A Phase 3, Open-Label, Multi-Center, Randomized Study Evaluating the Efficacy and Safety of TAR-200 in Combination with Cetrelimab or TAR-200 Alone Versus Intravesical Bacillus Calmette-Guérin (BCG) in Participants with BCG-naïve High-Risk Non-Muscle Invasive Bladder Cancer (HR-NMIBC)

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This study has been transitioned to CTIS with ID 2023-507187-39-00 check the CTIS register for the current data. The purpose of this study is to compare event-free survival (EFS) in participants with Bacillus Calmette-Guerin (BCG)-naive high-risk...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Bladder and bladder neck disorders (excl calculi)
Study type	Interventional

Summary

ID

NL-OMON56283

Source
ToetsingOnline

Brief title
SunRISe-3 / 17000139BLC3002

Condition

- Bladder and bladder neck disorders (excl calculi)

Synonym
'non-muscle invasive bladder cancer' and 'urothelial carcinoma'

Research involving
Human

Sponsors and support

Primary sponsor: Janssen-Cilag
Source(s) of monetary or material Support: Janssen-Cilag International N.V.

Intervention

Keyword: BCG, Cetrelimab, HR-NMIBC/ High-Risk Non-Muscle Invasive Bladder Cancer, TAR-200/Gemcitabine

Outcome measures

Primary outcome

Event-free Survival (EFS) is defined as the time from randomization to either the time of the first recurrence of high-grade disease progression, or death due to any cause, whichever occurs first. For participants with Carcinoma In-situ (CIS), persistent disease at 6 months (Week 24) is also considered an EFS event. Progression is defined as: an increase of stage from Ta to T1 or from CIS to T1 or progression to muscle invasive bladder cancer (MIBC) (T greater than or equal to [>=] 2) or to lymph node (N+) or to distant disease (M+), whichever occurs first.

Secondary outcome

* Overall Complete Response (CR) Rate: Overall CR will be measured by determining the percentage of participants with CIS who have no presence of high- grade disease at 6 months.

* Duration of CR: Duration of CR is defined from the time of first CR achieved to first evidence of recurrence, progression or death due to any cause

(whichever occurs first) for participants who achieve a CR.

* Recurrence-Free Survival (RFS): RFS is defined as the time from randomization to the time of the first recurrence of high-grade disease, or death due to any cause, whichever occurs first.

* Time to Progression (TTP): TTP is defined as the time from randomization to the date of first documented evidence of disease progression or death due to disease progression, whichever occurs first.

* Overall Survival (OS): OS is defined as the time from randomization to death, due to any cause.

* Cancer Specific Survival (CSS): CSS is defined as the time from randomization to the date of death due to bladder cancer.

* Frequency and grade of AE's, according to Common Terminology Criteria for Adverse Events (CTCAE)

* Change from baseline and time to symptom deterioration in EORTC-QLQ-NMIBC24 (European Organisation for Research and Treatment of Cancer Quality of life Questionnaire - Non-muscle Invasive Bladder Cancer 24)

Study description

Background summary

Bladder cancer is the tenth most common malignancy worldwide. About 75 percent (%) of bladder cancers are non-muscle invasive at diagnosis with approximately 25% of NMIBC patients have HR, NMIBC. The TAR- 200/gemcitabine (JNJ-17000139) product is an intravesical drug delivery system regulated as an investigational drug. The drug constituent consists of gemcitabine and osmotic minitablets. Cetrelimab (JNJ-63723283) is a fully human immunoglobulin G4 (IgG4) kappa monoclonal antibody (mAb) that binds programmed-cell death protein (PD)-1. The mainstay of treatment for HR-NMIBC is transurethral resection of bladder tumor,

followed by intravesical treatment with BCG. In this study metronomic dosing of intravesical gemcitabine, delivered via TAR-200, alone or in combination with cetrelimab will be evaluated and compared against intravesical BCG. The study consists of a Screening phase, Treatment phase, and Follow-up phase. The total duration of the study will be up to 5 years and 2 months. Efficacy, Safety, pharmacokinetics (PK), and biomarkers will be assessed at specific time points during the study.

