PRESERVE 1: A PHASE 3, RANDOMIZED, DOUBLE-BLIND TRIAL OF TRILACICLIB VERSUS PLACEBO IN PATIENTS RECEIVING FOLFOXIRI/BEVACIZUMAB FOR METASTATIC COLORECTAL CANCER

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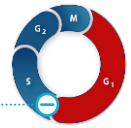
INTRODUCTION

- Multiagent chemotherapy remains the cornerstone of treatment for metastatic colorectal cancer (mCRC), with most patients receiving some combination of leucovorin, fluorouracil, oxaliplatin, and irinotecan in the first-line setting, often in combination with a monoclonal antibody targeting the epidermal growth factor receptor (EGFR) or vascular endothelial growth factor (VEGF) pathways[1,2]
- Improvements in overall survival (OS) and progression-free survival (PFS) gained from combining leucovorin, fluorouracil, oxaliplatin, and irinotecan (FOLFOXIRI) with bevacizumab have come at the expense of increased chemotherapy-induced toxicity, including myelosuppression, diarrhea, and mucositis[1–3]
  - As a result, the use of FOLFOXIRI is frequently limited to younger patients with fewer comorbidities
- Chemotherapy-induced myelosuppression, which commonly manifests as neutropenia, anemia, and/or thrombocytopenia, is a dose-limiting and potentially fatal complication of treatment that can result in hospitalization and the need for supportive care interventions
  - Symptoms of fatigue, and the development of infections and bleeding can seriously affect quality of life, and dose reductions and treatment delays may affect treatment response and long-term survival[4,5]
- Trilaciclib is an intravenous cyclin-dependent kinase 4/6 inhibitor indicated to decrease the incidence of chemotherapy-induced myelosuppression in adult patients when administered prior to a platinum/etoposide- or topotecan-containing chemotherapy regimen for extensive-stage small cell lung cancer[6]
- Data from 3 randomized, placebo-controlled, phase 2 clinical trials showed that administering trilaciclib prior to chemotherapy reduced the incidence of chemotherapy-induced myelosuppression, and reduced the need for supportive care interventions and chemotherapy dose reductions/delays[7–9]
- Additionally, in a randomized phase 2 trial in patients with metastatic triple-negative breast cancer, administering trilaciclib prior to gemcitabine plus carboplatin significantly improved OS compared with chemotherapy alone, potentially through protection and direct activation of immune function[10,11]

Trilaciclib Mechanism of Action

Trilaciclib (IV myeloprotection therapy)

- IV inhibitor of CDK4/6, administered prior to chemotherapy[6]
- Transiently arrests HSPCs and immune cells in the G_1 phase of the cell cycle during chemotherapy exposure, protecting them from chemotherapy-induced damage[6–9,12,13]



Myeloprotection impact[6–9]		Antitumor efficacy impact[10,11,14]
Reduces rate of hematologic adverse events (less neutropenia, anemia, and thrombocytopenia)	Protects multiple myeloid cell lineages	**Increases** patients' ability to receive longer duration of chemotherapy-based regimens
Decreases rescue interventions (fewer transfusions, less G-CSF, and fewer CIM-related hospitalizations)	Protects lymphoid cell lineages	**Protects** the immune system from damage by chemotherapy
Improves patients' quality of life (improved well-being and less fatigue)	Improves immune response	**Enhances** T-cell responses and favorably alters the tumor microenvironment

CDK4/6, cyclin-dependent kinase 4/6; CIM, chemotherapy-induced myelosuppression; G-CSF, granulocyte colony-stimulating factor; HSPC, hematopoietic stem and progenitor cell; IV, intravenous.

