A Randomized, Open-label, Phase 3 Study of Sacituzumab Govitecan Versus Treatment of Physician*s Choice in Patients With Previously Untreated, Locally Advanced, Inoperable or Metastatic Triple-Negative Breast Cancer Whose Tumors Do Not Express PD-L1 or in Patients Previously Treated With Anti-PD-(L)1 Agents in the Early Setting Whose Tumors Do Express PD-L1.

Published: 17-05-2022
Last updated: 10-01-2025

This study has been transitioned to CTIS with ID 2023-504195-14-00 check the CTIS register for the current data. •To compare progression-free survival (PFS) as assessed by blinded independent central review (BICR) between sacituzumab govitecan (SG)...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Breast neoplasms malignant and unspecified (incl nipple)
Study type	Interventional

Summary

ID

NL-OMON51786

Source
ToetsingOnline

Brief title
ASCENT-03

Condition

- Breast neoplasms malignant and unspecified (incl nipple)

Synonym
Breast cancer; Triple-negative breast cancer

Research involving
Human

Sponsors and support

Primary sponsor: Gilead Sciences
Source(s) of monetary or material Support: Gilead Sciences Inc.

Intervention

Keyword: inoperable Triple-Negative Breast Cancer, Open-label, Phase 3, Sacituzumab Govitecan, Untreated

Outcome measures

Primary outcome

• PFS is defined as the time from the date of randomization until the date of objective progressive disease (PD), as assessed by BICR per Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1, or death (whichever comes first).

Secondary outcome

• OS is defined as the time from the date of randomization until death due to any cause.

• ORR is defined as the proportion of patients who achieve a complete response (CR) or partial response (PR) that is confirmed at least 4 weeks after initial documentation of response as assessed by BICR per RECIST Version 1.1.

• DOR is defined as the time from the first documentation of CR or PR to the earlier of the first documentation of definitive PD or death from any cause

(whichever comes first) as assessed by BICR per RECIST Version 1.1.

• TTR is defined as the time from the date of randomization until the first documentation of CR or PR as assessed by BICR per RECIST Version 1.1.

• Incidence of treatment-emergent AEs (TEAEs) and clinical laboratory abnormalities.

• Mean change from baseline in the physical functioning domain of the EORTC QLQ C30 at week 25

• TTD of fatigue domain of the EORTC QLQ-C30 is defined as the time between the date of randomization and the date of assessment at which a patient experienced a deterioration (ie, >= 10 points worsening from baseline in the fatigue domain) or death

Exploratory End Points:

• Correlation of clinical outcome (PFS, OS, ORR, and DOR) with baseline tumor Trop-2 expression

• Correlation of clinical outcome (PFS, OS, ORR, and DOR) with tumor, tumor microenvironment, and blood biomarkers at baseline and post-SG treatment

• Clearance of circulating tumor DNA upon SG treatment

• Correlation of AEs to UGT1A1 status

• Correlation of pharmacokinetics and immunogenicity of SG

• Additional QOL end points include mean change from baseline, TTD (in addition to the subscales specified as secondary end points), time to improvement, proportion improved, and proportion worsened.

Study description

Background summary

Sacituzumab govitecan is a type of drug called an antibody-drug conjugate. Antibodies are proteins normally made by the immune system. The antibody attaches to a certain type of protein called Trop-2 found on many cancers, including breast cancer, and is conjugated (attached) to an anti-cancer drug. Paclitaxel, or nab-paclitaxel, or the combination of gemcitabine and carboplatin are commonly used chemotherapy treatments for previously untreated advanced TNBC.

Study objective

This study has been transitioned to CTIS with ID 2023-504195-14-00 check the CTIS register for the current data.

•To compare progression-free survival (PFS) as assessed by blinded independent central review (BICR) between sacituzumab govitecan (SG) versus treatment of physician*s choice (TPC)

Secondary Objectives:
•To compare overall survival (OS) between the 2 arms
•To compare objective response rate (ORR) as assessed by BICR between the 2 arms
•To compare duration of response (DOR) as assessed by BICR between the 2 arms
•To compare time to response (TTR) as assessed by BICR between the 2 arms
•To compare safety and tolerability between the 2 arms
•To compare mean change from baseline in the physical functioning domain and time to deterioration (TTD) in fatigue as measured by the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire, Core Questionnaire, Version 3.0 (EORTC QLQ-C30) between the 2 arms

