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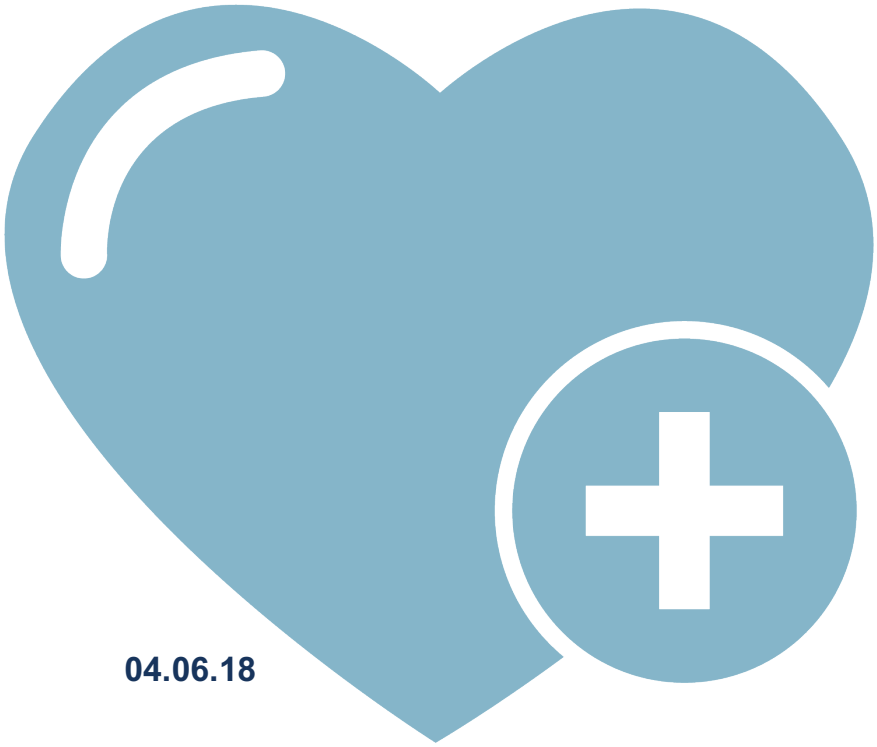
Grants Working Group Public Review Summary

Phase 1 Study of CD19/CD22 Chimeric Antigen Receptor (CAR) T Cells in Adults with Recurrent or Refractory B Cell Malignancies

Application Number: CLIN2-10846 (Revised Application)	Review Date: 29 March 2018

Clinical Trial Stage Project Proposal (CLIN2)



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APPLICATION NUMBER: CLIN2-10846 (Revised application)

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PROGRAM ANNOUNCEMENT: CLIN2 Clinical Trial Stage Projects

Therapeutic Candidate or Device

T cells genetically engineered to express a bispecific Chimeric Antigen Receptor (CAR) targeting CD19 and/or CD22

Indication

Patients with relapsed and refractory B cell malignancies

Therapeutic Mechanism

T cells expressing the bispecific CAR will recognize cancer cells expressing one or both of the target antigens. Upon recognition, the T cells will become activated, divide, and then kill the cancer cells. Progenitor T cells contained within the larger population will form memory stem cells that will persist and continue to survey the body and kill residual cancer. These cancer killing T cells are designed to persist for years following one treatment with CD19/22-CAR T cells.

Unmet Medical Need

50% or less of patients with diffuse large B cell lymphoma and B cell leukemia are cured with standard regimens that rely on chemotherapy for benefit. CD19/22-CAR T cells effectively kill chemotherapy resistant lymphoma and leukemia and thus could improve cure rates for these aggressive cancers.

Project Objective

Phase 1 trial completed

Major Proposed Activities

Demonstrate feasibility of producing CD19/22-CAR T cells

Assess toxicity of CD19/22-CAR T cells

Assess clinical activity of CD19/22-CAR T cells in adults with B-ALL and DLBCL.

