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

Transplant Eligible

Induction
3 drug combinations including PI and IMiD

Autologous stem cell transplantation, Early vs Deferred

Maintenance
Standard: Lenalidomide
High risk: Proteasome inhibitor or other combinations

Not Transplant Eligible

Induction
2 or 3 drug combinations

Maintenance

Supportive Care
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
Disparities in Access and Utilization of MM Therapy

Transplant Rates (Auto+Allo) per 10 Million

Global Approval of Lenalidomide and Bortezomib, as of 2018


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\(^1\)

2. Global Burden of Disease Study\(^2\)
   - Multiple myeloma incidence 2006-2015

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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: \( \frac{T}{MM \text{ incidence}} \times 100 \)
  • Transplants for MM in calendar year / gross annual MM incidence per region

• Separate analyses for all ages, and age < 70
Autologous HCT for MM: Baseline Numbers and Global Utilization

**Gross Numbers, Auto HSCT**

- **Global**
- **Europe/Central Asia**
- **North America**
- **Asia Pacific**
- **Latin America**
- **Africa/Middle East**

**Utilization, Auto HSCT**

- **30%**
- **North America**
- **Europe/Central Asia**
- **Global**
- **Latin America**
- **Asia Pacific**
- **Africa/Middle East**
Allogeneic HCT for MM, Baseline Numbers and Global Utilization

Gross Numbers, Allo HSCT

Utilization, Allo HSCT
Utilization of HCT, Age < 70

3a

% Utilization of Autologous H SCT, Age < 70

Region:
- Europe/Central Asia
- North America
- Latin America
- Asia Pacific
- Africa/Middle East

Year:

3b

% Utilization of Allogeneic H SCT, Age < 70

Region:
- Europe/Central Asia
- North America
- Africa/Middle East
- Latin America

Year:
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
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• Malek Benakli, MD
• Bazuaye G Nosa, MD
• 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
Instituto de Cancerología- Clínica las Américas
Medellín- Colombia
Disclosure

• I do not have any conflict of interest to declare
Hematopoietic Stem Cell Storage

Cryopreservation – disadvantages

- Expensive
- Time Consuming
- Needs lots of resources
- Labor intensive
- DMSO Potentially dangerous
1. HSC storage at 4°C, for 6 days, keeps enough clonogenic capacity to restore hematopoiesis after myeloablative chemotherapy.

1. This interval, 6 days, allows for the use of the most common conditioning for transplanting myeloma, but, also lymphoma.
Lab Data
Storage of noncryopreserved peripheral blood stem cells for transplantation

Samples from fourteen patients who underwent APBSCT were stored at 4°C for 8 days.

- In vitro analysis
  - Viability at 6th day: 80%
  - Clonogenic capacity at 5th - 6th day: 50%

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


- 47 patients - hematological malignancies - APBST
- APBSC kept at 4°C 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

80%
### Table 1. Cryopreservation Cell Concentrations and Cell Recoveries After Thawing

<table>
<thead>
<tr>
<th>Cryopreserved*</th>
<th>Mean ± SD</th>
<th>Range</th>
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</thead>
<tbody>
<tr>
<td>Nucleated cell count (× 10^9)</td>
<td>4.8 ± 3.4</td>
<td>0.6-14.9</td>
</tr>
<tr>
<td>Volume frozen (mL)</td>
<td>127 ± 45</td>
<td>34-300</td>
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<tr>
<td>Nucleated cell concentration (× 10^9/mL)</td>
<td>3.7 ± 1.9</td>
<td>0.4-8.0</td>
</tr>
<tr>
<td>Platelet concentration (× 10^9/mL)</td>
<td>2.9 ± 2.1</td>
<td>0.4-10.9</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>12.9 ± 7.2</td>
<td>2.8-44.7</td>
</tr>
<tr>
<td>Proportion mononuclear cells (%)</td>
<td>52.9 ± 27.2</td>
<td>10.5-100.0</td>
</tr>
<tr>
<td>Proportion viable cells (%)</td>
<td>97.9 ± 1.4</td>
<td>91.2-99.2</td>
</tr>
<tr>
<td>No. viable CD34+ cells (× 10^4)</td>
<td>9.3 ± 8.1</td>
<td>0.2-28.6</td>
</tr>
<tr>
<td>No. CFU-GM (× 10^3)</td>
<td>1.2 ± 1.2</td>
<td>0.0-7.2</td>
</tr>
<tr>
<td>No. BFU-E (× 10^3)</td>
<td>2.6 ± 2.3</td>
<td>0.2-28.6</td>
</tr>
</tbody>
</table>

