Updates in Multiple Myeloma, 2018

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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

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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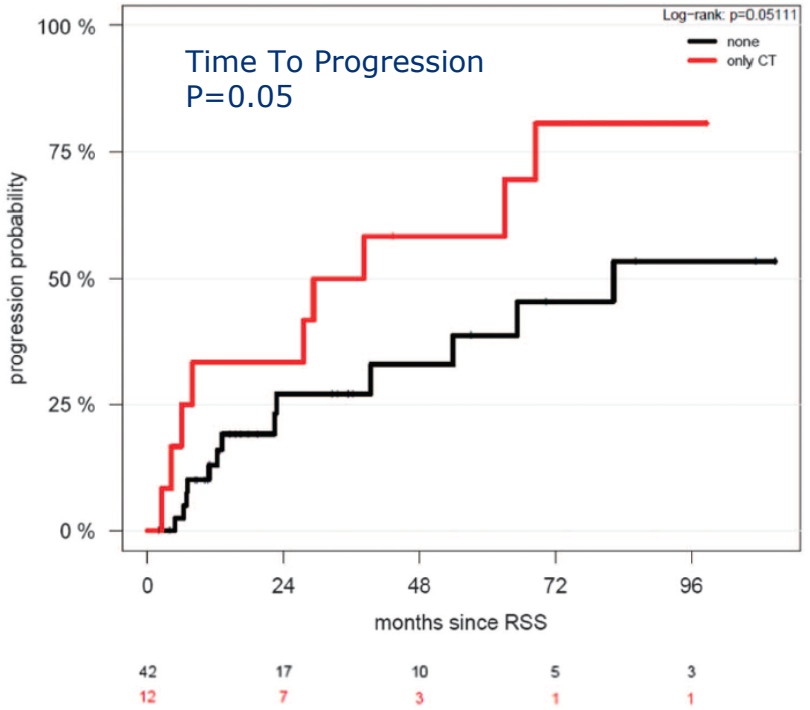
Skeletal Imaging: Smoldering Myeloma

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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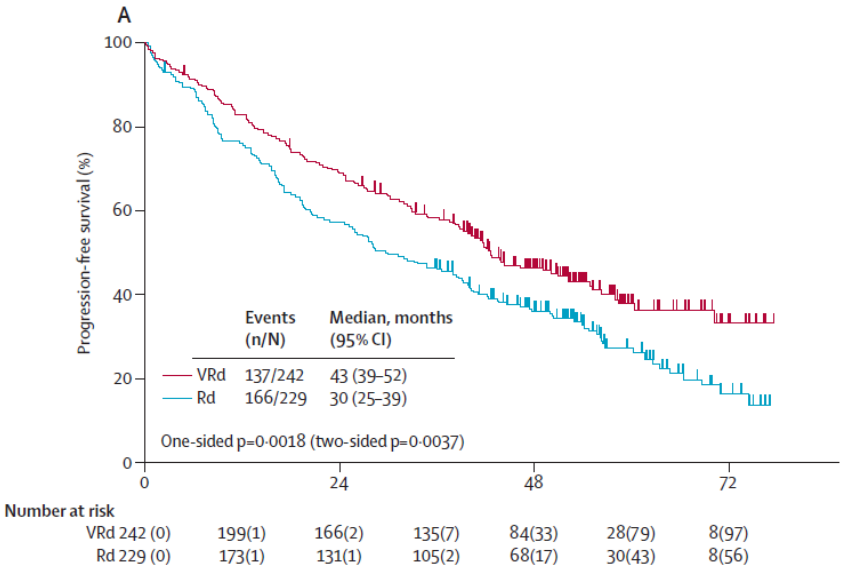
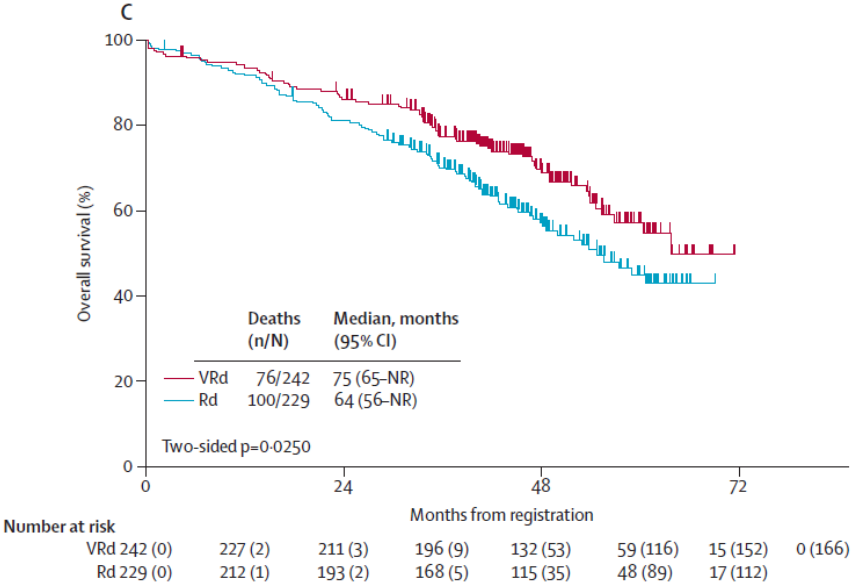
S0777 Rd vs RVd

