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New Immunotherapy Approaches for Relapsed/Refractory Myeloma

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First Randomized Trial in MM (Coke won….)

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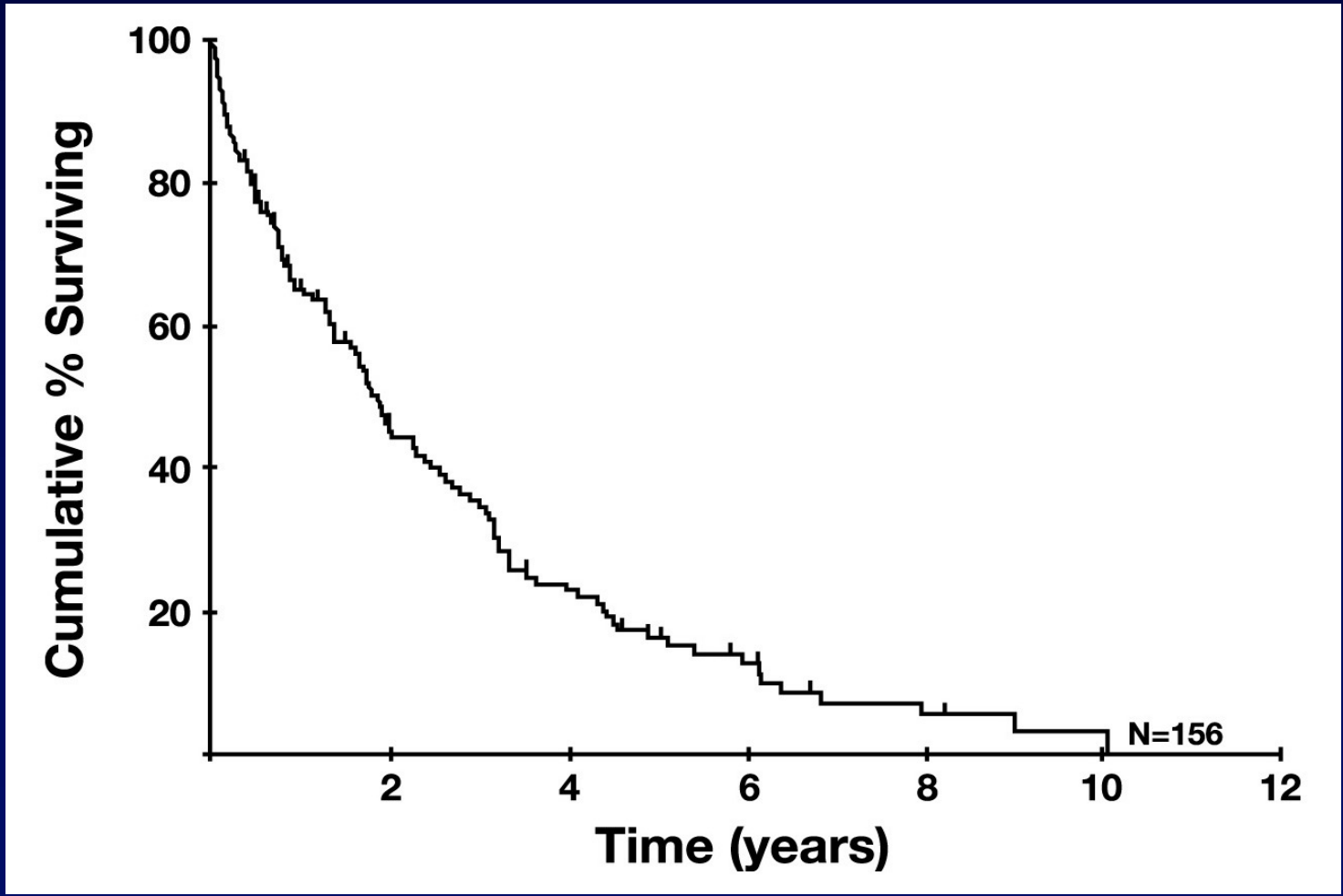
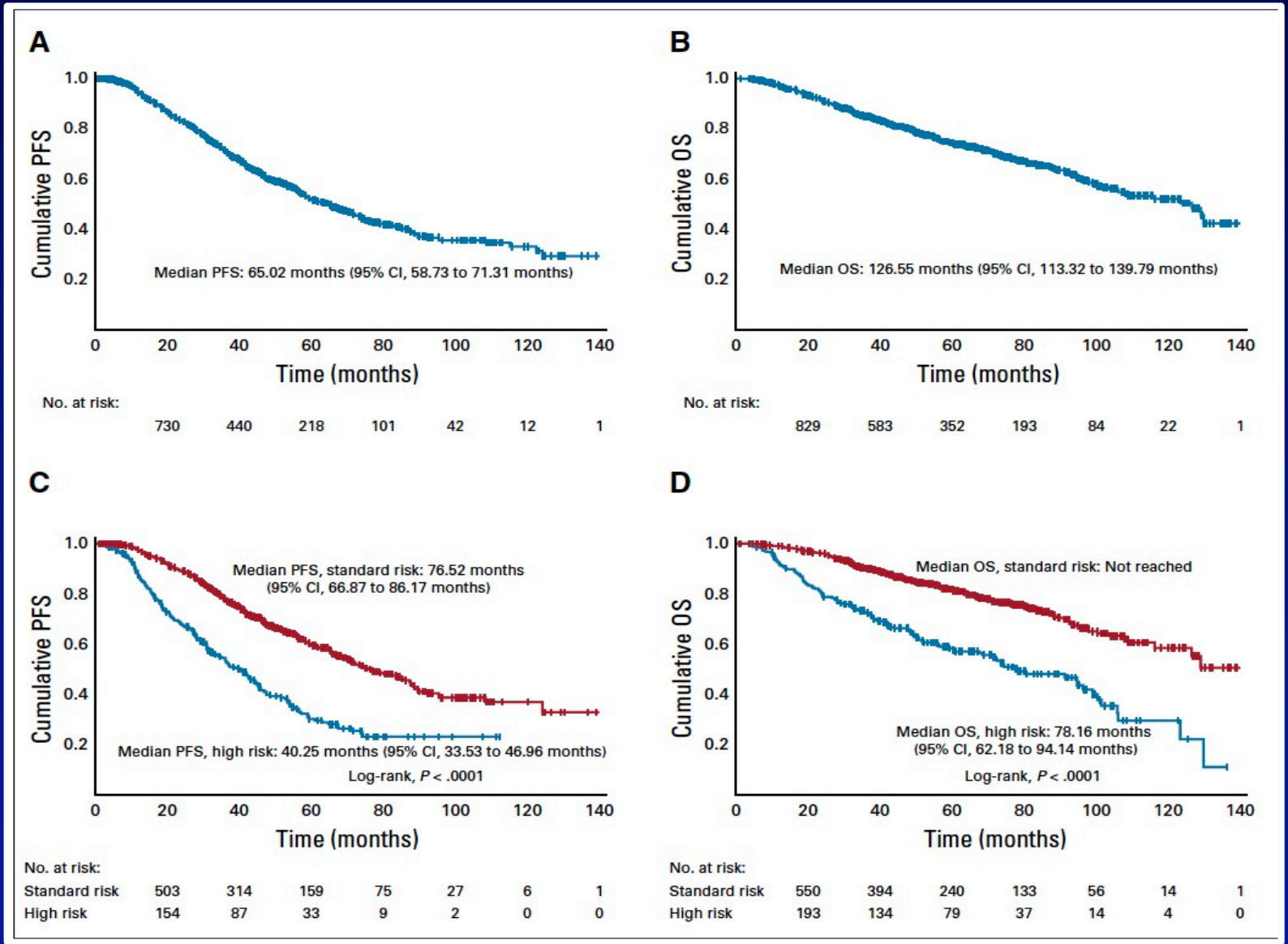
Overall Survival - Multiple Myeloma Patients (1980-1992)



Outcomes from RVD 1000 Cohort



Joseph et al, JCO 2020

Who are the Players

1990's

IMIDS

Thal/Len/Pom

Celmods

Iberdomide

mezigdomide

2015

MoAbs

Daratumumab

Elotuzumab

Isatuximab

ADC

Belamaf

2020

CART

BCMA

Ide-cel

cilta-cel

GPRC5D

MCar

2022

TCE

BCMA

Teclistimab

Elranatamab

5 others

GPRC5D

Talquetamab

FCRH5

Cevostamab

What is Immune Therapy?

