Application #	CLIN1-14080
Title (as written by the applicant)	Allogeneic mesenchymal stem cells loaded with oncolytic virus for cancer treatment
Therapeutic Candidate (as written by the applicant)	Allogeneic adipose-derived culture expanded mesenchymal stem cells loaded with oncolytic vaccinia virus
Indication (as written by the applicant)	-Metastatic melanoma -Triple negative breast cancer -Advanced Head & Neck Squamous Cell Carcinoma
Unmet Medical Need (as written by the applicant)	The proposal's targeted indications are associated with significant morbidity with limited treatment options and poor survival rates. Our new treatment approach will contribute to the effective treatment and improving quality of life of these patients.
Major Proposed Activities (as written by the applicant)	• Manufacturing of the final therapeutic drug product • Development and validation of assays for analysis of patient samples • IND-enabling animal model studies and electronic submission of the IND application to the FDA
Funds Requested	$3,111,467
GWG Recommendation	Tier 1: warrants funding
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: 1

Up to 15 scientific members of the GWG score each application. The final score for an application is the average of the individual member scores. Additional parameters related to the score are shown below.

Highest	1
Lowest	2
Count	14
Votes for Tier 1	12
Votes for Tier 2	2
Votes for Tier 3	0

- 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

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/RFA. Following the panel's discussion and scoring of the application, the members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

GWG Votes	Does the project hold the necessary significance and potential for impact?
Yes: 14	• Multiple different types of oncolytic viral therapies and other intralesional approaches are under development, as the investigators acknowledge. The investigators have presented theoretical rationale, including new preclinical data, for the potential superiority of their

	approach using oncolytic viral particles taken up by stem cells to limit the neutralization and degradation of the viral particles by the immune system. Whether this approach will translate into greater clinical efficacy can only be established through clinical testing. ● The proposed treatment is targeting multiple solid tumor types that are difficult to treat, and the treatment has the potential to overcome shortcomings in other attempts to use oncolytic viruses. ● Intralesional (intratumoral) therapy with an oncolytic virus could have substantial impact in treating a number of malignancies with accessible tumor sites with minimal systemic toxicity compared with other forms of treatment.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 13	● The resubmission is much clearer in explaining the rationale for loading cells with the virus, as well as the rationale for why the new process for producing allogeneic cells is expected to be better than the approach used in the previous clinical trial with autologous cells. ● The additional preclinical data in the resubmission is much clearer and supports the protective effect of the cells as well as the difference between using the proposed product compared to naked virus. ● A major concern in the prior application was the lack of a proper comparator in some of the in vivo efficacy experiments. The investigators have addressed this by presenting new data comparing inhibition of tumor growth after treatment with the stem cell-loaded virus with naked virus and shown significantly slower tumor growth with the stem-cell loaded virus in two different murine tumor models. They also present new data comparing the stem cell-loaded virus with a different, non-viral intralesional therapy and show statistically significantly slower tumor growth with the stem cell-loaded virus in a different murine tumor model. ● The investigators have responded to the prior critique regarding the transition from an autologous to an allogeneic approach, including providing new preclinical data. There are clear advantages to an allogeneic approach in terms of cost and convenience. ● Despite the evident advantages of an allogeneic approach, it remains unclear whether an allogeneic approach would result in clinically superior anti-tumor activity, which is particularly important given that the autologous approach did not show substantial efficacy in a phase 1 study, although the investigators cite the greater number of viral particles in the allogeneic product as a potential differentiator. ● While the new data is helpful, it is certainly not conclusive evidence that this allogeneic stem cell-loaded oncolytic virus preparation will be clinically efficacious, let alone superior to existing and upcoming alternative intralesional approaches.
No: 1	*none*
GWG Votes	**Is the project well planned and designed?**
Yes: 14	● The preclinical studies are aligned with both FDA requests and recommendations from the Grants Working Group. ● The investigators have satisfactorily addressed most of the critiques regarding design of the clinical project and manufacturing of the final product. ● It is encouraging to see that the manufacturing process has been transferred to a contract development and manufacturing company. ● If successful, the project would be very likely to create value that would advance CIRM's mission. ● The project timeline is appropriate to complete the essential work and seems to demonstrate an urgency that is commensurate with CIRM's mission.
No: 0	*none*
GWG Votes	**Is the project feasible?**
Yes: 14	● Overall, the project is considered feasible, and the intended objectives are considered potentially likely to be achieved within the proposed timeline. ● The proposed team is appropriately qualified and staffed and the team has access to the necessary resources to conduct the proposed activities, including manufacturing. ● Tech transfer of the manufacturing process to a GMP manufacturer has begun, and a contractor for pivotal preclinical studies has been selected. The team has considered and discussed potential risks with each proposed activity. ● The team has presented contingency plans to manage risks and delays.

	• The investigators have responded to critiques regarding the number and frequency of intralesional injections, but while they have reiterated their perception of the need for the stated approach the concerns about burden on patients remain considering the myriad of potential alternative approaches that patients may have. • The data sharing plan that was provided was extremely unclear. It appears the applicant has a limited understanding of what data sharing means, and/or this section has copying/pasting from documents that may not be relevant.
No: 0	*none*
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 13	• The applicants appear to understand the race, ethnicity, sex, gender, and age-based health disparities associated with the target indication. They have developed goals to achieve an inclusive distribution of subjects by race, ethnicity, sex, gender, and age in their future clinical trial of the product. • The applicant has provided data regarding the target indication, as well as detailed plans for outreach and engagement for the clinical trial. • The applicants assert that their allogeneic product will be cheaper to produce and available to provide multiple doses in comparison to the prior autologous product. While helpful, this in and of itself may not be sufficient to make this product serve the needs of underserved communities.
No: 1	*none*

DIVERSITY, EQUITY, AND INCLUSION IN RESEARCH

Following the panel's discussion of the application, the patient advocate and nurse members of the GWG were asked to indicate whether the application addressed diversity, equity and inclusion, and to provide brief comments. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

DEI Score: 7

Up to 7 patient advocate and nurse members of the GWG score each application. The final score for an application is the median of the individual member scores. Additional parameters related to the score are shown below.

Score	Patient Advocate & Nurse Votes	Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?
9-10: Outstanding response	0	*none*
6-8: Responsive	3	• The applicant is focused on recruiting patients with Advanced Metastatic Solid Tumors (AMST) in connection with certain diseases not adequately treated with current therapies, including triple-negative breast cancer. • There is data in the original application that depicts the race/ethnicity, and gender/identity of impacted populations.
3-5: Not fully responsive	0	*none*
0-2: Not responsive	0	*none*