PFS



OS



Durie et al Lancet 2017

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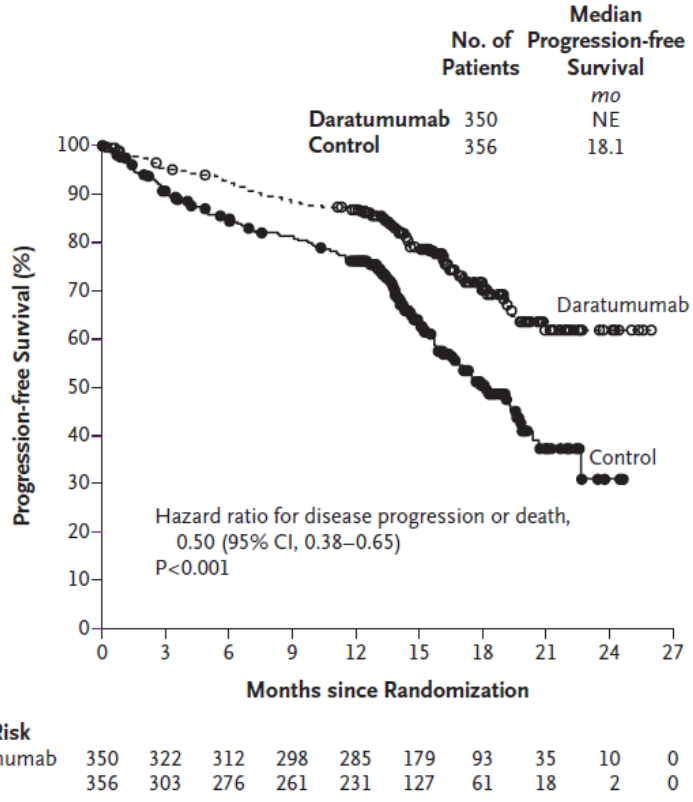
Dara-Bortez-Mel-Pred

