FDA Perspective on Dosage Optimization in Pediatric Oncology

Meeting of the Pediatric Oncology Subcommittee of the
Oncologic Drugs Advisory Committee
June 16, 2023

Kristin Wessel, MD, Division of Oncology 2 (DO2)
Ruby Leong, PharmD, LCDR USPHS, Division of Cancer Pharmacology I

Outline

- Importance of dosage optimization
- Unique aspects of pediatric oncology
- Misconceptions and potential issues
- Approaches to dosage optimization
- Opportunities for interactions with FDA

Dosage Optimization Definition

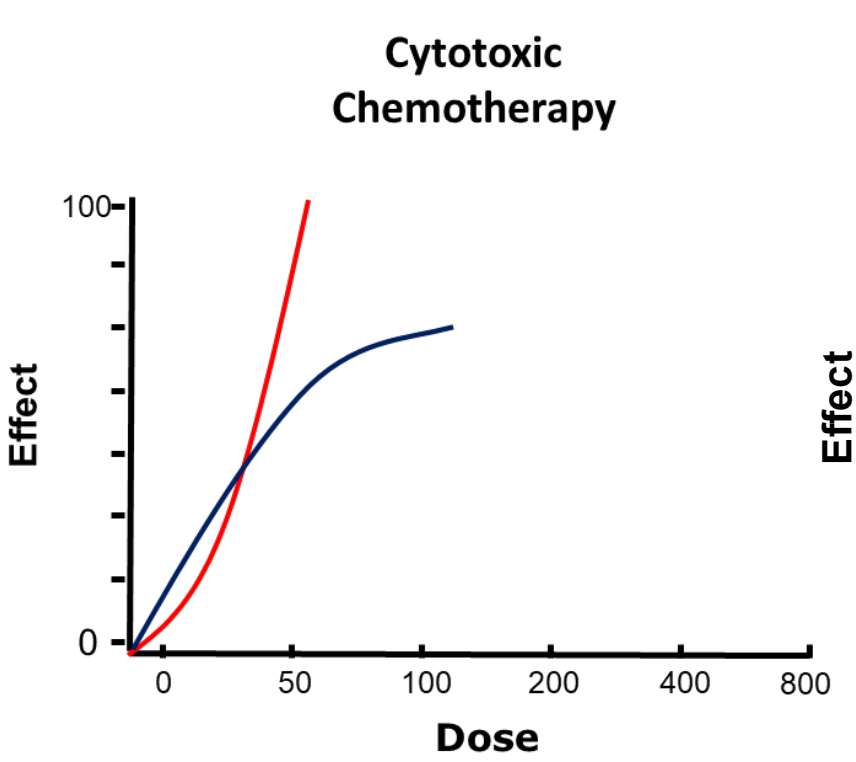
- **Dose**: quantity of drug
- **Dosage**: dose and schedule
- **Optimized dosage**: dosage that can maximize the benefit/risk profile or provide the desired therapeutic effect while minimizing toxicity

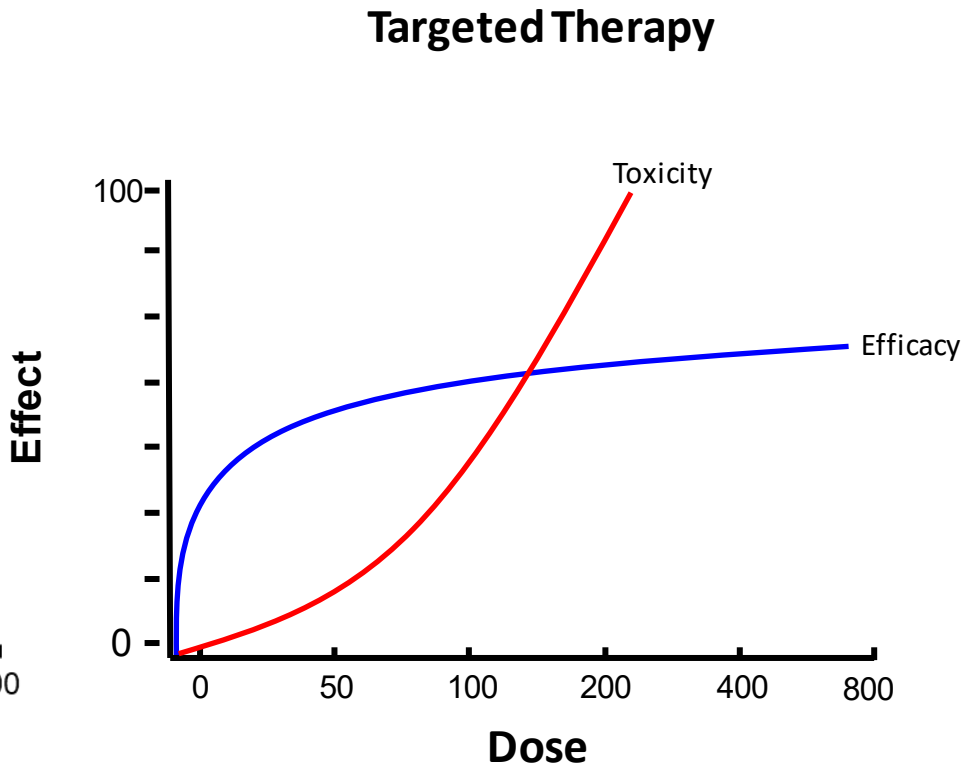
Optimizing the Dosage of Human Prescription Drugs and Biological Products for the Treatment of Oncologic Diseases | FDA

Importance of Dosage Optimization in Pediatric Oncology

- Maximization of benefit:risk balance
- Change in pediatric oncology drug landscape → more targeted therapies
- Unique considerations in pediatric vs. adult oncology

Dose-Response for Oncology Products





Key Differences

Cytotoxic Chemotherapies

- Steep dose-response, narrow therapeutic index
- MTD* reached
- Fixed number of cycles or short duration of treatment
- Many serious toxicities predictable, occur early
- Toxicities generally resolve with time off treatment

Molecularly Targeted Agents

- Different dose-response, potentially wide therapeutic index
- MTD may not be reached (or needed)
- Treatment for many months to years
- Long-term tolerability, including chronic symptomatic Grade 1-2 toxicities, very important
- Time off treatment less common for orally administered drugs

*MTD: maximum tolerated dose

Considering Low-Grade Toxicities

Diarrhea

DLT* →

Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Increase of <4 stools per day over baseline	Increase of 4-6 stools per day over baseline	Increase of ≥7 stools per day over baseline; hospitalization indicated	Life-threatening consequences (e.g., hemodynamic collapse)	Death

