Penn Medicine

Multiple Myeloma: ASH 2022 Highlights

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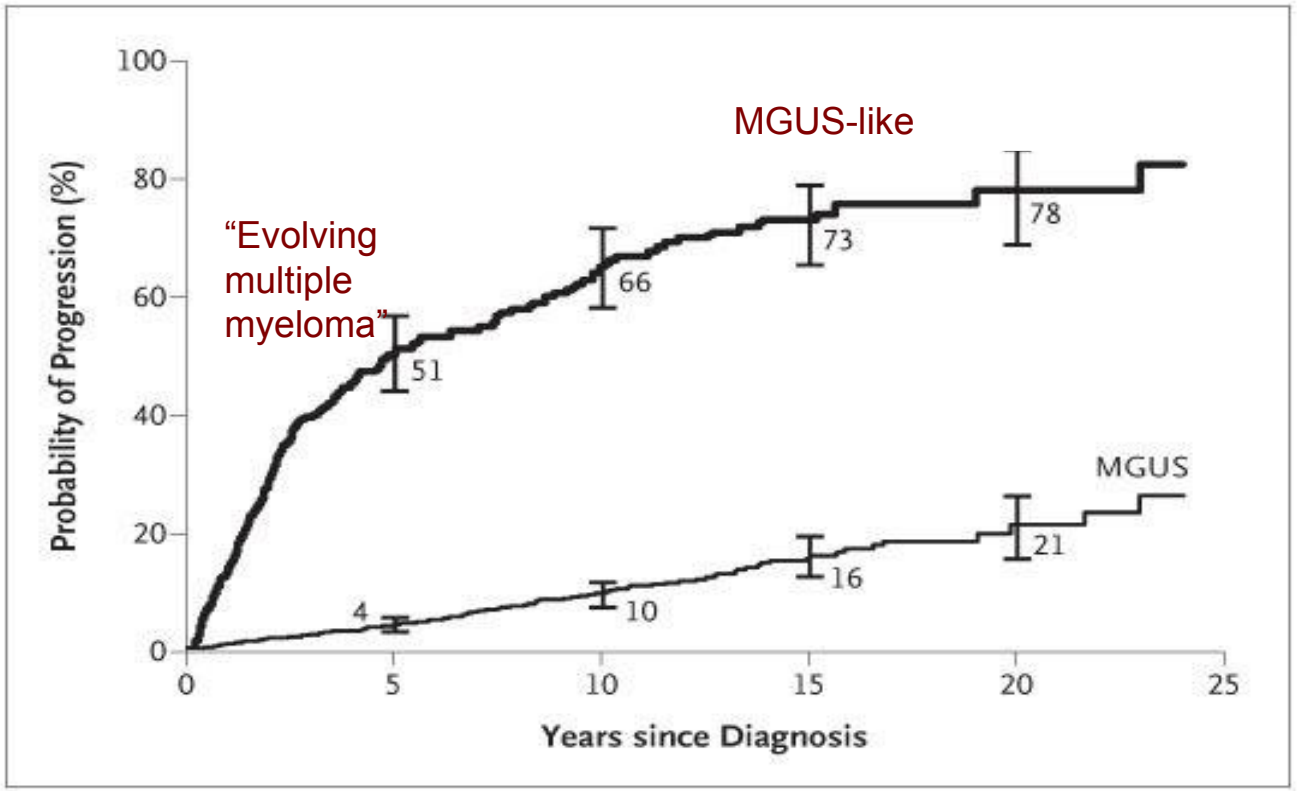
Questions:

1. Should we treat high-risk smoldering myeloma?
2. Should newly-diagnosed patients get 3 or 4 drugs as initial therapy?
3. Is there still a role for stem cell transplant in myeloma?
4. When is the best time to use CAR T cells for myeloma?
5. What's a bispecific antibody and how well do they work?
6. What else is new in therapy for myeloma?

Smoldering MM and MGUS have different risks of progression to MM

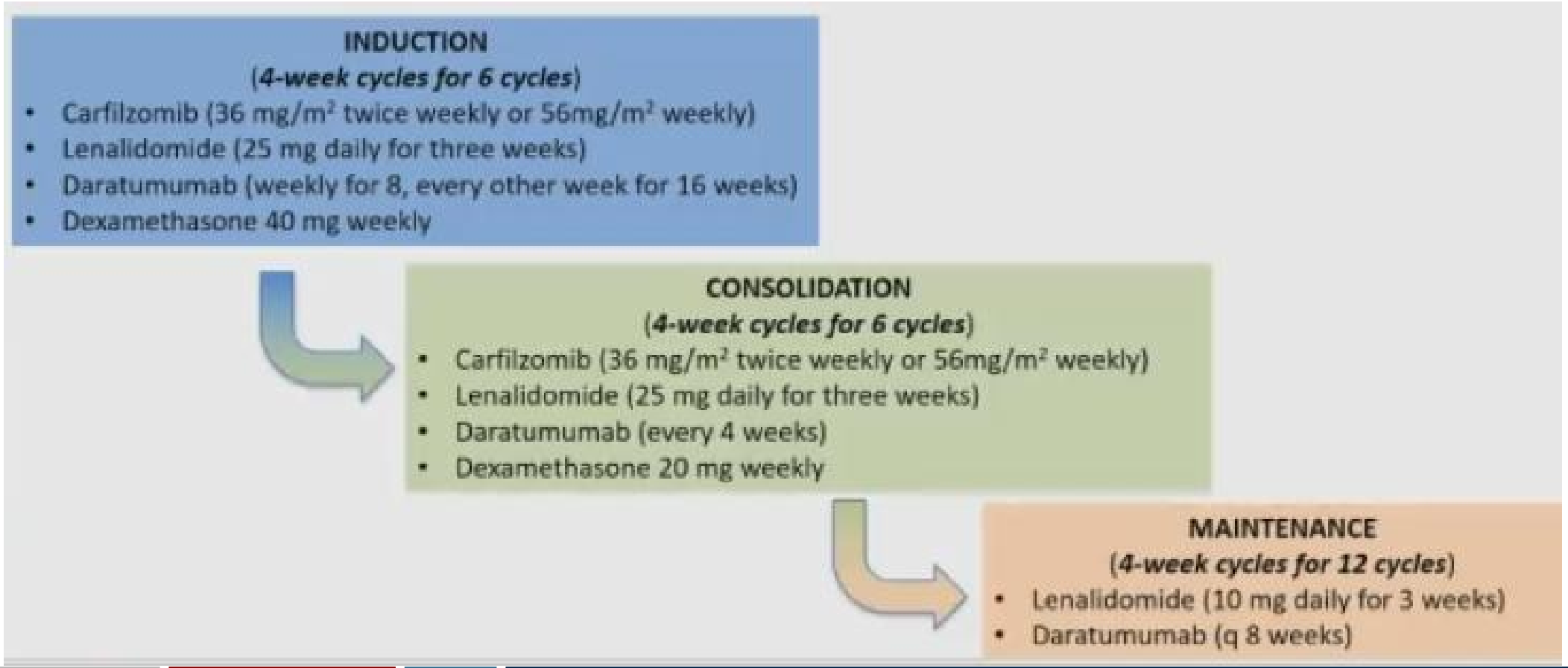
Smoldering multiple myeloma = heterogeneous group of patients with different disease biology



Kyle RA et al. NEJM 2007

ASCENT trial (NCT03289299)

- Inclusion criteria: High risk SMM per IMWG criteria: 2/20/20 > =2 points or score>= 9 using risk scoring system
- Primary endpoint of this trial = rate of confirmed sCR



Kumar, ASH 2022. Abstract #757

Results

Efficacy (n=87)

- Best ORR 97%
  - sCR 38%
  - ≥CR 64%
  - ≥VGPR 94%
- MRD negativity (10^{-5}) achieved in 73 (84%)
  - Median time to marrow negativity 6.6 months
- Survival (median f/up 26 months):
  - 4 patients have progressed (3 biochemically and 1 patient developed PCL 6 months after completing therapy)

Toxicity

- AE in 81 (92%) patients
- Grade 3 or higher:
  - 16 (18%) hematological
  - 44 (51%) non-hematological
- Dose reductions required for carfilzomib in 12 (14%), lenalidomide 12 (14%) and dexamethasone 14 (16%).
- 4 deaths: 2 Covid 19 (during consolidation), 1 RSV (consolidation), 1 disease progression (after completing therapy).

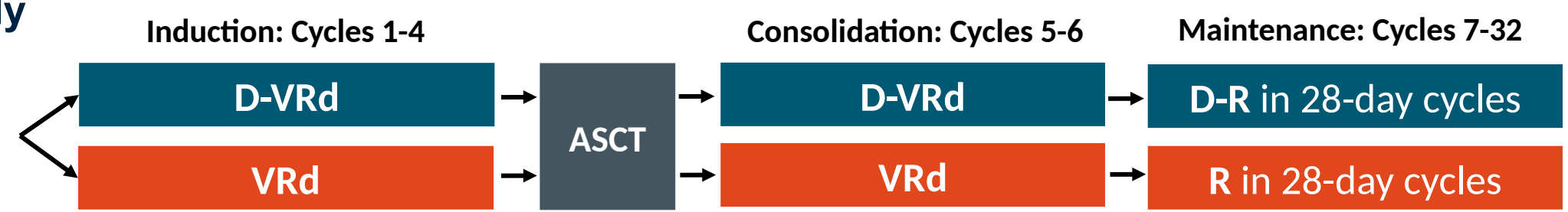
Kumar, ASH 2022. Abstract #757

Daratumumab + VRd

GRIFFIN study

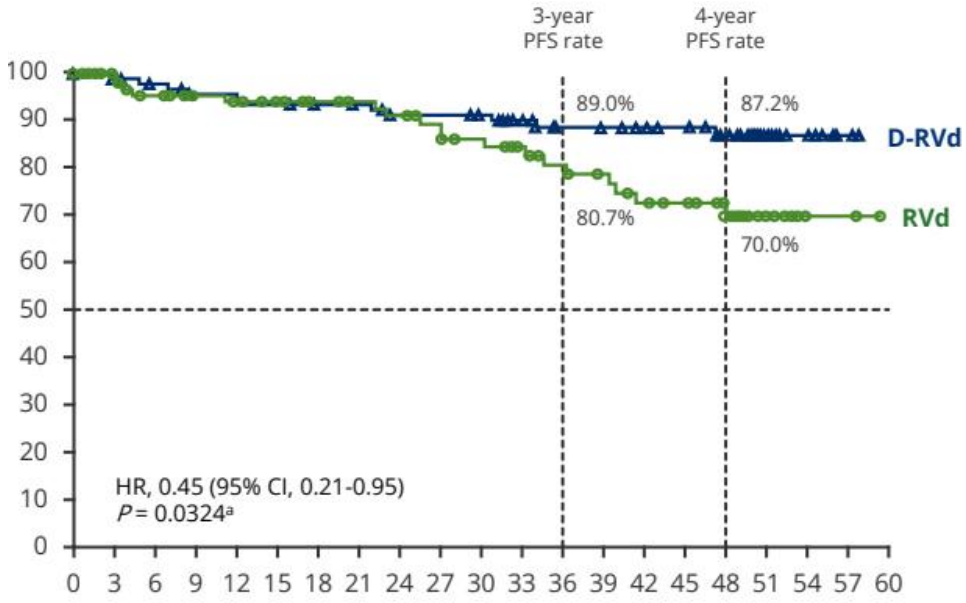
Primary endpoint: sCR by end of consolidation
Secondary endpoints: MRD, ORR, PFS, OS

