An Open-label, Randomized, Controlled Phase 3 Study of Disitamab Vedotin in Combination with Pembrolizumab Versus Chemotherapy in Subjects with Previously Untreated Locally Advanced or Metastatic Urothelial Carcinoma that Expresses HER2 (IHC 1+ and Greater)

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Primary Objectives:Associated pharmaceutical trial:To compare the efficacy of disitamab vedotin in combination with pembrolizumab to chemotherapy as first-line treatment in participants with advanced UC that expresses HER2Clinical...

Ethical review	Approved WMO
Status	Pending
Health condition type	Renal and urinary tract neoplasms malignant and unspecified
Study type	Interventional research previously applied in human subjects

Summary

ID

NL-OMON56748

Source
ToetsingOnline

Brief title
Disitamab Vedotin With Pembrolizumab vs Chemotherapy in Urothelial Cancer

Condition

- Renal and urinary tract neoplasms malignant and unspecified

Synonym
bladder cancer; kidney cancer

Research involving
Human

Sponsors and support

Primary sponsor: Seagen Inc., a wholly owned subsidiary of Pfizer
Source(s) of monetary or material Support: Seagen Inc., a wholly owned subsidiary of Pfizer

Intervention

- In-vitro diagnostic

Keyword: disitamab vedotin, HER2, previously untreated urothelial cancer

Explanation

N.a.

Outcome measures

Primary outcome

Associated pharmaceutical trial:
- PFS per Response Evaluation Criteria in Solid Tumors (RECIST) version (v)1.1
by blinded independent central review (BICR)
- Overall survival (OS)

Clinical Performance study:
The dual primary endpoints of the Study C5731001/SGNDV-001 are PFS per RECIST (v1.1)
according to BICR assessment among all randomized participants as well as OS. These endpoints will also serve as the dual primary endpoints for the diagnostic
protocol to inform on the clinical utility of these assays to identify participants
likely to benefit from treatment with the IMP in the Study C5731001/SGNDV-001
population.

Secondary outcome

Associated pharmaceutical trial:

• ORR, DOR, DCR per RECIST v1.1 by BICR
• ORR, DOR, DCR and PFS per RECIST v1.1 by investigator assessment
• Type, incidence, relatedness, severity, and seriousness of adverse events (AEs)
• Type, incidence, and severity of laboratory abnormalities
• Treatment discontinuation rate due to AEs
• Electrocardiogram abnormalities, including changes in corrected QT interval
• Effect on left ventricular ejection fraction
• Change from baseline to Week 16 in European Organisation for Research and
Treatment of Cancer core QoL questionnaire (EORTC QLQ-C30) Global Health Status (GHS)/QoL Score (Items 29+30)
• Time to Deterioration in EORTC QLQ-C30 GHS/QoL Score (Items 29 + 30)
• Time to pain progression

Study description

Background summary

The objective of this clinical performance study (CPS) is to characterize the clinical performance of the investigational in vitro diagnostic (IVD) assays used in the clinical trial C5731001/SGNDV-001 (Study C5731001/SGNDV-001).

Study C5731001/SGNDV-001, which is sponsored by Seagen Inc. (Seagen), a wholly owned subsidiary of Pfizer Inc. (Pfizer), is considered to be a combined clinical trial (as defined in the MDCG 2022-10 guidance) and is comprised of 2 studies:

• A pharmaceutical study assessing an investigational medicinal product (IMP) being developed by Pfizer:
o Disitamab vedotin (DV; RC48-ADC)

• A clinical performance study (CPS) evaluating 2 investigational IVDs manufactured by Ventana Medical Systems, Inc. (Ventana), also known as Roche Tissue Diagnostics (RTD)
o VENTANA human epidermal growth factor receptor 2 (HER2)/neu (4B5) Investigational Use Only (IUO) Assay (VENTANA HER2 (4B5) Assay)
o VENTANA HER2 Dual in situ hybridization (ISH) DNA Probe Cocktail (VENTANA HER2 Dual ISH).

