Clinical Trial Protocol

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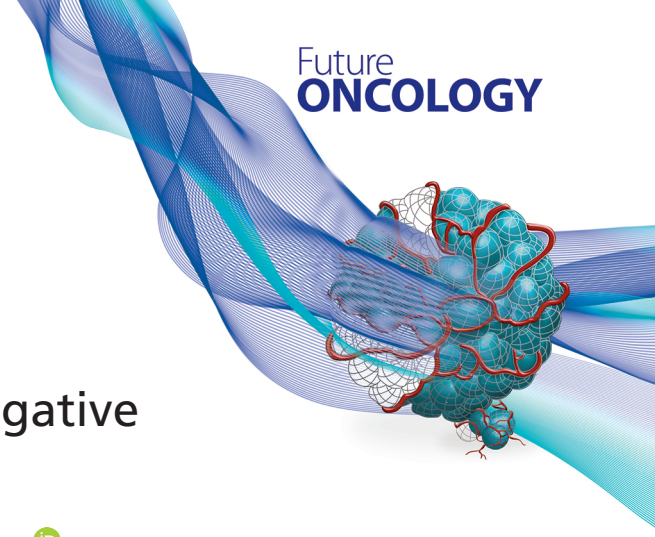

Trilaciclib prior to gemcitabine plus carboplatin for metastatic triple-negative breast cancer: phase III PRESERVE 2

Shom Goel*[,1], Antoinette R Tan[2], Hope S Rugo[3], Philippe Aftimos[4], Zoran Andrić[5], Andrew Beelen[6], Jingshan Zhang[6], John S Yi[6], Rajesh Malik[6] & Joyce O'Shaughnessy[7]

[1]Peter MacCallum Cancer Centre, Melbourne VIC 3000, Australia
[2]Levine Cancer Institute, Atrium Health, Charlotte, NC 28204, USA
[3]University of California San Francisco Comprehensive Cancer Center, San Francisco, CA 94158–1710, USA
[4]Institut Jules Bordet, Université Libre de Bruxelles, 1070 Brussels, Belgium
[5]Clinical Hospital Centre Bezanijska Kosa, 11080 Belgrade, Serbia
[6]G1 Therapeutics, Research Triangle Park, NC 27709, USA
[7]Baylor University Medical Center, Texas Oncology, US Oncology, Dallas, TX 75246, USA
*Author for correspondence: shom.goel@petermac.org

Triple-negative breast cancer (TNBC) is an aggressive malignancy for which cytotoxic chemotherapy remains the backbone of treatment. Trilaciclib is an intravenous cyclin-dependent kinase 4/6 inhibitor that induces transient cell cycle arrest of hematopoietic stem and progenitor cells and immune cells during chemotherapy exposure, protecting them from chemotherapy-induced damage and enhancing immune activity. Administration of trilaciclib prior to gemcitabine plus carboplatin (GCb) significantly improved overall survival (OS) compared with GCb alone in an open-label phase II trial in patients with metastatic TNBC, potentially through protection and direct activation of immune function. The randomized, double-blind, placebo-controlled, phase III PRESERVE 2 trial will evaluate the efficacy and safety of trilaciclib administered prior to GCb in patients with locally advanced unresectable or metastatic TNBC.

Clinical Trial Registration: NCT04799249 (ClinicalTrials.gov)

Tweetable abstract: Recruiting! PRESERVE 2: a randomized, phase III placebo-controlled trial assessing trilaciclib prior to first-line chemotherapy in patients with advanced or metastatic triple-negative breast cancer.

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Triple-negative breast cancer (TNBC), defined immunohistochemically by a lack of expression of ER, PR and HER2, accounts for approximately 15–20% of all breast cancer diagnoses worldwide [1,2]. TNBC is most prevalent in premenopausal women (aged <40 years) and has higher prevalence in African–American women compared with other ethnic groups [1,2]. TNBC tumors are frequently highly aggressive, high-grade tumors, and more than one-third of patients go on to develop metastatic disease, often involving the brain and visceral organs [3]. Compared with other breast cancer subtypes, TNBC is associated with a worse prognosis, including higher rates of relapse and shorter overall survival (OS) [1,3]. For patients with untreated metastatic TNBC, median OS is 8 months for relapsed disease and 11 months for *de novo* metastatic disease; this increases to 10 and 13 months, respectively, for patients who receive systemic chemotherapy in the real-world setting [4]. By contrast, patients with ER/PR-positive/HER2-negative breast cancers treated with oral CDK4/6 inhibitors plus fulvestrant have a median OS of ~35–54 months [5–7], while patients with HER2-positive disease have a median OS of ~57 months following treatment with pertuzumab plus trastuzumab and docetaxel [8].

As TNBC tumors lack ER, PR and HER2 expression, they are not sensitive to endocrine or HER2-targeted therapies [1]; however, TNBC is characterized by higher genomic instability, contributing to enhanced immunogenicity and chemosensitivity compared with other breast cancer subtypes [9].

