














Trilaciclib prior to FOLFOXIRI/bevacizumab for patients with untreated metastatic colorectal cancer: phase 3 PRESERVE 1 trial

Heinz-Josef Lenz , MD¹, Tianshu Liu , MD², Emerson Y. Chen , MD³, Zsolt Horváth , MD, PhD⁴, Igor Bondarenko , MD, PhD⁵, Iwona Danielewicz , MD⁶, Michele Ghidini , MD, PhD⁷, Pilar García-Alfonso , MD, PhD⁸, Robert Jones , PhD, MD^{9,10}, Matti Aapro , MD¹¹, Yanqiao Zhang, MD¹², Jufeng Wang, MD¹³, Wayne Wang , PhD¹⁴, Jennifer Adeleye, PhD¹⁴, Andrew Beelen , MD^{*14}, Joleen Hubbard , MD¹⁵

¹Department of Medicine, Keck School of Medicine, University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA 90033, United States

²Department of Medical Oncology, Zhongshan Hospital, Fudan University, Shanghai 200032, China

³Department of Medicine, Division of Hematology and Medical Oncology, Knight Cancer Institute, Oregon Health & Science University, Portland, OR 97239, United States

⁴Center of Oncoradiology, Bács-Kiskun County Teaching Hospital, Kecskemét 6000, Hungary

⁵Department of Oncology and Medical Radiology, Dnipropetrovsk State Medical Academy, City Multifield Clinical Hospital, Dnipropetrovsk 49102, Ukraine

⁶Department of Clinical Oncology, Szpital Pomorskie Sp. z o.o., Gdynia 81-519, Poland

⁷Operative Unit of Medical Oncology, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan 20122, Italy

⁸Department of Medical Oncology, Hospital General Universitario Gregorio Marañón, Instituto de Investigación Sanitaria (IiSGM), Universidad Complutense de Madrid, Madrid 28007, Spain

⁹Department of Cancer and Genetics, Cardiff University, Cardiff CF10 3AX, UK

¹⁰Velindre NHS Trust, Cardiff CF14 2TL, UK

¹¹Genolier Cancer Centre, Clinique de Genolier, Genolier 1272, Switzerland

¹²Department of GI Medical Oncology, Harbin Medical University Cancer Hospital, Nangang, Harbin, Heilongjiang 150040, China

¹³Department of Medical Oncology, Affiliated Cancer Hospital of Zhengzhou University, Henan Cancer Hospital, Zhengzhou 450008, China

¹⁴G1 Therapeutics, Inc., Research Triangle Park, NC 27709, United States

¹⁵Allina Health Cancer Institute, Abbott Northwestern Hospital, Minneapolis, MN 55407, United States

*Corresponding author: Andrew Beelen, MD, Incyclix Bio, 600 Park Offices Dr, Suite 355, Research Triangle Park, NC 27709, United States (andrew.beelen@gmail.com).

Present address: Jennifer Adeleye, Daiichi Sankyo, Inc., Basking Ridge, NJ 07920-2311, United States.

Present address: Andrew Beelen, Incyclix Bio, Research Triangle Park, NC 27709, United States.

Abstract

Background: In metastatic colorectal cancer (mCRC), improvements in survival from combining leucovorin/fluorouracil/oxaliplatin/irinotecan (FOLFOXIRI) with bevacizumab have come at the risk of increased rates of high-grade toxicities. Trilaciclib is indicated to decrease the incidence of chemotherapy-induced myelosuppression in patients receiving standard-of-care chemotherapy for extensive-stage small cell lung cancer.

Methods: Patients with untreated mCRC were randomly assigned 1:1 to trilaciclib (n = 164) or placebo (n = 162) prior to FOLFOXIRI/bevacizumab for up to 12 cycles (induction), followed by trilaciclib or placebo prior to fluorouracil/leucovorin/bevacizumab (maintenance). Co-primary endpoints were duration of severe (grade 4) neutropenia (DSN) in cycles 1-4 and occurrence of severe neutropenia (SN) during induction. Secondary endpoints included antitumor efficacy, survival, and safety.

Results: The study met its co-primary endpoints. Administering trilaciclib prior to FOLFOXIRI/bevacizumab resulted in significant reductions in DSN in cycles 1-4 vs placebo (mean, 0.1 vs 1.3 days; $P < .001$) and occurrence of SN during induction (1.3% vs 19.7%; adjusted relative risk [96% CI] = 0.07 [0.0 to 0.3]; $P < .001$). Grade 3/4 adverse events, including neutropenia, diarrhea, and leukopenia, were less frequent with trilaciclib vs placebo (64.8% vs 73.1%). Trilaciclib was associated with fewer chemotherapy dose reductions and delays and with reduced administration of supportive therapies, compared with placebo. Objective response rate (41.6% vs 57.1%; $P = .009$) and median progression-free survival (10.3 vs 13.1 months; $P < .001$) were significantly lower with trilaciclib vs placebo.

Conclusions: Administering trilaciclib prior to FOLFOXIRI/bevacizumab protected the neutrophil lineage from the effects of chemotherapy-induced myelosuppression. However, antitumor efficacy endpoints favored placebo.

Trial registration: [ClinicalTrials.gov](https://clinicaltrials.gov): NCT04607668.

Multigagent chemotherapy remains the cornerstone of treatment for metastatic colorectal cancer (mCRC), with most patients receiving some combination of leucovorin, fluorouracil, oxaliplatin, and

irinotecan plus a vascular endothelial growth factor (VEGF)- or epidermal growth factor receptor (EGFR)-targeting monoclonal antibody in the first-line setting.^{1,2} Approximately 95% of patients with

Received: July 8, 2024. Revised: October 11, 2024. Accepted: November 13, 2024

© The Author(s) 2024. Published by Oxford University Press.

This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs licence (<https://creativecommons.org/licenses/by-nc-nd/4.0/>), which permits non-commercial reproduction and distribution of the work, in any medium, provided the original work is not altered or transformed in any way, and that the work is properly cited. For commercial re-use, please contact journals.permissions@oup.com

mCRC have proficient mismatch repair/microsatellite stable (pMMR/MSS) disease.³ The recommended first-line treatment for these patients is a doublet chemotherapy backbone of FOLFOX (leucovorin, fluorouracil, and oxaliplatin), FOLFIRI (leucovorin, fluorouracil, and irinotecan) or capecitabine plus oxaliplatin, or triplet FOLFOXIRI (leucovorin, fluorouracil, oxaliplatin, and irinotecan), combined with VEGF-targeting bevacizumab.²

Combining FOLFOXIRI with bevacizumab prolongs overall survival (OS) and progression-free survival (PFS) vs chemotherapy doublets FOLFOX or FOLFIRI.⁴⁻⁶ However, increased toxicity is also observed, including myelosuppression, diarrhea, and mucositis.⁶⁻⁸ Consequently, FOLFOX and FOLFIRI doublets are still used in the general population despite inferior survival, and use of FOLFOXIRI is frequently limited to patients with high disease burden or younger patients with fewer comorbidities.

