Application #	CLIN2-14232
Title (as written by the applicant)	A Potent, First-In-Class KDM4 Inhibitor for Advanced Cancers
Therapeutic Candidate (as written by the applicant)	A first-in-class small molecule inhibitor of KDM4 histone demethylase, an epigenetic modifier important for cancer stem cell proliferation.
Indication (as written by the applicant)	Colorectal Cancer (CRC)
Unmet Medical Need (as written by the applicant)	Late-stage CRC patients receive chemotherapy with survival typically not exceeding two yrs. The product showed potent anti-tumor activity in CRC animal models, including MSI-H CRC which accounts for 15% of cases and do not respond to chemotherapy due to deficiency in DNA repair mechanisms.
Major Proposed Activities (as written by the applicant)	• Complete Phase 1a dose escalation study to assess safety and recommended phase 2 dose • Complete Phase 1b dose expansion study to assess effect of the product in specific cancer types (CRC and gastrointestinal cancers) • Complete analyses of blood samples from enrolled patients to assess genomic biomarkers that may inform of a responder population
Funds Requested	$7,141,843
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	13
Votes for Tier 1	7
Votes for Tier 2	6
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: 12	• The proposed product of this project is a first-in-class, small molecule inhibitor of KDM4 histone demethylase, an epigenetic modifier that plays an important role in cancer stem cell proliferation and other pathways relevant to progression of the bulk tumor (such as evasion of apoptosis and deficient DNA repair).

	• By inhibiting KDM4, the product reduces propagation of both tumor initiating cells and the bulk tumor in cancer models and was found to be especially potent in CRC with microsatellite instability-high (MSI-H) phenotype. • MSI-H CRC (occurring in ~15% of CRC) are deficient in DNA repair mechanisms and do not respond to chemotherapy. Despite the benefit of immune checkpoint inhibitors in a subset of patients, the lasting benefit is limited and thus additional therapeutic options for this population are greatly needed. • Yes, few options for treatment in advanced stages of the disease and this would add another tool. • There are no effective treatments at present; if successful, this would be a great impact.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 12	• Numerous publications have shown KDM4 to play an important role in promoting stem cell proliferation and maintenance, and KDM4 serves as the epigenetic control for stem-like features of CRC thus targeting it is sound. • In colorectal cancer, KDM4 overexpression is an unfavorable prognostic marker according to the human protein atlas. When overexpressed, KDM4 promotes genomic instability. Consequently, cells become deficient in DNA mismatch repair. • Trial starting dose is based on extensive animal model designs. • Trial design is complicated - may be difficult to execute by multiple sites.
No: 0	*none*
GWG Votes	**Is the project well planned and designed?**
Yes: 9	• An IND application has been filed with the FDA for the compound and approval has been received to proceed with a first-in-human clinical trial. The trial design is sound and well-planned. Because there are multiple sites, they are likely to accrue well, though accrual may not be as robust as planned. • The trial will follow a Bayesian optimal interval design where three patients will be enrolled in each cohort until the maximum tolerated dose (MTD) is reached. The product will be administered on an intermittent dosing schedule. Blood will be collected to assess pharmacokinetic parameters and to assess molecular biomarkers in circulating tumor DNA. Currently, there are no other KDM4 drugs in clinical development. This product will be the first in its class to enter human trials. • Study also includes robust correlative biomarkers. • Complicated trial design which may require additional personnel. • Although a safety study, dosing could potentially be addressed earlier. • Bayesian optimal interval design is good. There is a need to identify the study statistician who has experience with this type of design. • It is unclear if there is a statistician on the team. • In the second phase are multiple doses being studied as per FDA recommendations? • Data monitoring members who are investigators should be excluded.
No: 3	• Needs better investigation of dose response in addition to MTD estimation. • The data monitoring committee needs to be independent - not appropriate as constituted.
GWG Votes	**Is the project feasible?**
Yes: 9	• Feasible given the number of sites, IND approval, expertise of sites, and ability to improve access given the delivery of the drug. Despite advances such as checkpoint blockade, this disease is an unmet need. • This is a drug substance manufactured by professional contract manufacturing organization and tested by commercial testing companies. Two doses of the drug product have already completed manufacturing and are ready for clinical use. Additional material will be prepared to complete the dosing strategy. • The FDA has approved the manufacturing section and the IND as safe to proceed. The applicant has been asked to consider some additional comments. • Team is qualified; it will require lots of coordination to run the trial design at multiple sites, but I am satisfied with plan described and protocol contingencies. • The primary critique is whether to decrease the number of patients and pitch for non-MSI high to get safety signal initially, then perhaps lay groundwork for possible synergistic efforts in the future.

	• Recruitment may be an issue, but multiple sites will hopefully address this.
No: 3	• There may be problems with accrual and patient identification. • Needs more detail.
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 12	• The applicants do a good job of discussing incidence of CRC in underrepresented populations. Numerous strategies are outlined including engagement, cultural sensitivity training, and the sites involved have diverse populations. Interventions to ensure access to diverse and under resourced patients are also discussed. • Yes, well considered.
No: 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: 9.0

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	4	• Planned activities reflect an outstanding and comprehensive effort for outreach and engagement. • Well characterized patient population and outreach plan.
6-8: Responsive	0	*none*
3-5: Not fully responsive	0	*none*
0-2: Not responsive	0	*none*