ISRCTN11908197 https://doi.org/10.1186/ISRCTN11908197

Disitamab vedotin with pembrolizumab vs chemotherapy in previously untreated urothelial cancer expressing HER2

Submission date 24/04/2024	**Recruitment status** Recruiting	[X] Prospectively registered [ ] Protocol [ ] Statistical analysis plan [ ] Results [ ] Individual participant data [ ] Record updated in last year
Registration date 02/08/2024	**Overall study status** Ongoing	
Last Edited 10/09/2024	**Condition category** Cancer	

Plain English summary of protocol

Background and study aims
Patients with locally advanced unresectable or metastatic urothelial carcinoma (bladder cancer that has spread and cannot be removed by surgery) represent a population with a significant unmet medical need, with an average life expectancy of under 2 years. The majority of patients progress during or after first-line therapy and long-term survival is very rare despite the availability of subsequent therapies. New highly effective therapy is therefore needed. Disitamab vedotin has shown encouraging activity in advanced urothelial carcinoma. Initial experience suggests that there is potential for clinically meaningful effectiveness with a manageable safety profile when combined with other medications, such as pembrolizumab. This study compares the effectiveness of disitamab vedotin in combination with pembrolizumab (experimental arm, Arm A) versus platinum-containing chemotherapy (control arm, Arm B).

Who can participate?
Patients 18 years of age and older with locally advanced unresectable or metastatic urothelial carcinoma

What does the study involve?
Participants will be randomly allocated to one of the study arms. Following screening participants in Arm A will receive disitamab vedotin once every 2 weeks and pembrolizumab intravenous (into a vein) infusions every 6 weeks. Participants in Arm B will receive gemcitabine once a week for 2 weeks with either cisplatin or carboplatin once every 3 weeks. Patients will be permitted to have maintenance therapy, sequenced after chemotherapy which is currently the standard of care in the UK. Patients will be regularly examined by medical personnel, which include but are not limited to radiological tests (MRI or CT, with or without contrast, depending on tumour type), blood tests, and cardiogram, and may involve tumour biopsies, if not previously done. Results will be recorded and shared with the National Health Authorities (to decide if this drug should be used in other patients) but no patient's personal information will be disclosed.

What are the possible benefits and risks of participating?
The potential risks and burdens for this study are provided in the Participant Information Sheet

and Informed Consent Form(s) (PIS-ICF(s)). The participants will therefore know about these risks and burdens before taking part in the study. Due to the character limit for this question please refer to the PIS-ICF(s) for the risks and burdens. The management of these risks and burdens is presented below.
Safety will be evaluated by assessment of clinical laboratory tests, physical examinations, vital signs measurements at various time points during the study, and by the documentation of adverse events.
On a periodic basis, an Independent Data Monitoring Committee (IDMC) will monitor the safety of subjects participating in this trial. The IDMC will be responsible for evaluating the results of safety analyses and will make recommendations to the sponsor. Additional details are described in a separate IDMC charter.

Where is the study run from?
Seagen Inc. (Netherlands)

When is the study starting and how long is it expected to run for?
April 2024 to January 2031

Who is funding the study?
Seagen Inc. (Netherlands)

Who is the main contact?
Marcel Koopman, eu-regulatory@seagen.com

Plain English summary under review with external organisation

Contact information

Type(s)
Scientific

Contact name
Dr Andreea Iordache

Contact details
500 South Oak Way
Reading
United Kingdom
RG2 6AD
+44 (0)118 951 8583
iconregulatoryaffairs@iconplc.com

Type(s)
Principal investigator

Contact name
Dr Thomas Powles

Contact details
Barts Health NHS Trust – St Bartholomew’s Hospital
West Smithfield

London
United Kingdom
EC1A 7BE
+44 (0)7932048109
thomas.powles1@nhs.net

Type(s)
Public, Scientific

Contact name
Dr Marcel Koopman

Contact details
Evert Van De Beekstraat 1/104
Schiphol
Netherlands
1118 CL
+3 (0)120 238 2497
eu-regulatory@seagen.com