Chemotherapy-induced damage to hematopoietic stem and progenitor cells (HSPCs) can lead to multilineage myelosuppression, manifesting as neutropenia, anemia, and/or thrombocytopenia.⁹ Symptoms of multilineage myelosuppression can negatively affect the quality of life of patients undergoing chemotherapy and increase the likelihood of hospitalization and the need for supportive-care interventions, potentially affecting treatment response and long-term survival.^{10,11} Chemotherapy-induced myelosuppression is typically managed through chemotherapy dose reductions and delays. Current supportive-care agents, such as granulocyte colony-stimulating factor (G-CSF), erythropoiesis-stimulating agents (ESAs), and red blood cell (RBC) or platelet transfusions, are lineage-specific and typically administered reactively.⁹ In addition, although short-term administration of G-CSF may be used to address chemotherapy-induced neutropenia, care is warranted because G-CSF presence in the tumor microenvironment may promote malignancy progression and poor prognosis.¹²

Trilaciclib, an intravenously (IV) administered, small-molecule inhibitor of cyclin-dependent kinase 4/6, transiently induces cell cycle arrest in HSPCs during chemotherapy, thus protecting HSPCs from the cytotoxic effects of chemotherapy.^{13,14} Trilaciclib is indicated to decrease the incidence of chemotherapy-induced myelosuppression in adult patients when administered prior to a platinum/etoposide- or topotecan-containing regimen for extensive-stage small cell lung cancer (ES-SCLC).¹⁵ The approval was based on results from 3 randomized, placebo-controlled, phase 2 studies in patients with ES-SCLC, which showed that administering trilaciclib prior to chemotherapy reduced the incidence of myelosuppression and the need for supportive-care interventions and chemotherapy dose modifications.¹⁶⁻¹⁸

This study was designed to assess whether administering trilaciclib prior to FOLFOXIRI/bevacizumab could similarly reduce the incidence of chemotherapy-induced myelosuppression in previously untreated patients with pMMR/MSS mCRC.

Methods

Study design and participants

PRESERVE 1 was a multicenter, randomized, double-blind, placebo-controlled phase 3 trial (NCT04607668¹⁹) conducted at 88 sites in 8 countries (China, Hungary, Italy, Poland, Spain, Ukraine, the United Kingdom, and the United States). Eligible patients were aged ≥ 18 , had histologically or cytologically confirmed pMMR/MSS mCRC, unresectable and measurable or evaluable mCRC per Response Evaluation Criteria in Solid Tumours version 1.1, an Eastern Cooperative Oncology Group

performance status (ECOG PS) of 0 or 1, adequate organ function, no prior systemic therapy for mCRC, and no anticancer therapy ≤ 3 weeks prior to study treatment start. Known BRAF mutation status was a prerequisite for enrollment.

The study was designed and conducted in compliance with the principles of the Declaration of Helsinki and the Good Clinical Practice guidelines of the International Council for Harmonisation. The study protocol and all study-related materials were approved by the institutional review board or independent ethics committee of each investigational site. Written, informed consent was obtained from each patient before initiation of study procedures.

Randomization and procedures

Patients were randomly assigned 1:1 by an interactive web-response system to receive trilaciclib or placebo prior to FOLFOXIRI/bevacizumab. There were 3 stratification factors for randomization: (1) country, (2) prior therapy in adjuvant/neoadjuvant setting, and (3) BRAF V600E mutation status. These 3 factors could potentially impact myeloprotection and antitumor efficacy outcomes and hence were chosen as stratification factors.

During the induction phase, patients received trilaciclib or placebo IV on days 1 and 2 prior to FOLFOXIRI/bevacizumab in 14-day cycles for a maximum of 12 cycles. Irinotecan 165 mg/m², oxaliplatin 85 mg/m², leucovorin 400 mg/m² (or 200 mg/m² leucovorin), and bevacizumab 5 mg/kg were all administered IV on day 1. Fluorouracil 2400-3200 mg/m² (dosage per clinician discretion) was administered IV as a continuous infusion over 46-48 hours beginning on day 1. Trilaciclib 240 mg/m² or placebo (dextrose 5% in water or sodium chloride 0.9% solution) was administered IV over 30 (± 5) minutes prior to chemotherapy on days 1 and 2 of each cycle. During the maintenance phase, patients continued to receive trilaciclib or placebo (per randomization allocation) prior to IV fluorouracil and leucovorin plus bevacizumab at the same dose and schedule in 14-day cycles. Treatment was continued until disease progression, unacceptable toxicity, withdrawal of consent, discontinuation by the investigator, or the end of the study, whichever occurred first.

To facilitate an unbiased evaluation of the primary myeloprotection efficacy endpoints, primary prophylactic G-CSF was prohibited in cycle 1 of induction. Therapeutic G-CSF (administered in response to a febrile neutropenia [FN] event) in any cycle, and secondary prophylactic G-CSF beginning in cycle 2 and for all subsequent cycles, was allowed per standard guidelines and physician discretion. ESA administration and RBC or platelet transfusion were allowed per investigator discretion based on standard guidelines.

Outcomes

The primary objective of the study was to evaluate the effects of trilaciclib vs placebo on the neutrophil lineage in patients receiving FOLFOXIRI/bevacizumab for pMMR/MSS mCRC. The co-primary endpoints were duration of severe (grade 4) neutropenia (DSN) in cycles 1-4 and occurrence of severe neutropenia (SN) during induction. Both outcomes were chosen because they have been shown to correlate with the risk of FN and infections^{20,21}; therefore, a reduction in DSN during the timeframe when the risk for FN is highest (cycles 1-4) would decrease the risk of these events and improve the patient experience during chemotherapy.

SN was defined as an absolute neutrophil count (ANC) of $< 0.5 \times 10^9$ cells/L, per the Common Terminology Criteria for Adverse Events version 5.0 for grade 4 toxicity. DSN in cycles 1-4 was defined as the number of days for the first SN event that occurred in cycle 1, 2, 3, or 4 (ANC $< 0.5 \times 10^9$ cells/L to first ANC

$\geq 0.5 \times 10^9$ cells/L where no additional ANC values $< 0.5 \times 10^9$ cells/L were observed in that cycle) for patients who had at least 1 SN event in the first 4 cycles of induction. For patients without any SN in cycles 1-4, the DSN was recorded as 0. The occurrence of SN was a binary endpoint defined as those having 1 or more readings of ANC value $\leq 0.5 \times 10^9$ cells/L among all ANC measurements during induction. Hematology laboratory assessments were taken on days 1, 2, 4, 6, 8, 10, and 12 of cycle 1 and days 1 and 8 of subsequent cycles. The frequent assessments during cycle 1 better informed hematological parameters because they were not subject to potential bias from prophylactic G-CSF administration.

The key secondary objective of the study was to assess the effect of trilaciclib on OS compared with placebo. Secondary efficacy objectives included assessments for occurrence and/or number of several outcomes, including FN, grade 3/4 anemia or thrombocytopenia, G-CSF or ESA administration, all-cause dose reductions or cycle delays, objective response rate (ORR), best overall response, and PFS. Safety endpoints included the occurrence and severity of adverse events (AEs).

