Updates in Multiple Myeloma: 12 months in 10 minutes…

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Outline

- Standard of care for newly diagnosed MM
  - Imaging
  - Triplet Therapy
  - Dara for upfront MM?
- R/R MM
  - Daratumumab
    - Dara/Pom Dex
    - Dara retreatment
  - Pipeline/upcoming treatments

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Diagnosis of NDMM: How to Image the Skeleton

- Meta-analysis of 32 prospective and retrospective studies has illustrated increased detection rates of skeletal lesions using whole body CT, PET-CT or whole body MRI compared to skeletal survey
- 2014 IMWG diagnostic criteria incorporate whole body CT, PET-CT, and MRI into the recommendations for diagnosis of multiple myeloma
- Insurers have been slow to allow for advanced imaging in myeloma patients

Regelink, BJH 2013
Rajkumar, Lancet Onc 2014

Skeletal Imaging, Cont:

- Multi-center Retrospective study, IMWG sponsored
- 212 patients
  - 66 smoldering MM
  - 146 active MM

Table 2. Lytic bone lesions in CSS and WBCT, respectively, for the whole patient group

CSS	WBCT				
	Definitely present	*Probably present*	*Probably absent*	*Definitely absent*	*Total*
Definitely present	34 16.0%	2 0.9%	0 0%	5 2.4%	41 19.3%
Probably present	7 3.3%	0 0%	1 0.5%	6 2.8%	14 6.6%
Probably absent	11 5.2%	4 1.9%	2 0.9%	10 4.7%	27 12.7%
Definitely absent	33 15.6%	6 2.8%	8 3.8%	83 39.2%	130 61.3%
Total	85 40.1%	12 5.7%	11 5.2%	104 49.1%	212 100.0%

Abbreviations: CSS, conventional skeletal survey; WBCT, whole-body computed tomography.

54 (25%) of negative CSS had lesions present on WBCT

12 (6%) neg WBCT had positive CSS

Hillengass et al, Blood Cancer J, 2017

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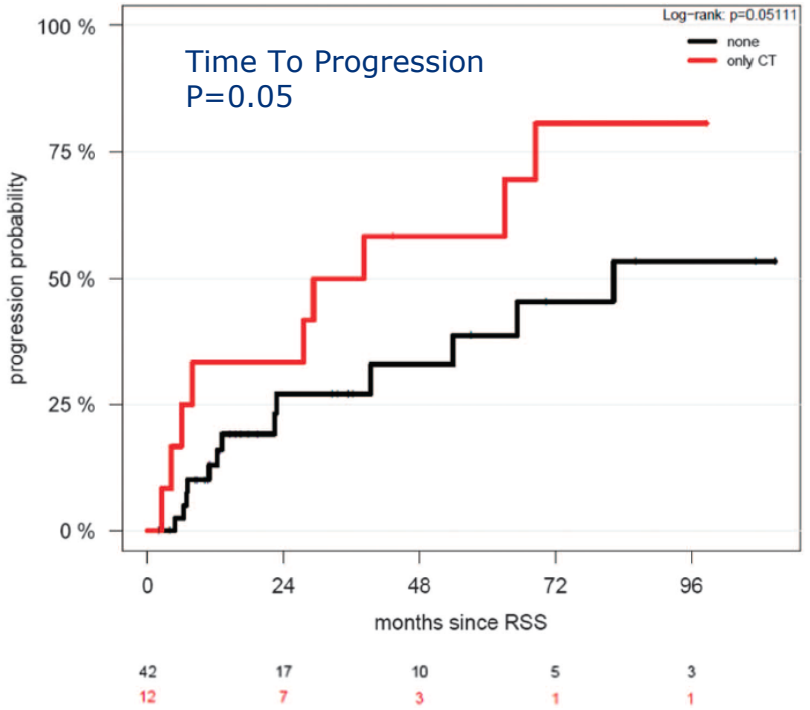
Skeletal Imaging: Smoldering Myeloma

