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Recommendations for Defining Chimeric Antigen Receptor T-Cell (CAR T) Dose-Limiting Toxicities (DLTs) for Future Early-Stage CAR T Therapy Studies

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BACKGROUND

- In 2022, the US FDA provided example dose-limiting toxicities (DLTs) (**Table 1**) as part of the draft guidance document, "Considerations for the Development of Chimeric Antigen Receptor (CAR) T Cell Products: Guidance for Industry" [1]
- The DLT definitions in the guidance do not reflect what was used in the early-phase studies for the approved CAR Ts. These studies defined DLTs as treatment-related, included exceptions, and/or allowed for time to resolve the adverse event
- Using DLT definitions from the FDA guidance could have prematurely stopped these early-phase studies of the approved CAR Ts
- An expert panel of academic cell therapists collaborated with industry partners at A2 Bio to review prior DLT definitions in early phase studies and assess the practical implications of the FDA guidance
- This led the panel to draft revised recommendations that integrated the permissibility of reversible events during dose-escalation for trial sponsors, investigators, health authorities, and other parties who may be involved in future CAR T therapy trials

DEFINING DLTS FOR CAR T THERAPIES IN ONCOLOGY TO ALLOW FOR REVERSIBLE EVENTS

- The expert panel guidelines (**Table 1**) integrate the history of cell therapy with its future curative potential by balancing the safety of patients in early-phase trials with the potential long-term therapeutic opportunities for patients with incurable, terminal malignancies

Table 1: DLT Definition Recommendations

	DLT Definitions Recommended by the Authors	DLT Definitions Recommended in the 2024 FDA Guidance[1]	DLT Definitions Included in Early-phase Studies of Approved CAR Ts Compared to the FDA Guidance 🟠=FDA Guidance for DLT criteria could have resulted in premature stopping of study 🟢=FDA Guidance for DLT criteria would have allowed study to proceed as conducted					
			tisagenlecleucel[3]	axicabtagene ciloleucel[4]	brexucabtagene autoleucel[5]	lisocabtagene maraleucel[6]	idecabtagene vicleucel[7]	ciltacabtagene autoleucel[8]
DLT window (days)	**Investigators should select a time frame consistent with the mechanism of action of the study treatment, including preconditioning lymphodepletion**	The observation period for DLTs should be adequate to capture both acute and delayed toxicities	21	30	30	28	21	21
Any treatment-related AE	*Included in recommendations below*	Recommend DLTs be defined independent of attribution to CAR Ts unless a clear alternative cause can be described	🟠	🟠	🟠	🟠	🟠	🟠
CRS[a]	Any grade 4 CRS (as defined by ASTCT[10]), with the **exception: grade 4 CRS per ASTCT due to use of CPAP or BiPAP that can be weaned** to high-flow nasal cannula, face mask, non-rebreather mask, or Venturi mask in ≤72 hours Any grade 3 (not higher) CRS that cannot be resolved to grade 2 or lower within 7 days **with appropriate treatment**	Any grade 4 or 5 CRS Any grade 3 CRS that does not resolve to grade ≤2 within 7 days	🟠	🟠	🟠	🟠	🟠	🟠
Neurotoxicity	Any grade 4 **ICANS** (as defined by ASTCT[10]) that cannot be resolved to grade 2 or lower within 3 days **with appropriate treatment** Any grade 3 (not higher) **ICANS** (as defined by ASTCT[10]) that cannot be resolved to grade 2 or lower within 7 days **with appropriate treatment**	Grade 3 and greater neurotoxicity	🟠	🟠	🟠	🟠	🟠	🟠
Allergic reaction	Any grade 3 or higher allergic reactions related to the cell therapy **that cannot be resolved to grade 2 or lower** within 48 hours of cell administration	Grade 3 and greater allergic reactions related to the cell infusion	🟠	🟠	🟠	🟠	🟠	🟠
Autoimmune	Any grade 3 or higher autoimmune toxicity **that cannot be resolved to grade 2 or lower** within 7 days with appropriate treatment	Any autoimmune toxicity grade ≥3	🟠	🟠	🟠	🟠	🟠	🟠
Organ toxicity	Grade 3 and higher organ toxicity (cardiac, dermatologic, gastrointestinal, hepatic, pulmonary, or renal/genitourinary) not preexisting or not due to the underlying malignancy and occurring within 30 days of cell infusion **that cannot be resolved to grade 2 or lower** within 7 days with appropriate treatment	Grade 3 and greater organ toxicity (cardiac, dermatologic, gastrointestinal, hepatic, pulmonary, or renal/ genitourinary) not preexisting or not due to the underlying malignancy and occurring within 30 days of cell infusion	🟠	🟠	🟠	🟠	🟠	🟠
Death	Any CTCAE v5.0 grade 5 AE **not due to progression of underlying disease**	Stopping rule: Any death within the 30 days after CAR T cell administration	🟠	🟠	🟠	🟠	🟠	🟠
Hematologic toxicity	Any grade 4 or higher life-threatening, study treatment-related hematologic toxicity lasting more than [21–30][b] consecutive days Any grade 4 or higher thrombocytopenia with clinically significant bleeding that cannot be resolved within 24 hours with appropriate treatment	Not mentioned	🟢	🟢	🟢	🟢	🟢	🟢
IEC-HS	Any grade 3 or higher IEC-HS lasting more than 28 days	Not mentioned	The term IEC-HS had not yet been identified at the time of study conduct					

