Myeloma Updates in 30 Minutes: An Impossible Task

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Disclosures

- Consultant for Janssen and Sanofi-Genzyme
- Grant/Research Support for Adaptive Biosciences

I will be discussing the off-label drugs: Daratumumab, Talquetamab, Elranatamab, Cevostamab, CC-92480 and Iberdomide

This presentation and/or comments will be free of any bias toward or promotion of the above referenced company(ies) or their product(s) and/or other business interests.

Cultural Linguistic Competency (CLC) & Implicit Bias (IB)

STATE LAW:

The California legislature has passed Assembly Bill (AB) 1195, which states that as of July 1, 2006, all Category 1 CME activities that relate to patient care must include a cultural diversity/linguistics component. It has also passed AB 241, which states that as of January 1, 2022, all continuing education courses for a physician and surgeon **must** contain curriculum that includes specified instruction in the understanding of implicit bias in medical treatment.

The cultural and linguistic competency (CLC) and implicit bias (IB) definitions reiterate how patients' diverse backgrounds may impact their access to care.

EXEMPTION:

Business and Professions Code 2190.1 exempts activities which are dedicated solely to research or other issues that do not contain a direct patient care component.

The following CLC & IB components will be addressed in this presentation:

- *Early explanation of the role of clinical trials in the management of advanced myeloma to underrepresented and minority communities.*

Learning Objectives

Newly Diagnosed MM

- Quad vs. Triplet
- Transplant vs. Non-Transplant

Brief Overview of Early Relapse

- Lenalidomide sensitive vs. Refractory
- Anti-CD38 as the new backbone

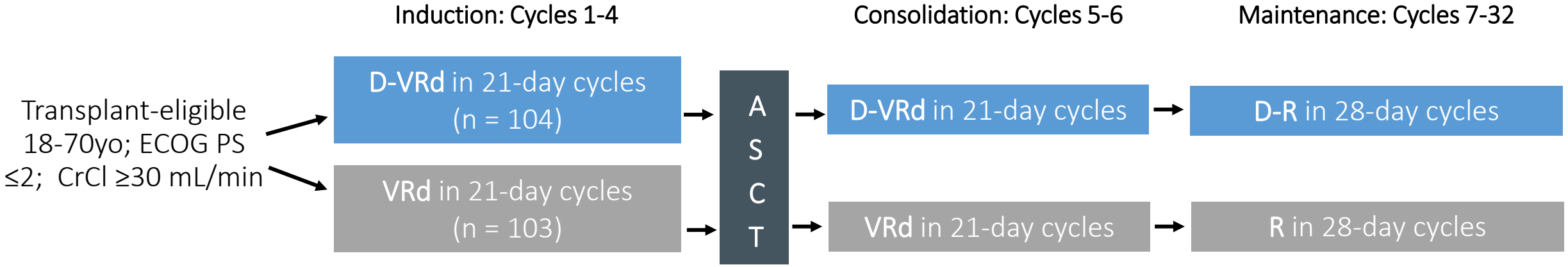
Later Relapse: SoC and Investigational

- CAR T
- Selinexor and Belantamab
- Bispecifics
- CELMoDs

Newly Diagnosed Multiple Myeloma: Quadruplets vs. Triplets ASCT vs. No ASCT

Chapter 1

Addition of anti-CD38 mAb improves outcomes in select populations



Primary endpoint: Stringent CR by end of consolidation (C6)

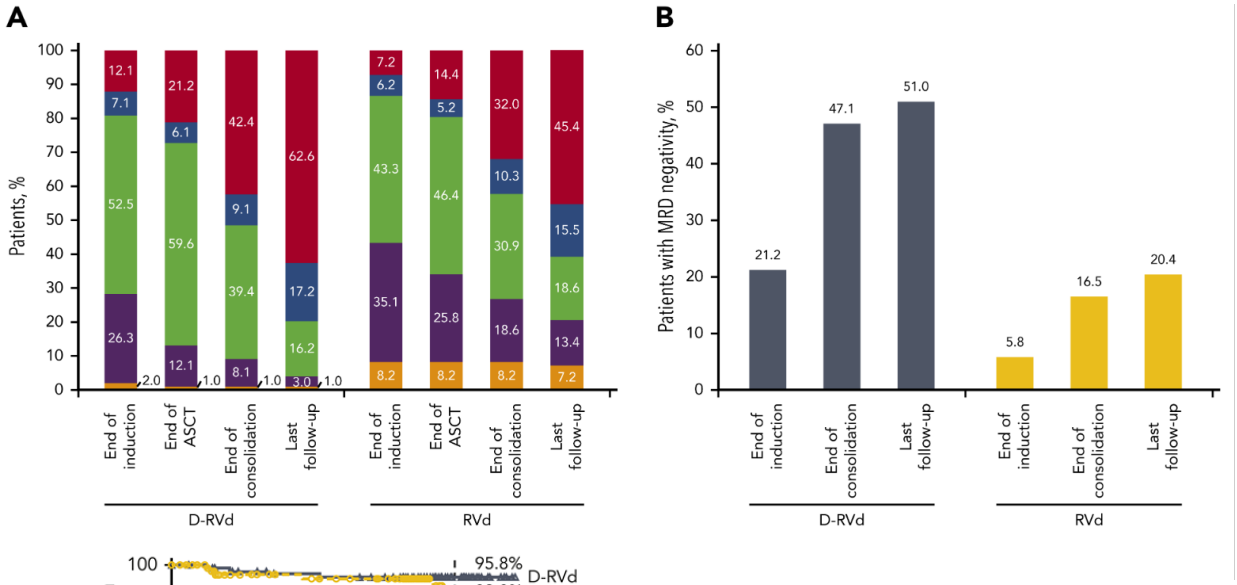
Key secondary endpoints:

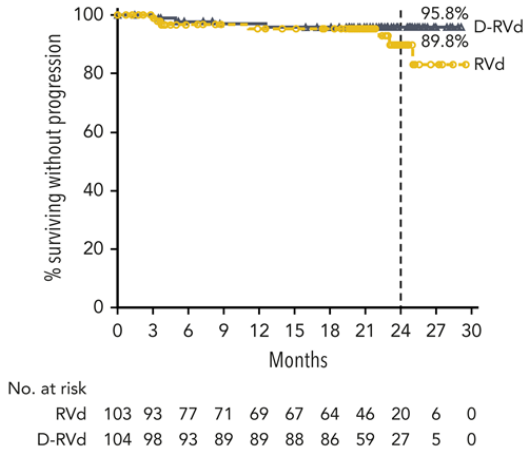
1. MRD-negativity by ClonoSEQ (10^{-5})
2. ORR, ≥VGPR, CR
3. PFS and OS

ISS disease stage, n (%)†	n = 104	n = 103
I	49 (47.1)	50 (48.5)
II	40 (38.5)	37 (35.9)
III	14 (13.5)	14 (13.6)
Missing	1 (1.0)	2 (1.9)
Baseline creatinine clearance, mL/min, n (%)	n = 104	n = 103
30-50	9 (8.7)	9 (8.7)
>50	95 (91.3)	94 (91.3)
Cytogenetic risk profile, n (%)‡	n = 98	n = 97
Standard	82 (83.7)	83 (85.6)
High risk	16 (16.3)	14 (14.4)

Vorhees et al. 2020; Laubach et al. ASH 2021;

GRIFFIN: Significant improvement in primary and secondary endpoints





Final Analysis

- Median follow-up 49.6 months
- All pt with ≥ 1yr of long-term follow-up
- Estimated 48-month PFS
  - Dara-RVd – 87.2% vs RVd – 70.0%
  - HR 0.45, 95% CI 0.21-0.95, *P* = 0.0324

Primary analysis

- sCR 42.4% vs. 32.0% - OR 1.57 95% CI 0.87-2.82; 1-sided *P* = .068 (significant)
- MRD$^-$ rate 51% vs. 20.4%, *P* <0.0001
- 24 mo PFS – 95.8% vs. 89.8%

Vorhees et al. 2020; Sborov et al. 2022

GRIFFIN: AEs and Caveats

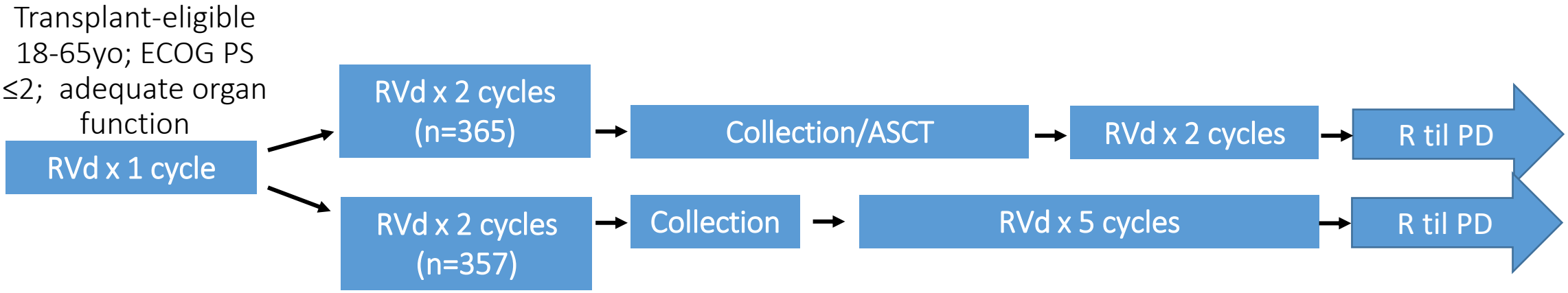
TEAE, %		D-RVd (n = 99)		RVd (n = 102)	
		Any	Grade 3/4	Any	Grade 3/4
Hematologic	▪ Neutropenia	64	46	40	24
	▪ Thrombocytopenia	44	15	35	9
	▪ Leukopenia	39	17	29	8
	▪ Anemia	37	9	32	6
	▪ Lymphopenia	31	23	28	23
Nonhematologic	▪ Fatigue	72	7	62	6
	▪ Upper respiratory tract infection	68	3	50	2
	▪ Diarrhea	67	7	55	5
	▪ Peripheral neuropathy	63	7	76	8
	▪ Cough	54	0	30	0

Critiques

- Phase 2 – not truly powered
  - PERSEUS Phase 3 ongoing
- Not re-randomized at maintenance
- Age limit of 70

Isa-RVd vs. RVd tested in the GMMG-HD7 trial – improved MRD negativity pre transplant

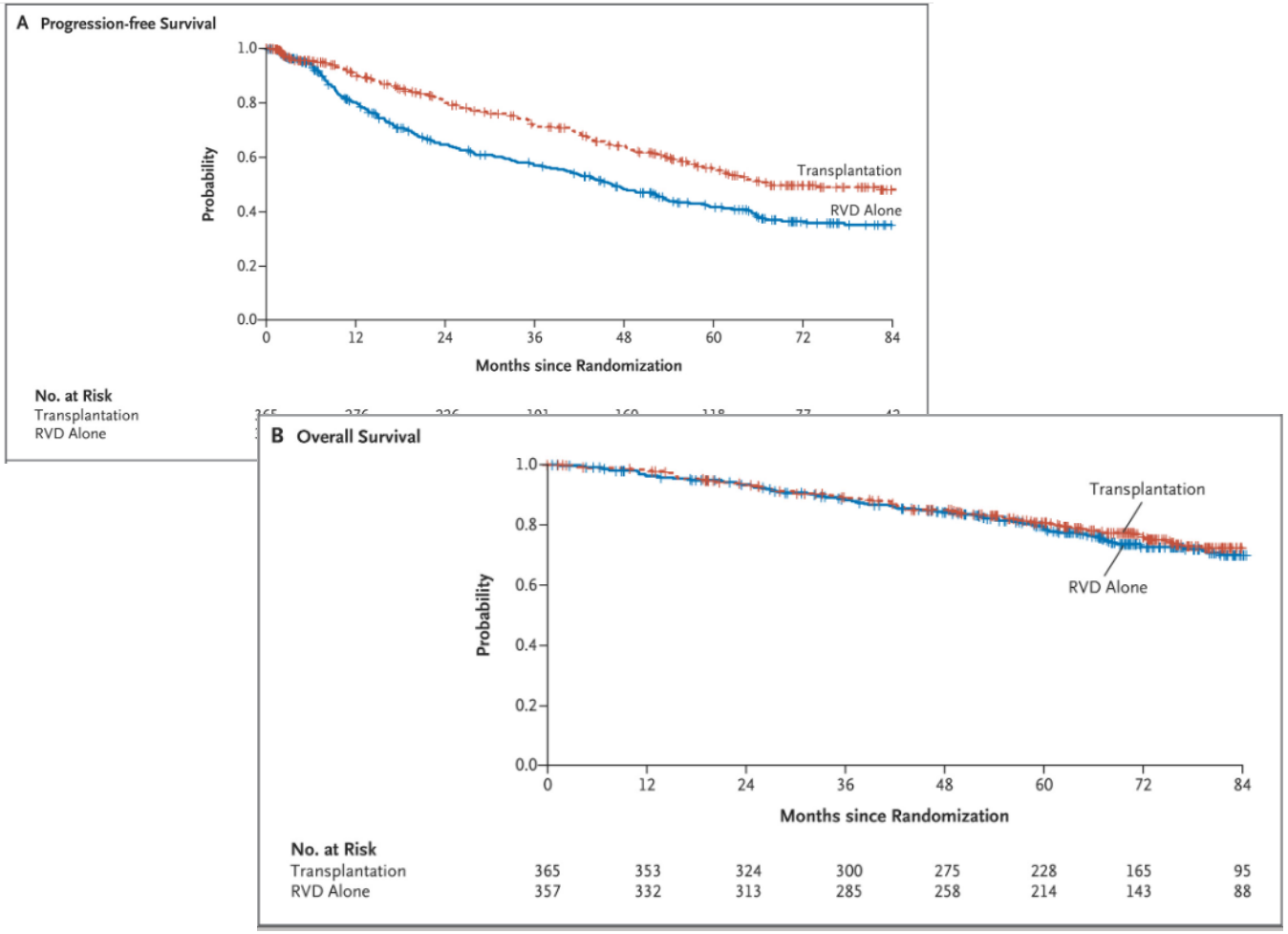
DETERMINATION: Triplet therapy, transplantation, and maintenance until progression



