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CALIFORNIA'S STEM CELL AGENCY

Grants Working Group Public Review Summary

Tumor stem cell-targeted immunotherapy for metastatic melanoma – a randomized phase 3 clinical trial

Application Number: CTS1-08239

PA 15-02: Clinical Trial Stage Projects

Review Number: 2015-04

THERAPEUTIC CANDIDATE
Tumor stem cell-targeted immunotherapy

INDICATION
Metastatic melanoma

UNMET MEDICAL NEED
There is an unmet need for treatments that can increase the long-term survival of patients with metastatic melanoma.

MAJOR PROPOSED ACTIVITIES
Completion of a Phase 3 (Ph3) pivotal trial conducted under SPA agreement with FDA.

Manufacturing of tumor stem cell-targeted immunotherapy.

Assessment of clinical safety and efficacy of the therapeutic candidate.

FUNDS REQUESTED
$17,731,554

RECOMMENDATION

Score: 1

Votes for Score 1 = 6 GWG members
Votes for Score 2 = 3 GWG members
Votes for Score 3 = 5 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

The clear strength of the proposed project and the basis of the fund recommendation is the compelling Ph2 clinical data reported by the applicant. Reviewers acknowledged the unmet medical need but were uncertain as to the proposed drug's impact on the patients with the highest unmet need when considered in comparison to recently available therapies. Reviewers considered the lack of mechanistic data and inadequate plan to gain understanding of therapeutic mechanism of action (MOA) to be a major weakness and expressed concern regarding the ability of the applicant to enroll the proposed pivotal Ph3 study as projected.

The GWG vote and recommendation to fund the project reflects both the high risk and the clear potential to impact unmet medical need. Although consensus could not be reached on balancing these two points, the GWG engaged in a robust and informed discussion that included perspectives from all reviewers.

REVIEW SUMMARY

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

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

- Metastatic melanoma in the proposed patient population represents an unmet medical need.
- The investigational drug has fast track designation with FDA in this indication, indicating it is considered an unmet medical need.
- Competing therapies recently approved or in development could limit the impact of the candidate therapy.

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

- This approach has the potential to improve outcomes with minimal toxicity as compared to currently available treatments thus improving the standard of care significantly.
- It may be possible to combine this treatment with other immune modulatory therapies with the potential to achieve greater efficacy.
- The data suggesting a favorable comparison of the candidate therapy to competing therapies was considered overstated and indeterminate.

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

- The proposed therapeutic offers a more tolerable mode of delivery and minimal toxicity compared to available therapies.
- The value proposition will likely depend upon the survival benefit and reliability of manufacturing the product. Despite the challenges and cost of delivering patient specific therapies, if the survival benefit observed in the Phase 2 trial is replicated, this drug is likely to be used by health care providers and elected by 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.

- Although based on a small number of patients, the data presented from the Phase 2 studies are compelling and show an impressive efficacy effect.
- There is a lack of sufficient data in the proposal to support the proposed mechanism of action (MOA).
- The rationale underlying the proposed MOA studies is weak.
- A cancer vaccine strategy for treating metastatic melanoma is sound.

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

- Data presented from the Phase 2 studies provide the single greatest support for progression to the proposed Phase 3 trial.
- A subset of reviewers were supportive of continued development but considered a pivotal trial to be premature and thought a confirmatory study would be more appropriate.

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 3 trial is appropriately planned, and the applicant has agreement with FDA on Special Protocol Assessment (SPA), indicating that the trial design is adequate to provide data to support a license application should the trial endpoint be met.
- There was concern that the trial design might be based on overly optimistic assumptions, and the study, therefore, underpowered.

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

- While the proposed trial is well-constructed, the proposed assays are not adequately designed to understand why some patients respond while others do not.
- Some of the proposed assays require a great deal of resources, and reviewers did not think the assays will yield useful data and recommended omitting these from the plan.

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

- The timeline does demonstrate an urgency that is commensurate with CIRM's mission, however, it might be overly ambitious.
- There are non-clinical hold manufacturing concerns that should be addressed during the course of the award to support timely approval and delivery to patients in the event the primary endpoint are met and approval granted.

Is the project feasible?

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

- The project plan and timeline are ambitious, and reviewers were concerned as to whether the trial could be enrolled as planned given the size of the trial; the number of competing therapies now available or in clinical trials; and the complexity of the manufacturing process.
- The number of trial sites proposed may be inadequate, so the applicant should consider increasing the number of sites to avoid enrollment problems.
- Recent improvements to the manufacturing process were thought to make the timeline more feasible.

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 was considered to be appropriate but with limited experience conducting large clinical studies.
- The team would likely benefit from additional internal commercial manufacturing expertise.

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

The contingency plan notes manufacturing and enrollment as risks, and the plans to address those risks were considered reasonable.