abbreviations: VTd, bortezomib, thalidomide, dexamethasone; D-VTd, daratumumab-VTd; RVd, lenalidomide, bortezomib, dexamethasone; D-RVd, daratumumab-RVd; KRd, carfilzomib, lenalidomide, dexamethasone; VGPR, very good partial response; CR, complete response; s-CR, stringent-CR; d, day.

Adapted from Harousseau JL., and Mohty M. Blood In Press

What about consolidation after auto-SCT?

EMN02/HO95 MM trial: study design



Stratification factor: ISS I vs. II vs. III

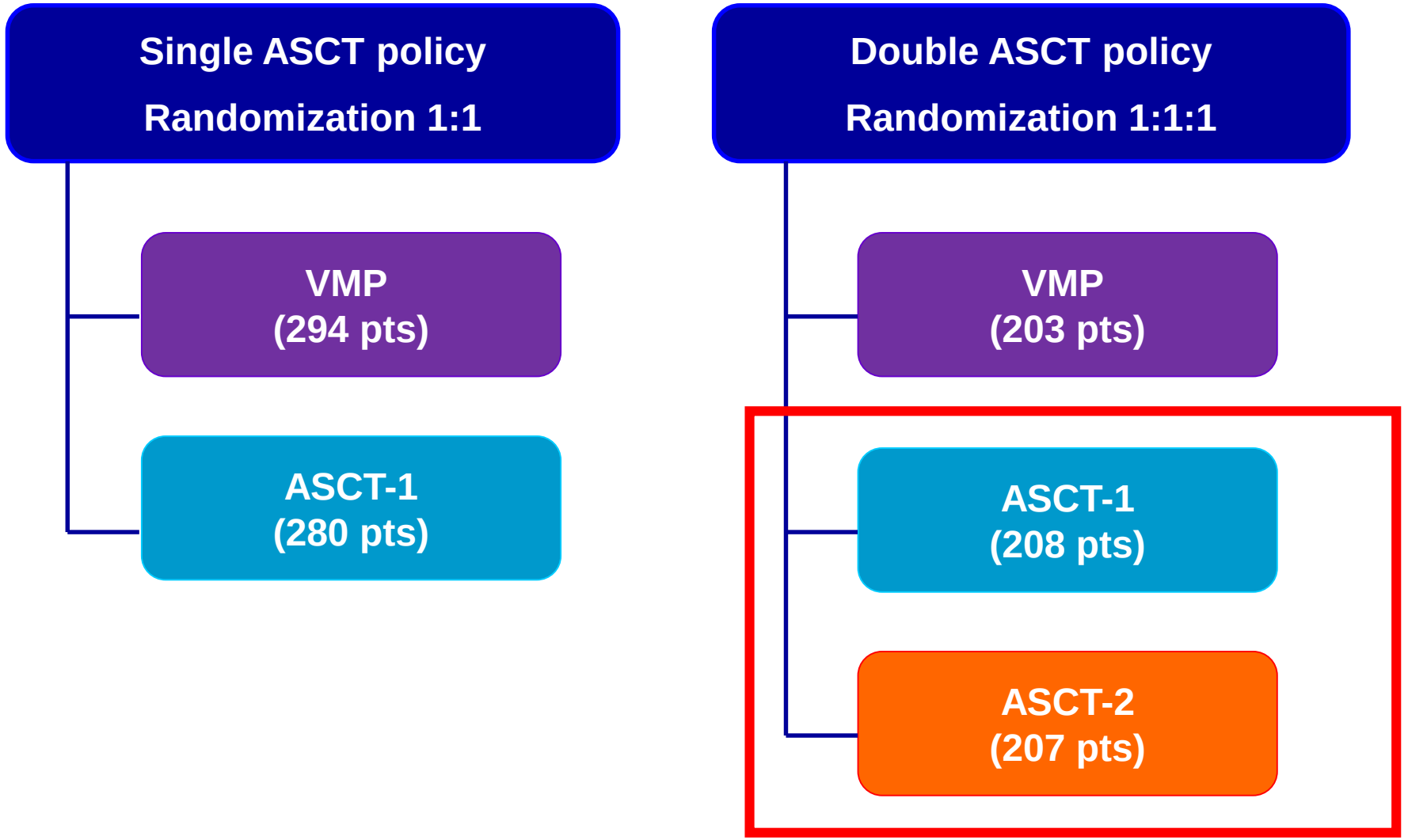
*** Randomization to VMP or HDM was 1:1 in centers with a fixed single ASCT policy**

*** Randomization to VMP or HDM-1 or HDM-2 was 1:1:1 in centers with a double ASCT policy**

Cavo M, et al. Lancet Haematol 2020;7:e456-e468.