Newly diagnosed MM, transplant-eligible N=207)

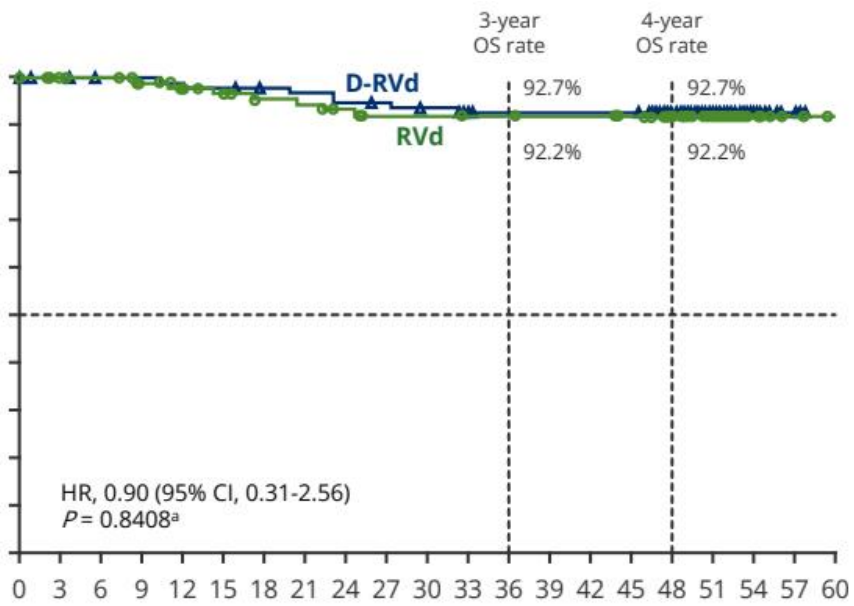


	D-VRd	VRd
ORR post ind.	98%	92%
sCR post cons.	42%	32%
sCR end of study (p=0.0005)	67%	48%

Progression-free Survival



Overall Survival



Sborov et al., IMS 2022

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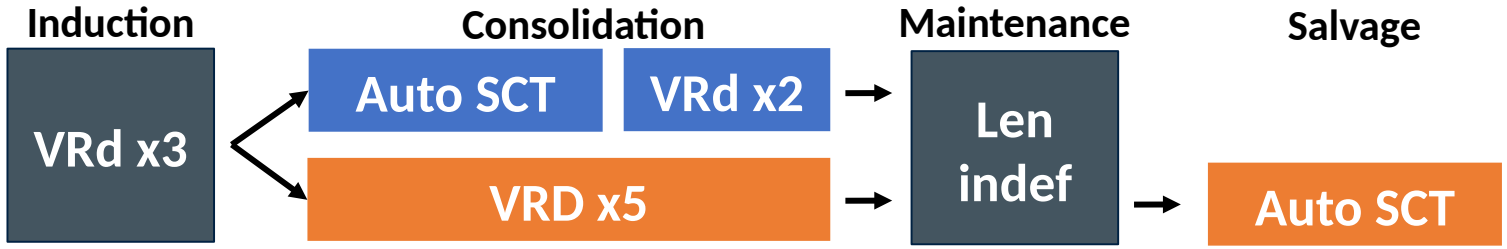
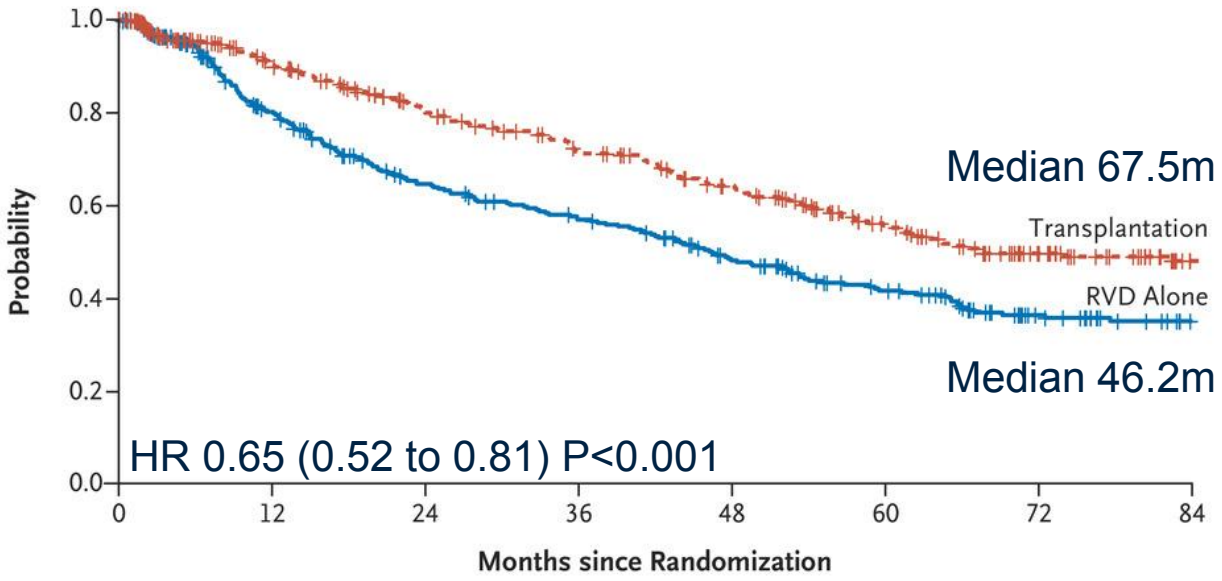
High-dose melphalan + auto SCT consolidation
DFCI-09 trial

Newly diagnosed MM, transplant-elig. N=729

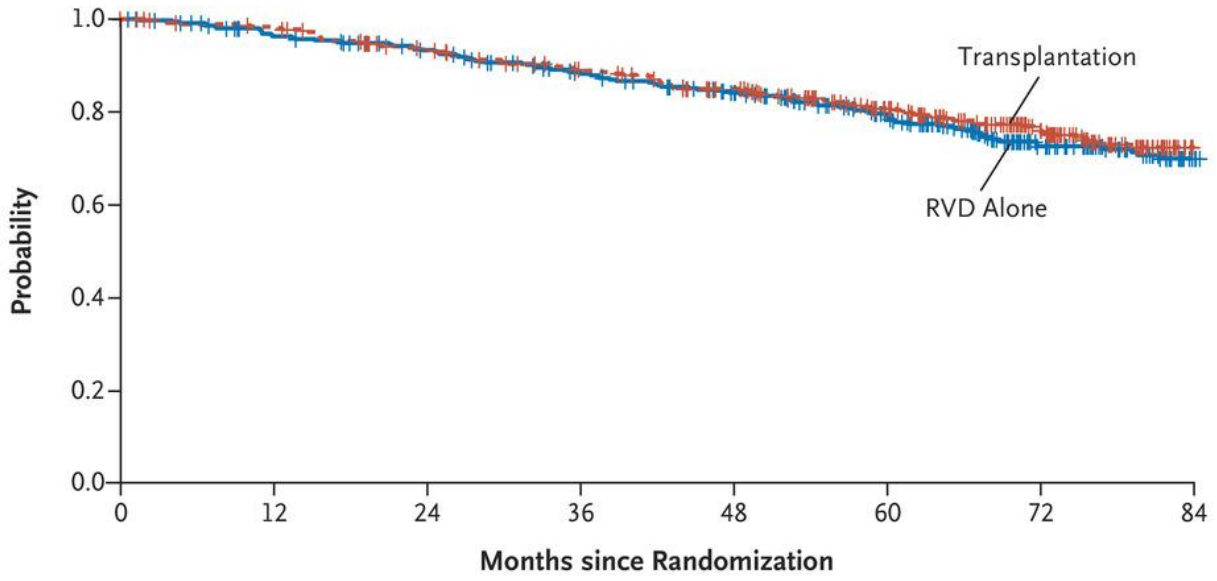


35% in delayed SCT arm who received salvage therapy eventually underwent auto-SCT

Progression-free Survival



Overall Survival



Median follow-up 76 months

Richardson et al., NEJM 2022, DOI: 10.1056/NEJMoa2204925

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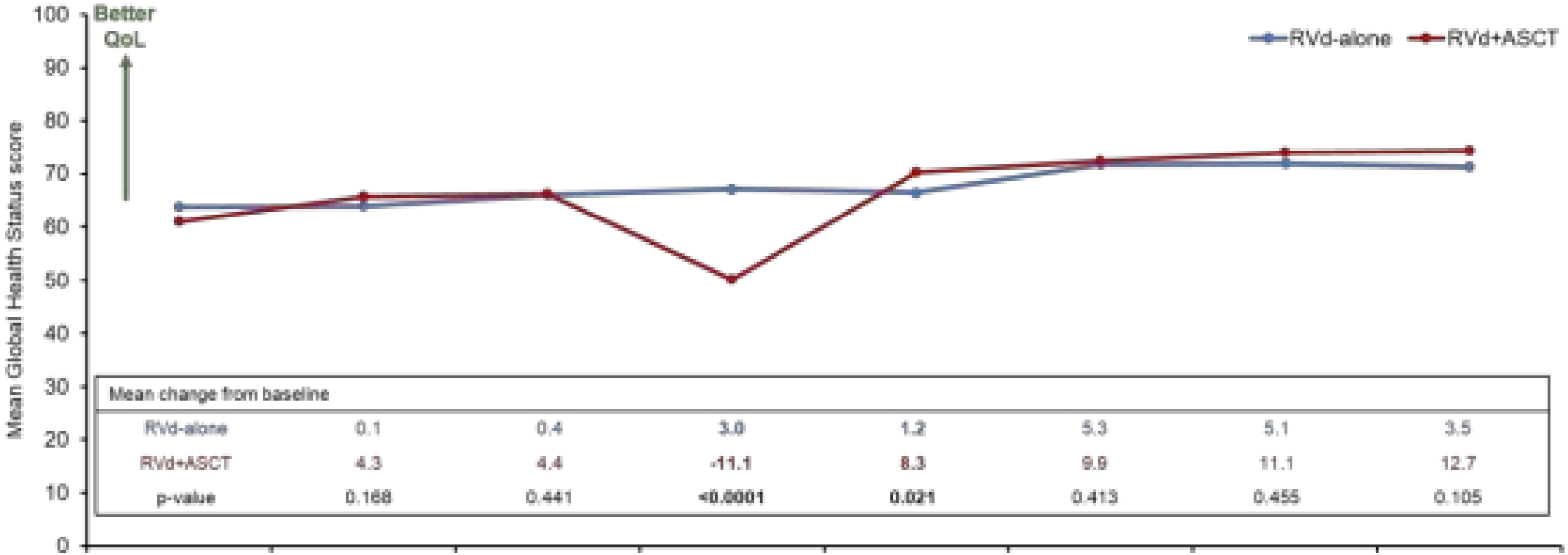
No difference in long-term quality of life