PRESERVE 1 STUDY

- PRESERVE 1 (NCT04607668) is a phase 3, multicenter, randomized, double-blind, placebo-controlled study evaluating the myeloprotective and antitumor efficacy of trilaciclib versus placebo administered prior to FOLFOXIRI/bevacizumab for patients receiving first-line treatment for proficient mismatch repair/microsatellite stable (pMMR/MSS) mCRC
- FOLFOXIRI is more efficacious and more myelosuppressive than other fluorouracil-based regimens used in the treatment of mCRC; therefore, patients should benefit from a reduction in the incidence of chemotherapy-induced myelosuppression and use of this regimen at the standard-of-care dose and schedule

STUDY OBJECTIVES

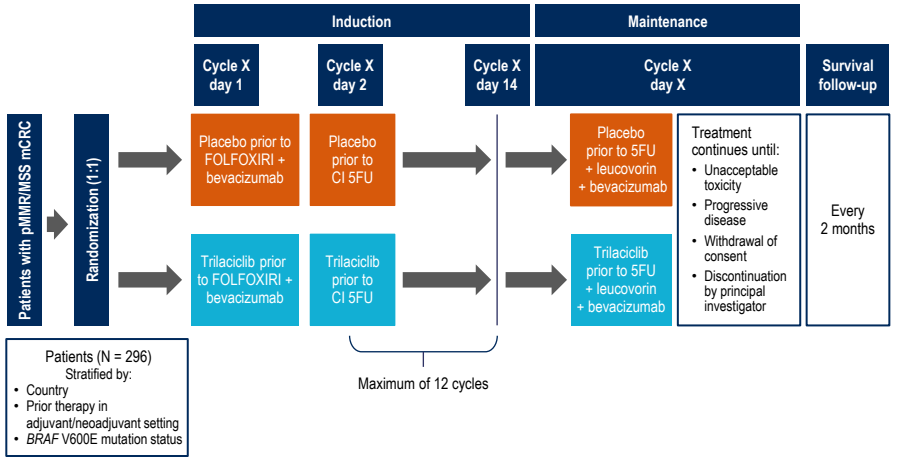
1 Primary Objective

- To evaluate the effects of trilaciclib versus placebo on the neutrophil lineage in patients receiving FOLFOXIRI/bevacizumab for pMMR/MSS mCRC

2 Key Secondary Objectives

- To assess the effects of trilaciclib versus placebo on chemotherapy-induced fatigue, measured using the Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F) scale
- To assess the effect of trilaciclib versus placebo on PFS and OS, per Response Evaluation Criteria in Solid Tumours version 1.1

STUDY DESIGN



5FU, fluorouracil; CI, continuous infusion; FOLFOXIRI, leucovorin, fluorouracil, oxaliplatin, and irinotecan; mCRC, metastatic colorectal cancer; pMMR/MSS, proficient mismatch repair/microsatellite stable.

Statistics

- To ensure strong control of family-wise type I error rate at the level of 2-sided 0.05, the following statistical considerations are specified in the protocol:
  1. Overall alpha (α) will be split for analyses between 2 groups:
     - Group 1: analyses of the 2 primary myelosuppression endpoints and time to first confirmed deterioration in fatigue (TTCD-fatigue) using $\alpha_1 = 0.04$
     - Group 2: analyses of PFS and OS using $\alpha_2 = 0.01$
  2. Hierarchical procedures are specified to test treatment effects within each group:
     - As coprimary endpoints, duration of severe (grade 4) neutropenia (DSN) in cycle 1, and occurrence of severe neutropenia (SN) during induction will each be tested at the 2-sided 0.04 level; if both are positive, α_1 will be passed to test treatment effect on TTCD-fatigue
     - Treatment effect for OS will be tested after the treatment effect for PFS is established at the α_2 level
  3. Recycling of α from Group 1 to Group 2:
     - If the treatment effects are established for all 3 endpoints in Group 1, PFS and OS will be tested at the 2-sided 0.05 level; otherwise, they will be tested at the 0.01 level
- The sample size is determined to support the primary efficacy analysis for the 2 primary efficacy endpoints:
  - 282 patients will be needed to detect treatment effect on DSN using a Mann-Whitney-Wilcoxon test, and on occurrence of SN using a chi-square test, with 90% power at the 2-sided significance level of 0.04
  - Assuming 5% of randomized patients will not have any postbaseline data, a total of 296 patients (148 per group) will be required for the study

