The Problem of Relapse in Myeloma

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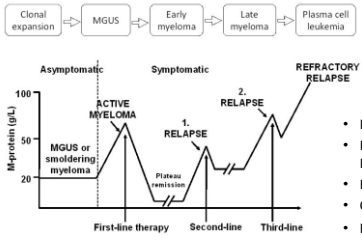
Relapse is the hallmark of multiple myeloma



- Definitions
- Relapse from CR / Biochemical Progression / Clinical Relapse
- Biological Correlates
- Choosing when to treat
- Risk Stratification of Relapse

Definitions- Relapse

- From CR
  - Mainly used for clinical trials
  - Reappearance of serum or urine M-protein by immunofixation or electrophoresis or abnormal FLC ratio
  - Development of ≥5% plasma cells in BM
  - Any other sign of progression (ie, new plasmacytoma, lytic bone lesion, or hypercalcemia)
- Clinical relapse
  - New CRAB findings
  - New plasmacytomas or bone lesions (fractures do not necessarily count)
  - Increasing size of existing plasmacytomas (≥50%)
  - Hyperviscosity related to paraprotein

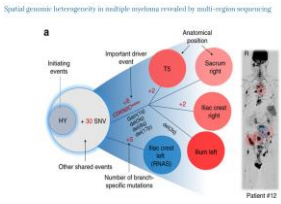
Kumar et al, *Lancet Oncol*, 2017

Definitions- *Progression*

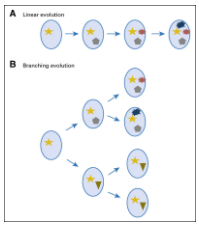
- Increase of 25% from lowest confirmed response value in one or more of:
  - Serum M-protein (absolute increase must be ≥0.5 g/dL)
  - Serum M-protein increase ≥1 g/dL, if the lowest M component was ≥5 g/dL
  - Urine M-protein (absolute increase must be ≥200 mg/24 h)
  - Light chain disease: the difference between involved and uninvolved FLC levels (absolute increase must be >10 mg/dL)
- Non-secretory: 25% increase in bone marrow plasma-cell percentage irrespective of baseline status (absolute increase must be ≥10%)
- Appearance of a new lesion(s), ≥50% increase from nadir
- ≥50% increase in circulating plasma cells (minimum of 200 cells per μL) if this is the only measure of disease

Kumar et al, *Lancet Oncol*, 2017

Multiclonal disease with spatial and temporal heterogeneity



- Acquired genomic events with progression



Rasche L et al *Nature Communications* **8**, Article number: 268(2017)

Case presentation

- 62 YO M with standard risk MM dx'd in 1/2013
  - Received RVD x 3→ nCR
  - Auto-HCT with melphalan 200 in 6/2013→ sCR
  - Maintenance lenalidomide started in 9/2013
- On routine bloodwork 4/2017 SPEP shows reappearance of M protein at 0.1 g/dL

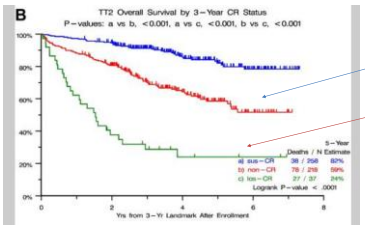
Now what??

Importance of full re-staging at suspected relapse/progression

- History- determine co-morbidities
- Physical- determine PS
- Labs – including PB flow for PCs
- Bone marrow, including FISH, cytogenetics, +/- GEP
  - Determine new clones
  - Risk stratification
  - Possibly help with clinical decision making (BCMA, 11:14)
- Imaging- beware of EMD
  - PET/CT
  - PET/MRI

Dingli et al, *Mayo Clin Proc*, 2017

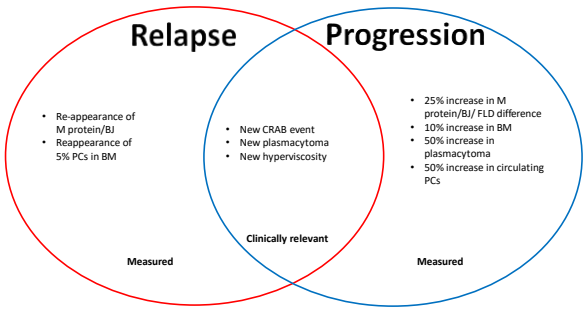
Loss of CR or Never CR or Sustained CR



Never CR

CR achieved and Lost

Hoering A et al Blood. 2009 Aug 13; 114(7): 1299–1305.



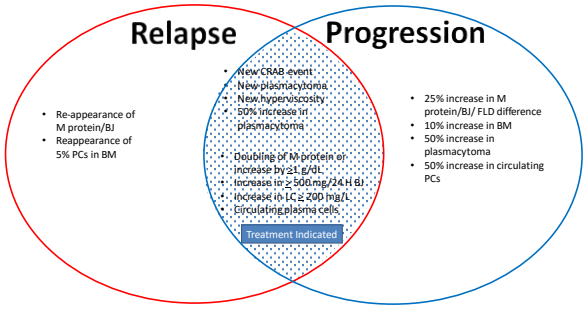
Making your decision

- Immediate treatment for relapse
- Closer follow-up
- Regular follow-up

Indications for treatment

- Clinical relapse (CRAB or plasmacytomas)
- Significant biochemical progression without clinical relapse
  - Doubling of the M-component in two consecutive measurements separated by 2 months with the reference value of 5 g/L, (=0.5 g/dL) or
  - In two consecutive measurements any of the following increases:
    - the absolute levels of serum M protein by ≥10 g/L (=1.0g/dL), or
    - an increase of urine M protein by ≥500 mg per 24 hours, or
    - an increase of involved FLC level by ≥20 mg/dL (= 200 mg/L) (plus an abnormal FLC ratio) or 25% increase (whichever is greater)

Ludwig et al, *The Oncologist*, 2014



Classification of relapsed multiple myeloma

High risk	Intermediate risk	Standard risk

• Primary refractory disease
• Relapse <12 months from ASCT
• Progression within the first year of diagnosis
• FISH
  • Deletion 17p
  • t(14;16)
  • t(14;20)
• High risk GEP
	• FISH
	  • t(4;14)
	  • 1q amp
	• High "S" phase
		All others including
		• Trisomies
		• t(11;14)
		• t(6;14)

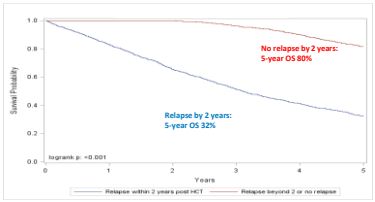
Dingli et al, *Mayo Clin Proc*, 2017

When to treat if only biochemical relapse/progression

- Aggressive clinical disease at diagnosis
- Short treatment-free interval/ suboptimal response to previous treatment line
- Imminent risk for organ dysfunction (pts with previous light chain-induced renal impairment)
- Unfavorable cytogenetics (t(4;14) or del17p)

Ludwig et al, *Oncologist*, 2014

Natural History of early relapse after transplant



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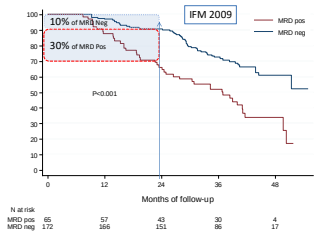
Kumar S et al Tandem BMT meetings 2017

How many pts relapse early?



Attal M et al NEJM 2017

Back to the case…

- 62 YO M with standard risk MM dx'd in 1/2013
  - Received RVD x 3→ nCR
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  - Maintenance lenalidomide started in 9/2013
- On routine bloodwork 4/2017 SPEP shows reappearance of M protein at 0.1 g/dL
- BM: 5% involvement by plasma cells, normal cytogenetics/FISH
- PET/CT negative
- Followed q3 months with labs
- 10/2013 M protein = 0.7
- 11/2013 M protein = 1.1

Gray areas

- On maintenance with an M protein rise 0.2→0.6
  - Should we treat earlier if the patient is already on maintenance?
- High-risk patients with increasing light chains, but not quite at progression
- Persistently PET avid plasmacytomas
- True biochemical progression but questionable performance status

Next Talks

- Choosing a regimen at relapse
  - Early Relapse
  - Refractory Relapse

- Options for the multirelapsed and refractory patient
  - Immunotherapy
  - Clinical Trials of Newer Novel Agents

Early Relapse: Choosing Among Different Second Line Regimens

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Disclosures

- Advisory board: Celgene, Amgen, Novartis, Spectrum, Pharmaceuticals and Adaptive technologies

Clinical Vignette

72-year-old female with diagnosis of standard risk myeloma (hyperdiploidy on FISH studies) received induction therapy with RVd regimen. She underwent upfront transplant and achieved stringent CR. She opted not to go for maintenance therapy, and was monitored closely. Four years from her transplant, she started showing evidence of biochemical progression, and now she is anemic.

