A Phase 2, Open-Label, Multi-Center, Randomized Study of TAR-200 in Combination with Cetrelimab and Cetrelimab Alone in Participants with Muscle-Invasive Urothelial Carcinoma of the Bladder who are Scheduled for Radical Cystectomy and are Ineligible for or Refusing Platinum-Based Neoadjuvant Chemotherapy

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This study has been transitioned to CTIS with ID 2023-507189-17-00 check the CTIS register for the current data. 2. Objective of the study (in English): The main purpose of this study is to determine the anti-tumor effects of TAR-200 + IV cetrelimab...

Ethical review	Approved WMO
Status	Pending
Health condition type	Renal and urinary tract neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON54183

Source
ToetsingOnline

Brief title
SunRISe-4 / 17000139BLC2002

Condition

- Renal and urinary tract neoplasms malignant and unspecified

Synonym
Bladder cancer

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Cetrelimab, MIBC, Radical Cystectomy, TAR-200/Gemcitabine

Outcome measures

Primary outcome

6. Primary study parameters/outcome of the study (in English):

Outcome Measure: Percentage of Participants with Pathologic Complete Response

(pCR)

Time frame: Up to Week 15

Description: Percentage of participants with a pathologic complete response

(pCR) or no evidence of pathologic intravesical disease and nodal involvement

(ypT0N0) derived from analysis of radical cystectomy (RC) bladder specimen will

be reported.

Secondary outcome

7. Secondary study parameters/outcome of the study (if applicable) (in English):

Outcome Measure: Recurrence-Free Survival (RFS)

Time frame: Up to Week 108

Description: RFS is defined as the time from randomization to first radiologic (as assessed by response evaluation criteria in solid tumors [RECIST] 1.1 criteria) or histologic evidence of nodal or metastatic disease or death due to any cause.

Outcome Measure: Number of Participants with Adverse Events (AEs) by Grades According to Common Terminology Criteria for Adverse Events (CTCAE)

Time frame: Up to Week 108

Description: Number of participants with AEs by severity grade as assessed by CTCAE version 5 will be reported. Grade refers to the severity of AE as follows: Grade 1- Mild; Grade 2- Moderate; Grade 3- Severe; Grade 4- Life-threatening; Grade 5- Death related to adverse event.

Outcome Measure: Number of Participants with Change from Baseline in Laboratory Abnormalities

Time frame: Up to Week 108

Description: Number of participants with change from baseline in laboratory abnormalities will be reported. Severity will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0. Severity scale ranges from Grade 1 (Mild) to Grade 5 (Death). Grade 1= Mild, Grade 2= Moderate, Grade 3= Severe, Grade 4= Life-threatening, and Grade 5= Death related to adverse event.

Study description

Background summary

1. Background of the study (in English):
Gemcitabine, an anti-metabolite routinely used in the systemic treatment of various forms of cancer, has demonstrated activity across all stages of urothelial cancer, from organ-confined recurrent low-grade tumors to metastatic disease. TAR-200 is a passive, non-resorbable investigational drug-device combination product whose primary mode of action is the controlled release of gemcitabine into bladder urine. Cetrelimab (JNJ-63723283)is a fully human immunoglobulin G4 (IgG4) kappa monoclonal antibody (mAb) that binds programmed-cell death protein (PD)-1. In this clinical study, we hypothesize that metronomic gemcitabine dosing via TAR-200, in combination with cetrelimab, a PD-1 inhibitor, will not only have marked local cytotoxic effects on bladder tumors, but will have a systemic priming effect, increasing tumor antigen presentation
as well as tumor antigen specific T-cell activation and maintenance. When these T cells are activated by co-treatment with cetrelimab, this systemic anti-tumor activity will result in material benefits in patients with MIBC, including those groups that are not suitable for platinum-based chemotherapy.

Study objective

This study has been transitioned to CTIS with ID 2023-507189-17-00 check the CTIS register for the current data.

