Memorial Sloan Kettering Cancer Center

# Immunotherapy in Multiple Myeloma

Sham Mailankody, MBBS
Research Director, Myeloma Service
Clinical Director, Cellular Therapy Service
Memorial Sloan Kettering Cancer Center, New York

# Disclosures

- Grant support: National Cancer Institute
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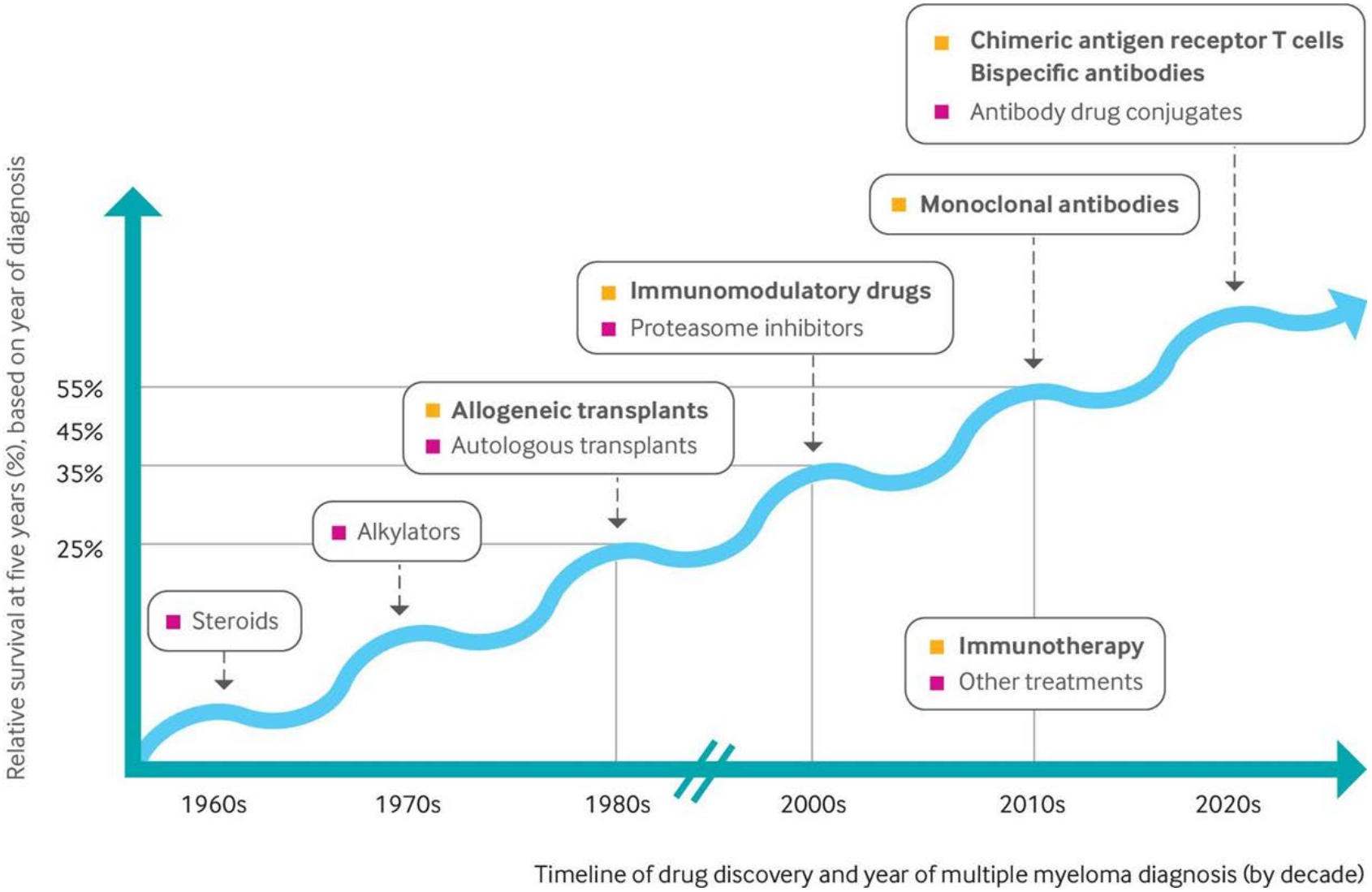
- Honoraria: Physician Education Resource, Plexus education, MJH Life Sciences
- Consultancy: Legend Biotech, Evicore, Janssen, Optum

# Outline

- Review clinical data for recent approved BCMA targeted immune therapies in multiple myeloma
- Off-the-shelf/Allogeneic cellular therapies: ALLO-715
- Alternate targets: Highlight emerging data for GPRC5D targeted therapies
- Mechanisms of Resistance and possible next steps
- Future directions

# Six Decades of Drug Discovery in Myeloma

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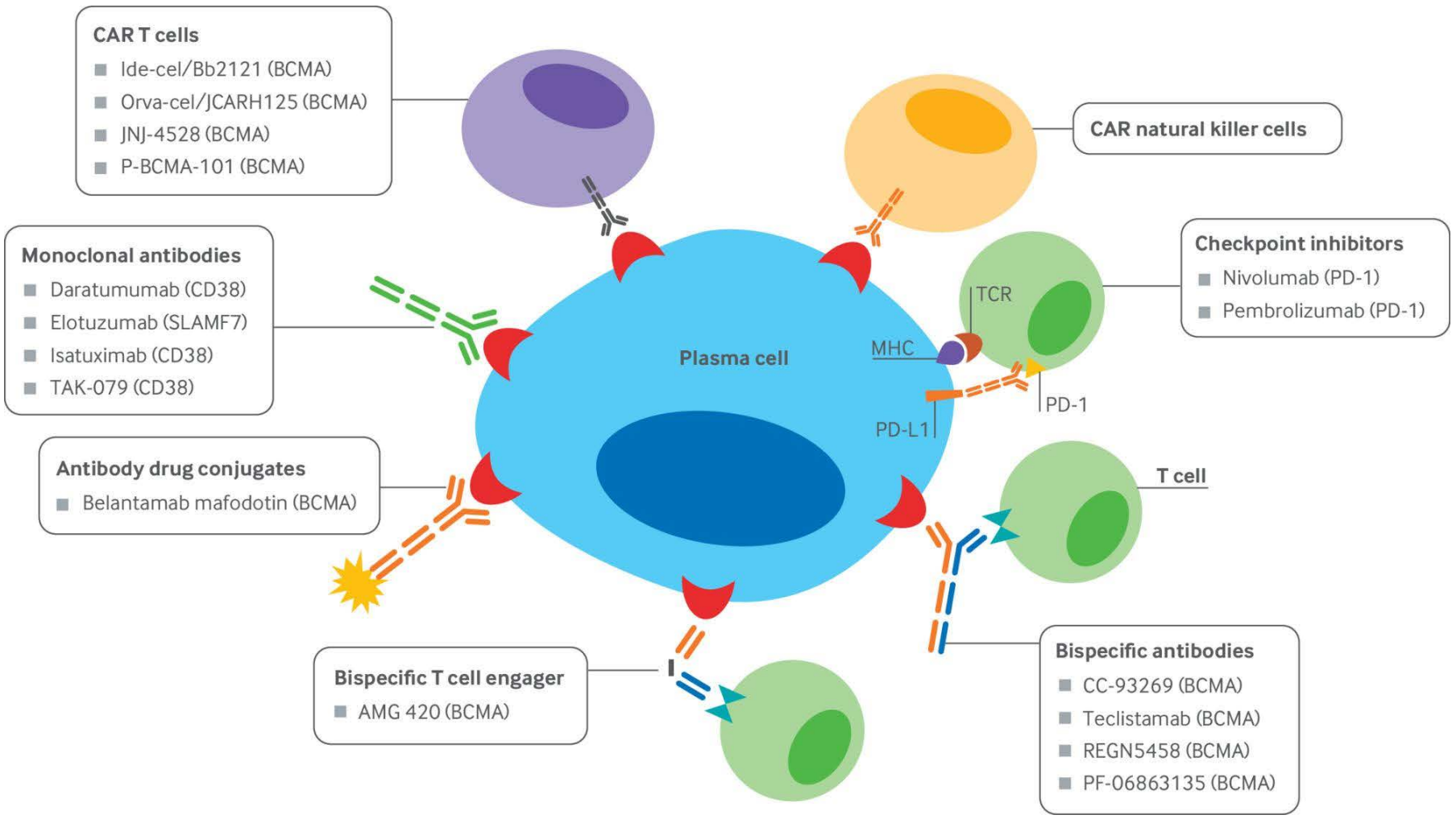
Shah U, Mailankody S. BMJ 2020

# Emerging Immunotherapies for Myeloma

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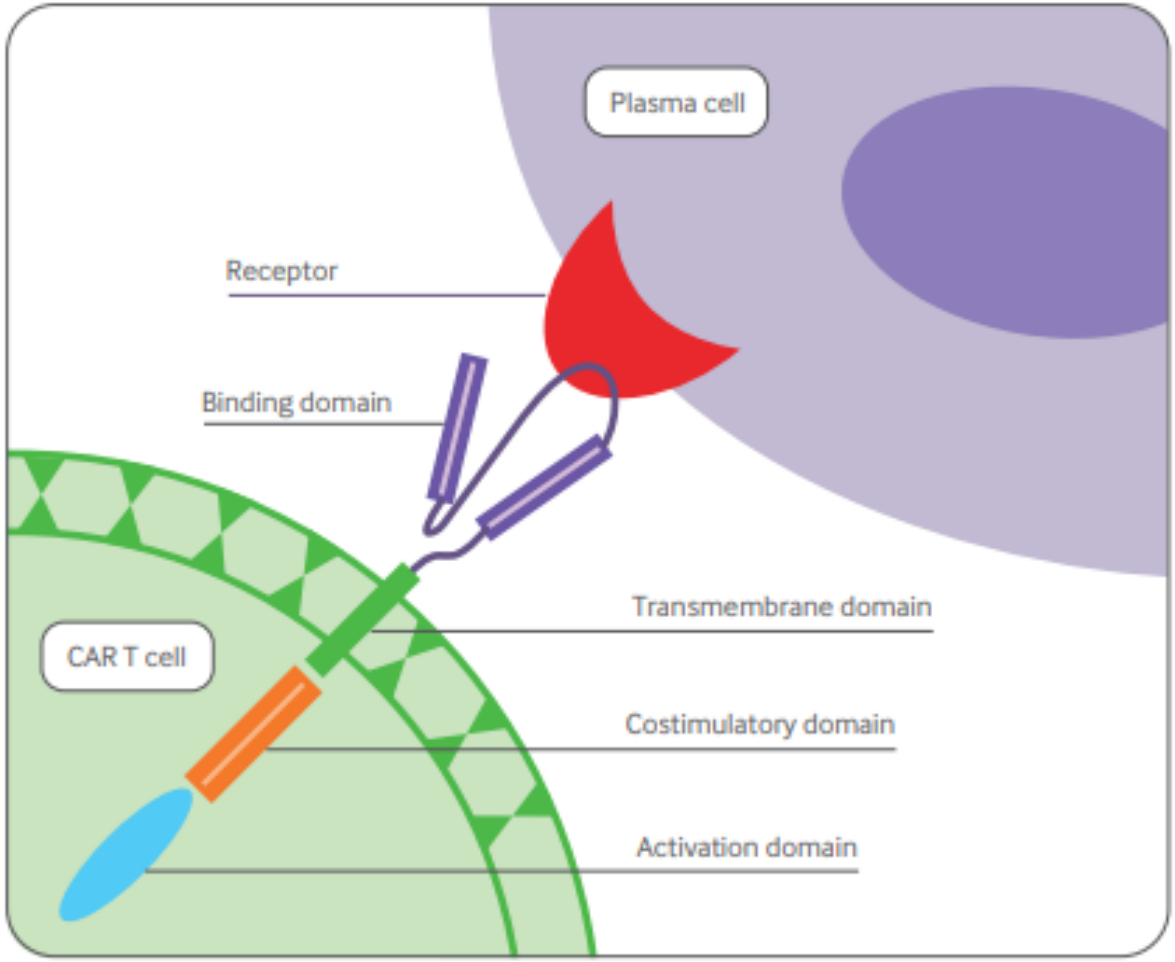
# CART cell therapy: Construct

