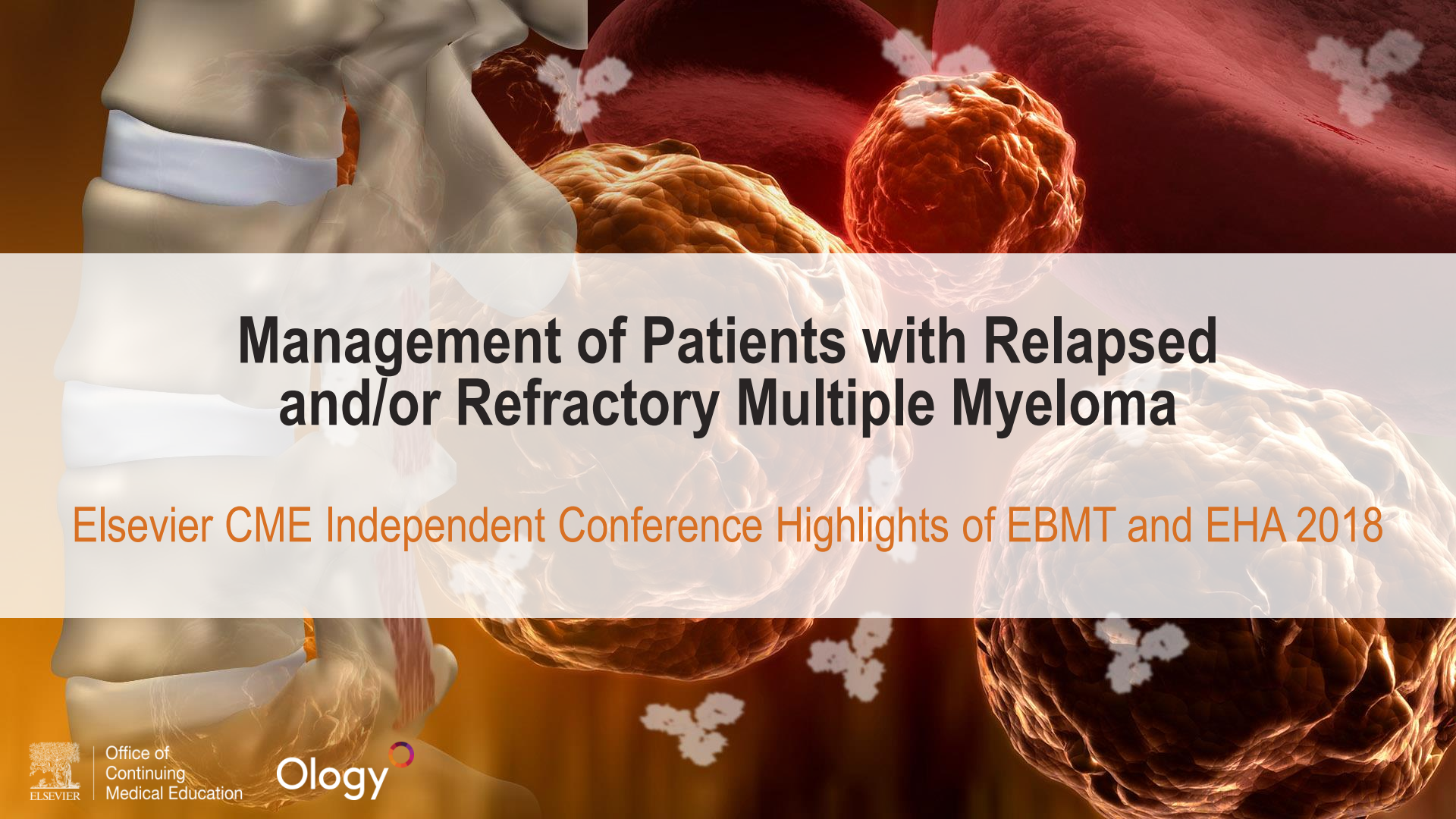

Management of Patients with Relapsed and/or Refractory Multiple Myeloma

Elsevier CME Independent Conference Highlights of EBMT and EHA 2018

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Faculty

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Spain

Multiple Myeloma Background

- Plasma cell malignancy
  - Malignant cells accumulate in the bone marrow, leading to marrow failure and bone destruction[1]
- Second most common hematological malignancy[2]
  - 30,770 new cases and 12,770 deaths estimated for 2018 in the USA[3]
- New treatments have been improving outcomes
  - 5-year survival was 34.6% in 2000 and was 53% in 2010[3]
  - Median survival has improved from 3-4 years to 7-8 years in the past 2 decades[4]
- Successes mainly due to[4]:
  - HDT-ASCT in transplant-eligible patients
  - IMiDs (e.g. lenalidomide, thalidomide) and PIs (e.g. bortezomib, carfilzomib)
  - Improvements in supportive care

HDT-ASCT, high-dose chemotherapy plus autologous stem cell transplantation; IMiD, immunomodulatory agent; PI, proteasome inhibitor.

1. National Comprehensive Cancer Network (NCCN). Multiple Myeloma. v4. 2018.
2. Mahajan S, et al. Ther Adv Hematol. 2018;9:123-33.
3. SEER Stat Fact Sheets: Myeloma. 2018. Available from: https://seer.cancer.gov/statfacts/html/mulmy.html. Accessed June, 2018.
4. Nijhof IS, et al. Drugs. 2018;78:19-37.

Unmet Needs in RRMM

Prolong remission with effective, well-tolerated therapies

- Most patients with MM experience relapse[1]
- Prognosis is particularly poor in patients who have received > 2 lines of therapy and are refractory to both PIs and IMiDs[1]
- Optimal combinations of novel PIs, IMiDs, and monoclonal antibodies have to be defined[2,3]
- Dosing regimens of current agents and combinations have to be improved[3]
- The role of autologous and allogeneic SCT after relapse has to be clarified[4]
- The role of new immunotherapy agents in development must be defined[4]

MM, multiple myeloma; RRMM, relapsed/refractory multiple myeloma; SCT, stem cell transplantation.

1. Nijhof IS, et al. Drugs. 2018;78:19-37.
2. Chim CS, et al. Leukemia. 2018;32:252-62.
3. Sonneveld P, et al. Crit Rev Oncol Hematol. 2017;112:153-70.
4. Mahajan S, et al. Ther Adv Hematol. 2018;9:123-33.

Treatment Strategy for Newly Diagnosed Patients With Active MM

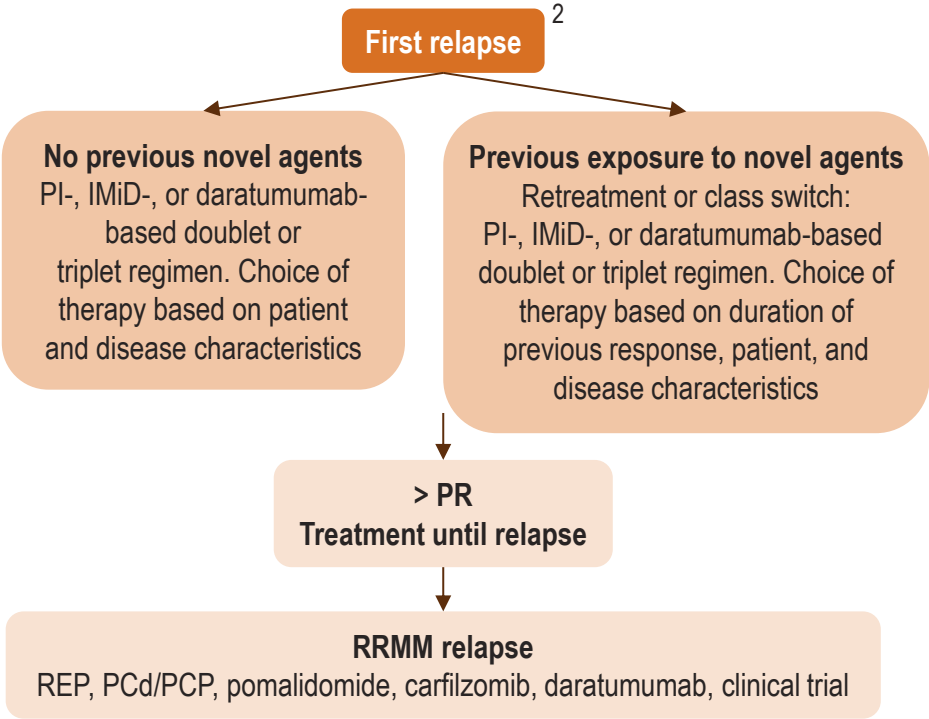
- Primary high-dose systemic therapy followed by SCT for eligible patients
- Less aggressive systemic treatment for patients with comorbidities
- Maintenance important both after SCT and in transplant-ineligible patients
  - Shown to improve OS and PFS after SCT

OS, overall survival; PFS, progression-free survival.