Additional identifiers

Clinical Trials Information System (CTIS)
2022-501105-12

Integrated Research Application System (IRAS)
1006741

ClinicalTrials.gov (NCT)
NCT05911295

Protocol serial number
SGNDV-001/KN-D74, IRAS 1006741, CPMS 54786

Study information

Scientific Title
An open-label, randomized, controlled Phase III study of disitamab vedotin in combination with pembrolizumabversus chemotherapy in subjects with previously untreated locally advanced or metastatic urothelial carcinoma that expresses HER2 (IHC 1+ and greater)

Study objectives
Primary objective:
1. To compare the efficacy of disitamab vedotin in combination with pembrolizumab to chemotherapy as first-line treatment in subjects with advanced UC that expresses HER2

Secondary objectives:
1. To compare objective response rate (ORR) between treatment with disitamab vedotin in combination with pembrolizumab versus chemotherapy.
2. To compare the duration of response (DOR) between treatment with disitamab vedotin in

combination with pembrolizumab versus chemotherapy.
3. To compare disease control rate (DCR) between treatment with disitamab vedotin in combination with pembrolizumab versus chemotherapy.
4. To compare progression-free survival (PFS) by investigator between treatment with disitamab vedotin in combination with pembrolizumab versus chemotherapy.
5. To evaluate the safety profile of each treatment regimen.
6. 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 subject's perspective.

Ethics approval required
Ethics approval required

Ethics approval(s)
approved 17/06/2024, South Central - Hampshire A Research Ethics Committee (Health Research Authority, 2 Redman Place, Stratford, London, E20 1JQ, United Kingdom; +44 (0)207 104 8210; hampshirea.rec@hra.nhs.uk), ref: 24/SC/0161

Study design
Open-label randomized controlled parallel-group trial

Primary study design
Interventional

Study type(s)
Safety, Efficacy

Health condition(s) or problem(s) studied
Previously untreated locally advanced or metastatic urothelial carcinoma that expresses HER2 (IHC 1+ and greater)

Interventions
This study will enrol participants with urothelial cancer (UC). UC can include cancer of the bladder, kidney, or the tubes that carry pee through the body (ureter, urethra). This study will try to find out if the drugs disitamab vedotin with pembrolizumab work better than platinum-containing chemotherapy to treat patients with UC. This study will also test what side effects happen when participants take these drugs together. A side effect is anything a drug does to the body besides treating the disease.

Participants in this study will have cancer that has spread through the body (metastatic) or spread near where it started (locally advanced).

The method of randomisation is by stratified randomisation. Participants will be randomized in a 1:1 ratio to experimental or control arm based on the following stratification factors: cisplatin eligibility (eligible or ineligible), presence of liver metastases (yes or no), HER2 status (positive (high) or low), and intent of avelumab maintenance use (yes or no).

Participants in the disitamab vedotin arm will get the study drug disitamab vedotin once every 2 weeks and pembrolizumab once every 6 weeks. Participants in the standard-of-care arm will get gemcitabine once a week for 2 weeks with either cisplatin or carboplatin once every 3 weeks.

All study medication will be given by intravenous administration at the following doses:

Arm A:
Disitamab Vedotin 1.5 mg/kg
Pembrolizumab 400 mg

Arm B:
Gemcitabine 1000 mg/m2
Carboplatin AUC 4.5 or 5
Cisplatin 70 mg/m2

Intervention Type
Drug

Phase
Phase III

Drug/device/biological/vaccine name(s)
Disitamab vedotin, pembrolizumab, cisplatin, gemcitabine, carboplatin

Primary outcome(s)
1. Progression-free survival (PFS) measured per Response Evaluation Criteria in Solid Tumors (RECIST) version (v)1.1 by blinded independent central review (BICR). Tumour assessments will occur every 8 weeks (±7 days), starting from randomization. Starting after Week 72, tumour assessments will be undertaken every 12 weeks (±14 days). Responses (CR or partial response [PR]) are to be confirmed with repeat scans at least 4 weeks after the first documentation of response.
2. Overall survival (OS), after progression and discontinuation of study treatment, is measured every 12 weeks (±1 week) in person, by phone, or by consulting public records.

