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THERAPEUTIC STRATEGIES TARGETING B-CELL MATURATION ANTIGEN (BCMA) IN MM

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Disclosures

Consulting Agreements	Amgen Inc, Bioclinica, Bristol-Myers Squibb Company, Celgene Corporation, CRISPR Therapeutics, Janssen Biotech Inc, Karyopharm Therapeutics, Kite Pharma Inc, Servier, Takeda Oncology
Contracted Research	AbbVie Inc, Acetylon Pharmaceuticals Inc, Amgen Inc, bluebird bio, Bristol-Myers Squibb Company, Celgene Corporation, Constellation Pharmaceuticals, Curis Inc, Genentech, Glenmark, Janssen Biotech Inc, Kesios Therapeutics Ltd, Lilly, Novartis, Poseida Therapeutics, Sanofi Genzyme, Takeda Oncology, Teva Oncology, Vivolux
Data and Safety Monitoring Board	Prothena

Case Presentation: Dr Lamar

48-year-old man

- Diagnosis: IgG-kappa multiple myeloma [1q-/1q+, t(4;14), del(13)]
  - Multiple plasmacytomas
  - Testicular involvement
  - Multiple lytic spinal lesions
- VRd → rapid PD

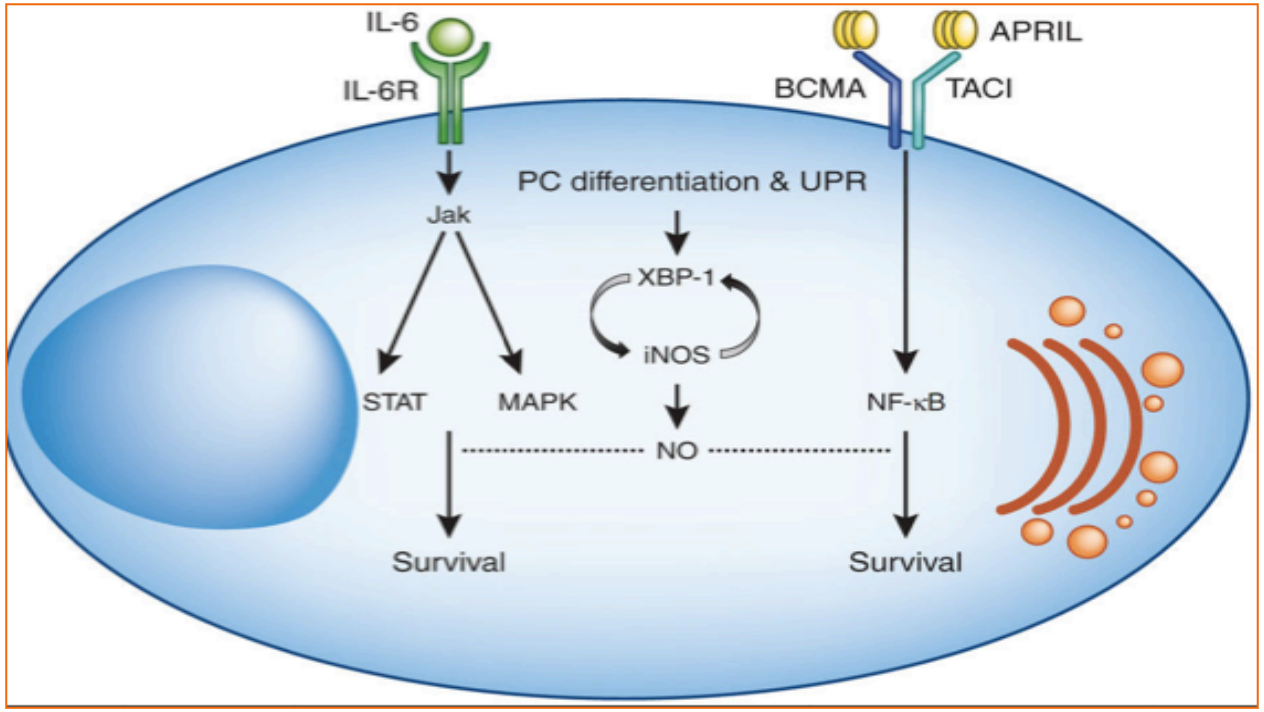
MOVING BEYOND THE NAKED MONOCLONAL ANTIBODIES…