National Comprehensive Cancer Network (NCCN). Multiple Myeloma. v4. 2018.

Therapy for Previously Treated MM

- Preferred regimens[1]
  - Repeat primary induction therapy (if relapse at > 6 months)
  - Bortezomib, lenalidomide, dexamethasone
  - Carfilzomib, dexamethasone
  - Carfilzomib, lenalidomide, dexamethasone
  - Daratumumab, bortezomib, dexamethasone
  - Daratumumab, lenalidomide, dexamethasone
  - Elotuzumab, lenalidomide, dexamethasone
  - Ixazomib, lenalidomide, dexamethasone



PCd, pomalidomide, cyclophosphamide, dexamethasone;
PCP, pomalidomide, cyclophosphamide, prednisone;
PR, partial response; REP, lenalidomide, cyclophosphamide, prednisone.

1. National Comprehensive Cancer Network (NCCN). Multiple Myeloma. v4. 2018.
2. Nijhof IS, et al. Drugs. 2018;78:19-37.

Discussion Outline

Parameswaran Hari Jesús San Miguel	Noopur Raje	Jesús San Miguel	Parameswaran Hari	Final Discussion
Role of Proteasome Inhibitors	Role of IMiDs	Role of Monoclonal Antibodies	Allogeneic Stem Cell Transplantation	

IMiDs, immunomodulatory drugs.

Role of Proteasome Inhibitors

- EHA-PF561: Subgroup Analysis of ENDEAVOR
- EBMT-B229 / EHA-PS1309: ASPIRE and ENDEAVOR by Prior ASCT Status
- EHA-S849: A.R.R.O.W. Trial: Carfilzomib Dosing
- EHA-PF554: MUK Five Study: Carfilzomib Maintenance

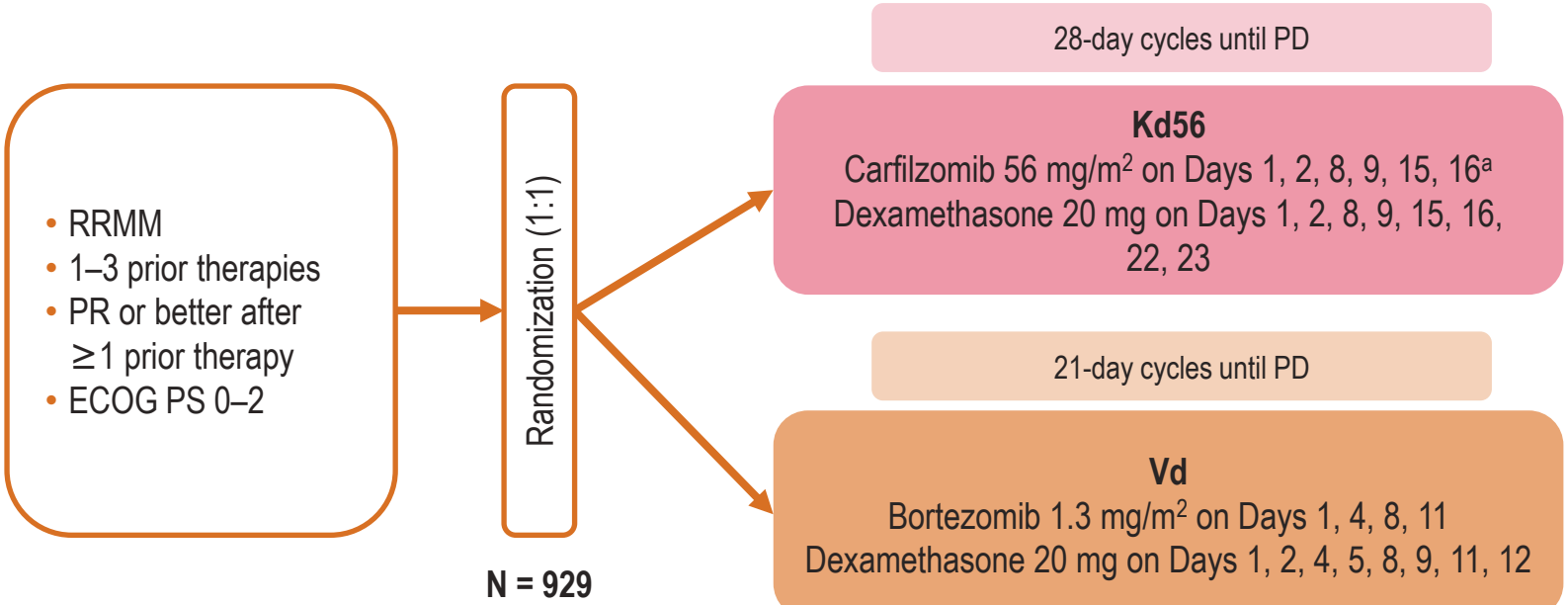
EHA-PF561: Subgroup Analysis of ENDEAVOR

Robert Z. Orlowski, Philippe Moreau, Heinz Ludwig, Albert Oriol Rocafiguera, Wee Joo Chng, Hartmut Goldschmidt, Zhao Yang, Amy S. Kimball, Meletios Dimopoulos

- **Objective:** Report additional OS and safety data from the Phase 3 ENDEAVOR trial after an additional 6 months of follow-up

Orlowski RZ, et al. Presented at EHA 2018. Abstract PF561.

ENDEAVOR (Kd vs Vd): Study Design



Primary endpoint of study: PFS

[a] Starting dose was 20 mg/m^2 on Days 1 and 2 of Cycle 1.
ECOG PS, Eastern Cooperative Oncology Group performance status; Kd, carfilzomib, low-dose dexamethasone; PD, progressive disease; PR, partial response; Vd, bortezomib, low-dose dexamethasone.

Dimopoulos MA, et al. Lancet Oncol. 2016;17:27-38.
Orlowski RZ et al. Presented at EHA 2018. Abstract PF561.
Goldschmidt H, et al. Presented at EBMT 2018. Abstract B229. and EHA 2018. Abstract PS1309.

Results: OS in ENDEAVOR Follow-Up

	Kd56 (n = 464)	Vd (n = 465)
Median OS, mos	47.8	38.8
HR (Kd56/Vd) (95% CI)	0.761 (0.633–0.915)	
p value	0.0017	

- 9-month improvement in OS with Kd56 compared with Vd
- OS benefits were observed in patient subgroups (elderly patients, high-risk cytogenetics, subgroups defined by prior treatment)

CI, confidence interval; HR, hazard ratio; Kd56, carfilzomib, dexamethasone.

Orlowski RZ et al. Presented at EHA 2018. Abstract PF561.

