Predictive Role of the Gut Microbiome in Abemaciclib-Associated Diarrhea: A Prospective Translational Pilot Study

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Abstract

Background: Abemaciclib, a CDK4/6 inhibitor, is approved for the treatment of both early-stage and metastatic HR+/HER2− breast cancer. While it improves survival outcomes, diarrhea remains the most frequent and dose-limiting adverse event, often resulting in treatment interruption, dose reduction, or discontinuation. Maintaining full-dose intensity is particularly crucial in the metastatic setting, where drug exposure is directly correlated with efficacy. We hypothesize that baseline gut microbiome characteristics are associated with the incidence, severity, and trajectory of abemaciclib-induced diarrhea. Findings may support the development of microbiome-informed strategies to enhance drug tolerability and support sustained dosing, which is essential for maximizing therapeutic efficacy and ultimately improving patient survival.

Methods: This is a prospective, double-arm pilot translational study enrolling 90 patients with HR+/HER2− breast cancer initiating CDK4/6 inhibitor therapy. Participants will be assigned to two cohorts: one receiving abemaciclib, and the other receiving a comparator CDK4/6 inhibitor with minimal GI toxicity (e.g., palbociclib or ribociclib). The primary objective is to evaluate the association between baseline gut microbiome composition and function with the severity of abemaciclib-induced diarrhea. Stool samples will be collected at baseline (pre-treatment) and one month after treatment initiation. Comprehensive multi-omic analyses will be performed, including shotgun metagenomics for microbial genome reconstruction and functional pathway annotation using tools such as KEGG, MetaCyc, and MAC. Stool metabolomic profiling will be conducted to elucidate potential mechanistic pathways. Systemic biomarkers such as circulating cytokines, intestinal fatty acid-binding protein (I-FABP), and lipopolysaccharide-binding protein (LBP) will also be assessed to evaluate epithelial damage and microbial translocation. The primary endpoint is the association between baseline microbiome features and diarrhea severity, graded using CTCAE v5.0. Secondary endpoints include longitudinal microbiome changes, treatment adherence, dose intensity, and patient-reported GI symptoms. Exploratory analyses will identify microbial taxa and metabolic pathways linked to susceptibility or resilience to GI toxicity. This pilot study aims to elucidate the role of the gut microbiome in modulating abemaciclib-associated diarrhea and to identify predictive biomarkers of toxicity. Findings may support the development of microbiome-informed strategies to enhance drug tolerability and maintain therapeutic intensity in HR+/HER2− breast cancer.

Introduction

CDK4/6 inhibitors have become a cornerstone of treatment for HR+/HER2− breast cancer, demonstrating substantial improvements in progression-free survival and overall survival across multiple disease settings. These agents enhance endocrine therapy responsiveness, delay resistance, and have reshaped the therapeutic landscape for both metastatic and early-stage disease. Among the available CDK4/6 inhibitors, abemaciclib holds a distinct clinical position due to its continuous dosing schedule, broader kinase inhibition profile, and consistent efficacy observed in endocrine-resistant and high-risk populations. In the adjuvant MONARCH-E trial, abemaciclib became the first CDK4/6 inhibitor to significantly reduce invasive disease recurrence in high-risk early-stage breast cancer. However, nearly 20% of patients discontinued therapy due to adverse events, highlighting the need for strategies that improve tolerability and support adequate dose exposure to maximize clinical benefit.

Although abemaciclib provides meaningful clinical benefit, gastrointestinal toxicity—particularly diarrhea—remains the most common adverse event associated with its use. In MONARCH-E, diarrhea occurred frequently and was the earliest-onset toxicity, often necessitating dose interruptions and dose reductions, which were reported in more than half of treated patients. While the majority of events were grade 1–2, their persistence and cumulative burden contributed to the overall 18–20% rate of adverse-event–related treatment discontinuation in the adjuvant abemaciclib arm. Preclinical studies suggest that abemaciclib's distinctive gastrointestinal toxicity may be driven, at least in part, by off-target inhibition of GSK3β, resulting in Wnt/β-catenin pathway activation and epithelial hyperproliferation. However, the marked inter-individual variability in toxicity severity indicates that additional biological determinants—such as the gut microbiome—may influence susceptibility to clinically significant diarrhea.