Table 3. Lytic bone lesions identified by CSS and WBCT, respectively, for SMM patients

CSS	*WBCT*				
	Definitely present	*Probably present*	*Probably absent*	*Definitely absent*	*Total*
Probably absent	1 (1.9%)	1 (1.9%)	2 (3.7%)	5 (9.3%)	9 (16.7%)
Definitely absent	10 (18.5%)	0 0%	2 (3.7%)	33 (61.1%)	45 (83.3%)
Total	11 (20.4%)	1 (1.9%)	4 (7.4%)	38 (70.4%)	54 (100.0%)

Abbreviations: CSS, conventional skeletal survey; SMM, smoldering multiple myeloma; WBCT, whole-body computed tomography.



Hillengass et al, Blood Canc J, 2017

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S0777: Defining SOC for Newly Diagnosed Myeloma

- Randomized phase III trial
- Induction (8 x 21 day cycles)
  - RVd (21 d): R: 25 mg, d1-14; D: 20 mg d 1,2, 4,5, 8,9, 11,12; V: 1.3mg/m2 1,4, 8, 11
  - Rd (28 d): R: 25 mg d1-21; D: 40 mg, d 1, 8, 15, 22
- Maintenance: Len 25 mg d 1-21 of 28 days, Dex 40 mg weekly
- Transplant Deferred
  - 525 patients randomized
  - Slight age and sex imbalances, accounted for in analysis of results

S0777: Response Rates

	Patients given bortezomib with lenalidomide and dexamethasone (VRd group; n=216)*	Patients given lenalidomide and dexamethasone (Rd group; n=214)*
Confirmed response	34 (15·7%)	18 (8·4%)
Very good partial response	60 (27·8%)	50 (23·4%)
Partial response	82 (38%)	85 (39·7%)
Overall response rate (partial response or better)	176 (81·5%)	153 (71·5%)
Stable disease	34 (15·7%)	52 (24·3%)
Stable disease or better	210 (97·2%)	205 (95·8%)
Progressive disease or death	6 (2·8%)	9 (4·2%)

* The p value for differences in those with confirmed response was 0·02. The results section provides more details (unconfirmed responses are collapsed into the response category one level below).

Table 3: Confirmed response in assessable patients

≥ VGPR: 43% vs 32%

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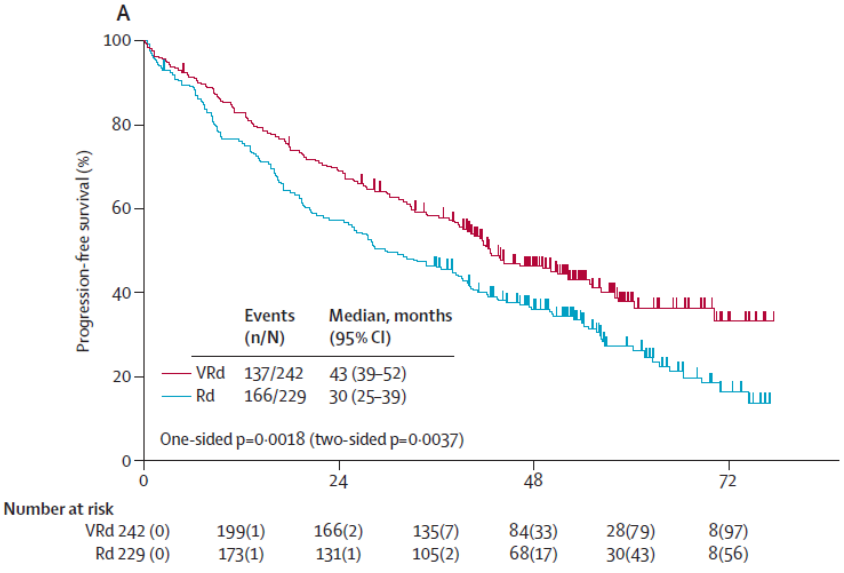
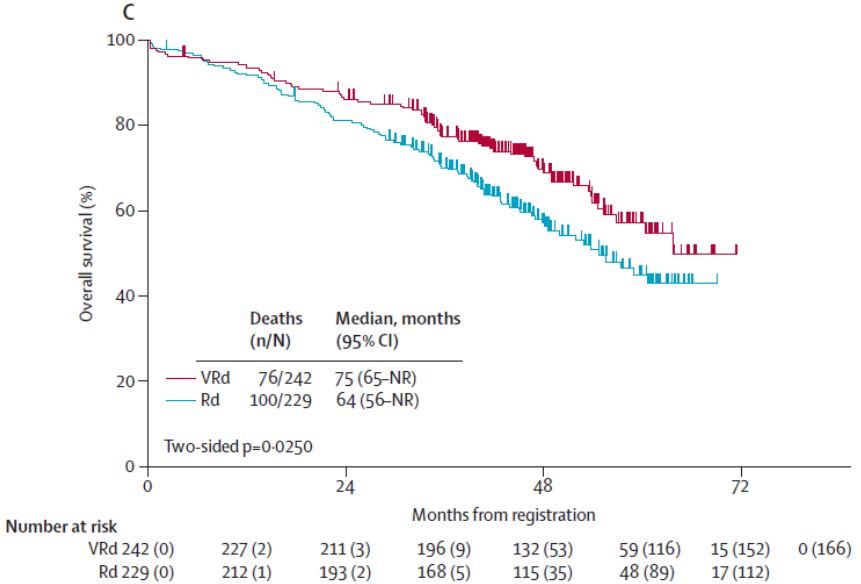
S0777 Rd vs RVd

