U.S. FOOD & DRUG ADMINISTRATION

Clinical Considerations for Cancer Cell Therapy: US FDA Perspectives

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Disclosure

None

Outline

- Basis for US regulatory approvals
- Overview of US FDA cancer cell therapy approvals
- Regulatory perspectives for clinical considerations on CAR-Ts
- Summary

Basis for Regulatory Approval

- Determination of substantial evidence to support the claims of effectiveness
  - Primary basis: adequate and well-controlled investigations
- Acceptable safety (in the context of effectiveness, favorable benefit-risk profile)
- Product labeling
  - Defines an appropriate patient population
  - Provides adequate information to enable safe and effective use

Two Types of Approvals

- Regular (Full) Approval

  Direct clinical benefits

  - Prolongation of overall survival (live longer)
  - Improvement of symptoms (live better)
  - Favorable effect on established surrogate

- Accelerated Approval

Accelerated Approval

The product*

- Treats serious or life-threatening illnesses
- Provides meaningful therapeutic benefit to patients over existing treatments
- Is tested in adequate and well-controlled clinical trials
- Has an effect on a **surrogate endpoint** that is **reasonably likely**, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, **to predict clinical benefit**, or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity
- Subject to the post-marketing requirement to verify and describe its clinical benefit

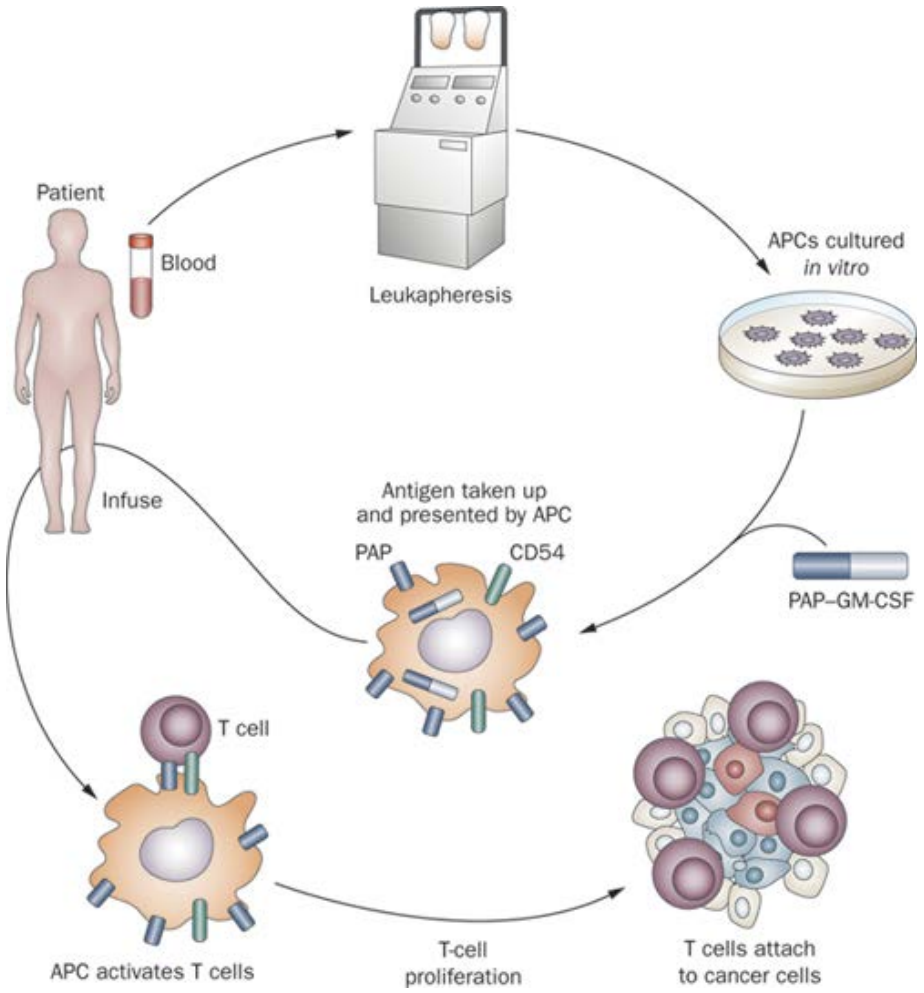
* 21 CFR 314.510 for drugs (subpart H) *21 CFR 601.41 for biologics (subpart E)

