Myeloma as a Paradigm for Targeting Tumor in its Microenvironment

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DISCLOSURES OF COMMERCIAL SUPPORT

Name of Company	Research support	Employee	Consultant	Stockholder	Speaker's Bureau	Scientific Advisory Board	Other
Pfizer			x				
Astrazeneca			x				
Janssen			x				
C4 Therapeutics				x		x	
Dynamic Cell Therapies				x		x	
Window Therapeutics				x		x	
Starton Therapeutics				x		x	
NextRNA				x			
Oncopep				x		x	

Therapeutic Advances in Multiple Myeloma

Proteasome inhibitors: bortezomib, carfilzomib, ixazomib; immunomodulatory drugs: thalidomide, lenalidomide, pomalidomide; HDAC inhibitor: panobinostat; monoclonal antibodies: elotuzumab, daratumumab, and isatuximab; nuclear transport inhibitor: selinexor; Immunotoxin: belantomab mafodotin; CAR T cell: idecel, ciltacel; bispecific T cell engager: teclistamab

Target MM in the BM microenvironment, alone and in combination, to overcome conventional drug resistance *in vitro* and *in vivo*

Effective in relapsed/refractory, relapsed, induction, consolidation, and maintenance therapy; now under evaluation earlier in disease course, SMM

Minimal residual disease negativity (MRD-) associated with prolonged PFS and OS in NDMM (transplant-eligible and -ineligible) and RRMM

31 FDA approvals (16 agents), median patient survival prolonged 3-4 fold, from 3 to at least 8-10 years, and MM is a chronic illness in many patients

Treatment Targeting Myeloma in its Bone Marrow Microenvironment

Novel strategies to overcome drug resistance and immunosuppression:
Triggering immunogenic cell death to overcome high risk MM
EZH2 inhibitor to increase CD38/48 expression and ADCC

Earlier Use/Improved Efficacy/Availability of CAR T cells:
Novel constructs (PHE855, CC98633, BAT CAR, SMAR)
Monitoring both target antigen expression and immune profile to inform therapy

Improve Therapeutic Index of Bispecific T cell Engagers:
Scientifically-informed combinations: ie, with immunogenic cell death inducers
Monitoring target antigen expression and immune profile to inform use/improve therapeutic index
Novel constructs (RG6234, trispecific T and NK cell engagers)

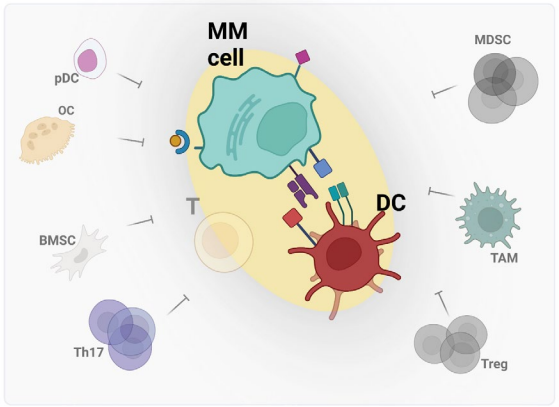
Both persistent minimal residual disease negativity and normalization of immune profile as goals of therapy

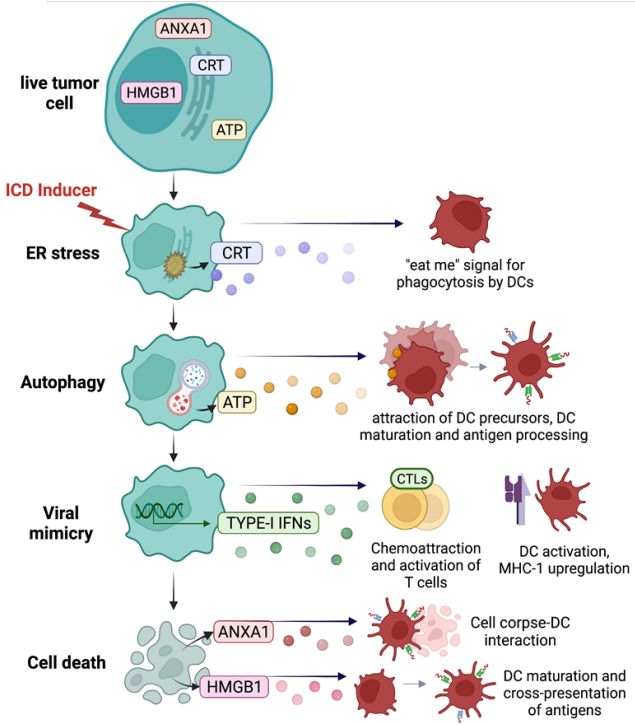
Triggering Immunogenic Cell Death in the Immunosuppressive MM Microenvironment

***Immunogenic cell death* (ICD)** → **Immune activation**

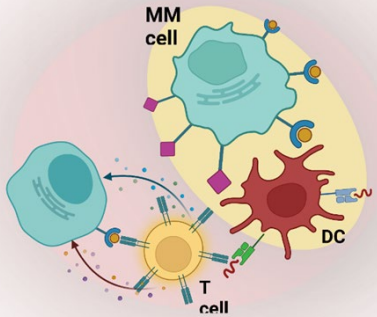
Can we overcome high risk disease?

Immunosuppressive MM Microenviroment





Immune activation



Johnstone M. et al Cells 2022

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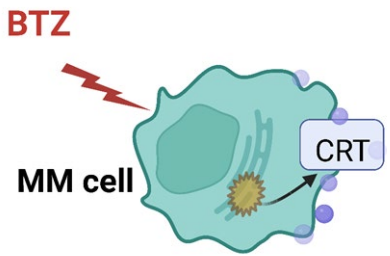
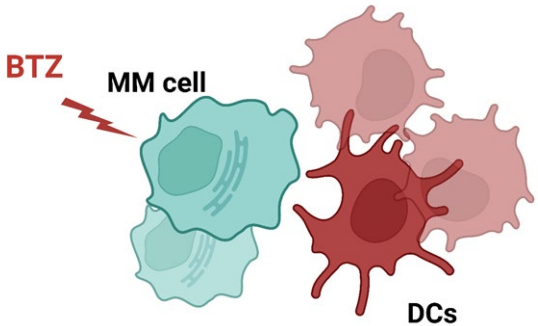
Bortezomib Induces Immunogenic Cell Death (ICD) in MM

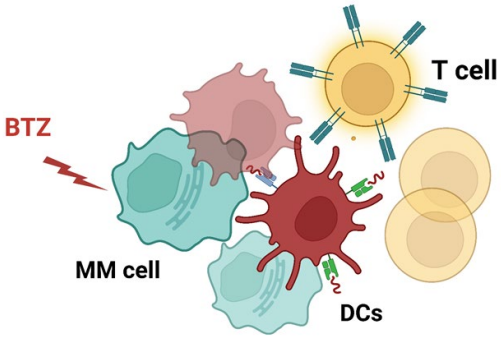
1. Cell death and DAMPs

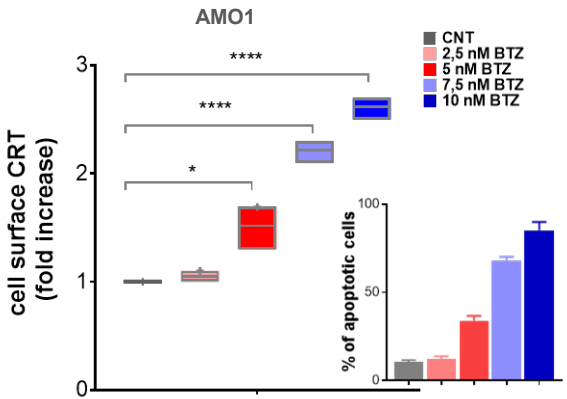


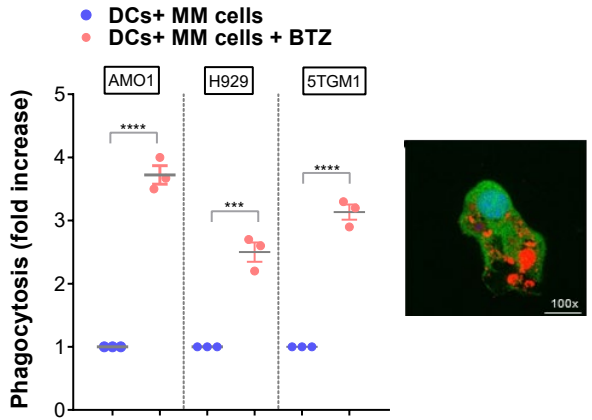
2. DCs recruitment and maturation

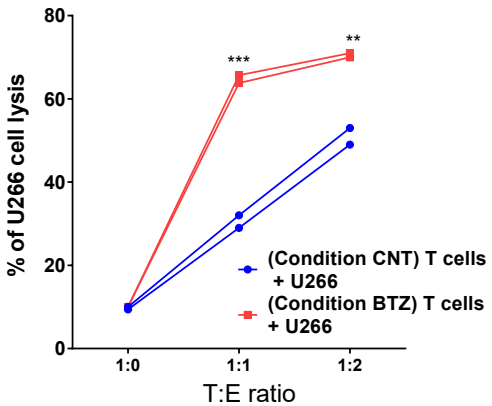


3. T cell recruitment and priming









Gulla et al, Blood Cancer Discovery 2021; 2: 468-83; ASH 2022

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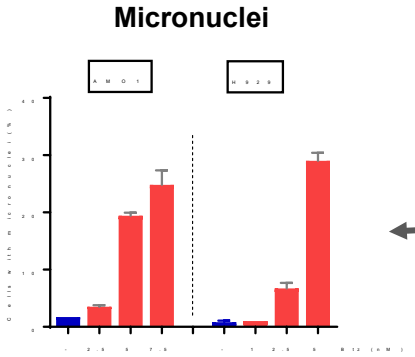
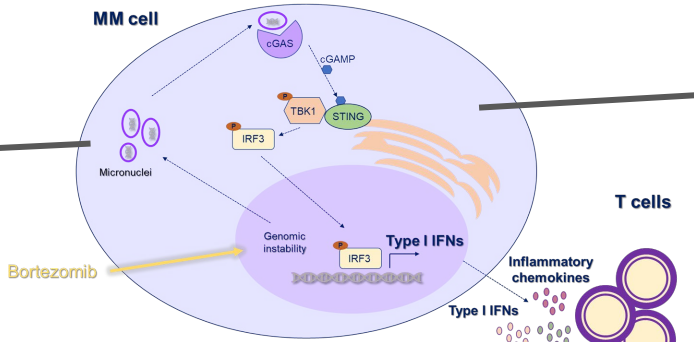
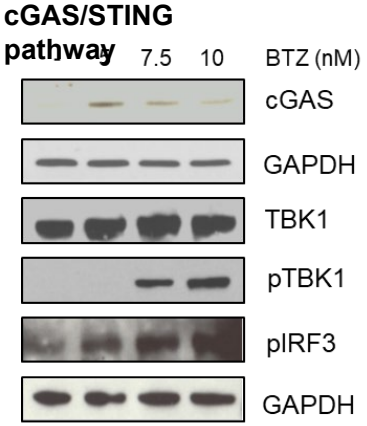
Bortezomib Induces Immunogenic Cell Death via cGAS/STING Pathway and Type I IFN Response

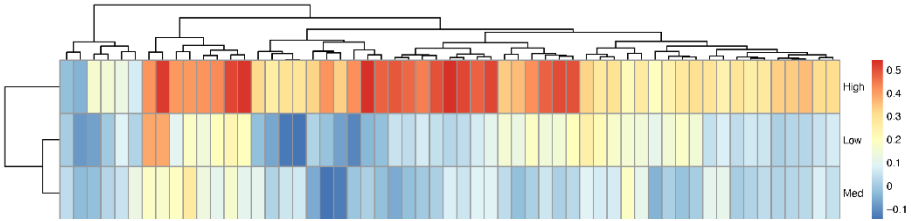






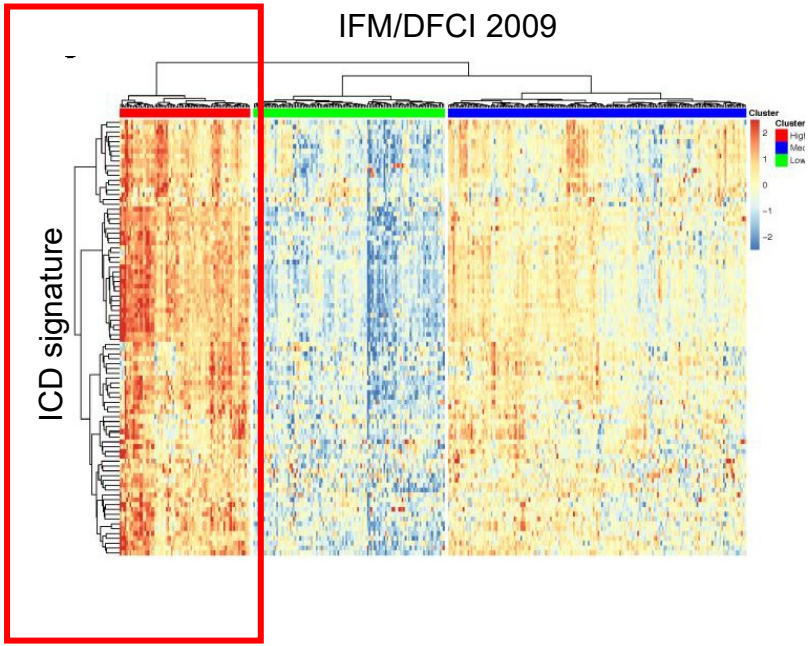
Sting Agonist to Induce Immunogenic Cell Death in MM

