

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

JOLEEN M. HUBBARD¹; MATTI AAPRO²; SATISH SHAH³; AFSHIN ELI GABAYAN⁴; RICHARD SIEGEL⁵; YILI PRITCHETT⁶; JOHN YI⁶; JANET HORTON⁶; AND FORTUNATO CIARDIELLO⁷

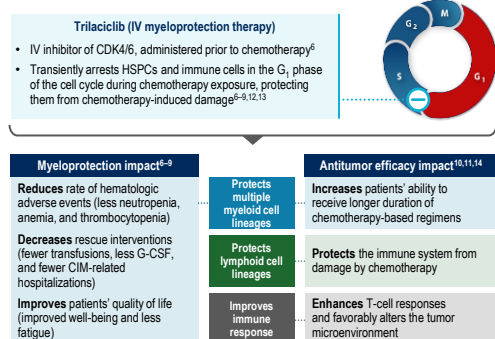
¹MAYO CLINIC, ROCHESTER, MN, USA; ²GENOLIER CANCER CENTER, CLINIQUE DE GENOLIER, GENOLIER, SWITZERLAND; ³GETTYSBURG CANCER CENTER, GETTYSBURG, PA, USA; ⁴BEVERLY HILLS CANCER CENTER, BEVERLY HILLS, CA, USA; ⁵ILLINOIS CANCER SPECIALISTS, ARLINGTON HEIGHTS, IL, USA; ⁶G1 THERAPEUTICS, INC., RESEARCH TRIANGLE PARK, NC, USA; ⁷UNIVERSITY OF CAMPANIA LUIGI VANVITELLI, NAPLES, ITALY



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 mucositis¹⁻³.
- 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 cancer⁶.
- 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/delays⁷⁻⁹.
- 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



