Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

Immunotherapy for the Treatment of Hematologic Malignancies

Jacalyn Rosenblatt, MD

Beth Israel Deaconess Medical Center

Associate Professor of Medicine, Harvard Medical School

AAEM AMERICAN ACADEMY OF EMERGENCY MEDICINE CHAMPION OF THE EMERGENCY PHYSICIAN

ACCC Association of Community Cancer Centers

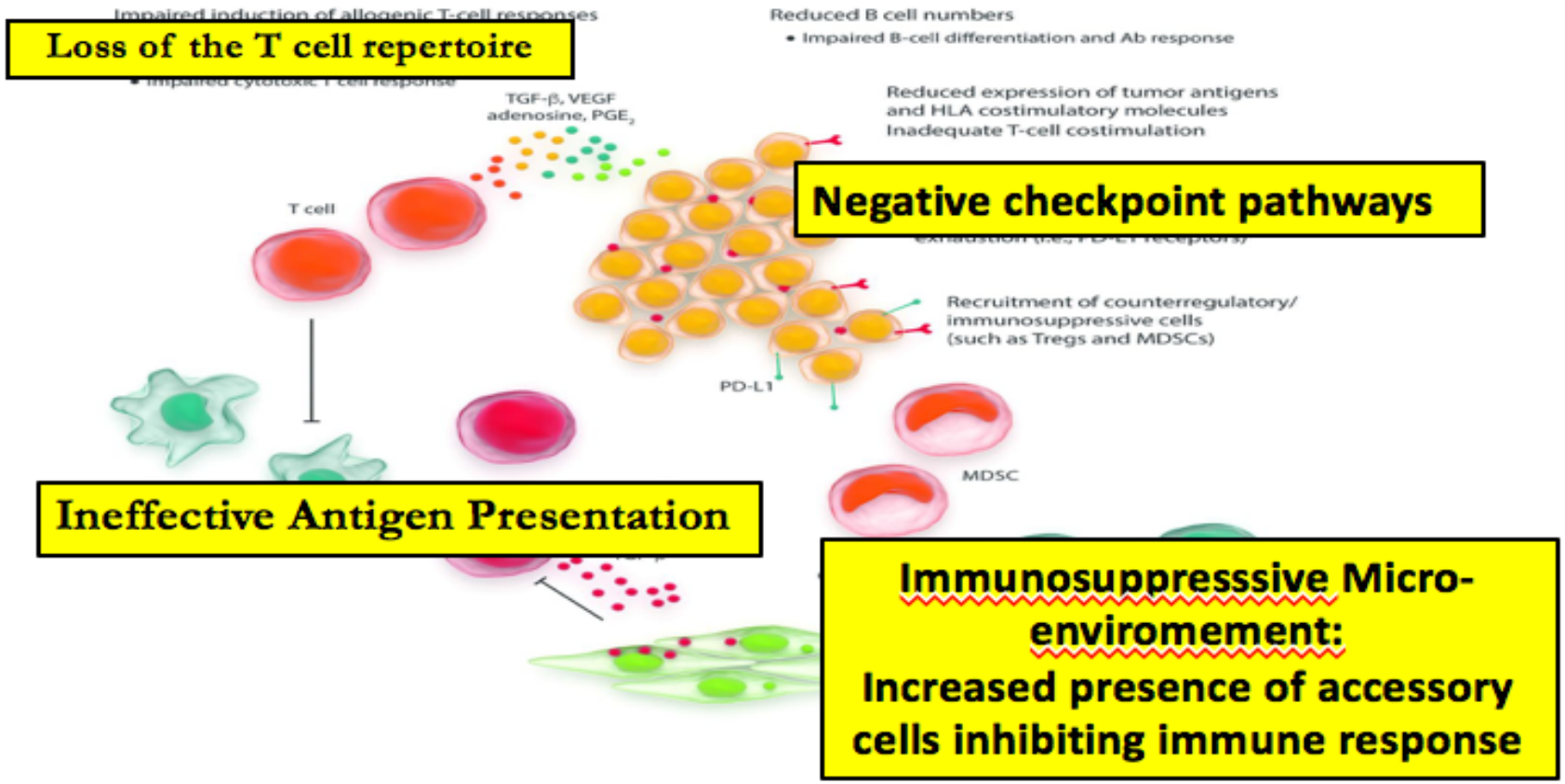
HOPA Hematology/Oncology Pharmacy Association

Society for Immunotherapy of Cancer

DISCLOSURES

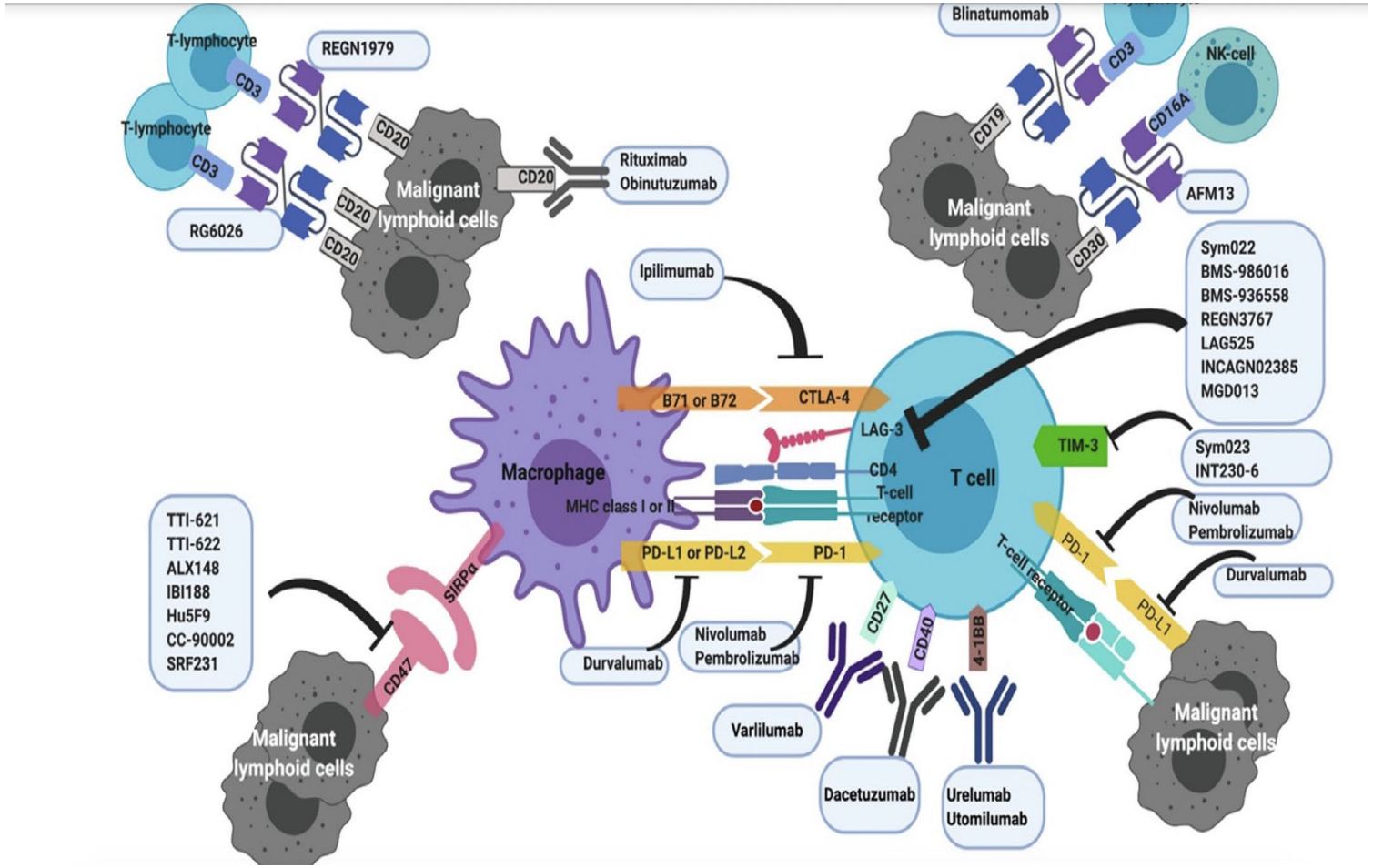
- I will be discussing non-FDA approved indications during my presentation
- Consultant: Celgene, BMS, Amgen, Merck, Partner TX, Parexel, and Imaging Endpoints
- Other: Research Support: Celgene, BMS, Dava Oncology, Education: Dava Oncology

Immune Tolerance in Malignancy



Paula Rodríguez-Otero et al. Haematologica 2017;102:423-432

IMMUNE THERAPY FOR LYMPHOID MALIGNANCY



- Checkpoint Blockade: Hodgkins Disease, NHL
- ADC: NHL
- BITE: ALL
- CAR T cells: NHL, ALL

A.M. Tun and S.M. Ansell Cancer Treatment Reviews 88 (2020) 102042

FDA-approved Checkpoint inhibitors: Lymphoma

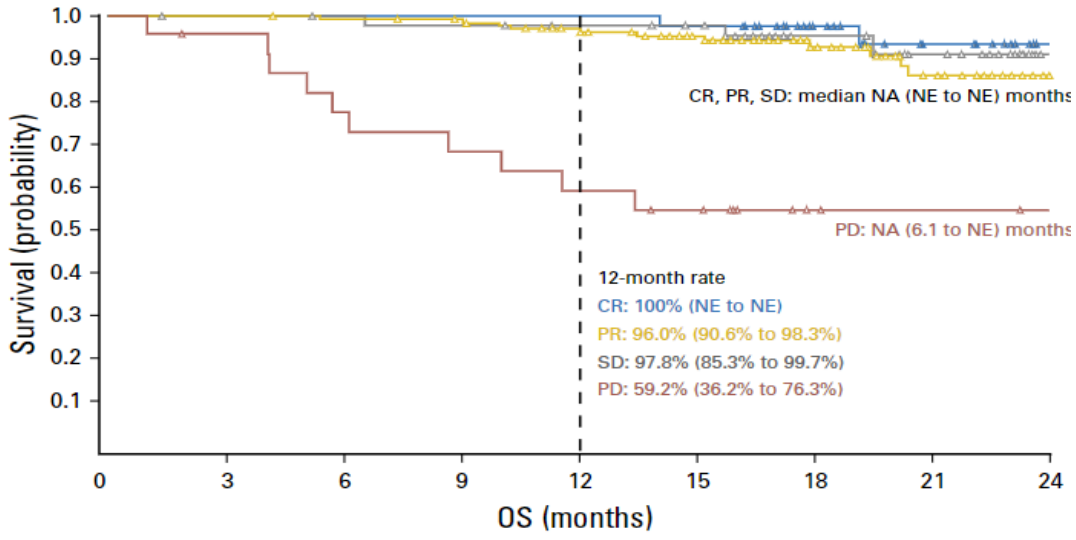
Drug	Approved	Indication	Dose
Nivolumab	2016	Classical Hodgkin lymphoma, relapsed after HSCT and brentuximab vedotin or ≥3 previous therapies	240 mg q2w or 480 mg q4w
Pembrolizumab	2017	Adult/pediatric refractory classical Hodgkin lymphoma or relapsed after 3 previous therapies	200 mg q3w adults 2 mg/kg (up to 200 mg) q3w (pediatric)
Pembrolizumab	2018	Adult/pediatric refractory primary mediastinal large B-cell lymphoma or relapsed after 2 previous therapies	200 mg q3W adults 2 mg/kg (up to 200 mg) q3w (pediatric)

Checkpoint inhibitors: Hodgkin Lymphoma

Checkmate-205

ORR = 69%

CR = 16%



No. at risk:

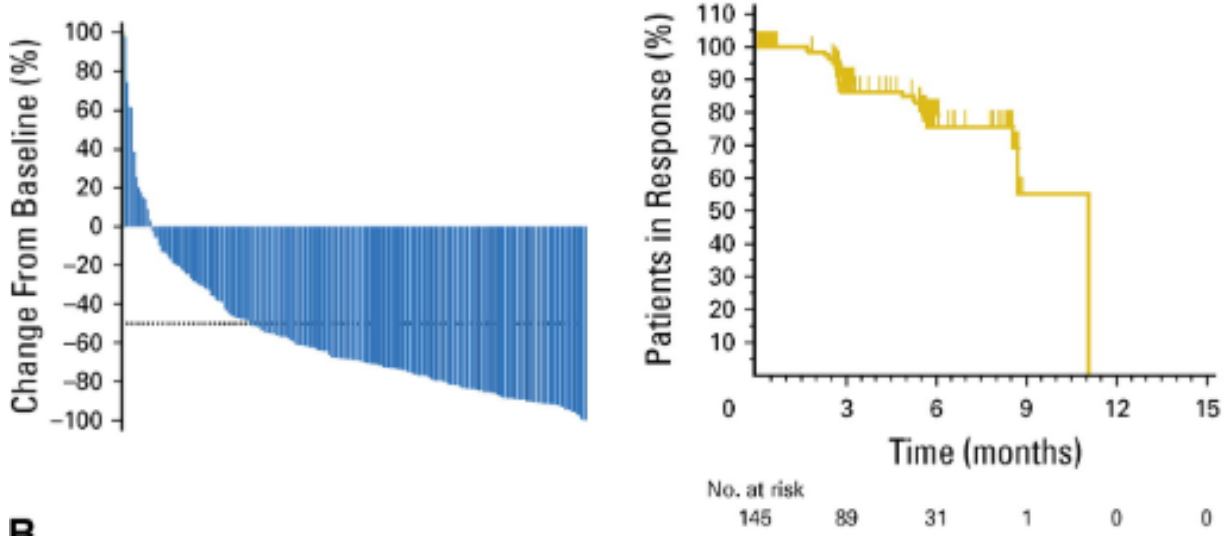
CR	40	40	40	40	40	39	26	16	7
PR	128	128	126	123	113	97	59	34	10
SD	47	46	45	44	42	39	25	16	3
PD	23	21	17	15	13	11	5	4	3

Keynote-087

ORR = 69%

CR = 22.4%

Activity seen regardless of PD-L1 expression



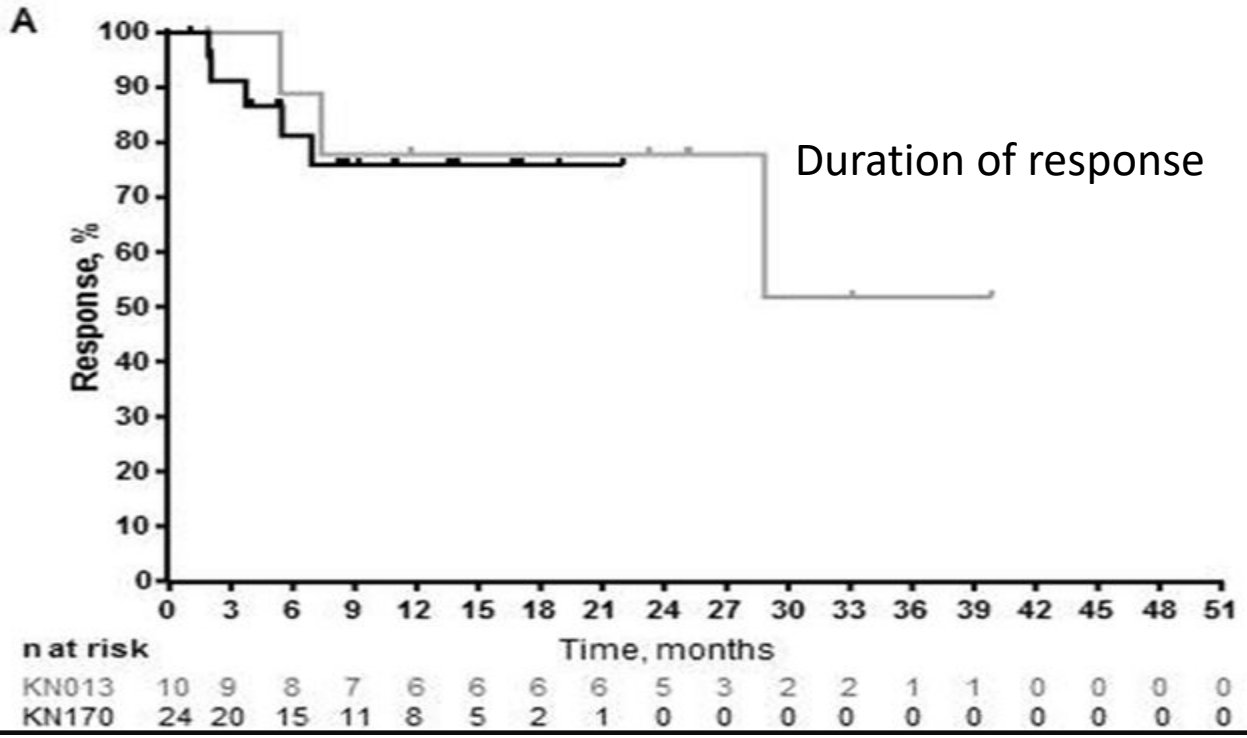
Armand, J Clin Oncol 2018.

Chen, J Clin Oncol 2017.

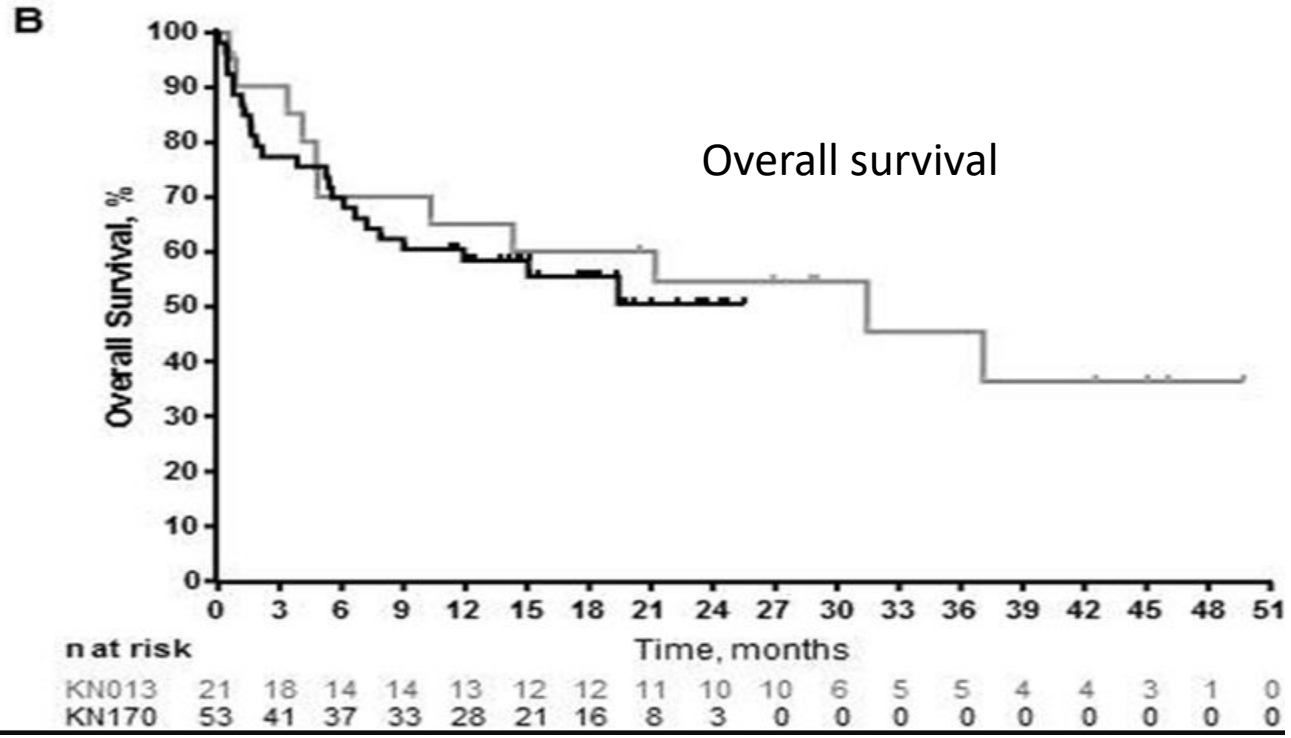
Pembrolizumab in Primary Mediastinal B cell Lymphoma

Grey = KEYNOTE-013 (rrPMBCL with failed, ineligible, or refused ASCT)
Black = KEYNOTE-170 (rrPMBCL with relapse or ineligible for ASCT with >= 2 prior therapies)

- ORR was 41% (7/17); 6 additional patients (35%) had stable disease
- Median DOR and OS NR



Duration of response

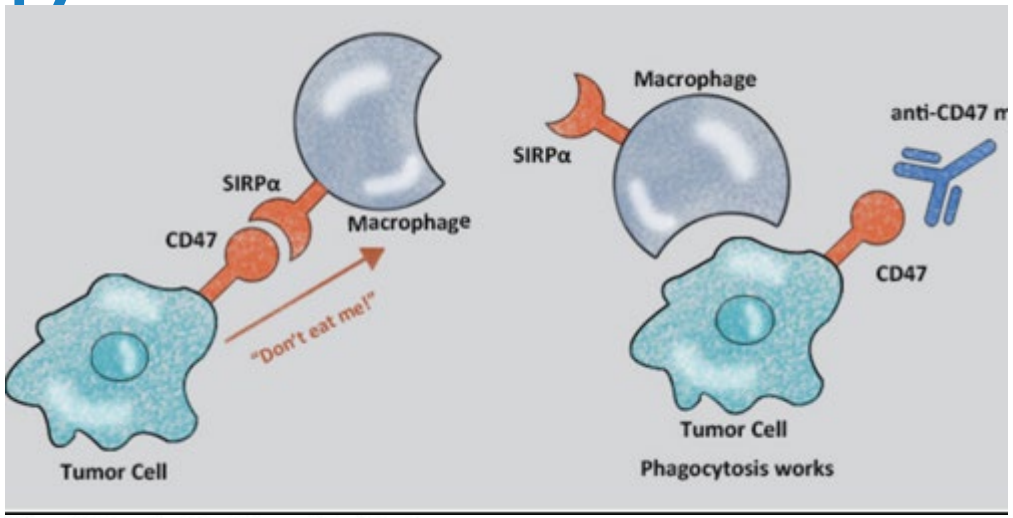


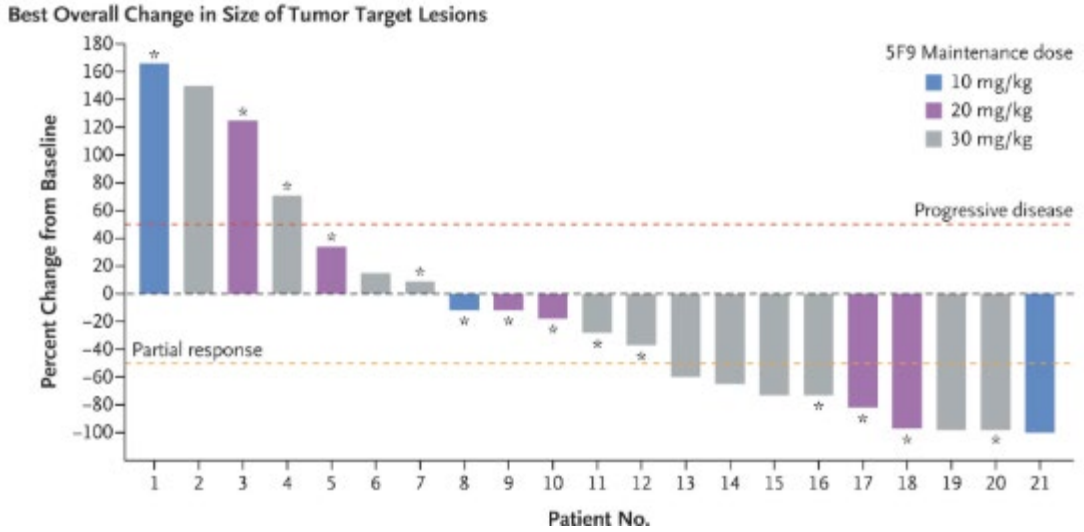
Overall survival

Armand, Blood 2018.

