Living Well with Myeloma Teleconference

Sorting Out the Approach to Relapse

Brian GM Durie

Thursday, October 10, 2019

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IMWG INTERNATIONAL MYELOMA WORKING GROUP
A Research Division of International Myeloma Foundation

BLACK SWAN RESEARCH INITITATIVE

What is Relapse?

- New Disease

- "Biochemical" [Lab Tests Only]

  or

- "Clinical" [New Active Disease]

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Current Strategies

- Document definite progression
  - Repeat lab tests if necessary
- Decide if early treatment is warranted
- Consider “tweaking” ongoing or prior therapy
  - Add DEX/Increase dose(s)
- If “clinical relapse,” opt for new triple therapy

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Factors Affecting Decisions About Relapse

- Initial Therapy: VRd/Other
- On/Off Maintenance: REV/PI/Other
- Depth of Best Response: PR/VGPR/CR/MRD Neg
- Treatment Tolerance
- High Risk or Not [17 p-; Ig+ …]
- Which Relapse: 1st, 2nd, 3rd….

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Current Expectations in 2019

EXAMPLE

	VRd+ASCT	Dara Rd [Pollux]	Dara Vd [Castor]	Isa Pd [Icaria]
Median PFS for Each Remission	50 months	44.5 months	16.7 months	11.5 months

TOTAL = OVER 10 YEARS OF REMISSIONS

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Broad Recommendations in 2019

- Treat Relapse Early
- Use TRIPLET to get best results
- Personalize Treatment Selection

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Drug Classes Available for Relapsed Myeloma

- **IMIDs**
  - Lenalidomide (Revlimid)
  - Pomalidomide (Pomalyst)
- **Proteasome inhibitors**
  - Bortezomib (Velcade)
  - Carfilzomib (Kyprolis)
  - Ixazomib (Ninlaro)
- **Alkylating Agents**
  - Cyclophosphamide (Cytoxan)
  - Melphalan (Alkeran)
  - Bendamustine (Treanda)
- **Histone deacetylase inhibitors**
  - Panobinostat (Farydak)
- **Monoclonal antibodies**
  - Elotuzumab (Empliciti)
  - Daratumumab (Darzalex)
  - Isatuximab
- **Exportin-1 inhibitors**

  Selinexor (Xpovio)

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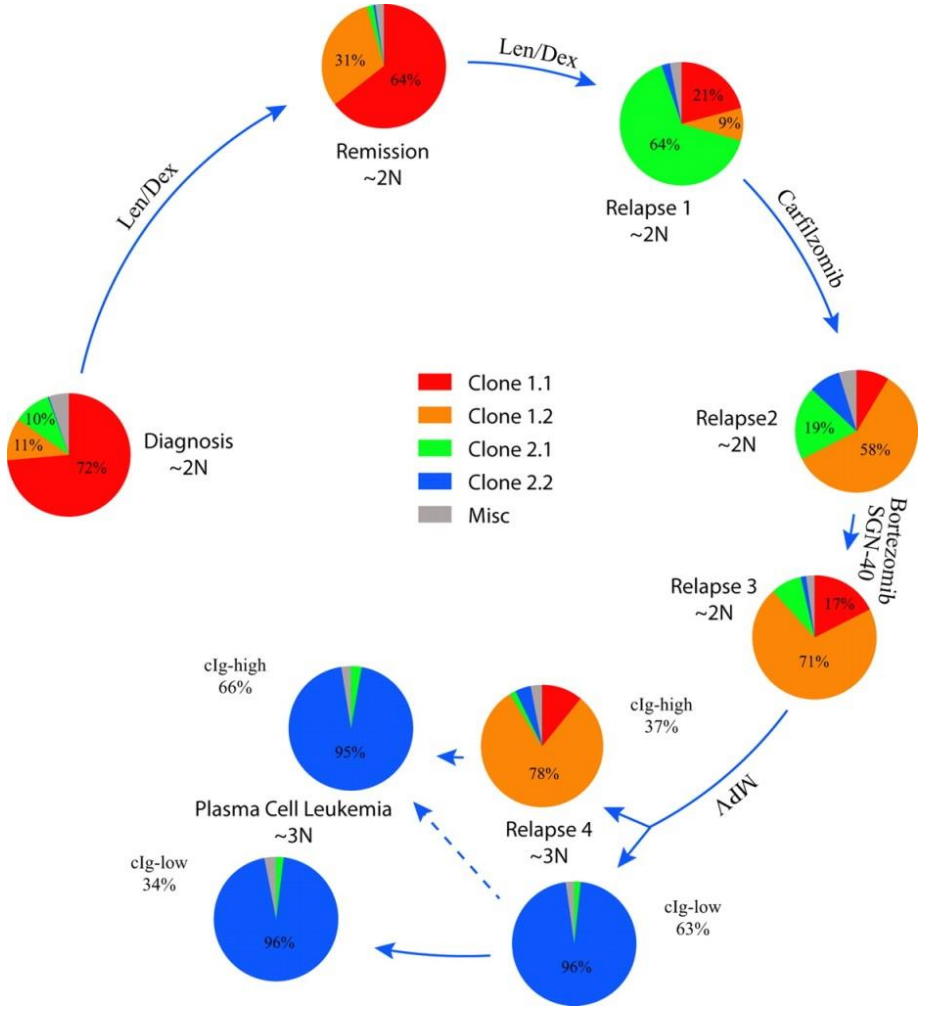
Clonal Heterogeneity Over Time

FISH analysis of a patient with t(4;14) MM over time



Keats J J et al. Blood 2012;120:1067-76

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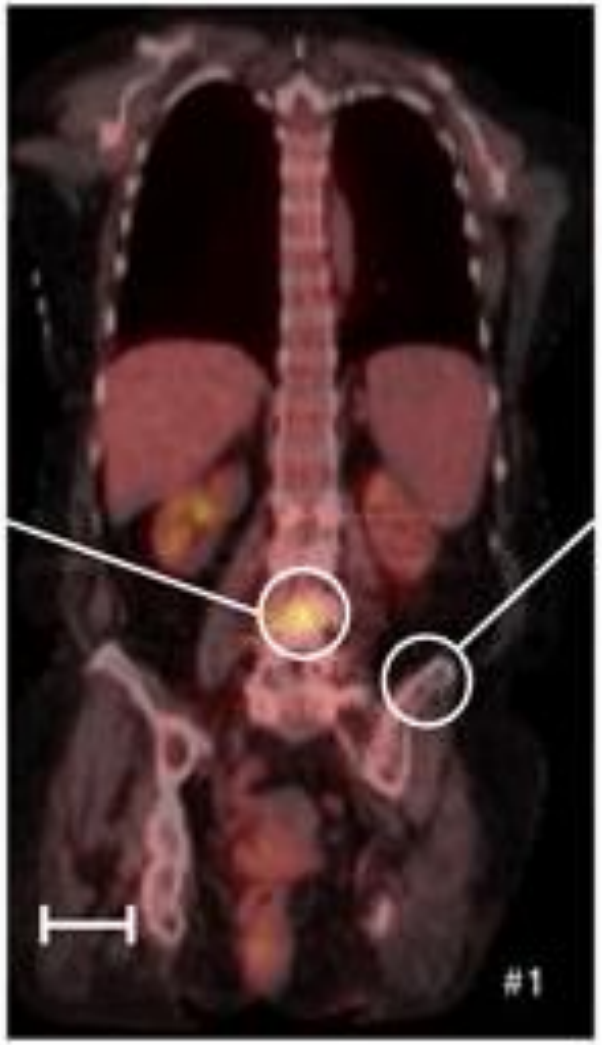
Clonal Heterogeneity Throughout the Body

Focal lesion at 4th lumbal vertebra:

- GEP70 high risk
- Non-Hyperdiploid
- Del(1p12)
- Del(1p32)
- Del(13q)
- Biallelic *TP53* del

High Risk



Left iliac crest:

- GEP70 low risk
- Hyperdiploid
- t(MYC)
- $BRAF^{V600E}$

Low Risk

Rasche L, et al. Nat Commun 2017;8:268.