US FDA Approvals for Cancer Cell Therapy

- sipuleucel T
- tisagenlecleucel (Kymriah)
- axicabtagene ciloleucel (Yescarta)

sipuleucel-T

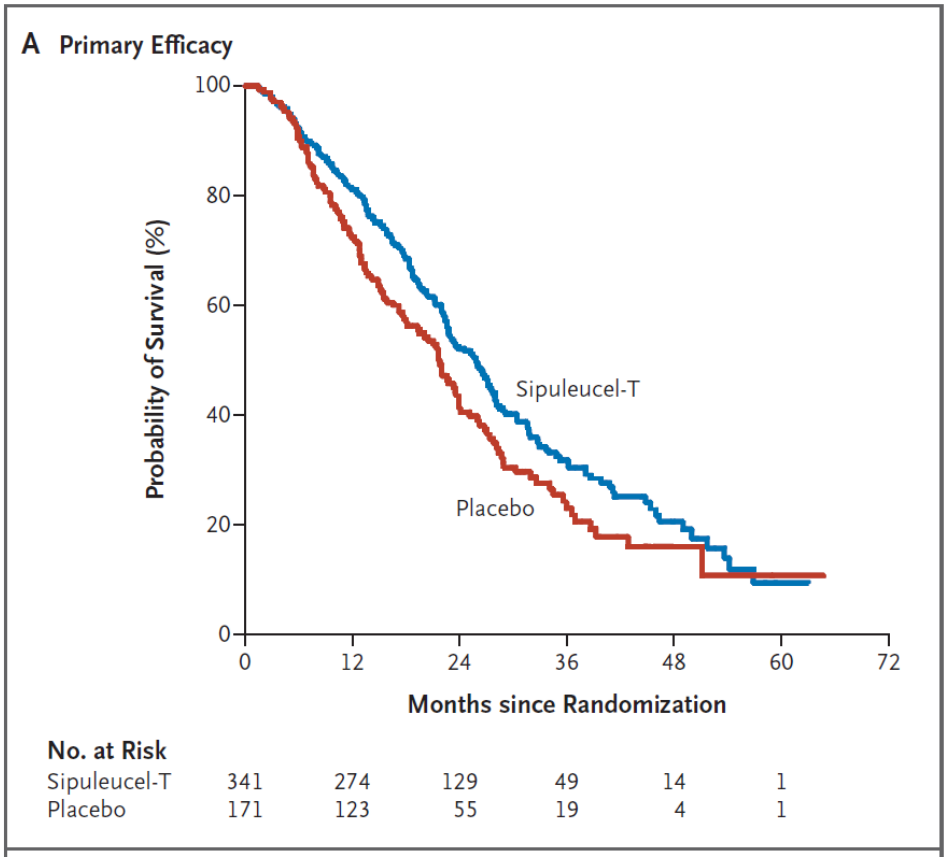
Antigen-presenting Cells (APC) pulsed with PAP-GM-CSF