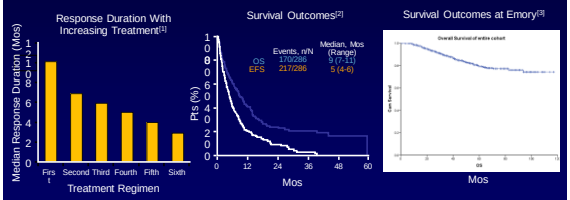
You suggest that the following second line regimen delivers the best depth of response (≥VGPR) based on the data from available lenalidomide based phase III studies:

1. Elotuzumab with lenalidomide and dexamethasone
2. Daratumumab with lenalidomide and dexamethasone
3. Ixazomib with lenalidomide and dexamethasone
4. Carfilzomib with lenalidomide and dexamethasone

Why is it important to choose the best second line regimen?

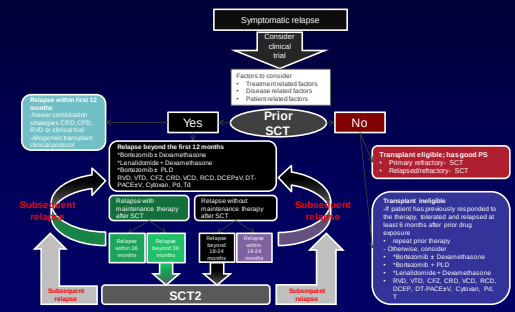
Relapsed myeloma: previously treated myeloma that progresses in the absence of any therapy and requires the initiation of salvage therapy.

Response duration in refractory myeloma



1. Kumar SK, et al. Mayo Clin Proc. 2004;79:867-874.
2. Kumar SK, et al. Leukemia. 2012;26:149-157.
3. Nooka A, et al. institutional data, unpublished.

Treatment Options for Relapsed and Refractory Myeloma (RRMM)



Nooka, et al. *Blood*. 2015;125(20):3085-99.

Factors to Consider to for Treatment Selection a Relapse: Disease related Factors

- Nature of relapse
  - indolent vs aggressive
- Risk stratification
  - Genetics of initial and relapsed marrow
- Disease burden
  - High vs low
- R-ISS staging
  - 1 vs 2-3

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.

Factors to Consider to for Treatment Selection a Relapse: Treatment related Factors

- Previous therapy
  - Pts with PD receiving IMiDs, PIs, or cytotoxic doublet/triplet therapies can benefit from next-generation regimens
  - Avoid agents of previous regimen-related toxicity
  - Maintenance therapy
- Regimen-related toxicity
  - Toxicity profile should be considered in light of pt comorbidities
  - Neuropathy: consider neuropathy sparing durgs (avoid bortezomib, thalidomide)
  - Cardiac issues (uncontrolled HTN, CHF): careful consideration of carfilzomib
  - 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 an option if pt had 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.

Factors to Consider to for Treatment Selection a Relapse: Patient related Factors

- Renal insufficiency: disease related or due to comorbidities (hypertension, vascular disease, diabetes, nephrotoxicity)[1]
- Hepatic impairment common in pts with RRMM[1]
- Comorbidities and frailty[1]
  - Treatment decisions complicated in elderly
    - ↑ toxicity due to ↓ organ function, physiologic reserve
    - European Myeloma Network vulnerability assessment algorithm anticipates regimen-related toxicities and assists individualizing therapy with least potential for interruption[2,3]
- Patient preferences
  - Convenience, ease of travel, insurance and other social factors

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.

Lenalidomide and Bortezomib-Based Early Relapse Regimens: PFS and OS

Trial	Regimen	PFS (mon)	ORR (%)	VGPR (%)	PFS (HR, 95% CI)	OS (HR, 95% CI)
ASPIRE[1] N=792	Rd + Carfilzomib	26.3	87.1	69.9	.69 (.57-.83) *P*=.0001	.79 (.63-.99) *P*=.04
	Rd	17.6	66.7	40.4		
TOURMALINE-MM-1[2] N=722	Rd + Ixazomib	20.6	78.3	48.1	.74 (.59-.74) *P*=.01	NR
	Rd	14.7	71.5	39		
ELOQUENT-2[3] N=646	Rd + Elotuzumab	19.4	79	33	.70 (.57-.85) *P*<.01	.78 (.63-.96)
	Rd	14.9	66	28		
POLLUX[4] N=569	Rd + Daratumumab	NR	93	75.8	.37 (.28-.50) *P*<.0001	.63 (.42-.95)
	Rd	18.4	76	44.2		
PANORAMA[5] N=768	Vd + Panobinostat	11.99	60.7	28	.63 (.52-.76) *P*<.0001	.87 (.69-1.10) *P*=.26
	Vd	8.08	54.6	16		
CASTOR[6] N=498	Vd + Daratumumab	NR	83	59	.39 (.28-.53) *P*<.0001	.63 (.42-.96)
	Vd	7.2	63	29		
ENDEAVOR[7] N=929	Carfilzomib + Dex	18.7	76.7	54	.53 (.44-.65) *P*<.0001	.79 (.58-1.08) *P*=.06
	Vd	9.4	62.3	29		

1. Stewart K, et al. *N Engl J Med* 2015;372:142-52. 2. Moreau P, et al. *N Engl J Med* 2016; 374:1621-1634.
3. Lonial S, et al. *N Engl J Med* 2015; 373:621-631. 4. Dimopoulus M, *et al. N Engl J Med* 2016; 375:1319-1331.
5. San Miguel J, *Lancet Oncol* 2014; 15: 1195–206. 6. Palumbo A, et al. *N Engl J Med* 2016; 375:754-766.
7. Dimopoulos M, et al. *Lancet Oncol*. 2016;17:27-38.

FDA Approvals of Novel Agents for Patients with RRMM

Novel Agent or Regimen	FDA Approval Date	Patient Population
Panobinostat + bortezomib/dexamethasone	February 23, 2015	• Patients with ≥2 prior standard therapies, including bortezomib and an IMiD agent
Carfilzomib + lenalidomide/dexamethasone	July 27, 2015	• Patients with relapsed disease who had received 1-3 prior lines of therapy
Daratumumab	November 16, 2015	• Patients with at least 3 prior treatments
Ixazomib + lenalidomide/dexamethasone	November 20, 2015	• Patients who had received at least 1 prior therapy
Elotuzumab + lenalidomide/dexamethasone	November 30, 2015	• Patients with 1-3 prior therapies
Carfilzomib + dexamethasone	January 21, 2016	• Patients with relapsed disease and 1-3 prior therapies
Daratumumab + bortezomib/dexamethasone	November 21,2016	• Patients who had received at least 1 prior therapy
Daratumumab + lenalidomide/dexamethasone	November 21,2016	• Patients who had received at least 1 prior therapy
Daratumumab + pomalidomide/dexamethasone	June 16, 2017	• Patients who had received ≥2 prior standard therapies, including bortezomib and an IMiD agent

Orłowski RZ, Lonial S. *Clin Cancer Res.* 2016;22:5443.

Available Regimens in Early Relapse *NCCN Guidelines*

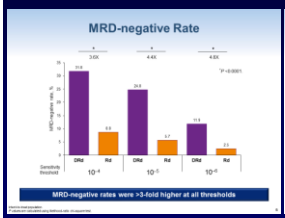
Preferred Regimens	Other Regimens
Level 1 Regimens **Doublets** • Bortezomib/dexamethasone • Carfilzomib/dexamethasone • Lenalidomide/dexamethasone **Triplets** • Elotuzumab/lenalidomide/dexamethasone • Daratumumab/lenalidomide/dexamethasone • Ixazomib/lenalidomide/dexamethasone • Carfilzomib/lenalidomide/dexamethasone • Daratumumab/bortezomib/dexamethasone **Other Regimens** • Repeat primary induction therapy (if relapse at >6 months) • Bortezomib/cyclophosphamide/dexamethasone • Bortezomib/lenalidomide/dexamethasone	**Level 1 Regimens** • Bortezomib/liposomal doxorubicin • Panobinostat/bortezomib/dexamethasone **Other** **PI-Based** • Ixazomib/dexamethasone • Elotuzumab/bortezomib/dexamethasone **Alkylator-Based** • Bendamustine/bortezomib/dexamethasone • Bendamustine/lenalidomide/dexamethasone • Cyclophosphamide/lenalidomide/dexamethasone • DCEP (dex/cyclophosphamide/etoposide/cisplatin) • DT-PACE (dex/thalidomide/cisplatin/doxorubicin/cyclophosphamide/etoposide) ± bortezomib (VTD-PACE) • High-dose cyclophosphamide

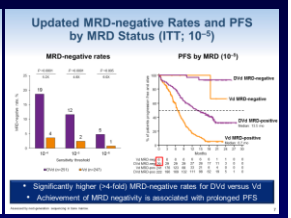
Note: NCCN Guidelines do not break out regimens into separate categories of early and late relapse

NCCN Guidelines, Version 3.2017. Accessed August, 2017.