2. Objective of the study (in English):
The main purpose of this study is to determine the anti-tumor effects of TAR-200 + IV cetrelimab (cohort 1) and IV cetrelimab alone (cohort 2).
The secondary objectives are to evaluate the safety and tolerability of up to 4 dosing cycles of TAR-
200 + IV cetrelimab (cohort 1) and IV cetrelimab (cohort 2) alone prior to RC and to determine the recurrence-free survival (RFS) in participants receiving TAR-200 + IV cetrelimab (cohort 1) and IV cetrelimab alone (cohort 2).

Study design

3. Study design (in English):
This study is a phase 2, open-label, multi-center, parallel group assignment, randomized study of TAR-200 in combination with cetrelimab (cohort 1) and cetrelimab alone (cohort 2) in participants with MIBC who are scheduled for Radical Cystectomy and are ineligible for or refuse platinum-based neoadjuvant chemotherapy.
The study consists of a Screening phase, Treatment phase and Follow-up phase.

The total duration of study will be up to 2 years and 6 months. Efficacy and safety will be assessed at specific time points during this study.

Intervention

5. Intervention (if applicable) (in English):
Study Arms:
Cohort 1: TAR-200 + IV Cetrelimab (Participants will receive TAR-200 in combination with IV cetrelimab.)
Cohort 2: IV Cetrelimab (Participants will receive IV cetrelimab.)

Participants in Cohort 1 will have the TAR-200 drug-device combination product (225 mg gemcitabine per TAR-200 system) inserted every 3 weeks, until Week 12. Cetrelimab (360mg) will be administered intravenously (IV) every 3 weeks until Week 9.

Participants in Cohort 2 will receive 360 mg of IV Cetrelimab every 3 weeks until Week 9.

Study burden and risks

2.3. Benefit-Risk Assessment
The standard of care in MIBC includes RC with urinary diversion and is considered the preferred
treatment option for patients who are considered surgical candidates. Systemic neoadjuvant
chemotherapy for these patients is associated with increased OS. Specifically, pathologic partial
and complete responses, as well as negative lymph node status, correlate with meaningful diseasefree
and OS benefits (Sonpavde 2009). However, systemic chemotherapy is associated with
significant toxicity, and up to 80% of patients may refuse or be ineligible for neoadjuvant and/or
adjuvant regimens (Haseebuddin 2015). There is a significant unmet need for efficacious and more
tolerable neoadjuvant treatments, specifically for patients who are ineligible for cisplatin-based
chemotherapy. A clinical benefit has been demonstrated in this platinum-ineligible patient
population utilizing checkpoint inhibitor monotherapy (anti-PD-1/PDL-1) and provides rationale
for potential efficacy of single-agent cetrelimab. (Necchi 2019, Powles 2019). In addition, it is
postulated that the sustained antineoplastic local therapy of TAR-200, in combination with an

efficacious anti-PD1 immunotherapy, could potentially provide comparable CR rates to neoadjuvant chemotherapy, without an overlapping toxicity profile.
Intravesical gemcitabine has consistently exhibited activity and a good toxicity profile in bladder cancer, albeit in the setting of non-muscle invasive disease (Shelley 2012). Ongoing clinical studies in MIBC and NMIBC have demonstrated good tolerability of intravesical dosing. Prior clinical trials evaluating the safety of TAR-200 itself have noted an excellent tolerability ad safety profile.
For safety details of intravesical gemcitabine and the TAR-200 drug device combination product, refer to the most recent version of the IB.
Overall, the safety profile of IV cetrelimab monotherapy is well-tolerated and generally consistent across completed and ongoing clinical trials. Most adverse events (AEs) were low-grade (Grade 1 to 2) with relatively few related high-grade (Grade 3 to 4) AEs. There was no pattern in the incidence, severity, or causality of AEs with respect to cetrelimab dose level.