**Thawed**

<table>
<thead>
<tr>
<th>Recovery (%)</th>
<th>Mean ± SD</th>
<th>Range</th>
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<tbody>
<tr>
<td>Recovery of nucleated cells (%)</td>
<td>75.4 ± 13.0</td>
<td>43.2-102.8</td>
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<tr>
<td>Proportion viable cells (%)</td>
<td></td>
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<tr>
<td>All cells</td>
<td>63.6 ± 15.2</td>
<td>31.2-85.0</td>
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<tr>
<td>Mononuclear cells</td>
<td>84.4 ± 5.5</td>
<td>73.8-95.2</td>
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<tr>
<td>Recovery of viable CD34+ cells (%)</td>
<td>71.4 ± 51.9</td>
<td>8.9-226.5</td>
</tr>
<tr>
<td>Recovery of CFU-GM (%)</td>
<td>45.3 ± 45.9</td>
<td>0.0-217.8</td>
</tr>
<tr>
<td>Recovery of BFU-E (%)</td>
<td>48.8 ± 33.9</td>
<td>0.0-170.7</td>
</tr>
</tbody>
</table>

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**From the Clinical Research Division, Fred Hutchinson Cancer Center**

*Blood, Vol 83, No 9 (May I), 1994 pp 2731-2736*
Clinical Results
Hematopoietic Autologous Stem Cell Transplant Without Cryopreservation. LATAM experience in patients with Myeloma and Lymphoma


✓ 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


✓ A simplified method for stem cell autografting in multiple myeloma: a single institution experience. Bone Marrow Transplantation (2009) 00, 1–5

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

L. Wannesson¹, T. Panzarella², J. Mikhail¹ & A. Keating¹

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country of origin</th>
<th>Source</th>
<th>Peer-reviewed source (Y/N)</th>
<th>Type of article</th>
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<tr>
<td>Kingston et al. [38]</td>
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<td>British Journal of Haematology</td>
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<td>Retrospective review of a multicentric case series</td>
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<td>Retrospective, single-center cohort comparison</td>
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<td>Papadimitriou et al. [29]</td>
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<td>Greece</td>
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<td>Holowiczi et al. [36]</td>
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<td>Poland</td>
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<td>Ruiz-Angelíes et al. [33]</td>
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<td>Mabed and Al-Kgodary [47]</td>
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<td>Bone Marrow Transplantation</td>
<td>Y</td>
<td>Retrospective review of a single-center case series</td>
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</table>

- 16 studies, **560** patients.
- Engraftment rate 99.5%
- Heterogeneous diseases - Heterogeneous preparative regimens
- Heterogeneous time of storage
Recent Information
Homogeneous Diseases
Homogeneous Conditioning
Retrospective analysis

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

Consecutive patients with myeloma or lymphoma Transplanted without cryopreservation

2002 to 2016

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

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

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
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*

Department of Haematology, Christian Medical College, Vellore, India

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

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<tbody>
<tr>
<td>No. of patients</td>
<td>224</td>
<td>92</td>
<td>59</td>
<td>216</td>
<td>29</td>
</tr>
<tr>
<td>Mobilization strategy</td>
<td>G</td>
<td>G</td>
<td>G, n = 38</td>
<td>G, n = 189</td>
<td>G ± P</td>
</tr>
<tr>
<td></td>
<td></td>
<td>G, n = 8</td>
<td>C, n = 16</td>
<td></td>
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<td></td>
<td></td>
<td>P + G, n = 8</td>
<td>P, n = 11</td>
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<td></td>
<td>C + P, n = 3</td>
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<td></td>
<td></td>
<td>C, n = 2</td>
<td></td>
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<tr>
<td>Median CD34 dose, ×10⁶/kg</td>
<td>4.87</td>
<td>2.9</td>
<td>2.8</td>
<td>3.6</td>
<td>5.1</td>
</tr>
<tr>
<td>Graft Failure</td>
<td>1/224</td>
<td>0/92</td>
<td>1/59</td>
<td>0/216</td>
<td>0/29</td>
</tr>
<tr>
<td>Medium day of neutrophil</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>engraftment (range)</td>
<td>12</td>
<td>10</td>
<td>10</td>
<td>14</td>
<td>8</td>
</tr>
<tr>
<td>Medium day of platelet</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>engraftment (range)</td>
<td>17</td>
<td>14</td>
<td>11</td>
<td>16</td>
<td>10</td>
</tr>
<tr>
<td>TRM, %</td>
<td>3.1</td>
<td>3.2</td>
<td>3.2</td>
<td>1.7</td>
<td>1.4</td>
</tr>
</tbody>
</table>

