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Design and Demonstration of Potent in vitro and in vivo Activity for CART-ddBCMA, a BCMA-Targeted CAR-T Cell Therapy Incorporating a Non-scFv Binding Domain

Janine M Buonato, Justin Edwards, Liubov Zaritskaya, Ankit Gupta, Laura Richman, David Hilbert, David LaFleur, David Tice

Arcellx, Inc.

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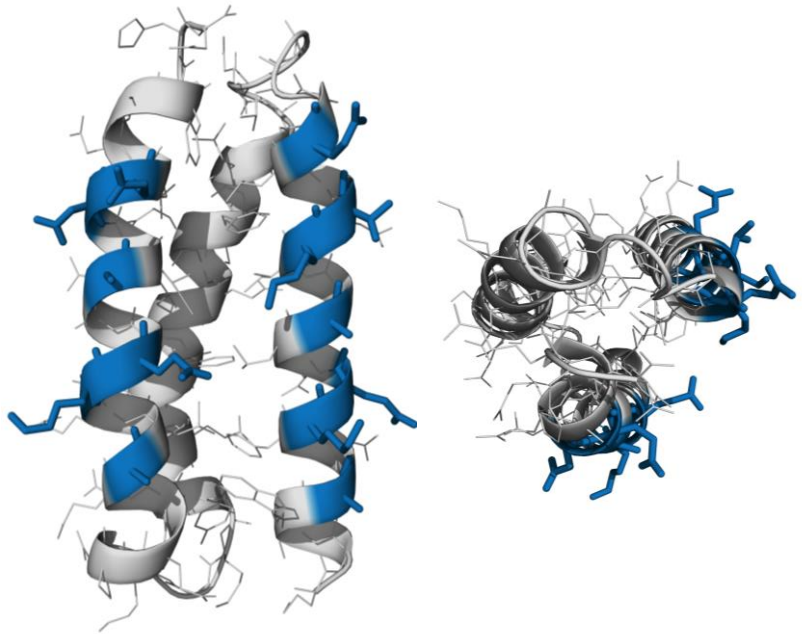
Disclosures

Employment: Arcellx

ddBCMA: a BCMA specific D domain for targeting multiple myeloma tumors

Arcellx's D domain platform for novel binding domain discovery

- Phage display libraries with 'face' of 12-14 randomized positions
- Based on a 73 aa (~8kDa) synthetic protein with no disulfide bonds (α3D; Qin *Mol Therapy* 2019)
- Can produce hits to variety of antigens with affinities as low as subnanomolar



ddBCMA:

Therapeutic solutions needed for relapsed and refractory myeloma patients – **BCMA** demonstrated as an effective therapeutic target in multiple myeloma

ddBCMA isolated from D-domain phage libraries

- **K_D = 40 nM**
- Engineered for reduced immunogenicity

ddBCMA CAR construction and transduction

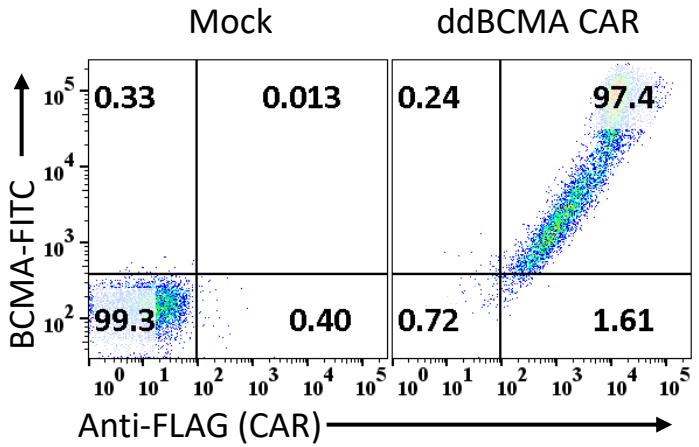
CAR Architecture

ddBCMA binding domain incorporated into lentiviral expression cassette encoding standard CAR elements

