



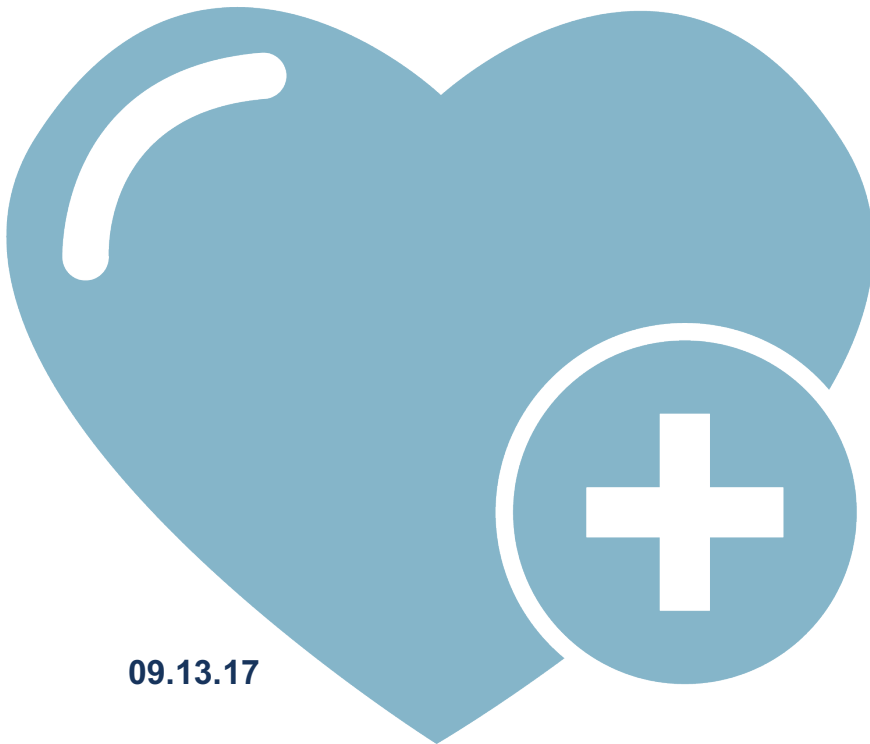
Grants Working Group Public Review Summary

Phase I Study of Chimeric Antigen Receptor Engineered Central
Memory T cells for the Treatment of Malignant Glioma

Application Number: CLIN2-10248
(Revised Application)

Review Date: 29 August 2017

Clinical Trial Stage Project Proposal (CLIN2)



09.13.17

CLINICAL



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Summary

Phase I Study of Chimeric Antigen Receptor Engineered Central Memory T cells for the Treatment of Malignant Glioma

APPLICATION NUMBER: CLIN2-10248 (Revised application)

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PROGRAM ANNOUNCEMENT: CLIN2 Clinical Trial Stage Projects

Therapeutic Candidate or Device

A promising immunotherapy utilizing a patient's memory T cells engineered to express chimeric antigen receptors (CAR) for targeted tumor killing.

Indication

Malignant glioma (WHO III and IV), including glioblastoma (WHO IV), that express the tumor-associated antigen IL-13 receptor alpha 2 (IL13R α 2).

Therapeutic Mechanism

A promising immunotherapy utilizing a patient's memory T cells genetically engineered to express chimeric antigen receptors for targeted tumor killing. Upon adoptive transfer the CAR T cell product specifically recognizes and directly destroys malignant glioma cells expressing IL13R α 2.

Unmet Medical Need

This proposal seeks to address the unmet medical need for more effective therapy against malignant glioma by engineering de novo antitumor immunity using patient-specific CAR-modified T cells.

Project Objective

Phase I trial completed

Major Proposed Activities

Manufacture and clinically evaluate intraventricular versus dual intraventricular and intratumoral delivery of CAR T cells

Evaluate safety, feasibility and preliminary evidence of efficacy across all routes of administration.

Develop and establish reagents and methods for a phase II clinical trial

Funds Requested

\$12,753,854 (\$0 Co-funding)

Recommendation

Score: 1

Votes for Score 1 = 15 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

This is a revised application that previously received a score of “2”. In the initial review of the application, reviewers supported the rationale for extending an ongoing phase 1 study to evaluate intratumoral and intraventricular delivery methods for a promising central memory CAR T cell treatment for malignant gliomas. They found the complete response observed in the single patient profiled in the proposal extremely compelling. However, they raised concerns about risks associated with intraventricular delivery and about the inadequately detailed safety data on the other patients treated to date. The reviewers also requested that the applicant provide additional rationale for not performing enrichment on the cell product. The revised application provided additional information on risks to patient, safety data on patients treated to date and justification for not performing cell enrichment on the manufactured product. The reviewers were satisfied with the applicant’s responses and 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.

- There is an unmet need for malignant glioma (MG) treatments and a number of clinical trials with CAR T cells are underway. Given the specific cell surface expression of IL13R α 2 in malignant glioma cells, IL13R α 2 is a promising target in malignant gliomas.

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

- The proposed treatment has the potential to reduce or eliminate recurrence and thereby improve the standard of care for MG patients.

c) Consider whether the proposed treatment offers a sufficient, impactful, and practical value proposition for patients and/or health care providers.

- While the treatment is difficult to scale up, the disease is very dire and the prevalence is small. Thus, setting up centers of excellence to administer the treatment could be worthwhile if meaningful results are achieved in MG patients.
- Some reviewers expressed concern that intraventricular delivery for the CAR T cell product could be technically challenging.

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Is the rationale sound?

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

- There is sound scientific rationale for targeting IL13R α 2 on malignant glioma cells.
- Observed results on the single patient treated on a compassionate use basis with intraventricular delivery of the CAR T cell product were compelling. The response observed in the other patients were not as compelling but reviewers did note a potential survival benefit.
- The treatment appears to be safe based on the safety outcomes in the patients treated to date with this approach.

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

- The complete response observed in the single compassionate use patient and overall safety observed in the phase 1 study support continued development of the therapeutic candidate.

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 achieve meaningful outcomes to support further development of the therapeutic candidate.

- The study design to test both intraventricular and intratumoral CAR T cell delivery methods is a particular strength of the proposal.
- The data obtained from this extended phase I study will add critical insights to the next study phases and eventually will have an impact on commercialization of the therapeutic candidate.
- In the initial review of this application reviewers expressed concern about the potential risks associated with the intraventricular delivery method. They were satisfied with the applicant's response, which identified the associated risks and provided additional safety data on the patients treated to date with this method.
- In the initial review of this application reviewers were unclear whether the product should be enriched for central memory T cells. They were satisfied with the applicant's response, which noted that risk of product loss, contamination and treatment delays did not outweigh the potential benefits of cell enrichment.

b) Consider whether this is a well-constructed, quality program.

- This is a well-planned project.

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- Data analytics to perform deep correlative analysis are well designed. From even a small number of patients, these analyses should allow for a much-improved phase 2 protocol and, most importantly, to the best outcomes possible.

c) Consider whether the project plan and timeline demonstrate an urgency that is commensurate with CIRM's mission.

- The project plan and timeline demonstrate 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 applicants have demonstrated the ability to execute a clinical trial investigating CAR T cells in malignant glioma.
- Enrollment estimates are reasonable and achievable given the number of eligible patients seen annually at the applicant institution.

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 well qualified and has specific expertise in CAR T cells and the cell delivery methods to be studied in this trial.

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

- The team has identified appropriate manufacturing risks and has a viable contingency plan.

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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).