In development: Macrophage checkpoint: CD47

- Phase 1b: Hu5F9-G4 + rituximab in rituximab refractory disease
- DLBCL – ORR = 40%, CR = 33%
- Follicular lymphoma – ORR = 71%, CR = 43%





Advani, NEJM 2018.

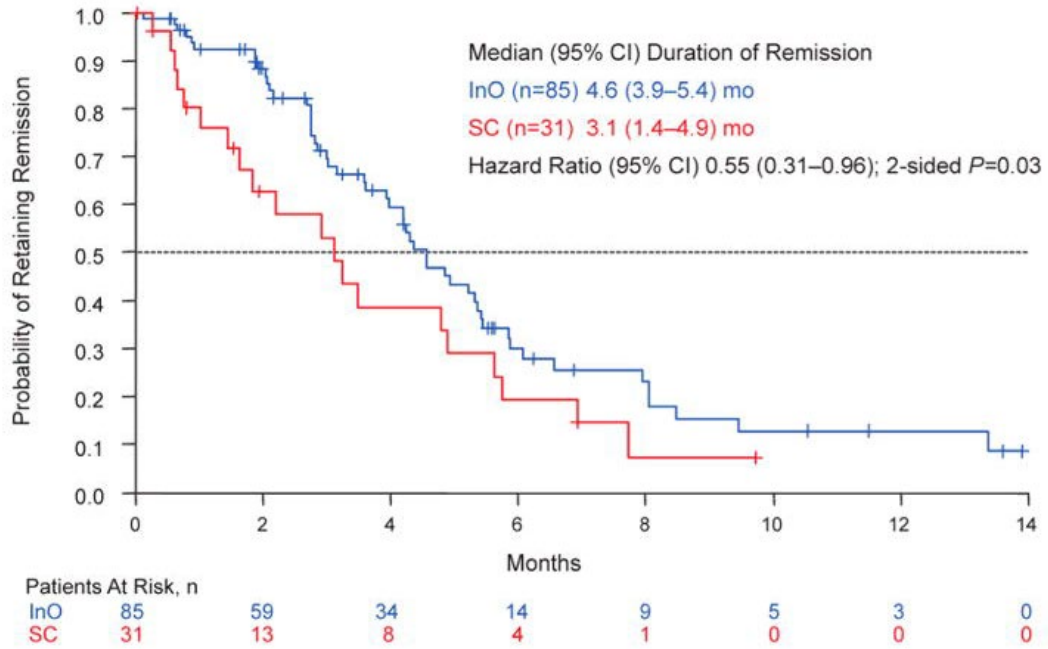
Antibody-drug conjugates (ADC)

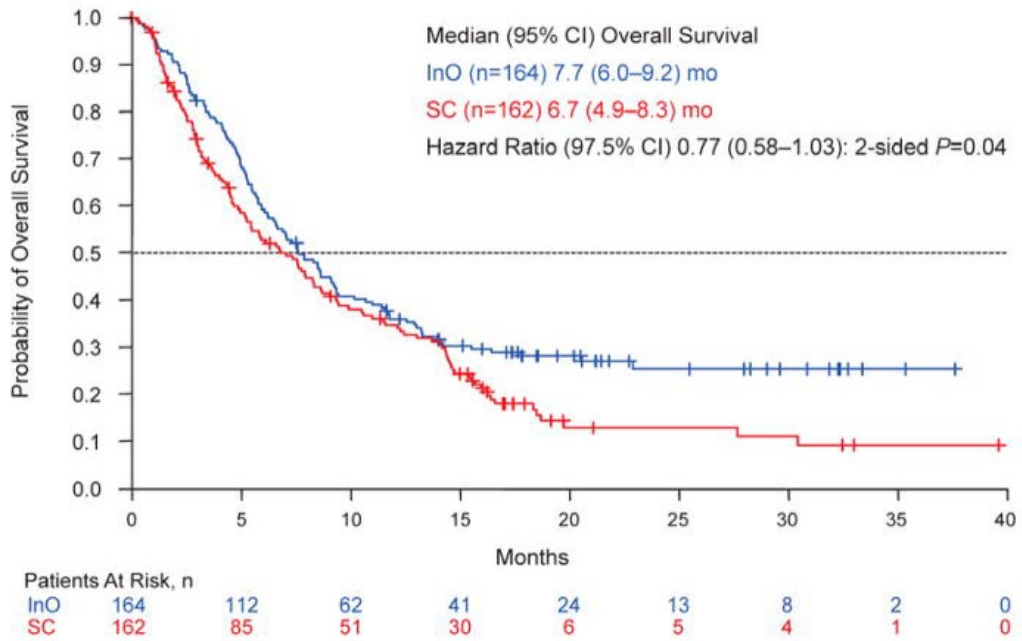
FDA-Approved Antibody-Drug Conjugates

Drug	Target antigen	Year of approval	Indication
Brentuximab vedotin	CD30	2011	• Classical Hodgkin lymphoma, relapsed after HSCT or ≥2 previous therapies • Anaplastic large cell lymphoma ≥ 1 previous therapies
		2018	cHL - first line with combination chemo
Inotuzumab ozogamicin	CD22	2017	Relapsed/refractory/MRD+ B-cell ALL
Polatuzumab vedotin (w/ bendamustine & rituximab)	CD79b	2019	DLBCL ≥ 2 previous therapies

Inotuzumab ozogamicin for ALL

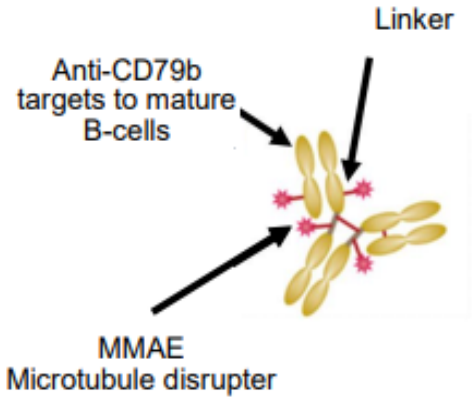
- Anti-CD22 antibody conjugated to calicheamicin
- Higher response, MRD-negativity, PFS, and OS than standard-of-care

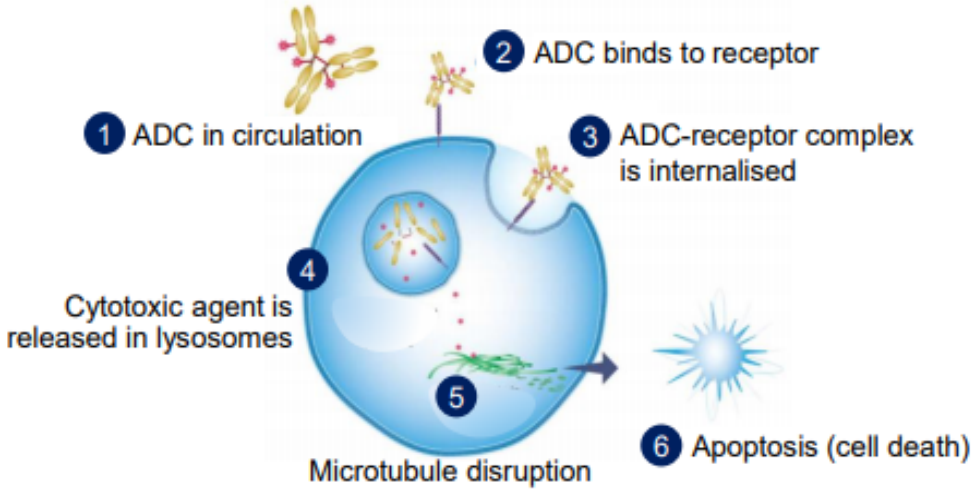




Kantarjian, NEJM 2016.

Polatuzumab vedotin: DLBCL





Polatuzumab vedotin has demonstrated efficacy in R/R DLBCL in combination with rituximab[1,2] and rituximab-bendamustine[3]

Treatment	Best overall response
Pola +/- rituximab	51–56%[1,2]
Pola + rituximab + bendamustine	68%[3]

ADC, antibody-drug conjugate; MMAE, monomethyl auristatin E

1. Palanca-Wessels A, et al. Lancet Oncol 2015;16:704–15; 2. Morschhauser F, et al. Lancet Hematology 2019;6:e254–65; 3. Sehn H, et al. Blood 2018;132:1683

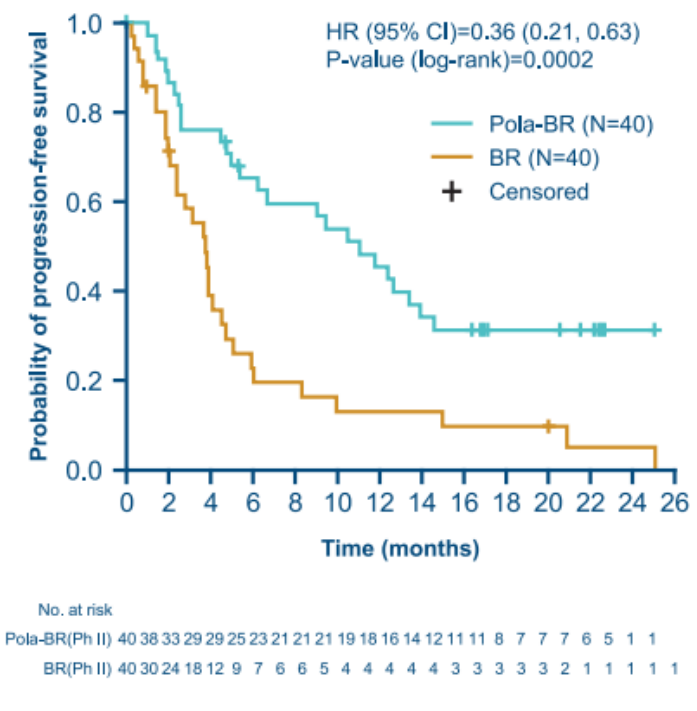
Slide credit: Tilly et al. ICML 2019

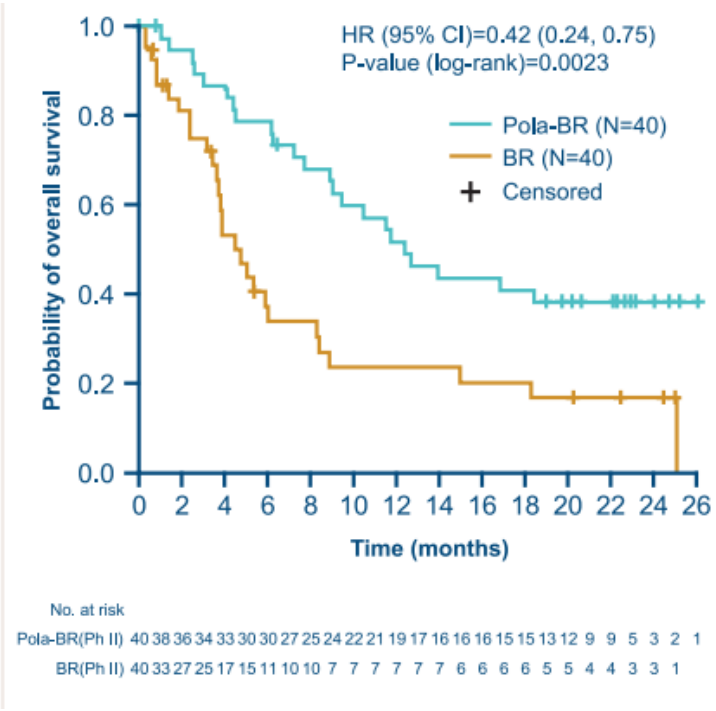
Polatuzumab vedotin: DLBCL

- Randomized phase 2 study
- Pola-BR vs. BR in R/R DLBCL

- Higher CR = 40% vs. 18% (p: 0.03)
- Median PFS = 7.6 m (HR=0.34, p<0.01)
- Median OS = 12.4 m (HR=0.42, p<0.01)

- Ongoing phase 3 (POLARIX)
- Frontline DLBCL- R-CHOP vs R-CHP+Pola



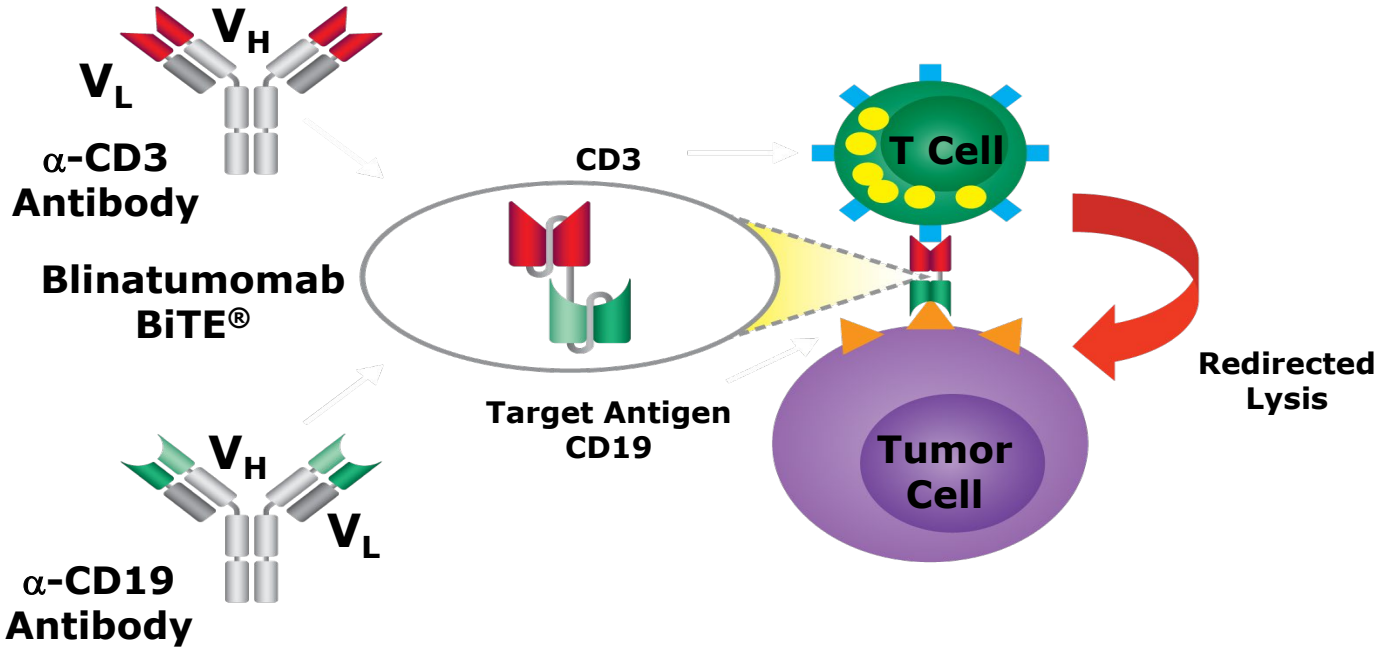


Sehn, Blood 2018.

Bi-specific T-cell engagers (BiTEs)

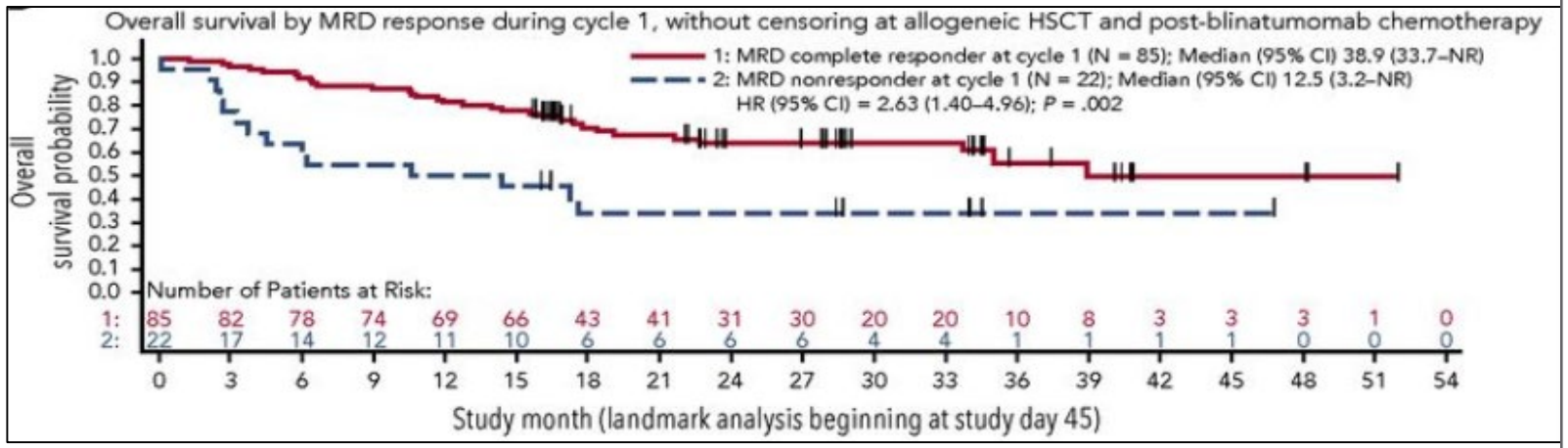
BiTE (Blinatumomab) Therapy

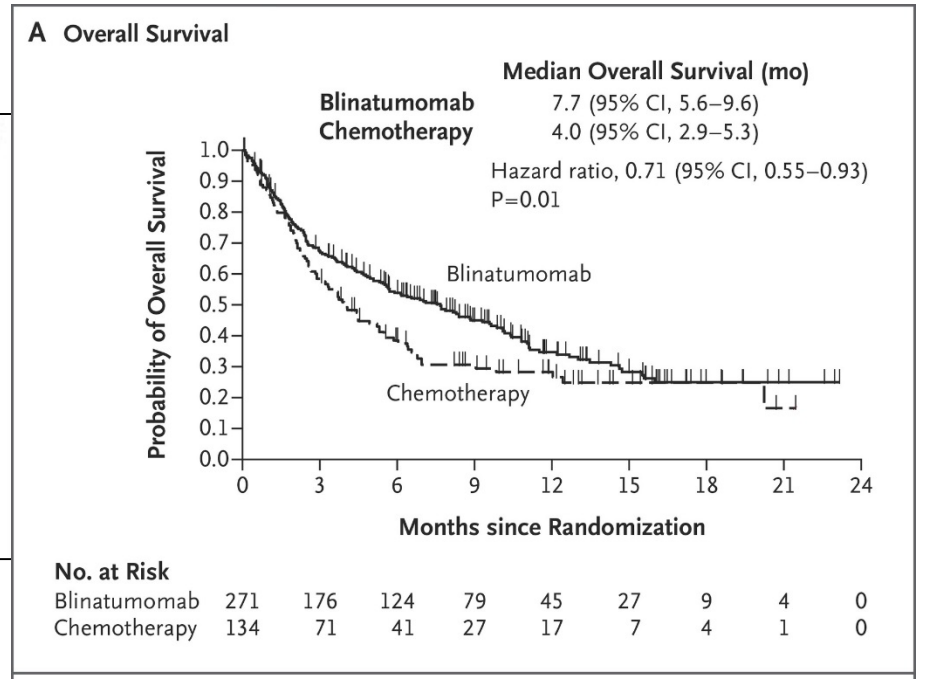
- Facilitates T cell engagement with CD19+ tumor cells (Similar to CD19 CAR T)
- Approval:
- Adult/pediatric R/R B-cell precursor acute lymphoblastic leukemia
- Adult/pediatric B-cell precursor acute lymphoblastic leukemia in 1st or 2nd complete remission, MRD ≥ 0.1%



Bargou et al. Science 2008

Blinatumomab: B-ALL





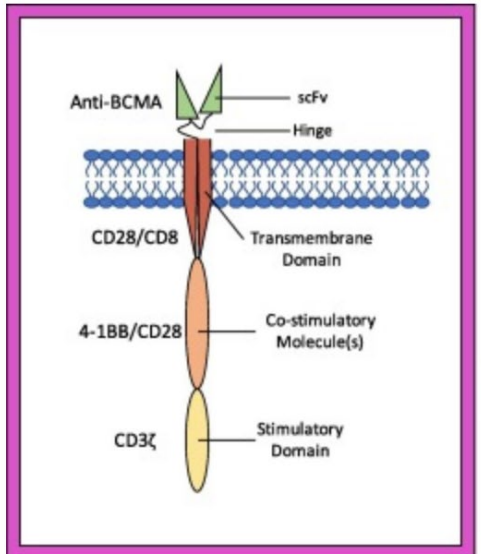
Gökbuget, Blood 2018.
Kantarjian, NEJM 2017.