- 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

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

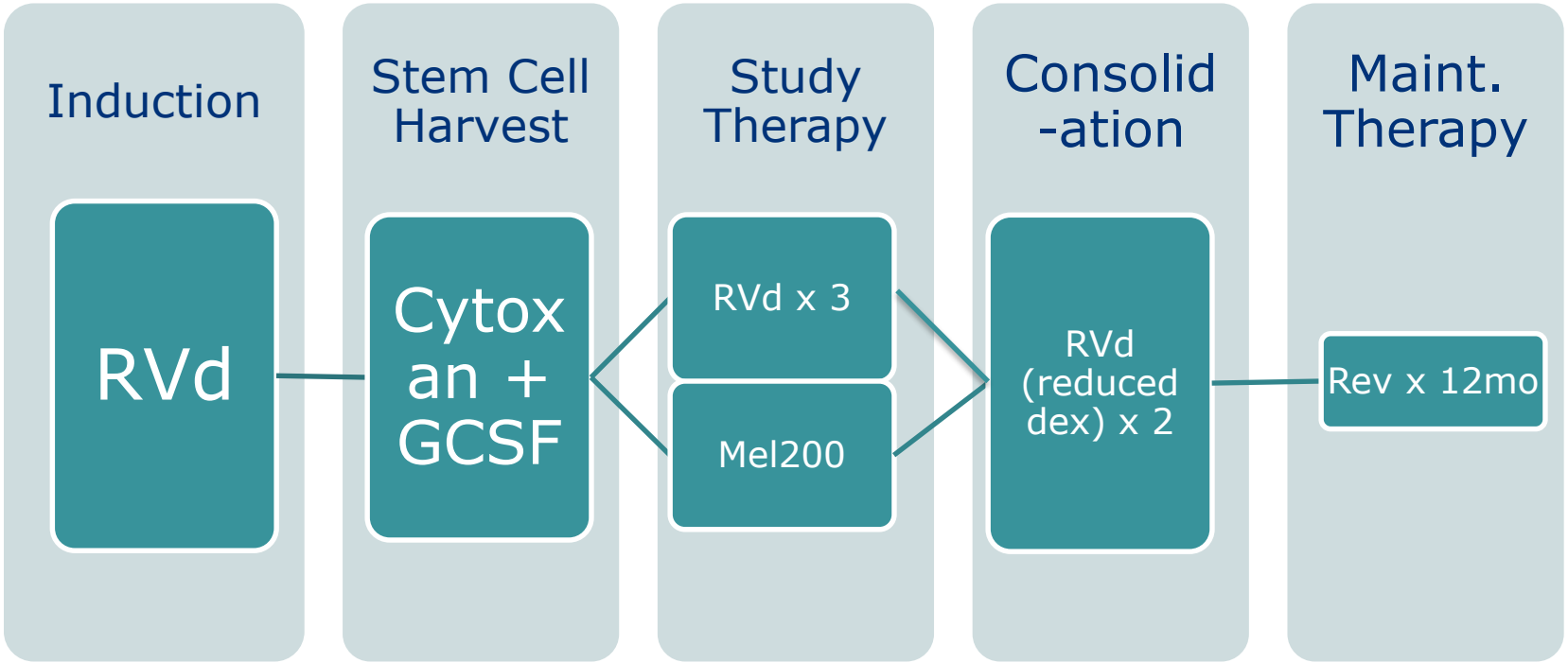
Has the role of transplant changed in 2017-2018?

IFM-2009

- Designed to address role of aHSCT in setting of modern induction therapy
- Patients age ≤ 65, normal liver function, estimated creatinine clearance ≥ 50