EMN02/HO95 MM trial: Randomization 1

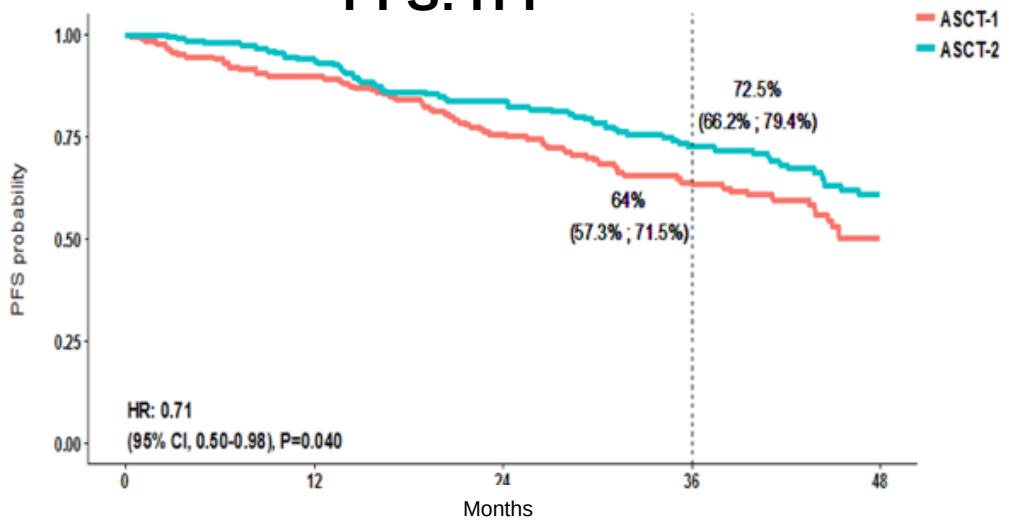
1192 pts were eligible for R1



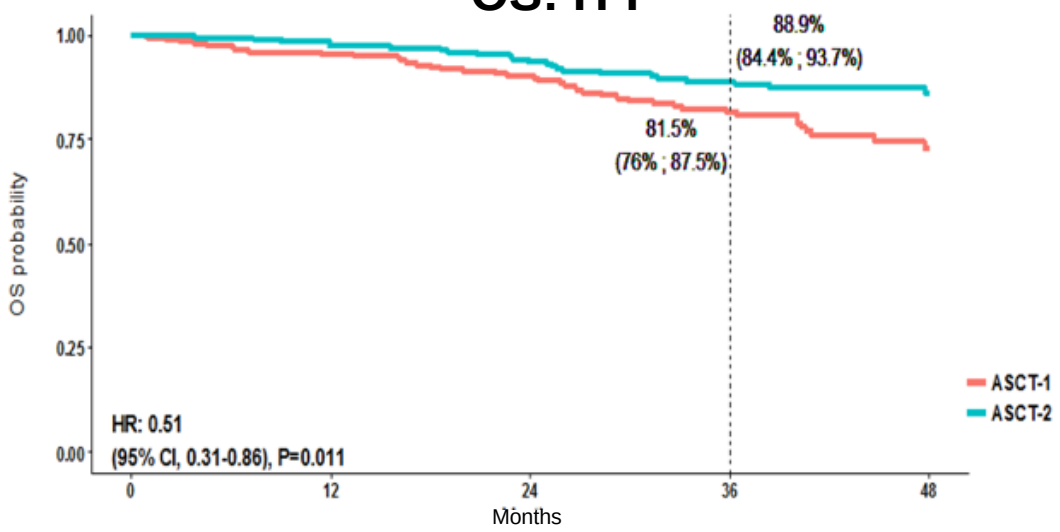
Cavo M, et al. Lancet Haematol 2020;7:e456-e468.