Pivotal study	Study population	Primary outcome	Other key outcomes
NCT02013167 (TOWER) [43]	R/R Ph– BCP-ALL (Adult)	Median OS: 7.7 months (95% CI, 5.6–9.6 months)	CR within 12 weeks of treatment initiation: 91/267 (34%) (95% CI, 28.0–39.5%; $p < 0.001$) CRh within 12 weeks of treatment initiation: 119/267 (44%) (95% CI, 37.9–50.0%; $p < 0.001$) EFS (6-month estimate): 31% MRD remission (defined as an MRD level below 0.0001): 76% Adverse events (grade ≥ 3): 231/267 (87%)
NCT01466179 (Study MT103-211) [40]	R/R Ph– BCP-ALL (Adult)	CR or CRh: 81/189 (43%) (95% CI, 36–50%) within the first two cycles of treatment	Median RFS in patients with CR/CRh: 5.9 months (95% CI, 4.8–8.3 months) Median OS: 6.1 months (95% CI, 4.2–7.5 months) alloHSCT after blinatumomab-induced remission: 32/81 (40%) 100-day mortality following alloHSCT: 11% (95% CI, 0–23%) MRD response: 60/73 (82%) (95% CI, 72–90%) Adverse events (grade ≥ 3): 71 (38%)
NCT01207388 (BLAST) [39]	MRD-positive BCP-ALL (Adult)	Complete MRD response: 88/113 (78%) patients after one cycle of treatment	Median OS: 36.5 months (95% CI, 19.8 months to not estimable) Median RFS: 18.9 months (95% CI, 12.3–35.2 months) Duration of hematologic remission: not reached
NCT02000427 (ALCANTARA) [49]	R/R Ph+ BCP-ALL (Adult)	CR or CRh: 16/45 (36%) (95% CI, 22–51%) within the first two cycles of treatment	Complete MRD response: 14/16 (88%) (95% CI, 62–98%) during the first two cycles of treatment Median RFS: 6.7 months (95% CI, 4.4 months to not estimable) Median OS: 7.1 months (95% CI, 5.6 months to not estimable) alloHSCT after blinatumomab-induced remission: 4/16 (25%) (95% CI, 7–52%) Adverse events (grade ≥ 3): 37/45 (82%)
NCT01471782 (Study MT103-205) [29]	R/R BCP-ALL (Pediatric)	Maximum-tolerated dosage: 15 mg/m^2/day CR: 27/70 (39%) (95% CI, 27–51%)	Median RFS in responders (n = 27): 4.4 months (95% CI, 2.3–7.6 months) Median OS (n = 70): 7.5 months (95% CI, 4.0–11.8 months) alloHSCT after blinatumomab treatment: 24/70 (34%) Complete MRD response (< 10^{-4}): 14/27 (52%) (95% CI, 32–71%) Adverse events (grade ≥ 3): 61 (87%)

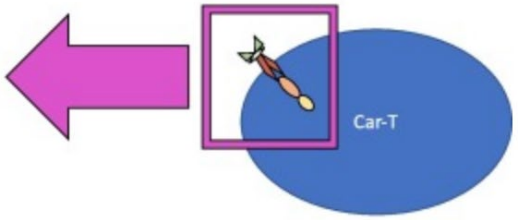
Andreas Viardot, *Annals of Hematology* (2020)

Chimeric Antigen Receptor Therapy (CAR T)

CAR T CONSTRUCT



T CELLS TRANSDUCED WITH CAR T CONSTRUCT



Single-chain variable fragment (scFv): derived from the variable region of an antibody specific for tumor surface antigen

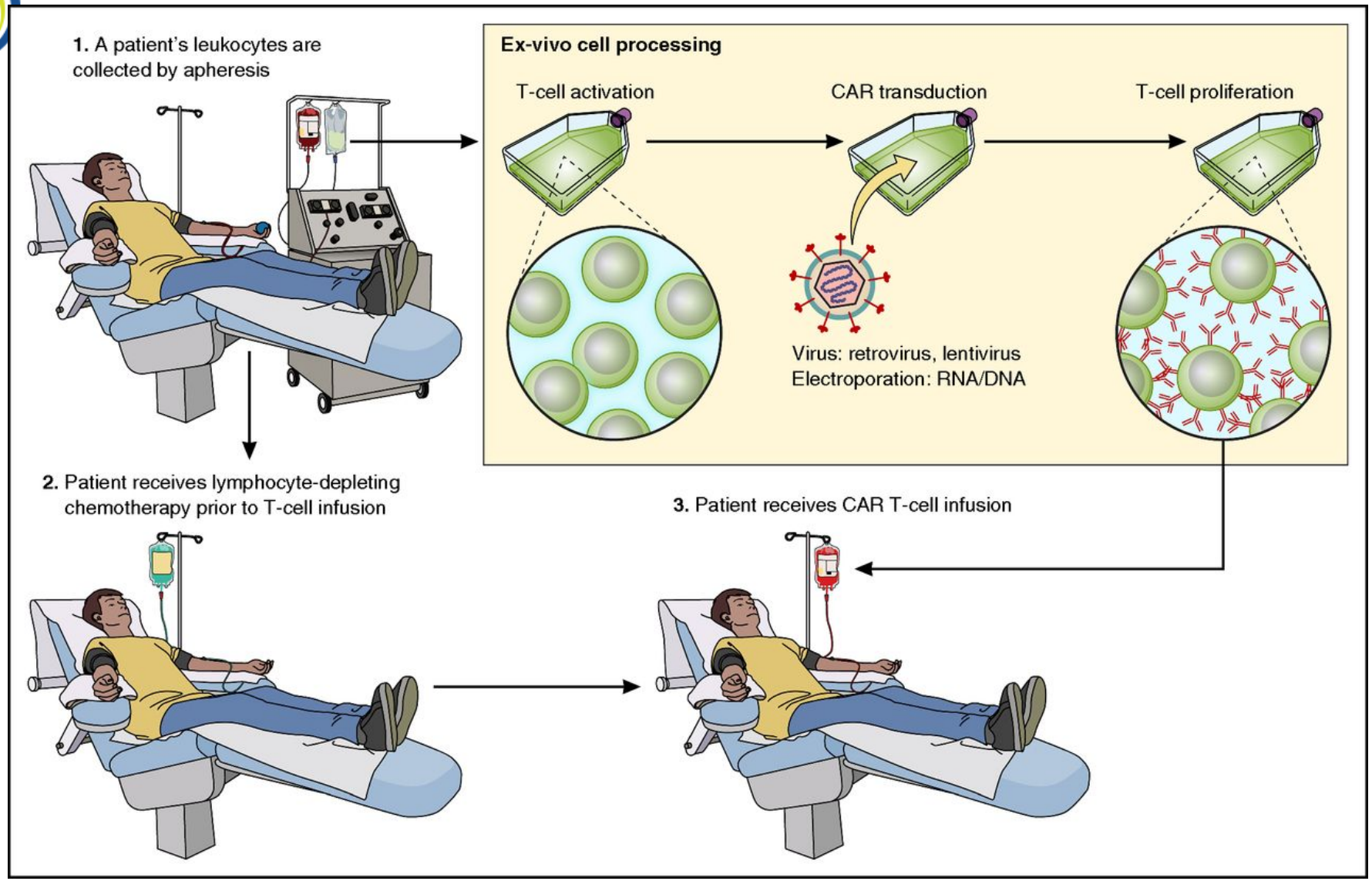
Transmembrane domain: hydrophobic α-helix derived from CD8, CD28 or immunoglobulin that is inserted into the membrane lipid bilayer spanning the cell membrane. Anchors the CAR in the T cell membrane

Costimulatory molecule(s): required for T cell activation

Stimulatory molecule: : required for T cell activation

David Feinberg et al Cell Immunol. 2019

Process of generation and delivery of CAR-T therapy



Lekha Mikkilineni, and James N. Kochenderfer Blood 2017;130:2594-2602

FDA-Approved CAR T cell therapies

DRUG	APPROVED	INDICATION	DOSE
Axicabtagene ciloleucel	2017	Adults with r/r large B-cell lymphoma. Including diffuse large B-cell lymphoma, primary mediastinal large B-cell lymphoma, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma	2 x 10^6 CAR-positive, viable T-cells per kg bodyweight (up to 2x10^8)
Tisagenlecleucel	2017	Patients ≤25 yr with refractory B-cell acute lymphoblastic leukemia or in 2+ relapse	0.2-0.5x10^6 CAR-positive, viable T-cells per kg if under 50 kg 0.1-2.5x10^8 CAR-positive, viable T-cells if over 50 kg
Tisagenlecleucel	2018	Adults with r/r large B-cell lymphoma after 2+ therapies Including DLBCL, high-grade B-cell lymphoma, DLBCL arising from follicular lymphoma	0.6-6.0 x 10^8 CAR-positive, viable T-cells

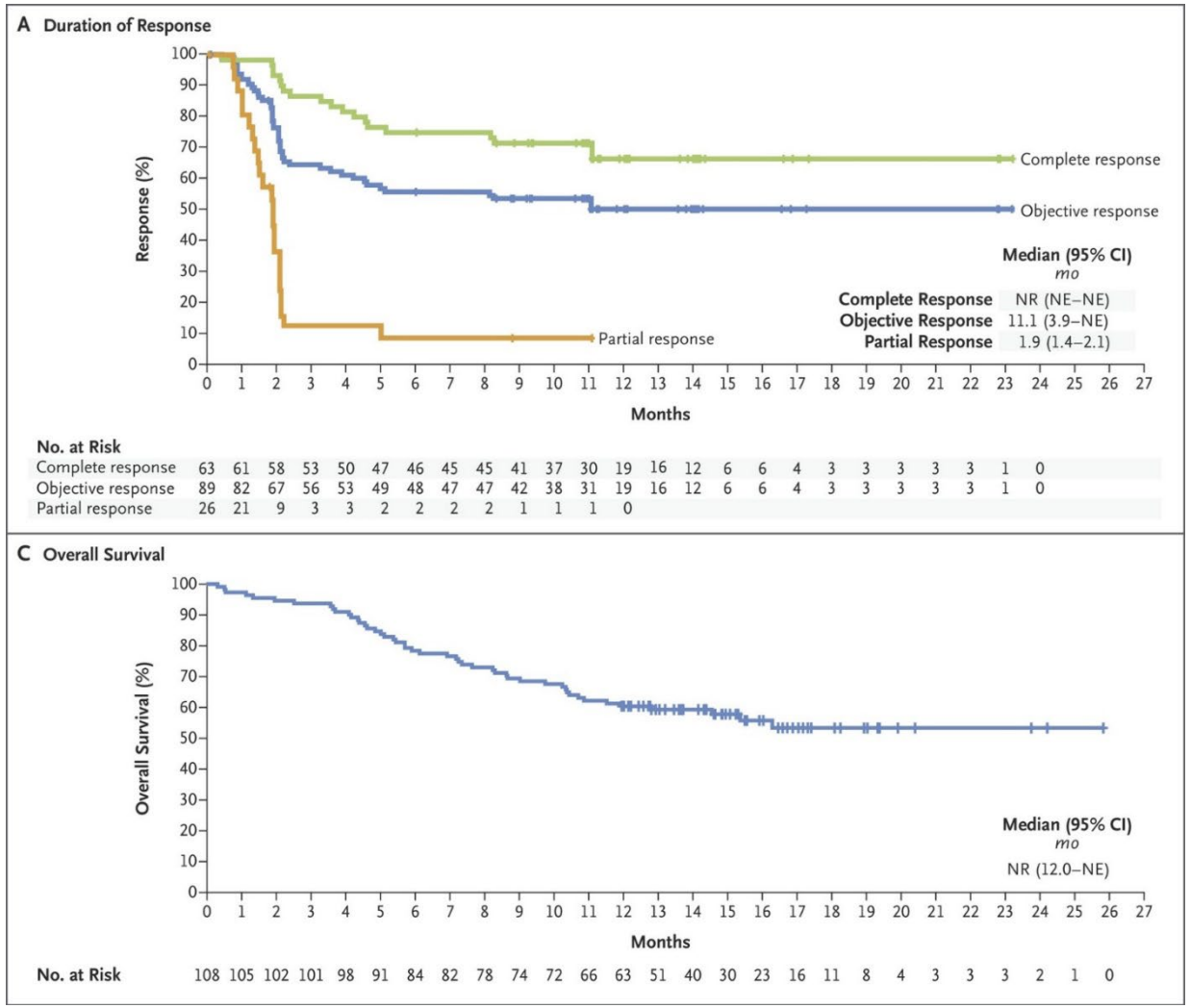
CAR T cell therapy in lymphoma

CAR T cell product	Axicabtagene ciloleucel (Yescarta)	Tisagenlecleucel (Kymriah)	Lisocabtagene maraleucel
Costimulation domain	CD-28	4-1BB	4-1BB
Vector	Retrovirus	Lentivirus	Lentivirus
Conditioning regimen	Fludarabine, cyclophosphamide	Fludarabine, cyclophosphamide, or bendamustine	Fludarabine, cyclophosphamide
Pivotal trial	ZUMA-1 ($N = 108$)	JULIET ($N = 111$)	TRANSCEND-NHL-001 ($N = 102$)
Histology	DLBCL, tFL, PMBCL	DLBCL, tFL	DLBCL,PMBCL, FL, tFL
CAR T cell dosage	2×10^6 cells/kg	3×10^8 cells/kg	1×10^8 cells/kg
ORR	83%	52%	75%
CR	58%	40%	55%
Median DOR (months)	11.1 (95% CI, 4.2—NE)	NR (95% CI, 10—NR)	NA
Overall survival	24-month survival, 50.5% (95% CI 40.2–59.7)	11.7 months (95% CI, 6.6—NE)	NA
Any grade CRS/NT	93%/64 %	58%/21%	37%/25 %
Grade ≥ 3 CRS	13%	22%	1%
Grade ≥ 3 NT	28%	12%	15%
Tocilizumab/steroid usage	43%/27%	15%/10%	17%/21%
Grade 5 AEs	4%	None	None

Sabarish Ayyappan, Kami Maddocks
J Hematol Oncol. 2019; 12: 82.

CD19 CAR in DLBCL- ZUMA1 (Axi-cel)

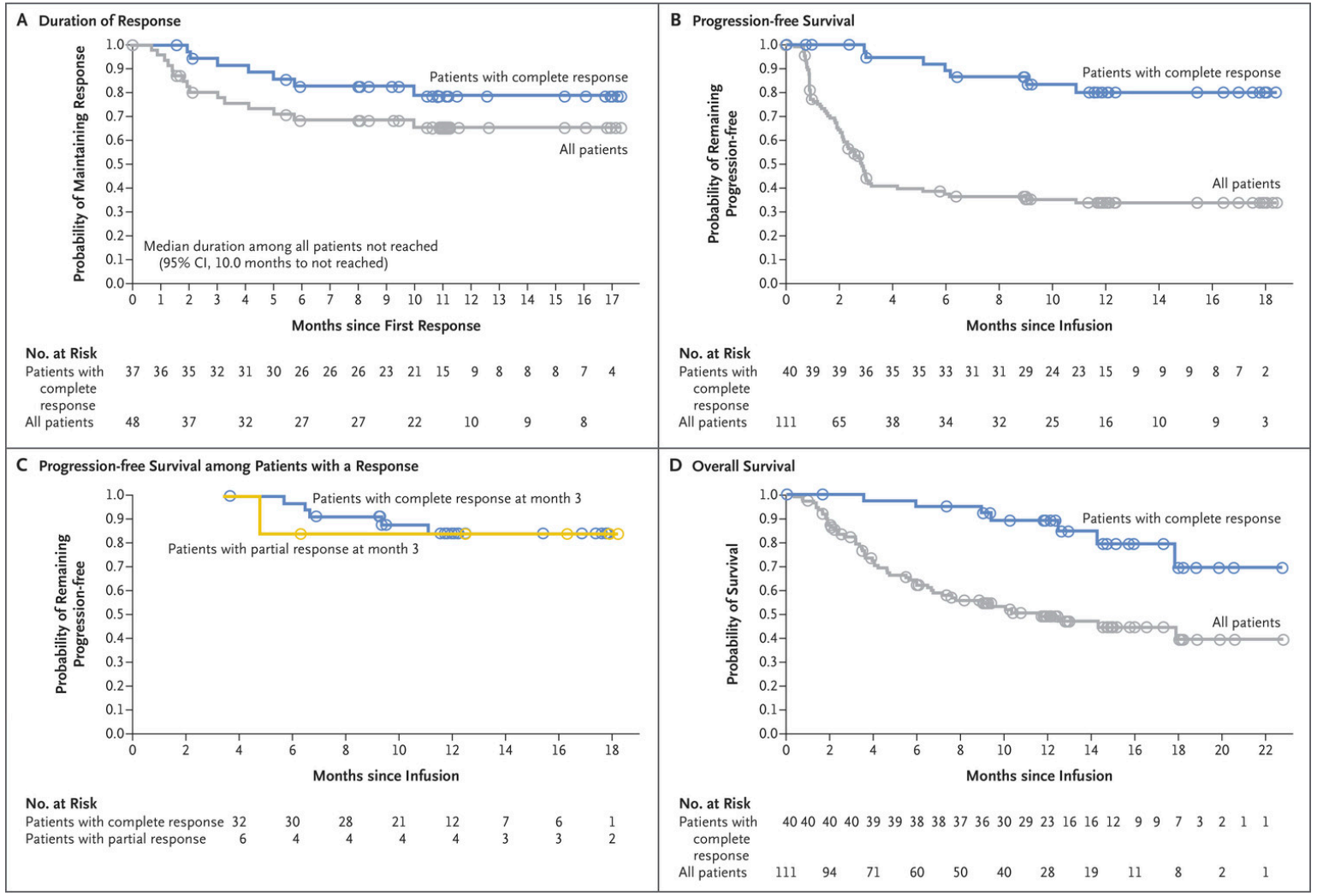
- CD19/CD28ʒ
- ORR = 82%
- CR = 54%
- 1.5-yr estimated OS = 52%
- CRS grade ≥3 = 13%
- Neurotox grade ≥3 = 28%



Neelapu, NEJM 2017.