- Well balanced
  - Median age ~56
  - ~24% underrepresented minorities
  - ~20% high risk cytogenetics

Richardson et al. NEJM 2022

DETERMINATION: Improved PFS with ASCT compared to non-ASCT, no OS difference, transient lower QOL



- Median follow-up 76 mo
- Median PFS
  - RVD alone – 46.2 mo
  - ASCT group – 67.5 mo
  - HR 1.53 (95% CI, 1.23 to 1.91; P<0.001)
  - High risk cytogenetic subgroup
    - RVD alone – 17.5 mo
    - ASCT group – 55.5 mo
- No difference in OS regardless of HR cyto
  - 28% underwent ASCT later in the RVD-alone group
- SPMs – overall comparable; signal for myeloid malignancies post-ASCT (0% vs. 2.7%, P=0.002)

Richardson et al. NEJM 2022; Richardson et al. IMW 2022

NDMM Updates – Summary and Questions

- Addition of CD38 monoclonal antibody to RVd appears to improve response, MRD^-, PFS
  - Not necessarily powered, but data are suggestive - phase 3 trial data awaited
  - Patients were not rerandomized at maintenance – variable insurance coverage for DR maintenance
  - Hematologic toxicities are significant, but non-hematologic toxicities comparable
  - Upper age assessed was 70 years old
- ASCT continues to demonstrate improved PFS compared to non-ASCT with triplet induction, indefinite maintenance
  - OS not different at this point – which outcome is most meaningful?
  - Will delayed ASCT be the equalizer or not?
  - How will quads, novel immunotherapies (bispecifics, CAR T) change this landscape?

Treatment at first relapse: Len refractoriness, mAb-based regimens, and beyond

Chapter 2

Most patients will have progressive-disease while on lenalidomide, therefore have len-refractory disease

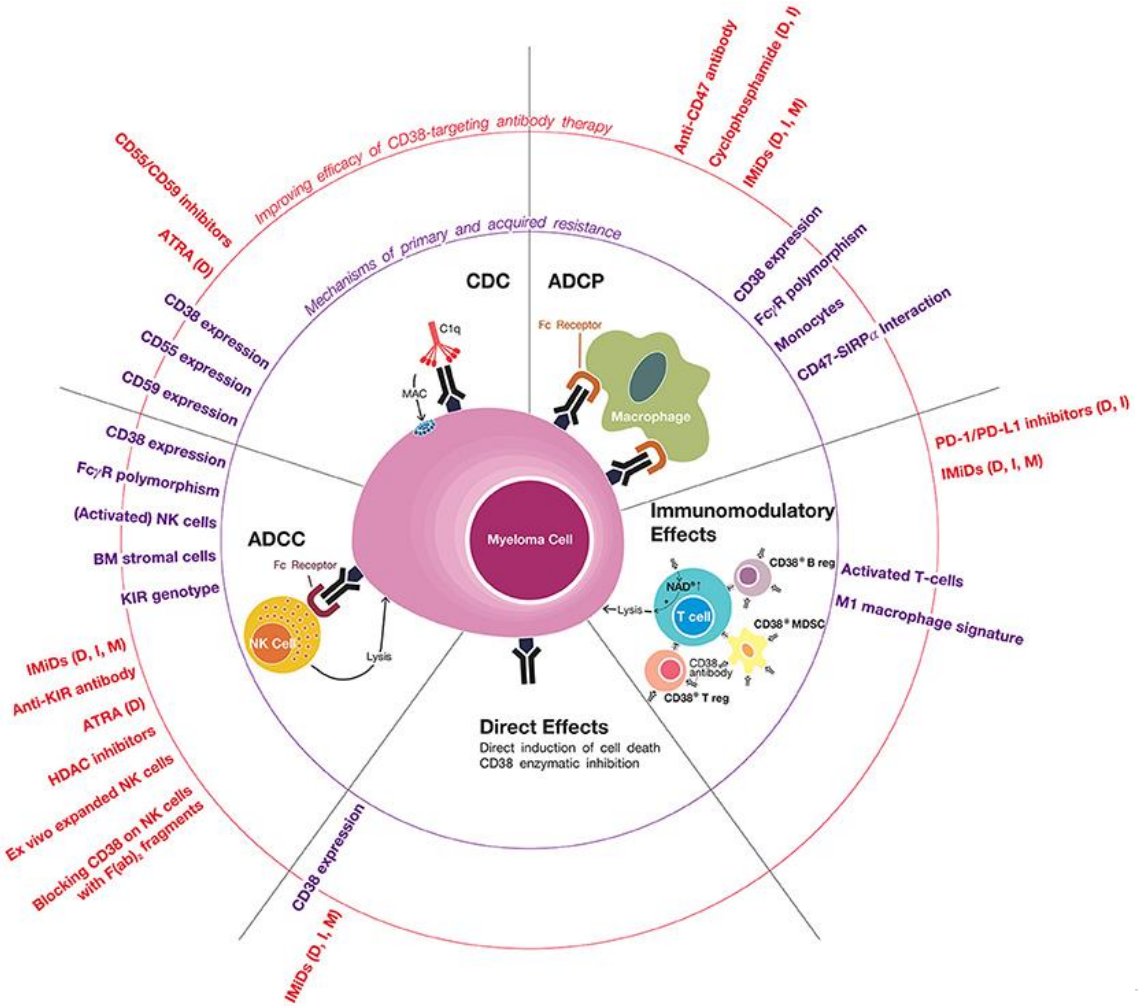
Moreau et al. (2021)

At first relapse, lenalidomide-combinations are preferred in those NOT len-refractory

Trial(s)	ASPIRE	POLLUX	ELOQUENT-2	TOURMALINE-MM1
Regimen	KRd vs. Rd	DRd vs. Rd	Elo-Rd vs. Rd	Ixa-Rd vs. Rd
Indication	RRMM with 1-3 LOT	RRMM ≥ 1 LOT	RRMM with 1-3 LOT	RRMM ≥ 1 LOT
ORR	87.1 vs. 66.7%	93 vs. 76%	79% vs. 66%	78% vs. 72%
DOR	28.6 vs. 21.2 mo	NR vs. 25.2 mo	21.9 vs. 17.1 mo	20.5 vs. 15.0 mo
PFS	mPFS – 26.3 vs. 17.6 mo; HR 0.69	mPFS – NR vs. 19.6 mo** HR 0.42 42-mo PFS 57.3% vs. 27.8%	mPFS – 19.4 vs. 14.9 mo HR 0.70	20.6 vs. 14.7mo HR
OS	mOS - 48.3 mo vs. 40.4 mo HR 0.79	mOS – 67.6 vs. 51.8mo HR 0.73	mOS – 48.3 vs. 39.6 mo HR 0.82	mOS – 53.6 vs. 51.6 mo HR 0.939 (NS)

Richardson et al. (2021); Dimoppolous et al. (2022); Moreau et al. (2021); Facone et al. (2016); Bahlis et al. (2020); Stewart et al. (2015)

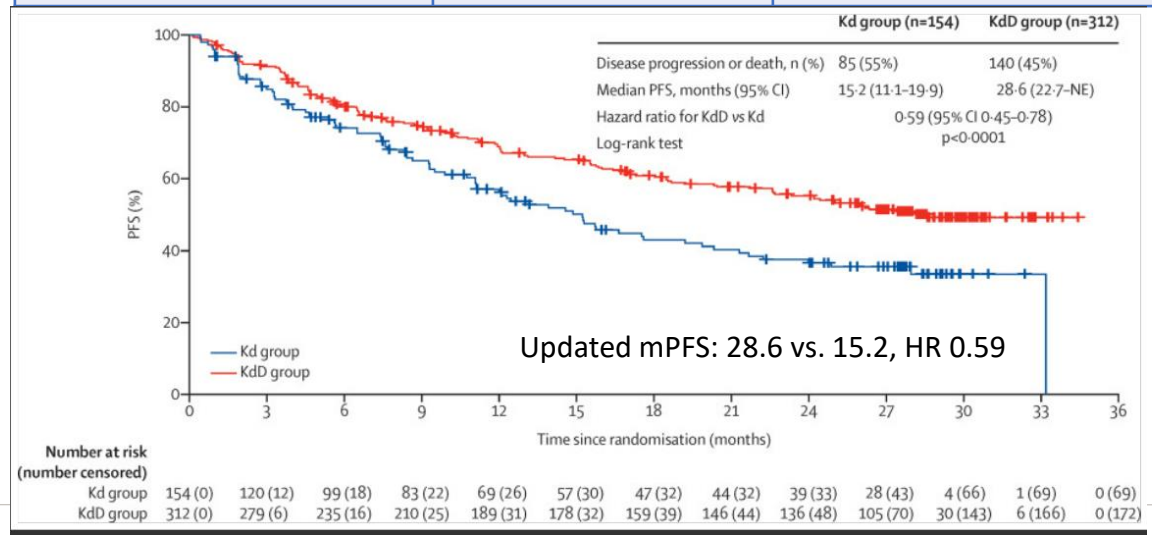
Given that most are len-refractory, CD38 monoclonal antibodies are the current backbone of RRMM treatment



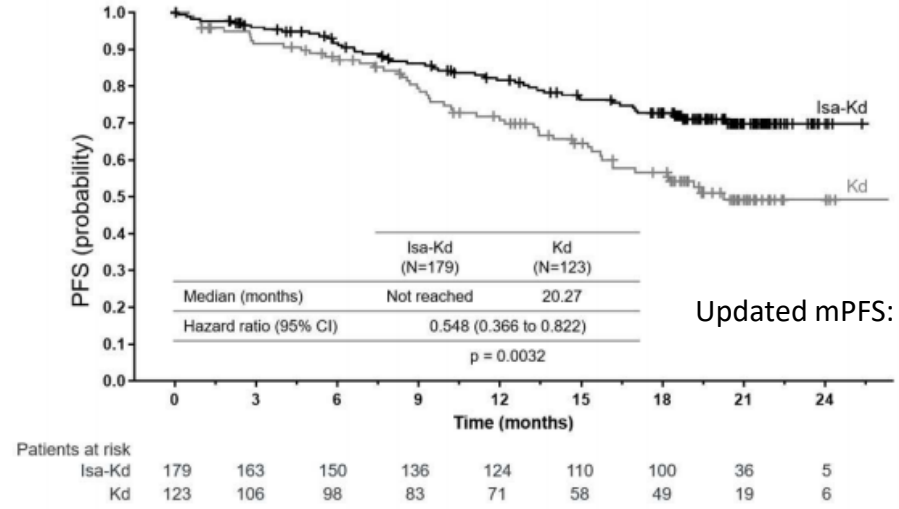
Van de Donk and Usmani. (2018)

Dara and Isa, when combined with Kd, improve outcomes over Kd alone

	CANDOR – DKd vs. Kd		IKEMA- IKd vs. Kd	
Age– med (range)	64 (29-84)		64 (30-90)	
Prior lines – med (range)	2 (1-3) – 29% BTZ-ref, 33% len-ref		2 (1-4) – 21% double refractory	
High Risk Cyto	16%		24% (42% gain 1q)	
Arm	**DKd**	**Kd**	**IKd**	**Kd**
ORR, %, (95% CI)	84 (80-88)	75 (67-81)	86.6 (80.7-91.2)	82.9 (75.1-89.1)
CR, %	28	10	44.1	35



Updated mPFS: 28.6 vs. 15.2, HR 0.59



Updated mPFS: 35.7 vs. 19.2, HR 0.58

Usmani et al. (2022); Moreau et al. (2022); Moreau et al. (2021)