FLAG tag in research vector*

α3D (ddNC) and C11D5.3 scFv (scFv) CAR constructs tested in parallel

ddBCMA CAR expression and target capture



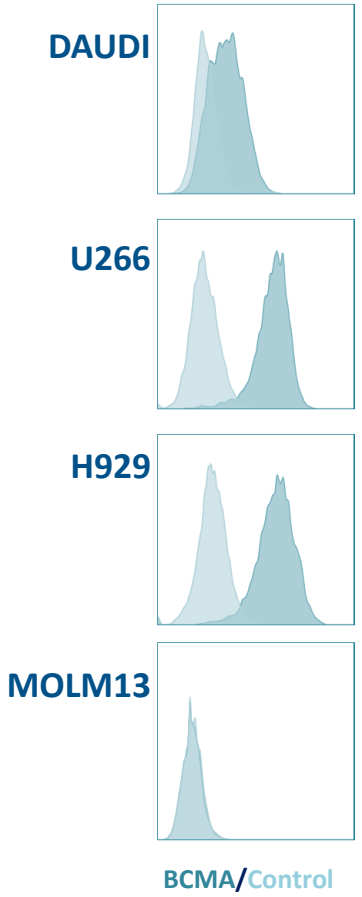
Normal donor T cells transduced with ddBCMA CAR

Stained for CAR expression and soluble BCMA binding

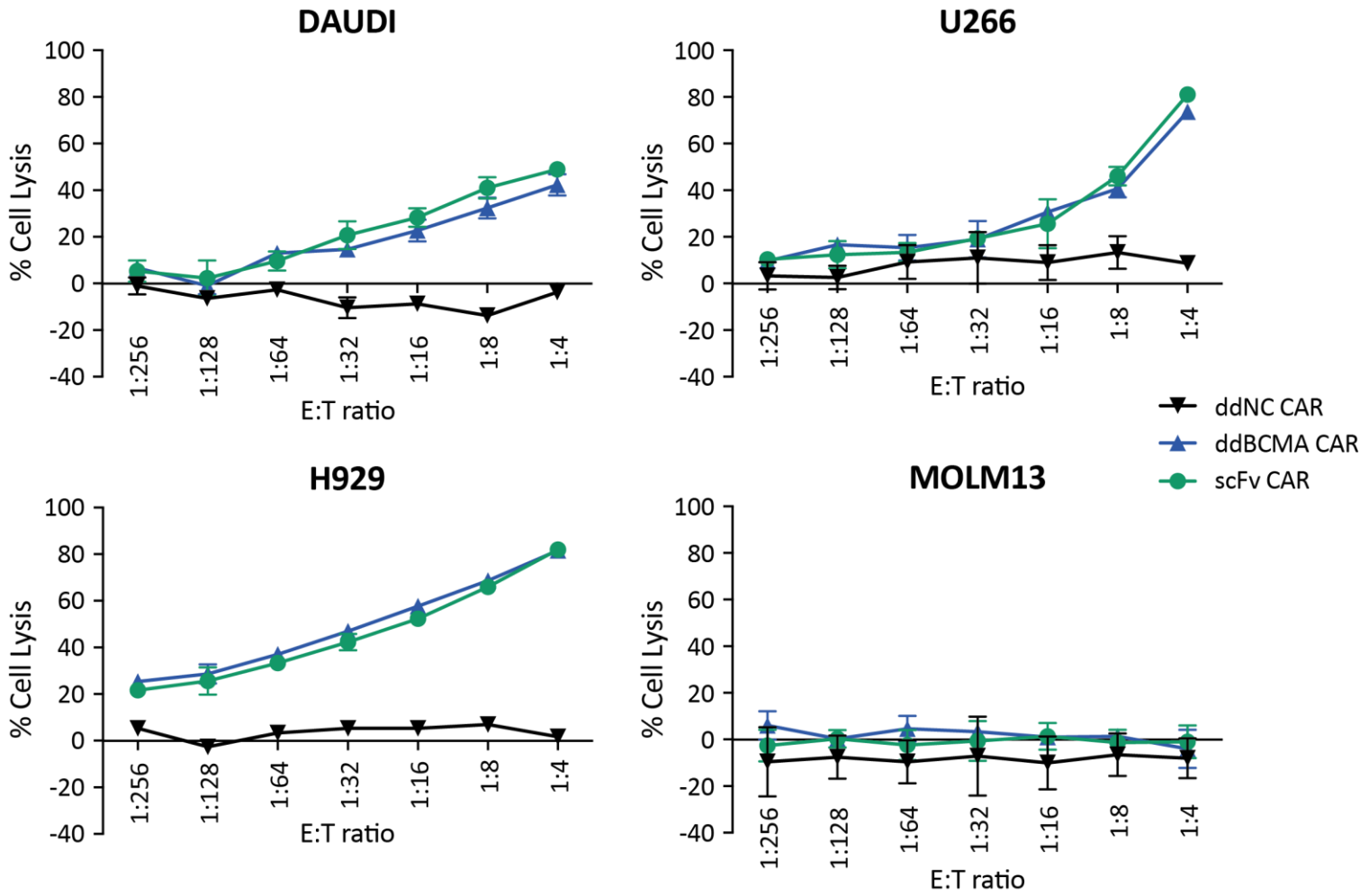
*Preclinical data throughout was generated with related but distinct cells from CART-ddBCMA to support its clinical development.