Depth of response

➢ MRD negative rate POLLUX MRD negative rates CASTOR

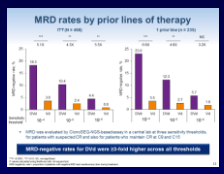




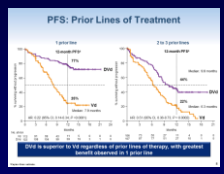
Moreau P, et al. *N Engl J Med* 2016; 374:1621-1634
Palumbo A, et al. *N Engl J Med.* 2016;375(17):754-766.

Benefit of antibodies as earlier lines of therapy: MRD negativity and PFS from CASTOR

MRD –ve rate with DVd as 1st line vs ITT

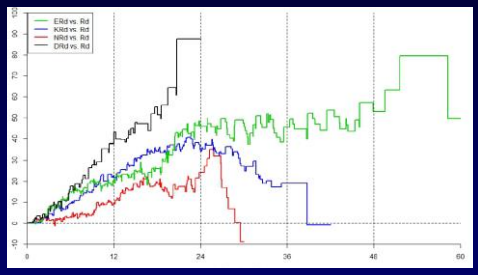


PFS with DVd as 1st line vs 2-3



Mateos MV, et al. *Blood*. 2016;128: Abstract 1150.

Relative Benefit of PFS: Possibility of delivering therapy over long term



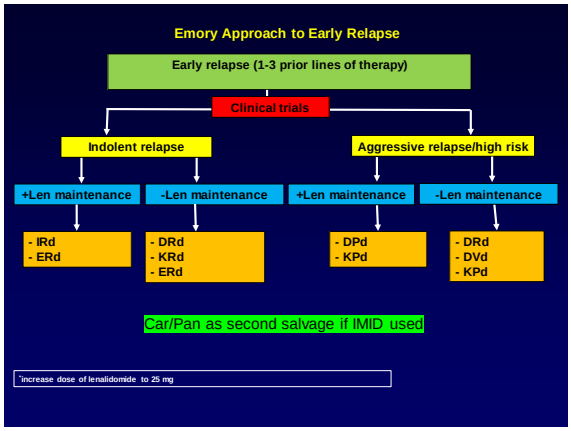
Betts K, et al. *haematologica*. 2017;102: Abstract E1300.

Salvage ASCT in the Relapsed Setting

- Data from Mayo Clinic Transplant Center suggests that ASCT2 appears safe and effective treatment for relapsed MM (N = 98)
  - ORR: 86%; median PFS: 10.3 mos; median OS: 33 mos
  - Rate of TRM: 4%, suggesting a favorable benefit-to-risk ratio
- Shorter TTP after ASCT1 predicts shorter OS post–ASCT2

TTP After ASCT1	Median From ASCT2, Mos (Range)	
	PFS	OS
< 12 mos	5.6 (3-8)	12.6 (4-23)
< 18 mos	7.1 (6-8)	19.4 (10-42)
< 24 mos	7.3 (6-10)	22.7 (13-62)
< 36 mos	7.6 (7-12)	30.5 (19-62)

Gonsalves WI, et al. Bone Marrow Transplant. 2013;48:568-573.



Clinical Vignette

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4. Carfilzomib with lenalidomide and dexamethasone

Conclusions

- Novel agents in combination can achieve prolonged responses even in relapsed disease
  - Depth of response is key even in relapsed disease
- There are many right ways to treat patients with multiple myeloma in relapse
  - There are also wrong ways to do it, know your options
  - Regimen with good tolerability, and efficacy (monoclonal antibodies)
- Despite major advances and newer options, a few challenges that we face today are
  - how to sequence the available regimens?
  - how to personalize therapy to derive the maximize benefit (eg: biomarkers)?
  - how to tailor therapy to minimize toxicity yet retain efficacy

Questions??

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Approach to the Patient with Refractory and Multiply Relapsed Multiple Myeloma

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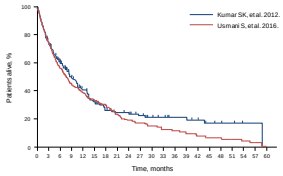
Member, Plasma Cell Disorders Program

Levine Cancer Institute

Relapsed/Refractory Disease : Outcomes

- Despite the introduction of IMiDs and PIs, most patients relapse and outcomes are poor in relapsed or refractory patients[1]
  - Median OS of 9 months in patients refractory to bortezomib and ≥1 IMiD[1]
  - Median OS of 8 months in patients with relapsed or refractory MM who were double refractory or had relapsed after ≥3 prior lines of therapy, including pomalidomide and carfilzomib[2]



MM, multiple myeloma; IMiD, immunomodulatory drug; PI, proteasome inhibitor; OS, overall survival.

1.Kumar SK, et al. *Leukemia*. 2012;26(1):149-157.
2.Usmani S, et al. *Oncologist*. 2016. doi:10.1634/theoncologist.2016-0104.

Outline

- Available Therapeutic Regimens for later relapse
- General Principles to Guide Therapy Decisions
- Treatment of Later Relapse / Progression (≥2 prior lines of therapy and/or lenalidomide/bortezomib refractory)
- Emerging therapeutics
- Conclusions

Available Regimens in Late Relapse: NCCN Guidelines

Preferred Regimens	Other Regimens
Late Relapse (≥2 prior lines or len/bort refractory) Level 1 Regimens Doublets • Pomalidomide/dexamethasone Other Regimens • Pomalidomide/bortezomib/dexamethasone • Pomalidomide/carfilzomib/dexamethasone • Pomalidomide/daratumumab/dexamethasone • Daratumumab	Late Relapse (≥2 prior lines or len/bort refractory) • Panobinostat/bortezomib/dexamethasone • Panobinostat/carfilzomib • Pomalidomide/cyclophosphamide/dexamethasone • DCEP (dex/cyclophosphamide/etoposide/cisplatin) • DT-PACE (dex/thalidomide/cisplatin/doxorubicin/ cyclophosphamide/etoposide) ± bortezomib (VTD-PACE) • High-dose cyclophosphamide

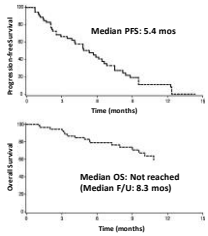
Note: NCCN Guidelines do not break out regimens into separate categories of early and late relapse

NCCN Guidelines, Version 3.2017, accessed August, 2017.

PANORAMA-2: A Phase 2 Study of Bortezomib, Dexamethasone and Panobinostat

- 55 pts with relapsed and bortezomib-refractory multiple myeloma (54 prior lenalidomide tx)
- Median prior regimens: 4 (2 – 11)
- Median time since diagnosis: 54.8 mos (7.5 – 263.6)
- 21-day cycle. Bort 1.3 mg/m^2 IV D1, 4, 8, 11 (D1, 8 for cycle 9+); Dex 20 mg day of and after bort; Pano/Placebo 3x/week for the first 2 weeks of the cycle.

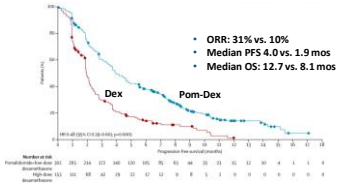
Response Category	%
ORR (≥PR)	34.5
CBR (≥MR)	52.7
CR	0.0
nCR	1.8
PR	32.7
MR	18.2
SD	36.4
PD	5.5



Richardson PG et al. Blood 2013;122:2331-7.

Pomalidomide-Dex vs Dex for Relapsed/Refractory Multiple Myeloma

- Randomized, phase III study of Pom-Dex vs Dex in relapsed/refractory myeloma
- Baseline characteristics: 1) Median number of prior therapies = 5; 2) Len and bort refractory 75%



- ORR: 31% vs. 10%
- Median PFS 4.0 vs. 1.9 mos
- Median OS: 12.7 vs. 8.1 mos

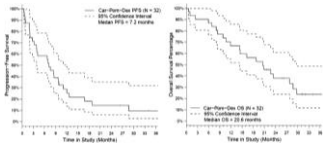
Miguel JS, et al. *Lancet Oncol.* 2013;14:1055-1066.

Carfilzomib, Pomalidomide and Dexamethasone for Relapsed/Refractory Multiple Myeloma

- MTD in phase I: 4-week cycle. CFZ 27 mg/m^2 D1, 2, 8, 9, 15, 16; Pom 4 mg D1-21; Dex 40 mg D1, 8, 15, 22
- Median lines of therapy: 6 (2–12)
- Len-refractory: 100%
- Bortezomib-refractory: 93.5%

Median PFS 7.2 months, Median OS 20.6 months

Best Overall Response	N=32
VGPR	16%
PR	34%
MR	16%
SD	25%
PD	9%



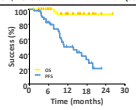
Shah JJ, et al. *Blood.* 2015;261:2284-2290.

