CAR T CELL THERAPY
(CHIMERIC ANTIGEN RECEPTOR T CELL THERAPY)

ESMO PRECEPTORSHIP PROGRAM IMMUNO-ONCOLOGY 20-21 NOV. 2019

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2019-11-21

DISCLOSURES

I have no disclosures to declare.

CONTENTS

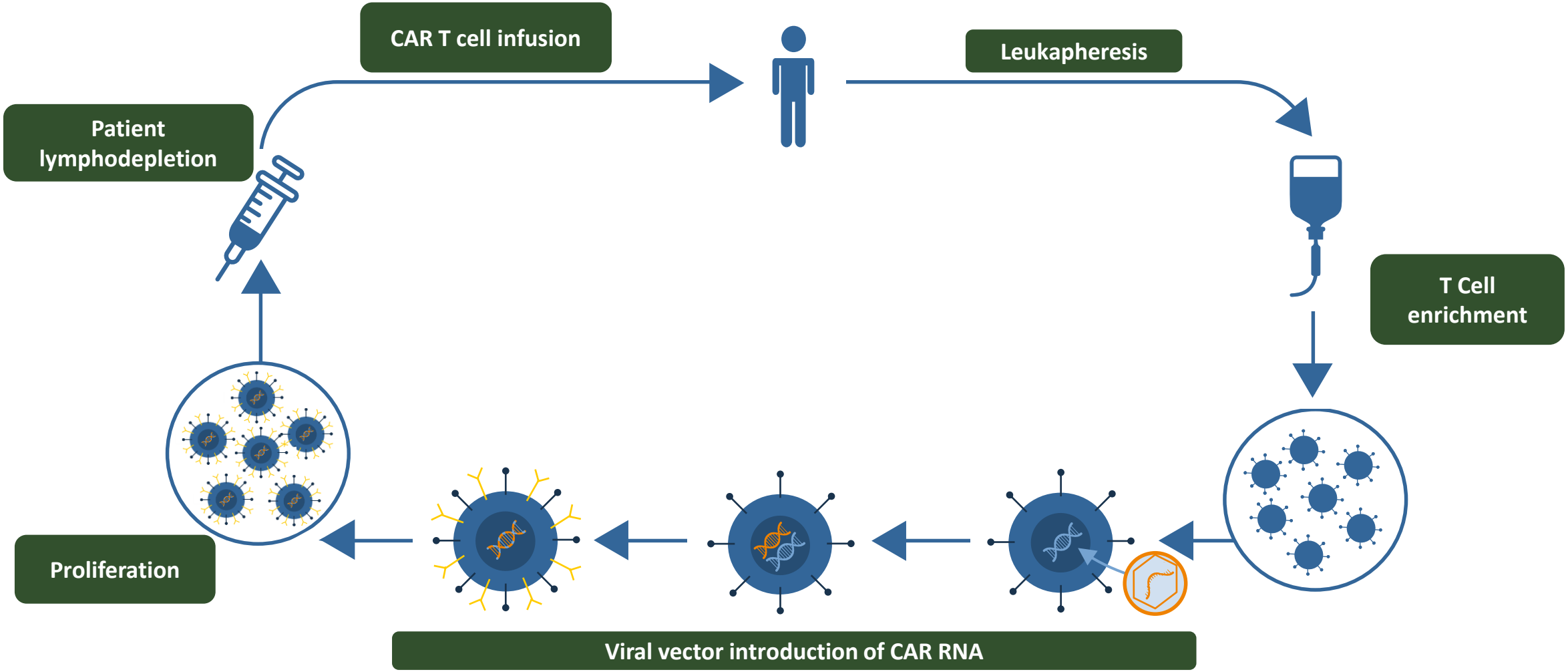
- What is CAR T cell therapy and how does it works ?
- CAR T cell trials and approved therapies in hematological malignancies.
- CAR T cell therapies targeting BCMA in Multiple Myeloma.
- Future directions for CAR T Cell Therapy.

CAR T Cell Therapy

- **What is CAR T cell therapy and how does it works ?**
- CAR T cell trials and approved therapies in hematological malignancies.
- CAR T cell therapies targeting BCMA in Multiple Myeloma.
- Future Directions for CAR T Cell Therapy.

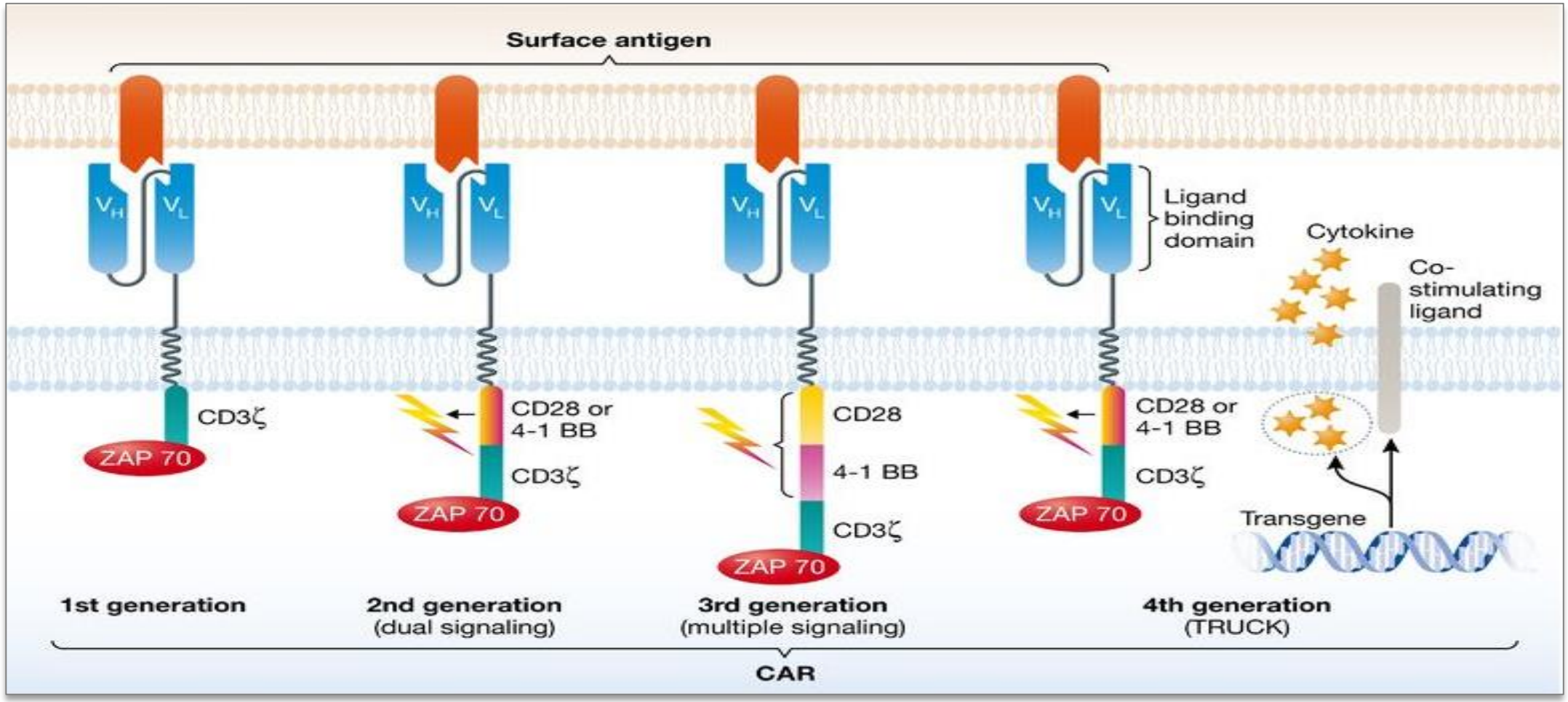
Chimeric Antigen Receptor (CAR) T Cell Therapy

- Adoptive cell therapy that utilizes autologous T cells engineered to express CARs.



CARs

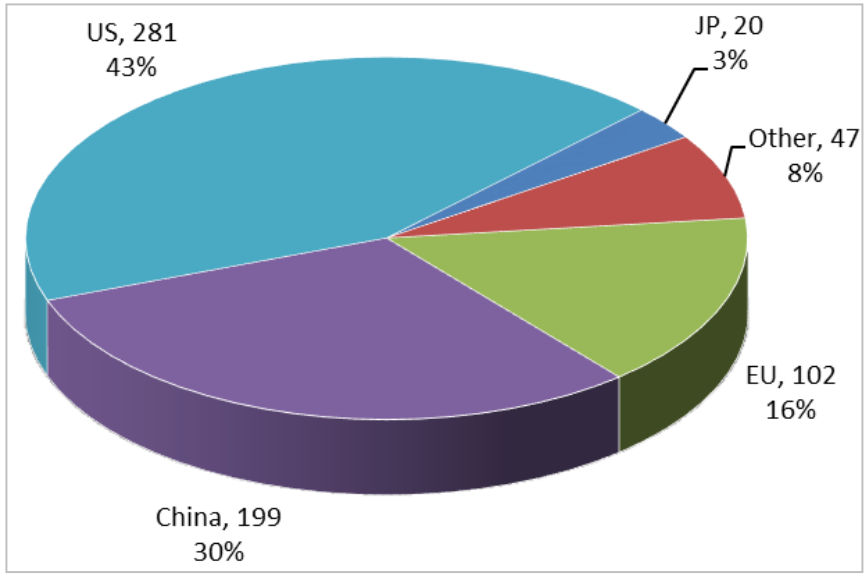
- CARs consist of extracellular antigen binding domain, a transmembrane domain, and an intracellular activation domain.