Dara or Isa combined with Kd increase risk of respiratory infections

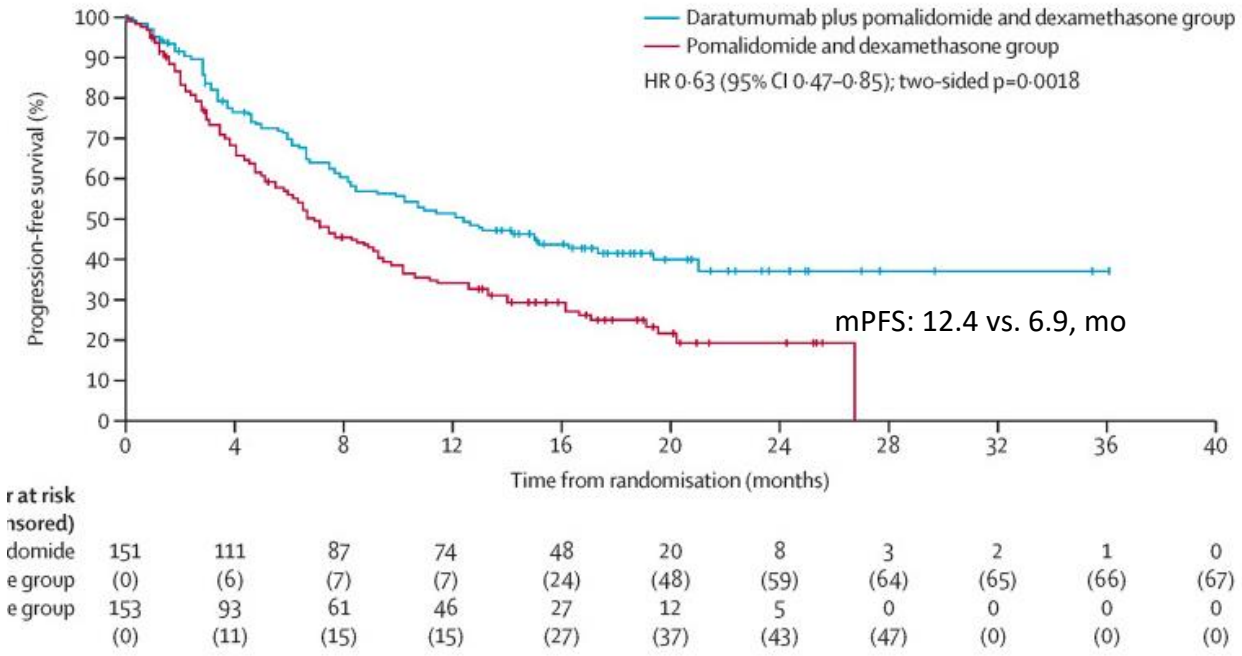
- Do not appear to increase risk of cardiac complications

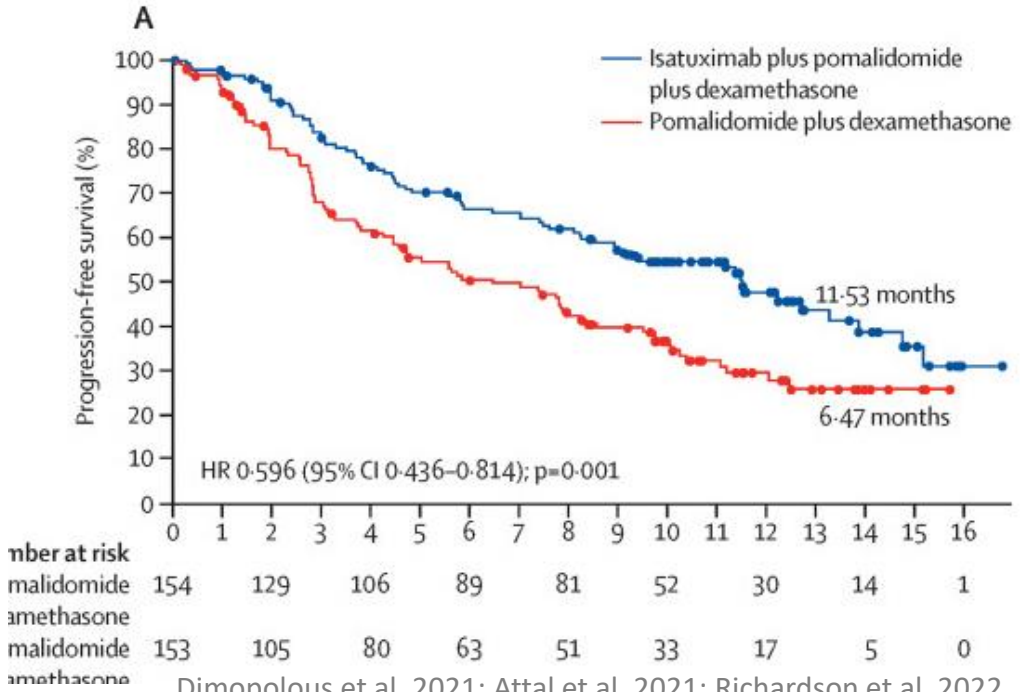
Arm	DKd	Kd	IKd	Kd
Grade ≥3, %	87	76	77	67
Hypertension	21	15	20	20
Pneumonia	17	9	23	14
Thrombocytopenia	25	16	30	24
Cardiac Failure	3	2	4	4
Fatal, %	9	5	3	3
Cardiac	2	0	NR	NR
Infections	5	3	NR	NR
Respiratory	1	1	NR	NR

Usmani et al. (2022); Moreau et al. (2022); Moreau et al. (2021)

CD38 mAb plus Pd for len-refractory MM

	APOLLO – DPd vs. Pd		ICARIA-MM – IPd vs. Pd	
Age– med (range)	67 (42-86)		67 (36-86)	
Prior lines – med (range)	**2 (1-5); 80% len ref, 48% PI-ref, 42% double**		**3 (2-11); 93% len-ref, 76% PI-ref, 73% double-refractory**	
High Risk Cyto	35%		20%	
Arm	**DPd**	**Pd**	**IPd**	**Pd**
ORR, %, (95% CI)	69 (61-76)	46 (38-55)	86.6 (80.7-91.2)	82.9 (75.1-89.1)
CR, %	25	4	44.1	35





Dimopolous et al. 2021; Attal et al. 2021; Richardson et al. 2022

Daratumumab regimens for RRMM

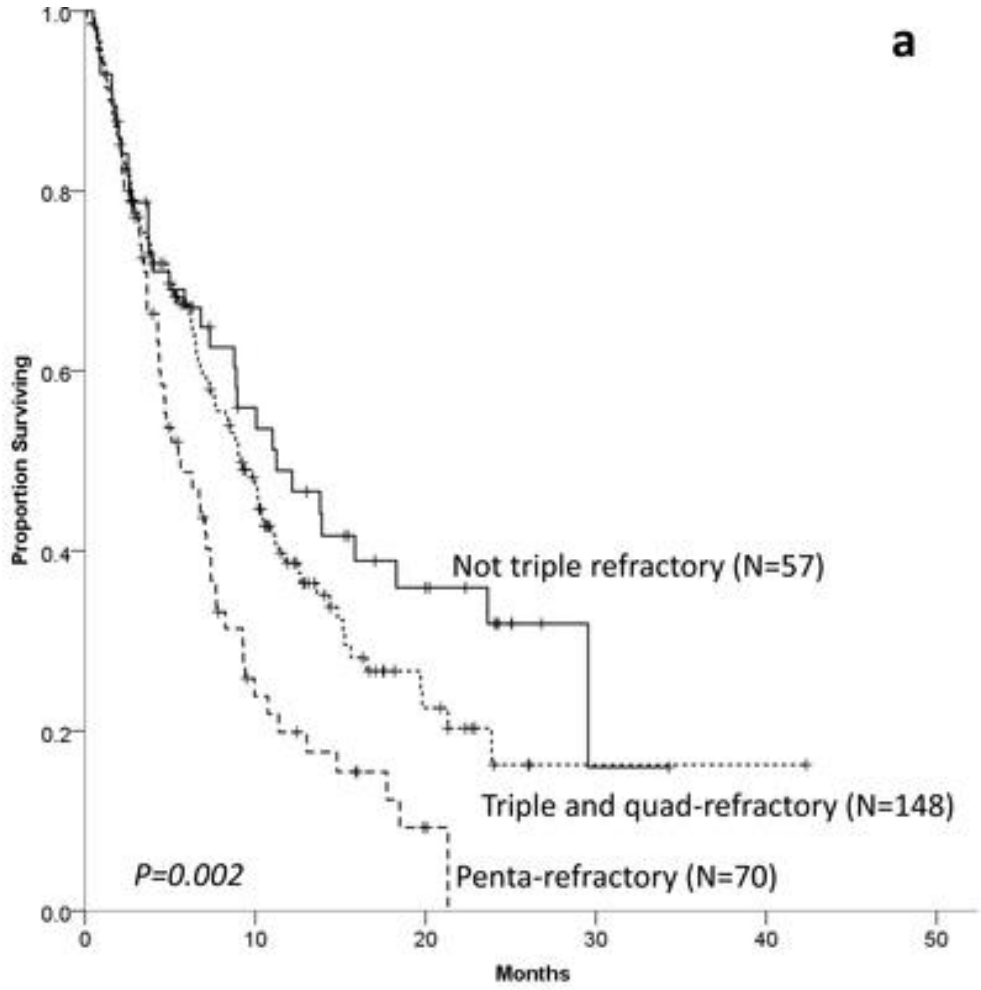
Trial(s)	SIRIUS GEN501	POLLUX	EQUULES APOLLO	CASTOR	EQUULES CANDOR
Regimen	Monotherapy	DRd vs. Rd	DPd DPd vs. Pd	DVd vs. Vd	DKd vs. Kd
Indication	• ≥3 lines OR • PI/IMID refractory	• ≥1 line	• ≥2 line (approved) • ≥1 line (off-label)	• ≥1 line	• ≥1-3 line
ORR	29.2% (20.8-38.9) 36% (21.6 – 52)	92.9% vs. 76.4%	60% APOLLO: ≥VGPR 51.0% vs. 19.6%	85% vs. 63%	84% 84% vs. 75%
DOR	7.4 mo (5.5 – NE)	NR	EQUULES: 6 mo: 85% 12 mo: 68%	NR	NE vs. 16.6
PFS	3.7 mo (2.8 – 4.6)	44.5 vs. 17.5 mo	APOLLO: 12.4 vs. 6.9 mo	16.7 vs. 7.1 mo	CANDOR: 18-month PFS 62% vs. 43%
OS	17.5 mo (13.7 – NE)	42-month OS rate: 65% vs. 57%	APOLLO: HR for OS 0.91 (95% CI 0.6-1.4)	NR	CANDOR: HR for OS 0.75 (95% CI 0.49-1.13)

CAR T Therapy Revolutionizes Treatment for Advance RRMM

Chapter 3

Refractoriness to anti-CD38 associated with poor OS

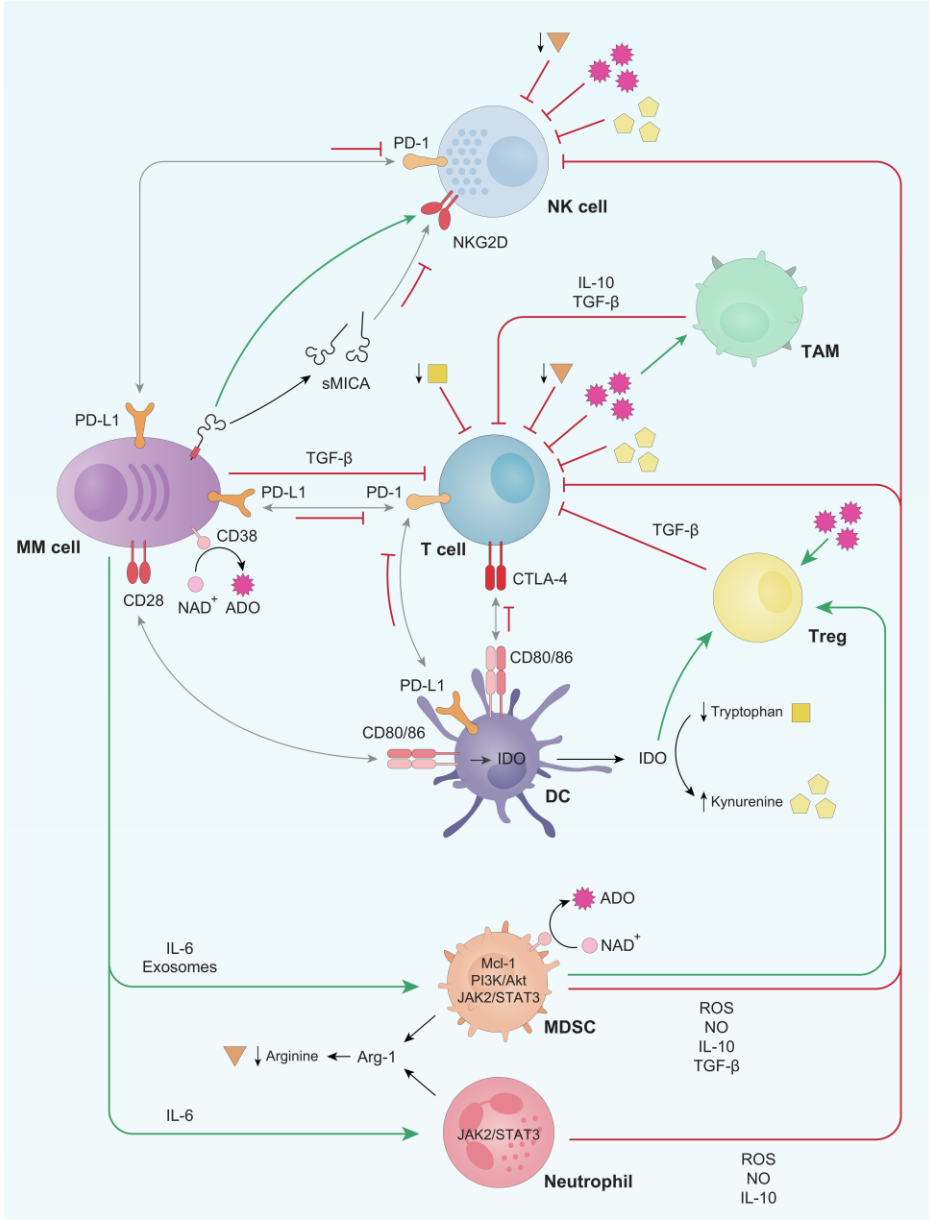
- Median OS for triple refractory 10 mo, penta-refractory 5.6 mo
- Limited responses to subsequent therapies after anti-CD38