Attal et al, NEJM 2017

IFM-2009



Attal et al, NEJM 2017

IFM 2009 Response Rates

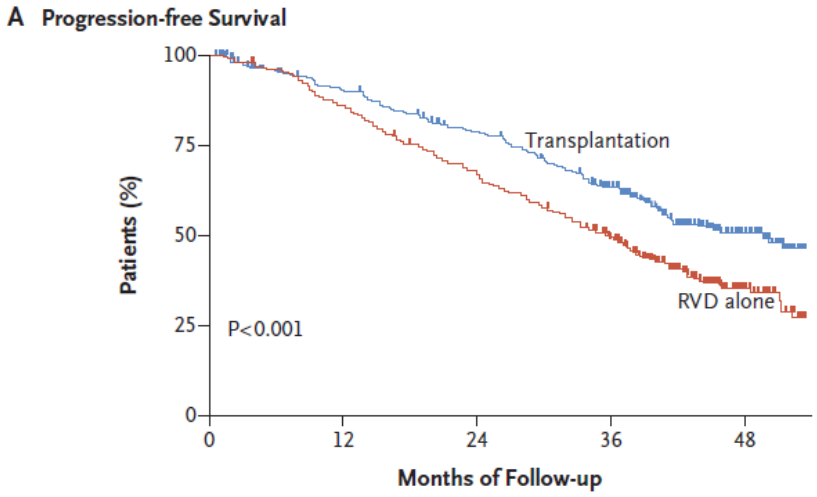
Table 2. Response to Treatment.*

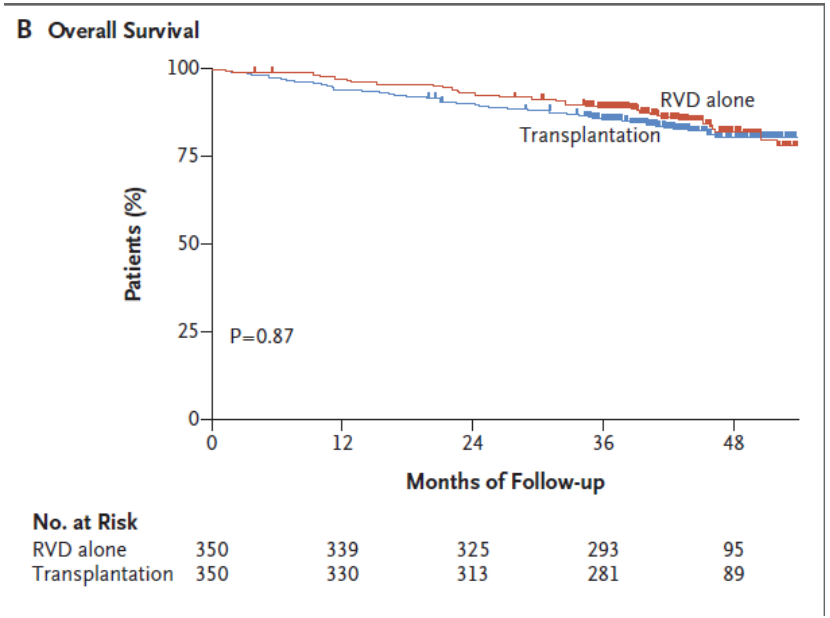
Outcome	RVD-Alone Group (N=350)	Transplantation Group (N=350)	Adjusted P Value†
Best response during the study — no. (%)			0.02
Complete response	169 (48)	205 (59)	
Very good partial response	101 (29)	102 (29)	
Partial response	70 (20)	37 (11)	
Stable disease	10 (3)	6 (2)	
Complete response — no. (%)	169 (48)	205 (59)	0.03
Complete response or very good partial response — no. (%)	270 (77)	307 (88)	0.001
Minimal residual disease not detected during the study — no./ total no. with complete or very good partial response (%)‡	171/265 (65)	220/278 (79)	<0.001

* Responses were assessed according to the International Uniform Response Criteria for Multiple Myeloma. Percentages may not total 100 because of rounding.
† P values were adjusted for multiplicity with the use of the Holm procedure to control the family-wise error rate at 0.05.
‡ Minimal residual disease was detected by means of flow cytometry. As a result of decisions made by the patient or the investigator, 5 patients in the RVD-alone group and 29 patients in the transplantation group were not tested.