Phase 1/2 Trial: Pomalidomide, Bortezomib and Dexamethasone

Median 2 prior lines
Prior lenalidomide 100%, prior bortezomib 57%
Refractory to immediate prior line 28%

OS and PFS[1]

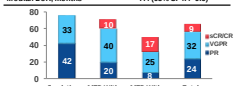
Median follow-up: 12 months	N = 47
Response rate, n (%)	40 (85)
Median OS	NA
Event free at 6 months (%)	100
Event free at 12 months (%)	95
Median PFS, months	10.7 (95% CI 9.4–18.5)
Median DoR, months	13.7 (95% CI 8.5–16.8)



Median 2 prior lines
Prior lenalidomide 100%, prior bortezomib 97%

ORR and DOR[2]

Median follow-up: 12 months	N = 34
Response rate, n (%)	22 (65)
Median DoR, months	7.4 (95% CI 4.4–9.6)

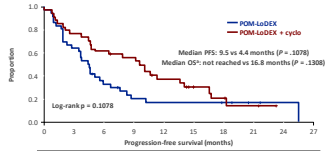


	Escalation (n = 12)	MTD With IV BORT (n = 10)	MTD With SC BORT (n = 12)	Total (N = 34)
Median TTR, mos (95% CI)	1.1 (0.7-5.1)[a]	1.4 (0.9-3.2)[a]	0.8 (0.7-1.0)[a]	1.0 (0.7-5.1)
Median DOR, mos (95% CI)	5.8 (1.2-10.1)	7.4 (4.1-NE)	NE (3.2-NE)	7.4 (4.4-9.6)

1. Lacy MQ, et al. *Blood.* 2014;124 (suppl, abstr 304). 2. Richardson PG, et al. *Blood.* 2015;124 (suppl, abstr 3036).

Phase 1/2 Trial: Pomalidomide, Cyclophosphamide and Dexamethasone

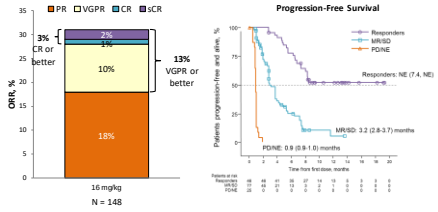
- Median number of prior therapies 4
- Must have been refractory to lenalidomide
- Refractory to bortezomib 71%



Arm	N	Event	Censored	Median (95% CI)
POM-LoDEX	36	30 (83%)	6 (17%)	4.4 (2.3, 6.0)
POM-LoDEX + cyclo	34	26 (76%)	8 (24%)	9.5 (4.6, 13.6)

Baz R, et al. *Blood.* 2016;127(21):2561-8.

Daratumumab as Monotherapy for Relapsed/Refractory Multiple Myeloma

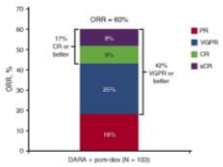


- Median OS: 19.9 months

Usmani S, et al. *Blood.* 2016;128:37-44.

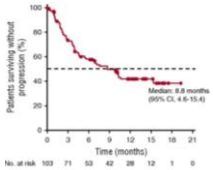
Pomalidomide, Dexamethasone and Daratumumab for Relapsed/Refractory MM

Median number of prior lines of therapy: 4 (range 1 – 13), 71% PI and IMiD refractory, 25% with high risk CGs



Of 17 pts in ≥CR, 35%, 29% and 6% were MRD- at thresholds of 10-4, 10-5 and 10-6, respectively

Median OS = 17.5 months (85% CI 13.3 – NE)



Median PFS in high risk CG disease (N=22): 3.9 months (95% CI 2.3 – NE)

Chari, A, et al. *Blood* 2017;130:974-81.

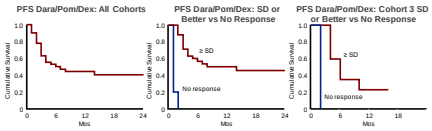
Analysis of Daratumumab, Pomalidomide and Dexamethasone in Relapsed/Refractory Multiple Myeloma

Best Response	Dara and Pom Naive (n = 19)	Dara and/or Pom Refractory (n = 22)	Dara and Pom Refractory (n = 12)
ORR, n %	17 (89.0)	9 (40.9)	4 (33.3)
sCR, n %	7 (36.8)	0	0
CR, n %	1 (5.3)	0	0
VGPR, n %	3 (15.8)	1 (4.5)	1 (8.3)
PR, n %	8 (42.1)	8 (36.4)	3 (25.0)
MR/SD, n %	1 (5.3)	9 (40.9)	6 (50.0)
PD, n %	1 (5.3)	4 (18.2)	2 (16.7)
Median cycles of tx, n (range)	15 (1-23)	3 (1-8)	3 (1-8)

Nooka AK, et al. *Blood.* 2016;128:492.

12

Analysis of Daratumumab, Pomalidomide and Dexamethasone in Relapsed/Refractory Multiple Myeloma



Efficacy, Mos	All Cohorts (N = 41)	Dara and Pom Naive (n = 19)	Dara and Pom Refractory (n = 12)
Median PFS	7	NR	3
Median follow-up	16	17	8

Nooka AK, et al. *Blood*. 2016;128:492.

General Treatment Principles

- Overlap between early and late relapse treatment choices
  - An early or late relapse regimen may be appropriate as 2nd – 4th line therapy (1 – 3 prior lines) depending on the circumstances
- The role of doublets and monotherapy is limited
  - Several novel triplets now available with good toxicity profiles
  - Consider in the more frail, heavily pretreated patients
- Prior treatment toxicity, disease resistance patterns and co-morbidities figure particularly prominently into the decision making process for these patients
- Assess for the presence of t(11;14)
- Always think about a clinical trial

PABST: The Blue Ribbon Approach to Therapy Decisions for Previously Treated Multiple Myeloma

- **P**ast medical history
  - What co-morbidities will impact tolerability of therapy?
- **A**dverse events
  - What toxicities were experienced with prior therapy?
- **B**iochemical vs clinical relapse/progression
- **S**tandard vs high-risk disease biology
- **T**reatment history
  - Is the disease resistant to specific drug classes?

Biochemical vs Clinical Progression

- **Biochemical progression:**
  - Progression of disease based on M protein parameter increase only
  - Timing of therapy institution / escalation dependent on numerous factors
    - Pace of progression
    - Original clinical presentation
    - Standard vs high-risk disease biology
    - Patient / physician comfort level
- **Clinical relapse:**
  - "Direct indicators of increasing disease and/or end organ dysfunction (CRAB features) related to the underlying clonal plasma-cell proliferative disorder"
  - Mandates immediate institution / escalation of therapy

IMWG Consensus Criteria for Response in MM

Biochemical Progression	Clinical Relapse
↑ of ≥25% from nadir response value in one or more of the following: 1) Serum M protein (absolute increase ≥0.5 g/dL; ≥1 g/dL if nadir ≥5 g/dL) 2) Urine M protein (absolute increase ≥200 mg/24 hours) 3) Measurable by serum FLC testing only: difference between involved and uninvolved FLCs (absolute increase ≥10 mg/dL) 4) Non-secretory: bone marrow PC % (absolute increase ≥10%)	1) Development of new soft tissue plasmacytomas or bone lesions (osteoporotic fractures do not constitute progression) 2) Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and >=1 cm) increase as measured serially by the SPD§§ of the measurable lesion 3) Hypercalcaemia (>11 mg/dL); 4) Decrease in haemoglobin of >=2 g/dL not related to therapy or other non-myeloma-related conditions 5) Rise in serum creatinine by 2 mg/dL or more from the start of the therapy and attributable to myeloma 6) Hyperviscosity related to serum paraprotein
≥50% increase in circulating plasma cells (minimum 200 cells / uL) if this is the only disease measure available	

Kumar S et al. Lancet Oncol 2016;17:328-46

Standard vs High-Risk Disease Biology: IMWG Consensus on Risk Stratification

	High-Risk	Standard-Risk	Low-Risk
Parameters	ISS II/III and t(4;14) or del(17p13)	Others	ISS I/II and absence of t(4;14), del(17p13) and +1q21 and age <55
% of Patients	20%	60%	20%
Median OS	2 years	7 years	>10 years

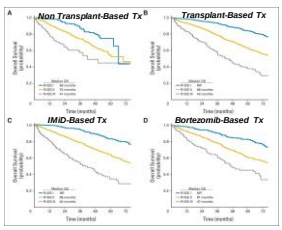
- Other factors: Gene expression profile, LDH. circulating plasma cells, response to prior therapy