PFS



OS



Durie et al. Lancet

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Dara-Bortez-Mel-Pred

- Transplant Ineligible (age >65 or comorbidity)
  - AST/ALT <2.5x ULN, T. Bili <1.5x ULN
  - eCrCl >40
  - ECOG 0-2
- Randomized to VMP (9 x 6 week cycles) vs Dara-VMP (9 x 6 week cycles -> dara montly)
- Primary Endpoint PFS
- 706 patients
- Reported at 2nd interim analysis (at ASH 2017, then in NEJM)

Mateos el al, NEJM 2018

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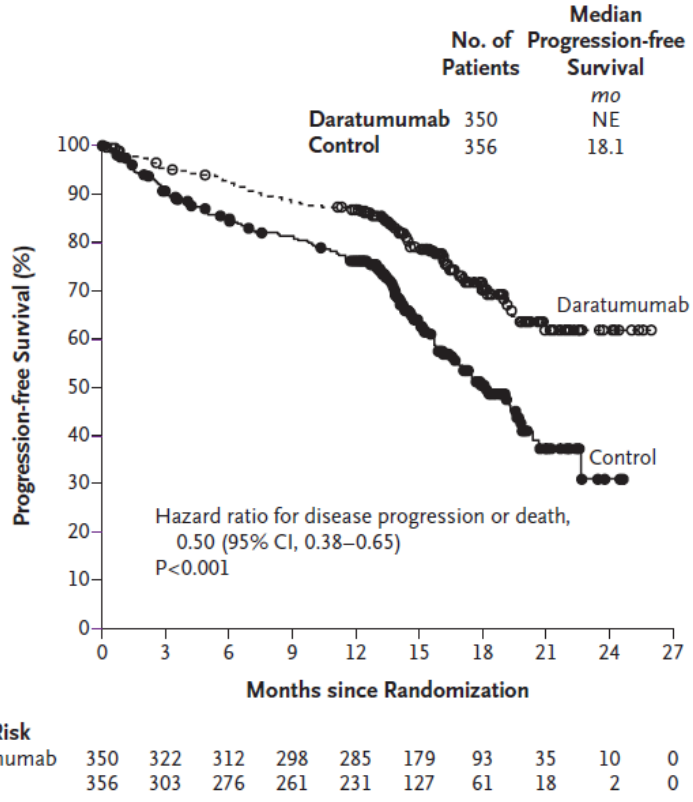
Dara-Bortez-Mel-Pred