Key secondary outcome(s))
1. Objective response rate (ORR) measured per RECIST v1.1 by BICR every 8 weeks (±7 days), starting from randomization. Starting after Week 72, tumour assessments will be undertaken every 12 weeks (±14 days).
2. ORR measured per RECIST v1.1 by investigator every 8 weeks (±7 days), starting from randomization. Starting after Week 72, tumour assessments will be undertaken every 12 weeks (±14 days).
3. Duration of response (DOR) measured per RECIST v1.1 by BICR every 8 weeks (±7 days), starting from randomization. Starting after Week 72, tumour assessments will be undertaken every 12 weeks (±14 days).
4. DOR measured per RECIST v1.1 by investigator every 8 weeks (±7 days), starting from randomization. Starting after Week 72, tumour assessments will be undertaken every 12 weeks (±14 days).
5. Disease control rate (DCR) measured per RECIST v1.1 by BICR every 8 weeks (±7 days), starting from randomization. Starting after Week 72, tumour assessments will be undertaken every 12 weeks (±14 days).
6. DCR measured per RECIST v1.1 by investigator every 8 weeks (±7 days), starting from randomization. Starting after Week 72, tumour assessments will be undertaken every 12 weeks (±14 days).
7. PFS measured per RECIST v1.1 by the investigator every 8 weeks (±7 days), starting from randomization. Starting after Week 72, tumour assessments will be undertaken every 12 weeks

(±14 days).
8. Type, incidence, relatedness, severity, and seriousness of adverse events (AEs) measured by investigators at pre-screening, screening, and baseline.
9. Type, incidence, and severity of laboratory abnormalities measured by local laboratories every 2 weeks for Arm A patients and every week for Arm B patients
10. Treatment discontinuation rate due to AEs measured as captured in the CRF
11. Electrocardiogram abnormalities, including changes in QTc measured by an ECG at screening
12. Effect on left ventricular ejection fraction measured by ECG at screening
13. Change from baseline to Week 16 in quality of life measured using the European Organization for Research and Treatment of Cancer core QoL questionnaire (EORTC QLQ C30) Global Health Status (GHS)/QoL Score (Items 29+30).
14. Time to deterioration in quality of life measured using EORTC QLQ-C30 GHS/QoL Score (Items 29 + 30). Collected on Day 1 of Cycle 1 before study treatment, then every 2 weeks until Week 24, every 8 weeks until Week 72, and every 12 weeks for the remainder of the study until disease progression (per BICR) or last dose of study treatment, whichever is later, and EoT.
15. Time to pain progression measured by questionnaire on Day 1 of Cycle 1 before study treatment, then every 2 weeks until Week 24, every 8 weeks until Week 72, and every 12 weeks for the remainder of the study until disease progression (per BICR) or last dose of study treatment, whichever is later. Electronic patient-reported outcomes (ePROs) should also be collected at the end of treatment (EOT).

Completion date
31/01/2031

Eligibility

Key inclusion criteria
Due to the character limit, please find the full list of inclusion criteria in the protocol

1. Age ≥18 years at the time of informed consent (IC).
2. Following baseline lab data, lab values collected within 7 days prior to randomization are acceptable:
2.1. Hb ≥9 g/dL without transfusion
2.2. ANC ≥1.5 × 109/L
2.3. Platelet count ≥100 × 109/L
2.4. ALT and AST ≤2.5 × upper limit of normal (ULN) without liver metastases or ≤5 × ULN with liver metastases
2.5. Serum total bilirubin ≤1.5 × ULN or direct bilirubin ≤ ULN for subjects with total bilirubin >1.5 × ULN; serum total bilirubin ≤3 × ULN for subjects with Gilbert's syndrome
2.6. CrCl ≥30 mL/min, as calculated using the Cockcroft-Gault formula
2.7. International normalized ratio (INR) or prothrombin time (PT) ≤1.5 × ULN and activated partial thromboplastin time (aPTT) ≤1.5 × ULN. Subjects receiving anticoagulant therapy are eligible and are required to have INR/PT and aPTT within therapeutic range. Note: In subjects transfused before the study, the transfusion (such as red blood cell, whole blood, or plasma transfusion) must be ≥14 days prior to start of therapy to establish adequate lab parameters independent from transfusion support
3. Subjects of childbearing potential under the following conditions:
3.1. Must have a negative serum pregnancy test result within 72 hrs prior to the first dose
3.2. Must agree not to try to become pregnant during the study and for at least 2 months after the final dose of disitamab vedotin and 4 months after the final dose of pembrolizumab
3.3. Must agree not to breastfeed or donate ova, from the time of IC and continuing through 2

