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

Authors: Heinz-Josef Lenz, MD,[1] Tianshu Liu, MD,[2] Emerson Y. Chen, MD,[3] Zsolt Horváth, MD, PhD,[4] Igor Bondarenko, MD, PhD,[5] Iwona Danielewicz, MD,[6] Michele Ghidini, MD, PhD,[7] Pilar García-Alfonso, MD, PhD,[8] Robert Jones, PhD, MA,[9] Matti Aapro, MD,[10] Yanqiao Zhang, MD,[11] Jufeng Wang, MD,[12] Wayne Wang, PhD,[13] Jennifer Adeleye, PhD,[13†] Andrew Beelen, MD,[13*‡] Joleen Hubbard, MD[14]

Affiliations

[1]Department of Medicine, Keck School of Medicine, University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA, USA.

[2]Department of Medical Oncology, Zhongshan Hospital, Fudan University, Shanghai, China.

[3]Oregon Health & Science University, Department of Medicine, Division of Hematology and Medical Oncology, Knight Cancer Institute, Portland, OR, USA.

[4]Center of Oncoradiology, Bács-Kiskun County Teaching Hospital, Kecskemét, Hungary.

[5]Dnipropetrovsk State Medical Academy, City Multifield Clinical Hospital, Dnipropetrovsk, Ukraine.

[6]Szpitale Pomorskie Sp. z o.o. Gdynia, Poland.

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

[8]Hospital General Universitario Gregorio Marañón, Instituto de Investigación Sanitaria (IiSGM), Universidad Complutense de Madrid, Madrid, Spain.

[9]Cardiff University and Velindre NHS Trust, Cardiff, UK.

[10]Genolier Cancer Centre, Clinique de Genolier, Genolier, Switzerland.

[11]Harbin Medical University Cancer Hospital, Nangang, Harbin, Heilongjiang, China.

[12]Department of Medical Oncology, Affiliated Cancer Hospital of Zhengzhou University, Henan Cancer Hospital, Zhengzhou, China.

[13]G1 Therapeutics, Inc., Research Triangle Park, NC, USA.

[14]Allina Health Cancer Institute, Abbott Northwestern Hospital, Minneapolis, MN, USA.

*Correspondence to: Andrew Beelen, MD, Incyclix Bio, 600 Park Offices Dr., Suite 355, Research

Triangle Park, NC 27709, USA (email: andrew.beelen@gmail.com).

[†]Present affiliation: Daiichi Sankyo, Inc., Basking Ridge, NJ, USA.

[‡]Present affiliation: Incyclix Bio, Research Triangle Park, NC, USA.

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 randomized 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 versus 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, 0.3]; $P < .001$). Grade 3/4 adverse events, including neutropenia, diarrhea, and leukopenia, were less frequent with trilaciclib versus placebo (64.8% vs. 73.1%). Trilaciclib was associated with fewer chemotherapy dose reductions and delays, and 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 versus 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: NCT04607668

Keywords: trilaciclib, bevacizumab, colorectal cancer, FOLFOXIRI, metastatic, myeloprotection,

myelosuppression

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Multiagent 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 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) versus 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 impact 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

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warranted as 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 three 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 (NCT04607668 (19)) 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.

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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 randomized 1:1 by an interactive web-response system to receive trilaciclib or placebo prior to FOLOFXIRI/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 FOLOXIRI/bevacizumab in 14-day cycles for a maximum of 12 cycles. Irinotecan 165 mg/m^2, oxaliplatin 85 mg/m^2, leucovorin 400 mg/m^2 (or 200 mg/m^2 levoleucovorin), and bevacizumab 5 mg/kg were all administered IV on day 1. Fluorouracil 2400-3200 mg/m^2 (dosage per clinician discretion) was administered IV as a continuous infusion over 46-48 hours beginning on day 1. Trilaciclib 240 mg/m^2 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

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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 versus 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 as 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 as 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 (US, 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 randomized 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 randomized patients. To account for potential data integrity issues resulting from the war in Ukraine, a modified (m)ITT population was utilized as the primary analysis population for all efficacy evaluations, which included all patients randomized in countries other than Ukraine and all patients in Ukraine who were randomized before September 9, 2021. The safety population included all randomized 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 randomized 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 post 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 randomized to the trilaciclib (n = 164) or placebo (n = 162) group (**Figure 1**). Of these, 319 (98%) patients received ≥1 dose of study drug (safety population) and 296 patients were included in the mITT population. Following study termination, all patients discontinued study drug and study participation.