Statistical analysis

The treatment group difference in DSN in cycles 1-4 (primary endpoint) was evaluated using a nonparametric analysis of covariance (ANCOVA). The rank-transformed baseline ANC (within each stratum) was included as a covariate in the model. The assumed treatment effect on occurrence of SN during induction (primary endpoint) was analyzed using a modified Poisson regression model with the same terms as used in the nonparametric ANCOVA model for DSN in cycles 1-4, with baseline ANC value as a covariate, and the log-transformed number of cycles used as the offset. Adjusted relative risk (trilaciclib vs placebo) and its 96% confidence interval (CI) was calculated along with the 2-sided *P* value.

Region (United States, Eastern Europe, Western Europe, and China) was used instead of country as a stratification factor in the statistical analysis models to account for regional differences in clinical practice. The assumed treatment effect on PFS was primarily evaluated using a stratified log-rank test accounting for the 3 stratification factors. The magnitude of treatment effect, hazard ratio (trilaciclib vs placebo), along with its 95% CI was estimated using a Cox proportional hazard model controlling for the same factors as included in the stratified log-rank test. The assumed treatment effect on ORR was evaluated using a Cochran–Mantel–Haenszel test accounting for the 3 stratification factors. The adjusted proportion difference (trilaciclib vs placebo) and its 95% CI were calculated using Cochran–Mantel–Haenszel weight. For patients who achieved confirmed complete or partial response as best overall response, the duration of response was calculated and analyzed.

The planned study sample size was 282 patients (141 per group), which was calculated to support the evaluation of each co-primary endpoint with 90% power at a 2-sided significance level of 0.04. Assuming 5% of randomly assigned patients would have no postbaseline data, 296 patients (148 per group) were required. Subsequently, 30 additional patients were planned for enrollment to replace patients affected by the war in Ukraine for the efficacy analyses (326 patients overall).

The intention-to-treat (ITT) population included all randomly assigned patients. To account for potential data integrity issues resulting from the war in Ukraine, a modified (m)ITT population was used as the primary analysis population for all efficacy evaluations, which included all patients randomly assigned in

countries other than Ukraine and all patients in Ukraine who were randomly assigned before September 9, 2021. The safety population included all randomly assigned patients who received ≥ 1 dose of any study drug, with data analyzed by actual received treatment.

The first planned analysis of myeloprotection, tumor response, and safety endpoints took place when all randomly assigned patients had completed up to 12 cycles or discontinued during induction (data cutoff: December 13, 2022). The final clinical database lock was planned to take place when 157 deaths had been observed or 52 months after first randomization, whichever came first. However, owing to early antitumor efficacy data favoring the placebo group in the first planned analysis, the trial was discontinued and the final analyses of safety and selected antitumor efficacy endpoints were conducted on April 17, 2023.

Results

Participants and treatment

Between January 6, 2021, and March 31, 2023, 458 patients were screened, and 326 eligible patients (ITT population) were randomly assigned to the trilaciclib ($n = 164$) or placebo ($n = 162$) group (Figure 1). Of these, 319 (98%) patients received ≥ 1 dose of the study drug (safety population) and 296 patients were included in the mITT population. After study termination, all patients discontinued the study drug and study participation.

Baseline demographic and clinical characteristics were similar between treatment groups (Table 1) and between the mITT and ITT populations (Table S1).

Myeloprotection efficacy

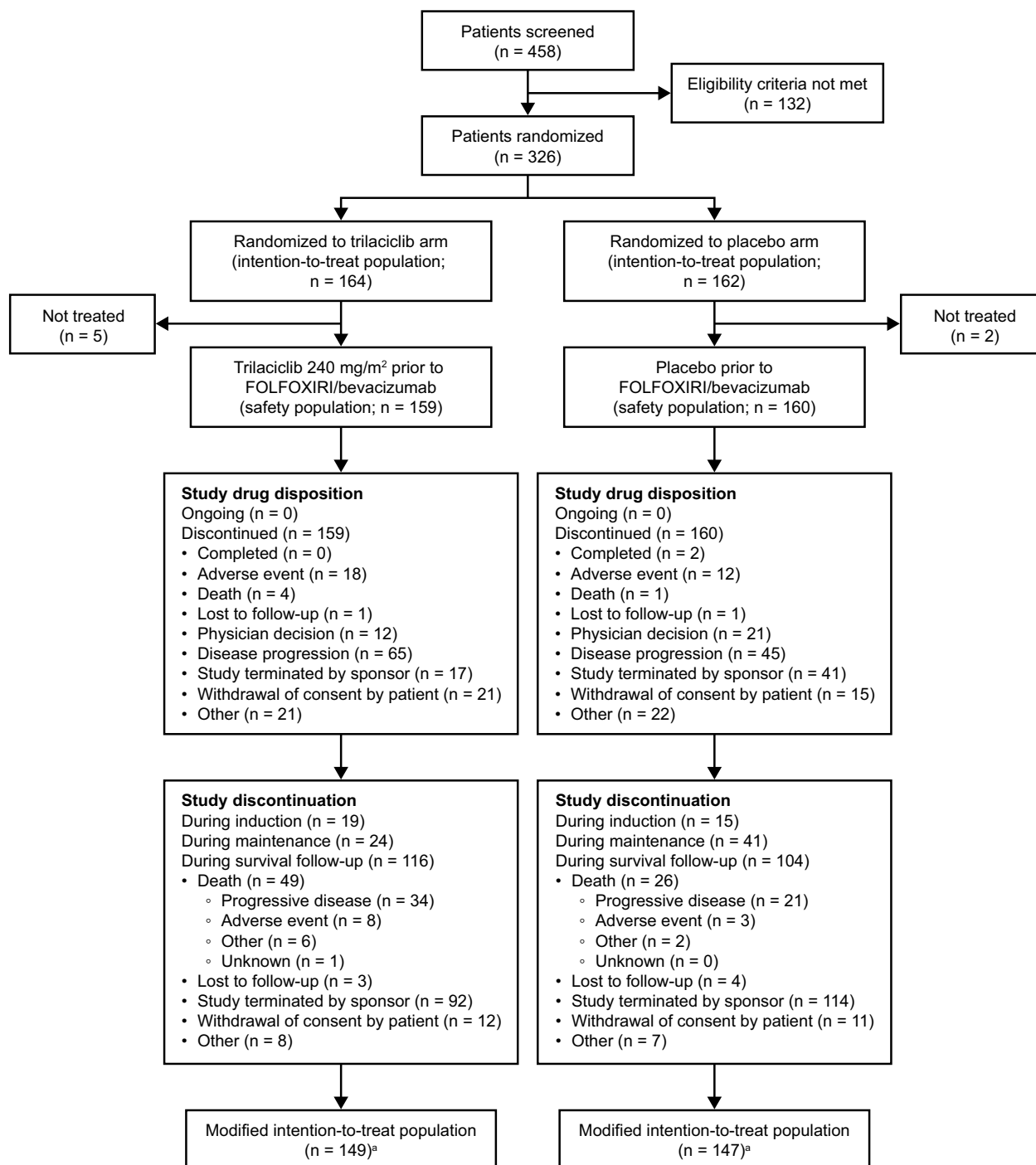
In the mITT population, trilaciclib administered prior to FOLFOXIRI/bevacizumab significantly reduced chemotherapy-induced neutropenia vs placebo (Figure 2). Mean (standard deviation) DSN in cycles 1-4 was 0.1 (0.8) days with trilaciclib vs 1.3 (3.1) days with placebo (mean [96% CI] difference = -1.2 [-1.7 to -0.6] days; $P < .001$). SN during induction was reported in 2 (1.3%) vs 29 (19.7%) patients treated with trilaciclib vs placebo, respectively (adjusted relative risk [96% CI] = 0.07 [0.0 to 0.3]; $P < .001$).

