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FDA Introductory Remarks

Tisagenlecleucel
Novartis Pharmaceuticals Corporation

Oncologic Drugs Advisory Committee Meeting

July 12, 2017

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Office of Tissues and Advanced Therapies (OTAT)
Center for Biologics Evaluation and Research (CBER)

Proposed Indication

Tisagenlecleucel is an autologous genetically modified immunocellular therapy indicated for the treatment of pediatric and young adult patients 3 to 25 years of age with relapsed/refractory (r/r) B-cell acute lymphoblastic leukemia (ALL)

Issues for Committee Discussion

- Product Quality
- Safety
  - Cytokine Release Syndrome and Neurotoxicity
  - Secondary Malignancy and Long-Term Follow-up
- Benefit – Risk Profile


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Tisagenlecleucel

CMC presentation

Oncologic Drugs Advisory Committee Meeting

July 12, 2017

BLA 125646

tisagenlecleucel

Novartis Pharmaceuticals Corporation

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CBER/OTAT
Division of Cellular and Gene Therapies

Overview

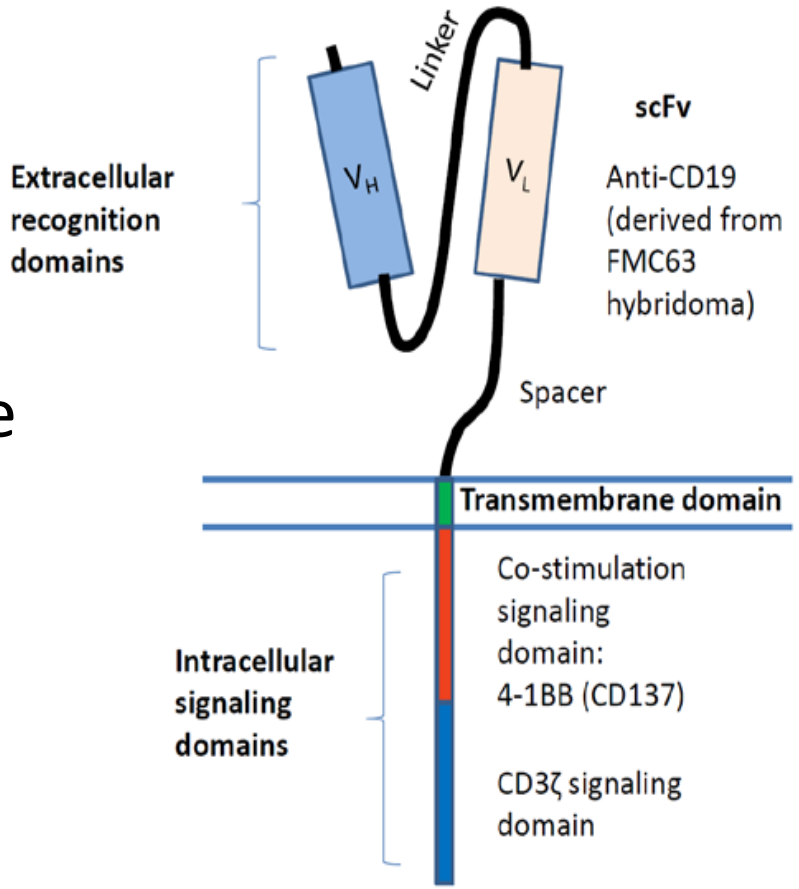
- Tisagenlecleucel: A chimeric antigen receptor (CAR) T cell therapy
- CAR structure
- Mechanism of action
- Vector design and safety profile
- Manufacturing process and control
- Product consistency
- Discussion questions

Tisagenlecleucel

- Genetically-modified autologous cellular immunotherapy
  - Patient's own T cells are modified (transduced) with a retroviral (HIV-1-based) vector to express a CD19-directed CAR
- Targets CD19-expressing cells
  - Intended target: B cell tumors
  - Unintended, but expected: Normal B lineage cells
- A dynamic “living” biologic
  - Can expand and differentiate during manufacturing, and after administration to patients

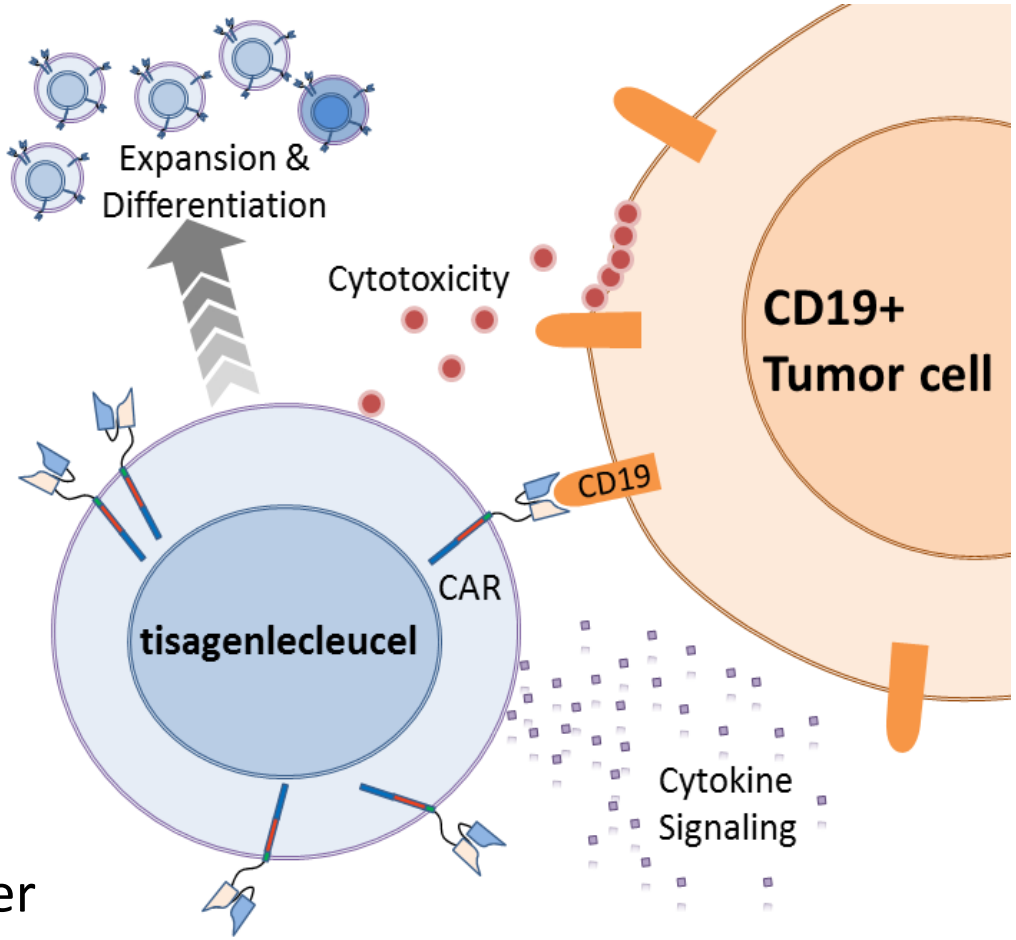
Tisagenlecleucel CAR design

- scFv domain
  - Specific for CD19
- Spacer & transmembrane
  - Important for CAR structure and function
- Intracellular signaling domains
  - T cell activation: CD3ζ
  - Co-stimulation signal: 4-1BB



