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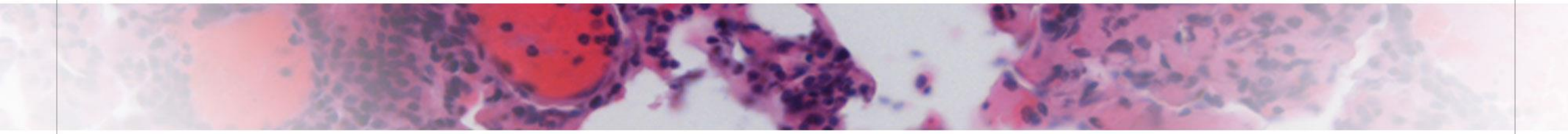


Development of a Phase 1 Study Evaluating the Activity of Modular CAR T for Multiple Myeloma (MCARTY) Targeting BCMA and CD19 for Improved Persistence

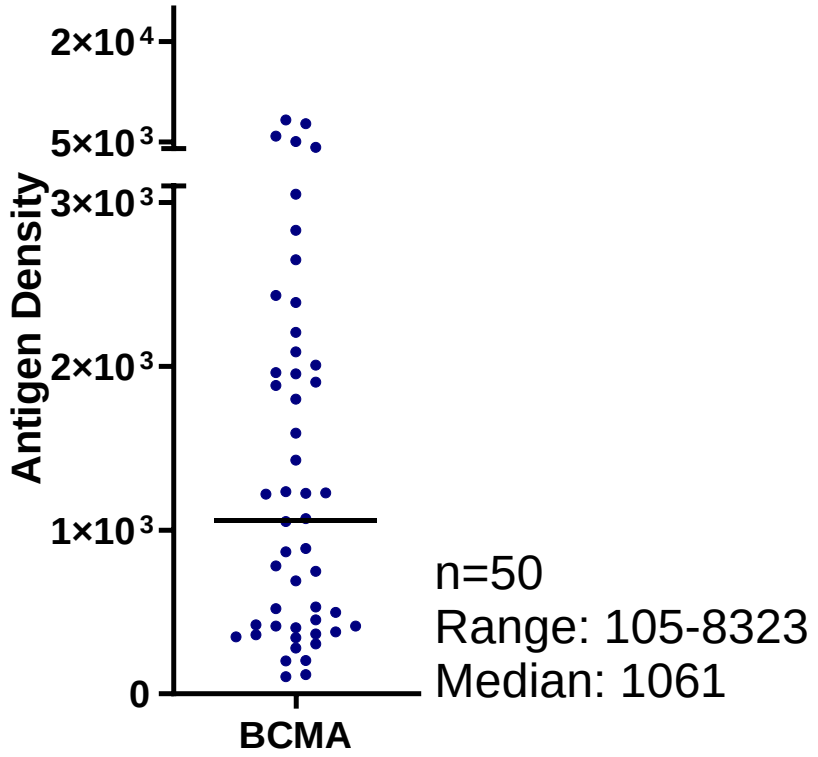
Lydia Sarah Hui Lee,[1,2] Wen Chean Lim,[3] Catriona Mactier,[4] Juliana Dias Alves Pinto,[5] Vitória Pereira,[5] Mhairi Vaughan,[5] Louisa Green,[5] Evie Lewin,[5] John Garcia,[5] Giulia Agliardi,[5] Yashma Pathak,[6] Riaz Jannoo,[6] Leigh Wood,[2] Bilyana Popova,[7] Helen Holmes,[7] Simon Thomas,[3] Victoria Spanswick,[6] William Wilson,[7] Christopher Parrish,[8] Rakesh Popat,[2] Claire Roddie,[1,2] Kwee Yong,[1,9] Martin Pule[1,3]

[1]Research Department of Haematology, University College London Cancer Institute, London, UK; [2]Department of Haematology, University College London Hospitals NHS Foundation Trust, London, UK; [3]Autolus Therapeutics, London, UK; [4]University College London, London, UK; [5]Centre for Cell, Gene & Tissue Therapeutics, University College London Cancer Institute, London, UK; [6]UCL ECMC GCLP Facility, University College London Cancer Institute, London, UK; [7]Cancer Research UK & UCL Cancer Trials Centre, University College London Cancer Institute, London, UK; [8]Leeds Teaching Hospitals NHS Trust, Leeds Cancer Centre, Leeds, UK; [9]Department of Haematology, University College London, London, UK

Background

- BCMA CAR T cells are highly effective in multiple myeloma, but long-term outcomes may be limited
- BCMA CAR T cell targeting is challenging
  - Low and variable BCMA surface expression
  - Myeloma stem/progenitor cells may not express BCMA
  - Persistence of BCMA CAR T cells is limited
- We sought to
  - Develop an ultrasensitive BCMA CAR
  - Co-target CD19 using a CAR with proven persistence
  - Test in an iterative clinical study

