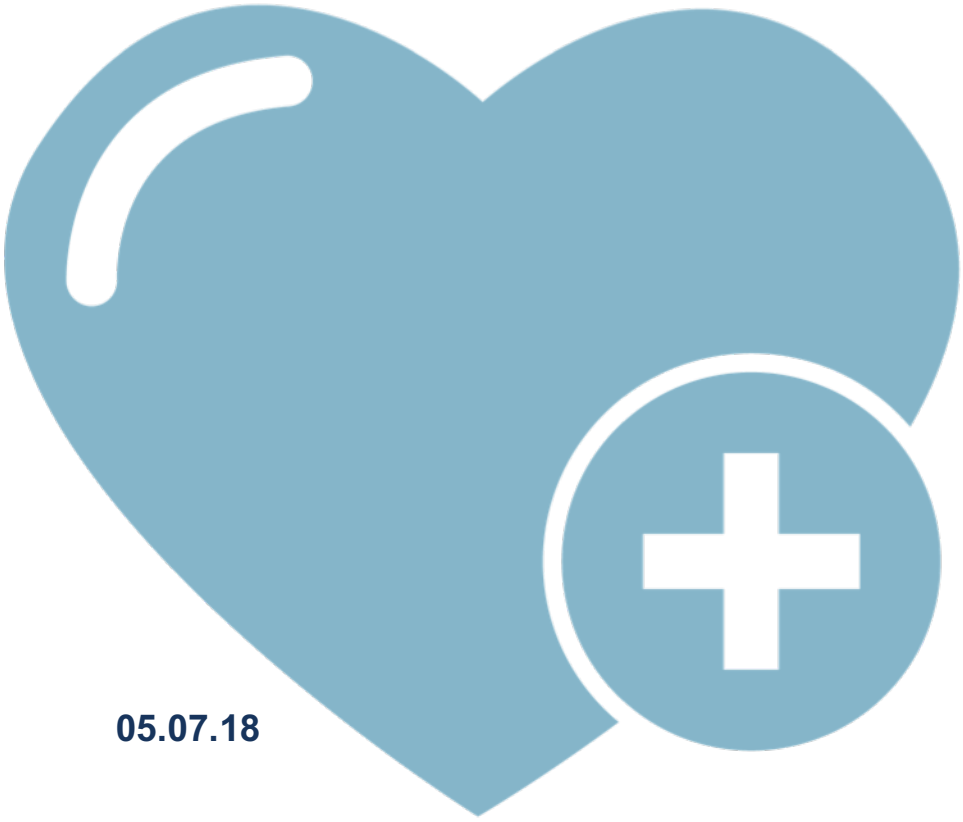
CIRM
CALIFORNIA'S STEM CELL AGENCY

Grants Working Group Public Review Summary

A phase I trial of intratumoral administration of CCL21-gene modified dendritic cell (DC) combined with intravenous pembrolizumab for advanced NSCLC

Application Number: CLIN2-10784 (Revised Application)	Review Date: 26 April 2018

Clinical Trial Stage Project Proposal (CLIN2)



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A phase I trial of intratumoral administration of CCL21-gene modified dendritic cell (DC) combined with intravenous pembrolizumab for advanced NSCLC

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PROGRAM ANNOUNCEMENT: CLIN2 Clinical Trial Stage Projects

Therapeutic Candidate or Device

Combination therapy with adenoviral CCL21 gene-modified DC and pembrolizumab

Indication

Patients with confirmed and measurable stage IV NSCLC expressing PD-L1 in less than 50% of cells who are naïve to systemic treatment for NSCLC.

Therapeutic Mechanism

The central rationale this approach is to utilize in situ vaccination with intratumoral injection of functional antigen presenting cells that take advantage of the full repertoire of available tumor antigens. We, and others, have found that this can convert the tumor site into a lymph node-like environment and thus promote specific T lymphocyte activation both locally and systemically.

Unmet Medical Need

Approximately 80% of NSCLC patients treated with anti-PD-1 do not respond. We have found that IT injection of Ad-CCL21-DC can induce tumoral CD8 T lymphocyte, enhance tumor antigen presentation in situ, and trigger systemic antitumor immunity. This supports the rationale for combination therapy.

Project Objective

Completion of phase 1 combination therapy trial

Major Proposed Activities

GMP manufacture of gene modified autologous cellular product

Phase 1 dose escalation and expansion cohorts for combination therapy

Monitoring of clinical and immune responses

Funds Requested

$11,993,073 ($400,000 Co-funding)

Recommendation

Score: 1

Votes for Score 1 = 15 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.

