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THERAPY FOR MULTIPLE MYELOMA
FIRST RELAPSE

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DANA-FARBER
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Disclosures

Consulting Agreements	Celgene Corporation, Janssen Biotech Inc, Merck, OncoPep, Pfizer Inc, Takeda Oncology
Ownership Interest	OncoPep

Case presentation 5: Dr Matt-Amaral

68-year-old man with COPD, pulmonary hypertension, obesity

- 2017: Thoracic spine pain, fracture at T7: IgA kappa MM
- Oct 2017: RVD
- Currently: Patient not doing well, may be early progression
- Not considered a candidate for ASCT

Case presentation 6: Dr Nadeem

66-year-old man

- Feb 2016: IgA lambda MM
- Cytogenetics: t(11;14)
- RVD x 4 → CR
- June 2016: Autologous transplant
- Lenalidomide maintenance 10 mg for 1.5 years; no tolerability issues
  - Biochemical relapse: Slowly progressive M-spike and kappa-lambda ratio
  - Bone marrow biopsy: 8%-9% plasma cells

How Do We Decide: Factors to be Considered for Treatment Selection

Disease-related Factors

- Nature of relapse
  - indolent vs aggressive
- Risk stratification
  - Genetics at Diagnosis & Relapse
- Disease burden
  - High vs low
- R-ISS staging
  - 1 vs 2-3

Patient-related Factors

- Renal insufficiency: disease related or due to comorbidities
- Cytopenia common in pts with RRMM[1]
- Comorbidities and frailty[1]
  - Treatment decisions complicated in elderly
- Patient preferences
  - Convenience, ease of travel, insurance and other social factors, Variation in patient goals/ preferences

1. Nooka AK, et al. Blood. 2015;125:3085-3099.
2. Palumbo A, et al. N Engl J Med. 2011;364:1046-1060.
3. Palumbo A, et al. Blood. 2011;118:4519-4529.
4. Orlowski RZ, Lonial S. *Clin Cancer Res.* 2016;22:5443.

How Do We Decide: Factors to be Considered for Treatment Selection

Prior Treatment-related Factors

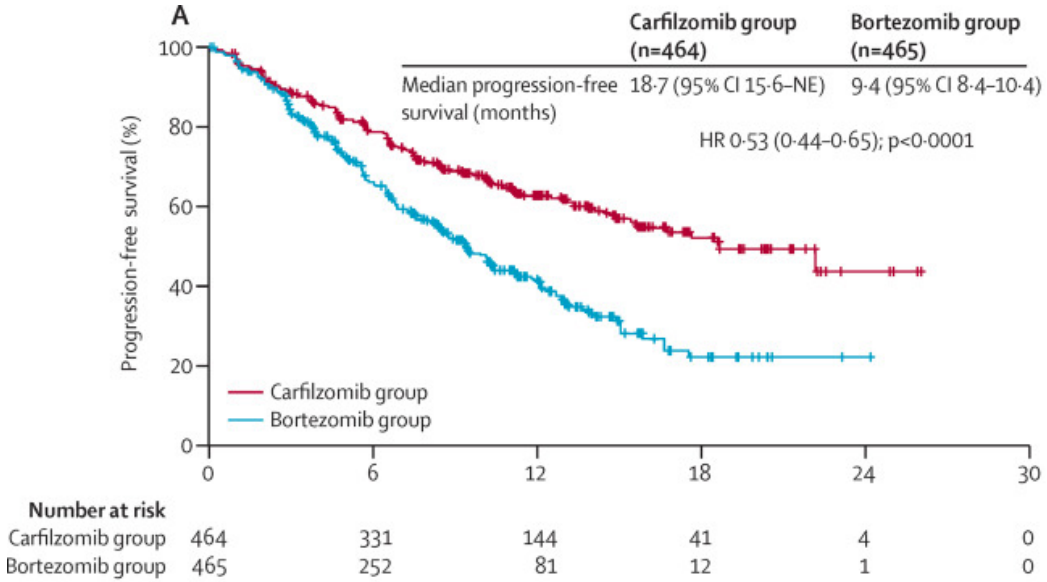
- Sensitivity versus Resistance to Previous therapy
- Regimen-related toxicity
  - Neuropathy
  - Cardiac issues
  - Cytopenia
  - COPD: monoclonal antibodies with caution (daratumumab)
  - DVT/PE: use anticoagulation with IMiDs
- Depth and duration of previous response, tumor burden at relapse
- Retreatment with previous therapies if previous response to the treatment, acceptable tolerance, and relapse occurred at least 6 mos after previous exposure

1. Nooka AK, et al. Blood. 2015;125:3085-3099.
2. Palumbo A, et al. N Engl J Med. 2011;364:1046-1060.
3. Palumbo A, et al. Blood. 2011;118:4519-4529.
4. Orlowski RZ, Lonial S. *Clin Cancer Res.* 2016;22:5443.