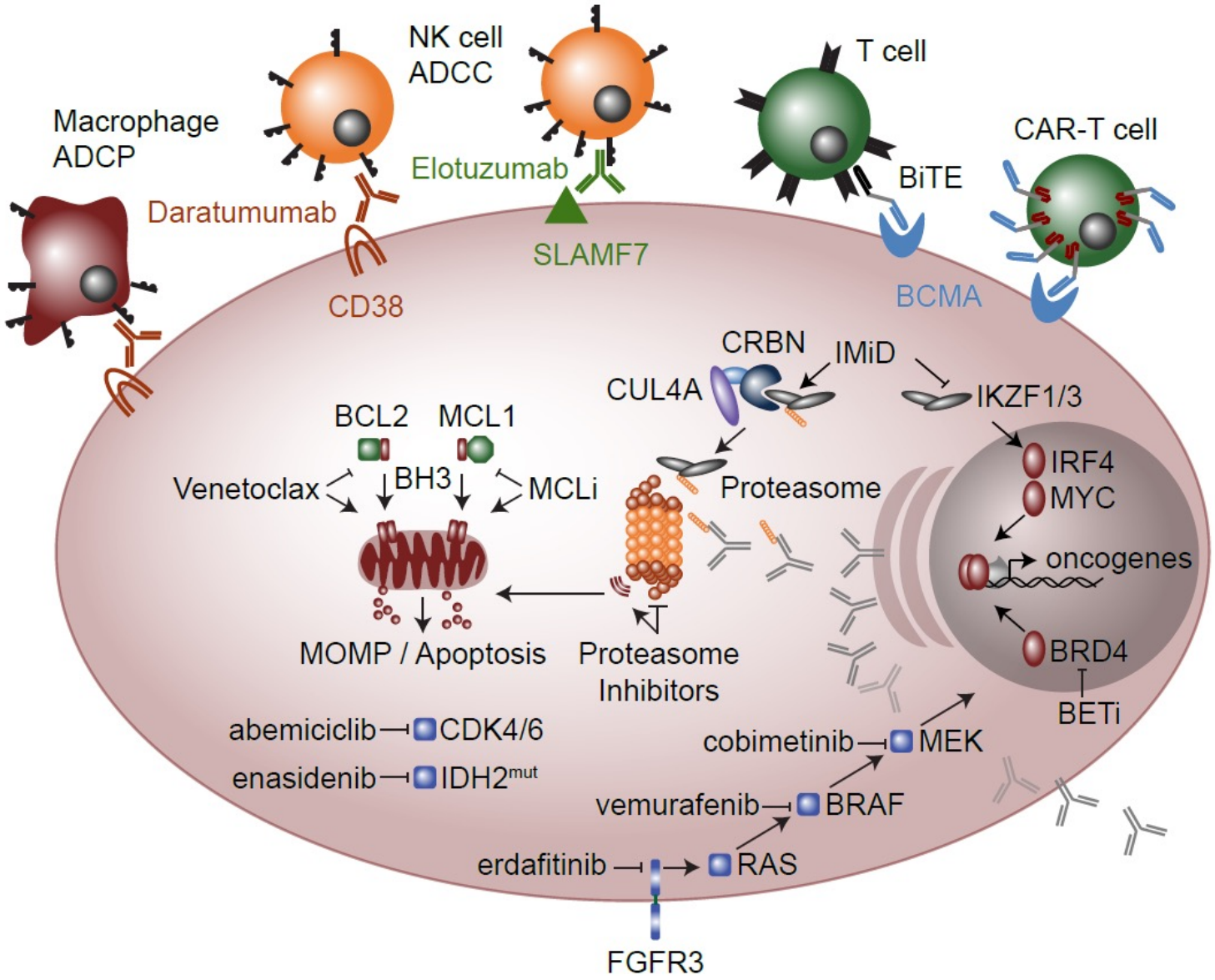
Immunotherapy

Passive/Active	Passive Immunity	Adjuvant Therapy	Active Therapy
Ab based T-cell	targeting a receptor	Immune Booster	Delivering Cells
T-Cell Engager	MoAB Direct Indirect	Dendritic cell or Peptide Vaccine	Allo Transplant, Car T-Cells
Pros/Cons of both	Truly 'Targeted' Therapy	'Connecting Flights'	Risk 'Off Target' effects

Immune Landscape circa 2010

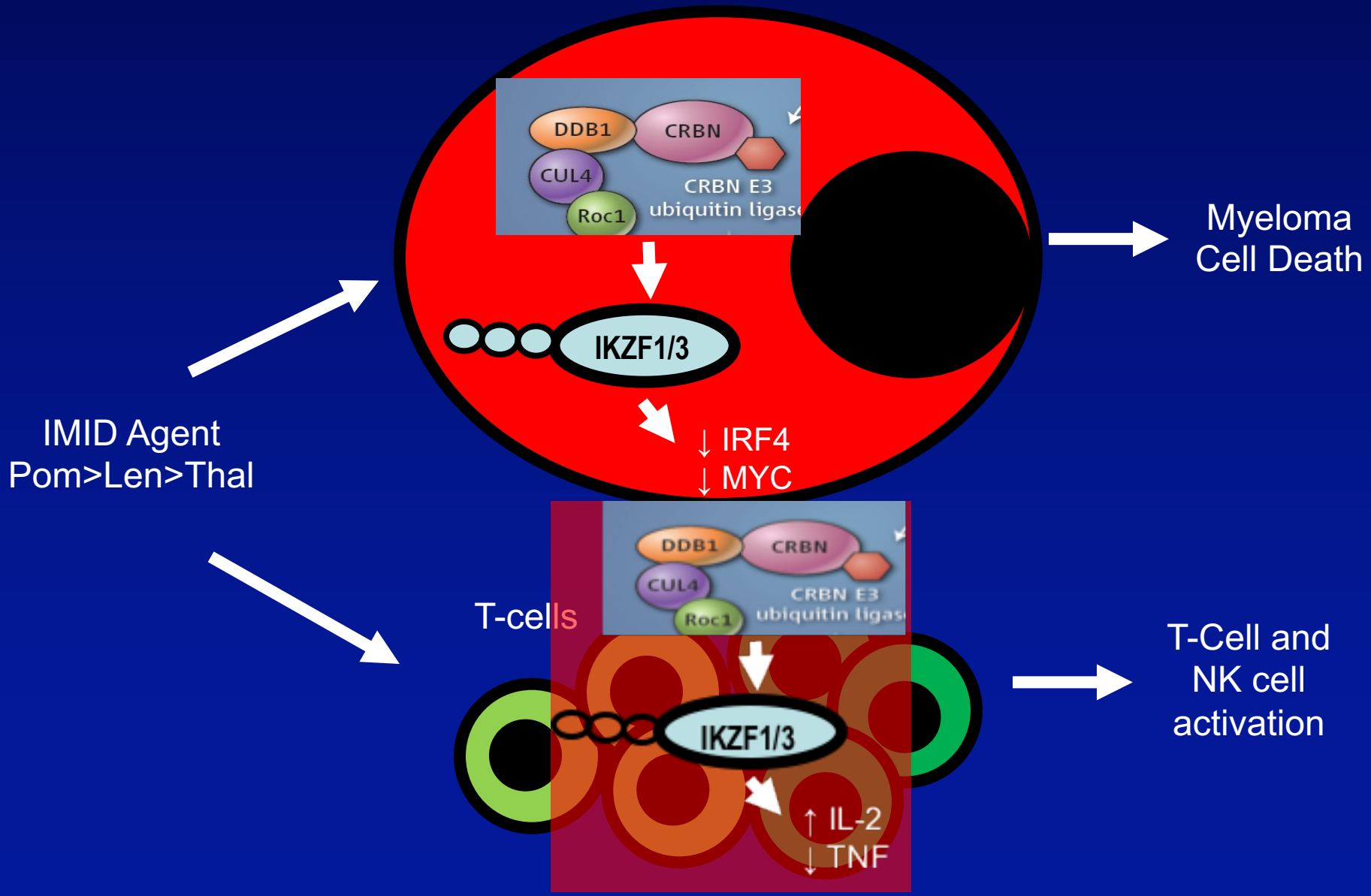
- Only immune player on the scene was thalidomide or lenalidomide
- How these agents worked remained a mystery
- Allo transplant remained a mainstay using the ‘cure’ argument, in the absence of solid data
- Oncologic Irony: A disease that produces too much antibody did not have a therapeutic monoclonal antibody

Therapeutic modalities in multiple myeloma



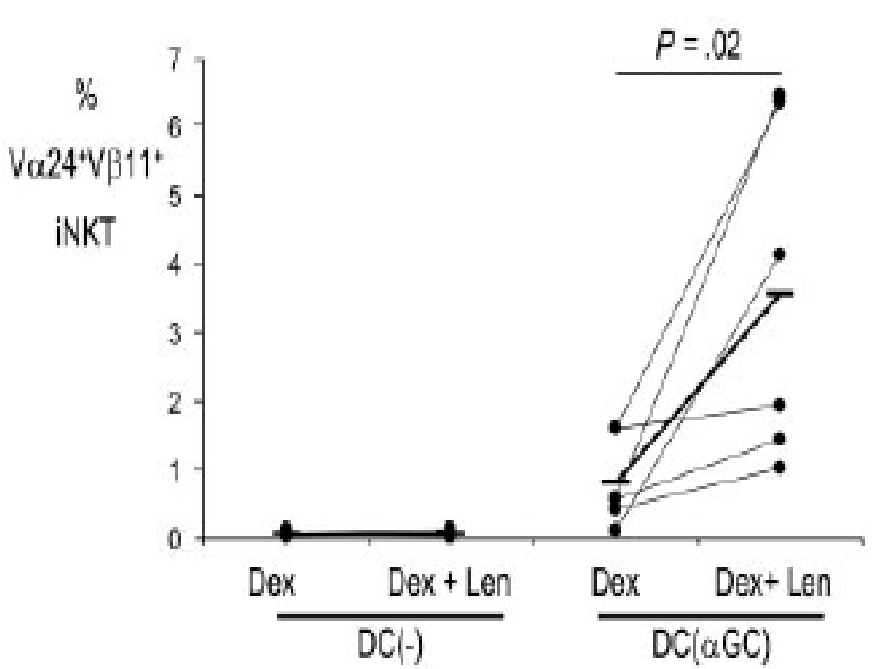
Barwick et al.
Frontiers Immunology, 2019