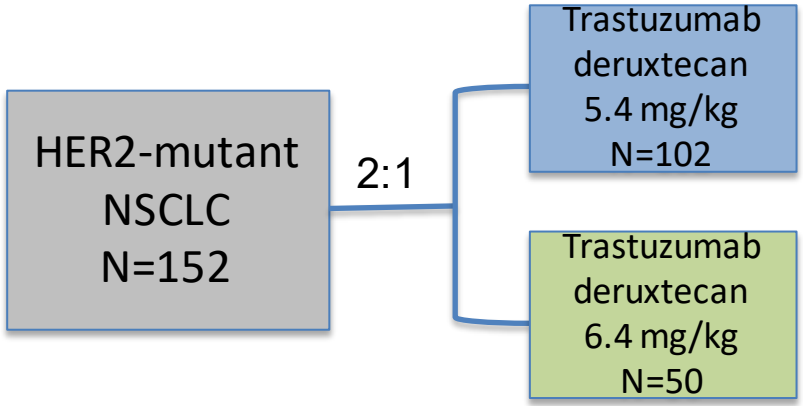
National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm

*DLT: Dose Limiting Toxicity

Real-World Example of Dosage Optimization in Adult Oncology

- Trastuzumab deruxtecan (T-DXd)
  - Initial accelerated approval in 2019 for HER2-positive breast cancer; dosage 5.4 mg/kg every 3 weeks
  - Boxed warning: Interstitial lung disease (ILD)/pneumonitis
- Accelerated approval in 2022 for non-small cell lung cancer (NSCLC) with activating HER2 mutations
  - DESTINY-Lung01: Single arm trial: T-DXd 6.4 mg/kg every 3 weeks
  - DESTINY-Lung02: Randomized dosage-optimization trial

DESTINY-Lung02 Study Schema



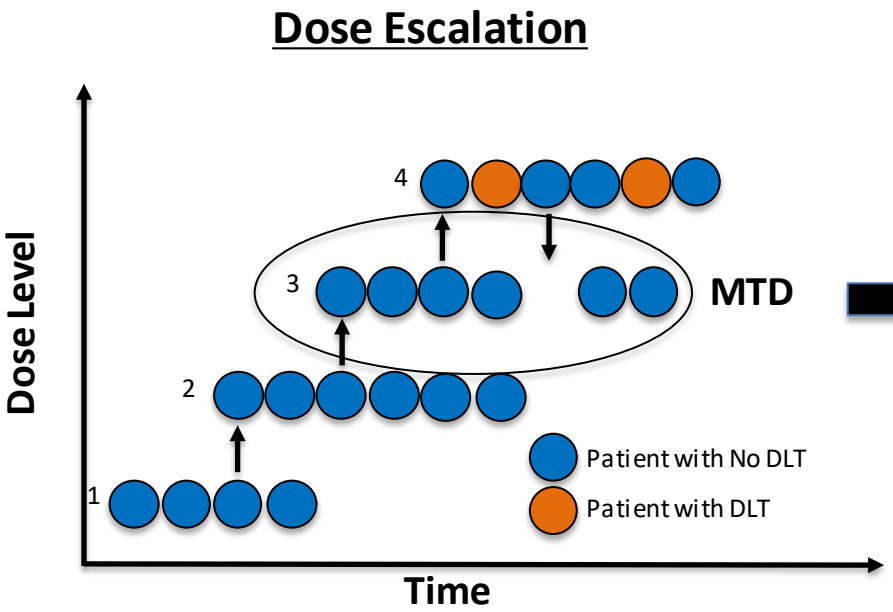
- Efficacy similar between groups
- Greater toxicity (ILD/pneumonitis) with higher dose → **5.4 mg/kg every 3 weeks**

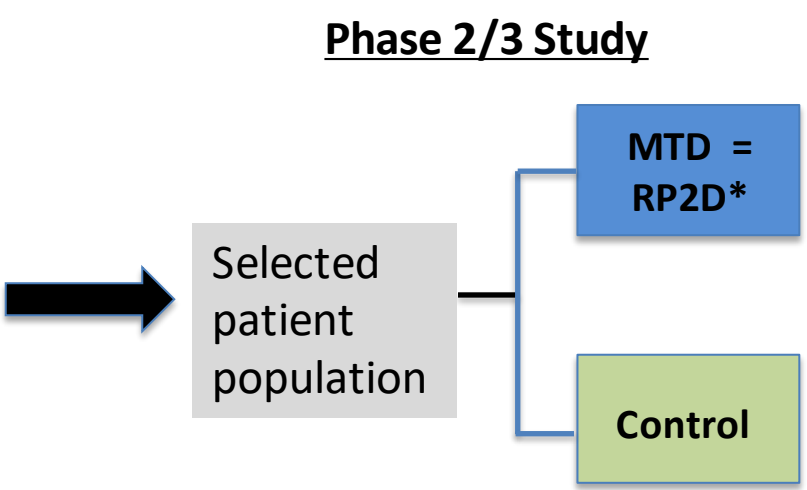
Real-World Example of Dosage Optimization in Pediatric Oncology

- **Crizotinib** approved in 2021 for pediatric patients 1 year of age and older and young adults with relapsed or refractory anaplastic lymphoma kinase-positive systemic anaplastic large cell lymphoma
- Based on **single-arm study with 26 patients** (ADVL0912)
  - dosage 280 mg/m^2 orally twice daily (**MTD**; n=20)
    - overall response rate (ORR) 90% (95% CI; 70%-97%)
  - dosage 165 mg/m^2 orally twice daily (n=6)
    - ORR 83% (95% CI; 44%-97%)
- **Exposure-efficacy relationship: flat** for ORR, complete response
- **Exposure-safety relationship:** increased incidence of **neutropenia and vision disorder** with higher exposure
- **Postmarketing commitment issued** to assess efficacy at lower dose that may provide a better benefit-risk profile

Merino et al, 2022 *Pediatr Blood Cancer*

Traditional Dosage Selection Strategy





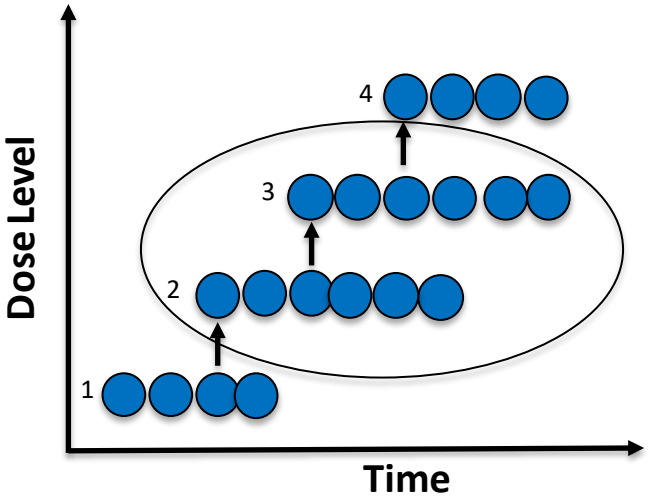
Hallmarks:

- Few patients at each dosage
- Short observation period for DLTs
- Emphasis on DLTs, but not other safety

*RP2D=Recommended Phase 2 dose

Example: Updated Dosage Selection Strategy

Dosage Escalation

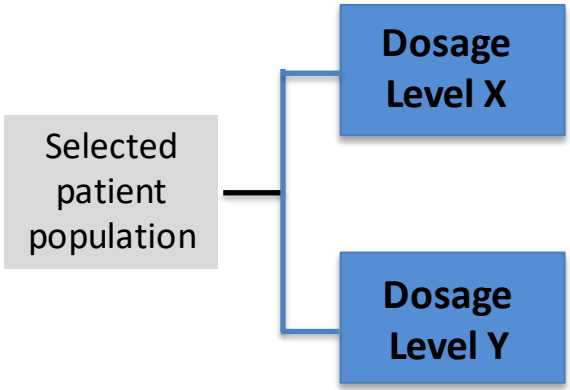


Identify target dosage range

Evaluate available data:

- PK*
- PD*
- Safety
- Tolerability
- Activity
- Adult data

Dosage Optimization

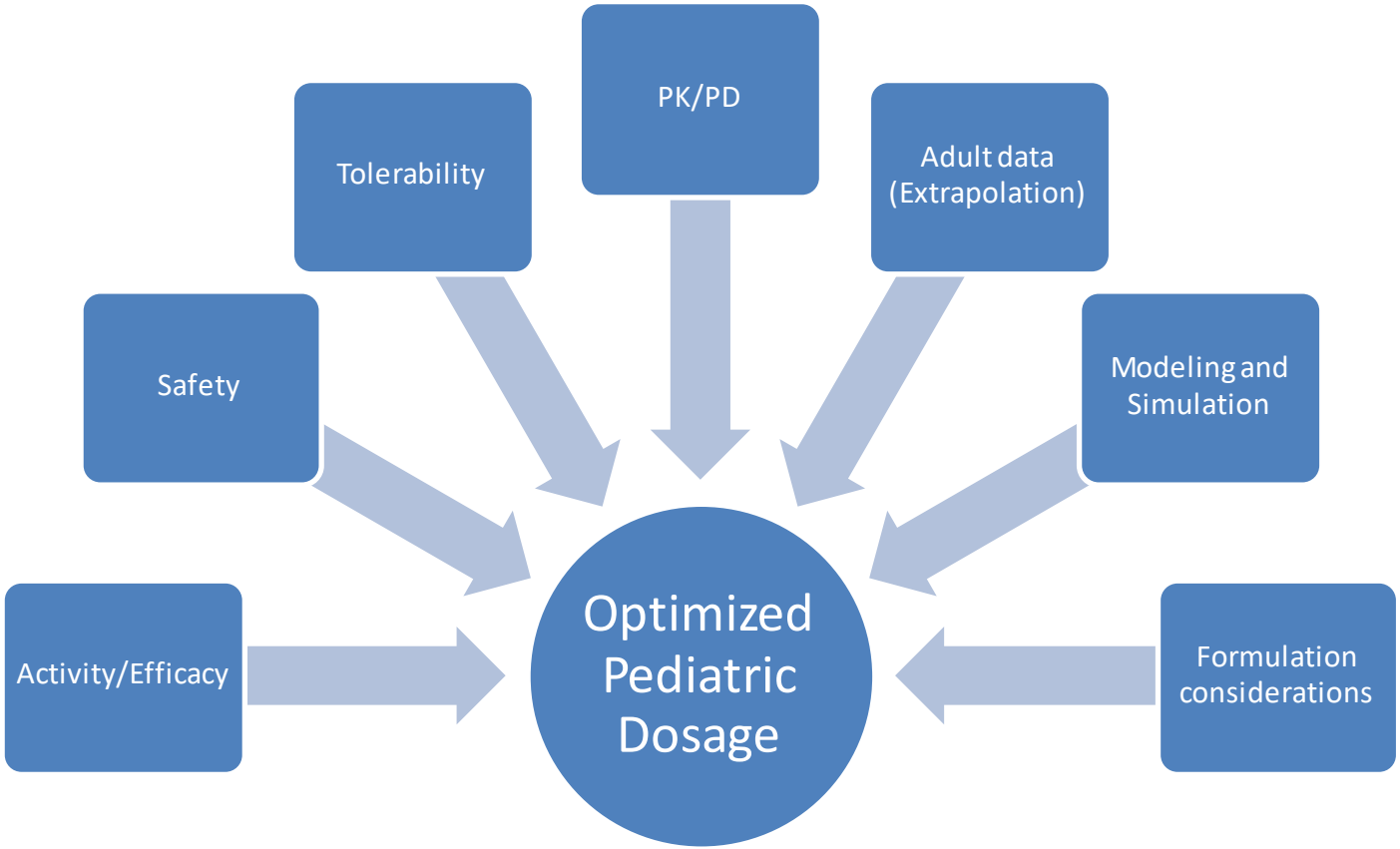


*PK: Pharmacokinetics
*PD: Pharmacodynamics

Unique Considerations in Pediatric Oncology

- PK/PD variability by patient age, organ function, body weight and body surface area (BSA)
  - Are different dosing strategies needed based on age?
  - PK and PD sampling schedules
- Formulation → ability to swallow, palatability, food effect
- Long term effects on growth, cognitive, and sexual development
- Rare cancers, small populations

Identifying Optimized Dosage



U.S. FOOD & DRUG ADMINISTRATION

Misconceptions

Misconceptions

- Identification of optimized dosage in adults is needed prior to initiation of trials in children
  - Drugs with potential to benefit pediatric patients should be studied as early as possible
  - First-in-human (FIH) trial can occur in pediatric patients with sufficient scientific justification and preclinical information

Misconceptions

- Pediatric monotherapy RP2D should be established prior to evaluation in combination
  - Early data from monotherapy can help support appropriate starting dosage for combinations
  - Consider overlapping toxicities, drug interactions, additive/synergistic activity

Misconceptions

- Dosage optimization is not feasible in rare cancers
  - Possible to incorporate principles of dosage optimization while tailoring to specific development program

U.S. FOOD & DRUG ADMINISTRATION

Potential Issues in Pediatric Oncology Dosing

Potential Issues in Pediatric Oncology Dosing

1. MTD-based dosage selection

- Dosage selection based on only short-term safety

- **Dosage should be selected based on the totality of PK, PD, activity/efficacy, and safety/tolerability data**

Totality of Data to Inform Dosage in Pediatric Oncology

- Pharmacokinetics/pharmacodynamics
  - Identify appropriate PK sampling schedules for age/size
- Activity/efficacy
  - Incorporate understanding of adult data as applicable
- Safety
  - Incorporate understanding of adult data as applicable
  - Short-term and long-term monitoring as appropriate
- Tolerability
  - Patient reported outcome data (e.g., National Cancer Institute's Pediatric Patient Reported Outcome-Common Terminology Criteria for Adverse Events [ped-PRO-CTCAE])

Totality of Data to Inform Dose in Pediatric Oncology: Tolerability

- Clinical outcome assessment (COA) data
  - By patients
  - By caregivers
- May provide complementary data to inform dosage optimization

Ped-PRO-CTCAE® ITEMS-ENGLISH

Item Library Version 1.0

PRO-CTCAE® Symptom Term: Diarrhea
a. In the past 7 days, how often did you have runny or watery poop?
○ Never
○ Sometimes
○ Most of the time
○ Almost all the time
b. In the past 7 days, how much did having runny or watery poop keep you from doing things you usually do?
○ Not at all
○ Some
○ A lot
○ A whole lot