Chng WJ et al. Leukemia 2014;28:269-77

Revised International Staging System

- ❑ R-ISS stage 1: normal LDH, no high risk cytogenetic abnormality (CA)*, ISS stage 1 disease
- ❑ R-ISS stage 2: not stage 1 or 3
- ❑ R-ISS stage 3: ISS stage 3 disease PLUS high LDH OR high risk CA

**High risk CA = del(17p) and/or t(4;14) and/or t(14;16)*



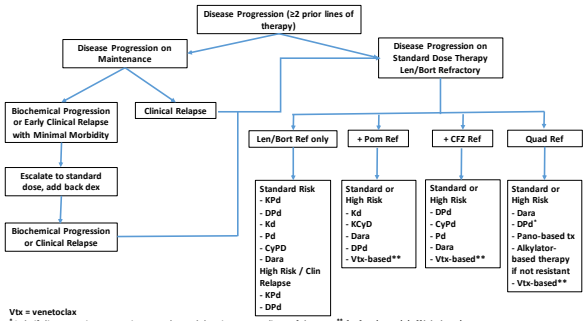
Palumbo et al. JCO 2015;33:2863-2869

Treatment History

- What regimen(s) has the patient had in earlier lines of therapy?
- Is the disease refractory to a specific treatment?
  - Refractory per the IMWG guidelines: disease progression on or within 60 days of the last dose of therapy
    - Lack of response (stable disease) with prior therapy has been included in the definition of refractory in some studies
  - Carfilzomib has activity in bortezomib-refractory disease but the reverse has not been well studied
  - Pomalidomide has activity in lenalidomide-refractory disease but the reverse has not been well studied
- If refractory, did the patient have disease progression on standard dosing, reduced dosing due to prior toxicity or maintenance dosing?
  - If dose reduced for toxicity, what were the toxicities, and how could they be better managed?
  - For patients on maintenance, it is common practice to optimize therapy prior to changing to a non-cross resistant regimen.
    - Increase the dose of lenalidomide and reincorporate dexamethasone for a patient with progression on lenalidomide maintenance. A 3rd agent is often included in such a scenario (e.g. elotuzumab) but patients with lenalidomide-refractory disease were not allowed to participate in the ELOQUENT-1 study and the additional impact of this maneuver has not been well studied

Treatment Choice Algorithm

- First Step
  - Review resistance pattern with prior therapy
  - Determine biochemical vs clinical relapse
  - Assess standard vs high risk disease
    - High risk FISH: del(1p), gain 1q, t(4;14), t(14;16), t(14;20), del(17p)
    - High LDH, circulating plasma cells, plasma cell leukemia, extramedullary disease
- Second Step
  - Refine choice based on co-morbidities and tolerability of previously used drug classes



Vtx = venetoclax

*Only if disease resistant to prior pom-dex and dara in separate lines of therapy. **If + for t(11;14) (off label use)

Venetoclax Monotherapy (N=66)

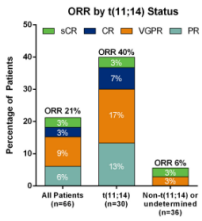
Design: Phase I, open label, study of venetoclax monotherapy

Study Population: RRMM
- Median age: 63 yrs
- ISS stage I/II/III: 62%
- Median prior therapies: 5 (1-5)
- Prior BTZ: 94% (70% ref)
- Prior REV: 94% (77% ref)

Dosing & Schedule:
VEN: initial 2 week lead in period with weekly dose-escalation
- Final doses: daily at 300 mg, 600 mg, 900 mg, or 1200 mg
- Patients who progressed could receive VEN + dex and remain on study

- **Median time on VEN: 2.5 mo (0.2-23); 26% received VEN + dex for a median of 1.4 mo (0.1-11)**

Safety, n (%)	Venetoclax
Gr 3/4 (≥10%)	Thrombocytopenia (26%), neutropenia (20%), lymphopenia (15%), anemia (14%), and decreased white blood cells (12%)
SAEs ≥2 pts	Pneumonia (n=5), sepsis (3), pain, pyrexia, cough, and hypotension (2 each)
Deaths	8 (all considered unrelated to VEN)



Kumar S, et al. ASH 2016. Abstract 488.

Venetoclax + Vd (N=66)

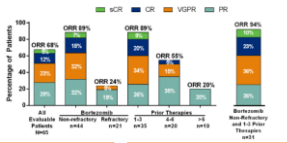
Design: Phase Ib, open label, dose escalation study of venetoclax + Vd

Study Population: RRMM
- Median age: 64 yrs
- ISS stage II/III: 59%
- Median prior therapies: 3 (1-13)
- Prior BTZ: 32% ref
- Prior REV: 56% ref

Dosing & Schedule:
VEN: daily, 50 mg – 1200 mg dose escalation
- RP2D: 800 mg qd

Vd: Dose and schedule not reported

Objective Responses Rates for Patients with R/R MM



Safety, n (%)	Venetoclax
Gr 3/4 (≥10%)	Thrombocytopenia (29%), anemia (15%) and neutropenia (14%)
SAEs ≥2 pts	Febrile neutropenia, thrombocytopenia, cardiac failure, pyrexia, influenza, lower respiratory tract infection, pneumonia, sepsis, acute kidney injury, respiratory failure, embolism, and hypotension 1 DLT: lower abdominal pain (1200 mg Ven)
Deaths	5 (4=PD, 1=RSV infection)

Efficacy	All	1-3 Priors
DOR	8.8 mo	V non-ref: 10.6 mo V naïve: 15.8 mo
TTP	8.6 mo	V non-ref: 11.3 mo V naïve: 17.1 mo

Efficacy	With t(11;14)	Without t(11;14)
ORR	78%	66%

- **Discontinuations:** 43 (65%), PD (33), AE (5), withdrawn consent (2), not specified (3)

Moreau P, et al. ASH 2016. Abstract 975.

STORM: Selinexor + Dex (N=79)

Design: Phase II study of Sd

Study Population: RRMM
- 48 pts refractory to REV, POM, V, K (Quad)
- 33 pts refractory to above + anti-CD38 mAbs (Penta)

Dosing & Schedule:
S: 80 mg BIW for 6 or 8 doses of a 28 d cycle
D: 20 mg BIW

Median age: 68 yrs

Efficacy	All	Quad	Penta
ORR	21%	21%	20%
CBR	32%	29%	37%

Efficacy	ORR, n (%)
Standard Risk	4 (17)
High Risk	6 (33)
t(17p13)	3 (38)
t(14;16)	1 (100)
t(4;14)	2 (50)

Efficacy	All	Responders	Non-responders
mOS	9.3 mo	NR (>11 mo)	5.7 mo
PFS	2.1 mo		
DOR		5 mo	

Safety, n (%) Gr 3/4 (≥10%)	All patients
Thrombocytopenia	58
Neutropenia	21
Anemia	25
Fatigue	14
Hyponatremia	20

- **Most quad patients (83%) received 6 doses/cycle; penta patients (65%) received 8 doses/cycle**

Vogl DT, et al. ASH 2016. Abstract 491.

PAVO: SC Daratumumab (N=41)

Design: Ph Ib, open label, multicenter, dose-escalation study of SC Dara with rHuPH20 (Dara-PH20)

Study Population: N=41
- ≥2 prior lines of therapy
- Prior therapy included an IMiD and a PI

Dose & Schedule:
D (cohort 1): 1200 mg in 60 mL over 20 min (n=8)
D (cohort 2): 1800 mg in 90 mL over 30 min (n=33)

Dara-PH20 was infused via a syringe pump in rotating areas on the abdomen in 4-week treatment cycles: QW for 8 weeks, Q2W for 16 weeks, and Q4W thereafter

Efficacy	1200 mg	1800 mg
ORR	25%	41%

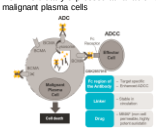
Safety	
Gr 3/4	Fatigue (2 pts), influenza, hypertension, dyspnea, and tumor lysis syndrome ONLY SEEN IN 1200 MG DOSE
IRR (most Gr 1/2)	Chills, fever, rigors, vomiting, itching, edema of the tongue, non-cardiac chest pain, and wheezing; all occurred at 1st infusion and were controlled with treatment NO GRADE 3 IRR SEEN IN 1800 MG DOSE

- Part 2 of the study will examine the RP2D of Dara-PH20 vs IV Dara monotherapy
- 1800 mg was selected as the RP2D

Usmani S, et al. ASH 2016. Abstract 1149.