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

* Platelet count above 50 × 10⁹/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%
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.
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 4°C with preservation of enough clonogenic capacity to restore the hematopoiesis.

Is possible to perform APBS transplant in lymphoma without cryopreservation.
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 \( r : 0.116; p:0.14 \)
Hematopoietic Autologous Stem Cell Transplant
Without Cryopreservation

Conclusion:
Autologous transplant with PBSC storage at 4°C, is feasible, safe, and produces a reliable engraftment

Advantages:
Simplicity
Low cost
*It can be used with the more common conditioning regimens*
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

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David Gómez-Almaguer
Monterrey- México

Francisco Cuéllar Ambrosi
Medellín- Colombia

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

Prof. Mohamad MOHTY
Clinical Hematology and Cellular Therapy Dpt.
Sorbonne University
Hôpital Saint-Antoine
Paris, France
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/m² Melphalan followed by ASCT

↓

Maintenance
Lenalidomide

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

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

**Induction therapy**

---

**ESMO Guidelines 2017**

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.

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**Meta-analysis bortezomib-based induction vs non bortezomib**

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

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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.


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)

Post-consolidation Depth of Response

- 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

\( P < 0.0001 \)
New findings in transplant-eligible MM: Daratumumab-VTD vs VTD

**PFS From First Randomization**

- **18-month PFS**: 93% for D-VTd arm, 85% for VTd arm.
- **P value**: <0.0001
- **HR (95% CI)**: 0.47 (0.33-0.67)

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

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

HR, hazard ratio; OS, overall survival; PFS, progression-free survival.

*Kaplan-Meier estimate.*
New findings in transplant-eligible MM: VRD vs VTD induction integrated analysis

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

**Event-free PFS in GEM studies**

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


---

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

### Key eligibility criteria:
- Transplant-eligible NDMM
- 18-70 years of age
- ECOG PS score 0-2
- CrCl ≥30 ml/min

### Induction:
**Cycles 1-4**
- **D-RVd**
  - D: 16 mg/kg IV Days 1, 8, 15
  - R: 25 mg PO Days 1-14
  - V: 1.3 mg/m² SC Days 1, 4, 8, 11
  - d: 20 mg PO Days 1, 2, 8, 9, 15, 16

### Consolidation:
**Cycles 5-6**
- **D-RVd**
  - D: 16 mg/kg IV Day 1
  - R: 25 mg PO Days 1-14
  - V: 1.3 mg/m² SC Days 1, 4, 8, 11
  - d: 20 mg PO Days 1, 2, 8, 9, 15, 16

### Maintenance:
**Cycles 7-32**
- **D-R**
  - D: 16 mg/kg IV Day 1
  - Q4W or Q8W
  - R: 10 mg PO Days 1-21
  - Cycles 7-9;
  - 15 mg PO Days 1-21 Cycle 10+

### Key points:
- **Primary endpoint:** sCR rate (by end of consolidation); 1-sided alpha of 0.1
  - 80% power to detect 15% improvement (50% vs 35%), N = 200
- **Secondary endpoints:** rates of MRD negativity (NGS 10⁻⁵), CR, ORR, >VGPR

---

*Lenalidomide dose adjustments were made for patients with CrCl ≤50 mL/min.
*Cyclophosphamide-based mobilization was permitted if unsuccessful.
*Consolidation was initiated 60-100 days post transplant.
*Patients who complete maintenance cycles 7-32 may continue single-agent lenalidomide thereafter.
*Protocol Amendment 2 allowed for the option to dose daratumumab Q4W, based on pharmacokinetic results from study SMM2001 (NCT02316106).
GRIFFIN phase 2 study: primary endpoint sCR by the end of consolidation