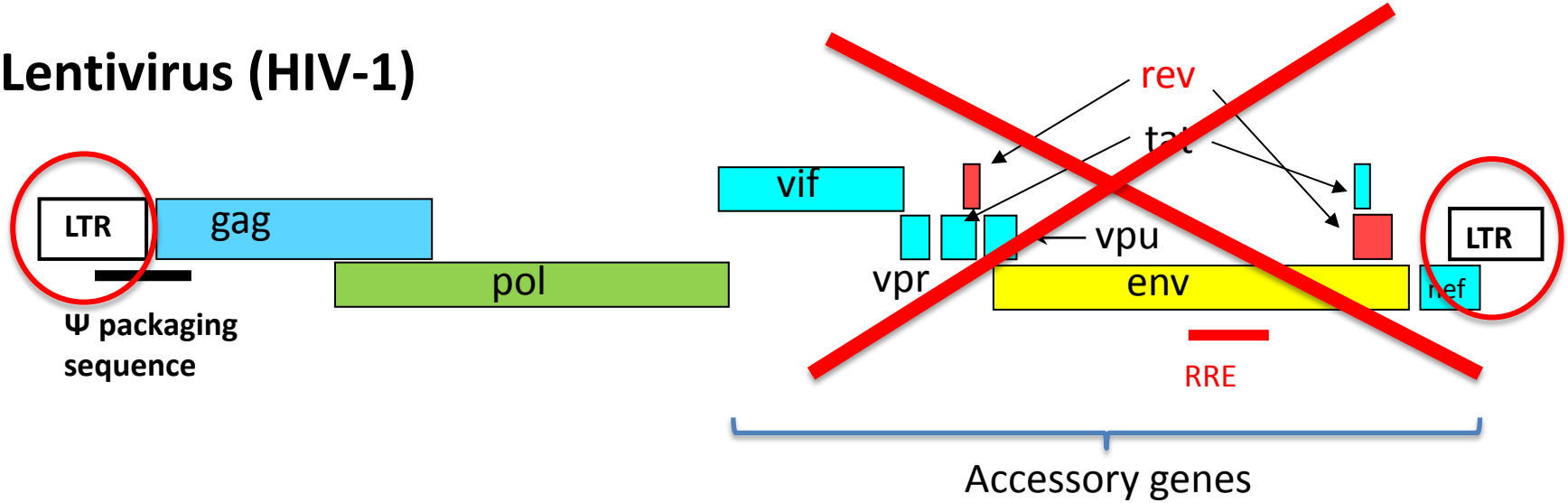
Mechanism of action

- CAR scFv binds to CD19 on B cell tumors
  - Not restricted by HLA
- Binding of CAR to CD19 activates tisagenlecleucel
  - Promotes cell expansion and differentiation
  - Triggers effector functions:
    - Lysis of $CD19^{+}$ cells
    - Cytokine signaling
    - Stimulation of bystander immune cells

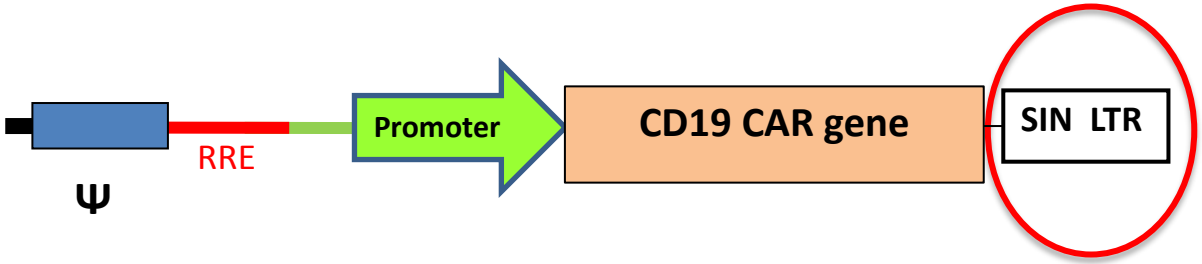


Tisagenlecleucel vector

Lentivirus (HIV-1)

