Application #	CLIN2-12149 #2
Title (as written by the applicant)	Phase 1 Clinical Development of a First-in-Class Antibody Targeting LILRB4, for the Treatment of AML with Monocytic Differentiation and CMML
Therapeutic Candidate (as written by the applicant)	A first-in-class antibody targeting leukocyte immunoglobulin-like receptor B4 (LILRB4), an immune inhibitory receptor
Indication (as written by the applicant)	Acute myeloid leukemia (AML) with monocytic differentiation and chronic myelomonocytic leukemia (CMML)
Unmet Medical Need (as written by the applicant)	AML is the most common acute leukemia in adults. Nearly 20,000 new cases are expected in the U.S. in 2020. Despite advances in treatment, less than 30 percent of AML patients are alive five years after initial diagnosis. CMML is a malignant hematopoietic stem cell disorder with dismal survival.
Major Proposed Activities (as written by the applicant)	• Conduct a Phase 1 study to evaluate the antibody in relapsed/refractory patients with AML with monocytic differentiation and CMML.
Funds Requested	$6,000,000
GWG Recommendation	Tier 1: warrants funding

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	12
Tier 1 (75 - 100): Fund	11
Tier 2 (65 - 74): Undecided	1
Tier 3 (1 - 64): Do not fund	0

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA. 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: 12	• Current therapies have limited impact and survival is limited. There is a need for targeted therapies to reduce the morbidity of potent but non-specific chemotherapeutic agents. • Refractory AML with monocytic features has a very bad prognosis and clearly needs new therapies. • High unmet need. Survival rates are very low. A $6M request increases the value of this proposal. • This proposal to focus on targeting the LILRB4 receptor found on monocytic cells and stem cells provides a novel targeted approach. • Yes. This subset of AML and CMML has poor prognosis and there is currently no treatment regimen that impacts these subsets. • The product targets LILRB4 in CMML, which is highly expressed in this subgroup of patients with negative prognosis. Therefore, there is a significant potential for impact. • Other targeted AML therapies that target mutations are not active in monocytic AML. A promising AML combination of two other chemotherapy agents appears to have little activity in monocytic AML. • The product can be used for a population refractory to current therapies for AML. • If the clinical trial supports the efficacy shown in preclinical models, this treatment has the potential to provide a therapy that could have great utility either as a monotherapy or in combination with other existing therapies.

No: 0	*none*
GWG Votes	Is the rationale sound?
Yes: 12	● In summary, preclinical efficacy and safety data support clinical evaluation in patients with monocytic AML and CMML. ● The target (human LILRB4) is highly expressed in AML and the deletion of the target decreases AML formation. New preclinical data is compelling. ● The rationale is sound with the target LILRB4 being very relevant in these tumor subtypes. ● The new explanations of the pre-clinical data make it more convincing. ● Preclinical data demonstrate binding of the antibody to the LILRB4 receptor, which is associated with several effects, including inhibition of the immune inhibitory pathway and increasing T-cell cytotoxicity against AML cells. It also has the potential to kill cells. ● Efficacy was demonstrated in mouse models including an AML xenograft model, in an AML syngeneic model, and a human AML patient-derived xenograft model. ● The preclinical data is somewhat underwhelming but establishing the xenograft model is quite challenging, so it is rational to take the modest efficacy signal seen in the preclinical work and test it in the clinic. ● Preclinical data is not striking, but adequate. ● Microscopic findings in the brains of large animal studies showed partially reversible mild multifocal gliosis at certain doses, so clinical studies will require careful evaluation for neurotoxicity.
No: 0	*none*
GWG Votes	Is the proposal well planned and designed?
Yes: 11	● The team has addressed the previous review questions very well. ● They responded well to the previous critiques. ● A standard ascending and dose escalation phase 1 study is proposed and has been cleared by FDA. ● The decision plan for monotherapy seems reasonable: to evaluate the overall response rate in the proposed number of patients and then consider monotherapy development based on discussion with FDA if a threshold complete response rate is seen. If this bar is not met, the applicant plans to evaluate the antibody activity in combination with other agents. ● Yes, I think so. Whether a single antibody agent is able to impact these diseases is debatable so maybe follow up trials will need the antibody to be used in combination with cytotoxic agents or other modalities. ● After hearing the concerns about CMML, I hope that they are still going to follow-up on those patients during the course of the study. I think their reasons for enrolling them are reasonable.
No: 1	● The inclusion of CMML patients remains questionable. ● The LSC correlative studies remain weak and should include functional analyses.
GWG Votes	Is the proposal feasible?
Yes: 12	● Excellent team and will likely complete the studies. ● The staff appears to be well qualified and experienced. ● Given the rareness of monocytic AML, multiple sites will be used to accrue patients for the dose-escalation phase, and additional sites will be added to accrue the patients in the expansion phase. While the duration of phase 1 studies is difficult to predict, this approach seems reasonable. ● Yes, they have the GMP antibody and a large number of clinical sites ready to initiate the study. ● A detailed mitigation plan is outlined.
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: 10