- Antibody Drug Conjugates (ADC)
- Bispecific antibodies or BiTEs
- Chimeric Antigen Receptor T Cells (CART)

- Most important target to date - BCMA

BCMA (B Cell Maturation Antigen)

- Member of the TNF receptor superfamily
- Receptor for BAFF and APRIL
- Expressed on cell surface
- Expression largely restricted to plasma cells and some mature B cells (absent on naive and memory B cells)
- Important in B cell maturation and long lived plasma cell survival



Njau & Jacob. Nat Immunol 2014. 15:219.

GSK2857916 (Belantamab mafodotin) an Antibody Drug Conjugate Against BCMA

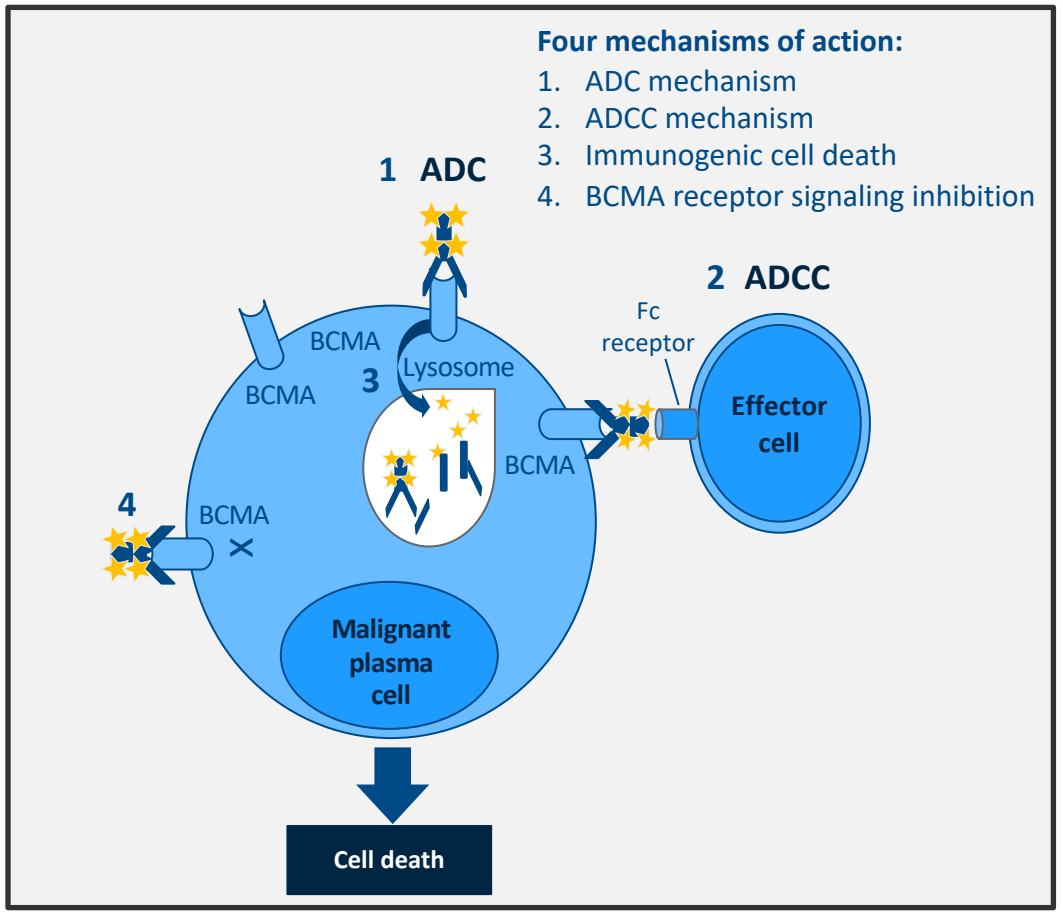
Background

- Antibody
  - Humanized, afucosylated IgG1 anti-BCMA ab
- Payload:
  - MMAF (monomethyl auristatin-F)

GSK2857916

Cytotoxic agent	– MMAF (non-cell permeable, highly potent auristatin)
Afucosylation	– Enhanced ADCC
Linker	– Stable in circulation

[1]Tai YT, et al. Blood 2014;123(20):3128-38.