- **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 \( P = 0.068 \)

- **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**

\[ \text{Patients (\%)} \]

<table>
<thead>
<tr>
<th></th>
<th>Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>D-RVd (n = 99)</td>
<td>42.4</td>
</tr>
<tr>
<td>RVd (n = 97)</td>
<td>32.0</td>
</tr>
</tbody>
</table>

\[ \text{Patients (\%)} \]

<table>
<thead>
<tr>
<th></th>
<th>Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
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<td>42.4</td>
</tr>
<tr>
<td>RVd (n = 97)</td>
<td>32.0</td>
</tr>
</tbody>
</table>

\[ \text{PR} \]

\[ \text{VGPR} \]

\[ \text{CR} \]

\[ \text{sCR} \]

\[ \text{Voorhees PM, et al. ASH 2019; abstract 691; Voorhees PN, et al. Blood 2020 [online ahead of print]} \]
**GRiffin:** responses deepened over time

**D-RVd**

<table>
<thead>
<tr>
<th>Time</th>
<th>≥CR</th>
<th>CR</th>
<th>PR</th>
<th>sCR</th>
<th>sCR Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>End of induction</td>
<td>12.1</td>
<td>21.2</td>
<td>52.5</td>
<td>7.1</td>
<td></td>
</tr>
<tr>
<td>End of ASCT</td>
<td>21.2</td>
<td>59.6</td>
<td>26.3</td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td>End of consolidation</td>
<td>42.4</td>
<td>39.4</td>
<td>21.2</td>
<td>0.0</td>
<td></td>
</tr>
</tbody>
</table>
| Clinical cutoff       | 62.6| 17.2| 16.2| 0.0 | 1.98 (95% CI, 1.12-3.49; P = 0.0177)

**RVd**

<table>
<thead>
<tr>
<th>Time</th>
<th>≥CR</th>
<th>CR</th>
<th>PR</th>
<th>sCR</th>
<th>sCR Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>End of induction</td>
<td>7.2</td>
<td>14.4</td>
<td>43.3</td>
<td>6.2</td>
<td></td>
</tr>
<tr>
<td>End of ASCT</td>
<td>25.8</td>
<td>46.4</td>
<td>35.1</td>
<td>8.2</td>
<td></td>
</tr>
<tr>
<td>End of consolidation</td>
<td>8.2</td>
<td>10.3</td>
<td>30.9</td>
<td>8.2</td>
<td></td>
</tr>
</tbody>
</table>
| Clinical cutoff       | 45.4| 15.5| 18.6| 7.2 | 2.53 (95% CI, 1.33-4.81; P = 0.0045)

- 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

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

Voorhees PM, et al. ASH 2019; abstract 691;
GRIFFIN: MRD (10⁻⁵) Negativityᵃ at Clinical Cutoff

Randomized (N = 207)

D-RVd (ITT,ᵇ n = 104)
- MRD negative 51.0%
- MRD negative & ≥CR 47.1%
- ≥CR (n = 79)
- MRD negative 62.0%
- MRD evaluableᵈ (n = 77)
- MRD negative 68.8%

RVd (ITT,ᵇ n = 103)
- MRD negative 20.4%
- MRD negative & ≥CR 18.4%
- ≥CR (n = 59)
- MRD negative 32.2%
- MRD evaluableᵈ (n = 65)
- MRD negative 32.3%

P <0.0001ᶜ

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

ᵃThe threshold of MRD negativity was defined as 1 tumor cell per 10⁵ 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.ᵇFor the ITT population, patients with a missing or inconclusive assessment were considered MRD positive.ᶜP-values were calculated from the Fisher’s exact test.ᵈThe 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.

