Application #	CLIN2-12823 #2
Title (as written by the applicant)	Phase 1, open label, dose escalation study of oncolytic virus (OV)-loaded cytokine induced killer (CIK) cells in patients with advanced solid tumors
Therapeutic Candidate (as written by the applicant)	Immune cells loaded with a cancer-killing virus that targets cancer tissue but not healthy tissue.
Indication (as written by the applicant)	Advanced, refractory solid tumors: colorectal cancer (CRC), hepatocellular carcinoma (HCC), osteosarcoma, triple negative (NNN) breast cancer, ovarian cancer, gastric cancer
Unmet Medical Need (as written by the applicant)	We address the unmet need of resistant and recurring cancers by combining activated cytokine-induced killer cells (CIK) and an oncolytic virus (OV). These have been thoroughly tested in humans and have excellent safety profiles but, when taken as individual therapies, have limited efficacy.
Major Proposed Activities (as written by the applicant)	• Manufacture OV-CIK cell product • Assess Safety and Tolerability • Determine Maximum Tolerated Dose
Funds Requested	$7,999,689
GWG Recommendation	***Tier 1: Has exceptional merit and warrants funding, if funds are available.***
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	15
Votes for Tier 1	14
Votes for Tier 2	1
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 proposal have the necessary significance and potential for impact?
Yes: 14	• Yes. Resistant, recurring, and incurable cancers including those the applicant proposes to address represent an area of unmet need. • Yes. Oncolytic virus (OV)-loaded cytokine induced killer (CIK) cells (OV-CIK) pose a unique approach to immunotherapy. The applicants are testing the approach in diseases for which the available data do not robustly support currently available immune approaches. • Overall, yes. However, in the applicant's current clinical protocol, the patient must undergo therapeutic infusion of OV-CIK very near a specialized production facility due to time constraints on the product's viability in transit. This limits the current geographic reach of the treatment. • The application clearly details the proposed therapeutic's significance and potential for impact.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 14	• Yes. The rationale for the treatment is that intravenous (IV)-administered OV alone infects only tumor cells surrounding the vasculature, while OV-CIK can carry the oncolytic virus into the tumor mass. The CIK cells also protect the OV from virus-neutralizing antibodies. • The application includes a reasonable rationale for the planned dosing, based on pre-clinical and clinical studies of the individual components (OV and CIK). • The applicant has addressed my concerns from the first round of review: (i) references related to mechanisms of action are now provided, (ii) data that describe the cellular composition of OV-CIK are now included, and (iii) the applicants have provided a detailed plan for the development of the potency assay. • Overall, yes. I do recommend that, before proceeding further, the applicants characterize the viral transduction efficiency of OV-CIK and the potential rate of viral shedding within patients. • References related to mechanisms of action were provided in the revision. • The rationale is generally sound.
No: 0	*none*
GWG Votes	**Is the proposal well planned and designed?**
Yes: 13	• The tumor-related, exploratory endpoint to assess viral presence in the TME seems critical for this study. It does not appear that any subjects have had this biopsy to date, as the biopsy is optional. I recommended that the biopsies be mandatory in the expansion phase of this program. • It is important that the study outcomes are independently and objectively reviewed. The safety monitoring committee (SMC) members may not be sufficiently objective. As of now, the applicants plan to convene an independent data safety monitoring board (DSMB) after the successful recruitment of five patients. • The protocol needs amendments. An independent DSMB is now being convened after CIRM's original feedback, but it would be nice to see the proposed DSMB charter draft. • Note that FDA does not have to review protocol amendments in active INDs. The sponsor seems to believe FDA approval is required for amendments. However, I appreciate that communication with FDA is wise to facilitate cooperation and collaboration, to avoid any unexpected clinical holds, and to incorporate FDA feedback in a timely manner. • Sponsor should consider amending the protocol or Investigator's Brochure (IB) or both to ensure documentation of expectations on handling risks (e.g., late arrival of cells). The applicant is working to address these issues and has amended the CIRM proposal, but it will be important to have clear instructions in the investigator-facing trial documents. • Data sharing has been enhanced in the revised proposal. Data that will be required for successful patent filing will not be shared; all other data, including sequencing data, will be shared.

