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CCO LIVE

Triple-Class Refractory: Selecting BCMA-Directed Therapy?

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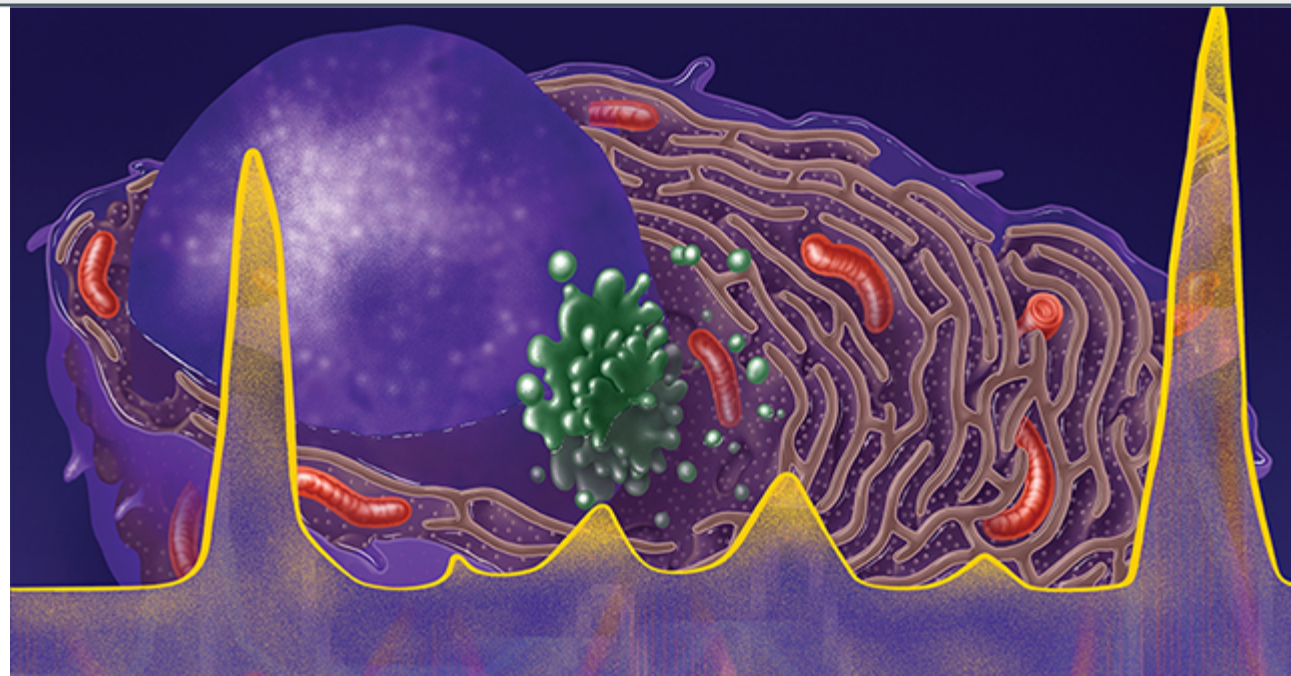

Faculty

Thomas G. Martin, MD
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Thomas G. Martin, MD, has disclosed that he has received consulting fees from GSK and funds for research support from Amgen, Johnson & Johnson – Janssen, Sanofi, and Seattle Genetics.

Patient Scenario

- 67-year-old male presented with standard risk IgG kappa MM
  - B2M 3.4, Alb 3.6, LDH 150, Cr 1.1, Ca 8.7, FISH: hyperdiploid (+5, +9, +15)
- He has received **3** prior lines of therapy
  - RVd for 6 cycles followed by ASCT and continuous R maintenance for 36 months (progresses on maintenance –refractory to R 10 mg QD)
  - DaraKd for 19 months achieves VGPR then progresses (Triple class refractory)
  - EloPd for 6 cycles achieves PR then PD (3 prior lines: refractory to R/P/K/Dara)
- Options for **triple-class drug refractory** (IMiD, PI, CD38) are limited

Presurvey 5: In your current practice, what would you recommend next for this patient?

1. Triplet or quadruplet combination with previously used agents
2. Cyclophosphamide-based combination chemotherapy
3. Selinexor + dexamethasone
4. Belantamab mafodotin
5. BCMA-targeted CAR T-cell
6. BCMA-targeted bispecific T-cell engager
7. Salvage ASCT
8. Salvage AlloSCT
9. Uncertain

Expert Recommendations

Expert Recommendations	
Brian G.M. Durie, MD	BCMA-targeted CAR T-cell
Shaji Kumar, MD	BCMA-targeted CAR T-cell
Thomas G. Martin, MD	BCMA-targeted CAR T-cell
Philippe Moreau, MD	BCMA-targeted CAR T-cell
S. Vincent Rajkumar, MD	Cyclophosphamide-based combination chemotherapy
Jesús San-Miguel, MD	BCMA-targeted CAR T-cell

Poll 5: What would be your expectation for survival in patients with R/R MM?