Attal et al, NEJM 2017

IFM 2009: PFS and OS





Attal et al, NEJM 2017

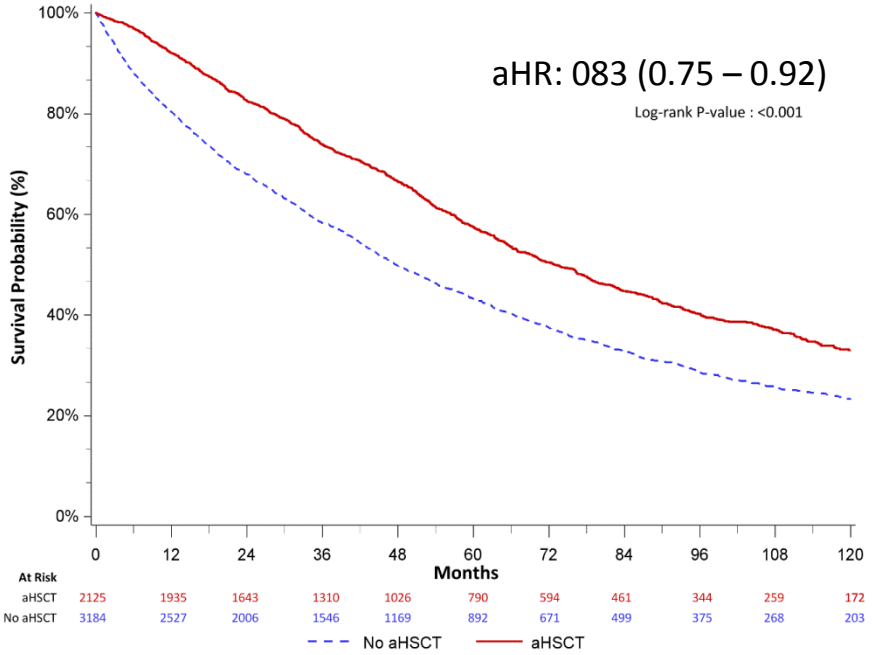
IFM 2009 Conclusions

- Clear PFS to aHSCT use, without a hint of OS benefit
- First aHSCT randomized trial utilizing strategies similar to those used in the US
- Caveats:
  - Maintenance was only 1 year
  - Post aHSCT consolidation is not commonly employed in the US
  - 207 patients in the non-aHSCT arm progressed, of these 172 (83%) went on to second line therapy. Of those, 136 (79%) went onto planned aHSCT
  - Thus this is not an aHSCT vs non-aHSCT trial, as a large proportion of patients went onto delayed aHSCT

Attal et al, NEJM 2017

CCR-OSHPD (Our Data)

- All patients with MM diagnosed 1998 – 2014
- Overall survival compared between those undergoing aHSCT vs those not



Rosenberg et al JNCI 2018 (in press)

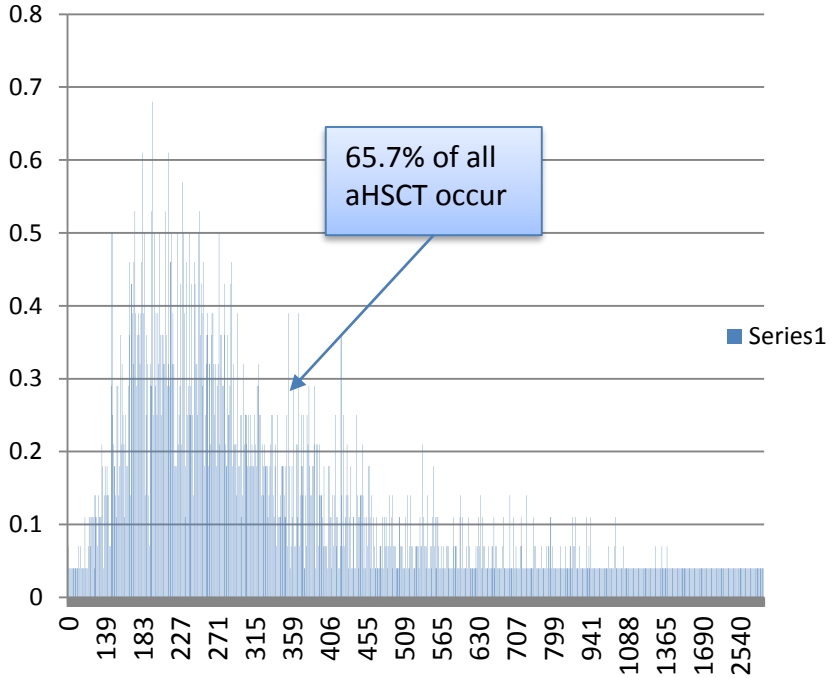
CCR-OSHPD

Effect of aHSCT on OS by Era of Diagnosis

Era	IPW			Propensity Score Matched			Traditional Cox		
	HR*	(95% CI)	P-Value †	HR	(95% CI)	P-Value †	HR	(95% CI)	P-Value†
1998-2002	0.97	(0.84, 1.11)	0.61	0.81	(0.72, 0.90)	<.001	0.81	(0.73, 0.89)	<.001
2003-2007	0.72	(0.60, 0.86)	<.001	0.68	(0.62, 0.76)	<.001	0.66	(0.60, 0.73)	<.001
2008-2012	0.81	(0.61, 1.08)	0.15	0.53	(0.45, 0.62)	<.001	0.53	(0.45, 0.62)	<.001
$P_{Interaction}$‡	0.21			<0.001			<0.001		

Adjusting for: Sex, Race/Ethnicity, Age at Diagnosis, Neighborhood Socioeconomic Status, Marital Status, Insurance type, First line therapy, Rural vs Urban location, Year of Diagnosis

Time from Diagnosis to Transplant



Rosenberg et al JNCI 2018 (in press)

aHSCT: Should We Still Consider This the Standard for Newly Diagnosed MM Patients?

