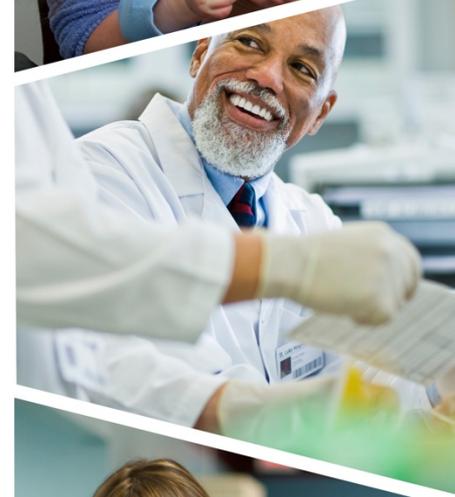


Gene Transfer Safety Assessment Board (GTSAB) Report

Recombinant DNA Advisory Committee December 14, 2016



Charge to the GTSAB

- 1) Review in closed session as appropriate safety information from gene transfer trials for the purpose of assessing toxicity and safety data across gene transfer trials
- 2) Identify significant trends or significant single events
- 3) Report significant findings and aggregated trend data to the RAC

Process enhances review of new protocols, improves the development, design, and conduct of human gene transfer trials, promotes public understanding and awareness of the safety of human gene transfer research studies, and informs decision-making of potential research participants

GTSAB Roster

Richard Whitley, MD (*Chair*)

Michael Atkins, MD

William Curry, MD

J. Kevin Donahue, MD

Howard Kaufman, MD

Dean Lee, MD, PhD

Joseph Pilewski, MD

Denise Gavin, PhD (*FDA Representative*)

Ramjay Vatsan, PhD (*FDA Representative*)



Serious Adverse Events (since June 2016)

3rd Quarter: 84 serious adverse events (SAEs) including initial & follow-up reports from 24 were shared and discussed with GTSAB.

4th Quarter: 63 additional SAEs including initial & follow-up reports from 20 protocols were received and reviewed by the NIH OSP Medical Officer.

SAEs – not CRS-related

Protocol 1243: **Listeria bacteremia** occurring more than 200 days after the last dose of study product (**CRS-207**). Bacteremia resolved with antibiotic treatment. Subject's chemoport may have been involved in the infection.

Protocol 1439: One case of **elevated LFTs** & one case of **liver failure**. Both cases occurred after intrahepatic administration of study product (**Talimogene Laherparepvec**).

Protocol 1484: Subject with advanced metastatic melanoma to lungs, pleura, & lymph nodes developed **dyspnea** 10 days after the last dose of the study drug (intralesional administration of **Talimogene Laherparepvec**). Imaging showed **pleural effusions** & pleural fluid analysis showed **tumor cells & immune cells**. Subject died three weeks after the onset of dyspnea likely due to progressive disease.

CAR T cell Trials with CRS-related SAEs

Protocol 1147: Two SAEs involved CRS, **decreased ejection fraction (EF)** & later **neurotoxicity**. MRI in one case showed enhancement in prior areas of CNS disease and subject was treated with systemic & intrathecal corticosteroids. Both subjects recovered with complete remission.

Protocol 1320: A subject with relapsed CD19 negative acute lymphoblastic leukemia (ALL) & **hemophagocytic lymphohistiocytosis (HLH)** after participating in a CD19 CAR T cell trial enrolled in an Emergency IND under this **anti-CD22 CAR** trial. Subject's course was complicated by **severe CRS, invasive fungal pneumonia, coagulopathy, & lactic acidosis**. Despite treatment, subject died with massive **bronchopulmonary hemorrhage** likely due to invasive pneumonia.

Protocol 1351: Multiple cases of **CRS & neurotoxicity** submitted in annual report.

Protocol 1431: Few cases of CRS reported. One subject developed **CRS, hypoxia, pleural effusions, thrombocytopenia/epistaxis, encephalopathy & Tumor Lysis Syndrome**. Subject was recovering as per last follow-up.

CAR T cell Trials with CRS-related SAEs (Cont.)

Protocol 1413: One SAE involved a subject with ALL who developed **fever & neurotoxicity (Grade 4)** with seizure. Subject recovered two weeks after event.

Another SAE involved a subject with refractory ALL who developed **severe CRS**, complicated by **cardiac arrest & multi-organ failure** & died few days after T cell infusion.

CAR T cell Trials with CRS-related SAEs (Cont.)

Protocol 1213: A subject with ALL & CNS disease developed **neutropenic fever** after lymphodepletion (LD) chemotherapy & CD19 CAR T cell infusion. Subject's course was complicated by sepsis during a **2nd course of LD chemotherapy** despite antibiotics. The cause of death was considered to be **cardiopulmonary arrest due to sepsis** in the setting of chemotherapy with refractory ALL.

GTSAB noted cardiac toxicities in T cell immunotherapy trials. Similar SAEs were previously noted in older subjects with comorbidities in other trials. GTSAB members discussed the enrollment criteria for cardiac function in these trials.

CAR T cell Trials with CRS-related SAEs (Cont.)

Protocol 1339: A subject with diffuse large B cell lymphoma (DLBCL) developed **neurotoxicity**, complicated by **decreased EF**, and **HLH**. Encephalopathy worsened & subject died.

Another subject with DLBCL developed **severe CRS & neurotoxicity**, complicated by **cardiac arrest**, & **severe lactic acidosis**. Subject died later. SAE assessed by PI/sponsor as Grade 5 anoxic brain injury after a myocardial infarction.