ddBCMA CAR mediates BCMA-specific target cell killing

Target cells



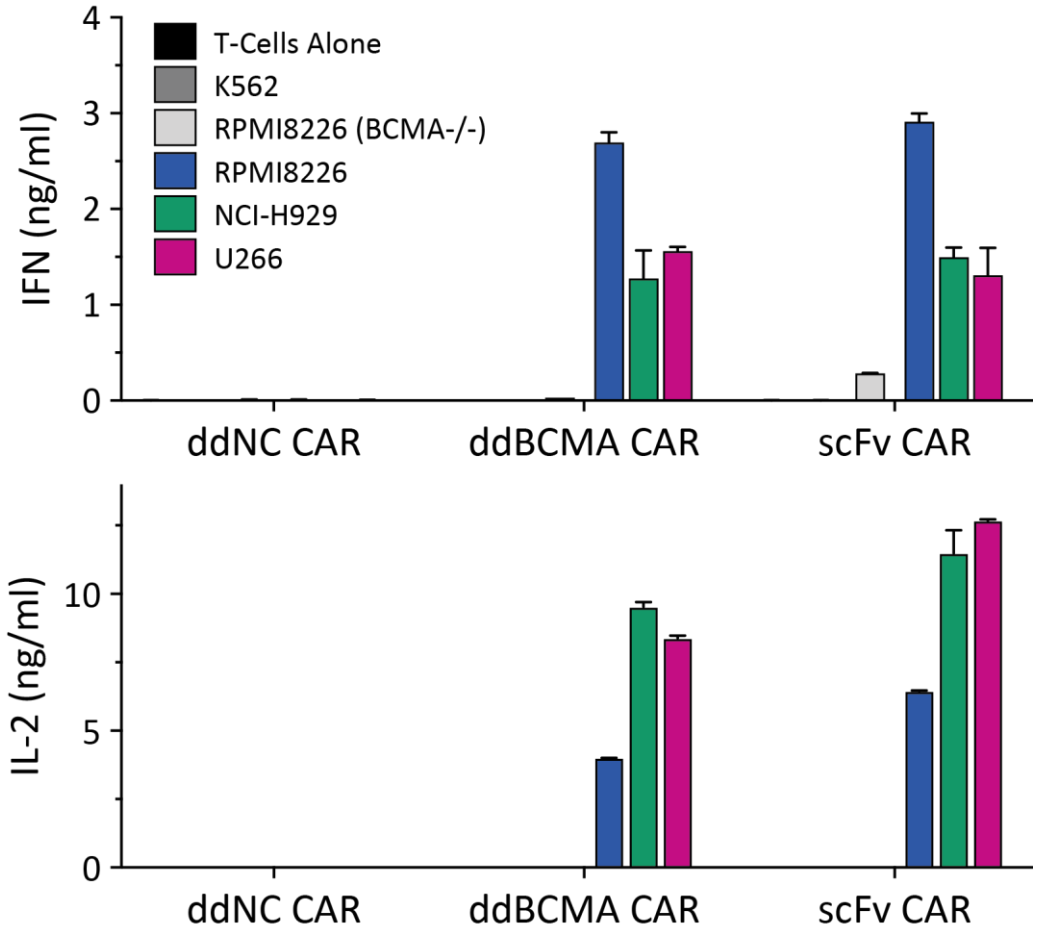
T cell mediated target lysis



Cell lysis measured after 16 hr co-culture with CAR-T cells

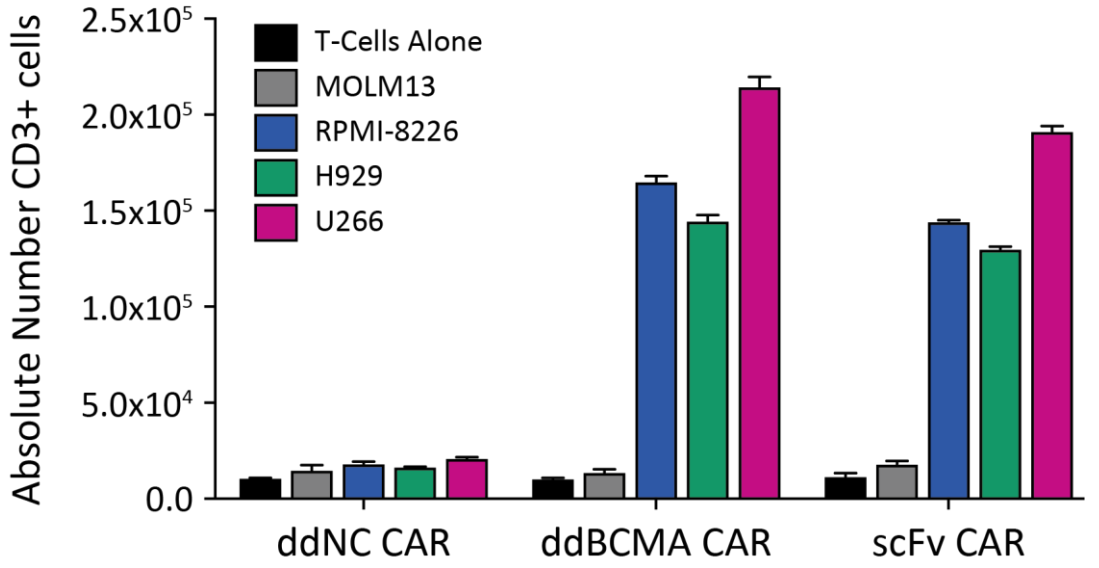
ddBCMA CAR induces cytokine secretion and T cell proliferation