Hartmann et al. 2017 EMBO Mol Med: e201607485

Current Landscape of CAR T Cell Therapy

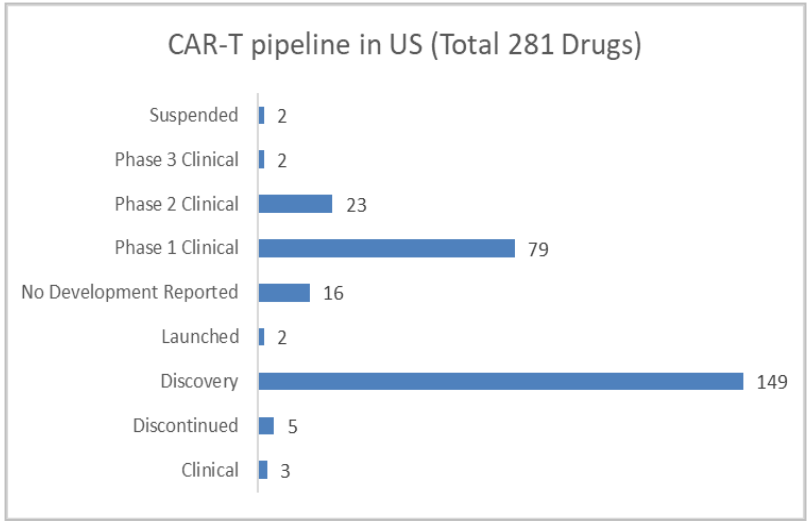
CAR-T pipeline in US, China, EU and JP

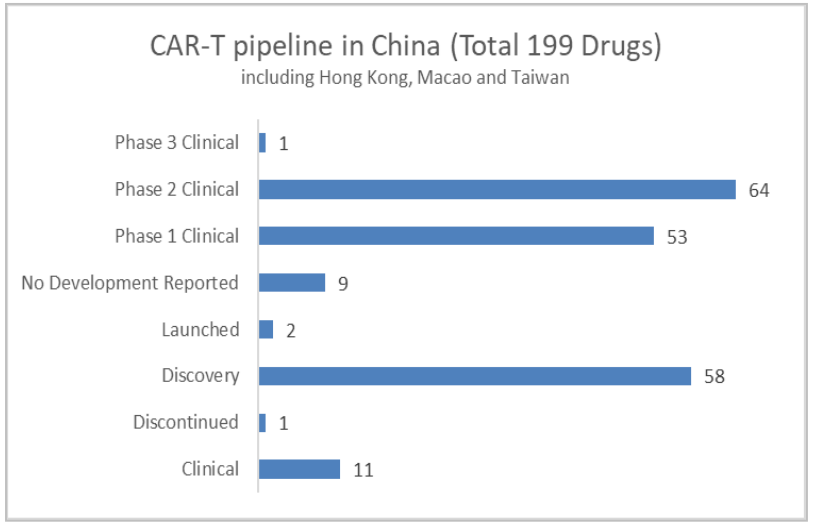


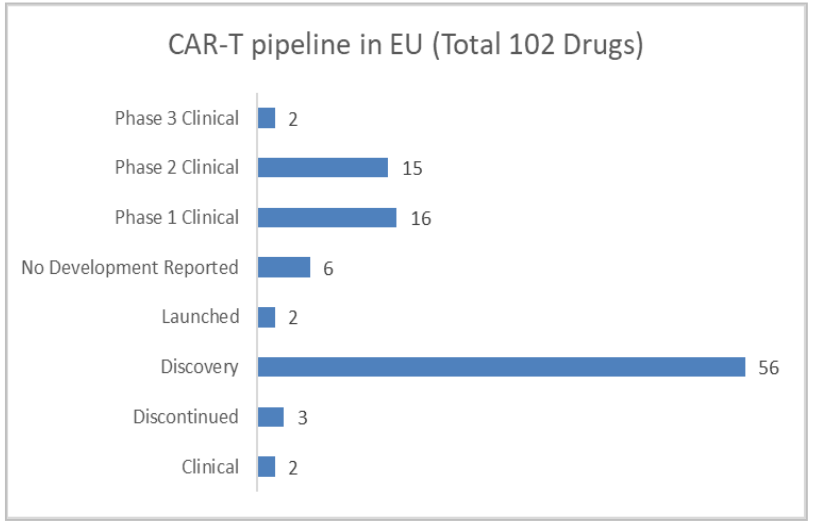
RESULTS

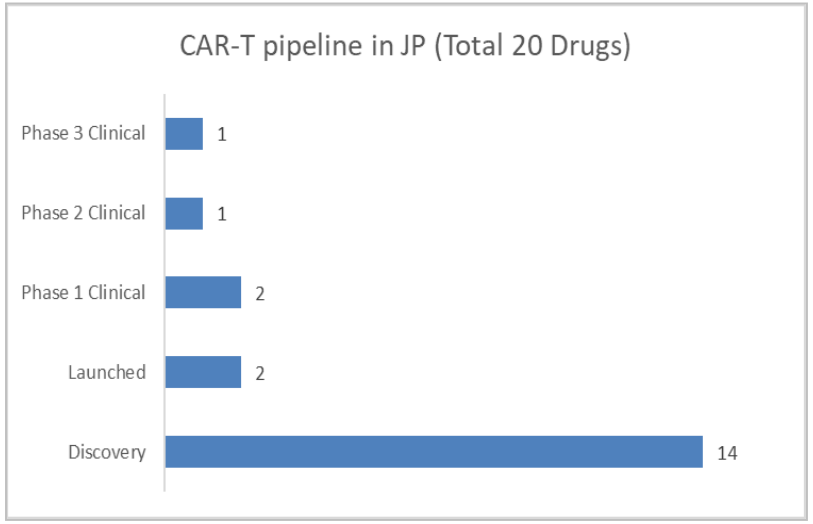
Source: Cortellis

Created: 08-Oct-2019



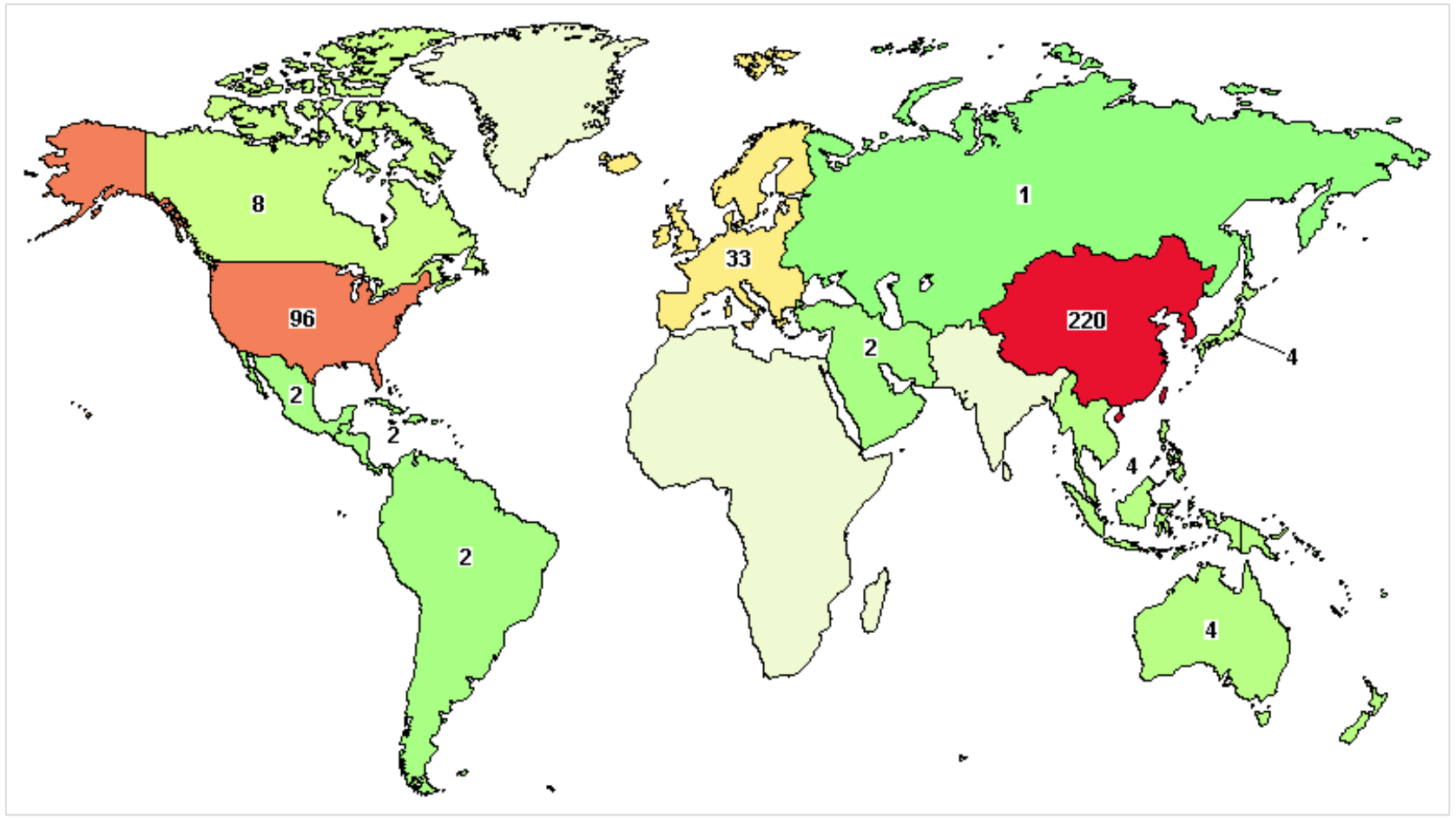






Current Landscape of CAR T Cell Therapy

365 Studies found for : **CART** (2019.11.9)



Region Name	Number of Studies
World	365
Central America	2
East Asia	220
Japan	4
Europe	33
Middle East	2
North America	102
Canada	8
Mexico	2
United States	96
North Asia	1
Pacifica	4
South America	2
Southeast Asia	4

Source: https://ClinicalTrials.gov

Current Landscape of CAR T Cell Therapy

- 365 clinical study focused on CAR T cell therapy registered on ClinicalTrials.gov
  - ~96 in the US; ~220 in China[a]; 33 in Europe[a].
  - China is a dominant player in the field.
- Majority of CAR T cell trials are for hematologic malignancies
  - ~69% of registered CAR T clinical studies.
  - 2 FDA-approved CAR T cell therapies.
- CAR T cell approaches for solid tumors, autoimmune disease
  - e.g. EGFRvIII for glioblastoma; HER2 for breast cancer; mesothelin for ovarian cancer; NKG2DL for gastric caner; Anti-GPC3 HCC.
- Other modified CAR T cells
  - e.g. PD-1 expression/knock out; Dural/Bi-specific antigens; Gene edited Universal CAR T cells.