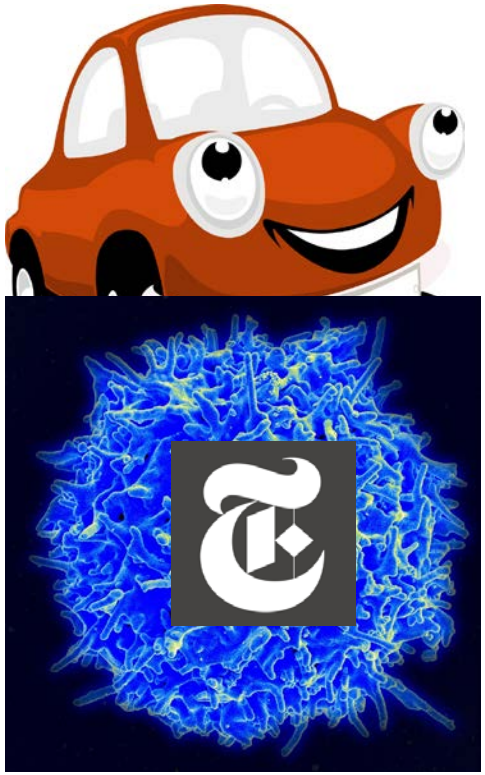
Nat. Rev. Clin. Oncol. c.2011.72

sipuleucel T

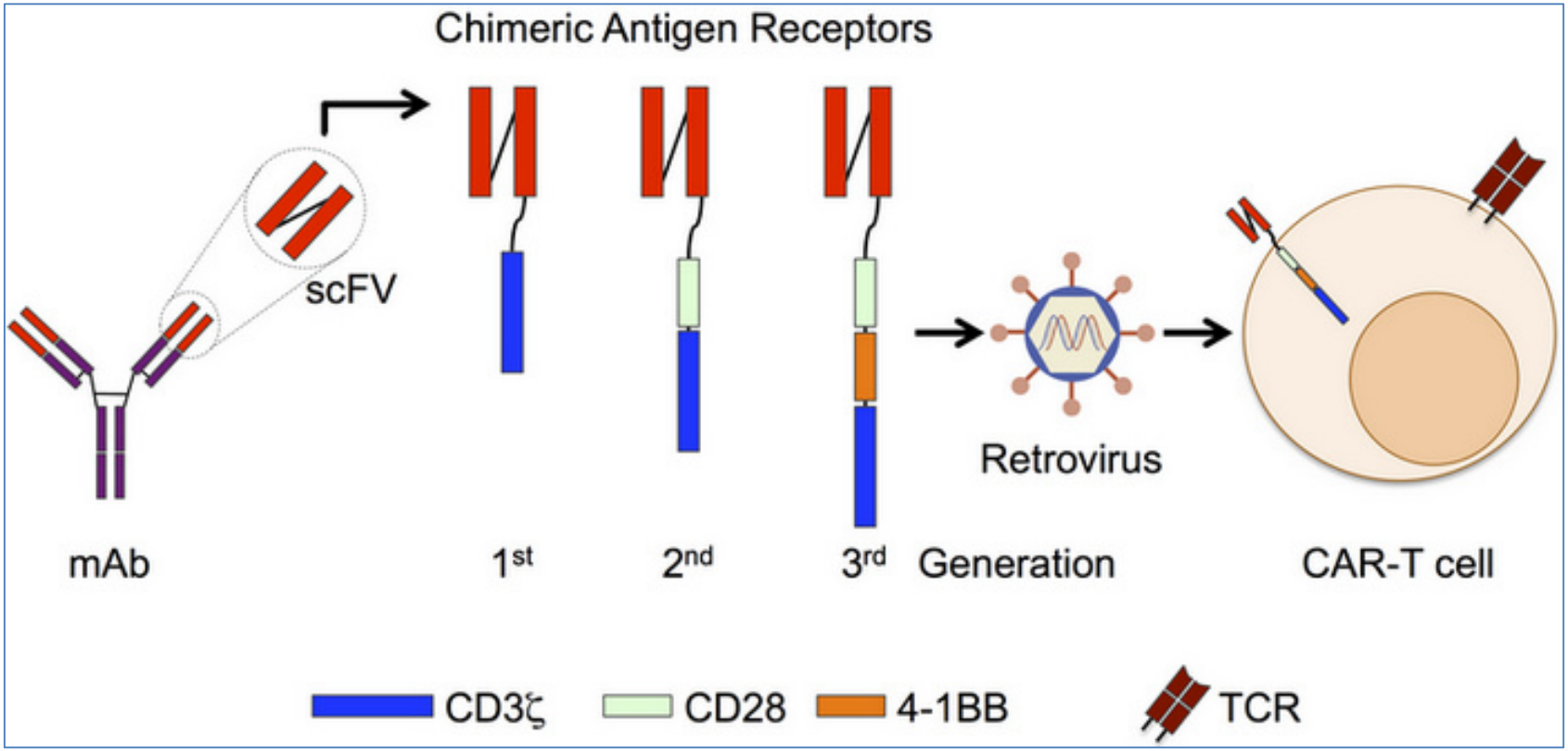
PROVENGE is an autologous cellular immunotherapy indicated for the treatment of asymptomatic or minimally symptomatic metastatic castrate resistant (hormone refractory) prostate cancer.