Exploratory Objectives:
•To assess tumor expression of Trop-2 as a potential biomarker of response to SG
•To explore blood and tumor biomarkers that may be associated with response to SG
•To explore the relationship of adverse events (AEs) to uridine diphosphate glucuronosyltransferase A1A (UGT1A1) status
•To characterize the pharmacokinetics and immunogenicity of SG
•To compare additional QOL outcomes as measured by EQ-5D-5L, the European Organisation for Research and Treatment of Cancer Breast Cancer-specific Quality of Life Questionnaire (EORTC QLQ-BR23), EORTC QLQ-C30, Patient Global Impression of Change/Patient Global Impression of Severity (PGIC/PGIS), and Functional Assessment of Cancer Therapy - General item GP5 (FACT--GP5) between the 2 arms

Study design

This is an international, multicenter, open-label, randomized, Phase 3 study in patients with locally advanced, inoperable or metastatic triple-negative breast cancer (TNBC) who have not received previous therapy for advanced disease and whose tumors are either:
• PD-L1 negative at screening (defined using the PD-L1 IHC 22C3 assay as tumors with a combined positive score (CPS) < 10), OR
• PD-L1 positive at screening (defined using the PD-L1 IHC 22C3 assay as tumors with a CPS >= 10) if they previously received a checkpoint inhibitor in the adjuvant or neoadjuvant setting or if they cannot be treated with a checkpoint inhibitor due to a comorbidity.
Enrolled patients may have received adjuvant or neoadjuvant chemotherapy with or without an anti-PD-L1 or anti-PD-1 agent and/or radiotherapy in the curative TNBC setting. However, at least 6 months must have elapsed between the completion of systemic (neo)adjuvant breast cancer therapy or surgery (whichever occurred last), and first local or distant recurrence. Adjuvant radiotherapy is not included in the 6-month interval, but patients must not have received radiotherapy treatment within 2 weeks prior to randomization. Patients with brain metastases who have been treated and are radiographically stable for at least 4 weeks are eligible, if they have also been clinically stable for at least 2 weeks on a prednisone-equivalent dose of <= 10 mg daily.
Patients meeting eligibility will be randomly assigned (1:1) to 1 of 2 arms:
· Arm A: sacituzumab govitecan (SG) 10 mg/kg intravenously on Days 1 and 8 of 21-day cycles
· Arm B: treatment of physician*s choice (TPC)
The TPC will be limited to 1 of the following treatment regimens:
• Gemcitabine 1000 mg/m2 with carboplatin area under the curve (AUC) 2 intravenously on Days 1 and 8 of 21-day cycles
• Paclitaxel 90 mg/m2 intravenously on Days 1, 8, and 15 of 28-day cycles
• nab-Paclitaxel 100 mg/m2 intravenously on Days 1, 8, and 15 of 28-day cycles
No other treatment regimen is permitted and no combination or crossovers of the 3 choices are permitted. Treatment will be administered until BICR verified disease progression, unacceptable toxicity, consent withdrawal, or death.
Randomized patients will be stratified by the following factors:
• De novo versus recurrent disease within 6 to 12 months from completion of treatment in the curative setting versus recurrent disease occurring > 12 months from completion of treatment in the curative setting
* Curative treatment interval is defined as systemic (neo)adjuvant breast cancer therapy or surgery (whichever occurred last) and first local or distant recurrence. Adjuvant radiotherapy is not included in the 6-month interval
• Geographic region (US/Canada/Western Europe versus rest of world)
Tumor assessments will be obtained by computed tomography (CT) or magnetic resonance imaging (MRI) scans every 6 weeks for the first year, then every 12 weeks thereafter until BICR-verified progression of disease or initiation of any new therapy. For each patient, the same imaging modality should be used

throughout the study. Images will be evaluated for tumor status by a BICR committee and assessment by a central imaging vendor as per RECIST Version 1.1. Complete responses and PRs must be confirmed by a follow-up scan at least 4 weeks from the date the response was first documented. Additional CT or MRI scans may be performed at the discretion of the treating physician to assess disease status as medically indicated. Scans will be archived for review by the BICR. In case of progression on clinical grounds, the investigator will make every effort to document progression radiographically for review by the BICR. An end of treatment visit will be conducted within 30 days (± 7 days) after the last dose of study treatment. Following BICR verified radiographic progression and study treatment discontinuation, patients who were randomized to the control arm may be eligible to receive SG in the crossover phase of this study. All patients, including those who prematurely terminate study treatment, will be followed every 12 weeks (± 7 days) or more frequently for survival until death or withdrawal of consent.
Patients will undergo screening, tumor, safety, laboratory, biomarker, pharmacokinetics (PK), immunogenicity and QOL evaluations.