1. Triple-class refractory: expected OS > 2 years
2. Triple-class refractory: expected OS 1-2 years
3. Triple-class refractory: expected OS < 10 months
4. Penta-refractory: expected OS > 6 months
5. Survival not measurable with novel BCMA-targeted therapies
6. Uncertain

Expert Recommendations

Expert Recommendations	
Brian G.M. Durie, MD	Triple-class refractory: expected OS > 2 years
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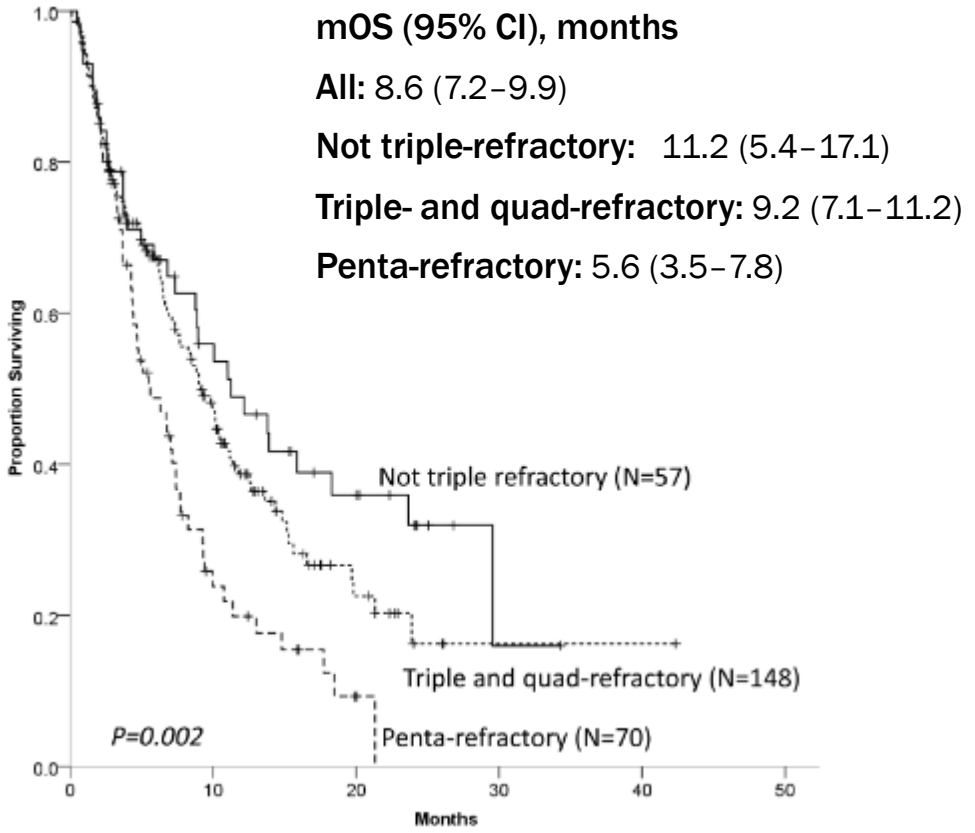
S. Vincent Rajkumar, MD	Triple-class refractory: expected OS > 2 years
Jesús San-Miguel, MD	Triple-class refractory: expected OS 1-2 years

Patients with Triple-Class Refractory MM

- The unmet need with poor prognosis

- MAMMOTH Study
  - Retrospective review of R/R MM
    - 275 patients
    - PI, IMiD, and CD38 exposed
  - Median OS was **< 9 months** in MAMMOTH in patients with disease refractory to anti-CD38 mAbs
  - Median OS was < 6 months if penta-refractory
  - **Current treatment options** include conventional chemotherapy, salvage ASCT, recycling previous regimens, selinexor + dexamethasone, belantamab mafodotin and clinical trials

Median OS in MAMMOTH study from T_0



Gandhi. Leukemia. 2019;33:2266.

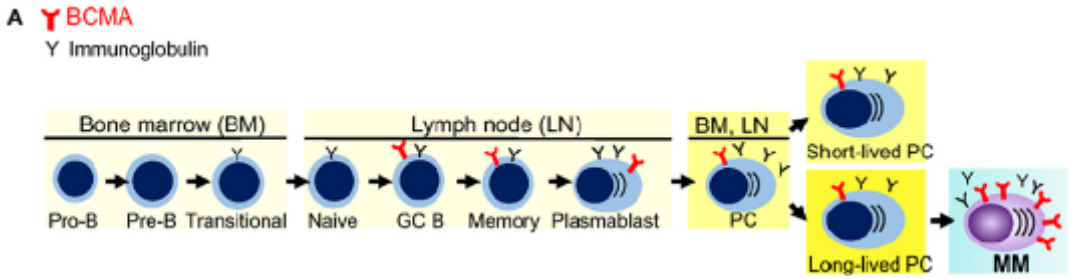
Triple-Class Refractory: *When All Else Fails*

Chemotherapy	HDAC / *ADC* XPO inhibitors	**Monoclonal Antibodies**	**IMiDs / CELMoDs/ Novel Drugs**	**BCMA Abs** Bispecifics/ ADCs	**Cellular therapies** BCMA CARs
Doxorubicin, Liposomal doxorubicin	Panobinostat/ Vorinostat	Next Gen 38 SAR442085	**CC-220** (Iberdomide), **CC-92480**	**Teclistamab AMG-701,** CC-93269	**Cilta-cel (JNJ-4528) Ide-cel (bb2121),** Orva-cel (JCARH125)
Cyclophosphamide, Bendamustine, Melphalan	**Belantamab Mafodotin**	TAK-079, TAK-573, TAK-169	**Venetoclax Melflufen**	**TNB-3838, REGN5458 PF-06863135**	LCAR-B38M, **bb21217, P-BCMA-101**
PACE, HyperCAD	**Selinexor**	MOR202, Others	**BFCR4350A Talquetamab**	**MEDI2228,** CC-99712 FOR46	**Lummicar-2 (CT053) ALLO-715** ALLO-605 (TurboCAR)

