Tables

Supplementary Table 1. Risk factors for CRS and/or ICANS

Risk factor	Description
Tumor Burden	Higher tumor burden increases the risk of severe complications and therapy-related mortality.
Age	Lower age increases the likelihood of severe CRS and ICANS
Cell Dosing	Higher doses of CAR-T cells may lead to more severe side effects.
Comorbidities	Pre-existing health conditions can exacerbate complications and increase the risk of mortality.
Tumor Progression	The timing of therapy in relation to disease progression affects the severity of complications.
Specific CAR-T Cell Product	Different CAR-T cell products have varying profiles of side effects and associated risks (Co-stimulatory domain CD28 associated with more severe CRS/ICANS than 4-1BB)
Prior Neutropenia	Profound pre CAR-T bone marrow suppression can lead to severe neutropenia, increasing infection risk and complications.

Supplementary Table 2. TIAN Grading system according to Common Terminology Criteria for Adverse Events (CTCAE)

TIAN Grade	Symptoms
1	Mild symptoms such as headaches with fever or minor worsening of existing neurological symptoms. Results in minor functional deficits. Managed with observation or symptomatic treatment.
2	Moderate changes in the neurological exam from baseline that substantially affect function.
3	Severe neurological signs and symptoms that may affect critical cardiorespiratory functions, or symptoms of increased intracranial pressure (>20 mmHg) responsive to intervention. In patients with spinal cord tumors, grade 3 TIAN can occur with the risk of debilitating loss of cord function.
4	Life-threatening, clinically significant elevated ICP (>20 mmHg) refractory to CSF drainage with no improvement in clinical symptoms in response to CSF drainage, possibly warranting urgent neurosurgical intervention (such as with emergent EVD or VPS placement). Signs and symptoms of impending/early herniation, or severe medullary dysfunction requiring airway protection and/or mechanical ventilation.

Supplementary Table 3. Prophylactic and Therapeutic algorithm for ICAHT

Prophylactic and/or Therapeutic Intervention	Description
Antiinfective prophylaxis	Antiinfective prophylaxis and treatment due to the risk of infections with consideration of depth

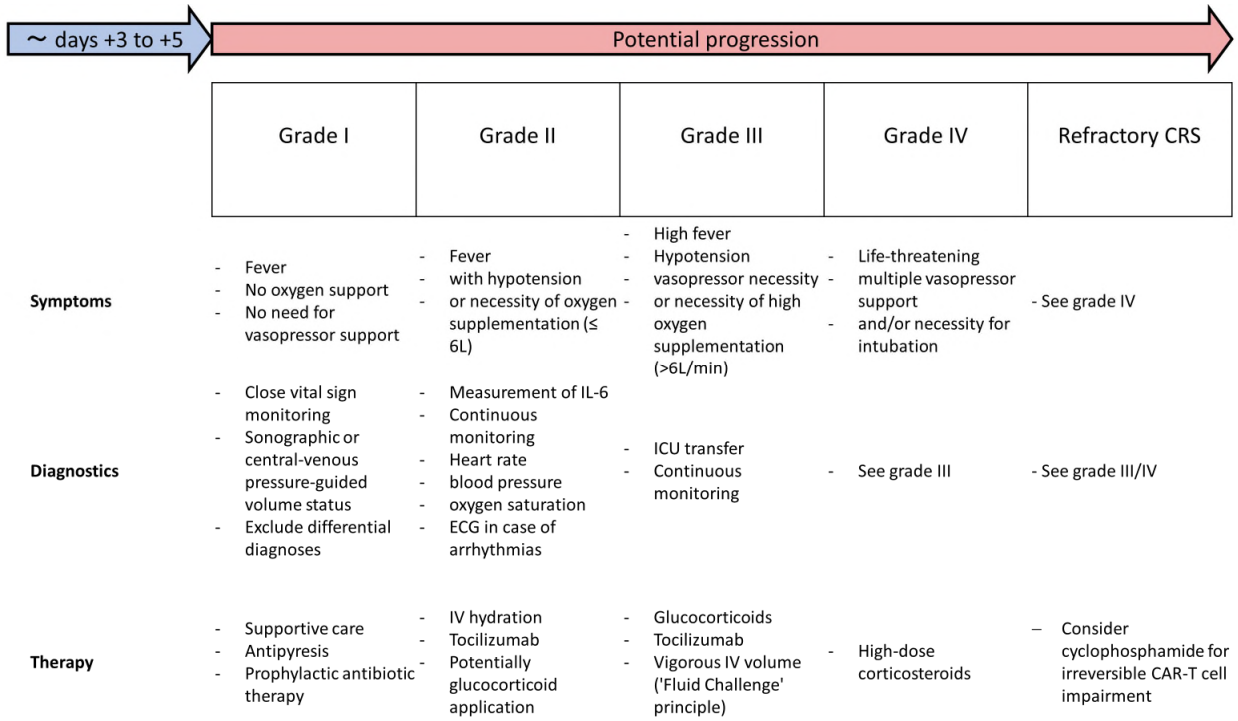
	and duration of neutropenia and prior infections/colonization
Prophylactic collection of stem cells pre-CAR-T cell therapy	Collection of autologous stem cells before CAR-T cell therapy in patients at high-risk for ICAHT in order to perform an autologous stem cell boost to re-establish proper hematopoietic function For G-CSF refractory ICAHT, autologous stem cell boost considered, with infused cell doses ranging between 1.1 to 11.5 $x10^6$ CD34+/kg.
Bone marrow aspiration/biopsy	Diagnostic bone marrow aspiration and biopsy in cases of high-risk HEMATOTOX Scoring to rule out other causes of prolonged cytopenia.
Use of growth factors	Heterogeneous practice: G-CSF use avoided in co-occurring ICANS. Standard use between days 5 and 14 post-CAR infusion, or in prolonged neutropenia.
TPO agonists	Without autologous stem cell backup, TPO agonists such as romiplostim (1-15 µg/kg weekly) for thrombocytopenia and darbepoetin alfa (2.25 µg/kg weekly) for anemia are recommended.
Transfusion support	Regular transfusions often necessary with higher frequency when infectious complications co-occur.
Anti-cytokine agents	In cases of hematotoxicity with high cytokines, such as CRS or infections, agents like anakinra up to 12 mg/kg/day IV are recommended. Bone marrow aspiration recommended before anakinra application.
Allogeneic stem cell boost	Considered for therapy-resistant cytopenia and in cases of persistent refractory ICAHT. Only applicable for patients with prior allogeneic stem cell transplantation and with complete donor chimerism.

