

September 21, 2026

Dear Application Review Committee,

We thank the Scientific Review Group for its thoughtful and valuable critiques. We thank the committee for recognizing the high value proposition of the oral route of administration and the potential applicability to both solid and hematologic malignancies, addressing significant unmet medical needs across California. The committee also recognized the particularly important opportunity in metastatic microsatellite-stable colorectal cancer (MSS CRC), noting:

*“The specific case of metastatic CRC causes over 5,000 deaths in California and 50,000 deaths in the U.S. per year. In populations of low socioeconomic status and minority populations, this leads to later-stage diagnosis and worse outcomes. Currently, there is no FDA approved therapy or emerging therapies targeting CSCs for solid tumors. The proposed transition from an ongoing Phase 1 study into a Phase 2 expansion minimizes development delays while potentially improving patient access, particularly for patients in rural or underserved communities.”*

The committee further noted that *“The team has strong academic discovery and investigator-initiated trial credentials.”* We appreciate these comments and address the major concerns as follows.

1. *“FTEs (all TBD), resources, and plan are insufficient to ensure a timely execution of the proposed single-site clinical trial.”* We apologize for not using individual names in the original budget justification. The ongoing first-in-human clinical trial is supported by an experienced and dedicated clinical research team with long-standing expertise in clinical trial operations, regulatory affairs, patient safety, and clinical research. The proposed salary support is based on the actual salaries and effort requirements of existing personnel who are already supporting the trial. Thus, the proposed budget reflects an established clinical infrastructure rather than a need to build a new clinical team. Names of personnel on the established clinical operational team that are listed TBD are provided here:

| Role | Project Manager | Data Project Manager | Clinical Trial Coordinators  | Research Associate |
|------|-----------------|----------------------|------------------------------|--------------------|
| Name | Kim Ruben       | Shikha Shaji         | Natalia Ortuno & Jena Plevin | Magalie Dosset     |

2. *“Enrollment challenges are anticipated with resources also not set in stone.”* The apparently slow enrollment does not reflect a lack of eligible patients or clinical resources. **More than 70 patients are currently on the waiting list to participate in the trial at UC San Diego alone.** The primary reason for the measured enrollment rate is the intentional safety-first approach required for a first-in-human, dose-escalation study. Importantly, the trial has not experienced a shortage of patient interest.

To date, there is **no treatment-related serious adverse events (SAEs)**, while disease control has been observed in the ongoing study. With accumulating safety experience and continued patient demand, we are now accelerating enrollment as appropriate while maintaining the safety requirements of the dose-escalation design.

3. *“There were limited clinical responses in solid tumors with a related drug, and it is not clear whether this drug, which is a covalent allosteric inhibitor, will be more active.”* We agree that the clinical activity of related compound provides important context for the development of this first-in-class therapy. However, the therapeutic rationale targeting **cancer stem cells (CSCs)** is distinct from conventional therapies that primarily target bulk tumor cells. CSC populations are very small in a tumor, and consequently, we do not expect a CSC-directed therapy to produce rapid or profound shrinkage of the entire tumor as monotherapy. Instead, it is expected to inhibit tumor recurrence, metastasis, and therapeutic resistance in **combination therapy**, thereby complementing therapies that eliminate the bulk tumor population. The oral bioavailability and safety further

provide an opportunity to develop sustained combination regimens that would be difficult to implement with intravenously administered agents.

Nearly all anticancer agents show diminished activity when given late in the disease course to heavily pretreated patients, and this may have contributed to the limited responses observed with the related drug. With increasing lines of prior therapy, tumor cells acquire resistance mechanisms that confer broad drug resistance, such as increased expression of drug efflux pumps that reduce intracellular drug accumulation. Detecting a signal of efficacy therefore depends on enriching the study population and treating patients earlier in their disease course. Because the study is currently conducted at a single site, we work closely with referring physicians to assess suitability for treatment and to enroll patients at a more optimal time, based on their sequence of prior therapy and pace of disease. We are applying this approach during the ongoing Phase 1 dose escalation and will continue it in the Phase 2 portion, leveraging the established infrastructure and patient access at UC San Diego to prioritize patients with fewer prior lines of therapy. We will also perform pre- and on-treatment tumor biopsies for biomarker analysis.

4. *“The program plans to enroll all patients at a single site.”* We propose to complete the Phase 1 dose-escalation portion of the study at UC San Diego, where the trial is already operational with weekly meetings and where **more than 70 patients are currently on the waiting list at UC San Diego alone**, which allows us to select patients at an optimal point in their treatment course. This approach minimizes the time and resources required to establish additional sites during the critical first-in-human dose-escalation phase while maintaining rigorous safety oversight.

At the same time, we are actively exploring expansion of the clinical trial to other sites including City of Hope and other University of California medical school campuses, where we have close collaborating colleagues.

Expansion through these California Institutions would provide a practical pathway to broaden patient access across California, including patients who may be underserved or geographically distant from UC San Diego. Thus, while UC San Diego provides an efficient and well-established site for completion of Phase 1, our longer-term strategy is to leverage the statewide institutions to support multicenter development and improve access for California patients.

Overall, the ongoing Phase 1 study has established a strong clinical foundation for the proposed Phase 2 development. The combination of substantial patient interest, an experienced clinical team, an established regulatory and clinical infrastructure, and an opportunity to expand through other California, institutions positions this therapy for efficient clinical development while maintaining the highest priority on patient safety.

Sincerely,



Peter Vu, M.D., PI  
Associate Clinical Professor



Yuan Chen, Ph.D., co-I  
Professor