Mean change from baseline							
RVd-alone	0.1	0.4	3.0	1.2	5.3	5.1	3.5
RVd+ASCT	4.3	4.4	11.1	8.3	9.9	11.1	12.7
p-value	0.168	0.441	<0.0001	0.021	0.413	0.455	0.105

Patients, N	Baseline	Cycle 2	Pre-mobilization	RVd cycle 5 / post-ASCT	RVd cycle 8 / RVd cycle 5	Maintenance	2 years	3 years
RVd-alone	309	258	231	239	224	186	107	89
RVd+ASCT	322	282	235	170	206	191	128	99

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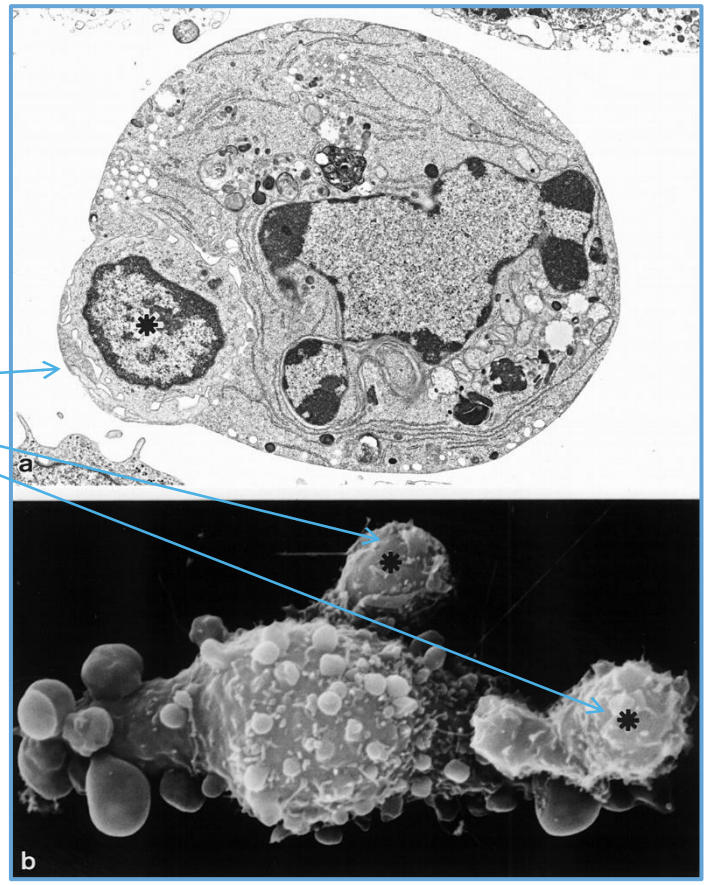
T cells can recognize and kill cancer cells

T cell



Groscurth P, Filgueira L. *Physiology*. 1998;13:17-21.

BUT…in patients

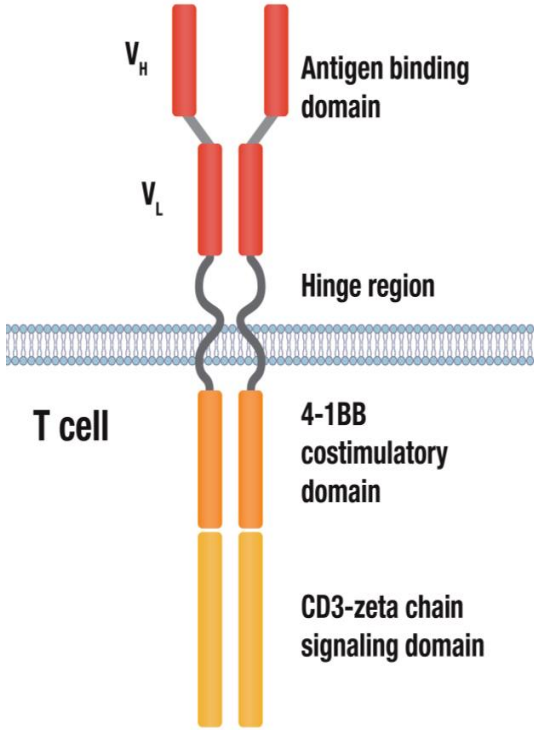
- **Cancer cells learn to evade the T cells**
- **T cells lose their activity over time**

HOW TO OVERCOME THIS?

- **Checkpoint blockade**
- **Cellular therapy**
- **Bispecific antibodies/T cell engagers (BiTEs)**

CAR (Chimeric Antigen Receptor)

Chimera

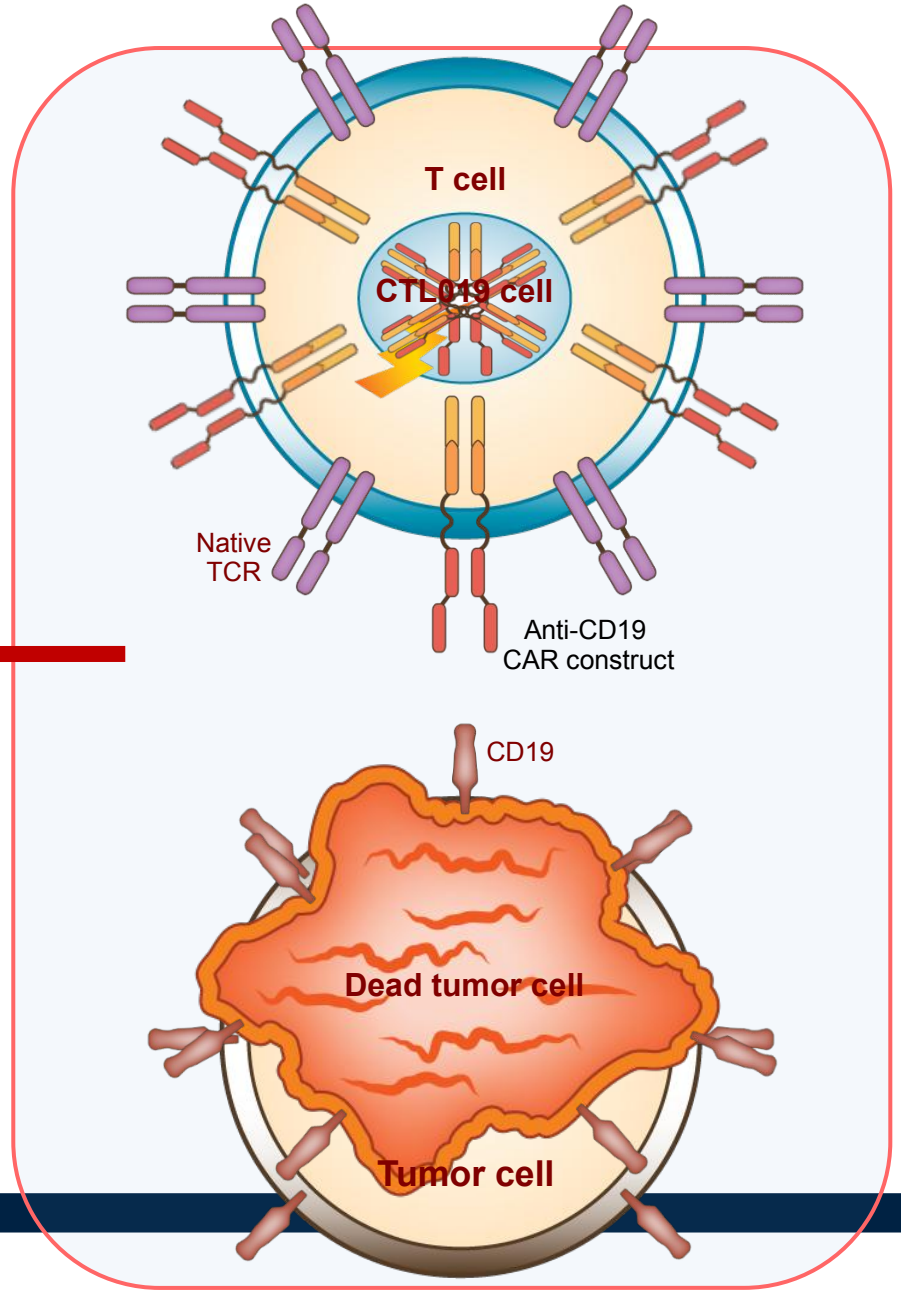


- Combines recognition domain of antibody with signaling domain of T cell
- Uses gene transfer (eg. lentiviral vector) to stably express CAR on T cells → allows recognition of cancer cell
- Addition of co-stimulatory domains (CD28, 4-1BB) augments proliferation and survival of the T cells

Building CAR T cells

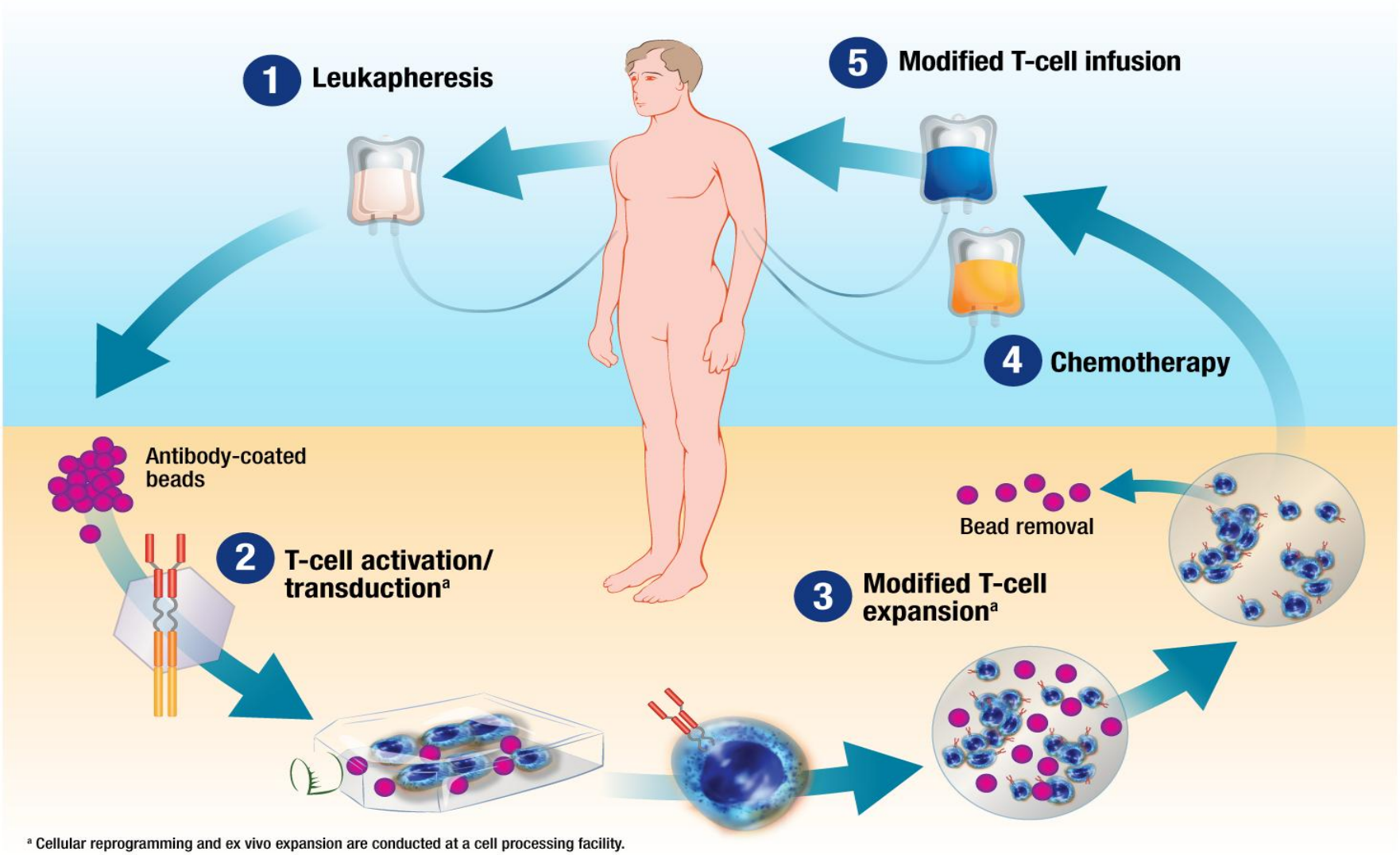
1. **Cytotoxicity**
2. **Cytokine production**
3. **Long-term persistence**