- Only 45 and 48 deaths in dara and control arms
- Unknown cross-over rates

Mateos el al, NEJM 2018

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Newly Diagnosed Myeloma: Standard Approach

- Triplets are THE standard of care
  - In my practice only those patients with multiple comorbidities, and high risk of death from other causes, don't get imid and PI combinations
- Plain films are inadequate to rule out skeletal disease
  - Unclear how much advanced imaging adds much in patients with bone disease on skeletal survey
- Daratumumab is now approved for transplant ineligible patients, along with VMP
  - VMP not commonly used in the US – but indication creep seems likely
  - Cross-over rates will be important for interpretation of OS data

Relapsed/Refractory MM

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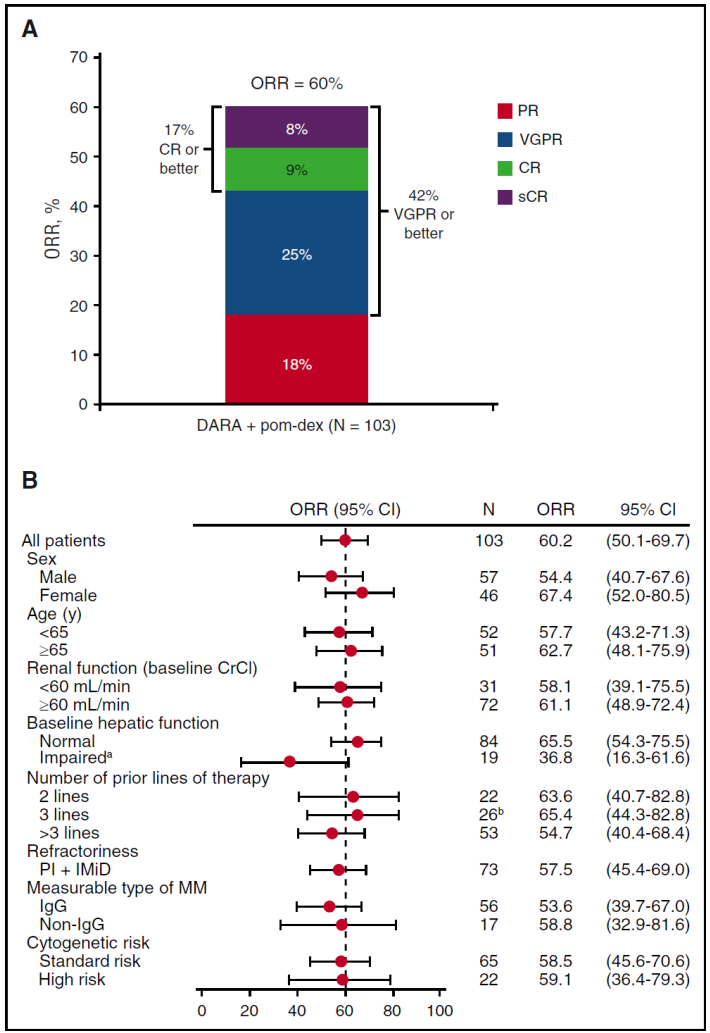
Daratumumab, Pomalidomide, Dex

- Pom and Dara naïve
- 103 pt
- Median prior tx: 4 (1-13)
  - 74% had ≥ 3 tx



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Daratumumab, Pomalidomide, Dex

- 99% of patients have grade 3-4 AE
  - Driven by neutropenia
- Is 4mg of Pom the right dose?