	• It would improve the application (and the research program generally) if that applicant (i) stated that qualified researchers would have access to de-identified trial data and (ii) outlined the criteria for a 'qualified researcher.' They do mention data sharing opportunities through American Association for Cancer Research (AACR). Publication is effective, and clinicaltrials.gov posting is useful, but access to raw datasets allows others to validate conclusions and conduct exploratory studies.
	• While the second therapeutic infusion is justified, it may result in substantially different toxicities as compared to the first infusion. I encourage the applicants to collect adverse events (AEs), toxicity and safety issues from the second infusion separately. These separate data will be invaluable in the future when the applicants must decide whether to proceed with a second infusion in the treatment protocol.
	• Given that patients with superficial cutaneous lesions receiving the parent OV had vaccinia necrosum, the investigators should collect data on any toxicities seen in patients with cutaneous involvement of their cancer.
	• The GWG had a substantial discussion about the safety, infectivity, and potential for reversion of the proposed OV to a competent virus. It would be valuable to include a discussion of all clinical findings to date on prior intratumoral or intravenous (IV) exposure to the parent OV or the OV-CIK product, including any FDA safety review(s).
	• The applicants need to improve the organization of the grant. Reviewers were provided voluminous information and literature sources; however, these were not laid out in a user-friendly manner.
	• The applicant should plan for detection and management of safety signals related to OV-CIK. The plan should include a method for residual OV detection in the blood, urine, and ascites, and describe safeguards to prevent infection of normal tissues.
	• A few questions about manufacturing/CMC remain:
	  ◦ The transduction efficiency of CIK with OV should be defined.
	  ◦ The minimal % CIK cells in the product could be adjusted to 10% based on the results of engineering runs and experience with the first four patients
	• The potency assay for fresh product should be performed as close to the harvest day/day of infusion as possible.

No: 1	• The applicant should plan for risk mitigation related to viral shedding and uncontrolled growth of virus.
GWG Votes	**Is the proposal feasible?**
Yes: 14	• The dose escalation part of the trial appears to be feasible and, in fact, is near completion. • The industry - academia collaborations appear to be working well. • In clinical practice, the required delay for product ex vivo activation and handling of the autologous product may be significantly problematic for patients with aggressive cancers. • The requirement that infusion needs to be done at a geographically close location due to transfer time from production facility limits the geographic applicability of this treatment, at least using current manufacturing and transfer requirements. • Biopsies need to be mandatory in situations where access to malignant tissue is possible.
No: 0	*none*
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 14	• The revised proposal now includes a reasonable outreach plan with clear goals. A key limitation is the reliance on the enrolling clinics to recruit and retain members of underserved communities. Outreach could be strengthened with IRB-approved advertising through social media or direct communication to community oncologists. However, the plan represents a significant improvement. • The revised application includes targets for patient enrollment and recruitment that include underserved and underrepresented patient populations. • The applicant will utilize Diversity Coordinators at the clinical sites along with training for the clinical site teams, including the Principal Investigators (PIs). The budget also

	includes company-internal Diversity Coordinators that will perform outreach to the PIs and the sites. Outreach to patient advocacy groups is also planned. • The applicant has developed inclusive enrollment targets: eight women with ovarian cancer including two from underserved populations; five women with colorectal cancer (CRC) including two from underserved populations; five women with triple negative (NNN) breast cancer including two from underserved populations; two women with gastric cancer, two women with osteosarcoma, and two women with hepatocellular carcinoma (HCC). • As of January 2022, the applicant has enrolled five patients with a total of two indications across three clinical sites. Of the five enrolled participants, three are women and two represented a racial or ethnic minority. • The applicant has a well-developed approach for recruiting trial participants from underserved communities.
No: 0	*none*

DIVERSITY, EQUITY, AND INCLUSION IN RESEARCH

Following the panel's discussion of the application, the patient advocate 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: 8.0

Up to 7 patient advocate 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 Votes	Has the applicant sufficiently addressed how they have or will incorporate perspectives from individuals with diverse experience and from underserved groups in the implementation of the proposed project?
9-10: Outstanding response	0	*none*
6-8: Responsive	4	• The patient inclusion criteria and clinical site selection are designed to facilitate inclusion of trial participants from underserved groups. • The applicant states their intention to recruit from both underrepresented and underserved populations, and proposes the budget, training, outreach, and participant services they will need to achieve their recruitment goals. • The applicant will collaborate with diversity programs to facilitate the enrollment and treatment of a trial population that is representative of the patient population. • The applicant states that all three of their clinical trial sites prioritize diversity and inclusion of underrepresented and underserved communities in both trial recruitment and hiring practices. • The applicant provides enrollment targets for women and minority participants. • The Proposal includes provision to participants of reimbursement for transportation and lodging. • The inclusion of a Diversity Coordinator is a strength of this application. • Strengths include the catchment areas, strong track record of success in recruiting from underserved populations at two of the clinical trial sites, and the patient demographic analysis included in the application. • If the therapy is approved for marketing, it may be advantageous to patients from underserved groups for these reasons: one hour infusion, no overnight stay, and potential for reimbursement.
3-5: Not fully responsive	0	*none*
0-2: Not responsive	0	*none*