

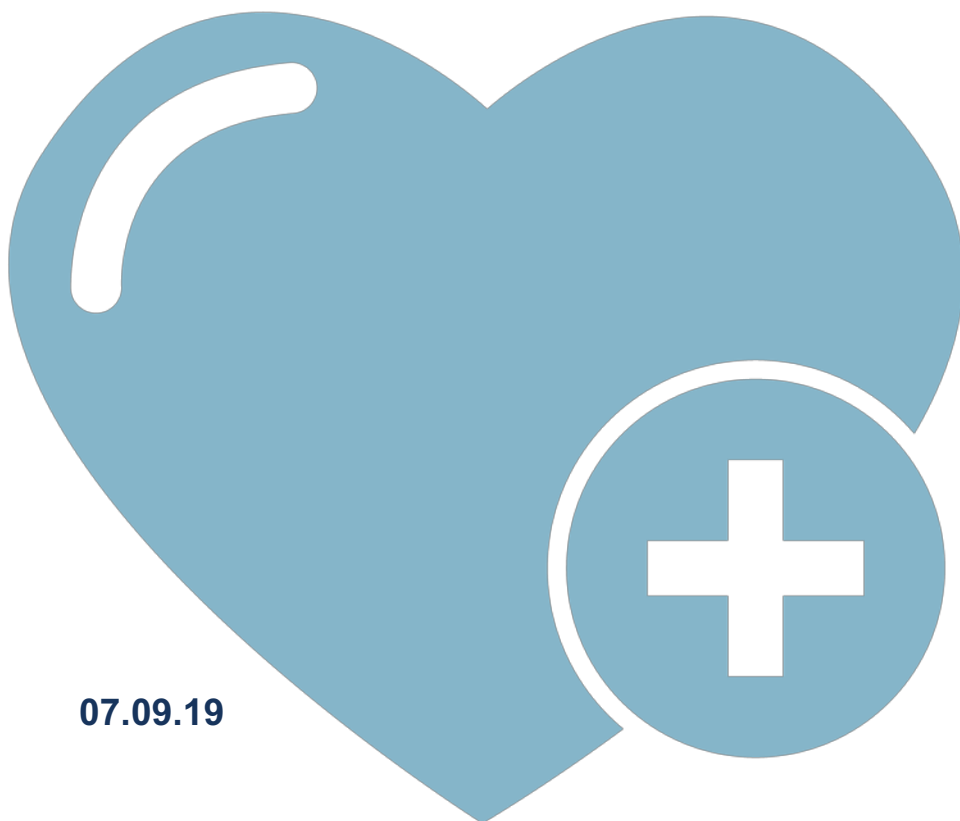
Grants Working Group Public Review Summary

A Phase 1 Study of Chimeric Antigen Receptor Engineered Stem/Memory T Cells for the Treatment of HER2-Positive Brain Metastases

Application Number: CLIN2-11574

Review Date: 25 June 2019

Clinical Trial Stage Project Proposal (CLIN2)



07.09.19

A Phase 1 Study of Chimeric Antigen Receptor Engineered Stem/Memory T Cells for the Treatment of HER2-Positive Brain Metastases

APPLICATION NUMBER: CLIN2-11574

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PROGRAM ANNOUNCEMENT: CLIN2 Clinical Trial Stage Projects

Therapeutic Candidate or Device

Autologous naïve-stem/memory T cells engineered with a chimeric antigen receptor targeting the HER2 antigen (HER2BBζ-Tn/mem)

Indication

HER2-positive brain and/or leptomeningeal metastases, primarily from breast cancer

Therapeutic Mechanism

The proposed therapy aims to provide a safe and effective treatment option for patients with HER2-positive cancers that have metastasized to the central nervous system via direct chimeric antigen receptor (CAR) T cell-mediated tumor cytotoxicity.

Unmet Medical Need

Currently, there are no effective treatment options that provide durable and life-extending therapies to patients with HER2-positive brain and/or leptomeningeal metastatic disease.

Project Objective

Phase 1 trial completed

Major Proposed Activities

Phase 1 clinical testing of regional intraventricular delivery of HER2BBζ-Tn/mem CAR T cell therapy

Achieve primary, secondary, and correlative study objectives in phase 1 trial

Phase 1 clinical trial activities to accelerate initiation of phase 2 trial

Funds Requested

\$9,288,375 (\$0 Co-funding)

Recommendation

Score: 1

Votes for Score 1 = 11 GWG members

Votes for Score 2 = 4 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.

Review Overview

A significant proportion of breast cancer patients will develop HER2+ brain metastases; many will undergo aggressive treatment including a combination of radiation, chemotherapy and surgery and still succumb to the disease. The proposed CAR-T cell therapy has potential to be a major breakthrough in extending survival for these patients. Reviewers agreed that the proposed HER2 targeted CAR-T cell therapy approach is based on sound rationale and is strongly supported by the applicants' preclinical and clinical studies.

Some reviewers were unconvinced that the proposed manufacturing improvement, which enriches for naïve-stem/memory T (Tn/mem) cells, will dramatically improve potency and persistence of the CAR-T cell product. Other reviewers thought it prudent to wait until the CIRM-funded clinical trial of a related CAR-T cell product for glioblastoma reads out more data prior to supporting this trial. However, the majority of the reviewers were strongly supportive of this project and recommended it for funding.