Supplementary Table 4. HLH after CAR-T cell therapy according to HLH-2004 diagnostic criteria [1] and H-score[2]

Step / Measure	Description
Initial Diagnostic Criteria (5/8 criteria must be fulfilled)	- fever - splenomegaly - cytopenia (hemoglobin < 90 g/L, thrombocytes < $100x10^9$/L, ANC < $1x 10^9$/L) - hypertriglyceridemia (≥3 mmol/L) and/or hypofibrinogenemia (< 1.5 g/L) - elevated ferritin (≥500 µg/L) - elevated sCD25 (≥2.400 U/ml) - decreased NK cell activity - hemophagocytosis in bone marrow, cerebrospinal fluid or lymph nodes
H-score	- same parameters - Based on a point system - Calculates probability of HLH - Quantifies HLH likelihood better

Figures

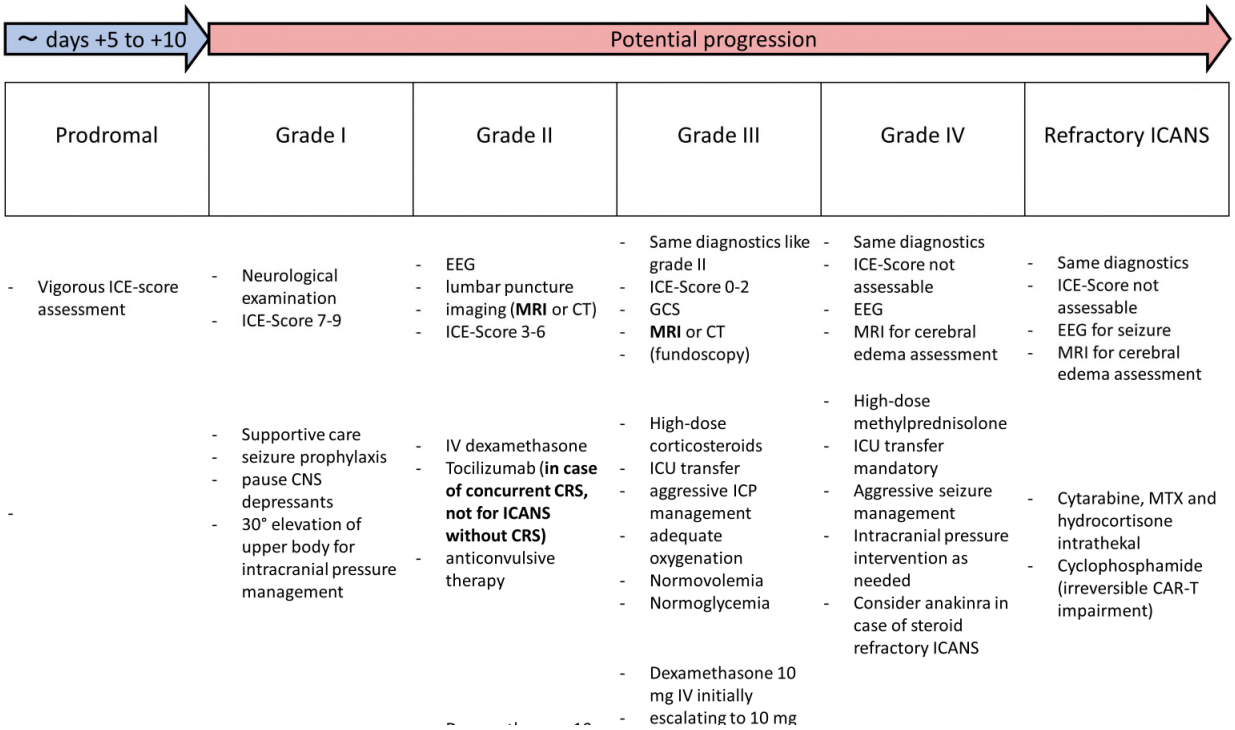
Supplementary Figure 1 – Cytokine Release Syndrome - clinical procedure