Table 2. Most common (>25%) TEAEs

	Daratumumab plus pom-dex (N = 103)	
	Any grade	Grade 3/4
Total AEs	103 (100)	102 (99)
Neutropenia	82 (80)	79 (77)
Anemia	56 (54)	29 (28)
Fatigue	54 (52)	12 (12)
Diarrhea	44 (43)	4 (4)
Thrombocytopenia	43 (42)	20 (19)
Cough	39 (38)	1* (1)
Leukopenia	38 (37)	25 (24)
Constipation	35 (34)	0 (0)
Dyspnea	33 (32)	8 (8)
Nausea	32 (31)	0 (0)
Pyrexia	31 (30)	2 (2)
Back pain	29 (28)	6 (6)
Upper respiratory tract infection	29 (28)	3 (3)
Muscle spasms	28 (27)	1 (1)

Values represent n (%) of patients.
*Reported as "productive cough."

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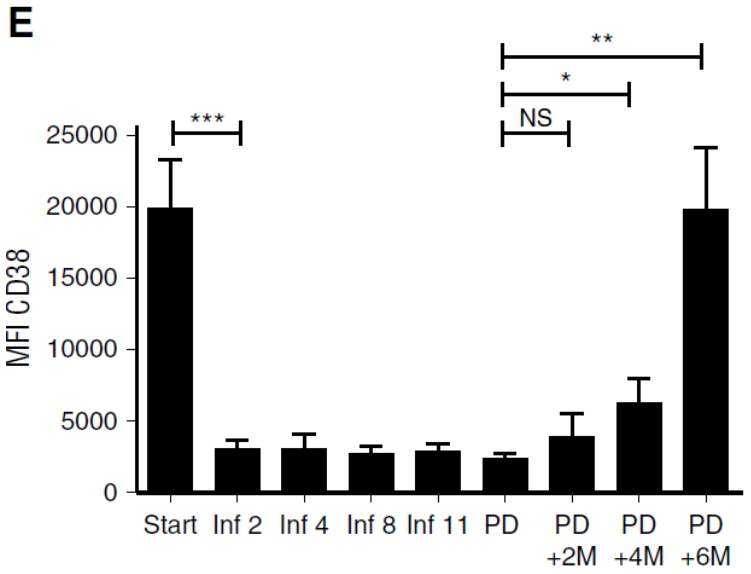
Retreatment with Daratumumab

- Mechanism of dara resistance is yet to be fully elucidated
- Patients on dara have lower CD38 expression than prior to treatment, though this expression returns to baseline 6 months post dara
- Given tolerability of dara, understanding *how* to re-treat with it is an important question moving forward



Nijhof et al, Blood 2016

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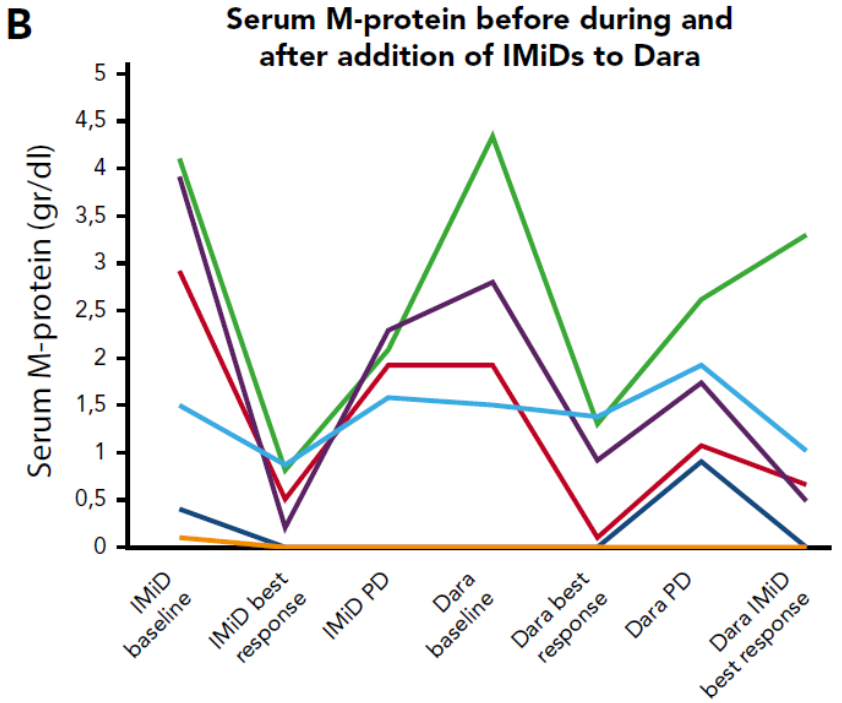
2 provocative retrospective studies