As per sponsor a 'Dear Investigator Letter' was sent informing sites of risks of **cardiac arrest & acidosis** in the setting of CRS and these risks are added to the informed consent form (ICF).

Other SAEs included multiple cases of **CRS**, and **early neurotoxicity**, some complicated by atrial fibrillation, all resolved after treatment.

Protocol Update

Protocol 1339: As of June 2016, 75 subjects were dosed in this trial (6 in phase 1 & 69 in phase 2).

- One related death occurred in phase 1 (dose limiting toxicity (DLT) due to **severe CRS** complicated by **intracranial hemorrhage** in setting of **severe thrombocytopenia** (reviewed by GTSAB last year)
- Two related deaths reported in phase 2 (one case of **HLH**, & one case of **cardiac arrest/severe acidosis/anoxic brain injury** (reviewed by GTSAB in Sept. 2016).
- As per sponsor, 2 additional subjects had reversible **Grade 4 CRS** & 2 additional subjects had **Grade 4 neurotoxicity** (one case still resolving & the other completely resolved).

As per sponsor as of mid October 2016, 122 subjects have been dosed with KTE-C19 among the ZUMA trials (cumulative data across all trials).

- 17 cases of **Grade 3 or higher CRS** observed, 13 occurred in ZUMA-1 (1339).
- 11 of the 17 cases were Grade 3 CRS,
- 4 were Grade 4 CRS,
- 2 were Grade 5 CRS.
- 13 of the 17 cases involved subjects who completely recovered from CRS.

According to news releases this trial has recently completed dosing of all enrolled subjects.

CAR T cell Trials with CRS-related SAEs: Brain edema

Protocol 1419: Three SAEs were reported earlier involving young subjects with ALL who developed **severe CRS & neurotoxicity (encephalopathy)**, complicated by **diffuse brain edema**, leading to **death**.

These three cases of **fatal brain edema** were assessed by the PI & Sponsor as related or likely related to T cells with possible contribution by lymphodepletion (LD) chemotherapy with cyclophosphamide (Cy) & fludarabine (Flu). All three cases were reported to the GTSAB in real-time.

The protocol was put on hold by the FDA and news releases indicated that sponsor initially assessed that a recent intensification of LD chemotherapy (i.e., addition of Flu) may have contributed to the SAEs, since the trial previously used Cy alone. The hold was lifted a few days later and the sponsor removed Flu from the LD chemotherapy regimen for this protocol.

CAR T cell Trials with CRS-related SAEs: Brain edema (Cont.)

Two recent SAE reports involving subjects with ALL who developed signs of CRS & neurotoxicity, complicated by **brain edema** leading to **death** were reported. Brain imaging was initially negative, but repeat imaging showed **diffuse brain edema**.

According to recent news releases, a voluntary hold on this trial was initiated by the sponsor.

These two cases of fatal brain edema bring the total number of deaths due to brain edema in this trial to five. These two cases were recently shared with the GTSAB in real-time and were the subject of several news releases.

Brain edema across all CAR T cell trials

NIH OSP Analysis – source: GeMCRIS® database:

- **Nine total cases** of serious adverse events (SAE) involving **brain edema** were found among **CAR T cell protocols** targeting hematologic malignancies.
- **Eight of these cases** were in subjects with **acute lymphoblastic leukemia (ALL)** treated with CD19 CAR T cells & one case was in a subject with **multiple myeloma** treated with an anti-BCMA CAR (an SAE of Grade 4 neurotoxicity involving brain edema noted in a recent annual report for NIH Protocol 1410).
- **Seven of the nine cases were fatal** (all seven in subjects with ALL)
 - Five of which occurred in NIH Protocol 1419 and
 - Two cases occurred in NIH Protocol 1213.
- **Six of the fatal cases** involved **diffuse brain edema** in relatively **young adult** subjects with ALL, which appeared to **progress very rapidly**.
 - Two cases in NIH Protocol 1419 involved **hyponatremia**, and
 - Few of the nine cases involved **seizure(s)**, evidence for **anoxic brain injury** or **decreased perfusion**, and **herniation**.

Brain edema across all CAR T cell trials

Overall Findings:

Our analysis indicates that

- To date approximately > 300 subjects with ALL have been dosed in CAR T cell immunotherapy trials
- Most of these are CD19 CAR T cell trials
- Brain edema appears to be
 - a rare event
 - relatively confined to subjects with ALL
 - reported in few protocols
 - and more common in young adults.

Research Updates (Publications)

- **Identification of Predictive Biomarkers for Cytokine Release Syndrome after Chimeric Antigen Receptor T-cell Therapy for Acute Lymphoblastic Leukemia.** David T. Teachey, et al. (2016) *Cancer Discov*; 664-79.
 - Regression modeling accurately predicted which patients would develop severe CRS.
- **CRISPR-Cas9-mediated multiplex gene editing in CAR-T cells.** Letter to the Editor by Xiaojuan Liu et al., (2016) *Cell Research* advance online publication 2 December 2016; doi:10.1038/cr.2016.142.
 - Mutant engineered T cells were tested in vitro & in pre-clinical murine models, which suggests potential for clinical application.
- **Multiplex Genome-Edited T-cell Manufacturing Platform for "Off-the-Shelf" Adoptive T-cell Immunotherapies.** Laurent Poirot et al. (2015), *Cancer Res*; 75(18):3853-64.
 - Demonstrates the applicability of TALEN-mediated genome editing to a scalable process, which enables manufacturing of 3rd party CAR T cells against tumor targets in an 'off-the-shelf' manner.

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