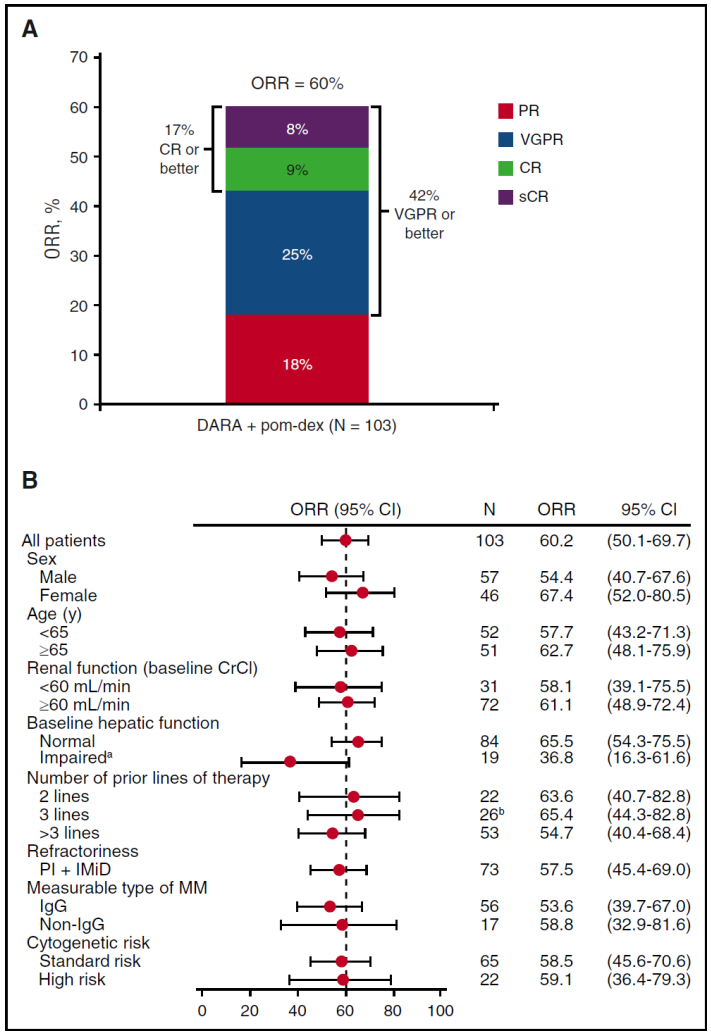
- Yes.

- Clear PFS benefit (and 40-50% of patients will progress with symptoms)
- In trials with lower cross-over to aHSCT use, OS benefit demonstrated
- Retrospective/observational data in CCR-OSPHD shows ongoing OS benefit regardless of era
  - Majority of aHSCT occurs within first year of diagnosis, and almost all within the first 2 years, thus seems like late transplant is not done
- Timing of aHSCT may *not* matter (only that all effective strategies are employed/available), but patients don't get younger over time, and thus become harder to transplant

Relapsed/Refractory MM

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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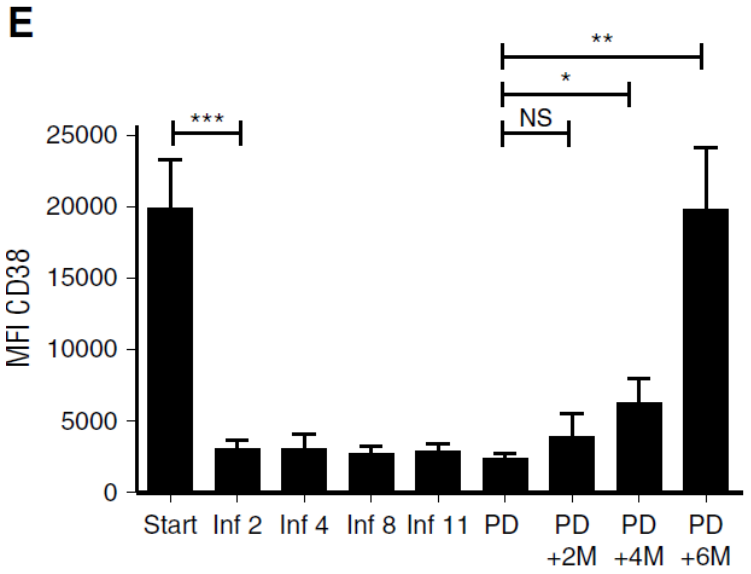
Retreatment with Daratumumab