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CD38 mAbs for Relapsed/Refractory Multiple Myeloma

	POLLUX		CASTOR		ICARIA	
	Rd	DRd	Vd (N=247)	DVd (N=251)	Pd (N=153)	Isa-Pd (N=154)
Key Eligibility Criteria	≥1 prior, len naïve / sensitive		≥1 prior line, bort naïve / sensitive		≥2 prior lines, len/PI exposed	
Median Follow-Up	13.5 months		7.4 months		11.6 months	
Median Lines of Tx	1 (1 – 8)	1 (1 – 11)	2 (1 – 10)	2 (1 – 9)	3 (2 – 10)	3 (2 – 11)
Len Refractory	IMID: 3.9%	IMID: 3.5%	--	--	91.5%	93.5%
Bort Refractory	16.3%	19.9%	--	--	PI: 75.2%	PI: 76.6%
ORR sCR CR ≥VGPR	76.4% 7.2% 12.0% 44.2%	92.9% 18.1% 24.9% 75.8%	63.2% 2.1% 6.8% 29.1%	82.9% 4.6% 14.6% 59.2%	35.3% CR/sCR: 2.0% 8.5%	60.4% CR/sCR: 4.5% 31.8%
MRD	4.6%	22.4%	--	--	0%	5.2%
Median PFS, mos	17.5	44.5	7.1	16.7	6.47	11.53
PFS HR	0.44 (95% CI 0.35 – 0.55, P<0.001)		0.31 (95% CI 0.24 – 0.39, P<0.001)		0.596 (95% CI 0.436 – 0.814)	
Median OS, mos	NR	NR	NR	NR	12-mo: 63%	12-mo: 72%

Dimopoulos, MA, et al. NEJM 2016;375:1319-31.

Dimopoulos, MA, et al. Haematologica 2018;103:2088-96.

Palumbo, A, et al. NEJM 2016;375:754-66.

Spencer, A, et al. Haematologica 2018;103:2079-87.

Richardson, P, et al. EHA 2019.

Bahlis, N, et al. ASH 2018.

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Carfilzomib, Dexamethasone and Daratumumab for Relapsed/Refractory MM

	All Pts	Len Refractory
ORR	84%	79%
sCR	18.3%	18.8%
CR	14.6%	10.4%
VGPR	37.8%	39.6%
PR	13.4%	10.4%

Median Follow-Up: 16.6 months

12-month PFS Standard Risk CGs: 80%
12-month PFS High Risk CGs: 62%

Chari, A, et al. *Blood* 2019;134:421-31

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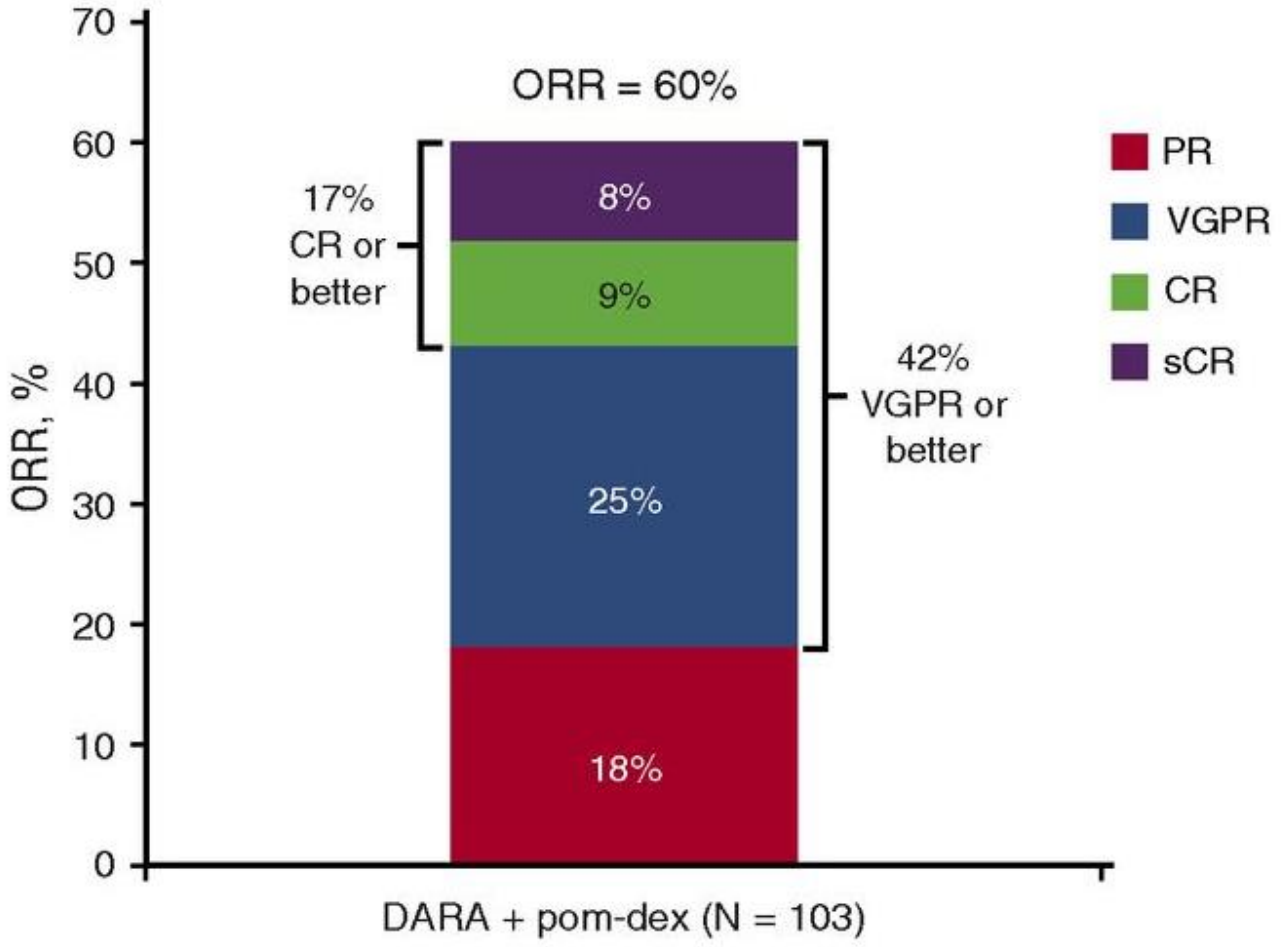
Pomalidomide, Dexamethasone and Daratumumab for Relapsed/Refractory MM