CD19 CAR in DLBCL - JULIET (Tisa-cel)

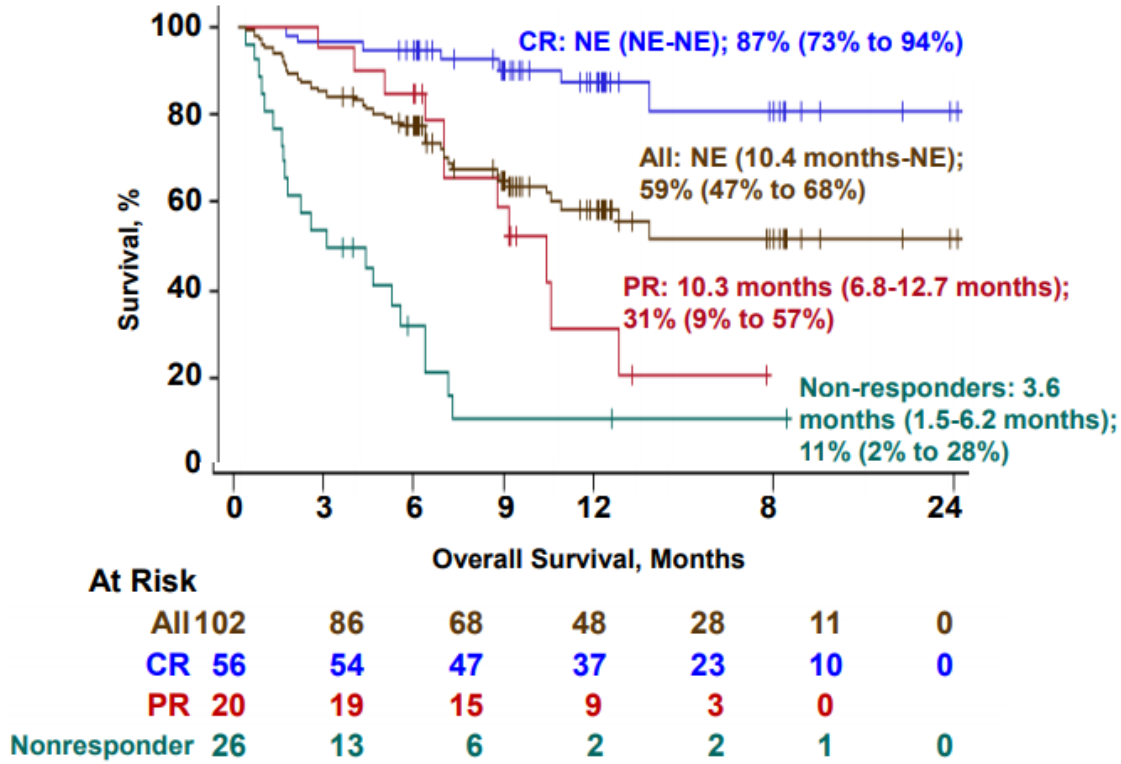
- CD19/4-1-BB
- ORR = 52%
- CR = 40%
- 1-yr estimated OS = 49%
- CRS grade ≥3 = 18%
- Neurotox grade ≥3 = 11%



Schuster, NEJM 2019.

CD19 CAR in DLBCL - TRANSCEND (Liso-Cel)

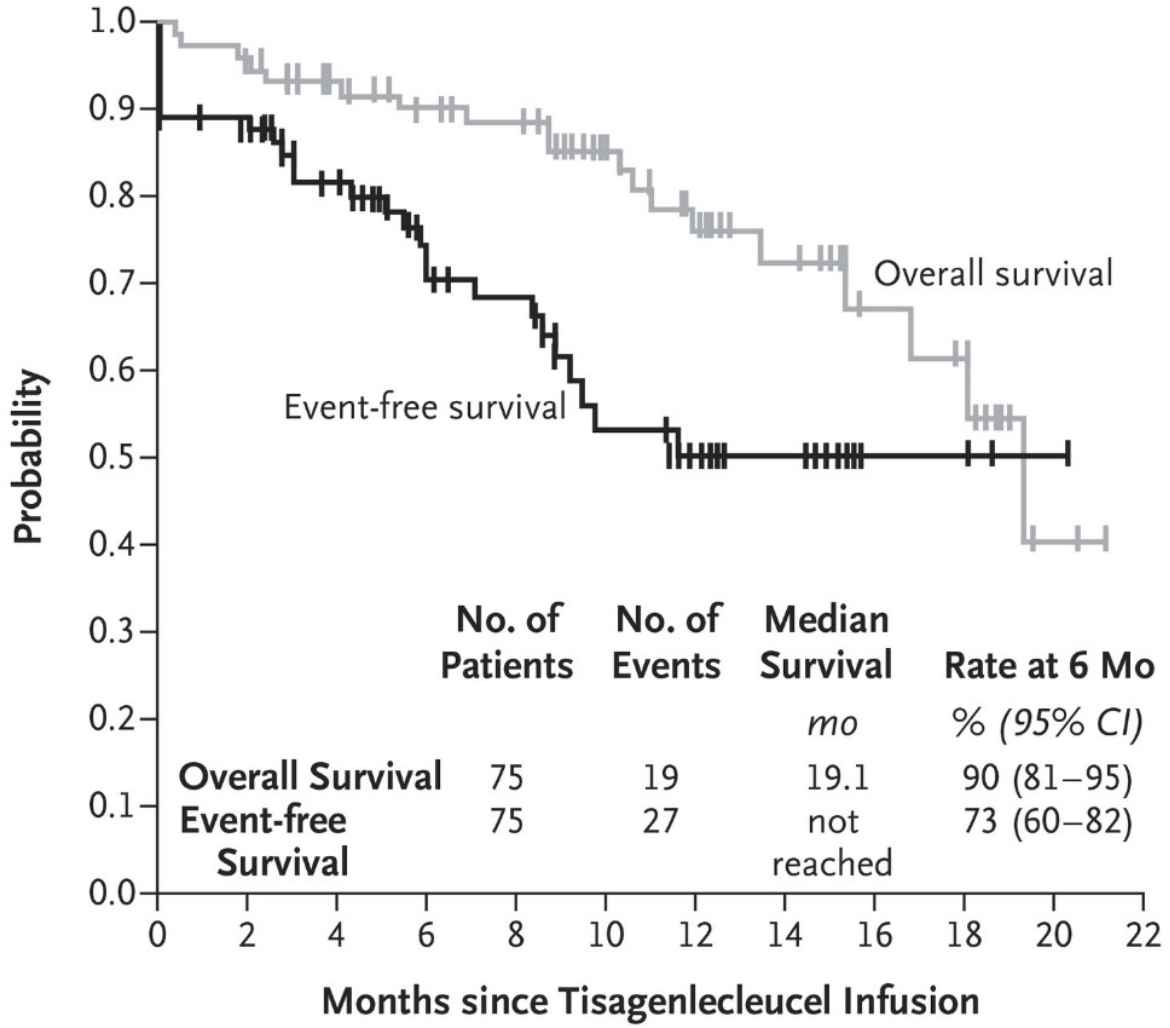
- CD19/4-1-BB, CD4:CD8 = 1:1
- ORR = 75%
- CR = 55%
- 1-yr estimated OS = 59%
- CRS grade ≥3 = 1%
- Neurotox grade ≥3 = 13%



Abramson JS, et al. HemaSphere. 2018;2(S1): Abstract S800.

CD19 CAR in B-ALL: ELIANA (Tisa-cel)

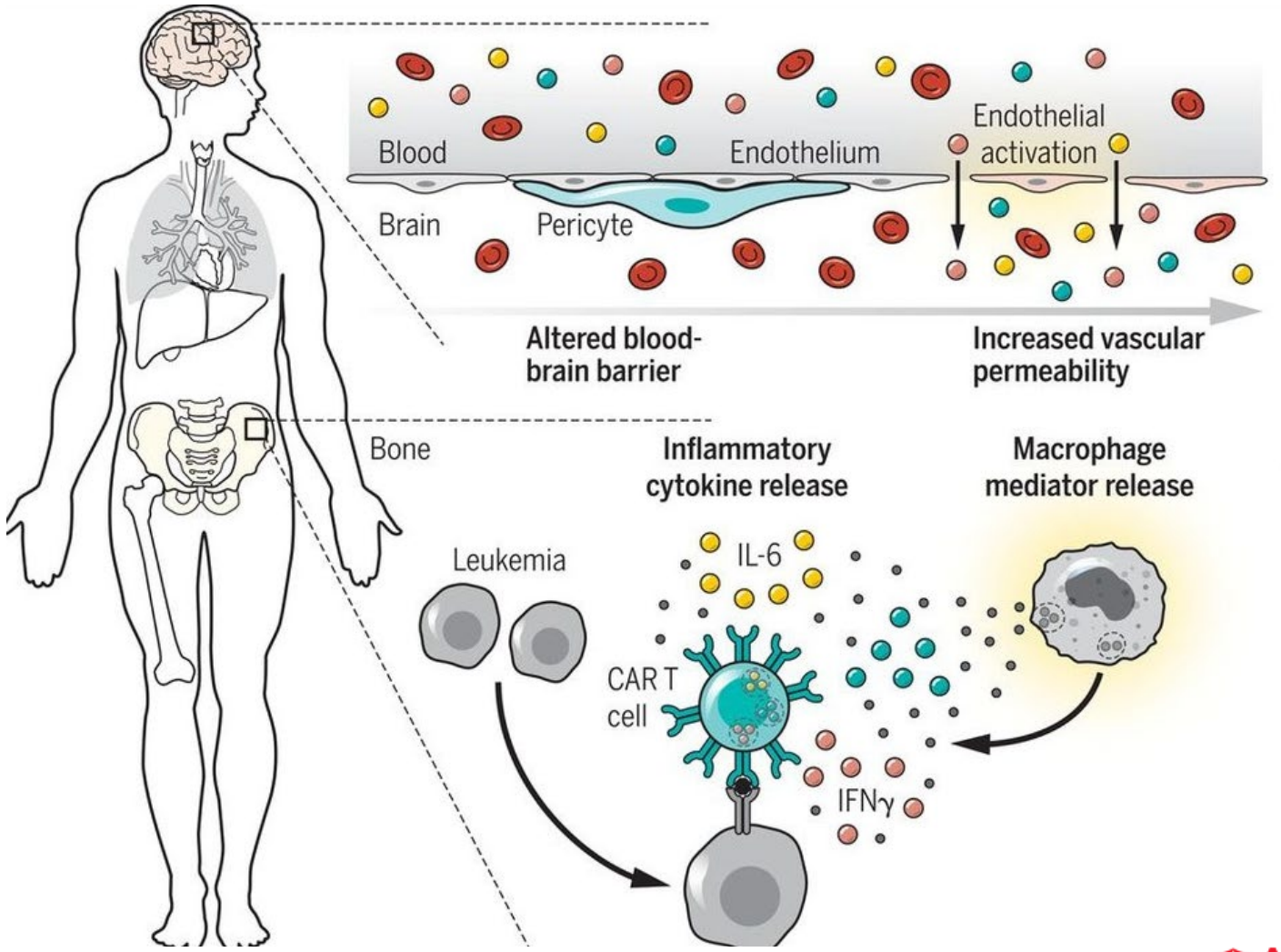
- CD19/4-1-BB
- ORR = 81%
- CR = 60%, CRi = 21%
- CRS grade ≥3 = 47%
- Neurotox grade ≥3 = 13%



	No. of Patients	No. of Events	Median Survival	Rate at 6 Mo
			mo	*% (95% CI)*
Overall Survival	75	19	19.1	90 (81–95)
Event-free Survival	75	27	not reached	73 (60–82)

Maude et al. NEJM 2018

CAR T Side Effects



Neurotoxicity
Delirium
Aphasia
Seizures
Cerebral edema
Intracranial hemorrhage

Hemodynamic instability
Tachycardia
Hypotension
Capillary leak syndrome

Organ dysfunction
AST and ALT elevation
Hyperbilirubinemia
Respiratory failure

Treatment

Steroids
Anti-epileptics

Tocilizumab
Steroids

June et al. Science 2018

CAR T Side Effects

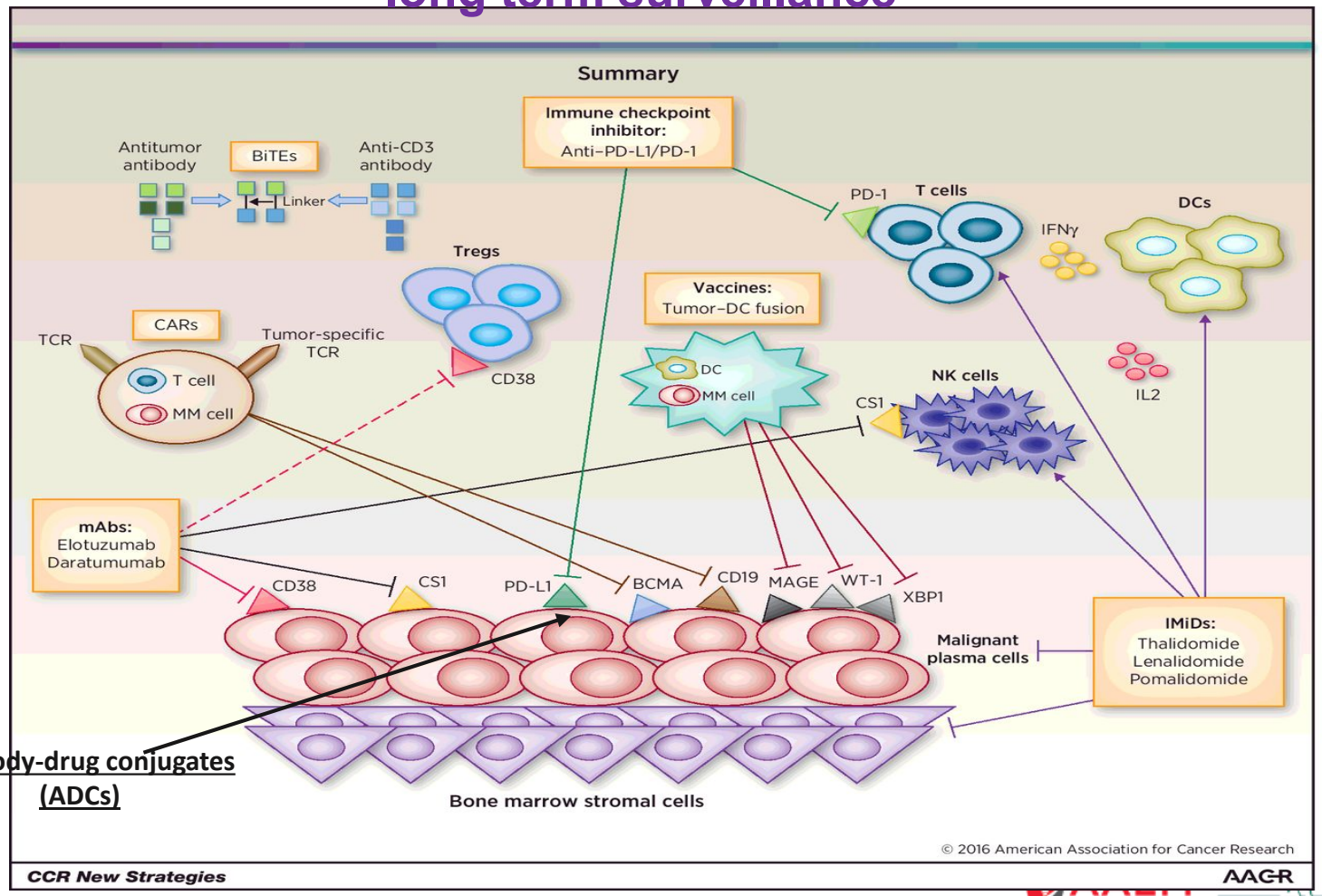
- Cytokine Release Syndrome (CRS)
- Neurotoxicity
- B Cell aplasia
- Macrophage Activation Syndrome (MAS)/HLH

Eligibility considerations for CAR

- Disease
  - Relative stability during CAR T manufacturing (~2-6 weeks)
  - Bridging therapy (chemo, RT, steroids, lenalidomide, ibrutinib)
  - CNS control
- Patient
  - Adequate cell counts
  - DVT, bleeding, infection, neuro disorders
  - Functional status: at screen vs. day of CAR T infusion
- Other
  - Social support, reimbursement

PROMISE OF IMMUNOTHERAPY IN MM

Great potential to incorporate **Immune based therapy** in order to **overcome resistance** and provide the **potential for memory and long term surveillance**



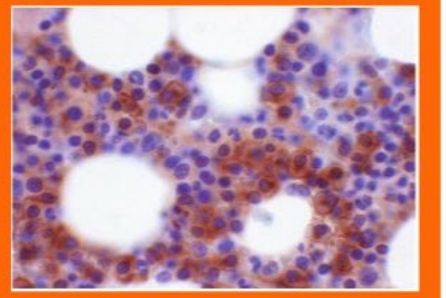
Clinical Cancer Research

Paola Neri et al. Clin Cancer Res 2016;22:5959-5965

BCMA: A promising target in MM

B cell maturation antigen (BCMA)

- A member of the TNF receptor superfamily
- Expression is largely restricted to plasma cells and mature B cells
- Not detectable in any other normal tissues
- Expressed nearly universally on multiple myeloma cells
- Anti-MM efficacy validated in initial studies[1]



Multiple myeloma cells expressing BCMA

(brown color = BCMA protein)

Raje ASCO 2018

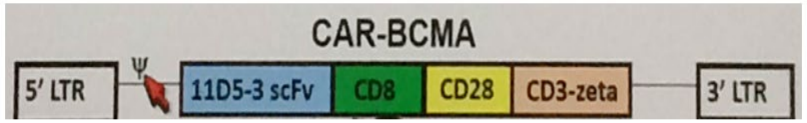
Table 1. Characteristics of trials evaluating BCMA-targeted CAR T-cells in MM.

	NCI	UPenn (Novartis)	bb2121 (Bluebird)	LCAR-B38M (Legend)	MCARH171 MSK/Juno Therapeutics
Reference (Clinicaltrials.gov identifier)	Brudno and colleagues[125] (NCT02215967)	Cohen and colleagues[127] (NCT02546167)	Raje and colleagues[126,129] (NCT02658929)	Zhang and colleagues[130] (NCT03090659)	Smith and colleagues[131] (NCT03070327)
Ag-binding domain	scFv (murine)	scFv (human)	scFv (murine)	Bispecific variable fragments of lama heavy-chain antibodies	scFv (human)
Signaling domains	CD3ζ/CD28	CD3ζ/4-1BB	CD3ζ/4-1BB	CD3ζ/4-1BB	CD3ζ/4-1BB
Suicide gene	None	None	None	None	EGFRt
Lymphodepletion	Flu/Cy	± Cy	Flu/Cy	Cy	Cy or Flu/Cy
BCMA expression required	Yes	No	In dose-escalation phase required, not is expansion cohort	Yes	Yes
Number of patients included	26	24	43	35	6
Number of prior therapies (median)	10	7	7	4	7.5
High-risk cytogenetics	38% (31% del(17p))	96% (71% del(17p) or *TP53* mutation)	Del(17p); t(4;14); t(14;16): dose-escalation cohort: 38%; expansion cohort: 41%	NA	67%
CAR T dose/kg	9×10^6	Cohort 1: $1–5 \times 10^8$ Cohort 2: Cy+$1–5 \times 10^7$ Cohort 3: Cy+$1–5 \times 10^8$	$50–800 \times 10^6$	Median dose: 4×10^6	Mean dose: $72–137 \times 10^6$
⩾PR	81%	Cohort 1: 44% Cohort 2: 20% Cohort 3: 60%	$150–800 \times 10^6$ cells ($n = 36$): 81%	100%	5 evaluable patients: 80%
CR	13%	Cohort 1: 11% Cohort 2: 0% Cohort 3: 10%	$150–800 \times 10^6$ ($n = 36$): 47%	63% (sCR)	5 evaluable patients: 0%
CRS (all grades)	81%	83%	63%	83%	50%

Ag, antigen; BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; CR, complete response; CRS, cytokine-release syndrome; Cy, cyclophosphamide; EGFRt, truncated Endothelial Growth Factor Receptor; Flu, fludarabine; NA, not available; NCI, National Cancer Institute; NCT, ClinicalTrials.gov identifier; PR, partial response; scFv, single-chain variable fragment; sCR, stringent complete response.