CAR-T



Chimeric Antigen Receptor (CAR) T cells

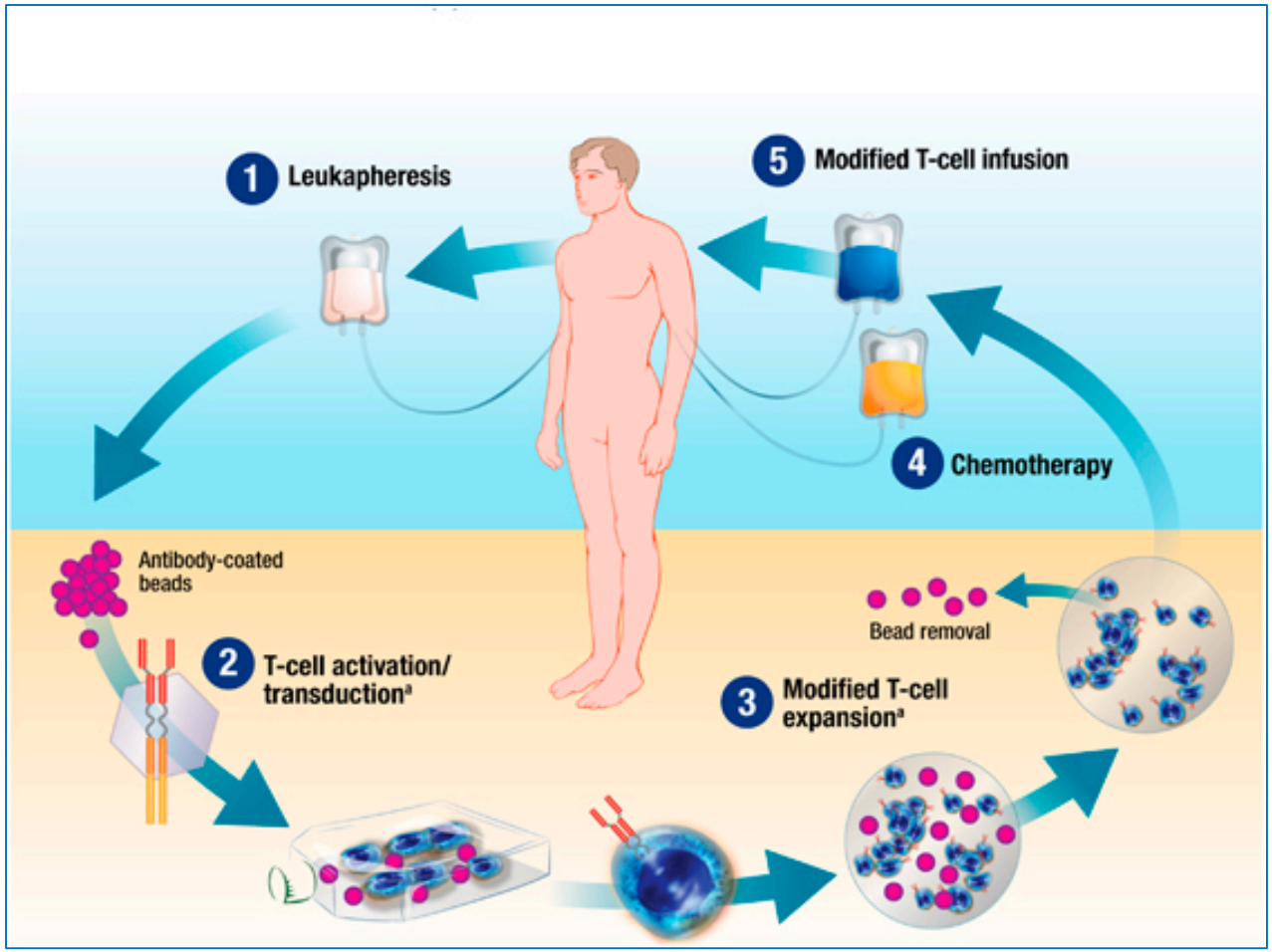


Michael S. Magee, Adam Snook. Discovery Medicine, Vol 100, November 17, 2014

CAR-T Cell Therapy

Performance-enhancing drugs: design and production of redirected (CAR) T cells

B L Levine
Cancer Gene Therapy (2015) 22, 79–84



KYMRIAH

A CD19-directed genetically modified autologous T cell immunotherapy indicated for the treatment of patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse

KYMRIAH Efficacy

Results	N=63
CR/CRi[1,2]	52 (83%)
95% CI	(71%, 91%)
	p<0.0001
CR[3]	40 (63%)
CRi[4]	12 (19%)
CR or CRi with MRD-negative bone marrow[5,6]	52 (83%)
95% CI	(71%, 91%)
	p<0.0001
Duration of Remission[7]	**N=52**
Median (months)	Not reached
95% CI	(7.5, NE[8])

YESCARTA

A CD19-directed genetically modified autologous T cell immunotherapy indicated for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma.