Single-Arm, Phase II Study



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

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Elotuzumab for Relapsed / Refractory Multiple Myeloma

	ELOQUENT-2		ELOQUENT-3		Elo-Bortezomib-Dex	
	Rd (N=325)	ERd (N=321)	Pd (N=57)	EPd (N=60)	Vd (N=75)	Elo-Vd (N=77)
Key Eligibility Criteria	1 – 3 prior lines, len naïve / sensitive		≥2 prior lines, ref to last line		1 - 3 prior lines, PI naïve / sensitive	
Median Follow-Up	24.5 months		Minimum 9.1 months		NR	
Median Lines of Tx	2 (1 – 4)	2 (1 – 4)	3 (2 – 8)	3 (2 – 8)	1 (1 – 3)	1 (1 – 3)
Len Refractory	--	--	84%	90%	NR	NR
PI Refractory	NR	NR	82%	78%	--	--
ORR sCR CR ≥VGPR	66% 7% (+CR) -- 28%	79% 4% (+CR) -- 33%	26% 0% 2% 9%	53% 3% 5% 20%	63% 1% 3% 27%	66% 0% 4% 36%
MRD	NR	NR	NR	NR	0%	5.2%
Median PFS, mos	14.9	19.4	4.7	10.3	6.9	9.7
PFS HR	0.70 (95% CI 0.57 – 0.85, P<0.001)		0.54 (95% CI 0.34 – 0.86, P=0.008)		0.72 (70% CI 0.59 – 0.88)	
Median OS, mos	40	48	NR	NR	12-mo: 74%	12-mo: 85%

Lonial, S, et al. NEJM 2015;373:621-31.

Dimopoulos, M, et al. NEJM 2018;379:1811-22.

Jakubowiak, A, et al. Blood 2016;127:2833-40.

Proteasome Inhibitor Triplets for Relapsed / Refractory Multiple Myeloma

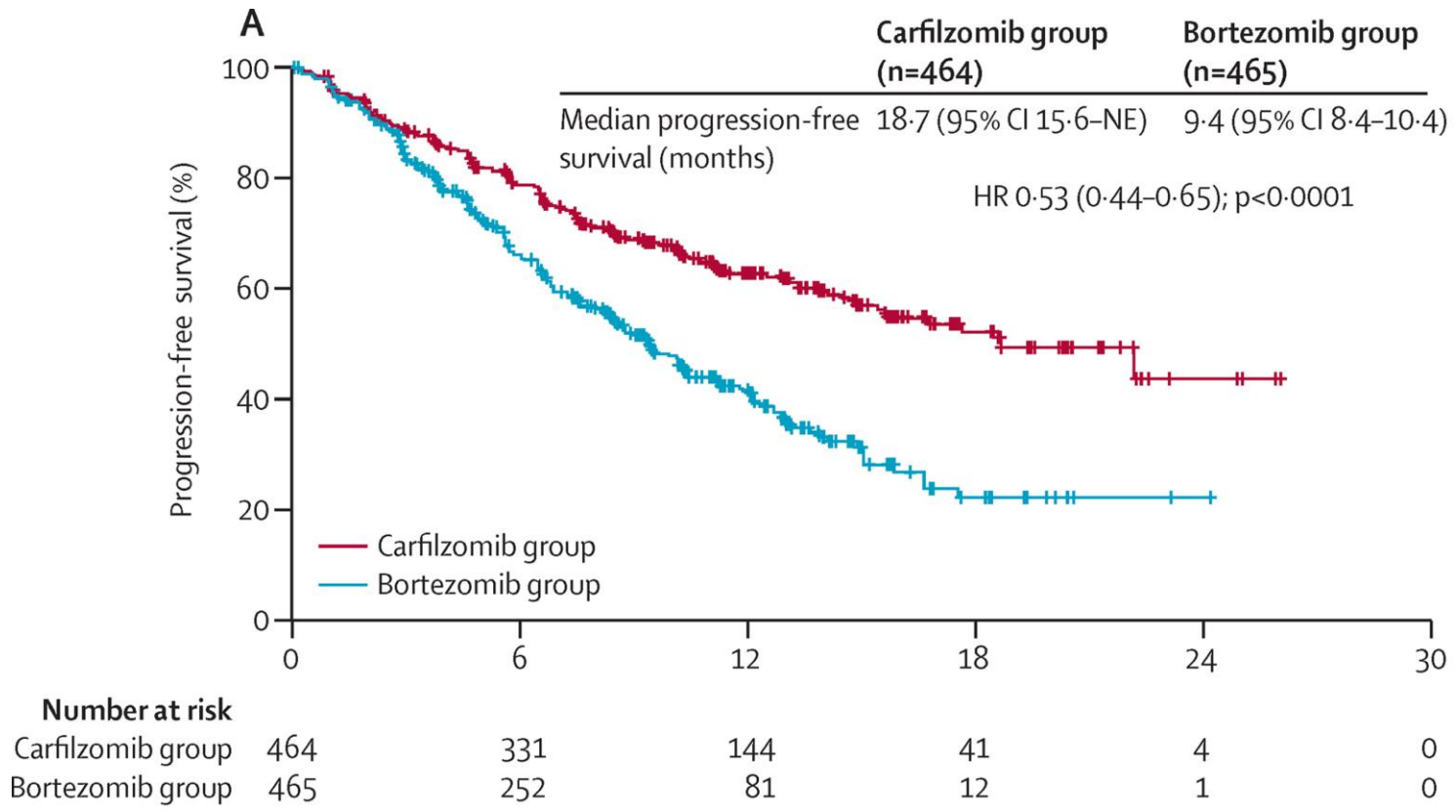
	TOURMALINE-MM1		ASPIRE		OPTIMISMM	
	Rd (N=362)	IRd (N=360)	Rd (N=396)	KRd (N=396)	Vd (N=278)	PVd (N=281)
Key Eligibility Criteria	1 – 3 prior lines, len/PI naïve / sensitive		1 - 3 prior lines, len/PI naïve / sensitive		1 - 3 prior lines PI naïve / sensitive	
Median Follow-Up	14.6 and 14.8 months		31.5 and 32.3 months		15.9 months	
Median Lines of Tx	2 (1 – 3)	2 (1 – 3)	2 (1 - 3)	2 (1 – 3)	2 (1 – 2)	2 (1 – 2)
Len Refractory	--	--	--	--	69%	71%
PI Refractory	--	--	--	--	13%	13%
ORR sCR CR ≥VGPR	71.5% <1% 7% 39%	78.3% 2% 12% 48%	66.7% 4.3% 5.1% 40.4%	87.1% 14.1% 17.7% 69.9%	50% 0.7% 3.2% 18.3%	82.2% 3.2% 12.5% 52.7%
MRD	NR	NR	NR	NR	NR	NR
Median PFS, mos	14.7	20.6	17.6	26.3	7.1	11.2
PFS HR	0.74 (95% CI 0.59 – 0.94, P=0.01)		0.69 (95% CI 0.57 – 0.83, P=0.0001)		0.61 (70% CI 0.49 – 0.77, P<0.0001)	
Median OS, mos	NR	NR	40.4	48.3	NR	NR

Siegel, DS, et al. J Clin Oncol 2018;36:728-34.
Richardson, PG, et al. Lancet Oncol 2019;20:781-94.
Moreau, P, et al. NEJM 2016;374:1621-34.
Stewart, AK, et al. NEJM 2015;372:142-32.