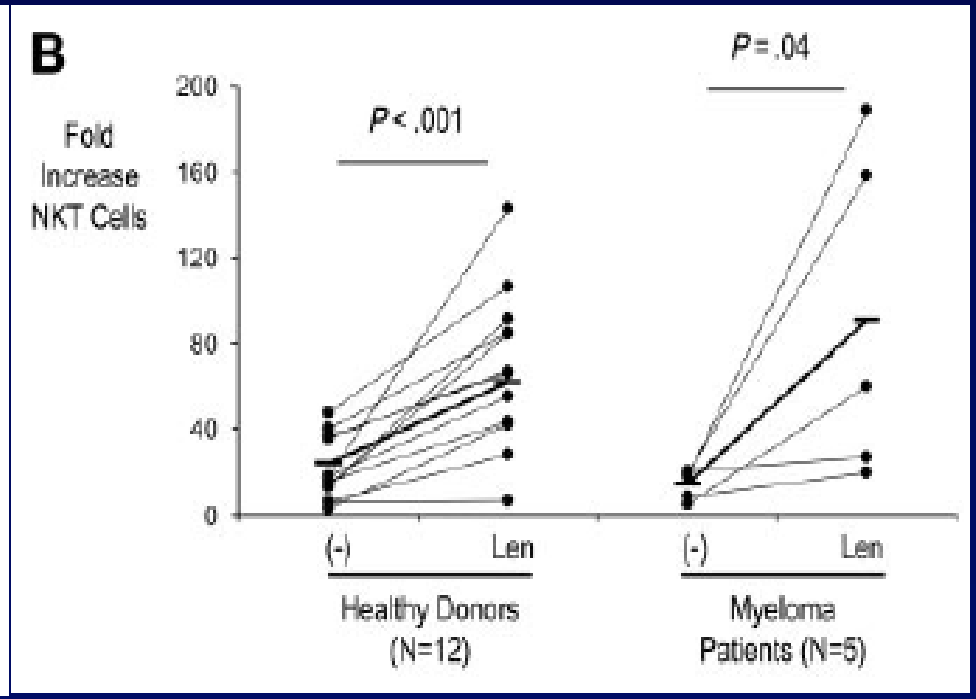
Differential Effects the Same Target



Enhancement of ligand-dependent activation of human natural killer T cells by lenalidomide: therapeutic implications

David H. Chang, Nancy Liu, Virginia Klimek, Hani Hassoun, Amitabha Mazumder, Stephen D. Nimer, Sundar Jagannath, and Madhav V. Dhodapkar



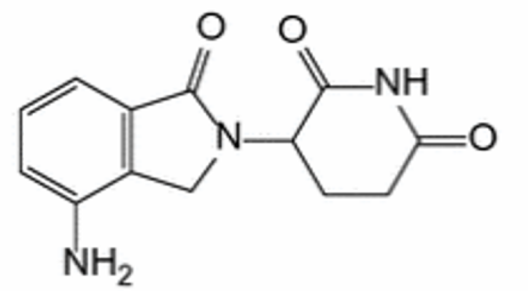


Blood 2007

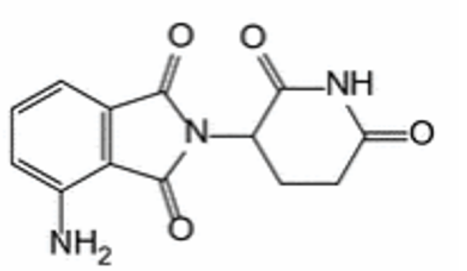
Novel cereblon E3 ligase modulators (CELMoD® agents) in development

LEN and **POM**
(a subgroup of CELMoD® agents)
helped to **transform therapy and drive survival** in MM[1-3]

LEN



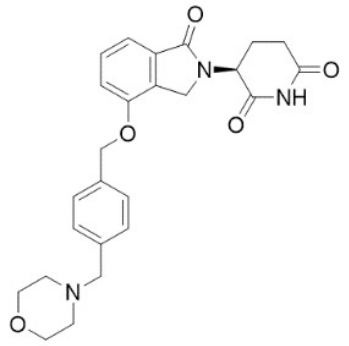
POM



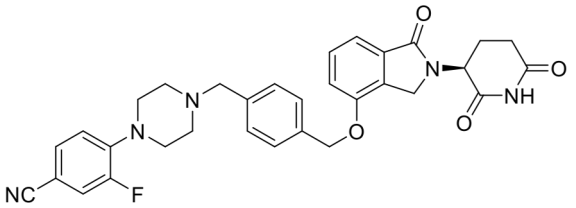
Rational selection of molecules based on **deep scientific understanding of CRBN and MM biology: iberdomide (IBER; CC-220) and mezigdomide (CC-92480)**[4-6]

2019 and 2020: First clinical data for IBER and CC-92480 in MM

IBER



CC-92480



Iberdomide (IBER; CC-220) and mezigdomide (CC-92480) are investigational products, currently not approved by any regulatory agency.

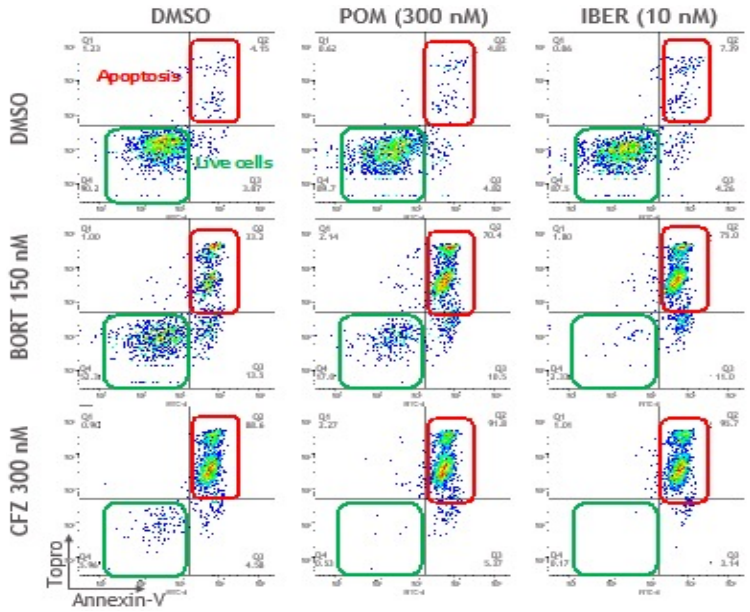
CRBN, cereblon; IBER, iberdomide; LEN, lenalidomide; MM, multiple myeloma; POM, pomalidomide.

1. Rajkumar SV, et al. Lancet Oncol. 2010;11:29-37. 2. Facon T, et al. Blood. 2018;131:301-10. 3. Durie BGM, et al. Blood Cancer J. 2020;10:53. 4. Ito T, Handa H. Int J Hematol. 2016;104:293-9.
5. Matyskiela ME, et al. J Med Chem. 2018;61:535-42. 6. Hansen JD, et al. J Med Chem. 2020;63:6648-67.

Iberdomide (IBER) and mezigdomide (CC-92480) synergize with other anti-myeloma agents

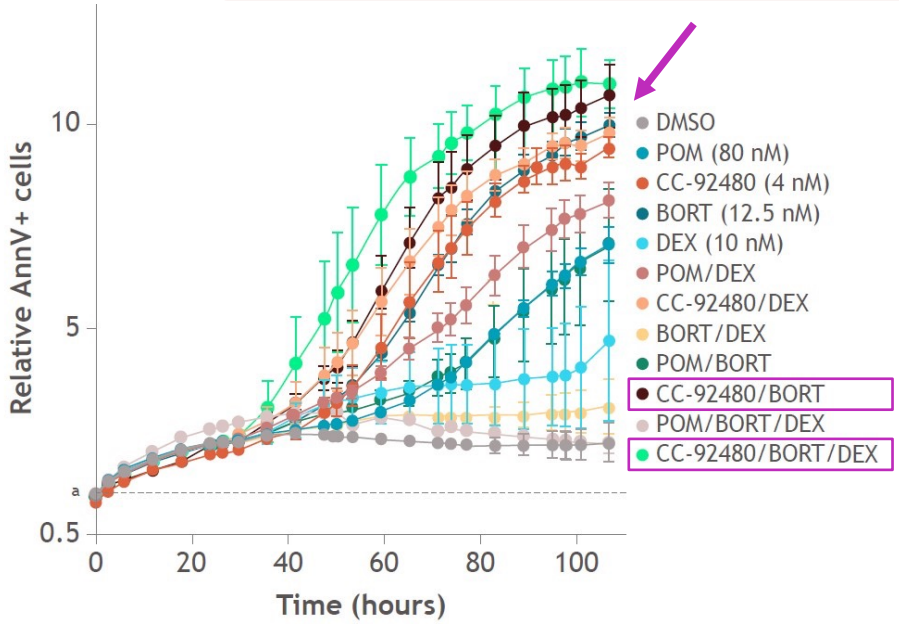
Preclinical studies indicate that IBER and mezigdomide synergize with other anti-MM agents including PIs and DARA, demonstrating deep induction of apoptosis and enhanced antibody-dependent cellular cytotoxicity

KMS12 BM cells



IBER induces deeper cell killing in combination with PIs vs POM

Pro-apoptosis



CC-92480 increased induction of apoptosis compared with POM (40% vs 20%)

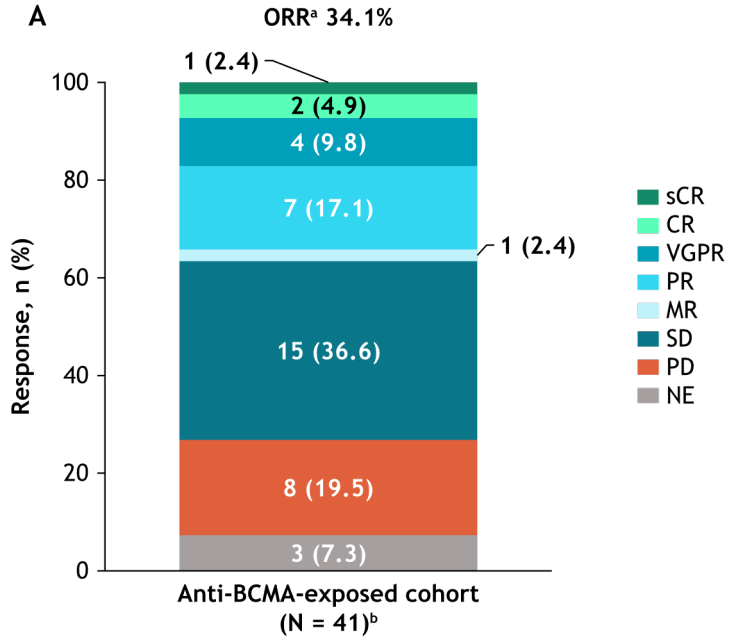
Iberdomide (IBER; CC-220) and CC-92480 are an investigational products, currently not approved by any regulatory agency.