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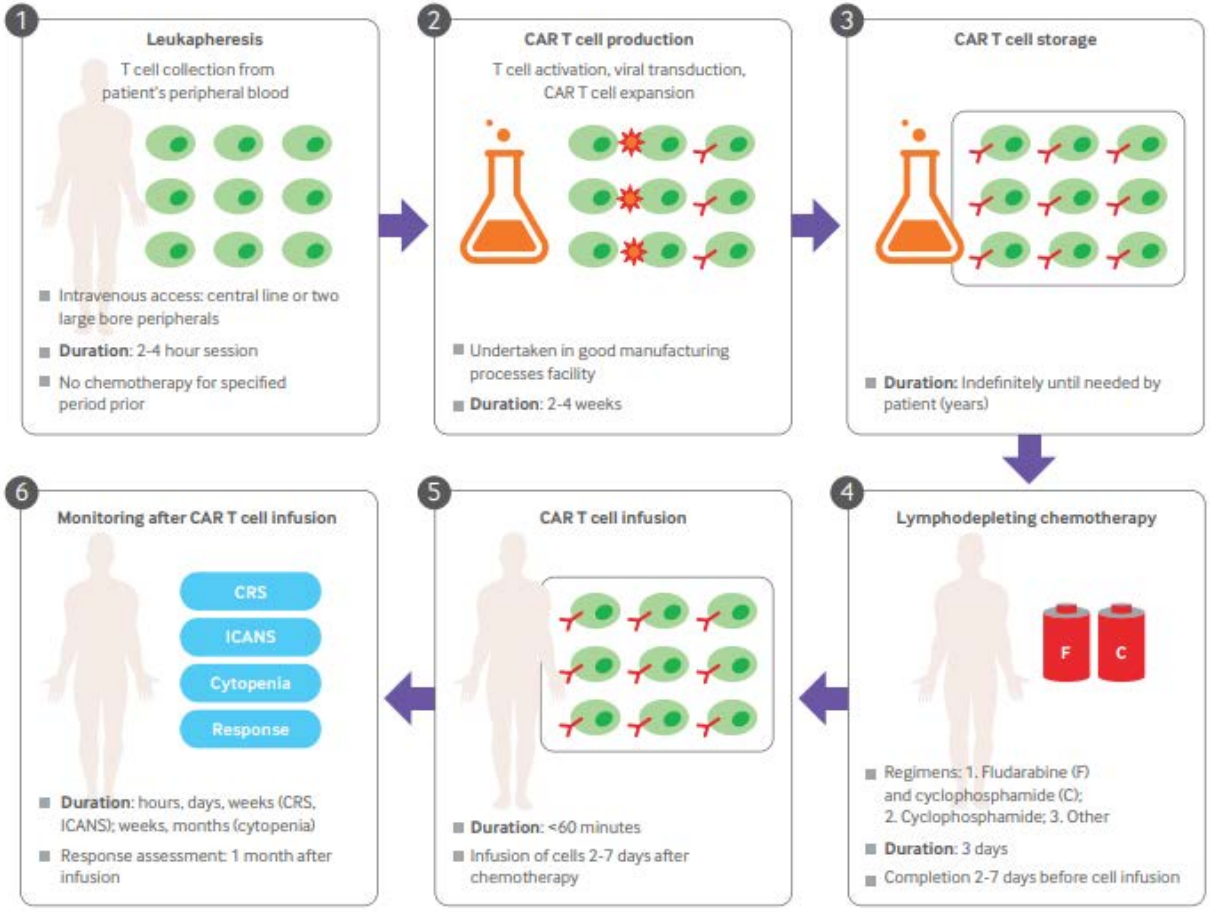
# Transitioning to the clinic

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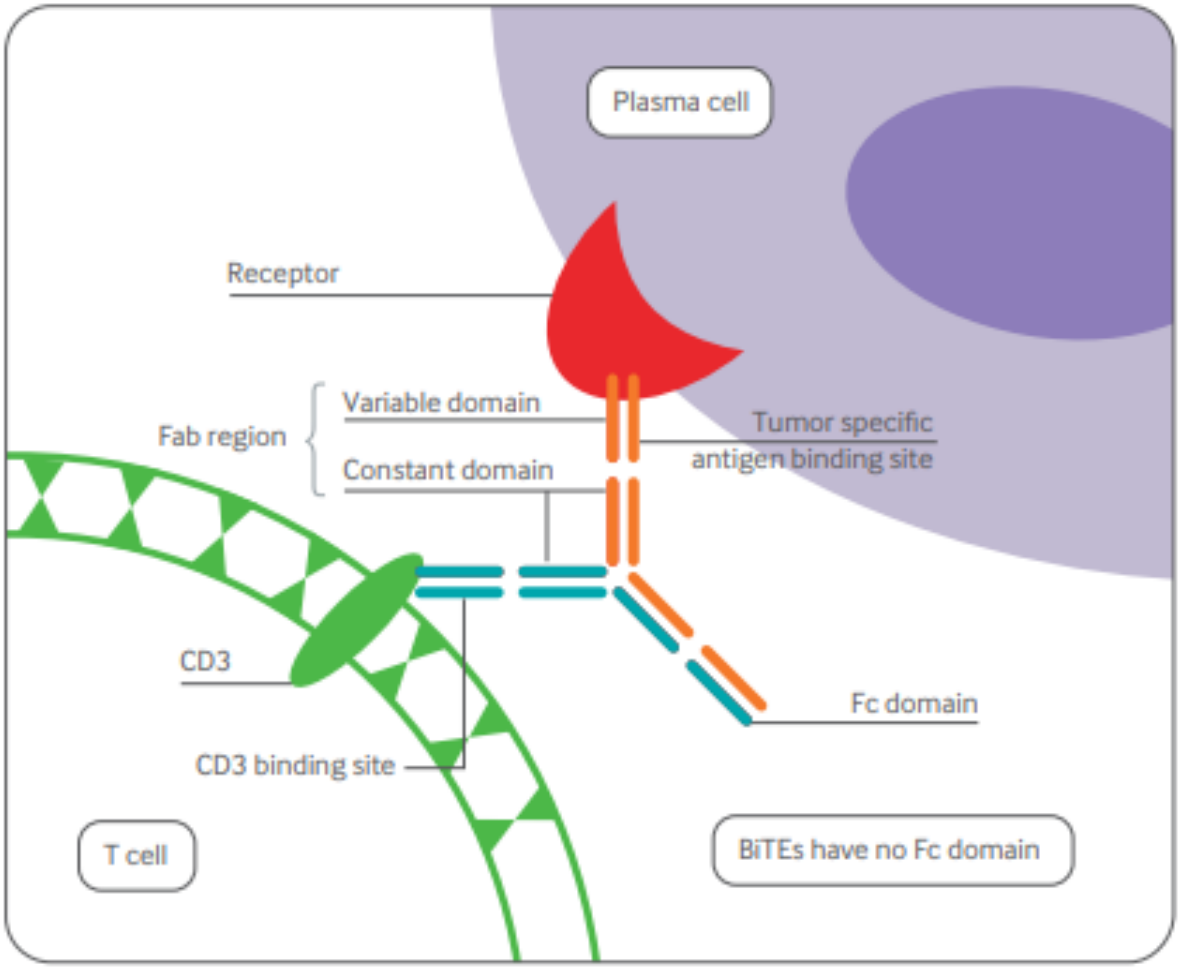
# Bispecific Antibodies

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# Baseline Characteristics: Ide-cel vs. Cilta-cel vs. Teclistamab

| Characteristic | Ide-cel | Cilta-cel | Teclistamab | T |
|---|---|---|---|---|
| Median age, years (range) | 61 (33-78) | 61 (56-68) | 64 (33-84) | 6 |
| Extramedullary disease, n (%) | 50 (39) | 13 (13) | 28 (17) | 2 |
| R-ISS stage III, n (%) | 21 (16) | 14 (14) | 20 (12) | 2 |
| High risk cytogenetics, n(%) | 45 (35) | 23 (24) | 38 (26) | 3 |
| Number of prior lines, n (range) | 6 (3-16) | 6 (4-8) | 5 (2-14) | 5 |
| Triple-refractory disease, n (%) | 108 (84) | 85 (88) | 128 (78) | 1 |

Munshi et al. NEJM 2021; Berdeja et al. Lancet 2021;
Martin et al. JCO 2022; Moreau et al. NEJM 2022

# Adverse Events: Ide-cel vs. Cilta-cel vs. Teclistamab

| Outcome | Ide-cel | Cilta-cel | Teclistamab | Te |
|---|---|---|---|---|
| CRS, any grade, % | 84 | 95 | 72 | 72 |
| CRS, grade 3 or higher, % | 5 | 4 | 1 | 1 |
| Neurotoxicity, any grade, % | 18 | 21 | 15 | 15 |
| Neurotoxicity, grade 3 or higher, % | 3 | 9 | 1 | 1 |
| Non relapse deaths, % | 7 | 9 | 16 | 16 |