EMN02/HO95 MM trial: Single vs double ASCT: outcomes

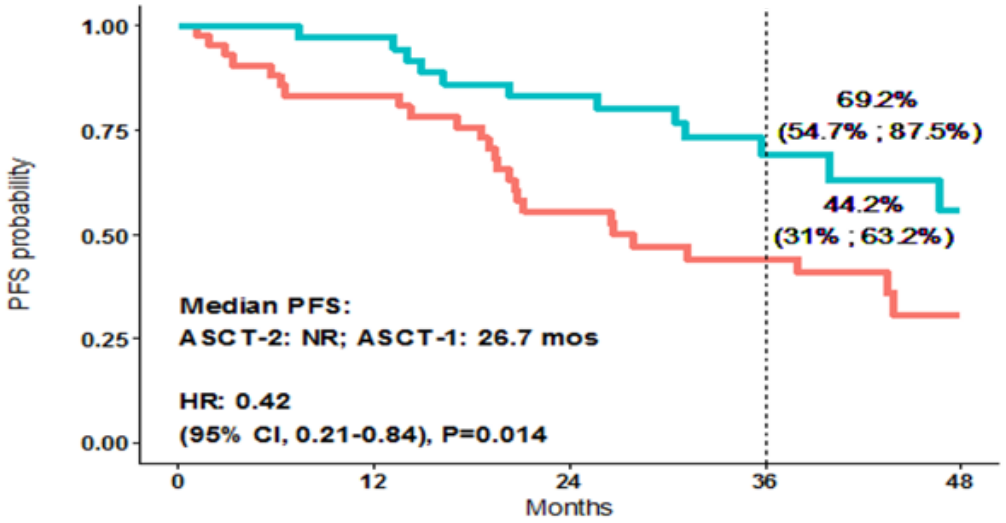
PFS: ITT



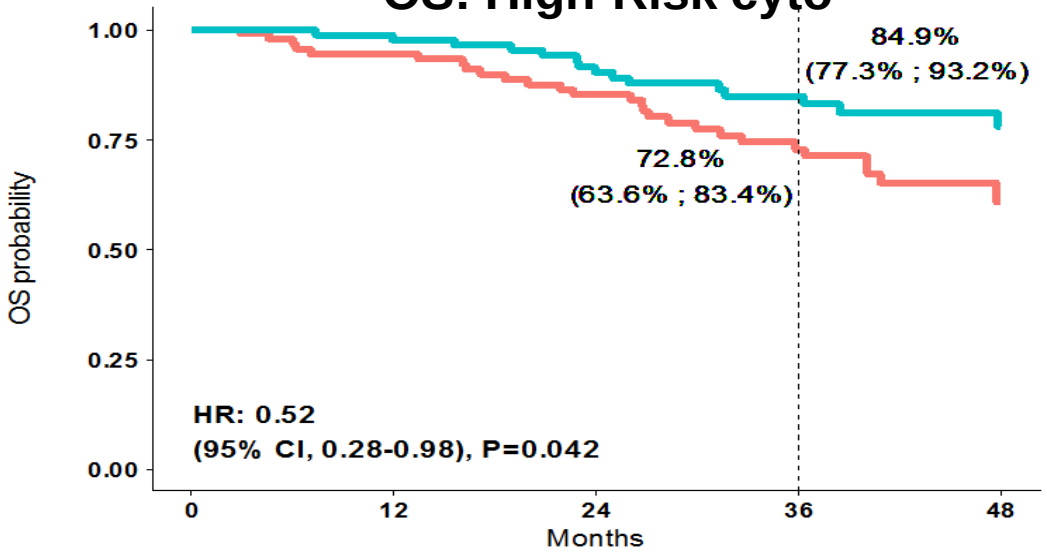
OS: ITT



PFS: High-Risk cyto

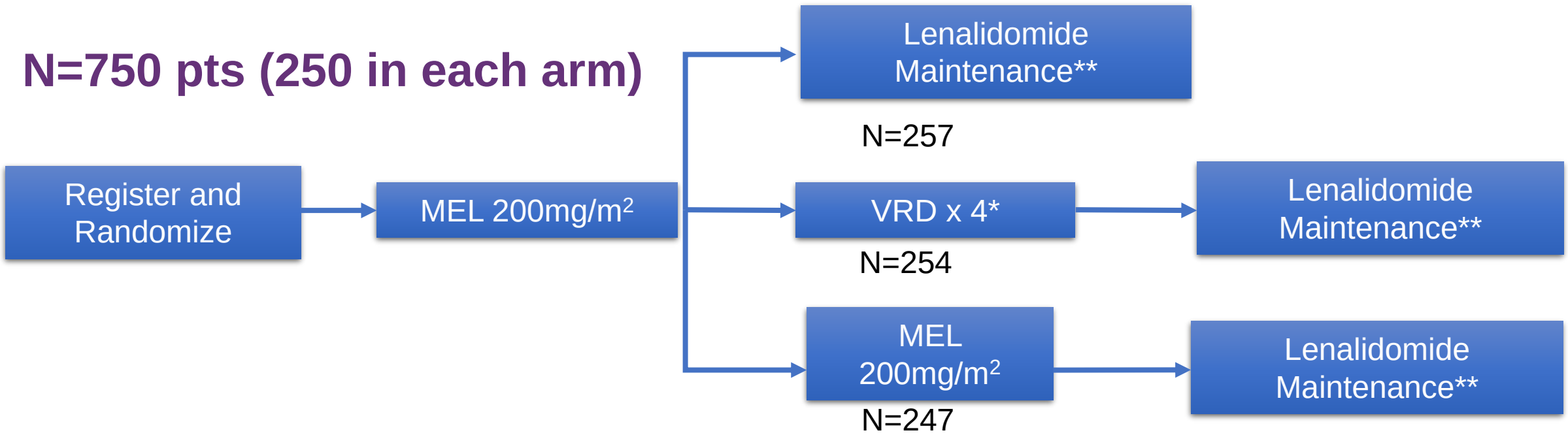


OS: High-Risk cyto



Cavo M, et al. Lancet Haematol 2020;7:e456-e468.