What is the Best Proteasome Inhibitor in Relapsed Myeloma?

- Phase 3 study comparing carfilzomib-dex to bortezomib-dex in relapsed multiple myeloma
  - Treatment given until disease progression or unacceptable toxicity
- Eligibility criteria: 1 – 3 prior lines of therapy

	Vd	Kd
ORR	**63%**	**77%**
sCR	**2%**	**2%**
CR	**4%**	**11%**
≥VGPR	**29%**	**54%**



Dimopoulos, MA, et al. Lancet Oncol 2017;18:1327-37.

Dimopoulos, MA, et al. Lancet Oncol 2016;17:27-38.

Median Overall Survival: 40.0 vs 47.6 months in favor of Kd

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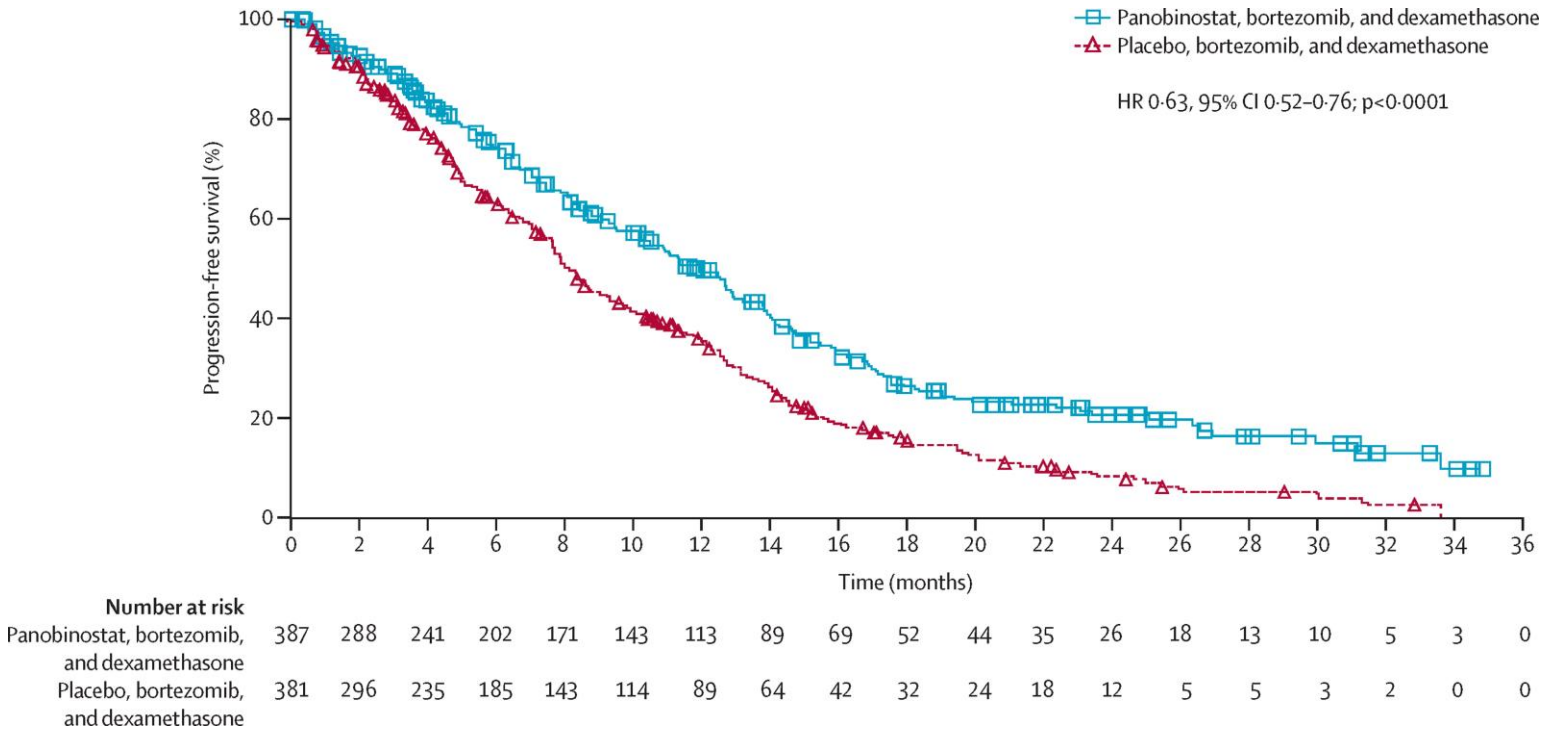
Panobinostat in Relapsed / Refractory Myeloma: PANORAMA-1

PANORAMA-1: A phase 3 study of panobinostat + bortezomib-dex vs placebo + bortezomib-dex for patients with relapsed or relapsed and refractory myeloma



	Vd (N=381)	Pano-Vd (N=387)
ORR	54.6%	60.7%
CR	6%	11%
≥nCR	15.7%	27.6%

- Median PFS for patients who have received ≥2 prior lines of therapy, including an IMID and bortezomib: 4.7 vs 12.5 months (95% CI 0.31 – 0.72)

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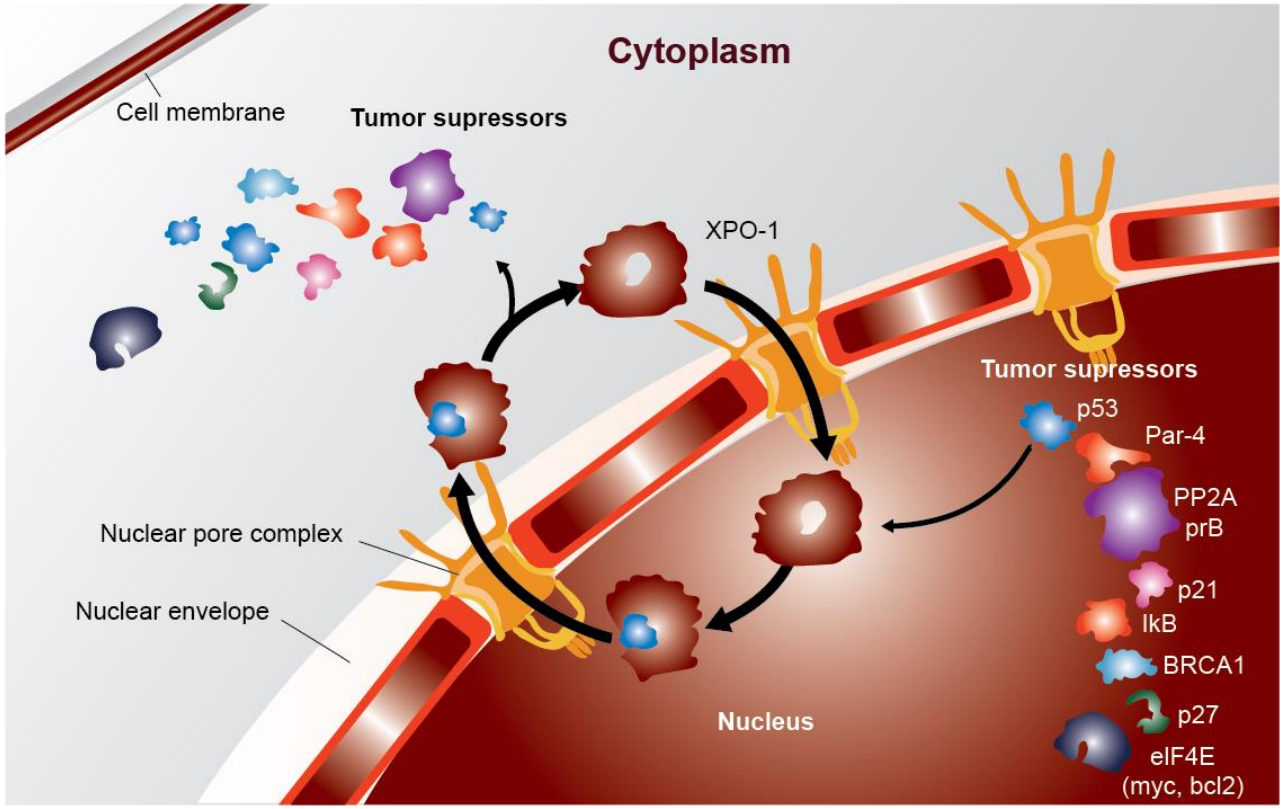
San Miguel JF et al. Lancet Oncol 2014;15:1195-206.

