A Phase Ib Trial to Evaluate the Efficacy and Safety of Bintrafusp Alfa Monotherapy in Metastatic or Locally Advanced/Unresectable Urothelial Cancer with Disease Progression or Recurrence Following Treatment with a Platinum Agent

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Main objective:- Evaluate the anti-tumor activity per RECIST 1.1 in participants with metastatic or locally advanced/unresectable urothelial cancer treated with bintrafusp alfa. Secondary objectives: - Evaluate other measures of antitumor activity...

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

Summary

ID

NL-OMON50165

Source
ToetsingOnline

Brief title
GSK213152

Condition

- Renal and urinary tract neoplasms malignant and unspecified

Synonym
Bladder cancer, urothelial cancer

Research involving
Human

Sponsors and support

Primary sponsor: GlaxoSmithKline Research & Development Ltd.
Source(s) of monetary or material Support: Pharmacuetical Industry

Intervention

Keyword: Anti-PD-L1, Bintrafusp alfa, TGF-□ inhibitor, Urothelial cancer

Outcome measures

Primary outcome

Confirmed Overall Response per RECIST 1.1 assessed by investigator.

Secondary outcome

- Duration of response (DOR), progression free survival (PFS), according to

RECIST 1.1, assessed by the investigator.

- Confirmed Overall Response, DOR, PFS, per RECIST 1.1 as assessed by the IRC

(independent review committee).

- Overall survival.

- Frequency and severity of AEs using NCI-CTCAE v5.

- Observed bintrafusp alfa serum concentrations at the end (Ceoi) and right

before infusions (Ctrough).

- Number and percentage of participants that develop anti-drug antibodies

against bintrafusp alfa.

Study description

Background summary

Worldwide 549,393 new cases of bladder cancer are diagnosed each year. Urothelial cancer is the most common histological type of bladder cancer, accounting for 90% of diagnoses in the US and Europe. In addition to the bladder, urothelial cancers can be diagnosed in the urethra, ureters, and renal pelvis. Approximately 25% of urothelial cancer patients, at diagnosis, will have disease that invades the detrusor muscle (muscle-invasive bladder cancer; MIBC) or is metastatic. Patients with MIBC and metastatic disease are typically treated with surgery, radiation, and/or (cisplatin-based) chemotherapy as determined by the stage of disease. Prognosis declines with more advanced disease. The development of immune checkpoint inhibitors has changed the treatment landscape and is improving the outlook for patients that have progressed after or are ineligible for cisplatin-based therapy. Overall response rates have ranged from 14% to 21% for patients that have received cisplatin to 23% to 29% for untreated patient*s ineligible for cisplatin.

Study objective

Main objective:
- Evaluate the anti-tumor activity per RECIST 1.1 in participants with metastatic or locally advanced/unresectable urothelial cancer treated with bintrafusp alfa.

Secondary objectives:
- Evaluate other measures of antitumor activity in participants with metastatic or locally advanced/unresectable urothelial cancer treated with bintrafusp alfa (RECIST 1.1).
- To evaluate clinical efficacy based on Overall Survival.
- Evaluate the safety and tolerability of bintrafusp alfa in participants with urothelial cancer.
- Characterize the PK of bintrafusp alfa.
- Evaluate the immunogenicity of bintrafusp alfa.

Study design

A Phase Ib open-label, global, multicenter, single-arm trial.

Intervention

Bintrafusp alfa will be administered intravenously (IV) at a dose of 1200 mg once every 2 weeks (Q2W) until confirmed disease progression, death, unacceptable toxicity, study withdrawal, or up to 24 months after a confirmed complete response (CR).

Study burden and risks

Known side effects of treatment with bintrafusp alfa mostly are immune related,

as bintrafusp alfa activates the immune system. Therefore, it could well be that patients experience immune related side effects as their immune system attacks normal organs and tissues in any area in the body. These side effects may be temporary, long-term, permanent, life threatening or even deadly. However, most of these side effects are reversible once treatment with bintrafusp alfa is stopped or are to be treated with drugs decreasing the immune system function (immunosuppressant drugs).

Bintrafusp alfa has been administered to approximately 700 participants in Phase I development and is currently in Phase II and III development for multiple indications. Bintrafusp alfa has a favorable safety profile with known risks consistent with the bifunctional mechanism of action. In Phase I, bintrafusp alfa has shown encouraging efficacy outcomes, in particular, for participants with non-small cell lung cancer (NSCLC) and biliary tract cancer (BTC). The Phase I studies of bintrafusp alfa did not include participants with urothelial cancers.

Bintrafusp alfa has a favorable safety profile with known risks consistent with the bifunctional mechanism of action. The bifunctional activity of bintrafusp alfa is well-suited for evaluation in urothelial cancer. Anti-programmed cell death 1/ligand 1 (PD-1/L1) receptor antibodies are approved for the treatment of locally advanced and metastatic urothelial cancers. However, TGF-* pathways are implicated in blunting the activity of these antibodies in this setting. Bintrafusp alfa interferes with both PD-1/L1 and TGF-* pathways, and therefore, has the potential to be more active than currently approved checkpoint modulators.