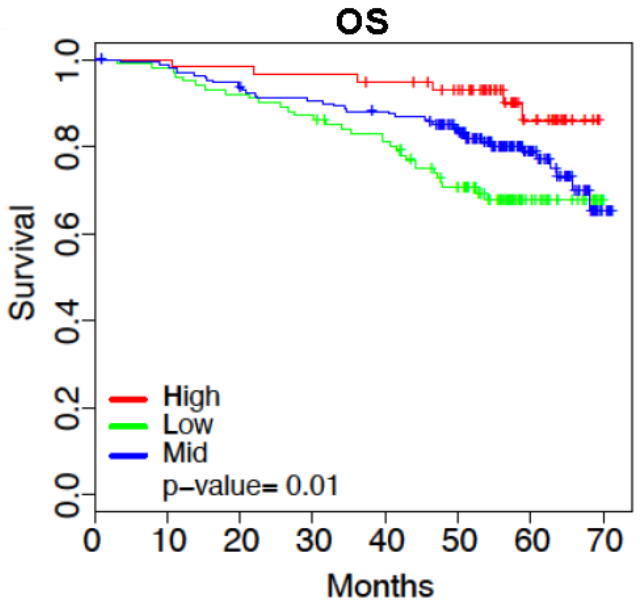
STING correlates with ICD (Type I IFN) -signature in MM patients



Gulla et al, Blood Cancer Discovery 2021; 2: 468-83; ASH 2022

Induction of ICD Contributes to Therapeutic Response to BTZ in Myeloma





Gulla et al, Blood Cancer Discovery 2021; 2: 468-83; ASH 2022

Delineating Mechanisms of Resistance to BTZ-Induced ICD in High Risk MM

Newly diagnosed MM patients (IFM/DFCI)

LongTermSurvival (>5years)
versus
ShortTermSurvival (<1.5years)

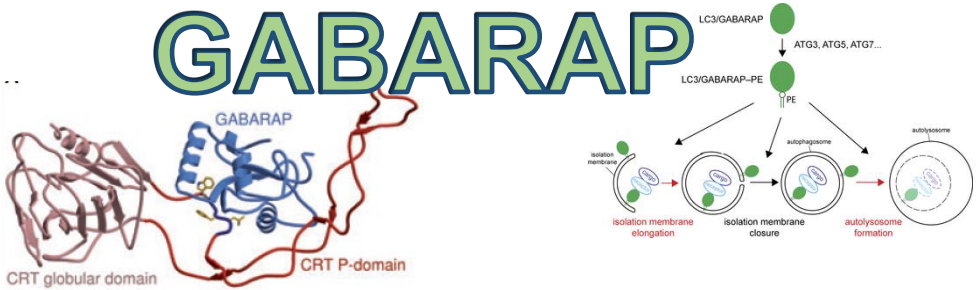
↓

differentially expressed genes

Genes correlated with MM patient OS

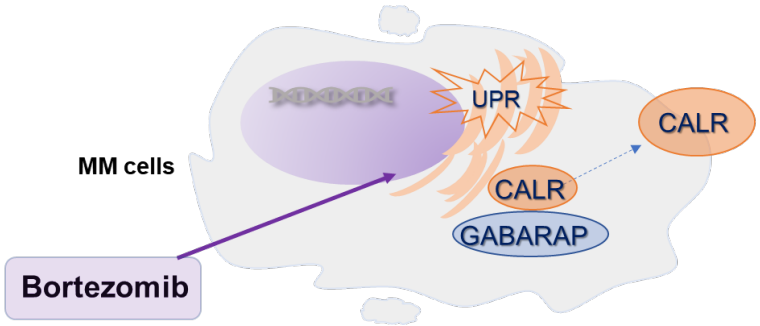
Genes involved in ICD mechanisms

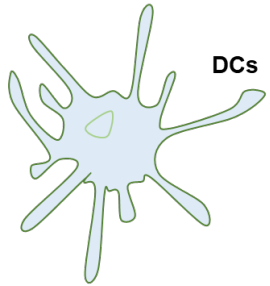
Gulla et al, Blood Cancer Discovery 2021; 2: 468-83; ASH 2022

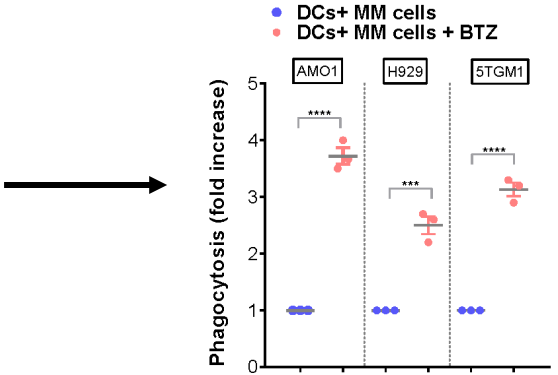


Thielmann Y. *et al.* (2009) *FEBS J.*
Martens S. (2016) J Cell Biol

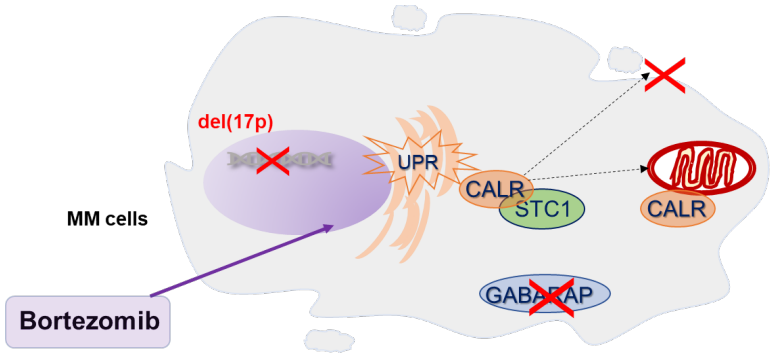
Bortezomib induces ICD in Standard Risk MM

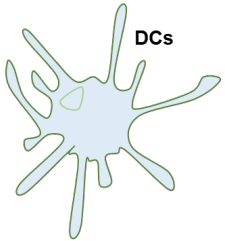


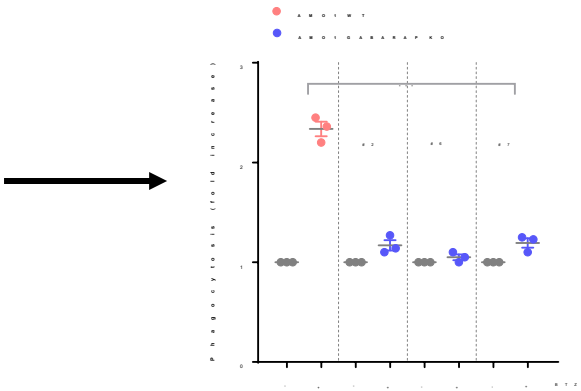




Loss-of-function of GABARAP (on 17p) in High Risk MM Abrogates ICD





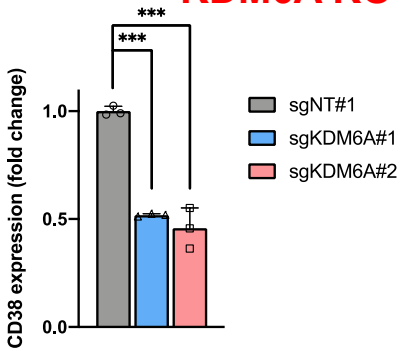


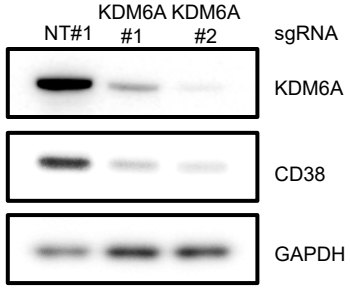
Novel Therapies (Stanniocalcin Inhibitor or Autophagy Inducers) to Trigger ICD in HR MM

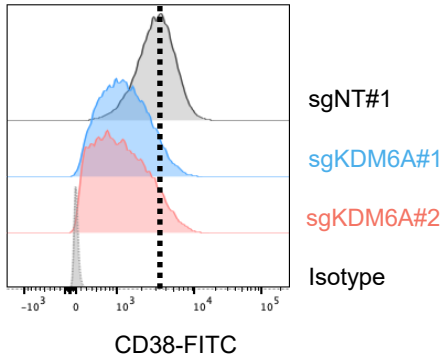
Gulla et al, Blood Cancer Discovery 2021; 2: 468-83; ASH 2022

Genome-wide CRISPR-Cas9 Screen Identifies KDM6A As A Modulator of Daratumumab Sensitivity in MM

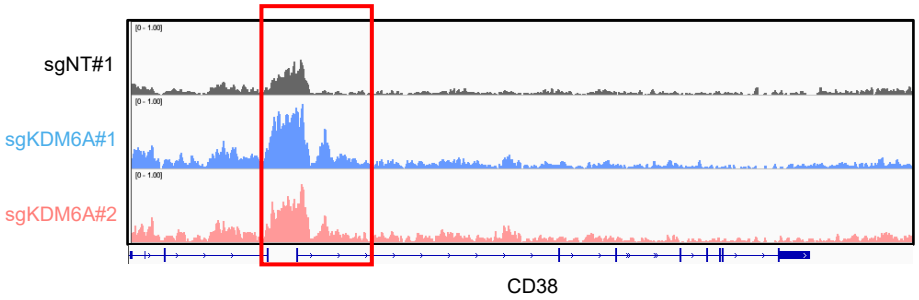
KDM6A KO decreases CD38 expression in MM cells