Trilaciclib also reduced FN (0% vs 5.0%), grade 3/4 anemia (3.1% vs 4.4%), and grade 3/4 thrombocytopenia (1.9% vs 2.5%) vs placebo (Figure 2). Furthermore, the need for G-CSF administration and ESA use was lower with trilaciclib than with placebo (Figure 2); G-CSF administration was significantly reduced in the trilaciclib group compared with placebo (19.5% vs 43.5%; adjusted relative risk [95% CI] = 0.48 [0.33 to 0.69]; nominal $P < .001$).

Safety

Median duration of treatment was 32.7 weeks (median 13 cycles) in the trilaciclib group and 37.8 weeks (median 16 cycles) in the placebo group. The incidence of chemotherapy dose reductions and cycle delays was lower with trilaciclib vs placebo (34.0% vs 48.1% and 79.2% vs 86.9%, respectively).

Overall, 157 (98.7%) patients in the trilaciclib group and 159 (99.4%) patients in the placebo group had ≥ 1 AE (Table 2). The most common any-grade AEs across both treatment groups were diarrhea (63.0%), nausea (58.6%), neutropenia (48.0%), anemia (37.0%), vomiting (37.3%), and fatigue (32.9%). The incidences of diarrhea, stomatitis, neutropenia, and epistaxis were $\geq 10\%$ lower with trilaciclib vs placebo. Grade 3/4 AEs were reported in 103 (64.8%) patients in the trilaciclib group vs 117 (73.1%) in the



^aIncluded all patients randomized in countries other than Ukraine and all patients in Ukraine who were randomized before September 9, 2021. FOLFOXIRI = folinic acid, 5-fluorouracil, oxaliplatin and irinotecan.

Figure 1. Trial profile.

placebo group, most commonly neutropenia (17.6% vs 40.0%), hypertension (12.6% vs 9.4%), diarrhea (6.92% vs 12.5%), vomiting (4.4% vs 6.88%), leukopenia (3.1% vs 8.8%), and neutrophil count decreased (3.8% vs 6.3%). No patients had an AE of FN with trilaciclib vs 8 (5.0%) patients with placebo. The percentage of patients with grade 3/4 neutropenia, diarrhea, and leukopenia was $\geq 5\%$ lower with trilaciclib vs placebo. Grade 3 neurotoxicity was reported in 1 (0.6%) patient in the trilaciclib group and 2 (1.3%) patients in the placebo group; 1 (0.6%) patient in the

trilaciclib group and 3 (1.9%) patients in the placebo group discontinued treatment due to neurotoxicity.

Treatment (trilaciclib or placebo)-related AEs (TRAEs) were reported in 212 (66.5%) patients overall, including 109 (68.6%) in the trilaciclib group and 103 (64.4%) in the placebo group. The most common TRAEs reported in $\geq 10\%$ of patients overall were nausea (27.0% with trilaciclib vs 25.0% with placebo), fatigue (13.2% vs 14.4%), diarrhea (10.7% vs 20.0%), neutropenia (10.7% vs 14.4%), and vomiting (10.1% vs 10.0%). The incidence of TRAEs

Table 1. Baseline demographic and clinical characteristics for the mITT population (N = 296).

	Trilaciclib prior to FOLFOXIRI/bevacizumab (n = 149)	Placebo prior to FOLFOXIRI/bevacizumab (n = 147)
Age, y		
Median (range)	58 (26-81)	55 (30-79)
<65, n (%)	108 (72.5)	115 (78.2)
≥65, n (%)	41 (27.5)	32 (21.8)
Sex, n (%)		
Female	55 (36.9)	56 (38.1)
Male	94 (63.1)	91 (61.9)
Race, n (%)		
White	104 (69.8)	97 (66.0)
Black or African American	4 (2.7)	9 (6.1)
Asian	32 (21.5)	33 (22.4)
Other	3 (2.0)	0
Not reported	6 (4.0)	8 (5.4)
Region, n (%)		
United States	61 (40.9)	64 (43.5)
Europe	62 (41.6)	56 (38.1)
China	26 (17.4)	27 (18.4)
ECOG PS, n (%)		
0	70 (47.0)	70 (47.6)
1	73 (49.0)	75 (51.0)
Site of primary tumor, n (%)		
Colon	105 (70.5)	108 (73.5)
Rectum	44 (29.5)	39 (26.5)
Primary tumor site laterality, n (%)		
Left	43 (28.9)	42 (28.6)
Right	35 (23.5)	39 (26.5)
BRAF V600E mutation, n (%)	10 (6.7)	8 (5.4)
KRAS mutation, n (%)	63 (42.3)	69 (46.9)
Prior adjuvant or neoadjuvant systemic therapy, n (%)	28 (18.8)	30 (20.4)

Abbreviations: ECOG PS = Eastern Cooperative Oncology Group performance status; FOLFOXIRI = folinic acid, 5-fluorouracil, oxaliplatin, and irinotecan; (m)ITT = (modified) intention-to-treat.

was similar between the trilaciclib and placebo groups except for diarrhea, which was lower with trilaciclib than with placebo (10.7% vs 20.0%). Injection-site and infusion-related reactions were reported in 4 (2.5%) and 6 (3.8%) vs 0 and 4 (2.5%) patients with trilaciclib vs placebo, respectively.

Grade 3/4 TRAEs were observed in 56 (17.6%) patients overall, most commonly neutropenia (in 16 [5.0%] patients). The percentage of patients with grade 3/4 TRAEs was similar between the trilaciclib and placebo groups (17.6% vs 17.5%, respectively), except for neutropenia, which was lower in the trilaciclib group than the placebo group (2.5% vs 7.5%, respectively).

Serious AEs were reported in 94 (29.5%) patients overall, including 47 (29.6%) in the trilaciclib group and 47 (29.4%) in the placebo group. AEs leading to death were observed in 8 (5.0%) patients in the trilaciclib group (acute respiratory failure [n = 1], pulmonary thrombosis [n = 1], respiratory failure [n = 1], intestinal sepsis [n = 1], hypertension [n = 1], gastrointestinal obstruction [n = 1], general disorders and administration-site conditions [n = 1], and psychiatric disorder [n = 1]) and 3 (1.9%) patients in the placebo group (acute respiratory failure [n = 1], COVID-19 [n = 1], and syncope [n = 1]). The primary reason for death was progressive disease.

Antitumor efficacy

Among patients evaluable for response (trilaciclib, n = 137; placebo, n = 140), the confirmed ORR (95% CI) was 41.6% (33.3% to 50.3%) in the trilaciclib group vs 57.1% (48.5% to 65.5%) in the

placebo group (adjusted proportion difference [trilaciclib—placebo] [95% CI] = −0.156 [−0.274 to −0.038]; P = .009) (Table S2). The confirmed disease control rate (95% CI) was similar in the trilaciclib and placebo groups (90.5% [84.3% to 94.9%] vs 92.9% [87.3% to 96.5%], respectively; adjusted proportion difference [trilaciclib—placebo] [95% CI] = −0.022 [−0.087 to 0.044]; P = .517). The median (95% CI) duration of confirmed response was 9.1 (7.9 to 10.2) months in the trilaciclib group vs 12.7 (9.5, not estimable [NE]) months in the placebo group.