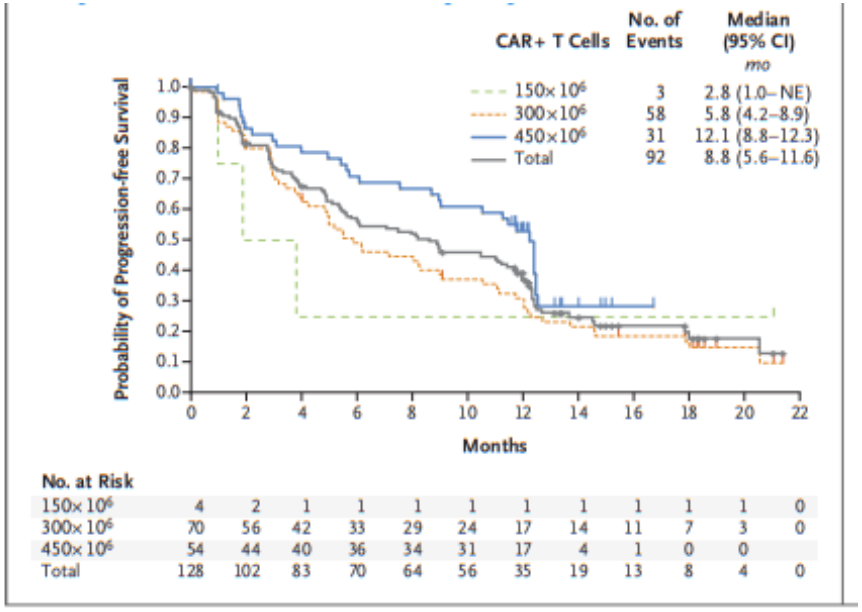
Munshi et al. NEJM 2021; Berdeja et al. Lancet 2021;
Martin et al. JCO 2022; Moreau et al. NEJM 2022

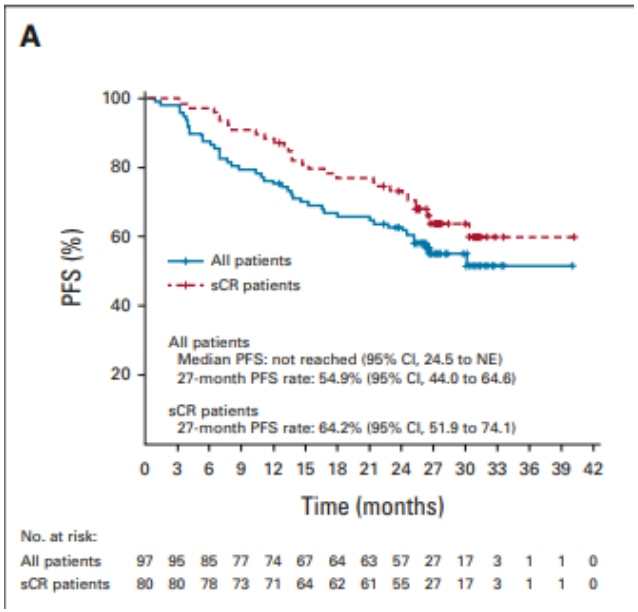
# Efficacy: Ide-cel vs. Cilta-cel vs. Teclistamab

| Outcome | Ide-cel | Cilta-cel | Teclistamab |
|---|---|---|---|
| Overall response rate, % | 73 | 97 | 63 |
| Complete response rate, % | 33 | 67 | 39 |
| Duration of response, months | 10.7 | NR | 18.4 |
| Median PFS, months | 8.8 | NR (27-month PFS: 55%) | 11.3 |
| Median follow-up, months | 13 | 12.4 | 14.1 |

Munshi et al. NEJM 2021; Berdeja et al. Lancet 2021;
Martin et al. JCO 2022; Moreau et al. NEJM 2022

# Deep responses and impressive PFS




Median PFS
Ide-cel: 8.8 months

Median PFS
Cilta-cel: NR (55% progression free at 27 months)

Munshi et al. NEJM 2021; Berdeja et al. Lancet 2021; Martin et al. JCO 2022

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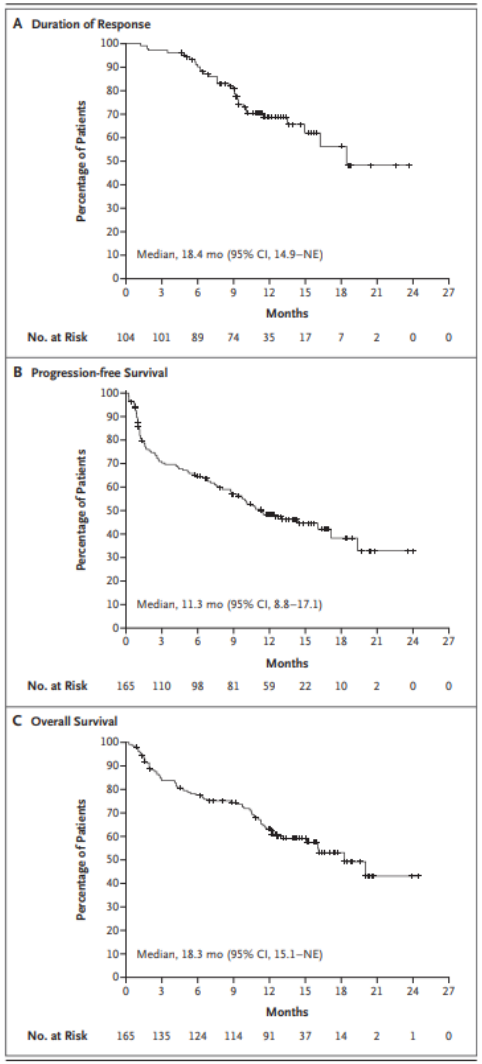
# Teclistamab: Efficacy




DOR: 18.4 months (95% CI: 14.9-NE)

PFS: 11.3 months (95% CI: 8.8-17.1)

OS: 18.3 months (95% CI: 15.1-NE)

Moreau et al. NEJM 2022

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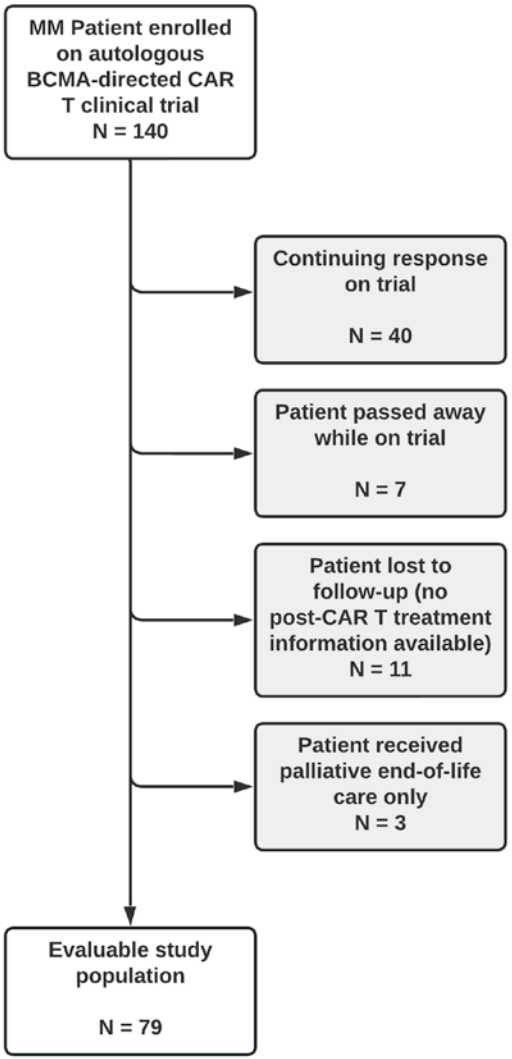
# Outcomes after progression post CAR T therapies




Median lines of therapy post CAR T progression: 2 (1-10)

Van Oekelen, Nath et al. Blood 2022

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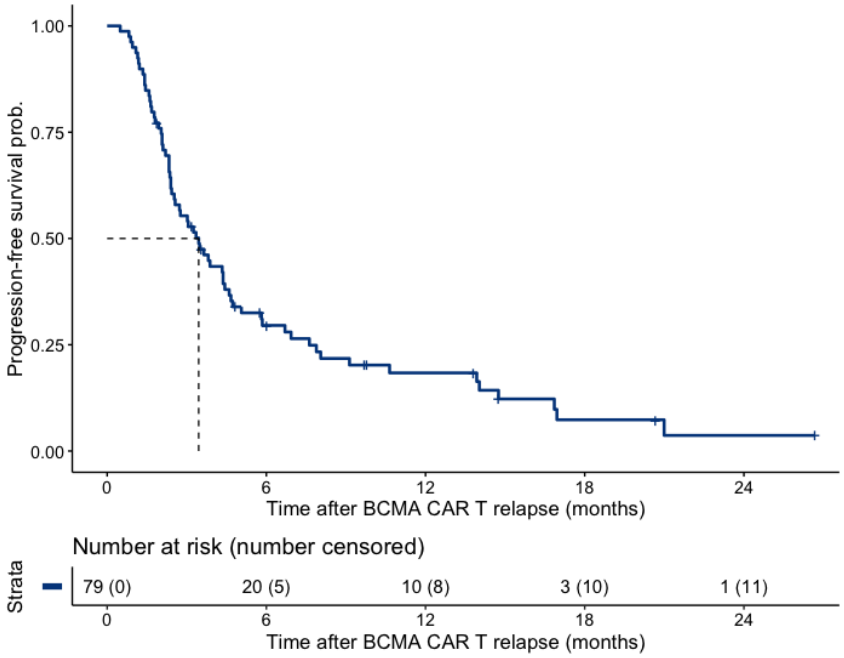
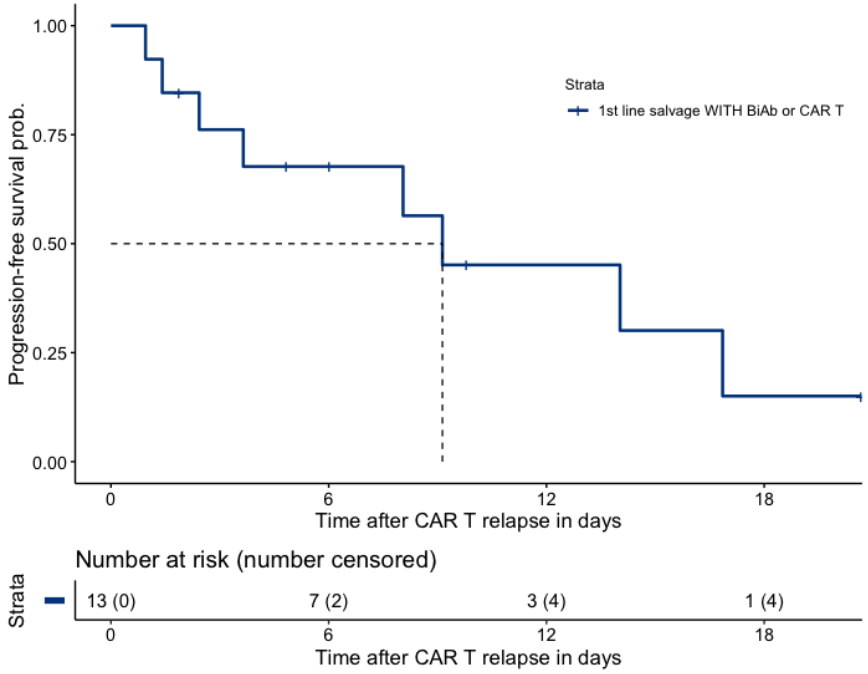
# Median Progression free survival