First in Human Study with GSK2857916, An Antibody Drug Conjugated to Microtubule-disrupting Agent Directed Against B-cell Maturation Antigen (n=30)

- BCMA expression is restricted to B cells at later stages of differentiation and is requisite for the survival of long lived plasma cells
- BCMA is broadly expressed at variable levels on malignant plasma cells



- GSK2857916 was well tolerated with no DLTs up to 4.6 mg/kg q3w; MTD was not reached
- AEs were manageable with ocular toxicity emerging as the most frequent reason for dose modifications
- Hematologic toxicities such as thrombocytopenia and anemia are expected in the disease under study
  - 66.7% ORR including a stringent CR observed at higher doses of GSK2857916 in this refractory population
- 3.4 mg/kg was selected as the dose to investigate in the expansion phase of the study based on the totality of the data from Part 1
- Pharmacodynamic and correlative analyses are ongoing

Cohen A, et al. ASH 2016.

B-cell Maturation Antigen (BCMA)-specific chimeric antigen receptor T cells (CART-BCMA) for MM

	Anti-BCMA CAR	Bb2121	LCAR-B38M	CART-BCMA
Group/Company	NCI	Bluebird/Celgene/NCI	Nanjing Legend Biotech	Novartis/UPenn
Binder/co-stimulatory signaling	Murine/CD3 & CD28	Murine/CD3 & 41-BB	Murine/CD3 & 41-BB	Fullay human/CD3 & 41-BB
Transfection	Gamma-retroviral	Lentiviral	Lentiviral	Lentiviral
Trial ID	NCT02215967	NCT02658929	NCT03090659	NCT02546167
BCMA expression required?	Yes	Yes	Yes	No
Median prior lines of therapy	7	7	3	9
Latest efficacy	1 CR (relapsed), 7 PRs in 16 patients	4 CRs, 12 PRs in 18 patients	15 CRs and 13 PRs in 35 patients	1 CR, 3 PRs in 9 patients
Safety summary	Substantial but reversible	1 death, cardiopulmonary arrest (unrelated)	Transient CRS	1 death – progressive disease/candidaemia

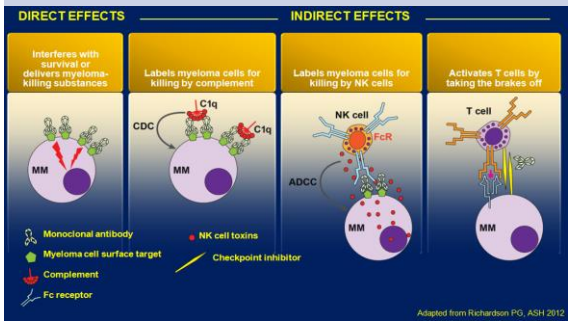
Conclusions

- There are many right ways to treat patients with multiple myeloma in relapse
  - There are also wrong ways to do it
- As long as you have a PABST (review PMHx, adverse events, biochemical vs clinical relapse, standard vs high-risk disease, treatment history), you will come to a good answer for your patient
- Use your local/regional Myeloma Specialists as a resource when questions arise about risk status, when to change treatment in biochemical relapse, optimal therapy when the preferred regimens may not be good options
- Always consider a clinical trial, especially in increasingly refractory and / or high risk disease. We have gotten better at treating this disease but have a long ways to go!

2017 Trends in MM Rx: Restoring Immune Function

- Immunomodulatory drugs, other small molecules (eg, HDACi's)
- Monoclonal antibodies
- Checkpoint inhibitors
- Vaccines
- Cellular therapies

Monoclonal Antibodies Kill MM Through Multiple Mechanisms



ELOQUENT 2: Elotuzumab-Rd (ERd) vs Rd

N=646
RRMM
1–3 prior lines
Not LEN-refractory

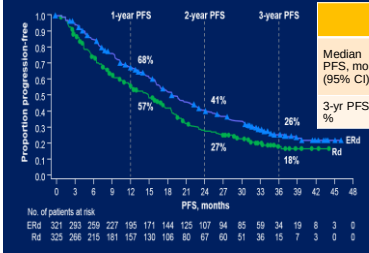
ERd (n = 321)
ELO: 10 mg/kg, d1, 8, 15, 22 (cycles 1–2); d1, 15 (cycles ≥ 3);
LEN: 25 mg, d1–21
DEX: weekly equivalent, 40 mg
28-day cycles until progression

Rd (n = 325)
LEN: 25 mg, d1–21
DEX: 40 mg, d1, 8, 15, 22
28-day cycles until progression

- **Primary end points: PFS, ORR**
- **Secondary end points: OS, DoR, QoL, safety**

Lonial S et al. *N Engl J Med.* 2015;373:621.

ELOQUENT-2: ERd vs Rd
Progression-Free Survival

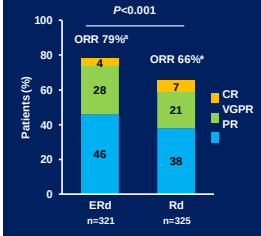


	ERd (n=321)	Rd (n=325)
Median PFS, mos (95% CI)	19.4 (16.6–22.2)	14.9 (12.1–17.2) HR=0.73 (95% CI 0.60–0.89; *P*=0.0014)
3-yr PFS, %	26	18

Dimopoulos MA et al. *Blood*. 2015;126: Abstract 28.

ELOQUENT-2: ERd vs Rd
Efficacy

Responses[1]



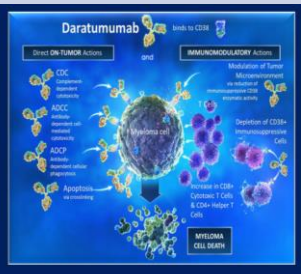
	ERd (n=321)	Rd (n=325)	HR; *P* value
Median PFS, months[2]	19.4	14.9	0.73; 0.0014
Median TTNT, months[2]	33	21	0.62 (95% CI 0.50–0.77)
Median OS, months[2]	43.7	39.6	0.77; 0.0257
Median DoR, months[1]	20.7	16.7	NR

*Values may not sum due to rounding.

1. Lonial S et al. *N Engl J Med*. 2015;373:621–31.
2. Dimopoulos MA et al. *Blood*. 2015;126: Abstract 28.

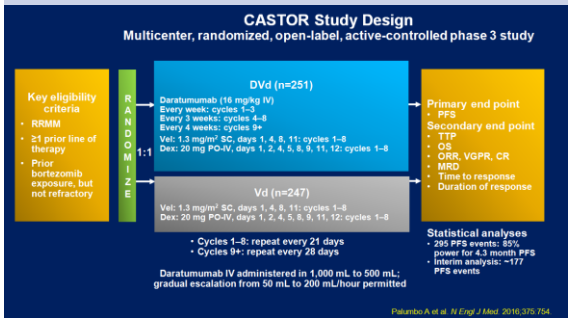
Daratumumab: Mechanism of Action

- Human CD38 IgGκ monoclonal antibody
- Direct and indirect anti-myeloma activity[1-5]
- Depletes CD38+ immunosuppressive regulatory cells[5]
- Promotes T-cell expansion and activation[5]



1. Lammerts van Bueren J et al. *Blood*. 2014;124: Abstract 3474. 2. Jansen JHM et al. *Blood*. 2012;120: Abstract 2974.
3. de Weers M et al. *J Immunol*. 2011;186:1840. 4. Overdijk MB et al. *MAbs*. 2015;7:311.
5. Krejcik J et al. *Blood*. 2016;128:384.

Phase 3 Randomized Controlled Study of DVd *vs* Vd in Pts With Relapsed or Refractory MM: CASTOR



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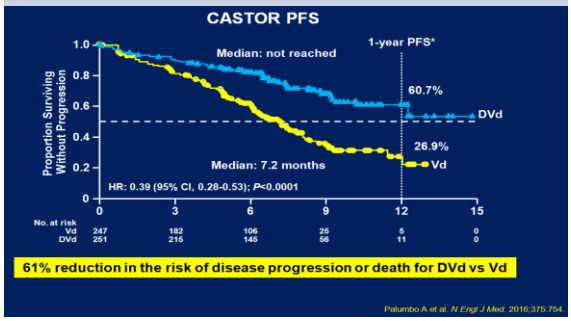
Phase 3 Randomized Controlled Study of DVd *vs* Vd in Pts With Relapsed or Refractory MM: CASTOR



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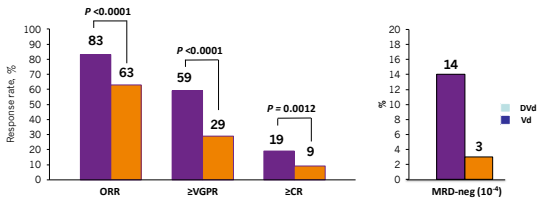
Overall Response Rate[a]