Randomized trial of Btz-Dex combinations

Trial	Regimen	Control	N	>=PR	>=VGPR	>=CR	PFS (months)
ENDEAVOR	Cfz-Dex	Btz-Dex	464	76	54	13	18.7 (vs. 9.4)
PANORAMA	Pano-Btz-Dex	Btz-Dex	387	61	28	11	12 (vs. 8)
CASTOR	Dara-Btz-Dex	Btz-Dex	251	83	59	19	NR (vs. 7.2)
Randomized Phase 2	Elo-Btz-Dex	Btz-Dex	77	67	37	4	9.7 (vs. 6.9)

Carfilzomib-Dexamethasone

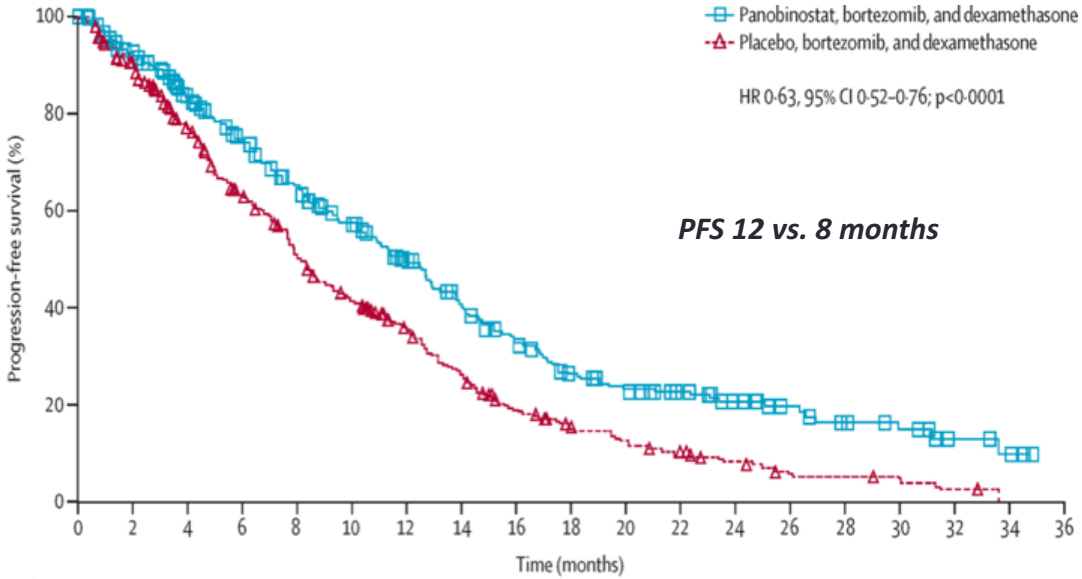


ORR	**76%**
>=VGPR	**54%**
>=CR	**13%**

- Twice weekly infusion
- High rates of cardiovascular and renal toxicity

Dimopoulos et al, Lancet 2016

PANORAMA: Panobinostat-Btz D

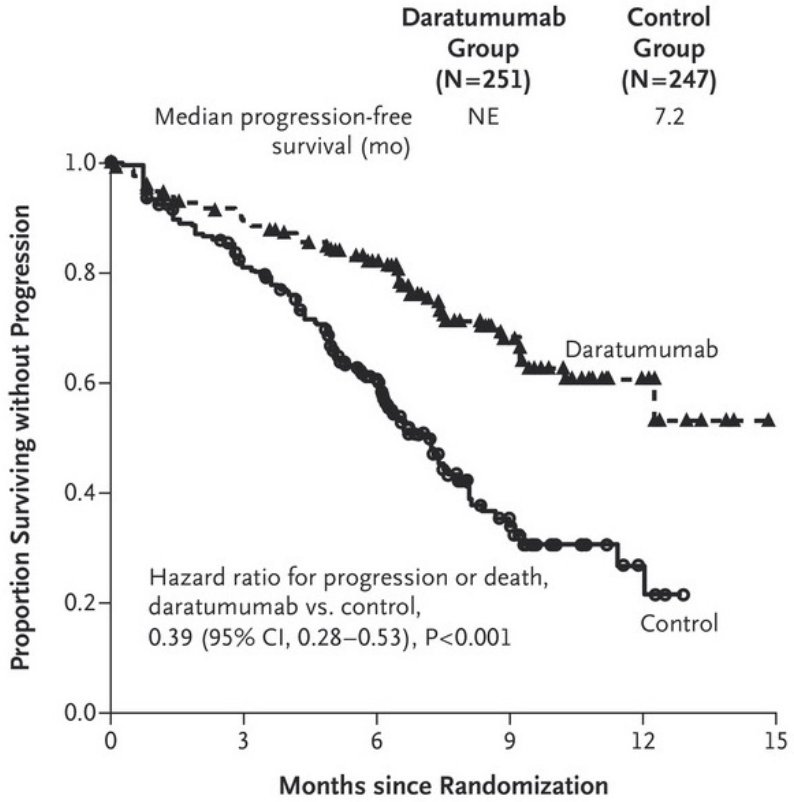


ORR	61%
>=VGPR	28%
>=CR	11%

- Twice weekly infusion
- High rates of cardiovascular and renal toxicity