Fransenn et al. Ther Adv Hematol. Jan 2019

NCI BCMA-specific CAR in rel/ref MM



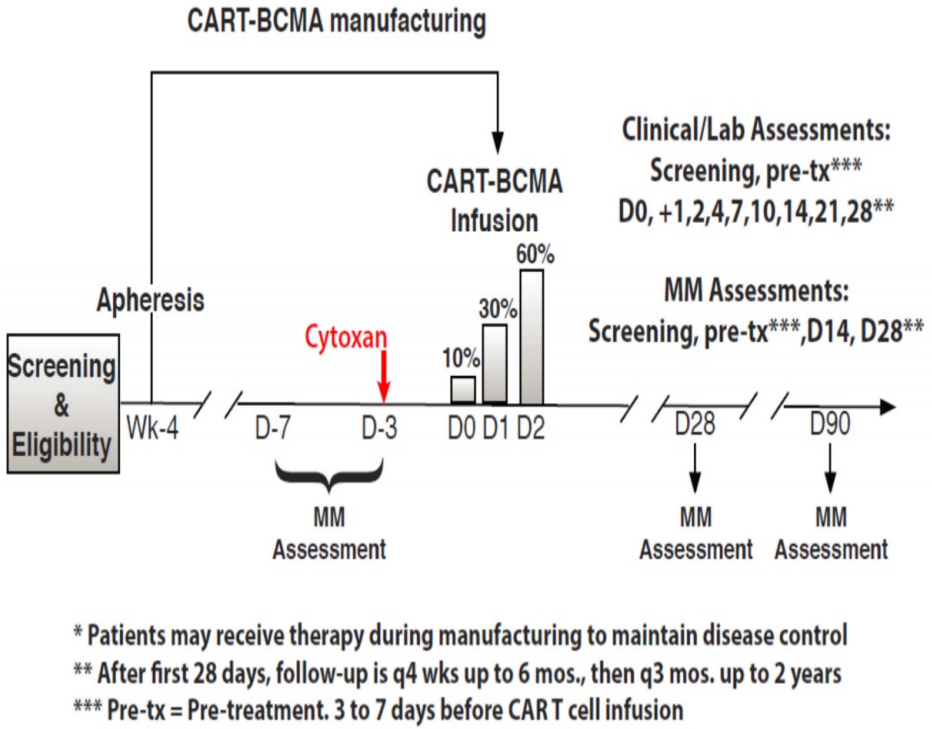
- Dose: 9X10^6 BCMA CAR T cells/kg after fludarabine and cytoxan lymphodepletion
- 16 patients treated
- Median 10 prior lines of therapy
- 6/16 (38%) had high risk cytogenetics; 5/16 (31%) deletion p53

- **ORR: 81%; 63% VGPR or CR**
- **Median EFS: 31 weeks**
- High peak blood CART cells was associated with response

- The latter 14 patients required to have a low burden of myeloma in the bone marrow to limit toxicity related to cytokine release syndrome (CRS). All patients had < 30% plasma cells by IHC of the core biopsy**.**

Brudno et al. J Clin Oncol. **2018** Aug 1;36(22):2267-2280

UPENN



- 24 subjects
- 96% high risk cytogenetics
- 7 prior lines of therapy

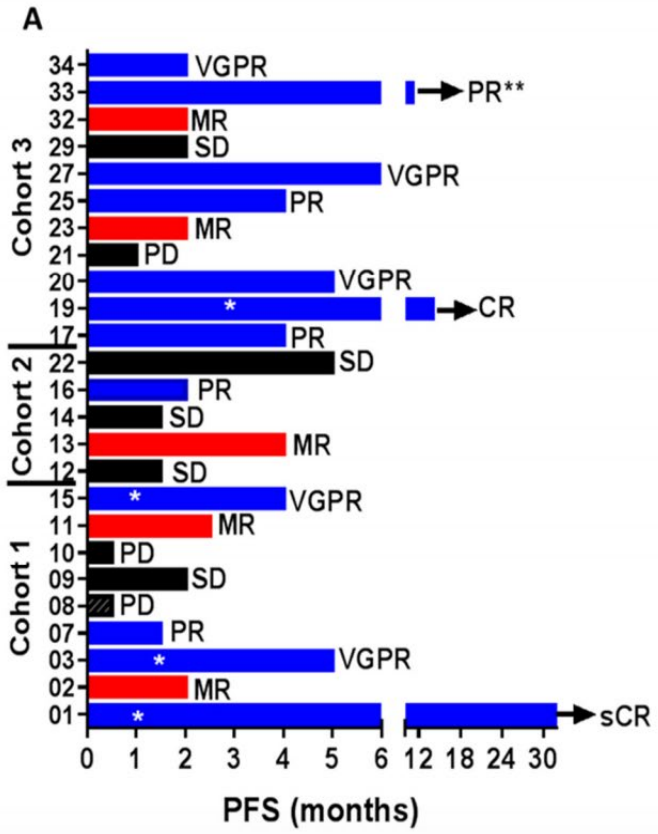
Adam Cohen et al. J Clin Invest. 2019 Mar 21;130. pii: 126397

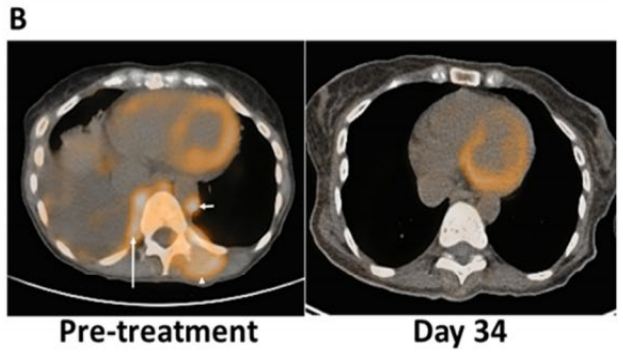
ORR

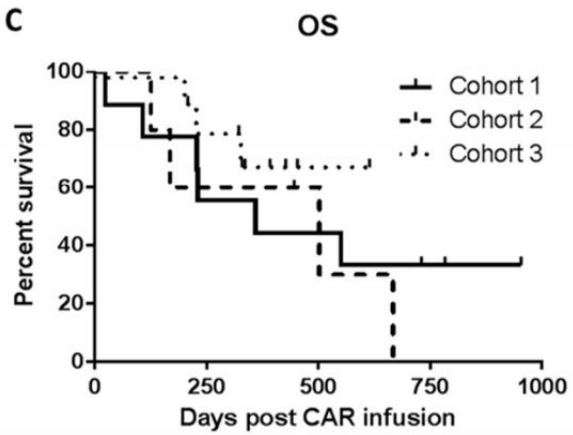
Cohort 1: 44%
Cohort 2: 20%
Cohort 3: 64%

Median Duration Of response: 124.5 days

3 patients ongoing Remission more than 11 months, 1 sCR>2.5 YRS







Adam Cohen et al. J Clin Invest. 2019 Mar 21;130. pii: 126397

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Anti-BCMA CAR T-Cell Therapy bb2121 in Relapsed or Refractory Multiple Myeloma

Noopur Raje, M.D., Jesus Berdeja, M.D., Yi Lin, M.D., Ph.D., David Siegel, M.D., Ph.D., Sundar Jagannath, M.D., Deepu Madduri, M.D., Michaela Liedtke, M.D., Jacalyn Rosenblatt, M.D., Marcela V. Maus, M.D., Ph.D., Ashley Turka, Lyh-Ping Lam, Pharm.D., Richard A. Morgan, Ph.D., Kevin Friedman, Ph.D., Monica Massaro, M.P.H., Julie Wang, Pharm.D., Ph.D., Greg Russotti, Ph.D., Zhihong Yang, Ph.D., Timothy Campbell, M.D., Ph.D., Kristen Hege, M.D., Fabio Petrocca, M.D., M. Travis Quigley, M.S., Nikhil Munshi, M.D., and James N. Kochenderfer, M.D.

New England Journal of Medicine380;18 nejm.org May 2, 2019

Table 1. Baseline Characteristics of the Safety Population.*

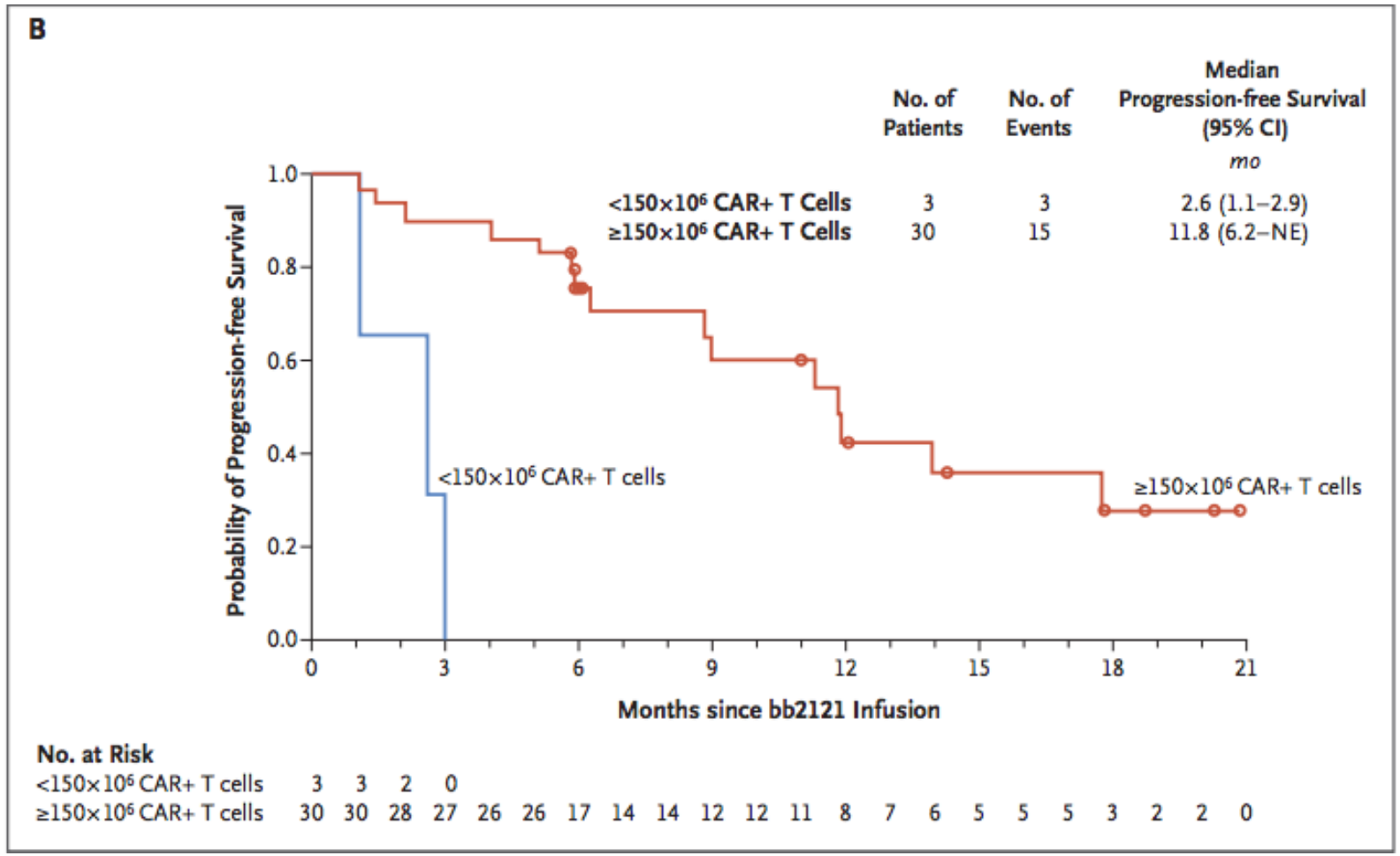
Characteristic	Dose-Escalation Cohort (N=21)	Expansion Cohort (N=12)	Total (N=33)
Median age (range) — yr	57 (37–74)	64 (46–75)	60 (37–75)
Male sex — no. (%)	13 (62)	8 (67)	21 (64)
Median time since diagnosis (range) — yr†	4 (1–16)	6 (1–36)	5 (1–36)
High tumor burden — no. (%)‡	11 (52)	5 (42)	16 (48)
Extramedullary disease — no. (%)	4 (19)	5 (42)	9 (27)
Tumor BCMA expression ≥50% — no. (%)§	21 (100)	2 (17)	23 (70)
ECOG performance-status score — no. (%)¶			
0	8 (38)	2 (17)	10 (30)
1	11 (52)	10 (83)	21 (64)
2	2 (10)	0	2 (6)
High-risk cytogenetic profile — no. (%)‖	8 (38)	7 (58)	15 (45)
Bridging therapy — no. (%)**	7 (33)	7 (58)	14 (42)
Progressive disease during most recent line of therapy — no. (%)	11 (52)	10 (83)	21 (64)
Median no. of previous antimyeloma regimens (range)	7 (3–14)	8 (3–23)	7 (3–23)
Previous autologous stem-cell transplantation — no. (%)	21 (100)	11 (92)	32 (97)
Previous therapies — no. (%)			
Bortezomib			
Exposed	21 (100)	12 (100)	33 (100)
Refractory	13 (62)	7 (58)	20 (61)
Carfilzomib			
Exposed	19 (90)	11 (92)	30 (91)
Refractory	12 (57)	7 (58)	19 (58)
Lenalidomide			
Exposed	21 (100)	12 (100)	33 (100)
Refractory	17 (81)	7 (58)	24 (73)
Pomalidomide			
Exposed	19 (90)	12 (100)	31 (94)
Refractory	14 (67)	12 (100)	26 (79)
Daratumumab			
Exposed	15 (71)	12 (100)	27 (82)
Refractory	9 (43)	9 (75)	18 (55)

New England Journal of Medicine380;18 nejm.org May 2, 2019

Table 3. Tumor Response According to Dose of Chimeric Antigen Receptor–Positive (CAR+) T Cells.*

Variable	50×10^6 CAR+ T Cells (N=3)	150×10^6 CAR+ Tells (N=8)	450×10^6 CAR+ T Cells		800×10^6 CAR+ T Cells (N=3)	150×10^6–800×10^6 CAR+ T Cells (N=30)	50×10^6–800×10^6 CAR+ T Cells (N=33)
			<50% BCMA (N=8)†	≥50% BCMA (N=11)†			
Objective response‡							
No. of patients with a response	1	6	8	10	3	27	28
Rate — % (95% CI)	33 (1–91)	75 (35–97)	100 (63–100)	91 (59–100)	100 (29–100)	90 (74–98)	85 (68–95)
Best overall response — no. (%)							
Stringent complete response	0	5 (63)	3 (38)	4 (36)	0	12 (40)	12 (36)
Complete response	0	0	0	1 (9)	2 (67)	3 (10)	3 (9)
Very good partial response	0	0	4 (50)	4 (36)	1 (33)	9 (30)	9 (27)
Partial response	1 (33)	1 (12)	1 (12)	1 (9)	0	3 (10)	4 (12)
Stable disease	2 (67)	1 (12)	0	1 (9)	0	2 (7)	4 (12)
Progressive disease	0	1 (12)	0	0	0	1 (3)	1 (3)
Median duration of response (95% CI) — mo	1.9 (NE–NE)	NE	7.7 (5.3–14.8)		12.9 (10.9–12.9)	10.9 (7.2–NE)	10.9 (7.2–NE)
Negativity for MRD§							
No. of patients with a response who could be evaluated for MRD	0	4	11		1	16	16
Rate — %	0	100	100		100	100	100

New England Journal of Medicine380;18 nejm.org May 2, 2019



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Zhao et al. Journal of Hematology & Oncology (2018) 11:141
https://doi.org/10.1186/s13045-018-0681-6

Journal of Hematology & Oncology

RESEARCH Open Access

A phase 1, open-label study of LCAR-B38M, a chimeric antigen receptor T cell therapy directed against B cell maturation antigen, in patients with relapsed or refractory multiple myeloma

Wan-Hong Zhao[1†], Jie Liu[1†], Bai-Yan Wang[1†], Yin-Xia Chen[1], Xing-Mei Cao[1], Yun Yang[1], Yi-Lin Zhang[1], Fang-Xia Wang[1], Peng-Yu Zhang[1], Bo Lei[1], Liu-Fang Gu[1], Jian-Li Wang[1], Nan Yang[1], Ru Zhang[1], Hui Zhang[1], Ying Shen[1], Ju Bai[1], Yan Xu[1], Xu-Geng Wang[1], Rui-Li Zhang[1], Li-Li Wei[1], Zong-Fang Li[2], Zhen-Zhen Li[2], Yan Geng[3], Qian He[3], Qiu-Chuan Zhuang[4], Xiao-Hu Fan[4], Ai-Li He[1,2] and Wang-Gang Zhang[1*]

PNAS

Exploratory trial of a biepitopic CAR T-targeting B cell maturation antigen in relapsed/refractory multiple myeloma

Jie Xu[a,1], Li-Juan Chen[b,1], Shuang-Shuang Yang[a,1], Yan Sun[a,1], Wen Wu[a], Yuan-Fang Liu[a], Ji Xu[b], Yan Zhuang[c], Wu Zhang[a], Xiang-Qin Weng[a], Jing Wu[a], Yan Wang[a], Jin Wang[a], Hua Yan[a], Wen-Bin Xu[a], Hua Jiang[c], Juan Du[c], Xiao-Yi Ding[d], Biao Li[d], Jun-Min Li[a], Wei-Jun Fu[c], Jiang Zhu[a], Li Zhu[e], Zhu Chen[a,2], Xiao-Hu (Frank) Fan[e,2], Jian Hou[c,2], Jian-Yong Li[b,2], Jian-Qing Mi[a,2], and Sai-Juan Chen[a,2]

[a]State Key Laboratory of Medical Genomics, Shanghai Institute of Hematology, National Research Center for Translational Medicine, Ruijin Hospital affiliated with Shanghai Jiao Tong University School of Medicine, 200025 Shanghai, China; [b]Department of Hematology, Jiangsu Province Hospital, First Affiliated Hospital of Nanjing Medical University, 210029 Nanjing, China; [c]Department of Hematology, Changzheng Hospital, The Second Military Medical University, 200003 Shanghai, China; [d]Department of Radiology and Nuclear Medicine, Ruijin Hospital affiliated with Shanghai Jiao Tong University School of Medicine, 200025 Shanghai, China; and [e]Nanjing Legend Biotech, 210008 Nanjing, China

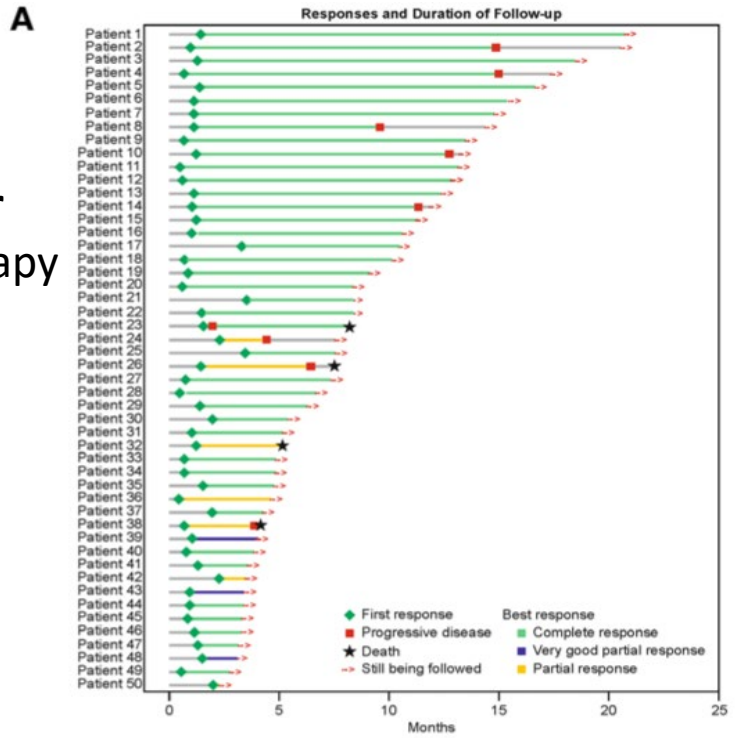
Contributed by Zhu Chen, December 17, 2018 (sent for review November 19, 2018; reviewed by Didier Blaise and Genhong Cheng)

Table 2 Adverse events that occurred in at least 10% of patients

AE, *n* (%)	All grade	Grades 1–2	Grade ≥ 3
Pyrexia	52 (91)	41 (72)	11 (19)
Cytokine release syndrome[a]	51 (90)	47 (83)	4 (7)
Thrombocytopenia	28 (49)	15 (26)	13 (23)
Leukopenia	27 (47)	10 (18)	17 (30)
AST increased	22 (39)	10 (18)	12 (21)
Anemia	17 (30)	7 (12)	10 (18)
Hypotension	12 (21)	9 (16)	3 (5)
ALT increased	10 (18)	10 (18)	0
Cough	10 (18)	10 (18)	0
Disseminated intravascular coagulation	10 (18)	9 (16)	1 (2)
Hypocalcemia	9 (16)	7 (12)	2 (4)
Hyponatremia	8 (14)	5 (9)	3 (5)
Dyspnea	6 (11)	6 (11)	0
Nausea	6 (11)	6 (11)	0

Mean **3 prior** Lines of therapy

ORR 88%
CR 68%



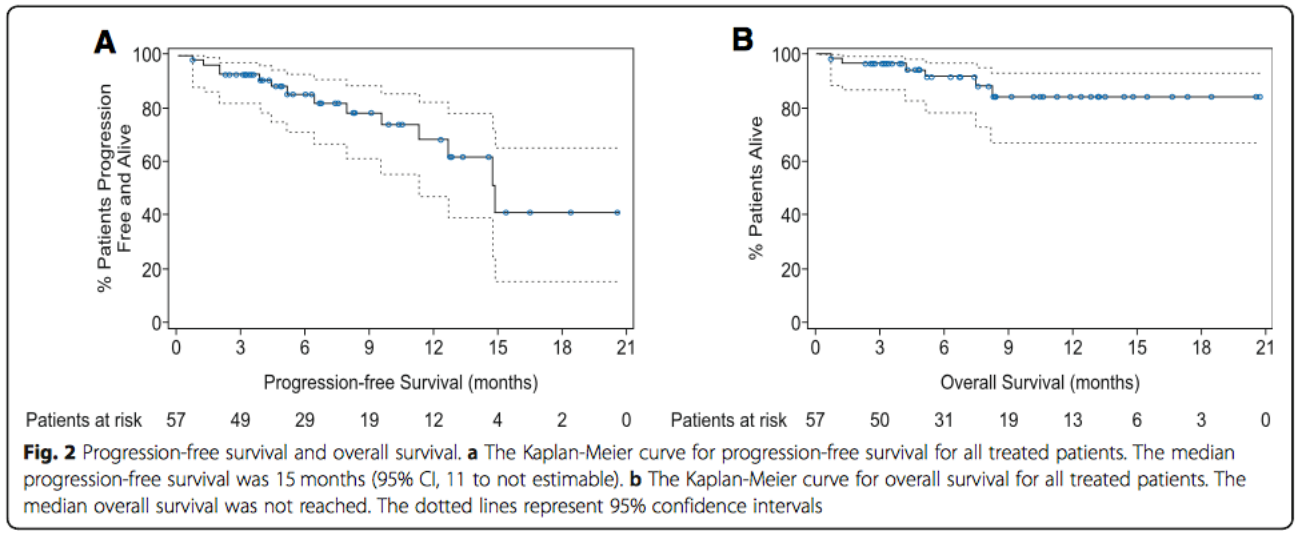


Fig. 2 Progression-free survival and overall survival. **a** The Kaplan-Meier curve for progression-free survival for all treated patients. The median progression-free survival was 15 months (95% CI, 11 to not estimable). **b** The Kaplan-Meier curve for overall survival for all treated patients. The median overall survival was not reached. The dotted lines represent 95% confidence intervals