Ghandi et al. 2019

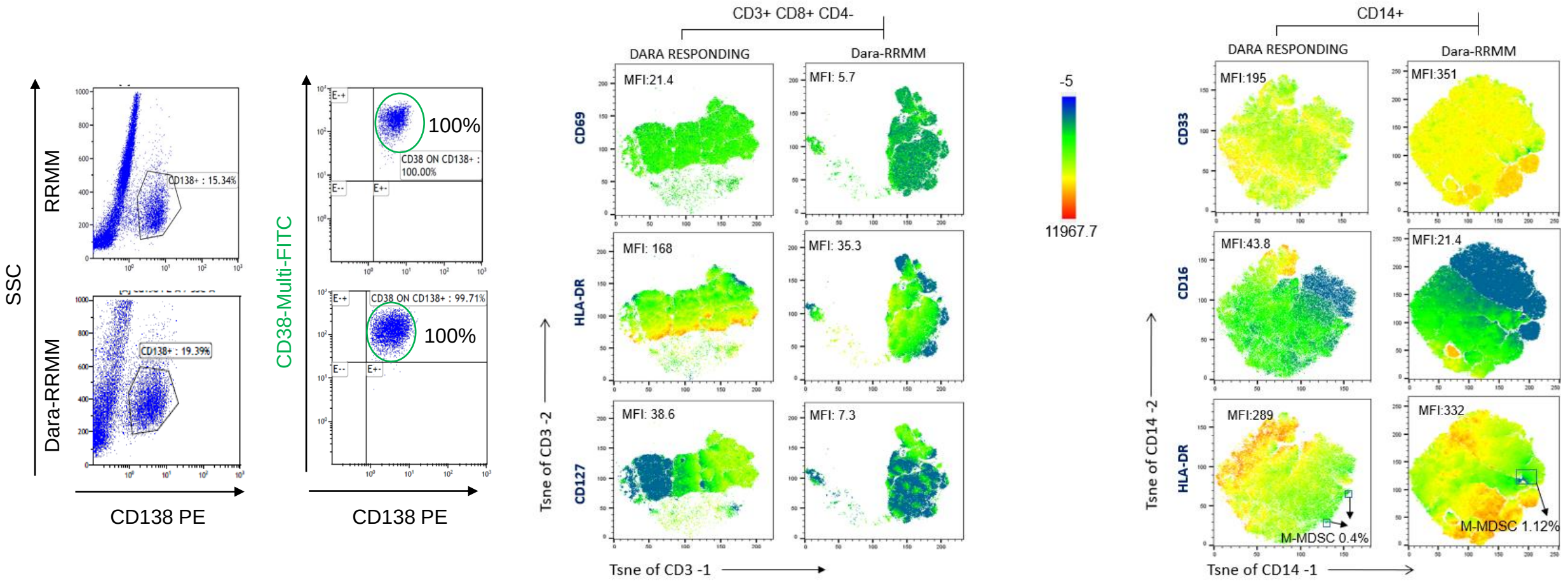
Myeloma is caused by and causes immunosuppression

- MGUS cells kept in check by NK and T-cells
  - …until they're not
- Selection for MM cells that activate MDSCs, Tregs, inactivate T-cells and NK cells
- Contact inhibition (increased PD-L1) and secreted factors



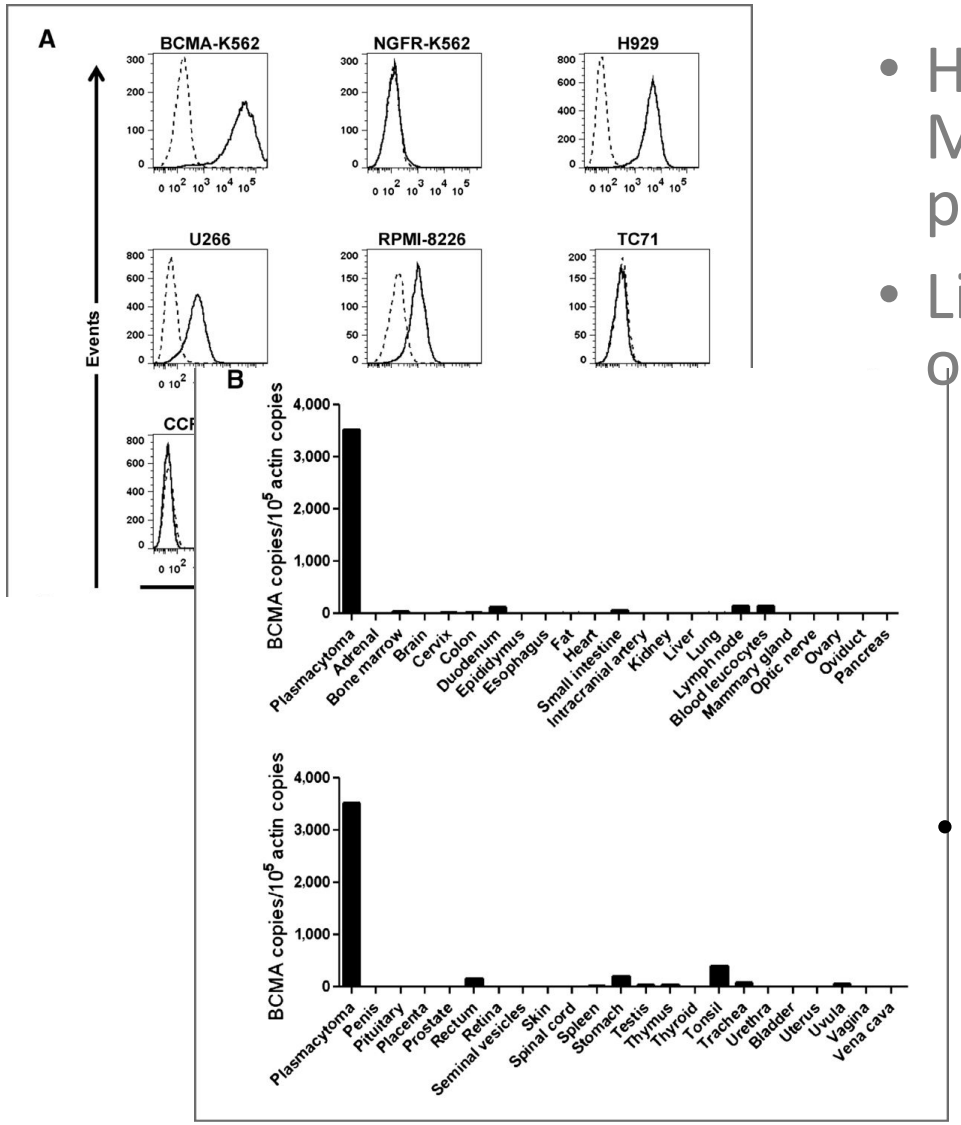
Díaz-Tejedor, A et al. *Cancers* 2021,

Resistance to daratumumab associated with exhaustion phenotype T and NK cells, not CD38 loss

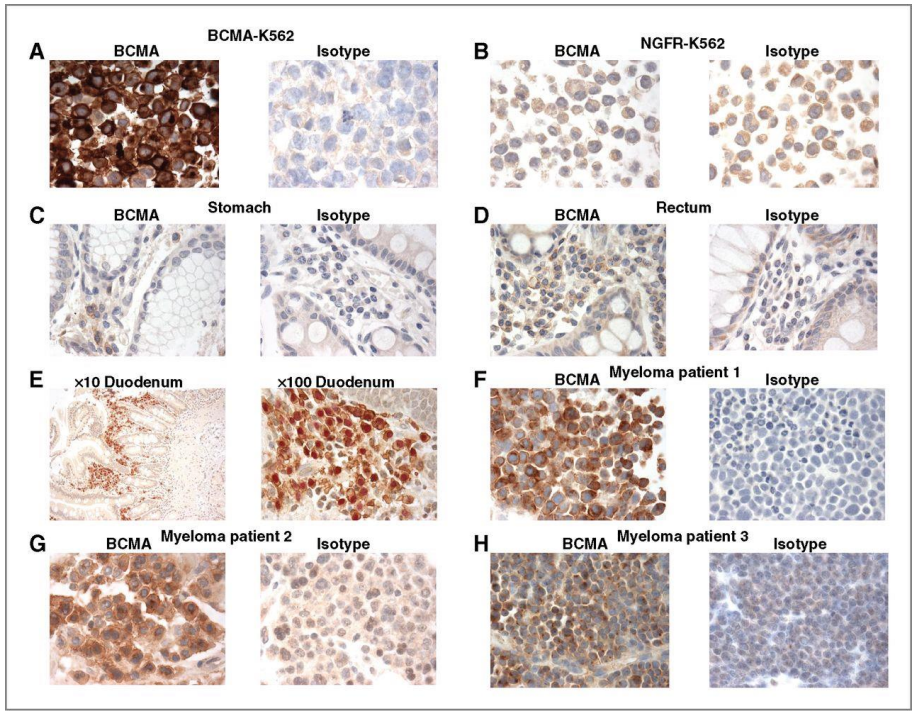


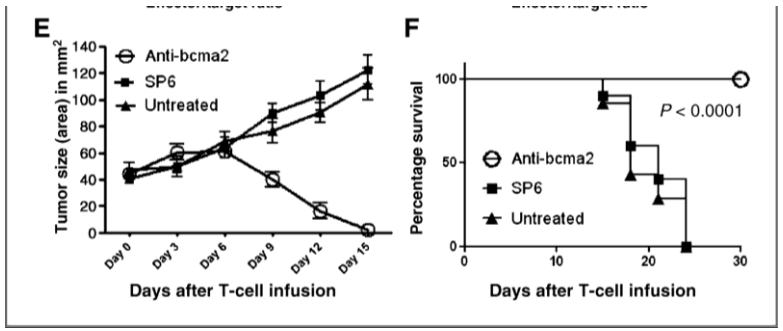
Leukemia, 2021 Jan;35(1):189-200

B-cell Maturation Antigen – aka BCMA, TNFRSF1, or CD269



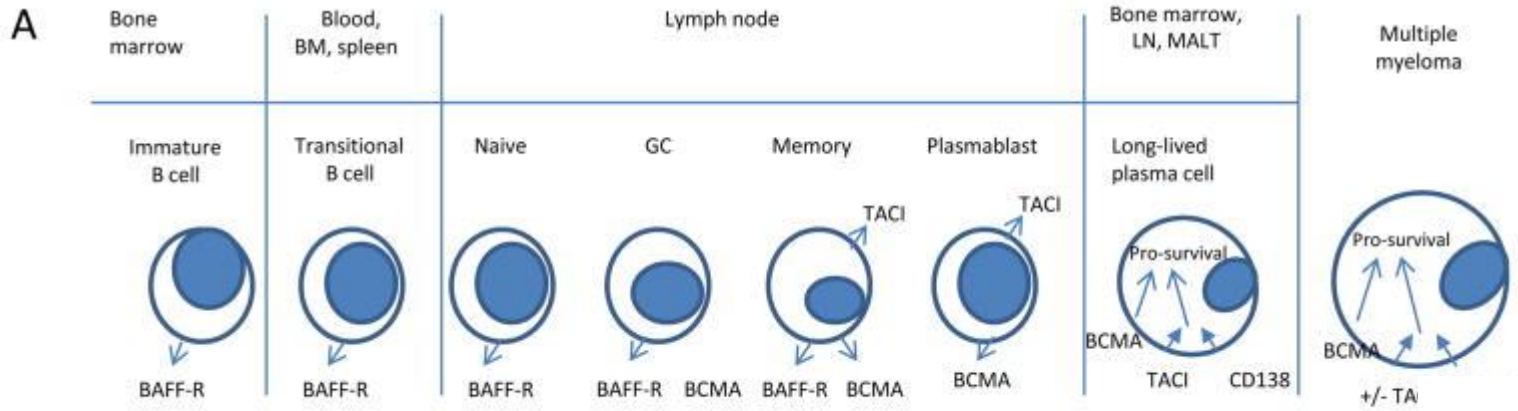
- Highly expressed in MM cell lines and primary tissues
- Limited expression outside of tumor
- Excellent *in vivo* activity of BCMA-CD28-CD3ζ CAR T



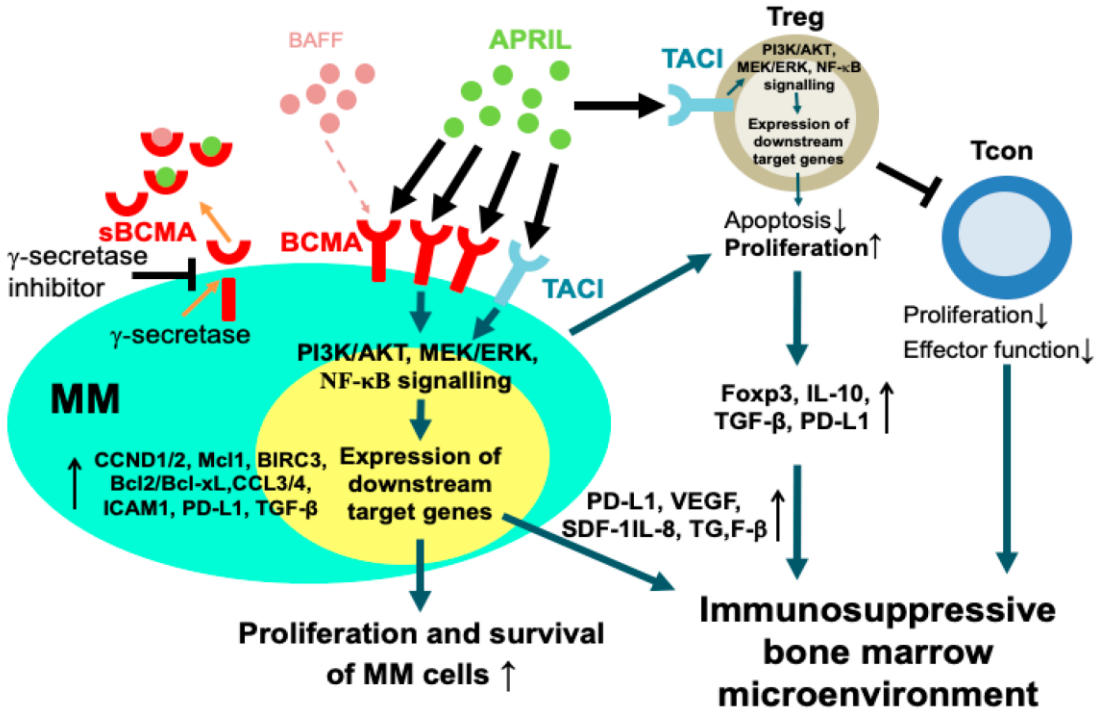


Carpenter et al. Clin Cancer Res. 2013;19(8)

But what does BCMA do?