Sequential, single-agent chemotherapy is the backbone of treatment for metastatic, PD-L1–negative TNBC, with recommended first-line treatment options including platinum-based chemotherapy (e.g., carboplatin, cisplatin), particularly for patients with *BRCA1/2*-mutant TNBC, as well as anthracyclines (e.g., doxorubicin, epirubicin), taxanes (e.g., paclitaxel, docetaxel) and antimetabolites (e.g., capecitabine, gemcitabine) [10–13]. Chemotherapy combinations may also be considered for patients with a high tumor burden, significant visceral disease or rapidly progressing disease, with some taxane- and platinum-based combination regimens having demonstrated efficacy in clinical trials [13,14]. For example, in a phase III study of gemcitabine plus carboplatin (GCb) with or without iniparib, first-line treatment with GCb resulted in a median progression-free survival (PFS) of 4.6 months and median OS of 13.9 months [14,15].

Patients with tumors that display PD-L1 protein expression above predefined levels (combined positive score ≥10 with the PD-L1 22C3 pharmDx assay or PD-L1 expression ≥1% with the Ventana PD-L1 [SP142] assay) may be treated with a combination of pembrolizumab plus chemotherapy as the preferred option in the first-line setting [10,11,16,17]. For patients with PD-L1–positive TNBC and a disease-free interval of ≤12 months, atezolizumab plus nab-paclitaxel is also a first-line treatment option in European countries where this indication is approved [10,11]. In the phase III KEYNOTE-355 trial (NCT02819518), patients who received first-line therapy for PD-L1–positive metastatic TNBC had improved median OS with pembrolizumab plus chemotherapy compared with chemotherapy alone (23.0 vs 16.1 months, respectively) [17]. However, patients with PD-L1–negative TNBC do not derive clinical benefit from treatment with immune checkpoint inhibitors [18,19], and not all patients with PD-L1–positive disease are appropriate candidates for immune checkpoint inhibitors, owing to potential toxicities.

For patients with metastatic TNBC harboring germline *BRCA1/2* mutations, PARP inhibitors (olaparib and talazoparib) have demonstrated PFS benefits compared with physician's choice of chemotherapy, although their comparative efficacy compared with platinum-based agents, anthracyclines and taxanes is not known [10,11,20,21]. Finally, following the results of the phase III ASCENT trial (NCT02574455), the antibody–drug conjugate sacituzumab govitecan has been approved for the treatment of patients with locally advanced or metastatic TNBC who have received two or more prior therapies, including at least one for metastatic disease [10,11,22,23].

Trilaciclib

Trilaciclib (COSELA™; G1 Therapeutics) is a selective and reversible CDK4/6 inhibitor that is administered via intravenous (IV) infusion prior to chemotherapy to proactively protect hematopoietic stem and progenitor cells and immune cells from chemotherapy-induced damage (myeloprotection) [24]. Hematopoietic stem and progenitor cells and lymphocytes are dependent on CDK4/6 activity for proliferation and, upon exposure to trilaciclib, become transiently arrested in the G_1 phase of the cell cycle, preventing proliferation in the presence of cytotoxic chemotherapy (Figure 1) [24]. In February 2021, the US FDA approved trilaciclib to decrease the incidence of chemotherapy-induced myelosuppression in adult patients when administered prior to a platinum/etoposide-containing or topotecan-containing regimen for extensive-stage small cell lung cancer (ES-SCLC) [25]. The FDA approval was based on the results of three randomized, double-blind, placebo-controlled, Phase II clinical trials in patients with ES-SCLC (NCT03041311, NCT02514447, NCT02499770) [26–28]. In each individual study and in an integrated analysis of all three trials, administering trilaciclib prior to chemotherapy resulted in significant reductions in the duration and occurrence of severe (grade 4) neutropenia (SN; primary end points). Compared with placebo, trilaciclib administered prior to chemotherapy also reduced the need for supportive care interventions and hospitalizations due to chemotherapy-induced myelosuppression or sepsis, reduced the incidence of grade 3/4 hematologic adverse events (AEs) and improved several health-related quality of life (QoL) domains, including fatigue and physical and functional well-being [26–30].