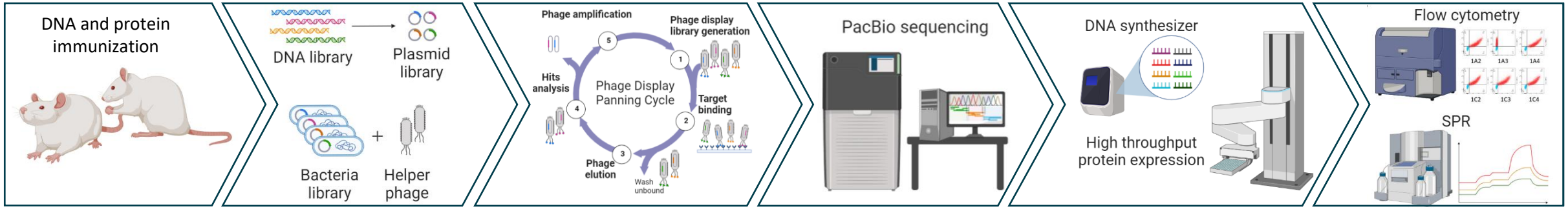
Distribution of BCMA expression on primary CD138^{+} myeloma cells[1]



[1]Lee L et al., Blood 2018;131(7):746–58

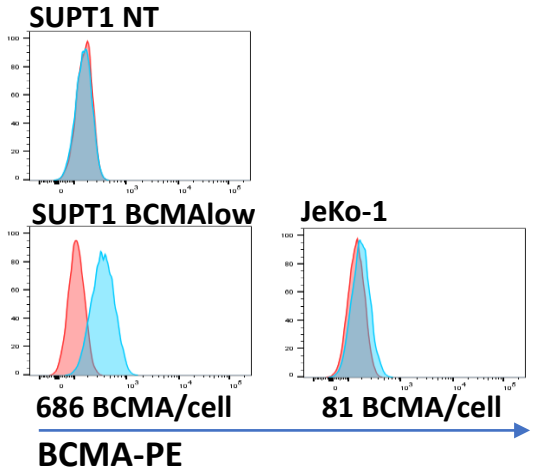
Part 1: Identification of a highly sensitive BCMA CAR

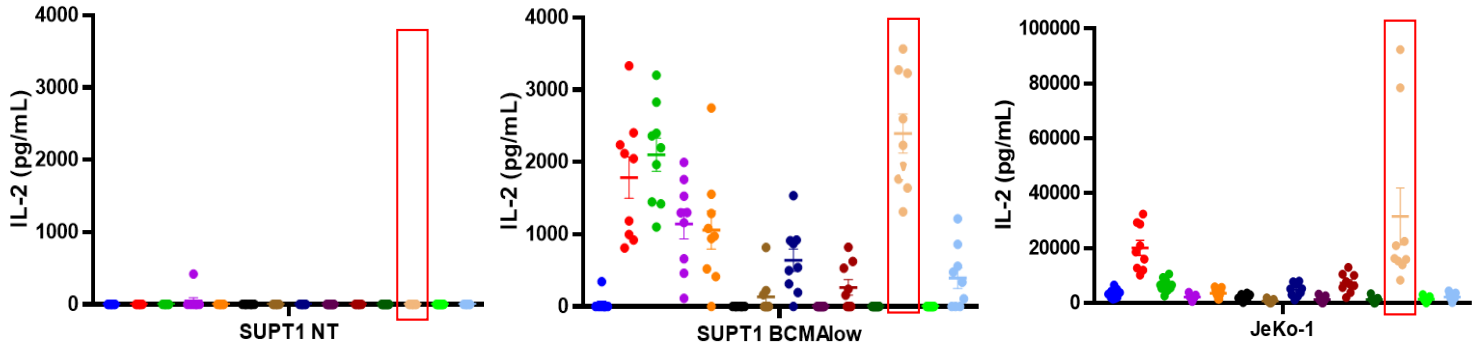
BCMA binders were generated from a rat library



Rat immunization | cDNA isolation and library construction | Phage display | Next generation sequencing analysis | DNA synthesis and protein production | Antibody biophysics and QC