Study objective

This study has been transitioned to CTIS with ID 2023-507187-39-00 check the CTIS register for the current data.

The purpose of this study is to compare event-free survival (EFS) in participants with Bacillus Calmette-Guerin (BCG)-naive high-risk non-muscle invasive bladder cancer (HR-NMIBC), including high-grade papillary Ta, any T1, or carcinoma in situ (CIS), between TAR-200 plus cetrelimab (Group A) and TAR-200 alone (Group C) versus intravesical BCG (Group B).

The secondary objectives are:
* BCG-naïve CIS patients (Group A and Group C versus Group B): compare overall complete response (CR) rate and duration of CR
* BCG-naïve HR-NMIBC high-grade papillary Ta or any T1 patients (Group A and Group C versus Group B): compare recurrence-free survival (RFS)
* compare following parameters in participants with BCG-naïve HR-NMIBC, high-grade papillary Ta or any T1 or CIS (Group A and Group C versus Group B):
- Time to progression
- Overall survival
- Cancer specific survival
- safety and tolerability
- health-related quality of life

Study design

An Open-Label, Randomized Study Evaluating the Efficacy and Safety of TAR-200 in Combination with Cetrelimab or TAR-200 Alone Versus Intravesical Bacillus Calmette-Guérin (BCG) in Participants with BCG-naïve High-Risk Non-Muscle Invasive Bladder Cancer.
Treatment Group A: TAR-200 + Cetrelimab.
Treatment Group C: TAR-200.
Treatment Group B: Bacillus Calmette- Guerin (BCG) Vesiculture.

Intervention

Treatment Group A: intravesical TAR-200 + i.v. Cetrelimab. Participants will have visits every 3 weeks for the first 51 weeks, then every 12 weeks through

week 96.
Treatment Group C: intravesical TAR-200. Participants will have visits every 3 weeks for the first 24 weeks, then every 12 weeks through week 96.
Treatment Group B: Bacillus Calmette- Guerin (BCG) Vesiculture. Participants will receive intravesical BCG once every week for 6 weeks (induction) and then followed by once every week for 3 weeks starting at Weeks 12, 24, 48, 72, and 96 (maintenance).

Study burden and risks

Possible Discomforts, Side Effects and Risks Associated with Cetrelimab
Very common (affects more than 1 in 10 people):
• Physical weakness and loss of strength
• Feeling tired or weak
• Shortness of breath
• Cough
• Diarrhea
• Nausea
• Vomiting
• Decreased appetite
• A fever
• Pain in specific regions such as in the muscles, bones, back, stomach or joints
• Skin rash, dry or red skin, itching
• Increase in liver enzymes in the blood
• Changes in blood levels of electrolytes (such as sodium or potassium), enzymes (such as amylase or lipase) or metabolites (such as creatinine)
• Allergic reaction or reaction to the medicine infusion which may cause fever, chills or rash

Common side effects observed to date in the first Phase 1b clinical trial with TAR-200 in MIBC (muscle invasive bladder cancer) in 23 study participants:
• Very common (may occur more than 10% of the time): Pollakiuria (frequent daytime urination)
• Common (may occur less than 10% of the time): urinary urgency, urinary tract infection, urinary incontinence

Potential Discomforts, Side Effects and Risks Associated with Gemcitabine
Gemcitabine chemotherapy may be associated with some side effects, which might persist after treatment. These include:
• Nausea and vomiting
• Flu-like symptoms
• Rash
• Low blood cell count, which can lead to fatigue, easy bruising or bleeding, or increased risk of infection

• Hair loss
• Constipation
• Mouth sores
• Muscle weakness
• Numbness and tingling

Possible Discomforts, Side Effects and Risks Associated with BCG
Most likely (greater than 10% -1 in 10 patients):
• Burning sensation or pain whit urination
• A sense of needing to urinate often or urinating small amounts often
• Flu-like syndrome of fatigue, joint or muscle pain, chills and fever less than 38°C
• Blood in the urine
• A fever

Risks and inconveniences related to blood draws, bladder biopsies/TURBT, urinary catheter, cystocopy procedure, radiological scans and radiation risk.