Median PFS 15 months
Median OS not reached

Zhao et al. Journal of Hematology & Oncology (2018) 11:141

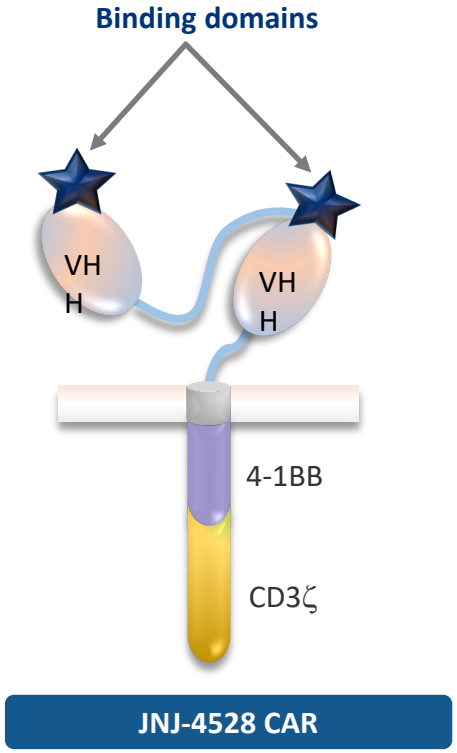
Results from CARTITUDE-1: A Phase 1b/2 Study of JNJ-4528, a CAR-T Cell Therapy Directed Against B-Cell Maturation Antigen (BCMA), in Patients with Relapsed and/or Refractory Multiple Myeloma (R/R MM)

Deepu Madduri,[1] Saad Z. Usmani,[2] Sundar Jagannath,[1] Indrajeet Singh,[3] Enrique Zudaire,[3] Tzu-Min Yeh,[4] Alicia J. Allred,[3] Arnob Banerjee,[3] Jenna D. Goldberg,[4] Jordan M. Schecter,[4] Sen Zhuang,[4] Jeffrey R. Infante,[3] Syed Rizvi,[5] Frank Fan,[6] Andrzej Jakubowiak,[7] Jesus G. Berdeja[8]

[1]Mount Sinai Medical Center, New York, NY, USA; [2]Levine Cancer Institute-Atrium Health, Charlotte, NC, USA; [3]Janssen R&D, Spring House, PA, USA; [4]Janssen R&D, Raritan, NJ, USA; [5]Legend Biotech USA Inc., Piscataway, NJ, USA; [6]Nanjing Legend Biotech, Nanjing, China; [7]University of Chicago, Chicago, IL, USA; [8]Sarah Cannon Research Institute, Nashville, TN, USA

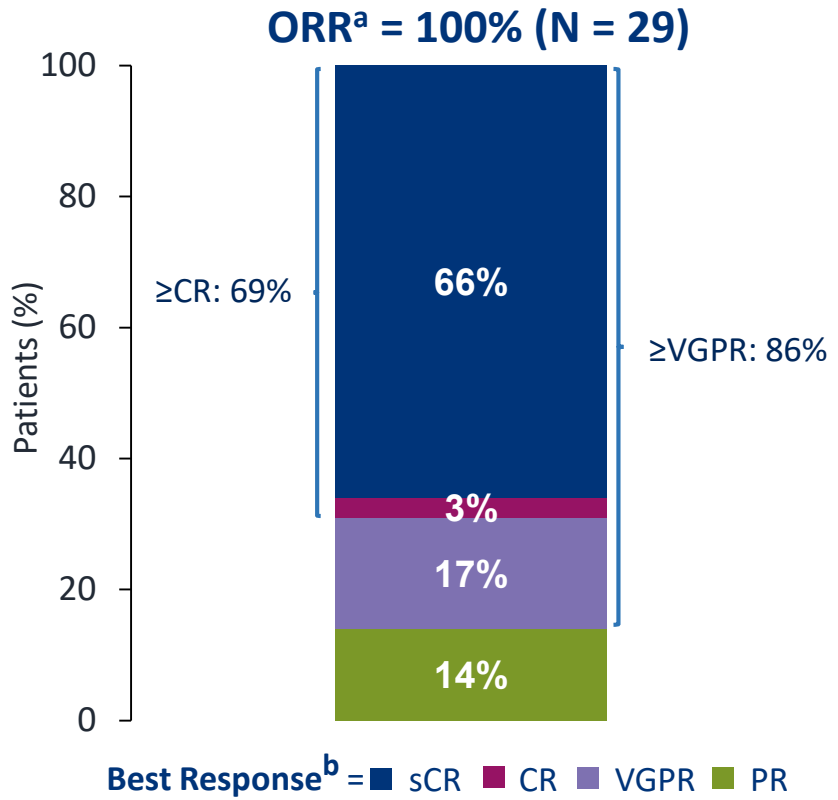
JNJ-4528: BCMA-targeted CAR-T Cell Therapy

- **JNJ-68284528 (JNJ-4528) is a structurally differentiated chimeric antigen receptor T (CAR-T) cell therapy**
  - Contains a CD3ζ signaling domain and 4-1BB costimulatory domain
  - 2 BCMA-targeting single domain antibodies designed to confer avidity
  - Identical to the CAR construct used in the LEGEND-2 study
- **LEGEND-2 (N = 74): Phase 1 investigator-initiated study conducted in China**
  - High, deep, and durable overall response and manageable safety in R/R MM[a,b]



[a]Zhao et al. *JHO* 2018;11(1):141; [b]Xu et al. *PNAS* 2019;116(19):9543; BCMA=B-cell maturation antigen; MM=multiple myeloma; R/R=relapsed/refractory; VHH=single variable domain on a heavy chain

CARTITUDE-1: Overall Response Rate

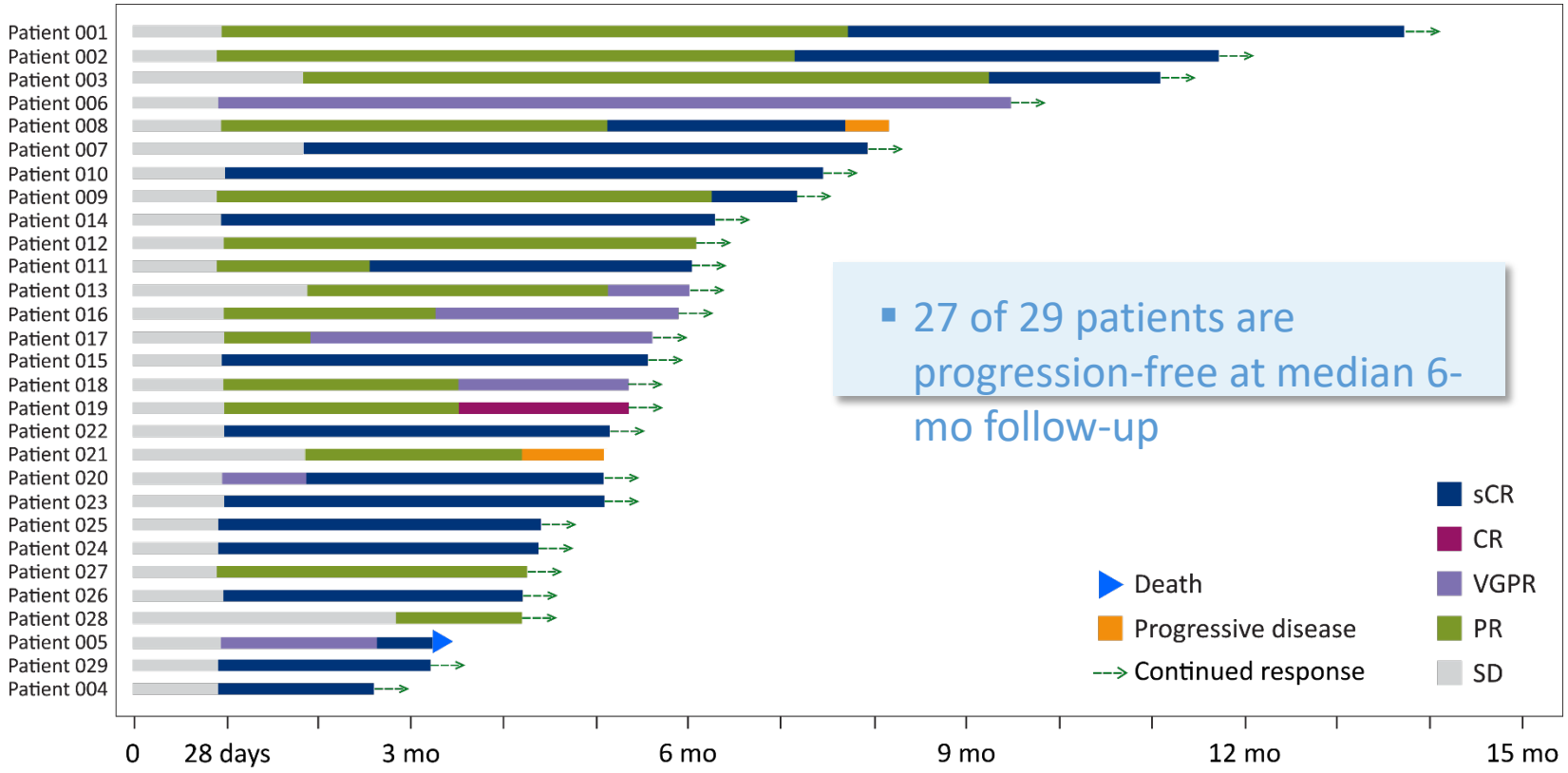


- ORR and depth of response were independent of BCMA expression on MM cells at baseline
- Median time to first response = 1 mo (1 – 3)
- Median time to ≥CR = 1 mo (1 – 9)

[a]PR or better; Independent Review Committee-assessed, [b]No patient had stable disease or progressive disease as best response. CR=complete response; ORR=overall response rate; PR=partial response; sCR=stringent complete response; VGPR=very good partial response

ASH Annual Meeting; Madduri et al Abstract #577

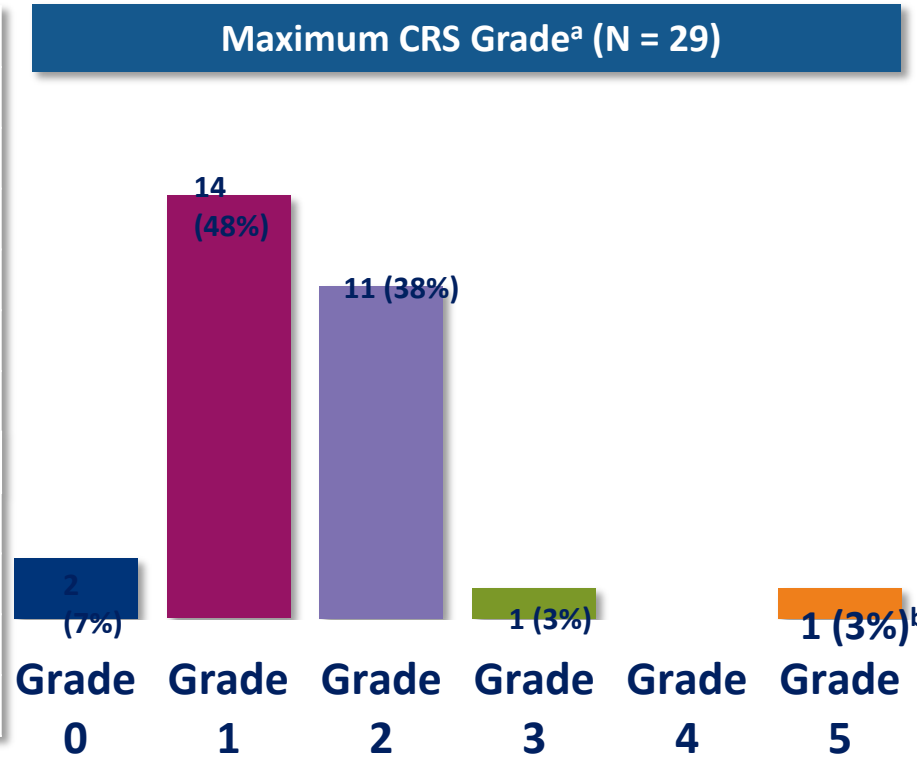
CARTITUDE-1: Duration of Response



- 27 of 29 patients are progression-free at median 6-mo follow-up

CARTITUDE-1: Safety

Hematologic AEs (≥25% All Grade)	N = 29	
	All Grade	Grade ≥3
Neutropenia	27 (93)	27 (93)
Anemia	25 (86)	16 (55)
Thrombocytopenia	25 (86)	20 (69)
Leukopenia	15 (52)	15 (52)
Lymphopenia	13 (45)	9 (31)
Non-Hematologic AEs (≥25% All Grade)		
Increased AST	9 (31)	2 (7)
Increased ALT	8 (28)	1 (3)
Diarrhea	8 (28)	1 (3)
Upper respiratory tract infection	8 (28)	0



ASH Annual Meeting; Madduri et al Abstract #577

CARTITUDE-1 Cytokine Release Syndrome and Neurotoxicity

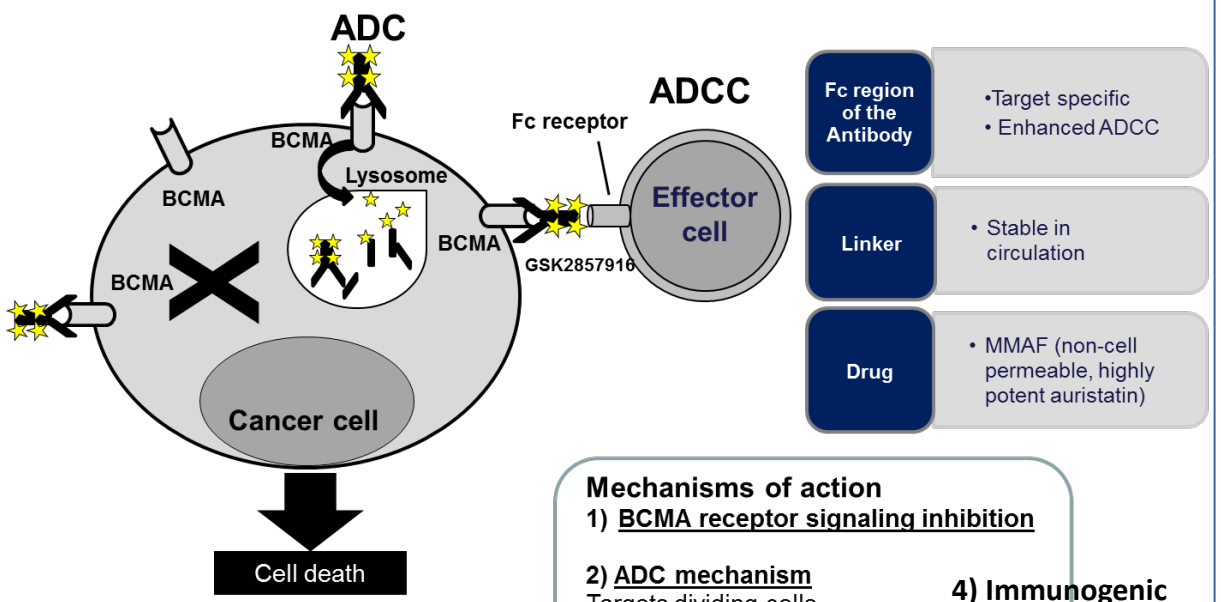
Cytokine Release Syndrome	Total (N = 29)
Patients with CRS, n (%)	27 (93)
Median time to onset of CRS, days (range)	7 (2 – 12)
Median duration of CRS, days (range)	4 (1 – 60)
Supportive Measure to Treat CRS	
Tocilizumab	22 (76)
Anakinra	6 (21)
Corticosteroids	6 (21)
Vasopressor used	2 (7)
Intubation/Mechanical Ventilation	1 (3)
Other[a]	22 (76)

CAR-T-associated AEs	N = 29	
	All Grade	Grade ≥3
Neurotoxicity consistent with ICANS[b]	3 (10)	1 (3)

ASH Annual Meeting; Madduri et al Abstract #577

Anti-BCMA ADC (Belantamab mafadotin, GSK2857916)

Figure 1. Mechanisms of action of GSK2857916



ADC, antibody-dependent cytotoxicity; ADCC, antibody-dependent cell-mediated cytotoxicity; BCMA, B cell maturation antigen; MMAF, monomethyl auristatin-F.

Anderson et al, AACR 2016, #CT034

DREAMM-1 Part 2: Adverse Events Regardless of Relationship

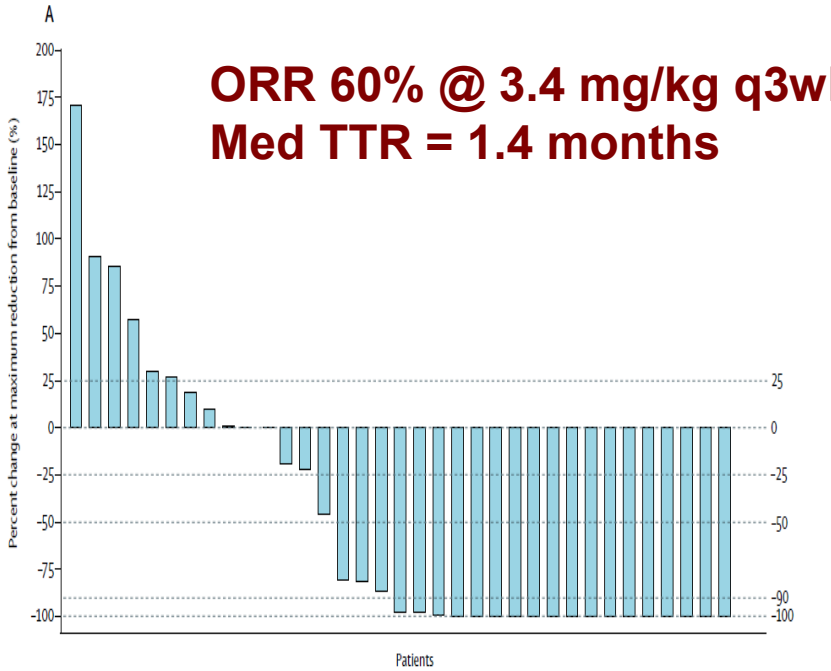
n (%)	N=35	
	Any grade	≥Grade 3*
Any event	35 (100)	28 (80)
Thrombocytopenia	20 (57)	12 (34)
Vision blurred	16 (46)	0
Dry eye	12 (34)	1 (3)
Anemia	10 (29)	5 (14)
AST increased	10 (29)	2 (6)
Cough	9 (26)	0
IRR	8 (23)	3 (9)
Nausea	8 (23)	0
Photophobia	8 (23)	0
Pyrexia	8 (23)	0
Chills	8 (23)	0
Fatigue	7 (20)	0

- Any ocular symptoms = 63%
  - Grade 3 = 9%
- Median time to onset= 23 days (range 1-84)
- Median duration = 30 days (range 5 – 224)
- Treat by dose delay and reduction
  - Artificial tears
  - Role of steroid eye drops?
- Corneal findings on exam in 89%
  - Microcystic changes, keratitis
  - Reversible

Trudel et al, ASH 2017, Lancet Onc 2018

Belantamab mafadotin

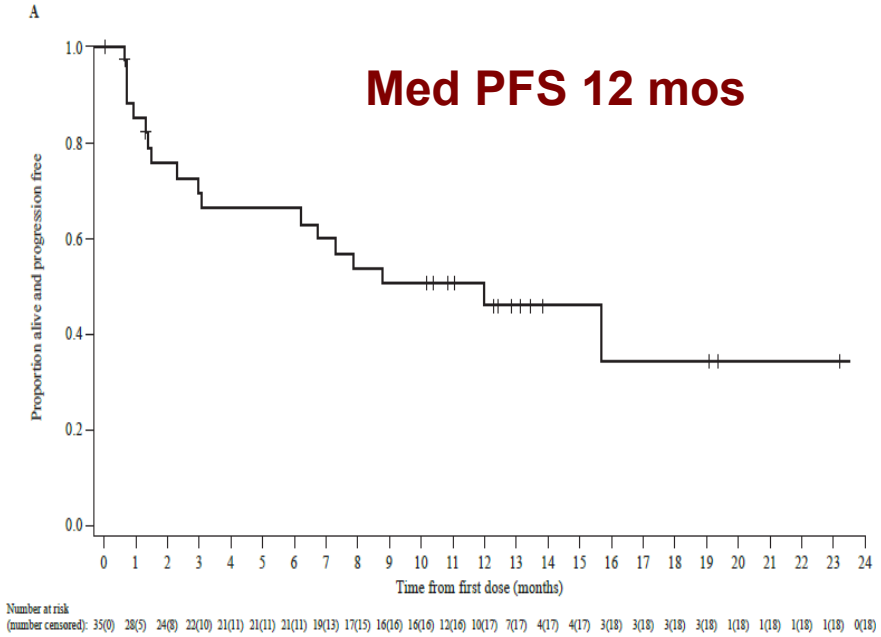
Part 2 expansion (n=35)



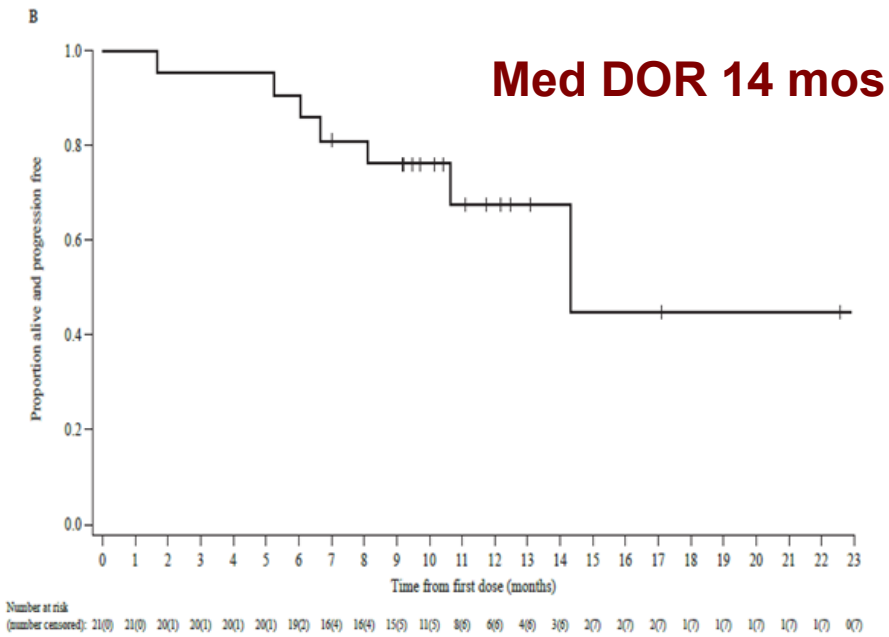
ORR 60% @ 3.4 mg/kg q3wks
Med TTR = 1.4 months

Trudel et al, Lancet Onc 2018; Trudel et al, Blood Cancer J 2019

Belantamab mafadotin



Med PFS 12 mos



Med DOR 14 mos

PI/IMID/Dara-ref (n=13)
ORR 39%, PFS 6 mos.

