A Randomized, Open-label, Phase 3 Study of Sacituzumab Govitecan and Pembrolizumab Versus Treatment of Physician's Choice and Pembrolizumab in Patients With Previously Untreated, Locally Advanced Inoperable or Metastatic Triple-Negative Breast Cancer, Whose Tumors Express PD-L1

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This study has been transitioned to CTIS with ID 2023-504194-21-00 check the CTIS register for the current data. Primary Objective:- To compare progression-free survival (PFS) as assessed by blinded independent central review (BICR) between...

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

Summary

ID

NL-OMON51425

Source
ToetsingOnline

Brief title
ASCENT-04

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: Sponsor

Intervention

Keyword: inoperable triple negative breast cancer, Open-label, Pembrolizumab, 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 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 objective 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.

* TTD of physical functioning domain of the EORTC QLQ-C30

* TTD of role functioning, global health status/QOL, pain, and fatigue subscale

domains of the EORTC QLQ-C30

Exploratory Endpoints:

* 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 after SG

plus pembrolizumab treatment

* Clearance of circulating tumor DNA upon SG plus pembrolizumab treatment

* Correlation of AEs to UGT1A1 status

* Correlation of PK and immunogenicity of SG

* Additional QOL endpoints include mean change from baseline, TTD (in addition

to the subscales specified as secondary endpoints), time to

improvement, proportion improved, and proportion worsened

Study description

Background summary

- Sacituzumab govitecan (Trodelvy®) is currently approved by the United States (U.S.) Food and Drug Administration (FDA) and the European Medicines Agency*s (EMA) for previously treated advanced TNBC. It is also approved by the U.S. FDA for the treatment of patients with bladder cancer and cancers of the urinary tract.
- Pembrolizumab is approved by the U.S. FDA and other regulatory agencies for the treatment of certain types of TNBC. It is also approved for the treatment of several different types of other cancers.
The purpose of this study is to see if sacituzumab govitecan in combination with pembrolizumab can improve lifespans of patients with advanced, PD-L1 positive TNBC and their tumor does not grow or spread when compared to pembrolizumab in combination with chemotherapy (paclitaxel, or nab-paclitaxel, or the combination of gemcitabine and carboplatin).
Sacituzumab govitecan will be administered at a dose of 10 mg/kg intravenously on Days 1 and 8 of 21-day cycles, with dose modifications permitted as specified.
Pembrolizumab will be administered at a dose of 200 mg intravenously on Day 1 of 21-day cycles, with dose modifications permitted as specified.

Study objective

This study has been transitioned to CTIS with ID 2023-504194-21-00 check the CTIS register for the current data.

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

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 evaluate duration of response (DOR) as assessed by BICR between the 2 arms
- To evaluate time to onset of response (TTR) as assessed by BICR between the 2 arms
- To evaluate safety and tolerability between the 2 arms
- To compare time to deterioration (TTD) in physical functioning as measured by European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30 [Version 3.0]) between the 2 arms
- To evaluate TTD in role functioning, global health status/quality of life

(QOL), pain, and fatigue as measured by the EORTC QLQ-C30 (Version 3.0) between the 2 arms

Exploratory Objectives:
- To assess tumor expression of trophoblast cell surface antigen-2 (Trop-2) as a potential biomarker of response to SG plus pembrolizumab
- To explore blood and tumor biomarkers that may be associated with response to SG plus pembrolizumab
- To explore the relationship of adverse events (AEs) to uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1) status
- To characterize the PK and immunogenicity of SG
- To evaluate additional QOL outcomes as measured by 5-level EuroQoL (EQ-5D-5L), theEuropean Organisation for Research and Treatment of Cancer, Breast Cancer Module (EORTC QLQ-BR23), EORTC QLQ-C30, and FACT-GP5 between the 2 arms

Study design

Study Design:
This is an international, multicenter, open-label, randomized, Phase 3 study in participants with locally advanced inoperable or metastatic triple-negative breast cancer (mTNBC) who have not received previous therapy for advanced disease and whose tumors are PD-L1 positive (defined using the PD-L1 IHC 22C3 assay as tumors with a combined positive score [CPS] >= 10) at screening. Enrolled participants 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. Participants 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.
Participants meeting eligibility will be randomly assigned (1:1) to one of 2 arms:
- Arm A: SG 10 mg/kg intravenously on Days 1 and 8 of 21-day cycles and pembrolizumab 200 mg on Day 1 of 21-day cycles. Pembrolizumab will be administered for a maximum of 35 cycles (approximately 2 years).
- Arm B: TPC; 21 or 28-day cycles and pembrolizumab 200 mg on Day 1 of 21-day cycles. Pembrolizumab will be administered for a maximum of 35 cycles (approximately 2 years). The TPC will be limited to one 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.If institutional dose and regimen guidelines
differ, the site may utilize institutional guidelines if approved by the sponsor or designee.
Randomized participants 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 the time between 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
- Geographic region (US/Canada/Western Europe versus rest of world)
- Prior exposure to anti-PD-1 or anti-PD-L1 agent (yes or no)
Tumor assessments will be obtained by computed tomography (CT) or magnetic resonance imaging (MRI) scans every 8 weeks during the first 18 months and then every 12 weeks thereafter until BICR-verified progression of disease or initiation of any new anticancer therapy. Bone scans may be conducted as clinically indicated. For each participant, 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 (CR) and partial response (PR) will 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 collected 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 (EOT) 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, participants who were randomized to the control arm (pembrolizumab + TPC
chemotherapy) may be eligible to receive SG in the crossover phase of this study. Participants who discontinue study treatment without BICR-verified progression should be followed for disease status with imaging studies per protocol until verification of progression or start of new anticancer therapy, whichever occurs first. 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.
Participants will undergo screening, tumor, safety, laboratory, biomarker, PK, immunogenicity and QOL evaluations.