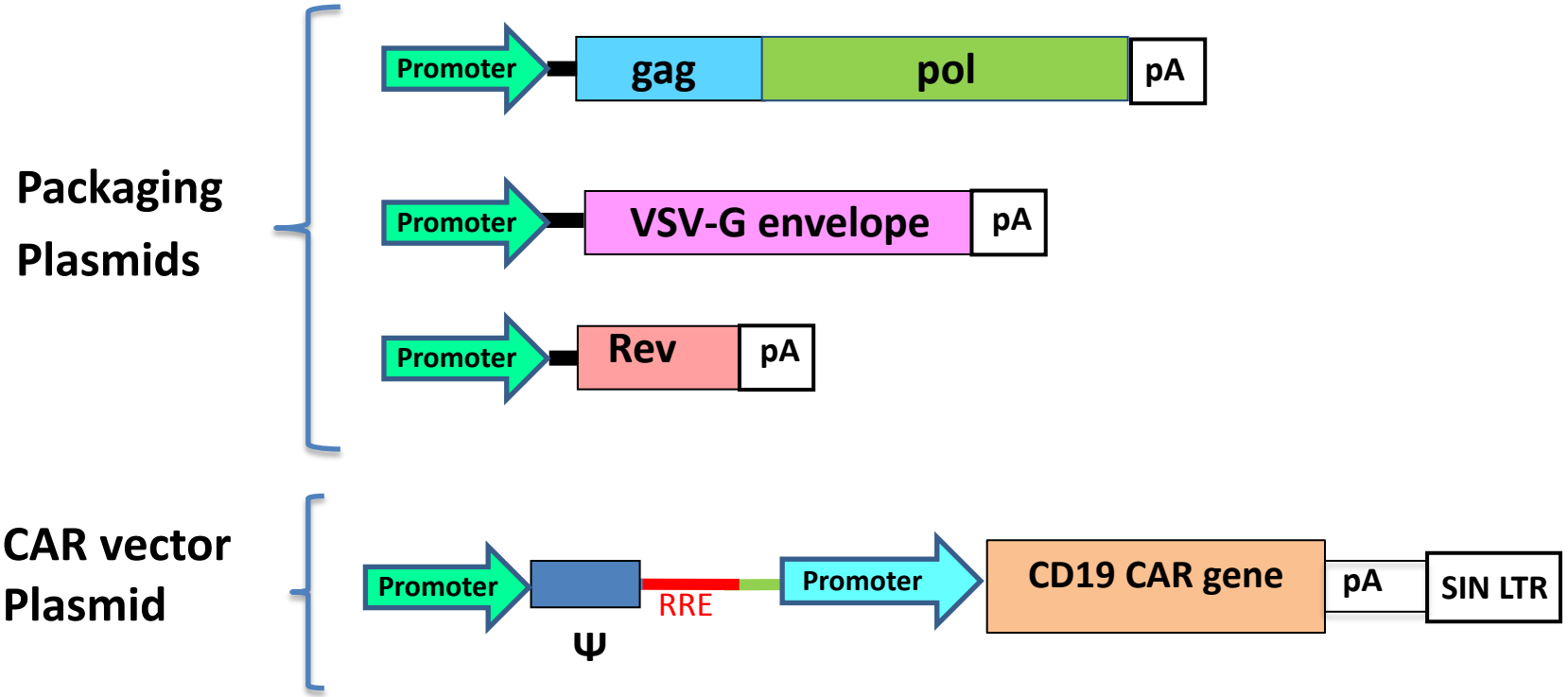


Tisagenlecleucel vector



LTR: long terminal repeat
SIN: self-inactivating
RRE: rev response element

Vector packaging system



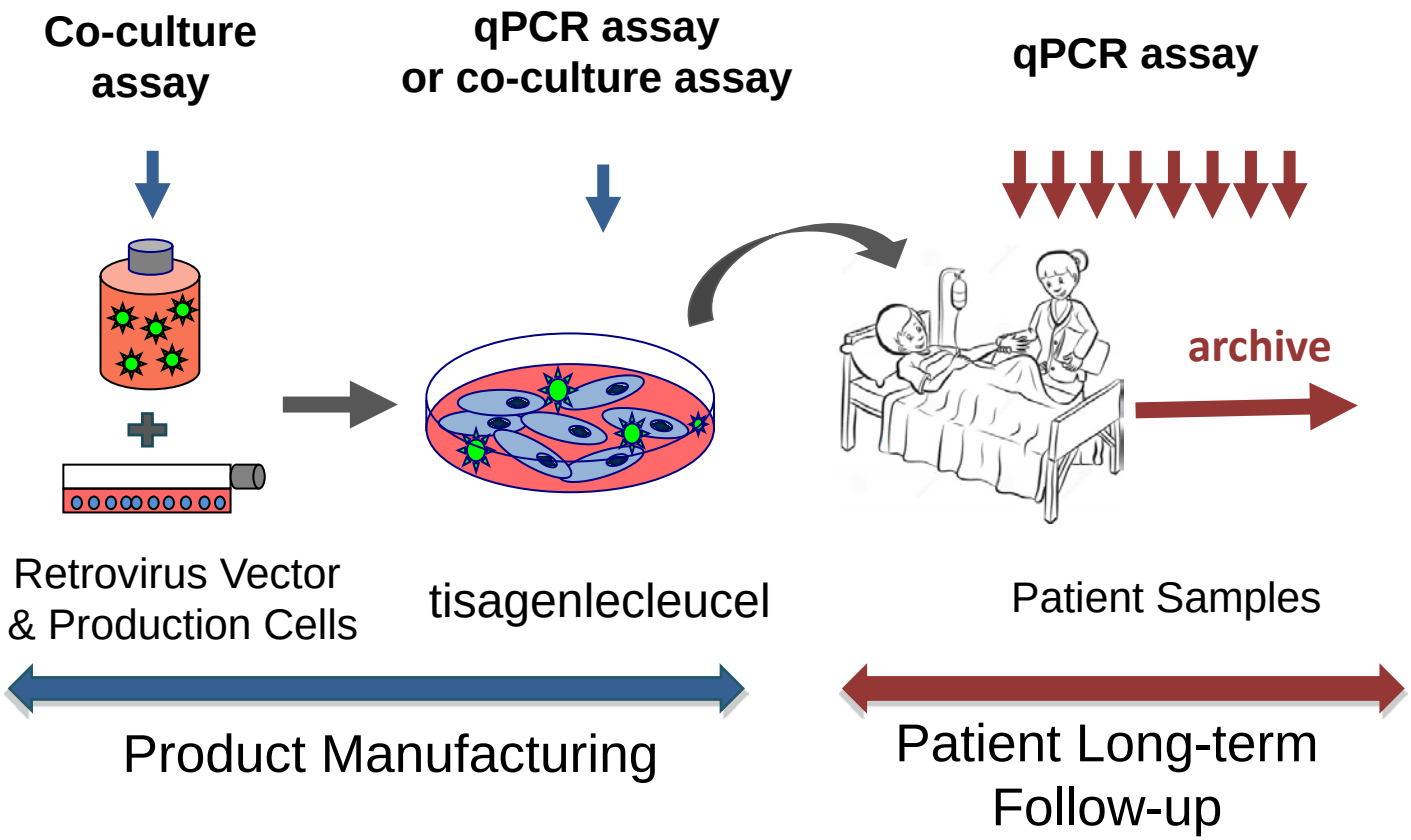
Replication defective

1. Split plasmid design with little sequence homology
2. Removal of accessory viral genes
3. Self-inactivating

Potential for RCR generation

- Slight risk of formation during vector manufacture
  - Replication competent retrovirus (RCR) were observed in early gammaretroviral vectors
- RCR risks are reduced by design features of the tisagenlecleucel retroviral vector
  - Minimal homology between packaging plasmids and vector sequences
  - Segregation on 4 different DNA plasmids
  - Deletion of HIV accessory genes

RCR testing during IND studies



- All RCR results were reported to be negative for tisagenlecleucel
  - Vector lots (≥ 13)
  - Patient-specific tisagenlecleucel lots (≥ 72)

Proposed RCR testing of commercial tisagenlecleucel

- Each vector batch and production cells
  - Co-culture assay
- Each patient's batch of tisagenlecleucel
  - qPCR assay
- Note: Negative RCR test results during manufacturing do not eliminate all risk of RCR
- Novartis does not plan to collect patient samples for RCR testing

Vector insertional mutagenesis risk

- Retroviral vector integration into a chromosome may change activity of host genes
  - Gene mutation or disruption
  - Increased activity of nearby genes due to enhancers in vector
- Insertional mutagenesis from gammaretroviral vectors has led to leukemia in multiple clinical studies using stem cells
- No vector-associated leukemia to date with tisagenlecleucel or other vector-modified T cell products
- Tisagenlecleucel uses a “self-inactivating” (SIN) vector design
  - SIN vectors lack retroviral enhancer sequences
  - Less likely to activate nearby genes, and therefore less risk of oncogenesis

Vector integration site analysis

- Vector integration sites were characterized in 14 batches of tisagenlecleucel.
- Distribution of integration sites was similar to other lentiviral vectors.
- No evidence for targeting to specific genes
  - Integration sites were highly polyclonal
  - No favoring of integration near oncogenes
- **Caveat:** This type of analysis cannot predict whether a rare mutated T cell will preferentially expand in vivo, possibly leading to oncogenesis.

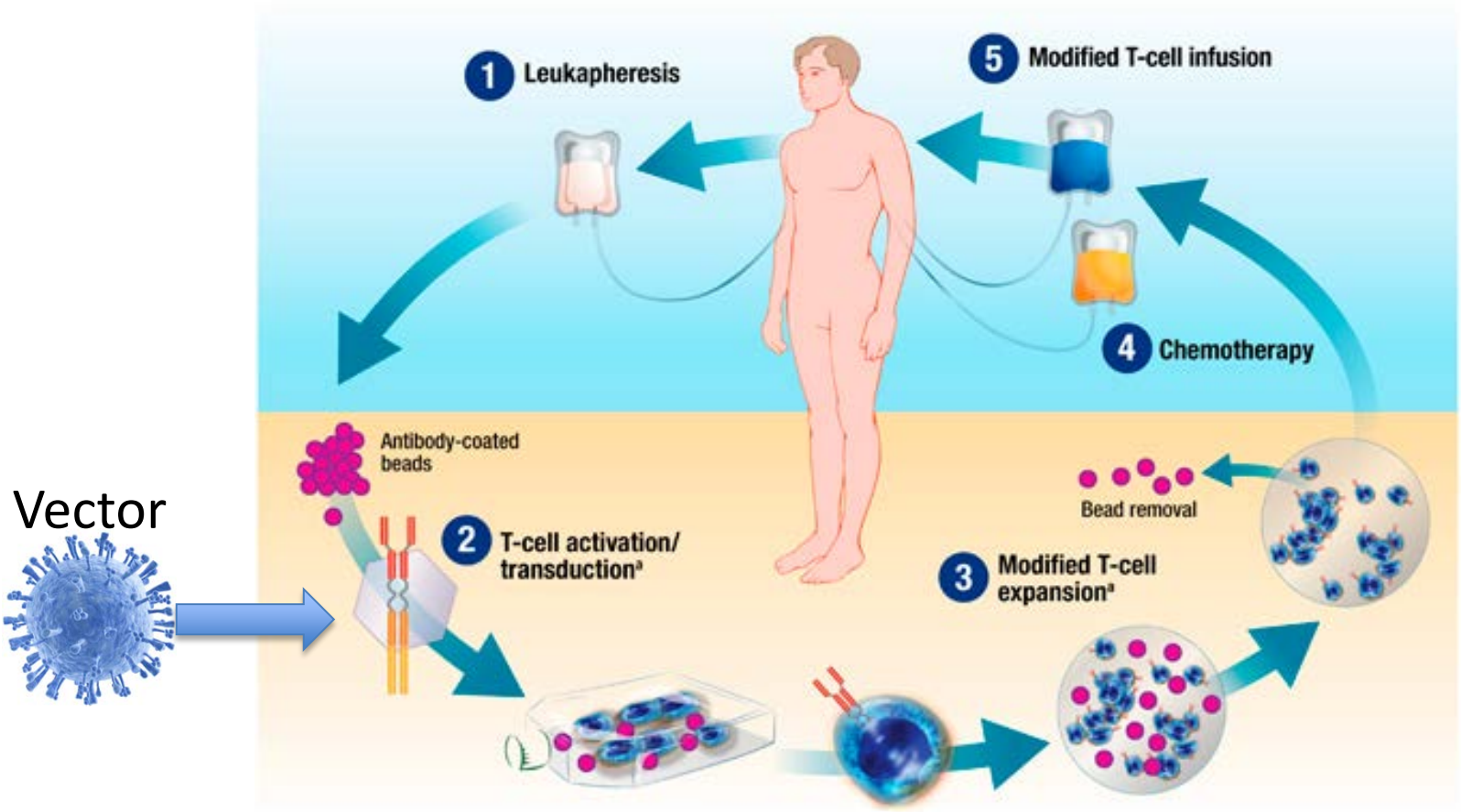
Monitoring for insertional mutagenesis

- During clinical trials of tisagenlecleucel:
  - Patient cell samples were regularly monitored for:
    - Product persistency
    - Clonal expansion
  - No instances of clonal expansion or vector-associated oncogenesis were detected
- The applicant does not propose routine patient monitoring for vector persistence or clonal T cell expansion, if tisagenlecleucel is licensed

Summary of potential risks associated with the vector

- Replication-competent retrovirus (RCR)
  - Vector design features
  - Testing for RCR
  - Patient monitoring (during IND, but not proposed if licensed)
- Insertional mutagenesis
  - SIN vector design
  - Patient monitoring (during IND, but not proposed if licensed)
- Vector-associated risks are low, but not entirely eliminated.
- Patient long-term follow-up for vector risk factors will be discussed by the advisory committee.