[a]www.ClinicalTrials.gov

Advantages and Drawbacks of CAR T Cell Therapy

ADVANTAGES

- Target specificity
- HLA independent
- Lower potential for graft versus host disease (GVHD)
- “Living drug”
- Immunotherapy/gene therapy

Advantages and Drawbacks of CAR T Cell Therapy

DRAWBACKS

- Adverse reactions :

  Toxicity— “4S”:

  - CRS
  - ICANS/ CRES
  - HLH/MAS
  - TLS

  on-target/off-tumor recognition

- Relapse (hard to predict)
- Individualized manufacturing process, Complicated chain identity, logistics issue
- Disease progression during manufacture; Manufacturing failure; Contamination with tumor cells
- Cost (US$373,000 to US$475,000)

CRS=Cytokine release syndrome; ICANS=Immune effector cell-associated neurotoxicity syndrome ; CRES=CAR T cell-related encephalopathy syndrome; HLH=Haemophagocytic lymphohistiocytosis; MAS=macrophage activation syndrome; TLS=Tumor Lysis Syndrome; MDT=Multi-Disciplinary Treatment. Grading systems: Lee et al, Penn Grading Scale, MSKCC Grading System, CARTOX Working Group, ASBMT Consensus

CAR T Cell Therapy

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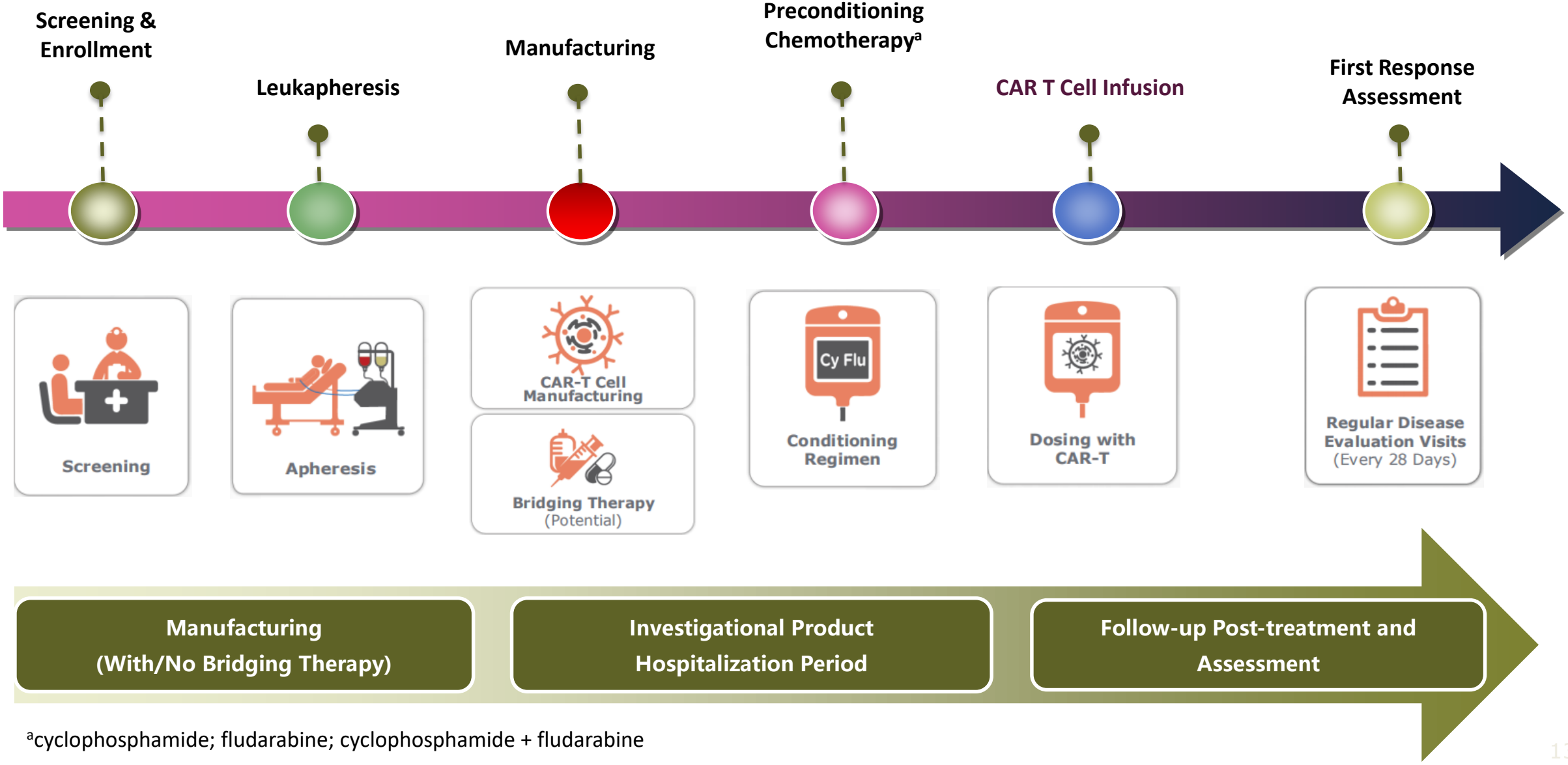
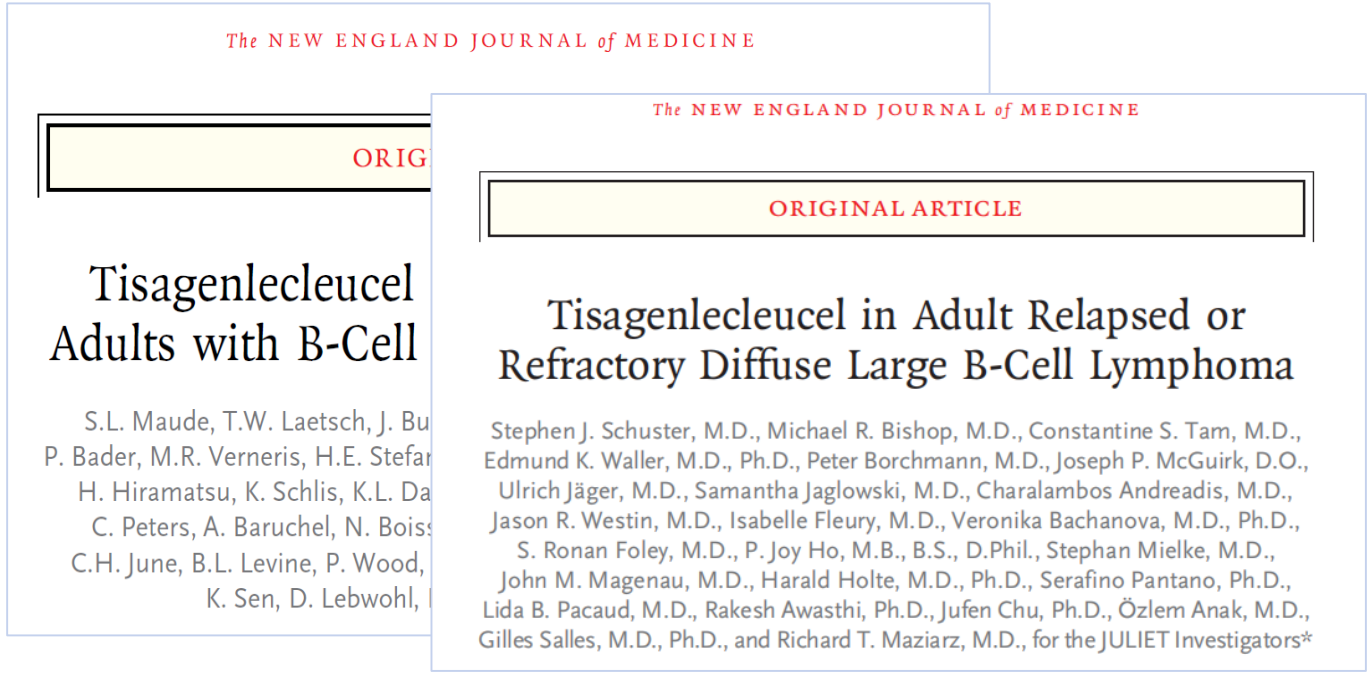
- **CAR T cell trials and approved therapies in hematological malignancies.**
- CAR T cell therapies targeting BCMA in Multiple Myeloma.
- Future Directions for CAR T Cell Therapy.