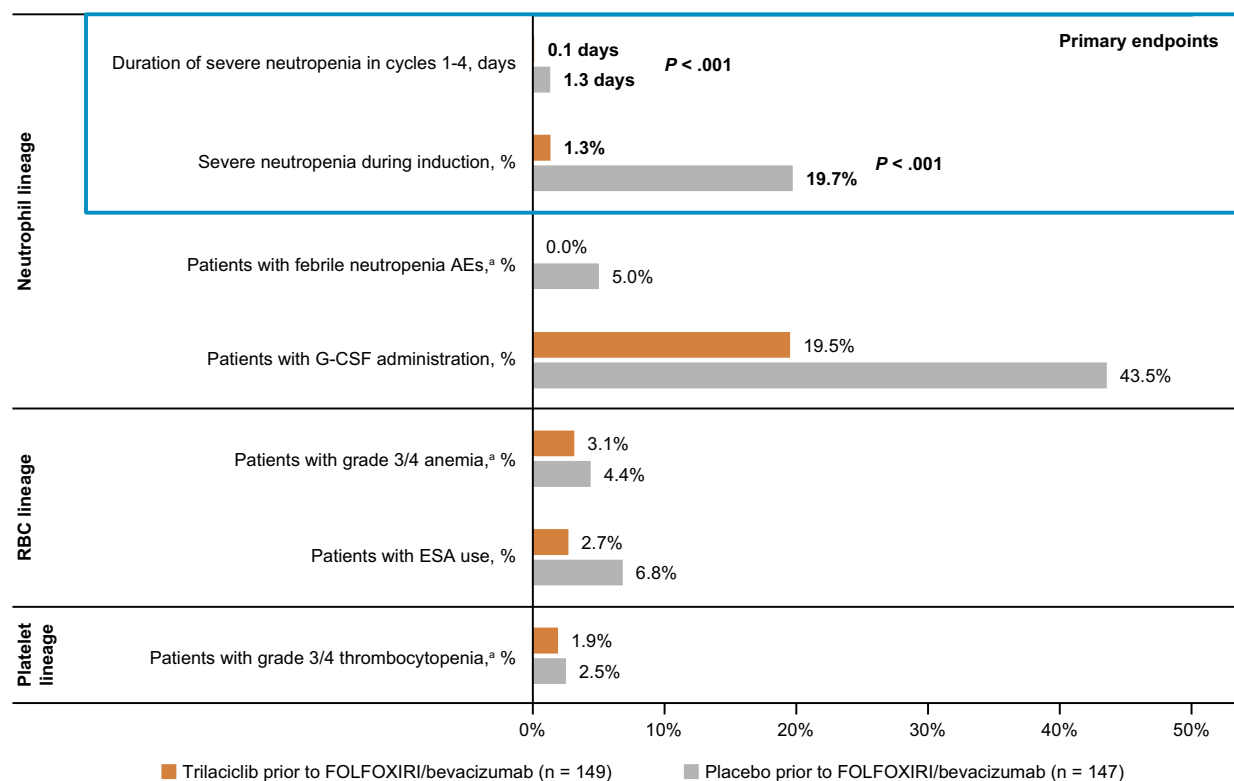
Median (range) PFS was 10.3 (8.6–11.0) months in the trilaciclib group vs 13.1 (11.0–18.5) months in the placebo group (hazard ratio = 1.94 [95% CI = 1.34 to 2.79]; P < .001; with separation of the curves after approximately 6 months/start of maintenance; Figure 3). Of PFS events in the trilaciclib group, 54 and 18 were events of disease progression and death without disease progression, respectively, compared with 45 and 7 with placebo. The planned OS analysis was not performed because the number of survival events did not meet the prespecified threshold when the trial was discontinued.

Discussion

This was the first clinical evaluation of trilaciclib in conjunction with fluorouracil-based chemotherapy. Results from this study showed that administering trilaciclib prior to FOLFOXIRI/bevacizumab was associated with significant reductions in DSN in cycles 1-4 and occurrence of SN during induction vs administering placebo, suggesting that trilaciclib is effective in protecting the neutrophil lineage from the effects of chemotherapy-induced myelosuppression. However, despite this study achieving its primary and other myeloprotection and safety endpoints, early survival indicators, including the confirmed ORR and PFS, did not favor trilaciclib over placebo.

The mechanism by which trilaciclib may attenuate the anti-tumor activity of FOLFOXIRI is not fully understood. One potential explanation is the presence of a drug-drug interaction whereby trilaciclib may inhibit transport proteins responsible for intracellular 5-fluorouracil accumulation. Differences in immunogenicity within the tumor microenvironment of various tumor types may also be worthy of consideration. Preclinical studies have shown that trilaciclib enhances T-cell activation and T-cell function, strengthening antitumor immunity.^{22,23} Although the “immune-cold” nature of pMMR/MSS mCRC tumors could explain a lack of antitumor efficacy in this patient population,²⁴ it does not account for the low antitumor response rates observed in this study. Additional mechanistic studies to help understand the observed attenuated antitumor efficacy with trilaciclib are required.

The antitumor efficacy results are inconsistent with those observed with trilaciclib when administered with different chemotherapy backbones and other tumor types. Clinical evidence to date in patients with ES-SCLC has not shown detriment to chemotherapy efficacy or adverse survival signals with the addition of trilaciclib to standard platinum/etoposide- or topotecan-containing chemotherapy regimens,^{16-18,25} and in a randomized phase 2 trial in patients with metastatic triple-negative breast cancer (TNBC), administering trilaciclib prior to gemcitabine plus carboplatin (Gcb) significantly improved OS vs Gcb alone (median 19.8 vs 12.6 months, respectively).^{25,26} The reasons for this improvement in survival among patients with TNBC are not yet fully understood; however, preclinical and clinical findings suggest that trilaciclib may protect immune cells from chemotherapy-induced damage and modulate the composition and response of



^aSafety population: trilaciclib, n = 159; placebo, n = 160.

AE = adverse event; ESA = erythropoiesis-stimulating agent; FOLFOXIRI = folinic acid, 5-fluorouracil, oxaliplatin and irinotecan; G-CSF = granulocyte colony-stimulating factor; RBC = red blood cell.

Figure 2. Summary of myeloprotection endpoints.

immune cell subsets to enhance the efficacy of GCB.^{23,25-27} In addition, the ORR for the placebo arm in our study (FOLFOXIRI/bevacizumab) is numerically lower than that observed in studies evaluating the same regimen (57% vs 65%, respectively)⁶; however, the reasons underlying this discrepancy are unclear.