Because the primary mechanism by which CDK4/6 inhibitors induce arrest in the G_1 phase of the cell cycle is inhibition of phosphorylation of the Rb protein [31], there is potential for trilaciclib to antagonize the intended efficacy of chemotherapy in Rb-proficient tumor types. SCLC tumor cells progress through the cell cycle independently of CDK4/6 owing to obligate loss of the Rb gene (*RB1*), and TNBC tumors are predominantly functionally CDK4/6 independent due to mutation or loss of the *RB1* gene or low expression of the Rb protein [32]. Therefore, there is minimal risk that trilaciclib administered prior to chemotherapy would induce G_1 arrest in these

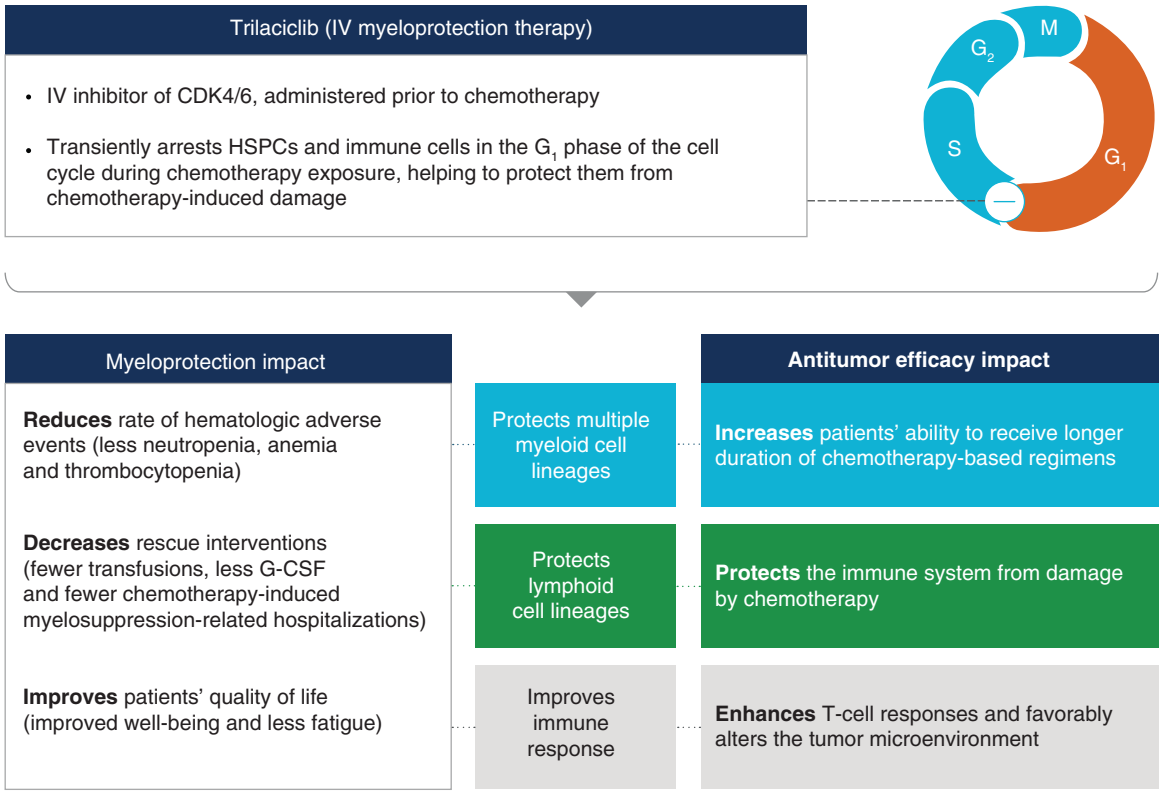

Figure 1. Trilaciclib mechanism of action.
G_1: Gap 1; G_2: Gap 2; HSPC: Hematopoietic stem and progenitor cell; IV: Intravenous; M: Mitosis; S: Synthesis.

tumor types. Additionally, data from the phase II studies in patients with ES-SCLC showed that trilaciclib does not antagonize chemotherapy efficacy [26–28]. However, the interactions between CDK4/6 inhibitors and chemotherapy are not yet fully understood [33].

Preclinical data suggest that, as well as protecting immune cells from cytotoxic damage, trilaciclib directly activates immune function by enhancing T-cell immunity. In preclinical tumor models, the addition of trilaciclib to chemotherapy plus immune checkpoint inhibitor combinations enhanced antitumor responses, in part by modulating the composition of T-cell subsets in the tumor microenvironment [34]. Transient arrest of intratumoral T-cell subsets on exposure to trilaciclib was followed by faster recovery of cytotoxic T cells compared with regulatory T cells. Moreover, within the tumor environment, trilaciclib-induced cell cycle arrest of immune cells resulted in more robust T-cell clonal expansion and enrichment of proinflammatory gene signatures, leading to enhanced T-cell effector function [34]. CDK4/6 inhibition has also been shown to enhance antitumor immunity by de-repressing the NFAT family of transcription factors and their targets, resulting in increased production of cytokines that enhance immune system function [31,35].

The PRESERVE 2 study

Herein, we describe the rationale and design of the multinational, randomized, double-blind, placebo-controlled, phase III PRESERVE 2 study (ClinicalTrials.gov identifier: NCT04799249) to evaluate the efficacy and safety of trilaciclib versus placebo administered prior to first-line GCb in patients with locally advanced unresectable or metastatic TNBC. The study is sponsored by G1 Therapeutics.