AnnV, annexin V; BM, bone marrow; BORT, bortezomib; CFZ, carfilzomib; DARA, daratumumab; DEX, dexamethasone; DMSO, dimethyl sulfoxide; PI, proteasome inhibitor.

Amatangelo M, et al. Blood. 2018;132:abstract 1935. Bjorklund CC, et al. Poster presentation at ASH 2021; abstract 2669.

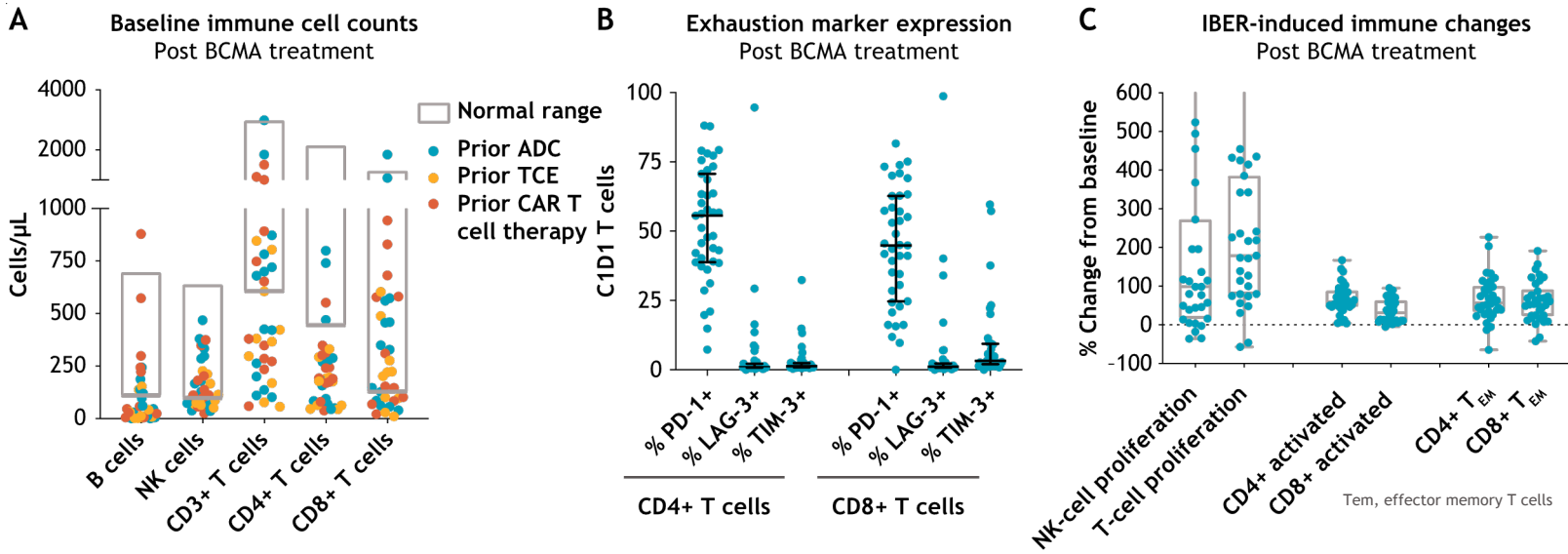
CC-220-MM-001 IBER+DEX (Cohort I) efficacy and safety in patients with heavily pretreated, anti-BCMA-exposed RRMM

Efficacy (ORR) and safety of IBER+DEX in anti-BCMA-exposed patients with RRMM



[a]PR or better; [b]Data cutoff: August 1, 2022; [c]Includes viral pneumonia, bacterial pneumonia, COVID-19 pneumonia, *Pneumocystis jirovecii* pneumonia, and pseudomonal pneumonia.
COVID-19, coronavirus disease 2019; MR, minimal response; NE, not evaluable; SD, stable disease; TEAE, treatment-emergent adverse event.

IBER is immune-stimulatory post-BCMA therapy



Most frequent (≥ 20% all grade) TEAEs and events of interest,[b] n (%)	Anti-BCMA-exposed cohort IBER + DEX (N = 41)		
	All grades	Grade 3	Grade 4
Hematologic TEAEs			
Neutropenia	23 (56.1)	11 (26.8)	10 (24.4)
Febrile neutropenia	1 (2.4)	1 (2.4)	0
Anemia	15 (36.6)	11 (26.8)	0
Thrombocytopenia	12 (29.3)	4 (9.8)	4 (9.8)
Leukopenia	12 (29.3)	6 (14.6)	4 (9.8)
Lymphopenia	9 (22.0)	2 (4.9)	6 (14.6)
Non-hematologic TEAEs			
Fatigue	15 (36.6)	2 (4.9)	0
Diarrhea	10 (24.4)	1 (2.4)	0
Constipation	10 (24.4)	0	0

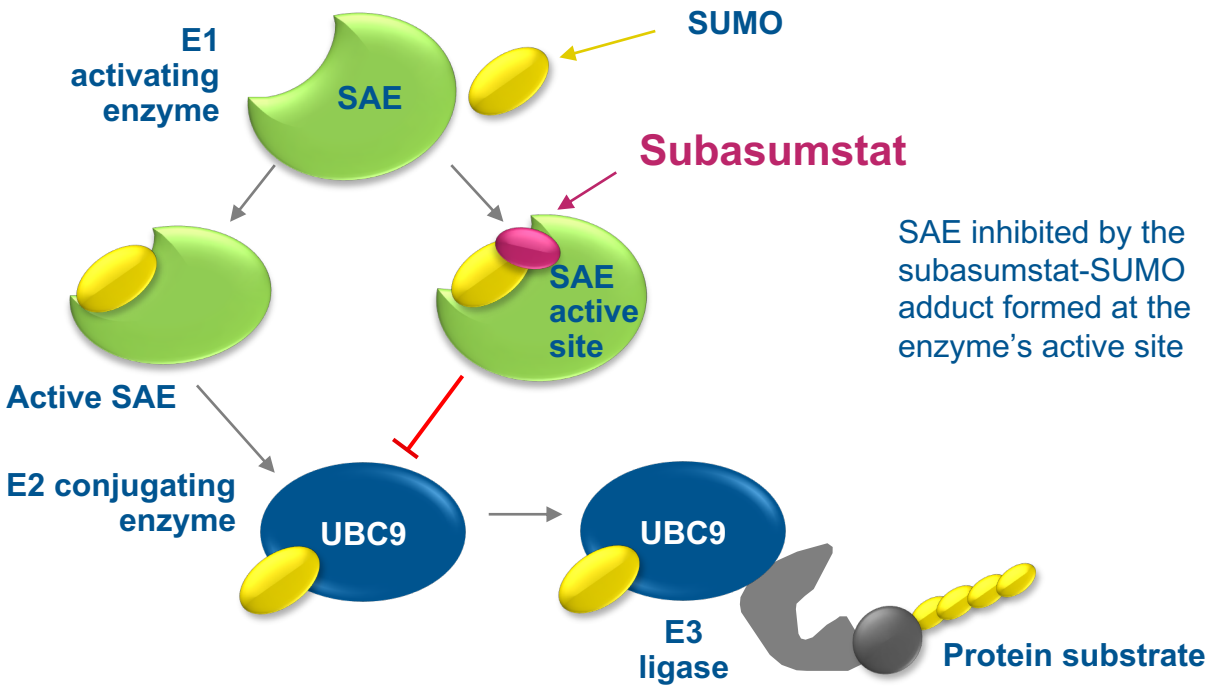
[a]PR or better; [b]Data cutoff: August 1, 2022; [c]Includes viral pneumonia, bacterial pneumonia, COVID-19 pneumonia, *Pneumocystis jirovecii* pneumonia, and pseudomonal pneumonia.
COVID-19, coronavirus disease 2019; MR, minimal response; NE, not evaluable; SD, stable disease; TEAE, treatment-emergent adverse event.

Lonial S, et al. ASH 2022; CC-220-MM-001 Study

Subasumstat (TAK-981)

- First-in-class, small-molecule inhibitor of SUMO-activating enzyme[1]
  - Blocks SUMOylation, a reversible post-translational modification analogous to ubiquitination that regulates IFN-I expression
  - Increases IFN-I production and signaling in innate immune cells[2]
- In ex-vivo assays, subasumstat:
  - Activated the IFN-I pathway
  - Increased phagocytic activity of monocyte-derived macrophages
  - Increased NK-cell cytotoxicity via IFN-I signaling[2]

Inhibition of the SUMOylation cascade by subasumstat[1]