Across our study, safety outcomes were consistent with previous clinical trial experience with trilaciclib. Toxicities were generally consistent with those of the chemotherapy regimen, and trilaciclib-related AEs were adequately managed and primarily low-grade and self-limiting.^{16-18,25}

Results from a pooled analysis of 8 randomized controlled studies in mCRC suggest that first-line FOLFOXIRI is associated with improvements in efficacy outcomes compared with FOLFOX or FOLFIRI, but risk of grade ≥ 3 AEs is increased, including neurotoxicity, neutropenia, and diarrhea, and AE-related treatment withdrawal.²⁸ In the current study, trilaciclib administration reduced the incidence of diarrhea, stomatitis, neutropenia, and epistaxis vs the placebo group. Additionally, fewer patients in the trilaciclib group experienced grade 3/4 AEs and chemotherapy dose reductions or delays vs those receiving placebo, suggesting that the addition of trilaciclib may enable patients to remain on the standard-of-care dose and schedule of FOLFOXIRI/bevacizumab.

Furthermore, since trilaciclib was associated with fewer supportive-care interventions, including ESA or G-CSF administration, vs placebo, adding trilaciclib may reduce the risks associated with supportive care (including prophylactic G-CSF administration) and reduce financial burden for patients and healthcare systems. Also of note, a retrospective cohort study showed that FN incidence in intermediate- to high-risk patients with metastatic cancer who did not receive G-CSF prophylaxis in cycle 1 was $\sim 16\%$,²⁹ which is close to the $\geq 20\%$ threshold at which

primary prophylactic G-CSF is recommended.³⁰ In our study, the incidence of FN was very low, supporting the reduced need for prophylactic G-CSF; however, careful interpretation is warranted given the reported lack of antitumor efficacy in our study.

Data from ongoing or recently completed clinical trials in patients with TNBC and bladder cancer will help inform the potential myeloprotection, antitumor efficacy, and safety of trilaciclib in combination with cytotoxic therapies and other anti-cancer agents. Active clinical trials with trilaciclib include a phase 3 trial of trilaciclib vs placebo prior to GCB in patients with locally advanced unresectable or metastatic TNBC (PRESERVE 2; NCT04799249); a phase 2 trial of trilaciclib prior to sacituzumab govitecan in pretreated patients with metastatic TNBC (NCT05113966); and a phase 2, randomized study of trilaciclib prior to first-line platinum-based chemotherapy and avelumab maintenance therapy in patients with untreated metastatic urothelial carcinoma (PRESERVE 3; NCT04887831).

Acknowledgments

The authors thank and acknowledge all the patients, their families, and clinical study site personnel for participating in the study. Medical writing assistance was provided by Philip Reardon, PhD, of Envision Pharma Group, funded by G1 Therapeutics, Inc.

Author contributions

Heinz-Josef Lenz, MD (Conceptualization; Investigation; Writing—review & editing), Tianshu Liu, MD (Investigation; Writing—review & editing), Emerson Y. Chen, MD (Investigation;

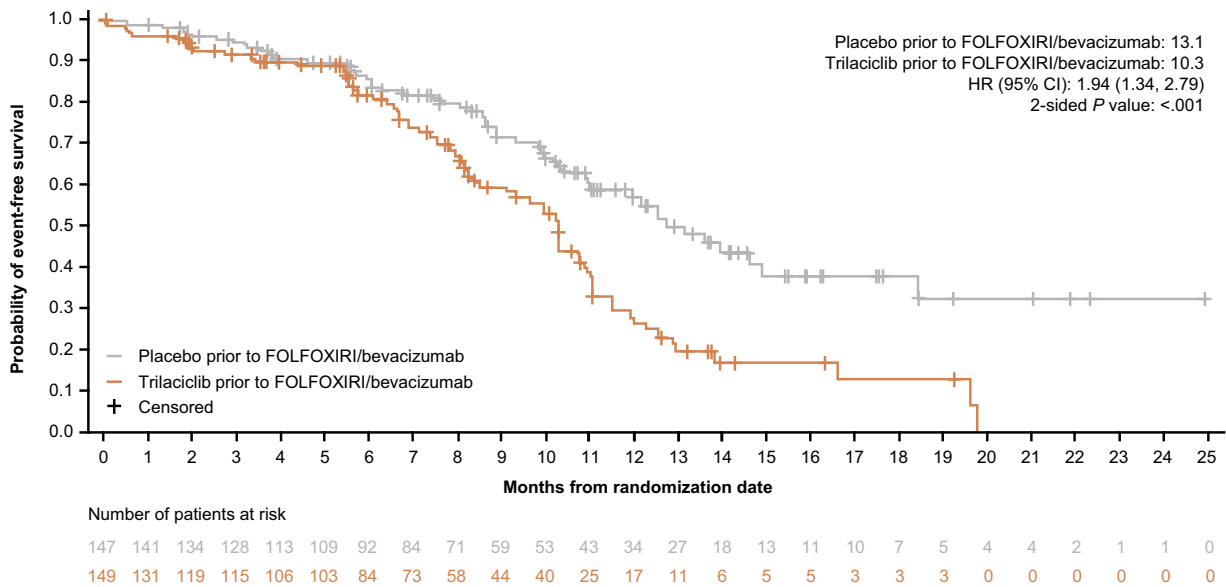
Table 2. Summary of adverse events occurring in ≥10% of all patients (safety population).

	Trilaciclib prior to FOLFOXIRI/bevacizumab (n = 159)			Placebo FOLFOXIRI/bevacizumab (n = 160)		
	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4
Any AE, n (%)	157 (98.7)	93 (58.8)	8 (5.03)	159 (99.4)	81 (50.6)	32 (20.0)
Hematological AE, n (%)^a						
Neutropenia	61 (38.4)	26 (16.4)	2 (1.26)	92 (57.5)	40 (25)	24 (15)
Anemia	57 (35.8)	5 (3.14)	0	61 (38.1)	7 (4.38)	0
Thrombocytopenia	34 (21.4)	2 (1.26)	2 (1.26)	36 (22.5)	4 (2.50)	0
Leukopenia	27 (17.0)	5 (3.14)	0	5 (9.4)	11 (6.88)	3 (1.88)
Nonhematological AE, n (%)^a						
Nausea	86 (54.1)	5 (3.14)	0	101 (63.1)	3 (1.88)	0
Diarrhea	83 (52.2)	11 (6.92)	0	118 (73.8)	19 (11.9)	1 (0.63)
Fatigue	54 (34.0)	7 (4.40)	0	52 (32.5)	7 (4.40)	0
Vomiting	53 (33.3)	7 (4.40)	0	65 (40.6)	11 (6.88)	0
Constipation	39 (24.5)	3 (1.89)	0	29 (18.1)	3 (5.7)	0
Peripheral sensory neuropathy	37 (23.3)	3 (1.89)	3 (1.89)	34 (21.3)	13 (8.13)	0
Neuropathy peripheral	36 (22.6)	13 (8.18)	0	26 (16.3)	1 (0.63)	0
Decreased appetite	36 (22.6)	1 (1.9)	0	39 (24.4)	0	0
Hypertension	35 (22.0)	20 (12.6)	0	35 (21.9)	14 (8.75)	1 (0.63)
Abdominal pain	34 (21.4)	3 (1.89)	0	37 (23.1)	4 (2.50)	0
Headache	32 (20.1)	0	0	26 (16.3)	0	0
Asthenia	28 (17.6)	5 (3.14)	0	28 (17.5)	3 (1.88)	0
Stomatitis	25 (15.7)	9 (5.66)	0	42 (26.3)	18 (11.3)	4 (2.50)
Alopecia	23 (14.5)	0	0	25 (15.6)	0	0
Hypokalemia	21 (13.2)	21 (13.2)	1 (0.63)	21 (13.1)	4 (2.50)	0
Paresthesia	20 (12.6)	0	0	15 (9.38)	0	0
Weight decreased	20 (12.6)	0	0	29 (18.1)	11 (6.88)	3 (1.88)
ALT increased	20 (12.6)	1 (0.63)	1 (0.63)	24 (15.0)	1 (0.63)	0
AST increased	20 (12.6)	1 (0.63)	0	24 (15.0)	1 (0.63)	0
Muscle spasms	20 (12.6)	0	0	9 (5.63)	0	0
COVID-19	19 (11.9)	21 (13.2)	0	22 (13.8)	1 (0.63)	0
Proteinuria	19 (11.9)	3 (1.89)	0	25 (15.6)	0	0
Pyrexia	17 (10.7)	1 (0.63)	0	25 (15.6)	0	0
Mucosal inflammation	17 (10.7)	1 (0.63)	0	18 (11.3)	2 (1.25)	0
Dizziness	14 (8.81)	0	0	25 (15.6)	0	0
Epistaxis	7 (4.4)	1 (0.63)	0	28 (17.5)	2 (1.25)	0