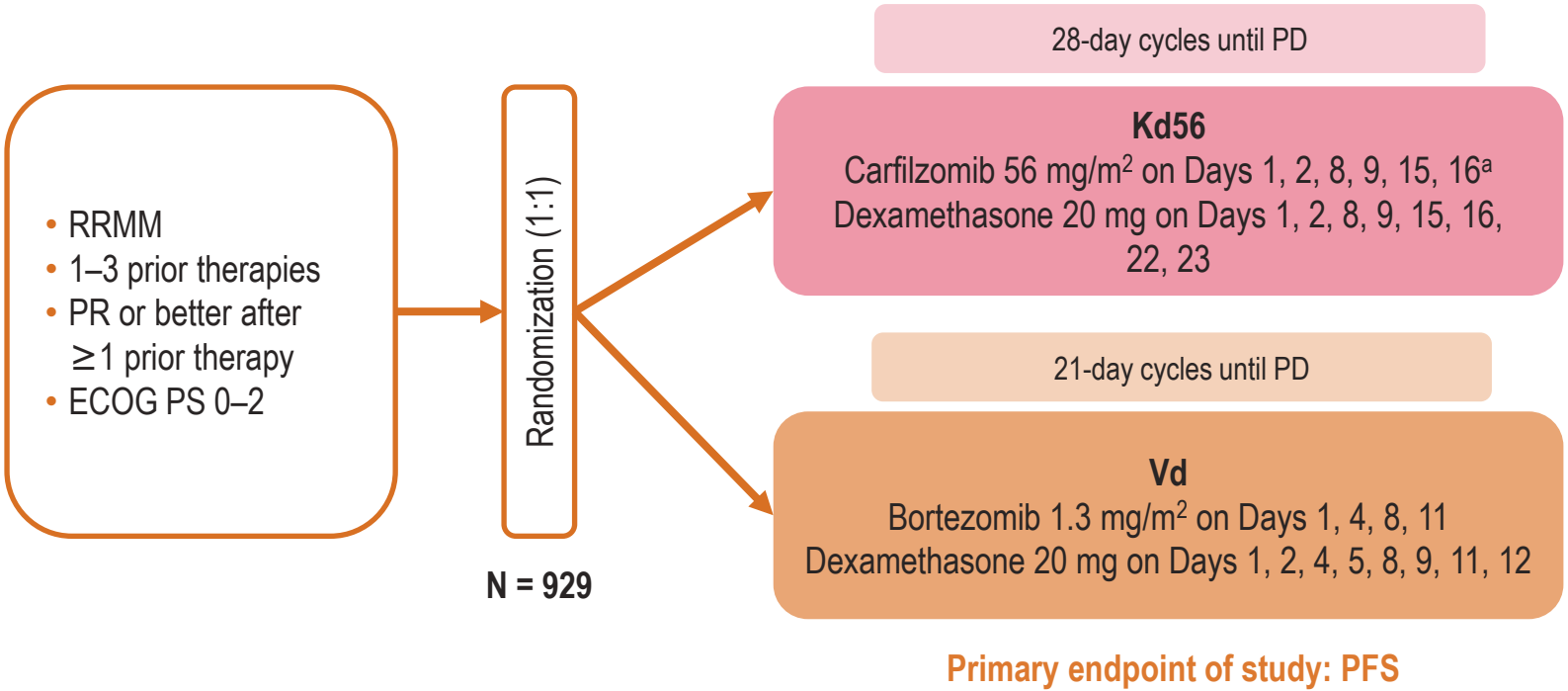
EBMT-B229 / EHA-PS1309:
ASPIRE and ENDEAVOR by prior ASCT status

Hartmut Goldschmidt, Maria-Victoria Mateos, David Siegel, Rafat Abonour, Heinz Ludwig, Mihaela Obreja, Karim Saad Iskander, Parameswaran Hari

- **Objective:** To evaluate OS of patients who participated in the Phase 3 ASPIRE (carfilzomib, lenalidomide, and dexamethasone vs lenalidomide and dexamethasone) or ENDEAVOR trials (carfilzomib and dexamethasone vs bortezomib and dexamethasone) in RRMM according to their prior ASCT status

Goldschmidt H, et al. Presented at EBMT 2018. Abstract B229 and EHA 2018 abstract PS1309.

ENDEAVOR (Kd vs Vd): Study Design

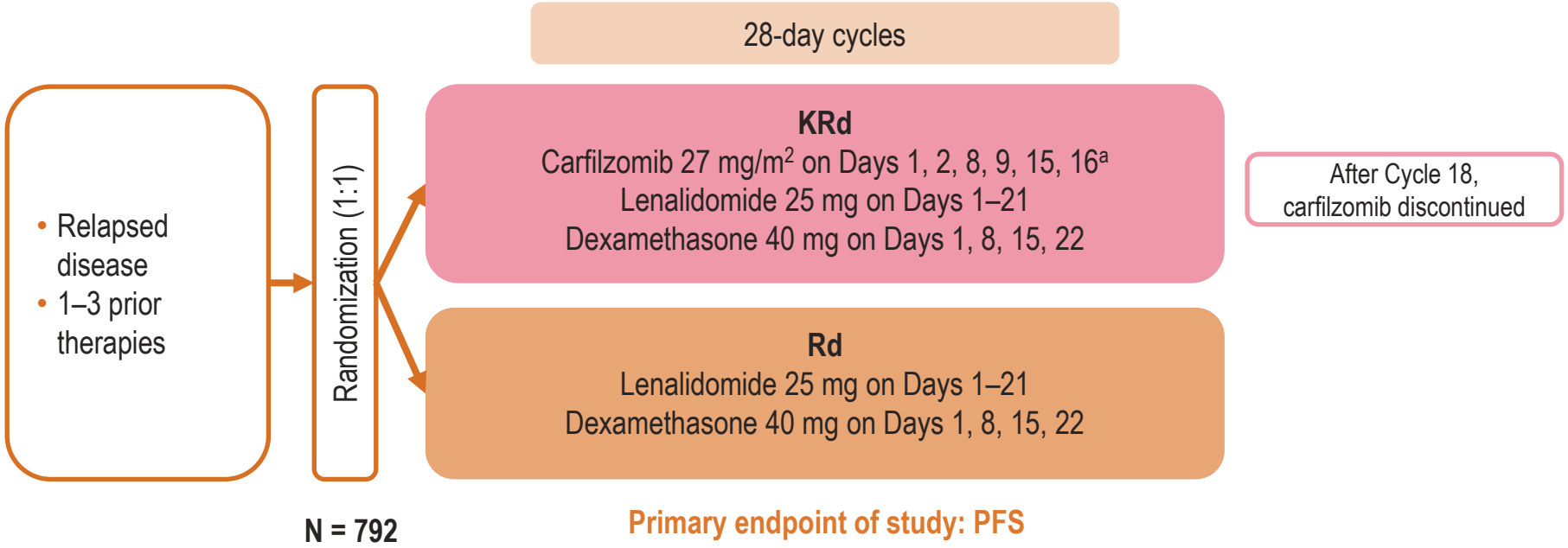


Primary endpoint of study: PFS

[a] Starting dose was 20 mg/m^2 on Days 1 and 2 of Cycle 1.

Dimopoulos MA, et al. Lancet Oncol. 2016;17:27-38.
Goldschmidt H, et al. Presented at EBMT 2018. Abstract B229. and EHA 2018. Abstract PS1309.

ASPIRE (KRd vs Rd): Study Design

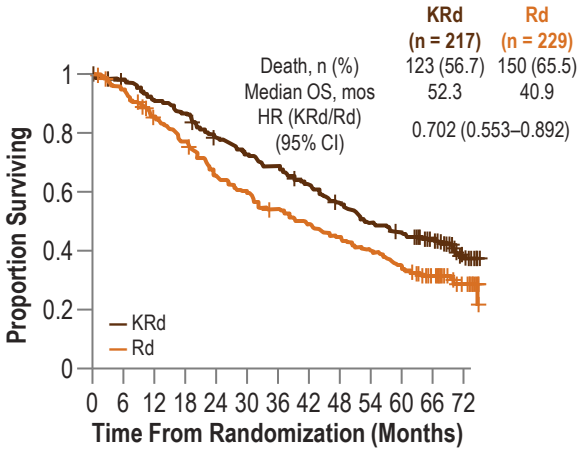


[a] Starting dose was 20 mg/m^2 on Days 1 and 2 of Cycle 1.
KRd, carfilzomib, lenalidomide, low-dose dexamethasone; Rd, lenalidomide, dexamethasone.

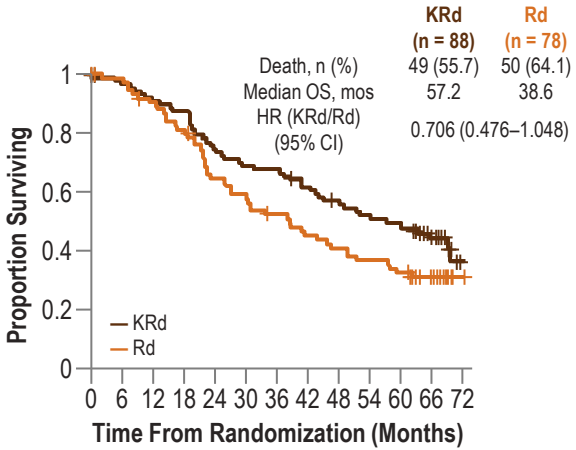
Stewart AK, et al. N Engl J Med. 2015;372:142-52.
Goldschmidt H, et al. Presented at EBMT 2018. Abstract B229. and EHA 2018. Abstract PS1309.