13 binders were screened by function with low and ultra-low cell lines



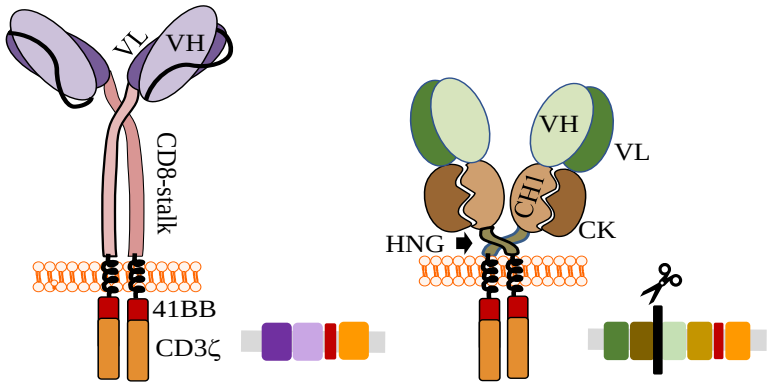


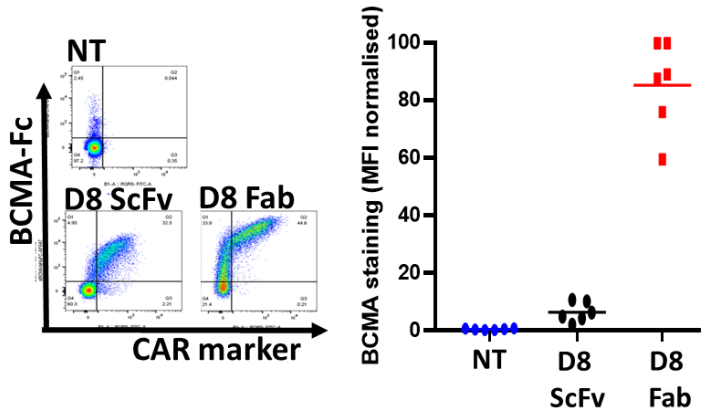
Binder D8 was selected

D8 Fab CAR vs D8 scFv CAR

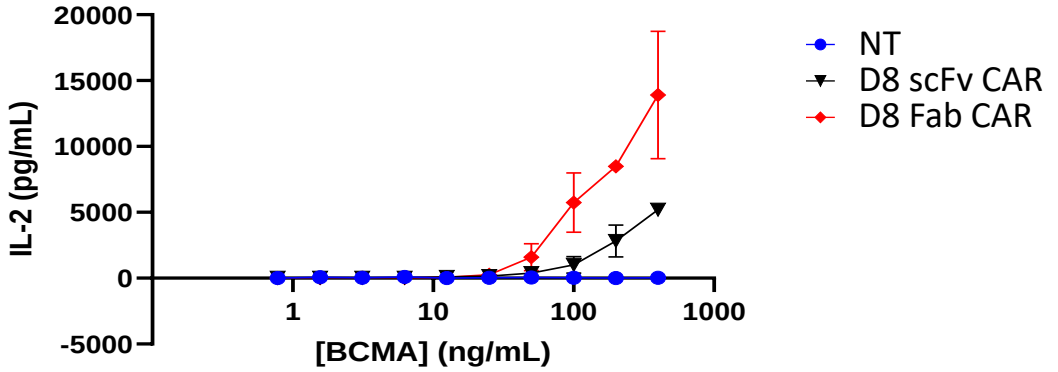
- Fab CAR format demonstrated increased surface CAR expression and greater sensitivity

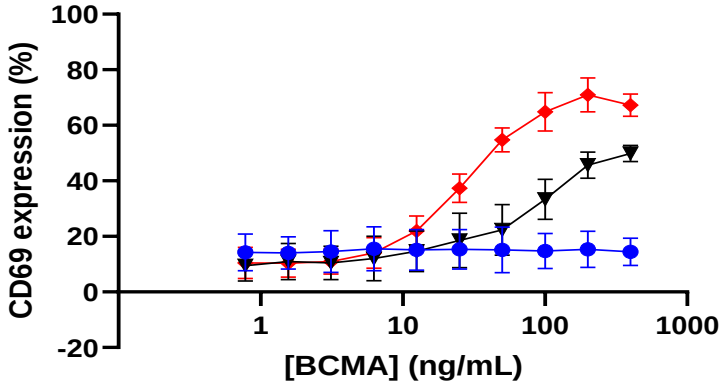
Increased BCMA binding by D8 Fab





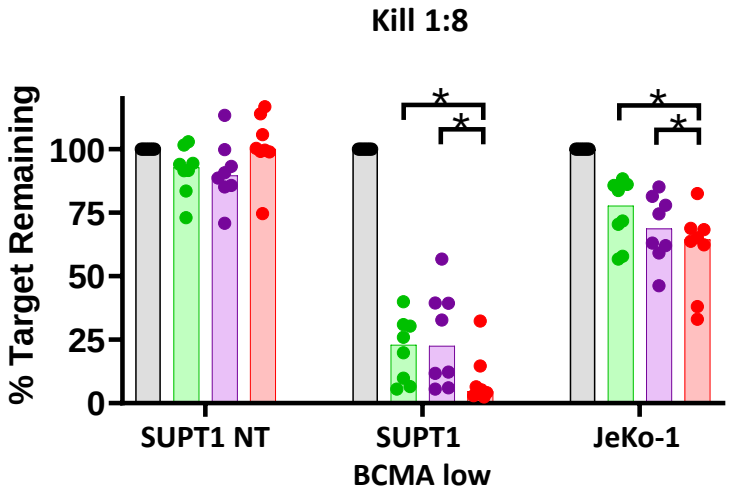
Increased activation by low level BCMA by D8 Fab