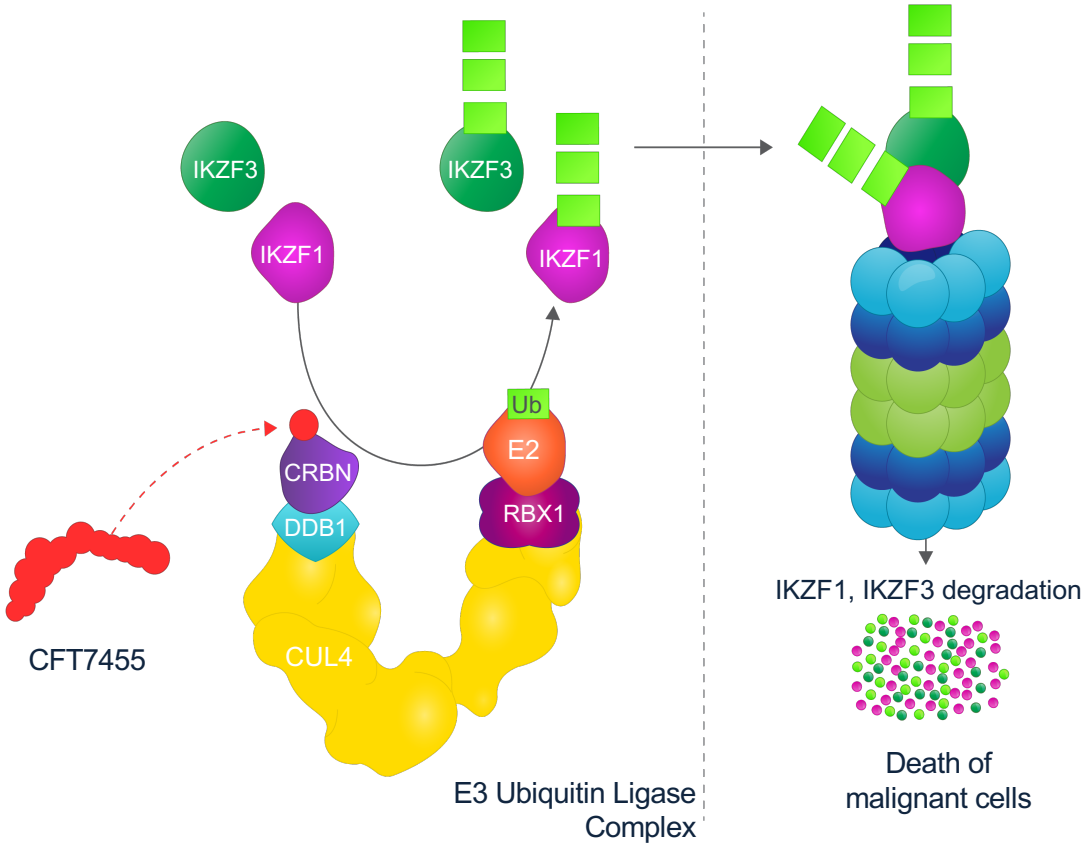
IFN-I, Type I interferon; NK, natural killer; SAE, SUMO-activating enzyme subunit; SUMO, small ubiquitin-like modifier

1. Langston SP, et al. J Med Chem 2021;64:2501–20
2. Nakamura A, et al. Cancer Res 2019;79(13 Suppl):Abstract #1523

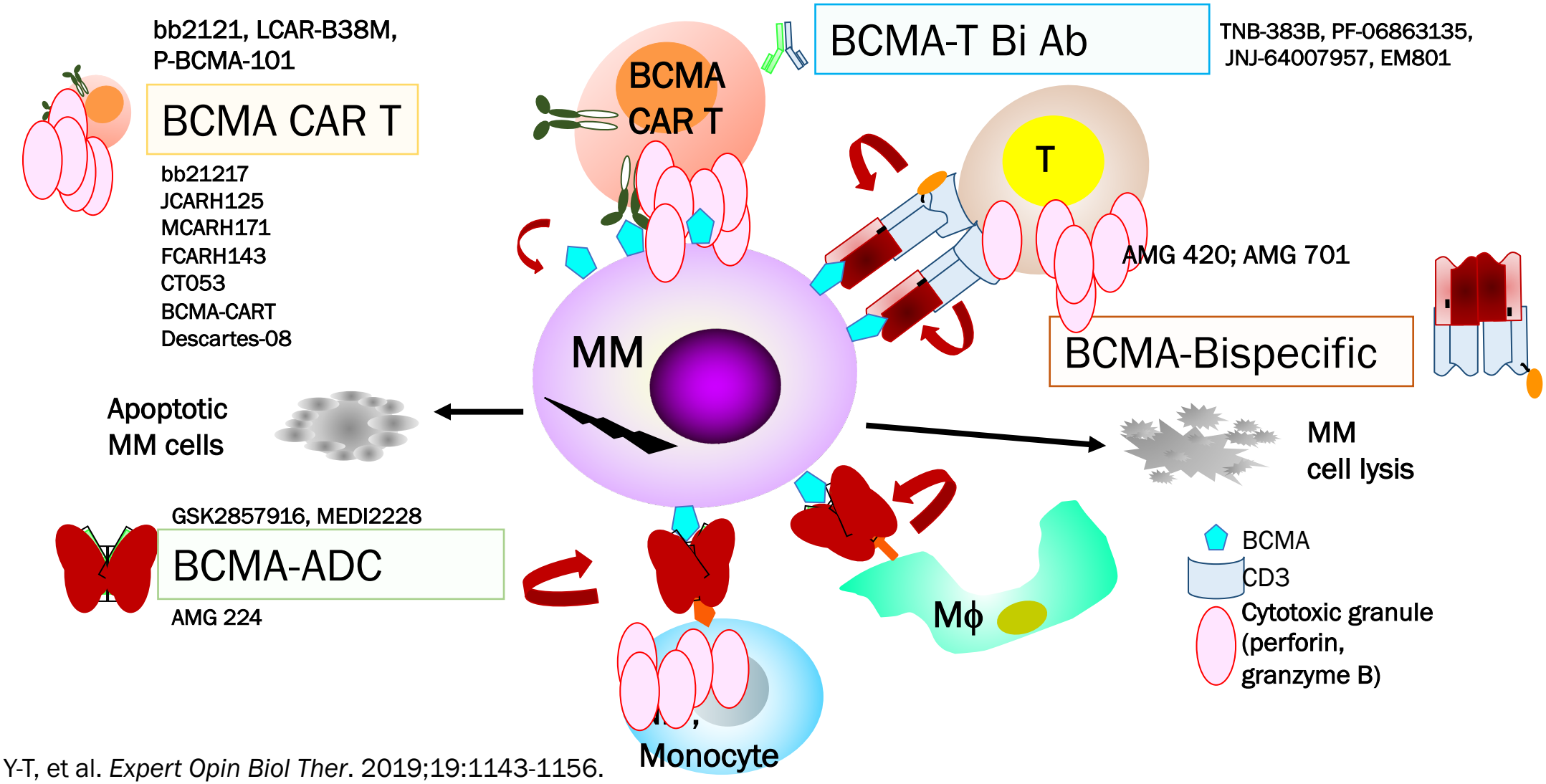
CFT7455 Background

- Novel protein degrader that binds to cereblon E3 ligase, creating a new surface on CRBN resulting in increased interaction with the transcription factors IKZF1/3 (Figure 1.) with increased potency compared to other immunomodulatory agents
- CFT7455 selectively degrades IKZF1/3 which are ubiquitinated by the CRBN E3 ligase and degraded by the proteasome (Figure 1.)
- The high CRBN binding affinity (IC50=0.9nM) of CFT7455 enables rapid and deep degradation of IKZF1/3 resulting in potent activity in MM and several subtypes of NHL in both *in vitro* and *in vivo* xenograft models

Figure 1: Mechanism of Action for CFT7455

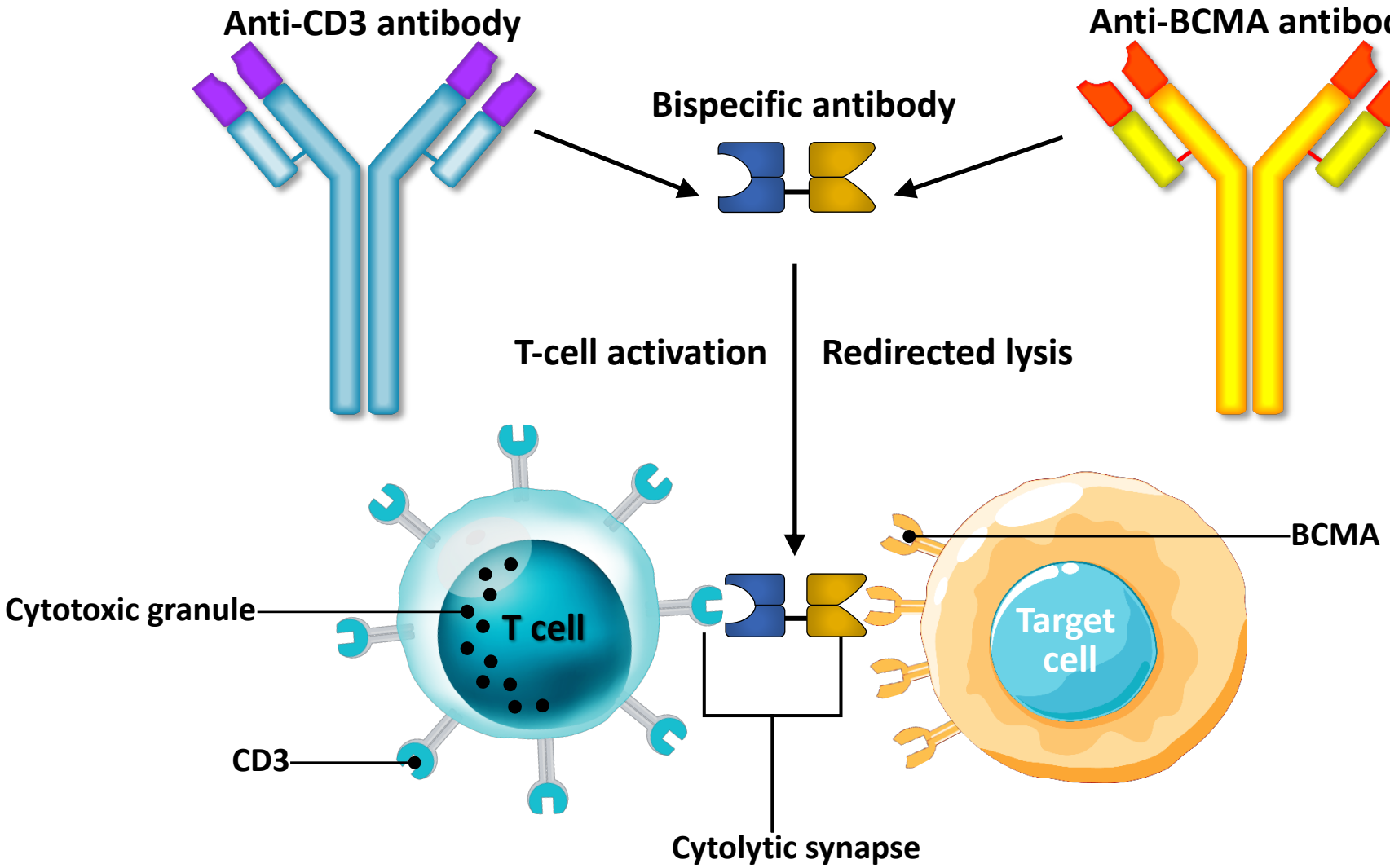


BCMA-Targeted Immunotherapy in MM



- Tai Y-T, et al. *Expert Opin Biol Ther*. 2019;19:1143-1156.