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.

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?

Score 10 – 0 (Best – Lowest)	Count	Comments
10	3	● *The applicant's leadership team and clinical trial team included individuals from diverse backgrounds, including the CMO who grew up in a rural environment and was the first person in his family to attend college.* ● *The clinical trial is purposely being conducted in different U.S. geographies to ensure a diverse patient population that represents the demographics of the U.S.* ● *The applicant has adopted policies to ensure equitable opportunities for individuals of any race, color, ethnicity, nationality, religion, socioeconomic status, veteran status, education, marital status, language, age, gender, gender expression, gender identity, sexual orientation, mental or physical ability, genetic information, and learning style.*
9	0	*none*
8	0	*none*
7	0	*none*
6	0	*none*
5	0	*none*
4	0	*none*
3	0	*none*
2	0	*none*
1	0	*none*
`0	0	*none*

Application #	CLIN2-12153 #2
Title (as written by the applicant)	Phase I Study of Antigen Targeting CAR T Cells After Lymphodepletion for Children with Refractory or Recurrent Malignant Brain Tumors
Therapeutic Candidate (as written by the applicant)	Autologous chimeric antigen receptor T cells derived from naive/memory T cells and engineered to target an antigen on pediatric malignant brain tumors.
Indication (as written by the applicant)	Recurrent/refractory malignant pediatric brain tumors that express the tumor-associated antigen.
Unmet Medical Need (as written by the applicant)	This proposal addresses the critical unmet medical need for effective therapies to treat aggressive pediatric brain tumors, including glioblastoma, medulloblastoma, atypical teratoid/rhabdoid tumor, diffuse midline glioma, and others.
Major Proposed Activities (as written by the applicant)	• manufacture and release of antigen-Tn/mem CAR T cells • evaluate safety and feasibility of intraventricularly-delivered CAR T cells administered after lymphodepletion in pediatric patients • develop and establish methods and target populations for Phase 2 clinical trial
Funds Requested	$8,401,309
GWG Recommendation	Tier 1: warrants funding

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
Tier 1 (75 - 100): Fund	11
Tier 2 (65 - 74): Undecided	4
Tier 3 (1 - 64): Do not fund	0

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA. 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: 12	• The current treatments for pediatric brain tumors are currently underwhelming and there is an urgent need for medicines that address this unmet need. • Current treatments can at best extend life a short period of time, so these tumors are basically a death sentence for a young person. • The proposal has a potential impact on the field of pediatric brain tumors. It is a big unmet medical need. • The proposal meets an unmet medical need in that pediatric patients with brain tumors are in need of novel directed therapeutics. The current approach has significant potential to improve standard of care for the intended patient population. Given refractory nature of these malignancies, CAR-T cell therapy, although complex, would be a significant advance for the field. While there should be greater clarity on how limitations will be overcome with a single antigen targeted strategy, the progress made by the investigative team and wealth of preclinical data are very attractive. • Pediatric brain tumors are a highly unmet need.