Trudel et al, Blood Cancer J 2019

Lancet Oncol. 2020 Feb;21(2):207-221. doi: 10.1016/S1470-2045(19)30788-0. Epub 2019 Dec 16.

Belantamab mafodotin for relapsed or refractory multiple myeloma (DREAMM-2): a two-arm, randomised, open-label, phase 2 study.

Lonial S[1], Lee HC[2], Badros A[3], Trudel S[4], Nooka AK[5], Chari A[6], Abdallah AO[7], Callander N[8], Lendvai N[9], Sborov D[10], Suvannasankha A[11], Weisel K[12], Karlin L[13], Libby E[14], Arnulf B[15], Facon T[16], Hulin C[17], Kortüm KM[18], Rodríguez-Otero P[19], Usmani SZ[20], Hari P[21], Baz R[22], Quach H[23], Moreau P[24], Voorhees PM[20], Gupta I[25], Hoos A[25], Zhi E[25], Baron J[25], Piontek T[25], Lewis E[26], Jewell RC[26], Dettman EJ[25], Popat R[27], Esposti SD[28], Opalinska J[25], Richardson P[29], Cohen AD[30].

- Phase 2 study
- Patients with three or more lines of therapy
- refractory to immunomodulatory drugs and proteasome inhibitors, and refractory or intolerant (or both) to an anti-CD38 monoclonal antibody
- 2·5 mg/kg or 3·4mg/kg belantamab mafodotin via intravenous infusion every 3 weeks on day 1 of each cycle until disease progression or unacceptable

DREAM-2 DATA

- 196 were included (97 in the 2·5 mg/kg cohort and 99 in the 3·4 mg/kg cohort).
- ORR:

  31%; in the 2·5 mg/kg cohort

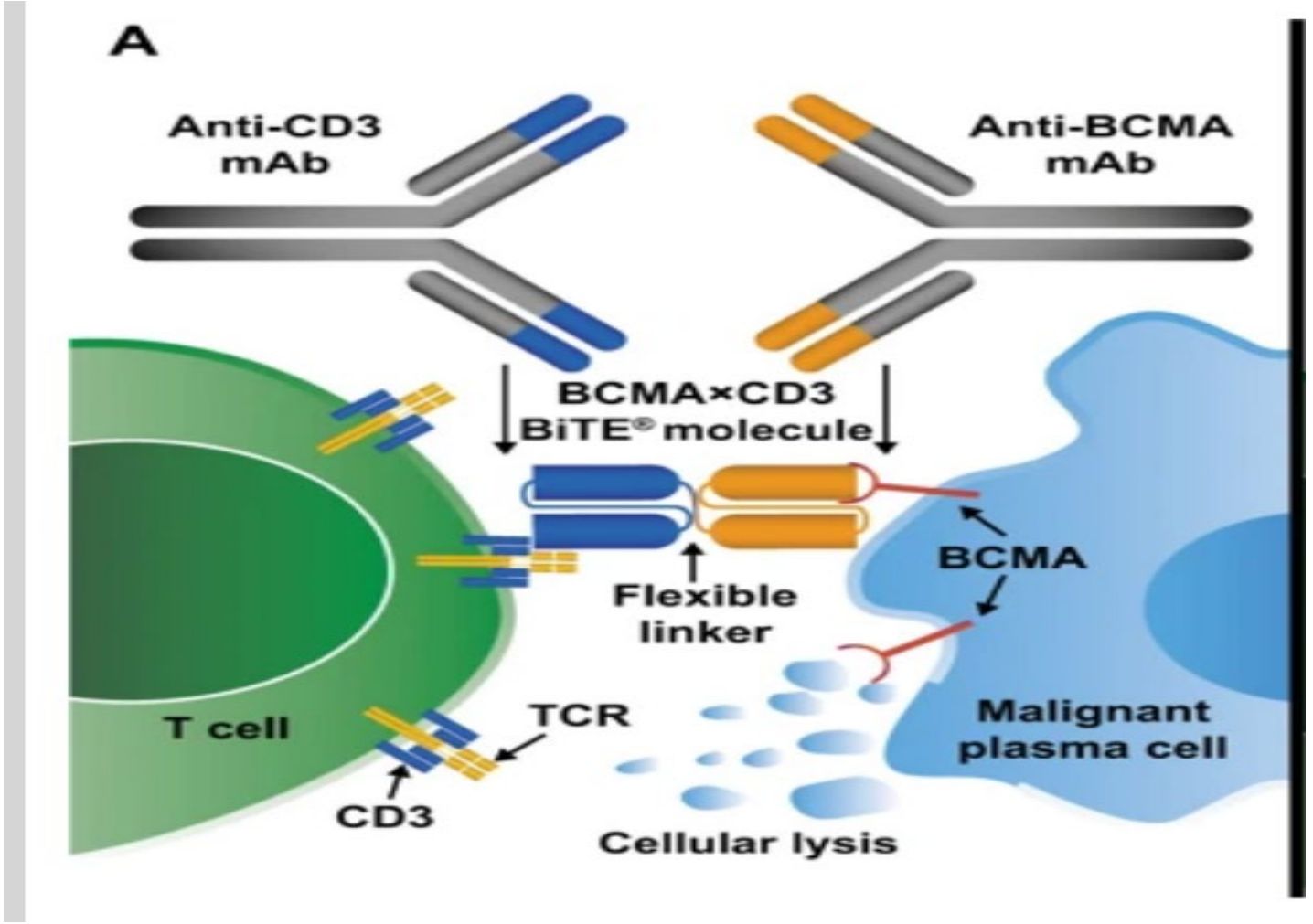
  34% in the 3·4 mg/kg cohort achieved an overall response.

Most common grade 3-4 adverse events :

- keratopathy 27% in the 2·5 mg/kg cohort and 21% in the 3·4 mg/kg cohort),
- thrombocytopenia 20% , 33%
- anaemia 20% and 25%
- Two deaths were potentially treatment related (one case of sepsis in the 2·5 mg/kg cohort and one case of haemophagocytic lymphohistiocytosis in the 3·4 mg/kg cohort.

- Single-agent belantamab mafodotin shows anti-myeloma activity with a manageable safety profile in patients with relapsed or refractory multiple myeloma.

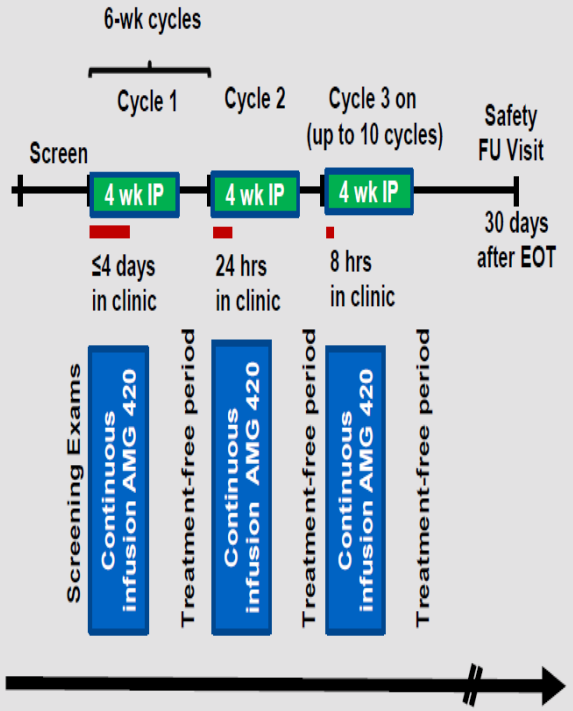
BITE



Shah et al Leukemia 2020

BCMA BiTE: AMG 420 Phase 1

AMG 420: STUDY SCHEMATIC/ OBJECTIVES



- First-in-human (FIH) phase I dose escalation study* of AMG 420 for up to 10 cycles, depending on response.
- Single-patient cohorts [0.2-1.6 µg/day (d)] were followed by cohorts of 3-6 patients (3.2-800 µg/d).
- Objectives of this phase 1 study of AMG 420 in patients with relapsed and/or refractory (R/R) MM included:
  - Assessing safety and tolerability
  - Determining the maximum tolerated dose (MTD)
  - Assessing anti-tumor activity

*NCT02514239. EOT, end of treatment; FU, follow-up; IP, investigational product.

Topp et al, ASH 2018, #1010

TABLE 3. Cytokine Release Syndrome and Serious AEs

Variable	No. (%)	No. of Patients With AEs at Each Grade				
		1	2	3	4	5
No. of patients	42					
Infections serious AEs						
All	14 (33)	—	4	8	—	2[b]
Pulmonary[a]	6 (14)	—	3	3	—	—
Central line/port infections	5 (12)	—	—	5	—	—
Adenovirus[b,c]	1 (2)	—	—	—	—	1
Aspergillosis/influenza[b]	1 (2)	—	—	—	—	1
Infection of unknown origin (fever)[d]	1 (2)	—	1	—	—	—
Treatment-related serious AEs						
Peripheral polyneuropathy	2 (5)	—	—	2	—	—
Edema	1 (2)	—	—	1	—	—
Cytokine release syndrome						
All treatment related, maximum grade	16 (38)	13	2	1	—	—

Abbreviation: AE, adverse event.

[a]Includes pneumonia (n = 4) and 1 each of bronchiopulmonary infection and infectious pneumopathy.

[b]One patient died as a result of aspergillosis/influenza and 1 as a result of fulminant hepatitis related to adenovirus infection; neither death was treatment related.

[c]Death in 400 μg/d cohort as a result of fulminant hepatitis related to adenovirus infection in the setting of immunosuppression not considered related to AMG 420. The trial sponsor held enrollment of new patients while responding to regulatory questions; subsequently, it was decided to halt enrollment after 10 patients had enrolled at 400 μg/d because an additional study of AMG 420 was being initiated.

[d]Accompanied by treatment-related SAE of grade 1 fever.

Topp; et al. ; *Journal of Clinical Oncology* 2020 epub Ahead of Print

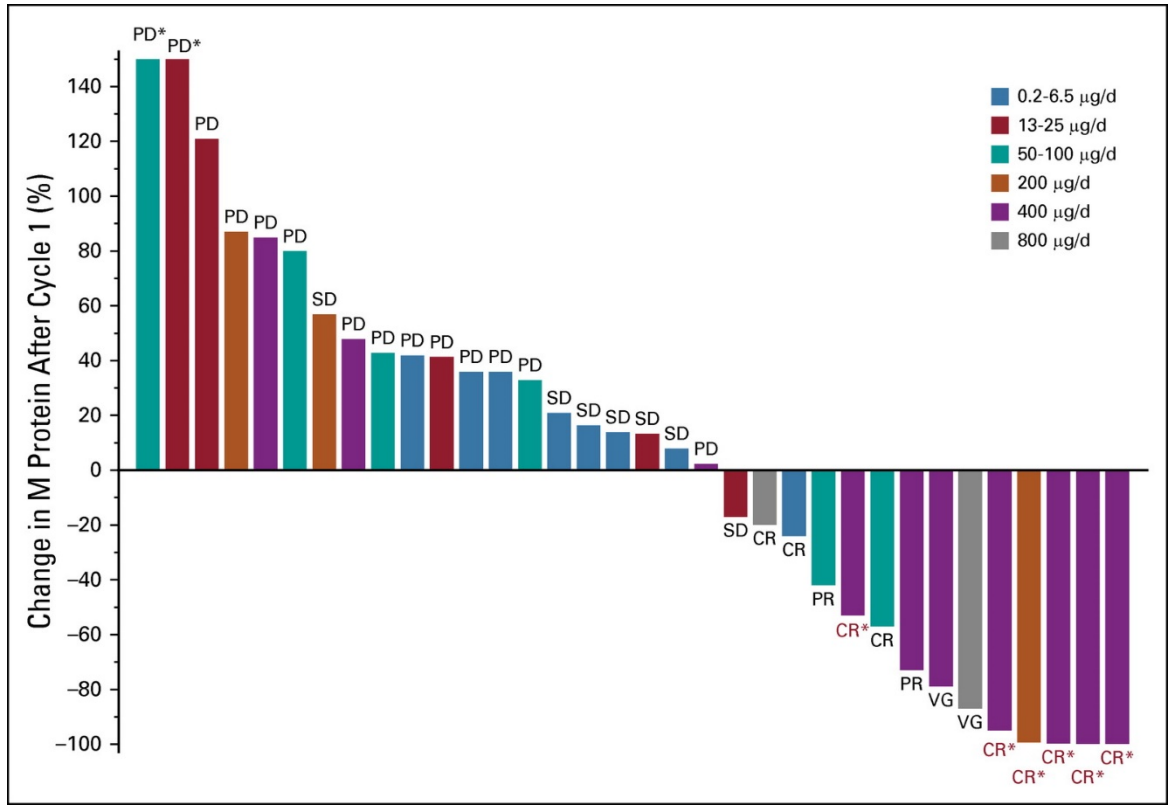


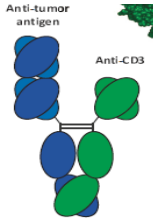
FIG A2. Cycle 1 change in M protein with best overall response. Best overall responses per investigator are shown next to percent change in M protein in the first cycle. Patients who lacked baseline M-protein values (n = 2), M-protein values at least 2 weeks postbaseline (n = 3), or postbaseline response assessments (n = 3 of whom 2 were treated ≤ 14 days before discontinuation because of an adverse event) were not included in this graph. CR, complete response; CR, minimal residual disease–negative CR; PD, progressive disease; PD*, progressive disease with increase in M protein > 150%; PR, partial response; SD, stable disease; VG, very good partial response.*

ORR : 31%

AT THE MTD OF 400 ug/d: ORR 70%

Published in: Max S. Topp; Johannes Duell; Gerhard Zugmaier; Michel Attal; Philippe Moreau; Christian Langer; Jan Krönke; Thierry Facon; Alexey V. Salnikov; Robin Lesley; Karl Beutner; James Kalabus; Erik Rasmussen; Kathrin Riemann; Alex C. Minella; Gerd Munzert; Hermann Einsele; *Journal of Clinical Oncology* Ahead of Print
DOI: 10.1200/JCO.19.02657

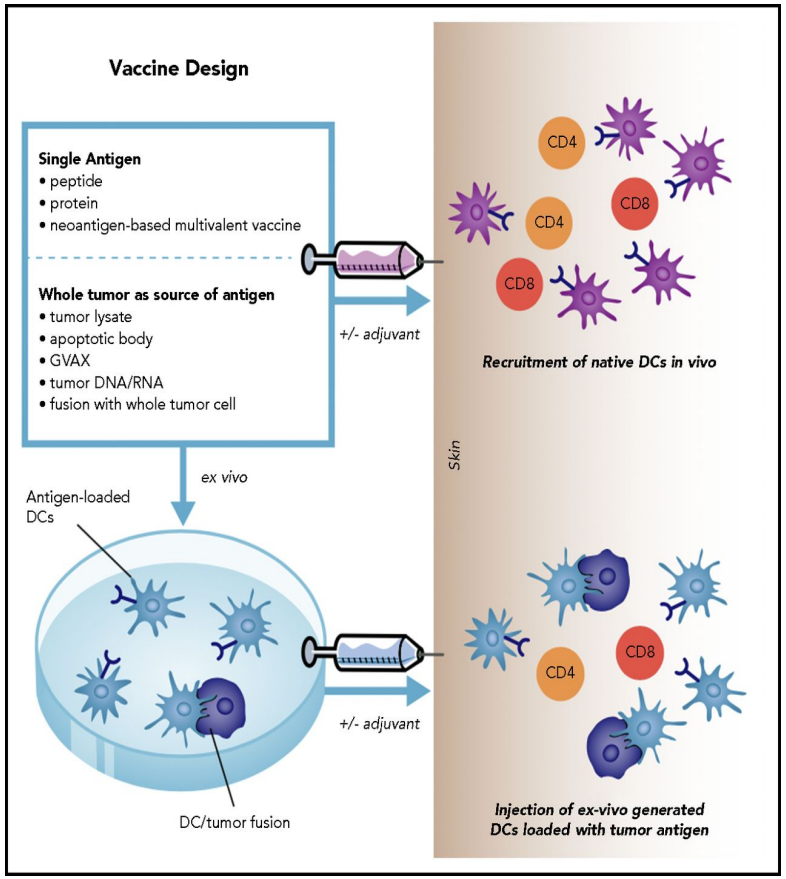
Newer Bispecific Antibodies for Myeloma



	IgG-like molecules	Non-IgG-like molecules
Fc domain	Yes	No
Half-life	Long	Short
	AMG701 (BCMA) **PF-06863135 (BCMA)** **JNJ-64007957 (BCMA)** **EM801 (BCMA)** **CC-93269/EM901 (BCMA)** **REGN5458 (BCMA)** **HPN217 (BCMA)** **TNB-383B (BCMA)** **AFM26 (BCMA)** **BFCR4350A (FcRH5)** **GBR1342 (CD38)** **AMG424 (CD38)** **JNJ-64407564 (GPRC5D)**	**AMG420 (BCMA)** **Blinatumumab (CD19)**

Designing an Effective Cancer Vaccine

- Expansion and activation of tumor specific lymphocytes to eliminate disease and prevent recurrence
- Selective targeting of malignant cells
- Capturing tumor heterogeneity
- Creation of memory for long term immune surveillance
- Reversal of the immune suppression of the tumor microenvironment Combinatorial strategies