[a]cyclophosphamide; fludarabine; cyclophosphamide + fludarabine


The NEW ENGLAND JOURNAL of MEDICINE

ORIG

Tisagenlecleucel
Adults with B-Cell

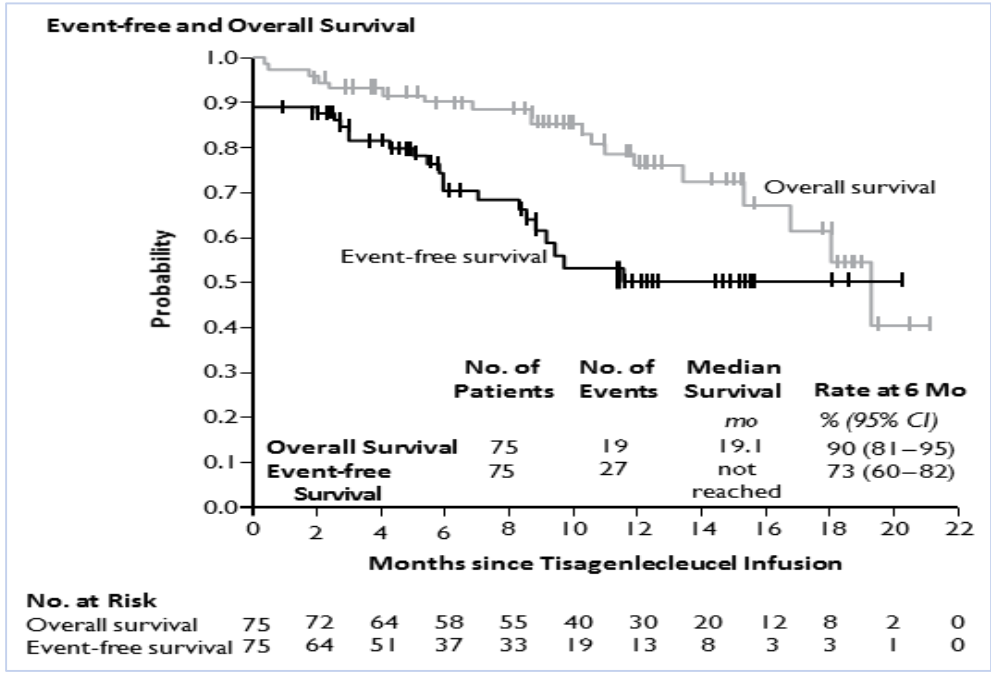
S.L. Maude, T.W. Laetsch, J. Bu
P. Bader, M.R. Verneris, H.E. Stefar
H. Hiramatsu, K. Schlis, K.L. Da
C. Peters, A. Baruchel, N. Boiss
C.H. June, B.L. Levine, P. Wood,
K. Sen, D. Lebwohl,

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Tisagenlecleucel in Adult Relapsed or Refractory Diffuse Large B-Cell Lymphoma

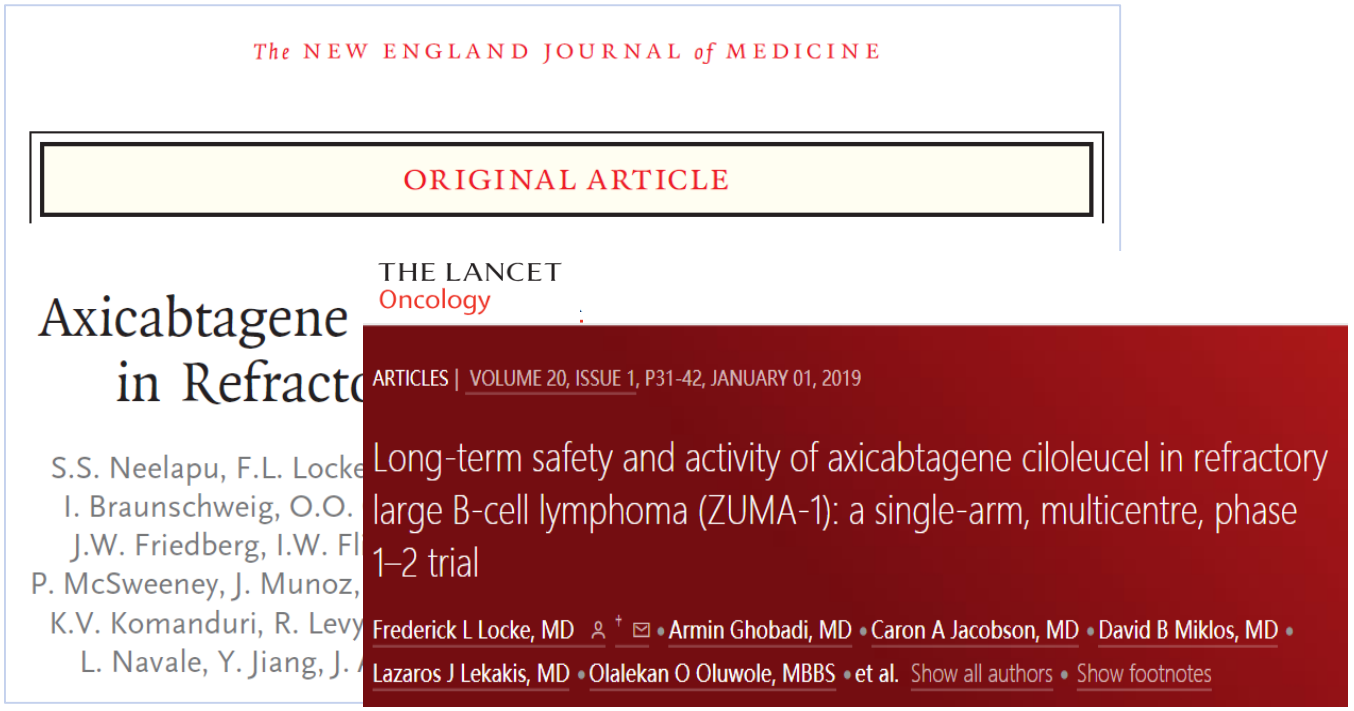
Stephen J. Schuster, M.D., Michael R. Bishop, M.D., Constantine S. Tam, M.D., Edmund K. Waller, M.D., Ph.D., Peter Borchmann, M.D., Joseph P. McGuirk, D.O., Ulrich Jäger, M.D., Samantha Jaglowski, M.D., Charalambos Andreadis, M.D., Jason R. Westin, M.D., Isabelle Fleury, M.D., Veronika Bachanova, M.D., Ph.D., S. Ronan Foley, M.D., P. Joy Ho, M.B., B.S., D.Phil., Stephan Mielke, M.D., John M. Magenau, M.D., Harald Holte, M.D., Ph.D., Serafino Pantano, Ph.D., Lida B. Pacaud, M.D., Rakesh Awasthi, Ph.D., Jufen Chu, Ph.D., Özlem Anak, M.D., Gilles Salles, M.D., Ph.D., and Richard T. Maziarz, M.D., for the JULIET Investigators*