Background & rationale

In addition to the studies in patients with ES-SCLC, trilaciclib was evaluated in an exploratory, randomized, open-label, phase II trial (NCT02978716) that investigated the efficacy and safety of administering trilaciclib prior to GCb in patients with TNBC who had previously received up to two lines of therapy in the metastatic setting. To demonstrate superiority of trilaciclib plus GCb over GCb alone with 90% power for at least one primary end point

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(either duration of severe neutropenia in cycle 1 or occurrence of severe neutropenia), a total of 102 patients were required. Patients in group 1 received GCb alone on days 1 and 8 (n = 34), group 2 received GCb and trilaciclib on days 1 and 8 (n = 33) and group 3 received GCb on days 2 and 9 and trilaciclib on days 1, 2, 8 and 9 (n = 35). The trial did not meet its primary end point because trilaciclib neither reduced the occurrence nor duration of severe neutropenia. However, Kaplan–Meier analyses showed that administering trilaciclib prior to GCb resulted in longer PFS (median 9.4 months in group 2 and 7.3 months in group 3 vs 5.7 months in group 1) and significantly longer OS (a key secondary end point) compared with GCb alone (median 20.1 months for groups 2 and 3 combined vs 12.6 months for group 1; hazard ratio [HR], 0.36; p = 0.0015) [36]. Mature results were consistent with the primary analysis, confirming that administering trilaciclib prior to GCb enhanced antitumor efficacy, with numerically higher response rates and longer PFS, and statistically significant improvements in OS (median 19.8 for groups 2 and 3 vs 12.6 months for group 1; HR, 0.37; $p < 0.0001$) [37]. In addition to improved OS, the results indicated an improvement in patient-reported outcomes (PROs) as measured by Functional Assessment of Cancer Therapy (FACT) scales, and a manageable safety profile [38].

Notably, efficacy outcomes in the phase II TNBC trial were comparable regardless of CDK4/6 dependence status and immune signatures [37]. Moreover, administering trilaciclib prior to GCb prolonged OS versus GCb alone irrespective of PD-L1 status, albeit with greater benefit in the PD-L1–positive population (PD-L1–positive: median 32.7 vs 10.5 months, respectively; HR, 0.34; PD-L1–negative: median 17.8 vs 13.9 months, respectively; HR, 0.48) [37]. Exploratory data from immune subtyping analyses and T-cell receptor immunosequencing suggested that administering trilaciclib prior to GCb enhanced T-cell activation [37]. Furthermore, there were significant increases in newly detected expanded clones among trilaciclib-treated patients who responded to GCb, and patients with an enrichment of T-cell clones appeared to have greater improvement in survival with trilaciclib [37]. Together with the preclinical data described above, these findings suggest that trilaciclib has the potential to enhance the efficacy of chemotherapy and chemotherapy plus ICI combinations by protecting immune cell populations from chemotherapy-induced damage and by enhancing T-cell immunity via multiple mechanisms [34,37]. However, the observed immune-mediated effects of trilaciclib are not yet fully understood, and further investigation regarding the association between enhanced antitumor immunity and improved OS among patients with metastatic TNBC is ongoing [37].

Given the encouraging evidence of improved patient outcomes in patients with TNBC, the phase III PRESERVE 2 trial has been designed to confirm the survival benefit observed in the phase II study of trilaciclib in patients with metastatic TNBC. The primary objective is to evaluate the effect of trilaciclib versus placebo on OS in patients receiving GCb for locally advanced unresectable or metastatic TNBC. The key secondary objective is to assess the effects of trilaciclib versus placebo on patients' QoL, as measured by time to confirmed deterioration in fatigue (TTCD-fatigue).

Design

Study design

PRESERVE 2 was designed as a two-cohort study (Figure 2). In cohort 1, the effects of trilaciclib in patients receiving first-line treatment for locally advanced unresectable TNBC or metastatic TNBC will be evaluated. Cohort 2 was designed to evaluate the effects of trilaciclib in patients with locally advanced unresectable TNBC or metastatic TNBC previously treated with a PD-1/PD-L1 inhibitor; however, this cohort was closed to accrual as of 24 January 2022, owing to the changing treatment landscape for patients receiving second-line treatment for TNBC. Patients currently enrolled in cohort 2 (n = 7) will continue to receive treatment per protocol, and data will be collected as planned.