- APRIL binds BCMA, induces further differentiation and survival of PCs
- MM with higher BCMA expression → proliferation, survival, **increased Treg/Tcon = immunosuppressive BMBx**

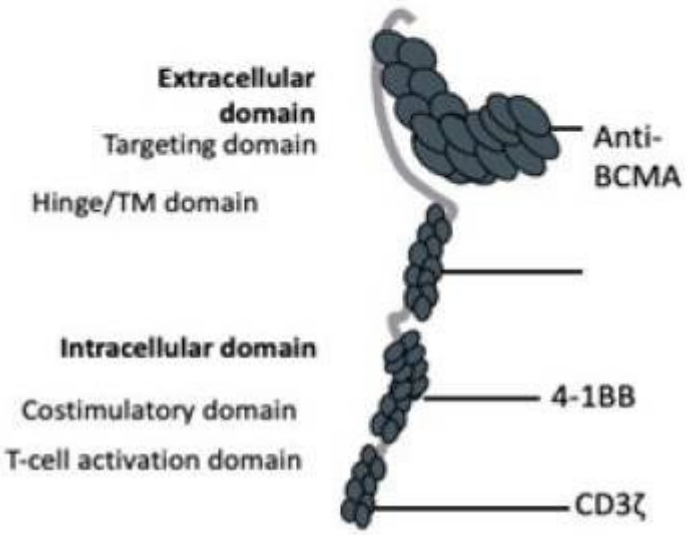


Maus MV et al. *Clin Cancer Res*. 2013; Cho et al. *Cancers*. 2020

BCMA CAR T construct differences

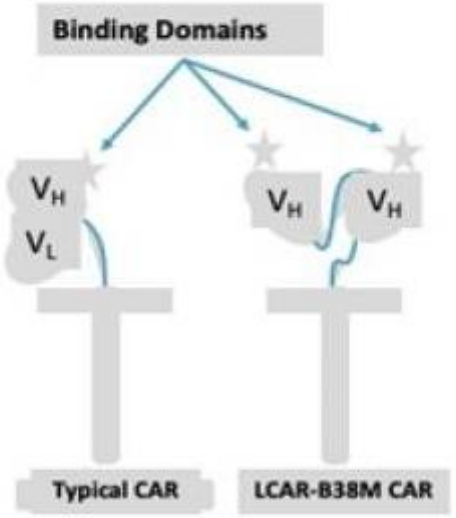
Idecabtagene Vicleucel

- Autologous T-cells transduced with a lentiviral vector encoding CAR specific for BCMA
- Targeting domain: Anti-BCMA
- Costimulatory domain: 4-1BB
- T-cell activation domain: CD3 ζ



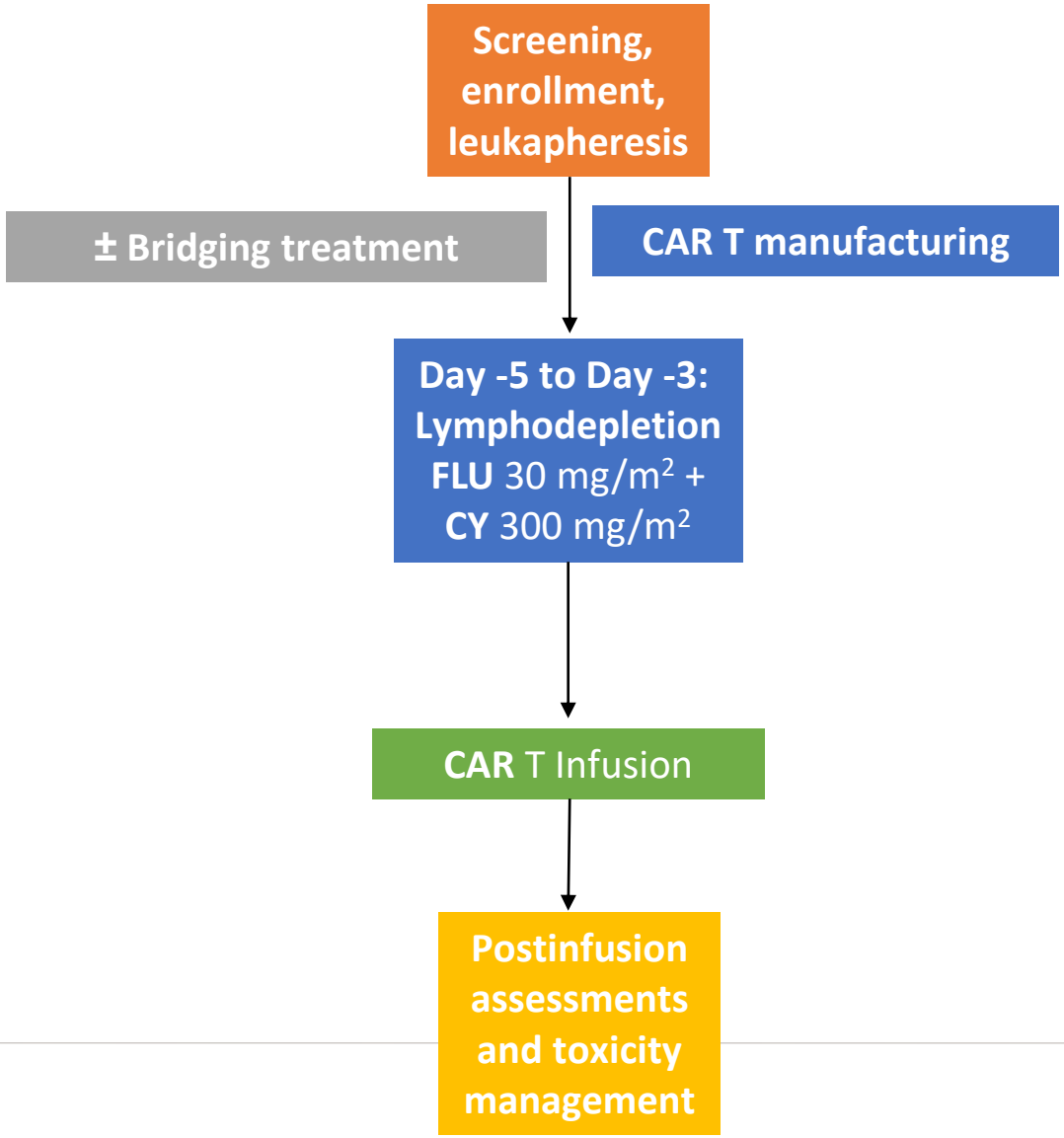
Ciltacabtagene Autoleucel

- Lentiviral vector-based + 4-1BB costimulatory domain;
- BCMA-catching domain targets 2 different epitopes simultaneously



Martino M et al. *Cancers.*

KarMMa and CARTITUDE-1 Study Designs

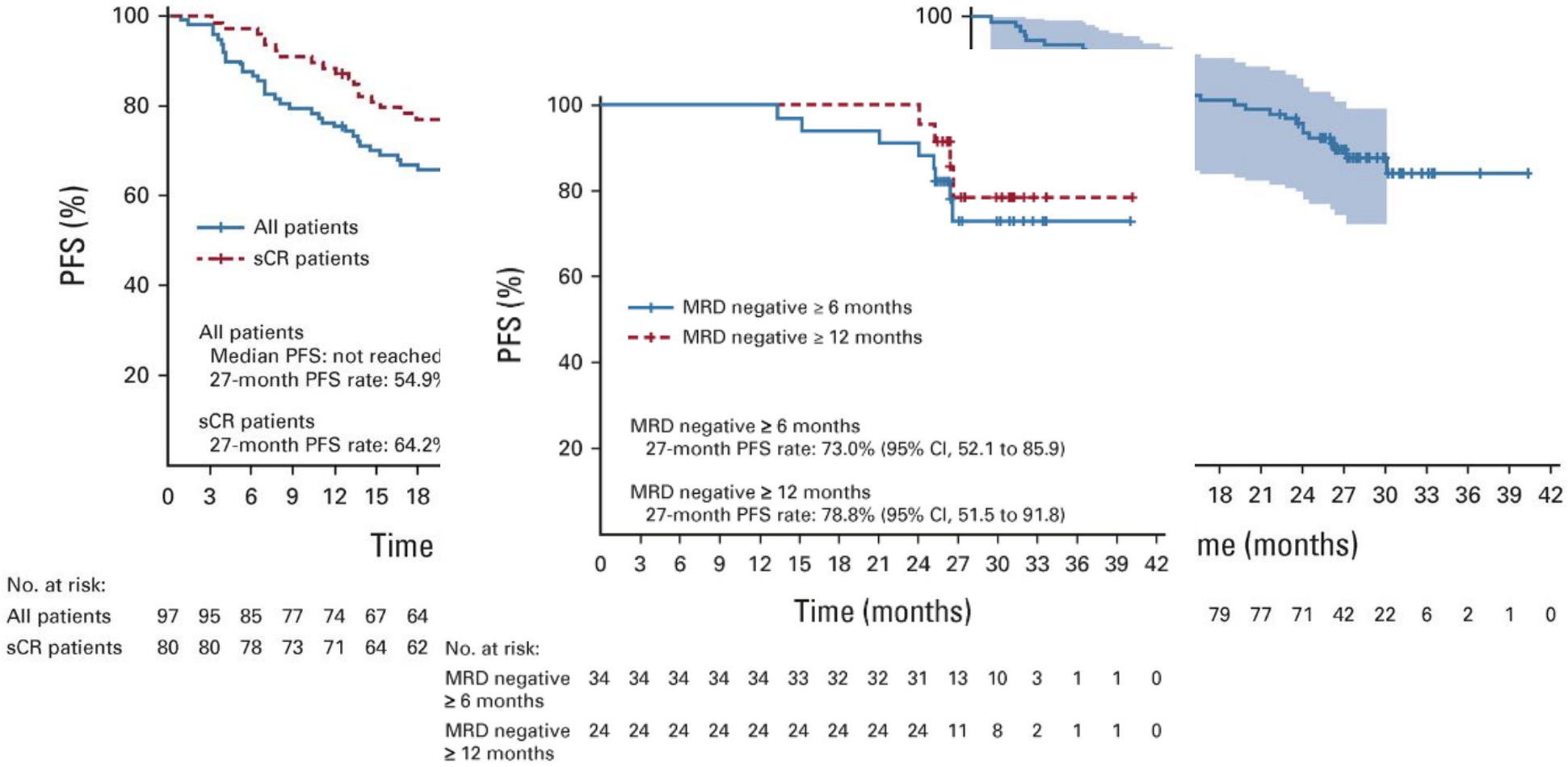


BCMA CAR T Trials - Baseline Characteristics

Trial	KarMMa	CARTITUDE-1
CAR T product	Ide-cel	Cilta-cel
N	128	97
Median age, y	61	61
Male, %	76	59
Extramedullary disease, %	39	13
ECOG-0 Performance Status, %	45	40
ISS Stage III, %	16	14
High-risk cytogenetics, %	35	24
Prior LOT (median)	6	6
Penta-refractory, % Triple-class refractory, %	26 84	42 88