Given the high frequency of gastrointestinal toxicity and its impact on dose intensity, there is a critical need for predictive tools capable of identifying patients at risk for clinically significant diarrhea before initiating abemaciclib. The gut microbiome—an essential regulator of mucosal immunity, epithelial turnover, and drug response—represents a promising source of host-derived biomarkers that may explain the observed variability in toxicity. We hypothesize that baseline microbiome composition and functional capacity are associated with the incidence, severity, and trajectory of abemaciclib-induced diarrhea. This prospective translational pilot study aims to characterize microbiome features linked to susceptibility or resilience to gastrointestinal toxicity and to generate predictive signatures that could ultimately inform personalized dosing strategies and improve treatment tolerability in HR+/HER2− breast cancer.

Methods and Materials

Study Design

- This is a prospective, two-arm, single-center translational pilot study designed to compare the tolerability, adherence, and dose intensity of different CDK4/6 inhibitors in patients with HR+HER2− breast cancer initiating treatment.
- The trial utilizes a non-randomized, pragmatic design where patients are allocated to one of two treatment arms based on CDK4/6 inhibitors, aiming to reflect real-world treatment decisions while prospectively collecting high-quality data.

Primary Objective: To identify predictive gut microbiome and metabolomic biomarkers associated with the severity of abemaciclib-induced diarrhea.

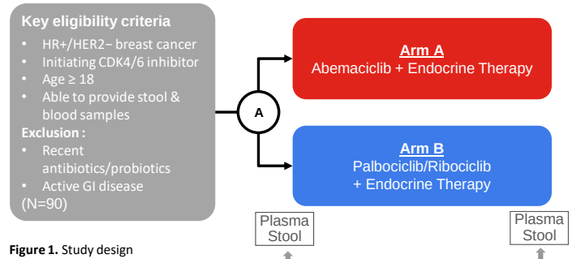


Figure 1. Study design

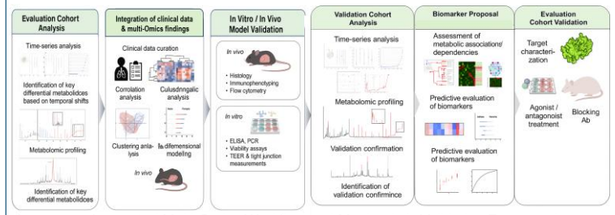


Figure 2. Integrated Multi-Omics Workflow and Mechanistic Validation Framework

Methods and Materials

Microbiome & Metabolome Profiling: Stool samples undergo shotgun metagenomic sequencing to characterize taxonomic composition and functional pathways (KEGG, MetaCyc) associated with abemaciclib-induced diarrhea. Targeted metabolomics using NMR (SCFAs) and LC/MS/MS (bile acids, tryptophan derivatives) is integrated to map metabolic alterations linked to toxicity.

Integrated Multi-Omics Analysis Combined microbiome, metabolome, and clinical datasets are analyzed using multivariate modeling (PLS-DA) and network analysis to identify microbial taxa, pathways, and metabolites associated with GI toxicity and treatment response.

In Vitro & In Vivo Mechanistic Evaluation Candidate microbial and metabolic features undergo functional testing in intestinal epithelial cell models, assessing viability, cytokine/chemokine secretion, TEER, and gene expression. Parallel in vivo models evaluate the impact of candidate metabolites on histology, epithelial permeability, and immune-cell dynamics under abemaciclib exposure.

Validation Cohort Analysis A separate validation cohort is analyzed using identical metagenomic and metabolomic workflows to assess reproducibility of microbiome–metabolite associations with the primary outcome and other clinical endpoints.

Predictive Biomarker Identification Microbial taxa and metabolites consistently associated with GI toxicity across both the evaluation and validation cohorts are proposed as predictive biomarkers for abemaciclib-induced diarrhea.

Therapeutic Target Discovery Mechanistic studies identify epithelial receptors, downstream signaling pathways, and transcriptomic changes modulated by key metabolites. These findings guide the development of candidate therapeutic agents aimed at mitigating abemaciclib-associated gastrointestinal toxicity.

Planned timeline

Current Status

- The study protocol has been finalized and IRB approval has been obtained.(KNUCH 2025-09-008-002).
- A total of 10 patients have been enrolled to date.
- Patient enrollment is expected to continue through December 2026, with completion of data analysis planned for 2027.

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