Intervention

Please refer to tables 1-3 of the Main ICF.

Study burden and risks

Please refer to section E9 of this form.

Contacts

Public
Gilead Sciences

Lakeside Drive 333
Foster City CA 94404
US
Scientific
Gilead Sciences

Lakeside Drive 333
Foster City CA 94404
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Patients must meet all of the following inclusion criteria to be eligible for participation in this study (no waivers for patient eligibility will be offered or permitted):
1) Female or male patients, regardless of race and ethnic group, who are 18 years of age or older, able to understand and give written informed consent.
2) Patients with locally advanced, inoperable, or metastatic TNBC who have not received previous systemic therapy for advanced disease and whose tumors are PD-L1 negative at screening. Alternatively, patients whose tumors are PD-L1 positive at screening will be eligible if they received an anti-programmed death (ligand) 1 (anti-PD-[L]1) agent (ie, checkpoint inhibitor) in the adjuvant or neoadjuvant setting or if they cannot be treated with an anti-PD-(L)1 agent due to a comorbidity.
a) Patients must have completed treatment for Stage I-III breast cancer, if indicated, and >= 6 months must have elapsed between completion of treatment with curative intent (eg, date of primary breast cancer surgery or date of last (neo)adjuvant chemotherapy administration [including anti-PD-(L)1 treatment], whichever occurred last) and first
documented local or distant disease recurrence. Dates of postoperative radiotherapy are not included in this calculation.
i) Patients who received taxane, gemcitabine, or platinum agents in the (neo)adjuvant setting can be treated with same class of chemotherapy (taxane or gemcitabine/carboplatin) if >= 12 months have elapsed between the completion of treatment with curative intent (eg, date of primary breast tumor surgery or date of last (neo)adjuvant chemotherapy administration, whichever occurred last) and first documented local or distant disease recurrence.
ii) Patients enrolled should have received prior anthracycline in the (neo)adjuvant setting or be considered not eligible for anthracyclines as assessed by the treating physician.
b) Patients presenting with de novo metastatic TNBC are eligible for this study.

c) TNBC status and tumor PD-L1 CPS will be confirmed centrally on a recent or archival tumor specimen. Patients must have histologically or cytologically documented TNBC, according to current ASCO/CAP criteria, defined as negative for ER, progesterone receptor, and HER2. Patients initially diagnosed with hormone receptor-positive or HER2-positive breast cancer must have central confirmation of TNBC in a tumor biopsy obtained from a local recurrence or distant metastasis prior to entry. Tumor combined positive score (CPS) < 10 using the PD-L1 IHC 22C3 assay will be required for eligibility. Alternatively, patients with tumor CPS >= 10 will be eligible if they received an anti--PD--(L)1 agent (ie, checkpoint inhibitor) in the adjuvant or neoadjuvant setting or if they cannot be treated with an antiPD-(L)1 agent due to a comorbidity.
d) Patients must have measurable disease by CT or MRI as per RECIST Version 1.1 criteria as evaluated locally. Tumor lesions situated in a previously irradiated area are considered measurable if unequivocal progression has been documented in such lesions since radiation.
3) Have provided representative formalin-fixed paraffin-embedded (FFPE) tumor specimen in blocks (preferred) or have at least 20 to 25 freshly sectioned unstained slides from fresh biopsy tissue (preferred) or archival tissue block for central testing of ER, progesterone receptor, HER2, and PD-L1 and additional biomarker testing. A baseline biopsy is required if archival tissue is not available and this procedure must be performed prior to the first dose of study treatment and after the patient provides written informed consent. Fine needle aspirates and bone biopsies are not suitable samples.
Note: Tumor tissue quality must be confirmed by the central laboratory. Submission of another tumor specimen may be required if provided specimen is not adequate for assessment. A discussion with the medical monitor is required if only 15 to 19 unstained slides are available and it is not clinically feasible to obtain a new biopsy.
4) ECOG performance status score of 0 or 1
5) Life expectancy >= 3 months
6) Recovered from major surgery for >= 2 weeks
7) Adequate hematologic counts without transfusional or growth factor support within 2 weeks of study treatment initiation (hemoglobin >= 9 g/dL, ANC >= 1500/mm3, and platelets >= 100,000/µL).
8) Adequate hepatic function (bilirubin <= 1.5 x ULN, AST and ALT <= 2.5 x ULN or <= 5 x ULN if known liver metastases, and serum albumin > 3 g/dL).
9) Creatinine clearance >= 30 mL/min as assessed by the Cockcroft-Gault equation.
10) International Normalized Ratio (INR)/PT and PTT or aPTT <= 1.5 ULN unless patient is currently receiving therapeutic anticoagulant therapy.
11) Male patients and female patients of childbearing potential who engage in heterosexual intercourse must agree to use protocol-specified method(s) of contraception as described in protocol Appendix 3.
12) Patients with HIV must be on antiretroviral therapy (ART) and have a well-controlled HIV infection/ disease