Patients will be randomly assigned (1:1) to receive placebo or trilaciclib 240 mg/m^2 as a 30-min i.v. infusion, completed ≤4 h prior to chemotherapy on each day that chemotherapy is administered. Gemcitabine (1000 mg/m^2) and carboplatin (area under the curve = 2 using the Calvert formula [maximum 300 mg]) will be administered by i.v. infusion on days 1 and 8 of each 21-day cycle. The rationale for using GCb derives from the results of previous studies that showed higher response rates with doublet chemotherapy than single-agent chemotherapy [16], and a favorable safety and tolerability profile [36–38]. Randomization in cohort 1 will be stratified on the basis of tumor PD-L1 status, as confirmed by the Ventana SP-142 *in vitro* diagnostic assay (positive [≥1% tumor-infiltrating immune cells] vs negative [<1%]); disease-free interval between end of last treatment with curative intent (not including [neo]adjuvant PD-1/PD-L1 inhibitors) and disease progression (≥6 to <12 months vs ≥12 months or *de novo* metastatic TNBC); and country. Treatment will continue until disease progression, unacceptable toxicity,

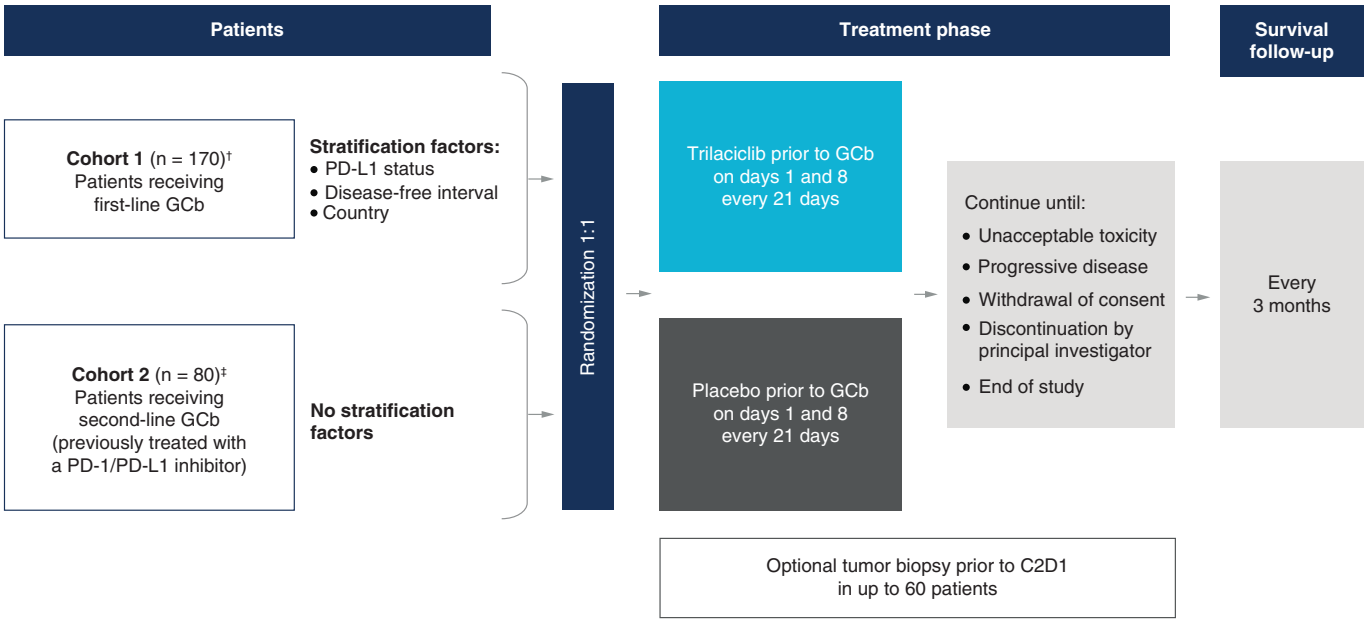

Figure 2. PRESERVE 2 study design.
†The proportion of PD-L1–negative patients in cohort 1 will be limited to approximately 60%.
‡Closed to accrual as of 24 January 2022.
C: Cycle; D: Day; GCb: Gemcitabine plus carboplatin.

Table 1. Key eligibility criteria for PRESERVE 2.

Key inclusion criteria	Key exclusion criteria
All patients: – Adult patients (≥18 years of age) – Confirmed locally advanced unresectable or metastatic TNBC – Archival tumor tissue available, or fresh biopsy to be obtained – ECOG performance status of 0 or 1 – Adequate organ function as demonstrated by laboratory values – Resolution of nonhematologic toxicities from prior therapy to grade ≤1 – Predicted life expectancy of ≥3 months – Vaccination against COVID-19 permitted Cohort 1 only: – No prior systemic therapy in the locally advanced unresectable/metastatic setting – Time between completion of last treatment with curative intent and first metastatic recurrence must be ≥6 months† Cohort 2 only‡: – Prior PD-1/PD-L1 inhibitor for ≥4 months' duration and documented PD-L1–positive status	All patients: – Prior treatment with gemcitabine – Prior treatment with carboplatin in the locally advanced unresectable/metastatic setting and in the (neo)adjuvant/curative setting if completed ≤6 months prior to first metastatic recurrence – Malignancies other than TNBC within 3 years prior to randomization – Symptomatic CNS metastases and/or leptomeningeal disease requiring immediate treatment with radiation therapy or steroids – Receipt of any cytotoxic chemotherapy or PD-1/PD-L1 inhibitor therapy (if relevant) ≤14 days prior to first dose of study drugs – Receipt of any investigational medication ≤30 days or ≤5 half-lives (whichever is greater) prior to the first dose of study drugs – Known hypersensitivity to carboplatin or other platinum-containing compounds, or mannitol – Pregnant or lactating women