Overview of tisagenlecleucel manufacturing process



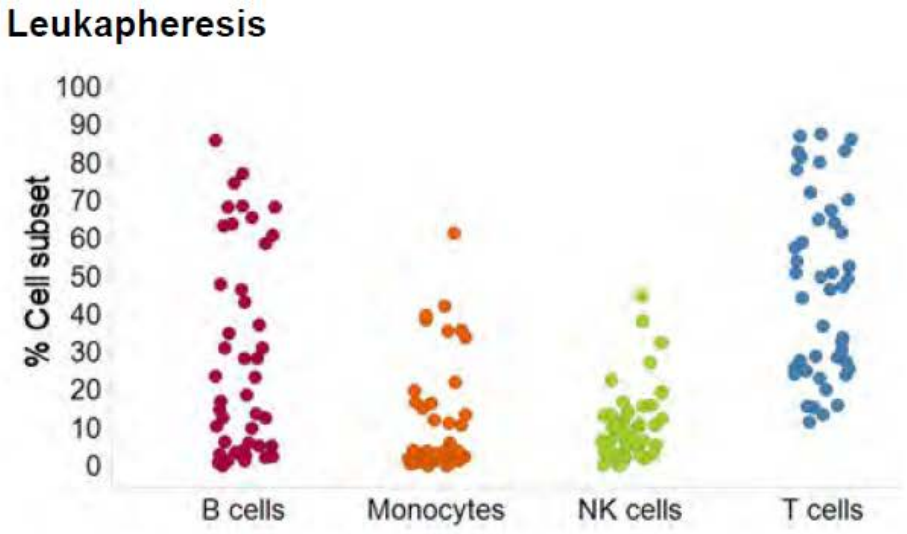
Cancer Gene Therapy (2015) **22,** 79–84

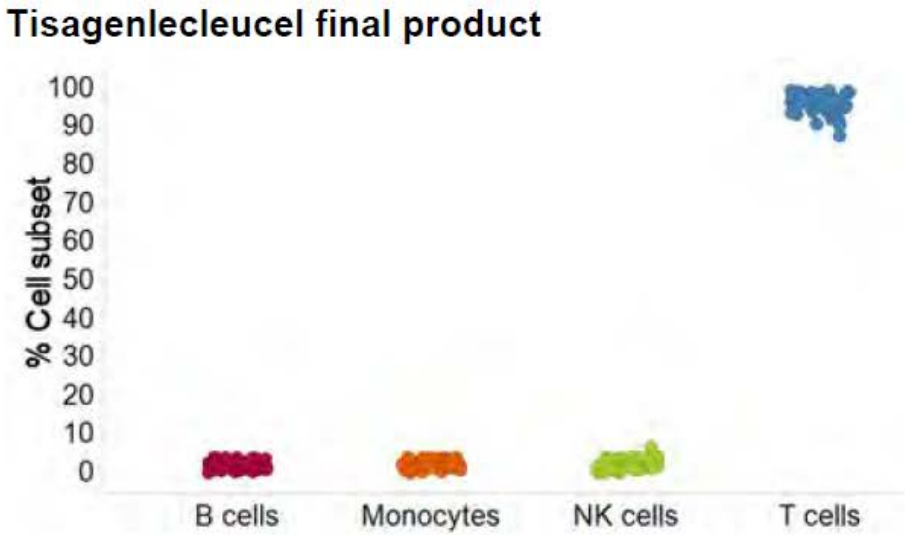
Control of tisagenlecleucel manufacturing and quality

- Qualify critical components
  - Leukapheresis
  - Vector
- Establish critical process parameters
- Validate the manufacturing process
- Monitor through in-process testing
- Meet lot release specifications
- Characterize additional product attributes

Variability of leukapheresis cells

- Autologous cells are collected from patient by apheresis
- Heterogeneous composition:
  - T cells, B cells, monocytes, tumor blasts, NK cells, RBC, etc.
  - Composition influenced by genetics, disease, age, prior treatment history, etc.





Source: Novartis BLA Briefing Document

Characteristics of T cells in tisagenlecleucel

- Tisagenlecleucel contains mostly T cells
  - A subset of these T cells express the CAR
- Heterogeneous T cell populations
  - CD4/CD8 ratio
  - Central memory T cells, effector memory T cells, etc.
- Unknown which T cell subsets contribute to tisagenlecleucel activity
- T cells can change after administration
  - Expansion
  - Activation
  - Differentiation
  - Persistence

Tisagenlecleucel lot release testing

- Safety
  - RCR, sterility, endotoxin, mycoplasma
  - Integrated vector copies
- Identity and purity
  - Tracking, CAR+, % T cells
- Dose determination
  - Number of viable T cells expressing CAR
- Potency
  - Cytokine production

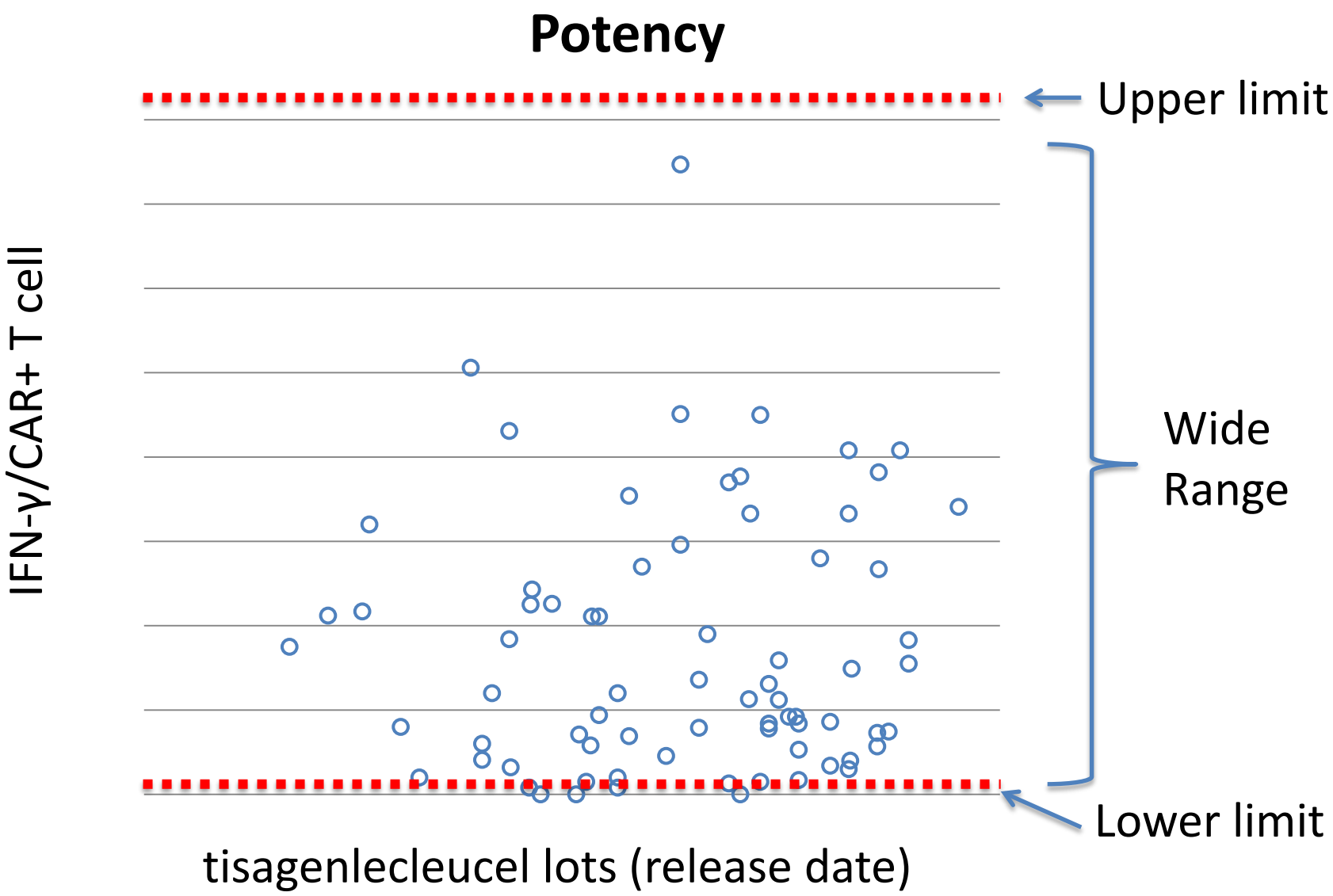
Tisagenlecleucel potency testing

- Quantitative measure of tisagenlecleucel biological activity
- Lot release: IFN-γ production upon stimulation by $CD19^+$ cells
- Additional characterization: killing of $CD19^+$ cells