Review Overview

This is a revised application that previously received a score of "2". Reviewers agreed that the vast majority of patients with advanced non-small cell lung cancer (NSCLC) currently lack effective treatment options. Reviewers thought that the rationale for proposing a combination immunotherapy of Ad-CCL21-DC and pembrolizumab for patients with <50% PD-L1 tumor cells was sound and was strongly supported by preclinical and clinical data. Reviewers thought that the design of the dose escalation and expansion phases of the trial and the focus on a treatment-naïve patient population were strengths of the proposal.

In the initial review of the application, reviewers raised concerns about the lack of functional characterization of the cell product, which they thought would complicate interpretation of trial results. The applicant adequately addressed reviewers' concerns in the revised submission by proposing a suite of assays to characterize functionality of the autologous cell product. Reviewers expressed strong overall enthusiasm for the project and unanimously recommended it for funding.

Review Summary

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

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

- The currently available therapies do not adequately benefit the majority of patients with advanced NSCLC. The proposed approach could improve the efficacy of immunotherapy in this patient population.
- There is also a need to evaluate novel therapeutics in a first line treatment-naïve setting before resistance mechanisms induced by conventional therapies have emerged. The treatment-naïve setting of this proposal is novel for this stage in development of the proposed treatment and a considerable strength of the application.

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

- The proposed combination immunotherapy is likely to provide improvement in outcome for advanced NSCLC patients with <50% PD-L1 expression in their tumors.

c) Consider whether the proposed treatment offers a sufficient value proposition that supports its adoption by patients and/or health care providers.

- If intra-tumoral injection of Ad-CCL21-DC is shown to improve responses to anti-PD1 immunotherapy then the proposed combination immunotherapy would offer excellent value to eligible patients, especially younger patients with locally advanced disease.

c) If a Phase 3 Trial is proposed is the therapy for a pediatric or rare indication or, if not, is the project unlikely to receive funding from other sources?

- N/A

2. Is the rationale sound?

a) Consider whether the proposed project is based on a sound scientific and/or clinical rationale, and whether the project plan is supported by the body of available data.

- The scientific rationale of converting the tumor into an active lymph node by administering Ad-CCL21-DC is sound and supported by strong preclinical data.
- The applicant has already gathered safety data on administration of Ad-CCL21-DC in a phase 1 trial

wherein Ad-CCL21-DC was studied as a single agent therapy.

- There is sound scientific rationale for combining intratumoral injection of Ad-CCL21-DC and administration of pembrolizumab, and it is supported by the applicant's strong preclinical data.
- The scientific and clinical rationale for use of pembrolizumab in this patient population is well established.

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

- The preclinical and clinical data strongly support clinical development of the combination immunotherapy.

3. 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 to achieve meaningful outcomes to support further development of the therapeutic candidate.

- The dose escalation and dose expansion phases of the trial are very well designed.
- The study of the combination immunotherapy in a treatment-naïve setting is appropriate and a strength of the proposal.
- In the initial review of the application, reviewers noted that a clear definition of an "evaluable" patient in the response population was not provided in the application.
    - Reviewers thought that the applicant provided a thorough and appropriate definition of an "evaluable" patient in the revised submission.
- In the initial review of the application, reviewers were concerned that the trial data would be difficult to interpret given the variability inherent in autologous cell products. Reviewers recommended that the applicant perform functional characterization assays on the cell products.
    - Reviewers were satisfied with the range of functional assays proposed by the applicant in the revised submission.

b) Consider whether the proposed experiments are essential and whether they create value that advances CIRM's mission.

- The proposed trial will inform clinical development of the combination immunotherapy for NSCLC.
- The extensive immunophenotyping and tumor characterization proposed in the application will provide useful information for interpreting outcomes in this trial. The studies may also inform the wider development of immunotherapies for NSCLC.

c) Consider whether the project timeline is appropriate to complete the essential work and whether it demonstrates an urgency that is commensurate with CIRM's mission.

- The proposed timeline is appropriate for execution and completion of the phase 1 trial.

4. Is the project feasible?

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

- The manufacturing, patient accrual and patient monitoring objectives are likely to be achieved within the proposed timeline.

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 has the necessary manufacturing, clinical and scientific resources to perform the phase 1 trial.

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

- The team has identified appropriate risks and has proposed an adequate contingency plan, both of which were informed by their previous clinical trial experience.

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).