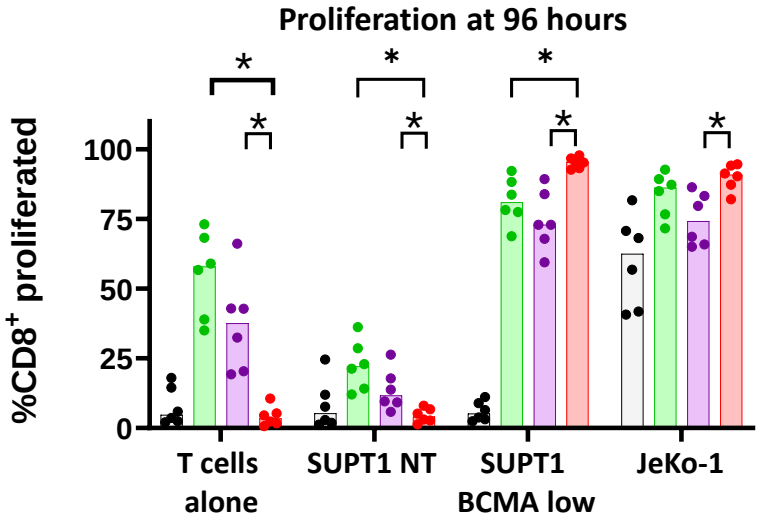


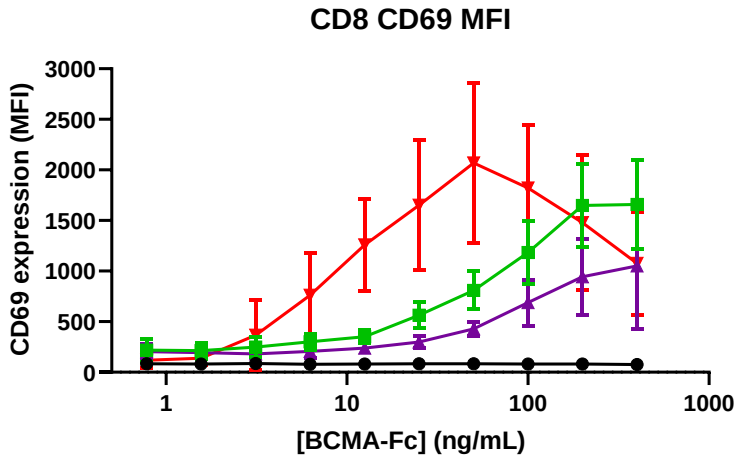


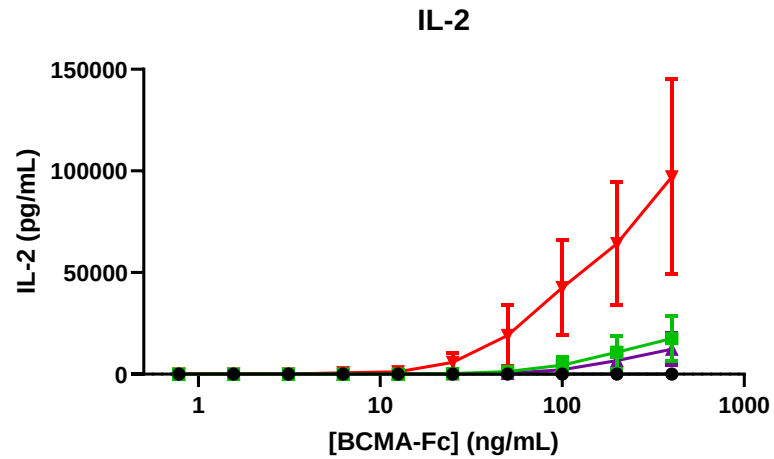
D8 Fab CAR vs other BCMA CARs

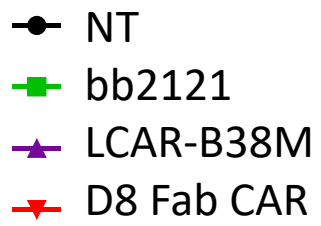
- D8 Fab CAR showed increased sensitivity to low-density antigen vs bb2121 and LCAR-B38M