**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

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>RVd</th>
<th>D-RVd</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>18/55 (32.7)</td>
<td>21/55 (38.2)</td>
<td>1.27 (0.58-2.78)</td>
</tr>
<tr>
<td>Female</td>
<td>13/42 (31.0)</td>
<td>21/44 (47.7)</td>
<td>2.04 (0.84-4.92)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65 yr</td>
<td>22/70 (31.4)</td>
<td>30/72 (41.7)</td>
<td>1.56 (0.78-3.10)</td>
</tr>
<tr>
<td>≥65 yr</td>
<td>9/27 (33.3)</td>
<td>12/27 (44.4)</td>
<td>1.60 (0.53-4.82)</td>
</tr>
<tr>
<td>ISS disease stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>11/48 (22.9)</td>
<td>19/48 (39.6)</td>
<td>2.20 (0.91-5.35)</td>
</tr>
<tr>
<td>II</td>
<td>12/35 (34.3)</td>
<td>17/37 (45.9)</td>
<td>1.63 (0.63-4.22)</td>
</tr>
<tr>
<td>III</td>
<td>7/13 (53.8)</td>
<td>6/14 (42.9)</td>
<td>0.64 (0.14-2.94)</td>
</tr>
<tr>
<td>Type of multiple myeloma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IgG</td>
<td>8/51 (15.7)</td>
<td>15/51 (29.4)</td>
<td>2.24 (0.85-5.88)</td>
</tr>
<tr>
<td>Non-IgG</td>
<td>23/46 (50.0)</td>
<td>25/45 (55.6)</td>
<td>1.25 (0.55-2.85)</td>
</tr>
<tr>
<td>Cyogenetic risk</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High risk</td>
<td>4/13 (30.8)</td>
<td>3/16 (18.8)</td>
<td>0.52 (0.09-2.90)</td>
</tr>
<tr>
<td>Standard risk</td>
<td>26/80 (32.5)</td>
<td>39/79 (49.4)</td>
<td>2.03 (1.06-3.85)</td>
</tr>
<tr>
<td>EC06 PS score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>13/39 (33.3)</td>
<td>16/38 (42.1)</td>
<td>1.45 (0.58-3.67)</td>
</tr>
<tr>
<td>1 or 2</td>
<td>18/58 (31.0)</td>
<td>25/60 (41.7)</td>
<td>1.59 (0.74-3.38)</td>
</tr>
</tbody>
</table>

---

### Minimal residual disease negativity by last follow-up

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>RVd</th>
<th>D-RVd</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>10/60 (16.7)</td>
<td>26/58 (44.8)</td>
<td>4.06 (1.73-9.54)</td>
</tr>
<tr>
<td>Female</td>
<td>11/43 (25.6)</td>
<td>27/46 (58.7)</td>
<td>4.13 (1.68-10.19)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65 yr</td>
<td>16/75 (21.3)</td>
<td>38/76 (50.0)</td>
<td>3.69 (1.81-7.52)</td>
</tr>
<tr>
<td>≥65 yr</td>
<td>5/28 (17.9)</td>
<td>15/28 (53.6)</td>
<td>5.31 (1.57-17.97)</td>
</tr>
<tr>
<td>ISS disease stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>6/50 (12.0)</td>
<td>25/49 (51.0)</td>
<td>7.64 (2.75-21.19)</td>
</tr>
<tr>
<td>II</td>
<td>10/37 (27.0)</td>
<td>20/40 (50.0)</td>
<td>2.70 (1.04-7.01)</td>
</tr>
<tr>
<td>III</td>
<td>5/14 (35.7)</td>
<td>8/14 (57.1)</td>
<td>2.40 (0.52-10.99)</td>
</tr>
<tr>
<td>Type of multiple myeloma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IgG</td>
<td>11/52 (21.2)</td>
<td>29/55 (52.7)</td>
<td>4.16 (1.78-9.73)</td>
</tr>
<tr>
<td>Non-IgG</td>
<td>10/51 (19.6)</td>
<td>22/46 (47.8)</td>
<td>3.76 (1.53-9.26)</td>
</tr>
<tr>
<td>Cyogenetic risk</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High risk</td>
<td>4/14 (28.6)</td>
<td>6/16 (37.5)</td>
<td>1.50 (0.32-6.99)</td>
</tr>
<tr>
<td>Standard risk</td>
<td>17/83 (20.5)</td>
<td>45/82 (54.9)</td>
<td>4.72 (2.37-9.40)</td>
</tr>
<tr>
<td>EC06 PS score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>5/40 (12.5)</td>
<td>21/39 (53.8)</td>
<td>8.17 (2.64-25.25)</td>
</tr>
<tr>
<td>1 or 2</td>
<td>16/62 (25.8)</td>
<td>32/62 (51.6)</td>
<td>3.07 (1.44-6.53)</td>
</tr>
</tbody>
</table>

---

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; 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.