YESCARTA Efficacy

Table 5. Response Rate

	Recipients of YESCARTA (N = 101)
Objective Response Rate[a]	73 (72%)
(95% CI)	(62, 81)
Complete Remission Rate	52 (51%)
(95% CI)	(41, 62)
Partial Remission Rate	21 (21%)
(95% CI)	(13, 30)

CI, confidence interval.

[a]*Per 2007 revised International Working Group criteria, as assessed by the independent review committee.*

Table 6. Duration of Response

	From N of 101
Number of Responders	73
DOR (Months)[a]	
Median[b]	9.2
(95% CI)	(5.4, NE)
Range[c]	0.03+, 14.4+
DOR if Best Response is CR (Months)	
Median[b]	NE
(95% CI)	(8.1, NE)
Range	0.4, 14.4+
DOR if Best Response is PR (Months)	
Median[b]	2.1
(95% CI)	(1.3, 5.3)
Range	0.03+, 8.4+
Median Follow-up for DOR (Months)[a, b]	7.9

Safety and REMS

Both CAR-T PIs carry the following boxed warnings

WARNING: CYTOKINE RELEASE SYNDROME AND NEUROLOGICAL TOXICITIES

See full prescribing information for complete boxed warning.

- **Cytokine Release Syndrome (CRS), including fatal or life-threatening reactions, occurred in patients receiving KYMRIAH. Do not administer KYMRIAH to patients with active infection or inflammatory disorders. Treat severe or life-threatening CRS with tocilizumab. (2.2, 2.3, 5.1)**
- **Neurological toxicities, which may be severe or life-threatening, can occur following treatment with KYMRIAH, including concurrently with CRS. Monitor for neurological events after treatment with KYMRIAH. Provide supportive care as needed. (5.2)**
- **KYMRIAH is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the KYMRIAH REMS. (5.3)**

WARNING: CYTOKINE RELEASE SYNDROME AND NEUROLOGIC TOXICITIES

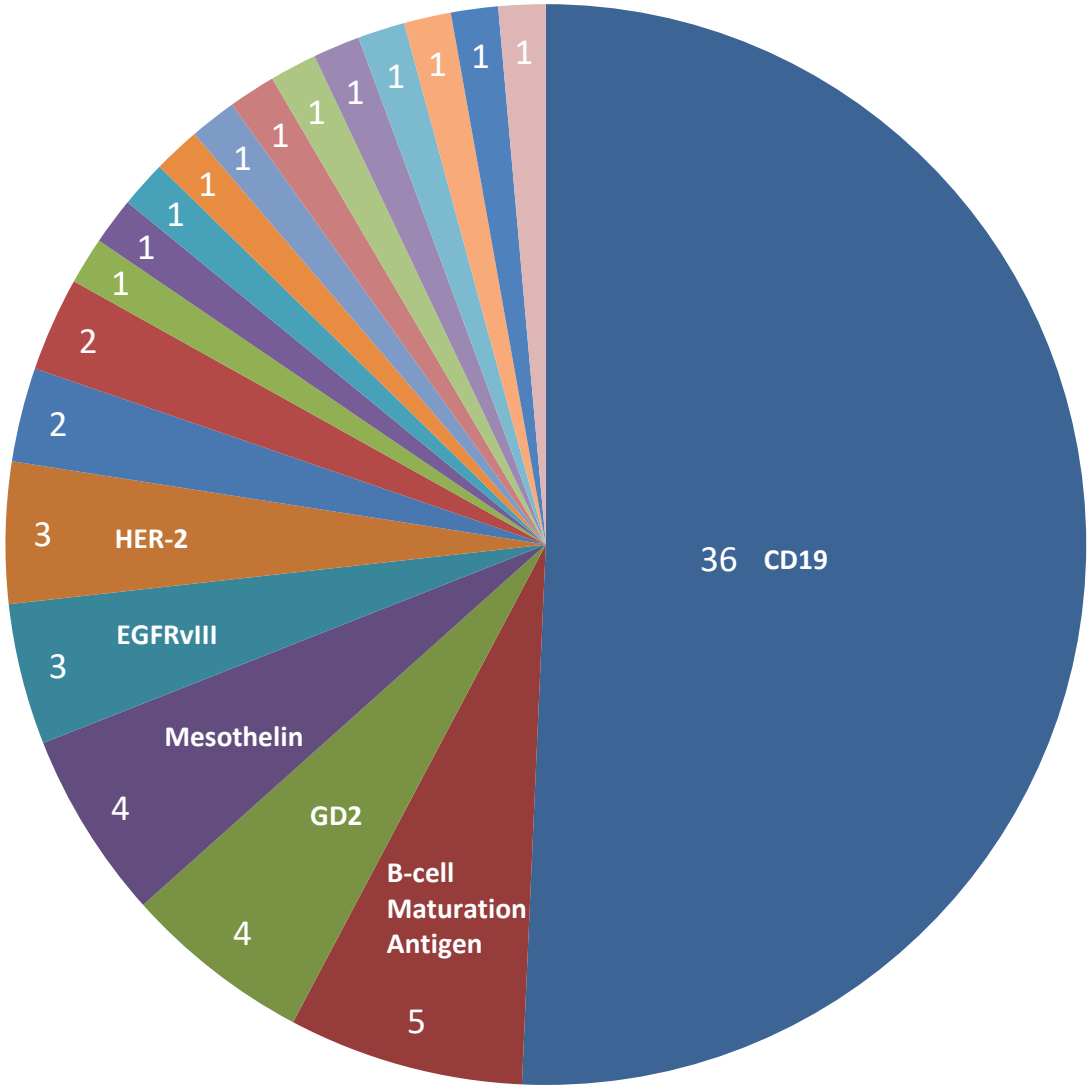
See full prescribing information for complete boxed warning.