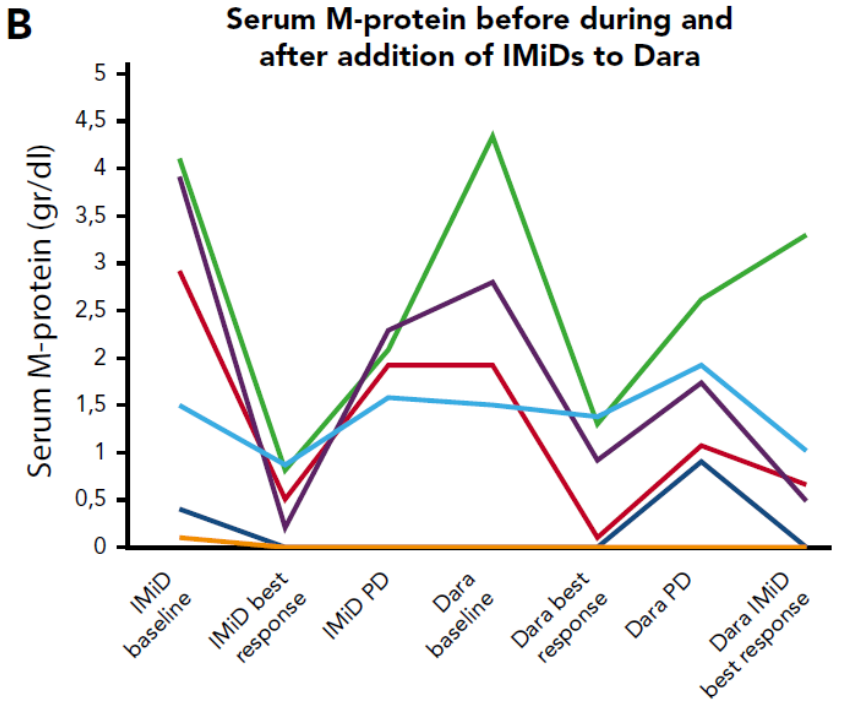
- Mechanism of dara resistance is yet to be fully elucidated
- Patients on dara have lower CD38 expression than prior to treatment, though this expression returns to baseline 6 months post dara
- Given tolerability of dara, understanding *how* to re-treat with it is an important question moving forward



Nijhof et al, Blood 2016

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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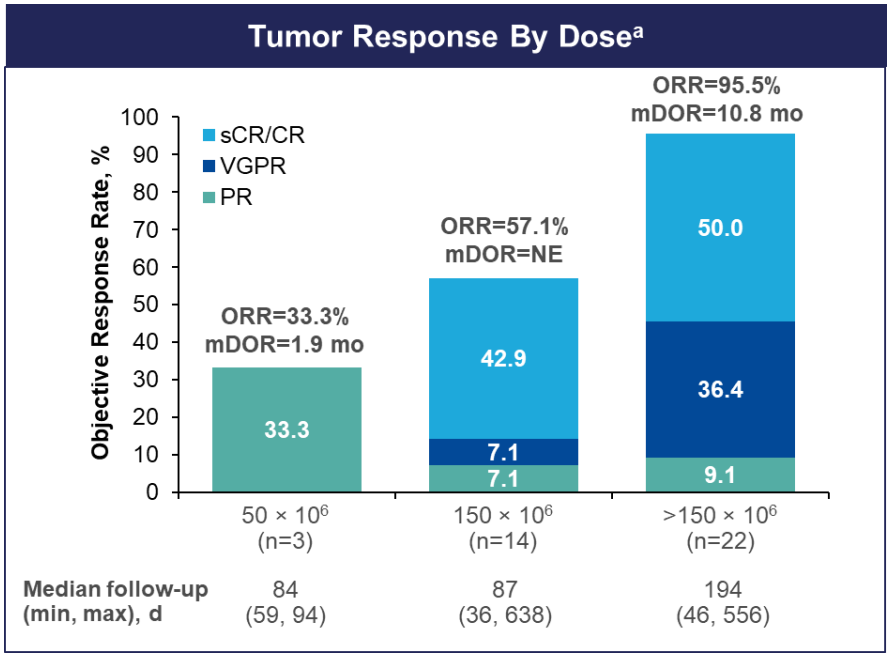
What's Coming Soon?

