



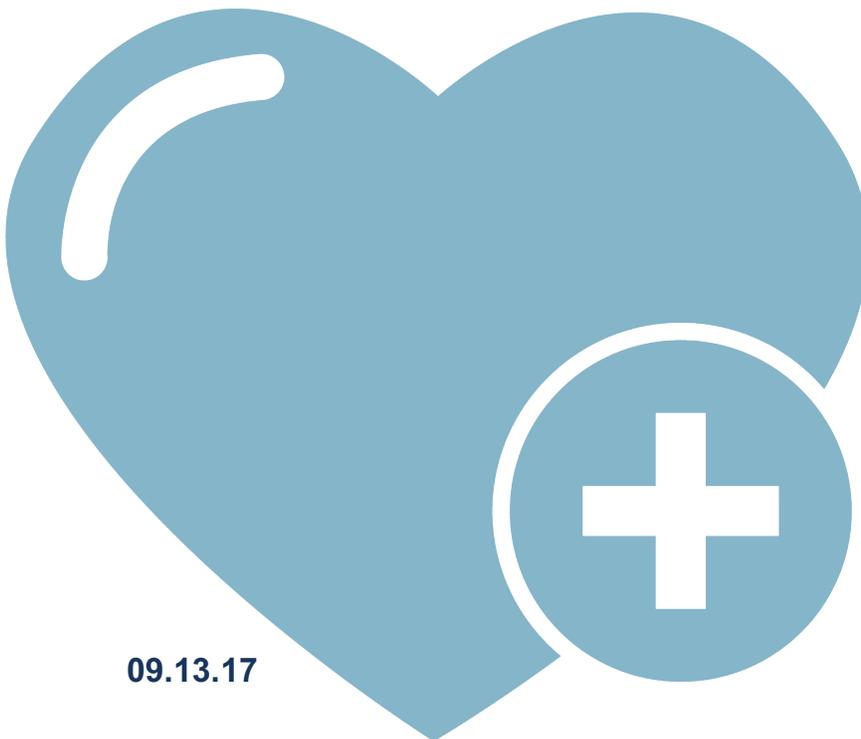
Grants Working Group Public Review Summary

A Phase 1b Trial of Hu5F9-G4 Monotherapy or Hu5F9-G4 in
Combination with Azacitidine in Patients with Acute Myeloid
Leukemia

Application Number: CLIN2-10144
(Revised Application)

Review Date: 29 August 2017

Clinical Trial Stage Project Proposal (CLIN2)



09.13.17

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A Phase 1b Trial of Hu5F9-G4 Monotherapy or Hu5F9-G4 in Combination with Azacitidine in Patients with Acute Myeloid Leukemia

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PROGRAM ANNOUNCEMENT: CLIN2 Clinical Trial Stage Projects

Therapeutic Candidate or Device

Hu5F9-G4 is a drug called an antibody that is designed to mobilize the body's immune system to eliminate cancer and cancer stem cells.

Indication

Patients with relapsed and/or refractory AML or newly diagnosed AML who cannot receive standard high dose chemotherapy.

Therapeutic Mechanism

This treatment targets cancer stem cells, which are cells thought to be responsible for how AML forms. Hu5F9-G4 targets a molecule on cancer cells called CD47, which acts as a "don't eat me" signal that cancer cells commandeer to avoid being ingested by the immune system. Hu5F9-G4 covers up this signal, allowing for the immune system to kill the cancer cells.

Unmet Medical Need

Acute myeloid leukemia (AML) affects over 13,000 adults annually and is one of the deadliest blood cancers in the United States. New therapies are needed as none available have been approved in over 40 years. Hu5F9-G4 alone or in combination has promising potential to benefit to AML patients.

Project Objective

Phase 1b trials completed.