months after the final dose of disitamab vedotin and 4 months after the final dose of pembrolizumab
3.4. If sexually active in a way that could lead to pregnancy, must consistently use at least 2 acceptable methods of contraception, starting at time of and continuing through ≥2 months after the final dose of disitamab vedotin and 4 months after the final dose of pembrolizumab
4. The subject must provide documented IC
5. Subject must be willing and able to comply with the trial procedures and the follow-up schedule
6. Subjects 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
7. Subjects must have measurable disease by investigator assessment according to RECIST v1.1. Note: Subjects 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
8. Subjects must not have received prior systemic therapy for locally advanced or metastatic UC with the following exceptions:
8.1. Neoadjuvant or adjuvant therapy, including PD-(L)1 inhibitors, is acceptable, if disease recurrence/progression occurred >12 months after the last dose of therapy
9. Subjects must be considered eligible to receive cisplatin- or carboplatin-containing chemotherapy, per the investigator's evaluation. Subjects meeting any of the following criteria should be considered cisplatin-ineligible, and will receive carboplatin:
9.1. CrCl <60 mL/min but ≥30 mL/min within 7 days of randomization (measured by the Cockcroft-Gault formula). Note: Subjects with a CrCl ≥50 mL/min and no other cisplatin ineligibility criteria may be considered cisplatin-eligible based on the investigator's clinical judgment.
9.2. ECOG performance status of 2 within 7 days of randomization (refer to Inclusion Criterion 8 for additional criteria for ECOG 2 subjects).
9.3. NCI CTCAE Grade 2 or higher hearing loss. Note: If a subject is determined to be cisplatin eligible, gemcitabine and cisplatin are to be administered without exception
Subjects must be willing and able to provide archived formalin-fixed paraffin-embedded tumor tissue blocks (or, alternatively, freshly sectioned slides; see lab 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 lab 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. Tumor tissue recommended to be collected within 12 months prior to enrollment, and after completion of the most recent (neo) adjuvant systemic therapy
10. HER2 expression of 1+ or greater on IHC determined by central lab
11. An ECOG performance status score of 0, 1, or 2 within 7 days prior to randomization.

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Key exclusion criteria
Due to the character limit, please find the full list of exclusion criteria in the protocol.