Richardson PG et al. Blood 2016;127:713-21.

SELINEXOR
Nuclear Export as a Therapeutic Target

- **Exportin 1 (XPO1) is the nuclear exporter for the majority of tumor suppressor proteins (TSPs), the glucocorticoid receptor (GR), and eIF4E-bound oncoprotein mRNAs**

- **Selinexor is a first-in-class XPO1 inhibitor that induces nuclear retention and activation of TSPs and the GR in the presence of steroids and suppresses oncoprotein expression**



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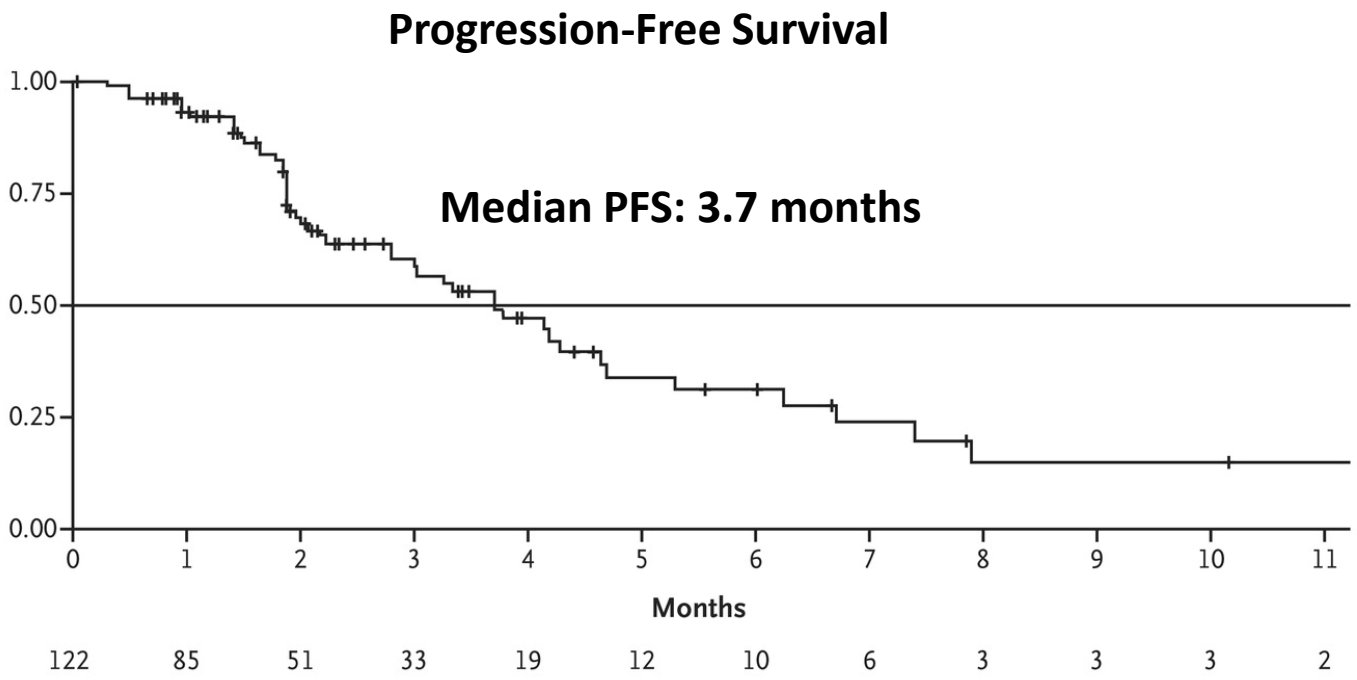
STORM: A Phase IIb Study of Selinexor + Dex for Triple Class Refractory Multiple Myeloma

- Median prior lines of therapy: 7 (3 – 18)
- All patients exposed to lenalidomide, pomalidomide, bortezomib, carfilzomib, daratumumab, glucocorticoids and an alkylating agent
- 96% refractory to carfilzomib, pomalidomide and daratumumab, 100% refractory to their most recent therapy

Response	N = 121
ORR (≥PR)	26%
CBR (≥MR)	39%
CR	2%
VGPR	5%
PR	20%
MR	13%

Median duration of response: 4.4 months



Median OS: 8.6 months

Chari A et al. NEJM 2019;381:727-38.

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1st Relapse (2nd Line Therapy)

Len Naïve or Sensitive / Bort Naïve or Sensitive	Len Refractory or Intolerant / Bort Naïve or Sensitive	Bort Refractory or Intolerant / Len Naïve or Sensitive	Len and Bort Refractory or Intolerant
Len-Based • DRd • KRd • ERd • IRd	Pom-Based • DPd • EPd† • KPd • PVd • PCd PI-Based • DKd • DVd • KCd • VCd • Kd††	Len-Based • DRd • KRd • ERd	Pom-Based • DPd • EPd† • KPd • PCd Carfilzomib-Based • DKd • KCd • Kd††

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2nd Relapse and Beyond (3rd Line Therapy+)

Len / Bort Refractory or Intolerant but Carfilzomib and Pomalidomide Naïve / Sensitive	Len / Carfilzomib Refractory or Intolerant, Pomalidomide Naïve or Sensitive	Pom / Bort Refractory or Intolerant but Carfilzomib Naïve or Sensitive	Pom / Carfilzomib Refractory or Intolerant
Dara Naïve / Sensitive • DPd • EPd • KPd • DKd • PCd • KCd **Dara Refractory** • KPd • EPd • PCd • KCd • Kd††	**Dara Naïve / Sensitive** • DPd • EPd • PCd **Dara Refractory** • EPd • PCd	**Dara Naïve / Sensitive** • DKd • KCd • Dara for frail patient • DPd **Dara Refractory** • KCd • Kd††	**Dara Naïve / Sensitive** • DPd • Dara for frail patient **Dara Refractory** • Sd • PI-PanoD • IMID-PanoD • IMID-Cd‡ • PI-Cd‡ • Cd for frail patient‡ • DPd ‡‡ • VtxD [for t(11;14)+ disease only]