†Prior PD-1/PD-L1 inhibitor in the (neo)adjuvant/curative setting does not have time/interval restrictions. Washout of at least 14 days from prior PD-1/PD-L1 inhibitor to the first dose of study drugs is required;
‡Closed to accrual as of 24 January 2022.
CNS: Central nervous system; ECOG: Eastern Cooperative Oncology Group; TNBC: Triple-negative breast cancer.

withdrawal of consent, investigator decision or the end of the study, whichever occurs first. Primary prophylaxis with G-CSF will be prohibited in cycle 1, although therapeutic G-CSF will be allowed. Following completion of cycle 1, G-CSF (prophylactic or therapeutic) will be permitted per standard guidelines. Erythropoiesis-stimulating agents and red blood cell or platelet transfusions will be allowed per investigator discretion.

Eligibility criteria

Key inclusion and exclusion criteria are described in Table 1. Patients must be aged ≥18 years, with locally advanced unresectable or metastatic TNBC (defined as <1% ER and PR by immunohistochemistry and HER2-negative by immunohistochemistry or *in situ* hybridization), an Eastern Cooperative Oncology Group performance status of 0 or 1, and adequate organ function based on laboratory values. Prior radiation therapy is permitted for

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recurrent disease. Patients are required to have archival tumor tissue available; if one is not available, a fresh biopsy must be obtained. Patients in cohort 1 must have received no prior systemic therapy in the locally advanced unresectable/metastatic setting, and the time between completion of last treatment with curative intent (excluding [neo]adjuvant PD-1/PD-L1 inhibitor) and first metastatic recurrence must be ≥6 months. Patients in cohort 2 are required to have a documented PD-L1–positive tumor and to have received PD-1/PD-L1 inhibitor treatment for ≥4 months as the most recent therapy for locally advanced unresectable or metastatic TNBC.

Planned sample size & study period

PRESERVE 2 will enrol patients at approximately 135 study sites in Australia, China, Europe, Russia and USA. The sample size was calculated to support the primary objective in cohort 1 of evaluating the effect of trilaciclib versus placebo on OS in patients with TNBC receiving first-line therapy. In cohort 1, 103 deaths would result in 84% power to detect an OS HR of 0.55 at a 2-sided significance level of 0.05, corresponding to a median OS duration of 29.1 months with trilaciclib and 16 months with placebo. With an assumed hazard rate of 0.0027 for loss to follow-up during the estimated 39 months of study duration, ≥170 patients are required. Study enrollment began in April 2021, with primary completion anticipated in June 2024 and study completion in October 2024.

Study procedures

Tumor response will be assessed per Response Evaluation Criteria in Solid Tumours version 1.1, using computed tomography or magnetic resonance imaging. Imaging will be performed at baseline, then every 9 weeks for the first 54 weeks, and every 12 weeks thereafter, with additional scans performed as clinically indicated. End-of-treatment visits will occur approximately 14 days following a patient's last dose of study drug, and patients will be followed for survival approximately every 3 months.

Safety will be assessed from the first dose of study drug through the safety follow-up visit, approximately 30 days following a patient's last dose of study drug. AEs will be assessed and graded based on the National Cancer Institute's Common Terminology Criteria for Adverse Events version 5.0. PROs will be assessed using Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F), FACT–General (FACT-G), FACT–Anemia (FACT-An), Patient Global Impression of Change (PGIC), Patient Global Impression of Severity (PGIS), and 5-level EuroQol 5-dimension (EQ-5D-5L) instruments. Myeloprotection will be assessed based on hematology assessments, related AEs and supportive care interventions (including transfusions). Blood sampling for pharmacokinetic (PK) and biomarker analysis will also be performed.

To evaluate the impact of trilaciclib on tumor-associated immune responses, immunophenotypic changes will be compared between tumor biopsies from patients receiving trilaciclib or placebo prior to GCb. For patients who consent to optional biopsy collection, fresh tumor biopsies from a recurrent/metastatic lesion will be collected at baseline and on treatment, prior to cycle 2. Archival tissue is acceptable for use as the baseline sample if no systemic therapy or local radiation has been administered between biopsy and randomization. The target participation for optional biopsy collection is 60 patients.