1. Known hypersensitivity to any excipient contained in the drug formulation of disitamab vedotin, cisplatin, carboplatin, gemcitabine, or pembrolizumab.
2. Subject 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. Subjects must have recovered from all radiation-related toxicities and must not require corticosteroids.
3. Subjects who previously received treatment with an MMAE agent or anti-HER2 therapy
4. Ongoing sensory or motor neuropathy Grade 2 or higher.
5. Subjects with acute, chronic, or symptomatic infections
6. Has a diagnosis of immunodeficiency condition/disorder (ie, immunoglobulin A [IgA] deficiency, etc.) or is receiving chronic systemic steroid therapy (dose >10 mg daily of prednisone or equivalent) or any other form of immunosuppressive therapy within 7 days prior to the first dose of study drug.
7. Subjects with a history of idiopathic pulmonary fibrosis, organizing pneumonia, drug-induced pneumonitis, noninfectious pneumonitis, interstitial lung disease, or idiopathic pneumonitis are excluded. Subjects with current pneumonitis or interstitial lung disease are also excluded.
8. Subjects with a history of another invasive malignancy within 3 years before the first dose of study intervention, or any evidence of residual disease from a previously diagnosed malignancy.
8.1. Subjects with adequately resected early-stage non-melanoma skin cancer or carcinoma in situ are allowed.
8.2. Subjects with a history of prostate cancer (T2NXMX or lower with Gleason score ≤7) treated with definitive intent (surgically or with radiation therapy), provided that the subject is considered prostate cancer free and the following criteria are met: Subjects who have undergone an adequate surgical resection must have undetectable prostate-specific antigen (PSA) for ≥1 yr and at screening. Subjects who have had radiation must have a PSA doubling time >1 yr (based on at least 3 values determined >1 month apart) and a total PSA value that does not meet Phoenix criteria for biochemical recurrence (ie, <2.0 ng/mL above nadir). Subjects with untreated low-risk prostate cancer (Gleason score ≤6) on active surveillance with PSA doubling time >1 month (based on at least 3 values determined <1 month apart) are also eligible.
8.3. Malignancies that can be cured after treatment (including but not limited to adequately treated thyroid cancer, cervical carcinoma in situ, basal or squamous cell skin cancer, or radical treatment of ductal carcinoma in situ to the breast).
9. Uncontrolled cardiac disease
10. Subjects who have received radiotherapy within 2 weeks prior to randomization
11. Subjects who have received major surgery within 4 weeks prior to randomization.
12. History of severe/life-threatening irAE with PD-(L)1 inhibitors are excluded. Please consult with medical monitor.
12.1. Grade ≥3 pneumonitis IMAEs, cardiomyopathy, etc
12.2. Grade 4 diarrhea/colitis IMAEs, hepatitis IMAEs, rash IMAEs c. Grade 3/4 adrenal insufficiency, hypophysitis, uveitis, hypothyroidism
13. Subjects requiring chronic oxygen therapy or have Grade ≥3 pulmonary disease unrelated to

underlying malignancy
14. CNS and/or leptomeningeal metastasis.
15. History of or active autoimmune disease that has required systemic treatment in the past 2 years
16. Subjects who have previously received any prior treatment with an agent directed to another stimulatory or coinhibitory T cell receptor (including but not limited to CD137 agonists, CAR-T cell therapy, CTLA-4 inhibitors, or OX-40 agonists) are excluded
17. Subjects with prior solid organ or bone marrow transplantation
18. Pleural effusion or ascites with symptoms or requiring symptomatic treatment

Date of first enrolment
31/08/2024

Date of final enrolment
30/09/2026

Locations

Countries of recruitment
United Kingdom

England

Scotland

Argentina

Australia

Austria

Belgium

Brazil

Bulgaria

Canada

Chile

France

Greece

Hungary

Ireland

Israel

Italy

Mexico

Netherlands

Norway

Peru

Portugal

Romania

Singapore

Spain

Sweden

Taiwan

Thailand

Türkiye

Study participating centre
Beatson West of Scotland Cancer Centre
1053 Great Western Road
Glasgow
United Kingdom
G12 0YN

Study participating centre
St. Bartholomews Hospital
West Smithfield
London
United Kingdom
EC1A 7BE

Study participating centre
Guys Hospital
Guys Hospital
Great Maze Pond

London
United Kingdom
SE1 9RT

Study participating centre
Charing Cross Hospital
Fulham Palace Road
London
United Kingdom
W6 8RF

Study participating centre
Royal Devon and Exeter Hospital
Royal Devon & Exeter Hospital
Barrack Road
Exeter
United Kingdom
EX2 5DW

Study participating centre
Weston Park Hospital
Whitham Road
Broomhall
Sheffield
United Kingdom
S10 2SJ

Sponsor information

Organisation
Seagen Inc.

Funder(s)

Funder type
Industry

Funder Name

Seagen

Alternative Name(s)
Seattle Genetics, Inc, Seagen Inc, Seagen Inc., Seagen, Inc., Cascadian Therapeutics, Seattle Genetics, Inc.

Funding Body Type
Private sector organisation

Funding Body Subtype
For-profit companies (industry)

Location
United States of America

Results and Publications

Individual participant data (IPD) sharing plan
The data-sharing plans for the current study are unknown and will be made available at a later date

IPD sharing plan summary
Data sharing statement to be made available at a later date