Study objective

Primary Objectives:

Associated pharmaceutical trial:
To compare the efficacy of disitamab vedotin in combination with pembrolizumab to chemotherapy as first-line treatment in participants with advanced UC that expresses HER2

Clinical performance study:
To assess the clinical performance of the investigational HER2 devices (VENTANA HER2 (4B5) and VENTANA HER2 Dual ISH assays) to identify participants with tumors with HER2 expression (HER2 low and HER2 positive), who will receive treatment per the Study C5731001/SGNDV-001.

Secondary Objectives:
Associated pharmaceutical trial:

- To compare objective response rate (ORR) between treatment with disitamab vedotin in combination with pembrolizumab versus chemotherapy
- To compare duration of response (DOR) between treatment with disitamab vedotin in combination with pembrolizumab versus chemotherapy
- To compare disease control rate (DCR) between treatment with disitamab vedotin in combination with pembrolizumab versus chemotherapy
-To compare progression-free survival (PFS) by investigator between treatment with disitamab vedotin in combination with pembrolizumab versus chemotherapy
- To evaluate the safety profile of each treatment regimen
- To compare the impact of treatment with disitamab vedotin in combination with pembrolizumab versus chemotherapy with respect to quality of life (QoL) and symptoms, including pain, from the participant's perspective

Clinical Performance study:
- To assess the staining performance of the VENTANA HER2 (4B5) assay in staining formalin-fixed, paraffin-embedded (FFPE) LA/mUC samples on the BenchMark ULTRA instrument in a clinical use setting.
- To assess the staining performance of the VENTANA HER2 Dual ISH assay in staining FFPE LA/mUC samples on the BenchMark ULTRA instrument in a clinical use setting.

Study design

In this combined clinical trial, the investigational IVD assays will be used to assess human epidermal growth factor receptor 2 (HER2) biomarker status as part of determining participant eligibility for inclusion in the pharmaceutical study.
The results of Study C5731001/SGNDV-001 are intended to support the safety and efficacy of both the IMP and the investigational IVD products used to select participants most likely to respond to the IMP.
The interventional CPS includes activities executed at the clinical sites, as described in the Study C5731001/SGNDV-001 clinical protocol and the clinical performance plan, as well as activities that take place at diagnostic testing site(s) (central laboratories) and described in the diagnostic testing sub-protocol (protocol RD006556, executed by Ventana).

Intervention

Group A: disitamab vedotin on Day 1, Day 15, and Day 29 of each 6 week cycle. Pembrolizumab on Day 1 of each 6-week cycle.
Group B: gemcitabine on Day 1 and Day 8 of each 3-week cycle. Cisplatin or carboplatin on Day 1 of each 3-week cycle.

Study burden and risks

There is a risk that the test might not work as expected because it is still being developed.
- The test could be wrong and show that a tumor makes HER2 when it does not make HER2. The patient could qualify for the drug study based on this result. If that happens, the patient could have the risks of side effects without the possible helpful effect of the study drug.
- Or the test could be wrong and show that a tumor does not make HER2, but it really does make HER2. The patient wouldn’t qualify for the drug study if this happens.

If a new biopsy needs to be taken, there could be risks from that procedure.

Contacts

Scientific
Seagen Inc., a wholly owned subsidiary of Pfizer
K. Sokolowski
30th Drive SE 21823
Bothell WA98021
United States
+14255999019
Public
Seagen Inc., a wholly owned subsidiary of Pfizer
K. Sokolowski
30th Drive SE 21823
Bothell WA98021
United States
+14255999019

Trial sites

Trial sites in the Netherlands

Amphia Ziekenhuis
Target size: 3

Antoni van Leeuwenhoek (AVL)
Target size: 3

Radboud Universitair Medisch Centrum
Target size: 3

HagaZiekenhuis
Target size: 3

Rijnstate Ziekenhuis
Target size: 3

Maastricht Universitair Medisch Centrum +
Target size: 3

Listed location countries

France, Hungary, Ireland, Netherlands, Portugal, Singapore, India, New Zealand, Australia, Greece, Argentina, Belgium, Brazil, Italy, Croatia, Norway, Taiwan, United Kingdom, Mexico, Canada, Czech Republic, Israel, Japan, Peru, Spain, Turkey, United States, Thailand