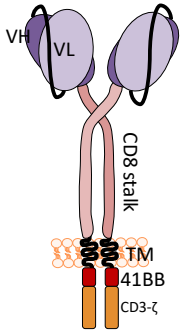




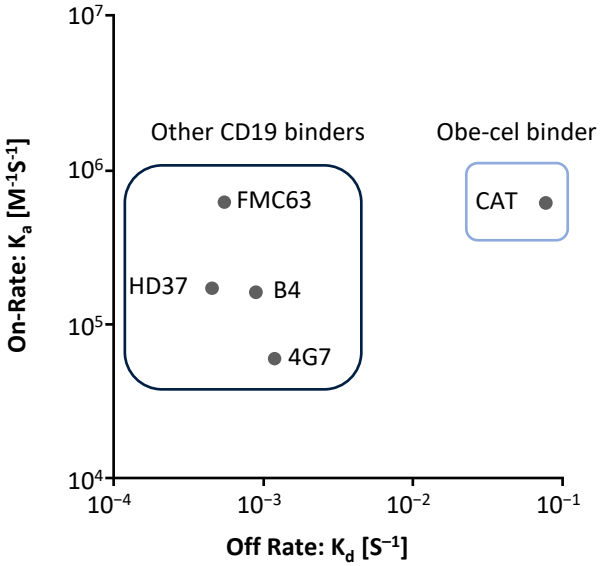


Part 2: Co-targeting CD19 with obe-cel

- Obecabtagene autoleucel (obe-cel, CAT-41BBζ) is a clinically proven fast off-rate CD19 CAR
- In adult ALL, obe-cel has demonstrated:[1–3]
  - High AUC
  - Low toxicity
  - Persistence
- Efficacy and persistence has also been demonstrated in B-NHL and CLL[4]
- Thus obe-cel is persistent and tolerable and suitable for a co-targeting strategy in multiple myeloma



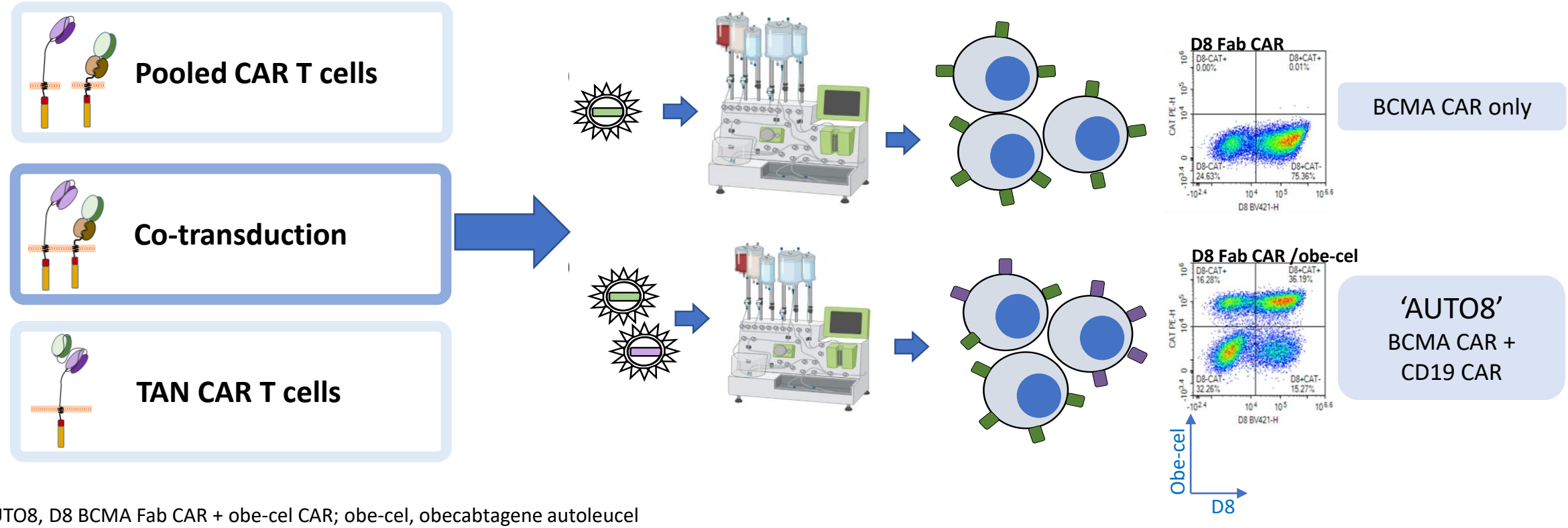
Fast-on, fast-off rate kinetics[5]