David Avigan, and Jacalyn Rosenblatt Blood 2018;131:2640-2650

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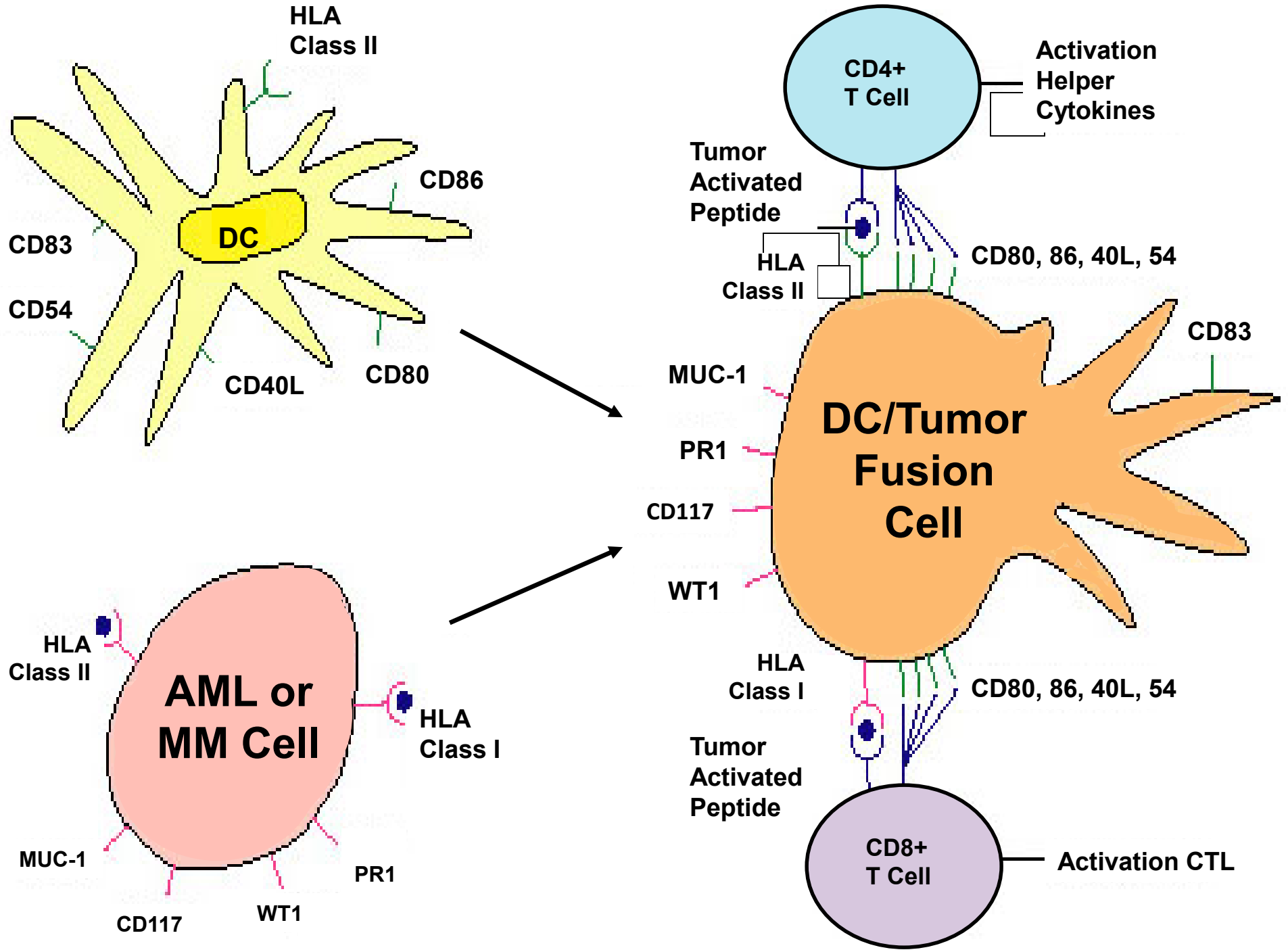
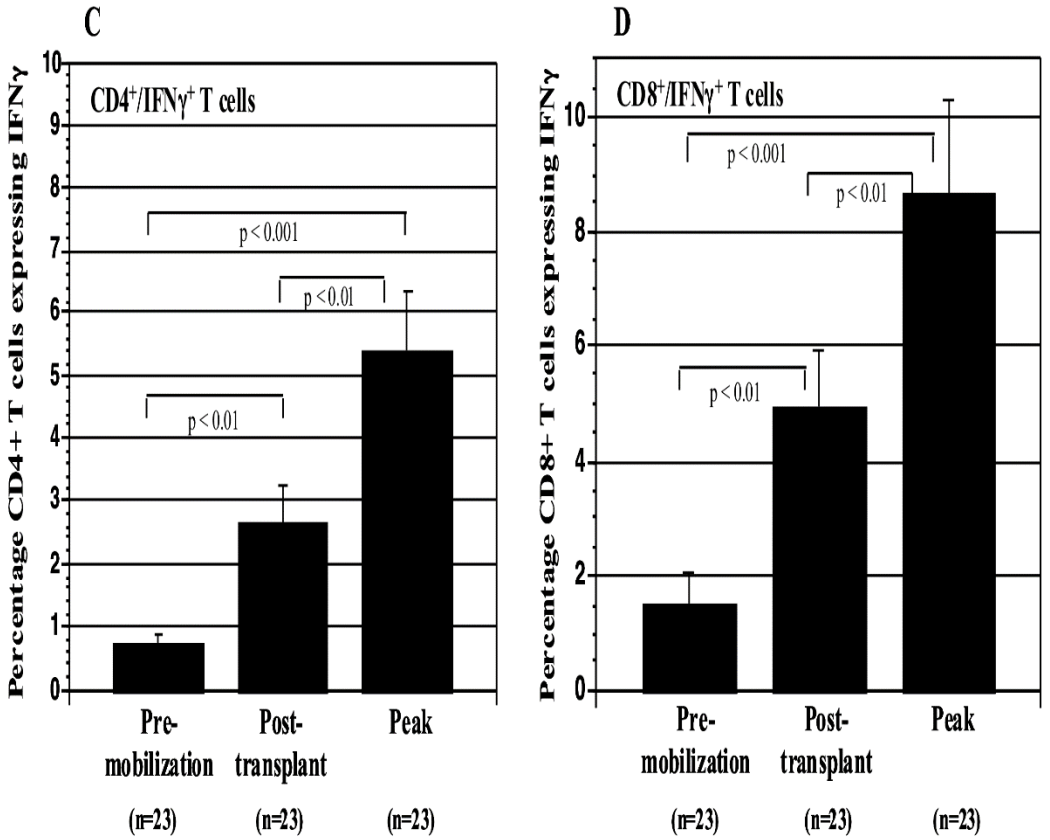
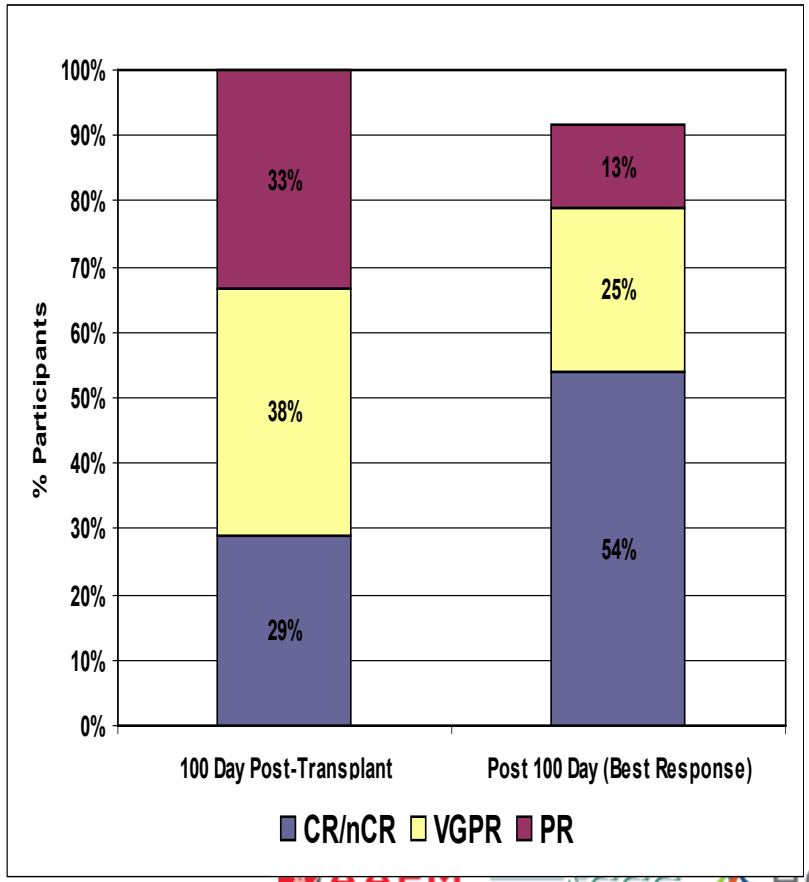
ADVANCES IN Cancer IMMUNOTHERAPY



Vaccination Induced Expansion of MM reactive T cells and Targeting of MRD





Rosenblatt et al CCR 2013

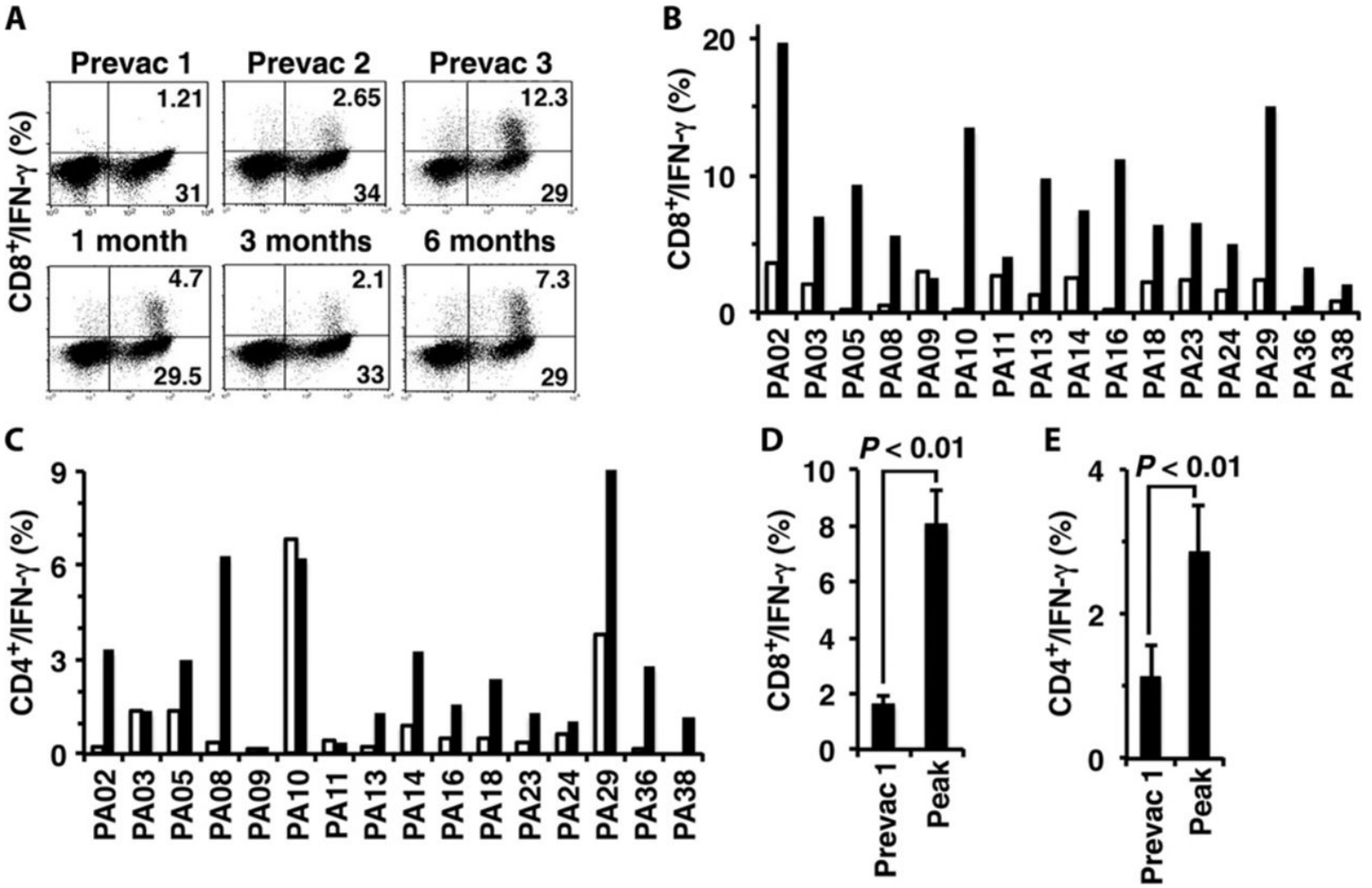
BMT CTN Protocol 1401

Phase II Multicenter Trial of Single Autologous Hematopoietic Cell Transplant Followed by Lenalidomide Maintenance for Multiple Myeloma with or without Vaccination with Dendritic Cell (DC)/Myeloma Fusions

(MY T VAX)

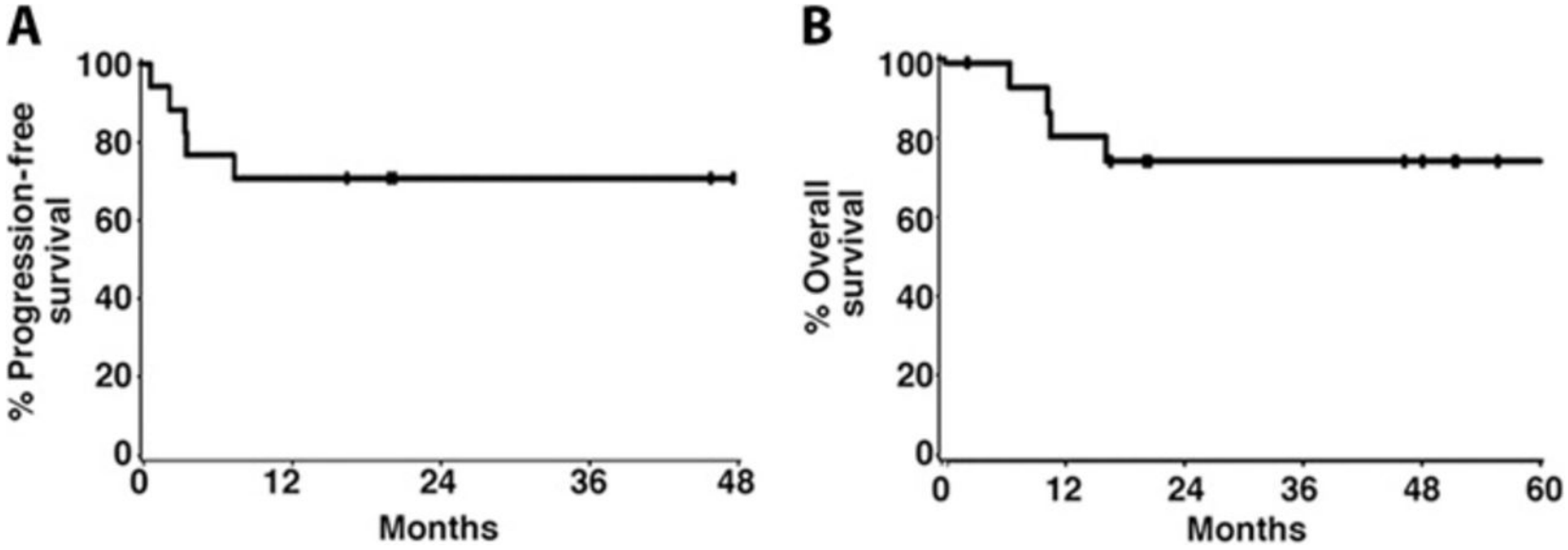
BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Expansion of leukemia-specific CD4+ and CD8+ T cells after vaccination



Rosenblatt et al Sci Transl Med 2016;8:368ra171

Clinical Outcome



- 12 of 17 patients who received at least one dose of vaccine remain alive and in remission (**71%**; 90% CI, 52 to 89%) at 16.7 to 66.5 months from initiating vaccination
- **Median follow-up: 57 months**

Sci Transl Med 2016;8:368ra171

Ongoing Clinical Trials in AML

- **Randomized phase II study evaluating DC/AML fusion vaccine versus control following remission**
- Patients 55 years or older who achieve remission are randomized to either
  - DC/AML fusion vaccine alone
  - observation
- Primary clinical endpoint: 2-year progression free survival
- Secondary clinical endpoint: overall survival

- **Clinical Trial of Vaccination with DC/AML fusions following allogeneic transplantation**

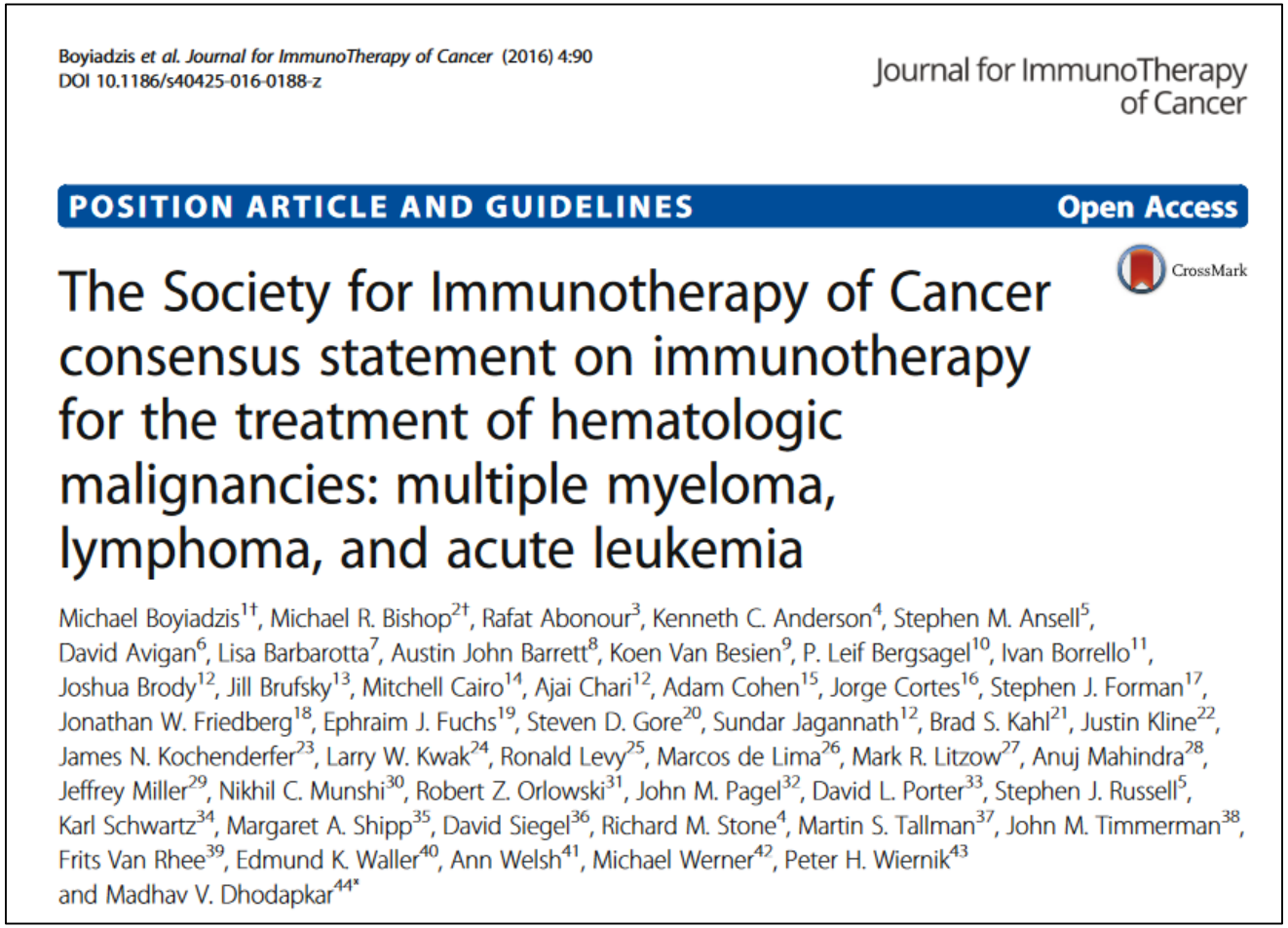
5R01CA212649

SPORE IN LEUKEMIA, 1 P50 CA 206963-01; PROJECT 4

Conclusions

- Many immunotherapy options for hematological malignancies
- Checkpoint inhibitors for Hodgkin lymphoma and PMBCL – high response rate, excellent tolerance, durable responses if CR
- Blinatumomab and inotuzumab for ALL – effective salvage, deeper remissions
- Polatuzumab vedotin for DLBCL – effective salvage, potential to become frontline
- CAR T therapy – ever-increasing indications; patient selection and toxicity management
- Critical to consider conbination therapy and biomarkers of response/resistance

Additional Resources



Boyiadzis *et al. Journal for ImmunoTherapy of Cancer* (2016) 4:90
DOI 10.1186/s40425-016-0188-z

Journal for ImmunoTherapy of Cancer

POSITION ARTICLE AND GUIDELINES Open Access

The Society for Immunotherapy of Cancer consensus statement on immunotherapy for the treatment of hematologic malignancies: multiple myeloma, lymphoma, and acute leukemia

Michael Boyiadzis[1†], Michael R. Bishop[2†], Rafat Abonour[3], Kenneth C. Anderson[4], Stephen M. Ansell[5], David Avigan[6], Lisa Barbarotta[7], Austin John Barrett[8], Koen Van Besien[9], P. Leif Bergsagel[10], Ivan Borrello[11], Joshua Brody[12], Jill Brufsky[13], Mitchell Cairo[14], Ajai Chari[12], Adam Cohen[15], Jorge Cortes[16], Stephen J. Forman[17], Jonathan W. Friedberg[18], Ephraim J. Fuchs[19], Steven D. Gore[20], Sundar Jagannath[12], Brad S. Kahl[21], Justin Kline[22], James N. Kochenderfer[23], Larry W. Kwak[24], Ronald Levy[25], Marcos de Lima[26], Mark R. Litzow[27], Anuj Mahindra[28], Jeffrey Miller[29], Nikhil C. Munshi[30], Robert Z. Orlowski[31], John M. Pagel[32], David L. Porter[33], Stephen J. Russell[5], Karl Schwartz[34], Margaret A. Shipp[35], David Siegel[36], Richard M. Stone[4], Martin S. Tallman[37], John M. Timmerman[38], Frits Van Rhee[39], Edmund K. Waller[40], Ann Welsh[41], Michael Werner[42], Peter H. Wiernik[43] and Madhav V. Dhodapkar[44*]