Cytokine release



1:1 ratio of CAR-T and target cells, 16 hr

T-cell proliferation

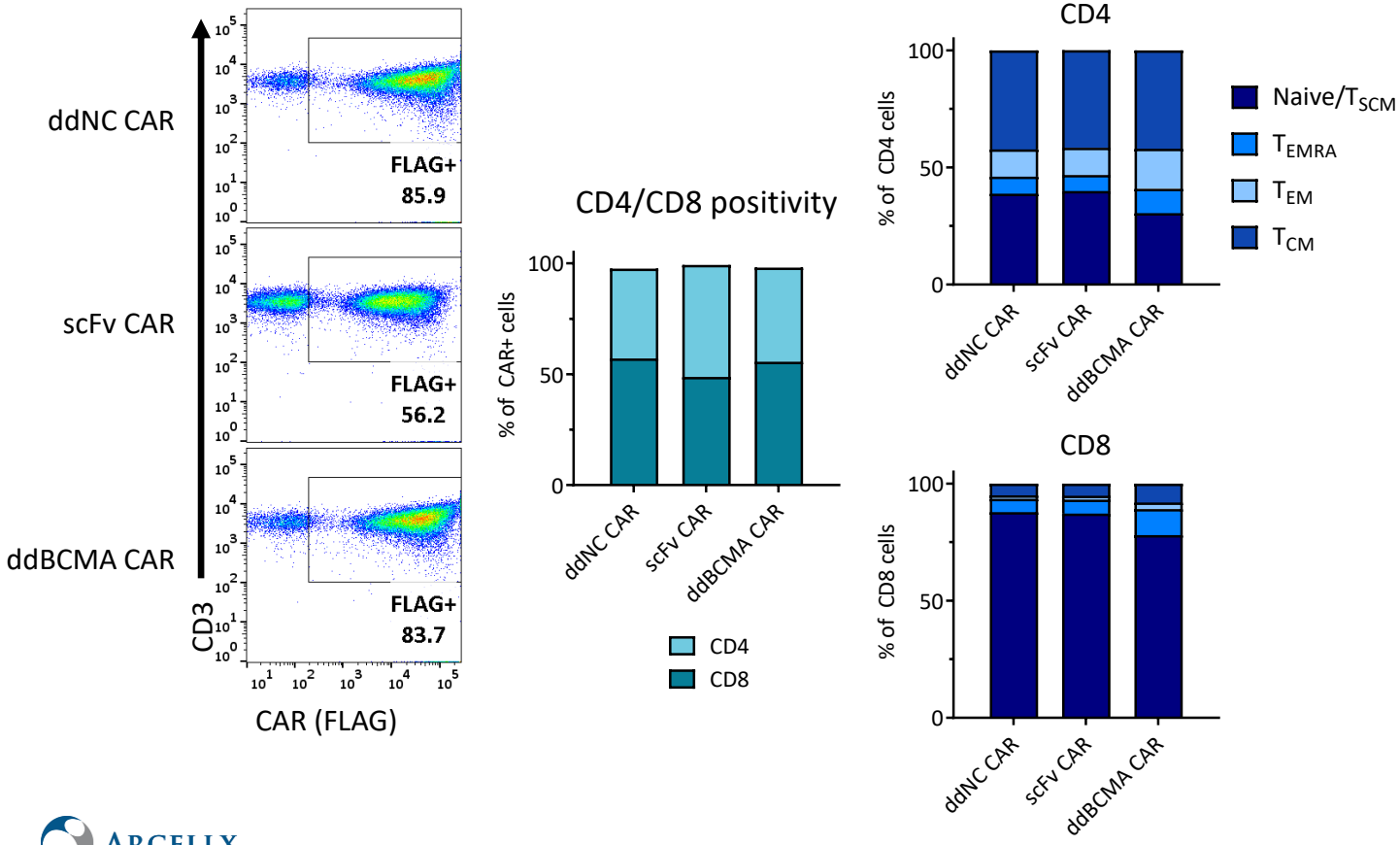