All patients: 3.5 months

Patients with T-cell engaging therapies: 9.1 months

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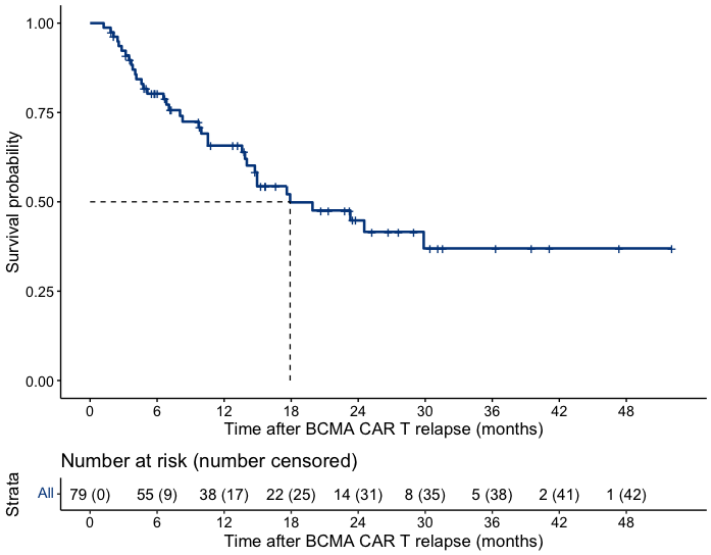
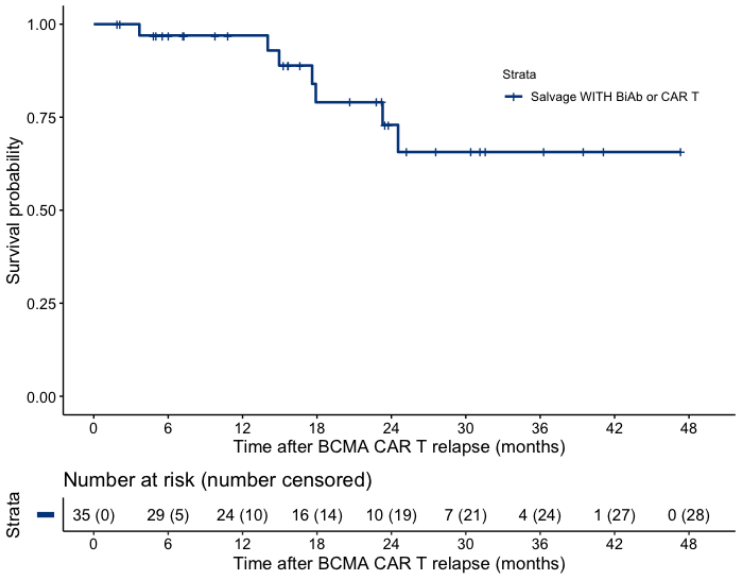
# Median overall survival




All patients: 17.9 months




Patients with T-cell engaging therapies: not reached

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# What's next? Moving up earlier lines of treatment

- Randomized trials of cilta-cel and ide-cel in patients with 1-3 (or 2-4) prior lines of treatment compared to standard of care

- Randomized trials of cilta-cel in newly diagnosed transplant eligible and transplant ineligible patients

Bristol Myers Squibb and 2seventy bio Announce Topline Results from KarMMa-3 Trial Showing Abecma (idecabtagene vicleucel) Significantly Improves Progression-Free Survival Versus Standard Regimens in Relapsed and Refractory Multiple Myeloma

08/10/2022

LATEST NEWS

**Janssen Announces Unblinding of Phase 3 CARTITUDE-4 Study of CARVYKTI® (cilta-cel) as Primary Endpoint Met in Treatment of Patients with Relapsed and Refractory Multiple Myeloma**

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# BCMA Bispecific Antibodies (select studies)

| | Teclistamab[1] | Elranatamab[2] | ABBV-383[3] |
|---|---|---|---|
| **Schedule** | Weekly SC | Weekly SC | IV q3W |
| **Patients** | 165 | 123 | 81 |
| **Median prior lines** | 5 | 5 | 4 |
| **Triple Class and Penta Refractory** | 78% and 30% | 97% and 42% | 81% and 41% |
| **Prior BCMA** | No | No | No |
| **CRS, All (Gr 3/4)** | 72% (0.6%) | 58% (0%) | 73% (4%) |
| **ICANS, All (Gr 3/4)** | 3% (0.6%) | 3% (0%) | 2% (NA) |
| **Infections, All (Gr3/4)** | 76% (45%) | 67% (35%) | 41% (23%) |
| **ORR** | 62% | 61% | 68% |
| **CR** | 39% | 28% | 36% |

1. Moreau et al. NEJM 2022; 2.Bahlis et al. ASH Abstract#159; 3. D'Souza et al. JCO 2022.

# Allogeneic CAR T cell therapy

1. Potential Advantages?
   **Bulk manufacturing, repeat dosing, no need for bridging, cell quality**

2. How do we address Graft-Versus-Host?
   **TCR Knockout, constrained specificity**

3. How do we address Host-Versus-Graft?
   **- Evasive: Δ B2m, Δ CIITA**
   **- Immunosuppressive: Δ CD52, Δ deoxycytidine kinase**

# Allogeneic CAR T cell therapy

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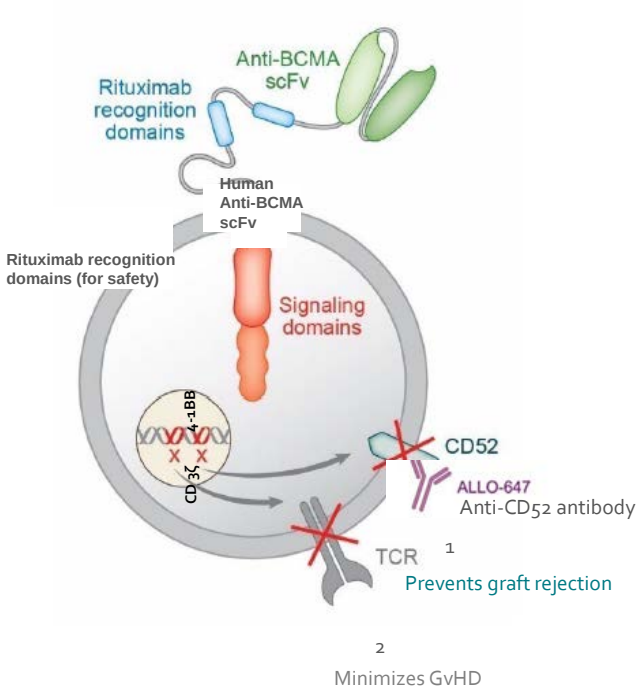
# First Allogeneic CAR T Therapy for Myeloma

- ALLO715 has human derived scFv with 4-1BB costimulatory domain and CD3z signaling domain
- Graft-Versus-Host: Knockout of TRAC gene
- Host-Versus-Graft: Knockout of CD52 allowing for lymphodepletion with anti CD52 antibody ALLO-647




1. TALEN-mediated CD52 KO allows selective lymphodepletion with ALLO-647
2. TALEN-mediated TRAC KO eliminates TCRα expression to minimize risk of GvHD

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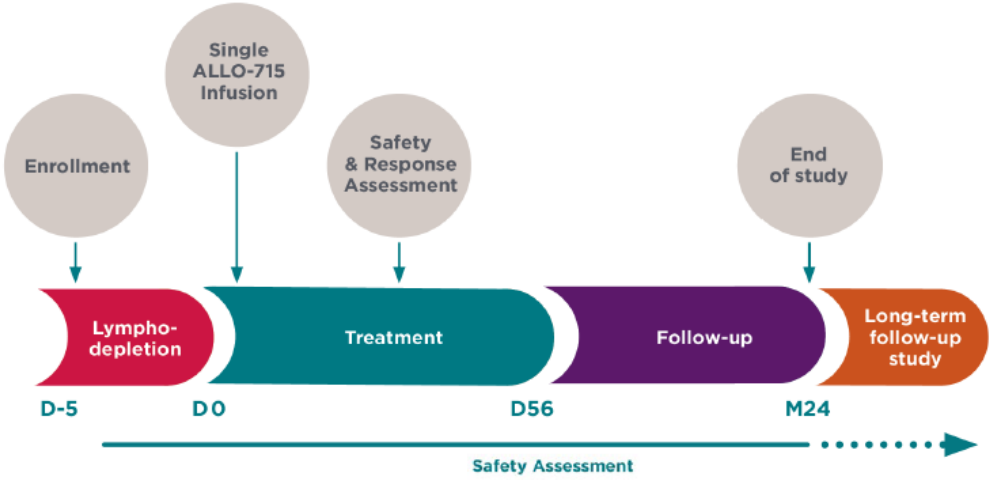
# UNIVERSAL: First Allogeneic BCMA CAR T in Multiple Myeloma

## Design for Part A*




| ALLO-715 Dose Escalation: 40, 160, 320, 480 x $10^6$ CAR+ T cells | |
|---|---|
| Lymphodepletion Regimens (FCA**, CA†) | Doses |
| Fludarabine | 30 mg/m²/day x 3 days |
| Cyclophosphamide | 300 mg/m²/day x 3 days |
| ALLO-647 | 13 to 30 mg x 3 days |

* Parts B (combination of ALLO-715 + nirogacestat) and C (consolidation regimen) are not reported here
** FCA conditioning with fludarabine, cyclophosphamide, and ALLO-647
† CA conditioning with cyclophosphamide and ALLO-647