San Miguel et al, Lancet Oncology, 2014, 5(11), 1195–1206

Daratumumab bortezomib Dex (CASTOR)

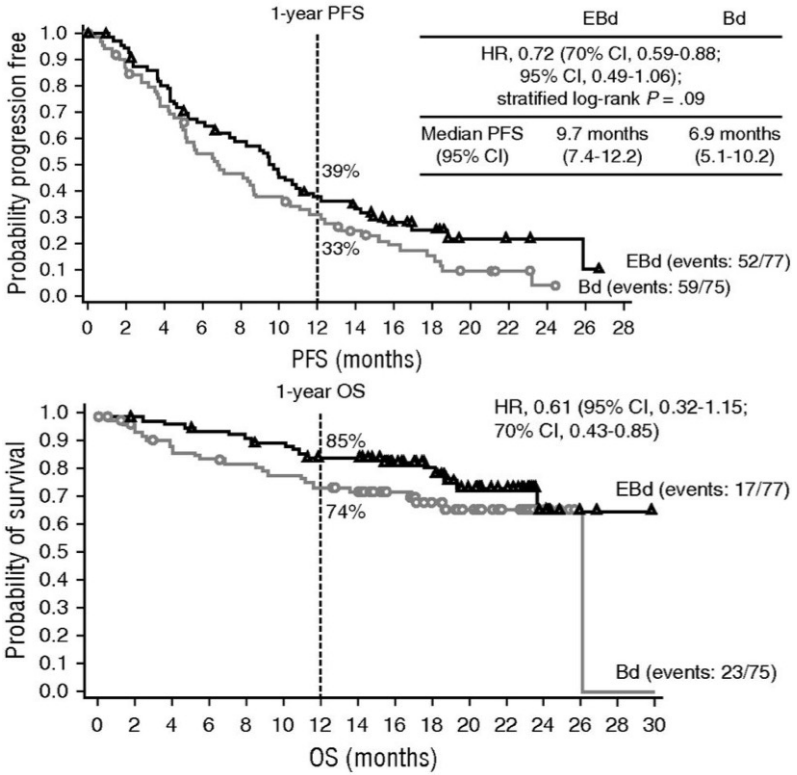


ORR	83%
>=VGPR	59%
>=CR	19%

- Twice weekly infusion
- High rates of cardiovascular and renal toxicity

N Engl J Med 2016; 375:754-766 August 25, 2016

Elotuzumab-Bortezomib-Dex

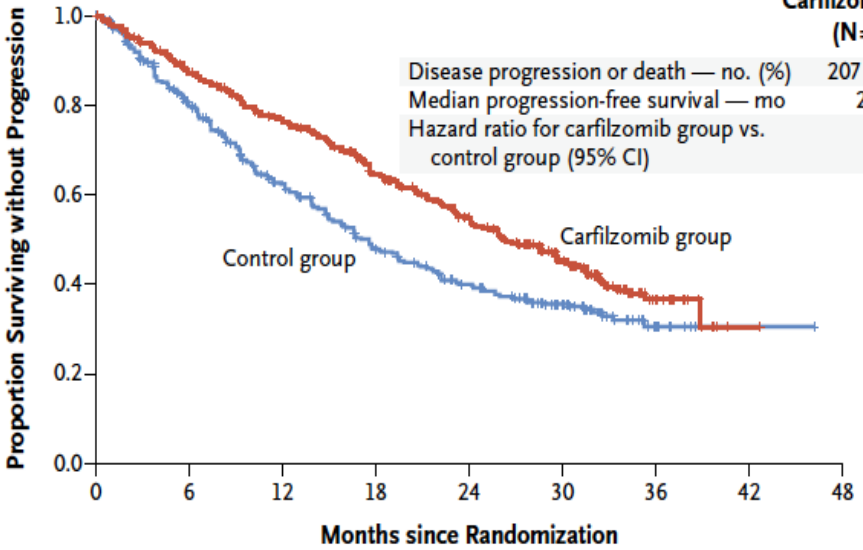


Jakubowiak et al, Blood 2016 127:2833-2840

Randomized trials of Len-Dex combinations

Trial	Regimen	Control	N	>=PR	>=VGPR	>=CR	PFS (months)
ASPIRE	Cfz-Len-Dex	Len-Dex	207	87	70	32	26.3 (vs. 17.6)
TOURMALINE	Ixa-Len-Dex	Len-Dex	360	78	48	12	20.6 (vs. 14.7)
POLLUX	Dara-Len-Dex	Len-Dex	286	87	70	32	NR (vs. 7.2)
ELOQUENT	Elo-Len-Dex	Len-Dex	299	79	33	4	19.4 (vs. 14.9)

