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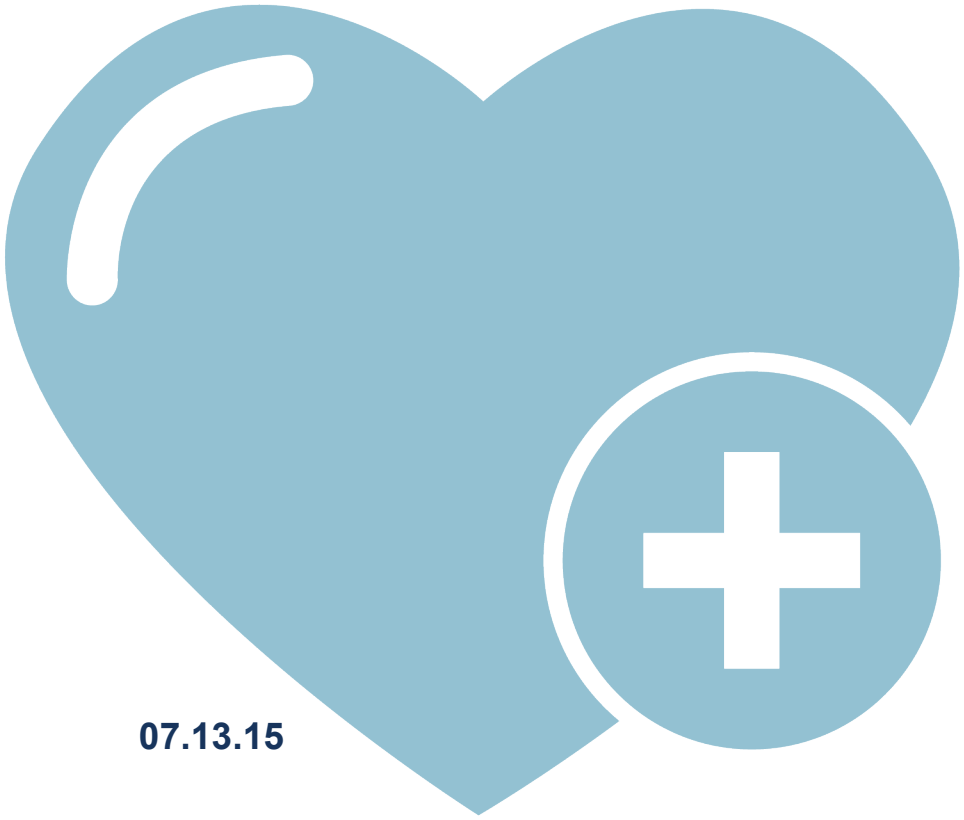
Grants Working Group Public Review Summary

A Phase 1B Extension Study to Determine the Safety, Pharmaco-kinetics and Pharmacodynamics of UC-961 (Cirmtuzumab) at the Recommended Phase 2 Dose for Patients with Chronic Lymphocytic Leukemia Previously Treated with Cirmtuzumab (UC-961)

Application Number: SAA1-08273	Review Number: CP2015 - June

Supplemental Accelerating Activities Project Proposal



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A Phase 1B Extension Study to Determine the Safety, Pharmacokinetics and Pharmacodynamics of UC-961 (Cirmtuzumab) at the Recommended Phase 2 Dose for Patients with Chronic Lymphocytic Leukemia Previously Treated with Cirmtuzumab (UC-961)

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PROGRAM ANNOUNCEMENT: Supplemental Accelerating Activities Projects

Therapeutic Candidate

UC-961 (Cirmtuzumab) - a humanized monoclonal antibody specific for ROR1, an enzyme that is a cancer stem-cell antigen

Indication

Chronic lymphocytic leukemia (CLL)

Unmet Medical Need

Persistence of cancer stem cells (CSC) can allow for cancer to relapse after apparent successful therapy. For this reason, many cancers including CLL are considered incurable. Cirmtuzumab targets ROR1 and may effect eradication of CSC, potentially saving the lives of those with intractable cancer. CLL is the lead indication; however, cirmtuzumab also has anti-cancer-stem cell activity in other cancers.