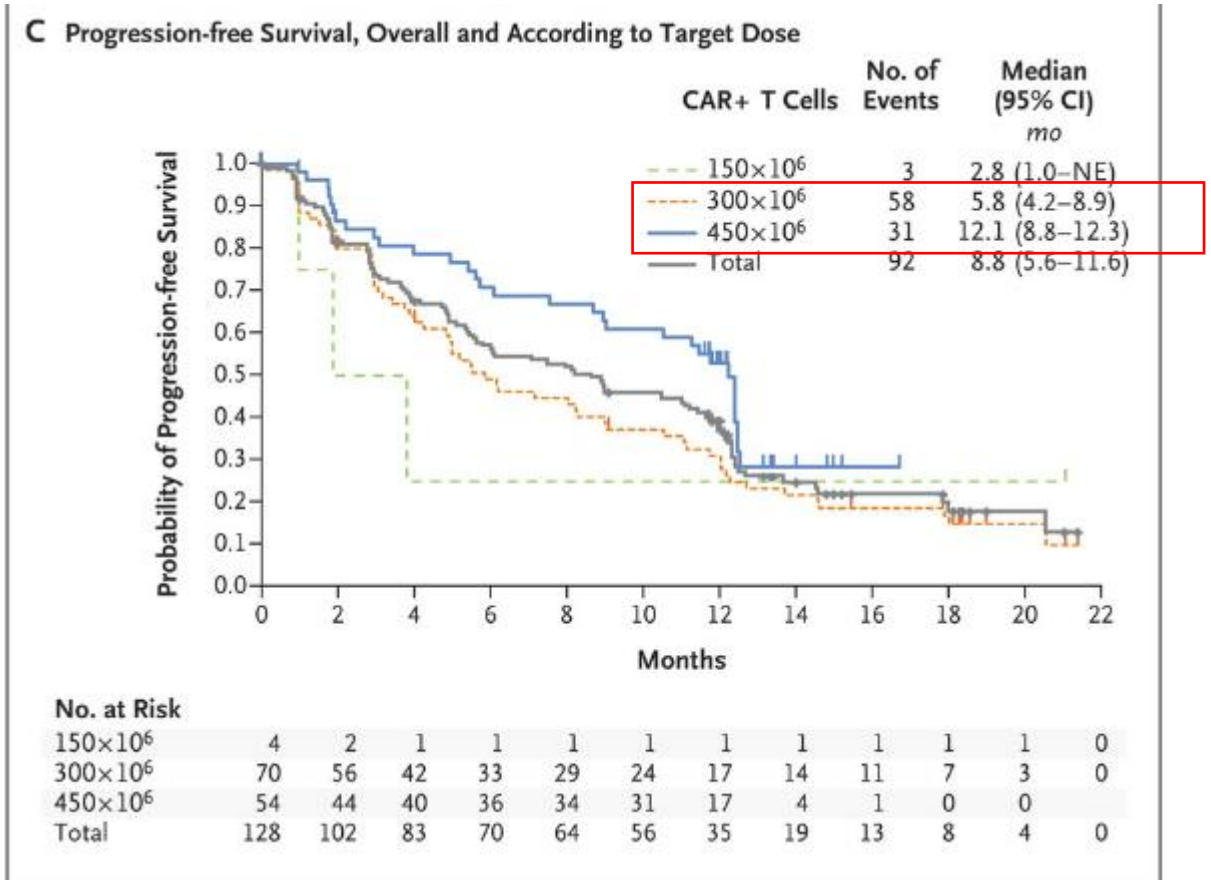
Munshi et ak. (2021); Berdeja et al. (2021)

CARTITUDE-1 Efficacy



Martin et al. (2022)

KarMMa Efficacy



Efficacy Outcomes of BCMA CAR T

Trial	KarMMa	CARTITUDE-1
CAR T product	Ide-cel	Cilta-cel
N	128	97
ORR, %	73	97.9
PFS (median)	8.6	NR (2-year PFS 60.5%)
OS (median)	NR (2-year OS 51%)	NR (1-year OS 89%)
MRD negativity, %	26	92

Munshi et ak. (2021); Berdeja et al. (2021)

Safety Outcomes of BCMA CAR T

Trial	KarMMa	CARTITUDE-1
CAR T product	Ide-cel	Cilta-cel
N	128	97
TEAE, any/≥Gr 3,%	100/99	100/94
CRS, Any, %	84	95
Gr 3/4	5	4
Gr 5	<1	1
Median onset, d	1	7
Median duration, d	5	4
NT, Any, %	18	21 (ICANS 17%, other NT 12%)
Gr 3/4	4	9 (ICANS 2%, other NT 8%)
Gr 5	0	1
Median onset, d	2	ICANS 8, Other 27
Median duration, d	5	ICANS 4, Other 74.5

Munshi et ak. (2021); Berdeja et al. (2021)

Real World Experience with Ide-Cel

	KarMMa-1	Real World
Median age, y	61 (33-78)	64 (36-78)
ECOG PS 0 or 1	98%	77%
Extramedullary disease	39%	53%
High risk cyto	35%	33%
Median LOT	6	6
Prior ASCT	94%	85%
Penta-refractory disease	26%	41%
ORR/CR	73%/33%	83%/34%
Grade ≥ 3 CRS and ICANS	5%, 3%	5%, 5%

Hansen et al. (2022)

Choosing Appropriate Patients for CAR T

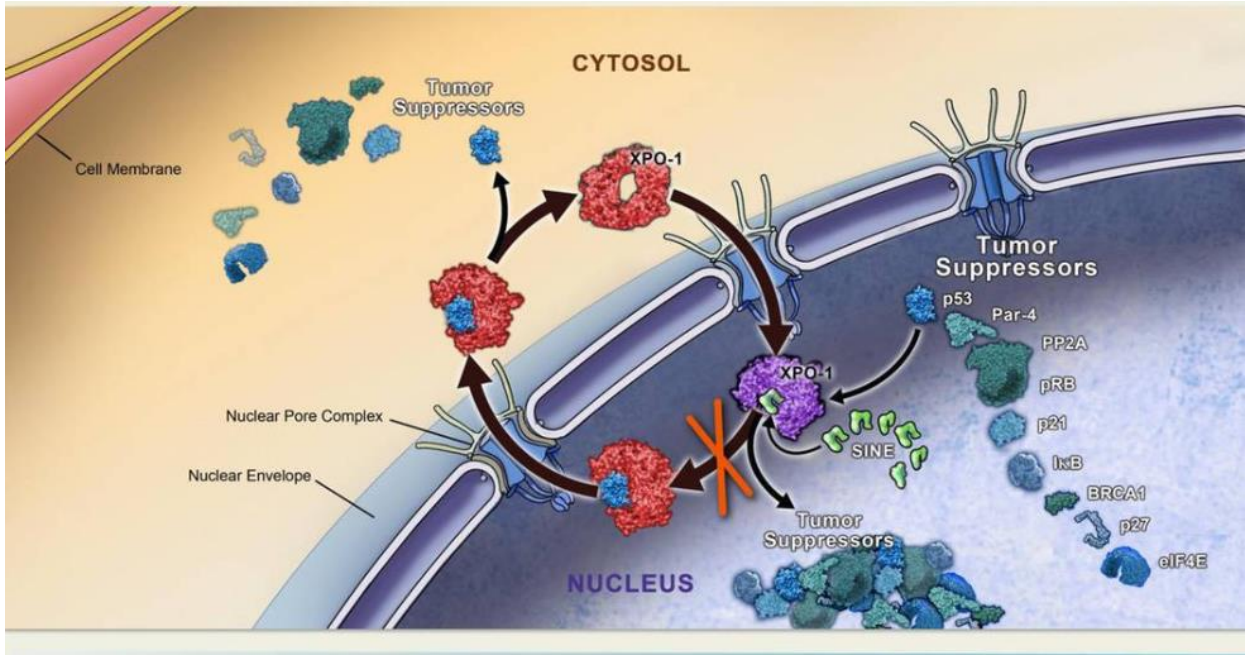
- Barriers
  - Availability
  - Manufacturing time
  - Rapidly progressing disease – inadequate bridging
  - Facilities that can administer therapies and manage toxicities
  - Cost and resources
- Considerations
  - Early referral and workup
  - Risk stratify for co-morbditities
  - Does patient have a bridging option to get them 5-8 weeks between leukapheresis and infusion
  - Disease burden is associated with risk of CRS and ICANS

Options for patients who cannot receive CAR T therapy

- Standard of Care
  - Belantamab mafodotin
  - Selinexor regimens
- Investigational
  - Bispecific antibodies/T-cell engagers
  - CELMoDs
  - Novel (allogeneic) CAR T

Selinexor

- Oral, selective inhibitor of XPO1
  - Retention of tumor suppressors, GR, and oncogene mRNA in nucleus
  - XPO1 overexpressed in MM



STORM: Sd for Triple-Class Refractory MM

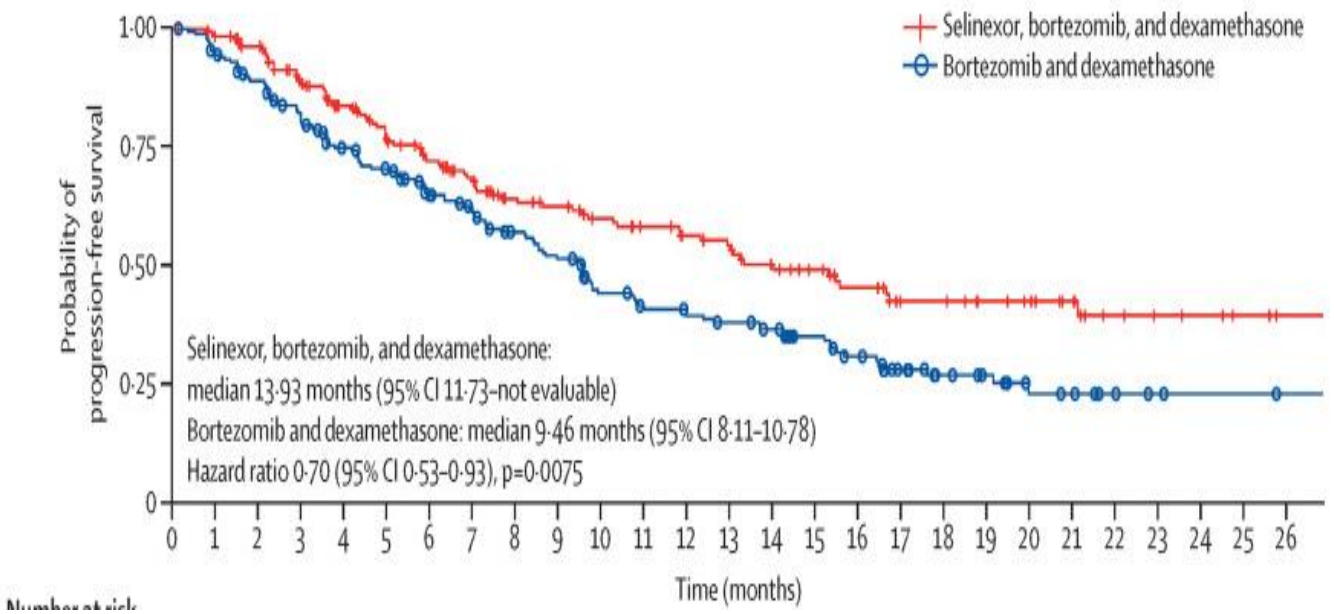
- Oral selinexor (80mg) with dex (20mg) on D1, D3 weekly
- 123 patients with penta-exposed, triple class refractory
  - Approved for penta-refractory, at least 4 prior lines (n=83)
  - mDOR 3.8 mo

Response	STORM (n=83)
Overall Response Rate (ORR)[a], n (%)	21 (25.3)
95% CI	16.4, 36
Stringent Complete Response (sCR)	1 (1)
Complete Response (CR)	0
Very Good Partial Response (VGPR)	4 (5)
Partial Response (PR)	16 (19)

a. Includes sCR + CR + VGPR + PR.

Chari et al. 2019. NEJM

BOSTON: PFS



	Selinexor, bortezomib, and dexamethasone group (n=195)	Bortezomib and dexamethasone group (n=207)
Overall response rate*	149 (76·4% [69·8–82·2])	129 (62·3% [55·3–68·9])
Best overall response†		
Stringent complete response	19 (10%)	13 (6%)
Complete response	14 (7%)	9 (4%)
Very good partial response	54 (28%)	45 (22%)
Partial response	62 (32%)	62 (30%)
Minimal response	16 (8%)	20 (10%)
Stable disease	25 (13%)	40 (19%)
Progressive disease	1 (1%)	10 (5%)
Non-evaluable	4 (2%)	8 (4%)
Negative status for minimal residual disease‡	9 (5%)	8 (4%)

Data are n (% [95% CI]) or n (%). *p=0·0012 for between-group comparison (Cochran-Mantel-Haenszel test). †Best overall response categories are mutually exclusive. ‡Minimal residual disease was assessed in patients with a stringent complete response or complete response; negative status was defined as an absence of malignant clones per 100 000 white blood cells.

Table 2: Efficacy data

Dimopoulos. ASCO 2020. Abstr 8501.; Grosicki et al. Lancet 2020; Gasparetto et al. ASH 2020.