ASPIRE: Carfilzomib-Rd



	Carfilzomib Group (N=396)	Control Group (N=396)
Disease progression or death — no. (%)	207 (52.3)	224 (56.6)
Median progression-free survival — mo	26.3	17.6
Hazard ratio for carfilzomib group vs. control group (95% CI)	0.69 (0.57–0.83)	

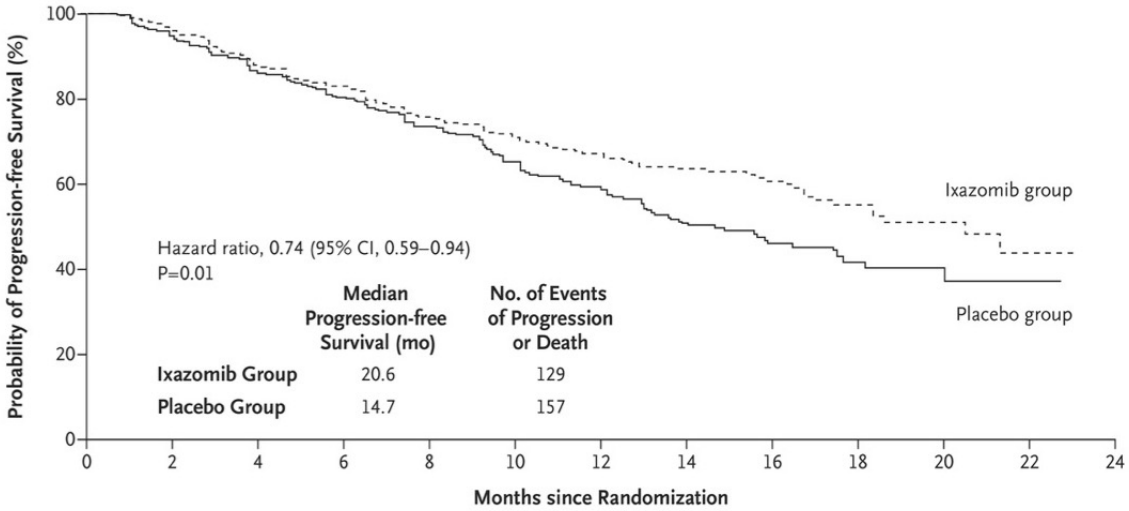
P=0.0001

ORR	87%
>=VGPR	70%
>=CR	32%

- Two infusions per week for 3/4 weeks
- Well tolerated

Stewart et al, NEJM 2015

TOURMALINE: Ixazomib-Rd

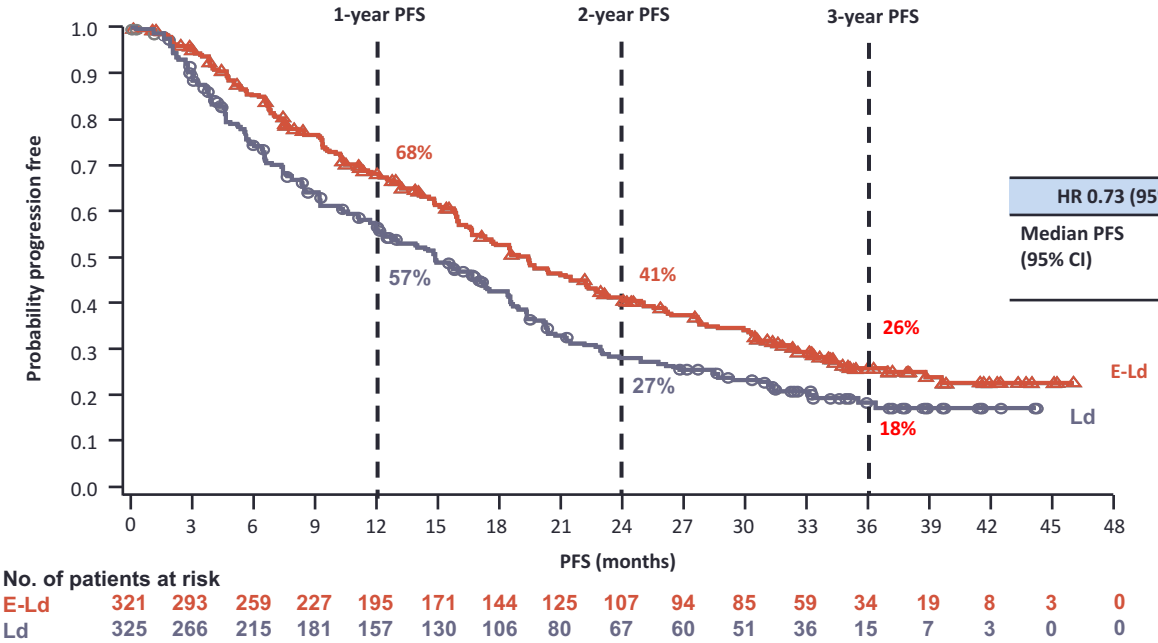


ORR	78%
>=VGPR	48%
>=CR	12%

- All oral regimen
- Well tolerated

Moreau P et al. N Engl J Med 2016;374:1621-1634

ELOQUENT: Elotuzumab-Rd

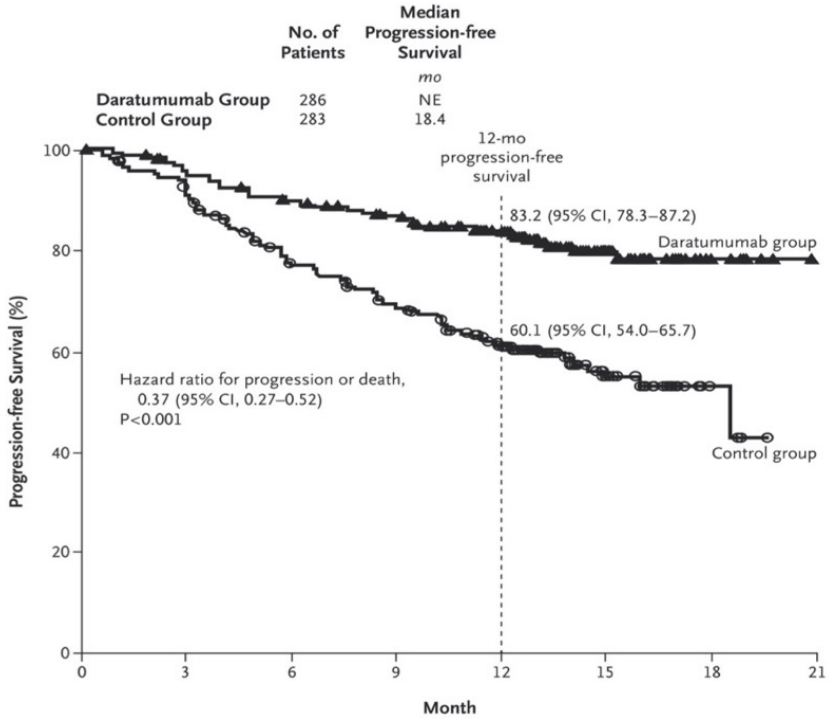


	E-Ld	Ld
HR 0.73 (95% CI 0.60, 0.89); p=0.0014		
Median PFS (95% CI)	19.4 mos (16.6, 22.2)	14.9 mos (12.1, 17.2)

ORR	79%
>=VGPR	33%
>=CR	4%

- One infusion every other week
- Well tolerated

Daratumumab-Rd (Pollux)



ORR	87%
>=VGPR	70%
>=CR	32%

- One infusion weekly for 8, every other week for 8, then monthly
- Well tolerated, infusion reactions cycle 1

N Engl J Med 2016; 375:1319-1331

FDA Approval of Daratumumab in Combination with Pomalidomide and Dexamethasone

June 16, 2017 – “The US Food and Drug Administration has approved the use of daratumumab in combination with pomalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received at least two prior therapies including lenalidomide and a proteasome inhibitor...

The approval was based on data from the phase I (MMY1001, EQUULEUS) study of daratumumab in combination with pomalidomide and dexamethasone in relapsed or refractory multiple myeloma.”