Major Proposed Activities

Investigating how safe and well tolerated Hu5F9-G4 alone or in combination with azacitidine is in AML patients

Investigating how effective Hu5F9-G4 alone or in combination with azacitidine in eliminating leukemic disease in AML patients

Investigating optimal dosing regimen of Hu5F9-G4 for the treatment of AML patients

Funds Requested

\$5,000,000 (\$7,390,868 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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Public Review
Summary

Review Overview

This is a revised application that previously received a score of “2”. In the initial review of the application, reviewers thought that there was compelling scientific and clinical rationale for studying Hu5F9-G4 in relapsed/refractory (R/R) and treatment naïve/unfit (TN/U) AML patients. However, they had concerns about the potential for overlap between the proposed phase 1b study and the ongoing phase 1 study being conducted in the UK. Reviewers also thought that the application had not provided adequate rationale for the combination therapy. They were also unclear on the safety and efficacy endpoints and leukemic stem cell (LSC) targeting analyses proposed in the phase 1b study. The applicant’s response, which clarified that the proposed study builds on the ongoing UK study, provided additional information on the endpoints and LSC target analyses and provided additional rationale for the combination therapy approach, was well received by the reviewers. Reviewers commended the phase 1b study design 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.

- The R/R and elderly subtypes of AML are not curable in most cases and few effective treatment options currently exist.
- Limited survival rates are thought to be due to persistence of drug resistant leukemic stem cells (LSC), which may be effectively targeted by the proposed treatment.

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 is shown to target leukemic stem cells it may improve long-term outcomes for patients with AML.
- The current standard of care for patients with AML is chemotherapy with or without bone marrow transplantation with a curative intent. The proposed treatment may improve outcomes by limiting the toxicities of the standard approaches.

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

- The development of a novel therapy for AML capable of improving survival rates carries significant impact. Alleviating the need for allogeneic stem cell transplantation may also provide significant cost savings to the healthcare system.
- The therapy is likely to be well tolerated. There is good rationale for efficacy. This remains a largely untested approach but, if it does work, it is likely to have

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Public Review
Summary

a significant impact on AML treatment.

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.

- The rationale for targeting CD47 as an anticancer approach is supported by the published preclinical data. These data suggest that CD47 is expressed at increased levels on AML cells compared to normal hematopoietic cells. LSC targeting is supported by the *in vivo* pre-clinical data. Clinical data on Hu5F9-G4 monotherapy further support the rationale.
- The rationale for combining Hu5F9-G4 with azacitidine isn't particularly strong but the applicant's *in vitro* data suggests that azacitidine enhances Hu5F9-G4 activity. The applicants also included compelling anecdotal information that patients who had previously failed azacitidine are responding well to the combination.

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

- The results from the phase 1 study in the UK show that Hu5F9-G4 is well tolerated and provide rationale for continued development of the proposed treatment.

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.

- In the initial review of the application, reviewers were unclear how the proposed phase 1b trial built on the ongoing phase 1 study being conducted by the applicant in the UK. Reviewers found the applicant's response, which noted that the proposed study enables exploration of higher doses, expands inclusion/exclusion criteria, incorporates preliminary efficacy analysis and tests the combination therapy, to be satisfactory and they commended the study design.
- Inpatient dose-escalation is a well-designed and appropriate method to optimize patient dosing, and the applicants provided appropriate justification.
- The planned correlative studies for evaluating LSC targeting are well designed and will provide important information.
- Reviewers thought the durability endpoint was especially relevant given that treatment durability is a major concern in R/R AML patients.

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Public Review
Summary

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

- The clinical trial is well designed to examine the safety and efficacy of the proposed treatment in AML patients.
- The manufacturing partner is appropriately qualified and has already supplied product for the ongoing trial.
- Reviewers questioned whether the data safety monitoring committee was appropriately setup to function as an independent body.

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

- The project timeline demonstrates 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 commitment from adequate centers to enroll patients.
- The applicants have demonstrated appropriate manufacturing capability to supply the trial.

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.

- This is a well-qualified team that has already shown the ability to successfully conduct an AML trial.

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

- The applicant identified some potential risks and proposed appropriate contingency plans for these risks. However, risks associated with the lack of AML activity or lack of LSC targeting were not discussed in the application.

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Public Review
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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).