Data Studio

1:00–2:30pm, Wednesday, 7 October 2020
Videoconference:
https://stanford.zoom.us/j/98567770260?pwd=QlA4MEJVeVZXZTF1RjhGSHVNR2FNQT09
Password: 489313

Investigator: **Lori Muffly** Blood & Marrow Transplantation
Investigator: **Evan Weber** Center for Cell Therapy

Title: Phase I Study of KTE-X19 + Dasatinib in Relapsed/Refractory Adult Acute Lymphoblastic Leukemia

Summary:

The Data Studio Workshop brings together a biomedical investigator with a group of experts for an in-depth session to solicit advice about statistical and study design issues that arise while planning or conducting a research project. This week, the investigator(s) will discuss the following project with the group.

A substantial proportion of adults with B-cell acute lymphoblastic leukemia (ALL) will develop relapsed or refractory (r/r) leukemia. Outcomes for this population are poor. The development and recent FDA approval of chimeric antigen receptor T-cell (CART) therapy directed at CD19 for ALL has revolutionized the approach to this disease. However, no commercial CART product exists for r/r ALL in adults. Among the published single center clinical trials of CART in adult ALL, response rates are universally high; 50-70% will achieve complete response. However, at least two major barriers to progress stand out. One is CAR-mediated toxicities (cytokine release syndrome [CRS] and neurotoxicity) induced by the early and rapid expansion and proliferation of these cells. The other is subsequent T-cell exhaustion with loss of clinical response.

We screened several small molecule kinase inhibitors on CAR T-cell functionality and identified dasatinib, an FDA-approved drug for the treatment of Ph+ ALL and chronic myeloid leukemia (CML). It is a potent and reversible inhibitor of CAR T cell cytotoxicity, cytokine secretion, and proliferation. Dasatinib inhibits CAR T-cell functionality in vitro and in vivo at nanomolar concentrations similar to those detected in the serum of Ph+ ALL and CML patients treated with dasatinib. These data suggest that dasatinib could be safely used as an OFF switch to prevent or mitigate CAR-mediated toxicities.

In a separate study, we discovered that transient disruption of CAR signaling (i.e. "rest") via downregulation of surface CAR could reprogram exhausted CAR T cells to resemble memory-like cells, thereby leading to functional reinvigoration. We hypothesized that transient application of dasatinib could recapitulate these results by inducing "rest". Indeed, using an in vitro model of CAR T-cell exhaustion, dasatinib treatment of exhausted CAR T-cells for 4-7 days enhanced the expansion of CD8+ cells, decreased the expression of canonical exhaustion markers, and enhanced antigen-dependent cytotoxicity and cytokine secretion. Notably, repeated 3-day dasatinib pulses prolonged the anti-tumor response and enhanced survival in 2 separate dasatinib-insensitive tumor xenograft murine models. Tumor-infiltrating CAR T-cells in mice treated with dasatinib exhibited an increased percentage of memory-like cells and enhanced degranulation when re-stimulated ex vivo. Collectively, these results indicate that CAR T-cell and dasatinib combination therapy may result in enhanced safety and efficacy.

Questions:

1. Dose and Dosing Schedule
   (a) How to choose/study both the dasatinib dose and dosing schedule post-CART infusion?
   (b) What are meaningful Phase I endpoints to clarify optimal dosing?
   (c) Time Window
      i. The CAR T-cells need some time to hit target and expand. Therefore, we think that we likely should not start dasatinib in most patients before Day +3-5, but this is debatable.
      ii. In SOC with this type of CART, most CAR T-cells are no longer detectable by Day +28.
   (d) Toxicities and Adverse Events (AEs)
      i. Do we set a fixed dasatinib schedule or modify based on toxicity? CRS and neurotoxicity typically have onset between Day +1 and Day +7 following CART infusion. Typically, as SOC we do not treat Grade 1 but will treat Grade 2 toxicity with steroids and tocilizumab. For example, if we plan that dasatinib starts on Day +3 for all patients and a patient develops grade I CRS on Day +1 do we start earlier? Similarly, if we plan for 3 day pulses do we continue longer if CRS is ongoing?
      ii. We think that prolonged cytopenias could be an AE of special interest and this may affect our dosing of dasatinib. Dasatinib can cause or worsen cytopenias. These patients are cytopenic due to the lymphodepletion chemo. Prolonged cytopenias are also a common issue after CART therapy.
2. How should we allocate the total sample size?
   (a) Should we use the entire sample size for finding the optimal dose and schedule?
   (b) If not, how should we choose between inclusion of an expansion cohort or a separate Phase II at the recommended dose and schedule?
3. Measurement of CAR persistence is not standardized in the lab. Therefore, although we hope this approach decreases exhaustion and increases persistence, these can really only be exploratory aims.

Zoom Meeting Information

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Join from PC, Mac, Linux, iOS or Android:
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Or iPhone one-tap (US Toll): +18333021536,,98567770260# or
                             +16507249799,,98567770260#

Or Telephone:
    Dial: +1 650 724 9799 (US, Canada, Caribbean Toll) or
          +1 833 302 1536 (US, Canada, Caribbean Toll Free)

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For more information about Data Studio:
http://med.stanford.edu/dbds/resources/data-studio.html