http://www.ascopost.com/News/57747

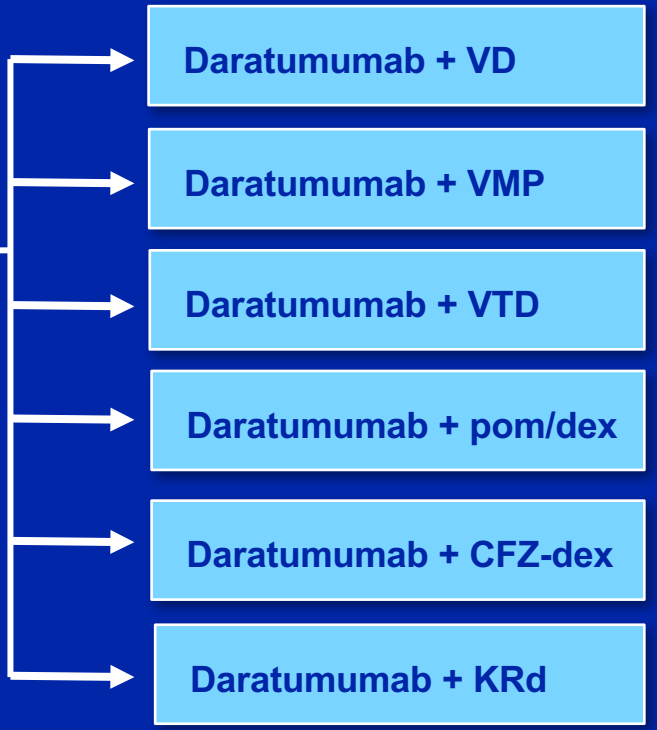
EQUULEUS: Phase Ib Study of Daratumumab in Combination with Backbone Regimens

NCT01998971

Eligibility

Symptomatic MM

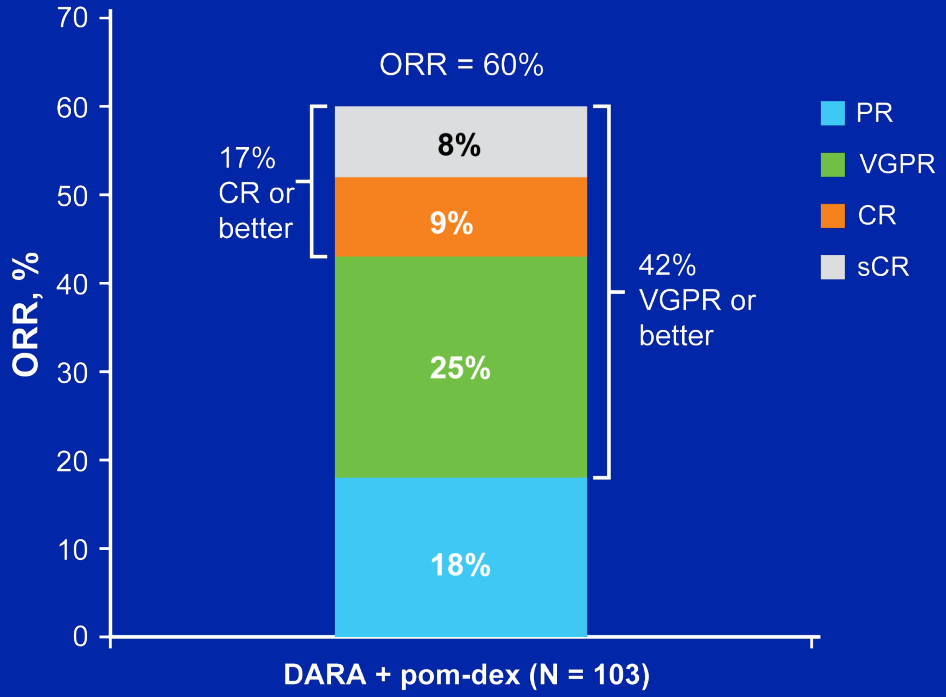
- For KRd regimen: newly diagnosed MM
- For CFZ-dex regimen: relapsed or refractory MM



KRd = carfilzomib/lenalidomide/dexamethasone
CFZ-dex = carfilzomib/dexamethasone
VD = bortezomib/dexamethasone
VMP = bortezomib/melphalan/prednisone
VTD = bortezomib/thalidomide/dexamethasone
Pom/dex = pomalidomide/dexamethasone

www.clinicaltrials.gov; Accessed December 2017.

EQUULEUS: Efficacy and Safety of Daratumumab with Pomalidomide and Dexamethasone



Select most common (>5%) Grade 3 and 4 adverse events	N = 103
Neutropenia	77%
Anemia	28%
Leukopenia	24%
Thrombocytopenia	19%
Lymphopenia	14%
Pneumonia	10%
Febrile neutropenia	8%

- Daratumumab infusion-related reactions: 50%

Chari A et al. *Blood* 2017;130(8):974-81.