National Cancer Institute (NCI) Pediatric Patient Reported Outcome (PRO) Common Terminology Criteria for Adverse Events (CTCAE), https://healthcaredelivery.cancer.gov/pro-ctcae/instrument-ped.html

Potential Issues in Pediatric Oncology Dosing

2. Dose is higher than adult RP2D without adequate justification

a. Escalation beyond adult RP2D without adequate justification

b. Investigational drug in combination with chemotherapy

- Proposed pediatric body weight-adjusted dose of the drug in combination is higher than the adult equivalent single agent dose
- **Due to potential overlapping toxicities with the combination, consider approaches such as reduction of the initial pediatric dose to lower than the adult equivalent single agent dose**

Potential Issues in Pediatric Oncology Dosing

3. No planned dosage exploration

- Evaluation of only one dose level

- **Exploration of more than one dose level to further understand dose and exposure relationships with efficacy and safety**

Potential Issues in Pediatric Oncology Dosing

4. Dosing issues due to oral formulation

- Lack of an age-appropriate formulation (e.g., lack of appropriate strengths to cover dosages needed for the intended age range)
- Manipulating solid dosage forms, such as crushing tablets or opening capsules and administering with a vehicle can impact drug exposure→ potential safety or efficacy concerns
  - **Early consideration of development of an age-appropriate formulation**
  - **Relative bioavailability study of the pediatric and adult formulations should also be conducted (in adults) as early as feasible**

Approaches to Dosage Optimization in Pediatric Oncology

1. Leveraging adult data to inform pediatric dosage

2. Pediatric extrapolation approach

3. Applications of model-informed drug development (MIDD)

How Adult Data Can Inform Dosage Selection in Pediatric Trials

Is there information in adults to inform pediatric dosing?

YES

- Is the adult dosage adequately supported?
- Is the adult approved dosage for the **same** indication or a **different** indication?
- If an adult RP2D has been identified, the adult data (safety, tolerability, efficacy, PK, PD) can be leveraged to inform dosing in pediatric studies

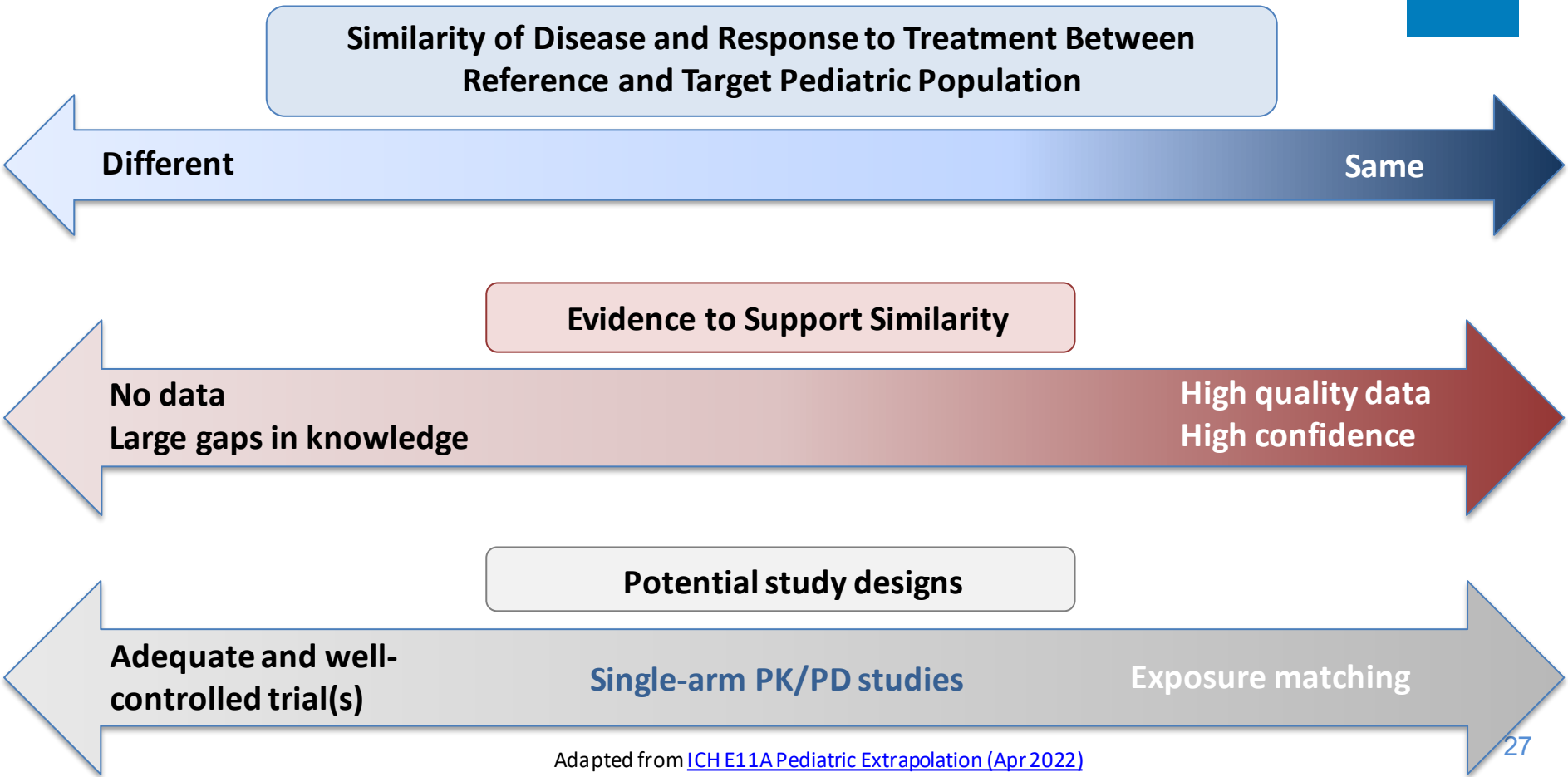
NO

- If FIH study is in pediatric population or if adult study is ongoing and an adult RP2D has not been identified

What other information (e.g., PK, PD, and safety) can be used to inform pediatric trial design and safety risks?

Leverage modeling and simulation for all the scenarios

Pediatric Extrapolation Approach



Adapted from ICH E11A Pediatric Extrapolation (Apr 2022)

Applications of Model-Informed Drug Development (MIDD)

Pediatric Dose Selection and Optimization	• Identify covariates (weight, BSA, age, etc.) • Incorporate pediatric ontogeny • Predict PK in various age groups
Leveraging Knowledge for Bridging Gaps	• Exposure-response for efficacy and safety • Leveraging prior knowledge from adults or other drugs from the same class
Informing Clinical Trial Design	• Determine appropriate dosages for evaluation across the pediatric age range, sample size, optimal PK sampling for pediatric patients

Adapted from Role of Model-Informed Drug Development in Pediatric Drug Development, Regulatory Evaluation, and Labeling (Bi et al. 2019)

Opportunities for Interactions with FDA

- Early discussions with FDA are recommended for input on dosage optimization strategies
  - Pre-Investigational New Drug (IND) meeting
  - End of Phase 1/2 meeting
  - Type D meeting – intended to focus on a narrow set of issues
- Public Meetings/Workshops
- International collaboration with European Medicines Agency
  - Pediatric Cluster teleconferences
  - Common Commentary Process
  - Formal Parallel Scientific Advice (PSA)