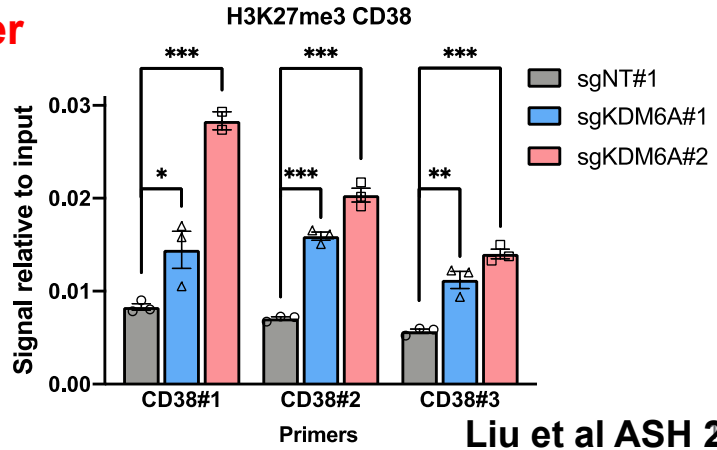






KDM6A KO Increases H3K27me3 on CD38 Promoter



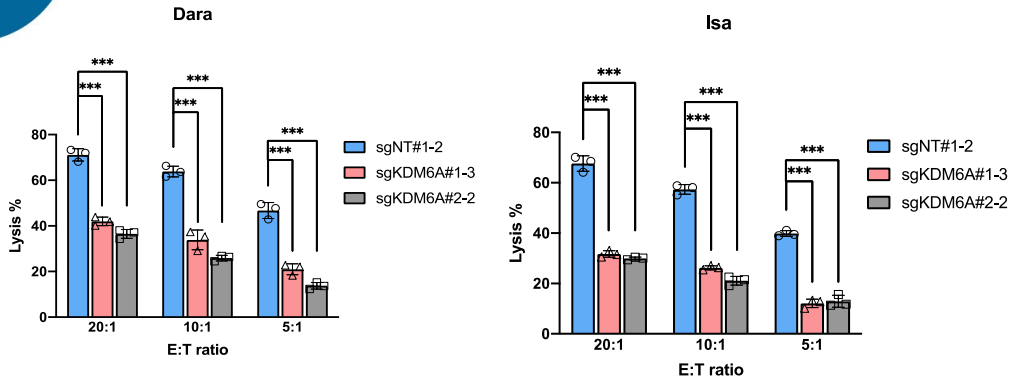


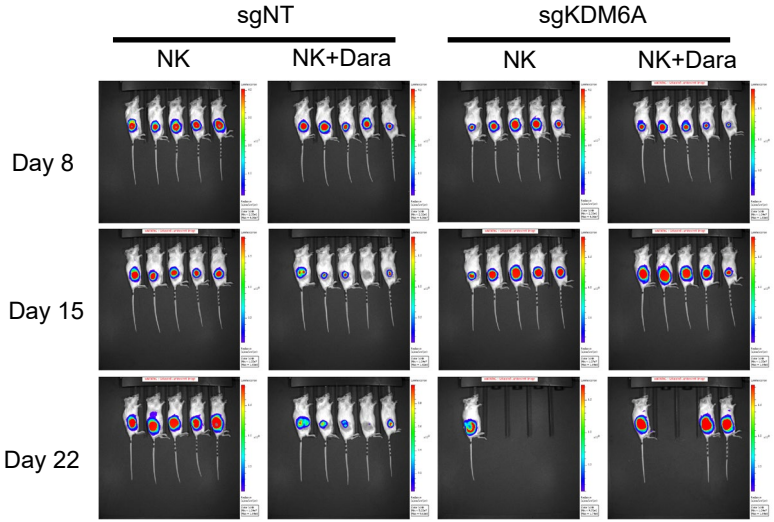
Dana-Farber Cancer Institute

Liu et al ASH 2022

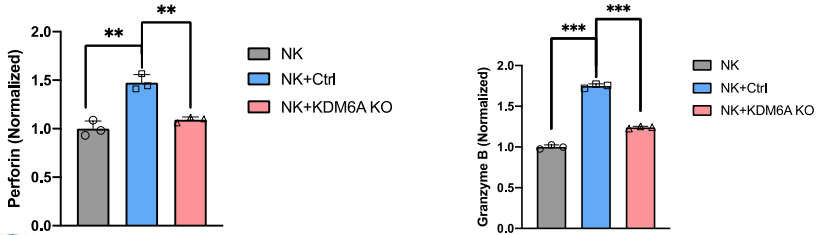
KDM6A KO Decreases In Vitro and In Vivo Cytotoxicity Induced by Daratumumab and Isatuximab

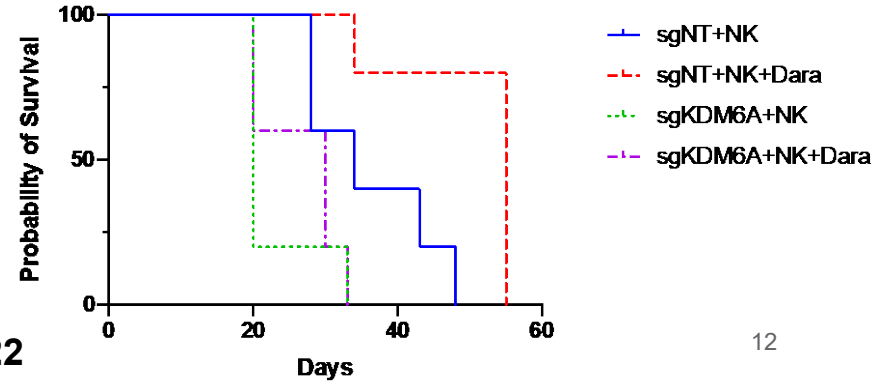
Decreased in Vitro NK lysis





Decreased Perforin/Granzyme B Release





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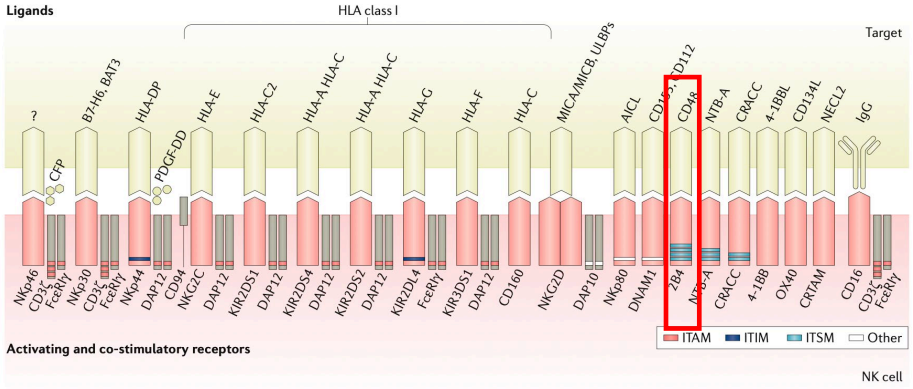
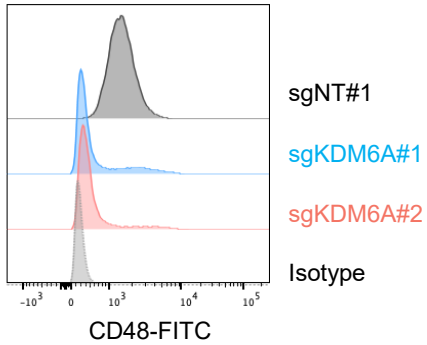
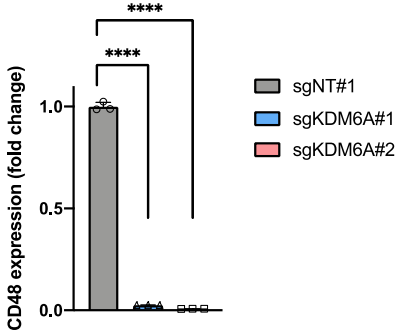
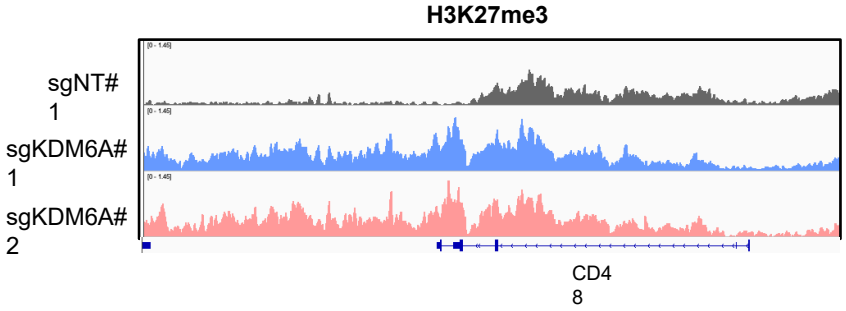
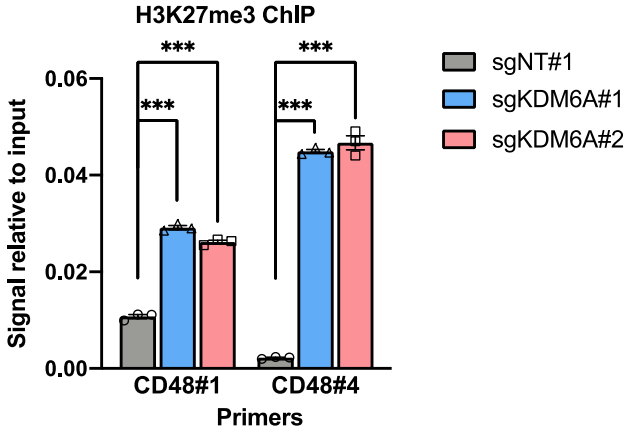
KDM6A KO Decrease CD48 Expression in MM cells











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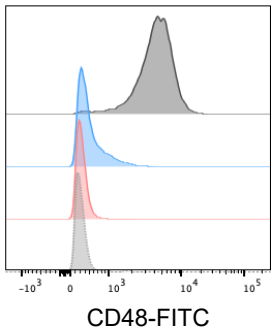
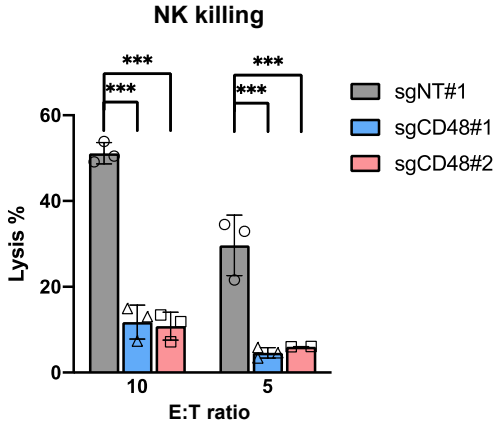
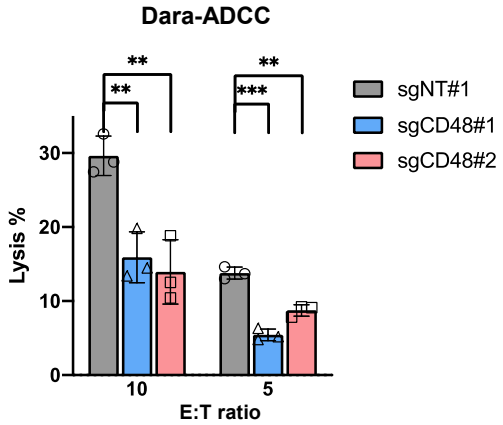
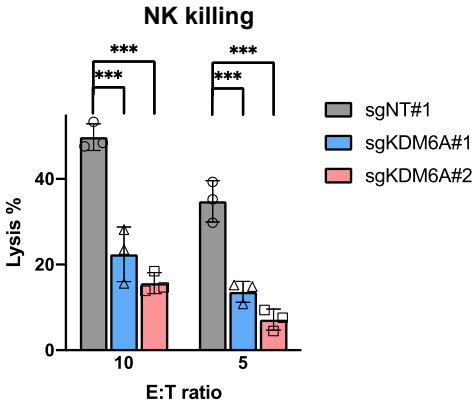
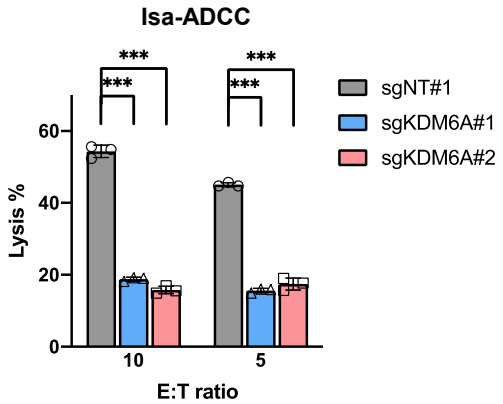
CD48 on MM Cells Modulates NK Cell-Mediated Cytotoxicity and ADCC











Liu et al ASH 2022

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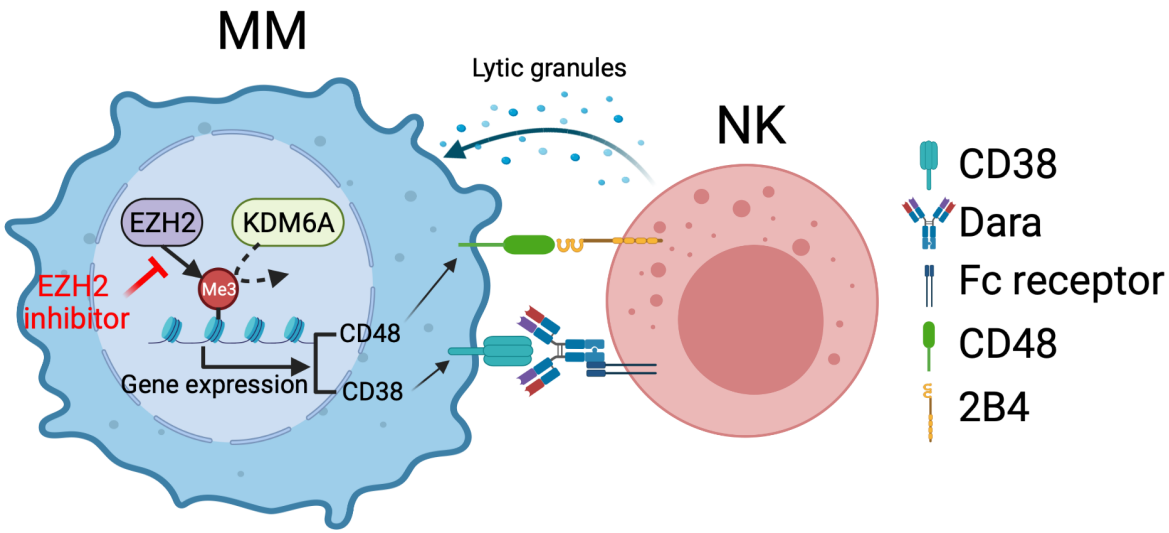
EZH2 Inhibition to Restore Expression of CD38/CD48

Balanced CD38/CD48 transcription

Inhibition of CD38/CD48 transcription

Liu et al, ASH 2022

EZH2 Inhibitor is a Novel Strategy to Increase CD38 and 48 Expression and ADCC

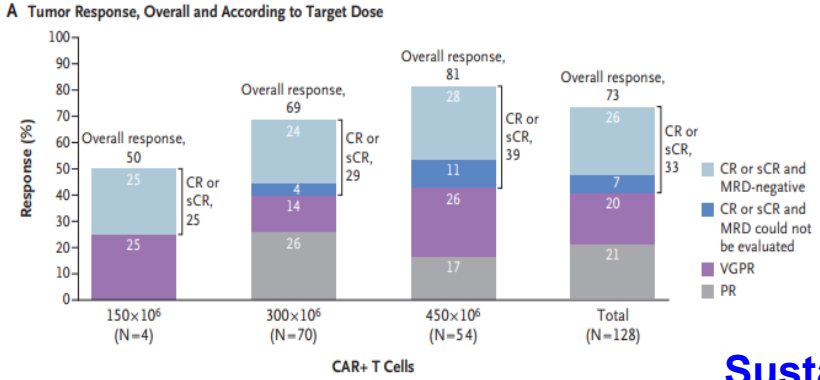


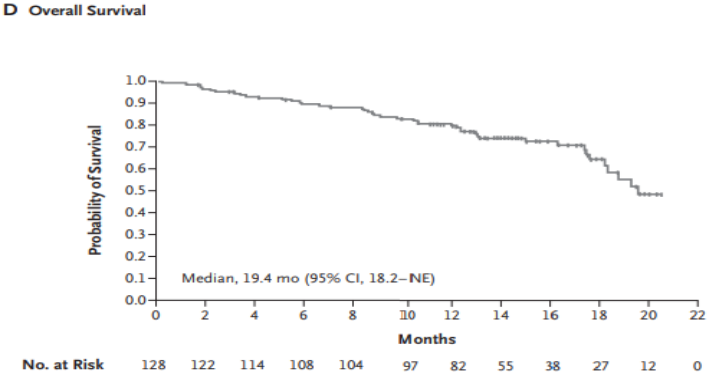
Inactivation of KDM6A downregulates CD38/CD48 expression through H3K27me3 regulation.