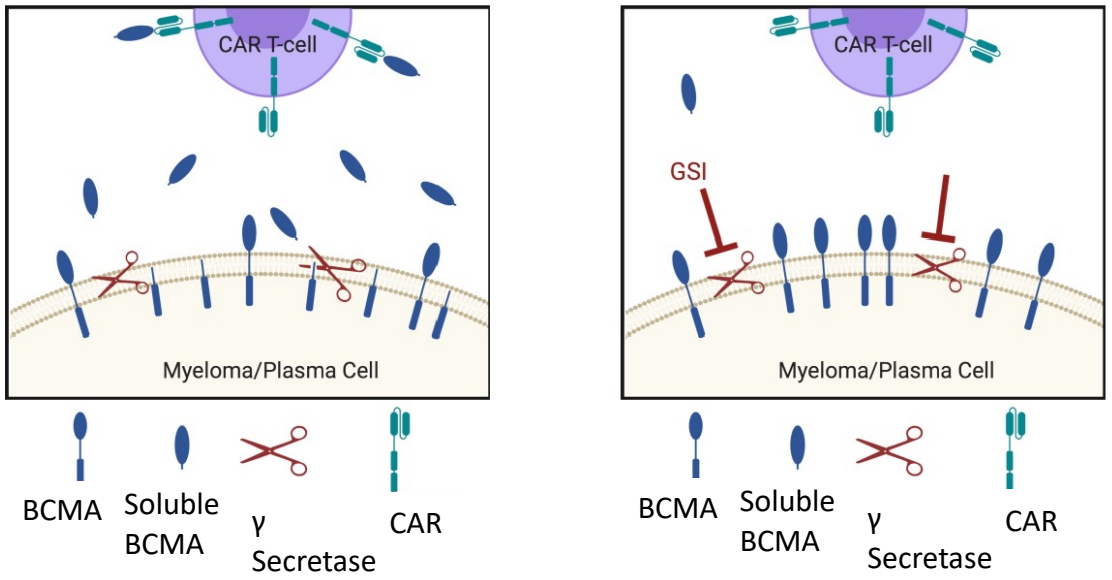
Bispecific T Cell Engagers



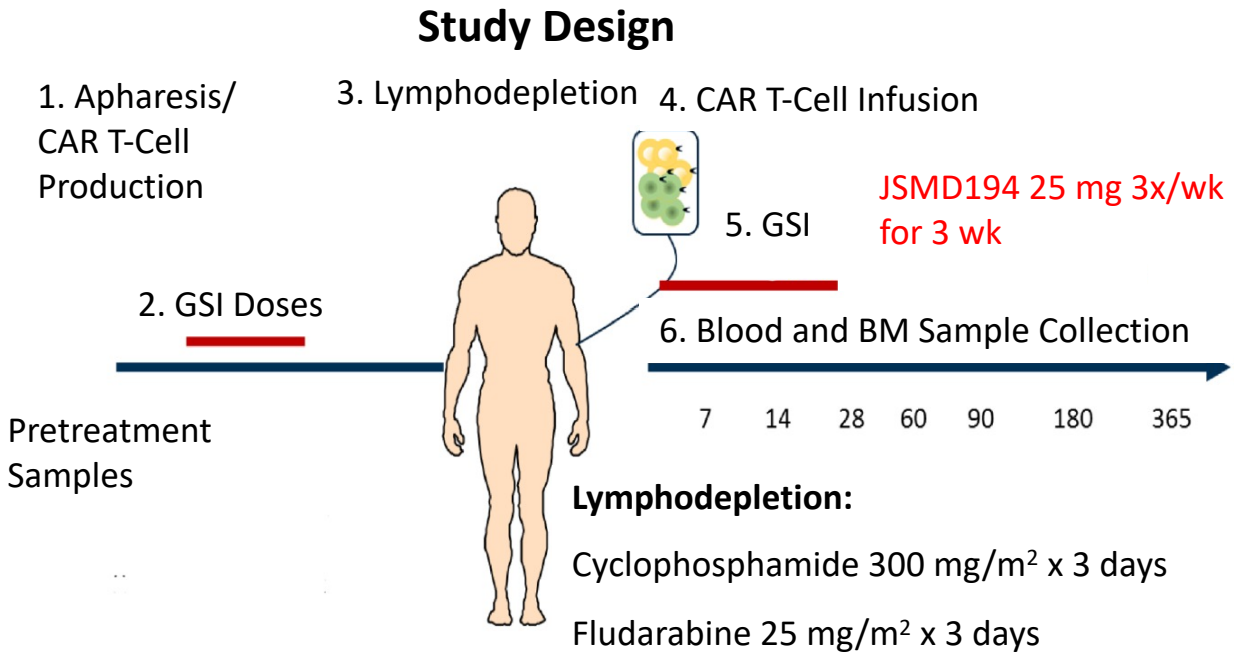
Baeuerle PA, et al. *Cancer Res*. 2009;69:4941-4944.

Fully Human BCMA CAR T-Cells Combined With γ Secretase Inhibitor to Increase BCMA Expression in R/R MM

γ Secretase Cleaves BCMA From Plasma Cells



Study Design



Pont. Blood. 2019;134:1585. Cowan. ASH 2021. Abstr 551.

Immune therapy challenges

- Poor T-cell health??
- Model for MM will require multiple infusions of cells or chronic therapy vs ALL model
- IS microenvironment remolds infused cells.
- Antigen loss is rarely the issue

Alternative Manufacturing May be a key Degradable Microscaffolds (DMS)

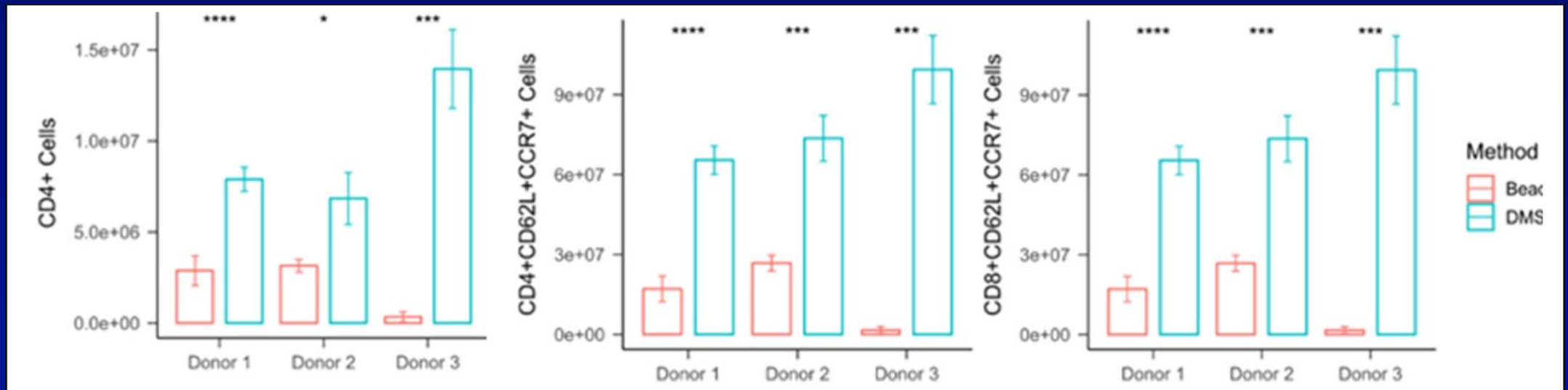


Figure 5: The DMS platform produces more CD4+ cells (**Left**), CD4+CCR7+CD62L+ (**Middle**), and CD8+CCR7+CD62L+ (**Right**) Naïve+T_{CM} cells than microbeads. Each data set represents three different primary healthy donor T cells.