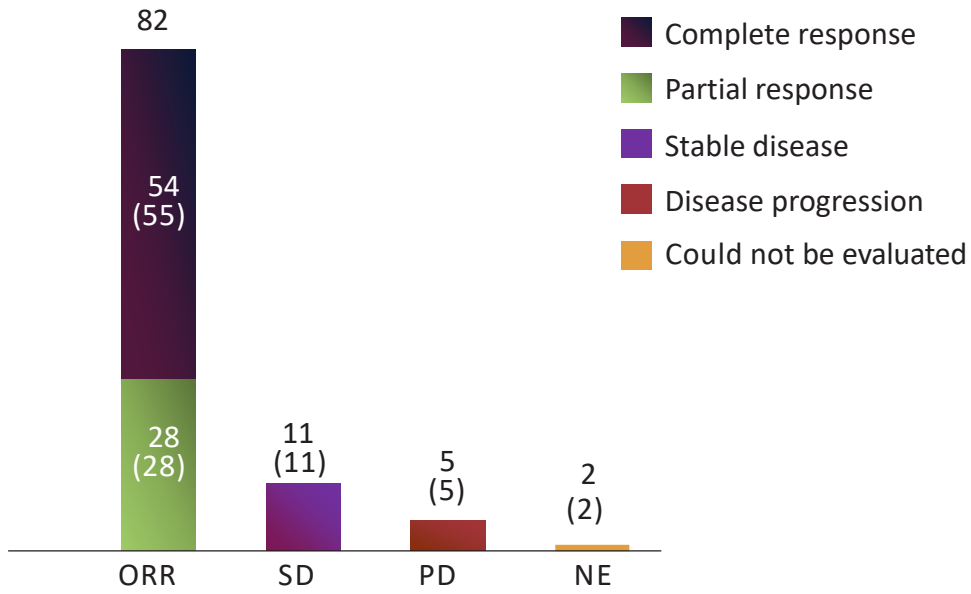


- First FDA-approved CAR T cell therapy - KYMRIAH®
  - CD19 CAR T cells (costimulatory molecule 4-1BB, murine single chain variable fragment (scFv))
  - Approved for acute lymphoblastic leukemia (ALL)[a] and diffuse large B-cell lymphoma (DLBCL)[b]
- ORR = 81% (ALL) and 52% (DLBCL)[C]
- Median EFS/RFS = not reached (ALL)a and 65% (RFS for DLBCL at 12 months)[b]
- Median OS = 19.1 months (ALL)a and 22.2 months (DLBCL)[b]

[a]Maude et al. 2018 *NEJM;* 378(5): 439-48
[b]Schuster et al. 2017 *NEJM*; 377(26): 2545-54
[C]Schuster et al. 2019 01; 380(1):45-56.

EFS=event-free survival; ORR=overall response rate; OS=overall survival
PFS=progression-free survival





- 2nd FDA-approved CD19 CAR T cell therapy - YESCARTA®
  - Approved for R/R DLBCL, DLBCL arising from FL, PMBCL, high-grade B-cell lymphoma
- ORR = 82% (CR 58%, median follow-up 15·4 months) [a], 83% (CR 58%, 27.1 months) [b]
- Median PFS = 5.8 months[a], 5.9 months[b]
- Median OS = not reached [a,b]

[a]Neelapu et al. 2017 *NEJM;* 377(26): 2531-44
[b]Frederick L Locke et al. Lancet Oncol. 2019 Jan; 20(1): 31–42.

FL=follicular lymphoma; R/R=relapsed/refractory;
PMBCL=primary mediastinal large B-cell lymphoma

Safety Summary of FDA-Approved CAR T Cell Therapies

	Kymriah® (ALL)[a]		Kymriah® (DLBCL)[a]		Yescarta® (DLBCL)[b]	
	All Grade	Grade ≥3	All Grade	Grade ≥3	All Grade	Grade ≥3
CRS	79%	49%	74%	23%	94%	13%
Neurologic toxicities	72%	21%	58%	18%	87%	31%
Prolonged cytopenia						
Anemia	-	0%	-	0%	-	3%[d]
Neutropenia	-	40%[c]	-	25%[c]	-	15%[d]
Thrombocytopenia	-	27%[c]	-	40%[c]	-	18%[d]

[a]Kymriah USPI; [b]Yescarta USPI; [c]Not resolved by Day 28; [d]Not resolved by Day 30

Other Hematologic CAR T Cell Targets

- CD20 for ALL, DLBCL, mantle cell lymphoma, FL, Non-Hodgkin lymphoma (NHL)
- CD22 for ALL, NHL, chronic lymphocytic leukemia, FL
- CD30 for Hodgkin lymphoma, anaplastic large cell lymphoma
- CD123 for acute myeloid leukemia
- CD138, CD38 and **B-cell maturation antigen (BCMA) for multiple myeloma**

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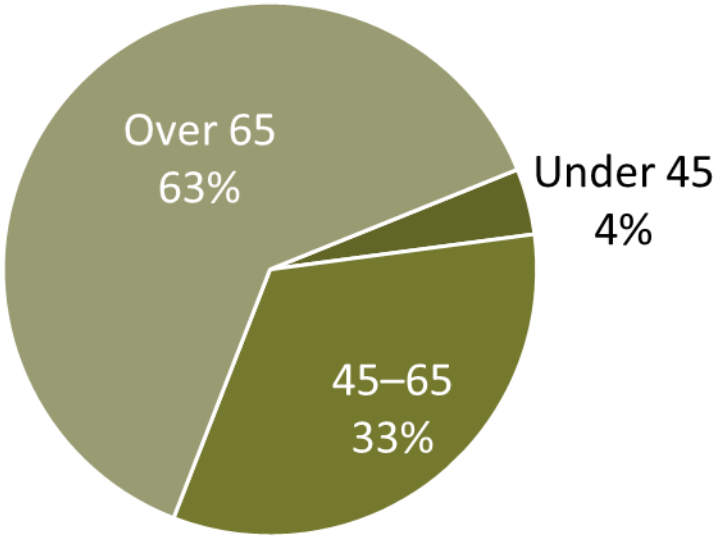
Pathophysiology and Epidemiology of Multiple Myeloma

Multiple myeloma (MM) is a clonal plasma cell malignant neoplasm

Age of Diagnosis[1]



230,000 5-year worldwide prevalence[2]

- US: 6.1 per 100,000[3]
- Europe: 4.5–6.0 per 100,000[4]
- China: 0.6 per 100,000[5]

1% of worldwide new cancer cases[2]

2.1% of all US cancer deaths[6]

50.7%
5-year survival rate[3]

1. Multiple Myeloma Research Foundation. Available: https://themmrf.org/multiple-myeloma/what-is-multiple-myeloma. Accessed October 3, 2018.
2. Ruzafa J, et al. *Pharmacoepidemiol Drug Saf*. 2016;25(8):871–9.
3. Costa 2017 Blood Adv; 1(4): 282-7;
4. Palumbo 2011 Blood; 118: 4519-39;
5. Ferlay 2012 GLOBOCAN 2012;
6. Cancer Stat Facts: Myeloma. National Cancer Institute: Surveillance, Epidemiology, and End Results Program. Available: https://seer.cancer.gov/statfacts/html/mulmy.html. Accessed October 3, 2018.

ESMO Guidelines for MM

Indolent MM	Immediate treatment not recommended
<70 years	Induction followed by high-dose therapy with ASCT as standard therapy
Elderly	Bortezomib/melphalan/prednisone (VMP) or lenalidomide + low dose dexamethasone (Rd)
R/R MM	Proteasome inhibitor- or lenalidomide-containing regimens
Advanced Cases	Pomalidomide + low-dose dexamethasone and daratumumab

Moreau et al. 2017 *Ann Oncol; 28(suppl 4)*: iv52-61

MM Treatment Challenges in Asia

- In Asia, ESMO and NCCN guidelines are used to guide treatment
- However, new drugs for patients with MM are not always available

  e.g., anti-CD38 antibody just on market in China on 2019.9.26, need about $45,000 for 2 cycles, Carfilzomib and Xgeva(denosumab) still not marketed in China
- High medical expenditures are often not covered by health insurance and patients cannot afford to cover costs
- Differences in dosage and treatment effects in Asian and Western populations; treatments require further optimization for Asian patients
- New treatments developed independently in China, such as CAR T cell therapy, offer a more affordable and more accessible treatment option for patients in Asia

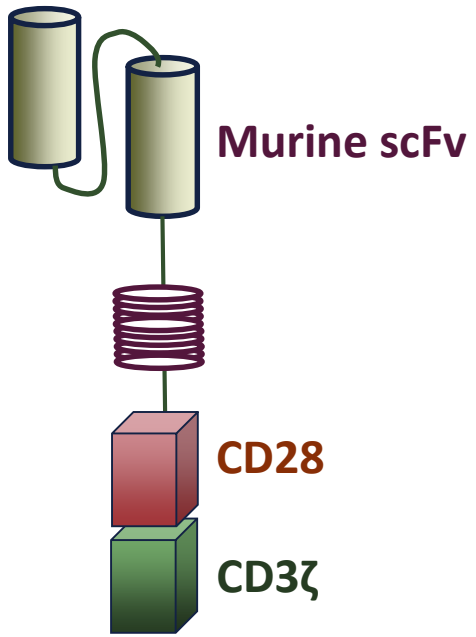
CAR T Cell Approaches for MM

- Many targets available for MM:
  - Integrin ß7, CD70, CD38, CD138, NKG2D, CD19, ƙ light chain, SLAMF7, Lewis Y and **BCMA**
- BCMA is an attractive target for MM
  - Member of the tumor necrosis factor family
  - BCMA expressed exclusively in B-cell lineages
  - Involved in B-cell maturation and differentiation
  - Widely expressed in malignant plasma cells
- **BCMA-targeted** CAR T cells are furthest in development
  1. BCMA CAR T – *National Cancer Institute (NCI)*
  2. bb2121 – *bluebird bio*
  3. LCAR-B38M – *Nanjing Legend Biotech*