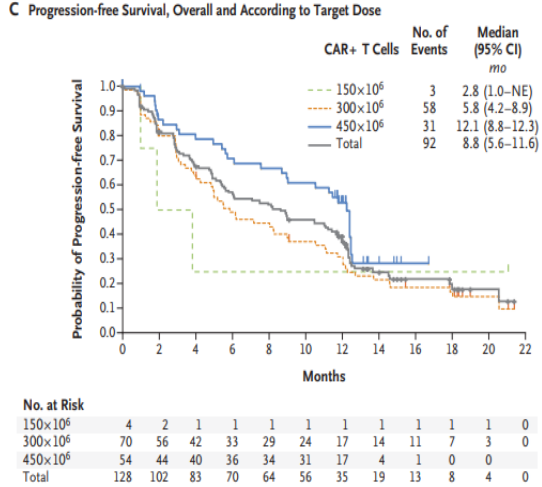
EZH2 inhibitor upregulates CD38/CD48 expression and enhances NK cell activity and Daratumamab/Isatuximab- mediated ADCC; may be useful to enhance ADCC triggered by other MoAbs as well.

Liu et al, ASH 2022

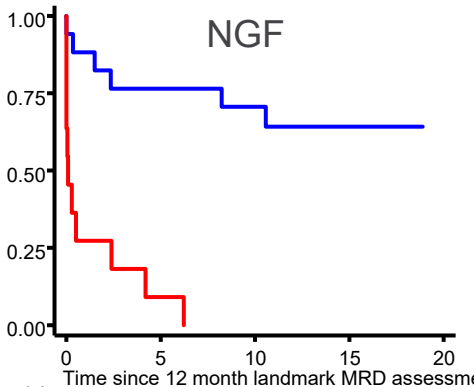
Idecel BCMA CAR T Cells in RRMM

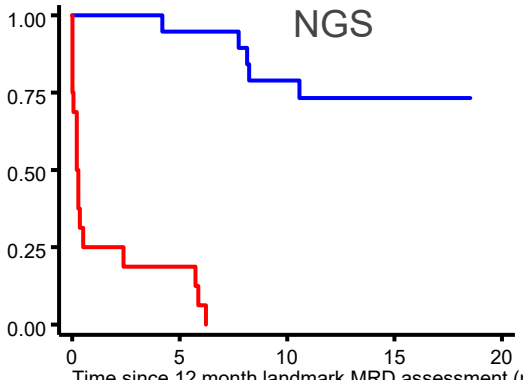






Sustained vs Unsustained MRD at 12 month landmark





Munshi et al NEJM 2021; 384: 705-16; Paiva et al ASH 2022

Ide-cel or Standard Regimens Earlier in RRMM

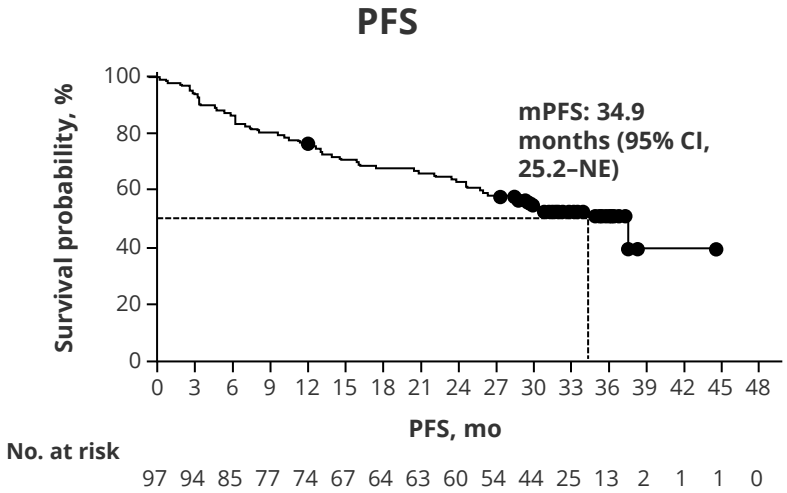
Phase III trial in RRMM after 2-4 regimens (IMiDs, PIs, Dara), refractory to last regimen
Randomized 2:1 to Ide-Cel or 1 of 5 standard regimens

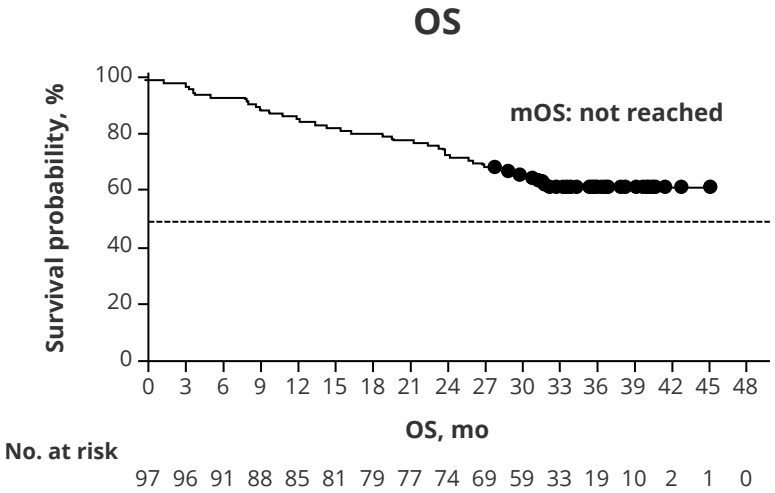
Results:
254 pts Ide-cel and 132 to standard regimen
66% triple refractory, 95% Dara refractory

At median 18.6 mos followup: PFS 13.3 mo Ide-cel vs 4.4 mo standard regimen HR 0.49, p<0.001); OS not mature
ORR: 71% Ide-cel vs 42% standard therapy (p<0.001)
Adverse events Grade $\geq$ 3: 93%% Idecel vs 75% standard therapy
Idecel: CRS 88%, 5% grade $\geq$ 3; Neurotoxocity 15%, 3% grade $\geq$ 3

Rodriguez-Otero P et al NEJM 2023; 16: 1002-14.

Final Results CARTITUDE-1 : Time-to-Event Outcomes (~3-Year F/U)





- Median DOR: 33.9 months (95% CI, 25.5–NE)
- An estimated 62.9% of patients were alive at 3-year follow-up

Munshi et al EHA 2023

DOR, duration of response; mPFS, median PFS; mOS, median OS; NE, not estimable; OS, overall survival; PFS, progression-free survival.
1. Berdeja JG, et al. *Lancet* 2021;398:314-24. 2. Martin T, et al. *J Clin Oncol* 2023;41:1265-74.

CARTITUDE-4: 1 to 3 Prior Therapies
Primary Endpoint – PFS (ITT Population)

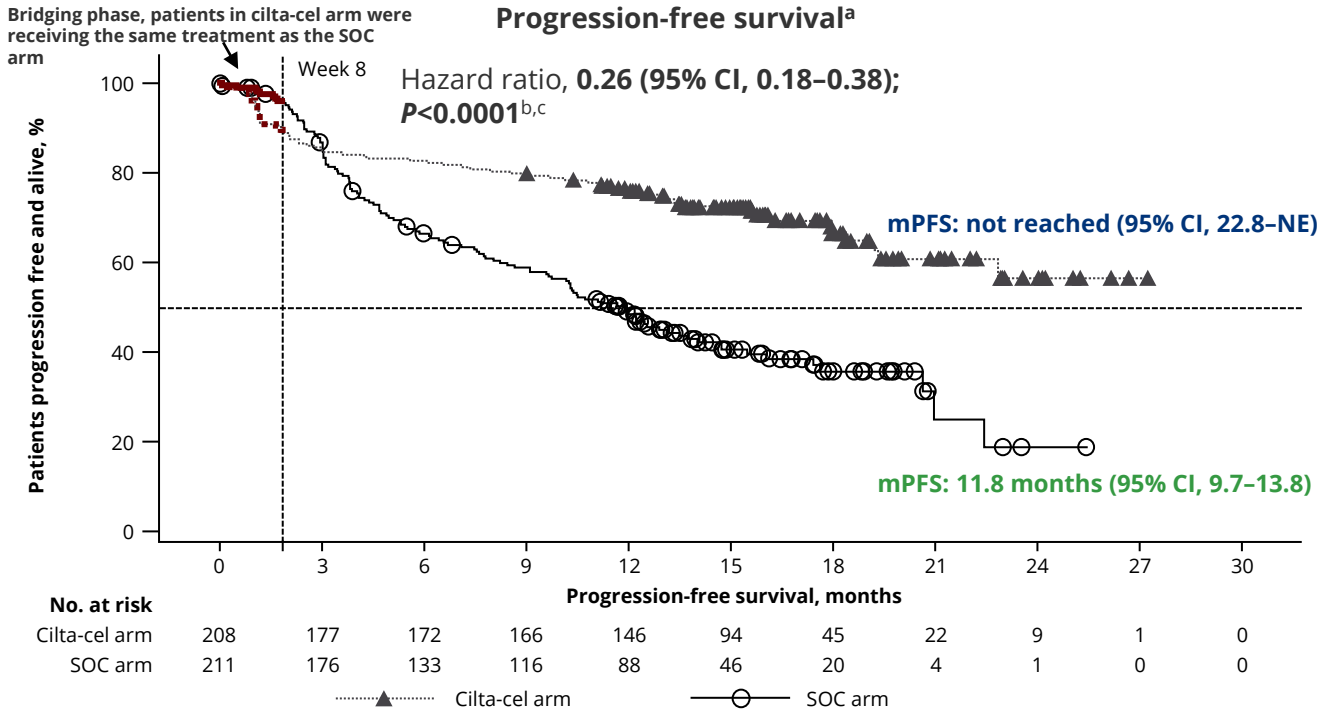
Cilta-cel vs SOC

Len Refractory

SOC Dara Pom Dex or Dara Vel Dex

12-month PFS rate: 76% vs 49%

SOC performed as expected



San Miguel et al ASCO, EHA 2023 NEJM 2023

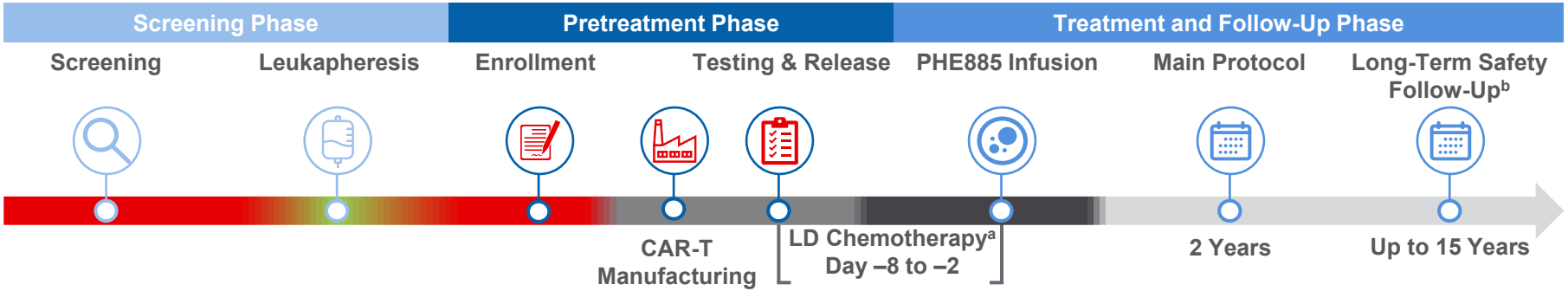
PHE885: Study Design

- **PHE885 is an autologous, fully human, BCMA-directed CAR-T cell therapy manufactured in <2 days using the next-generation T-Charge™ platform**