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# ALLO715: Patient Flow

***Median Time from Enrollment to Start of Treatment for All Patients: 5 Days***

Part A Enrolled (N=48)

*5 patients became ineligible due to organ failures from rapidly progressing disease*

Part A Safety Population (N=43)

Part A Efficacy Population (N=43)

| CAR+ T Cell Dose | Lymphodepletion Regimen | | | |
|---|---|---|---|---|
| | FCA39 | FCA60 | FCA90 | CA39 |
| 40 x $10^6$ Cells (DL1) | 3 | – | – | – |
| 160 x $10^6$ Cells (DL2) | 4 | – | – | 3 |
| 320 x $10^6$ Cells (DL3) | 11 | 10 | 3 | 3 |
| 480 x $10^6$ Cells (DL4) | 3 | 3 | – | – |

*Overall median follow-up time = **4 Months***

- Patient flow includes patients enrolled in Part A of study
  - Part A was a single dose of ALLO-715 cells in dose escalation which was previously presented
  - Multiple LD regimens were evaluated at DL3 and DL4

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# ALLO715: Baseline Characteristics

| Characteristics | | (N=43) |
|---|---|---|
| Age, median (range), years | | 64 (46-77) |
| Gender, % | Male | 63 |
| | Female | 37 |
| ECOG PS, % | 0 | 49 |
| | 1 | 51 |
| ISS Stage III, % | | 19 |
| High-risk cytogenetics*, % | | 37 |
| Extramedullary disease, % | | 21 |
| High tumor burden at screening†, % | | 33 |
| Time since initial diagnosis, median (range), years | | 4.9 (0.9, 26.4) |
| Number of prior anti-myeloma regimens, median (range) | | 5 (3-11) |
| Prior autologous SCT, % | | 91 |
| Triple-refractory, % | | 91 |
| Penta exposed/Penta-refractory, % | | 42 |

* High-risk cytogenetics is defined as del 17p, t(4;14), or t(14;16)
† High tumor burden considered when more than 50% plasma cells in bone marrow

- Patients had advanced disease
  - 19% of patients had ISS Stage III
  - 21% of patients had extramedullary disease
- Heavily pretreated patients in study
  - Median of 5 prior lines of therapy
  - All patients were refractory to last line
    - 91% were triple refractory and 42% were penta-refractory
- **No patient received bridging therapy**

Data Cutoff Date: October 14, 2021

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# ALLO-715 and ALLO-647 Demonstrated Manageable Safety Profile

| Key adverse events (N=43) | Any Grade | ≥Grade 3 |
|---|---|---|
| | n (%) | |
| Cytokine Release Syndrome | 24 (56) | 1 (2.3) |
| Neurotoxicity† | 6 (14) | 0 |
| Graft-versus-Host Disease | 0 | 0 |
| Infection‡ | 23 (54) | 11 (23) |
| Infusion Reaction to ALLO-647 | 12 (28) | 0 |

- Manageable safety profile with low-grade and reversible CRS and neurotoxicity
  - Low use of tocilizumab 23% and steroids 14%
- No GvHD
- CMV reactivation in 12 patients
- Low grade and reversible infusion related reactions

- 3 Grade 5 infections- fungal pneumonia, adenoviral hepatitis, and sepsis

† Analysis done using a broad SMQ of noninfectious encephalopathy/delirium with adjudication by clinical review
‡ All infections (bacterial, fungal, and viral) included

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# Efficacy of ALLO-715 and ALLO-647

## Encouraging Efficacy Seen with Additional Patients at DL3

| Cell Dose & LD Regimen | DL3 (320M CAR+ T Cells)* | | | | DL4 (480M CAR+ T Cells) | |
|---|---|---|---|---|---|---|
| | FCA39 N=11 | FCA60 N=10 | FCA90 N=3 | FCA ALL N=24 | FCA39 N=3 | FCA60 N=3 |
| **ORR†, n (%)** (95% CI) | **7 (64)** (31, 89) | **8 (80)** (44, 98) | **2 (67)** (9, 99) | **17 (71)** (49, 87) | **1 (33)** (0.8, 91) | **2 (67)** (9, 99) |
| **VGPR+ Rate, n (%)** | 5 (46) | 5 (50) | 1 (33) | 11 (46) | 0 | 2 (67) |
| **CR/sCR Rate, n (%)** | 3 (27) | 3 (30) | 0 | 6 (25) | 0 | 0 |
| **mDOR, months (95% CI)** | 8.3 (3.4, 11.3) | NE (5.6, NE) | 3.1 (2.4, 3.1) | 8.3 (3.4, 11.3) | 1.4 (NE, NE) | NE (1.5, NE) |
| **Median follow-up, months (range)**** | 3.3 (0.5, 3.8) | 3.8 (3.1, 11.2) | -- | 3.8 (0.5, 11.2) | -- | 7.4 (7.4, 7.4) |

- In the FCA 320M CAR+ cell dose group, 17 patients **(71%) achieved an overall response rate (ORR)**
  - 11 (46%) were VGPR+, of those 6 (25%) were CR/sCR

* Three patients treated with 320M CAR+ cells and the CA LD regimen are not included above. Two of those responded with one pt achieving a CR
† Clinical response evaluation was based on IMWG response criteria, Kumar et al, 2016
** Median follow-up is for censored pts

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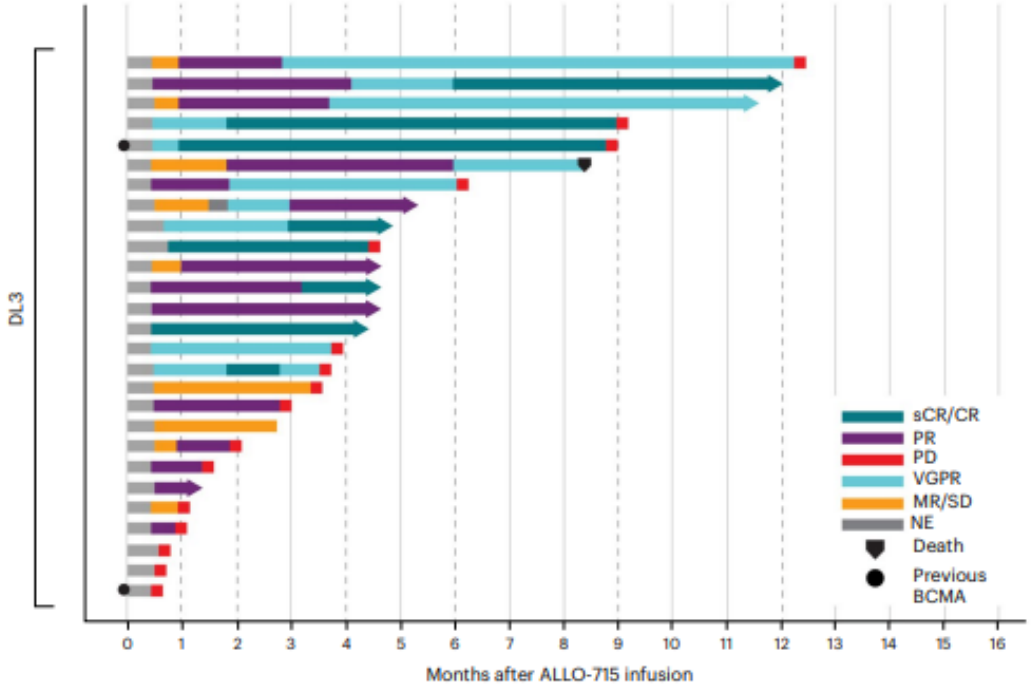
# 320M CAR T+ Cell Dose Achieves Durable Responses




**Median time to response was 16 days**

In the expansion of DL3 FCA, 9 pts with an initial response remain in response with median duration of response of 8.3 months

- Of those with a confirmed response of VGPR+, **92% were MRD negative**
- MRD negativity is associated with a durable response and period of progression-free survival

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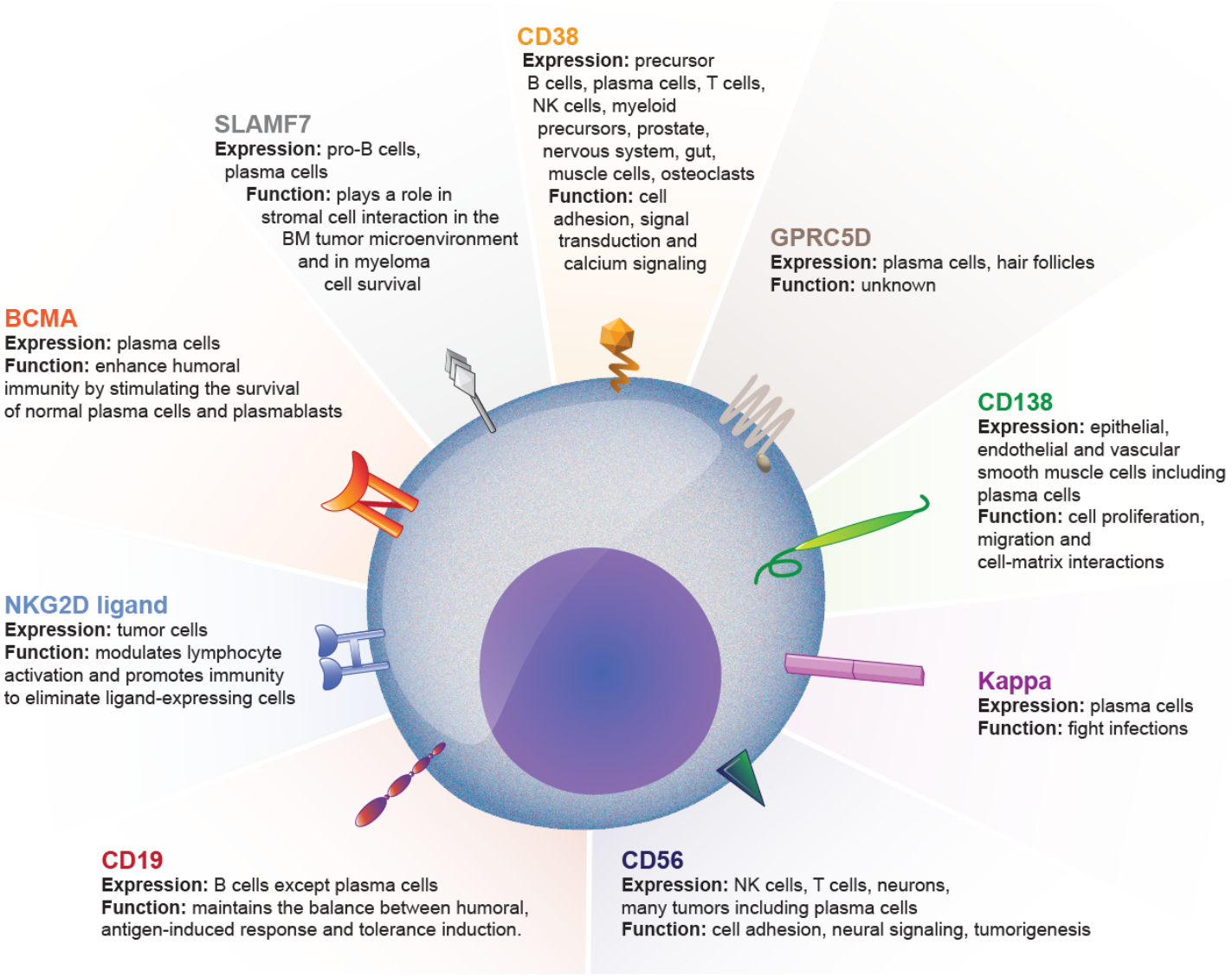
# CAR T Therapy Targets: Beyond BCMA