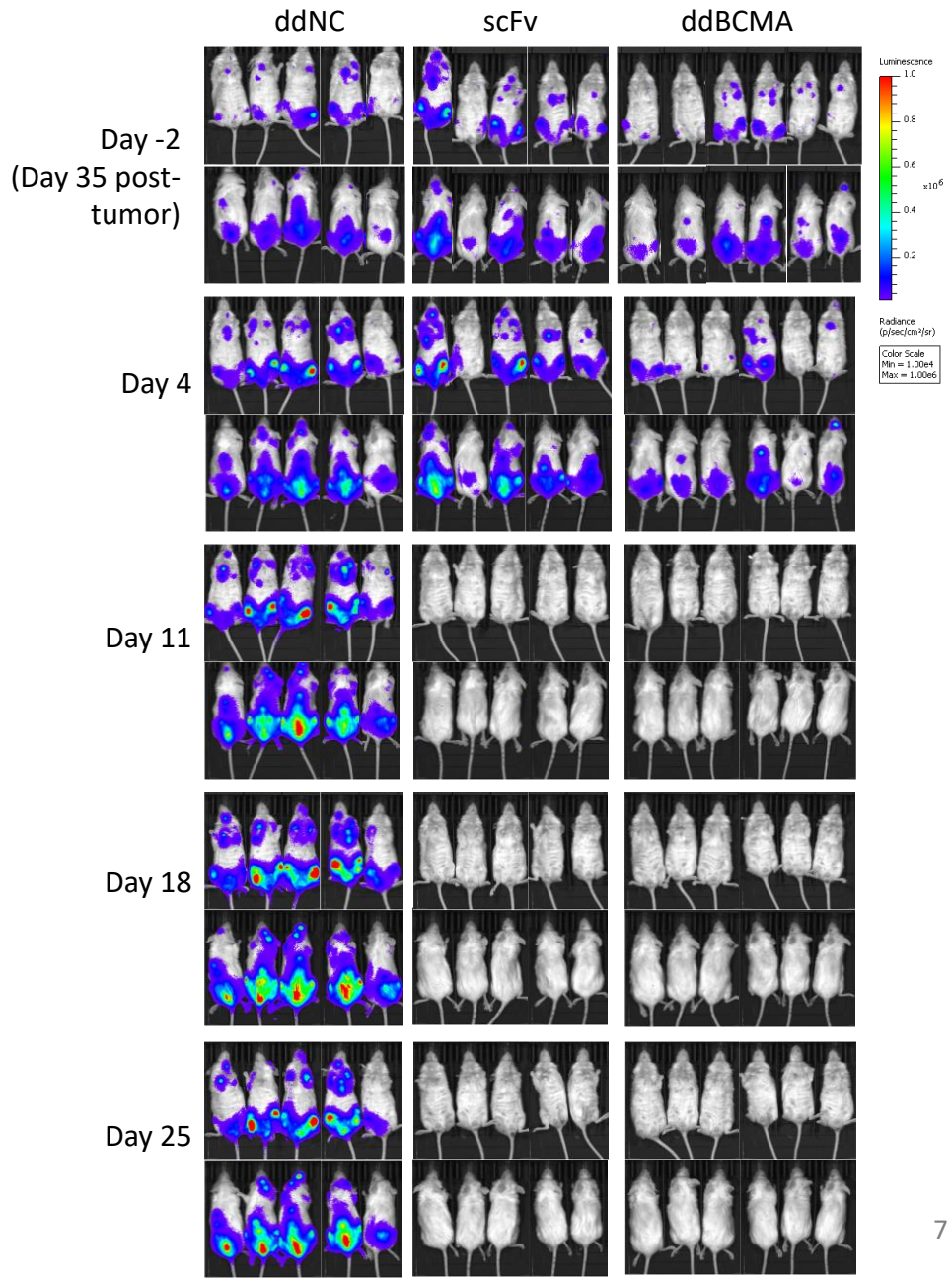
1:1 ratio of CAR-T and target cells, 4 days