[1]Roddie C et al., J Clin Oncol 2021;39(30):3352–63; [2]Roddie C et al., J Clin Oncol 2023;41[16 Suppl]:7000; [3]Roddie C et al., ASH 2023 abstract 2114; [4]Roddie C et al., Blood 2022;140(Suppl 1):7452–3, ASH abstract; [5]Ghorashian S et al., NatMed 2019;25(9):1408–14

Dual targeting CAR by co-transduction

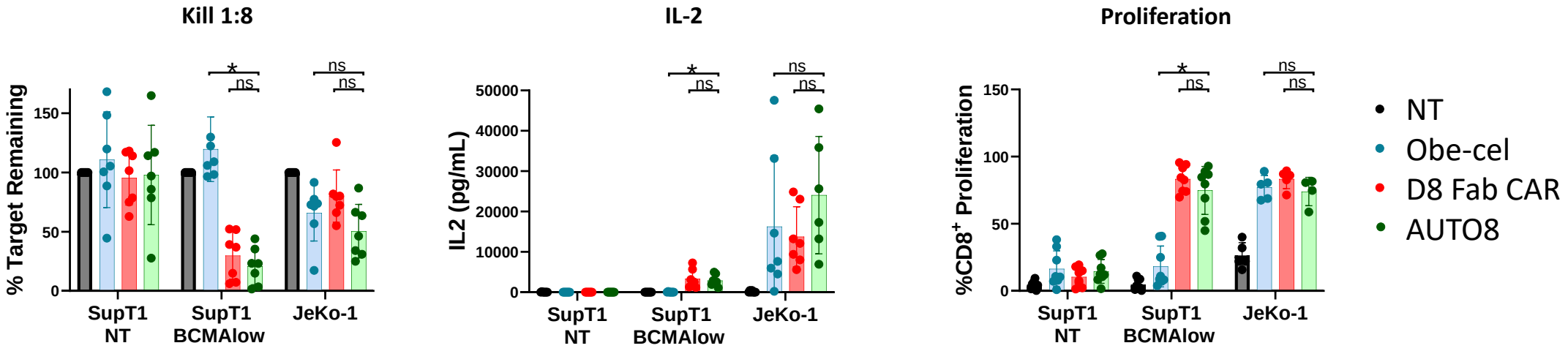
- Co-transduction is simple and does not disrupt obe-cel or D8 Fab CAR expression
  - Several potential co-targeting strategies
  - Dual transduction approach chosen for ease, to leave both CARs intact



AUTO8, D8 BCMA Fab CAR + obe-cel CAR; obe-cel, obecabtagene autoleucel

D8 BCMA CAR vs AUTO8 dual targeting CAR

- AUTO8 can target both CD19 and BCMA



*p<0.05
AUTO8, D8 BCMA Fab CAR + obe-cel CAR; ns, not significant

Part 3: MCARTY trial

- Staggered dose-escalation study design testing both D8 BCMA CAR and AUTO8: Phase 1 study evaluating the activity of **M**odular **CAR T** for M**Y**eloma (MCARTY)

Screening → **Leukapheresis** → **Academic manufacture**
- T cell selection
- Prodigy based lentiviral transduction with AKTVIII*
- 6–8 day expansion

→ **Lymphodepletion**
- Cy 300mg/m^2
- Flu 30mg/m^2
- Day -5/-4/-3

→ **CAR infusion** → **Follow up**

Iterative, staggered trial design for direct comparison (rolling 6 design)

Cohort 1: BCMA CAR	**50 x 10^6 CAR T cells**	**150 x 10^6 CAR T cells**
Cohort 2: AUTO8	**50 x 10^6 CAR T cells**	**150 x 10^6 CAR T cells**

Key eligibility criteria

- R/R multiple myeloma
- Secretory disease
- Triple exposed (IMID, PI, anti-CD38) including ASCT (unless ineligible)
- Refractory to last line of therapy
- ECOG PS 0/1
- CrCl≥40ml/min, ANC≥1, plt≥50, Hb≥80
- No selection based on BCMA expression

Primary endpoints

- Safety
- Feasibility

Secondary endpoints

- Response and survival
- CAR persistence

Screened
N = 13

→ Progressive disease
n = 1

Successfully manufactured products
N = 12

Infused
N = 11

Median vein to vein time:
55 days

*Mehra et al JITC 2023 11(9). Data cut off: 13 Nov 2023

AUTO8, D8 BCMA Fab CAR + obe-cel CAR; cy, cyclophosphamide; flu, fludarabine; obe-cel, obecabtagene autoleucel