Setting lot release specifications

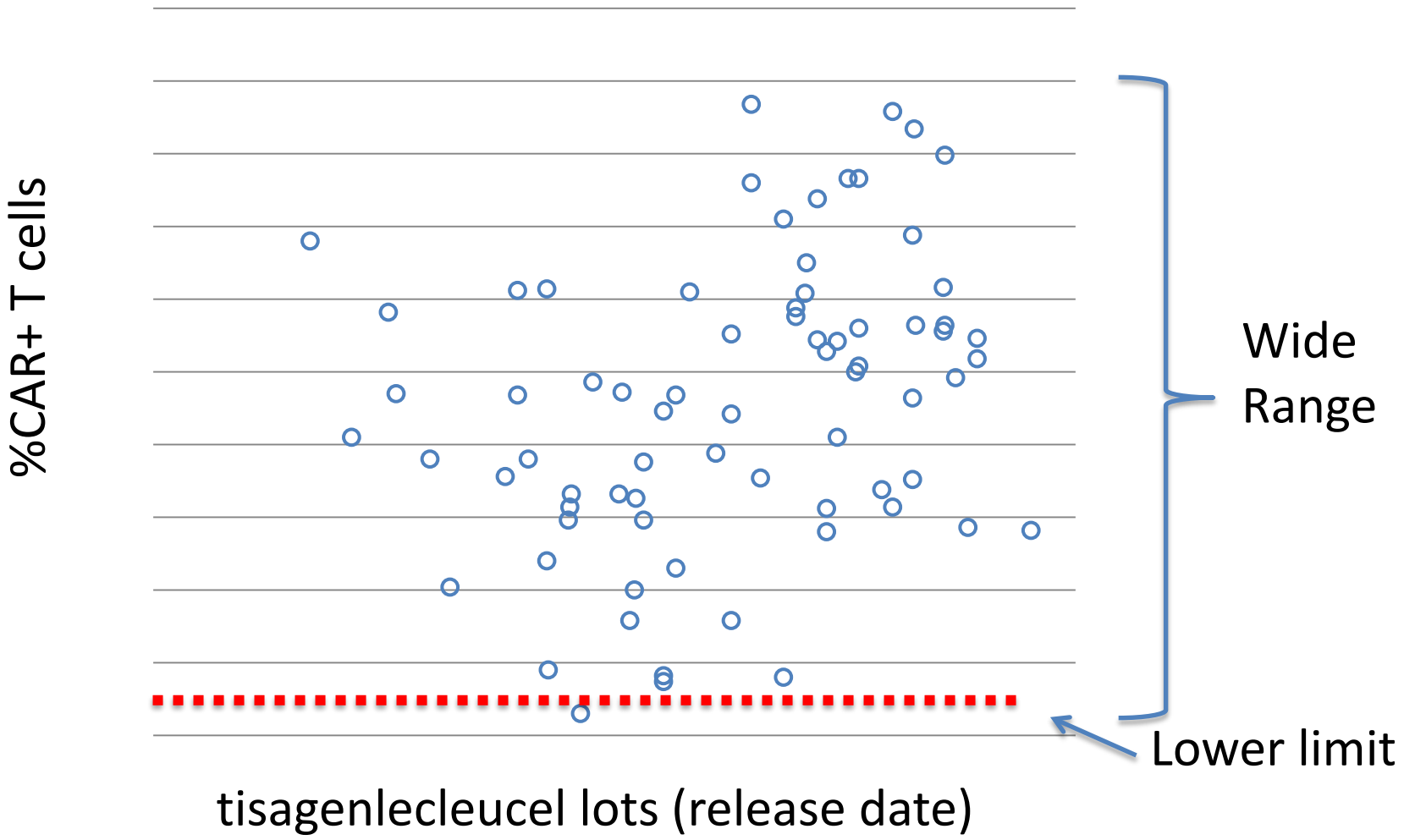
- Lot release specifications ensure a consistently safe, pure, and potent product
- The proposed lot release specifications were based on statistical analysis of historical data
- Patient safety and efficacy outcomes occurred within a broad range of tisagenlecleucel characteristics, for instance:
  - IFN-γ production
  - Transduction efficiency (% CAR+ T cells & vector copy numbers)

Example of lot release data



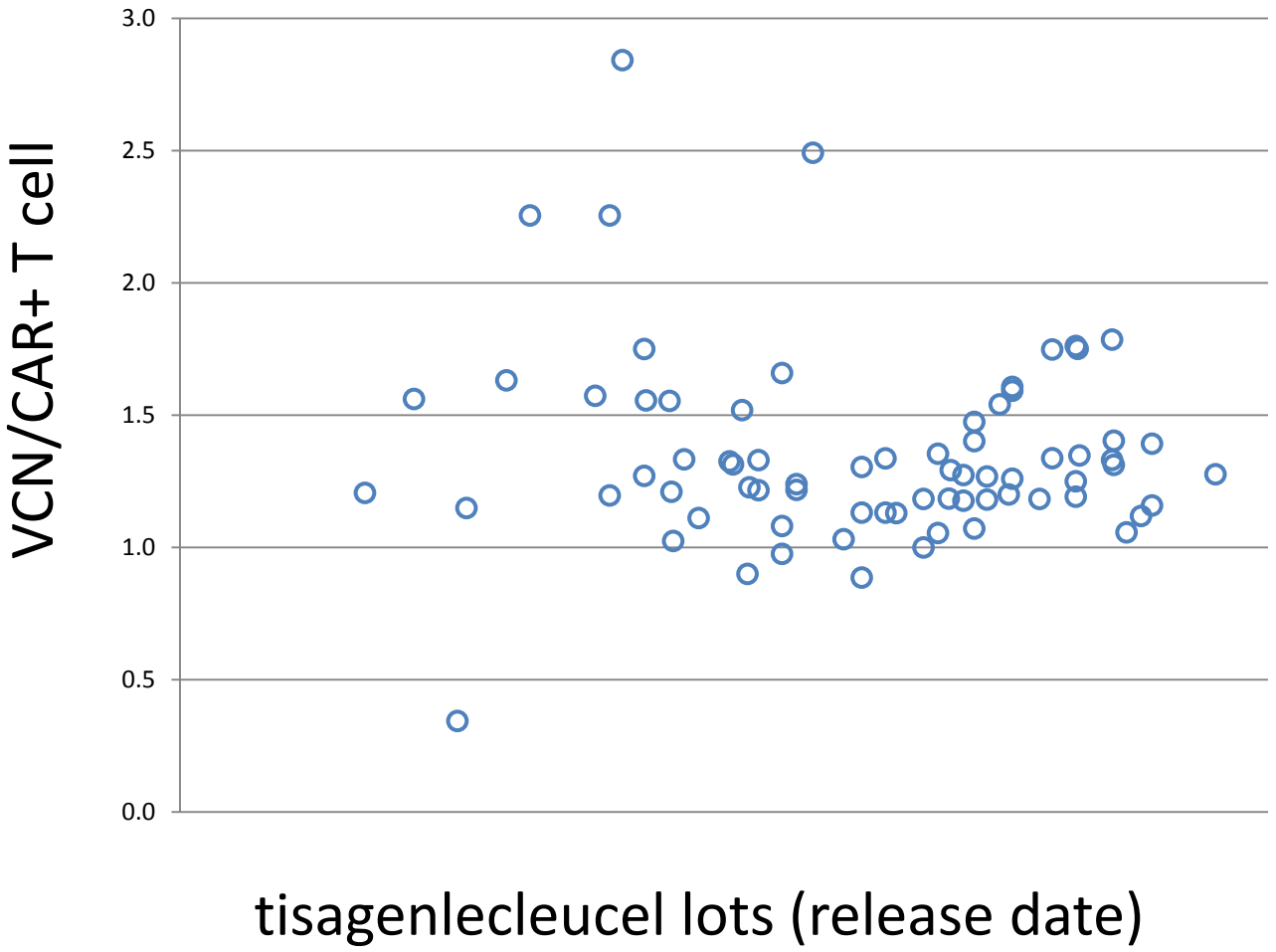
Example of lot release data

Transduction efficiency



Example of lot release data

Integrated vector



Tisagenlecleucel quality summary

- Dynamic product with the capacity to expand and differentiate following administration.
- Process controls are necessary to assure product consistency.
- Some of the product attributes are variable and may have limited value for predicting safety and efficacy.
- Products with variable characteristics were administered during clinical studies.
- The risks of RCR and insertional mutagenesis are minimized through vector design.
  - RCR has not been detected in tisagenlecleucel cell products or vectors.
  - Clonal dominance has not been observed.
  - Long-term follow-up of study subjects is still underway.