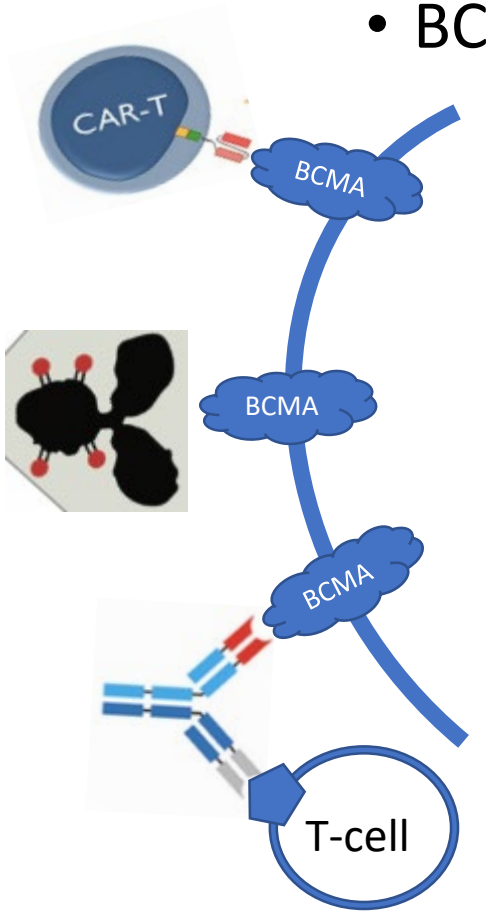
*Blue = approved Green = ongoing clinical trials

Immunotherapy for MM

- Targets and Therapeutics



- Current MM <u>Targets</u>
  - **BCMA**
  - <u>GPRC5D</u>
  - <u>FcRH5</u>
  - CD138
  - CD38
  - CD19
  - SLAMF7
  - ASCT2
  - CD229
  - Kappa light chain

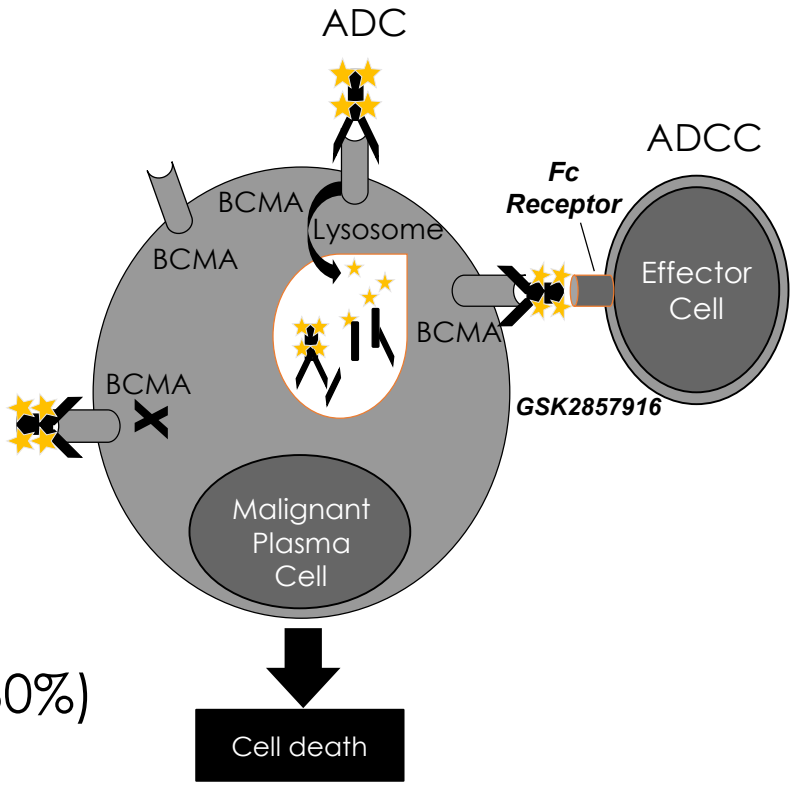


- BCMA <u>Therapeutics</u>
  - **CARs**
    - **Idecaptagene Vicleucel**
    - **Ciltacabtagene autoleucel**
  - **ADCs**
    - **Belantamab mafodotin**
    - **MEDI2228**
  - **Bispecific antibodies**
    - **Teclistamab**
    - **~6 others at ASH2020**

Cho. Front Immunol 2018; 9:1821

Belantamab Mafodotin (GSK2857916): A BCMA-Targeted Antibody Drug Conjugate

- Belantamab mafodotin
  - humanized, IgG1
  - afucosylated anti-BCMA
  - Toxin – **MMAF**
  - **Phase I study**
    - Part 2: 3.4 mg/kg Q3W
    - Potent activity (ORR ~60%)
    - Ocular toxicity (~63%)
    - Thrombocytopenia (34%)



Mechanisms of Action:
1. **ADC mechanism**
2. **ADCC mechanism**
3. **Immunogenic cell death**

Fc region of the antibody	**–Target specific –Enhanced ADCC**
Linker	**–Stable in circulation**
Drug	**–MMAF (non-cell permeable, highly potent auristatin)**

Tai. Blood. 2014;123:3128.
Trudel. Lancet Oncol. 2018;19:1641.