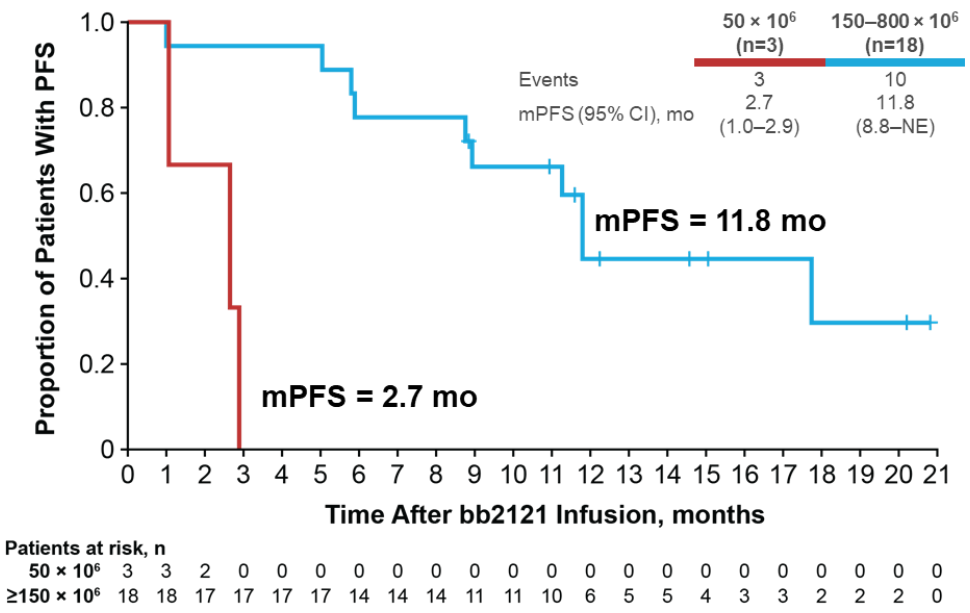
- The therapeutic pipeline remains robust
- Recent data with Isatuximab and Selinexor both have encouraging data
- 156 Phase I trials are currently recruiting in multiple myeloma
  - PD1/PDL1 inhibitors are being explored (cautiously)
  - CART-cell therapy
  - BCMA bi-specific t-cell engagers
  - New 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.

Clinical Trials in MM at UCDCC

- Newly diagnosed MM
  - **E1A11: ENDURANCE**
    - Randomization 1: RVd vs KRd
    - Randomization 2: 2 years len maintenance vs indefinite maintenance
- Relapsed MM:
  - **UCHMC 1502**: Pomalidomide + Ixazomib + Clarithromycin + Dex (PICd)
    - Phase I/II, all oral therapy for RRMM
    - Correlative studies to determine the mechanism of clarithromycin's anti-MM properties
  - **PHI-100**: KRd + AMG 232
    - MDM2 inhibitor, should increase p53 activity
    - No del(17p) patients, or those with cryptic p53 mutations
  - **Atezolizumab + daratumumab**, open later this year
    - PDL-1 inhibitor, better known in the solid-tumor circles
    - Has arms with and without pomalidomide
- Phase Ib trials in MM
  - **AMG 176**: MCL-1 inhibitor, currently open and enrolling
  - **SGN-48a**: anticipate opening Q1 2019, novel antibody drug conjugate

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