MASTER Phase 2 study: design

**Dara-KRd**
- Daratumumab 16 mg/m² Days 1,8,15,22 (days 1,15 C 3-6; day 1 C >6)
- Carfilzomib (20) 56 mg/m² Days 1,8,15
- Lenalidomide 25 mg Days 1-21
- Dexamethasone 40 mg PO Days 1,8,15,22

**Induction**
- Dara-KRd x 4

**AHCT**

**Consolidation**
- Dara-KRd x 4
- MRD assessment by NGS

**Consolidation**
- Dara-KRd x 4
- 2nd MRD (-) (<10⁻⁵)

**Treatment-free observation and MRD surveillance**

**Lenalidomide Maintenance**

- 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

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

Best MRD response by phase of therapy:
- Post Induction (N=67)
- Post Transplant (N=38)
- MRD-directed consolidation (N=38)

Best IMWG response by phase of therapy:
- Post Induction Cycle 2 (N=81)
- Post Induction Cycle 4 (N=70)
- Post Transplant (N=42)
- MRD-based consolidation (N=42)

Costa L, et al. ASH 2019; abstract 860
## Response to induction with or without daratumumab

<table>
<thead>
<tr>
<th></th>
<th>VTd 28 d Cassiopeia trial</th>
<th>D-VTd 28 d Cassiopeia trial</th>
<th>RVd 21 d IFM2009 trial</th>
<th>RVd 28 d GEM2012 trial</th>
<th>RVd 21d</th>
<th>Dara-VRd 21d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nº of cycles of induction</td>
<td>4</td>
<td>4</td>
<td>3</td>
<td>6</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Nº of patients</td>
<td>542</td>
<td>543</td>
<td>350</td>
<td>458</td>
<td>102</td>
<td>99</td>
</tr>
<tr>
<td>Response Post-induction</td>
<td>≥ VGPR 56.1 8.9 6.5</td>
<td>≥ CR 65 14 7</td>
<td>47</td>
<td>67 33</td>
<td>57 13 7</td>
<td>72 19 12</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

EMN02/HO95 MM trial: Randomization 1

1192 pts were eligible for R1

Single ASCT policy
Randomization 1:1

- VMP (294 pts)
- ASCT-1 (280 pts)

Double ASCT policy
Randomization 1:1:1

- VMP (203 pts)
- ASCT-1 (208 pts)
- ASCT-2 (207 pts)

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

**PFS: ITT**
- Median PFS: ASCT-2: NR; ASCT-1: 28.7 mos
- HR: 0.42 (95% CI, 0.21-0.84), P=0.014

**OS: ITT**
- HR: 0.51 (95% CI, 0.31-0.86), P=0.011

**PFS: High-Risk cyto**
- Median PFS: ASCT-2: NR; ASCT-1: 28.7 mos
- HR: 0.42 (95% CI, 0.21-0.84), P=0.014

**OS: High-Risk cyto**
- HR: 0.52 (95% CI, 0.28-0.98), P=0.042

BMT CTN0702 (STAMINA) study design

N=750 pts (250 in each arm)

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

Lenalidomide Maintenance**
- N=257

Lenalidomide Maintenance**
- N=254

Lenalidomide Maintenance**
- N=247

* Bortezomib 1.3mg/m² 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

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

What about maintenance after auto-SCT?
What we know today for transplant-eligible patients with MM: Maintenance with lenalidomide

### Lenalidomide

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

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

Bortezomib

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

* Bortezomib administered at 1.3mg/m² IV in both studies

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)

**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**

**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**

**1:1 Randomization**

**Continue until PD or 36 cycles**

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

- Presentation
- PR
- VGPR
- CR
- stringent CR

- Total number of tumor cells
- MRD
- Undetectable MRD

- Time to progression
- Diagnosis
- End of therapy

MRD by:
- Flow (NGF)
- Sequencing (NGS)
- Imaging (PET)

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.
Thank you for attending!

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