ADC, antibody-drug conjugate; ADCC, antibody-dependent cell-mediated cytotoxicity; BCMA, B-cell maturation antigen; IgG, immunoglobulin G; MMAF, monomethyl auristatin-F

Trudel et al. The Lancet Oncology. 2018 Dec 1;19(12):1641-53

GSK2857916 (Belantamab mafodotin): Results from Part 2 of Study BMA117159 (DREAMM-1)

Population

- 35 pts in expansion phase
- 3.4 mg/kg IV q 3 wk
- Med priors 5
- 40% dara exposed/refractory

AEs of interest

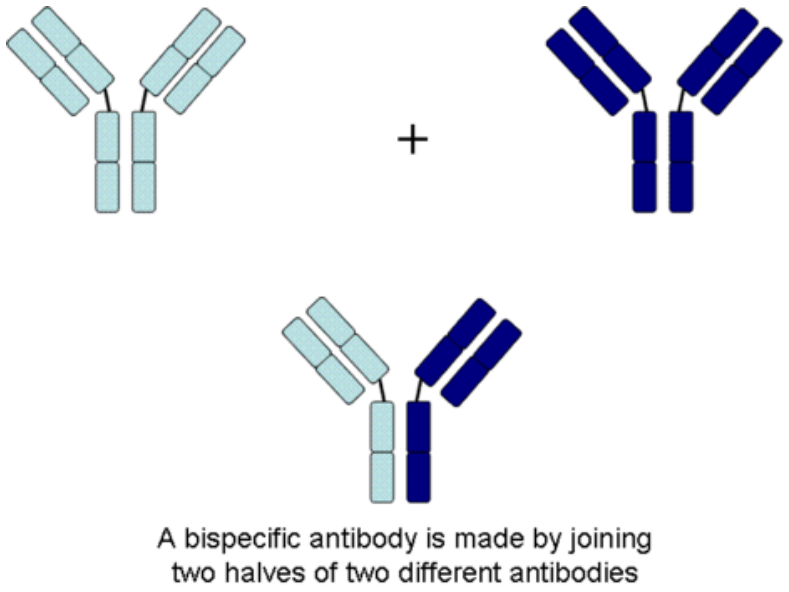
- IRR 29% (Gr 1/2 in first dose only)
- Gr 3 Thrombocytopenia 26%
- Corneal events 69%
  (blurred vision, photophobia,dry eyes)