“Living drug”



Courtesy of D. Porter

Overview of CAR T cell therapy



Courtesy of D. Porter

CD19-specific CAR T cells for B-cell cancers

- Acute lymphoblastic leukemia (ALL)
- Chronic lymphocytic leukemia (CLL)
- B-cell Non-Hodgkin lymphomas

- Initial trials reported in 2010-2011
  - Memorial Sloan Kettering Cancer Center/New York
  - University of Pennsylvania/Philadelphia
  - National Institutes of Health/Bethesda
  - Fred Hutchinson Cancer Center/Seattle

- Dramatic responses seen in highly-refractory patients
  - Can be durable, >10 years in some earliest-treated patients

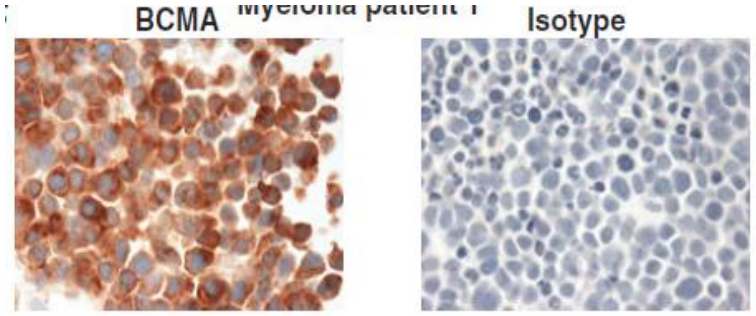
https://vimeo.com/54668275

4 FDA approved CD19 CAR T products:
Kymriah
Yescarta
Tecartus
Breyanzi

www.emilywhiteheadfoundation.org

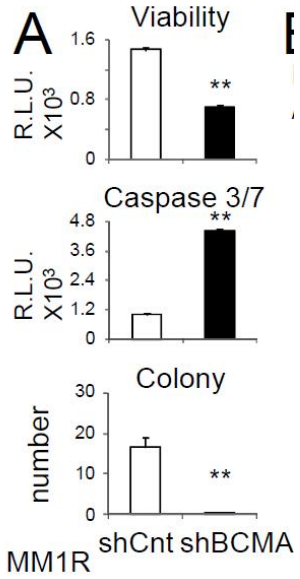
BCMA (B-cell Maturation Antigen): a new target for myeloma

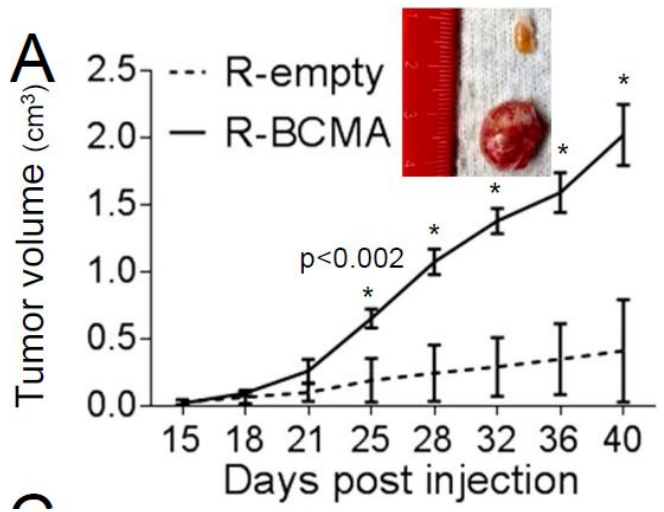
- Expressed on normal plasma cells
- Highly expressed on myeloma cells
- Soluble BCMA in patient serum



- **Promotes MM growth and survival**

- **Multiple approaches targeting BCMA**
  - Antibody-drug conjugates
  - Bispecific Antibodies
  - CAR T cells





Myeloma immunotherapy in 2023

Aug. 2020

FDA grant[illegible]ccelerate[illegible]pproval to belantam[illegible]lotin[illegible]r multiple

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On August 5, 2020, [illegible]ted approval to belantamab mafodo[illegible]oSmi[illegible]nts with relapsed or refractory multiple m[illegible]ve received at[illegible]erapies, including an anti-CD38 monoclonal anti[illegible] proteasome inhibitor,[illegible]mmunomodulatory agent..

Mar. 2021

FDA Approves First Cell-Based Gene Therapy for Adult Patients with Multiple Myeloma

Share **Ide-cel** Print

For Immediate Release: March 27, 2021

The U.S. Food and Drug Administration approved Abecma (idecabtagene vicleucel), a cell-based gene therapy to treat adult patients with multiple myeloma who have not responded to, or whose disease has returned after, at least four prior lines (different types) of therapy. Abecma is the first cell-based gene therapy approved by the FDA for the treatment of multiple myeloma.

Feb. 2022

U.S. FDA Approves CARVYKTI™ (ciltacabtagene autoleucel), Janssen's First Cell Therapy, a BCMA-Directed CAR-T Immunotherapy for the Treatment of Patients with Relapsed or Refractory Multiple Myeloma

In the pivotal clinical study, 98 percent of patients with relapsed or refractory multiple myeloma responded to a one-time treatment with ciltacabtagene autoleucel and 78 percent of patients who responded experienced a stringent complete response

HORSHAM, Pa., February 28, 2022 – The Janssen Pharmaceutical Companies of Johnson & Johnson announced today the U.S. Food and Drug Administration (FDA) has approved CARVYKTI™ (ciltacabtagene autoleucel; cilta-cel) for the treatment of adults with relapsed or refractory multiple myeloma (RRMM) after

Oct. 2022

FDA approves teclistamab-cqyv for relapsed or refractory multiple myeloma

Share Tweet LinkedIn Email Print

On October 25, 2022, the Food and Drug Administration granted accelerated approval to teclistamab-cqyv (Tecvayli, Janssen Biotech, Inc.), the first bispecific B-cell maturation

Late 2023

Talquetamab??
Elranatamab??

- >25 unique BCMA-targeted therapies have entered trials
  - Bispecific Ab, mAb, ADC, auto and allo CAR-T, CAR-NK

Efficacy and Safety of Cilta-cel in Patients With Progressive Multiple Myeloma after Exposure to Non-cellular Anti-BCMA Immunotherapy

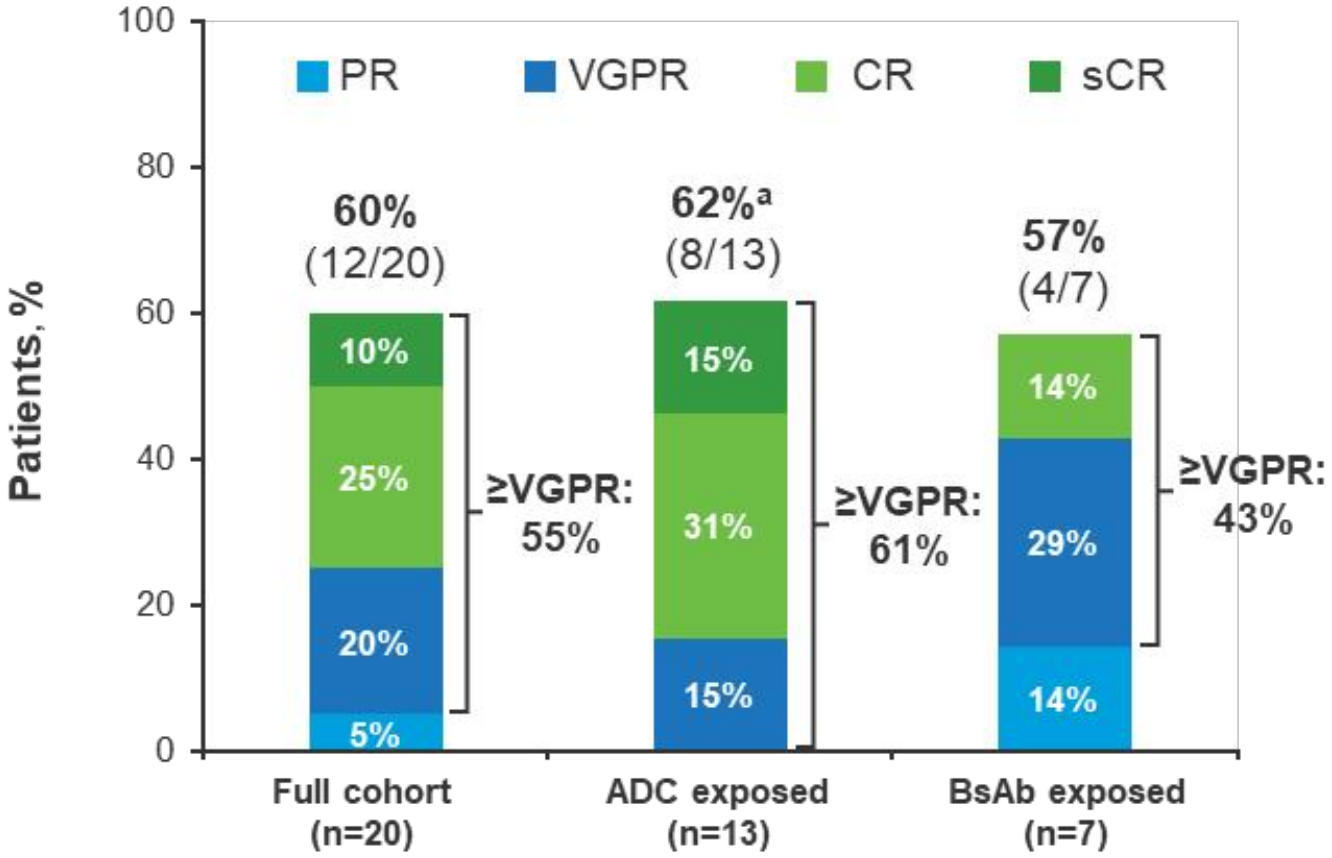
Adam D Cohen[1], María-Victoria Mateos[2], Yael C Cohen[3], Paula Rodriguez-Otero[4], Bruno Paiva[4], Niels WCJ van de Donk[5], Thomas G. Martin[6], Attaya Suvannasankha[7], Deepu Madduri[8]*, Christina Corsale[9], Jordan M Schecter[9], Kevin C De Braganca[9], Carolyn C Jackson[9], Helen Varsos[9], William Deraedt[10], Tito Roccia[11], Pankaj Mistry[12], Xiaoying Xu[9], Katherine Li[13], Enrique Zudaire[13], Muhammad Akram[14], Lida Pacaud[14], Irit Avivi[3], Jesús San-Miguel[4]