- **Cytokine Release Syndrome (CRS), including fatal or life-threatening reactions, occurred in patients receiving YESCARTA. Do not administer YESCARTA to patients with active infection or inflammatory disorders. Treat severe or life-threatening CRS with tocilizumab or tocilizumab and corticosteroids (2.2, 2.3, 5.1).**
- **Neurologic toxicities, including fatal or life-threatening reactions, occurred in patients receiving YESCARTA, including concurrently with CRS or after CRS resolution. Monitor for neurologic toxicities after treatment with YESCARTA. Provide supportive care and/or corticosteroids, as needed (2.2, 2.3, 5.2).**
- **YESCARTA is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the YESCARTA REMS (5.3).**

Regulatory Perspectives for CAR-Ts

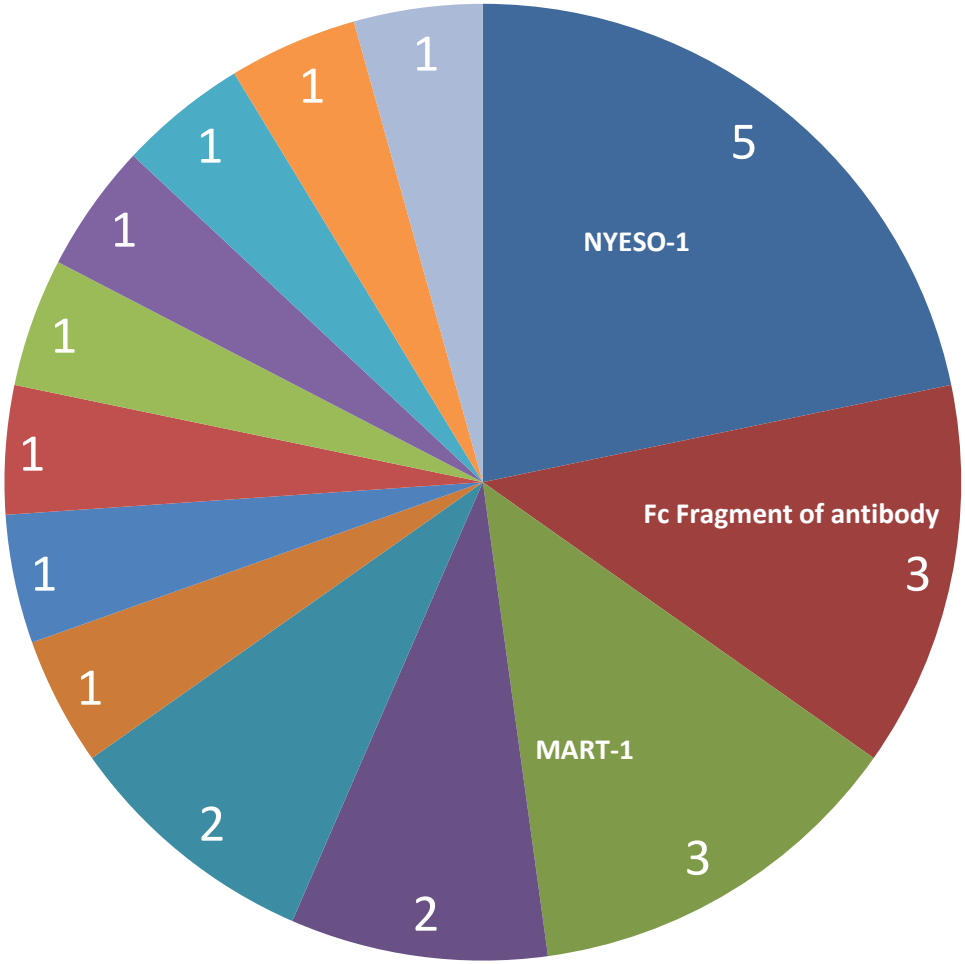
- Landscape analysis
- Clinical Considerations