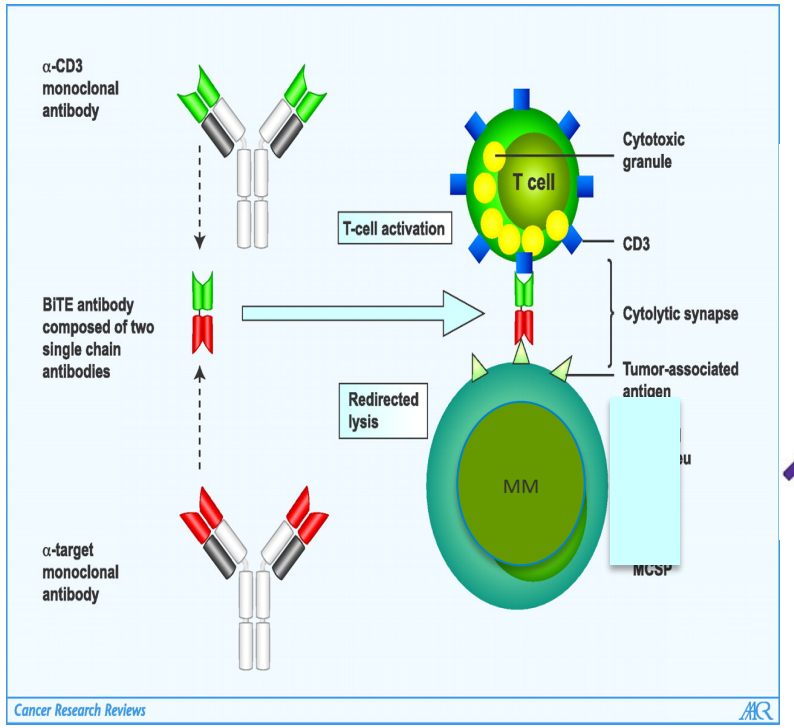
Efficacy

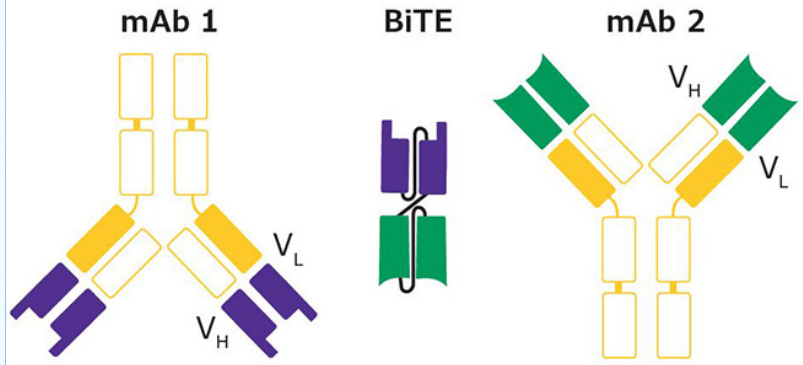
- Entire population (n=35)
  - ORR 60% (most ≥ VGPR)
  - Med PFS 12.0 mos
  - Med DOR 14.4 mos
- Dara exposed/refractory (n=14)
  - ORR 42.9%
  - Med PFS 6.8 mos

Trudel et al. Blood Cancer Journal(2019)9:37

DREAMM studies underway in many combinations in the relapsed and frontline settings







Bispecifics

- Targets in MM
- **BCMA:CD3**
- GPRC5D:CD3
- CD38:CD3
- FcRH5:CD3

AMG 420 (BCMA:CD3 BiTE): Updated Results of a First-in-Human Phase 1 Dose Escalation Study

Population
- 42 pts in dose escalation
- Med prior therapies 4
- MTD 400 ug/d CIV
- CIV infusions 4wks on, 2 wks off

Toxicity
- 3 DLTs
  - Gr 3 CRS (@ 800ug/d)
  - Gr 3 PN (@400 and 800ug/d)
- 2 Deaths - unrelated
  - ARDS due to flu/aspergillosis
  - Hepatitis due to adenovirus

Efficacy

- Entire population (n=42)
  - ORR 31%
- @MTD 400ug/d (n=10)
  - ORR 70%
  - 5 of 7 with MRD- CR*
  - Med DOR 9 mos