[1]Abramson Cancer Center, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA; [2]Hospital Clinico Universitario de Salamanca, Salamanca, Spain; [3]Tel-Aviv Sourasky (Ichilov) Medical Center, and Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel; [4]Clinica Universidad de Navarra, CCUN, Centro de Investigacion Medica Aplicada (CIMA), Instituto de Investigacion Sanitaria de Navarra (IDISNA, CIBERONC), CIBER-ONC CB16/12/00369, Pamplona, Spain; ; [5]Amsterdam University Medical Center, Vrije Universiteit Amsterdam, Amsterdam, Netherlands; [6]UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, CA, USA; [7]Indiana University Simon Cancer Center, Indiana University and Roudebush VAMC, Indianapolis, IN, USA; [8]Mount Sinai Medical Center, New York, NY, USA; [9]Janssen Research & Development, Raritan, NJ, USA; [10]Janssen Research & Development, Beerse, Belgium; [11]Janssen Global Services, Raritan, NJ, USA; [12]Janssen Research & Development, High Wycombe, UK; [13]Janssen Research & Development, Spring House, PA, USA; [14]Legend Biotech USA Inc., Piscataway, NJ, USA

*Currently an employee of Janssen

Presented at the 64th American Society of Hematology (ASH) Annual Meeting; December 10–13, 2022; New Orleans, LA, USA.

Cilta-cel after prior BCMA therapy: CARTITUDE-2 cohort C



Median 8 priors
55% penta-refractory

Median DOR and PFS			
Estimate, months (95% CI)	Full cohort (N=20)	ADC exposed (N=13)	BsAb exposed (N=7)
DOR	12.3 (7.2–NE)	13.3 (7.2–NE)	8.2 (4.4–NE)
PFS	9.1 (1.5–13.2)	9.5 (1.0–15.2)	5.3 (0.6–NE)

Cohen et al, ASH 2022, #2028

Integration with other MM therapies: Best time to use CAR T?

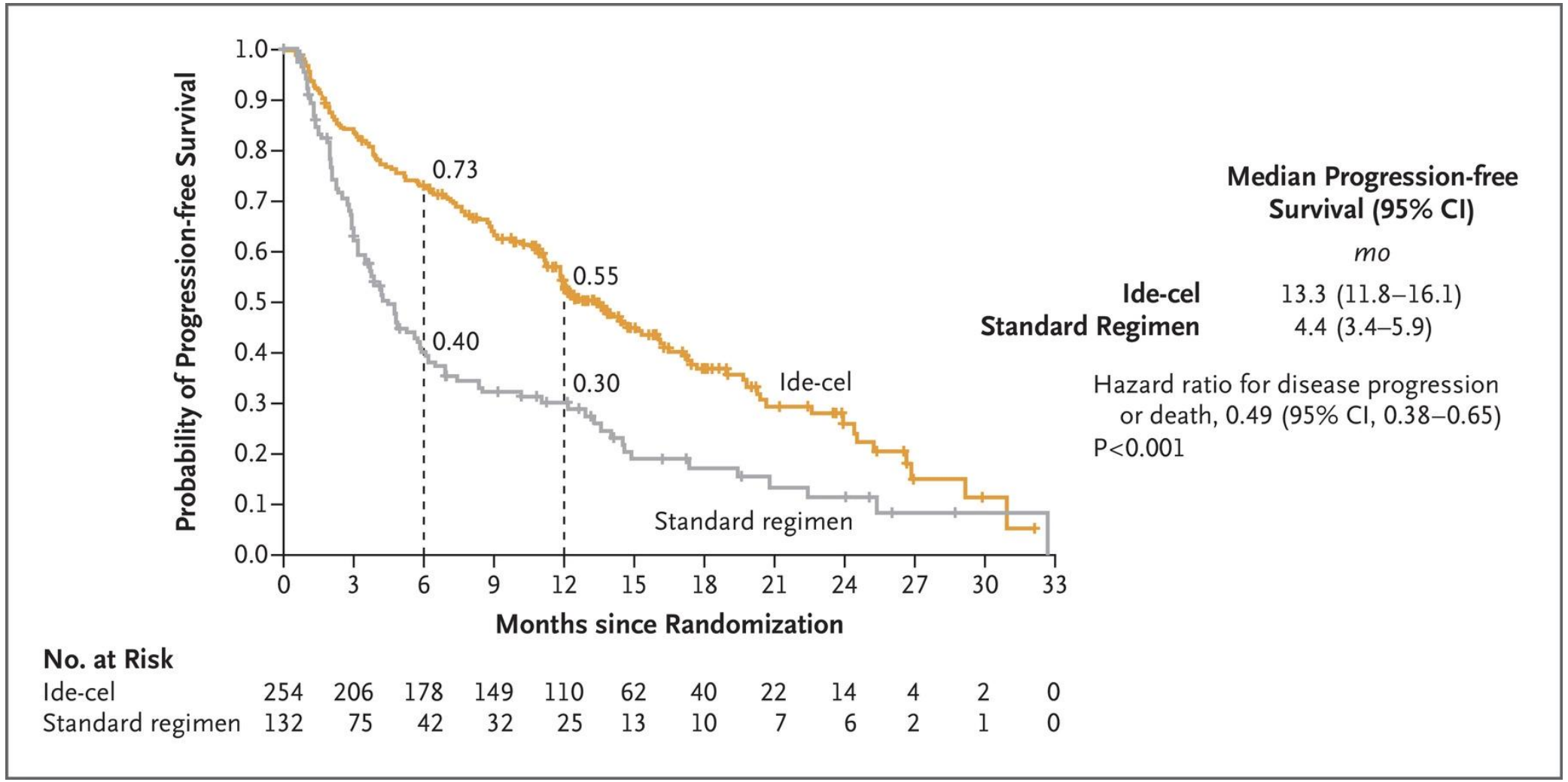
Ide-cel

- KarMMa-2
  - Phase 2 study in r/r MM and high-risk MM (relapse early after induction)
- KarMMa-3
  - Phase 3 randomized study of ide-cel vs SOC in r/r MM **(2-4 priors)**
- KarMMa-4
  - Phase 1 study in newly dx'd high-risk MM
- KarMMa-7
  - Phase 1/2 combo study in r/r MM
- BMT-CTN 1902
  - Phase 2 in MM pts with <CR s/p autoSCT + 6 months Len maint.

Cilta-cel

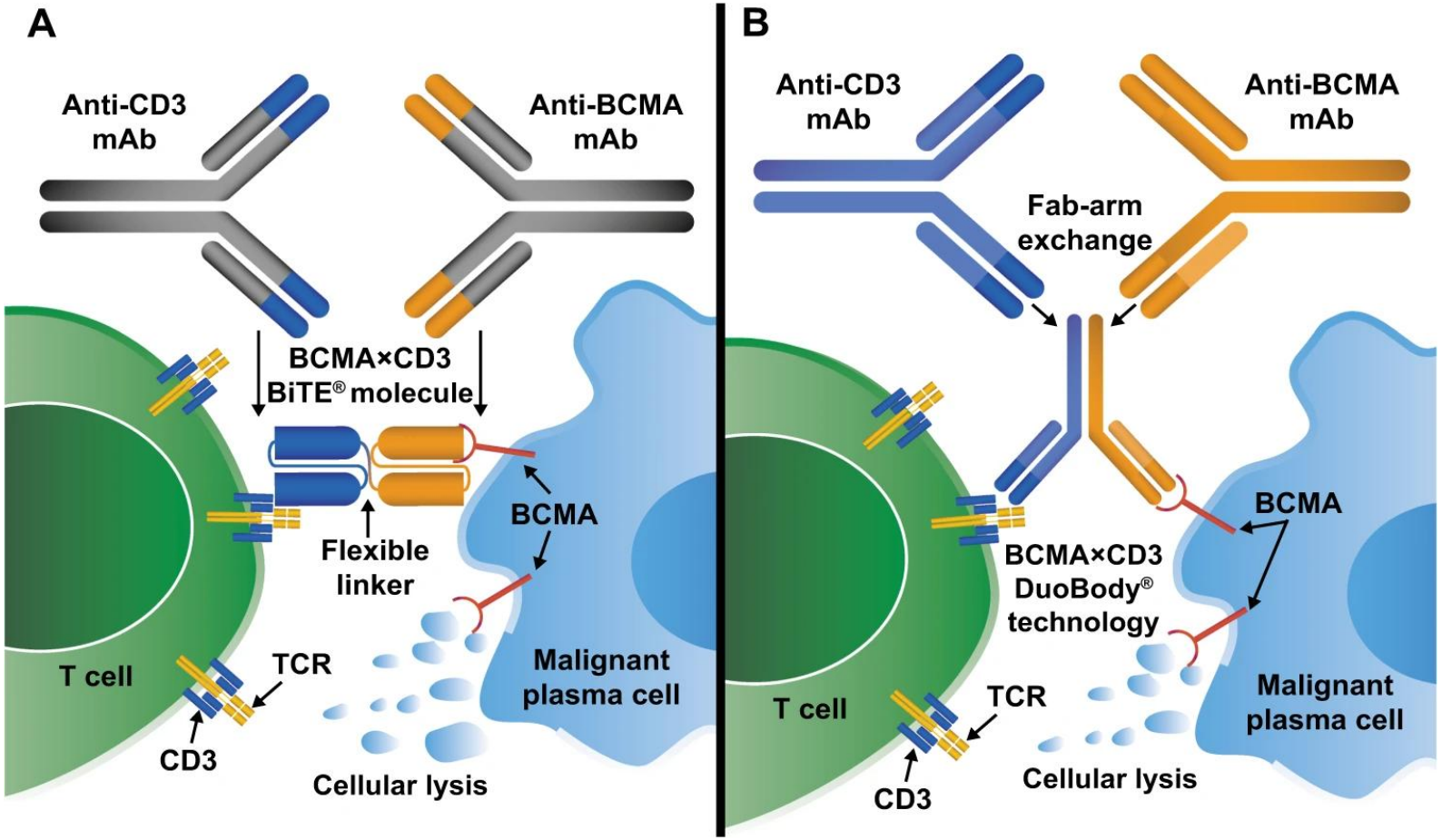
- CARTITUDE-2
  - Phase 2 study in multiple cohorts
    - Early relapse, post-induction
- CARTITUDE-4
  - Phase 3 randomized study of cilta-cel vs SOC in r/r MM **(1-3 priors)**
- CARTITUDE-5
  - Phase 3 randomized study of cilta-cel vs Rd maint after VRd induction for NDMM
- CARTITUDE-6
  - Phase 3 randomized study of cilta-cel vs autoSCT after D-VRd induction for NDMM