DREAMM-2 Study Design

A phase II, open-label, randomized 2-dose study in RR MM after an anti-CD38 therapy. Primary analysis of DREAMM-2 completed at median follow-up of 6.3 and 6.9 months for the 2.5 mg/kg and 3.4 mg/kg cohorts, respectively. Additional analysis was completed at 13 months of follow-up.

*Patients stratified based on number of previous lines of therapy (≤4 vs >4) and presence or absence of high-risk cytogenetic features; **According to International Myeloma Working Group 2016 criteria.

POPULATION

- Measurable disease
- ECOG PS 0-2
- **3 or more prior lines** of antimyeloma therapy
- **Refractory to a PI and an IMiD and progression on an anti-CD38 antibody**
- Prior anti-BCMA therapy excluded
- Prior auto-SCT allowed; allo-SCT excluded

RANDOMIZE 1:1*

Treatment until disease progression or unacceptable toxicity

- **Belantamab mafodotin 2.5 mg/kg** IV, every 3 weeks (n=97)
- **Belantamab mafodotin 3.4 mg/kg** IV, every 3 weeks (n=99)

Primary Outcome

ORR: % of patients with ≥PR**

Key Secondary Outcomes

- DOR (time from ≥PR until PD or death due to PD
- Other efficacy: CBR, PFS, OS, TTBR, TTR
- Safety, including keratopathy (MECs)

Key baseline characteristics=>

Characteristic	2.5 mg/kg	3.4 mg/kg
Median prior Lines	7 (3-21)	6 (3-21)
Triple class exposed	~100%	~100%

BCMA, B-cell maturation antigen; CBR, clinical benefit rate; DOR. duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; IMiD, immunomodulatory imide drug; IV, intravenous; MEC, microcyst-like epithelial change; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; RRMM, relapsed/refractory multiple myeloma; SCT, stem-cell transplantation; TTBR, time to best response; TTR, time to response.

1. Lonial. *Lancet Oncol*. 2020;21:207-221. 2. Lonial. Poster presented at: ASCO 2020. Abstr 436.

DREAMM-2 Results

Key efficacy data

Response	2.5 mg/kg N = 97	3.4 mg/kg N = 99
Follow-up	13 months	
ORR, n (%)	**31 (32%)**	**35 (35%)**
sCR	2 (2%)	2 (2%)
CR	5 (5%)	3 (3%)
VGPR	11 (11%)	18 (18%)
PR	13 (13%)	12 (12%)
Median PFS (95% CI), mo	2.8 (1.6-3.6)	3.9 (2.0-5.8)
Median DoR estimate, mo	**11**	**6.2**
Median OS estimate, mo	**13.7**	**13.8**

- ORRs were comparable in both HR and SR patients

Key safety data

AE, n (%)	2.5 mg/kg N = 95	3.4 mg/kg N = 99
Grade 3-4 AE (≥20%)		
Keratopathy	44 (46%)	42 (42%)
Thrombocytopenia	21 (22%)	32 (32%)
Anemia	20 (21%)	27 (27%)
Serious AE	40 (42%)	47 (47%)
SAE leading to death	3 (3%)	9 (9%)

- Overall safety at 2.5 mg/kg
  - Keratopathy (Gr 1-4) 72%
  - Thrombocytopenia (Gr 1-4) 38%
- 2 deaths were considered potentially treatment related:
  - 2.5 mg/kg: sepsis (n = 1)
  - 3.4 mg/kg: hemophagocytic lymphohistiocytosis (n = 1)
- Overall rates of anemia and thrombocytopenia were higher in HR than SR

Lonial. Lancet Oncol. 2020;21:207-221.
Lonial. 2020 ASCO Annual Meeting. Abstr 436.

ADC Summary in RRMM

- **What more do we need?**
  1. Improved response rates and durability with combinations
     Trudel et al. ASH 2020, Abstr 725: Belantamab + Pom
     Popat et al. ASH 2020 , Abstr 1419: Belantamab + Vd
  2. Improved safety
     Split/intermittent dosing of Belantamab
     Novel toxin:
     Kumar et al. ASH 2020 , Abstr 179 – MEDI2228 [pyrrolobenzodiazepine dimer]
     Shah et al. ASH 2020, Abstr 3030 – STRO-001 [maytansinoid]
  3. Additional targets
     CD74/CD46/SLAMF7
  4. Mechanism of resistance
     Antigen loss
     P-glycoprotein

BCMA CAR T-Cell Studies: Efficacy

	Ide-cel (bb2121) PhII			bb21217			Cilta-cel (JNJ-4528)	Orva-cel (JCAR-H125)		
Cell Dose	150	300	450	150	300	450	0.75 x 10^6 / kg	300	450	600
Median follow-up, mos		13.3		17.6	4.0	3.3	11.5 (3.0 – 17.0)	9.5	8.8	2.3
Response Rate										
ORR	50%	69%	82%	83%	43%	57%	100%	95%	89%	92%
CR	25%	29%	39%	33%	0%	14%	86%	37%	42%	29%
MRD										
Evaluable for MRD, #	4	70	54	7	6	4	21	11	11	3
MRD- (%)	50%	31%	48%	100%	83.3%	100%	85.7%	72.7%	90.9%	100%
Median DoR, mos	NR	9.9	11.3	11.1	NR	NR	NR	NR	NR	NR
Median PFS	2.8	5.8	12.1	NR	NR	NR	NR	9.3	NR	NR