	● Compelling unmet need. ● Unmet need in treating pediatric brain tumors. ● Continued extremely high unmet need. ● Clear unmet need without other options. ● Yes, unmet need with few effective long-term options. ● Dire clinical situation.
No: 0	*none*
GWG Votes	Is the rationale sound?
Yes: 11	● In response to previous reviewer comments, the authors provided more pre-clinical data, based on published studies and manufacturing feasibility data. It makes the rationale for this clinical study even stronger. ● A well written and well-crafted response. I am more convinced that this make sense to move forward if nothing else to give some hope and test the ability to do this in a pediatric population. ● The authors acknowledge the potentially high cost of the developed product in their response. They noted that the goal of the study is to get clinical data as soon as possible and that they would not improve/change the manufacturing process at this point, short-term. ● Pre-clinical data are impressive and the use of lymphodepletion seems warranted based on the data. ● Concerns about past failure of a toxin conjugate in glioblastoma should not rule out trying a CAR-T study. ● I think the use of a CAR-T therapies is warranted based on the pre-clinical data. There was some contention that expression of the target antigen is variable and heterogenous amongst the various tumor types and that might mask important positive results. ● Although there is some concern around tumor heterogeneity with regard to target antigen expression, this is a desperate disease. ● The applicants were very responsive to the previous review; however, it still remains unclear how this approach will overcome the tumor microenvironments within pediatric brain tumors. Target expression is likely not uniformly expressed and these tumors may have axes of resistance. How will these limitations be overcome with a single antigen targeted strategy? ● Overall, yes. But there is a concern regarding the highly variable target antigen expression. There will be highly variable outcomes with the different tumors and conditions that are being targeted. Nevertheless, some patients will no doubt benefit from such a therapy. They use old technologies that are inferior and generate less Tcm and Tscm than currently available technologies. Strongly suggest at scale manufacturing with a process that generates more memory phenotype. ● Yes, although the prospect of efficacy for antigen targeted therapy is influenced by prior clinical studies in which the antigen targeting has not been successful.
No: 1	*none*
GWG Votes	Is the proposal well planned and designed?
Yes: 12	● The proposal is well planned and designed. ● The applicants were very responsive to previous criticisms and investigators have a great deal of expertise in target antigen screening and immuno-monitoring. ● Well-designed study. ● Excellent plan.
No: 0	*none*
GWG Votes	Is the proposal feasible?
Yes: 11	● The team proved the feasibility of similar projects funded by CIRM before. The proposed timeline looks appropriate. The team is very well qualified and has experience in treatment of adult patients with corresponding manufacturing runs with a similar product. ● The authors added data from the first 2 patients, enrolled in the study and infused with a product. They also noted that several more patients are in the process. It proves that the study is feasible. ● Treatment is feasible. ● Concerns remain about enrollment at a single institution. Having additional sites already onboarded would allay these concerns. ● Applicant institution has the required skills to undertake this project. There was some question about their ability to recruit patients but given the heterogeneity of tumors this probably isn't a problem, although this heterogeneity may make it harder to draw clear cut conclusions. ● Overall feasible, but the proposal does not account for variability that will be encountered. ● Some questions, but not enough to stop the study.
No: 1	*none*

Does the project serve the needs of underserved communities?

- Complicating issues regarding availability of a proposed therapy to underserved communities include the nature of the target disorder, incidence, and level of medical care required for the proposed therapy.
- Pediatric brain tumors are rare and devastating disorders that require expensive, high technology treatments to extend quality of life even by a few months.
- Current standard of care involves neurosurgical procedures coupled with radiation therapy or radiation therapy alone for invasive tumors in critical brain structures that are inoperable. The proposed therapy will require an even higher level of in-hospital support than current standard of care. It's impossible to imagine how this could be implemented out of the setting of a major medical center in underserved areas of the state.
- The document provides ample information regarding plans to ensure inclusion of underserved populations as participants in the trial. The trial sites here are both major medical centers in the greater metropolitan area of Southern California that serve a highly diverse population and the material includes information about ongoing institutional programs to increase accrual of patients into clinical research overall.

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: 9

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.

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?
Score 10 – 0 (Best – Lowest)	**Count**	**Comments**
10	1	• This is a revised version of a proposal originally submitted before new review criteria regarding availability for underserved communities and DEI were implemented. However, the applicant provided supplemental material that did address the new criteria. • Regarding the specific question of the new DEI requirement, "how perspectives from individuals with diverse experience and from under-represented groups will be considered in the implementation of the proposed project", the supplemental material outlines how planning and implementation engage the existing minority and outreach programs of the institution. The description makes it clear that there will be extensive consideration of diverse perspectives in implementing this project. The only minor weakness is that information is not provided about whether there is diversity in the members of the research team.
9	2	*none*
8	1	*none*
7	0	*none*
6	0	*none*
5	0	*none*
4	0	*none*
3	0	*none*
2	0	*none*
1	0	*none*
0	0	*none*