Exclusion criteria

Patients who meet any of the following exclusion criteria are not eligible to be enrolled in this study (no waivers for patient eligibility will be offered or permitted):
1) Positive serum pregnancy test or women who are lactating.
2) Known or severe (>= Grade 3) hypersensitivity or allergy to sacituzumab govitecan and/or the chemotherapy regimen of choice in the TPC arm (eg, nab-paclitaxel, paclitaxel, gemcitabine, or Carboplatin), their metabolites, or formulation excipient.
3) Requirement for ongoing therapy with or prior use of any prohibited medications listed in section 5.6.1 of the protocol.
4) Patients may not have received systemic anticancer treatment (with the exception of endocrine therapy) within the previous 6 months or radiation therapy within 2 weeks prior to enrollment. Patients must have recovered (ie, > Grade 2 is considered not recovered) from AEs due to a previously administered agent at the time of study entry.
- Note: patients with any grade neuropathy or alopecia are an exception to this criterion and will qualify for the study.
- Note: if patients received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.
5) Patients may not be participating in a study with an investigational agent or investigational device within 4 weeks prior to randomization. Patients participating in observational studies are eligible.
6) Have previously received topoisomerase 1 inhibitors or antibody drug conjugates containing a topoisomerase inhibitor.
7) Have an active second malignancy.
8) Have known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Patients with previously treated brain metastases may participate (with the exception of those treated with chemotherapy) provided they have stable CNS disease (defined as radiographic stability demonstrated with a minimum of 2 posttreatment brain imaging assessments; one performed during screening) for at least 4 weeks prior to enrollment and all neurologic symptoms have returned to baseline, have no evidence of new or enlarging brain metastases, and have also been clinically stable for at least 2 weeks while taking <= 10 mg/day of prednisone or its equivalent. All patients with carcinomatous meningitis are excluded regardless of clinical stability.
9) Met any of the following criteria for cardiac disease:
a) Myocardial infarction or unstable angina pectoris within 6 months of enrollment.
b) History of serious ventricular arrhythmia (ie, ventricular tachycardia or ventricular fibrillation), high-grade atrioventricular block, or other cardiac arrhythmias requiring antiarrhythmic medications (except for atrial fibrillation that is well controlled with antiarrhythmic medication); history of QT interval prolongation.

c) New York Heart Association Class III or greater congestive heart failure or known left ventricular ejection fraction of < 40%.
10) Have active chronic inflammatory bowel disease (ulcerative colitis, Crohn*s disease) or GI perforation within 6 months of enrollment.
11) Have active serious infection requiring antibiotics.
12) Patients positive for HIV-1 or 2 with a history of Kaposi sarcoma and/or Multicentric Castleman Disease.
13) Have active HBV (defined as having a positive HbsAg test) or HCV.
a) For patients with a history of HBV infection, a hepatitis B core antibody test should be conducted at screening. If positive, hepatitis B DNA testing will be performed and if active HBV infection is ruled out, the patient may be eligible.
b) Patients who are HCV antibody positive with undetectable HCV viral load may be eligible.
14) Have other concurrent medical or psychiatric conditions that, in the investigator*s opinion, may be likely to confound study interpretation or prevent completion of study procedures and follow-up examinations.
15) Has received a live vaccine within 30 days prior to randomization.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	09-03-2023
Enrollment:	16
Type:	Actual

Medical products/devices used

Registration:	No
Product type:	Medicine
Brand name:	Carboplatin
Generic name:	Carboplatin
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Gemcitabine
Generic name:	Gemcitabin Aurobindo
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	nab-Paclitaxel
Generic name:	Abraxane
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Paclitaxel
Generic name:	Paclitaxel
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Sacituzumab govitecan
Generic name:	Trodelvy
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	17-05-2022
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	24-10-2022
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO	

Date:	04-01-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	12-01-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	30-10-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	09-01-2024
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	01-07-2024
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	22-07-2024
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EU-CTR	CTIS2023-504195-14-00
EudraCT	EUCTR2021-005743-79-NL
CCMO	NL81012.028.22