Summary

- Timely dosage optimization important to ensure best possible quality of life, minimize potential for dosage interruptions and discontinuations, and minimize chance of late effects, while maintaining efficacy

- Consider totality of data and approaches such as pediatric extrapolation and MIDD

- No one size fits all approach; acknowledge need for flexibility

- Early discussions with FDA are recommended to facilitate integration of dosage optimization with seamless drug development

Dosage Optimization Resources

Multi-Stakeholder Meetings

- Friends of Cancer Research Annual Meeting 2021
- Friends of Cancer Research White Paper 2021
- FDA- ASCO Workshop: "Getting the Dose Right"

Publications

- The Drug-Dosing Conundrum in Oncology- When Less is More
- How to Get the Dose Right
- Improving Dose-Optimization Processes Used in Oncology Drug Development to Minimize Toxicity and Maximize Benefit to Patients

Guidance Documents

- ICH E4: Dose-Response Information to Support Drug Registration
- Exposure- Response Relationships
- Optimizing the Dosage of Human Prescription Drugs and Biological Products for the Treatment of Oncologic Diseases

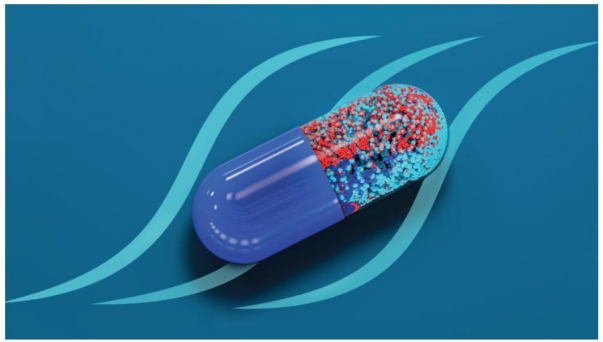
Oncology Center of Excellence

Project Optimus

Mission: To ensure that dosages of cancer drugs are optimized to maximize efficacy as well as safety and tolerability

Who We Are: A multidisciplinary team of medical oncologists, clinical pharmacologists, biostatisticians, toxicologists, and other scientists with expertise in key facets of dosage optimization

More Info: Project Optimus website



Pediatric Development and MIDD Resources

Publications

- Role of Model-Informed Drug Development in Pediatric Drug Development, Regulatory Evaluation, and Labeling

Guidance Documents

- ICH E11A Pediatric Extrapolation
- General Clinical Pharmacology Considerations for Pediatric Studies of Drugs, Including Biological Products Guidance for Industry
- Considerations for the Inclusion of Adolescent Patients in Adult Oncology Clinical Trials

FDA MIDD Program

- Model-Informed Drug Development Paired Meeting Program


FDA
U.S. FOOD & DRUG
ADMINISTRATION

U.S. FOOD & DRUG ADMINISTRATION

Dosage Optimization Considerations for Chimeric Antigen Receptor (CAR) T-Cell Products

Meeting of the Pediatric Oncology Subcommittee of the
Oncologic Drugs Advisory Committee
June 16, 2023

Xiaofei Wang, PhD

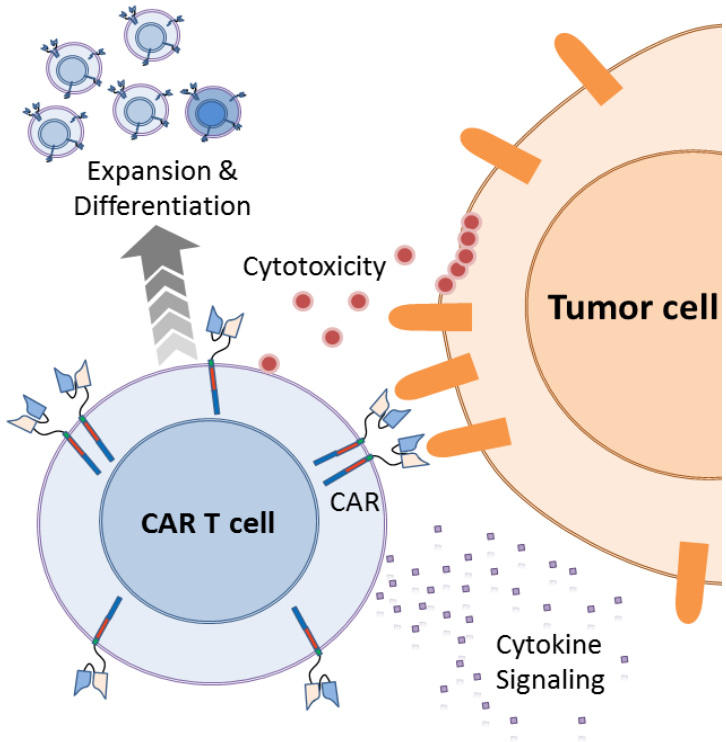
Office of Clinical Evaluation
Office of Therapeutic Products
Center for Biologics Evaluation and Research

Outline

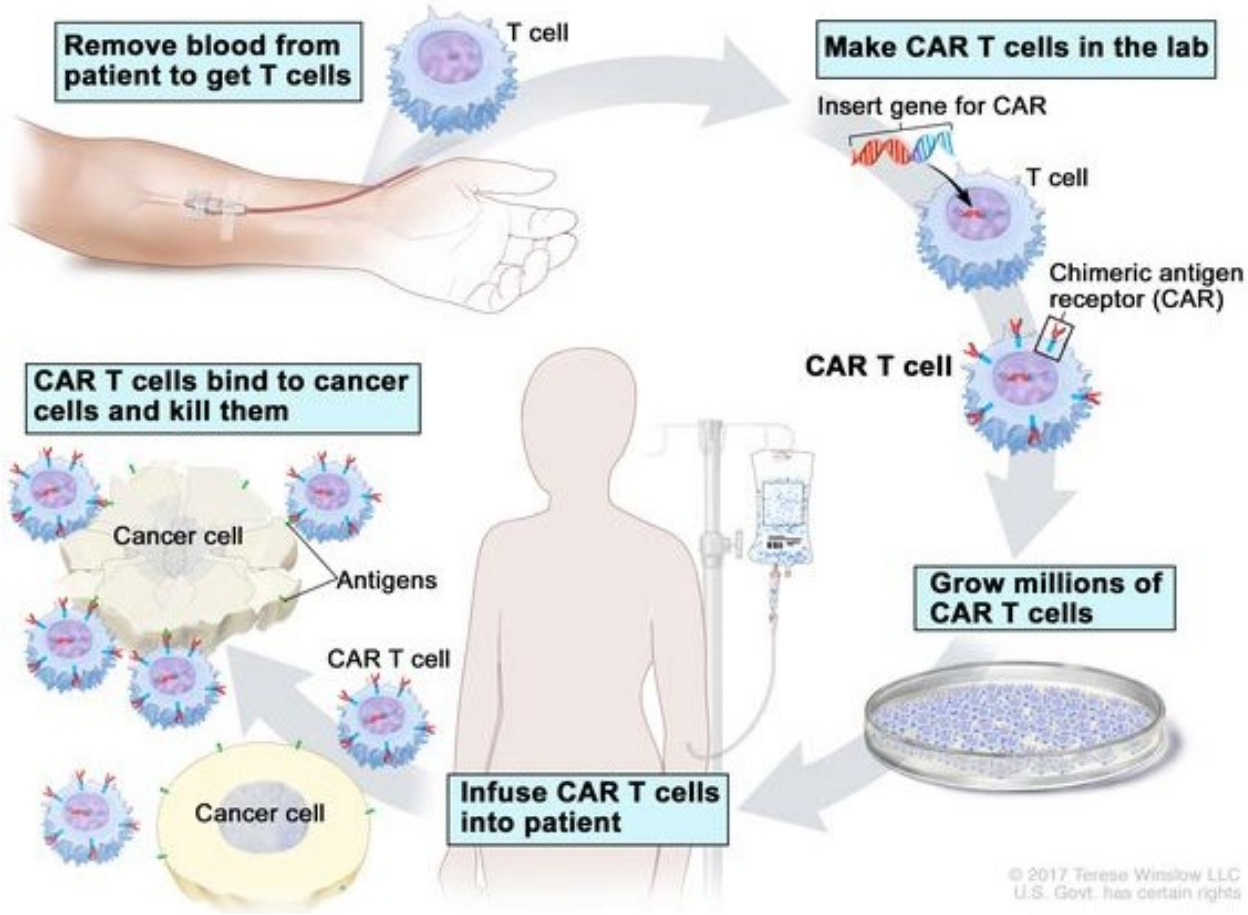
- CAR T-cell therapy
- Dose considerations in the development of CAR T-cell therapy
- Overview of dose/exposure-response relationships for approved CAR T-cell products
- Dose optimization in the development of CAR T-cell therapy
- Regulatory resources