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)
Adolescents (16-17 years)

Inclusion criteria

Inclusion criteria for the pharmaceutical study and the performance study in the combined trial are the same:

Participants must meet all of the following inclusion criteria to be eligible for enrollment into the study:

1. Age 18 years and older at the time of consent or considered an adult by local regulations.
2. Participants must have LA/mUC with histopathological confirmation (Stage IIIB-IV per American Joint Committee on Cancer, Cancer Staging Atlas 8th ed.), including UC originating from the renal pelvis, ureters, bladder, or urethra. Mixed-cell type tumors are eligible as long as urothelial (transitional cell histology) carcinoma is the predominant cell type.

3. Participants must have measurable disease by investigator assessment according to RECIST v1.1.

   Note: Participants with prior definitive radiation therapy must have measurable disease per RECIST v1.1 that is outside the radiation field or has demonstrated unequivocal progression since completion of radiation therapy.

4. Participants must not have received prior systemic therapy for locally advanced or metastatic UC with the following exceptions:
   1. Neoadjuvant or adjuvant therapy, including PD-(L)1 inhibitors, is acceptable, if

disease recurrence/progression occurred more than 12 months after the last dose of therapy.

5. Participants must be considered eligible to receive cisplatin- or carboplatin-containing chemotherapy, per the investigator's evaluation. Participants meeting any of the following criteria should be considered cisplatin-ineligible, and will receive carboplatin:
    1. CrCl <60 mL/min but ≥30 mL/min within 7 days of randomization (measured by the Cockcroft-Gault formula).
    2. ECOG performance status of 2 within 7 days of randomization (refer to Inclusion Criterion 8 for additional criteria for ECOG 2 participants).
    3. NCI CTCAE Grade 2 or higher hearing loss.
6. Participants must be willing and able to provide archived formalin-fixed paraffin-embedded tumor tissue blocks (or, alternatively, freshly sectioned slides; see laboratory manual for details) from a muscle-invasive or metastatic UC lesion or a biopsy sample of metastatic UC. This must be obtained prior to study treatment initiation and will be sent to a sponsor-designated central laboratory for biomarker analysis. If archival tissue is not available, then a newly obtained "fresh" baseline biopsy of an accessible tumor lesion is required within 28 days prior to Cycle 1 Day 1. Biopsy must provide adequate tissue for HER2 testing.
    1. Tumor tissue recommended to be collected within 12 months prior to enrollment or most recent sample. Tumor tissue obtained after completion of the most recent (neo) adjuvant systemic therapy is preferred.
7. HER2 expression of 1+ or greater on IHC determined by central laboratory.
8. An ECOG performance status score of 0, 1, or 2 within 7 days prior to randomization.
    1. Participants with ECOG 2 must meet additional criteria: Hb ≥10 g/dL, CrCl ≥50 mL/min, and heart failure severity less than New York Heart Association (NYHA) Class III.
9. Adequate baseline cardiac parameters:
    1. LVEF ≥50%
    2. Fridericia's corrected QT interval (QTcF) <470 ms
10. The following baseline laboratory data, laboratory values collected within 7 days prior to randomization are acceptable:
    1. Hb ≥9 g/dL without transfusion
    2. ANC ≥1.5 × 109/L
    3. Platelet count ≥100 × 109/L
    4. ALT and AST ≤2.5 × upper limit of normal (ULN) without liver metastases or ≤5 × ULN with liver metastases
    5. Serum total bilirubin ≤1.5 × ULN or direct bilirubin ≤ ULN for participants with total bilirubin >1.5 × ULN; serum total bilirubin ≤3 × ULN for participants with Gilbert's syndrome

Exclusion criteria

Exclusion criteria for the pharmaceutical study and the performance study in the combined trial are the same:

Participants meeting any of the following exclusion criteria are ineligible for enrollment into

the study:

1. Known hypersensitivity to any excipient contained in the drug formulation of disitamab vedotin, cisplatin, carboplatin, gemcitabine, or pembrolizumab.
2. History of severe/life threatening IMAE with PD-(L)1 inhibitors are excluded. Please consult with medical monitor.
    1. Grade ≥3 cardiomyopathy
    2. Grade 4 diarrhea/colitis IMAEs, hepatitis IMAEs, rash IMAEs
    3. Grade 3/4 adrenal insufficiency, hypophysitis, uveitis, hypothyroidism
3. CNS and/or leptomeningeal metastasis.