PATIENT ELIGIBILITY CRITERIA

Key inclusion criteria

- Aged ≥ 18 years; patients aged > 70 years must have a G8 Health State Screening Tool (geriatric screening tool) score > 14
- Histologically or cytologically confirmed pMMR/MSS adenocarcinoma of the colon or rectum
- *BRAF* mutant or wild-type eligible; status must be known prior to randomization
- Unresectable and measurable or evaluable mCRC per RECIST v1.1
- ECOG performance status of 0 or 1
- Archival or fresh tumor specimen for retrospective biomarker analysis
- Adequate organ function

Key exclusion criteria

- Prior systemic therapy for mCRC
- Receipt of any anticancer therapy ≤ 3 weeks prior to study treatment start
- Symptomatic peripheral neuropathy
- Personal/family history of long QT syndrome
- History of interstitial lung disease
- Uncontrolled hypertension (BP ≥ 150/90 mmHg)
- History of prior abdominal fistula or perforation within 6 months prior to randomization, or clinically significant hemorrhage within 1 month prior to randomization

BP, blood pressure; ECOG, Eastern Cooperative Oncology Group; mCRC, metastatic colorectal cancer; pMMR/MSS, proficient mismatch repair/microsatellite stable; RECIST v1.1, Response Evaluation Criteria in Solid Tumours version 1.1.

ENDPOINTS

Primary endpoint

- Duration of severe (grade 4) neutropenia in cycle 1
- Occurrence of severe neutropenia during induction

Key secondary endpoints

- TTCD-fatigue during induction
- Progression-free survival
- Overall survival

Other secondary endpoints

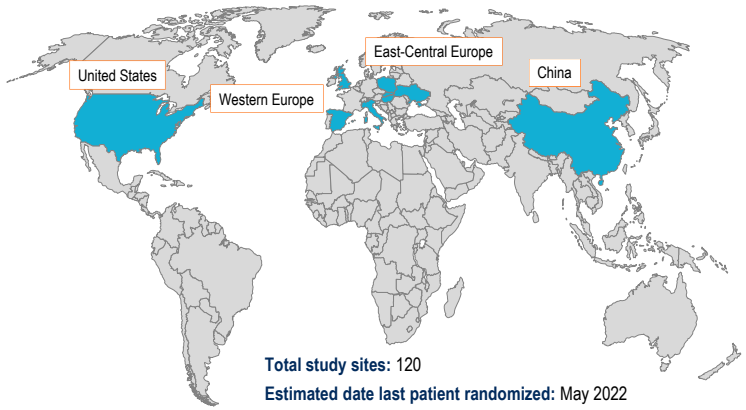
- Myeloprotection effects (across neutrophil, red blood cell, and platelet lineages)
- All-cause dose reductions or delays
- Relative dose intensity for FOLFOXIRI/bevacizumab
- Healthcare utilization (hospitalizations and antibiotic use)
- Antitumor activity (best overall response and duration of response)
- Occurrence and severity of adverse events

Exploratory endpoints

- Antitumor efficacy by CDK4/6-dependence status
- Pharmacokinetics of trilaciclib
- Quality of life using patient-reported outcome measures
- Receipt of subsequent anticancer therapy/therapies

CDK4/6, cyclin-dependent kinase 4/6; FOLFOXIRI, leucovorin, fluorouracil, oxaliplatin, and irinotecan; TTCD-fatigue, time to first confirmed deterioration of fatigue.

STUDY SITES



Total study sites: 120

Estimated date last patient randomized: May 2022

Estimated date myeloprotection analysis: Q1 2023

Estimated date PFS/OS analysis: Q3 2025

OS, overall survival; PFS, progression-free survival; Q, quarter.

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DISCLOSURES:
Study sponsored by G1 Therapeutics, Inc.
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