Ide-cel vs Standard regimens in MM pts with 2-4 prior therapies



Rodriguez-Otero et al, NEJM 2023

Bispecific Antibodies/T-cell Engagers for Myeloma



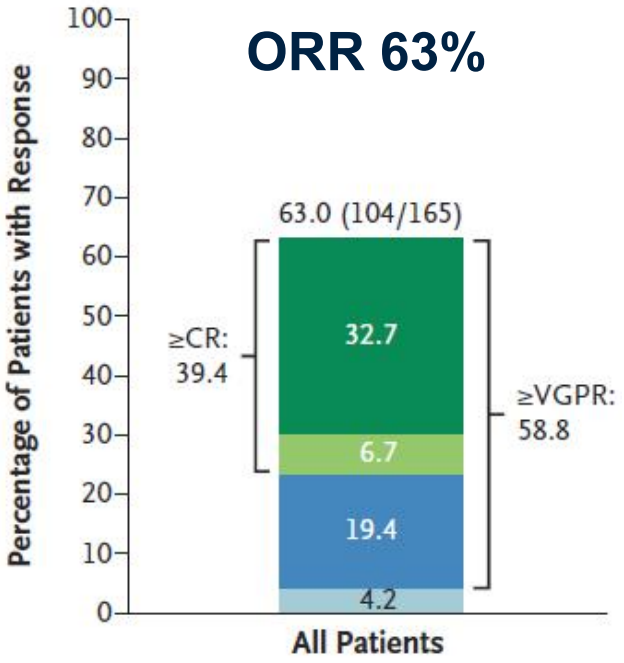
AMG420

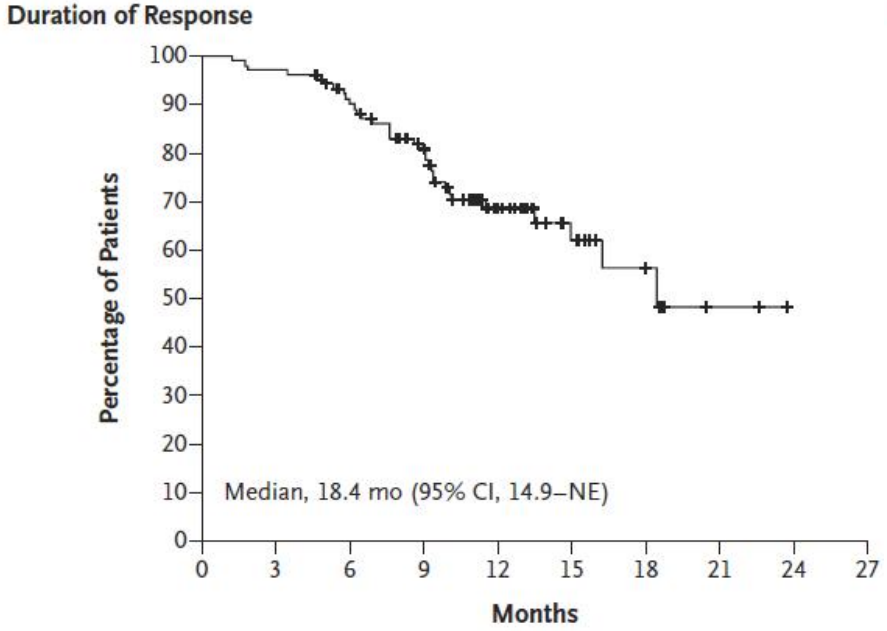
Target	
BCMA	AMG701 (Parvurutumab) PF-06863135 (Elranatamab) JNJ-64007957 (Teclistamab) CC-93269 (Alnuctumab) REGN5458 (Linvoseltamab) HPN217 ABBV-383/TNB-383B AFM26
FcRH5	BFCR4350A (Cevostamab)
CD38	ISB-1342 AMG424
GPRC5D	JNJ-64407564 (Talquetamab) RG6234

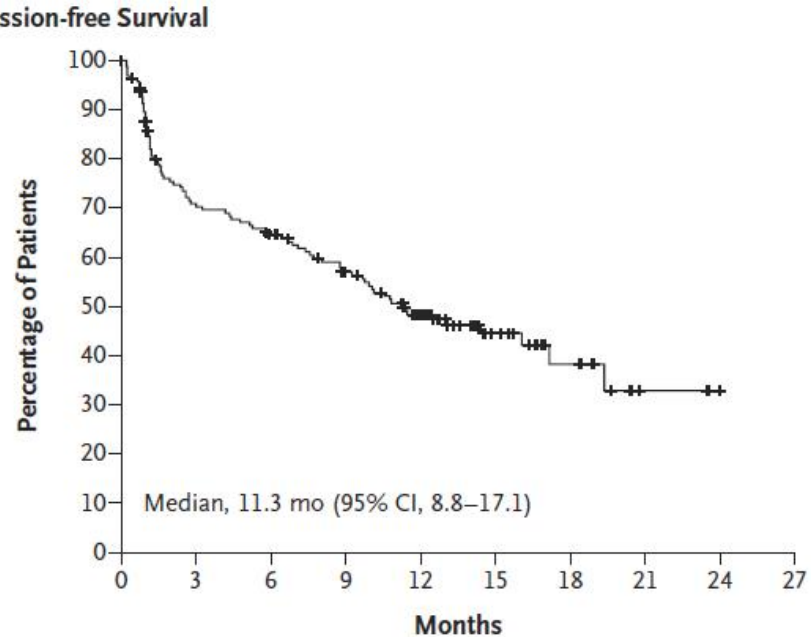
Shah N et al, Leukemia 2020

Teclistamab FDA approved for rel/ref MM

- 4 prior lines, including PI, IMID and anti-CD38 mAb
- MAJESTIC-1 phase 2 trial. n=165, med 5 priors, 77% TCR, 30% penta-drug ref (PDR)
- 1.5 mg/kg SQ weekly until PD or intolerance







Median OS = 18.3 mos

Moreau et al, NEJM 2022

Teclistamab toxicities and real world considerations

Table 2. Adverse Events in 165 Patients (Safety Population).*

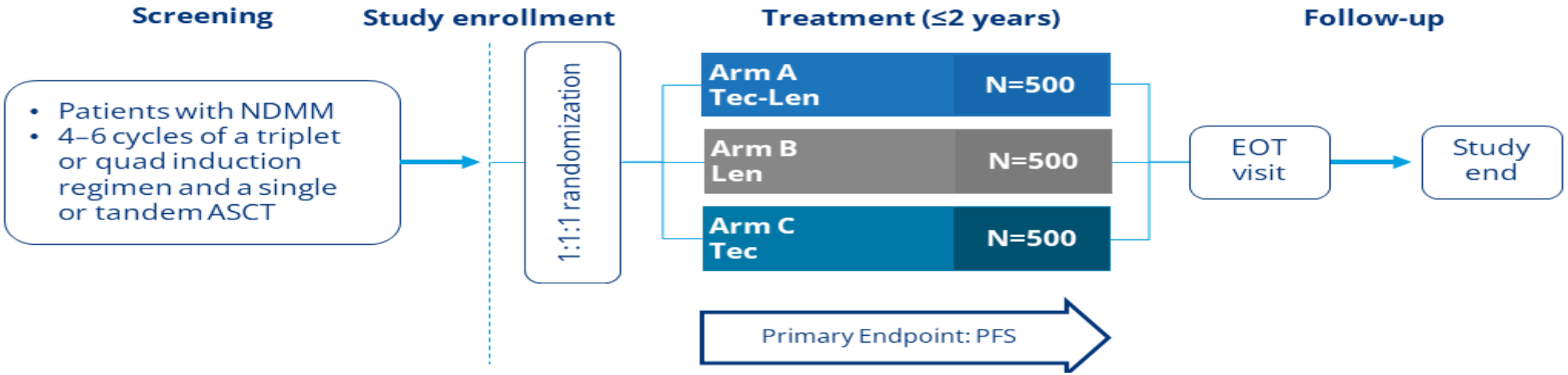
Event	Any Grade	Grade 3 or 4
	no. of patients (%)	
Any adverse event	165 (100)	156 (94.5)
Hematologic		
Neutropenia	117 (70.9)	106 (64.2)
Anemia	86 (52.1)	61 (37.0)
Thrombocytopenia	66 (40.0)	35 (21.2)
Lymphopenia	57 (34.5)	54 (32.7)
Leukopenia	29 (17.6)	12 (7.3)
Nonhematologic		
Diarrhea	47 (28.5)	6 (3.6)
Fatigue	46 (27.9)	4 (2.4)
Nausea	45 (27.3)	1 (0.6)
Injection-site erythema	43 (26.1)	0
Pyrexia	45 (27.3)	1 (0.6)
Headache	39 (23.6)	1 (0.6)
Arthralgia	36 (21.8)	1 (0.6)
Constipation	34 (20.6)	0
Cough	33 (20.0)	0
Pneumonia	30 (18.2)	21 (12.7)
Covid-19	29 (17.6)	20 (12.1)
Bone pain	29 (17.6)	6 (3.6)
Back pain	27 (16.4)	4 (2.4)
Cytokine release syndrome†	119 (72.1)	1 (0.6)
Neurotoxic event	24 (14.5)	1 (0.6)

- Step-up dosing to mitigate severe CRS
  - Days 1, 3, 5 (hospitalization 7-9 days)
  - 36% got Toci, 9% steroids
- Be vigilant for infections (76% incidence, 45% grade 3/4)
  - CMV, EBV, adenovirus, PJP, JC virus (PML)
  - Prophylax for VZV, PJP
  - IVIG for IgG <400
  - COVID preventive measures
  - GCSF for neutropenia
- Consider q2wk dosing after best response
  - Trial allowed q2wk dosing if in CR after 6 months
- May need repeat step up dosing after long interruption
  - Penn plan: outpatient single dose of 0.3 mg/kg → 1.5 mg/kg weekly

