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Open Letter to the CIRM Application Review Subcommittee
Re: CLIN2-19191 – TriLeukeVax (TLV)

Dear Members of the Application Review Subcommittee,

As a brief introduction, I am the current Chief of the UCSF Health Division of Hematology and Oncology and Physician-in-Chief of the UCSF Helen Diller Family Comprehensive Cancer Center. I have had the privilege of training at both UCLA and UCSF and a faculty career as a physician-scientist inside and outside of California, including at UCSF, the University of Texas M.D. Anderson Cancer Center and at the University of Miami's Sylvester Comprehensive Cancer Center, where I served as inaugural Chief of the Division of Transplantation and Cellular Therapy and also served as Medical Director of the cGMP Laboratory in the Interdisciplinary Stem Cell Institute. I have served in other positions relevant to this opinion, including as former President of the American Society for Transplantation and Cellular Therapy, as former Chair of the American Society of Hematology Scientific Committee on Immunology and Host Defense, and as a former member of the Boards of Directors for both the NMDP and the Foundation for the Accreditation of Cellular Therapy.

I am writing to provide perspective on the biological rationale underlying the TriLeukeVax (TLV) clinical program proposed by Dr. Karin Gaensler and colleagues at UCSF. Given my focus in hematologic malignancies and hematopoietic stem cell transplantation, my clinical and research work has focused on understanding the immune mechanisms that contribute to durable leukemia control. From that perspective, the scientific concept underlying the TLV platform addresses a critical and persistent problem in AML therapy: the ability to harness immune responses capable of eliminating residual leukemic cells while avoiding the risks of transplantation.

One of the most compelling demonstrations of immune-mediated leukemia control is the graft-versus-leukemia (GVL) effect observed following allogeneic hematopoietic stem cell transplantation (HSCT). Decades of clinical experience have established that donor-derived immune responses can recognize and eliminate residual leukemia, contributing to durable remission in a subset of patients. At the same time, HSCT remains associated with significant risks, including regimen-related toxicity, graft-versus-host disease, and infectious complications associated with immunosuppression that result in non-relapse mortality and limit its applicability and curative potential. Since the risk of developing AML increase with age, these risks are particularly relevant for the majority of AML patients who are older and often ineligible for HSCT or intensive conditioning regimens.

For this reason, a central goal in leukemia immunotherapy has been the development of strategies capable of reproducing the beneficial anti-leukemic immune effects of HSCT without exposing patients to its associated toxicities. Approaches that stimulate immune recognition of leukemia-associated antigens and promote cytotoxic immune responses against residual leukemic stem cells represent a promising strategy for achieving this objective

The TriLeukeVax platform is conceptually aligned with this goal. The approach is to engineer autologous leukemia cells to express the combination of 1) a co-stimulatory protein required to activate cytotoxic anti-leukemic immune responses, and 2) a powerful cytokine that enhances these T and NK immune cell responses directed against leukemia cells. In doing so, the strategy seeks to engage immune mechanisms analogous to those responsible for GVL effects while avoiding the immunologic and treatment-related complications associated with

HSCT. This autologous vaccine approach is particularly attractive in the setting of minimal residual disease, where immune-mediated elimination of residual leukemia could meaningfully reduce the risk of relapse. All too often, patients and the clinicians caring for them celebrate a "remission" only to witness relapse and progressive disease resulting ultimately in death—the strategies proposed here propose a novel and safe immunotherapy approach designed to improve outcomes in this all too familiar clinical scenario.

Immunotherapy has transformed oncology therapy across the spectrum of blood cancers and solid tumors. Although discovery of the GVL effects of allogeneic HSCT arguably kicked off the immunotherapy revolution, innovative immune-based strategies aimed at relapse prevention remain an important frontier in AML research. Approaches such as TLV reflect thoughtful efforts to translate well-established biological insights into new therapeutic approaches. This may expand treatment options for transplant-ineligible patients who face a substantial risk of disease recurrence, despite achieving remission.

For these reasons, I believe the TriLeukeVax program represents a scientifically grounded and innovative effort to explore immune-mediated control of residual disease in AML. The promise of this vaccine is supported by the Fast-Track and ODD designations recently awarded by the FDA. I appreciate the Committee's careful consideration of this proposal and its potential to contribute to the development of new strategies aimed at improving long-term outcomes for patients with this challenging disease and strongly urge you to support this innovative and important research.

I am deeply grateful for the Committee's efforts to advance science and clinical medicine and would be happy to respond to any queries regarding my support for this proposal.

Sincerely,

Krishna Komanduri, MD
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