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A phase 2 trial of loperamide and granulocyte colony-stimulating factors to improve sacituzumab govitecan tolerance in patients with unresectable locally advanced or metastatic triple-negative breast cancer: PRIMED

José Manuel Pérez-García[1,2], María Gion[3], Alejandro Martínez Bueno[4], Serafin Morales[5], Lourdes Calvo[6], Xavier Gonzalez[7], Salvador Blanch[8], Elena López-Miranda[3], Janat Fazal-Salom[1], Alexandros Lazaris[1], Eileen Shimizu[1], Patricia Cortez[9], María Isabel Blancas López-Barajas[10], Manuel Ruiz[11], Javier Cortés[1,2,12], Antonio Llombart-Cussac[1,13]

(1) Medica Scientia Innovation Research (MEDSIR), Barcelona, Spain and Ridgewood, New Jersey, USA; (2) International Breast Cancer Center (IBCC), Pangaea Group, Quiron Group, Barcelona, Spain; (3) Universitario Ramón y Cajal, Madrid, Spain; (4) Instituto Oncológico Dr. Rosell, Hospital Quiron Dexeus, Barcelona, Spain; (5) Hospital Universitario de Arnau de Villanova de Lleida, Lleida, Spain; (6) Complejo Hospitalario Universitario A Coruña, Coruña, Spain; (7) Hospital Universitario General de Cataluña, Barcelona, Spain; (8) Hospital Quirón Valencia, Valencia, Spain; (9) Hospital Quiron San Camio-Ruber Juan Bravo, Madrid, Spain; (10) Hospital Universitario Clínico San Cecilio de Granada, Granada, Spain; (11) Hospital Universitario Virgen del Rocío, Sevilla, Spain; (12) Universidad Europea de Madrid, Madrid, Spain; (13) Arnau de Vilanova, Valencia, Spain; Catholic University, Valencia, Spain

BACKGROUND

- Sacituzumab govitecan (SG) is an antibody-drug conjugate that targets Trop-2 to deliver SN 38 (the active metabolite of irinotecan, a topoisomerase I inhibitor) to malignant cells **[1].**
- SG has demonstrated a benefit in terms of progression-free survival and overall survival in patients with refractory triple-negative and hormone receptor (HR)-positive/human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancers in comparison with single agent chemotherapy **[2-5].**
- The most common adverse events related to SG administration include neutropenia and diarrhea, which when severe can lead to treatment delay, suppression, or discontinuation **[1-3].**
- Loperamide and granulocyte colony-stimulating factors (G-CSF) are commonly used to treat and prevent drug-associated diarrhea and neutropenia in cancer patients, respectively **[6,7].**
- PRIMED hypothesizes that prophylactic administration of loperamide (for diarrhea) and G-CSF (for neutropenia) can help mitigate these undesirable effects related to SG treatment and therefore reduce dose reductions or discontinuations.

TRIAL DESIGN

- This is a multicenter, open-label, single-arm, phase II clinical trial (NTC05520723).
- Patients will be treated with SG, loperamide, and G-CSF for two 21-day cycles and will then continue on SG until disease progression, unacceptable toxicity, or patient's/physician's decision.
- Loperamide and G-CSF can be extended after two cycles under physician's discretion.
- An overview of the study design is shown in **Figure 1.**

TRIAL ENROLLMENT

PRIMED study was opened to accrual in February 2023 and is currently recruiting in 10 institutions from Spain.

STUDY ENDPOINTS

Primary Endpoints

- Co-primary endpoints are incidence of grade ≥2 diarrhea and grade ≥3 neutropenia per NCI-CTCAE v.5.0 at cycle 2.

Secondary Endpoints

- Tolerability and safety per NCI-CTCAE v.5.0 at cycle 2.
- Discontinuation and dose reduction rates.
- Efficacy in terms of progression-free survival, objective response rate, clinical benefit ratio, time to response, duration of response, and best percentage of change in tumor burden per RECIST v.1.1.