Results: ASPIRE by prior ASCT status

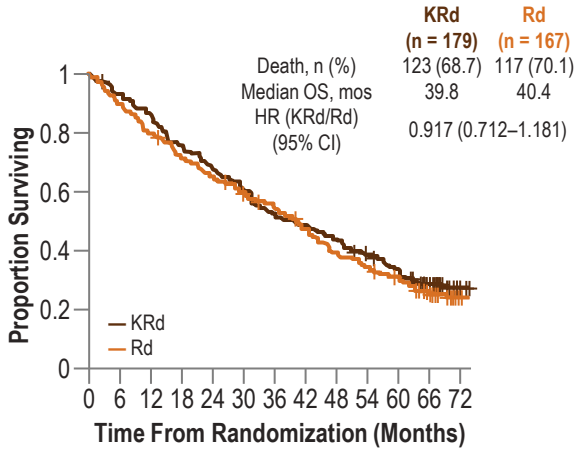
Prior ASCT



1R1T



No Prior ASCT



ASPIRE

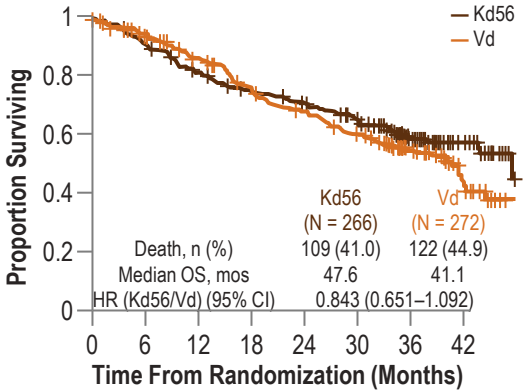
- Median OS improved by 11.4 months with KRd after prior ASCT
- For those after first relapse – median OS improved by 18.6 months

1R1T, first relapse after frontline ASCT.

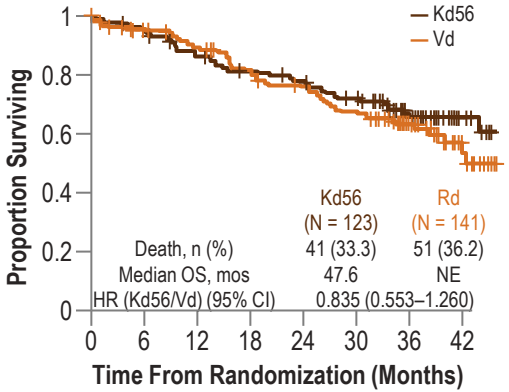
Goldschmidt H, et al. Presented at EBMT 2018. Abstract B229 and EHA 2018 abstract PS1309.

Results: ENDEAVOR by prior ASCT status

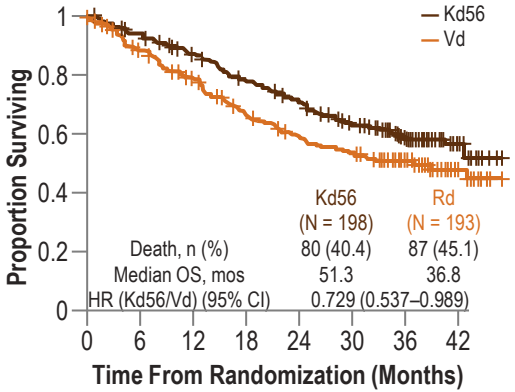
Prior ASCT



1R1T



No Prior ASCT



ENDEAVOR

- Benefit for Kd56 over Vd in all ASCT groups
- More evident in “no prior transplant” groups

Goldschmidt H, et al. Presented at EBMT 2018. Abstract B229 and EHA 2018 abstract PS1309.

Safety: ASPIRE and ENDEAVOR

- Safety data of the extended analyses of ASPIRE and ENDEAVOR were consistent with previous reports
- Carfilzomib was well tolerated independent of prior ASCT status

Goldschmidt H, et al. Presented at EBMT 2018. Abstract B229 and EHA 2018. Abstract PS1309.

EHA-S849: A.R.R.O.W. Trial – Carfilzomib Dosing

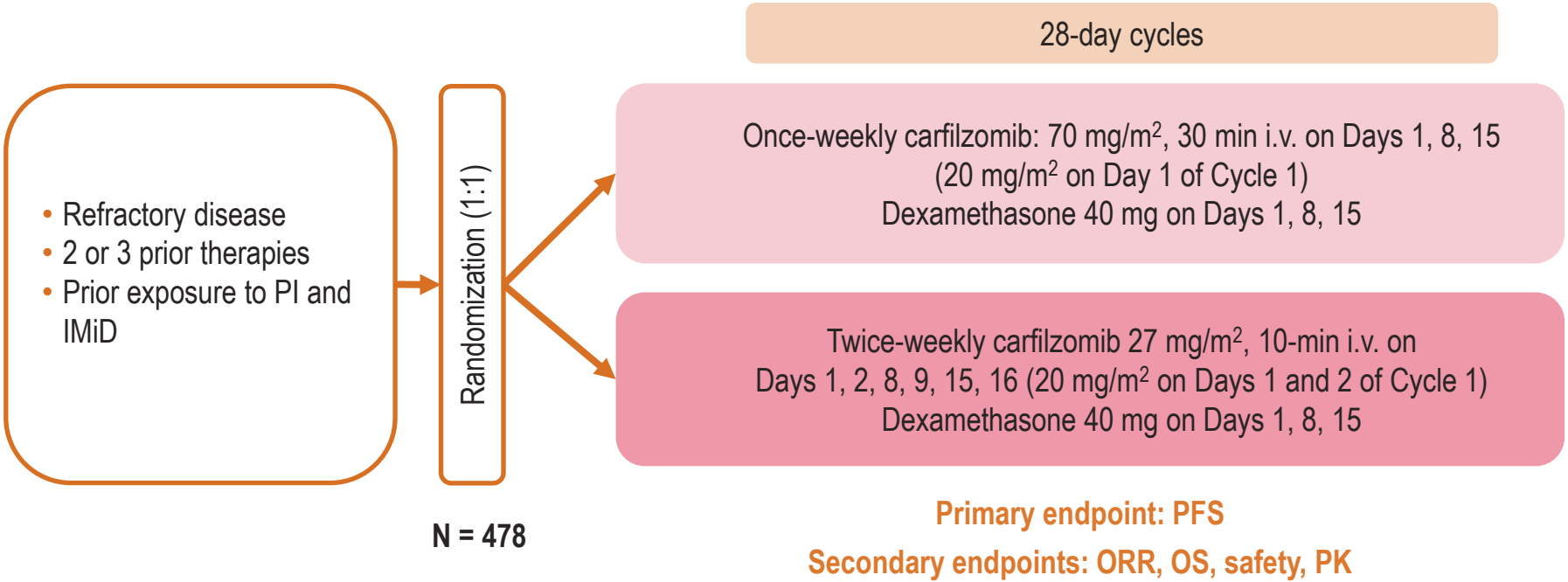
Maria-Victoria Mateos, Philippe Moreau, James R. Berenson, Katja Weisel, Antonio Lazzaro, Kevin Song, Meletios A. Dimopoulos, Mei Huang, Anita Zahlten-Kumeli, A. Keith Stewart

- **Background:** Improvement of carfilzomib dosing might increase adherence without impacting efficacy and safety of carfilzomib treatment

- **Objective:** To report data from the interim analysis of the phase 3 A.R.R.O.W. study of once-weekly vs twice-weekly carfilzomib plus dexamethasone in patients with RRMM

Mateos M-V, et al. Presented at EHA 2018. Abstract S849.
Moreau P, et al. Lancet Oncol. 2018;19:953-64.

A.R.R.O.W.: Study Design



ORR, overall response rate; PK, pharmacokinetics.

Mateos M-V, et al. Presented at EHA 2018. Abstract S849.
Moreau P, et al. Lancet Oncol. 2018;19:953-64.

A.R.R.O.W.: Results

- Baseline characteristics were well balanced

	Once Weekly	Twice Weekly	HR	p Value
PFS, months	11.2	7.6	0.69	0.0014
ORR, %	62.9	40.8		0.0001
≥ Grade 3 AE, %	67.6	61.7		
Grade 5 AE, %	2.1	0.9		
≥ Grade 3 hypertension, %	5.9	5.5		
≥ Grade 3 cardiac failure, %	2.9	4.3		

Once-weekly carfilzomib plus dexamethasone improved ORR and PFS compared with twice-weekly with similar safety

AE, adverse events.

Mateos M-V, et al. Presented at EHA 2018. Abstract S849.