Intervention

Please refer to Tables 1-3 in the Main ICF.

Study burden and risks

Please refer to section E9 of this request 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

Eligible participants include adults age >=18 years with locally advanced inoperable or metastatic TNBC who have not received previous systemic therapy for advanced disease and whose tumors are PD-L1 positive at screening. Participants must have completed systemic treatment for Stage I to III breast

cancer, if indicated, and >=6months must have elapsed between completion of treatment with curative intent and first documented local or distant disease recurrence. Participants presenting with de novo metastatic TNBC are eligible for this study. Tumors will be centrally confirmed for TNBC and PD-L1 status. Triple-negative breast cancer will be defined as negative for estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 (HER2; immunohistochemistry [IHC] 0, IHC 1+ or IHC 2+/in situ hybridization [ISH]) as per current American Society of Clinical Oncology or College of American Pathologists guidelines {Allison 2020, Wolff 2018}. Tumor PD-L1 status will be assessed using the PD-L1 IHC 22C3 assay and participants with tumors with a CPS>=10 will be eligible. Additionally, eligible participants must have an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1 and life expectancy of >=3months.

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 (Appendix 11.4) or women who are lactating.
2) Known or severe (>= Grade 3) hypersensitivity or allergy to SG, pembrolizumab, and/or the chemotherapy regimen of choice in the TPC arm (eg, nab-paclitaxel, paclitaxel, gemcitabine,
or carboplatin), their metabolites, or formulation excipient.
3) Have received prior therapy with an agent directed to another stimulatory or coinhibitory T-cell receptor (eg, CTLA-4, OX-40, CD137)
4) Requirement for ongoing therapy with or prior use of any prohibited medications listed in Section 5.6.1.
5) 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 from AEs due to a previously administered agent to <= Grade 1 or baseline at the time of study entry.
* Note: patients with <= Grade 2 neuropathy or any grade alopecia are an exception to this criterion and will qualify for the study. Patients with endocrine-related AEs Grade <=2 requiring treatment or hormone replacement may be eligible.
* Note: if patients received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.
6) 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.

7) Have previously received topoisomerase 1 inhibitors or antibody drug conjugates containing
a topoisomerase inhibitor.
8) Have an active second malignancy.
Note: patients with a history of malignancy that has been completely treated, with no
evidence of active cancer for 3 years prior to enrollment, or patients with surgically cured
tumors with low risk of recurrence (eg, nonmelanoma skin cancer, histologically confirmed
complete excision of carcinoma in situ, or similar) are allowed to enroll.
9) 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 post-treatment 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.
10) Have undergone an allogenic tissue or solid organ transplant.
11) 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%.
12) Have active chronic inflammatory bowel disease (ulcerative colitis, Crohn*s disease) or GI
perforation within 6 months of enrollment.
13) Have active serious infection requiring systemic antimicrobial therapy.
14) Patients positive for HIV-1 or 2 with a history of Kaposi sarcoma and/or

Multicentric
Castleman Disease.
15) 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.
16) 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.
17) Has a diagnosis of immunodeficiency or receiving systemic corticosteroid therapy (higher
than physiologic doses) >= 10 mg of prednisone per day or equivalent] or any other form of
immunosuppressive therapy within 14 days prior to randomization.
18) Has received a live or live-attenuated vaccine within 30 days prior to randomization.
Administration of killed vaccines are allowed.
19) Has an active autoimmune disease that has required systemic treatment in the past 2 years
(eg, with use of disease modifying agents, corticosteroids, or immunosuppressive drugs).
Replacement therapy (eg, thyroxine, insulin, physiologic corticosteroid replacement therapy
for adrenal or pituitary insufficiency) is not considered a form of systemic treatment and is
allowed.
20) Has a history of (noninfectious) pneumonitis/interstitial lung disease that required steroids or
has current pneumonitis/interstitial lung disease.
21) Has received prior radiotherapy within 2 weeks of start of study intervention. Patients must
have recovered from all radiation-related toxicities, not require corticosteroids, and not have
had radiation pneumonitis. A 1-week washout is permitted for palliative radiation (2 weeks
of radiotherapy) to non-CNS disease.

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):	13-04-2023
Enrollment:	18
Type:	Actual

Medical products/devices used

Registration:	No
Product type:	Medicine
Brand name:	Abraxane
Generic name:	nab-Paclitaxel
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Carboplatin
Generic name:	Carboplatin
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Gemcitabin Aurobindo
Generic name:	Gemcitabin
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:	23-08-2022
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	07-12-2022
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	28-01-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	20-02-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	25-01-2024
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	20-02-2024
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO	

Date:	02-07-2024
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	24-07-2024
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	CTIS2023-504194-21-00
EudraCT	EUCTR2021-005742-14-NL
CCMO	NL81639.028.22