BMT CTN0702 (STAMINA) study design

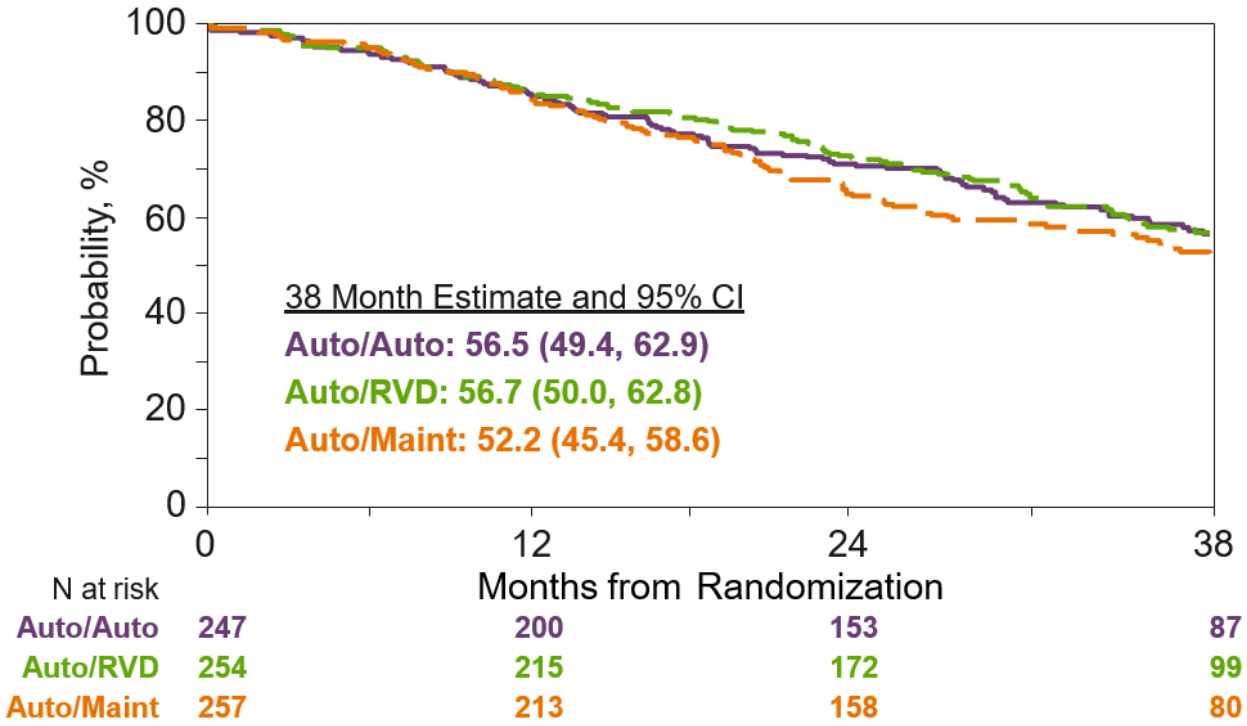


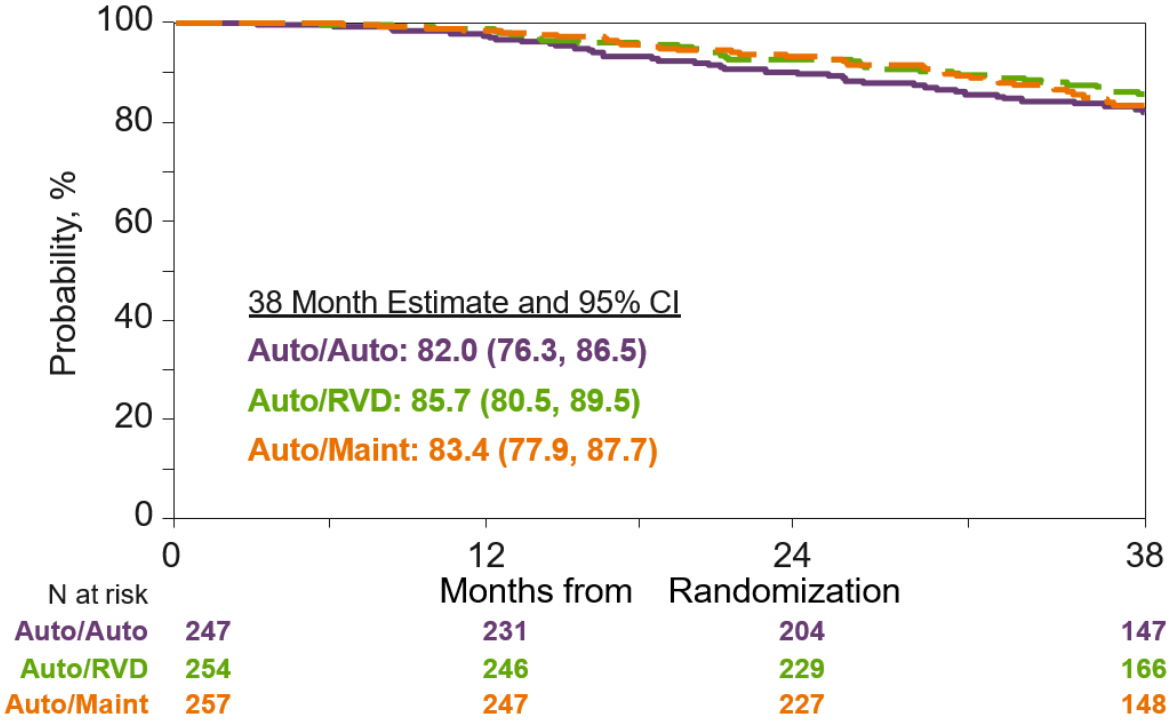
*Bortezomib 1.3mg/m^2 days 1, 4, 8,11
Lenalidomide 15mg days 1-15
Dexamethasone 40mg days 1, 8, 15
Every 21 days

**Lenalidomide x 3 years:
10mg/d for 3 cycles , then 15 mg/d
Amendment in 2014 changed Lenalidomide maintenance until disease progression after report of CALGB 100104

Stadtmauer EA, et al. J Clin Oncol. 2019;37:589-597.

BMT CTN0702 (STAMINA): PFS and OS according to randomization





Stadtmauer EA, et al. J Clin Oncol. 2019;37:589-597.

What about maintenance after auto-SCT?

What we know today for transplant-eligible patients with MM:
Maintenance with lenalidomide

Maintenance	**ESMO Guidelines 2017[1]** Lenalidomide maintenance is EMA-approved for the treatment of adult patients with newly-diagnosed MM who have undergone ASCT

Lenalidomide

Study details	n	Treatment	PFS	OS
Meta-analysis[2] Median follow-up: 80 months	605	Induction → ASCT → lenalidomide daily (or D 1–21/28) until progression	52.8 m	Not reached
	603	Placebo / Observation	23.5 m HR (95% CI) 0.48 (0.41 to 0.55)	86.0 m; p=0.001
MYELOMA XI[3] Median follow-up: 30.6 months	730	Transplant eligible: CTD or CRD → ASCT → lenalidomide D 1–21/28 until progression	56.9 m	87.5%
	518		30.1 m; p<0.0001	80.2%; p=0.0130

1. Moreau P, et al. Ann Oncol 2017;28(suppl_4):iv52-iv61; 2. McCarthy PL, et al. J Clin Oncol 2017;35: 3279-3289;
3. Jackson G et al. ASH 2017 (Abstract 436), oral presentation.