[updates at ASH2020: Cilta-cel PhII, bb2121 PhI, bb2121-7, Poseida BCMA-CAR, CD19-BCMA dual targeted CAR, Allo715-BCMA]

Munshi. ASCO 2020. Abstr 8503. Berdeja. ASH 2019. Abstr 927. Berdeja. ASCO 2020. Abstr 8505; Mailankody. ASCO 2020. Abstr 8504.

BCMA CAR T-Cell Studies: Safety

	Ide-cel (bb2121) PhII	bb21217	Cilta-cel (JNJ-4528)	Orva-cel (JCAR-H125)
Cytokine Release Syndrome				
All Grades	84%	66%	93%	89%
Grade 3 / 4 / 5	4% / <1% / <1%	5% / 0% / 3%	7%	3%
Median Onset, Days	1 (1 – 12)	3 (1 – 20)	7 (2 – 12)	2 (1 – 4)
Median Duration	5 (1 – 63)	4 (1 – 28)	4 (2 – 64)	4 (1 – 10)
Neurotoxicity				
All grades	18%	24%	10%	13%
Grade 3 / 4 / 5	3% / 0% / 0%	5% / 3% / 0%	3%	3%
Median Onset, Days	2 (1 – 10)	7 (3 – 24)	NR	4 (1 – 6)
Median Duration	3 (1 – 26)	NR	NR	4 (1 – 10)

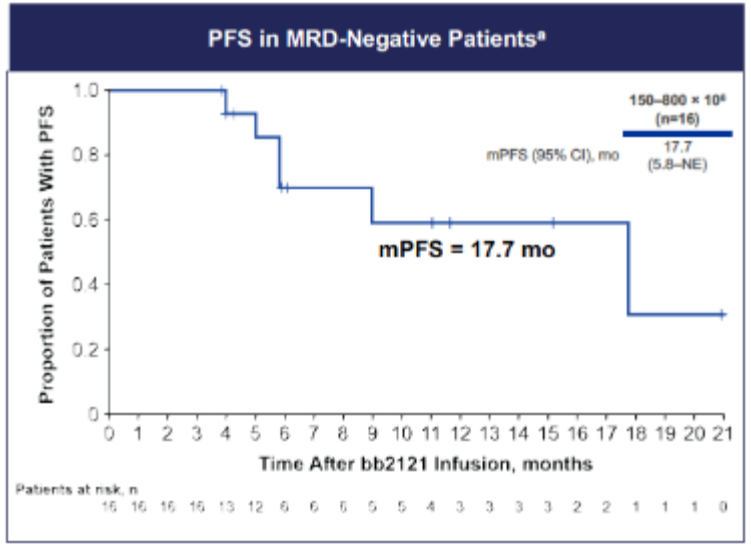
[updates at ASH2020: Cilta-cel PhII, bb2121 PhI, bb2121-7, Poseida BCMA-CAR, CD19-BCMA dual targeted CAR, Allo715-BCMA]

Munshi. ASCO 2020. Abstr 8503. Berdeja. ASH 2019. Abstr 927. Berdeja. ASCO 2020. Abstr 8505; Mailankody. ASCO 2020. Abstr 8504.

CAR T-Cell Summary in RRMM

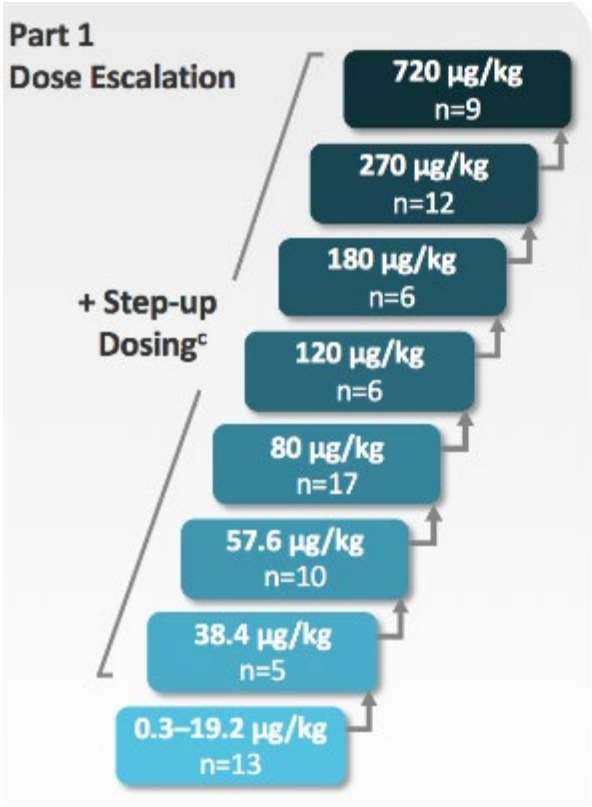
- **What more do we need?**
  1. Improved CARs
     - **Faster Manufacturing or *Off-the-shelf***
     - **Better T-cells – Tscm/cm**
     - **Persistence: a good "second wave"**
  2. Improved patient selection
     - **Early relapse (1-3 PLT)**
     - **Frontline: replace ASCT?**
     - **Lower burden of disease**
  3. Additional targets and combinations
     - **GPRC5D +/- BCMA**
     - **CD19 + BCMA**
     - **CAR + BISPECIFIC, CAR + CelMOD**
  4. Mechanism for resistance
     - **Antigen loss**
     - **Myeloma "stem cell"**

CARTITUDE 1 – JNJ-4528



Madduri. ASH 2019. Abstr 577. Raje. ASCO 2018. Abst 8007.