Baseline characteristics

Baseline characteristics	All treated patients (N = 11)
Male / female, n (%)	9 (82) / 2 (18)
Median age, years (range)	50 (33–66)
Median time since diagnosis, years (range)	4.6 (3.1–11.8)
ISS at baseline, n (%) I / II / III	 8(73) / 3 (27) / 0
Cytogenetic risk, n (%) Known High risk	 10 (91) 5 (45)
Extramedullary disease, n (%)	0 (0)
Median prior lines of therapy, n (range)	4 (3–8)
PI/IMID/CD38 exposed, n (%) PI refractory IMID refractory CD38 refractory Triple refractory Previous BCMA exposure	11 (100) 7 (64) 9 (82) 10 (91) 5 (45) 1 (9)
Baseline PCs on trephines, % (range)	30 (10–65)
BCMA expression on PCs (ABC by FACS), n (range)	409 (1–2530)

Note: high risk cytogenetics defined as t(4;14), t(14;16), t(14;20), del(17p), 1q gain, 1p loss

Safety

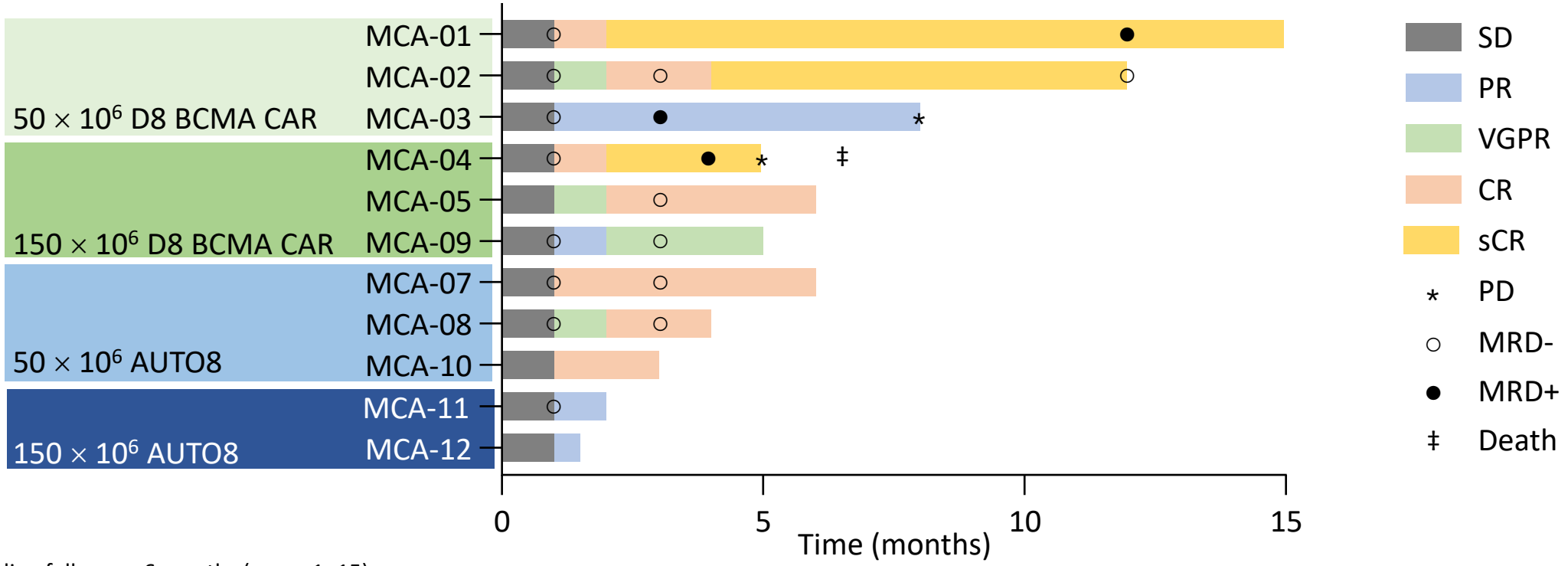
Adverse events, n (%)	D8 BCMA CAR 50 x 10^6 (N = 3)		D8 BCMA CAR 150 x 10^6 (N = 3)		AUTO8 50 x 10^6 (N = 3)		AUTO8 150 x 10^6 (N = 2)	
	Grade 1–2	Grade ≥3	Grade 1–2	Grade ≥3	Grade 1–2	Grade ≥3	Grade 1–2	Grade ≥3
Hematological								
Anemia	0	1 (33)	1(33)	2(67)	0	2 (67)	1(50)	1(50)
Neutropenia	0	3 (100)	0	3 (100)	0	3 (100)	0	2 (100)
Thrombocytopenia	1 (33)	1 (33)	1 (33)	2 (67)	0	2 (67)	0	1 (50)
CRS	3 (100)	0	3 (100)	0	2 (67)	0	2 (100)	0
ICANS	0	0	0	0	0	0	0	0