*MRD@10^{-4}

Topp et al. ASCO 2019, Abstract 8007

BISPECIFIC T CELL ENGAGERS/ANTIBODIES

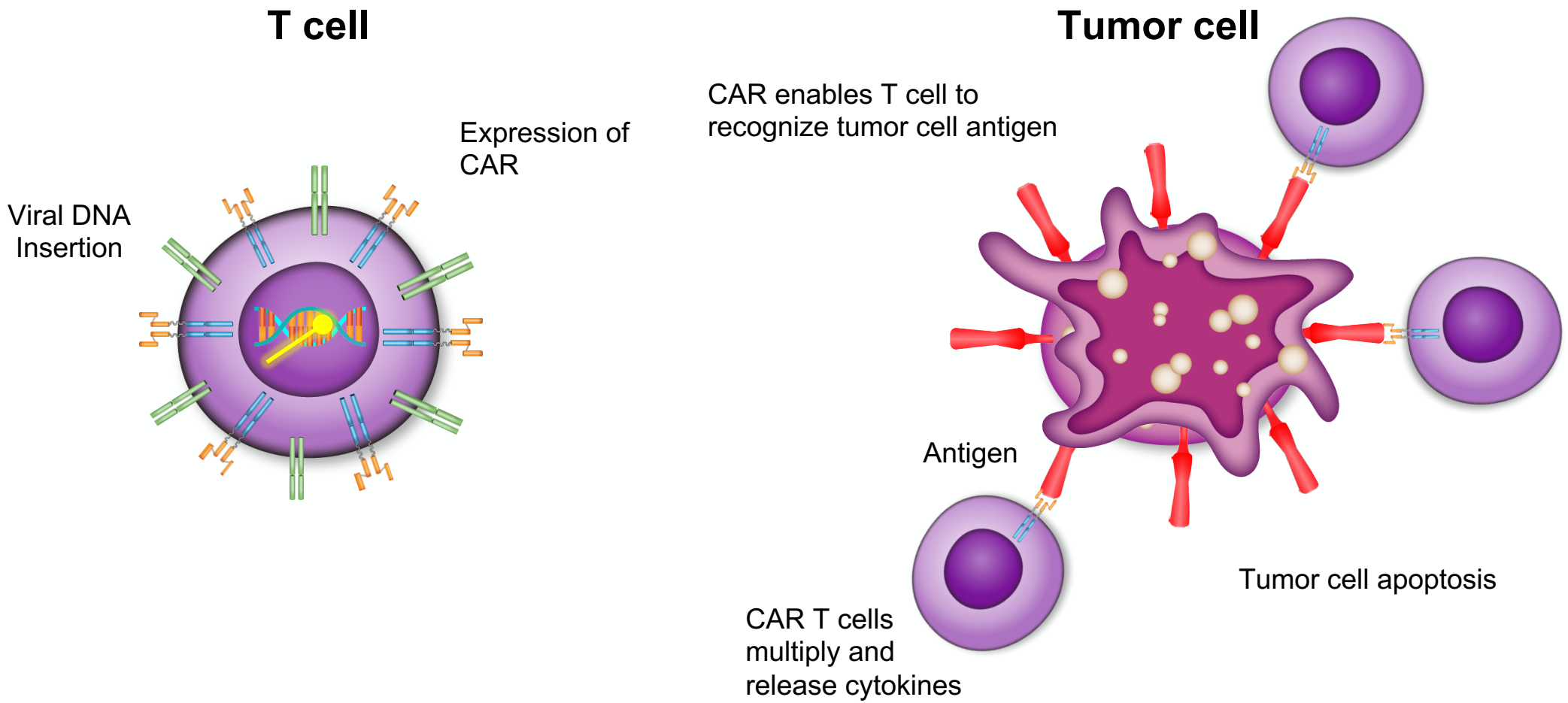
Name	Target	Structure	Trial ID
AMG-420	BCMA	BiTE	NCT02514239
AMG-701	BCMA	BiTE-HLE	NCT03287908
CC-93269	BCMA	BsAb	NCT03486067
PF-06863135	BCMA	BsAb	NCT03269136
REGN-5458	BCMA	BsAb	NCT03761108
TNB-383B	BCMA	BsAb	NCT03933735
JNJ-64007957	BCMA	DuoBody	NCT03145181
JNJ-64007564	GPRC5d	DuoBody	NCT03399799
GBR 1342	CD38	BsAb	NCT03309111
AMG-424	CD38	BsAb (XmAb)	NCT03445663
BFCR4350A	FcRH5	BsAb	NCT03275103