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

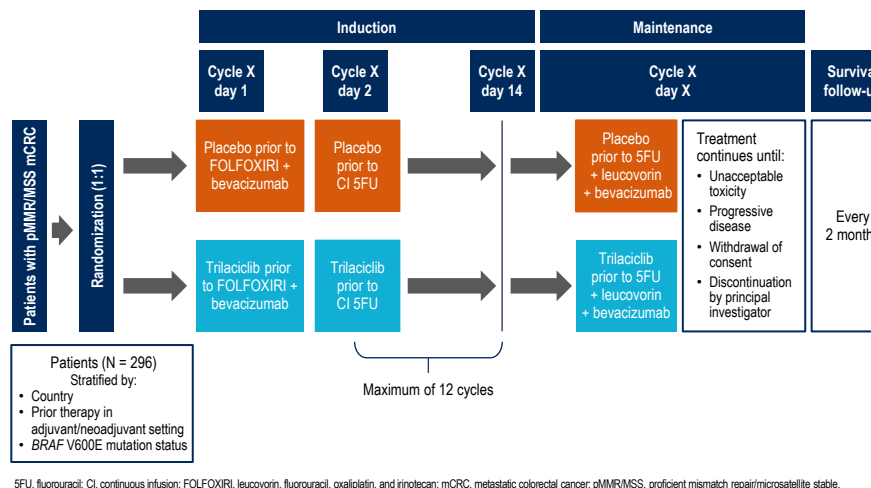
1 PRIMARY OBJECTIVE

- 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



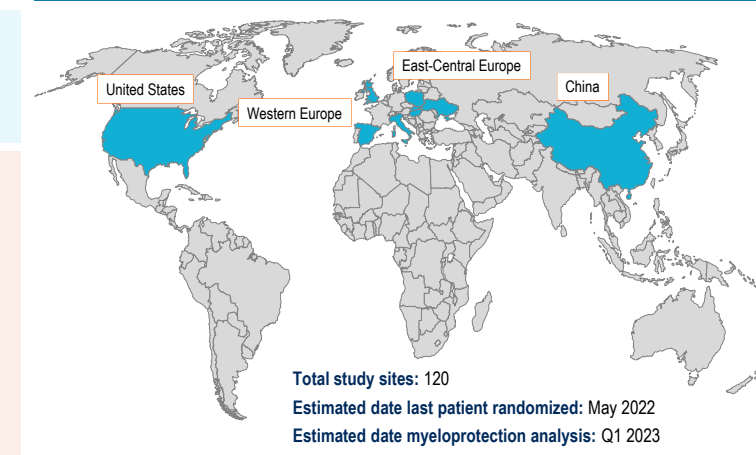
PATIENT ELIGIBILITY CRITERIA

Key inclusion criteria	Key exclusion criteria
Aged ≥ 18 years; patients aged > 70 years must have a G8 Health State Screening Tool (geriatric screening tool) score > 14	Prior systemic therapy for mCRC
Histologically or cytologically confirmed pMMR/MSS adenocarcinoma of the colon or rectum	Receipt of any anticancer therapy ≤ 3 weeks prior to study treatment start
BRAF mutant or wild-type eligible; status must be known prior to randomization	Symptomatic peripheral neuropathy
Unresectable and measurable or evaluable mCRC per RECIST v1.1	Personal/family history of long QT syndrome
ECOG performance status of 0 or 1	History of interstitial lung disease
Archival or fresh tumor specimen for retrospective biomarker analysis	Uncontrolled hypertension (BP ≥ 150/90 mmHg)
Adequate organ function	History of prior abdominal fistula or perforation within 6 months prior to randomization, or clinically significant hemorrhage within 1 month prior to randomization

ENDPOINTS

Primary endpoint	Key secondary endpoints
Duration of severe (grade 4) neutropenia in cycle 1	TTCD-fatigue during induction
Occurrence of severe neutropenia during induction	Progression-free survival
	Overall survival
Other secondary endpoints	Exploratory endpoints
Myeloprotection effects (across neutrophil, red blood cell, and platelet lineages)	Antitumor efficacy by CDK4/6-dependence status
All-cause dose reductions or delays	Pharmacokinetics of trilaciclib
Relative dose intensity for FOLFOXIRI/bevacizumab	Quality of life using patient-reported outcome measures
Healthcare utilization (hospitalizations and antibiotic use)	Receipt of subsequent anticancer therapy/therapies
Antitumor activity (best overall response and duration of response)	
Occurrence and severity of adverse events	

STUDY SITES



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.

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.

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

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

REFERENCES

- Montagna F, et al. *Colorectal Dis*. 2011;13:846–52.
- Loupakis F, et al. *N Engl J Med*. 2014;371:609–18.
- Sastre J, et al. *J Clin Oncol*. 2019;37:3507.
- Epstein RS, et al. *Adv Ther*. 2020;37:3606–18.
- Epstein RS, et al. *Patient Prefer Adherence*. 2021;15:453–65.
- COSSA™ (trilaciclib). Prescribing Information. <https://www.g1therapeutics.com/cosela/pi/>. Accessed August 2021.
- Daniel D, et al. *Int J Cancer*. 2021;148:2557–70.
- Weiss JM, et al. G1T28-02 Study Group. *Ann Oncol*. 2019;30:1613–21.
- Hart LL, et al. *Adv Ther*. 2021;38:2933–45.
- Tan AR, et al. *Lancet Oncol*. 2019;20:1587–801.
- O'Shaughnessy J, et al. SABCS poster presentation, 2020; abstract #PD1-06.
- He S, et al. *Sci Transl Med*. 2017;9:aaa0986.
- Li G, et al. *Cancer Chemother Pharmacol*. 2021;87:889–707.
- La AY, et al. *J Immunother Cancer*. 2020;8:e000847.

ACKNOWLEDGMENTS

Medical writing assistance was provided by Fathana Burnett, PhD, from Alligent Europe (Envision Pharma Group), funded by G1 Therapeutics, Inc.

DISCLOSURES

Study sponsored by G1 Therapeutics, Inc. JMM: no conflicts of interest to declare.

DISCLAIMER

For questions regarding the PRESERVE 1 trial, please contact clinicalinfo@g1therapeutics.com. Copies of this e-Poster obtained through QR, AR, and/or text key codes are for personal use only and may not be reproduced without written permission of the authors.