Outcome measures/end points

The primary end point is OS, defined as the time from randomization to death or to the last contact date when the patient was known to be alive for those who survive. The key secondary end point is TTCD-fatigue, as measured by FACIT-F. Other secondary antitumor end points include PFS, OS in the PD-L1–positive/negative subgroups (cohort 1), objective response rate, clinical benefit rate and duration of objective response. Other secondary PRO end points include change from baseline and/or TTCD in FACT-G domain scores (physical, social/family, emotional and functional well-being), FACT-An and EQ-5D-5L, and proportion of patients reporting deterioration/improvement using PGIC or PGIS fatigue items. Safety and tolerability will also be assessed as a secondary end point. Secondary myeloprotection efficacy end points include duration of SN in cycle 1, and occurrences of SN, grade 3/4 decreased hemoglobin and platelet counts and use of supportive care interventions. Exploratory end points include pharmacodynamic parameters in tumor biopsies and peripheral blood, antitumor efficacy in patients with CDK4/6-dependent, -independent or -indeterminate signatures and in PD-L1-positive/negative subgroups, and population PK parameters of trilaciclib when administered prior to GCb. A full list of study end points is provided in Table 2.

Table 2. PRESERVE 2 end points.

Type of end point	End point
Primary	OS† in the ITT population
Key secondary	TTCD-fatigue, as measured by the FACIT-F
Other secondary	
Antitumor efficacy	– OS† in the PD-L1–positive subgroup – OS† in the PD-L1–negative subgroup – PFS‡ in the ITT population per RECIST v1.1 – ORR (CR + PR) per RECIST v1.1 – CBR (confirmed CR + PR + SD lasting ≥24 weeks) per RECIST v1.1 – DOR per RECIST v1.1
PROs (myelosuppression-related symptoms)	Change from baseline and/or time to deterioration in: – FACT-G domain scores (physical, social/family, emotional and functional well-being) – FACT-An score – EQ-5D-5L score Percentage of patients reporting deterioration or improvement using: – PGIC fatigue item – PGIS fatigue item
Safety and tolerability	– Occurrence and severity of AEs (NCI-CTCAE v5) – Trilaciclib AESIs – Changes in laboratory parameters, vital signs and ECG parameters – Grade 3/4 abnormalities in serum chemistry laboratory parameters – Trilaciclib infusion interruptions – Chemotherapy dose modifications – RDI for gemcitabine and carboplatin
Myeloprotection efficacy	– Duration of severe (grade 4) neutropenia in cycle 1 – Occurrence of severe (grade 4) neutropenia – Occurrence of febrile neutropenia AEs – Occurrence of G-CSF administration – Occurrence of grade 3/4 decreased hemoglobin – RBC transfusions on/after week 5 (occurrence and number of transfusions) – Occurrence of ESA administration – Occurrence of grade 3/4 decreased platelet count – Platelet transfusions (occurrence and number of transfusions) – Occurrence and number of hospitalizations due to CIM – All-cause dose reductions (occurrence and number of reductions) – All-cause cycle delays (occurrence and number of delays)
Exploratory	– Differences in pharmacodynamic parameters, including those relating to immune-based mechanisms, in tumor biopsies and peripheral blood – OS†, PFS‡ and ORR per RECIST v1.1, in patients with CDK4/6-dependent, -independent and -indeterminant signatures – PFS‡, ORR, DOR and CBR in PD-L1 subgroups – Population PK parameters (as data permit)

†Time from randomization to death due to any cause for those who die, or time from randomization to last contact with living patient for those who survive in the study (censored cases);
‡Time from randomization to disease progression (per RECIST v1.1) or death due to any cause, whichever occurs first; for patients without disease progression or death, PFS will be calculated per censoring rules.
AE: Adverse event; AESI: Adverse event of special interest; CBR: Clinical benefit rate; CIM: Chemotherapy-induced myelosuppression; CR: Complete response; DOR: Duration of objective response; ECG: Electrocardiogram; EQ-5D-5L: 5-level EuroQol 5-dimension questionnaire; ESA: Erythropoiesis-stimulating agent; FACIT-F: Functional Assessment of Chronic Illness Therapy–Fatigue; FACT-An: Functional Assessment of Cancer Therapy–Anemia; FACT-G: Functional Assessment of Cancer Therapy–General; ITT: Intention-to-treat; NCI-CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events; ORR: Objective response rate; OS: Overall survival; PFS: Progression-free survival; PGIC: Patient Global Impression of Change; PGIS: Patient Global Impression of Severity; PK: Pharmacokinetics; PR: Partial response; PRO: Patient-reported outcome; RBC: Red blood cell; RDI: Relative dose intensity; RECIST: Response Evaluation Criteria in Solid Tumours; SD: Stable disease; TTCD-fatigue: Time to first confirmed deterioration of fatigue.

Statistics

Data from each cohort will be analyzed separately. The primary analysis population for efficacy will consist of all randomized (intention-to-treat) patients unless specified otherwise. The safety population will include all randomized patients who receive at least one dose of study drug. The PK population will include all patients who receive at least one dose of trilaciclib and have evaluable PK data.