T-Charge™

Has <2-day manufacturing time[6,7] and aim of <10-day door-to-door time in the United States	**Preserves T-cell stemness,[6-8]** maintaining the stem and central memory T cells[8]	**Enhances in vivo expansion[6,7]** with the potential to improve efficacy, and increase persistence and durability of response

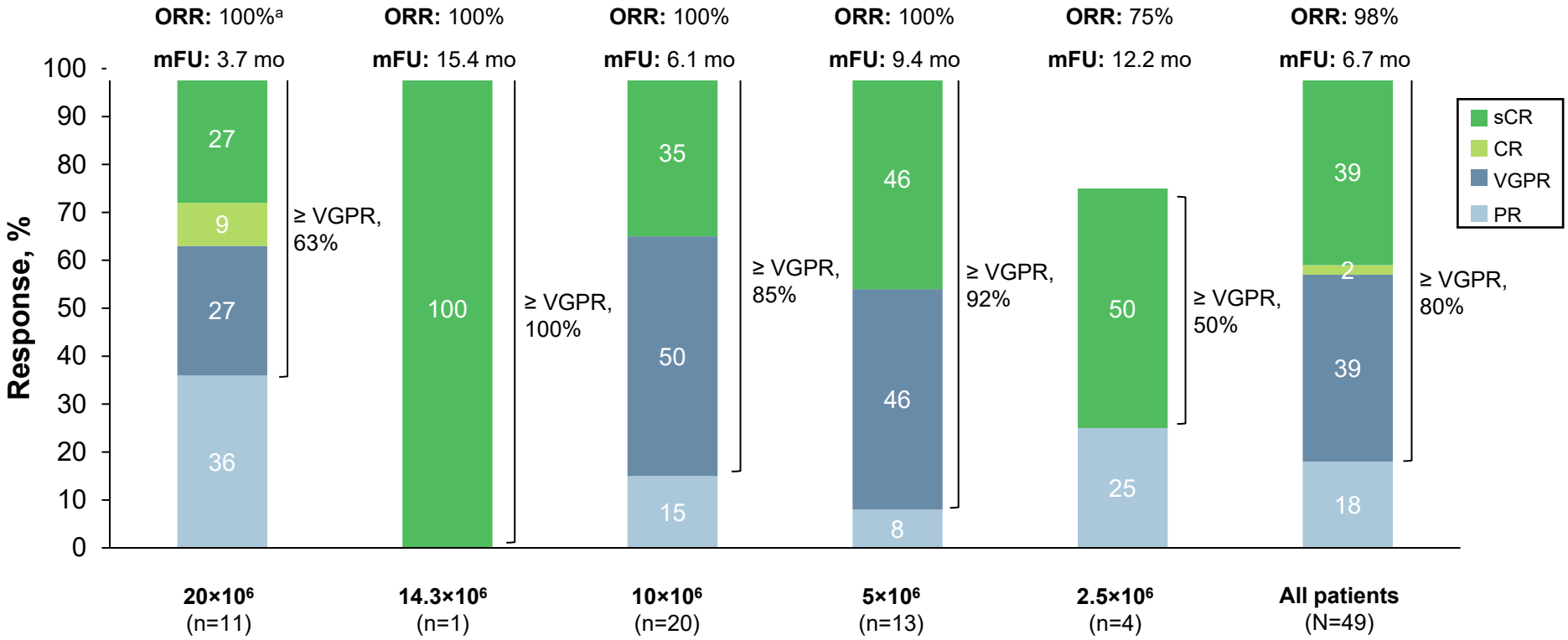
- This presentation focuses on updated clinical data from the Phase I trial (US only) with 50 patients treated (NCT04318327) and 6.7 months median follow-up (data cutoff March 28, 2023)



Sperling et al ASCO 2023

[a]LD of fludarabine/cyclophosphamide delivered over 3 continuous days within the Day –8 to Day –2 period prior to anti-BCMA CAR-T cell administration. [b]Long-term follow-up protocol conducted under a separate protocol per health authority guidance.

PHE885: 100% ORR at Active Doses of 10×10^6 and 20×10^6



- All but 1 patient at the dose of 2.5×10^6 achieved a clinical response[b]

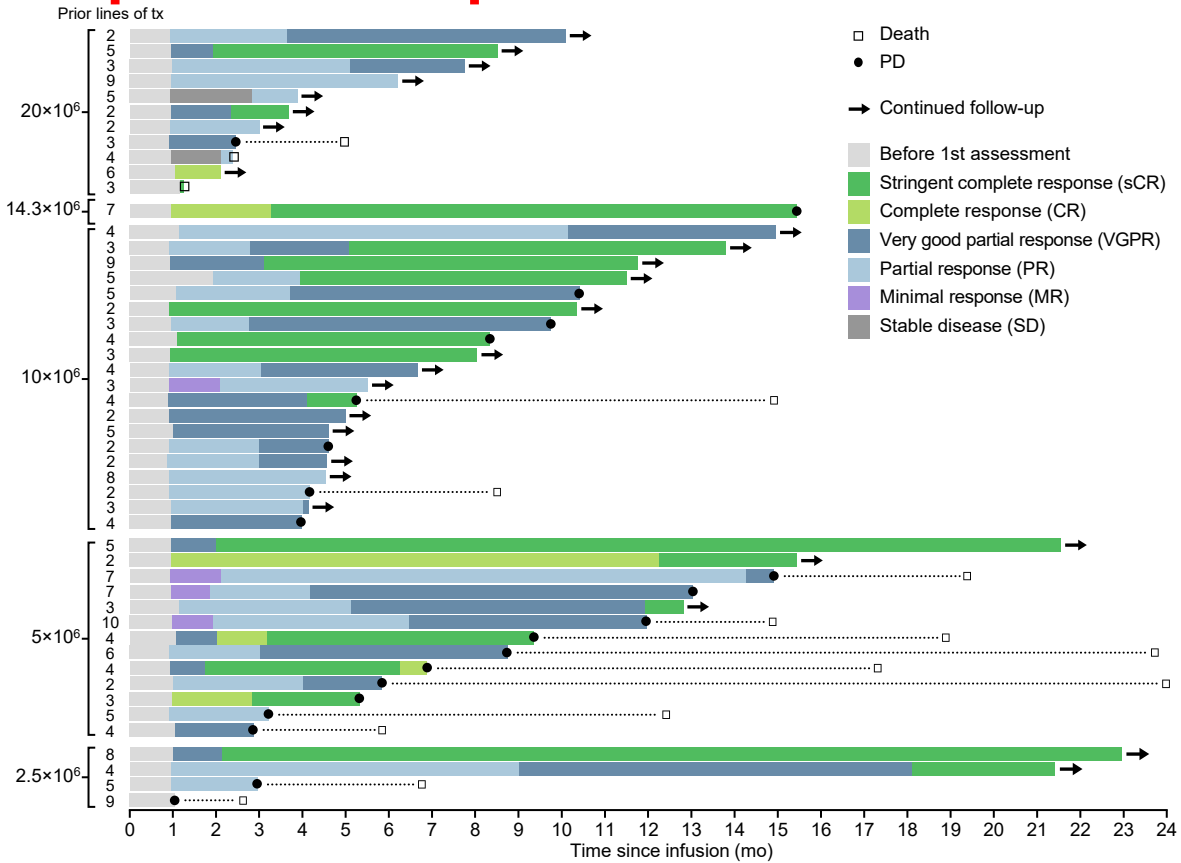
Sperling et al ASCO 2023

PHE885: Clinical Responses Deepen Over Time

- MRD negativity rate[a]:

Dose	Month 3	Month 6
20×10⁶	4/5 (80%)	3/3 (100%)
14.3×10⁶	1/1 (100%)	1/1 (100%)
10×10⁶	7/13 (54%)	5/7 (71%)
5×10⁶	6/11 (55%)	5/7 (71%)
2.5×10⁶	0/2 (0%)	0/1 (0%)
All doses	18/32 (56%)	14/19 (74%)

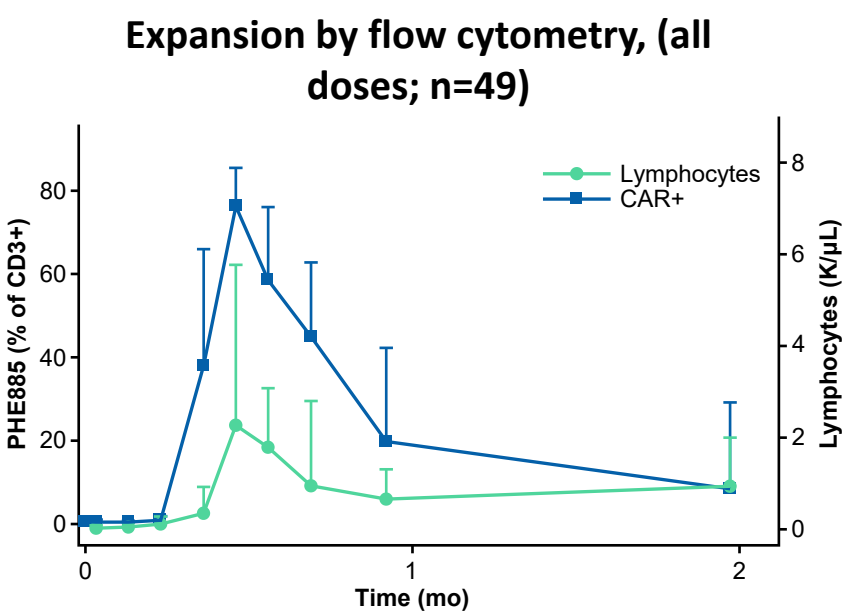
- Median time to first response was 0.95 (0.89-2.83) months and median time to best response was 2.76 (0.92-18.1) months
- **Conversion to CR/sCR occurred as late as 18 months after infusion**

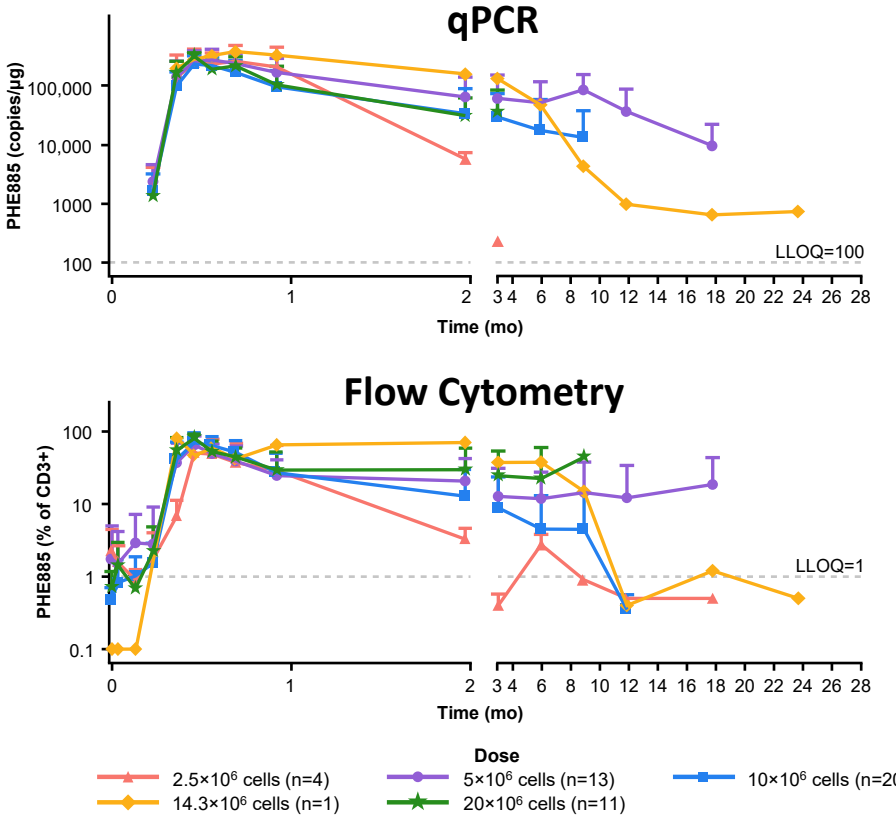


Sperling et al ASCO 2023

[a]MRD assessed by NGS with a sensitivity of 10^{-5} in all MRD-evaluable patients.