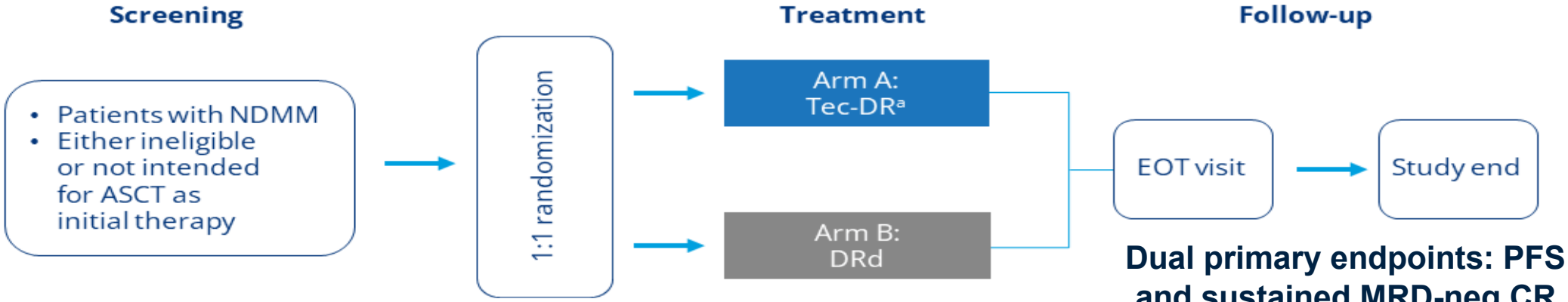
Moreau et al, NEJM 2022

Other teclistamab studies

MAJESTIC-4



MAJESTIC-7

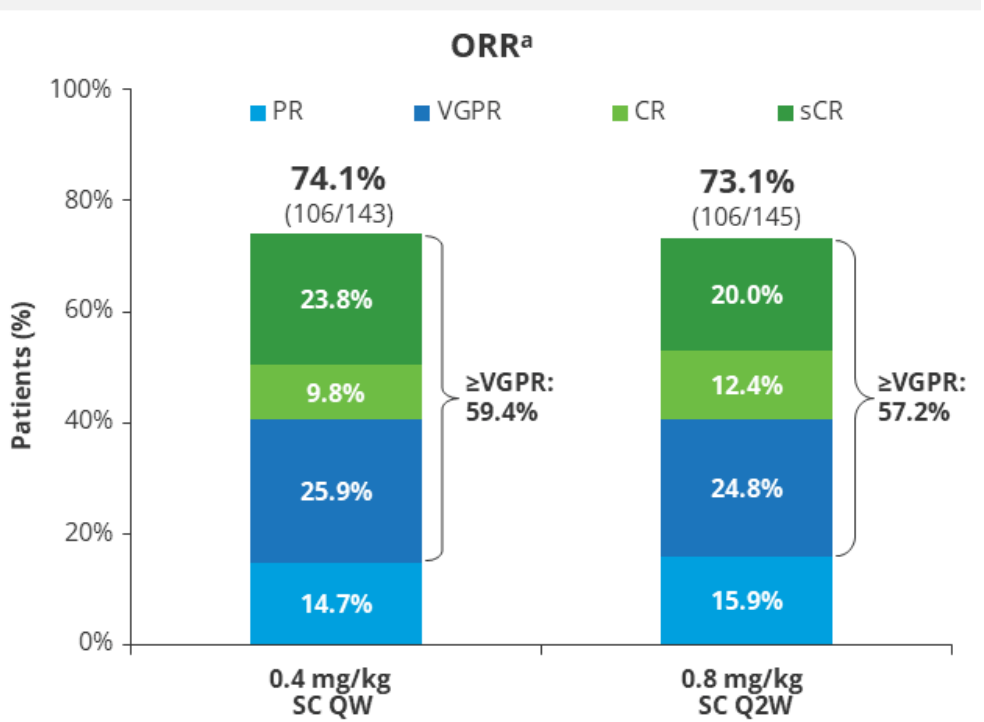


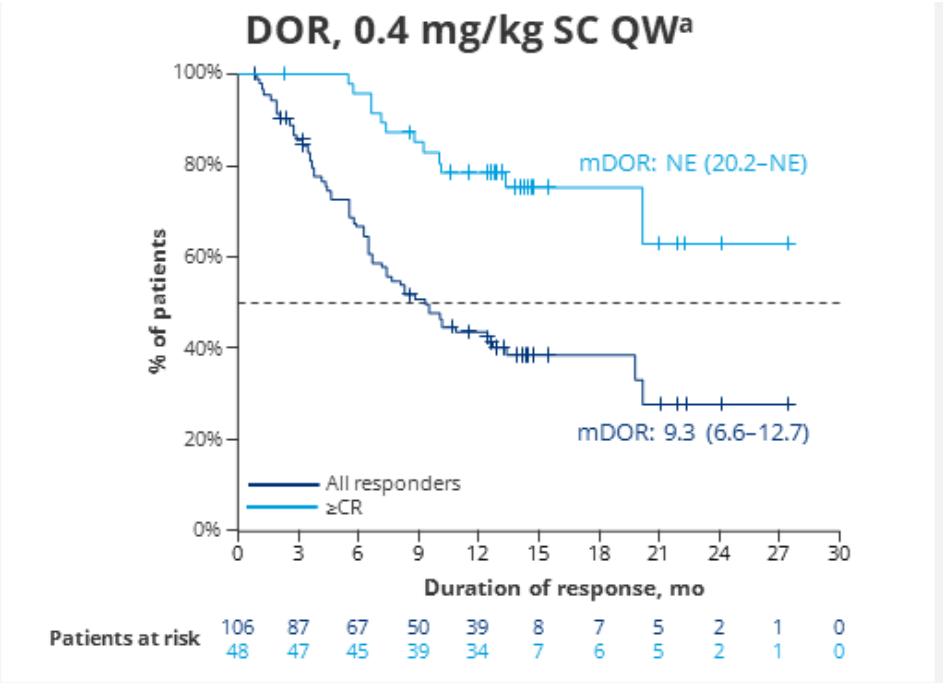
Dual primary endpoints: PFS and sustained MRD-neg CR

Zamagni et al, ASH 2022, #3242; Krishnan et al, ASH 2022, #4558

Talquetamab (GPRC5D x CD3 bsAb) phase 1/2 study

- MONUMENTAL-1. Dose: 0.4 mg/kg SQ qwk (n=143) or 0.8 mg/kg SQ q2wks (n=145)
- Med 5 priors, 72% TCR, 25% PDR, 25% EMD. 13% prior belantamab
- Med f/up 14.9 and 8.6 mos





mPFS: 7.5 months (95% CI: 5.7–9.4; 33% censored)

Chari et al, ASH 2022, #157

Modakafusp alfa is a first-in-class, innate immunity enhancer that functions through targeted next-generation IFN signaling

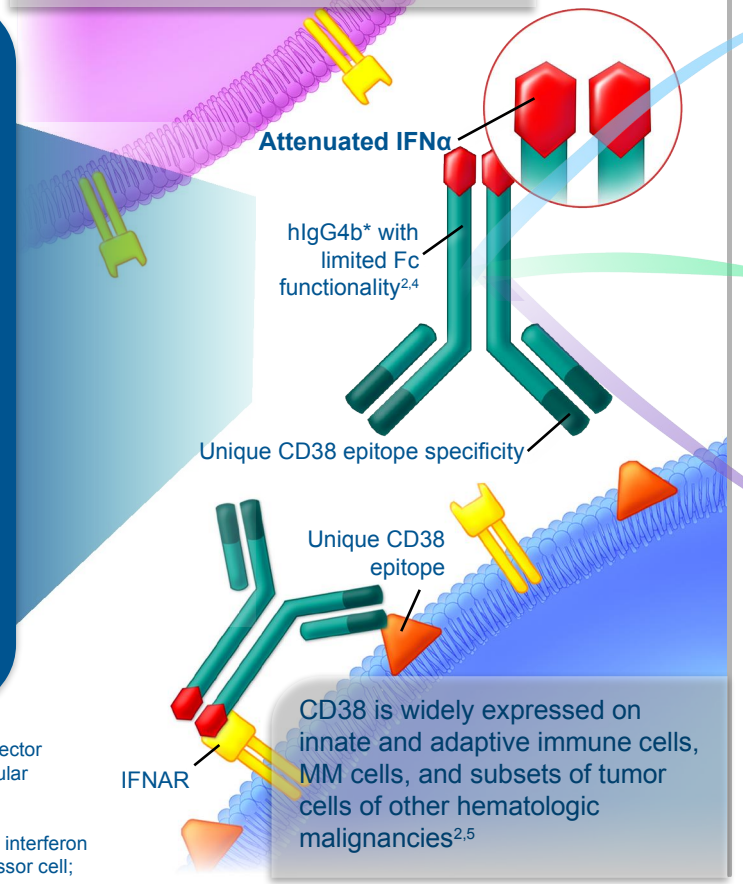
Modakafusp alfa

Binds with high affinity to unique epitope of CD38[1,2]

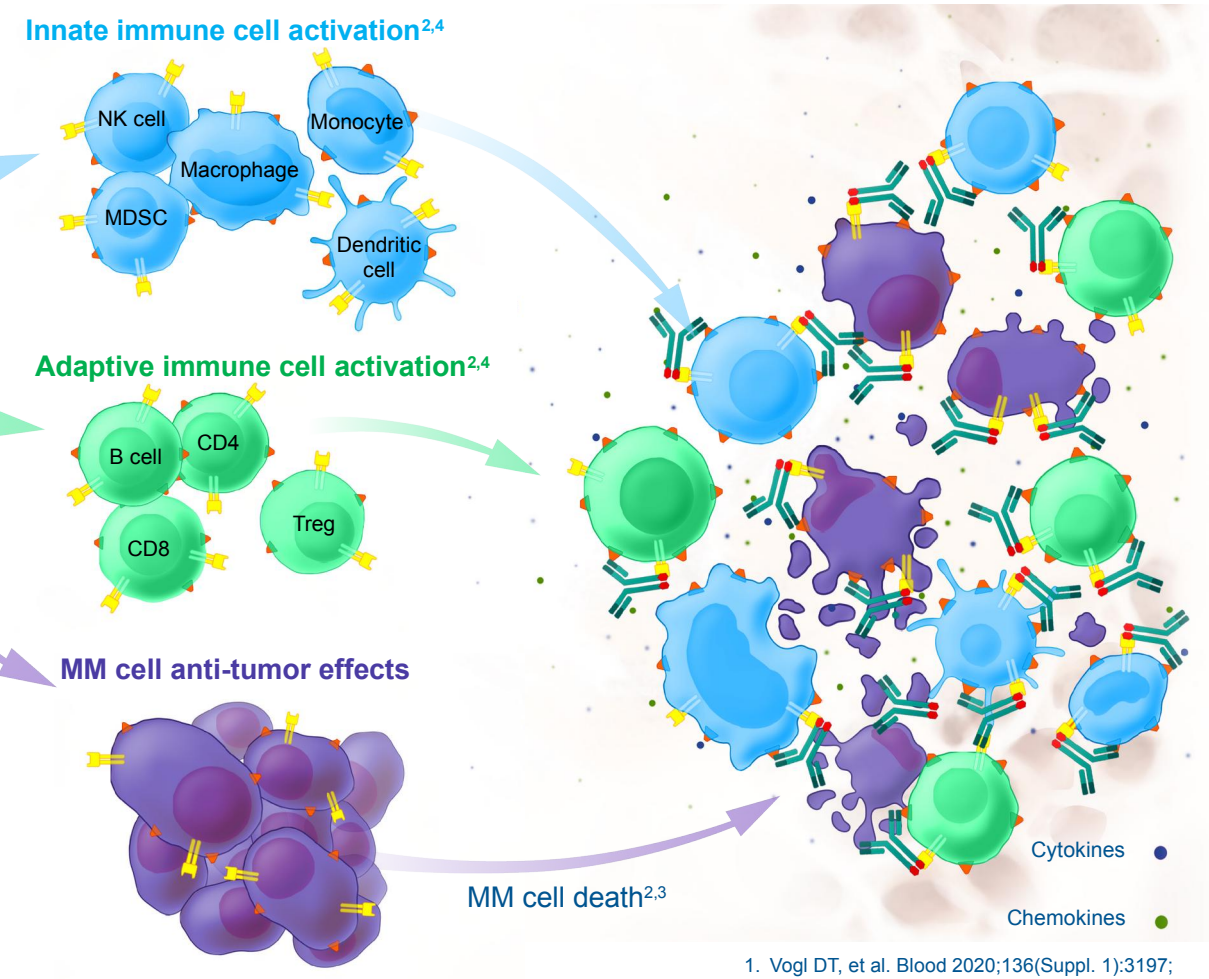
Signals through IFNAR to:[2]