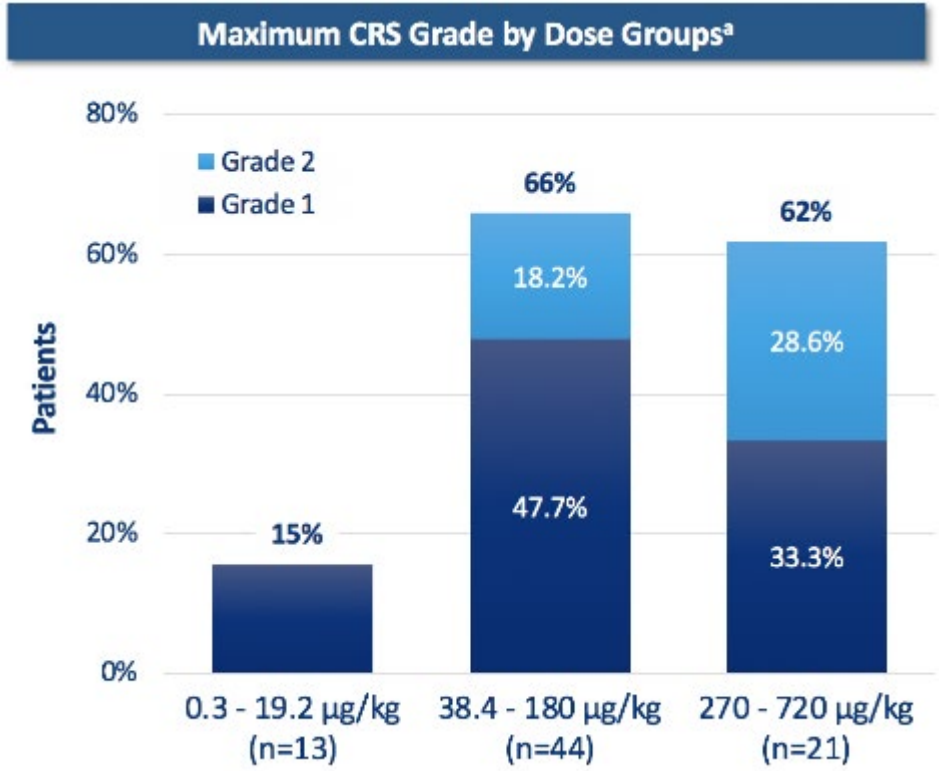
Teclistamab – ASCO 2020



Dosing
- Weekly step-up

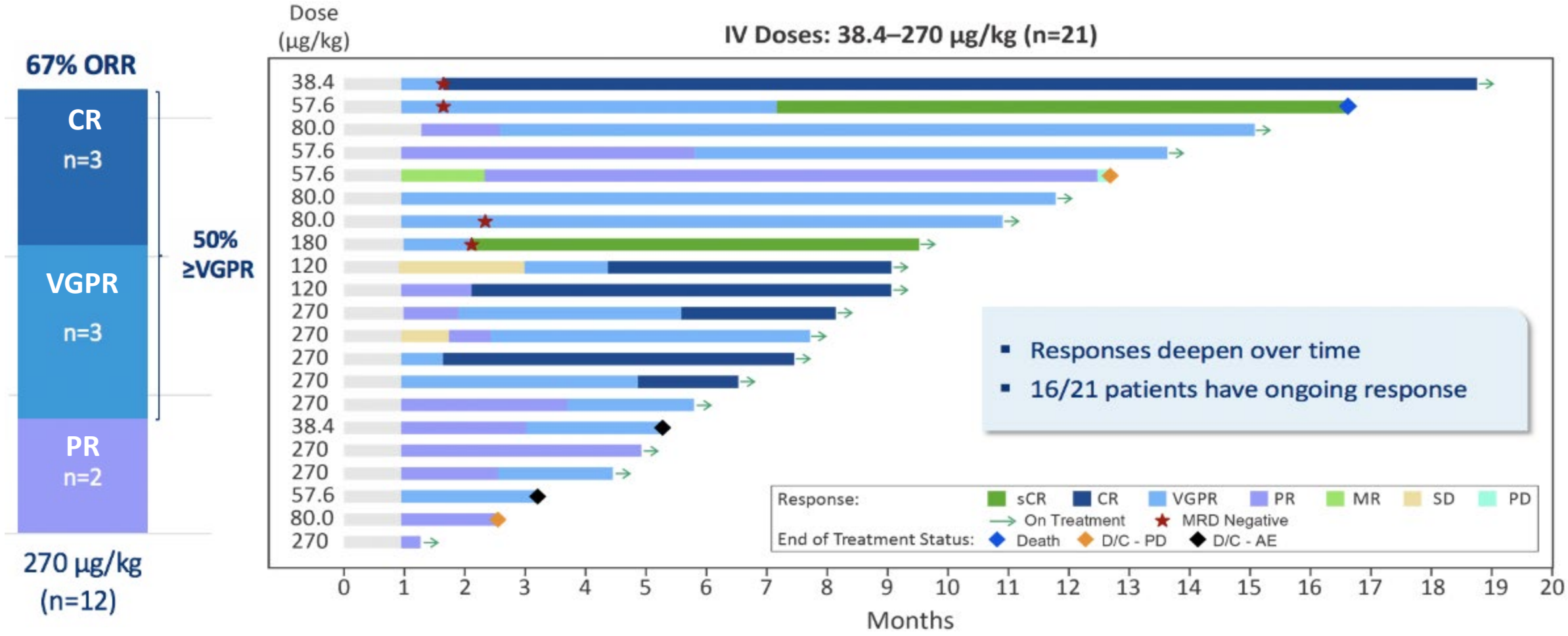
<u>STUDY ENROLLMENT AND RESULTS</u>
- 78 patients enrolled
- 6 PLT, 31% HR cytogenetics
- 80% triple class refractory