    1. Participants with treated CNS metastases (by whole brain radiation therapy, surgery or radiosurgery, etc.) are permitted on study if all of the following are met:

        i. CNS metastases have been clinically stable for at least 4 weeks and baseline scans show no evidence of new or worsening CNS metastasis.

        ii. Participant is on a stable dose of ≤10 mg/day of prednisone or equivalent for at least 2 weeks.

4. History of or active autoimmune disease that has required systemic treatment in the past 2 years (ie, with use of disease modifying agents, corticosteroids, or immunosuppressive drugs).
    1. Replacement therapy (eg, thyroxine, insulin, physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic disease-modifying treatment and is allowed, if disease is stable.
    2. Participants with vitiligo, psoriasis, type 1 diabetes mellitus, hypothyroidism, or resolved childhood asthma/atopy are allowed.
    3. Participants requiring intermittent use of bronchodilators, inhaled steroids, or local steroid injections are allowed.
    4. Participants with hypothyroidism that is stable with hormone replacement or Sjögren's syndrome are allowed.
5. Participants who have previously received any prior treatment with an agent directed to another stimulatory or co-inhibitory T cell receptor (including but not limited to CD137 agonists, CAR-T cell therapy, CTLA-4 inhibitors, or OX-40 agonists) are excluded.
6. Participants with prior solid organ or bone marrow transplantation.
7. Pleural effusion or ascites with symptoms or requiring symptomatic treatment.
8. Participants with an estimated life expectancy <12 weeks.
9. Participants with ongoing clinically significant toxicity associated with prior treatment that has not resolved to ≤ Grade 1 or returned to baseline, except for Grade 2 alopecia.

10. Participant has received prior radiotherapy to a metastatic site without the use of chemotherapy radiosensitization within 3 weeks of the first dose of study intervention, with the exception of palliative radiotherapy to bone lesions, which is allowed if completed 2 weeks before the start of study intervention. Participants must have recovered from all radiation-related toxicities and must not require corticosteroids.

    Note: Ongoing hormonal/antihormonal treatment (eg, for breast cancer) is allowed,

provided that the participant is eligible per exclusion criteria of prior malignancy.

11. Participants who previously received treatment with an MMAE agent or anti-HER2 therapy.
12. Ongoing sensory or motor neuropathy Grade 2 or higher.
13. Participants with acute, chronic, or symptomatic infections, including:
    1. Ongoing symptomatic severe acute respiratory syndrome-associated coronavirus 2 (SARS-CoV-2) infection except for participants who have recovered clinically but continue to have a detectable presence of SARS-CoV-2.
    2. History of human immunodeficiency virus (HIV) infection. Testing is not required unless mandated by local regulations.
    3. History of hepatitis

Study design

Design

Study phase:	N/A
Study type:	Interventional research previously applied in human subjects
Intervention model:	Other
Allocation:	Non controlled trial
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Other

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-03-2024
Enrollment:	14
Duration:	24 months (per patient)
Type:	Anticipated

WORLD

Recruitment status:	Pending
Start date (anticipated):	01-03-2024
Enrollment:	400
Type:	Anticipated

Medical products/devices used

Product type:	Medical device
Generic name:	VENTANA HER2/neu (4B5) IUO Assay and VENTANA HER2 Dual ISH DNA Probe Cocktail Assay
Registration:	Yes - CE outside intended use

IPD sharing statement

Plan to share IPD: Undecided

Plan description
N.a.

Ethics review

Approved WMO Date:	16-05-2024
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	24-04-2025
Application type:	Amendment
Review commission:	METC NedMec

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	2022-501105-12-00
CCMO	NL86149.000.24
Research portal	NL-005719