- Activate innate and adaptive immune cells[1]
- Elicit direct anti-proliferative/ apoptotic signals to tumor cells[2,3]

The CD38-targeted attenuated IFNα fusion protein displays a 10,000-fold greater specificity than native IFNα for CD38+ vs CD38− cells[2]



CD38 is widely expressed on innate and adaptive immune cells, MM cells, and subsets of tumor cells of other hematologic malignancies[2,5]

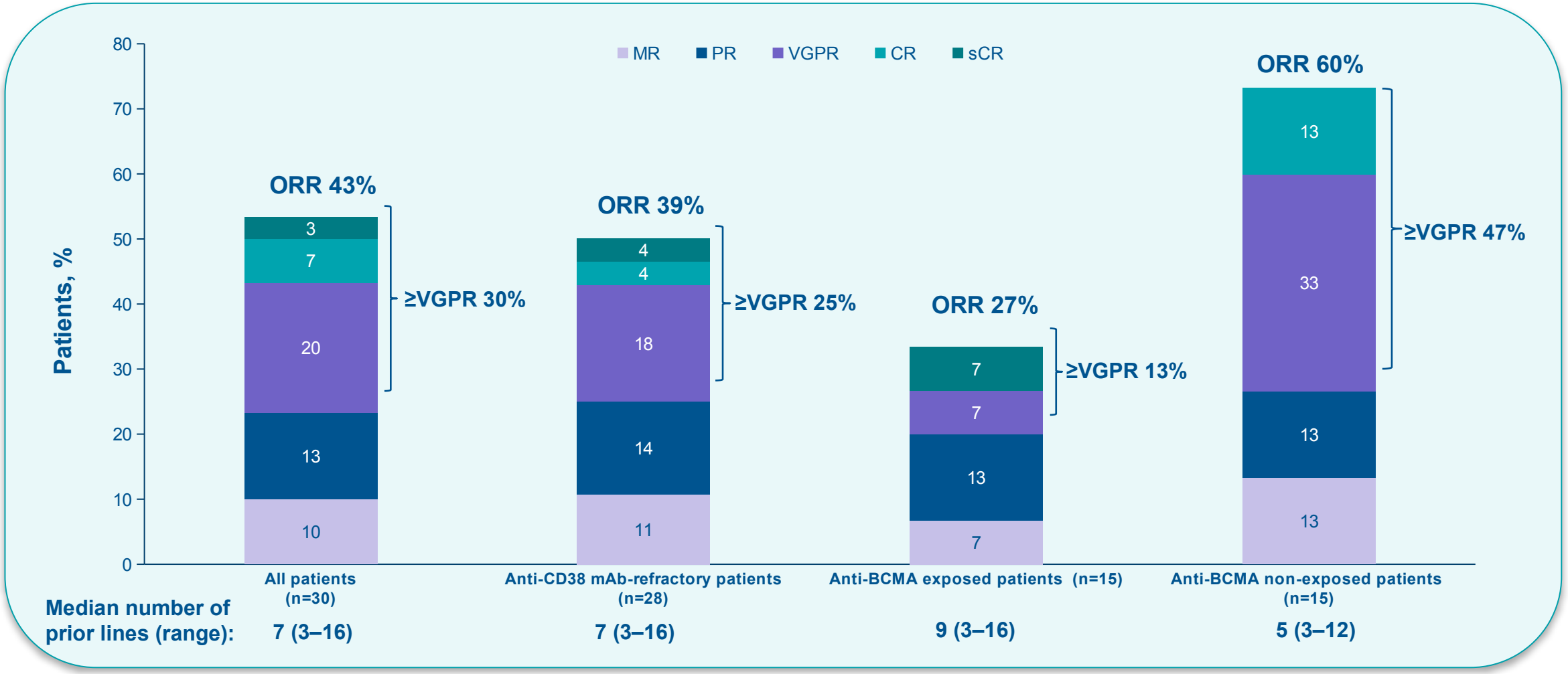


*hIgG4 is a poor inducer of Fc-mediated effector functions, such as antibody-dependent cellular cytotoxicity and phagocytosis.[4]

Fc, fragment crystallizable; hIgG4b, human immunoglobulin 4b; IFN, interferon; IFNAR, interferon α receptor; MDSC, myeloid-derived suppressor cell; MM, multiple myeloma; NK, natural killer; Treg, regulatory T cell

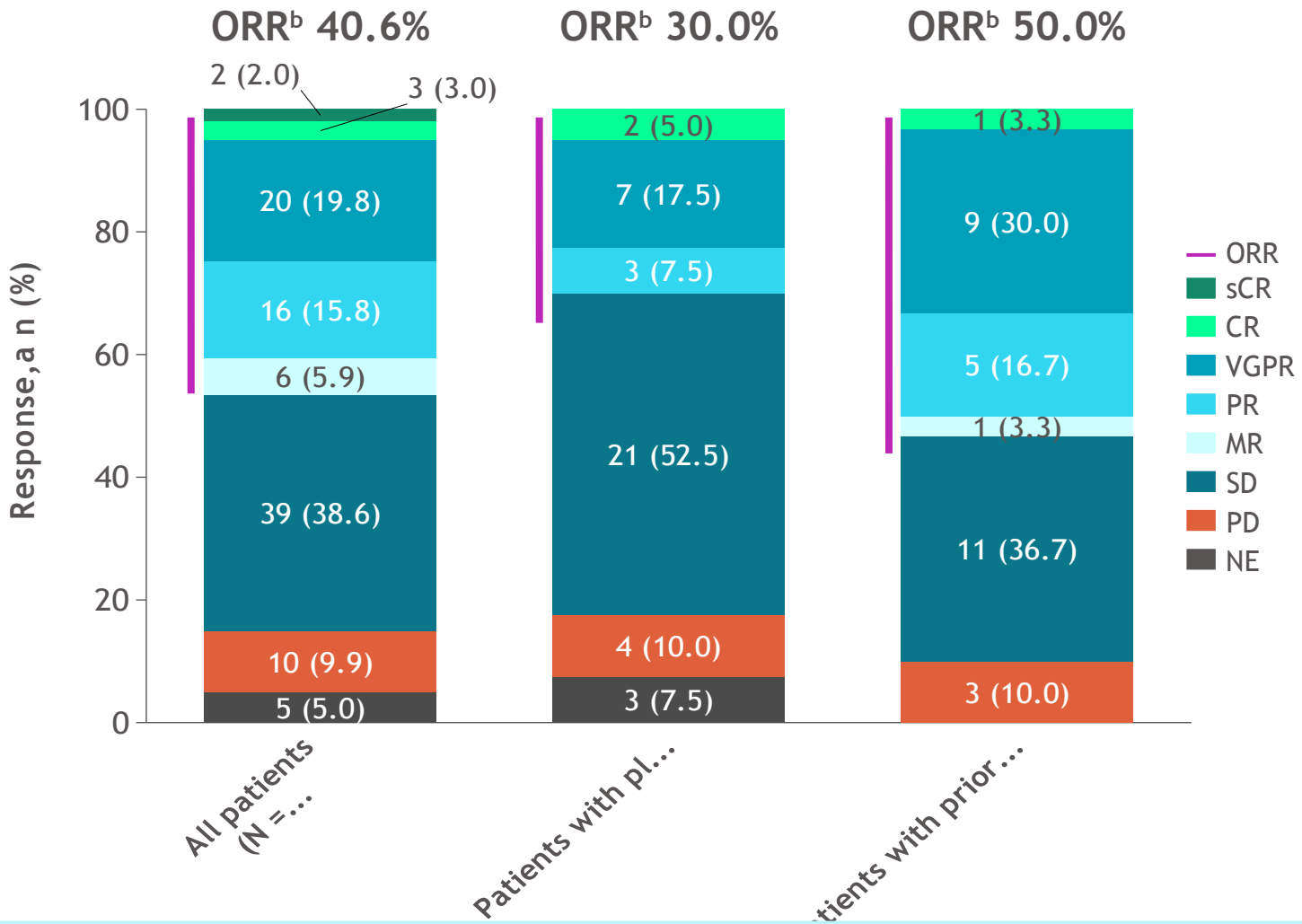
1. Vogl DT, et al. Blood 2020;136(Suppl. 1):3197;
2. Pogue SL, et al. PLoS One 2016;11:e0162472;
3. Anguille S, et al. Leukemia 2011;25:739–48;
4. Crescioli S, et al. Curr Allergy Asthma Rep 2016;16:7;
5. Calabretta E, Carlo-Stella C. Cells 2020;9:802

Responses were observed with modakafusp alfa 1.5 mg/kg Q4W regardless of prior therapies or refractory status



Vogl et al, ASH 2022, #565

Mezigdomide Response Rates



Time to first response, median (range), months	
All pts	0.95 (0.89-12.92)
Pts with plasmacytomas[c]	2.17 (0.92-5.26)
Pts with prior anti-BCMA therapy	2.10 (0.89-10.16)

Follow-up time,[d] median (range), months	
All pts	5.46 (0.03-17.49)
Pts with plasmacytomas[c]	6.10 (0.03-15.98)
Pts with prior anti-BCMA therapy	5.46 (0.03-15.98)

Activity of MEZI+DEX is promising in TCR pts, as well as those with plasmacytoma and/or prior anti-BCMA therapy

[a]Data cutoff: September 16, 2022; [b]PR or better; [c]Including extramedullary soft tissue only disease as well as soft tissue bone-related plasmacytomas; [d]From univariate analysis for all responders without adjusting for censoring.
CR, complete response; MR, minimal response; NE, not evaluable; PD, progressive disease; PR, partial response; sCR, stringent complete response; SD, stable disease; VGPR, very good partial response.

Richardson PG, et al. ASH 2022. Abstract #568.

Summary/Take-home points

- Standard of care of smoldering MM remains close observation
  - Treating high-risk patients is feasible, ?long term impact on survival
- Daratumumab added to VRd for newly-diagnosed MM improves depth and duration of response
- Autologous stem cell transplant after induction improves depth and duration of response
  - Impact on long-term survival?
- BCMA CAR T cells induce unprecedented responses in relapsed/refractory MM patients
  - “one and done” treatment
  - May be less effective after prior BCMA-targeted therapies
  - Optimal timing and sequencing under investigation
- BCMA and non-BCMA-targeted bispecific antibodies/T cell-engagers (BsAb/BiTEs) induce deep responses in relapsed/refractory MM patients
  - Response durability promising but follow-up shorter
  - Optimal dose/schedule to be determined
- Challenges: optimal sequencing, combining with standard myeloma drugs

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