Data represent any-grade AEs occurring in ≥10% of patients in either trilaciclib or placebo groups.

^a AEs are presented by MedDRA Version 24.1 Preferred Term.

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; FOLFOXIRI = folinic acid, 5-fluorouracil, oxaliplatin, and irinotecan; MedDRA = Medical Dictionary for Regulatory Activities.



CI = confidence interval; FOLFOXIRI = folinic acid, 5-fluorouracil, oxaliplatin and irinotecan; HR = hazard ratio.

Figure 3. Kaplan-Meier curve for PFS of the mITT population.

Writing—review & editing), Zsolt Horváth, MD, PhD (Investigation; Writing—review & editing), Igor Bondarenko, MD, PhD (Investigation; Writing—review & editing), Iwona Danielewicz, MD (Investigation; Writing—review & editing), Michele Ghidini, MD, PhD (Investigation; Writing—review & editing), Pilar García-Alfonso, MD, PhD (Investigation; Writing—review & editing), Robert Jones, PhD, MD (Investigation; Writing—review & editing), Matti Aapro, MD (Conceptualization; Data curation; Investigation; Writing—review & editing), Yanqiao Zhang, MD (Investigation; Writing—review & editing), Jufeng Wang, MD (Investigation; Writing—review & editing), Wayne Wang, PhD (Conceptualization; Formal analysis; Methodology; Writing—review & editing), Jennifer Adeleye, PhD (Conceptualization; Data curation; Formal analysis; Methodology; Writing—review & editing), Andrew Beelen, M.D. (Conceptualization; Data curation; Formal analysis; Methodology; Writing—review & editing), and Joleen Hubbard, MD (Conceptualization; Data curation; Investigation; Writing—review & editing).

Supplementary material

Supplementary material is available at JNCI Cancer Spectrum online.

Funding

This work was supported by G1 Therapeutics, Inc.

Conflicts of interest

Wayne Wang, Jennifer Adeleye, and Andrew Beelen are current or former paid employees of G1 Therapeutics, Inc. Andrew Beelen holds the following patents: US 2019/0374545 A1, US 2021/0030758 A1, and WO 2022/125829 A1. Jennifer Adeleye is a stockholder in G1 Therapeutics, Inc. Michele Ghidini reports payment or honoraria for presentations and lectures from Eli Lilly, Amgen, Roche, Italfarmaco, Servier, and Pfizer. Heinz-Josef Lenz reports institutional funding from NCI Moonshot U2C and NCI UG1, UM1 grants, has received consulting fees from Merck KG, Bayer, Merck, Isofol, Oncocyte, Invitae, Affini-T, 3T Biosciences, Repimmune, G1 Therapeutics, Inc., Jazz Therapeutics, Adagene, and Fulgent, was supported to attend ASCO by BMS, has served on the data safety monitoring/advisory board for Veloxis, and is a stockholder in Biobreak and Fulgent. Igor Bondarenko and Tianshu Liu declare no conflicts of interest.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

References

- Cervantes A, Adam R, Roselló S, et al. ESMO Guidelines Committee. Electronic address: clinicalguidelines@esmo.org. Metastatic colorectal cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Ann Oncol*. 2023;34:10-32. <https://doi.org/10.1016/j.annonc.2022.10.003>
- Morris VK, Kennedy EB, Baxter NN, et al. Treatment of metastatic colorectal cancer: ASCO guideline. *J Clin Oncol*. 2023;41:678-700. <https://doi.org/10.1200/JCO.22.01690>
- San-Román-Gil M, Torres-Jiménez J, Pozas J, et al. Current landscape and potential challenges of immune checkpoint inhibitors in microsatellite stable metastatic colorectal carcinoma. *Cancers (Basel)*. 2023;15:863. <https://doi.org/10.3390/cancers15030863>
- Falcone A, Ricci S, Brunetti I, et al.; Gruppo Oncologico Nord Ovest. Phase III trial of infusional fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) compared with infusional fluorouracil, leucovorin, and irinotecan (FOLFIRI) as first-line treatment for metastatic colorectal cancer: the Gruppo Oncologico Nord Ovest. *J Clin Oncol*. 2007;25:1670-1676. <https://doi.org/10.1200/JCO.2006.09.0928>
- Cremolini C, Loupakis F, Antoniotti C, et al. FOLFOXIRI plus bevacizumab versus FOLFIRI plus bevacizumab as first-line treatment of patients with metastatic colorectal cancer: updated overall survival and molecular subgroup analyses of the open-label, phase 3 TRIBE study. *Lancet Oncol*. 2015;16:1306-1315. [https://doi.org/10.1016/S1470-2045\(15\)00122-9](https://doi.org/10.1016/S1470-2045(15)00122-9)
- Loupakis F, Cremolini C, Masi G, et al. Initial therapy with FOLFOXIRI and bevacizumab for metastatic colorectal cancer. *N Engl J Med*. 2014;371:1609-1618. <https://doi.org/10.1056/NEJMoa1403108>
- Montagnani F, Chiriatti A, Turrisi G, Francini G, Fiorentini G. A systematic review of FOLFOXIRI chemotherapy for the first-line treatment of metastatic colorectal cancer: improved efficacy at the cost of increased toxicity. *Colorectal Dis*. 2011;13:846-852. <https://doi.org/10.1111/j.1463-1318.2010.02206.x>
- Sastre J, Vieitez JM, Gomez-España MA, et al; Spanish Cooperative Group for the Treatment of Digestive Tumors (TTD). Randomized phase III study comparing FOLFOX + bevacizumab versus folfoxiri + bevacizumab (BEV) as 1st line treatment in patients with metastatic colorectal cancer (mCRC) with ≥ 3 baseline circulating tumor cells (bCTCs). *J Clin Oncol*. 2019;37:3507.
- Lyman GH, Kuderer NM, Aapro M. Improving outcomes of chemotherapy: established and novel options for myeloprotection in the COVID-19 era. *Front Oncol*. 2021;11:697908. <https://doi.org/10.3389/fonc.2021.697908>
- Epstein RS, Aapro MS, Basu Roy UK, et al. Patient burden and real-world management of chemotherapy-induced myelosuppression: results from an online survey of patients with solid tumors. *Adv Ther*. 2020;37:3606-3618. <https://doi.org/10.1007/s12325-020-01419-6>
- Epstein RS, Basu Roy UK, Aapro M, et al. Cancer patients' perspectives and experiences of chemotherapy-induced myelosuppression and its impact on daily life. *Patient Prefer Adherence*. 2021;15:453-465. <https://doi.org/10.2147/PPA.S292462>
- Karagiannidis I, Salataj E, Said Abu Egal E, Beswick EJ. G-CSF in tumors: aggressiveness, tumor microenvironment and immune cell regulation. *Cytokine*. 2021;142:155479. <https://doi.org/10.1016/j.cyto.2021.155479>
- He S, Roberts PJ, Sorrentino JA, et al. Transient CDK4/6 inhibition protects hematopoietic stem cells from chemotherapy-induced exhaustion. *Sci Transl Med*. 2017;9:eaal3986. <https://doi.org/10.1126/scitranslmed.aal3986>
- Bisi JE, Sorrentino JA, Roberts PJ, Tavares FX, Strum JC. Preclinical characterization of G1T28: a novel CDK4/6 inhibitor for reduction of chemotherapy-induced myelosuppression. *Mol Cancer Ther*. 2016;15:783-793. <https://doi.org/10.1158/1535-7163.MCT-15-0775>
- COSELA® (trilaciclib) Prescribing Information. G1 Therapeutics, Inc.; 2023.
- Daniel D, Kuchava V, Bondarenko I, et al. Trilaciclib prior to chemotherapy and atezolizumab in patients with newly diagnosed