CAR T Cell Therapy:
Chimeric Antigen Receptor T-Cell Therapy

- Genetically engineered T-cell immunotherapy
- Targets cell surface antigen
  - Not restricted by human leukocyte antigen (HLA)
  - Retains endogenous T-cell receptors (TCRs); can be removed by genome editing
- Living drug
  - Dynamic cell population during manufacturing process
  - Promotes cell expansion and differentiation
- Activates T cell signaling
  - Lysis of tumor cells
  - Cytokine signaling
  - Stimulation of bystander immune cells



CAR T-Cell Therapy



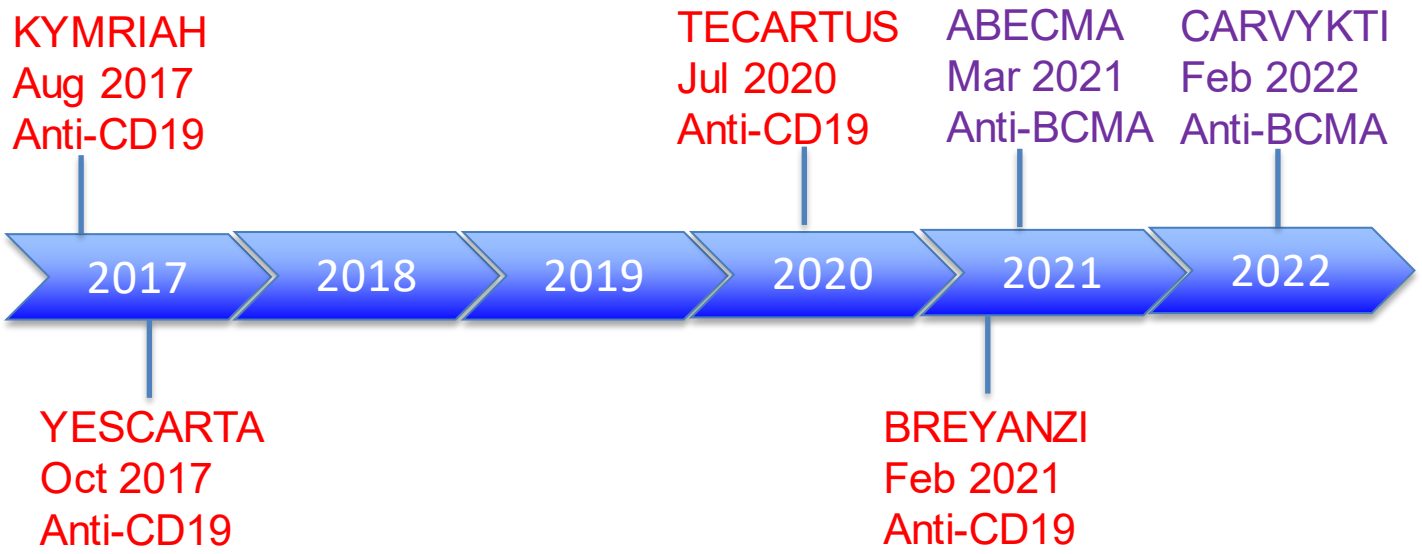
CAR T-Cell Therapy vs. Conventional Therapies

CAR T-Cell Therapy	Conventional Therapies
Ex vivo genetically modified T-cells	Small molecules, peptides, proteins, etc.
Drug composition: drug product comprised of different T-cell subsets, may be unique for each subject (e.g. autologous CAR T-cells)	Fixed drug product composition: single active pharmaceutical ingredient (API) or fixed-dose combination
Route of Administration: infusion, mostly intravenous infusion	Route of Administration: various
Dosing regimen: therapeutic effects may be achieved via single-dose treatment (e.g. autologous CAR T-cells for hematological malignancies)	Dosing regimen: generally therapeutic effects may be achieved via multiple-dose treatment
Pharmacokinetics: conventional absorption, distribution, metabolism, and excretion (ADME) concepts may not apply: a living drug, cells proliferate in vivo after administration (Mass balance concept does not apply)	Pharmacokinetics: conventional ADME concepts apply

Autologous vs. Allogeneic CAR T-Cell Therapy

Autologous CAR T-Cell Therapy	Allogeneic CAR T-Cell Therapy
From patients' own T-cells, unique for each subject (product heterogeneity)	From healthy donor's T-cells, universal "off-the-shelf" product
Increased risks of potential therapy delays or manufacturing failures	Decreased risks of potential therapy delays or manufacturing failures
Long-term persistence is observed	Concerns of long-term in vivo persistence
No concerns of graft-versus-host-disease (GvHD)	Concerns of GvHD

Approved CAR T-Cell Therapies



For pediatric cancer:

KYMRIAH® (tisagenlecleucel) Suspension for IV infusion

Patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (BCP ALL)

0.2 – 5.0 x 10^6 cells/kg (≤ 50 kg)
0.1 – 2.5 x 10^8 cell/kg (> 50 kg)

BCMA: B-cell maturation antigen

Dose Considerations in Clinical Development of CAR T-Cell Therapy

- Starting dose in first-in-human studies
  - Based on data from pre-clinical and available clinical experiences of the product or similar CAR T product(s)
- Dose escalation
  - Generally, do not recommend intra-subject dose escalation
- Dosing regimen
  - Autologous CAR T-cells for hematological malignancies: generally single dose
  - Autologous CAR T-cells for solid tumors: single or repeat doses
  - Allogeneic CAR T-cells: single dose and repeat doses
  - Considerations for repeat-doses:
    - potential safety issues with multiple rounds of lymphodepletion
    - observation of lower CAR T-cell expansion compared to first dose due to antigen escape and T cell exhaustion

Dose Considerations in Clinical Development of CAR T-Cell Therapy (cont.)