Funds Requested

$11,976,906 ($2,283,796 Co-funding)

Recommendation

Score: 1

Votes for Score 1 = 13 GWG members

Votes for Score 2 = 1 GWG members

Votes for Score 3 = 0 GWG members

- A score of “1” means that the application has exceptional merit and warrants funding;
- A score of “2” means that the application needs improvement and does not warrant funding at this time but could be resubmitted to address areas for improvement;
- A score of “3” means that the application is sufficiently flawed that it does not warrant funding, and the same project should not be resubmitted for review for at least six months after the date of the GWG’s recommendation.

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Review Overview

This is a revised application that previously received a score of "2." Reviewers agreed that effective and durable treatment options for patients with relapsed/refractory B cell acute lymphoblastic leukemia (B-ALL) and diffuse large B-cell lymphoma (DLBCL) are sorely needed. While reviewers generally agreed that CAR-T cell based approaches targeting CD19 and CD22 are based on strong scientific and clinical rationale and supported by convincing data, they had several concerns in the initial review of the application. Reviewers were not convinced that the bi-specific CAR-T cell approach offered sufficient value over single agent CAR-T therapies. Reviewers noted that the trial design should be revised to better delineate the B-ALL and DLBCL patient populations. Finally, reviewers were not convinced that the project adequately assessed the role of stem cells.

Reviewers thought that the applicant had adequately revised the study design to address their concerns about mixing the two patient populations. Some reviewers were not convinced that the applicant's inclusion of additional correlative studies assessing presence of stem T cells after administration would be informative. Overall, the reviewers thought that the applicant had made a good-faith effort to address reviewers concerns and that the study would provide valuable information on the utility of bispecific CAR-T cell therapies. Thus, they recommended it for funding.

Review Summary

Does the project hold the necessary significance and potential for impact?

a) Consider whether the proposed treatment fulfills an unmet medical need.

- Relapsed and refractory B-ALL and DLBCL patients have high rates of morbidity and mortality.
- The proposed treatment has the potential to address this unmet medical need.

b) Consider whether the approach is likely to provide an improvement over the standard of care for the intended patient population.

- The current standard of care in these patient populations involves various therapies targeting CD19 including recently approved CAR-T cells. A significant number of patients treated with these therapies relapse and a subset of these patients exhibit CD19 antigen loss.
- The proposed dual targeting approach could improve outcome for patients by overcoming the problem of CD19 negative relapse.

c) Consider whether the proposed treatment offers a sufficient value proposition that supports its adoption by patients and/or health care providers.

- Reviewers thought that the proposed bispecific CAR-T cell therapy product would provide an incremental benefit over single antigen CAR-T cell therapies. However, adoption would likely be dependent on cost and perceived benefit.
- In the initial review of the application, reviewers were not certain whether the proposed bispecific CAR-T cell therapy offered sufficient value over sequential or simultaneous treatment with monospecific CD19 and CD22 CAR-T cell therapies.
    - Reviewers thought that the applicant's response, which included additional justification and noted preclinical data demonstrating

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enhanced efficacy of bi-specific CAR-T over sequential administration of single antigen CAR-T, was adequate.

c) If a Phase 3 Trial is proposed is the therapy for a pediatric or rare indication or, if not, is the project unlikely to receive funding from other sources?

- N/A

Is the rationale sound?

a) Consider whether the proposed project is based on a sound scientific and/or clinical rationale, and whether the project plan is supported by the body of available data.