Roy Lab, Ga Tech CMAT Program

Alternative Manufacturing with BCMA

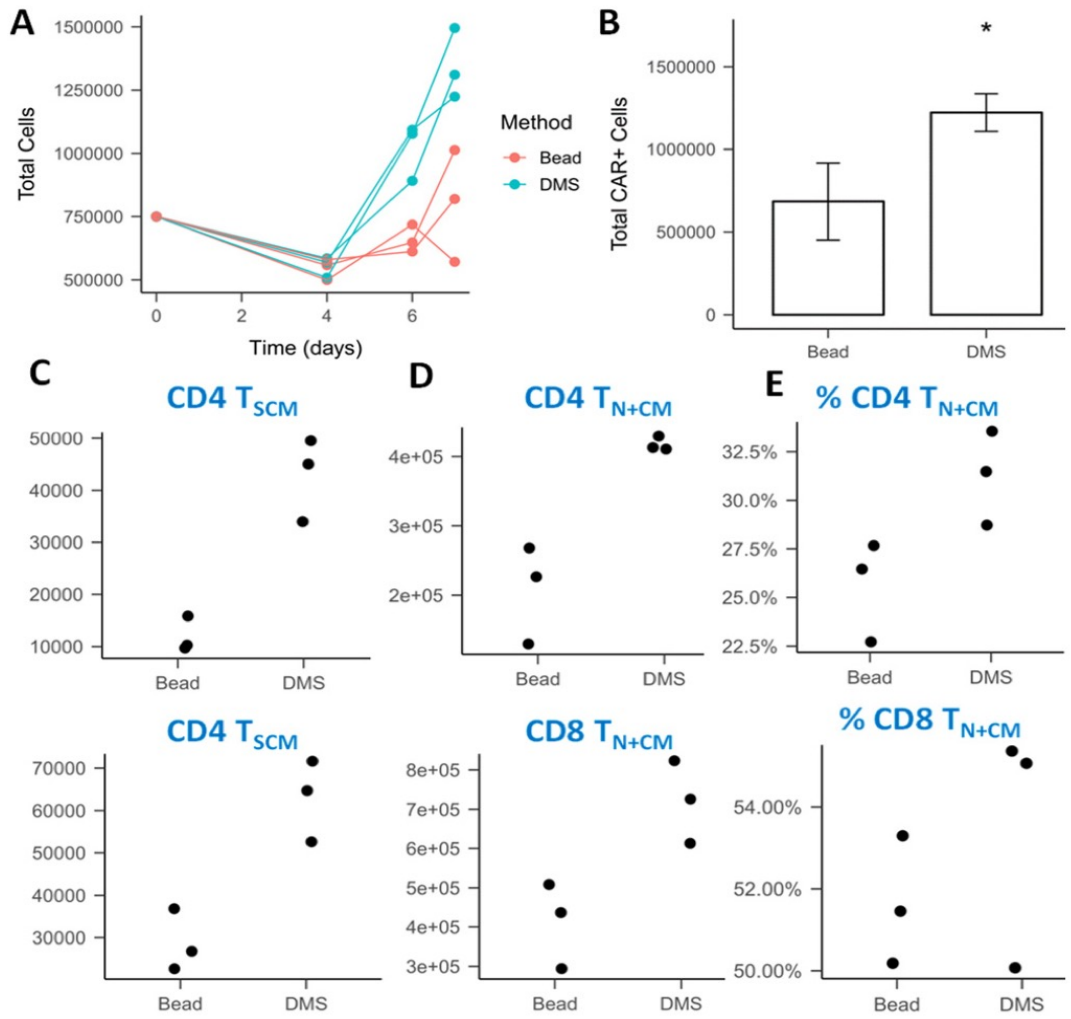


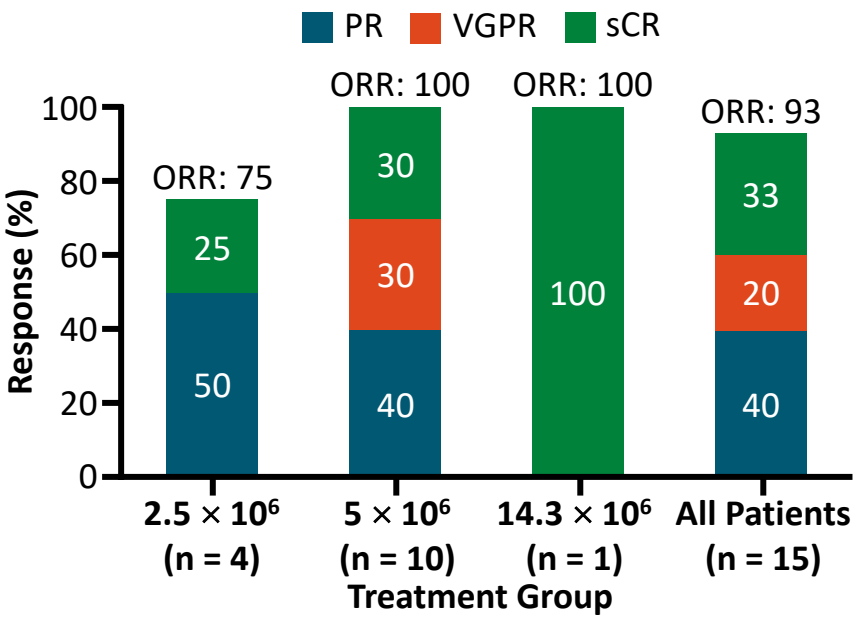
Figure 11: DMS-based BCMA CAR-T Manufacturing yields better expansion, more CAR+ cells, more total (and for CD4, more %) T_{SCM} (CD45RO-CD27+CD95+) and T_{N+TCM} (CD62L+CCR7+) cells, compared to bead-manufactured cells from the same donor.

Roy Lab, Ga Tech CMAT Program

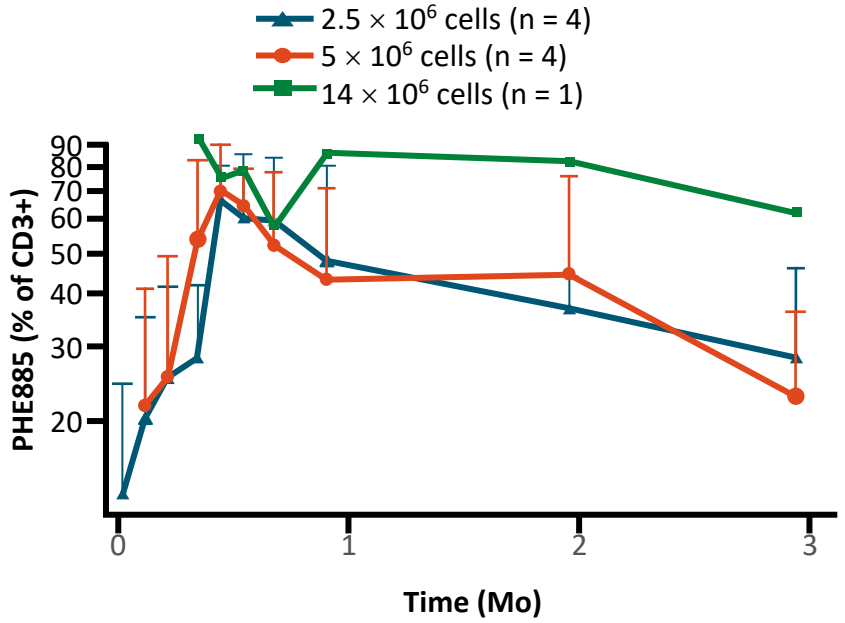
Phase I Trial of PHE885 in R/R MM: Rapid Production and Turnaround

- PHE885: anti-BCMA CAR T-cells manufactured ex vivo with culture time of approximately 24 hr; time to manufacture final product is <2 days, relying entirely on in vivo expansion after CAR T-cell infusion
- Phase I study in heavily pretreated patients with R/R MM

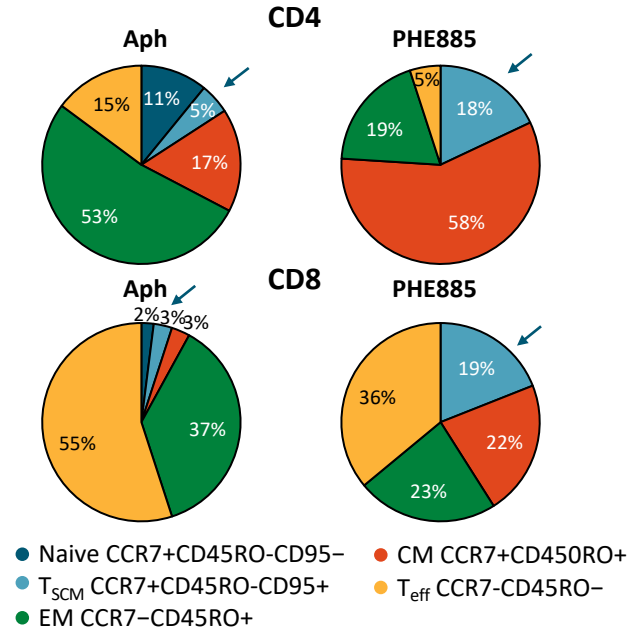
Tumor Response by Dose



Cellular Kinetics of PHE885 by Flow Cytometry



Manufacturing Process Preserves T-Cell Stemness



- Following PHE885 treatment, there is a shift toward naive/T_{SCM} phenotype
- Shift to T_{SCM}/T_{naive} population observed in CD4+ and CD8+ T-cells in patients with ≥ VGPR but not wi

Sperling. ASH 2021. Abstr 3864.

