CLINICAL

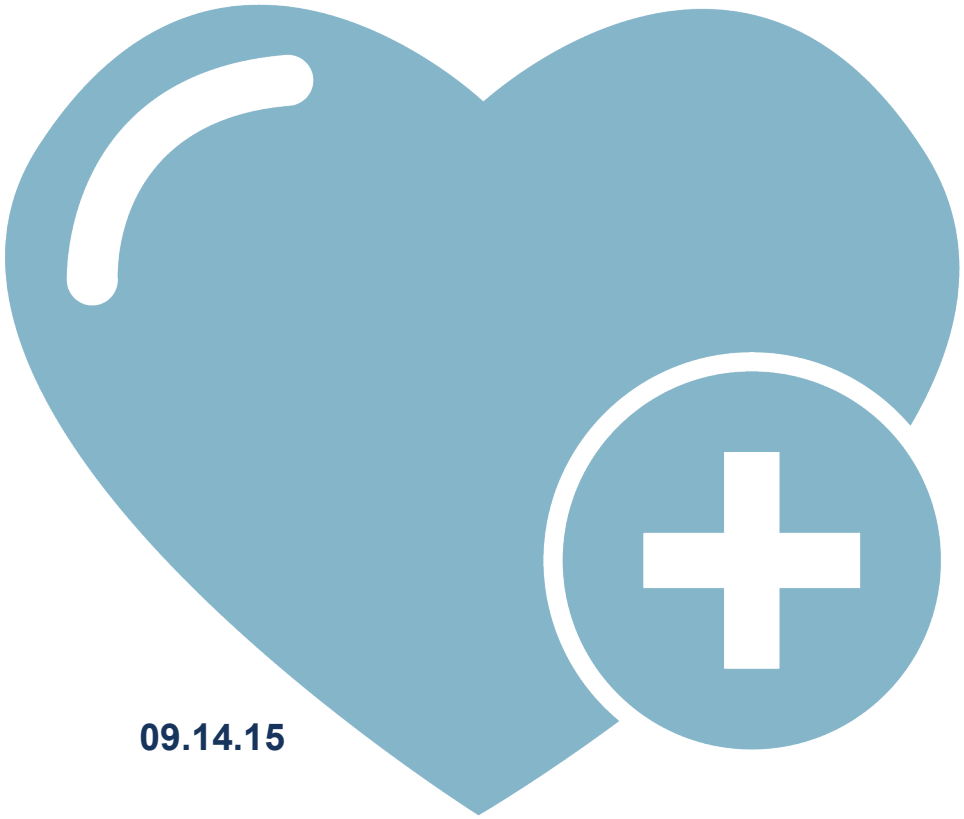
Agenda Item #8
ICOC Board Meeting
September 24th, 2015

Grants Working Group Public Review Summary

A Phase 3 randomized double-blind, controlled study of ICT 107 with maintenance temozolomide (TMZ) in newly diagnosed glioblastoma following resection and concomitant TMZ chemoradiotherapy

Application Number: CST1-08280 (Revised Application)	Review Date: August 25, 2015

Clinical Trial Stage Project Proposal (15-02)



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A Phase 3 randomized double-blind, controlled study of ICT 107with maintenance temozolomide (TMZ) in newly diagnosed glioblastoma following resection and concomitant TMZ chemoradiotherapy

APPLICATION NUMBER: CST1-08280 (Revised application)

REVIEW DATE: August 25, 2015

PROGRAM ANNOUNCEMENT: 15-02 Clinical Trial Stage Projects

Therapeutic Candidate

Autologous dendritic cells pulsed with HLA-specific peptides derived from tumor-associated antigens (ICT-107)

Indication

Newly diagnosed glioblastoma

Unmet Medical Need

Patients with glioblastoma, a rare brain cancer with orphan status, have a poor prognosis and limited lifespan despite current standard of care. Treatment options are limited to surgery, radiotherapy and a single chemotherapeutic agent. Tumor stem cells are resistant to current standard of care.

Major Proposed Activities

Manufacture autologous therapeutic product for each patient in the Phase 3 (Ph3) trial.

Conduct a multi-center, international Phase 3 clinical trial showing conclusive safety and efficacy of ICT-107 for newly diagnosed glioblastoma.