PHE885: In Vivo Expansion and Prolonged Persistence



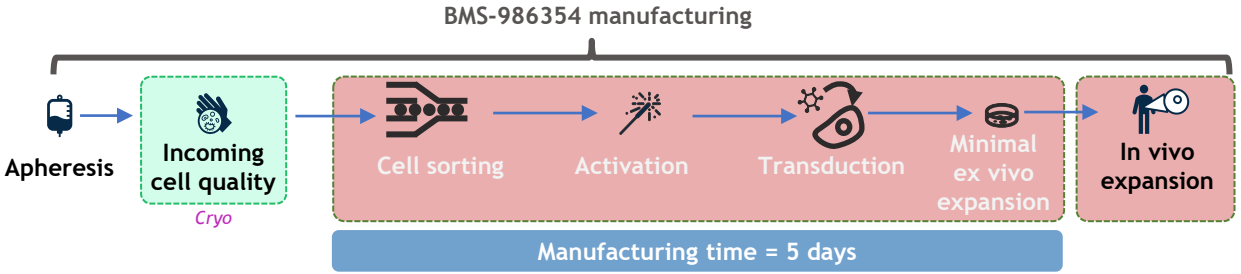


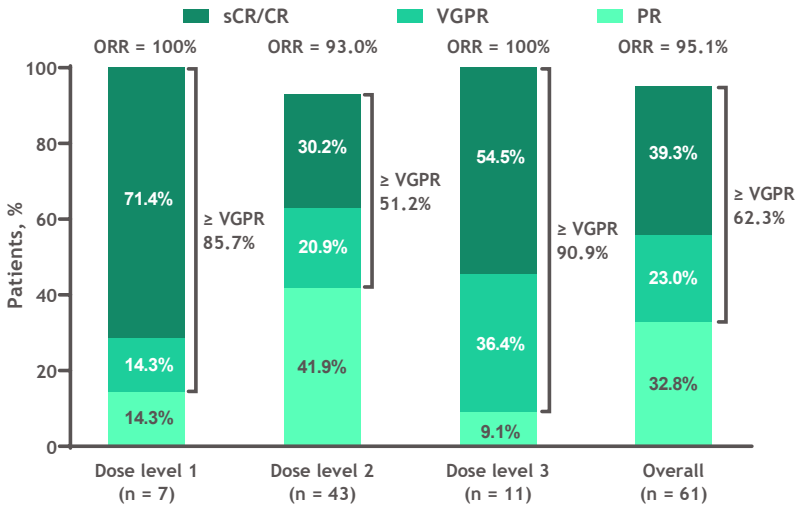
- **PHE885 cellular kinetics showed remarkable initial in vivo expansion and prolonged persistence**
- **Median time of last detectable transgene was 6 months (181 days[a])**

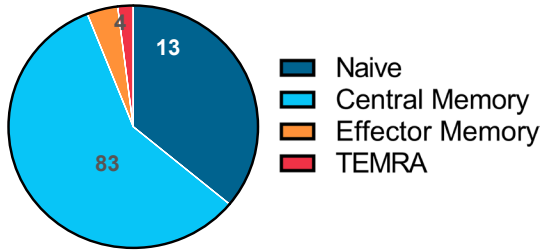
Sperling et al ASCO 2023

[a]For all patients dosed at least 9 months before the data cutoff, including patients with detectable transgene at the latest visit.

Phase 1 Trial of BCMA NEX-T CAR T Cell CC-98633/BMS-986354 in RRMM

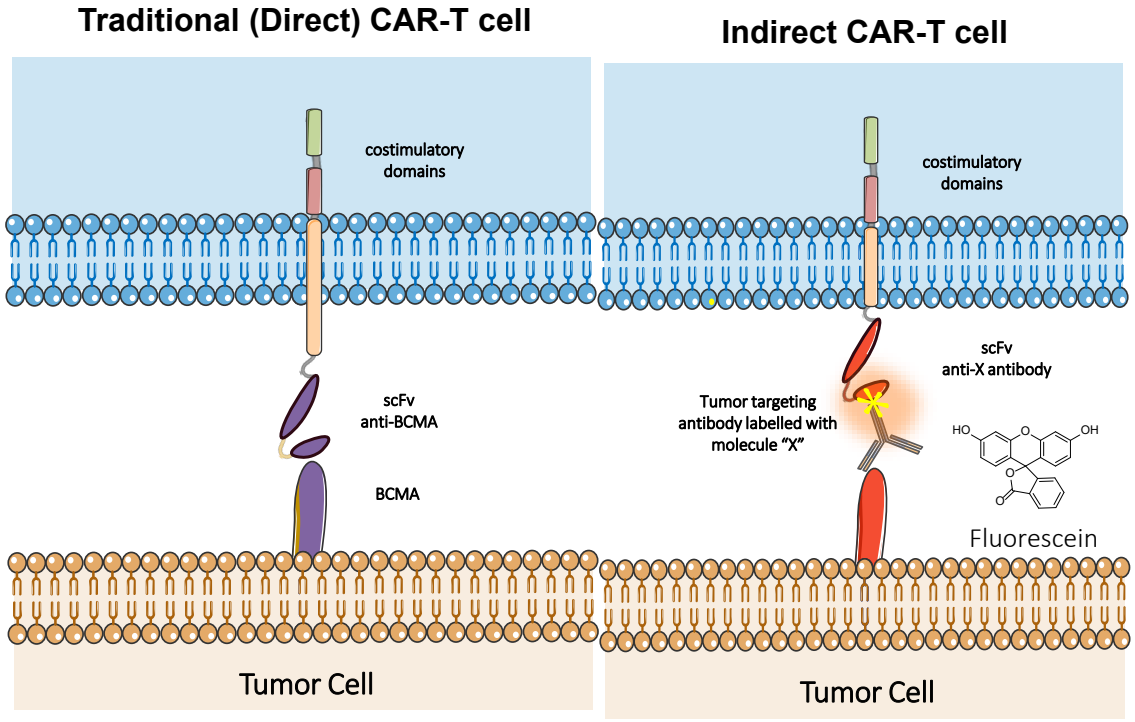


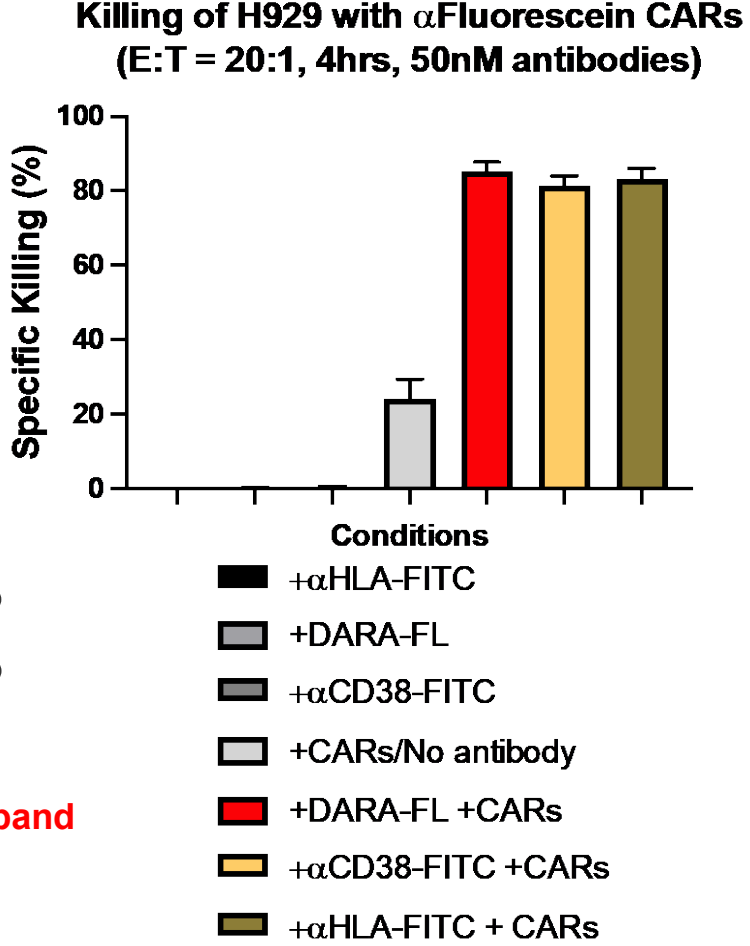




Costa LJ et al. ASH 2022

BAT-CAR: Binary Activated T Cell with Chimeric Antigen Receptor



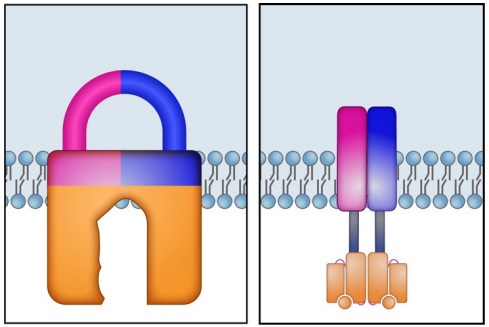


Titratability to improve therapeutic window; Multiplexability to expand use of existing targets; Redundancy to prevent antigen escape

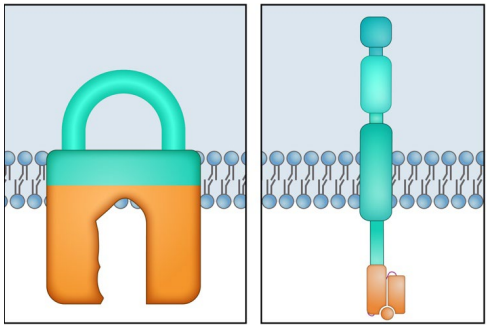
Kobayashi A et al Chem Med Chem 2022;20:17:e202100722.

Small Molecule Activated Receptors (SMARs): Receptors with Binding Specificity for Select Small Molecules

Chimeric Cytokine Receptor (CCR)



Chimeric Antigen Receptor (CAR)



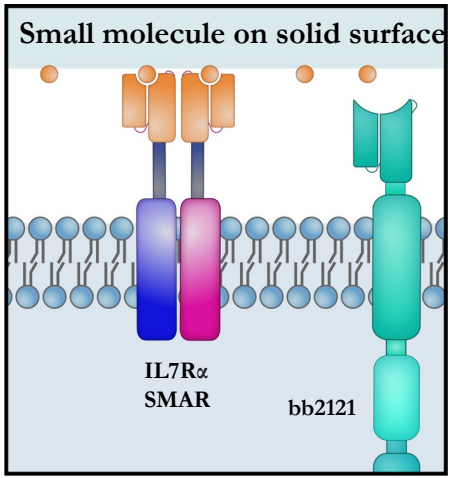
Chimeric cytokine receptors (CCRs) and chimeric antigen receptors (CARs) can both be delivered to the same cell.

When antigen and cytokine receptors are activated together:

- **Potent memory responses induced**
- **Potentiates CD8 memory T cell killing**
- **Potential for Treg memory**

Novina et al 2023

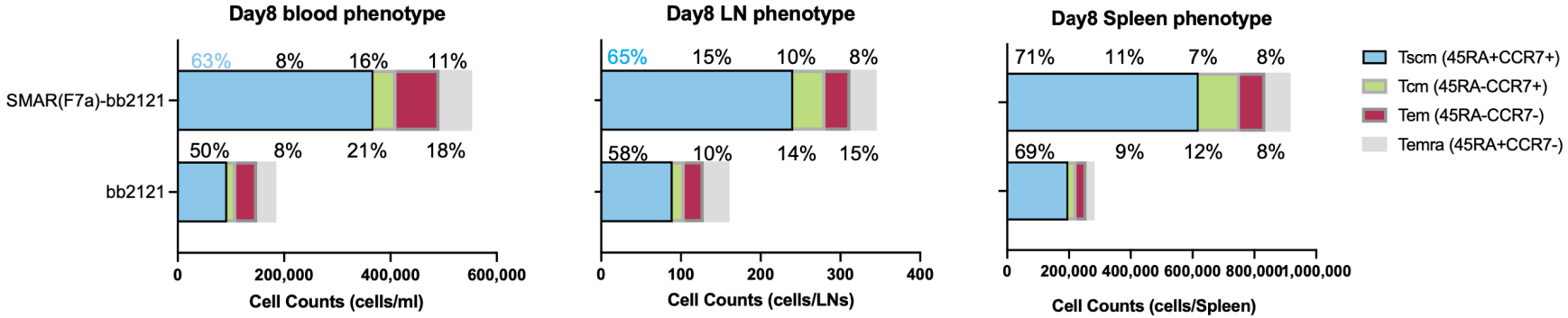
Activation of IL-7Ra SMAR *Ex Vivo* Generates Increased Memory CAR-T Cells *In Vivo*



Novina et al 2023

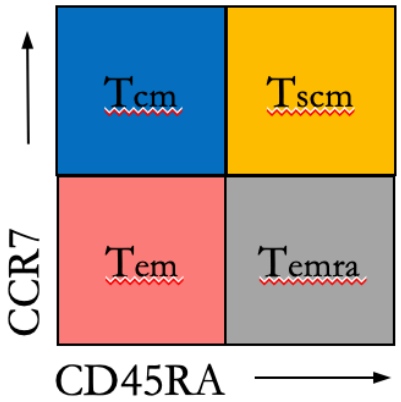
8 days after CAR-T cell dosing:

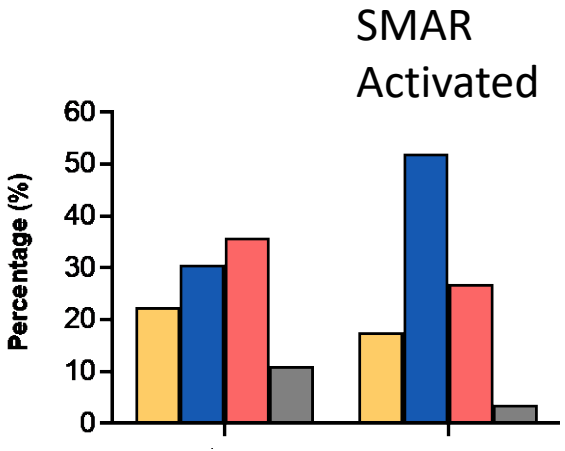
IL7Rα-bb2121 shows increased memory phenotype (CD45RA/CCR7) and cell expansion in MM.1S bearing mice



IL-7Rα SMAR Activation in Ciltacel Induces Tcm Phenotype

Phenotype of T cells

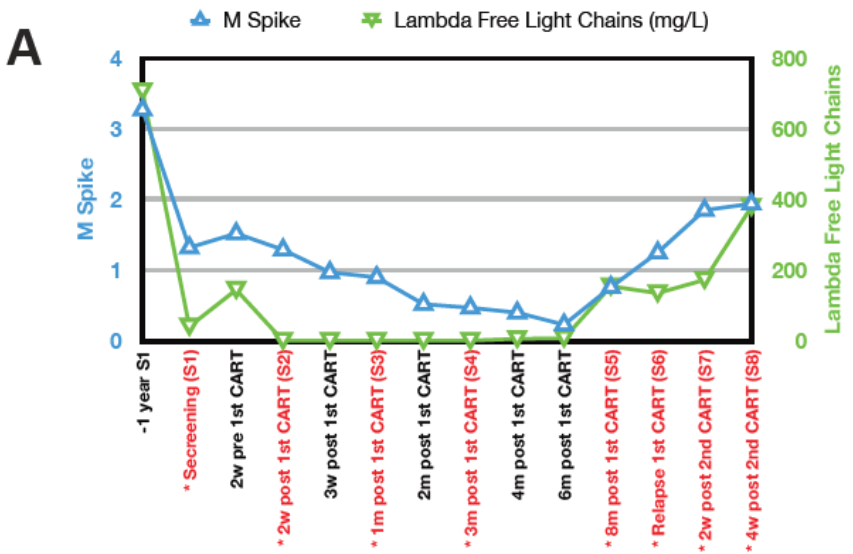


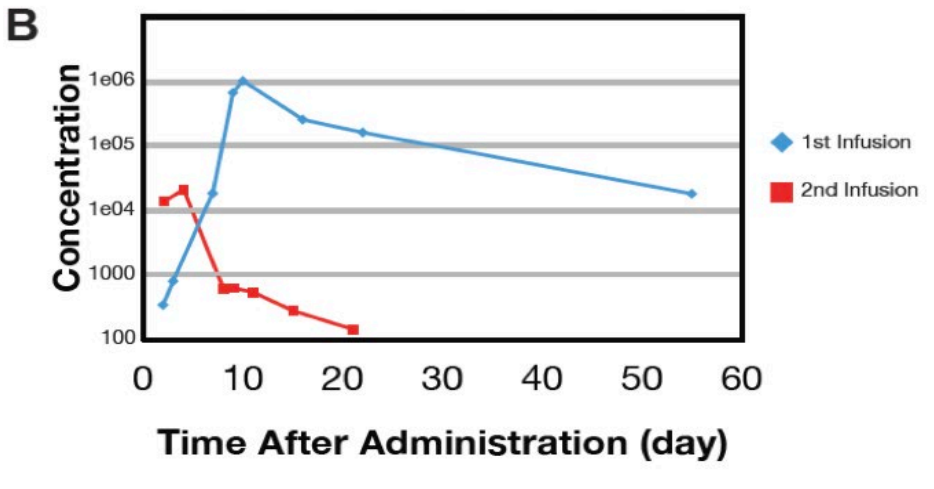


- Stem-cell memory (Tscm) CCR7+CD45RA+CD95+
- Central memory (Tcm) CCR7+CD45RA-
- Effector memory (Tem) CCR7-CD45RA-
- Terminally differentiated (Temra) CCR7-CD45RA+

Novina et al 2023

Biallelic BCMA Loss Confers Resistance to BCMA Immunotherapy





Monoallelic deletion of BCMA on 16p13.13 in 8.58% NDMM (n=2458) associated with del 1p (OR 19.37) and del 17p (OR 8.8); should we screen before BCMA therapy?

Alternative (dual) targets: GPRC5D, CD19, FcHR5, CD38, CD138, SLAMF-7

Samur et al Nat Comm 2021; 12: 868; Samur et al IMW 2022

Changes in Bone Marrow Tumor and Immune Cells Correlate with Durability of Remissions Following BCMA CAR T Therapy in Myeloma

Shorter PFS: Lower diversity of peripheral T cell (TCR) repertoire, hyperexpanded clones with exhausted phenotype, and BAFF+PD-L1+ myeloid cells

Longer PFS: Increased CLEC9A+ dendritic cells, CD27+TCF1+, T cells with diverse T cell receptors, and T cells with marrow residence genes

Residual tumor cells at time of response express stemlike genes

Tumor recurrence is associated with emergence of new dominant clones.

Dhodapkar et al Blood Cancer Discovery 2022; 3: 490-501.

CC-95266 GPRC5D-Targeting CAR-T Cell Therapy: Response

ORRa

ORR in patients with and without prior BCMA-targeting therapy

- ICANS-type neurotoxicity was infrequent, low grade and reversible with steroid treatment: Any grade 2 (6%), none were grade 3/4
- DLTs: prolonged neutropenia and/or thrombocytopenia, 2 patients (25 x 10^6 and 75 x 10^6 CAR-T cells)
- MTD has not been reached
- No deaths related to study treatment (1 death prior to treatment)

Berdeja J et al. ASH 2022

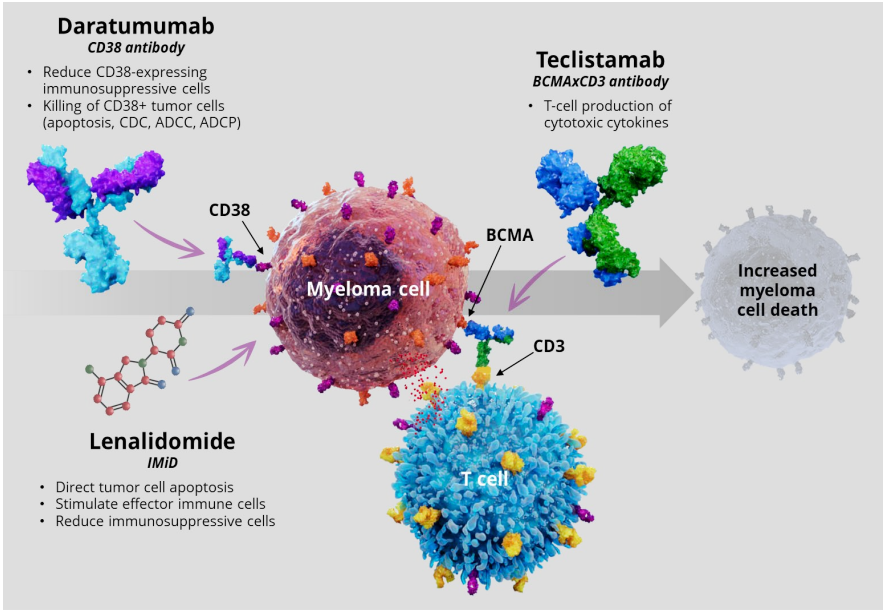
Teclistamab Alone and With SC Daratumumab and Lenalidomide in RRMM

- Teclistamab BCMA×CD3 bispecific antibody (Tec) FDA approved 165 pts 76% refractory to IMiD, PI, CD 38 Ab; median 5 lines prior therapy
- ORR 63%, CR 39%, 26% MRD-; Median PFS 11.3 mo, DOR 18.4 mo
- CRS 72.1% (0.6% grade 3); 64.2%, 37%, and 21.2% ≥ grade 3 low WBC, Hct, and Plts
- Infections 76.4% (44.8% grade 3)

Lenalidomide stimulates CTL/NK cells, downregulates Tregs; Daratumumab expands CTLs

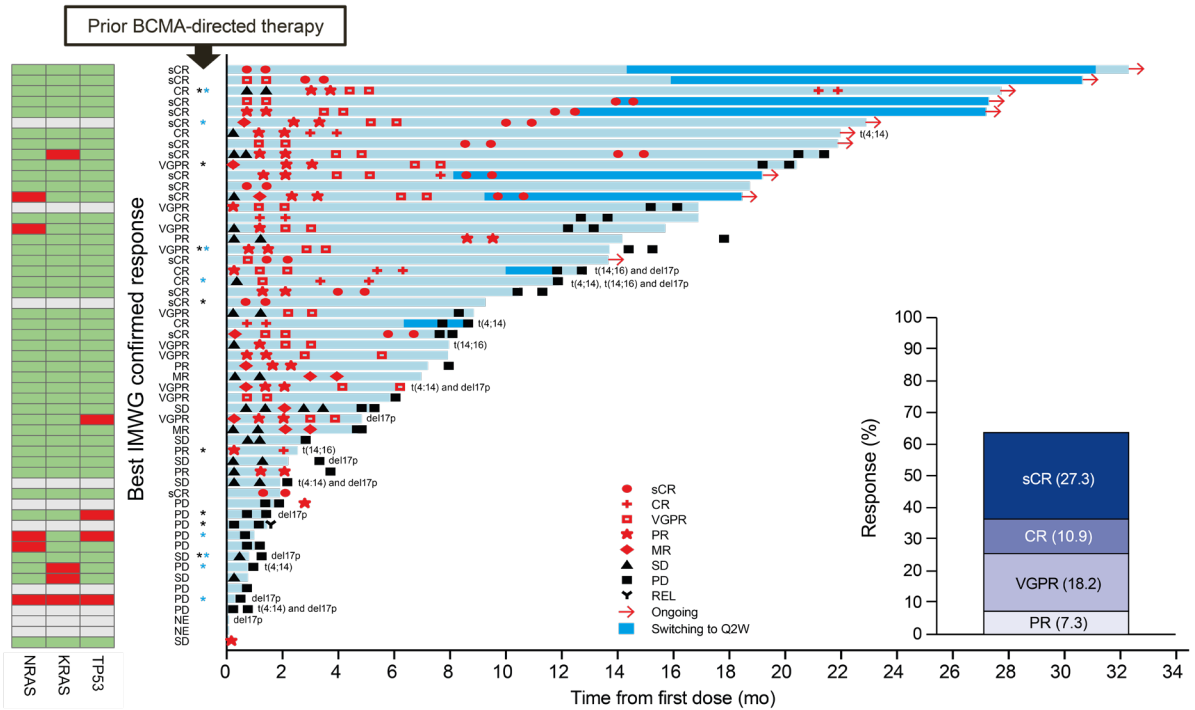
- Tec/Len/Dara: 93.5% ORR, 54.8% CR; 90.3% ≥ VGPR including Dara and/or Len refractory MM; 25/31 (80.6%) progression-free on treatment
- CRS 81% (no grade 3); 90.6% ≥ grade 3 AEs including low WBC, Hct, and Plts in 78.1%, 15.5%, and 12.5%
- Patients w > 1 infection 90.6% (37.5% grade ≥ 3, 2 deaths)

Combinations with immunogenic cell death inducers



Nooka A et al. ASCO 2022; Moreau P et al. NEJM 2022; 387:495; Searle et al ASH 2022

Elranatamab, a BCMA Targeted T-cell Engaging Bispecific Antibody, Induces Durable Clinical and Molecular Responses in RRMM



Median duration of follow-up 12.0 months (range 0.3–32.3)

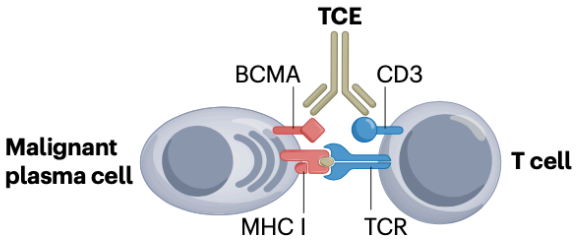
ORR 64% (95% CI, 50–75) and CR/sCR rate 38% (21/55)