EHA-PF554: MUK Five STUDY: Carfilzomib Maintenance

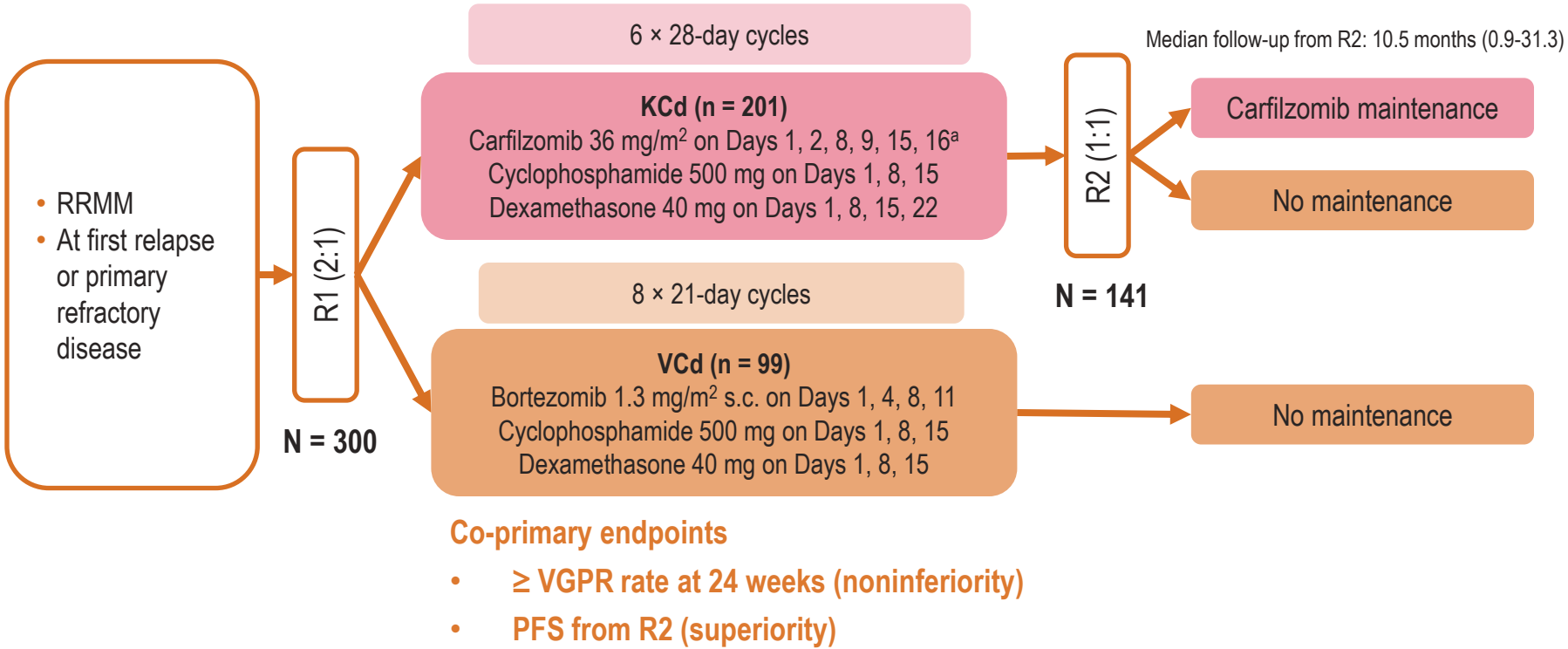
Kwee Yong, Samantha Hinsley, Debbie Sherratt, Sarah Brown, Louise Flanagan, Catherine Williams, Jamie Cavenagh, Martin Kaiser, Neil Rabin, Karthik Ramasamy, Mamta Garg, Holger Auner, Stephen Hawkins, Ceri Bygrave, Ruth De Tute, Gareth Morgan, Faith Davies, Roger Owen

- **Objective:** The MUK Five phase 2 study compared safety and activity of triplet therapy with KCd to VCd, as fixed-duration therapy for patients at first relapse, or refractory to 1 prior line. This analysis evaluated the activity and safety of maintenance carfilzomib vs observation after KCd

KCd, carfilzomib, cyclophosphamide, dexamethasone;
VCd, bortezomib, cyclophosphamide, dexamethasone.

Yong K, et al. Presented at EHA 2018. Abstract PF554.

Phase 2 MUK Five (KCd vs VCd at First Relapse): Study Design



Co-primary endpoints

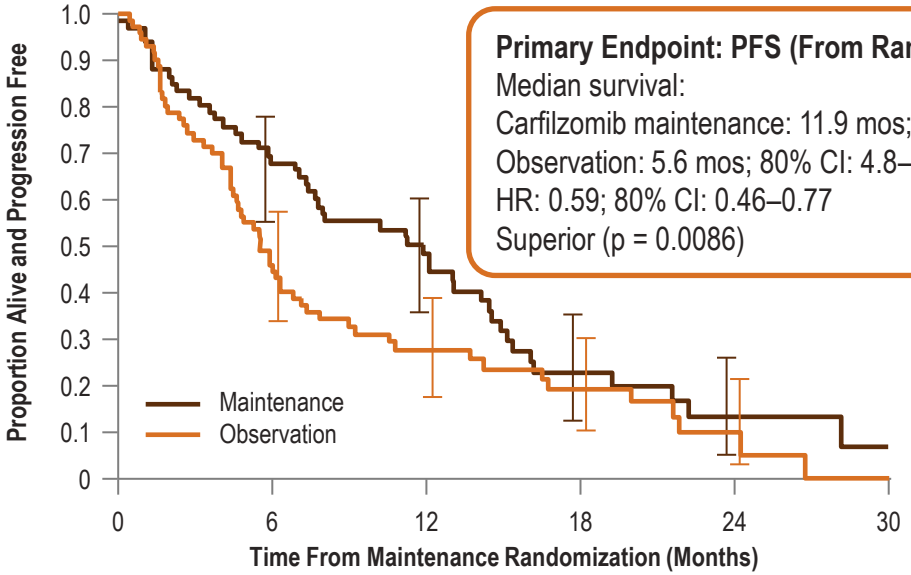
- **≥ VGPR rate at 24 weeks (noninferiority)**
- **PFS from R2 (superiority)**

[a] Starting dose was 20 mg/m^2 on Days 1 and 2 of Cycle 1.
R1, first randomization; R2, second randomization; s.c., subcutaneously; VGPR, very good partial response.

Yong K, et al. Presented at EHA 2018. Abstract PF554.
Brown S, et al. BMC Hematol. 2016;16:14.

MUK Five: Results

Maintenance Treatment: Efficacy (n = 141)



Primary Endpoint: PFS (From Randomization 2)
Median survival:
Carfilzomib maintenance: 11.9 mos; 80% CI: 8.0–13.1
Observation: 5.6 mos; 80% CI: 4.8–6.4
HR: 0.59; 80% CI: 0.46–0.77
Superior (p = 0.0086)

Primary endpoints at 24 weeks (R1)
≥VGPR:
KCD 40.2% vs VCD 31.9%
ORR:
KCD 84.0% vs VCD 68.1%
(p=0.0014, superior)

Maintenance therapy with carfilzomib was associated with longer PFS

AEs during maintenance were predominantly of Grade 1 and 2

Median PFS from randomization 1 for maintenance group: 18.1 months; 80% CI: 14.4–18.9

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

Yong K, et al. Presented at EHA 2018. Abstract PF554.

Discussion: Are These Results on Prolonged PI Therapy Guideline-Changing?

- It was already known that prolonged treatment with bortezomib was associated with longer PFS and disease control
- These data show that prolonged therapy with carfilzomib is also associated with improved efficacy in this setting
  - The data from these 2 studies are complementary, showing the tolerability of the once-weekly dose of carfilzomib and the efficacy of the maintenance regimen
  - It might even be possible to modify the maintenance regimen to a once-weekly or once every other week schedule with similar efficacy

Personal communication: Parameswaran Hari and Jesús San Miguel.

Discussion: Do You Consider Carfilzomib Standard of Care for RRMM?

- After first relapse
  - Yes, combinations including carfilzomib after prior lenalidomide therapy, for example, are going to be commonly used
- When to use doublet or triplet regimens
  - The data indicate that carfilzomib doublet treatment is more effective after the first relapse than the second relapse, but the triplet treatment is similar for both

Personal communication: Parameswaran Hari and Jesús San Miguel.

Discussion: How Do You Choose Between Carfilzomib Regimens?

- It seems that with carfilzomib, higher doses provide greater efficacy and most investigators will try to use the highest dose that can be tolerated
  - For patients who are not responding to a lower dose, such as 27 mg/m^2, but are tolerating it well, it makes sense to try a higher dose
- In patients with high-risk cytogenetics, triplet regimens that combine a PI and an IMiD are more effective than doublet regimens
- In the elderly, doublet regimens are very popular and the once-weekly regimen is also likely to be very popular in this patient population

Personal communication: Parameswaran Hari and Jesús San Miguel.

Discussion: Can You Discuss Novel PIs in Development?

- Novel PIs that are being investigated include oprozomib, an oral second-generation inhibitor, and marizomib
- The new oral PIs will likely have a great impact on treatment of all MM patients, but will have a particular impact in the maintenance phase of treatment

Personal communication: Parameswaran Hari and Jesús San Miguel.