What we know today for transplant-eligible patients with MM:
Maintenance with bortezomib

Bortezomib

Study details*	n	Treatment	PFS	OS
HOVON 65 MM / GMMG-HD4[1,2] Median follow-up: 96 months (Overall trial)	413	PAD x 3 → HDM → bortezomib every 2 weeks for 2 years	34 m	48%
	414	VAD x 3 → HDM → Thalidomide daily for 2 years	28 m; p<0.001	45%; p=0.24
PETHEMA/GEM[3] Median follow-up: 58.6 months (From maintenance start)	91	TV (thal daily, 1 cycle bortezomib every 3 m) for 3 years	50.6 m	Not significantly diffferent between arms
	88	Thal (daily for 3 years)	40.3 m	
	92	Interferon-α2b (3 x week for 3 years)	32.5 m; p=0.03	

*Bortezomib administered at 1.3mg/m^2 IV in both studies

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.

AURIGA Phase 3 study: Design

- Objective: to evaluate the conversion rate to MRD negativity after maintenance treatment with DARA SC plus len vs len alone in patients with NDMM who are MRD positive after ASCT

Key eligibility criteria

- NDMM with ≥VGPR
- MRD positive
- No prior anti-CD38 exposure
- Post ASCT
- 4-8 cycles of induction ± consolidation therapy

Stratified by cytogenetic risk (high vs standard/ unknown)

1:1 Randomization

Maintenance

28-day cycles

Len

Len: 10 mg PO Days 1-28
(15 mg PO daily, if well tolerated after 3 cycles)

Dara SC + Len

DARA: 1,800 mg SC QW Cycles 1-2, Q2W Cycles 3-6, Q4W thereafter
Len: 10 mg PO Days 1-28
(15 mg PO daily, if well tolerated after 3 cycles)

MRD by NGS at 12, 18, 24 and 36 months

Continue until PD or 36 cycles

Primary endpoint

- MRD-negativity conversion rate (10^{-5}) at 12 months

Secondary endpoints

- PFS
- Overall MRD-negativity conversion rate
- Durable MRD negativity
- CR/sCR
- OS
- Duration of CR/sCR
- HRQoL
- Safety