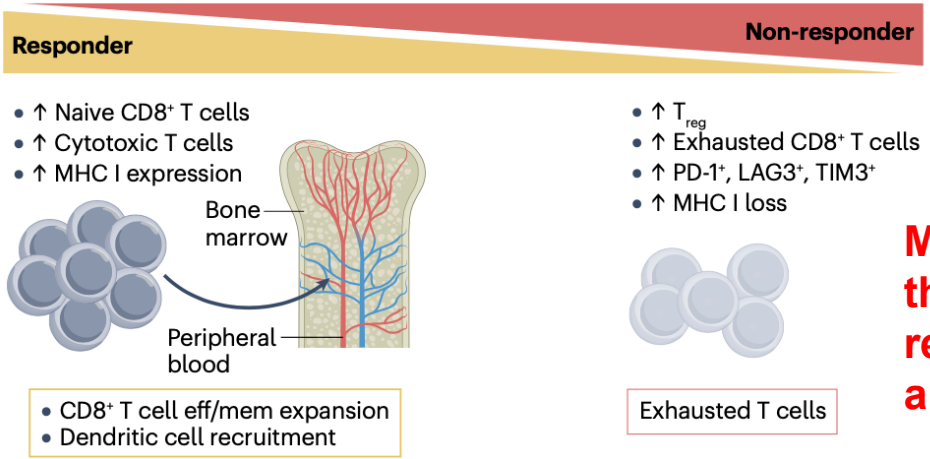
54% (7/13) of patients with prior BCMA-directed therapy achieved response

For responders (N=35), median time to response was 36 days (range 7–262)

Raje et al, ASH 2022

T Cell Landscape Determines Response to Bispecific T Cell Engagers (TCE) in Multiple Myeloma





Single-cell TCR tracing identifies conserved T cell responses to TCEs

Clonal expansion of effector CD8+ T cells is a driver of TCE therapy response

Naive T cells require additional MHC class I signal and differentiate upon TCE activation

The abundance of exhausted CD8+ clones predicts response failure

Monitoring immune profile before and during therapy can inform schedule of TCE to optimize response and limit T cell exhaustion, relapse, and increased risk of infection.

Friedrich, Neri, Rabb, Bahlis et al Cancer Cell 2023; 41: 1-15
Midha, Anderson Nat Rev Clin Oncol, in press

Antigen Escape is a Tumor Intrinsic Mechanism of Resistance to BCMA Targeted Immunotherapies

Combining bulk WGS and scCNV analysis in 18 RRMM patients identified 5 distinct genomic mechanisms leading to BCMA antigen escape:

Diploid 16p	**Focal biallelic loss of *TNFRSF17***
Subclone (<1%) with *TNFRSF17* biallelic loss	**Clonal *TNFRSF17* biallelic loss**
Diploid 16p	**16p monoallelic loss + mut. *TNFRSF17* c.R27P point mutation**
	16p monoallelic loss + mut. *TNFRSF17* in-frame deletion (p.Ser30del)
	16p monoallelic loss + mut. *TNFRSF17* in-frame deletion (p.Pro34del)

Lee, Neri, Bahlis et al. ASH 2022

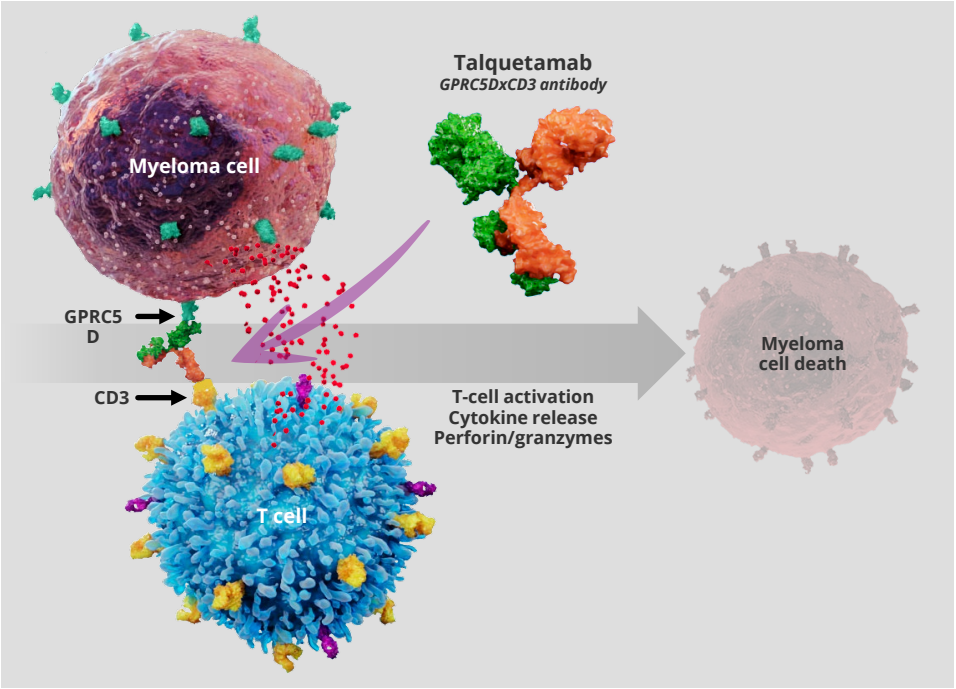
Talquetamab, a G Protein-Coupled Receptor Family C Group 5 Member D Bispecific Antibody in Relapsed Refractory Multiple Myeloma

Talquetamab: T-cell redirecting bispecific antibody directed against GPRC5D

GPRC5D: highly expressed on myeloma cells, limited expression in normal human tissues, including hematopoietic stem cells

Talquetamab: ORR 64–70% with QW and Q2W dosing in the phase 1 MonumenTAL-1 study

Most common AEs were CRS, skin and nail-related events, and dysgeusia

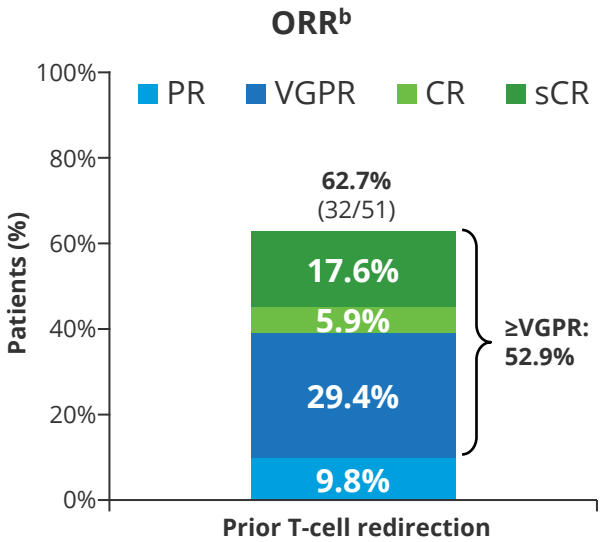


Chari et al NEJM 2022; 387: 2232-44, ASH 2022

Talquetamab GRRC5D BiTE in Patients With Prior T-Cell Redirection

Median 6 (3–15) prior lines of therapy
70.6% (n=36) prior CAR-T cell therapy
35.3% (n=18) prior bispecific antibody therapy
3 patients both
7.8% (n=4) refractory to belantamab
Most patients received QW (n=43) vs Q2W (n=8) talquetamab dosing

ORR 62.7%
72.2% ORR (26/36) prior CAR-T therapy
44.4% ORR (8/18) prior BiTE treatment
Median DOR: 12.7 months at median F/U 11.8 months

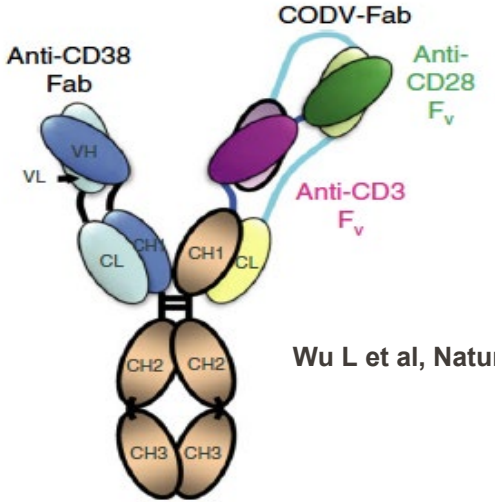


Chari et al ASH 2022

NB Biallelic *GPRC5D* loss post anti-GPRC5DxCD3Ɛ TCE (n=2)

Lee H, Neri, Bahlis et al. ASH 2022

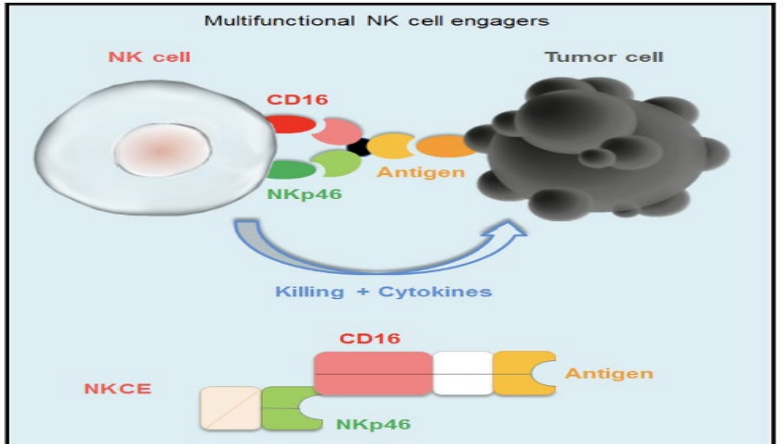
CD38 x CD28 x CD3 Trispecific Ab



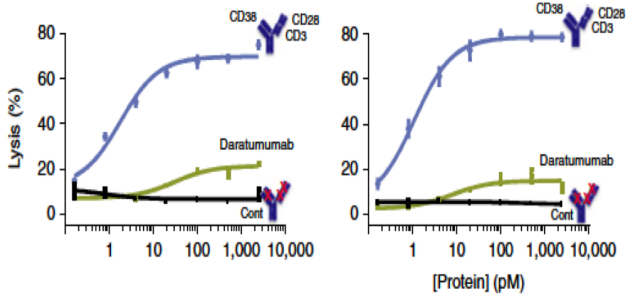
Wu L et al, Nature Cancer, 2020; 1(1) 86-98

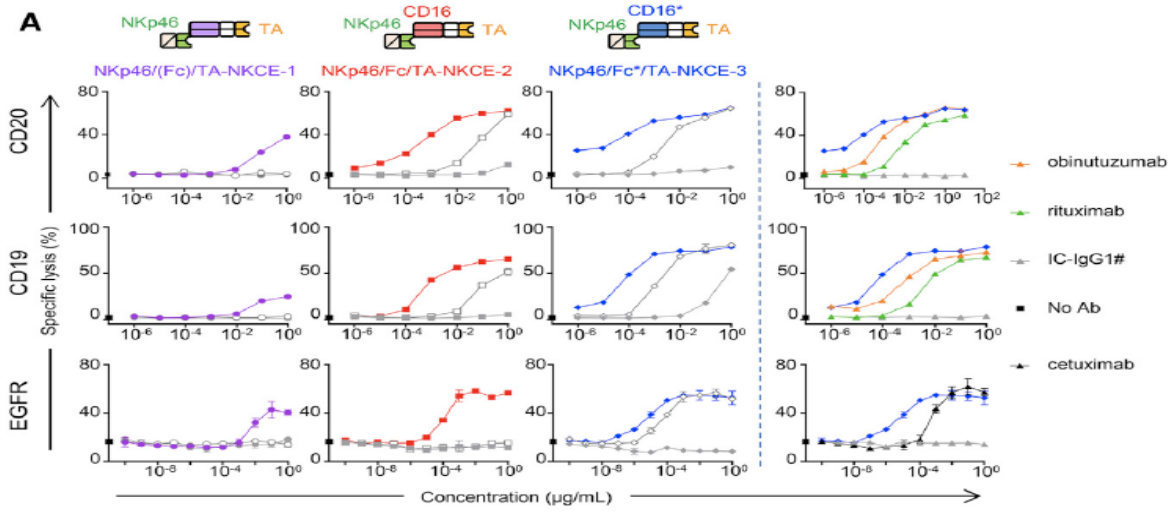
NK Trispecific Tumor Antigen x CD16 x p46NK

Gauthier et al, Cell, 2019; 177: 1701-13.



	RPM I8226	U266
CD38 per cell	129,000	14,000
CD28 per cell	84,000	170,000





1980 and Ongoing-Stem cell transplant
2000 and Ongoing- Novel agents
2020 and Ongoing-Immune therapies

Alfred Goldberg (1943-2023)
Described proteasomal protein degradation, PS-341 (bortezomib)

In the future, targeted and immune therapies Including CART/BiTEs will be incorporated into initial treatment of MM to achieve durable MRD- responses and restore memory anti-MM immunity, allowing patients to be disease free and off all therapy.

"Cure is Growing Old and Dying from Something Else"

Francesca Thompson, MD
1986