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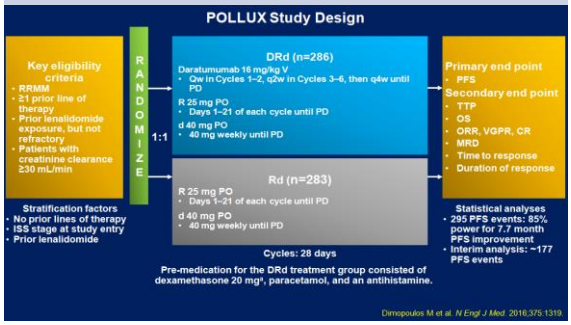
Phase 3 Randomized Controlled Study of DRd *vs* Rd in Pts With Relapsed or Refractory MM: POLLUX



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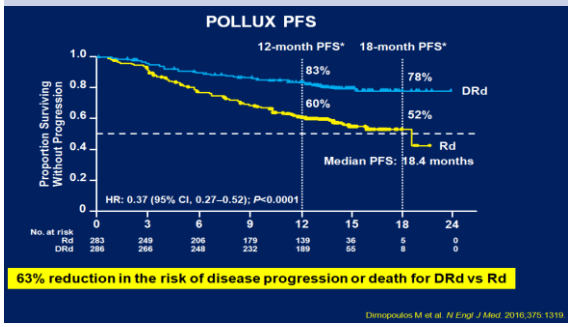
Phase 3 Randomized Controlled Study of DRd *vs* Rd in Pts With Relapsed or Refractory MM: POLLUX



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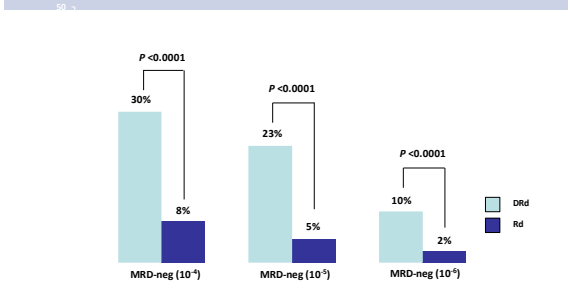
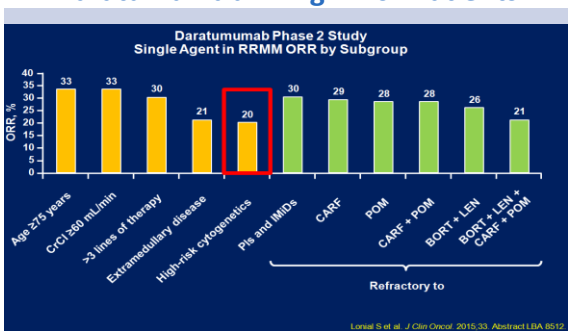
MRD-negative Rate



Daratumumab in High-Risk Patients



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Rationale for DARA + POM-D

- In a randomized, Phase 3 study, pomalidomide plus low-dose dexamethasone (POM-D) in patients relapsed from or refractory to previous treatment with bortezomib or lenalidomide[1] resulted in the following:
  - ORR = 31%
  - Median PFS of 4.0 months
  - Median OS of 12.7 months
- Pomalidomide increases CD38 expression in a time and dose-dependent fashion in multiple myeloma cells[2]

1. San Miguel J, et al. Lancet Oncol. 2013;14(11):1055-1066.
2. Boxhammer R, et al. Presented at 51st American Society of Clinical Oncology (ASCO) Annual Meeting; May 29- June 2, 2015; Chicago, IL. Abstract 8588.

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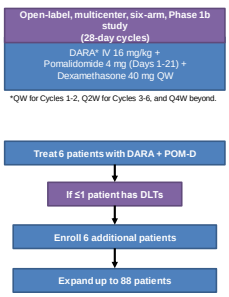
MMY1001: DARA + POM-D Arm

Eligibility criteria

- Refractory to last line of therapy
- ≥2 prior lines of therapy, including 2 consecutive cycles of lenalidomide and bortezomib
- Pomalidomide naïve
- ECOG score ≤2
- Absolute neutrophil count ≥1.0×10^9/L, and platelet count ≥75×10^9/L for patients with <50% plasma cells (>50×10^9/L, otherwise)
- Calculated creatinine clearance ≥45 mL/min/1.73 m^2



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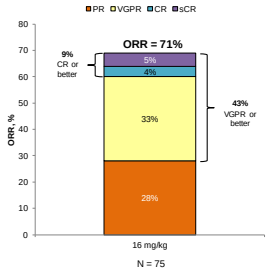
Overall Response Rate:
DARA + POM-D

	DARA + POM-D (N = 75)	
	n (%)	95% CI
Overall response rate (sCR+CR+VGPR+PR)	**53 (71)**	**59.0-80.6**
Best response		
sCR	4 (5)	1.5-13.1
CR	3 (4)	0.8-11.2
VGPR	25 (33)	22.9-45.2
PR	21 (28)	18.2-39.6
MR	2 (3)	0.3-9.3
SD	17 (23)	13.8-33.8
PD	3 (4)	0.8-11.2
VGPR or better (sCR+CR+VGPR)	32 (43)	31.3-54.6
CR or better (sCR+CR)	7 (9)	3.8-18.3



- ORR = 71%
- ORR in double-refractory patients = 67%
- Clinical benefit rate (ORR + minimal response) = 73%

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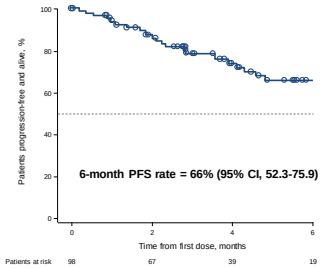
Progression-free Survival at 6 Months:
DARA + POM-D



- Median follow-up of 4.2 months

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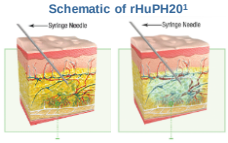
Coming Soon?;Recombinant Human Hyaluronidase

- ENHANZE™ platform of recombinant human hyaluronidase (rHuPH20) temporarily breaks down the hyaluronan barrier, allowing rapid absorption of injected drugs[1]
- Herceptin SC® and MabThera SC® are approved in Europe as co-formulate products with rHuPH20[2,3]
  - Dosing time is 5 to 8 minutes with SC versus 0.5 to 6 hours with IV[4-6]

Schematic of rHuPH20[1]



Aim: To determine the safety, pharmacokinetics, and efficacy of DARA as SC administration

1. Halozyme Therapeutics. Mechanism of action for Hylenex recombinant (hyaluronidase human injection). www.hylenex.com/mechanism-of-action. Accessed 11/8/2016.
2. European Medicines Agency. Herceptin: EPAR – product information. 2016
3. European Medicines Agency. MabThera: EPAR – product information. 2016.
4. Ismaeil G, et al. *Lancet Oncology*. 2012;13(9):869-878.
5. Shpilberg O, et al. *Br J Cancer*. 2013;109(8):1556-1561.
6. De Cock E, et al. *Plos One*. 2016;11(8):e0157957.

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PAVO: Study Design

Phase 1b, open-label, multicenter, dose-finding, proof of concept study

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.

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IRRs

	1,200 mg n = 8	1,800 mg n = 45
IRR, % (n)	**13** (1)	**24** (11)
Chills	**13** (1)	**9** (4)
Pyrexia	**0** (0)	**9** (4)
Pruritus	**0** (0)	**4** (2)
Dyspnea	**13** (1)	**0** (0)
Flushing	**0** (0)	**2** (1)
Hypertension	**0** (0)	**2** (1)
Hypotension	**0** (0)	**2** (1)
Nausea	**0** (0)	**2** (1)
Non-cardiac chest pain	**13** (1)	**0** (0)
Oropharyngeal pain	**0** (0)	**2** (1)
Paresthesia	**0** (0)	**2** (1)
Rash	**0** (0)	**2** (1)
Sinus headache	**0** (0)	**2** (1)
Tongue edema	**0** (0)	**2** (1)
Vomiting	**0** (0)	**2** (1)

- All IRRs in the 1,800-mg group were grade 1 or 2
- One grade 3 IRR of dyspnea in the 1,200-mg group
- No grade 4 IRRs were observed
- All IRRs occurred during or within 4 hours of the first infusion
- No IRRs occurred during subsequent infusions in either group
- Abdominal wall SC injections were well tolerated

Low IRR incidence and severity with DARA SC

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Immune Checkpoint Inhibitors in MM

- Target PD-1, PDL-1
- Allow T cells to function
- Current agents under investigation in MM: nivolumab and pembrolizumab
- Activity only in combination with other MM agents

Immune Checkpoint Inhibitors for Relapsed/Refractory Multiple Myeloma

	Keynote-023: Pembrolizumab + Lenalidomide and Dexamethasone[1]	Phase 2 of Pembrolizumab + Pomalidomide and Dexamethasone[2]
Patient population	RRMM for whom ≥2 prior therapies, including a proteasome inhibitor and an IMiD, have failed	RRMM for whom ≥2 prior therapies, including a proteasome inhibitor and an IMiD, have failed
Dosing		
Pembrolizumab	200 mg fixed dose*	200 mg IV every 2 weeks
IMiD	Lenalidomide: 25 mg	Pomalidomide: 4 mg daily × 21 days
Dexamethasone	40 mg (low-dose)	40 mg weekly
Response	17 patients; 76% response rate	11 of 22 evaluable patients (50% response rate)