Major Proposed Activities

GMP manufacture of cirmtuzumab to provide sufficient antibody for completion of the extension-therapy trial

Conduct extension protocol for patients in the Phase I study who require additional treatment with cirmtuzumab

Funds Requested

2,895,587 ($0 Co-funding)

Recommendation

Score: 2

Votes for Score 1 = 2 GWG members

Votes for Score 2 = 6 GWG members

Votes for Score 3 = 3 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.

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Review Overview

Reviewers expressed enthusiasm for the parent project and acknowledged the excellence of the team. However, they thought the proposed extension trial to be poorly designed and did not believe it would add value to the parent award, nor did they think it would accelerate or increase the likelihood of successful development of the therapeutic candidate.

Review Summary

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

a) Consider whether the proposed activities add value to the parent award.

- Reviewers did not think that the proposed extension trial would add value and expressed concern that it could be a distraction from the ongoing parent trial.
- Reviewers acknowledged that patients enrolled in the Phase 1 trial may be interested in ongoing treatment but did not consider the proposed Phase 1 extension trial to be an appropriate approach to addressing this issue.

b) Consider whether the conduct of these activities accelerates completion of the parent project, accelerates development of the therapy to patients, or increases the likelihood of successful development of the therapeutic candidate.

- The extension trial as proposed is not likely to accelerate development or increase the likelihood of success.
- Reviewers were concerned that repeat dosing of patients prior to determination of the maximum tolerated dose (MTD) could complicate understanding of the Phase 1 data, and, therefore, potentially detract from the parent trial.
- Reviewers agreed with the applicant that acceleration of the current dosing schedule is appropriate and could accelerate development of therapy. However, they thought acceleration could be better achieved by discussing the safety data collected to date with the FDA and proposing an accelerated and/or increased continuous dosing scheme in naïve patients.

Is the rationale sound?

a) Consider whether the proposed activities are justified and integral to the core objective of the parent award.

- Reviewers thought it premature to initiate repeat dosing trials when the MTD is not yet defined and toxicities associated with higher doses are not known.

b) Consider whether there is evidence that pursuing these activities is necessary and appropriate at this time.

- Reviewers agreed with the applicant that it is appropriate to accelerate the dosing scheme at this time but did not think the applicant proposed an appropriate plan to do so.

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

- Though it would be meaningful to obtaining additional dosing information to support clinical development, reviewers found the proposed extension trial to

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be poorly designed and did not think the applicant can obtain meaningful outcomes from the study as proposed.

- Some information on repeat dosing would be obtained in the proposed extension trial, but the data would likely to be difficult to interpret as single dose toxicities are not yet determined and repeat dosing is likely to complicate understanding of toxicities observed in the Phase 1 trial at higher doses.
- Reviewers were particularly concerned that inclusion of overlapping cohorts in the Phase 1 trial could complicate the ability of the applicant to determine the MTD, a critical element for moving the therapeutic candidate forward.
- Reviewers thought the plan to generate additional antibody for the study to be excellent.
- As previously mentioned, reviewers advised approaching the FDA with a new dosing scheme. However, if the FDA is not amenable, reviewers would be more receptive to an extension trial designed to demonstrate responses at higher doses and/or continuous doses in naïve patients.

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

- Reviewers acknowledged the high quality of the parent project but did not think the proposed extension trial was of similar high quality.

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

- Reviewers thought the trial as designed could delay completion of the existing Phase 1 trial without accelerating initiation of a true Phase 2 trial. A plan more commensurate with the urgency of CIRM's mission would be to complete the Phase 1 trial as soon as possible and initiate a well-designed Phase 2 trial.

Is the project feasible?

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

- Reviewers thought the applicant could execute the extension trial as proposed.
- The applicant may be overly optimistic regarding the number of patients that will enroll in the proposed trial and enrollment could take longer than planned.

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.

- Reviewers thought that the team is well qualified and has a clear track record of success. The team is a strength of the proposal.
- The team has access to all necessary resources.

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

- The team identified appropriate risks and has a solid and viable contingency plan to manage risks.

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CIRM Recommendation

The CIRM team met after the GWG to consider its recommendation to the Application Review Subcommittee. This section will be posted publicly.

RECOMMENDATION: Do not fund (CIRM concurs with the GWG recommendation)