- Toxicity:
  - CRS: overall 56%
  - Neurotox: 8% Gr 1-4 (3% Gr 3-4)



Usmani. ASCO 2020. Abstr 100.

Teclistamab - Results



Usmani. ASCO 2020. Abstr 100.

BCMA Bispecific mAb Studies: Efficacy

	AMG420	CC-93269	Teclistamab
Dose	400 ug/day	6→10 mg and 6 mg	270 ug / kg
N	10	9	12
Median follow-up, mos	NR	NR	NR
Response Rate			
ORR	70%	88.9%	67%
CR	50%	44.4%	25%
MRD			
Evaluable for MRD, #	10	NR	5
MRD- (%)	50%	NR	80%
Median DoR, mos	9.0 (range 5.8 – ≥13.6)	11 of 13 ongoing	16 of 21 ongoing

[Many bispecific antibody updates and new presentations at ASH 2020]

Topp. JCO. 2020;38:775. Abstr 8503. Costa. ASH 2019. Abstr 143. Usmani. ASCO 2020. Abstr 100

Bispecific Summary in RRMM

- **What more do we need?**
  1. Phase II study results
     Optimized step-up dosing
     Responses in RRMM including EMD and HR
     Convenient schedule for long-term dosing
  2. Improved safety
     Outpatient administration
     Prophylactic use of tocilizumab/other CRS mitigation strategies
  3. Additional targets
     CD38/SLAMF7/GPRC5D/FcRH5
  4. Improved response rates and durability with combinations
     Bispecific mAb + IMiDs, PIs, CD38 Abs
     Bispecific + CelMODs

BCMA Therapeutics – Advantages/Disadvantages

	Antibody–drug conjugate	CAR T-cells	Bispecific antibody
Advantages	Off-the-shelf	Personalized	Off the shelf
	Targeted cytotoxicity Not dependent on T-cell health	Targeted immuno-cytotoxicity	Targeted immuno-cytotoxicity
	No lymphodepletion No steroids	Single infusion (“one and done”)	No lymphodepletion Minimal steroids
	Available to any infusion center Outpatient administration	Potentially persistent	
Disadvantages		Fact accredited center required (hospitalization likely required)	Initial hospitalization required
	Currently requires REMS/Ophtho	CRS and Neurotoxicity; requires ICU and Neurology services	CRS and Neurotoxicity possible
	Single agent activity low in CD38 refractory patients	Dependent on T-cell health (manufacturing failures)	Dependent on T-cell health (T-cell exhaustion)
	Requires continuous administration	Requires significant support social – caregiver required	Requires continuous administration
	$$	$$$$	$$$

Sequencing of BCMA Targeted Therapeutics

- As of Now ➔ Belantamab Mafodotin [only FDA approved modality]
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  - BCMA Targeted CAR T-cell (Ide-cel) ➔ Fit, well-resourced, triple refract
  - Belantamab Mafodotin ➔ less fit, limited social support, rapidly progressive
  - 3rd/4th Quarter➔ potentially a second CAR – Cilta-cel may be approved