C=cyclophosphamide; D=daratumumab; d = dexamethasone; E=Elotuzumab; IMID=immunomodulatory drug; K=carfilzomib; P=pomalidomide; Pano=panobinostat; PI=proteasome inhibitor; S=selinexor; Vtx=venetoclax

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††Triplet combinations have outperformed doublet therapy consistently in phase III clinical trials and can be used in frail patients with appropriate dose / schedule modifications. As such, doublets should only be used in exceptional circumstances.
‡ Best suited for patients with alkylating agent sensitive / naïve disease
‡‡ For patients with disease refractory to pomalidomide and daratumumab in separate lines of therapy

New Agent: Updates

- GSK 2857916
- AMG 420 BiTE/BEATs
- CAR T
- CELMOD (CC220)
- VENETOCLAX

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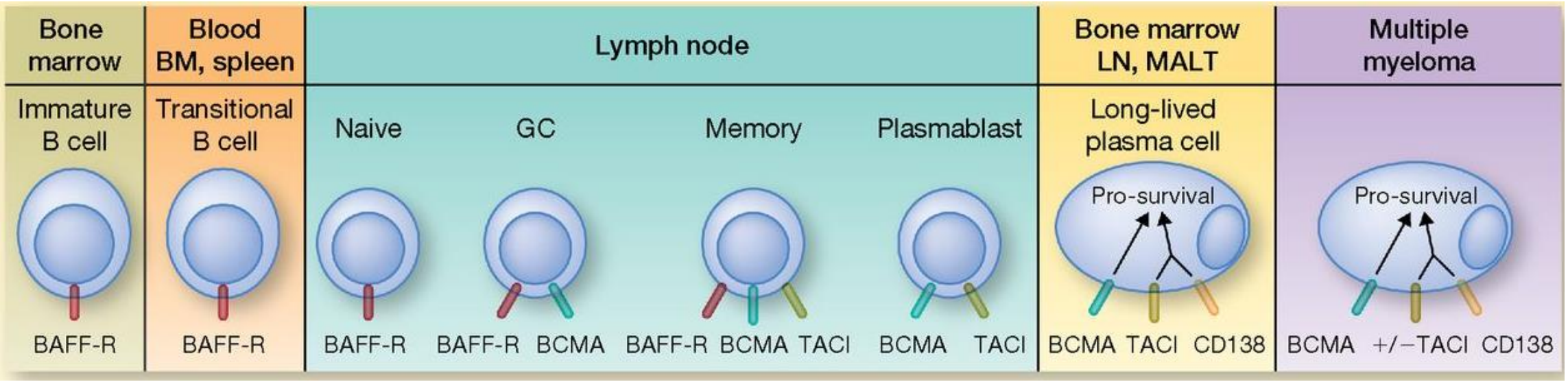
New Approaches to Therapy:
B-Cell Maturation Antigen (BCMA), a Near Perfect Target



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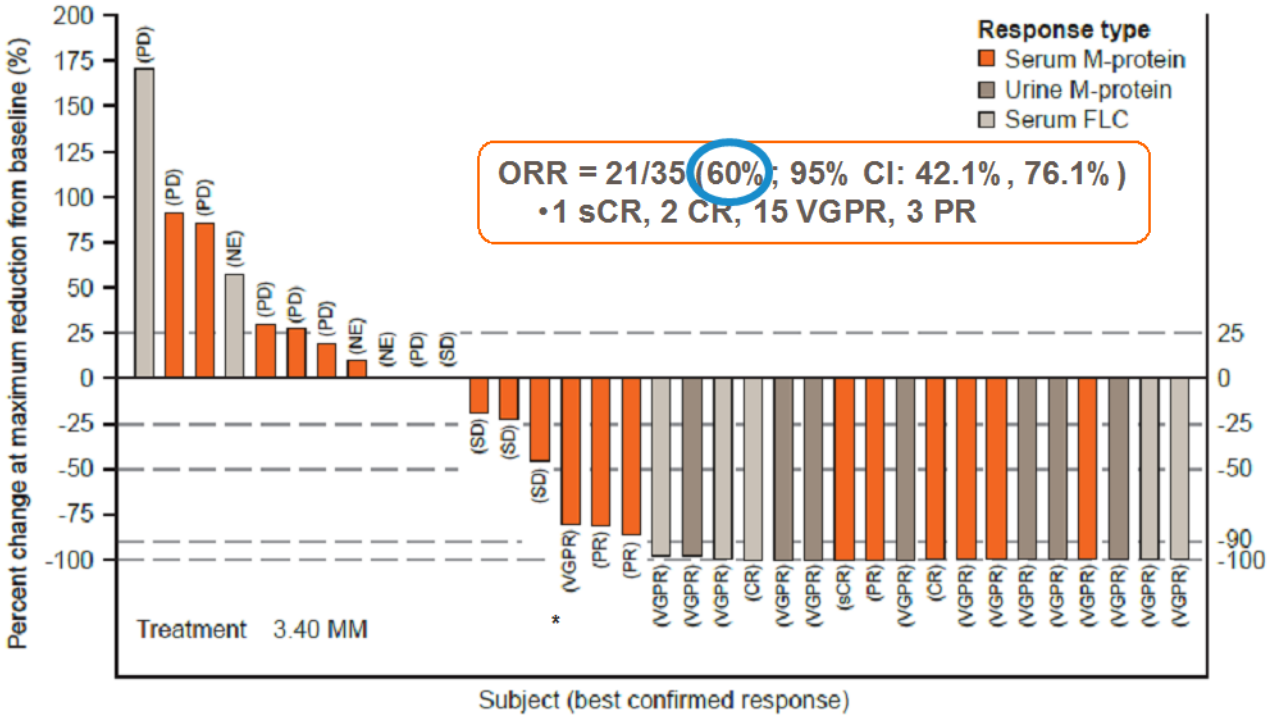
GSK-ADC: DREAMM1 Phase 2 Part 2