Role of Immunomodulatory Drugs

- EHA-S847: OPTIMISMM: Pomalidomide Regimen
- EHA-PS1292: MM-014 Trial: Pomalidomide Regimen

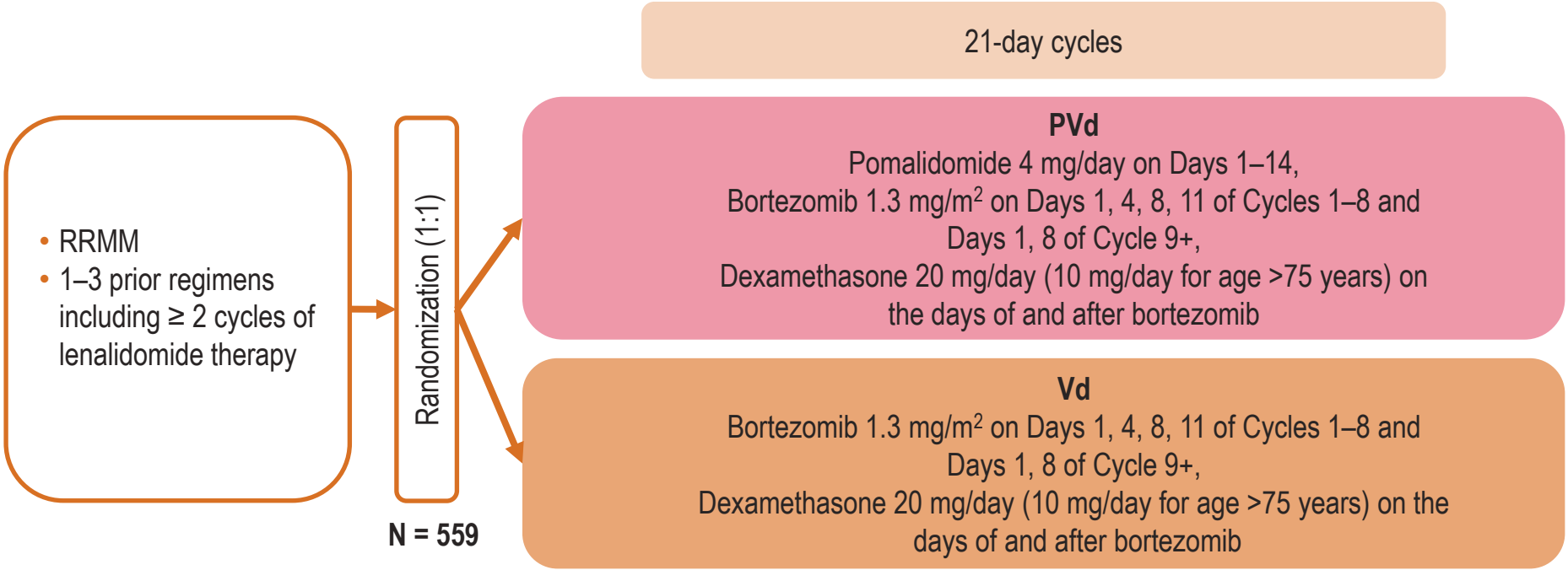
EHA-S847: OPTIMISMM: Pomalidomide Regimen

Paul Richardson, Albert Oriol Rocafiguera, Meral Beksac, Anna Marina Liberati, Monica Galli, Fredrik Schjesvold, Jindriska Lindsay, Katja Weisel, Darrell White, Thierry Facon, Jesus San Miguel, Kazutaka Sunami, Peter O'Gorman, Pieter Sonneveld, Pawel Robak, Sergey Semochkin, Steve Schey, Xin Yu, Thomas Doerr, Amine Bensmaine, Tsvetan Biyukov, Teresa Peluso, Mohamed Zaki, Kenneth Anderson, Meletios Dimopoulos

- **Objective:** Phase 3 trial to compare the safety and efficacy of pomalidomide, bortezomib, and low-dose dexamethasone with bortezomib and low-dose dexamethasone in patients with RRMM who were previously exposed to lenalidomide

Richardson P, et al. Presented at EHA 2018. Abstract S847.

OPTIMISMM: Study design



Richardson P, et al. Presented at EHA 2018. Abstract S847.

OPTIMISMM: Results

Efficacy	ITT		1 prior treatment line	
	PVd n = 281	Vd n = 278	PVd n = 111	Vd n = 115
PFS, months				
Median	11.20	7.10	20.73	11.63
HR (95% CI)	0.61 (0.49–0.77)		0.54 (0.36–0.82)	
p value	< 0.0001		NA	
ORR (≥ PR), %	82.2	50.0	90.1	54.8
≥ VGPR, %	52.7	18.3	61.3	22.6

PVd significantly improved PFS vs Vd in lenalidomide-exposed patients with RRMM

- Safety of pomalidomide-based treatment was consistent with previous reports
- Most frequently reported grade 3/4 treatment-emergent AEs:
  - Neutropenia (42% vs 9%), infections (31% vs 18%), and thrombocytopenia (27% vs 29%)

ITT, intention-to-treat; NA, not applicable.

Richardson P, et al. Presented at EHA 2018. Abstract S847.

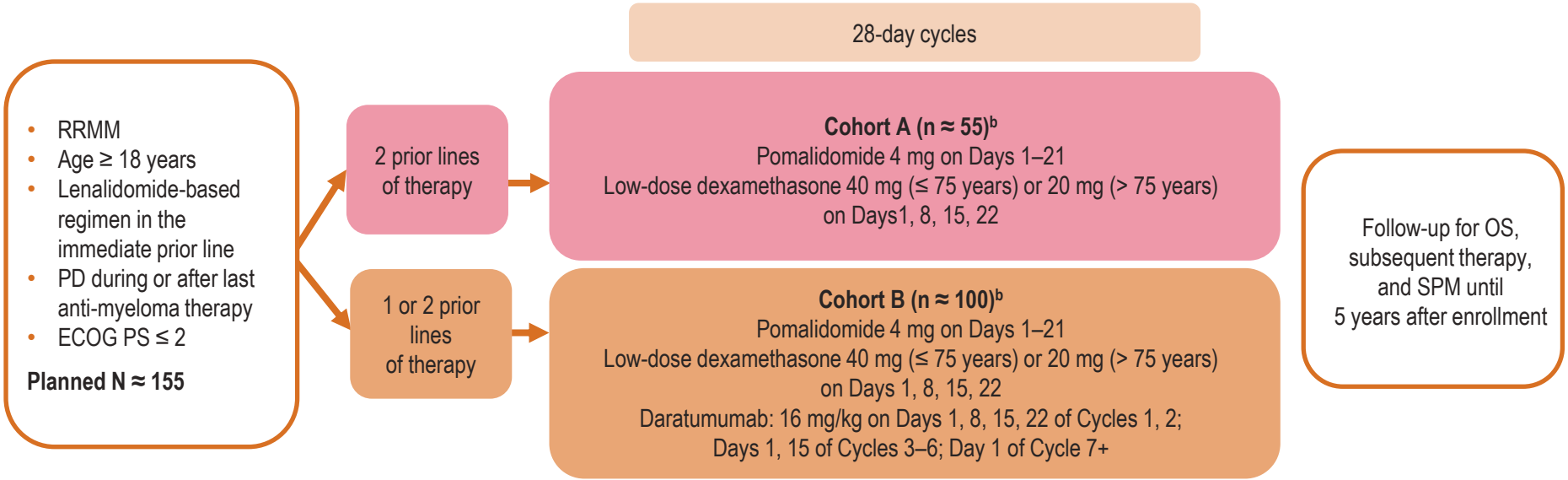
EHA-PS1292: MM-014 Trial: Pomalidomide Regimen

David S. Siegel, Gary J. Schiller, Christy Samaras, Michael Sebag, Jesus Berdeja, Siddharta Ganguly, Jeffrey Matous, Kevin Song, Christopher S. Seet, Giampaolo Talamo, Shanti Srinivas, Mirelis Acosta-Rivera, Michael Bar, Donald Quick, Bertrand Anz, Gustavo Fonseca, Donna Reece, Faiza Zafar, Weiyuan Chung, Nizar J. Bahlis

- **Objective:** To present efficacy and safety data for RRMM patients in the phase 2 MM-014 trial who received pomalidomide, low-dose dexamethasone, and daratumumab after lenalidomide-based treatment failure

Siegel DS, et al. Presented at EHA 2018. Abstract PS1292.