*Used in the phase 2 portion of study based on MTD/MAD

1. San Miguel J et al. Blood. 2015;126. Abstract 565
2. Badros AZ et al. Blood. 2015;126. Abstract 596

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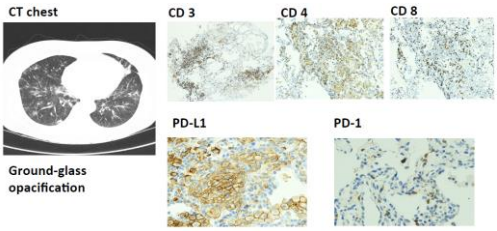
Pneumonitis



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Type	Trial	Patient Types	Study Phase	Site(s)
CAR T	CART-19 for multiple myeloma	Relapsed/ refractory	1	University of Pennsylvania
	Safety study of CAR-modified T cells targeting NKG2D-ligands	Relapsed/ refractory	1	Dana-Farber Cancer Institute
	Study of T cells targeting B-cell maturation antigen (BCMA) for previously treated multiple myeloma	Relapsed/ refractory	1	National Cancer Institute University of Pennsylvania
MILs	Tadalafil and lenalidomide maintenance with or without activated marrow infiltrating lymphocytes (MILs) in high-risk myeloma	Newly diagnosed; relapsed (without prior ASCT)	2	Sidney Kimmel Comprehensive Cancer Center
	Adoptive immunotherapy with activated marrow-infiltrating lymphocytes and cyclophosphamide graft-versus-host disease prophylaxis in patients with relapse of hematologic malignancies after allogeneic hematopoietic cell transplantation	Relapsed/ refractory	1	Sidney Kimmel Comprehensive Cancer Center
Affinity-enhanced T cells	Engineered autologous T cells expressing an affinity-enhanced TCR specific for NY-ESO-1 and LAGE-1	Relapsed/ refractory	1/2	City of Hope University of Maryland
DLI	CD3/CD28 activated Id-KLH primed autologous lymphocytes	Post-transplant	2	University of Pennsylvania

Myeloma CAR Therapy

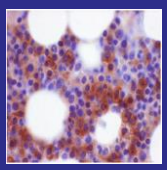
- **Which Target:**
  - **CD19, CD138, CD38, CD56, kappa, Lewis Y, CD44v6, CS1 (SLAMF7), BCMA**

- **Many questions remain about CAR design:**
  - **Optimal costimulatory domains**
  - **Optimal vector**
  - **Optimal dose and schedule**
  - **Need for chemotherapy**
  - **Perhaps "cocktails" of multiple CARs or CARs + chemotherapy will be required for best outcomes**

Which Target: BCMA

B cell maturation antigen (BCMA)

- A member of the TNF receptor superfamily
- Expression is largely restricted to plasma cells and mature B cells
- Not detectable in any other normal tissues
- Expressed nearly universally on multiple myeloma cells
- Anti-MM efficacy validated in initial studies[1]

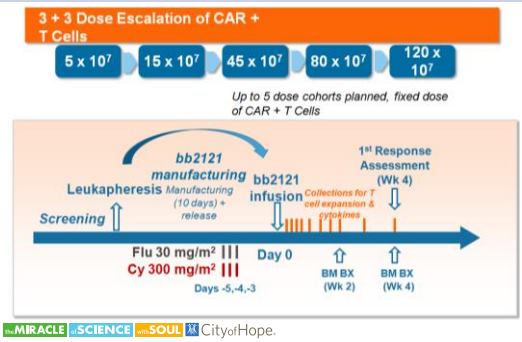


Multiple myeloma cells expressing BCMA

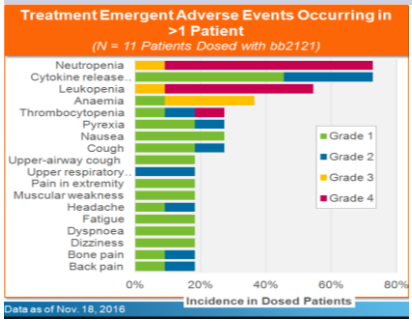
(brown color = BCMA protein)

1. Ali et al., *Blood* 2016 128: 1688. Cohen et al., ASH 2016, abstract 1147

CRB-401 Study Design



Adverse Events Generally Mild, No ≥ Grade 3 CRS* or Neurotoxicity



- No DLTs to date
- Cytopenias related to fludarabine/ cyclophosphamide lymphodepletion, as expected
- No ≥ Grade 3 cytokine release syndrome or neurotoxicity

*CRS uniformly graded according to Lee et al., *Blood* 2014;124:188-195

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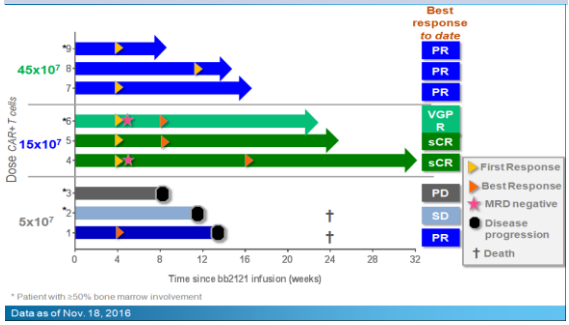
Best Response and Time Since bb2121 Infusion



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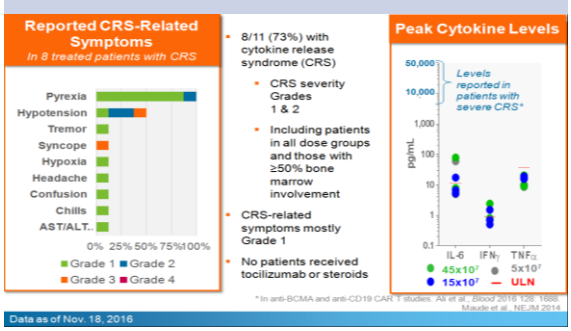
Cytokine Release Syndrome Summary



- 8/11 (73%) with cytokine release syndrome (CRS)
  - CRS severity Grades 1 & 2
  - Including patients in all dose groups and those with ≥50% bone marrow involvement
- CRS-related symptoms mostly Grade 1
- No patients received tocilizumab or steroids

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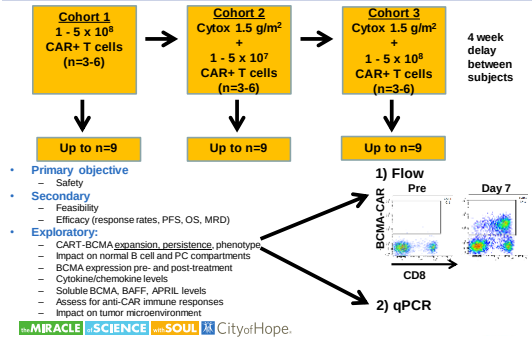
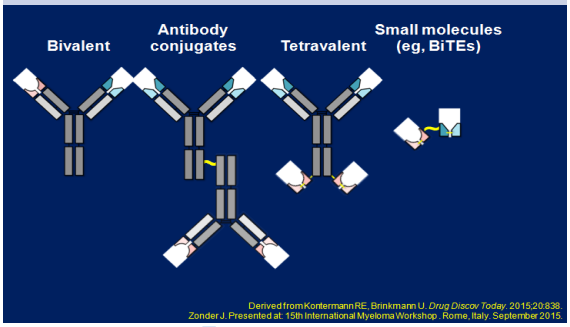
UPENN; BCMA CAR TRIAL



Patient characteristics – Cohort 1 (n=9)

Characteristic	Median (range) or %
Age	57 (44 – 70)
Gender	67% male; 33% female
Isotype	IgG (33%), IgA (44%), LC (22%)
Prior lines of therapy	9 (4-11)
Lenalidomide	100% (refractory: 78%)
Bortezomib	100% (refr: 89%)
Pomalidomide	100% (refr: 89%)
Carfilzomib	100% (refr: 89%)
Autologous SCT	78%
Cyclophosphamide	100% (refr: 67%)
Daratumumab	44% (refr: 44%)
Anti-PD1	33% (refr: 33%)
High-risk genetics -17p or *TP53* mutation	100% 67%
Extramedullary dz	33%
% BM plasma cells	80 (15 – 95)
Day 0 absolute CD3	258/μL (117 – 1354)

Bi-Specific Antibody (bsAb) Constructs



Conclusions

- **Immunotherapy is an active strategy for myeloma therapy**
- **Optimal targets for immunotherapy remain under study**