- Emory group identified 12 patients refractory to both Dara and pomalidomide who were treated with Dara-Pom-Dex
- 35% response rate (compared with 90% among patients naïve to both agents)
- Median F/U: 5mo
- Median PFS: 2.5 mo



Nooka et al, Blood 2016 128:492 (ASH abstract)
Gavriatopoulou et al, Blood 2018

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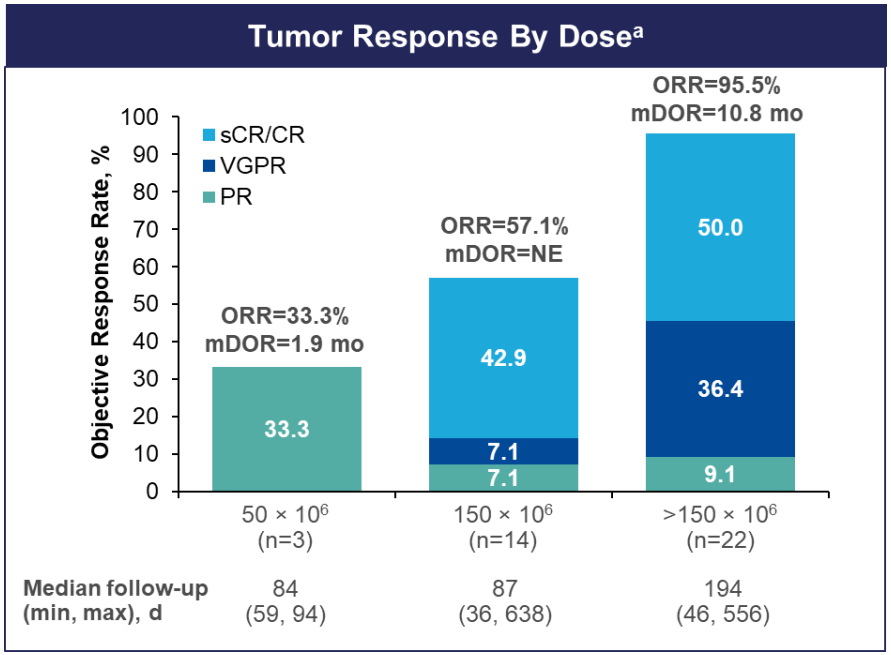
What's Coming Soon?