ddBCMA CAR mediates sustained tumor control in vivo

NSG™ mice were injected i.v. with 5 million U266 cells; transfer of 1.5 million CAR-positive T cells injected i.v. 37 days later (Day 0)

Phenotyping of CAR-T cell inputs

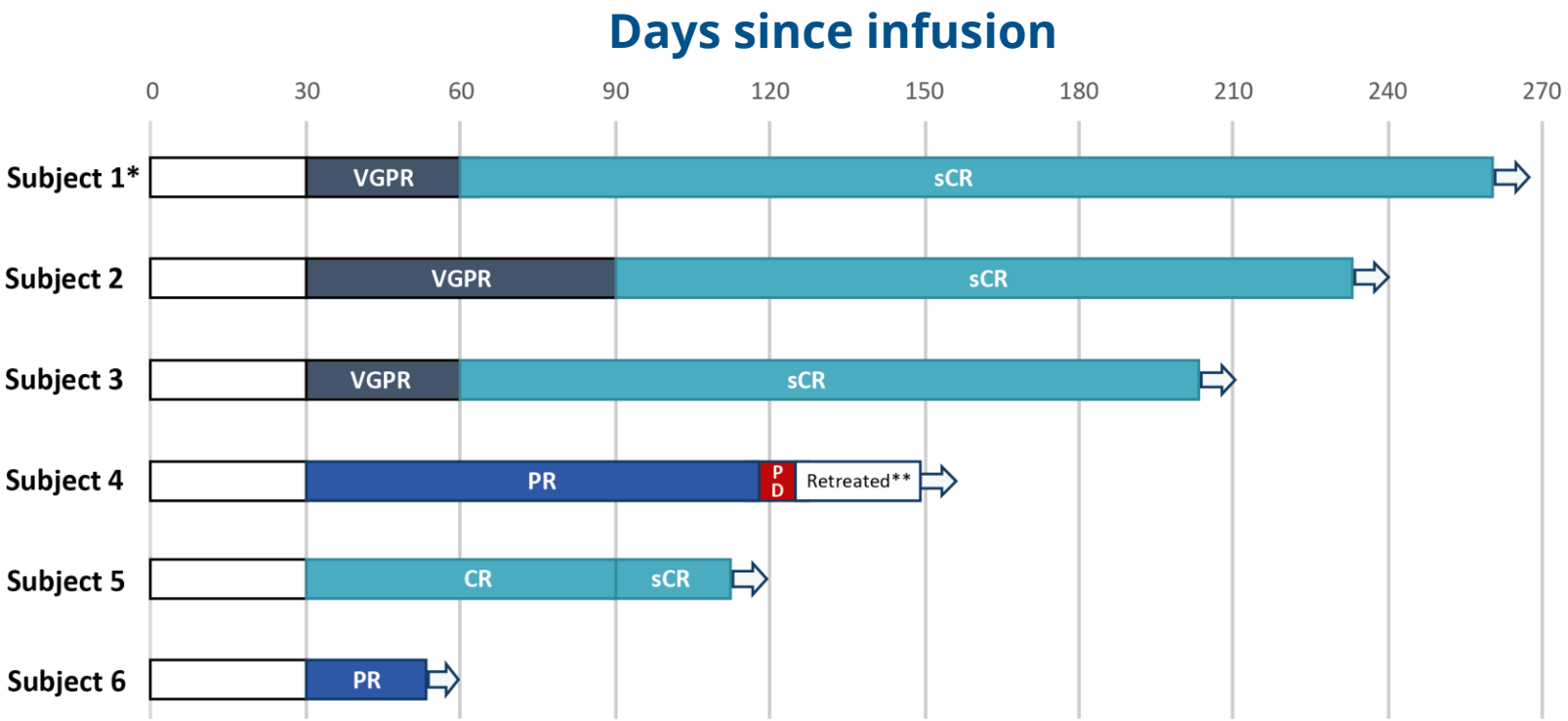




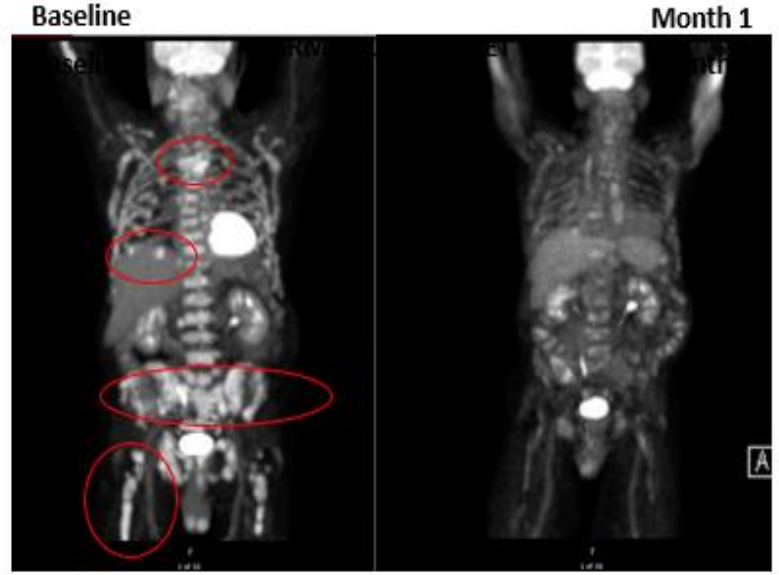
Time on Study from CART-ddBCMA Infusion (as of 29 Oct 2020)

Adapted from Frigault et al, ASH 2020 Abstract #3199; please refer to full ASH presentation for safety and efficacy data.

- First 6 patients received 100 million CAR+ cells and showed robust cell expansion
- CRS and neurotoxicity have been limited to Grade 1/2 with rapid resolution