Shah U and Mailankody S. Best Pra & Res: Clin Heme 2019

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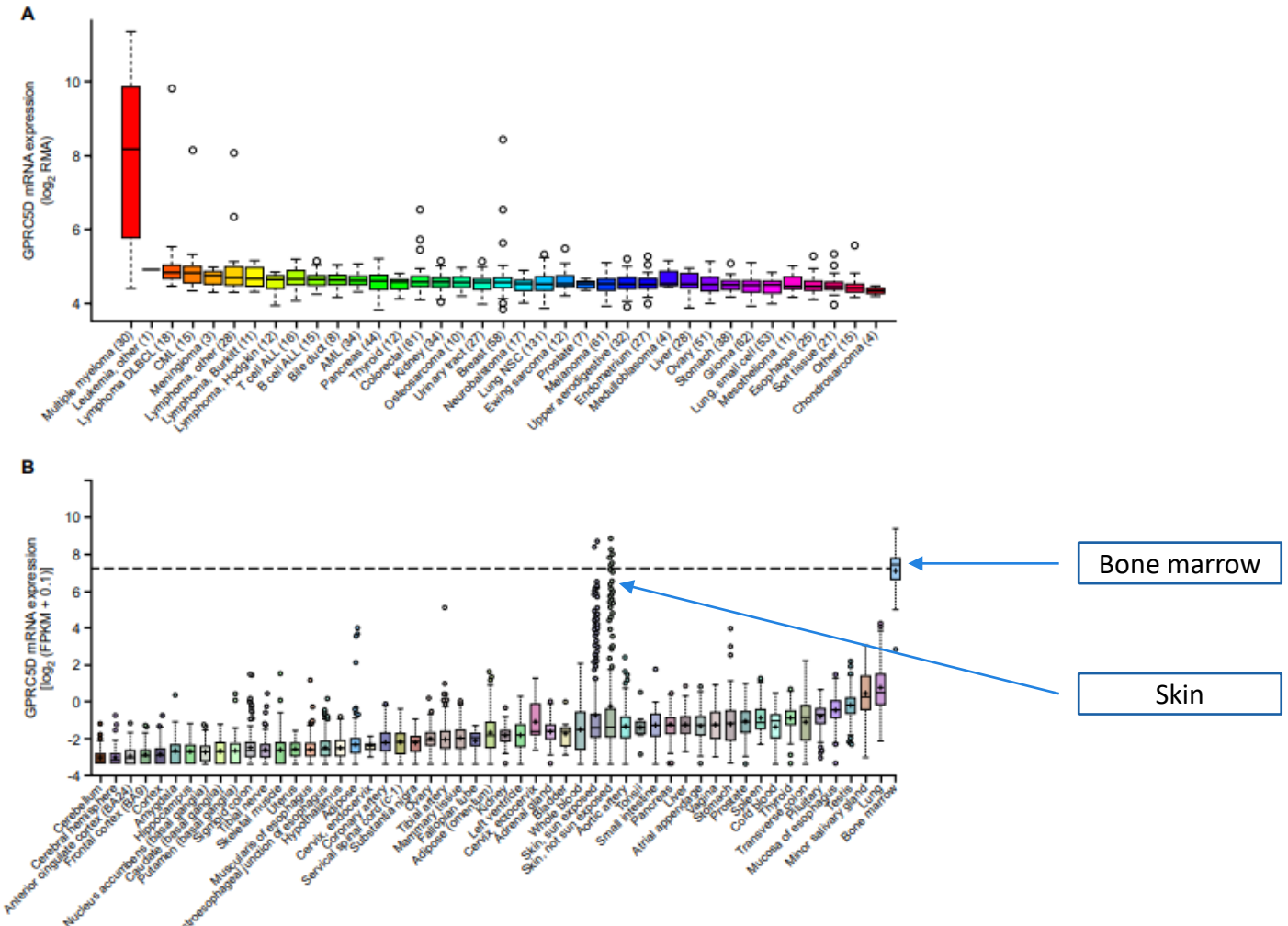
# GPRC5D: Highly expressed in myeloma; limited normal tissue expression




Smith EL. et al. Science Translational Medicine 2019

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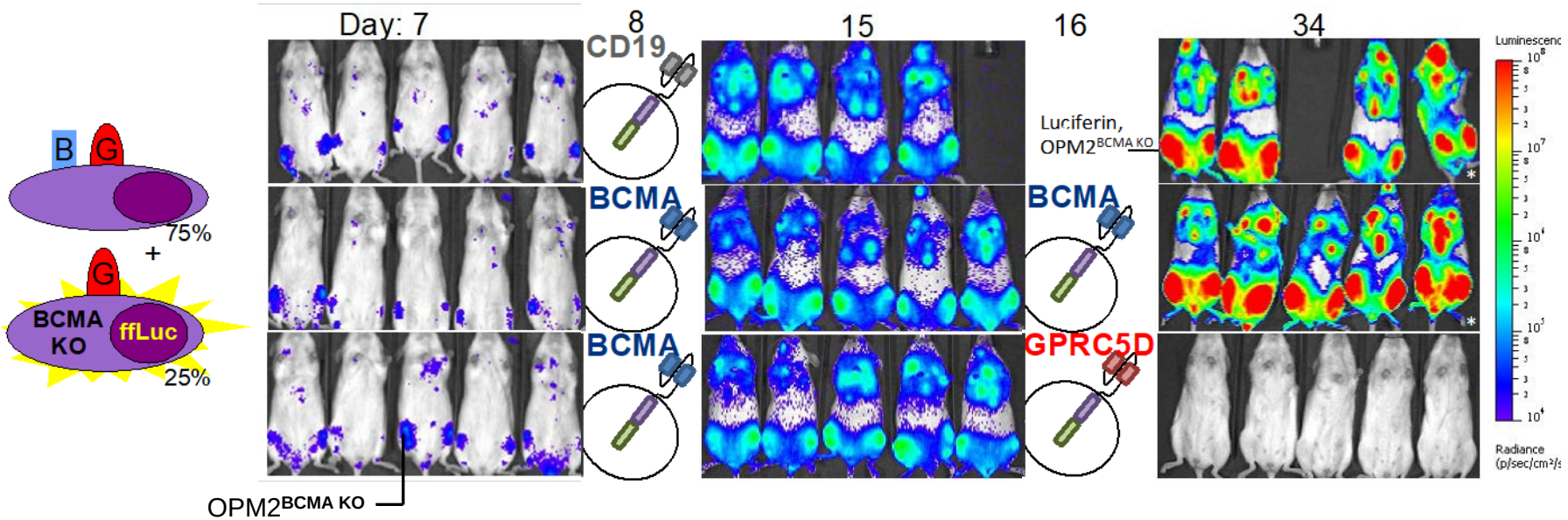
# GPRC5D-targeted CAR T cells rescued mice from BCMA negative tumor escape model




Smith EL. et al. Science Translational Medicine 2019

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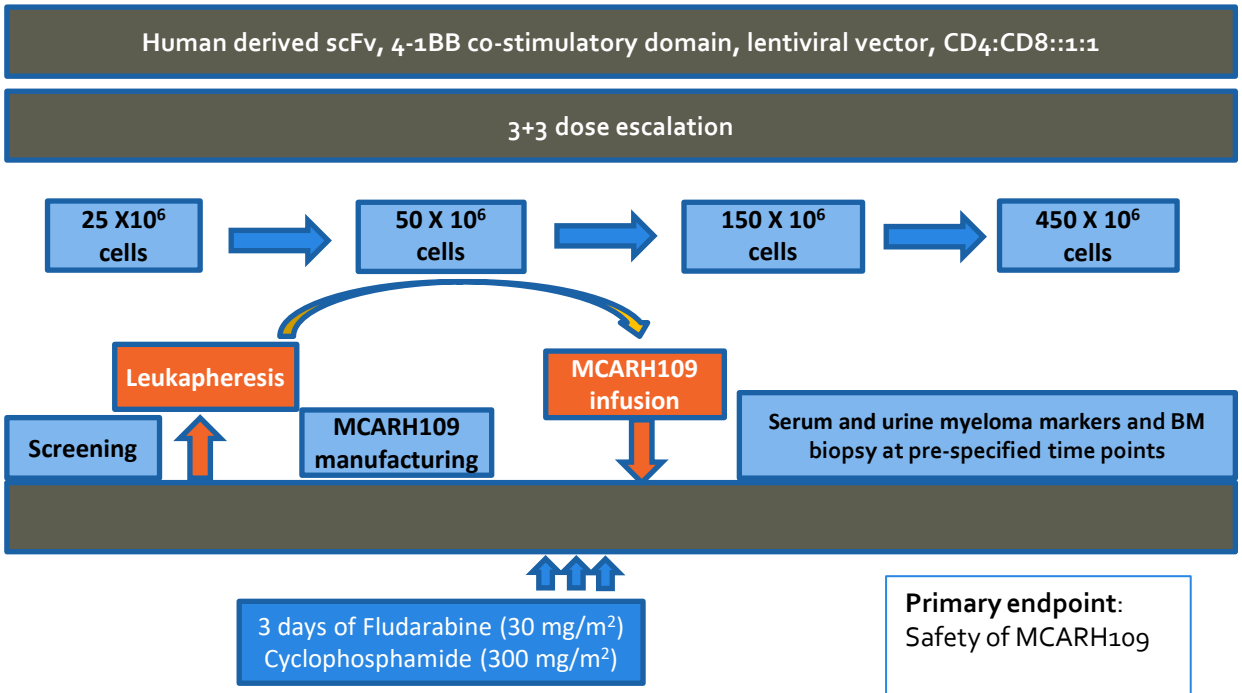
# MCARH109: Study Design