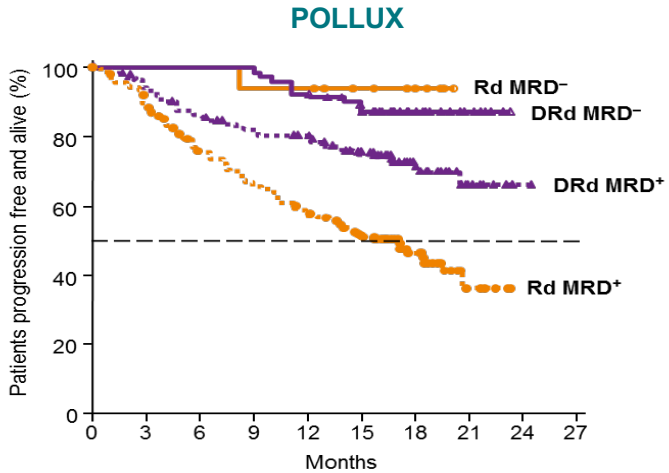
Many options

- Repeat induction regimen – e.g. bortezomib, lenalidomide, dex (VRd)
- Any of the triplets studied above
- VCd is another choice
- DCEP/DT-PACE in fulminant relapse

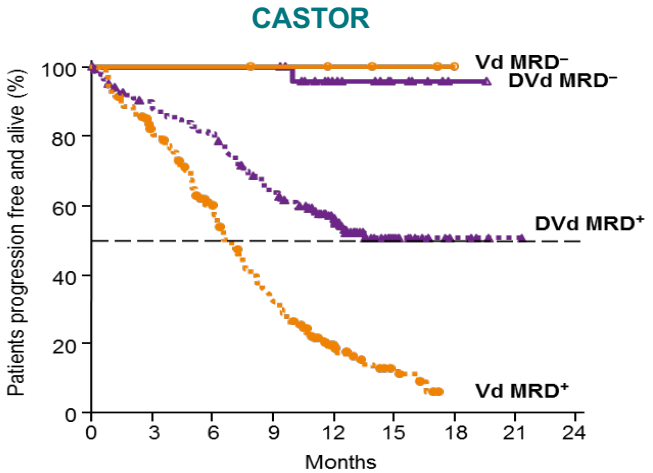
- Salvage/Second Autologous Transplant
- Emerging Choices

Achieving MRD Negativity Is Important Even in Relapsed Myeloma

CASTOR & POLLUX: PFS According to MRD Status at 10^{-5}



Patients at risk										
Rd MRD negative	16	16	16	15	15	12	10	0	0	0
DRd MRD negative	71	71	71	70	66	57	28	6	0	0
Rd MRD positive	267	233	190	166	144	120	38	5	0	0
DRd MRD positive	215	195	178	167	161	137	54	9	1	0



Patients at risk									
Vd MRD negative	6	6	6	5	3	2	0	0	0
DVd MRD negative	26	26	26	26	15	7	1	0	0
Vd MRD positive	241	176	123	68	20	7	0	0	0
DVd MRD positive	225	189	172	134	76	26	4	1	0

- Lower risk of progression in MRD-negative patients
- More patients achieve MRD negativity when adding daratumumab
- PFS benefit in MRD-positive patients who received daratumumab-containing regimens versus standard of care

Avet-Loiseau H, et al. Presented at ASH 2016 (Abstract 246), oral presentation.

Open-Label, Multicenter, Dose-Escalation Phase 1b Study to Assess the Subcutaneous Delivery of Daratumumab in Patients with Relapsed or Refractory Multiple Myeloma (PAVO): Proof of Concept Study Design

Key eligibility criteria
- RRMM with measurable disease
- ≥2 prior lines of treatment
- Not received anti-CD38 therapy

Group 1 (n = 8)
DARA: 1,200 mg
rHuPH20: 30,000 U

→

Group 2[a] (n = 45)
DARA: 1,800 mg
rHuPH20: 45,000 U

Primary endpoints
- C_{trough} of DARA at Cycle 3/Day 1
- Safety

Secondary endpoints
- ORR
- CR
- Duration of response
- Time to response

Dosing schedule
- Approved schedule for IV
  - 1 Cycle = 28 days

Infusion time
- 1,200 mg: 20-min infusion (60 mL)
- 1,800 mg: 30-min infusion (90 mL)

Pre-[b]/post-infusion medication
- Acetaminophen, diphenhydramine, montelukast, and methylprednisolone

RRMM, relapsed or refractory multiple myeloma; QW, weekly; Q2W, every 2 weeks; Q4W, every 4 weeks; C_{trough}, trough concentration; ORR, overall response rate; CR, complete response; PK, pharmacokinetic.

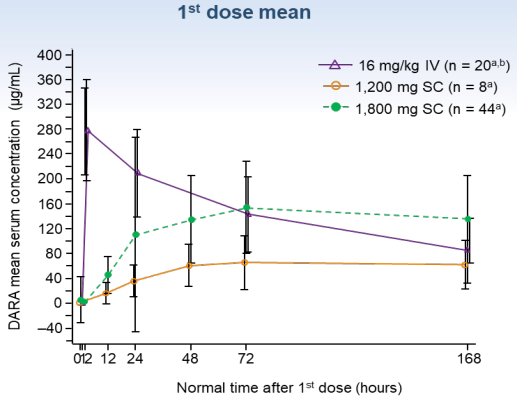
[a]Group 2 comprises 4 distinct cohorts, each treated with DARA 1,800 mg and rHuPH20 45,000 U. C_{trough} on Cycle 3/Day 1 in Group 1 supported dose selection for Group 2. The study evaluation team reviewed safety after Cycle 1 and PK after Cycle 3/Day 1 for each group.