- Rapid, deep, and durable responses have been observed at the first dose level (100 million CAR+ cells) in patients with poor prognostic factors



Subject #1

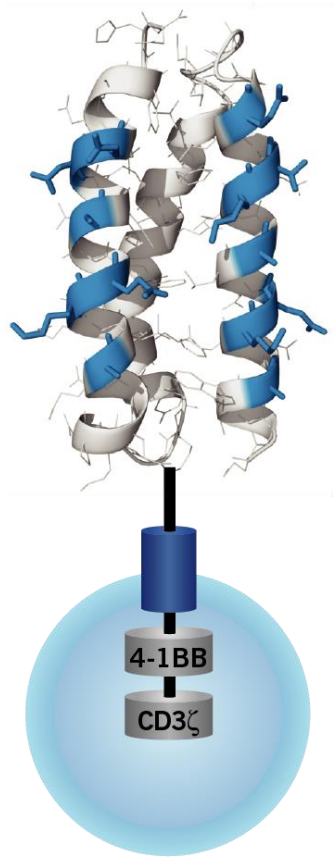


High disease burden (95% BMPC) at baseline with IgA myeloma, extra-medullary disease, penta-refractory, and high-risk cytogenetics

⇒ Month 1: bone marrow negative, MRD negative, PET-CT negative

Conclusions

CART-ddBCMA



- CART-ddBCMA utilizes a novel, non-scFv binding domain, that is highly stable and engineered to reduce immunogenicity
- Potent anti-tumor activity demonstrated in vitro and in vivo against BCMA-positive myeloma cells
- CART-ddBCMA facilitates deep and durable responses in patients with poor prognosis