- Results at 3.4 mg/kg IV Q3 Wk



Updated Results

- ORR 60%
- 2 sCR
- 3 CR
- 14 VGPR
- 2 PR

- PFS: 12 months
- DOR: 14.3 months

- D/PI/IMiD refractory
  - PFS 6.2 m

89% Double refractory;
34% double + Dara refractory
29% Cyto High-risk

Trudel et al. Ash 2017

Blood Cancer J 2019 Mar 20;9(4):37

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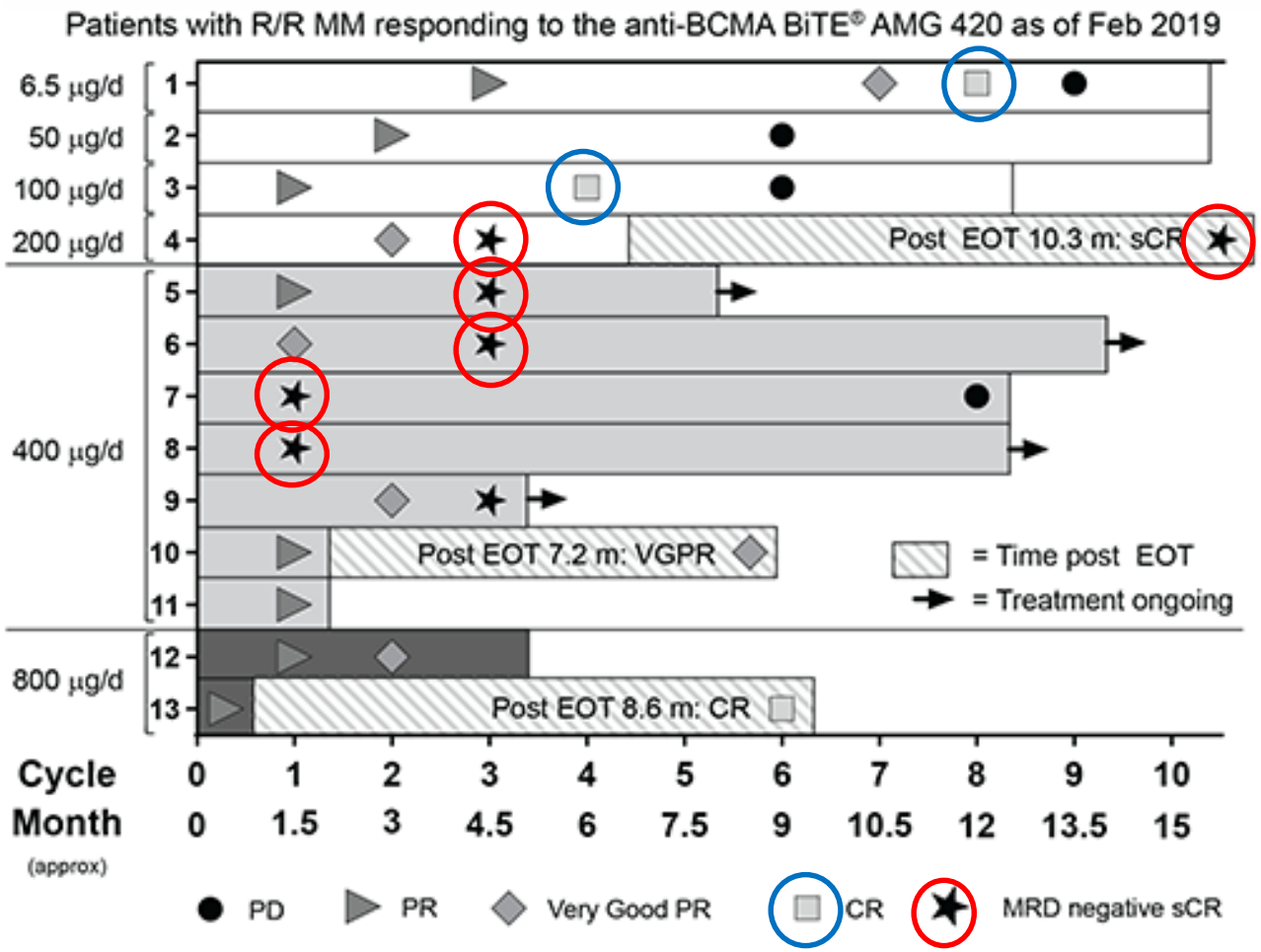
EVALUATION OF AMG 420, AN ANTI-BCMA BISPECIFIC T-CELL ENGAGER (BITE®) IMMUNOTHERAPY

R/R MULTIPLE MYELOMA (MM) PATIENTS: UPDATED RESULTS OF A FIRST-IN-HUMAN (FIH) PHASE 1 DOSE ESCALATION STUDY



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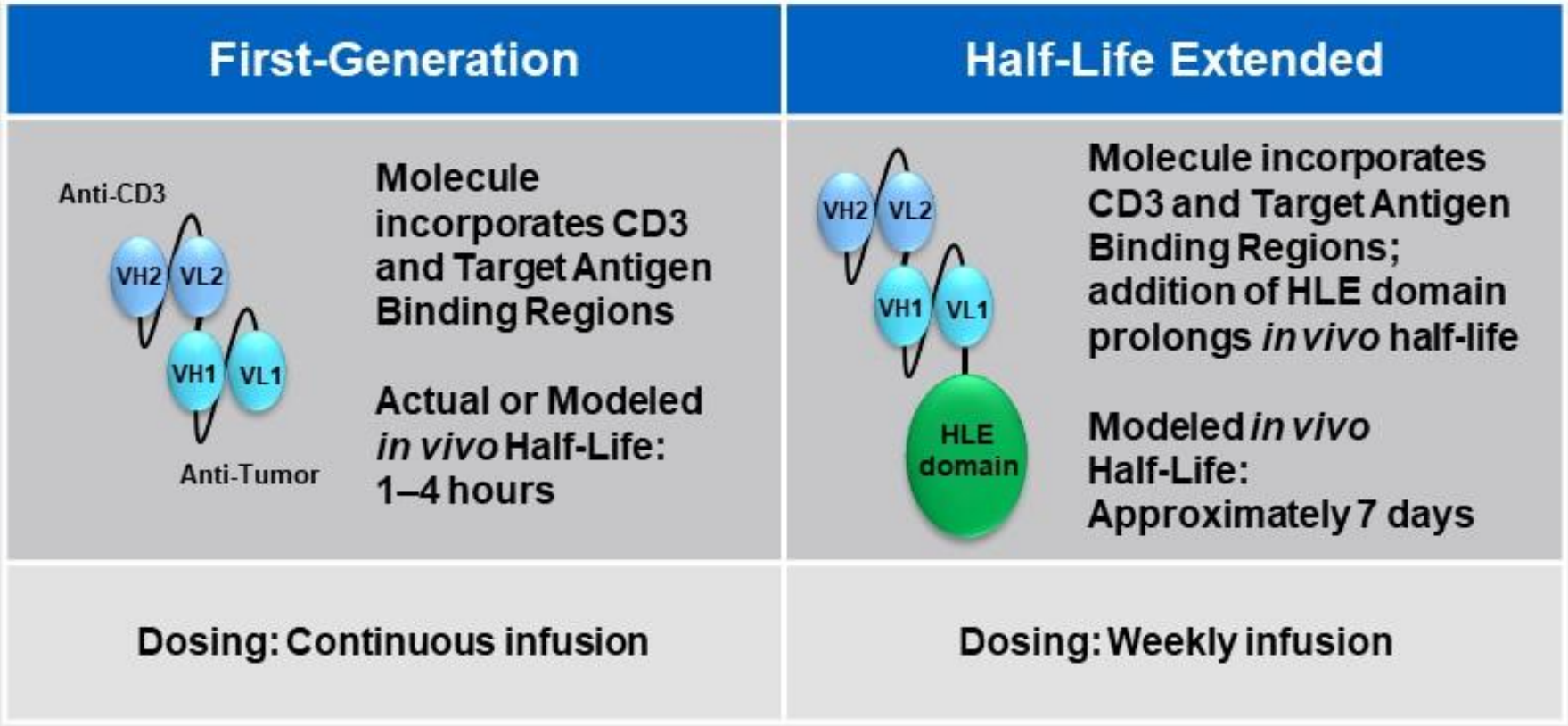
BiTE® FORMATS IN DEVELOPMENT



CD = cluster of differentiation; VH = variable domain, heavy chain; VL = variable domain, light chain

