| Application # | CLIN2-15094 |
|---|---|
| **Title** (as written by the applicant) | Phase I Trial of Locoregionally Delivered Autologous B7-H3 CAR T Cells (B7-H3CART) in Adults with Recurrent Glioblastoma Multiforme |
| **Therapeutic Candidate** (as written by the applicant) | Autologous T cells genetically engineered to express a Chimeric Antigen Receptor targeting B7-H3 (B7-H3CART) |
| **Indication** (as written by the applicant) | Brain tumors in adults: Glioblastoma Multiforme (GBM) |
| **Unmet Medical Need** (as written by the applicant) | Glioblastoma Multiforme (GBM) is the most common malignant primary brain tumor in adults. The long-term prognosis for GBM remains grim, and current treatments show limited improvement in overall survival. Thus, there is an urgent need for novel effective therapies. |
| **Major Proposed Activities** (as written by the applicant) | • Determine recommended Phase 2 dose of therapeutic for patients with GBM<br>• Assess toxicity of B7-H3CART cells<br>• Assess clinical activity of B7-H3CART cells in adults with GBM |
| **Funds Requested** | $11,999,991 |
| **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."<br><br>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 majority score of all of the individual member scores. If there is no majority score, the final score is 2. 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 project hold the necessary significance and potential for impact? |
|---|---|

| | |
|---|---|
| **Yes:**<br>15 | • The proposal addresses a disease characterized by limited therapeutic options and a challenging life expectancy.<br>• An important target population is affected by a severe lack of effective treatments for glioblastoma multiforme (GBM).<br>• This proposal holds promise, particularly due to the novelty of direct administration.<br>• This is an area of high unmet need. |
| **No:**<br>0 | *none* |
| **GWG Votes** | **Is the rationale sound?** |
| **Yes:**<br>15 | • The proposal includes compelling rationale and proof of concept.<br>• The applicant has good preliminary data.<br>• Administration into the tumor is a novel approach. The rationale for the trial is completely sound.<br>• This proposal is scientifically sound with a clinical rationale. |
| **No:**<br>0 | *none* |
| **GWG Votes** | **Is the project well planned and designed?** |
| **Yes:**<br>13 | • The applicant has a good protocol design. The trial is already enrolling participants.<br>• Enrollment at a single site is feasible.<br>• This project is well designed.<br>• Some of the milestones are confusing and need to be clarified.<br>  ◦ What is the purpose of milestone 5? An expansion of participants?<br>  ◦ One stated objective is to obtain IRB approval to proceed with the IND application, but the applicant has an approved IND and an open protocol.<br>  ◦ Milestone 5 repeats content from milestones 1 to 4, which is confusing. It can be unclear whether certain text actually refers to the expansion cohort.<br>• The therapeutic approach needs to be better considered for this particular tumor type. GBM has limited or no resection and no cavity for drug administration.<br>• About 80% of patients with diffuse intrinsic pontine glioma (DIPG) have a specific mutation (H3K27M). There are promising clinical trials underway of a targeted therapy for that particular mutation. If DIPG is included in this study, it must be as a separate arm from the glioblastoma. |
| **No:**<br>2 | • As this is an ongoing study, please clarify exactly what CIRM funds will allow/be used for (i.e. does this award accelerate something, additional arm, etc). It is not clear what the impact of the CIRM funds will be. Are CIRM funds needed to complete the study?<br>• The trial has a typical 3x3 design. Although not optimal for interpretation of clinical trial results, this design is suitable for this disease.<br>• The primary endpoint is unusual, and its impact on the patient is unclear.<br>• Regarding data sharing: the data sharing statement initially suggests that individual participant data will not be made publicly available. However, the data sharing plan document contradicts this, indicating that data will be shared after the clinical trial concludes, the database is locked, and all analyses are performed. At least two publications are anticipated by the end of the grant period in 2027, and trial outcomes will be published upon completion.<br>• The applicant's plans for evaluating DLTs (Dose-Limiting Toxicities) pose some risk, as DLTs reported from the trial will be limited to DLTs deemed related to treatment. Still, considering the patient population and FDA advice, this approach seems acceptable.<br>• The DSMB (Data Safety Monitoring Board) may not be entirely independent, but the large institution can likely exercise appropriate governance. The statistical section was comprehensible, but some parts should be deferred to an appendix or Statistical Analysis Plan (SAP). Linking the discussion on the Bayesian stopping rule back to the Maximum Tolerated Dose (MTD) discussion in 5.3.7 would be helpful. The DSMB should provide clear guidance on stopping criteria.<br>• The application needs cleanup to address discrepancies, clarify milestones, and describe conflicted analyses. Rectifying errors is crucial for an accurate project assessment, especially considering the substantial funding requested.<br>• Regarding the ongoing study, it's essential to specify how CIRM funds will be used. Will they accelerate progress or support an additional arm, for instance? The impact of CIRM funds on the study's completion should be made explicit. |
| **GWG Votes** | **Is the project feasible?** |

| | |
|---|---|
| **Yes:**<br>15 | • The trial is already in process. Feasibility of administration into tumor sites is yet to be determined.<br>• The team has an open protocol and has treated the first three patients. |
| **No:**<br>0 | *none* |
| **GWG Votes** | Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)? |
| **Yes:**<br>15 | • The applicant has an appropriate plan.<br>• The DEI plan is very well defined.<br>• The plans to reach the goals of DEI are appropriate, including outreach and assistance programs. |
| **No:**<br>0 | *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: 10

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** | 5 | • One of the best applications to date on DEI support elements from an outstandingly succcessful program with a great track record in place.<br>• The proposal includes excellent demographic / socioeconomic data including disease incidence, survival rates with information on access to radiation oncology centers and medicaid versus medicare.<br>• The institution's track record is very strong. By mining their own data, they have identified improvements to be made and are implementing these improvements.<br>• There is a very detailed plan as to how to provide patient support in addition to excellent outreach plans to advocacy groups.<br>• Social workers, materials in a variety of languages, and interpreters are all part of the process - both historically and going forward.<br>• The institution has an excellent catchment area for trial participants.<br>• Clear description of the patient population<br>• Strong patient support program.<br>• Well-stated DEI plans.<br>• Strong DEI plan. |
| **6-8: Responsive** | 0 | *none* |
| **3-5: Not fully responsive** | 0 | *none* |
| **0-2: Not responsive** | 0 | *none* |