Discussion question #1

DISCUSSION: During tisagenlecleucel development, the applicant established product quality specifications to assess Chimeric Antigen Receptor (CAR) expression and T cell activity, including transduction efficiency by flow cytometry, vector copy number per cell, and IFN-γ production following stimulation by CD19+ cells.

Discussion question #1 (continued)

Please discuss the following aspects of the control of product quality of tisagenlecleucel with respect to identity, safety, purity and potency:

a. The design of the CAR construct and viral vector.
b. The assessment of CAR expression and T cell activity through
    I. The number of transduced T cells
    II. The number of vector copies per cell
    III. Antigen-specific T cell function (e.g., IFN-γ production and cytotoxicity upon stimulation)
c. Any other measurements, such as T cell subpopulations (cell surface marker characterization), that could provide greater assurance of product quality.

Discussion question #2

DISCUSSION: Potential safety concerns with tisagenlecleucel and other retrovirus-based gene therapy products include generation of replication competent retrovirus (RCR) and insertional mutagenesis. Strategies to address these concerns include vector design and product testing.

Discussion question #2 (continued)

a. Please discuss how vector design impacts the risk of RCR.
b. Please discuss how vector design impacts the risk that insertional mutagenesis might cause secondary malignancies.
c. Please discuss the extent to which product testing can mitigate the risk of RCR and insertional mutagenesis.

Thank you!

BLA 125646

Tisagenlecleucel

Novartis Pharmaceuticals Corporation

Clinical Presentation
Oncologic Drugs Advisory Committee Meeting
July 12, 2017
Maura O'Leary, MD
CBER/OTAT
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Clinical Hematology Branch

Proposed Indication

Tisagenlecleucel is an autologous genetically modified immunocellular therapy indicated for the treatment of pediatric and young adult patients 3 to 25 years of age with relapsed/refractory (r/r) B-cell acute lymphoblastic leukemia (ALL)

Outline

- Issues for Discussion
- Disease Background and Current Therapies
- Study B2202 - Design
- Efficacy Results
- Safety Results
- Follow-up and Pharmacovigilance Study
- Overall Summary

Issues for Discussion

- Potential post-marketing considerations
  - Mitigation of short-term risks to patients from cytokine release syndrome (CRS) and neurotoxicities
  - Long-term follow-up to address potential risk of secondary malignancies from replication competent retroviruses (RCR) and insertional mutagenesis
  - Tisagenlecleucel persistence
- The overall benefit - risk profile for the treatment of pediatric and young adult patients with refractory or relapsed B-cell precursor ALL

Background

- **Pediatric ALL: 3100 cases in US per year in children and adolescents**
  - **80% are B cell precursor ALL (CD19 positive [CD19+])**
- **Relapse occurs in 15-20% of patients.**
- **Risk stratification for subsequent therapy after relapse is based on the time from initial diagnosis of ALL to relapse.**
- **Patients with refractory disease or relapse following salvage chemotherapy who achieve a remission are considered for allogeneic stem cell transplant (allo-SCT).**
- **Treatment options for patients who fail allo-SCT or have relapsed multiple times are limited and results are dismal.**

Treatment of Pediatric Relapsed ALL

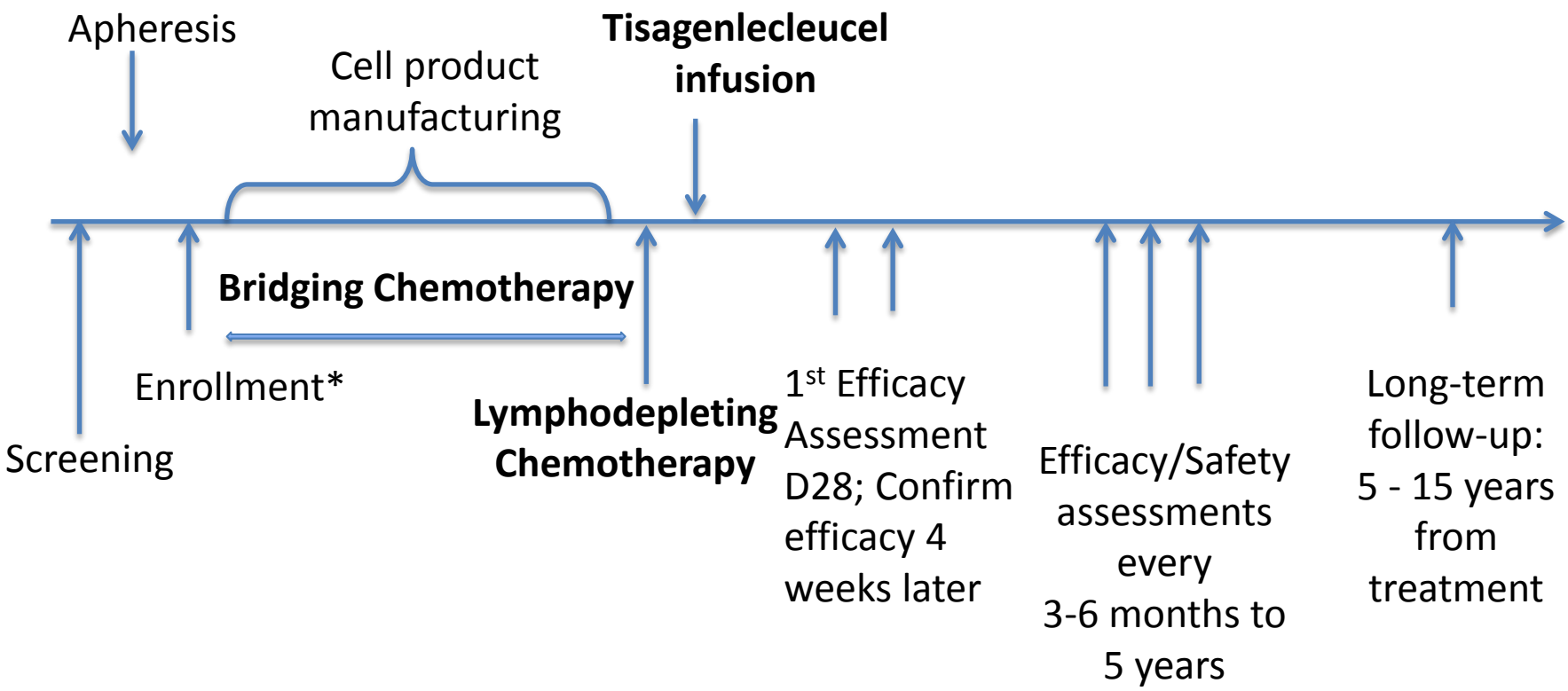
FDA-Approved Products	Approval Year	Endpoint	Clinical Benefit / Effect
BLINCYTO (n=70)	2014	ORR = CR + CRi	CR/CRh: 33% Median DOR – ORR: 6 months
CLOLAR (n=61)	2004	ORR = CR + CRi	CR/CRp: 19.7% Median DOR – ORR: 2.5 months

CR: complete remission; CRi: CR with incomplete hematologic recovery; DOR: duration of response; ORR: overall remission rate

Source: PI for BLINCYTO, CLOLAR

Published CR rates with chemotherapy for pediatric ALL in 2nd relapse 44%; 3rd marrow relapse 27% (Ko et al, 2010)