AMGEN

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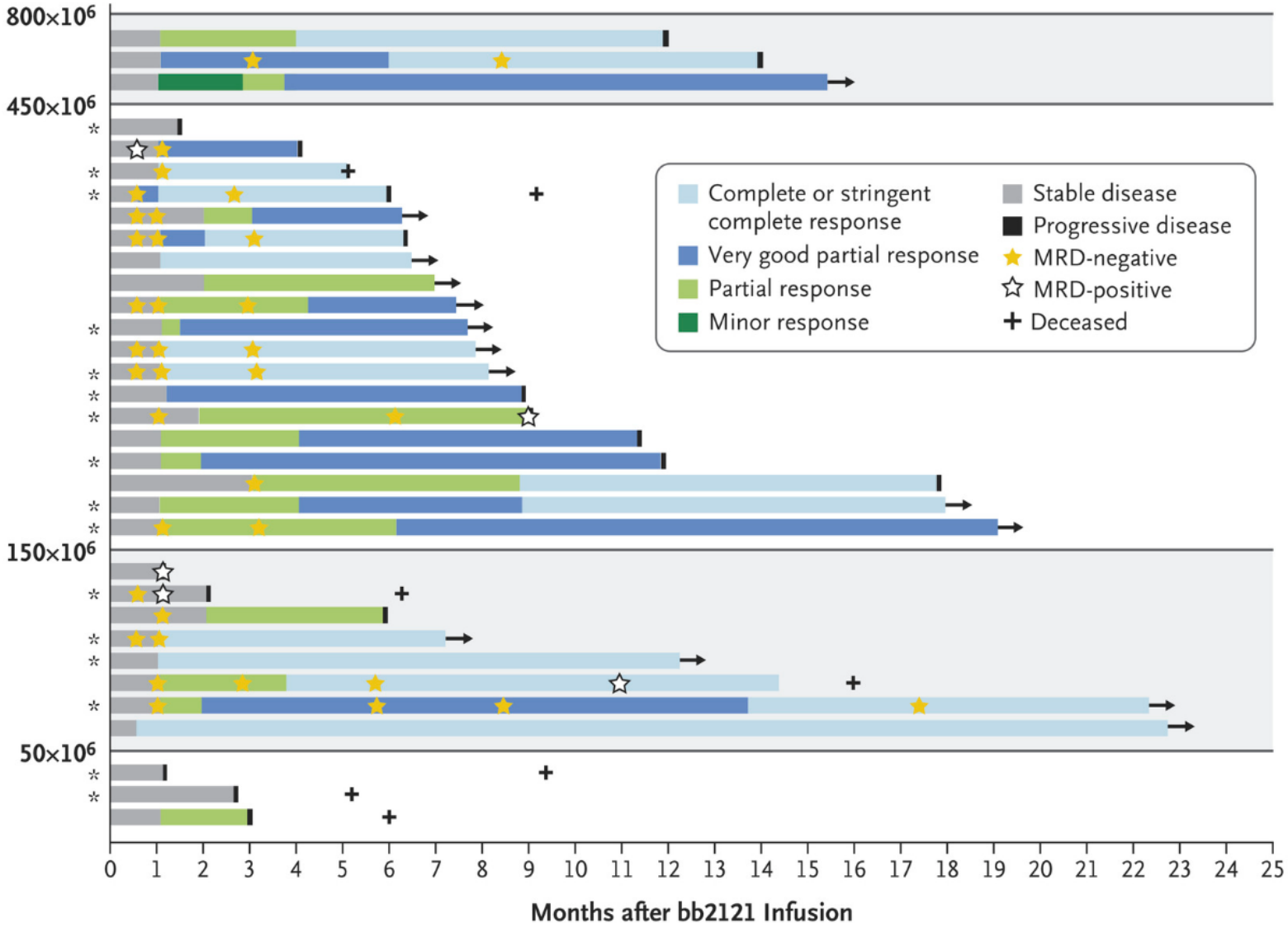
Anti-BCMA CAR T-Cell Therapy bb2121 in Relapsed or Refractory Multiple Myeloma*



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*NEJM May 2, 2019: pp 1726-1737

How Does BCMA Therapy Measure Up?

- In what order should we give these therapies?
- What line of therapy should we target?
- Will sequential BCMA therapies be possible
- Will CAR T cell therapy replace autoSCTx?

	GSK2857916	bb2121 (≥150 x 10^6 CAR T cells)	AMG-420
N	35	Escalation Group: 21	N = 42
Median Prior Lines of Therapy	57% ≥5 prior lines	7 regimens (3 – 14)	PLT. 4 (2-13)
Progression-free survival	12 months	11.8 months (17.7 months for MRD- pts)	PFS – NR
ORR CR/sCR VGPR PR	60% 9% 43% 9%	95.5% 50.0% 36.4% 9.1%	ORR 70% - 5 CR - 1 VGPR - 1 PR

GSK2857916: BCMA mAb Drug Conjugate
Vs
bb2121: BCMA CAR T Cell Therapy
Vs.
Bispecific – AMG-420

Trudel S et al. ASH 2017.
Raje N et al. ASCO 2018.
Olin RL et al. Bone Marrow Transplant 2009;43:417-22.
Cook G et al. Lancet Oncol 2014;15:874-85.

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FIRST CLINICAL (PHASE 1B/2A) STUDY OF IBERDOMIDE (CC-220; IBER)

A CELMOD, IN COMBINATION WITH DEXAMETHASONE IN PATIENTS WITH RELAPSED/REFRACTORY MULTIPLE MYELOMA

Table 1. Responses in evaluable patients

Efficacy	IBER dose 0.3–1.2 mg + DEX (N=51)
Very good partial response	1
Partial response (PR)	15
Minimal response (MR)	10
Stable disease (SD)	19
Progressive disease	6
Overall response (≥PR, %)	16 (31)
Clinical benefit (≥MR, %)	26 (51)
Disease control (≥SD, %)	45 (88)

DEX, dexamethasone; IBER, iberdomide

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Venetoclax Update

- Anti-BCl-2 therapy
- **BELLINI Trial:** 41/194 patients in Venetoclax Vd died: 13 linked to therapy plus infection and progression
- Both PFS and OS benefit in patients with t(11;14): EHA 2019

CANOVA Trial for t(11;14) patients
Re-opened: Venetoclax/dex vs Pom/dex

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Overall Guidelines in Selecting Relapse Therapy

KEY POINTS:

T iming of the Relapse
R esponse to Prior Therapy
A ggressivness of Relapse
P erformance Status at Relapse

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Principles

- Prefer Triplets
- At Least 2 New Drugs
- Consider Transplant if Eligible
- Clinical Trials if Appropriate

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Active Drugs in Multiple Myeloma

Old Drugs

- Alkylators
- Steroids
- Interferon
- Anthracyclines

Older Drugs (2003-2007)

- Bortezomib
- Thalidomide
- Lenalidomide
- Liposomal doxorubicin

Recently Approved Drugs (2013-2015)

- Carfilzomib
- Pomalidomide
- Panobinostat

- Ixazomib
- Daratumumab
- Elotuzumab

Future Drugs

- GSK 2857916
- AMG 420
- CAR-Ts

- Isatuximab
- Selinexor
- Venetoclax

- BiTEs [AMG 701 / EM 801 / JNJ 64007957]
- BEATs
- Anti CD 46 and 74
- CelMODs [220/ 9284]
- DTP 3
- BION 1301
- JNJ 42756493

Rajkumar SV. 2019

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Remember….

In 2019, treatment for relapse can achieve long, good quality remissions!

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Thank you to our sponsors!


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