Contacts

Public
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Age 1. Age >=18 years (or the legal age of consent in the jurisdiction in which the study is taking place) at the time of informed consent. Disease Characteristic 2. Criterion modified per Global Amendment 1 2.1 Criterion modified per Global Amendment 2 2.2 Histologically confirmed initial diagnosis by local pathology (within 90 days of the most recent signed informed consent) of HR-NMIBC (high-grade Ta,any T1 or CIS), [AJCC 2017], in participants who are BCG-nai*ve. Mixed histology tumors are allowed if urothelial differentiation (transitional cell histology) is predominant. However, the presence of neuroendocrine, micropapillary, signet ring cell, plasmacytoid, or sarcomatoid features will make a participant ineligible. Participants may have had a history of HR-NMIBC (defined as high-grade Ta, any T1, or CIS) as long as it has been >3 years from current/novel diagnosis of HR-NMIBC (high-grade Ta, any T1 or CIS). 3. BCG-nai*ve (participants who have not received prior intravesical BCG or who previously received but stopped BCG more than 3 years before date of randomization are eligible) (Kamat 2016). 4. Participants must be willing to undergo all study procedures (eg, multiple cystoscopies from Screening through the end of study and TURBT/bladder biopsy for assessment of recurrence/progression). 5. Criterion modified per Global Amendment 2 5.1 All visible papillary disease must be fully resected (absent) prior to date of randomization and documented at baseline cystoscopy. Local urine cytology at screening must be negative or atypical (for HGUC) for patients with papillary only disease (without CIS). 6. All AEs associated with any prior surgery and/or intravesical therapy must have resolved to CTCAE version 5.0 Grade <2 prior to date of randomization. Type of Participant 7. Eastern Cooperative Oncology Group (ECOG) performance status Grade 0, 1, or 2. 8. Thyroid function tests within normal range or stable per Investigator assessment. Investigators may consult an endocrinologist for participant eligibility assessment in the case of equivocal or marginal tests results. 9.1 Criterion modified per Global Amendment 1 9.2 Criterion modified per Global Amendment 2 Adequate bone marrow, liver, and renal function: A. Bone marrow function (without the support of cytokines or erythropoiesis stimulating agent in the preceding 2 weeks): i. Absolute neutrophil count (ANC) >=1,000/mm3 ii. Platelet count >=75,000/mm3 iii. Hemoglobin >=8.0 g/dL B. Liver function: i. Total bilirubin <=1.5 x ULN or direct bilirubin < ULN for participants with total bilirubin levels >1.5xULN (except participants with Gilbert*s Syndrome, who must have a total bilirubin <3.0 mg/dL), ii. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) <=2.5x institutional ULN C. Renal function: i. Creatinine clearance >30 mL/min

using the Cockcroft-Gault formula. (See Section 10.15: Appendix 15). Sex and Contraceptive/Barrier Requirements For inclusion criteria 10-11 Please see the protocol. Informed Consent 12. Criterion modified per Global Amendment 1 12.1 Participants must sign an informed consent form (ICF) (or their legally acceptable representative must sign) indicating that he or she understands the purpose of, and procedures required for, the study and is willing to participate in the study and agree to store samples when applicable. 13. Participants must be willing and able to adhere to the lifestyle restrictions specified in this protocol.