NCI BCMA CAR T

- Phase 1 study of 24 patients with R/R MM
- Results from 16 patients treated at highest dose

- ORR = 81%
- 94% of patients had decrease in myeloma marker
- CRS = 94%
- Neurotoxicity = confusion and delirium

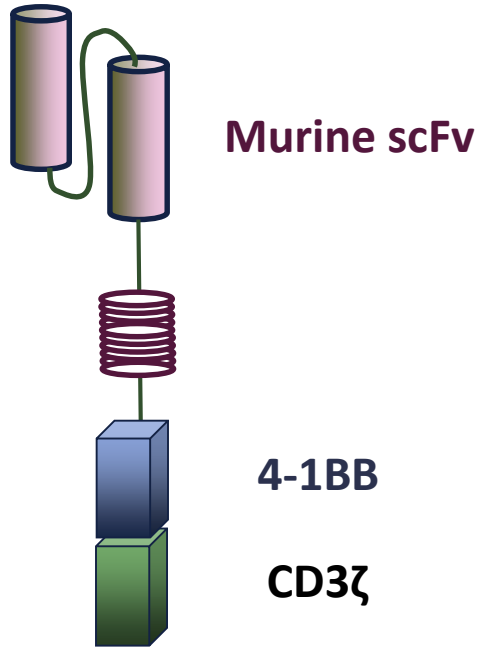


Brudno et al. 2018 *JCO*; 36(22): 2267-80

scFV=single chain variable fragment

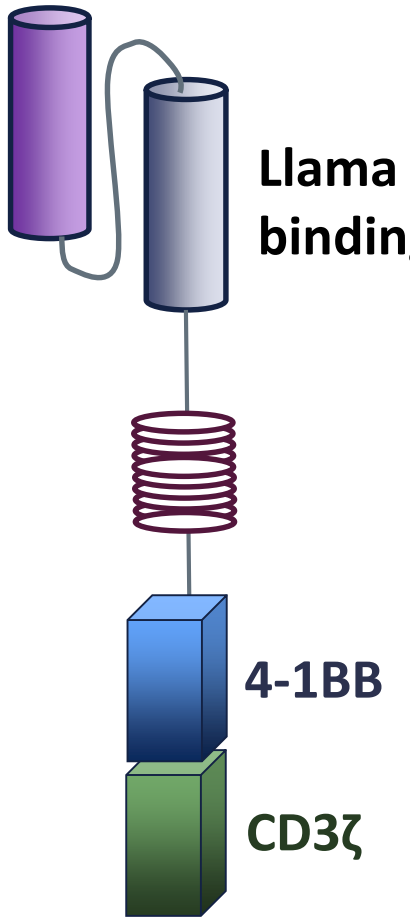
bb-2121 BCMA CAR T

- Phase 1 study in 43 patients with R/R MM
- ORR = 95.5% for 22 patients treated with >150x10^6 CAR+ T cells
- Median PFS = 11.8 months for 18 patients treated with 150-800x10^6 CAR+ T cells
- CRS = 63%
- Neurotoxicity = 33%



Raje et al. 2018 *JCO*; 36(suppl): abstr 8007

LCAR-B38M BCMA CAR T



Other CAR T players

LCAR-B38M VHH Dual-Epitope Binding CAR

LCAR-B38M Study Sites in China---LEGEND-2 (NCT03090659):

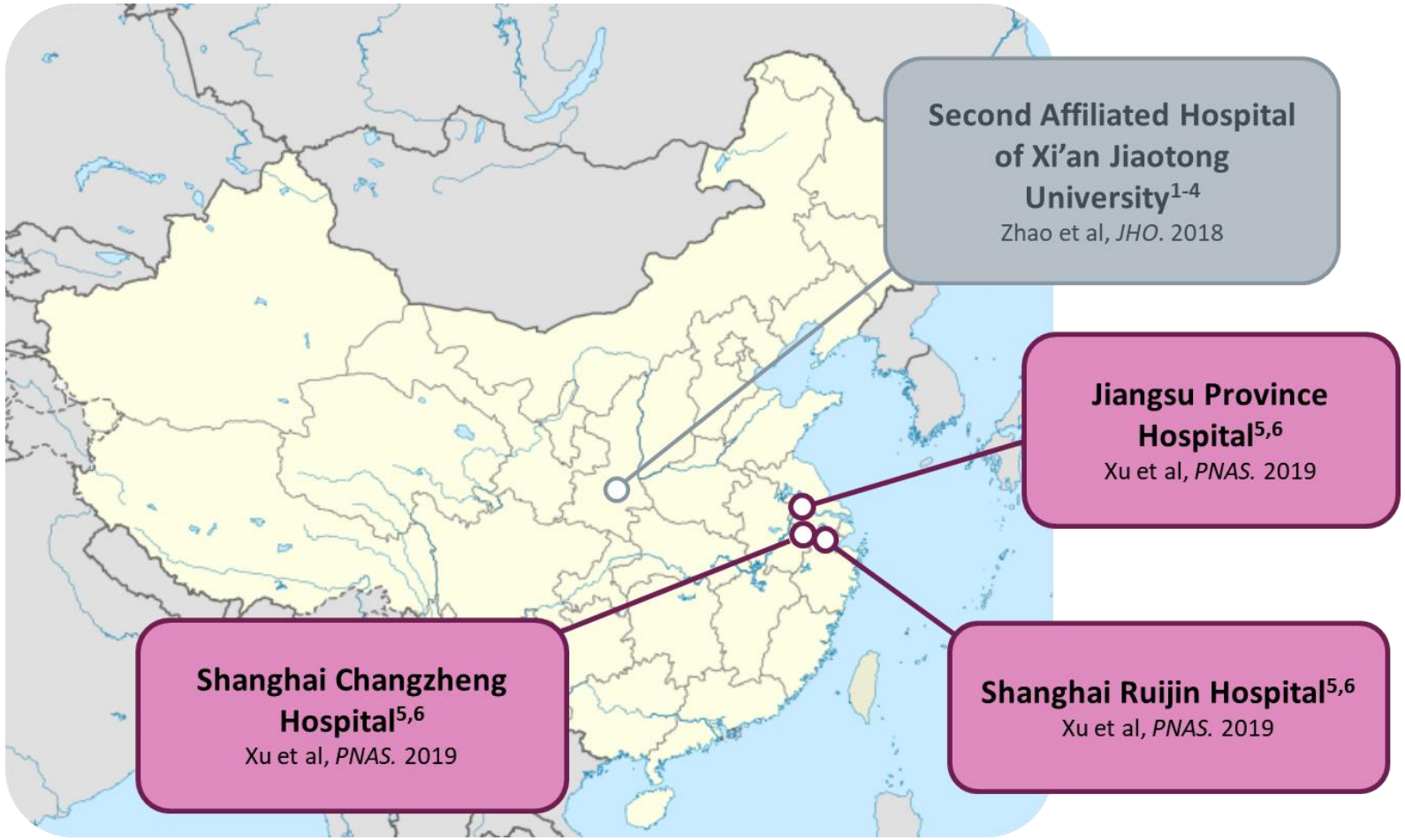
Phase 1 First-in-Human Study of LCAR-B38M in China

Investigator initiated studies:
•conducted 4 sites in China

Total 74 patients
•N= 57 Zhao WH, et al. JHO 2018
•N= 17 Xu J, et al. *PNAS.* 2019

Preconditioning
•Cy only (Xi'an, Jiangsu)
•Cy + flu (Changzeng, Ruijin)

LCAR-B38M infusion
•Split-dose (Xi'an, Changzeng, Ruijin)
•Single-dose (Jiangsu)



- 57 patients with R/R MM have been treated with LCAR-B38M in Xi'an Site
- Updated results will be presented at ASH 2019
- US Phase Ib/II study and China Phase II study is ongoing

1. Zhao W et al. ASCO 2017, Abstract LBA3001.
2. Zhang W, et al. EHA 2017. Abstract S107.
3. Zhao WH et al. *J Hem Onc* 2018, 11:141
4. Zhao WH et al. ASH 2018. Abstract 955.
5. Mi J-Q et al. ASH 2017, Abstract 3115.
6. Xu J et al. *Proc Nat Acad Sci*. 2019.