[a] The Lee 2014 CRS grading system[9] (used in studies of axicabtagene ciloleucel, brexucabtagene autoleucel, lisocabtagene maraleucel, and idecabtagene vicleucel) allowed greater flexibility in management of Grade 3 and 4 CRS than the current ASTCT CRS grading system[10].
[b] Investigators should select a time frame consistent with the mechanism of action of the study treatment, including the preconditioning lymphodepleting chemotherapy. In addition, AEs need to be closely monitored outside the DLT window for prolonged hematologic toxicities that could still be considered dose-limiting safety events.
Abbreviations: AE, adverse event; ASTCT, American Society for Transplantation and Cellular Therapy; BiPAP, bilevel positive airway pressure; CAR T, chimeric antigen receptor T cell; CPAP, continuous positive airway pressure; CRS, cytokine release syndrome; CTCAE, Common Terminology Criteria for Adverse Events; DLT, dose-limiting toxicity; FDA, US Food and Drug Administration; ICANS, immune effector cell-associated neurotoxicity syndrome; IEC-HS, immune effector cell-associated hemophagocytic lymphohistiocytosis-like syndrome.

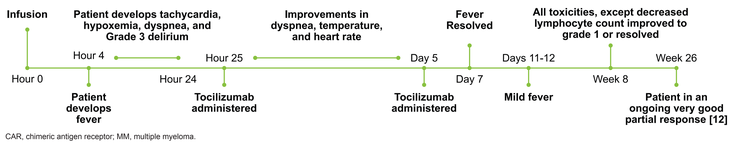
REVIEW OF THE LITERATURE: CASE STUDIES

- Here we present 2 patients with relapsed/refractory (R/R) hematologic malignancies who were treated with CAR T therapies and experienced safety events that could have been labeled as DLTs if appropriate time for intervention and resolution were not accounted for in the DLT definition, thereby limiting potential clinical development of the CAR T product

Patient 1: Male Adult With MM Treated With BCMA-targeted CAR T Therapy [11]

Patient 1

- Patient received 5 prior lines of therapy for his multiple myeloma
- Most recent therapy was cyclophosphamide, bortezomib, and dexamethasone; disease relapsed during first cycle
- Received an infusion of 9×10^6 CAR-BCMA T cells/kg



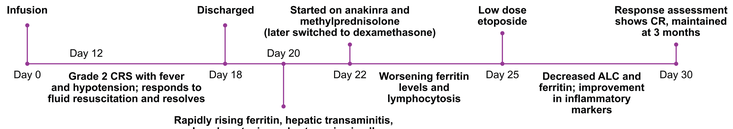
CAR, chimeric antigen receptor; MM, multiple myeloma.

- Per FDA guidance, this event of grade 3 neurotoxicity would be considered a DLT under the definition "grade 3 or greater neurotoxicity"
  - Whereas per the presented consensus guidelines, the definition of DLT includes time to resolution; consequently, this event would not be considered a DLT because symptoms had resolved

Patient 2: Female Adult With R/R B-ALL Treated With CD22-directed CAR T Therapy [13]

Patient 2

- 38-year-old female with B-ALL with CNS disease
- Previously received ASCT and tisagenlecleucel
- Treated with investigational CD22 CAR T therapy (NCT02315612)



ALC, absolute lymphocyte count; ASCT, autologous stem cell transplant; B-ALL, B-cell acute lymphoblastic leukemia; CAR T, chimeric antigen receptor T-cell; CNS, central nervous system; CR, complete response; CRS, cytokine release syndrome.

- For this patient, immune effector cell-associated hemophagocytic lymphohistiocytosis-like syndrome led to hospitalization and she did not respond to initial treatment; however, rapid resolution of symptoms occurred with second-line treatment, and the patient achieved a complete response; this example highlights the importance of including exceptions for events that resolve within a reasonable time frame when considering DLT definitions

CONCLUSIONS:

- DLT definitions in CAR T therapy phase 1 trials lack standardization, hindering proper safety assessment across studies
- While standardization is needed, DLT definitions must be reasonably tolerant since CAR T toxicities are typically predicable and manageable with experience
- An expert panel from academia and A2 Biotherapeutics, Inc. created guidelines for DLT definitions that allow time for proper management and resolution before classifying events as DLTs
- Following these optimized guidelines helps prevent unnecessary interruption of dose escalation while still capturing meaningful safety events

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