- D8 BCMA CAR and AUTO8 did not result in severe ICANS/CRS and were well tolerated with no DLTs
  - CRS in 10 patients (91%) and all low grade; median time to onset was 0.5 days (range 0–6) and median duration was 4 days (range 1–16)
  - No patients reported ICANS
  - Tocilizumab given to 7 patients (64%) and steroids to 2 patients (18%)

AUTO8, D8 BCMA Fab CAR + obe-cel CAR

Clinical responses

- Both D8 BCMA CAR and AUTO8 associated with high response rate
  - ORR 100%
  - 3 PR, 1 VGPR, 7 CR/sCR (all evaluable MRD-)
  - Two patients remained in sCR at >12 months; overall PFS was not reached



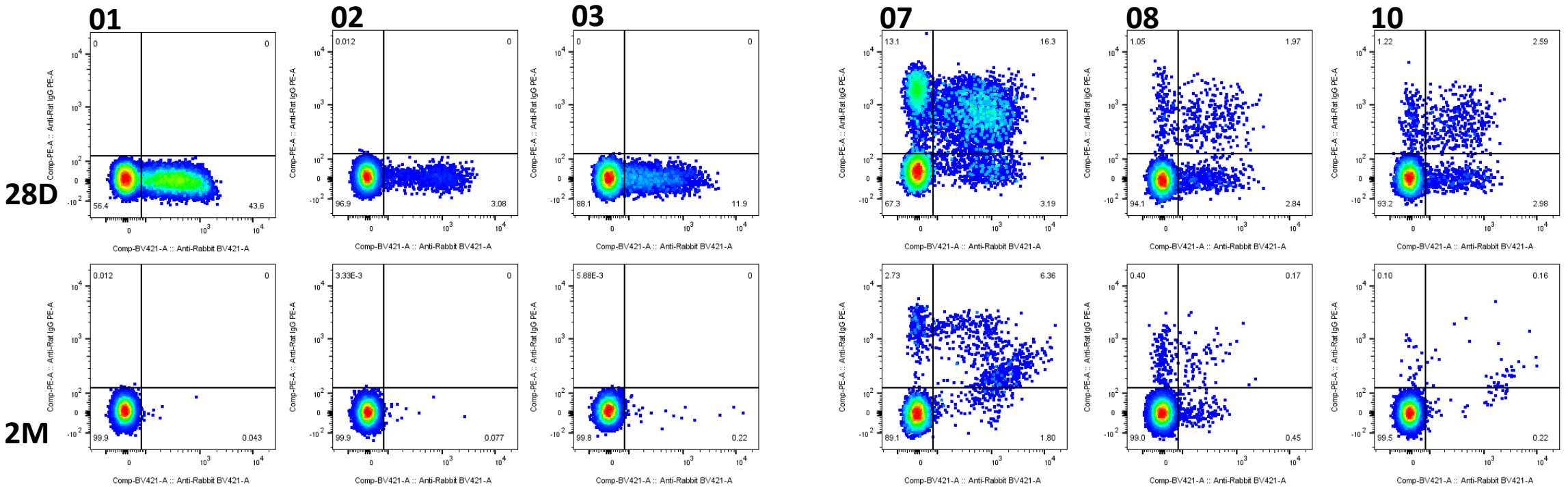
Median follow up 6 months (range 1–15)
AUTO8, D8 BCMA Fab CAR + obe-cel CAR

Persistence data D8 BCMA CAR vs AUTO8

- Increased CAR T cells detected by flow in patients treated with AUTO8

50 x 10^6 D8 BCMA CAR

50 x 10^6 AUTO8



Obe-cel

D8

AUTO8, D8 BCMA Fab CAR + obe-cel CAR

Conclusions

- D8 Fab CAR is a BCMA CAR with increased activity and sensitivity to low level antigens
- Co-targeting CD19 by co-transducing effector cells with the obe-cel CD19 CAR aims to increase the duration of CAR-mediated tumor control
- MCARTY is a recruiting Phase 1 trial for R/R multiple myeloma with two separate, parallel cohorts for direct comparison: i) D8 BCMA Fab CAR and ii) AUTO8: D8 BCMA Fab CAR + obe-cel CAR
- At median follow up of 6 months, there were no reported cases of ICANS and no grade ≥3 CRS; ORR was 100% with two cases of ongoing sCR >12 months
- Persistence data of the AUTO8 dual targeting cohort is immature but demonstrates expansion of three CAR populations and suggests a trend to increased persistence of D8 BCMA Fab CAR expressing T cells

AUTO8, D8 BCMA Fab CAR + obe-cel CAR; obe-cel, obecabtagene autoleucel

Thank you

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