Review Summary

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

YES	14	NO	0
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Reviewers considered the following:

- a) Whether the proposed treatment fulfills an unmet medical need.
- b) Whether the approach is likely to provide an improvement over the standard of care for the intended patient population.
- c) Whether the proposed treatment offers a sufficient value proposition such that the value created by it supports its adoption by patients and/or health care providers.
- d) 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?

Summary of Reviewers' Comments:

- This is a highly significant and critical unmet medical need given that approximately 25% of breast cancer patients are HER2+ and 50% of these patients will develop brain and leptomeningeal metastases.
- HER2+ brain metastatic patients have poor prognoses and many exhaust treatments that include some combination of surgery, radiation and chemotherapy. If this CAR-T therapy is as effective as the similar CAR-T approach in glioblastoma it is likely to be a major breakthrough in treatment options for these patients.
- The value proposition to the healthcare system and overall scalability of the treatment are unclear given the complexity and cost of administering the autologous engineered CAR-T cell therapy.

Is the rationale sound?

YES	12	NO	2
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Reviewers considered the following:

- a) 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.
- b) Whether the data supports the continued development of the treatment at this stage.

Summary of Reviewers' Comments:

- Reviewers agreed that targeting HER2+ brain metastases with HER2-targeted autologous CAR-T cell therapy is based on sound scientific rationale.
 - Pre-clinical studies have shown potent, selective and durable anti-tumor efficacy of this therapeutic approach in mouse tumor models. However, some reviewers cautioned that the mouse studies didn't effectively model human metastatic disease.
 - Reviewers were encouraged by the preliminary data from the 3 initial patients treated with the central memory T cell variant of this CAR-T cell therapy.
- Reviewers agreed that localized intraventricular delivery of this CAR-T therapy is based on sound scientific and clinical rationale. It is a straightforward, minimally invasive surgical procedure and is currently being utilized safely in the ongoing CAR-T trial in glioblastoma.
 - The delivery approach may have an upper limit on quantity of cells that can be infused.
 - It is likely that the cells will traffic out of the cerebrospinal fluid (CSF) into the blood and perhaps back into the brain. There is some HER2 expression in the choroid plexus and it is important to monitor for damage and inflammation there and on the pial lining.
- Switching to a manufacturing process that enriches for Tn/mem has significant potential to improve CAR-T cell persistence and potency. Some reviewers remained unconvinced whether it justifies the added cost and complexity compared to bulk T cell processing.
 - Reviewers acknowledged that without head-to-head comparison and significantly more clinical data there is no definitive way to tell if Tn/mem selection is more effective than using bulk T cell populations.
 - Data from the multiple ongoing clinical studies in different cancers using this manufacturing approach may eventually strengthen the rationale for it.
 - A potential advantage of selection is that a more homogenous cell product is infused into the patient.
- Some reviewers thought that while there is strong scientific and clinical rationale for this CAR-T therapy in HER2+ brain metastases, it would be prudent to wait and obtain safety and efficacy data from the glioblastoma CAR-T trial prior to funding this trial.

Is the project well planned and designed?

YES	14	NO	0
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Reviewers considered the following:

- a) 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.
- b) Whether the proposed experiments are essential and whether they create value that advances CIRM's mission.
- c) Whether the project timeline is appropriate to complete the essential work and whether it demonstrates an urgency that is commensurate with CIRM's mission.

Summary of Reviewers' Comments:

- The trial is appropriately designed to provide safety, maximum dose and initial efficacy data that will inform the phase 2 trial design.
- The thorough secondary analysis plan will provide important data on Tn/mem persistence, biodistribution and bioactivity, which will further inform the clinical development of this CAR-T cell therapy.
- There was some concern about the FDA-imposed limitation on patient enrollment to those with stable systemic disease. While appropriate for this stage of clinical study, interpretation of results for efficacy and applicability to the broader HER2+ metastatic brain cancer population will be more difficult.
- Some reviewers questioned the inclusion of patients with HER2+ metastases from cancers other than breast, which could make it difficult to interpret results.
 - Other reviewers noted that it is not an uncommon strategy for accelerating enrollment in such trials where the primary objective is safety.
 - They also noted that it may inform whether brain metastases from different HER2+ cancers result in differential responses to the CAR-T cell therapy.
- The intraventricular delivery approach being studied in this trial had broader implications for the field on the potential for regional delivery of CAR-T cells for solid tumors.

Is the project feasible?

YES	14	NO	0
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Reviewers considered the following:

- a) Whether the intended objectives are likely to be achieved within the proposed timeline.
- b) 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.
- c) Whether the team has a viable contingency plan to manage risks and delays.

Summary of Reviewers' Comments:

- The team is extremely well qualified and resourced to execute the proposed project activities.
 - The team has a track record of effective execution on similar CAR-T clinical trials.
 - This is one of the premier teams for lentiviral vector and CAR-T manufacturing.
- There are appropriate contingency plans in place to manage the identified risks.
- Some reviewers were concerned that while the technology is licensed to a commercialization partner, the partner is not providing financial support for this phase 1 trial.

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).