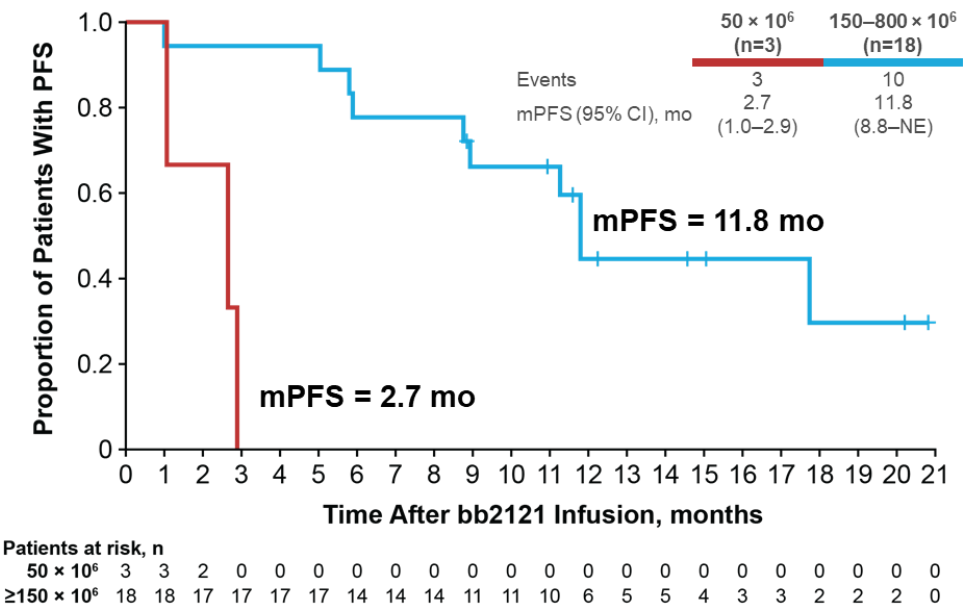
- The therapeutic pipeline remains robust
- Recent data with Isatuximab and Selinexor both have encouraging data
- 156 Phase I trials are currently recruiting in multiple myeloma
  - PD1/PDL1 inhibitors are being explored (cautiously)
  - CART-cell therapy
  - BCMA bi-specific t-cell engagers
  - New imids
  - New PIs
  - Small molecules (anti-MDM2, anti-MCL1)
  - Antibody drug conjugates

BB2121

- Anti-BCMA target CAR T-Cell therapy
- 43 pts total
- 4-1 BB co-stimulatory domain thought to promote more durable T-cell response while limiting acute toxicity
- All patients exposed to bortezomib, lenalidomide, most exposed to pom, dara, and carfilzomib
- CRS in 63%, only 5% grade 3
- MRD negativity in 16 pts (37%)

Response rates are dose dependent





Raje et al, ASCO abst 8007
Munshi et al ESA abst 2138
Curtesy of Celgene

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Carfilzomib dosing: Are we any closer to a standard approach?

Randomized trials

Trial	Carfilzomib Dose	Carfilzomib Schedule	Comparator	Outcome
ASPIRE	27mg/m2 (KRd)	2x/wk	Rd	OS benefit (2% X-over)
ENDEAVOR	56mg/m2	2x/wk	Vd	OS benefit (No X-over)
ARROW	70 mg/m2	Weekly	Kd 27 2x/wk	PFS benefit, more toxicity

KRd: carfilzomib, lenalidomide, dexamethasone; Kd: carfilzomib, dexamethasone; Rd: lenalidomide, dexamethasone; OS: overall survival; PFS: progression free survival; X-over: cross-over

Siegel et al JCO 2018
Dimopolous et al Lancet Onc 2017
Moreau et al Lancet Onc 2018

Carfilzomib dosing: Are we any closer to a standard approach?

Phase I-II Weekly KRd trials in relapse/refractory disease

Trial	Carfilzomib Dose	Number Patients	Response	Toxicity
Biran et al, ASCO 8022	Phase I: 56 ->70 mg/m2	56 mg: 10 70 mg: 46	ORR: 90% sCR/CR 20% (56mg) 30% (70mg)	~70% Grade 3-5 at both doses 2 cardiac deaths @70 mg
Richez et al ASCO 8017	56mg/m2	28	ORR: 93% ≥ CR: 60%	Heme AE ≥3 57% Non-Heme AE ≥3 37%

ORR: Overall Response Rate, CR: complete response; sCR: stringent complete response

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Carfilzomib dosing: Are we any closer to a standard approach?

- Probably not.
- Unclear if weekly Kd at 70 mg/m2 is non-inferior to Kd given at 56 mg/m2, though it is clearly effective, if slightly more toxic, than Vd
- Weekly KRd dosing is coming, and is being adopted by some physicians already.
  - 70 mg? 56 mg? 2 cardiac deaths at higher doses are worrisome – and longer term tolerability is going to be a major issue
  - Current SWOG/ECOG/ALLIANCE trial includes KRd using 36 mg/m2 twice weekly dosing - so we may be in a similar boat to Kd once results of randomized trials of weekly dosing begin reporting out.