- Considerations for dose selection
  - Product characteristics and manufacturing process
  - Lymphodepletion
  - Indications
  - Route of administration
  - Exposure-response relationships
  - Safety and efficacy profiles

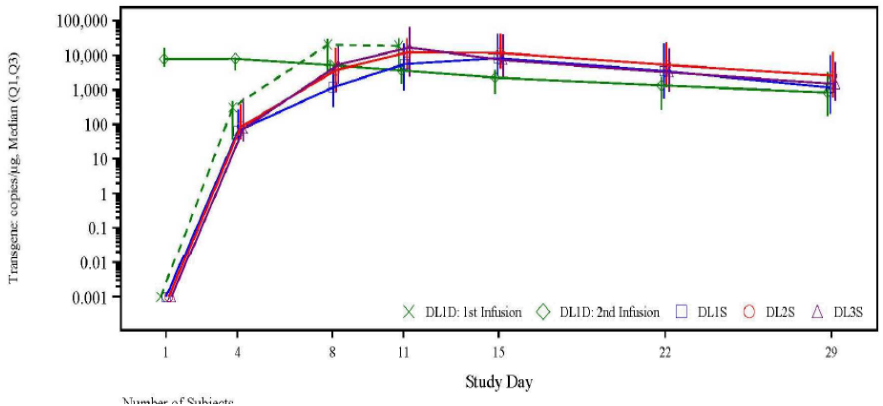
Clinical Development of CAR T-Cell Therapy for Pediatric Patients

- Experiences with Kymriah "indicated for patients up to 25 years of age with BCP ALL"
  - Wide dose range: no definitive dose-response due to limited data
- Data from adults may inform dosing in children
  - Inclusion of adolescents in adult trials is encouraged if scientifically justified
  - Distinct biologics of malignancies between children and adults
  - Early phase clinical studies may need to enroll both children and adults
- Dose of CAR T-cell therapy in pediatrics:
  - Body weight (BW) or body surface area (BSA)-based dosing rather than flat doing is recommended

Experiences with CAR T-Cell Therapy: Dose-Exposure Response Relationships

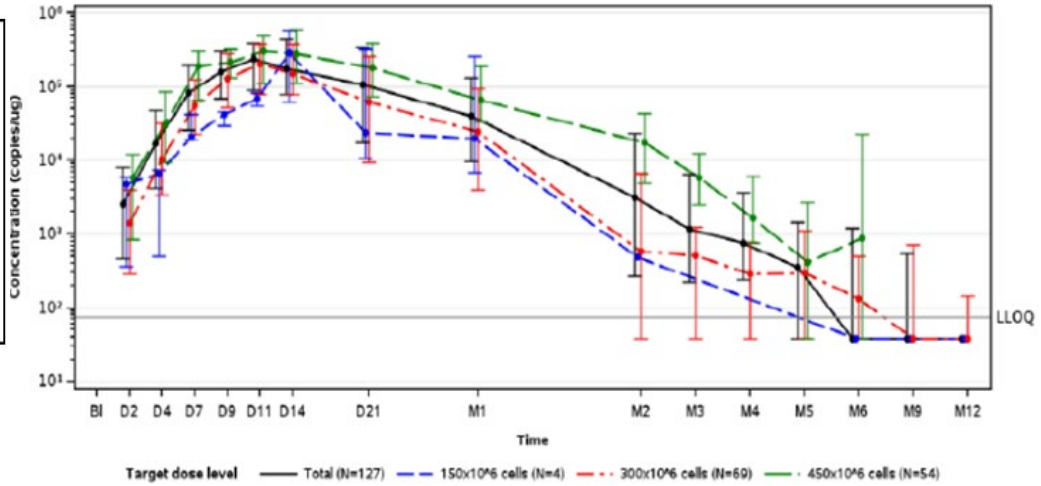
- Breyanzi (anti-CD19): no evident dose-exposure relationship
- Abecma (anti-BCMA): positive dose-exposure with overlaps between doses due to heterogeneity of drug product

Breyanzi



Dose level 1 (DL1): 50 x 10^6 CAR+ T cells
Dose level 2 (DL2): 100 x 10^6 CAR+ T cells
Dose level 3 (DL3): 150 x 10^6 CAR+ T cells

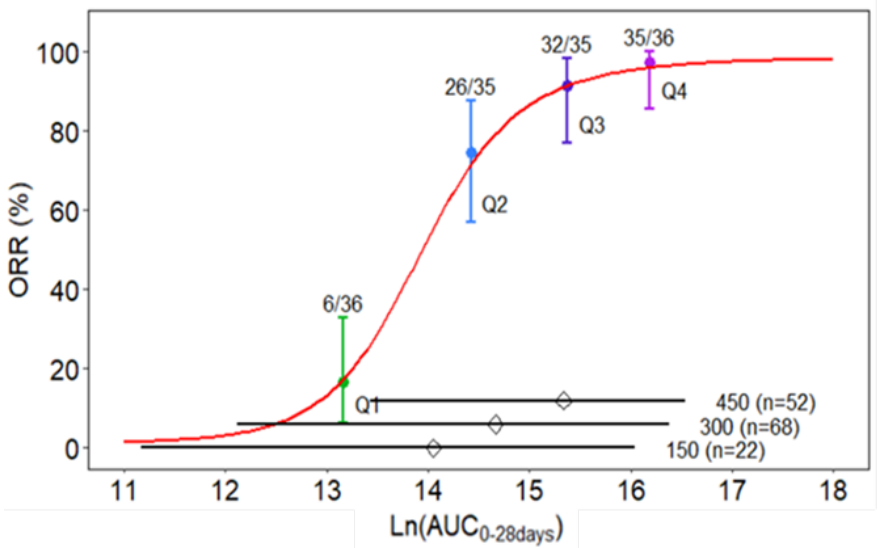
Abecma

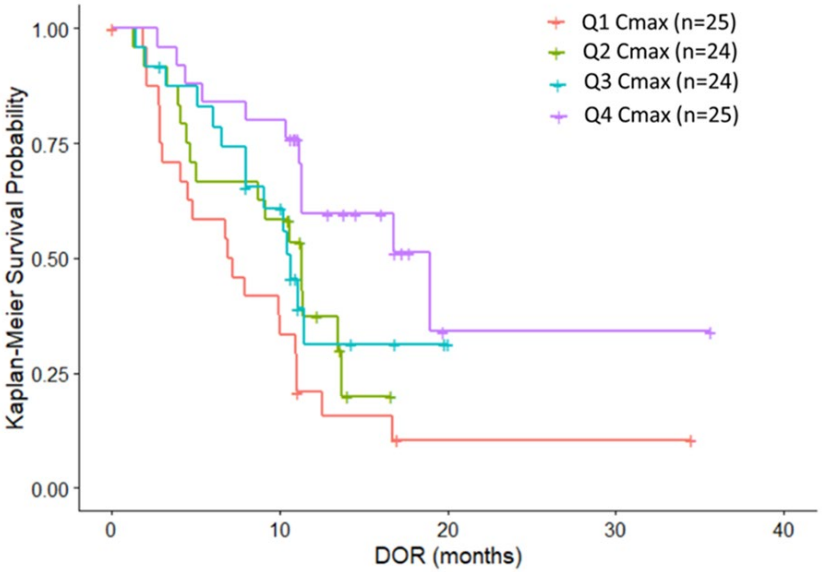


BLA 125714 & BLA 125736 clinical pharmacology reviews

Experiences with CAR T-Cell Therapy: Exposure-Response Relationships

- Efficacy
  - Treatment responders tend to have higher CAR T-cell expansion than non-responders