[b]Administered 1 hour prior to infusion.

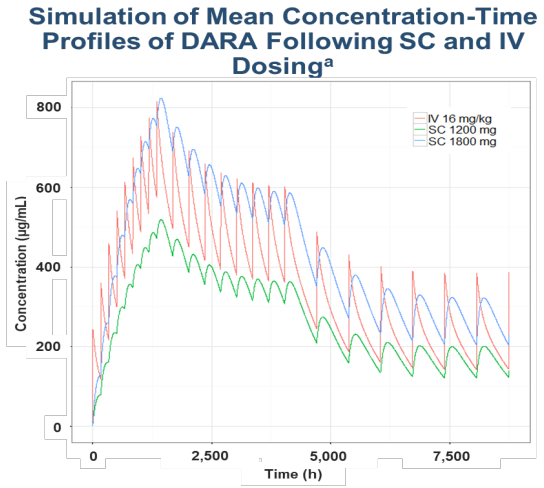
Usmani SZ et al. *Proc ASH* 2016;Abstract 1149.

Patient Disposition and PK

- Median (range) follow-up
  - 1,200 mg: 6.4 (1.6-12.0) months
  - 1,800 mg: 4.3 (0.8-8.6) months
- Median (range) duration of treatment
  - 1,200 mg: 2.6 (0.7-12.0) months
  - 1,800 mg: 3.4 (0.7-8.6) months

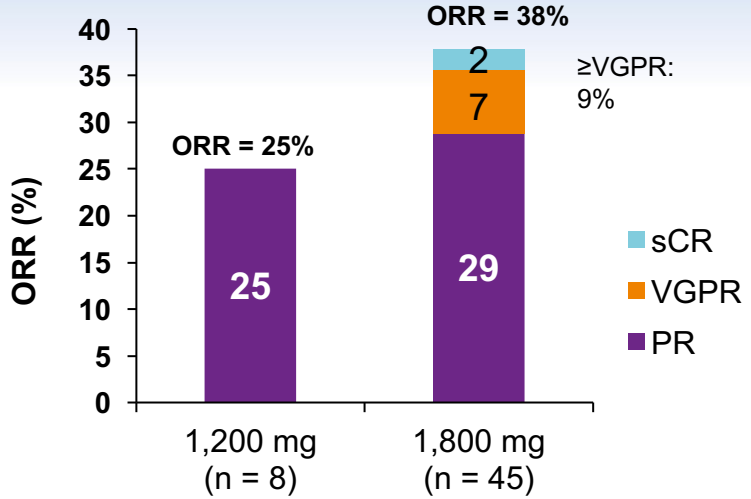


	1,200 mg n = 8	1,800 mg n = 45
Patients treated, n	**8**	**45**
Patients who discontinued Rx, % (n)	**88** (7)	**33** (15)
Reason for discontinuation		
Progressive disease	**63** (5)	**27** (12)
Withdrawal by patient	**13** (1)	**0** (0)
Physician decision	**0** (0)	**4** (2)
Death	**13** (1)	**2** (1)



PAVO Study Response

Response	1,200 mg n = 8	1,800 mg n = 45
ORR, % (n)	**25** (2)	**38** (17)
sCR	**0** (0)	**2** (1)
CR	**0** (0)	**0** (0)
VGPR	**0** (0)	**7** (3)
PR	**25** (2)	**29** (13)
MR	**13** (1)	**11** (5)
SD	**50** (4)	**38** (17)
PD	**13** (1)	**13** (6)



- Responses to DARA-PH20 were observed across both groups

Deeper responses were observed in the 1,800-mg group

AE profile of DARA-PH20 was consistent with IV DARA

Low IRR incidence and severity with ONE grade 3, NO grade 4 IRR of dyspnea with DARA SC with first dose, none with subsequent doses

Response-evaluable set.
sCR, stringent complete response; VGPR, very good partial response; PR, partial response; MR, minimal response; SD, stable disease; PD, progressive disease.

General Guiding Principles

- Duration of initial response defines biology
- Triplet (two active classes + dex) preferred over doublet
  - At least one drug from a non-refractory class
- Consider PS, age and comorbidities when selecting drug/ doses
- Take into account prior toxicities/ residual toxicities
- Treat to maximum response – MRD negativity is a goal
- Maintain on one drug till progression or tolerability