**Key eligibility criteria:**
- 3 or more lines of therapy
- Prior PI, ImiD, CD38 antibody based therapy
- Prior BCMA and CART allowed
- Non-secretory myeloma allowed
- Prior allogeneic SCT allowed




**Primary endpoint**: Safety of MCARH109

**Secondary endpoints**: Efficacy, MCARH109 expansion and persistence

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# MCARH109: Baseline Characteristics

| | 25 X10$^6$ CAR+ T cells (n=3) | 50 X10$^6$ CAR+ T cells (n=3) | 150 X10$^6$ CAR+ T cells (n=6) | 450 X10$^6$ CAR+ T cells (n=5) | Total (N=17) |
|---|---|---|---|---|---|
| **Median (range) age, years (range)** | 60 (38-76) | 50 (39-56) | 59 (40-74) | 65 (63-73) | 60 (38-76) |
| **Male, n (%)** | 2 (67) | 3 (100) | 4 (67) | 4 (80) | 13 (77) |
| **High-risk cytogenetics, n (%)*** | 3 (100) | 2 (67) | 3 (60) | 5 (100) | 13 (77) |
| **Extramedullary plasmacytoma, n (%)** | 3 (100) | 1 (33) | 3 (50) | 0 (0) | 7 (41) |
| **Non-secretory myeloma** | 2 (67) | 0 (0) | 1 (20) | 0 (0) | 3 (18) |
| **Prior Lines of Therapy, median (range)** | 6 (6-8) | 7 (4-8) | 7 (5-14) | 6 (5-12) | 6 (4-14) |
| **Refractory to last line, n (%)** | 3 (100) | 3 (100) | 5 (83) | 3 (60) | 14 (82) |
| **Penta-exposed, n (%)** | 3 (100) | 3 (100) | 6 (100) | 5 (100) | 17 (100) |
| **Triple-refractory, n (%)** | 3 (100) | 3 (100) | 6 (100) | 4 (80) | 16 (94) |
| **Prior Autologous Transplant, n (%)** | 3 (100) | 3 (100) | 6 (100) | 5 (100) | 17 (100) |
| **Prior Allogeneic Transplant, n (%)** | 0 (0) | 2 (67) | 1 (0) | 0 (0) | 3 (18) |
| **Prior BCMA therapy, n (%)**** | 1 (33) | 1 (33) | 4 (67) | 4 (80) | 10 (59) |
| **Prior CART therapy, n (%)** | 0 (0) | 1 (33) | 3 (50) | 4 (80) | 8 (47) |
| **Bridging therapy, n (%)** | 3 (100) | 3 (100) | 6 (100) | 4 (80) | 16 (94) |
| **Refractory to bridging, n (%)** | 3 (100) | 3 (100) | 5 (83) | 4 (80) | 15 (88) |

*includes t (4;14), 1q amplification, del 17p, t (14;16)
**includes any BCMA bispecific antibody, antibody drug conjugate, or CART therapy

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# MCARH109: Key Safety Events

| Adverse events (n=17) | Any Grade | Grade 3/4 |
|---|---|---|
| **Cytokine Release Syndrome, n (%)** | 15 (88) | 1 (6) |
| **ICANS, n (%)** | 1 (6) | 1 6) |
| **Macrophage Activation Syndrome, n (%)** | 1 (6) | 1 (6) |
| **Cerebellar disorder, n (%)** | 2 (12) | 2 (12) |
| **Infections, n (%)** | 3 (18) | 2 (12) |
| **Nail changes, n (%)** | 11 (65) | 0 (0) |
| **Maculo-papular rash, n (%)** | 3 (18) | 0 (0) |
| **Dysgeusia, n (%)** | 2 (12) | 0 (0) |
| **Hematologic Toxicities, n (%)** | | |
| Anemia | 15 (88) | 7 (41) |
| Thrombocytopenia | 15 (88) | 11 (65) |
| Neutropenia | 17 (100) | 17 (100) |

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# MCARH109: Clinical Responses

| Response | All Patients | | Previous BCMA therapies | | No previous BCMA therapies | |
|---|---|---|---|---|---|---|
| | All doses (n=17) | 25-150 million cells (n=12) | All doses (n=10) | 25-150 million cells (n=6) | All doses (n=7) | 25-150 million cells (n=6) |
| Partial Response or better, n (%) | 12 (71) | 7 (58) | 7 (70) | 3 (50) | 5 (71) | 4 (67) |
| Very Good Partial Response or better, n (%) | 10 (59) | 5 (42) | 6 (60) | 2 (33) | 4 (57) | 3 (50) |
| Complete Response or better, n (%) | 6 (35) | 3 (25) | 4 (40) | 2 (33) | 2 (29) | 1 (17) |
| BM MRD negativity*, n (%) | 8 (47) | 6 (50) | 3 (30) | 2 (33) | 5 (71) | 4 (67) |

* MRD assessment by multicolor flow cytometry (sensitivity: 1 in $10^5$)

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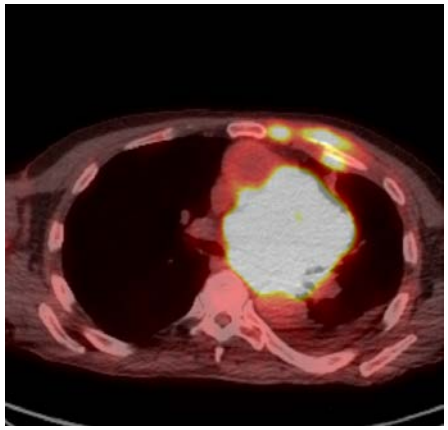
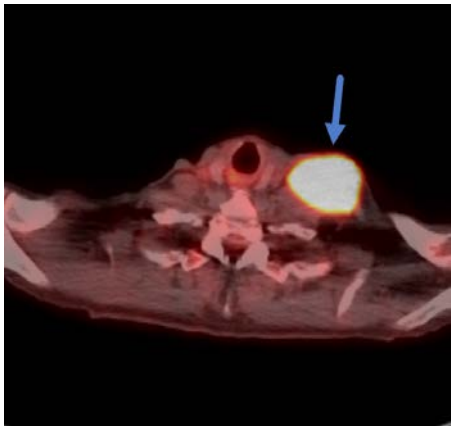
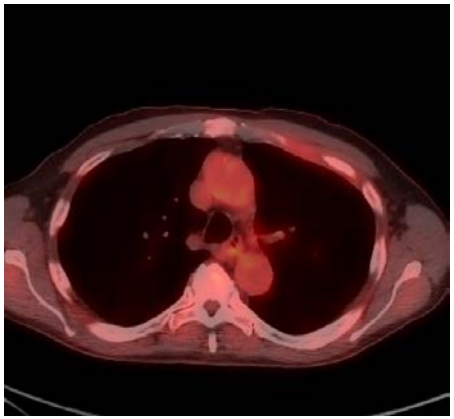
# Radiologic Response: Patient #1

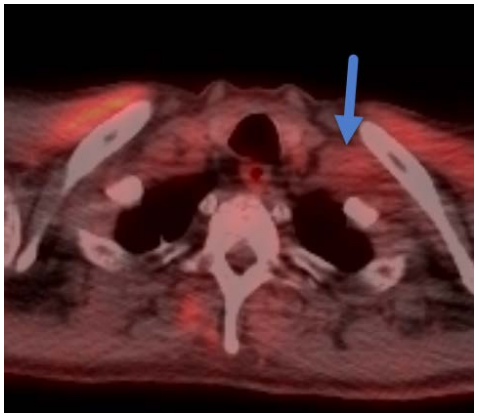


Pre-treatment





4 week follow-up



# GPRC5D directed therapies in clinical development

**Table 1 | GPRC5D-directed CAR-T-cell and bispecific-antibody therapies in clinical development for patients with relapsed and/or refractory multiple myeloma with triple-class exposure**

| Treatment | Efficacy outcomes | Common adverse events (grade ≥ 3) | Off-target, on-tumour toxicities (grade ≥ 3) |
|---|---|---|---|
| **CAR T cell therapies** | | | |
| MCARH109 (ref. [4]) (*n* = 17) | ORR 71% (≥CR in 35%), mDOR 7.8 months | CRS 88% (6%), neurotoxicities 6% (6%), cerebellar toxicities 12% (12%) | Nail changes 65% (0%), rash 18% (0%), dysgeusia 12% (0%) |
| CC-95266 (BMS-986393)[3] (*n* = 33) | ORR 89% (≥CR in 47%), mDOR NR | CRS 64% (6%), neurotoxicities 6% (0%) | Nail changes 9% (0%), skin toxicities 30% (0%), dysgeusia 15% (0%) |
| OriCAR-017 (ref. [5]) (*n* = 10) | ORR 100% (≥CR in 60%), mDOR NR | CRS 100% (0%), neurotoxicities 0% (0%) | Nail changes 30% (0%), skin toxicities NA, dysgeusia NA |
| **Bispecific antibodies** | | | |
| Talquetamab[7] (*n* = 74) | ORR 70% (≥CR in 23%), mDOR 10.2 months[a] | CRS 77% (3%), neurotoxicities 10% (0%)[a] | Nail changes 57% (0%), rash 47% (0%), non-rash skin toxicities 67% (0%), dysgeusia 63% (NA)[a] |
| | ORR 64% (≥CR in 23%), mDOR 7.8 months[b] | CRS 80% (0%), neurotoxicities 5% (0%)[b] | Nail changes 27% (2%), rash 30% (16%), non-rash skin toxicities 70% (2%), dysgeusia 57% (NA)[b] |
| RG6234 (ref. [9]) (*n* = 104) | ORR 64% (≥CR in 25%), mDOR 12.5 months[c] | CRS 79% (2%), neurotoxicities 12% (4%)[c] | Nail/hair changes 28% (0%), skin toxicities 86% (23%), mucosal toxicities 77% (5%)[c] |
| | ORR 71% (≥CR in 35%), mDOR 10.8 months[d] | CRS 82% (2%), neurotoxicities 10% (2%)[d] | Nail/hair changes 24% (0%), skin toxicities 78% (12%), mucosal toxicities 73% (0%)[d] |

CAR, chimeric antigen receptor; ≥CR, complete response or better; CRS, cytokine-release syndrome; mDOR, median duration of response; GPRC5D, G-protein-coupled receptor, class C, group 5, member D; NA, not available; NR, not reached; ORR, overall response rate. [a]Data for patients who received talquetamab at a subcutaneous dose of 405 µg/kg weekly. [b]Data for patients who received talquetamab at a subcutaneous dose of 800 µg/kg every other week. [c]Subcutaneous administration. [d]Intravenous administration.