Exploratory Objectives

- Evaluate predictive or prognostic biomarkers associated with disease activity status or response to treatment.
- Identify possible mechanisms of sensitivity/resistance to treatment through the comparative analysis of potential biomarkers from paired pre-treatment and post-progression blood samples and/or stool samples.

STATISTICS

Sample size

- It was based on a Simon's two-stage design, planned to attain an 80% power at nominal level of one-sided alpha of 0.05 to each endpoint.

Stage I (N=25)

- The trial will continue to final analysis if there are <6 patients (24%) with grade ≥2 diarrhea and <9 patients (36%) with grade ≥3 neutropenia. Otherwise, the recruitment will continue to achieve 50 patients.

Final analysis (N=50)

- The study will be declared positive if any of the following outcomes are achieved:

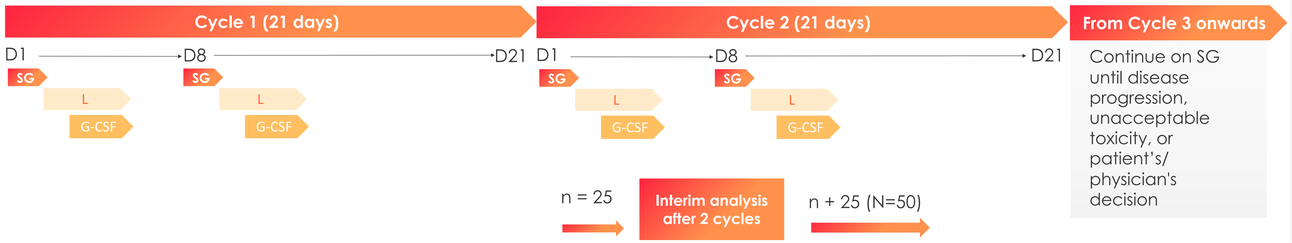
1. If there are ≤7 (14%) patients with grade ≥2 diarrhea (expected rate as the null hypothesis 25%).
2. If there are ≤14 (28%) patients with grade ≥3 neutropenia (expected rate as null hypothesis 40%).

AUTHOR DISCLOSURE AND CONTACT INFO

Maria Gion Disclosure:
Honoraria: Roche, Novartis, Gilead, Daiichi-Sankyo
Travel grants, accommodation: Roche, Pfizer
Contact Information: maria.gion@medsir.org

STUDY DESIGN

Figure 1. PRIMED Trial Design



Key Eligibility Criteria

- Patients ≥18 years with taxane-pretreated advanced triple-negative breast cancer*.
- At least one and up to two prior chemotherapeutic regimens for advanced disease.
- Earlier treatment in curative setting will be considered as one of the regimens if advanced disease occurred in <12 months after completion of chemotherapy.
- ECOG performance status 0 or 1.
- Measurable or non-measurable, but evaluable, disease per RECIST v.1.1. Patients with bone-only metastases are also eligible.

Study Treatment

SG
10 mg/kg IV on D1 and D8
+
Loperamide
2 mg PO BID, or 4 mg QD on D2, D3, D4, and D9, D10, D11
+
G-CSF
0.5 MU/kg/day SC QD on D3, D4, and D10, D11

Primary Endpoints

Incidence of grade ≥2 diarrhea and grade ≥3 neutropenia per NCI-CTCAE v.5.0 at cycle 2.

BID: Twice a day; **D:** Day; **ECOG**: Eastern Cooperative Oncology Group; **G-CSF:** Granulocyte-colony stimulating factor; **IV**: Intravenous; **L:** Loperamide; **NCI-CTCAE v.5.0:** National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0; **PO**: Orally; **QD**: Daily; **RECIST v.1.1**: Response Evaluation Criteria In Solid Tumors version 1.1; **SC**: Subcutaneous; **SG:** Sacituzumab govitecan

*** As of March 14, 2023, the protocol is pending approval of an amendment to also allow the inclusion of patients with HR-positive/HER2-negative advanced breast cancer.**

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Scan here to view a plain language summary of this trial.