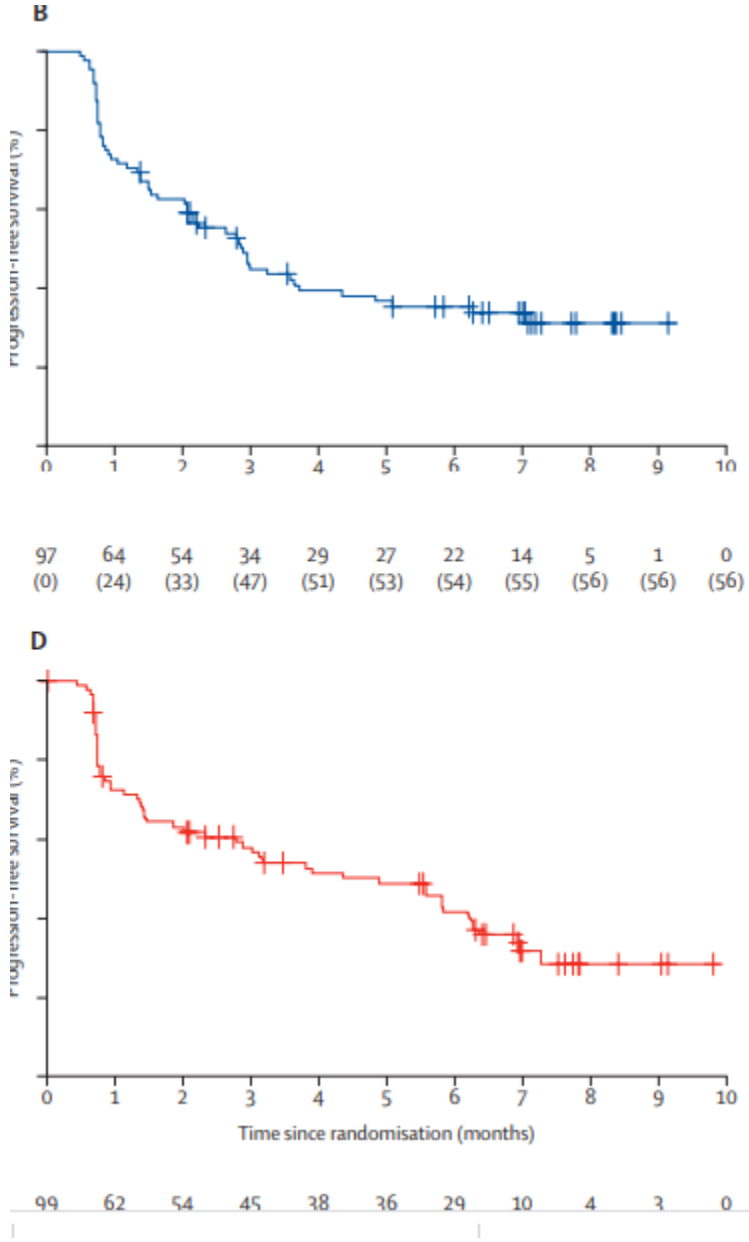
Management of Patients Treated with Seli

- High incidence of heme and non-heme toxicities
  - Fatigue, nausea, hyponatremia, anorexia
- Consensus guidelines on management (Mikhael et al. CLML 2020)
  - Set expectations with patients – 50% required dose reduction in STORM
  - Close monitoring, frequent communication
  - Weekly/2x weekly hydration
  - Nausea prophylaxis with NK1 receptor antagonist, ondansetron, +/- olanzapine (1-2 cycles)
  - Hyponatremia – salt tabs, dose holds, r/o paraproteinemia as cause
  - Anorexia- nutrition consult, dronabinol

Mikhael et al. 2021

Belantamab mafodotin

- BCMA antibody linked to MMAF payload
- DREAMM2 pivotal trial
  - 97 treated at **2.5mg/m2 q3wk**
    - 31% ORR, mPFS 2.9 mo, mDOR not reached
  - 99 treated at 3.4mg/m2 q3wk
    - 34% ORR, mPFS 4.9 mo, mDOR not reached
  - Frequent delays, mainly due to keratopathy
    - Responses not necessarily lost with delays
- **<u>Unclear if subsequent BCMA therapy affected</u>**

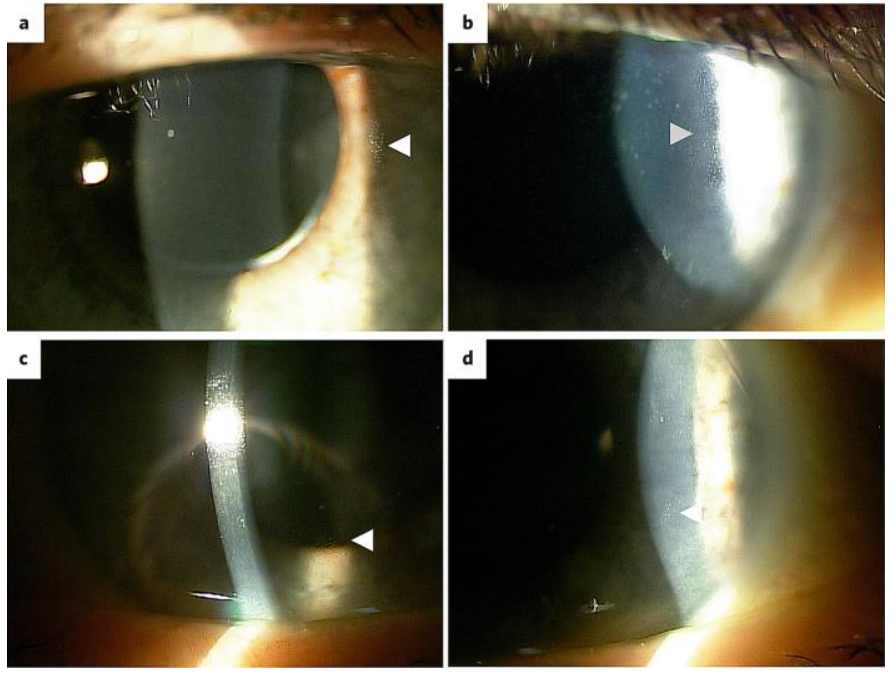


Lonial et al. Lancet 2020.

Ocular toxicity with belantamab mafodotin

- Median time to resolution of ocular toxicity requiring dose hold 21 days
- Few discontinuations due to ocular toxicity
  - Microcystic keratopathy
- Ophthalmologic exam: Baseline, predose, any complaint
- REMS
- **Steroid drops ineffective**

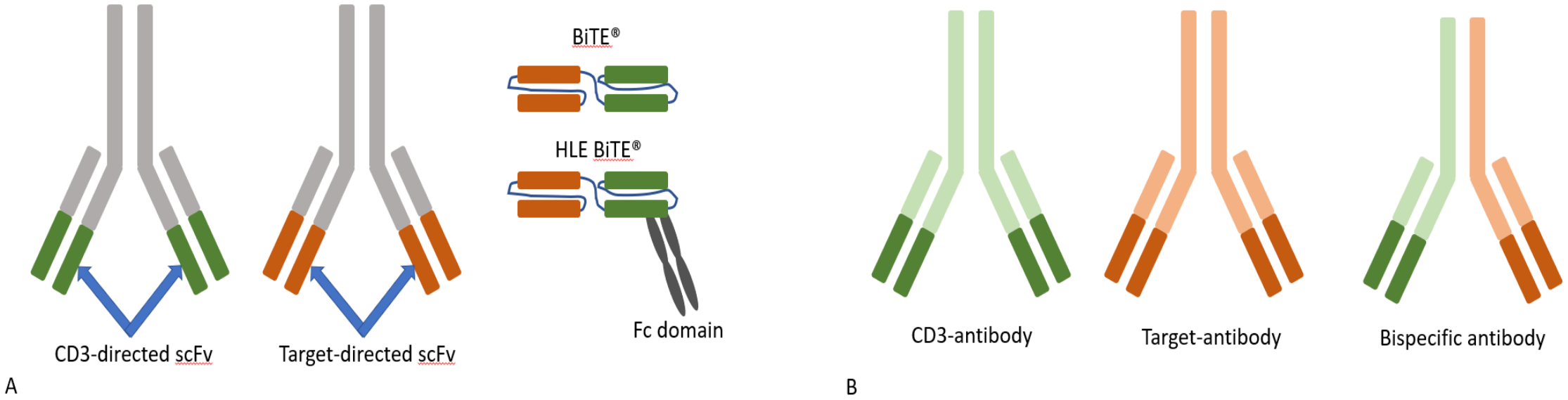
Adverse Reactions	N = 95	
	All Grades (%)	Grade 3-4 (%)
Eye disorders		
Keratopathy[a]	71	44
Decreased visual acuity[b]	53	28
Blurred vision[c]	22	4
Dry eyes[d]	14	1



Investigational Agents Promise New Treatment Paradigms for RRMM

Chapter 4

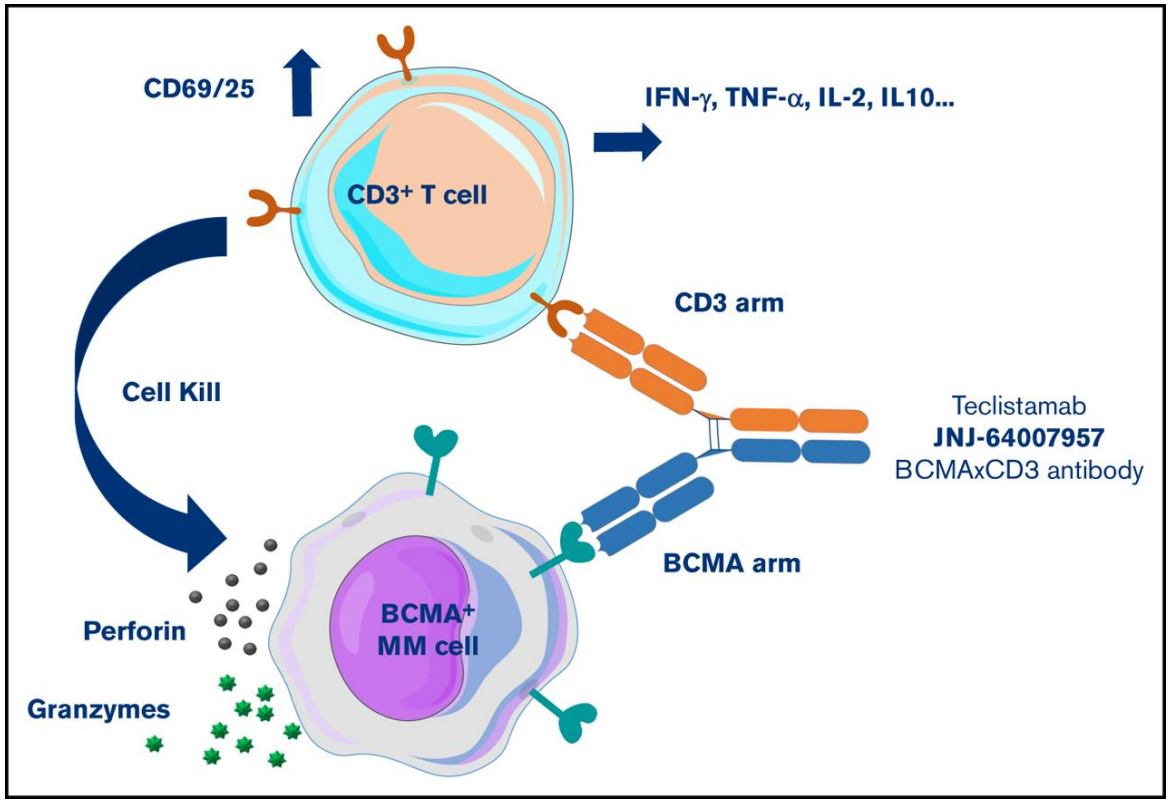
Bispecific Constructs Provide Off-the-Shelf T-cell Redirection to Combat Myeloma



Goldsmith et al. (2022)

Teclistamab – BCMA x CD3 DuoBody BSA

- Approximates CD3+ T-cells with BCMA+ MM cells
- Induces T-cell mediated cytotoxicity
- No BCMA agonization
- No null activity
  - Mutations in Fc region that reduce ADCC/ADCP

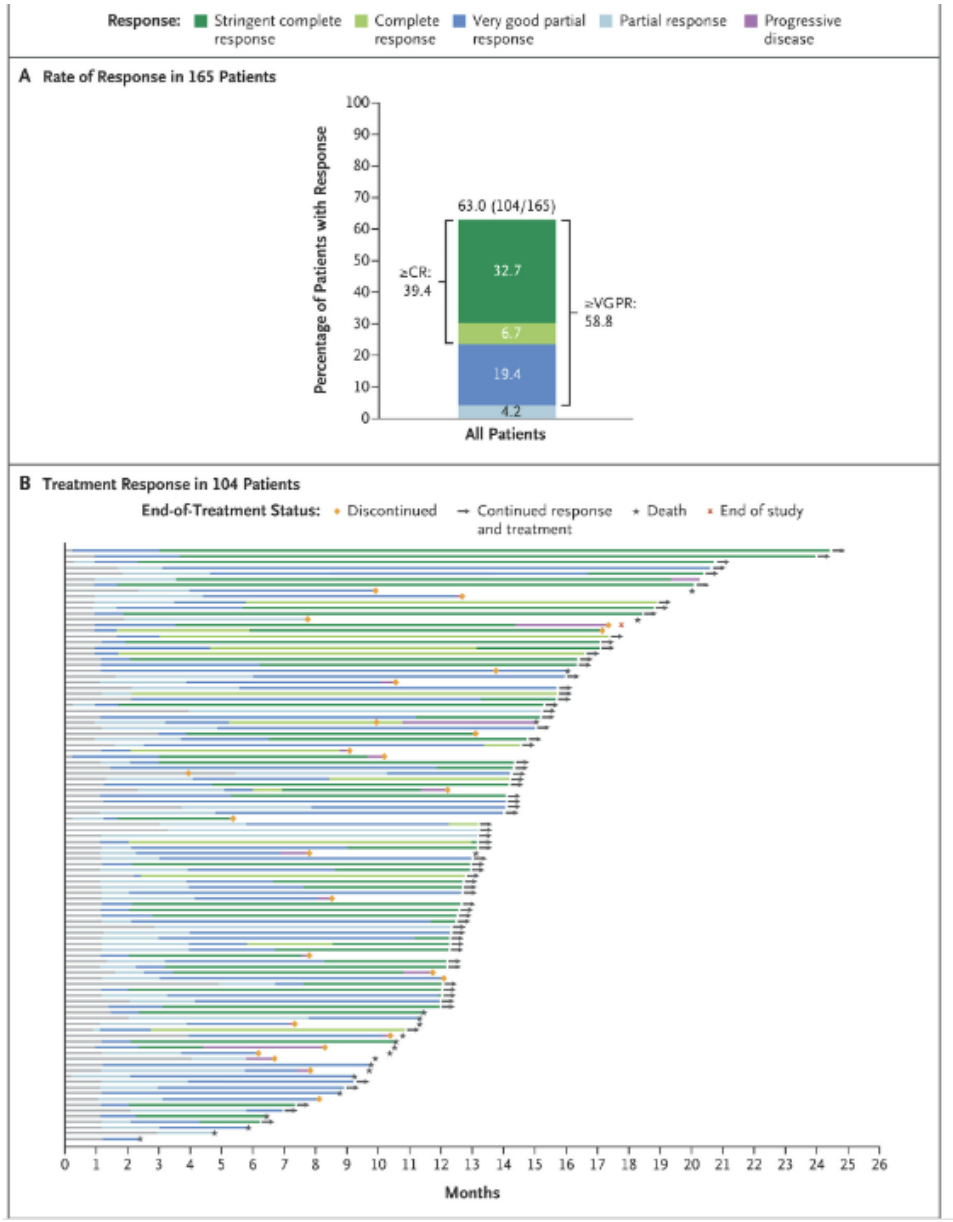


Pillarisetti et al. Blood Adv, 2020

MajesTEC-1 – Phase I/II trial in RRMM

- Dose escalation and expansion
  - Phase 1 (n=40), Phase 2 (n=125)
  - Median age 64
  - 17% extramedullary disease
  - 33.3% ECOG 0
  - 25.7% high-risk cyto
  - 100% triple-class refractory
  - **65% ORR, 6-month DOR of 90%**