Exclusion criteria

Disease Characteristics 1.Criterion modified per Global Amendment 1 1.1 Presence or history of histologically confirmed, muscle invasive, locally advanced, nonresectable, or metastatic urothelial carcinoma (ie, >=T2). 2. Must not have had urothelial carcinoma or histological variant at any site outside of the urinary bladder (ie, urethra, ureter, or renal pelvis). Ta/any T1/CIS of the upper urinary tract (including renal pelvis and ureter) is allowable if treated with complete nephroureterectomy more than 24 months prior to randomization. 3. Criterion modified per Global Amendment 2 3.1 N+ and/or M+ per blinded independent central review (BICR) of computed tomography/magnetic resonance (CT/MR) Urography and chest CT. Any history of HR-NMIBC (high-grade Ta, any T1 or CIS) <3 years from current diagnosis. Medical Conditions 4.1 Active malignancies (ie, progressing or requiring treatment change in the last 24 months prior to randomization) other than the disease being treated under study. Potential allowed exceptions include the following (others may be allowed with Sponsor approval). a. skin cancer (non-melanoma or melanoma) that is considered completely cured. b. non-invasive cervical cancer treated that is considered completely cured. c. adequately treated lobular carcinoma in situ (LCIS) and ductal CIS d. history of localized breast cancer and receiving antihormonal agents e. history of localized prostate cancer (N0M0) and receiving androgen deprivation therapy f. Locerion modified per Global Amendment 2alized prostate cancer (N0M0): i. with a Gleason score of 6, treated within the last 24 months or untreated and under surveillance, ii. with a Gleason score of 3+4 that has been treated more than 6 months prior to full study Screening and considered to have a very low risk of recurrence, iii. or history of localized prostate cancer and receiving androgen deprivation therapy and considered to have a very low risk of recurrence. 5. Presence of any bladder or urethral anatomic feature (eg, urethral stricture) that, in the opinion of the Investigator, may prevent the safe insertion, indwelling use, removal of TAR-200, or administration of intravesical BCG. Participants with tumors involving the prostatic urethra in men will be excluded. 6. A history of clinically significant polyuria with recorded 24-hour urine volumes greater than 4000 mL. 7.1 Received a live virus vaccine within 30 days prior to the initiation of study treatment. Inactivated (non-live, or non-replicating)

vaccines approved or authorized for emergency use (eg,COVID-19) by local health authorities are allowed. 8.1. Participants should not have a history of acute ischemic heart disease within 42 days of randomization, or history of uncontrolled cardiovascular disease including any of the following in the 3 months prior to randomization: a. unstable angina, b. myocardial infarction, c. ventricular fibrillation, d. Torsades de Pointes, e. cardiac arrest, or known congestive New York Heart Association Class III-IV heart failure, f. cerebrovascular accident, g. transient ischemic attack, or h. pulmonary embolism or other venous thromboembolism in the 3 months prior to randomization. 9. Indwelling catheters are not permitted; however, intermittent catheterization is acceptable. 10. Participants must not have clinically significant liver disease that precludes participant treatment regimens prescribed on the study (including, but not limited to active viral, alcoholic, or other autoimmune hepatitis, cirrhosis, or inherited liver disease). 11. Active hepatitis B or C infection (for example, participants with history of hepatitis C infection but undetectable hepatitis C virus polymerase chain reaction (PCR) test and participants with history of hepatitis B infection with positive HBsAg antibody and undetectable PCR are allowed). 12.1 Human immunodeficiency virus (HIV) infection, unless the participant has been on a stable anti-retroviral therapy regimen for the last 6 months or more prior to randomization and has had no opportunistic infections and a CD4 count of >350 in the last 6 months. 13. Participants with congenital immunodeficiencies. 14. Evidence of radiographic features associated with pulmonary fibrosis/ advance interstitial lung disease (ILD) (pulmonary consult may be required by the Investigator) as determined by BICR of chest CT, medical history of pneumonitis/ILD, or active non-infectious pneumonitis/ILD. 15. Evidence of active tuberculin infection (eg, positive Mantoux test). 16. Criterion removed per Global Amendment 2. 17. Major surgery and/or not fully recovered within 4 weeks before first dose (TURBT is not considered major surgery). For exclusion criteria 18-35 please see the protocol.

Study design

Design

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

Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	29-11-2023
Enrollment:	14
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Cetrelimab
Generic name:	Cetrelimab
Product type:	Medicine
Brand name:	TAR-200
Generic name:	TAR-200
Product type:	Medicine
Brand name:	VesiCulture
Generic name:	Mycobacterium bovis BCG (Bacillus Calmette-Guérin), Danish strain 1331, live attenuated

Ethics review

Approved WMO Date:	17-11-2022
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	02-02-2023
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	10-03-2023

Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	17-03-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	03-07-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	18-07-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	09-10-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	24-10-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	21-11-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

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	CTIS2023-507187-39-00
EudraCT	EUCTR2020-004506-64-NL
CCMO	NL82250.056.22