MM-014: Study Design

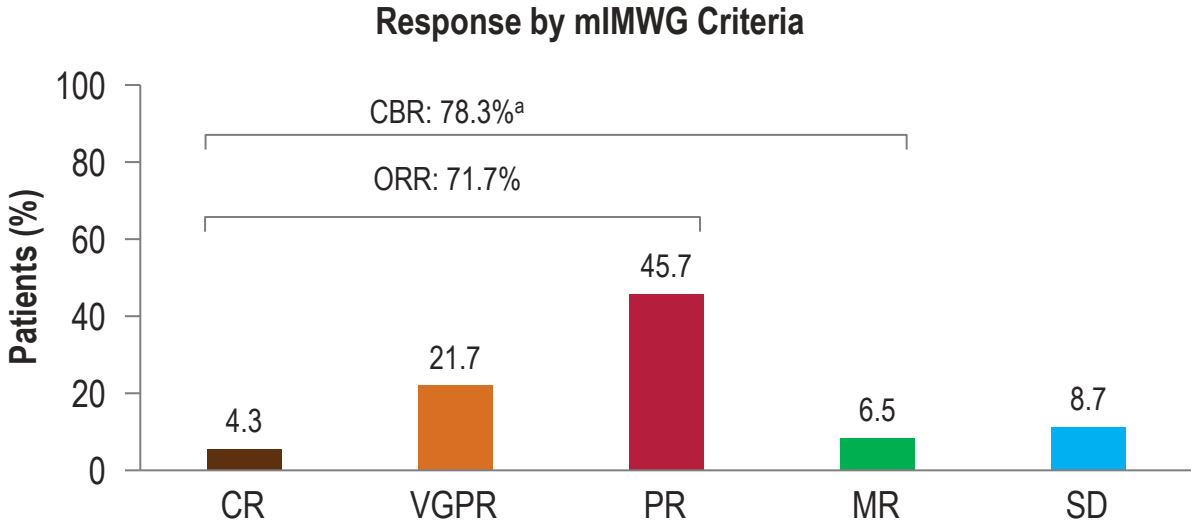


Primary endpoint: ORR by mIMWG criteria

SPM, second primary malignancy; mIMWG, modified International Myeloma Working Group criteria.

Siegel DS, et al. Presented at EHA 2018. Abstract PS1292.

MM-014: Results



- The most common grade 3/4 hematologic TEAE was neutropenia

ORR in the ITT was 71.7%
ORR in lenalidomide-refractory patients was 72.2%

[a] Due to rounding, percentages of CR, VGPR, PR, and MR may not add up to presented CBR value.
CBR, clinical benefit rate; CR, complete response; MR, minimal response; SD, stable disease; TEAE, treatment-emergent adverse effect.

Siegel DS, et al. Presented at EHA 2018. Abstract PS1292.

Discussion: The role of IMiD Regimens in RRMM

- Each of these studies highlights important data for lenalidomide-refractory disease
  - For those previously exposed to lenalidomide, pomalidome plus bortezomib provides significant benefit in early relapse
  - The addition of other drugs to pomalidomide in lenalidomide-refractory disease is of benefit and well tolerated
- These findings are relevant to practice in the USA where lenalidomide maintenance is standard practice
- IMiDs are well tolerated and seem to combine well with other regimens in this setting, particularly PIs and monoclonal antibodies
  - New combinations are being tested

Personal Communication: Noopur Raje.

Role of Monoclonal Antibodies

- EHA-LB2606: ELOQUENT-3 Study

EHA-LB2606: ELOQUENT-3 Study

Meletios A Dimopoulos, Dominik Dytfeld, Sebastian Grosicki, Philippe Moreau, Naoki Takezako, Mitsuo Hori, Xavier Leleu, Richard LeBlanc, Kenshi Suzuki, Marc S. Raab, Paul G. Richardson, Mihaela Popa McKiver, Ying-Ming Jou, Suresh G. Shelat, Michael Robbins, Brian Rafferty, Jesús San Miguel

- **Objective:** Phase 2 study to compare the efficacy and safety of elotuzumab, pomalidomide, and dexamethasone with that of pomalidomide and dexamethasone in patients with RRMM

Dimopoulos MA, et al. Presented at EHA 2018. Abstract LB2606.

ELOQUENT-3: Study Design

An international, open-label, randomized, phase 2 trial (NCT02654132), with a 2-sided α = 0.2 and 85% power to detect a true HR of 0.57

N = 117

- RRMM
- ≥ 2 prior lines of therapy
- Refractory to last therapy
- Refractory or relapsed and refractory to lenalidomide and a PI
- Prior pomalidomide not permitted

28-day cycles

EPd

Elotuzumab 10 mg/kg i.v. weekly on Cycles 1, 2

Elotuzumab 20 mg/kg i.v. every 4 weeks on Cycles 3+

Pomalidomide 4 mg orally on Days 1–21

Dexamethasone 40 mg[a] equivalent[b]; weekly

Pd

Pomalidomide 4 mg orally on Days 1–21

Dexamethasone 40 mg[a] orally; weekly

Endpoints

Primary
- PFS by investigator

Secondary
- ORR
- OS

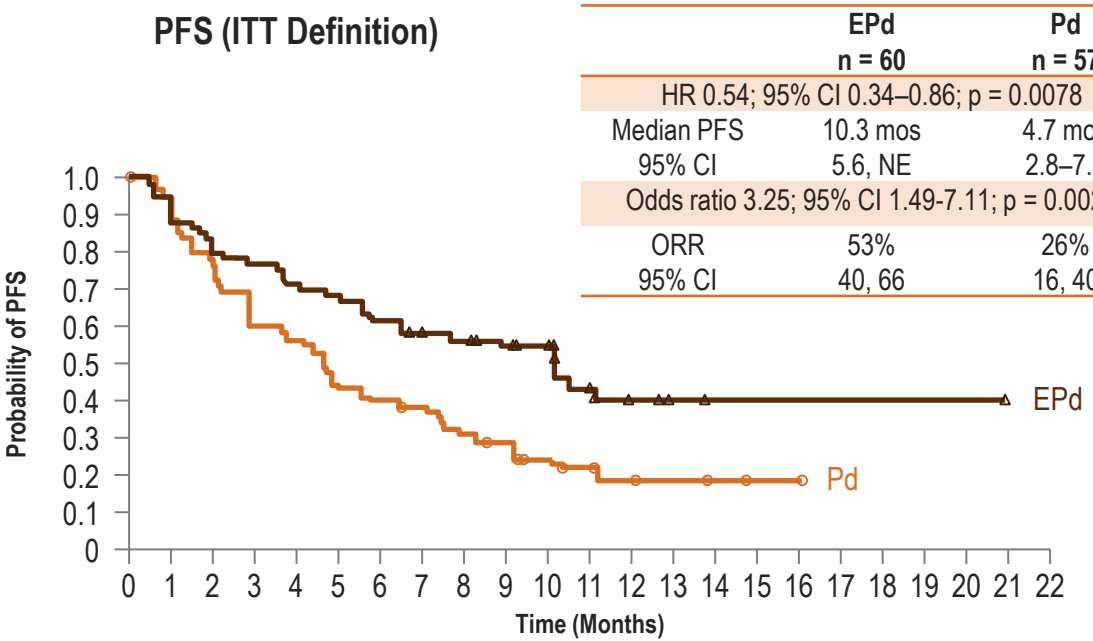
Exploratory
- Safety
- DOR

Database lock: Feb 21, 2018
Minimum follow-up: 9.1 months
Follow-up every 4 weeks[c]

[a] 20 mg in patients aged > 75 years.
[b] Dexamethasone was split between oral (28 or 8 mg in patients aged ≤ 75 or > 75 years) and i.v. (8 mg) doses on days with elotuzumab.
[c] Follow-up continued until PD; follow-up for survival occurred at least every 2 weeks.
DOR, duration of response; EPd, elotuzumab, pomalidomide, dexamethasone; Pd, pomalidomide, dexamethasone.

Dimopoulos MA, et al. Presented at EHA 2018. Abstract LB2606.

ELOQUENT-3: Results



	EPd n = 60	Pd n = 57
HR 0.54; 95% CI 0.34–0.86; p = 0.0078		
Median PFS	10.3 mos	4.7 mos
95% CI	5.6, NE	2.8–7.2
Odds ratio 3.25; 95% CI 1.49-7.11; p = 0.0029		
ORR	53%	26%
95% CI	40, 66	16, 40

- 46% reduction in risk of progression or death for EPd vs Pd
- Safety was similar to previous reports of elotuzumab and pomalidomide

Dimopoulos MA, et al. Presented at EHA 2018. Abstract LB2606.