An interim analysis for OS will be performed for cohort 1 when approximately 70% of required events (i.e., 72 deaths) have been observed. If the primary OS analysis is statistically significant, TTCD-fatigue will be analyzed. OS will be evaluated using a log-rank test, and a Cox proportional hazard model will be used to estimate the HR and its 95% confidence interval.

Within each country, randomization in cohort 1 will be stratified by tumor PD-L1 status and disease-free interval. The countries will be grouped into the factor of 'region' with three different entries of 1) United States; 2)

Western Europe and Australia; and 3) other countries (e.g., Eastern Europe, Russia, China). Region will be used instead of country in statistical analysis models to account for regional differences in clinical practice.

The planned statistical analyses for cohort 2 are no longer applicable; data from cohort 2 will be summarized as appropriate.

Conclusion

Trilaciclib is an IV CDK4/6 inhibitor that is administered prior to chemotherapy to provide multilineage myeloprotection in patients with ES-SCLC. Data from a Phase II study in patients with TNBC showed that administering trilaciclib prior to GCb resulted in clinically meaningful improvements in OS compared with GCb alone, potentially through both protection of immune cells and enhancement of T-cell effector function. The Phase III, randomized, multicenter PRESERVE 2 study will further explore the OS benefit of trilaciclib administered prior to GCb in patients with metastatic TNBC. The results of this study will help to define the role of trilaciclib in this setting and potentially improve standard treatment for metastatic TNBC by improving efficacy outcomes, reducing the incidence of chemotherapy-induced myelosuppression, and improving patients' QoL.

Executive summary

- Cytotoxic chemotherapy is the backbone of treatment for patients with metastatic triple-negative breast cancer (TNBC).
- Trilaciclib is an intravenous CDK4/6 inhibitor approved to decrease the incidence of chemotherapy-induced myelosuppression in adult patients when administered prior to a platinum/etoposide-containing or topotecan-containing regimen for extensive-stage small cell lung cancer.
- In addition to its myeloprotective effects, trilaciclib has been shown to improve antitumor immunity in preclinical models by protecting lymphocyte populations, enhancing T-cell responses, and favorably altering the tumor microenvironment.

Background & rationale

- Administration of trilaciclib prior to gemcitabine plus carboplatin (GCb) improved overall survival (OS) compared with GCb alone in a phase II trial in patients with metastatic TNBC.
- Efficacy outcomes were comparable regardless of CDK4/6 dependence status and immune signatures and administering trilaciclib prior to GCb prolonged OS irrespective of PD-L1 status.
- Trilaciclib potentially enhances chemotherapy efficacy through protection and direct activation of immune function; however, the observed immune-mediated effects of trilaciclib are not yet fully understood.
- Given the encouraging evidence of improved patient outcomes in patients with TNBC, the phase III PRESERVE 2 trial aims to confirm the OS benefit seen in the Phase II study of trilaciclib in patients with metastatic TNBC.

Study design & eligibility criteria

- PRESERVE 2 is a multinational, randomized, double-blind, placebo-controlled, phase III trial of trilaciclib administered prior to GCb in patients with locally advanced unresectable or metastatic TNBC.
- Eligible patients must be aged ≥18 years, with locally advanced unresectable or metastatic TNBC.
- Patients in cohort 1 must have received no prior systemic therapy in this setting.
- Cohort 2 was planned to enrol patients with prior PD-1/PD-L1 inhibitor treatment; however, this cohort was closed to accrual as of 24 January 2022.
- Approximately 170 patients will be enrolled in cohort 1.

Outcome measures/end points

- The primary end point is OS, and the key secondary end point is time to confirmed deterioration of fatigue, as measured by Functional Assessment of Chronic Illness Therapy–Fatigue.
- Other secondary end points include progression-free survival, objective response rate, clinical benefit rate, patient-reported outcomes, safety and myelosuppression.
- Tumor response will be assessed per Response Evaluation Criteria in Solid Tumors version 1.1, with imaging performed every 9 weeks for the first 54 weeks, and every 12 weeks thereafter.

Conclusion

- The PRESERVE 2 study will help to further define the role of trilaciclib administered prior to GCb in patients with metastatic TNBC.

Supplementary data

An infographic accompanies this paper. To view or download this infographic in your browser please click here: https://www.futuremedicine.com/doi/suppl/10.2217/fon-2022-0773

Author contributions

All authors contributed to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work. All authors contributed to drafting the work or revising it critically for important intellectual content. All authors provided final approval of the version to be published. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Financial & competing interests disclosure

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Ethical conduct of research

The study will be conducted in accordance with the consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines and applicable International Council for Harmonization Good Clinical Practice Guidelines. In addition, informed consent has been obtained from the participants involved.

Data sharing statement

G1 Therapeutics fulfils its commitment to publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov, the EudraCT, and other public registries in accordance with applicable local laws/regulations.

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