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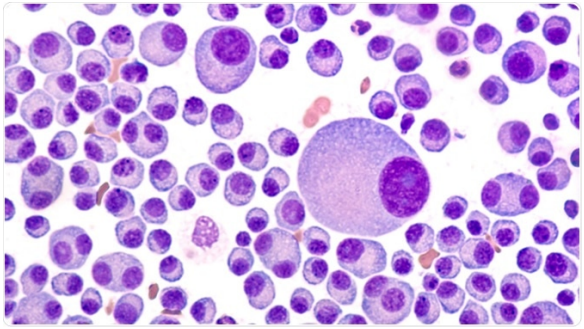
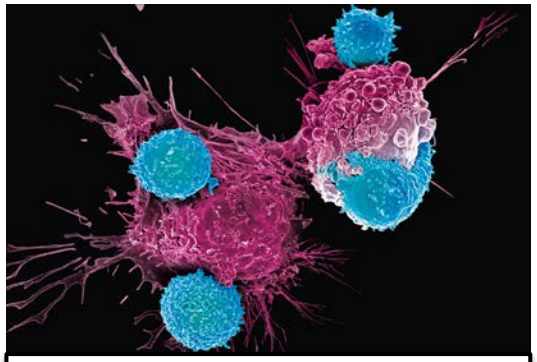
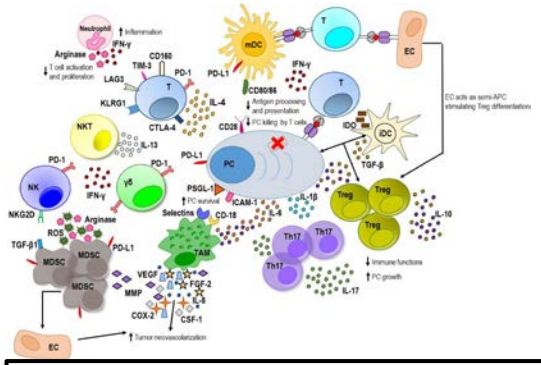
# Mechanisms of resistance to immune therapies



Plasma cell related



T cell related



Microenvironment related

Loss or decrease in BCMA expression

- CAR T constructs targeting low antigen density
- Alternate or dual targeting

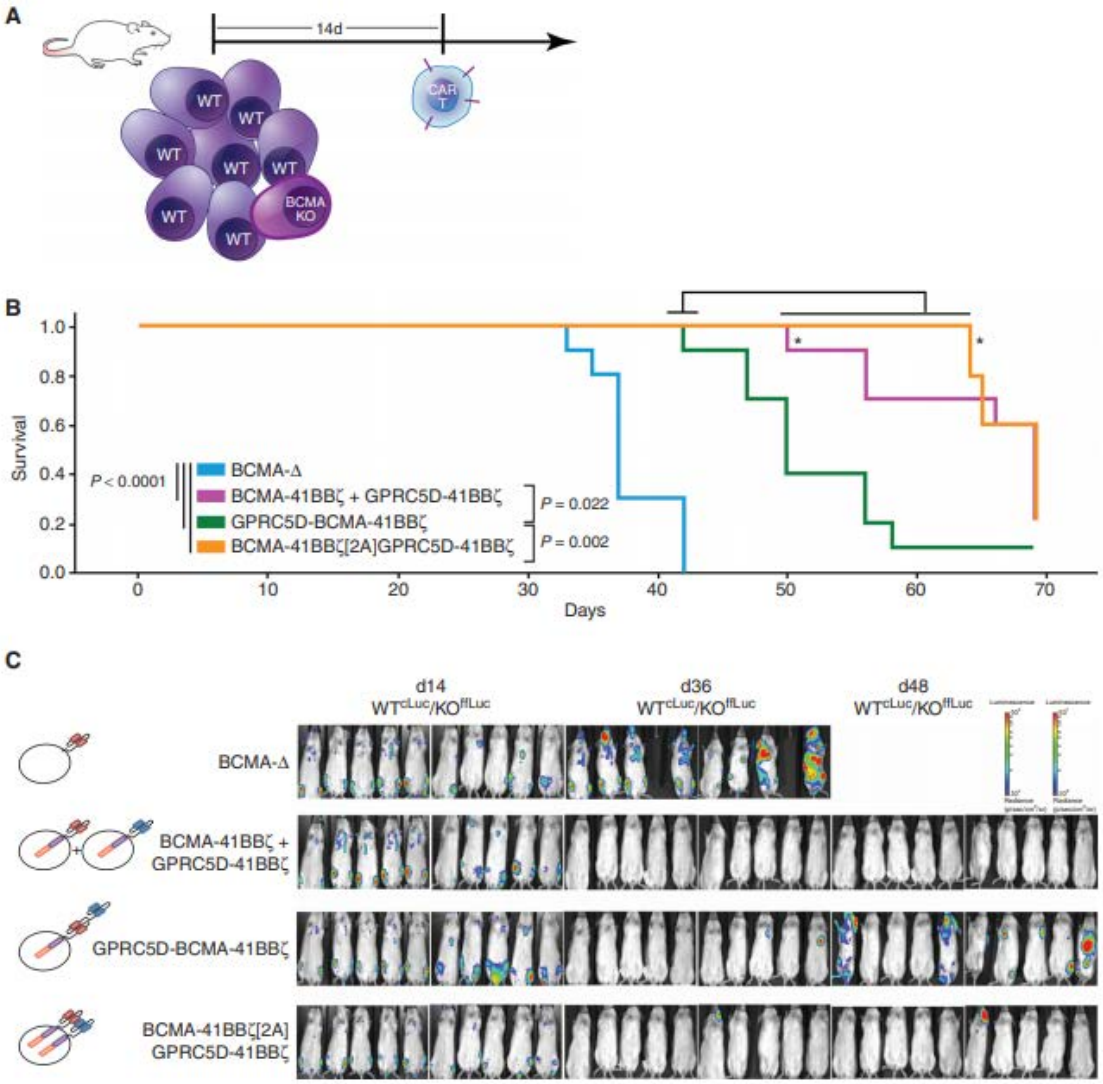
Lack of persistence or exhaustion of T cells

- T cell therapies at earlier stages of disease
- Allogeneic cell therapies
- Combination approaches

Extramedullary disease

- Combination approaches
- Radiation therapy

# Rationale for Targeting Both GPRC5D and BCMA

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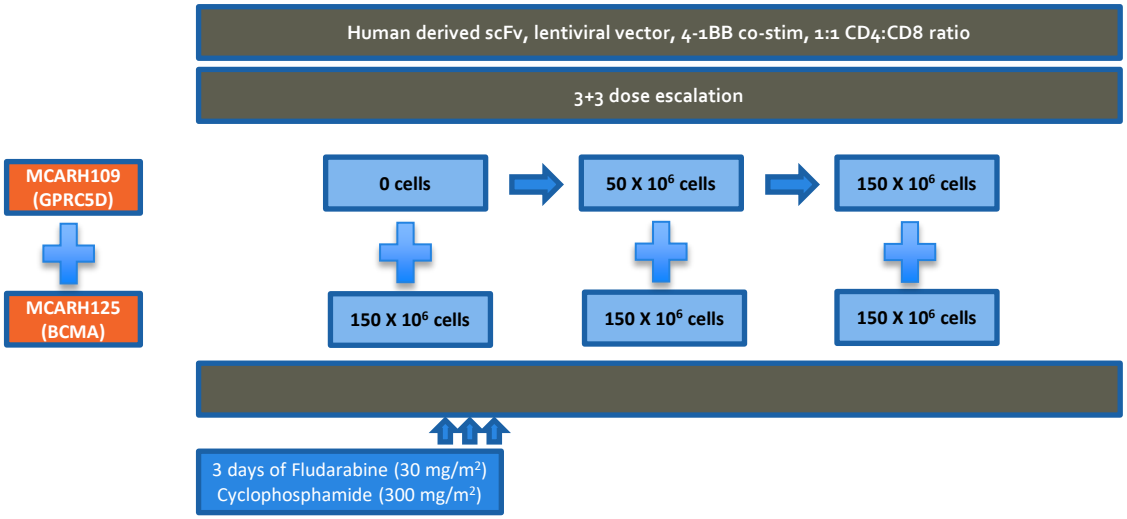
# BCMA and GPRC5D targeted CAR T cell therapy

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# Summary

- Two CART therapies and one bispecific antibody targeting BCMA are now FDA approved
- High overall responses and promising duration of response with these therapies
- Other potential immune therapies: allogeneic CAR T cells, bispecific antibodies
- Alternate targets like GPRC5D emerging as possible treatment options
- Relapses are common- mechanisms not entirely clear
- Potential for combinations and earlier use of these therapies in myeloma

# Thank you!

Sham Mailankody, MBBS
Associate Attending
Myeloma &
Cellular Therapeutics Service
Memorial Sloan Kettering
Cancer Center
New York, NY, USA
Email: mailanks@mskcc.org

**Myeloma Service**
Saad Usmani, MD, MBA
Hani Hassoun, MD
Alex Lesokhin, MD
Urvi Shah, MD
Neha Korde, MD
Malin Hultcrantz, MD, PhD
Carlyn Tan, MD
Dhwani Patel, MD

**BMT Service**
Sergio Giralt, MD
Heather Landau, MD
David Chung, MD, PhD
Michael Scordo, MD
Gunjan Shah, MD
Oscar Lahoud, MD
Parastoo Dahi, MD

**Pathology and Radiology**
Jonathan Landa, MD
Ahmet Dogan MD, PhD
Misha Roshal, MD

**Cellular Therapeutics Service**
Jae Park, MD
Briana Cadzin, RN
Bianca Santomasso, MD
Elena Meade, MD and many others

**Center for Hematologic Malignancies**
Omar Abdel-Wahab
Xiaoli Mi and team

**Cell Therapy and Cell Engineering Facility**
Michel Sadelain, MD, PhD
Karlo Perica, MD
Isabelle Riviere, PhD and team

**Immune Discovery and Modelling Service**
Kinga Hosszu
Devin Mcavoy

**External Collaborators**
Renier Brentjens, MD, PhD and lab (RPCI)
Eric Smith, MD, PhD and lab (DFCI)

**Thank you to our patients, families and caregivers!**

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