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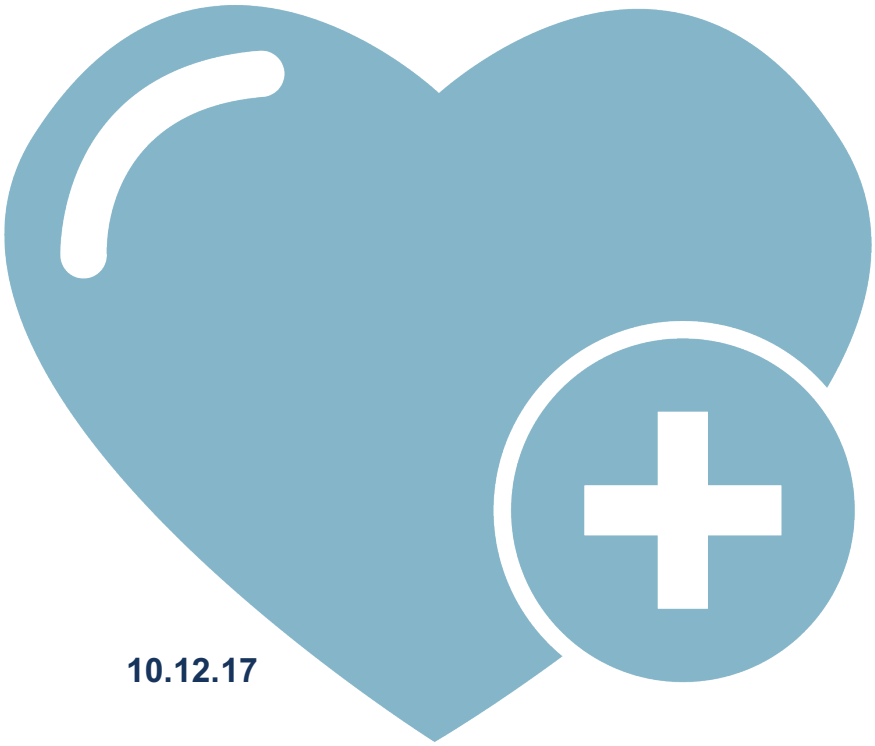
Grants Working Group Public Review Summary

Clinical Study of T stem cell memory (Tscm)-based CAR-T cells in Patients with Multiple Myeloma

Application Number: CLIN2-10395	Review Date: 26 September 2017

Clinical Trial Stage Project Proposal (CLIN2)



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Clinical Study of T stem cell memory (Tscm)-based CAR-T cells in Patients with Multiple Myeloma

APPLICATION NUMBER: CLIN2-10395

REVIEW DATE: 26 September 2017

PROGRAM ANNOUNCEMENT: CLIN2 Clinical Trial Stage Projects

Therapeutic Candidate or Device

Genetically engineered, Centyrin-based, stem cell memory CAR-T cells (CARTyrin T cells)

Indication

Multiple Myeloma

Therapeutic Mechanism

The Centyrin-based chimeric antigen receptor (CARTyrin) cells are cells that are removed from a myeloma patient's body and genetically engineered to express a receptor that binds to BCMA that is selectively found on myeloma cells, triggering the CARTyrin T cells to specifically kill the myeloma cells. Because the CARTyrin T cells are stem cell memory, they can persist for long periods and kill residual myeloma cells or recurrences.

Unmet Medical Need

Multiple myeloma is generally an incurable and fatal disease, running a course of multiple relapses and recurrences. Current therapies rarely produce long-term control in relapsed/refractory patients. Being stem cell memory CAR-T cells, the treatment could potentially produce long-term control.

Project Objective

Phase 1 trial completed

Major Proposed Activities

Manufacturing of products for the proposed trial

Enrollment, treatment and follow-up of patients to assess safety and efficacy of the therapy, followed by analysis and reporting of the results

Completion of nonclinical safety studies

Funds Requested

$19,997,927 ($8,571,294 Co-funding)

Recommendation

Score: 1

Votes for Score 1 = 10 GWG members

Votes for Score 2 = 0 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

Relapsed/refractory multiple myeloma is a significant unmet medical need. Reviewers thought that the proposed product has the potential to provide a very high rate of durable response in myeloma patients. There is strong scientific and clinical rationale for targeting BCMA on myeloma cells. Reviewers thought that the proposed improvements to the CAR T cell platform technology are highly innovative and could enhance the efficacy and durability of the treatment. Reviewers unanimously recommended the application 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/refractory multiple myeloma has a very poor prognosis and constitutes an unmet medical need.

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

- While there are a number of active agents producing responses in some patients lasting months to years, relapse is inevitable.
- Very high response rates have been reported for other CAR T cell approaches targeting the same BCMA antigen as this proposed product.

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

- If the proposed product is curative or provides a very high rate of durable responses it will offer a compelling value proposition.
- If successful, the proposed product and technology platform could be disruptive to the field of cancer immunotherapy.

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 BCMA target is widely expressed on myeloma cells.
- Clinical studies for other CAR T cell products targeting BCMA have demonstrated high response rates.
- The preclinical data for the proposed product showed powerful and durable efficacy in resistant myeloma models.

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- There is good scientific rationale that the use of a fully human CAR and a high percentage of stem cell memory T cells in the proposed product could increase efficacy and persistence *in vivo*.
- There is good scientific rationale for the proposed manufacturing improvements to the CAR T technology platform.

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

- The preclinical data on the proposed product and clinical data on related products targeting BCMA strongly support continued clinical development 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.

- The phase 1 study is appropriately designed to inform a go/no-go decision for the program.
- Reviewers noted that investigators participating in this study should not be on the safety committee.

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

- The proposed activities, including the rodent preclinical study for IND amendment, are appropriate and create value that advances CIRM's mission.
- The FDA follow-up correspondence indicates that only the rodent preclinical study is necessary for an IND amendment.

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 and demonstrates an urgency that is commensurate with CIRM's mission.

Is the project feasible?

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

- The manufacturing activities, clinical trial and preclinical studies are likely to be achieved in the proposed timeline.

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 team is highly qualified to conduct the clinical trial.

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

- While the clinical and manufacturing risks are minimally described, there is a financial contingency plan in place to address such risks.

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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).