

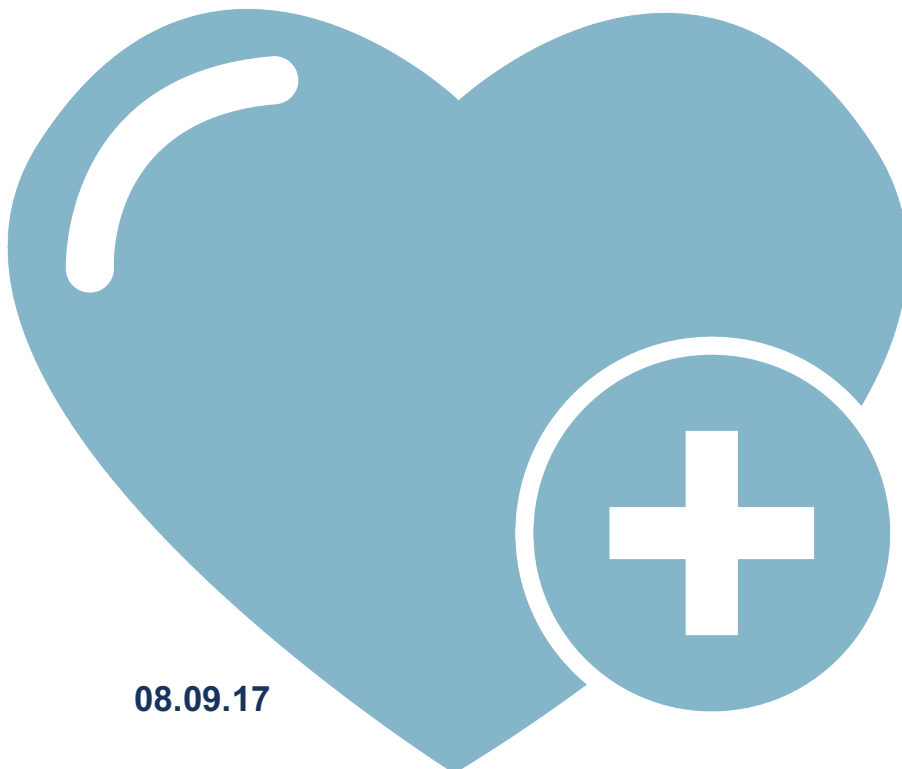


Grants Working Group Public Review Summary

A Phase 1b/2a Study of the ROR1-Targeting Monoclonal Antibody, Cirmtuzumab, and the Bruton Tyrosine Kinase Inhibitor, Ibrutinib, in B-Cell Cancers

Application Number: CLIN2-10192 (Revised Application)	Review Date: 25 July 2017
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Clinical Trial Stage Project Proposal (CLIN2)



08.09.17

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A Phase 1b/2a Study of the ROR1-Targeting Monoclonal Antibody, Cirmtuzumab, and the Bruton Tyrosine Kinase Inhibitor, Ibrutinib, in B-Cell Cancers

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PROGRAM ANNOUNCEMENT: CLIN2 Clinical Trial Stage Projects

Therapeutic Candidate or Device

Cirmtuzumab (UC-961) is a therapeutic monoclonal antibody that inhibits ROR1, a tumor-specific protein on the surface of many cancer stem cells

Indication

Cirmtuzumab will be used with the approved drug, ibrutinib, for patients with chronic lymphocytic leukemia or mantle cell lymphoma.

Therapeutic Mechanism

ROR1 is a cell surface protein which is present on tumors but not normal adult tissues, making it an attractive target for anticancer therapy. ROR1 is expressed on the malignant cells in >90% of patients with chronic lymphocytic leukemia or mantle cell lymphoma, and is commonly seen on multiple solid tumors, where it is a marker of cancer stem cells. Binding of cirmtuzumab inhibits ROR1 cellular actions, thereby disrupting processes important for cancer growth.

Unmet Medical Need

Ibrutinib, a current therapy for chronic lymphocytic leukemia and mantle cell lymphoma, causes complete disease remission in <20% of patients. Combining cirmtuzumab with ibrutinib is proposed to significantly increase the proportion of patients with complete remission and long-term cancer control.

Project Objective

Cirmtuzumab manufactured, Ph 1b/2a trial completed.

Major Proposed Activities

Manufacture cirmtuzumab monoclonal antibody for use in the Phase 1b/2a clinical trial.

Perform a Phase 1b/2a study to demonstrate the safety, pharmacology, and efficacy of cirmtuzumab when given together with ibrutinib.

Funds Requested

\$18,292,674 (\$13,341,842 Co-funding)

Recommendation

Score: 1

Votes for Score 1 = 14 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 combining cirtuzumab and ibrutinib for B-cell malignancies but expressed several concerns about the trial design. They raised concerns about the inclusion of both MCL and CLL patients, the statistical plan and the stopping rules in the proposed clinical trial. The revised proposal adequately addressed reviewers’ concerns by focusing the Phase 2 study portion on CLL patients and by introducing appropriate stopping rules. The applicants also provided sufficient additional information on the planned cancer stem cell correlative studies. Reviewers recommended the project 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.

- Curative strategies for patients with relapsed and refractory chronic lymphocytic leukemia (CLL) or mantle cell lymphoma (MCL) are limited to allogeneic bone marrow transplantation.
- The proposed treatment, if shown to target cancer stem cells, has the potential to address the unmet medical need for improved complete response rate in these disease indications.

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

- If the proposed treatment adequately targets CSCs and achieves long-term remission without need for bone marrow transplantation then it would be a significant advance over the standard of care.

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

- The agent may provide value by decreasing the need for stem cell transplantation or chronic use of ibrutinib or idelalisib.
- Pre-clinical data suggests that the combination of cirtuzumab and ibrutinib may provide a valuable new combination therapy that would significantly increase efficacy versus CLL with minimal added toxicity.

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.

- ROR1 is expressed on both CLL and MCL cells. The data gathered to date suggests that WNT5a activation of ROR1 leads to tumor cell proliferation. The published data in CLL and preliminary data for MCL convincingly show that cirtuzumab blocks ROR1 activation.

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

- *In vitro* and *in vivo* evidence supports development of the proposed combination. Phase 1 data from Cirmtuzumab monotherapy suggest pharmacokinetic/pharmacodynamic activity with minimal toxicity at the selected monotherapy dose. Early anecdotal clinical evidence suggests enhanced activity of the combination.

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 phase 1/2 trial was well-designed in the initial application, and has been improved by focusing the phase 2 study on CLL and inclusion of futility analyses.
- The clinical study design is acceptable for signal seeking and moving on to a comparative study, however even accelerated approval must show substantial evidence of effect.
- The applicant responded to reviewer concerns by incorporating and improving stopping rules during different stages of the trial.

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

- The program is well-constructed.
- The inclusion of investigators in the monitoring committee is not appropriate and not in the patients' best interest.

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

- The initial plan demonstrated urgency, and the changes to focus on CLL and include a futility analysis show additional 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 clinical trial objectives are clearly defined and evidence of efficacy should be obtained by the end of the proposed funding period.
- Patient accrual rate may be a concern in the Phase 2 portion of the study.

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 and investigators are well-suited to the protocol.

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- The PI has demonstrated timely performance on previous CIRM awards.
- c) **Consider whether the team has a viable contingency plan to manage risks and delays.**
- The team identified appropriate risks with respect to manufacturing, trial enrollment and trial outcome. The team proposed viable contingency plans for the identified 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).