Narrative Summary

Early-phase clinical trials play a critical role in identifying appropriate drug doses for subsequent development. Traditionally, dose selection is guided by safety, pharmacokinetics (PK), and clinician-reported adverse events, with the maximum tolerated dose paradigm remaining central in oncology and other therapeutic areas. However, clinician-reported toxicity often underestimates the frequency and severity of symptomatic adverse events experienced by patients. As a result, current dose-finding strategies may not fully capture the patient experience of treatment burden.

Patient-reported outcomes (PROs), such as the EORTC QLQ-C30 and EQ-5D-5L, directly measure patients' symptoms, functioning, and quality of life. Although regulatory agencies and the scientific community increasingly recognize the importance of PROs, these data are rarely incorporated quantitatively into early-phase dose selection. Instead, PROs are typically analyzed descriptively and not integrated into formal exposure–response modeling frameworks that guide dose optimization decisions.

One major barrier to PRO-informed dose selection is methodological. PRO data are noisy, highly variable, and frequently incomplete. Existing analytical approaches are not well suited to accommodate these characteristics, limiting the ability to link systemic drug exposure to patient-reported symptom trajectories. Our laboratory has developed a population modeling framework specifically designed to characterize longitudinal PRO data while accounting for variability and missingness. Using this approach, we have demonstrated that PRO trajectories can predict important clinical outcomes, including overall survival, supporting their validity as quantitative endpoints.

The objective of this project is to evaluate the feasibility of incorporating PROs into early-phase dose selection using population exposure–response modeling. We will conduct a secondary analysis of de-identified participant-level data from clinical trial NCT01381874. First, we will develop a population PK model to estimate individual drug exposure profiles. We will then characterize relationships between systemic exposure and longitudinal PRO domains, focusing on both toxicity-related and efficacy-related measures. Finally, we will conduct simulation analyses to evaluate whether alternative dosing regimens informed by exposure–PRO relationships could improve the balance between symptom burden and therapeutic benefit.

This study will be the first to formally evaluate whether quantitative exposure–PRO relationships can support PRO-driven dose selection in early-phase clinical trials. By establishing methodological feasibility and demonstrating practical application, this work aims to modernize dose optimization strategies and promote more patient-centered drug development. If successful, the modeling framework developed here will be generalizable across therapeutic areas and development programs, strengthening benefit–risk assessment and advancing public health decision-making.