Genetically Modified T cell Immunotherapy --- CAR-Ts



- A total of 71 CAR-T cell INDs as of 9/14/17
- 50% CD19 (6 commercial INDs)

Genetically Modified T cell Immunotherapy --- TCR-Ts



- A total of 23 TCR-T cell INDs as of 9/14/17
- 22% NYESO-1 (one commercial IND)

CAR-T Clinical Considerations

Efficacy

- Target identification
- Trial design
  - Study population
  - Efficacy endpoint
  - Evaluation

Safety

- Toxicity management
  - Cytokine-release syndrome (CRS)
  - Neurological toxicities

Underlying Challenge: Manufacturing and Quality Controls

Regulatory Considerations

Patient Population -1

Conventional

- Testing the efficacy and safety in a defined patient population with a given malignant type, e.g., CLL
- Move to another stage of the same tumor type or different disease

CAR-T

- Targeting a specific antigen regardless of tumor type
- May consider enrolling patients with different tumor histology as long as the tumors express the antigen that the CAR-T cells target (histology-agnostic)

Regulatory Considerations

Patient Population -2

- Challenges in enrolling patients with different tumor histology
  - –Prior treatment requirement
  - –Patient performance and organ function
  - –Companion diagnostic for identifying targeted antigen
- Because of toxicity concern, unclear role of CAR-T in earlier-stage disease

Regulatory Considerations
Trial Design

- Single-arm vs. randomized, controlled trials
- Controlled trial
  - Feasibility
  - Appropriate control
  - Other concurrent treatments tailored to patients with different tumor types
  - Other factors that may confound study results

Regulatory Considerations

Efficacy Endpoint

- Single-arm trial
  - Tumor response rate
  - Magnitude of the treatment effect
  - Duration

- Randomized controlled trial
  - Time to event
    - Overall Survival
    - Progression-free survival

- A substantial and durable confirmed response rate from single-arm trial(s) with a well-described study population could support approval (accelerated or traditional approval, e.g., KYMRIAH and YESCARTA)

CAR-T Toxicities

- Cytokine release syndrome
  - Importance of monitoring cytokine levels
  - Importance of monitoring the persistence of CAR-T cells
  - Consideration for early use of Tocilizumab
- Off-target effects
  - Pre-clinical studies
  - Clinical monitoring
- Optimal management for toxicities including neurological toxicities
  - REMS

CAR-T for Solid Tumor

- Challenges
  - Target identification
  - CAR-T trafficking and homing to tumor site
- Opportunities
  - Application of knowledge gained from CAR-T for hematological malignancies
  - New advances in technology
    - NGS for targeting identification
    - CRISPR to enhance CAR-T function

Combination of Cell therapy with Other Agents

- Trial design consideration to understand the contribution of the components
- Toxicity attribution and management

Summary

- A living drug, CAR-T therapy holds great promise for cure
- Trial design should consider the study population, endpoint, safety monitoring among other factors
- Much work needs to be done in solid tumor space with focus on target identification, understanding and enhancing cell tracking and homing to tumor site
- Combination of cell therapy with other agents poses more challenges in determining efficacy and safety
- Collaboration among stakeholders is the key for success

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- **OTAT Learn Webinar Series:**

  http://www.fda.gov/BiologicsBloodVaccines/NewsEvents/ucm232821.htm

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