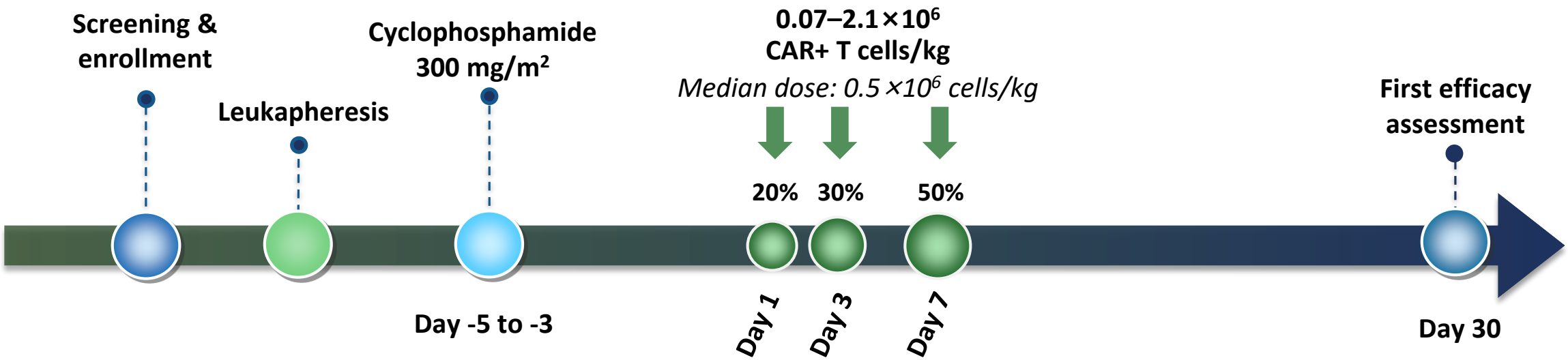
LEGEND-2 Study Design: Xi'an Site

Key Inclusion Criteria

- Active MM defined by IMWG criteria
- Relapsed on prior regimens

Key Objectives

- Primary: safety of LCAR-B38M CAR-T cells
- Secondary: anti-myeloma activity based on IMWG response criteria



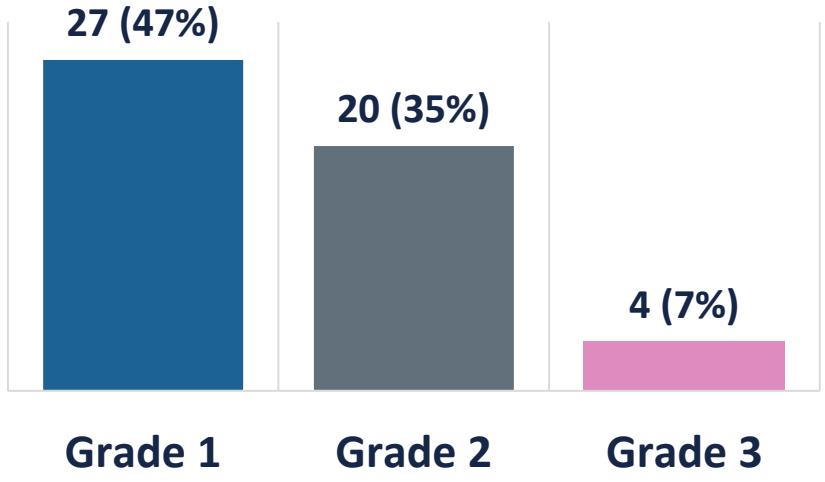
IMWG=International Myeloma Working Group.

Zhao W-H, et al. Presented at 60th ASH Annual Meeting; December 1–4, 2018; San Diego, CA; Abstract #955.

LCAR-B38M – Safety and Efficacy

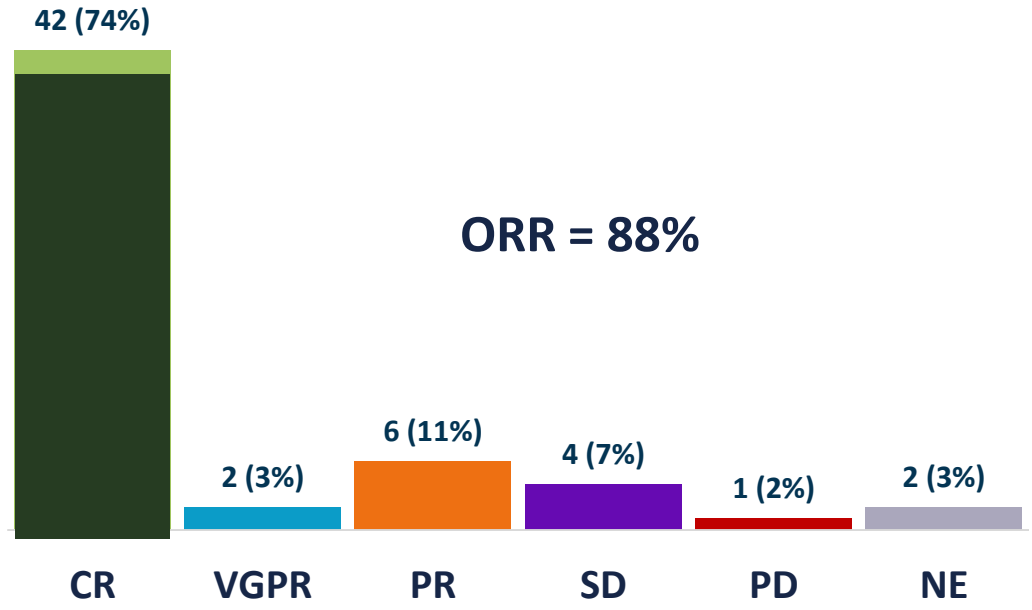
- Phase 1 study in 57 patients with R/R MM

Cytokine Release Syndrome



- Median time to onset = 9 days (range, 1–19)
- Median duration = 9 days (range, 3–57)
- One patient died of PE/ACS before resolution of grade 2 CRS
- No grade 4 CRS
- Tocilizumab (46%), oxygen (35%), vasopressor (11%), and intubation (2%) to treat CRS

Best Overall Response (N=57)



- mDOR = 16 mo (95% CI, 12–NR)
- mDOR for patients with CR = 22 mo (95% CI, 14–NR)
- Median time to initial response = 1 mo (0.4–3.6)

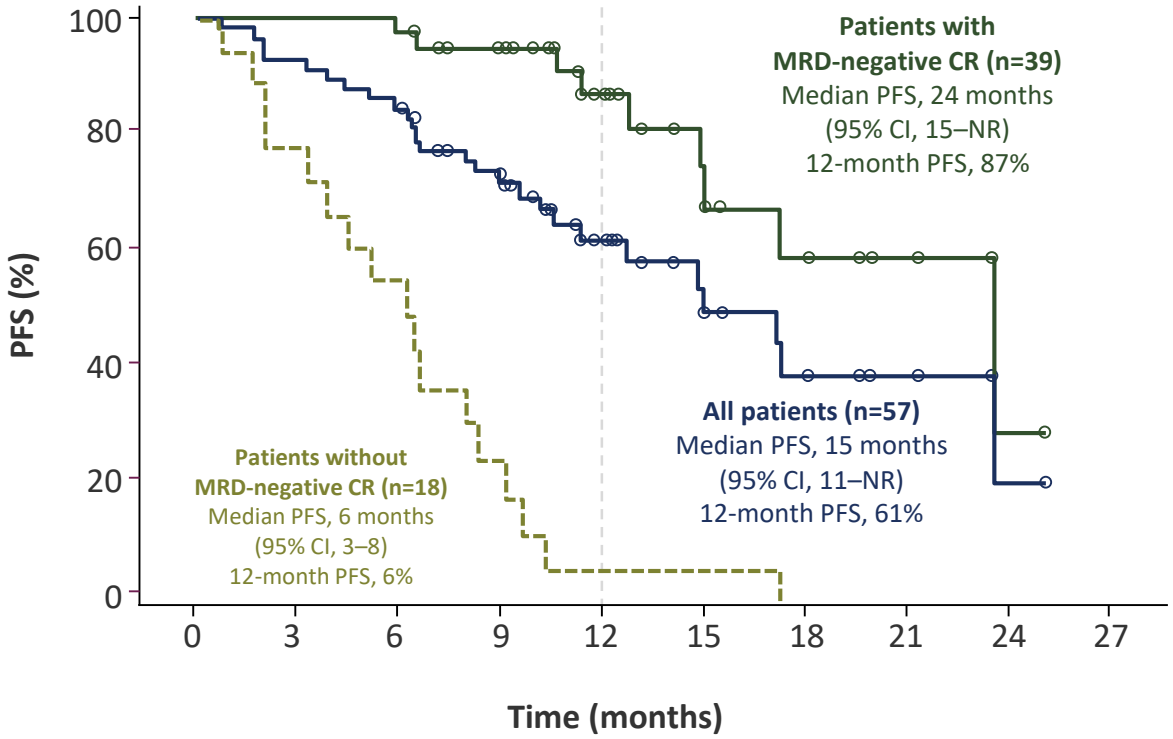
PE/ACS=pulmonary embolism/acute coronary syndrome
CR=complete response; mDOR=median duration of response; MRD-neg=minimal residual disease-negative; NE=not evaluable; ORR=overall response rate; PD=progressive disease; PR=partial response; SD=stable disease; VGPR=very good partial response

Zhao WH et al. *J Hem Onc* 2018, 11:141
Zhao W-H, et al. Presented at the 60th ASH Annual Meeting, December 1–4, 2018; San Diego, CA; Abstract 955.