Abbreviations: PAP - Positive airway pressure, ICU - Intensive Care Unit, ECG – Electrocardiogram

As Figure 2, sSupplementary Ffigure 1 describes the various gradings and respective measures for the most common side effect of CAR-T cell therapy - cytokine release syndrome (CRS). For a CRS I°, a systemic infection should be ruled out, and treatment with antipyretics and IV cristalloids should be administered. A CRS II° is defined by a temperature above 38 °C, decreased blood pressure, and/or the need for oxygen therapy with ≤ 6L/min. For a CRS II°, additionally the administration of tocilizumab 8 mg/kg IV should be carried out. In CRS III°, the administration of a vasopressor is necessary and/or oxygen therapy with > 6L/min is required. Transfer to the intensive care unit is necessary, and intravenous administration of dexamethasone is performed. For CRS IV°, the administration of > 1 vasopressor is required, and intubation or PAP is often necessary. In addition to the previously mentioned therapy, the administration of intravenous methylprednisolone must be performed.

Supplementary Figure 2 – Immune cell associated neurotoxicity syndrome - clinical procedure

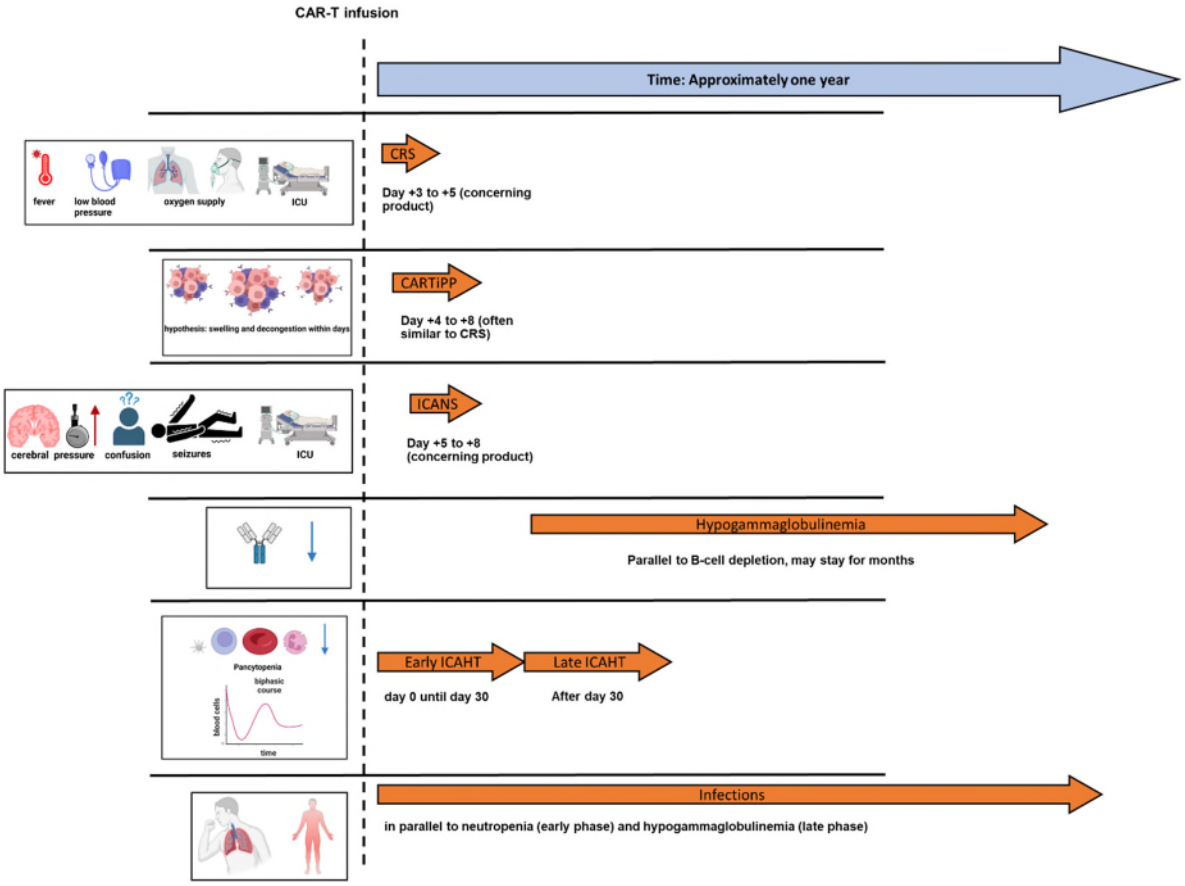


Abbreviations: CRS - Cytokine Release Syndrome, ICE-Score - Immune Effector Cell-Associated Encephalopathy Score, CNS - Central Nervous System, EEG - Electroencephalogram, ICP - Intracranial Pressure, MRI - Magnetic Resonance Imaging, ICU - Intensive Care Unit, ICANS - Immune Effector Cell-Associated Neurotoxicity Syndrome

As Figure 3, sSupplementary Ffigure 2 differentiates the grading and therapy of CAR-T cell-associated neurotoxicity (ICANS). In For ICANS I°, an ICE score of 7-9 out of a total of 10 points is mandatory. This is determined with a simple questionnaire. Grade 1 indicates a mild disturbance of consciousness,

where the patient is spontaneously arousable. Close monitoring of the patient should be carried out, and the prophylactic application of antiepileptics can be considered. ICANS II° is characterized by a disturbance of consciousness where the patient is arousable by speech. The application of intravenous dexamethasone must be carried out. Additionally, aspiration prophylaxis should be considered, and medications should no longer be administered orally. Cerebral imaging should be performed, and a lumbar puncture should be conducted. In ICANS III°, the disturbance of consciousness is more severe, and the patient only responds to tactile