Funds Requested

$19,919,449 ($35,412,355 Co-funding)

Recommendation

Score: 1

Votes for Score 1 = 9 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.

CIRM 2.0

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Public Review Summary

Review Overview

In the initial review of this application, reviewers were enthusiastic as glioblastoma represents a serious unmet medical need. Additionally, the applicant presented strong preclinical and clinical data to support the proposed Ph3 registration trial and there was a reasonable plan to obtain regulatory approval of the proposed therapeutic. However, reviewers had feasibility concerns regarding the applicant's ability to enroll the trial and maintain the reagent supply chain to support manufacturing of the product. Reviewers also had concerns with the trial design, which centered around selection of the patient population targeted in the registration trial and the lack of immune monitoring proposed in the trial. The applicant was provided the opportunity to address these concerns in a revised application, and their responses and modifications to the proposal reassured reviewers that the applicant could enroll and conduct the Ph3 trial as proposed and that, if endpoints are met, the trial design could support licensing approval by FDA.

Review Summary

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

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

- Glioblastoma represents a serious unmet medical need as median survival is just over a year.
- No effective treatments are currently available for glioblastoma and a new treatment that extends overall survival or progression free survival would impact the unmet medical need; even a therapy restricted to a subset of glioblastoma patients such as the proposed therapy.

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

- If successfully developed, the proposed therapeutic could become a new standard of care and extend survival of glioblastoma patients.

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

- The proposed immunotherapy approach is a popular one in the development of glioblastoma treatments and, if successfully developed, the therapeutic would likely face significant competition. The applicants acknowledged the competition and clearly articulated advantages offered by their candidate therapeutic, and its potential to offer a sufficient and impactful value proposition.
- The value proposition and utility of this therapy will depend on a clear demonstration of efficacy and a lack of undesirable side effects. The therapy has been well tolerated to date, so if endpoints in the registration trial are met, the therapy is likely to have utility for patients.

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 a strong clinical rationale to support the proposed Ph3 trail, which includes a tremendous survival response in the Ph1 trial.

- The scientific rationale is well thought out and supported by the preclinical and clinical data.

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

- The preclinical package is rational, well thought out, and supportive of clinical development of the proposed therapeutic.
- Though the survival response observed in the Ph1 trial was not fully replicated in the Ph2 trial, results are supportive of continued clinical development and of the Ph3 trial as designed.

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 applicants have described a scientifically appropriate and reasonable Ph3 trial design based upon the available Ph1 and Ph2 clinical data.
- The reviewers expressed concern that the project plan does not include sufficient monitoring of immune responses following administration of the therapeutic nor sufficient laboratory medicine to inform the hypothesis and development of a second generation product. However, the applicant acknowledged this weakness and has indicated a desire to work with CIRM to enhance this part of their project.
- The applicant has agreement with FDA on Special Protocol Assessment (SPA) indicating that the trial design and proposed analysis is adequate to provide the necessary data to support a license application, should the clinical trial endpoint be met.

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

- Overall, this is a high quality program as indicated by the trial site and patient selection, reagent production plans, data analysis, oversight and monitoring plans, and contingency plans.

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

- The plan and timeline demonstrate an urgency to deliver treatments to glioblastoma patients 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.

- Reviewers expressed concerns regarding the ability of the applicant to fully enroll the trial as proposed given the competitive landscape in immunotherapy trials for glioblastoma and the complex nature of the multisite trial. However, the applicant articulated a clear and compelling plan to engage trial sites and providers to enroll the trial and has selected an experienced Clinical Research Organization (CRO) to assist in clinical operations.
- Reviewers were concerned that manufacturing issues might hinder the ability of the applicant to achieve the objectives within the proposed timeline. Concerns included supply chain security, contract negotiations with the Contract Manufacturing Organization (CMO), and comparability issues with

FDA. The applicant provided additional detail that allayed such concerns, though reviewers noted these issues should be monitored until resolved.

- Reviewers recommended the applicant hold a type C meeting with FDA per the SPA letter and suggest submitting the comparability protocol as a CMC amendment before executing it.

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 excellent, appropriately staffed and has access to all necessary resources.

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

- The contingency plans are appropriate though slightly under-developed in terms of patient enrollment risks.

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).