B2202: Treatment Schema



*Cell product acceptance required prior to enrollment

B2202: Enrollment Eligibility

- Systemic relapsed or refractory (r/r) B cell precursor ALL
- 3 years to 21 years at the time of initial diagnosis
- Acceptable leukapheresis product at manufacturing site
- Excluded active central nervous system involvement by malignancy

B2202 Tisagenlecleucel Dose

Single intravenous infusion

- **For subjects ≤ 50 kg: 2 - 5 x 10e6 viable transduced T cells / kg body weight**
- **For subjects > 50 kg: single dose of 1 - 2.5 x 10e8 viable transduced T cells**

B2202: Primary Endpoint

- **Primary endpoint: ORR (CR+CRi) within 3 months after tisagenlecleucel administration, as assessed by an Independent Review Committee (IRC)**
- **Primary study hypothesis: Ho: ORR ≤ 20% vs. Ha: ORR > 20%**

ORR - Overall Remission Rate
CR – Complete Remission
CRi – CR with incomplete hematologic recovery
Per National Comprehensive Cancer Network (NCCN) guidelines

B2202: Risk Mitigation Measures

- Pre-infusion eligibility criteria
- Novel CRS definition and grading system
- Complex CRS treatment algorithm
- Supportive measures for multi-organ dysfunction
- Study site selection and training
- Study site monitoring

B2202: Pre-Infusion Eligibility Criteria for Tisagenlecleucel

- Negative rapid test for influenza
- Adequate pulmonary and cardiac function
- Absence of active infection
- Availability on site of tocilizumab

B2202: Study Site Selection and Training

- Selection
  - Tertiary care centers
  - Expertise in thawing and infusion of cellular products
- Training
  - Pre-emptive measures (e.g., availability of tocilizumab prior to infusion)
  - Cytokine release syndrome grading and treatment algorithm
  - Subject or caregiver education on the early recognition of CRS symptoms

B2202: Overview of Long-Term Follow-Up (LTFU)

- Follow up periods
  - Years 0-5 years – Study B2202
  - Years 5-15 years – Study A2205B
- Objectives
  - Potential risks from tisagenlecleucel
    - Replication competent retrovirus (RCR)
    - New malignancies
  - Adverse events related to tisagenlecleucel from B2202 (transgene persistence)
  - Delayed adverse events of childhood leukemia

B2202: LTFU Assessments

- Investigational site or remote sites
- Years 0-2
  - Persistence every 3-6 months, annually when negative
- Years 2-5
  - Every 6 months for 5 years – transgene persistence*
  - Annually for RCR ^
- Years 5-10 years on Study A2205B
  - Annually (if negative): transgene persistence and RCR samples are stored
- Survival data: every 6 months

*After 5 years, if transgene persistence is no longer detected by 2 consecutive assessments, subjects will be followed via mail or phone call biannually with annual storage of samples.
^After 1 year, if all RCR samples are negative, archiving of collected samples is planned.

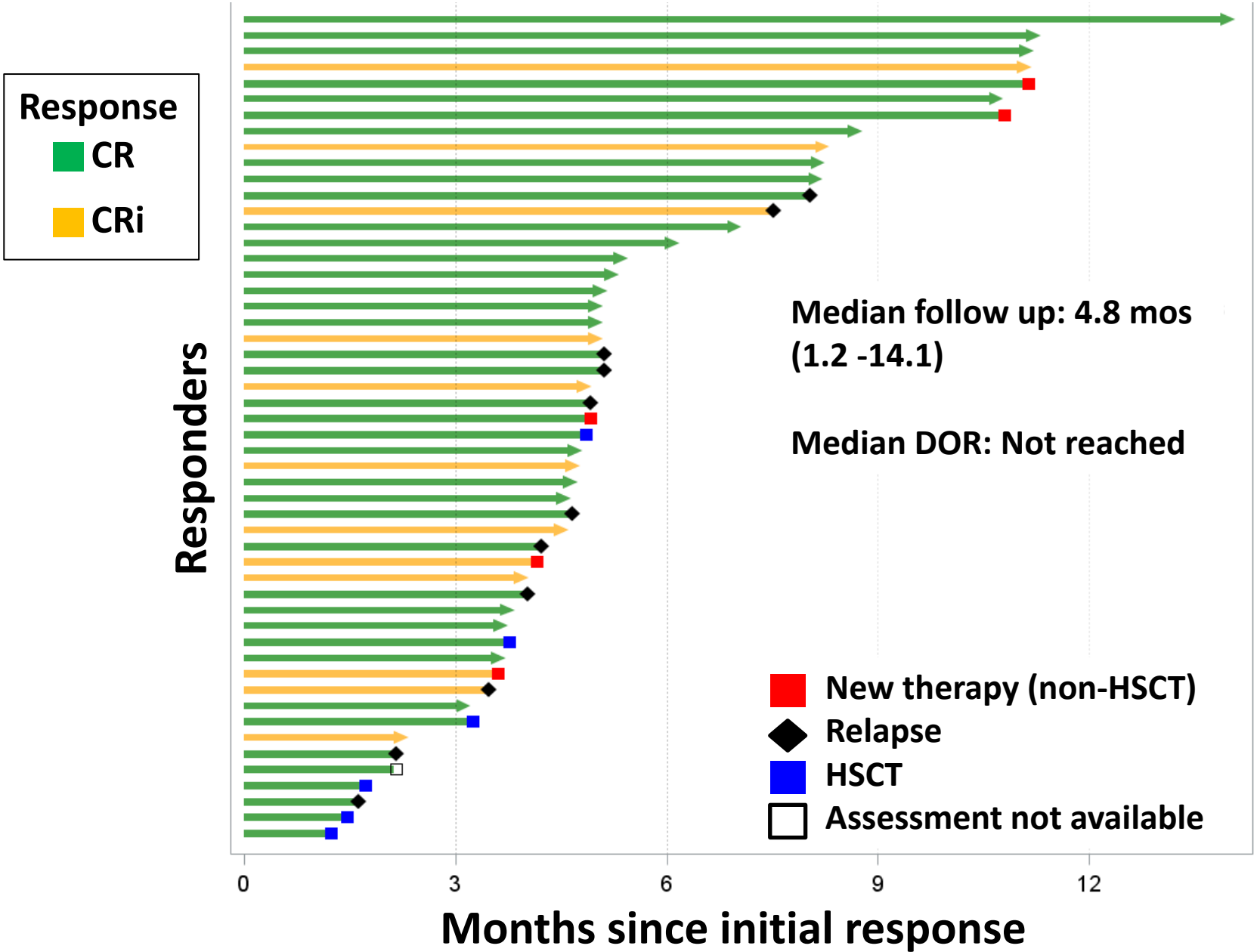
Efficacy Results: B2202

B2202 Efficacy Results

Primary Endpoint: ORR* (n=63)	
Response	**n (%)**
ORR* (95% CI)	52 [82.5%] (CI: 70.9, 91.0)
CR	40 (63%)
CRi	12 (19%)
No Response/Unknown	11 (18%)