- extensive-stage small cell lung cancer: a multicentre, randomised, double-blind, placebo-controlled Phase II trial. *Int J Cancer*. 2021;148:2557-2570. <https://doi.org/10.1002/ijc.33453>
17. Hart LL, Ferrarotto R, Andric ZG, et al. Myelopreservation with trilaciclib in patients receiving topotecan for small cell lung cancer: results from a randomized, double-blind, placebo-controlled Phase II study. *Adv Ther*. 2021;38:350-365. <https://doi.org/10.1007/s12325-020-01538-0>
 18. Weiss JM, Csozsi T, Maglakelidze M, et al.; G1T28-02 Study Group. Myelopreservation with the CDK4/6 inhibitor trilaciclib in patients with small-cell lung cancer receiving first-line chemotherapy: a phase Ib/randomized phase II trial. *Ann Oncol*. 2019;30:1613-1621. <https://doi.org/10.1093/annonc/mdz278>
 19. Trilaciclib, a CDK 4/6 inhibitor, in patients receiving FOLFOXIRI/bevacizumab for metastatic colorectal cancer (mCRC): (PRESERVE1). ClinicalTrials.gov identifier: NCT04607668. <https://www.clinicaltrials.gov/study/NCT04607668>
 20. Gustinetti G, Mikulska M. Bloodstream infections in neutropenic cancer patients: a practical update. *Virulence*. 2016;7:280-297. <https://doi.org/10.1080/21505594.2016.1156821>
 21. Li Y, Klippel Z, Shih X, Reiner M, Wang H, Page JH. Relationship between severity and duration of chemotherapy-induced neutropenia and risk of infection among patients with nonmyeloid malignancies. *Support Care Cancer*. 2016;24:4377-4383. <https://doi.org/10.1007/s00520-016-3277-0>
 22. Deng J, Wang ES, Jenkins RW, et al. CDK4/6 inhibition augments antitumor immunity by enhancing T-cell activation. *Cancer Discov*. 2018;8:216-233. <https://doi.org/10.1158/2159-8290.CD-17-0915>
 23. Lai AY, Sorrentino JA, Dragnev KH, et al. CDK4/6 inhibition enhances antitumor efficacy of chemotherapy and immune checkpoint inhibitor combinations in preclinical models and enhances T-cell activation in patients with SCLC receiving chemotherapy. *J Immunother Cancer*. 2020;8:e000847. <https://doi.org/10.1136/jitc-2020-000847>
 24. Huyghe N, Baldin P, Van den Eynde M. Immunotherapy with immune checkpoint inhibitors in colorectal cancer: what is the future beyond deficient mismatch-repair tumours? *Gastroenterol Rep (Oxf)*. 2020;8:11-24. <https://doi.org/10.1093/gastro/goz061>
 25. Tan AR, Wright GS, Thummala AR, et al. Trilaciclib plus chemotherapy versus chemotherapy alone in patients with metastatic triple-negative breast cancer: a multicentre, randomised, open-label, phase 2 trial. *Lancet Oncol*. 2019;20:1587-1601. [https://doi.org/10.1016/S1470-2045\(19\)30616-3](https://doi.org/10.1016/S1470-2045(19)30616-3)
 26. Tan AR, Wright GS, Thummala AR, et al. Trilaciclib prior to chemotherapy in patients with metastatic triple-negative breast cancer: final efficacy and subgroup analysis from a randomized phase II study. *Clin Cancer Res*. 2022;28:629-636. <https://doi.org/10.1158/1078-0432.CCR-21-2272>
 27. Tan AR, O'Shaughnessy J, Cao S, Ahn S, Yi JS. Investigating potential immune mechanisms of trilaciclib administered prior to chemotherapy in patients with metastatic triple-negative breast cancer. *Breast Cancer Res Treat*. 2023;201:307-316. <https://doi.org/10.1007/s10549-023-07009-8>
 28. Marques RP, Duarte GS, Sterrantino C, et al. Triplet (FOLFOXIRI) versus doublet (FOLFOX or FOLFIRI) backbone chemotherapy as first-line treatment of metastatic colorectal cancer: a systematic review and meta-analysis. *Crit Rev Oncol Hematol*. 2017;118:54-62. <https://doi.org/10.1016/j.critrevonc.2017.08.006>
 29. Averin A, Silvia A, Lamerato L, et al. Risk of chemotherapy-induced febrile neutropenia in patients with metastatic cancer not receiving granulocyte colony-stimulating factor prophylaxis in US clinical practice. *Support Care Cancer*. 2021;29:2179-2186. <https://doi.org/10.1007/s00520-020-05715-3>
 30. Crawford J, Becker PS, Armitage JO, et al. Myeloid growth factors, version 2.2017, NCCN clinical practice guidelines in oncology. *J Natl Compr Canc Netw*. 2017;15:1520-1541. <https://doi.org/10.6004/jnccn.2017.0175>

© The Author(s) 2024. Published by Oxford University Press.

This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs licence (<https://creativecommons.org/licenses/by-nc-nd/4.0/>), which permits non-commercial reproduction and distribution of the work, in any medium, provided the original work is not altered or transformed in any way, and that the work is properly cited. For commercial re-use, please contact journals.permissions@oup.com

JNCI Cancer Spectrum, 2024, 9, 1–9
<https://doi.org/10.1093/jncics/pkae116>
 Article