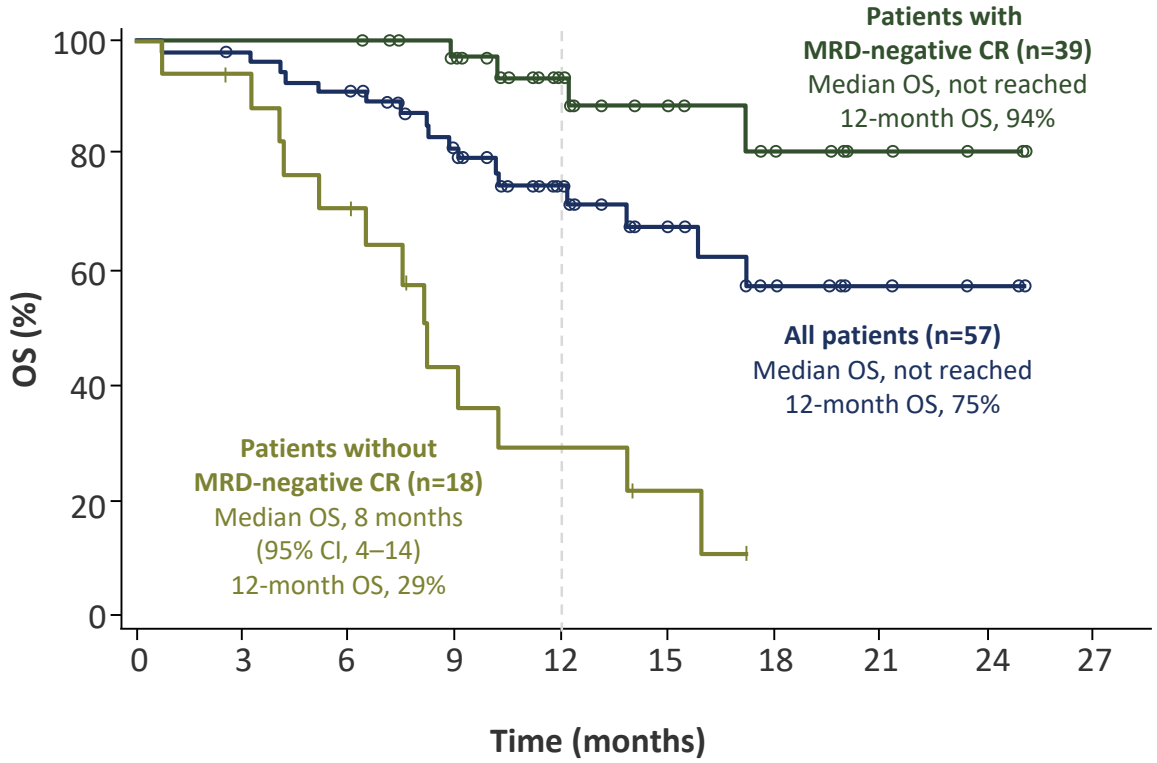
LEGEND-2 Phase I LCAR-B38M in R/R MM

Progression-Free (PFS) and Overall (OS) Survival

PFS



OS



Zhao W-H, et al. Presented at the 60th ASH Annual Meeting, December 1–4, 2018; San Diego, CA; Abstract 955.

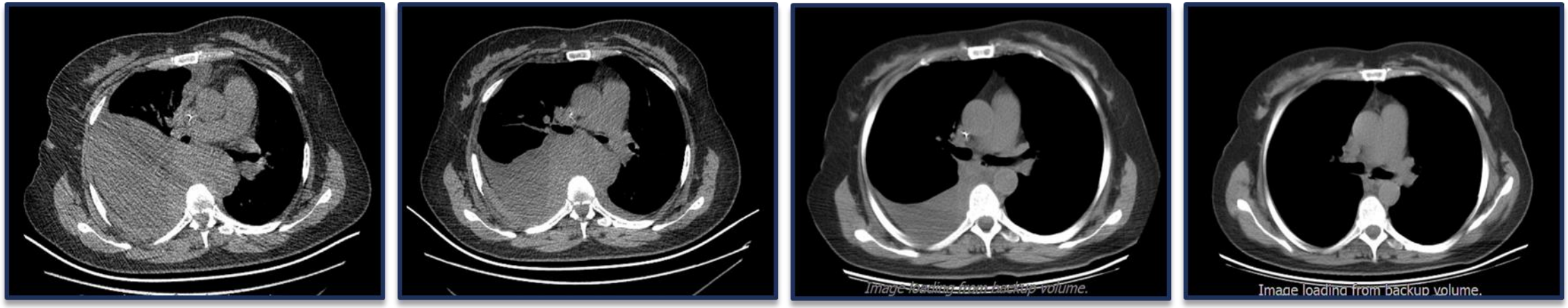
LCAR-B38M – Clinical Efficacy

Subject#6

Treatment baseline | Mid June 2016 | Late August 2016 | March 2019

LCAR-B38M – Clinical Efficacy

Subject#17



Baseline2016.11.24 2016.12.13 2017.1.3 2017.2.9

Subject#23

Baselinev2017.2.1 2017.4.19 2017.8.23

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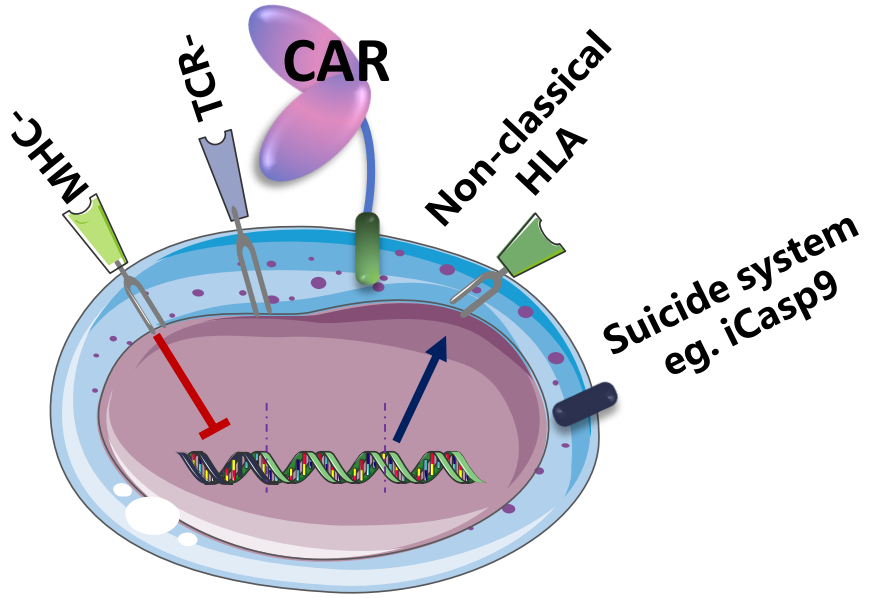
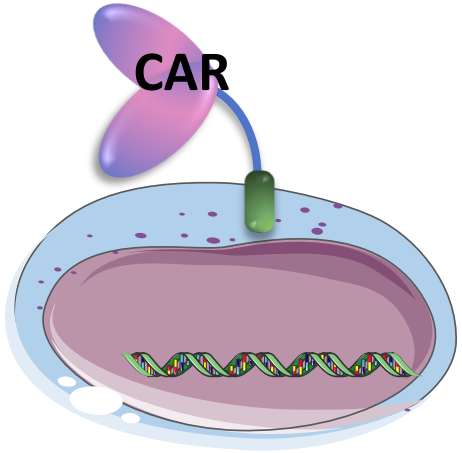
- **Future Directions for CAR T Cell Therapy.**

Future Directions for CAR T Cell Therapy

- Allogenic CAR T cell therapy
  - Universal, "off the shelf" CAR T cells[a]
- Fourth generation CAR T constructs
  - Inducible expression of cytokines (e.g. IL-12) within the tumor microenvironment[b]
- Gene editing technology (ZFN, TALEN, CRISPR)
  - Specific, directed insertion of CAR gene to T cell genome[c]
  - Disrupt TCR and CD52[d]
- Combination with other therapy
  - CAR T + stem cell transplant (SCT bridging)[e,f]
  - CAR T + targeted therapy
  - allogeneic transplantation + Multivirus-specific T cells



allogenic T cell



NK/Macrophage cell [g.H.i]

[a]Qasim et al. 2017 *Sci Transl Med*; 9(374); [b]Zhang et al. 2011 *Mol Ther*; 19(4): 751-9; [c]Ren et al. 2017 *Oncotarget*; 8: 17002-11;
[d]Torikai H et al 2012 Blood; 119(24):5697-705; [e]Maude et al. 2017 *JCO*; 35(suppl): 103; [f]Chong et al. 2017 *Blood*; 129: 1039-41;
[g]Heczey A et al. 2014 Blood. 124(18):2824-33; [h]Deniger DC et al. 2013 Mol Ther; 21(3):638-47; [i]Klichinsky M et al. 2017 Cancer research; 77(13 Supplement):4575

Take Home Messages

- CAR T cell therapy is an immunotherapy that utilizes patients' own engineered T cells to attack cancer cells
- Promising, possibly curative treatment for some hematologic malignancies
  - 2 FDA approved therapies (KYMRIAH® and YESCARTA®) for ALL and DLBCL
  - BCMA-targeted CAR T therapies for MM show encouraging results
- Future of CAR T therapy:
  - New generations of CAR constructs
  - Improved manufacturing/allogenic options and universal CAR T cells
  - More specific targets for broader range of indications
  - More safety management choices

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THANK YOU !

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