FPI May 2019

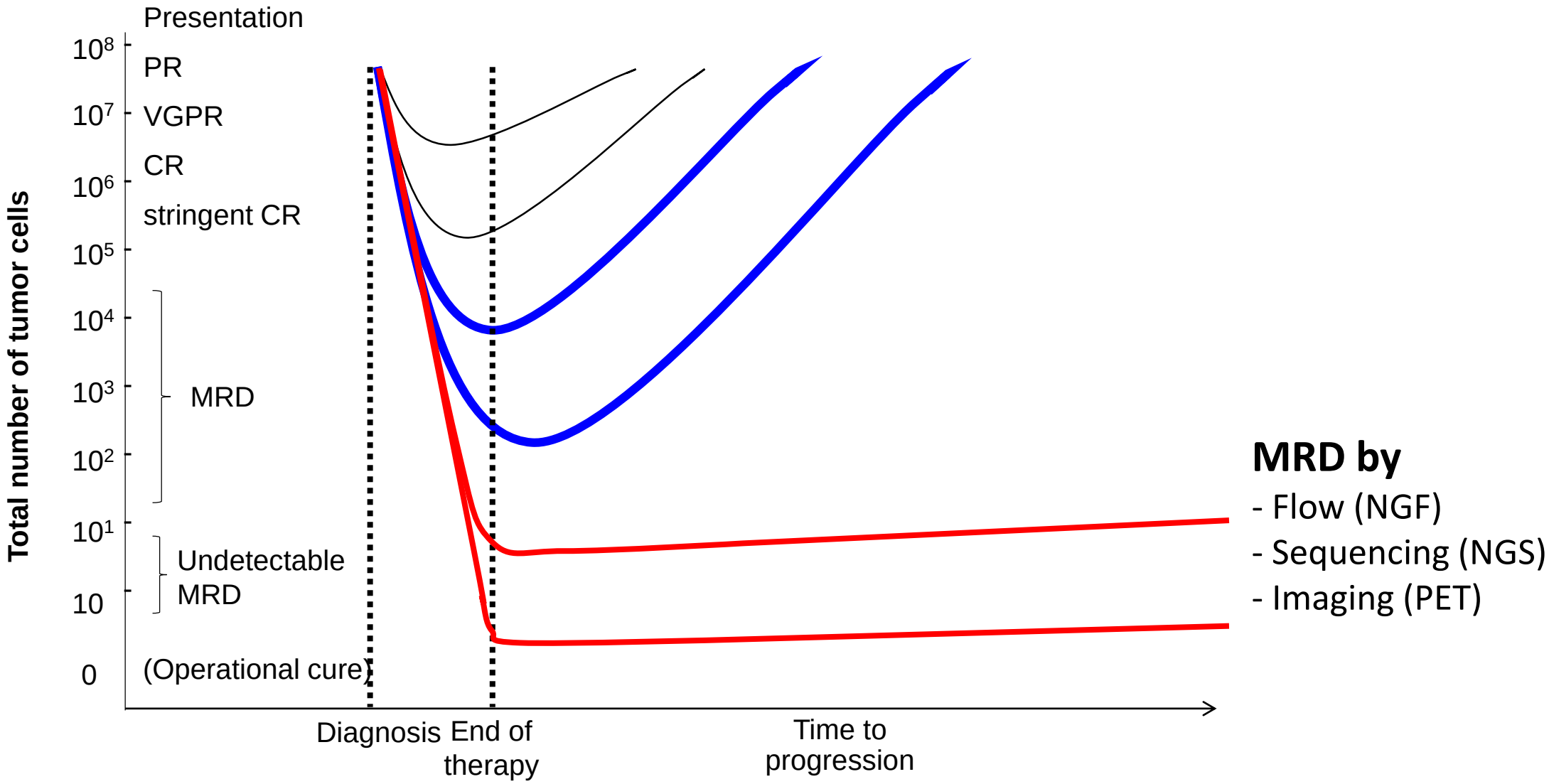
NDMM, newly diagnosed multiple myeloma; VGPR, very good partial response; MRD, minimal residual disease; ASCT, autologous stem cell transplant; len, lenalidomide; PO, oral; DARA SC, daratumumab subcutaneous; QW, weekly; Q2W, every 2 weeks; Q4W, every 4 weeks; NGS, next-generation sequencing; PD, progressive disease; PFS, progression-free survival; CR, complete response; sCR, stringent complete response; OS, overall survival; HRQoL, health-related quality of life; FPI, first patient in.

Shah N, et al. ASH 2019; abstract 1829

Summary
Transplant-eligible patients with MM

- **Induction therapy followed by ASCT is the standard treatment** in fit, newly-diagnosed patients with MM
  - **Three-drug bortezomib-dexamethasone-based combinations are the current standard of care** for induction
  - These triplets will be replaced in the near future by **four-drug combinations including a mAb combined with a PI and an IMiD**
- **Double ASCT likely improves outcomes**, especially in patients with unfavourable cytogenetic abnormalities
- **Lenalidomide maintenance is approved** for the treatment of patients with newly-diagnosed MM who have undergone ASCT
  - Some patient populations may benefit from alternative maintenance regimens

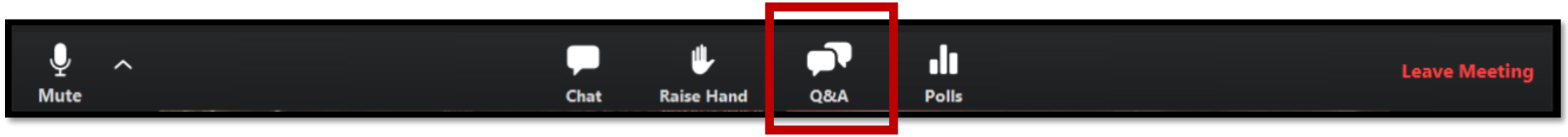
Goals of therapy in NDMM



Paiva B, Van Dongen JJ, Orfao A. Blood. 2015;125(20):3059-3068

Panel Discussion

Please submit any thoughts, comments or questions regarding this Webinar in the Zoom panel at the bottom of your screen.



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