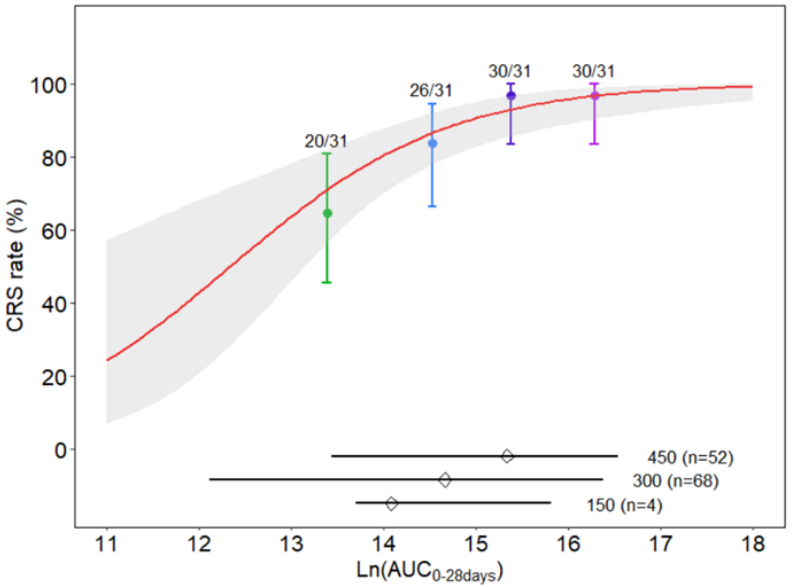


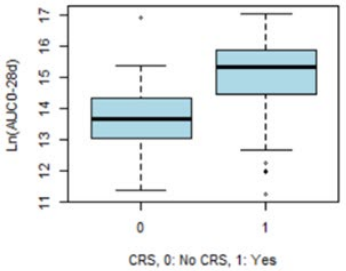
ORR: objective response rate; DOR: duration of response
Ln(AUC0-28days):natural log of area under the curve of 0-28 days

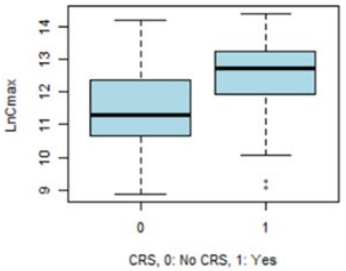
BLA 125736 Abecma clinical pharmacology review

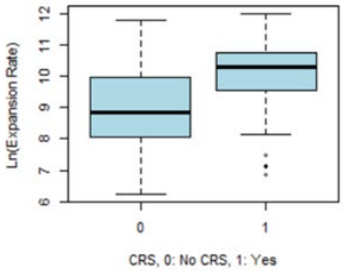
Experiences with CAR T-Cell Therapy: Exposure-Response Relationships (cont.)

- Safety – Cytokine Release Syndrome (CRS)
  - Subjects with CRS had higher CAR T-cell exposure, compared to subjects without CRS









BLA 125736 Abecma clinical pharmacology review

Dose Optimization for CAR T-Cell Therapy

- Dose optimization is critical in the development of CAR T-cell therapy
  - Hematological malignancies: generally single dose
- Dose optimization is challenging
  - Overlapping exposure profiles
- General principles of oncologic drug product dose optimization apply to CAR T-cell therapy:
  - Dose optimization is based on the totality of the data from safety, efficacy and pharmacokinetic /pharmacodynamic profiles
- Early communication with FDA review team is encouraged to receive advice on dose optimization
  - Novel study designs may be needed

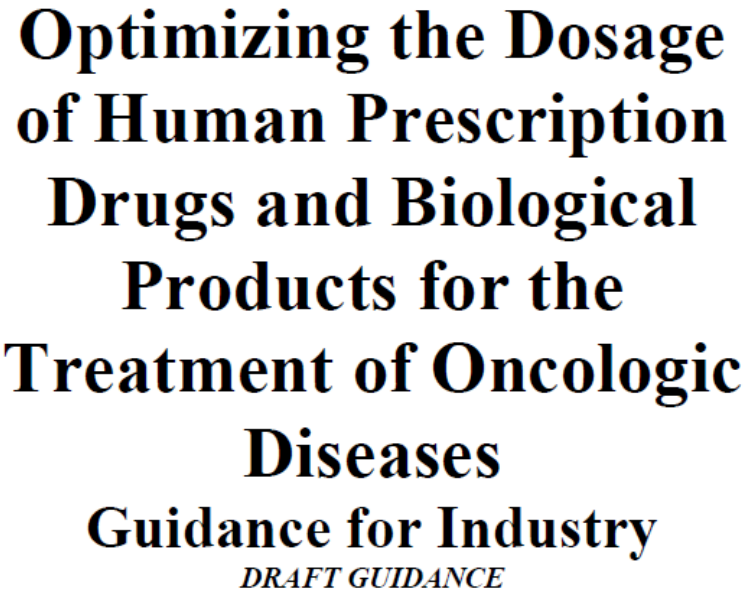
FDA Guidance Documents for Cell and Gene Therapies (Selected)

Cellular & Gene Therapy Guidance Website: https://www.fda.gov/vaccines-blood-biologics/biologics-guidances/cellular-gene-therapy-guidances

- Considerations for the Development of Chimeric Antigen Receptor (CAR) T Cell Products (Draft, March 2022) https://www.fda.gov/media/156896/download
- Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products (June 2015) https://www.fda.gov/media/106369/download
- Long Term Follow-Up After Administration of Human Gene Therapy Products (Draft, July 2018) https://www.fda.gov/media/113768/download
- Biomarker Qualification: Evidentiary Framework (Draft, December 2018) https://www.fda.gov/media/122319/download
- Preclinical Assessment of Investigational Cellular and Gene Therapy Products (November 2013) https://www.fda.gov/media/87564/download

FDA Guidance Documents (cont'd)

- Optimizing the Dosage of Human Prescription Drugs and Biological Products for the Treatment of Oncologic Diseases (https://www.fda.gov/media/164555/download)




FDA
U.S. FOOD & DRUG
ADMINISTRATION