For the recognized pattern of immune-related adverse events (irAEs) that are defined, management algorithms have been developed. Treatment plans for diarrhea/colitis, renal insufficiency, pneumonitis, transaminitis, asymptomatic thyroid stimulating hormone elevation, symptomatic endocrinopathy, retinopathy, suspicion of adrenal crisis, rash, and neurological toxicity are provided in Section 10.9, Appendix 9, Guidelines for Management of Immune-Related Adverse Events and Adverse Events of Clinical Interest. Most high-grade events were manageable with the use of corticosteroids or hormone replacement therapy (endocrinopathies) as instructed in these algorithms.
Additional details on the safety profile of cetrelimab, including results from other clinical studies, are also available in the cetrelimab IB.
Overall, for participants who are ineligible for cisplatin-based treatment, the treatment of TAR-200 in combination with IV cetrelimab (hereafter referred to as "TAR-200 + IV cetrelimab) or IV cetrelimab alone, has the potential to increase disease-free and survival periods relative to patients who are unable to receive neoadjuvant

chemotherapy. Little
systemic toxicity is expected from TAR-200 reducing the risks observed with systemic
chemotherapy.
Accounting for the measures taken to minimize AEs in participants
of this study, the identified potential risks of TAR-200 in combination with cetrelimab are justified
by the anticipated benefits that may be afforded to participants with MIBC who are scheduled for
radical cystectomy and ineligible for platinum chemotherapy.
From a risk-based alternative treatment perspective, chemoradiotherapy has been proposed
as an alternative to RC. Several organizations, including the AUA and the EAU, have updated
their guidelines to support chemoradiotherapy as an alternative to RC in patients with
muscle-invasive disease. However, chemoradiotherapy has been associated with both acute and latent toxicity,
including local and systemic symptoms. Such acute toxicities include anemia, fatigue, colitis, and
cystitis, while latent longer-term toxicities and side effects may include bladder contracture,
hemorrhagic cystitis, secondary malignancy, and urethral or rectal stricture. Therefore, while
participants in this clinical study should be counseled on all treatment options, RC
remains a standard of care.
More detailed information about the known and expected benefits and risks of TAR-200 and
cetrelimab may be found in the respective IBs for these study drugs.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Inclusion Criteria: - Histologically proven, cT2-T4a N0, M0 infiltrating urothelial carcinoma of the bladder. Initial diagnosis must have been within 120 days of randomization date. Participants with variant histologic subtypes are allowed if tumor(s) demonstrate urothelial predominance. However, the presence of small cell or neuroendocrine variants will make a participant ineligible - Participants with no residual tumor, or intravesical tumor size of less than or equal to <=3 centimeter (cm) following transurethral resection of bladder tumor (TURBT) are eligible; debulking TURBT for any residual disease is encouraged but not mandated. Participants with persistent tumors greater than (>)3 cm at screening must undergo a second debulking, re-staging TURBT. Participants will be ineligible if any individual tumor is greater than (>)3 cm after debulking TURBT - Deemed eligible for and willing to undergo RC by the operating urologist - Eastern Cooperative Oncology Group (ECOG) performance status Grade 0 or 1 - Thyroid function tests within normal range or stable on hormone supplementation per investigator assessment. Investigators may consult an endocrinologist for participant eligibility assessment in the case of equivocal or marginal tests results - All adverse events associated with any prior surgery must have resolved to common terminology criteria for adverse events (CTCAE) version 5.0 Grade less than (<) 2 prior to randomization

Exclusion criteria

Exclusion Criteria:
- Must not have received prior systemic chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to starting study treatment

- Participants must not have evidence of cT4b, or N1-3, or M1 disease based on central radiology staging (chest, abdomen, and pelvis must be performed using computed tomography [CT] or magnetic resonance imaging [MRI]) within 42 days prior to randomization
- Presence of any bladder or urethral anatomic feature that, in the opinion of the Investigator, may prevent the safe placement, indwelling use, or removal of TAR-200
- Prior systemic chemotherapy for urothelial cell carcinoma of the bladder at any time
- Currently participating or has participated in a study of an investigational agent and received study therapy or investigational device within 4 weeks prior to enrollment
- Participants with evidence of bladder perforation during diagnostic cystoscopy. Participant is eligible if perforation has resolved prior to dosing

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	05-07-2023
Enrollment:	8
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Cetrelimab
Generic name:	Cetrelimab

Product type:	Medicine
Brand name:	TAR-200
Generic name:	TAR-200

Ethics review

Approved WMO Date:	28-04-2022
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	26-04-2023
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	14-06-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	23-06-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	09-10-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	26-10-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	13-11-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	22-12-2023

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	CTIS2023-507189-17-00
EudraCT	EUCTR2020-005565-13-NL
CCMO	NL75605.028.22