stimulus. Epileptic seizures may occur but respond to intervention. A focal cerebral edema in imaging may also be present. Transfer to the intensive care unit should take place, and the application of methylprednisolone must be carried out. In ICANS IV°, severe disturbance of consciousness is observed, where the patient is not spontaneously arousable and only responds to repetitive tactile stimuli. Epileptic seizures are life-threatening. Higher degree motor deficits (hemi- or paraparesis) and diffuse cerebral edema in imaging may occur, accompanied by symptoms such as decorticate or decerebrate rigidity, abducens palsy, papilledema, or Cushing's reflex (increased intracranial pressure, increased blood pressure, decreased heart rate). The placement of intracranial pressure monitoring should and plasmapheresis may be considered. Additionally, further immunosuppressive drug strategies with anakinra IV amongst others may be applied.

Supplementary Figure 3 – Timeline CAR-T-associated complications



Supplementary figure 3 illustrates the timeline of various complications and their onset relative to CAR-T cell infusion, which occurs at the beginning of the timeline. The entire duration covered is approximately one year. CRS: This complication often occurs between day +3 to +5, depending on the product used. CARTiPP: This mostly develops around day +4 to +8, similarly to CRS, again depending on the product used. ICANS often occurs from day +5 to +8. Early ICAHT: This occurs from day 0 to day 30. Late ICAHT: This phase starts after day 30. Hypogammaglobulinemia: This condition accompanies B-cell depletion and can persist for months. Infections: Infections align with the phases of neutropenia (initial phase) and hypogammaglobulinemia (late phase) and can occur throughout the year. Infections may go along with neutropenia in an early phase. However, later on they are associated with Hypogammaglobulinemia.

Abbreviations: CRS (Cytokine Release Syndrome), CARTiPP (CAR-T Cell associated Pseudprogression), ICANS (Immune effector Cell-Associated Neurotoxicity Syndrome), ICAHT (Immune effector Cell-Associated Hematotoxicity), ICU (Intensive care unit)

1. Henter JI, Horne A, Aricó M, et al. HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer. 2007;48(2):124-131.

2. Debaugnies F, Mahadeb B, Ferster A, et al. Performances of the H-Score for Diagnosis of Hemophagocytic Lymphohistiocytosis in Adult and Pediatric Patients. Am J Clin Pathol. 2016;145(6):862-870.