Discussion: Role of Monoclonal Antibodies in RRMM

- The data shown here for the synergistic effects of elotuzumab with pomalidomide are even more exciting and interesting than the previous data for lenalidomide plus elotuzumab
- There is evidence that the benefits observed with the elotuzumab combination are durable in the long-term
- There are also reports that this combination has been used in multi-refractory patients with great success

Personal communication: Parameswaran Hari and Jesús San Miguel.

Discussion: Patient Selection for Combination Therapy With Elotuzumab Versus Daratumumab

- For rapid tumor debulking, a combination with daratumumab is useful
- In patients with non-aggressive relapse or slowly progressing disease, an elotuzumab combination may be very attractive
- It would be interesting to test the addition of elotuzumab to lenalidomide maintenance at the first indication of biochemical relapse
- In this study, after Cycle 2, elotuzumab was administered once every 4 weeks; this is very attractive to patients as well

Personal communication: Parameswaran Hari and Jesús San Miguel.

Role of Allogeneic Stem Cell Transplantation

- EBMT-OS4-2: Haploidentical Transplantation – EBMT/CIBMTR Report
- EBMT-B213: Allogeneic HSCT: Number of Prior Therapy Lines

HSCT, hemopoietic stem cell transplantation.

EBMT-OS4-2: Haploidentical Transplantation – EBMT/CIBMTR Report

Firoozeh Sahebi, Laurent Garderet, Abraham Kanate, Diderik-Jan Eikema, Nina Simone Knelange, Omar F Dávila Alvelo, Yener Koc, Didier Blaise, Qaiser Bashir, José M Moraleda, Peter Dreger, Stefan Ciurea, Harry Schouten, Nirav Shah, Mareike Verbeek, Wolf Rösler, Jose L Diez Martin, Stefan Schoenland, Anita D'Souza, Nicolaus Kröger, Parameswaran Hari

- **Objective:** Retrospective analysis of outcomes after haploidentical allogeneic SCT in patients with high-risk MM or RRMM

Sahebi F, et al. Presented at EBMT 2018. Abstract OS4-2.

Study Design and Patient Characteristics

- Retrospective analysis
- High-risk MM or RRMM
- Haploidentical ASCT
- 2008–2016 at an EBMT/CIBMTR center
- N = 96
  (63% male; median age 54.9 years)

ISS Stage	
I-II	44.8%
III	38.5%
Subtype	
IgG	42.7%
IgA	15%
Light chain	35.4%
Other/unknown	6.3%
Time from diagnosis > 24 months	**82%**
Prior ASCT	68.8%
> 1 prior	31.2%
Recipient/donor CMV status	
−/−	13.5%
−/+	8.3%
+/−	8.3%
+/+	40.6%
Gender-matched donor	49%
Conditioning	
Myeloablative with TBI	5.2%
Myeloablative no TBI	13.5%
Reduced intensity with TBI	54.2%
Reduced intensity no TBI	26%
GVHD prophylaxis	
Post-Cy	76%
No post-Cy	17.7%
ATG/alemtuzumab	41.7%
ATG alone	11.5%
Neither	41.7%

ATG, anti-thymocyte globulin; CMV, cytomegalovirus; Ig, immunoglobulin; ISS, International Staging System; GVHD, graft versus host disease; post-Cy, post-transplant cyclophosphamide; TBI, total body irradiation.

Sahebi F, et al. Presented at EBMT 2018. Abstract OS4-2.

Haploidentical Transplantation: Results

	Patients, % (range)
OS at 2 years	48 (36–59)
Cumulative risk of relapse	56 (45–67)
Non-relapse mortality	26 (17–36)
Incidence of cGVHD	45 (33–57)

- Median follow-up 19.9 (9.3–39.1) months

Univariate analysis

- Higher relapse rates:
  - ATG/alemtuzumab (p = 0.001)
  - TBI + Cy-based regimens (p = 0.001)
- Inferior OS:
  - ATG (p = 0.01)
  - TBI + Cy-based regimens (p = 0.01)
- Higher NRM:
  - ATG (p = 0.012)
  - TBI-based regimens (p = 0.005)
- CMV status had no impact on NRM or GVHD

cGVHD, chronic graft versus host disease;
Cy, cyclophosphamide; NRM, non-relapse mortality.

Sahebi F, et al. Presented at EBMT 2018. Abstract OS4-2.

EBMT-B213: Allogeneic HSCT: Number of Prior Therapy Lines

Christine Eisfeld, Eva Esseling, Martin Kropff, Andrea Kerkhoff, Christian Reicherts, Jörn C. Albring, Jan-Henrik Mikesch, Christoph Groth, Rolf Mesters, Christoph Schliemann, Torsten Kessler, Georg Lenz, Wolfgang E. Berdel, Matthias Stelljes

- **Objective:** To retrospectively evaluate outcomes for patients who received allogeneic HSCT for MM with regard to cytogenetic risk factors, prior therapies, and transplant characteristics

Eisfeld C, et al. Presented at EBMT 2018. Abstract B213.

Study Design and Patient Characteristics

- Retrospective analysis of data for 88 patients with MM
- Received allogeneic HCST between 1999 and 2016
- Collected data for cytogenetic risk factors, prior therapies, transplant characteristics

Patient characteristics (N = 88)	
Age at transplantation (median)	51 years
HLA-identical sibling donor	43%
HLA-matched (10/10) unrelated donor	45%
HLA-mismatched related donor	11%
Upfront tandem autologous–allogeneic transplantation	**34%**
Allogeneic HSCT after relapse[a]	**66%**
Cytogenetic abnormalities	**73%** **(26% high risk[b])**

[a] After 2–7 lines of treatment including 1 or 2 autologous SCTs.
[b] 17/17p deletion; 4;14 translocation; 14;16 translocation; and/or 1q amplification.
HLA, human leukocyte antigen.

Eisfeld C, et al. Presented at EBMT 2018. Abstract B213.

Allogeneic HSCT: Results

Outcomes after HSCT (median follow-up 5.6 years)	
Median OS from time of allogeneic HSCT, months	30.5
OS at 5.6 years follow-up, % (95% CI)	37 (26–48)
Median PFS from time of allogeneic HSCT, months	12.3
PFS at 5.6 years follow-up, % (95% CI)	24 (14–33)
Cumulative incidence of non-relapse death, %	
3 months	14
1 year	24
3 years	29
Cumulative incidence of relapse, %	
1 year	31
2 years	46
3 years	54

OS was significantly reduced for patients who received > 2 lines of therapy prior to SCT
(HR 3.4, 95% CI 1.3–8.6; p = 0.01)

Eisfeld C, et al. Presented at EBMT 2018. Abstract B213.

Discussion: Role of Allogeneic SCT in RRMM

- We only consider allogeneic transplantation in the early phases of the disease, not in the later phases due to poor outcomes
- The use of allogeneic transplantation has been a little more common in the USA in recent years due to changes in insurance coverage

Personal communication: Parameswaran Hari and Jesús San Miguel.

Discussion: Role of Haploidentical Transplantation in RRMM

- It is not a curative option, especially in multiple-relapsed MM, but can be attractive as a platform to build upon

Personal communication: Parameswaran Hari and Jesús San Miguel.

Discussion: CAR T-Cell Therapy

- **Phase 1 Study of anti-BCMA CAR T-cell therapy bb2121**
  - Data on 43 patients, heavily pretreated
- Preliminary data show promise in this patient population
- BCMA appears to be a promising target in MM for other treatment strategies as well

BCMA, B-cell maturation antigen; CRS, cytokine release syndrome.

Raje N, et al. Presented at EHA 2018. Abstract S138.
Personal communication: Noopur Raje.

Discussion: Impact of the Presented Data on Clinical Practice

- With new treatments, we are trying to move toward curative options for MM
- Intensive treatments such as transplantations and high-dose chemotherapy are still needed on the way to curing a substantial proportion of MM patients

Personal communication: Parameswaran Hari and Jesús San Miguel.

Discussion: Choosing the Optimal Treatment Regimen for Patients with MM

- It is important to lay out a long-term treatment strategy
- It is important to consider early treatment very carefully in terms of reducing the risk of minimal residual disease as much as possible
- It is important to detect the disease early and to treat as soon as possible after diagnosis and after biochemical relapse, not wait for clinical relapse

Personal communication: Parameswaran Hari and Jesús San Miguel.

Key Messages

- Novel combination regimens and schedules have been shown to improve outcomes for patients with RRMM
- Carfilzomib-based doublet and triplet regimens have demonstrated high response rates and OS benefit
- Pomalidomide-based treatments have shown promise in patients who have received previous lenalidomide
- The role and timing of allogeneic SCT in treatment strategies have to be further clarified

Personal communication: Parameswaran Hari.