Costa e al. ASH 2019 Oral Session: Abs 143, Sat 12/7/19:10:30am

Cooper et al. ASH 2019 Poster Session: Abs 3176, Sun 12/8/19

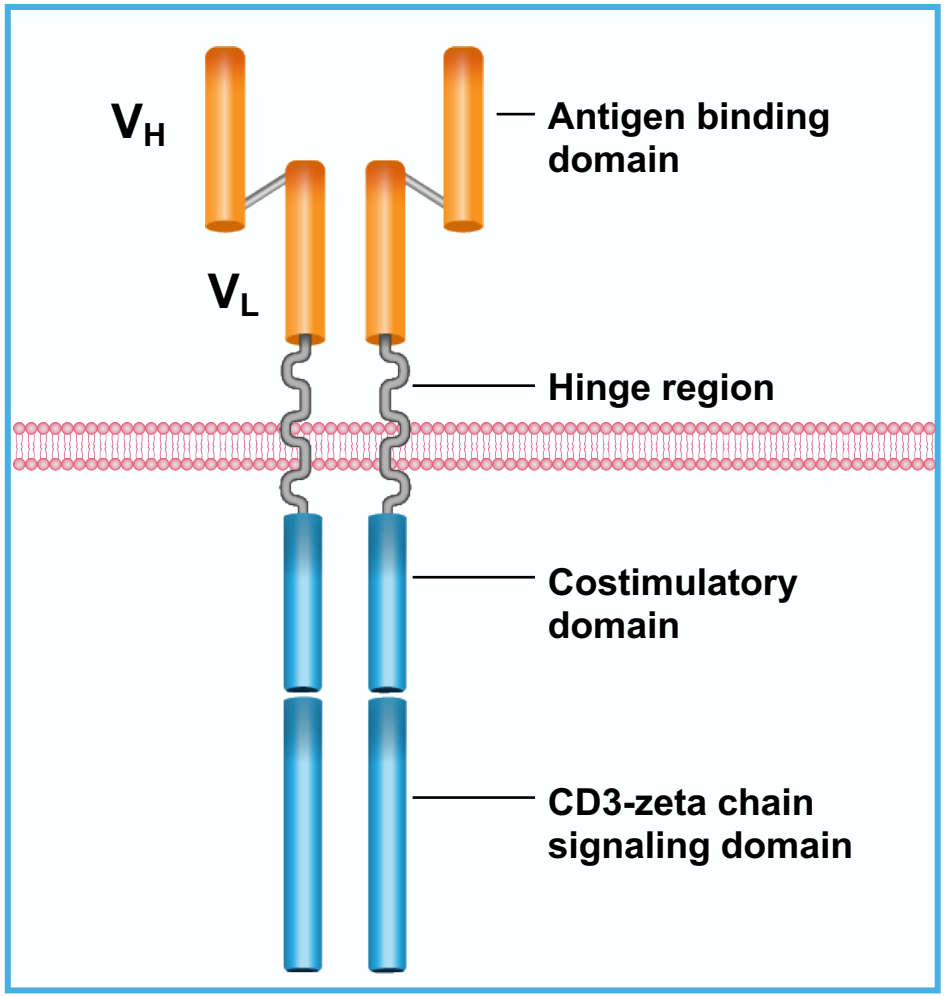
HLE, half-life extended; BsAb, bispecific antibody

CAR T Cells: Mechanism of Action



CAR T WORKING GROUP

Chimeric Antigen Receptors



scFv
Single-chain variable fragment (scFv) bypasses MHC antigen presentation, allowing direct activation of T cell by cancer cell antigens

Hinge region
Essential for optimal antigen binding

Costimulatory Domain: CD28 or 4-1BB
Enhances proliferation, cytotoxicity and persistence of CAR T cells

Signaling Domain: CD3ζ chain
Proliferation and activation of CAR T cells
CAR T-cell-mediated killing of tumor cells

CAR T
WORKING GROUP

BCMA-DIRECTED CAR T CELLS IN MULTIPLE MYELOMA

	BB2121(BLUEBIRD)	LCAR-B38M(LEGEND)*	JCARH125(JUNO)
Ag-binding domain	scFv (M)	2-VHH (C)	scFv (H)
Vector & Costimulatory Domain	Lentiviral, CD3/41BB	Lentiviral, CD3/41BB	Lentiviral, CD3/41BB
Special Qualities	Low tonic activity	2 epitopes	Equal # CD4/CD8
Population	33	57	44
# Prior Tx	7	3	7
CART Dose	50-800 $x10^6$	0.5(0.07-2.1)$x10^6$/kg	50-450 $x10^6$
ORR	85%	88%	82%
CR	45%	68%	27%
CRS All Grades (Grade 3/4)	76%(6%)	90%(7%)	80%(9%)
Neurotox All Grades (Grade 3/4)	42% (3%)	2%(0%)	25%(7%)
Med PFS	11.8 mos	15 mos	NR

Raje et al, NEJM 2019; Zhao et al, J Hem Onc 2018, Mailankody et al, ASH 2018

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*Wang et al. ASH 2019 Oral Session: Abs579, Mon 12/9/19: 7:30a