- The clinical rationale for CAR-T cells in hematologic malignancies is strong given recent FDA approvals for CD19 CAR-T cell products.
- There is strong scientific and clinical rationale for targeting CD19 and CD22, which are ubiquitously expressed in both B-ALL and DLBCL tumors.
    - Clinical trials for commercially available CD19 CAR-T cells support targeting CD19 in these indications.
    - The applicant's preliminary clinical experience with CD22 CAR-T cells strongly support targeting CD22 in these indications.
- There is scientific rationale for targeting both CD19 and CD22 to overcome antigen loss.
    - The loss of CD19 has been documented in patients relapsing from anti-CD19 CAR T cell therapy. This may be more frequent in ALL than DLBCL.
    - The applicant's pre-clinical *in vitro* and animal data support the bispecific CAR-T cell approach.
- Reviewers were concerned that the preliminary clinical results with CD22 CAR-T cell therapy suggest CD22 is more susceptible to antigen loss than CD19.
- In the initial review of the application, reviewers expressed concern that the use of murine CD19 CAR construct could increase the risk of immunogenicity.
    - Reviewers thought that the applicant's response, which justified the use of the construct based on clinical experience of the same murine CD19 CAR used in approved CAR-T cell therapy, was adequate.

b) Consider whether the data supports the continued development of the treatment at this stage.

- The preclinical data on the bi-specific CAR-T and the clinical experience with CD19 and CD22 single antigen CAR-T support clinical investigation of the treatment.

Is the project well planned and designed?

a) Consider whether the project is appropriately planned and designed to meet the objective of the program announcement and to achieve meaningful outcomes to support further development of the therapeutic candidate.

- In the initial review of the application, reviewers expressed strong concern with

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the phase 1 trial design, which mixed the B-ALL and DLBCL populations. Reviewers recommended that the expansion portion of the trial split the two patient populations into separate cohorts.

  - Reviewers thought that the applicant's response in the revised application, which included clear inclusion/exclusion criteria, endpoints, separate expansion cohorts for the two patient populations and futility analysis, was thorough and adequately addressed their concerns.

- In the initial review of the application, reviewers questioned whether this represented a stem cell project. They noted that the product wasn't characterized for stem cell composition and the role of the stem cells wouldn't be tracked after administration to the patient.
  - The applicant's response in the revised application included phenotypic characterization of the patient samples gathered to date and enumeration of stem cell memory and central memory T cells. The applicant also proposed to perform phenotypic characterization of the administered cells in correlative studies.
  - Some reviewers thought that the applicant's response did not adequately assess functionality of the stem cells. Other reviewers noted that phenotypic characterization was adequate at this stage.
- In the initial review of the application, reviewers were unclear whether the applicant had adequately addressed the FDA reviewers' feedback regarding definitions of dose limiting toxicities in the proposed phase 1 trial.
  - Reviewers thought that the applicant's response did not adequately address their concern but acknowledged that there may have been additional interaction with the FDA leading to the active IND.

b) Consider whether the proposed experiments are essential and whether they create value that advances CIRM's mission.

- The proposed experiments in the revised application will inform feasibility and mechanism of action questions about bi-specific CAR-T cells.
- The investigation of stem cell memory and central memory T cell subsets in correlative studies, as described in the revised application, will advance CIRM's mission.

c) Consider whether the project timeline is appropriate to complete the essential work and whether it demonstrates an urgency that is commensurate with CIRM's mission.

- The project timeline is appropriate.

Is the project feasible?

a) Consider whether the intended objectives are likely to be achieved within the proposed timeline.

- In the initial review of the application, reviewers had expressed concerns about feasibility of patient enrollment given the existence of commercial CD19 CAR-T cell therapy.
  - Reviewers thought that the applicant's response, which described the patient population and experience at the applicant institution, was adequate but not thoroughly convincing.

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b) Consider whether the proposed team is appropriately qualified and staffed and whether the team has access to all the necessary resources to conduct the proposed activities.

- The proposed team is well qualified and has the necessary resources to conduct the proposed phase 1 clinical trial activities.

c) Consider whether the team has a viable contingency plan to manage risks and delays.

- The identified risks and contingency plans are laid out well in the proposal.

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CIRM Recommendation to Application Review Subcommittee

The CIRM recommendation to the Application Review Subcommittee is considered after the GWG review and did not affect the GWG outcome or summary. This section will be posted publicly.

RECOMMENDATION: Fund (CIRM concurs with the GWG recommendation).