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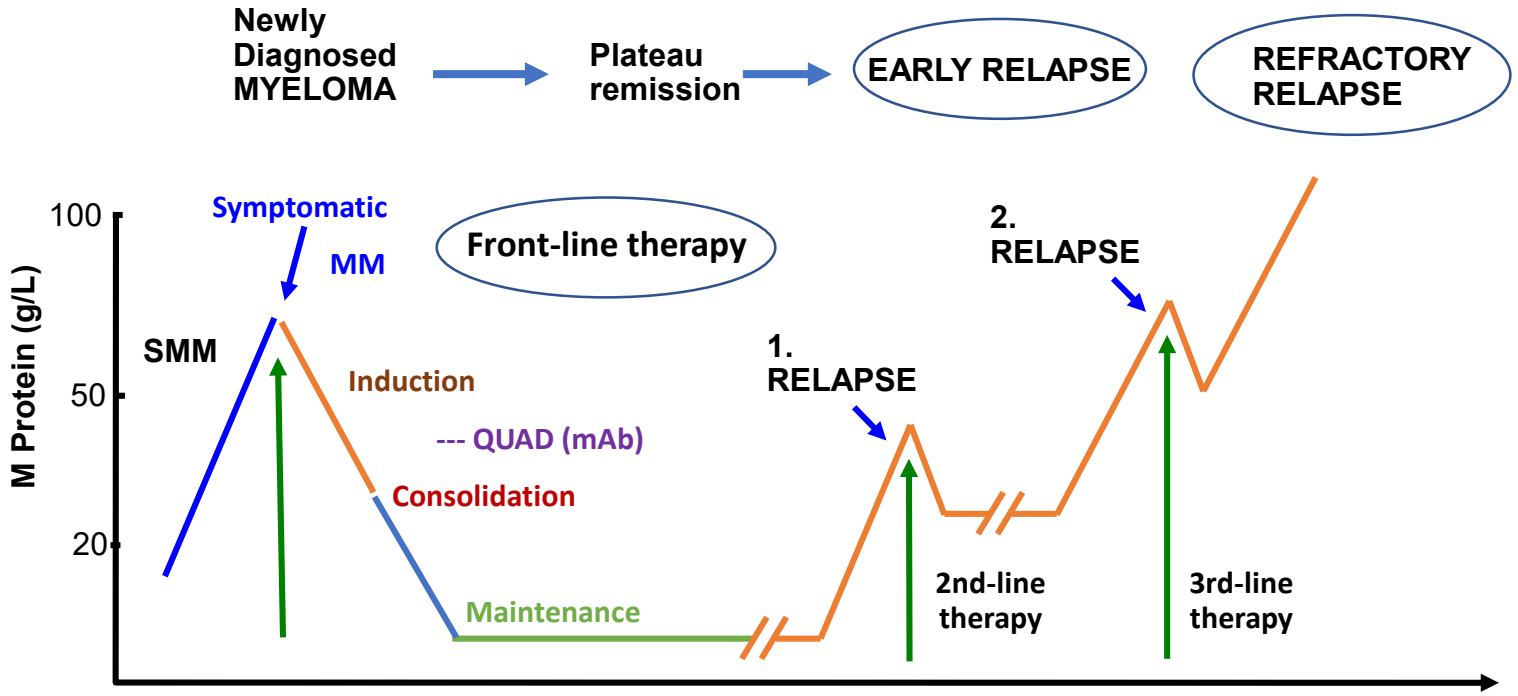
- In 2022 and beyond ➔ other CARs, ADCs and bispecific mAbs
  - CD38 + triplet (induction) → BCMA CAR consolidation → BCMA – ADC early relapse
  - CD38 + doublet/triplet for induction → bispecific maintenance → BCMA-ADC relapse
  - BCMA-ADC + doublet induction → GPRC5D CAR at relapse → FcRH5 bispecific RRMM

Future Strategies in Multiple Myeloma

Where and in what combination will immunotherapy have the most Impact?



<u>Frontline</u>
QUAD: No transplant

MRD (+): Consolidation: CAR vs. Bispecific
MRD (-): Maintenance: Len (CELMoD)/mAb vs. Bispecific

<u>Early Relapse (1-3 Prior Lines)</u>
Novel CAR (Different target)
Novel Ab: ADC vs. Trivalent Ab

<u>Late Relapse (*off-the shelf*)</u>
Third party cellular therapy (NK + T)
Crispr strategies

Conclusions: Next Generation Therapeutics

- Triple Class Refractory is an UNMET Need
  - Belantamab mafodotin: BCMA-ADC → approved in this population
  - BCMA directed CAR T-cell therapeutics → will be available soon
  - Initial bispecific antibody results promising
    - Off-the-shelf products, toxicity is manageable
    - Bind BCMA, GPRC5D, FCRH5
- Need better understanding mechanisms of resistance
  - Loss of antigen
  - T cell burnout/exhaustion
- Combinations of novel-novel drugs on-going
- Sequencing of these therapeutics will be important and future sequencing studies will be important

Now, let’s return to our patient case

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Patient Case Example: R/R MM

- 67-year-old male presented with standard risk IgG kappa MM
  - B2M 3.4, Alb 3.6, LDH 150, Cr 1.1, Ca 8.7, FISH: hyperdiploid (+5, +9, +15)
- He has received **3** prior lines of therapy
  - RVd for 6 cycles followed by ASCT and continuous R maintenance for 36 months (progresses on maintenance –refractory to R 10 mg QD)
  - DaraKd for 19 months achieves VGPR then progresses (Triple class refractory)
  - EloPd for 6 cycles achieves PR then PD (3 prior lines: refractory to R/P/K/Dara)
- Options for **triple-class drug refractory** (IMiD, PI, CD38) are limited
- Approved agents are available
  - Belantamab mafodotin
  - Selinexor + Dex
  - Alkylator therapy [cyclophosphamide-based, bendamustine, 2nd autologous SCT]

Assessment 5: Now, what would you recommend next for this patient?

1. Triplet or quadruplet combination with previously used agents
2. Cyclophosphamide-based combination chemotherapy
3. Selinexor + dexamethasone
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Panel Discussion:
BCMA-Directed Therapy

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