Cautions with New Approaches

- More effective treatments results in more severe immunosuppression
- Noted in the context of post covid vaccine responses
- Noted with higher use of IVIG
- Noted with more infectious AEs with TCE, MOAB, CART

- Continuous therapy models may not be optimal ways to deliver therapy

Neutralizing antibodies to COVID are blocked by potent Immune therapies

Treatment			
Line 1—including maintenance	100	2.00 (1.05 to 3.79)	.034
Line 2+ with anti-CD38 mAb	72	0.53 (0.27 to 1.05)	.069
Line 2+ without anti-CD38 mAb	66	—	—

Nooka et al, JCO 2021

Resistance Mechanisms

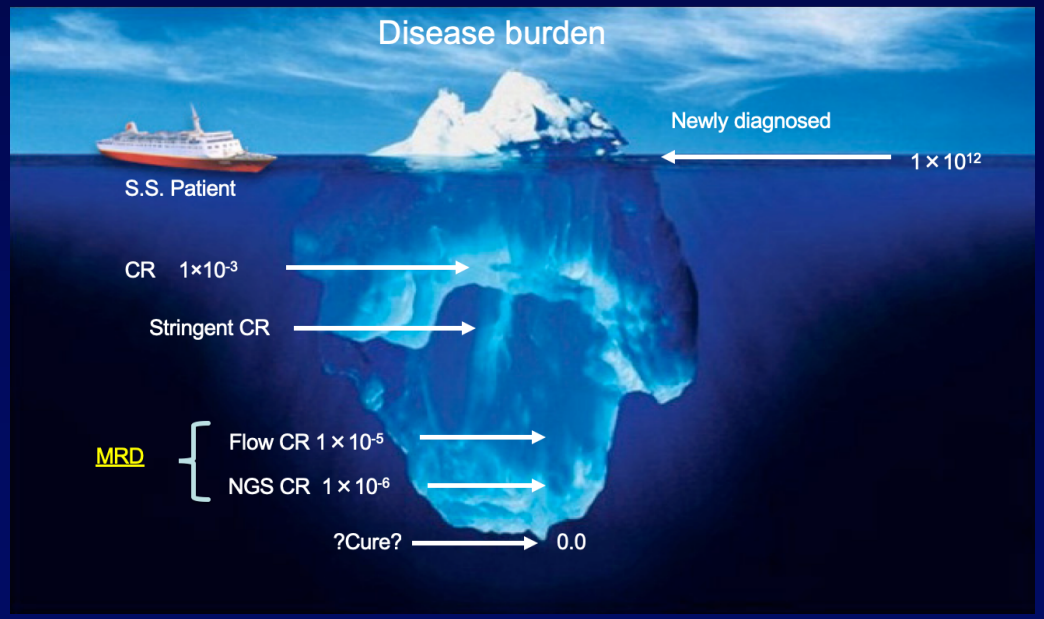
- CART resistance may be either primary (target loss, proliferation, IS microenvironment), or secondary (lack of persistence, induced exhaustion)
- TCE resistance maybe related to poor T-cell health, exhaustion, or target mutation/loss

Concerns with selective pressure on the receptor are a major concern with TCE

Model for elimination of the malignant clone
Depth ≠ Duration

Induction
(goal to achieve deep response)

Depth

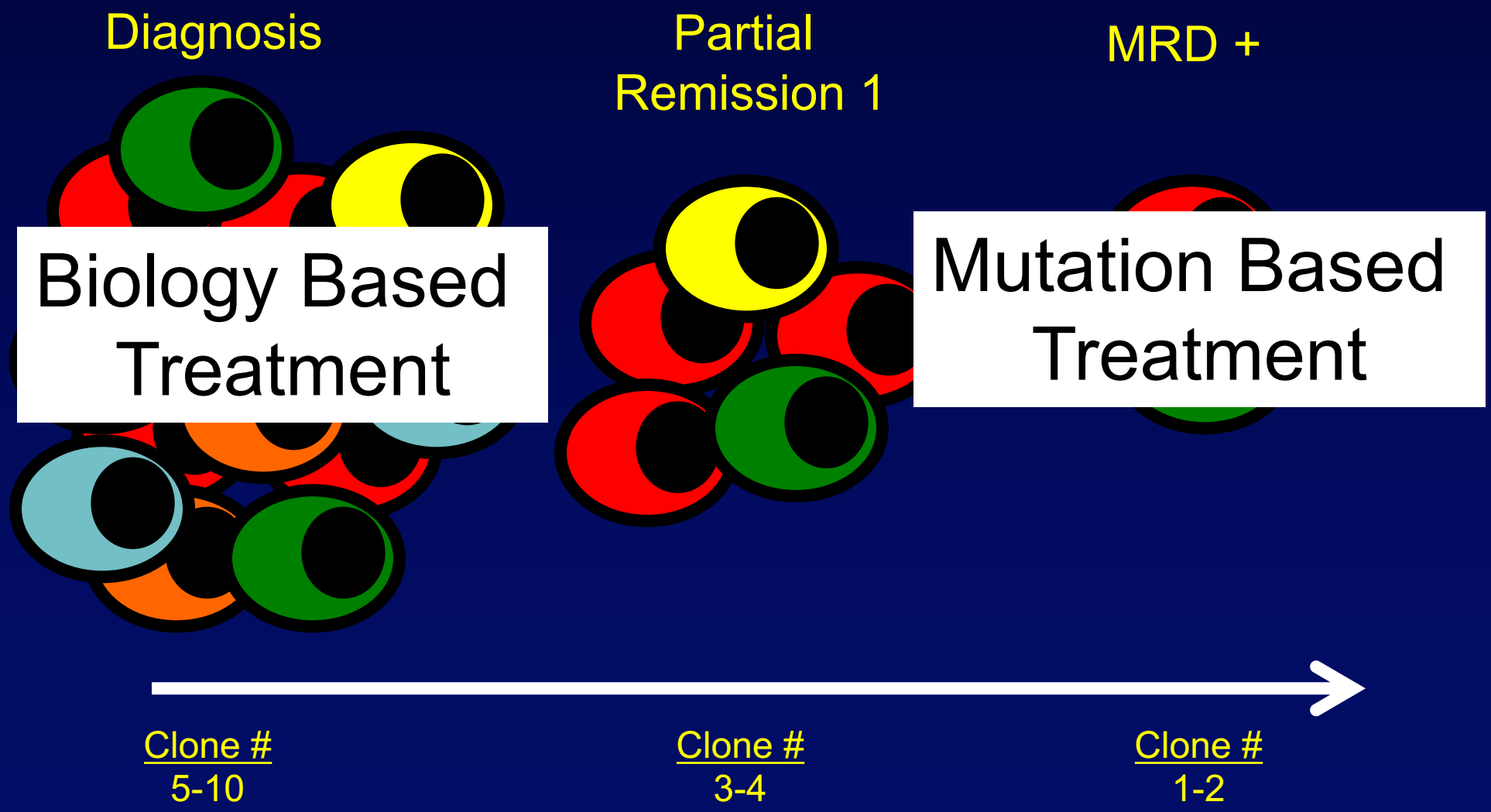


Probably different drugs
To address resistant clones

Duration

Consolidation/Maintenance
(to achieve Cure)

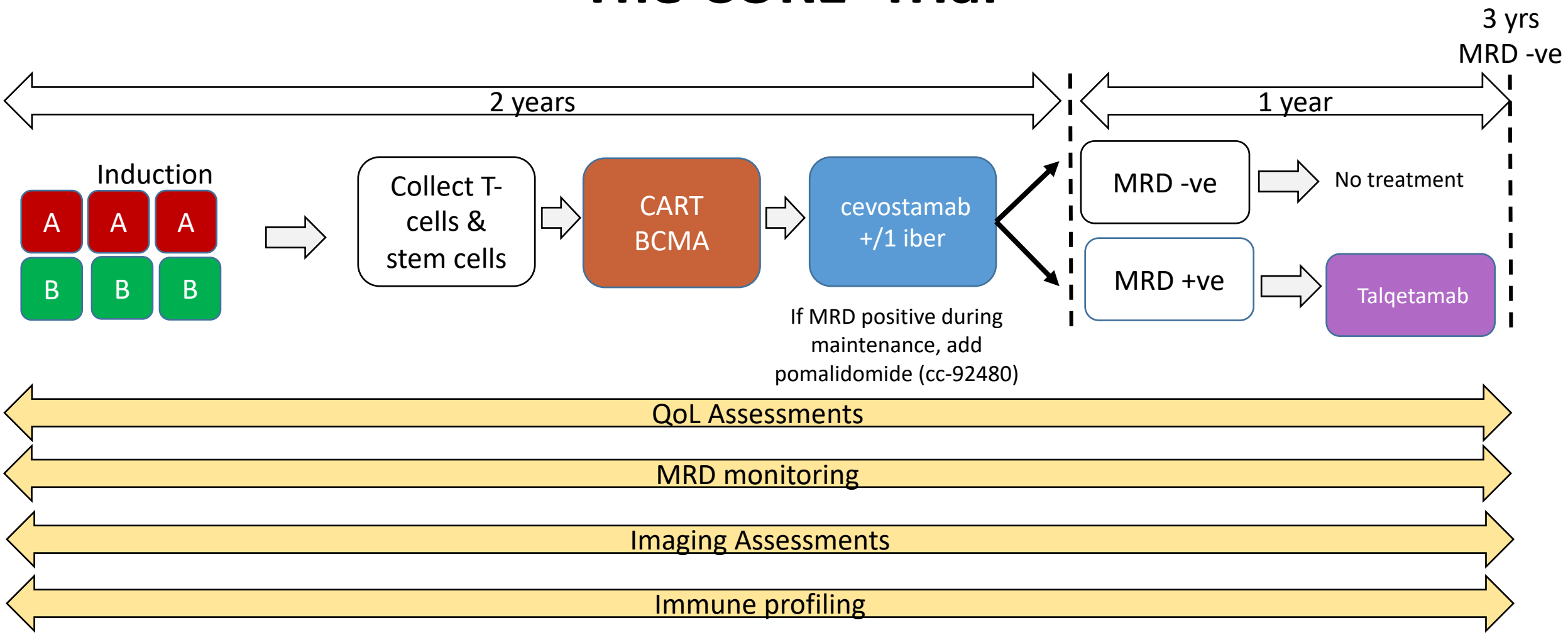
Clonal Evolution During Induction



Immune therapy circa 2021

- We now have multiple immune targets including CD38, SLAMF7, BCMA, GPRC5d and FCRH5
- Their expression is somewhat consistent across different genetic and treatment groups.
- Focus now needs to be on a strategy for integration of target and modality (CART vs Bispecific vs MOAB) and how we can enhance immune function to best optimize each of the above approaches.

The CURE Trial



A: Daratumumab/Carfilzomib/dexamethasone
B: iberdomide)/BCMA TCE/dexamethasone

What does the future look like?

- Combination therapy
- Mixing targets
- Post cart maintenance with imids/celmods, and possibly TCEs
- Limited duration therapy (another possible benefit of combination therapy)
- The backbones of disease treatment (IMIDS, Pis and CD38) will remain important ways to reduce tumor burden

Patients and Families

Thanks to:

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Larry Boise

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T.J. Martell Foundation

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