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

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Myeloprotection efficacy

In the mITT population, trilaciclib administered prior to FOLFOXIRI/bevacizumab significantly reduced chemotherapy-induced neutropenia versus placebo (**Figure 2**). Mean (standard deviation) DSN in cycles 1-4 was 0.1 (0.8) days with trilaciclib versus 1.3 (3.1) days with placebo (mean [96% CI] difference, −1.2 [−1.7, −0.6] days; *P* < .001). SN during induction was reported in 2 (1.3%) versus 29 (19.7%) patients treated with trilaciclib versus placebo, respectively (adjusted relative risk [96% CI], 0.07 [0.0, 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%) versus 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, 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 versus 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 ≥10% lower with trilaciclib versus placebo. Grade 3/4 AEs were reported in 103 (64.8%) patients in the trilaciclib group versus 117 (73.1%) in the 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

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trilaciclib versus 8 (5.0%) patients with placebo. The percentage of patients with grade 3/4 neutropenia, diarrhea, and leukopenia was ≥5% lower with trilaciclib versus 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 ≥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 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%) versus 0 and 4 (2.5%) patients with trilaciclib versus 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%, 50.3%) in the trilaciclib group versus 57.1% (48.5%, 65.5%) in the placebo group (adjusted proportion difference [trilaciclib – placebo] [95% CI], -0.156 [-0.274, -0.038]; *P* = .009) (**Supplementary Table 2)**. The confirmed disease control rate (95% CI) was similar in the trilaciclib and placebo groups (90.5% [84.3%, 94.9%] vs. 92.9% [87.3%, 96.5%], respectively; adjusted proportion difference [trilaciclib – placebo] [95% CI], -0.022 [-0.087, 0.044]; *P* = .517). The median (95% CI) duration of confirmed response was 9.1 (7.9, 10.2) months in the trilaciclib group versus 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 versus 13.1 (11.0-18.5) months in the placebo group (hazard ratio, 1.94 [95% CI: 1.34, 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 as 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 versus 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.

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The mechanism by which trilaciclib may attenuate the antitumor 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 versus 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 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.

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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 versus the placebo group. Additionally,

fewer patients in the trilaciclib group experienced grade 3/4 AEs and chemotherapy dose reductions

or delays versus 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, versus placebo, adding trilaciclib may reduce the risks associated with

supportive-care (including prophylactic G-CSF administration) and reduce financial burden for

patients and health care 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 ~16%,(29) which is close to the ≥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 anticancer agents. Active clinical trials with trilaciclib

include a phase 3 trial of trilaciclib versus placebo prior to GCb in patients with locally advanced

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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).

Data Sharing and Data Availability

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

Author Contributions

Matti Aapro, Joleen Hubbard, Andrew Beelen, and Jennifer Adeleye contributed to the design and implementation of the clinical research and to the acquisition of data. Wayne Wang, Jennifer Adeleye, and Andrew Beelen conceived and designed the analysis. All authors were responsible for the analysis and interpretation of results; provided critical feedback and helped shape the research, analysis, and development of the manuscript; and read and approved the final manuscript.

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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

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Figure Legends

Figure 1. Trial profile.

Figure 2. Summary of myeloprotection endpoints.

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

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Tables

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 (%)		
USA	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)

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

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

	Trilaciclib prior to FOLFOXIRI/bevacizumab (n = 159)			Placebo prior to 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)
Hematologic 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)
Nonhematologic 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.

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ᵃ AEs are presented by MedDRA Version 24.1 Preferred Term. AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; FOLFOXIRI = folinic acid, 5-fluorouracil, oxaliplatin and irinotecan; MedDRA = Medical Dictionary for Regulatory Activities.

Figure 1

Patients screened
(n = 458)

Eligibility criteria not met
(n = 132)

Patients randomized
(n = 326)

Randomized to trilaciclib arm
(intention-to-treat population;
n = 164)

Randomized to placebo arm
(intention-to-treat population;
n = 162)

Not treated
(n = 5)

Not treated
(n = 2)

Trilaciclib 240 mg/m^2 prior to
FOLFOXIRI/bevacizumab
(safety population; n = 159)

Placebo prior to
FOLFOXIRI/bevacizumab
(safety population; n = 160)

Study drug disposition
Ongoing (n = 0)
Discontinued (n = 159)
• Completed (n = 0)
• Adverse event (n = 18)
• Death (n = 4)
• Lost to follow-up (n = 1)
• Physician decision (n = 12)
• Disease progression (n = 65)
• Study terminated by sponsor (n = 17)
• Withdrawal of consent by patient (n = 21)
• Other (n = 21)

Study drug disposition
Ongoing (n = 0)
Discontinued (n = 160)
• Completed (n = 2)
• Adverse event (n = 12)
• Death (n = 1)
• Lost to follow-up (n = 1)
• Physician decision (n = 21)
• Disease progression (n = 45)
• Study terminated by sponsor (n = 41)
• Withdrawal of consent by patient (n = 15)
• Other (n = 22)