FUTURE DIRECTIONS OF MOST ADVANCED CART PRODUCTS

- Race to FDA Approval in the USA
  - Global Pivotal Trial (KarMMa) has completed enrollment
    - bb2121 dose range: 150-450 × 10^6 CAR+ T cells
  - Legend/Janssen enrolling on pivotal trial of JNJ-68284528 (LCAR-B38M)
- Use Beyond the Refractory Setting
  - Trials in earlier phase of disease
    - KarMMa 3 – randomized Phase 3 of bb2121 vs SOC in pts with 2-4 priors
    - KarMMa 2 – cohort of pts with early relapse, bb2121 as 2nd line
  - In conjunction with ASCT/Consolidation in MRD
    - KarMMa2, SZ-CART-MM 02 (BCMA and CART19)
  - Upfront in high risk patients
    - Studies in development

Madduri et al. ASH 2019 Oral Session Abs577, Mon 12/9/19: 7:00a

OVERCOMING RELAPSE OF CART THERAPY

- Increase persistence of CARTs - Select/augment memory phenotype
  - bb21217[1]
    - same construct as bb2121 but cultured w/ PI3Ki
    - 12 patients reported – ORR 83.3%, detectable CART out to 9 mos
  - P-BCMA-101[2]
    - piggyBac – non viral DNA delivery using transposons
    - CRS 9%, no Gr3/4; peak expansion 14-21 ds
- Decrease potential of BCMA escape/augment expression
  - Gamma secretase inhibitors
  - Dual and Tandem CARTs
    - Tandem BCMA and CD19 CAR
    - Dual BCMA and CD19
    - Dual BCMA and CD38
- Off the shelf
  - Allogeneic CART
    - "Better" T cells
    - Readily available

Berdeja et al. ASH 2019 Oral Session:
Abs 927, Mon 12/9/19: 6:45p

Cowan et al. ASH 2019 Oral Session:
Abs 204, Sat 12/7/19: 1:15p

Yan et al. ASH 2019 Oral Session:
Abs 578, Mon 12/9/19: 7:15a
Garfall et al. ASH 2019 Poster Session:
Abs 1863, Sat 12/7/19

Zhang et al. ASH 2019 Poster Session:
Abs 3147, Sun 12/8/19

Li et al. ASH 2019 Oral Session:
Abs 930, Mon 12/9/19: 7:30p

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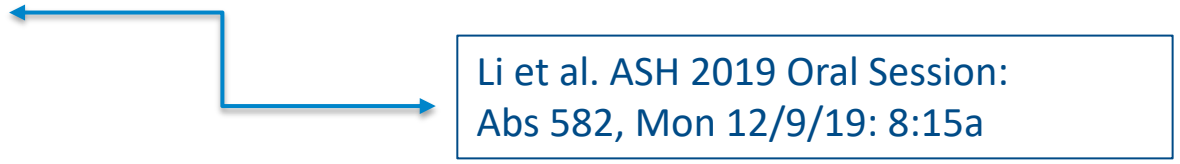
1. Shah et al: ASH 2018, Abs 488. 2. Gregory et al: ASH 2018.

How Will All These Modalities Fit Into Our Treatment Paradigm?

SOME UNANSWERED QUESTIONS

- ADCs
  - Will they be better than naked monoclonal antibodies or just different?
  - Is plan to replace the naked MoAbs?
    - DREAMM studies with belantamab mafodotin planned in many current daratumumab indications
  - Ocular toxicity of BM could be an issue – but this is payload specific
    - Will tox limit combination potential?
    - Will tox limit ability to be given continuously?
- CAR Ts vs BiTEs/Bispecifics
  - One time infusion vs frequent dosing/continuous infusion
  - Complex procedure vs "off the shelf"
- Targeting BCMA via ADCs, BiTEs or CAR Ts have produced impressive results in the relapsed/refractory setting
  - Is there a rational way of sequencing them?
  - Is there a role for retreatment?
- Will failure of one anti-BCMA therapy negate use of another?
  - Will depend on mechanisms of resistance
  - Clinical trials need to include patients who have relapsed post other anti BCMA therapies
    - CT103A, fully human BCMA CART – 4 pts with prior murine BCMA CAR – 100% RR, 3 sCR, 1VGPR (AB440, IMW 2019)



Li et al. ASH 2019 Oral Session:
Abs 582, Mon 12/9/19: 8:15a