* All were Minimum Residual Disease (MRD) negative

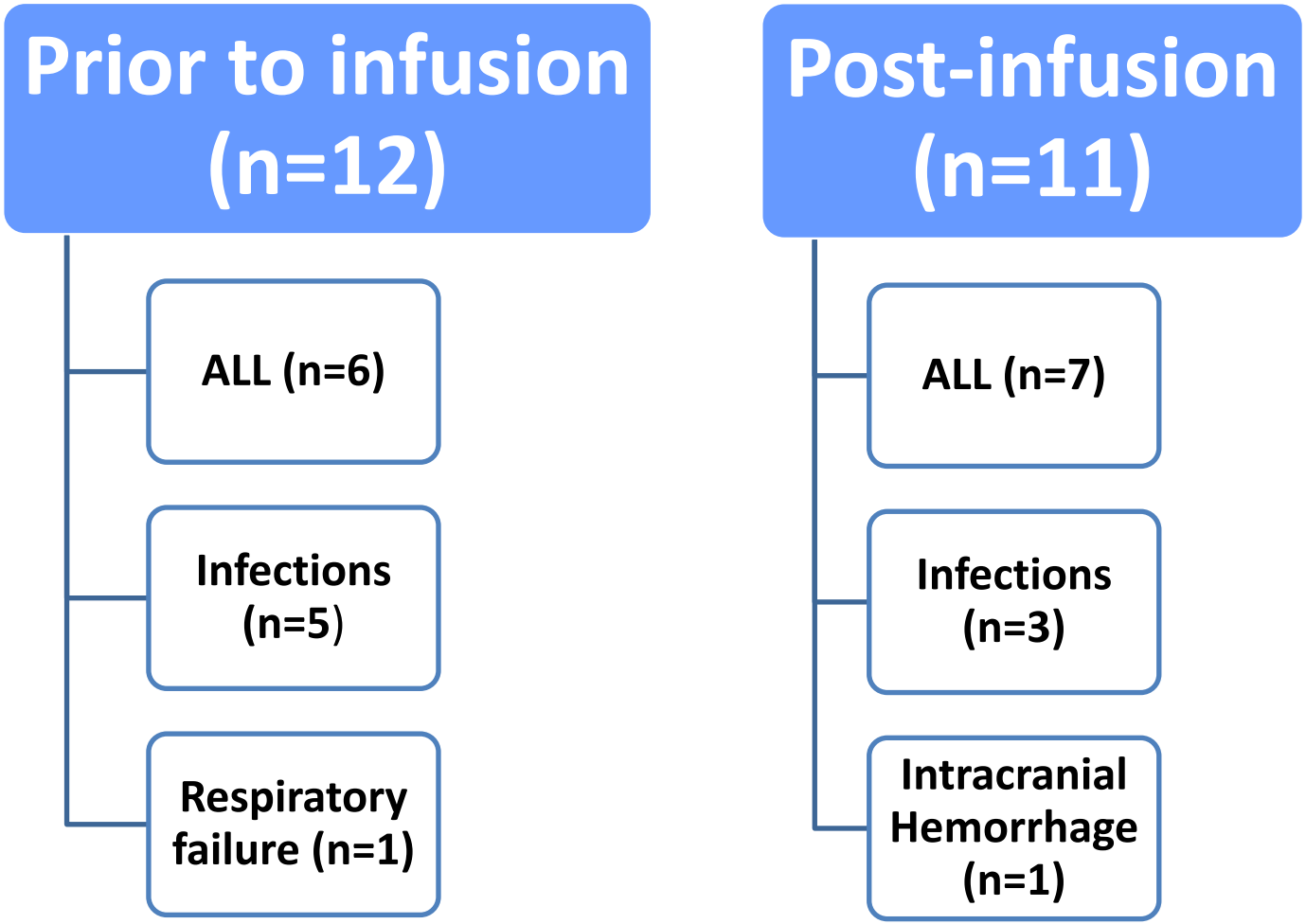
B2202: Duration of Response (DOR)



B2202: Safety

- Overview
- Deaths
- Cytokine release syndrome (CRS)
- Neurotoxicity
- Adverse events of special interest (AESI)
- Pharmacovigilance

B2202 Safety Results: Deaths



B2202 Safety Results: Cytokine Release Syndrome

- CRS - 78% of subjects
- Median time to onset: 3 days (1 - 22 days)
- Median duration of CRS: 8 days (1 - 36)
- Median time to Grade 3/4 CRS: 6 days (3 – 33)

- CRS severity was associated with high tumor burden of greater than 50% blasts in the bone marrow at screening

B2202 Neurotoxicity

- 30 subjects (44%) developed neurotoxicity
  - 10 subjects (15%) had Grade 3 events
  - 6/10 Grade 3 neurotoxic events were associated with Grade 3/4 CRS
  - No Grade 4 neurotoxicity
- One Grade 5 intracranial hemorrhage (ICH) due to coagulopathy
- Reversible
  - Supportive measures
  - Airway protection
  - Seizure prophylaxis
  - Corticosteroids +/- tocilizumab

B2202 CRS: Tocilizumab Use

- 68 subjects infused with tisagenlecleucel
- 53 subjects developed CRS (78%)
  - 14 Grade 3 (21%)
  - 18 Grade 4 (27%)
- Tocilizumab
  - 1 Treated with Grade 2
  - 7 Treated with Grade 3
  - 18 Treated with Grade 4
- 26 treated with tocilizumab for CRS, 16 – one dose, 7 – two doses, and 3 – three doses
- One patient received tocilizumab who did not have CRS

Supportive Care for CRS and Neurotoxicity

- Intensive Care Unit admissions
  - 31 subjects with a mean duration of 11 days
- Infections
  - 27 subjects with Grade 3/4 infections
- Assisted ventilation
  - 10 subjects
- Dialysis
  - 7 subjects with mean of 11 days
- Seizure prophylaxis
- Airway protection in encephalopathic subjects

B2202 Safety: Additional Adverse Events of Special Interest

Event	Grade	N (%)
Febrile Neutropenia	Grade 3/4	25 (37)
Cytopenias > 28 days	Grade 3/4	22 (33)
Infections	Grade 3/4	18 (27)
Congestive Heart Failure	Grade 3/4	3 (4)
Hemophagocytic Lymphohistiocytosis	Grade 3/4	3 (4)
Hypogammaglobulinemia	All Grades	20 (29)
Hypofibrinogenemia	Grade 3/4	32 (47)

B2202: Long-Term Safety Results

- Survival
  - Median overall survival (OS) has not been reached
  - The median follow-up time for survival is 6.9 months (9 days to 17.7 months)
- Generation of RCR – none
- Persistence – up to 366 days in responders
  - Hypogammaglobulinemia
  - Potential for malignant transformation

Summary of Safety Issues

- Post-Infusion: 0 - 60 days
  - 47% Grade 3/4 CRS events
  - 15% Grade 3 neurotoxicity
  - 27% Grade 3/4 infectious complications
  - 11 deaths post-infusion – progressive disease, infections, and one ICH
- Long-term follow-up
  - Limited duration of follow-up
  - No RCR or secondary malignancies
  - Persistence

Proposed Pharmacovigilance Plan (PVP)

- Post-Marketing Registry Study
  - Observational registry
  - Standard-of-care follow-up
  - No routine monitoring of RCR or persistence
- Post-marketing risk mitigation at treatment sites
  - Training for healthcare providers
  - Education for patients
  - Essential services

CCTL019B2401: Proposed Post-Marketing Registry Study

- Design
  - Multicenter, prospective, observational, non-interventional, planned safety study
- Enrollment
- Endpoints
  - Adverse events and laboratory abnormalities
  - Adverse Events of Special Interest
  - Growth and Development outcomes
  - Reproductive status and pregnancy outcomes
  - Disease outcomes (ORR, OS)
- Follow-up period (up to 15 years)

Potential Risk Mitigation Measures

- Risk Mitigation in the IND Phase
  - Treatment sites
    - Tertiary care
    - Expertise in thawing and infusion of cellular products
  - Training
    - Pre-emptive measures (e.g., availability of tocilizumab; reassessment of clinical status after lymphodepletion)
    - CRS grading and treatment algorithm
    - Subject or caregiver education - early recognition of CRS and neurotoxicities

Overall Summary

- Primary efficacy of MRD negative is ORR 82.5% (52/63)
- B2202 Study requirements
  - Site training
  - Complex CRS management algorithm and risk management
  - Site monitoring during the study
- Short-term risks
  - Life-threatening (CRS, neurotoxicity, coagulopathies and infections)
- Long-term risks
  - RCR and secondary malignancies: none reported, but short duration of follow-up
- Post-marketing studies
  - Registry study for known and potential adverse events
  - Mitigate acute risks related to CRS and neurotoxicity.

Discussion Question 3: Clinical

Please discuss risk mitigation measures for the serious risks of cytokine release syndrome and neurotoxicity with tisagenlecleucel.

Discussion Question 4: Clinical

For the tisagenlecleucel IND studies, the FDA requires 15 years of follow-up to monitor for subsequent malignant transformation.

Given the possibility of generation of replication-competent retrovirus and insertional mutagenesis, please discuss the duration of follow-up and the type of assessments that you would recommend for patients who receive marketed tisagenlecleucel.

Voting Question 5

Considering the efficacy and safety results of Study B2202, is the benefit-risk profile of tisagenlecleucel favorable for treatment of pediatric and young adult patients (age 3-25 years) with relapsed (second or later relapse) or refractory (failed to achieve remission to initial induction or reinduction chemotherapy) B-cell precursor acute lymphoblastic leukemia (ALL)?

Thank you for your attention