Study discontinuation
During induction (n = 19)
During maintenance (n = 24)
During survival follow-up (n = 116)
• Death (n = 49)
  ◦ Progressive disease (n = 34)
  ◦ Adverse event (n = 8)
  ◦ Other (n = 6)
  ◦ Unknown (n = 1)
• Lost to follow-up (n = 3)
• Study terminated by sponsor (n = 92)
• Withdrawal of consent by patient (n = 12)
• Other (n = 8)

Study discontinuation
During induction (n = 15)
During maintenance (n = 41)
During survival follow-up (n = 104)
• Death (n = 26)
  ◦ Progressive disease (n = 21)
  ◦ Adverse event (n = 3)
  ◦ Other (n = 2)
  ◦ Unknown (n = 0)
• Lost to follow-up (n = 4)
• Study terminated by sponsor (n = 114)
• Withdrawal of consent by patient (n = 11)
• Other (n = 7)

Modified intention-to-treat population
(n = 149)[a]

Modified intention-to-treat population
(n = 147)[a]

[a]Included 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.

Neutrophil lineage

Duration of severe neutropenia in cycles 1-4, days — **0.1 days** / 1.3 days — *P* < .001

Severe neutropenia during induction, % — **1.3%** / **19.7%** — *P* < .001

Patients with febrile neutropenia AEs,[a] % — 0.0% / 5.0%

Patients with G-CSF administration, % — 19.5% / 43.5%

RBC lineage

Patients with grade 3/4 anemia,[a] % — 3.1% / 4.4%

Patients with ESA use, % — 2.7% / 6.8%

Platelet lineage

Patients with grade 3/4 thrombocytopenia,[a] % — 1.9% / 2.5%

Primary endpoints

0% — 10% — 20% — 30% — 40% — 50%

■ Trilaciclib prior to FOLFOXIRI/bevacizumab (n = 149) ■ Placebo prior to FOLFOXIRI/bevacizumab (n = 147)

[a]Safety 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.

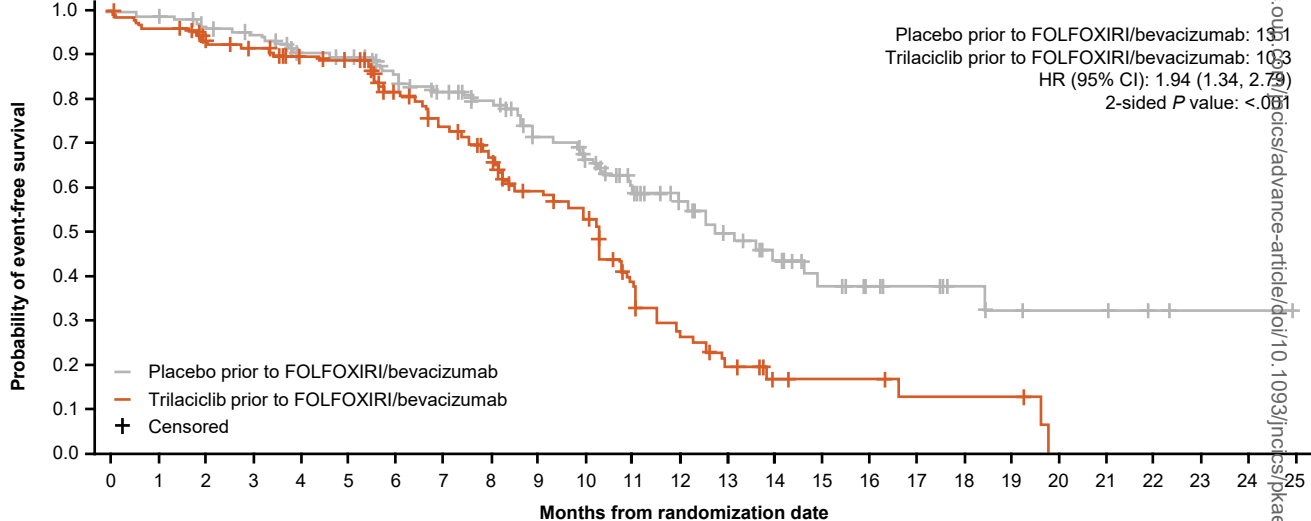Figure 3

Placebo prior to FOLFOXIRI/bevacizumab: 13.1
Trilaciclib prior to FOLFOXIRI/bevacizumab: 10.3
HR (95% CI): 1.94 (1.34, 2.79)
2-sided *P* value: <.001

Number of patients at risk

147	141	134	128	113	109	92	84	71	59	53	43	34	27	18	13	11	10	7	5	4	4	2	1	1	0
149	131	119	115	106	103	84	73	58	44	40	25	17	11	6	5	5	3	3	3	0	0	0	0	0	0

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