- Safety
  - 94.5% Grade 3/4 AEs, mostly heme
  - 72.1% CRS, one grade 3 event
  - 14.5% ICANS, mostly grade 1-2
  - 76.4% infections, 44.8% grade 3-4



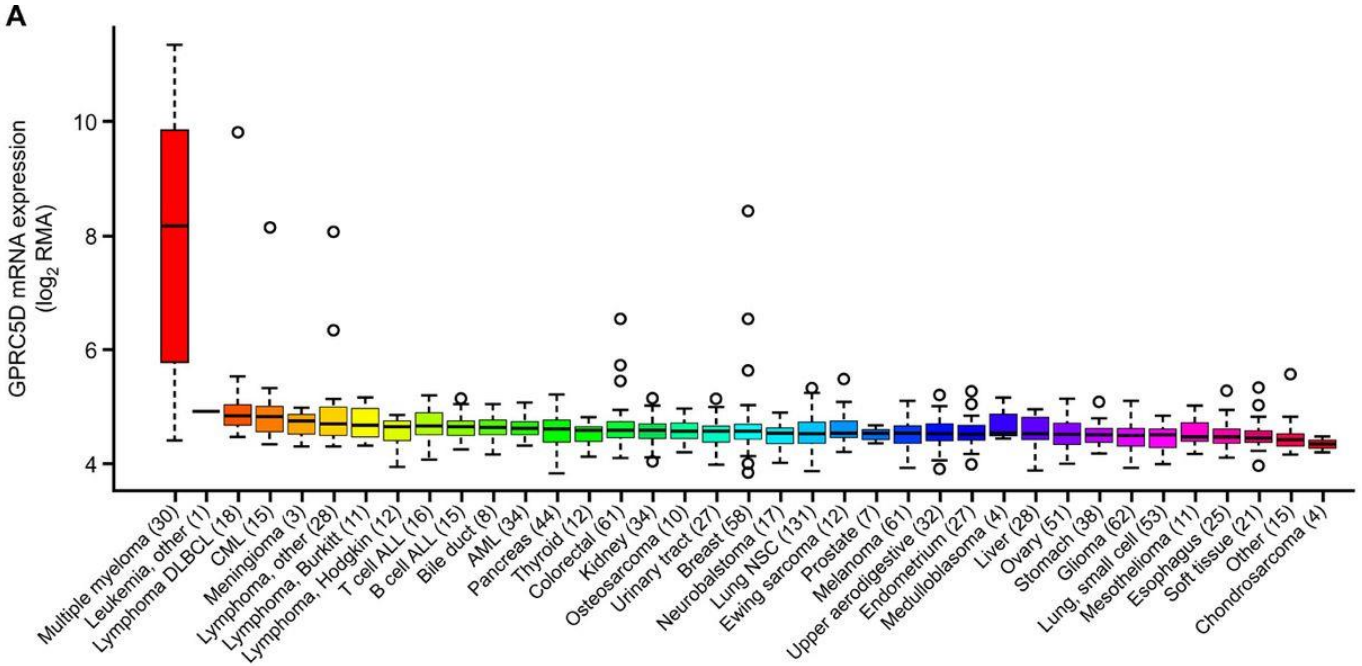
Moreau et al. (2022)

Agent	Trial Identification	Intervention	Phase	Median prior lines, n	Cycle 1 Dosing	Patients	ORR (%)	Time to Response (d)	DOR	CRS	ICANS	Infection
Teclistamab (JNJ-64007957)	NCT04557098 (MajesTEC-1) NCT03145181	Monotherapy	I/II	5 (2-15)	IV/SC Weekly	159	65%	28 (28-44.8)	NR; 6-month DOR 90%	67%	2.50%	60% (Grade 3: 22%)
	NCT04108195 (TRIMM-2)	Daratumumab + teclistamab ± pomalidomide; or daratumumab + talquetamab ± pomalidomide	I	5 (2-16)	SC Weekly	33	54.5%	28 (0-53.2)	NR	54.50%	0%	51.5% (Grade 3: 24.2%)
	NCT04586426	Talquetamab + teclistamab ± daratumumab	I	-	-	-	-	-	-	-	-	-
AMG-420 (BI 836909)	NCT02514239 NCT03836053	Monotherapy	I/II	3.5 (2-9)	IV Weekly	23	70%	-	23.5	38%	-	-
Pavurutamab (AMG-701)	NCT03287908 (ParadigMM-1B)	Monotherapy; or Pavurutamab + pomalidomide; or Pavurutamab + pomalidomide + dexamethasone	I/II	6 (2-25)	IV/SC Weekly	75	36%	28 (28-53.2)	3.8 (1.9-7.4)	61% (Grade 3: 7%)	-	17%
	NCT04998747 (ProxiMMity-1)	Monotherapy	I	-	-	-	-	-	-	-	-	-
CC-93269	NCT03486067	Monotherapy	I	5 (3-13)	IV/SC Weekly	30	43.3-88.9%	114.8 (112-366.8)	NR	77% (Grade 3: 3.33%)	-	30%
Elranatamab (PF-06863135)	NCT03269136 (MagnestisMM-1)	Monotherapy; or Elranatamab + dexamethasone; or Elranatamab + lenalidomide; or Elranatamab + pomalidomide	I/II	6 (2-15)	IV/SC Weekly	150	70-83%	22 (21-50)	NR	87.30%	-	-
	NCT04649359 (MagnestisMM-3	Monotherapy	II	-	-	-	-	-	-	-	-	-
	NCT05090566 (MagnestisMM-4)	Elranatamab + nirogacestat; or Elranatamab + lenalidomide + dexamethasone	II	-	-	-	-	-	-	-	-	-
Linvoseltamab (REGN-5458)	NCT03761108	Monotherapy	I/II	5 (2-17)	IV Weekly	68	73.30%	-	NR; ≥8-month DOR 92.1%	38%	-	-
TNB-383B (ABBV-383)	NCT03933735	Monotherapy	I	5 (1-15)	IV Every 3 Weeks	103	79%	-	-	52% (Grade 3: 3%)	-	28%

Goldsmith et al. (2022)

GPRC5D

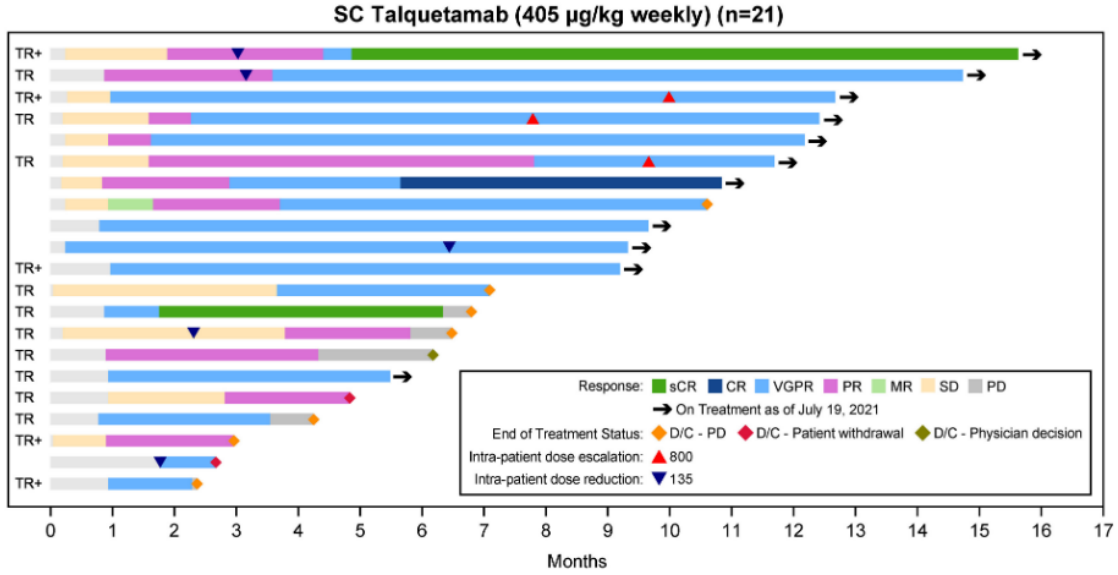
- Orphan G-coupled protein receptor
- Highly expressed in MM cells, also hair follicles and variably in salivary tissue
- Expression is independent of BCMA
- Bispecifics and CAR T in clinical development

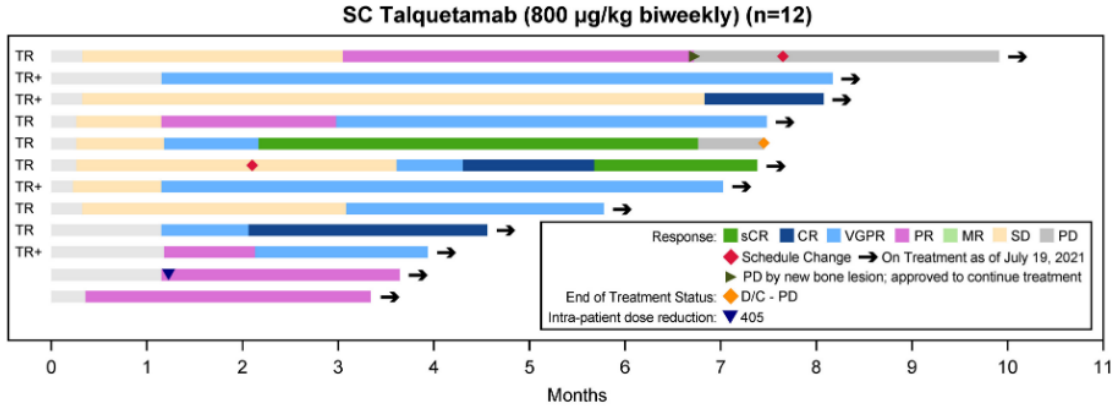


Smith et al. Sci Tran Med. 2019

MonumenTAL-1 – Talquetamab – GPRC5D x CD3 DuoBody

- Phase 1 trial
  - Pts with RRMM, refractory or intolerant to standard therapy
  - ~100% triple-class exposed, ~75% triple-class refractory
  - CRS~80%, mostly grade 1-2
  - Cytopenias common, reversible
  - Unique AEs
    - Skin exfoliation, dysgeusia
- Efficacy
  - ORR 70%, ≥VGPR 57%





+, penta-drug refractory; CR, complete response; D/C, discontinued; MR, minimal response; PD, progressive disease; PR, partial response; SC, subcutaneous; sCR, stringent complete response; SD, stable disease; TR, triple-class refractory; VGPR, very good partial response

Cevostomab – FcRH5 targeting bispecific antibody

- Results from ongoing Phase 1
  - Safety
    - CRS – 80%, mostly grade 1-2
    - ICANS – 13.1%, all grade 1-2
    - Infections – 18.8 grade 3-4
    - Most grade 3-4 toxicities were hematologic
  - Efficacy
    - ORR at 160mg dose 54.5%
    - ORR at 90mg dose 36.7%
    - Slightly lower in those with prior CAR T, BSA, ADC exposure previously
    - Estimated mDOR 15.6mo

Trudel et al. (2021)

CELMoDs overcome IMiD resistance

- Iberdomide
  - Enhanced tumoricidal and immunostimulatory effects
  - 20x greater affinity to CRBN than Len and Pom
  - 25-50% ORR in various combinations among heavily-pretreated patients
- Mezigdomide
  - Rapid degradation of Ikaros and Aiolos
  - 48% ORR in combination with dexamethasone
  - 75% ORR in combination with bortezomib
  - Responses regardless of IMiD refractoriness

Lonial et al. (2021); Richardson et al. (2021); Richardson et al. (2022)

Conclusions and Future Directions

- Multitude of standard and investigational options for RRMM
- Lack of head-to-head data and data on best sequence of therapies
- Choice of therapy influenced by prior therapy, comorbidities, pace of relapse, trial eligibility
- Early referral to and co-management with myeloma specialist important to expand options
- Novel agents will move toward frontline, requiring further innovation for those with RRMM

Thank you

- COH CME
- Dept. of Heme/HCT
- Patients and Families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