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

1. Can give signed informed consent/assent which includes compliance with the requirements and restrictions listed in the ICF and in this protocol
2. Eighteen (18) years at the time of signing the informed consent.
3. Histologically confirmed locally advanced or metastatic or locally advanced/unresectable urothelial carcinoma (including renal, pelvis, uterus, urinary bladder, urethra). Mixed histologies are acceptable provided transitional cell carcinoma is the predominant histology. a) Measurable disease per RECIST v1.1 criteria. b) Experienced disease progression or recurrence either (1) following platinum containing chemotherapy for metastatic or locally advanced/unresectable urothelial cancer or (2) within 12 months from completion of neo-adjuvant or adjuvant platinum-containing chemotherapy for localized muscle-invasive urothelial cancer.
4. Able to provide, a tumor tissue sample collected during screening and prior to administration of bintrafusp alfa (see SRM for details).
5. Able to provide an archival tumor sample (preferably from the most recent biopsy). Archival material is formalin fixed tumor tissue sample from a biopsy of a tumor lesion.
6. All prior treatment-related toxicities (defined by National Cancer Institute Common Toxicity Criteria for Adverse Events [NCI-CTCAE] v5.0) must be * Grade 1 at the time of enrollment, except alopecia, grade 2 neuropathy, or asymptomatic toxicities that are clinically stable with medical management (e.g. electrolyte abnormalities, etc.). ECOG PS 0 or 1.
7. Adequate organ system functions as defined by the laboratory assessments
8. Life expectancy of at least 12 weeks.
9. A female is eligible if she is not pregnant or breastfeeding, and at least one of the following conditions applies:
* Not a woman of childbearing potential (WOCBP). OR
* If a WOCBP, use a highly effective contraceptive method (i.e., with a failure rate of <1% per year), preferably with low user dependency, as described in the

following time periods:
o Before the first dose of the study intervention(s), if using hormonal contraception:
* -Has completed at least one 4-week cycle of an oral contraception pill and either had or has begun her menses.
OR
-Has used a depot contraceptive or extended-cycle oral contraceptive for least 28 days and has a documented negative pregnancy test using a highly sensitive assay.
o During the intervention period
o After the study intervention period (i.e., after the last dose of study intervention is administered) for at least 2 months. The Investigator evaluates the effectiveness of the contraceptive method in relationship to the first dose of study intervention.
Has a negative serum or highly sensitive urine pregnancy test, as required by local regulations, within 24 hours before the first dose of study intervention. If a urine test cannot be confirmed as negative (e.g., an ambiguous result), a serum pregnancy test is required.
Male participants:
* Contraceptive use by men should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.
* Male participants are eligible to participate if they agree to the following from the time of first dose of study until 125 days after the last dose of study treatment to allow for clearance of any altered sperm:
o Refrain from donating sperm.
PLUS, either:
* Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on long term and persistent basis) and agree to remain abstinent.
OR
* Must agree to use contraception/barrier as detailed below. Agree to use a male condom and female partner to use an additional highly effective contraceptive method with a failure rate of <1% per year when having sexual intercourse with a woman of childbearing potential who is not currently pregnant.
10. Archival tumor sample high for PD-L1 by central assay.

Exclusion criteria

1. Active brain and/or leptomeningeal disease that is symptomatic or requires therapeutic intervention. Participants with asymptomatic CNS metastases who are clinically stable as demonstrated by serial brain images and have no requirement for corticosteroids for at least 14 days prior to enrollment are eligible. 2. History of malignancy other than urothelial cancer within the last

3 years except for localized tumors that have been treated with curative intent or have not required therapy in the past 2 years. (e.g., resected non-melanoma skin cancer, etc.).
3. No more than 2 lines of systemic therapy for the treatment of meatastastic disease. If the most recent therapy was not a platinumbased regimen, the participant must have progressed on or after that therapy. 4. Cirrhosis or current unstable liver or bilary disease per investigator assessment defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminaemia, oesophageal or gastric varices, or persistent jaundice. NOTE: Stable non-cirrhotic chronic liver disease (including Gilbert's syndrome or asymptomatic gallstones) is acceptable if participant otherwise meets entry criteria.
5. Current pneumonitis or history of non-infectious pneumonitis that required systemic immunosuppressive treatment.
6. Active autoimmune disease that required systemic immunosuppressive treatment within the past 2 years.
7. Received prior allogeneic/autologous bone marrow or solid organ transplant.
8. Receiving systemic corticosteroids (10 mg daily oral prednisone or equivalent) or other immunosuppressive agent within 7 days prior to study treatment. Inhaled or topical steroids are permitted. Note: a) Physiologic doses of corticosteroids for treatment of endocrinopathies or steroids with minimal systemic absorption, including (e.g., topical, inhaled, intra-articular, ophthalmic, intranasal); corticosteroids may be continued if the participant is on a stable dose b) Steroids as premedication for hypersensitivity reactions (e.g., CT scan premedication) are permitted.
9. Known severe hypersensitivity reactions to monoclonal antibodies or any ingredient used in the study treatment formulation (Grade 3 NCICTCAE v5).
10. Active infection requiring systemic therapy.
11. Received any live vaccine within 30 days prior first dose of intervention.
12. Known history of positive test for human immunodeficiency virus (HIV) with the exception of participants with CD4+ T-cell (CD4+) counts greater than or equal to 350 cells/uL and no history of AIDS-defining opportunistic infections.
13. Active hepatitis B virus (HBV) (HBV surface antigen-positive).
14. Active hepatitis C virus (HCV) infection, or positive HCV antibody, with the exception of participants that (1) have HCV viral load below the limits of quantitation and (2) completed curative antiviral therapy or are receiving and compliant with antiviral therapy
15. History or evidence of cardiac abnormalities within the 6 months prior to first dose of intervention which include: a. Serious, uncontrolled cardiac arrhythmia or clinically significant electrocardiogram abnormalities including second degree (Type II) or third-degree atrioventricular block or QTc interval > 450 msec (or QTc > 480 msec for participants with bundle branch block). b. Cardiomyopathy, myocardial infarction, acute coronary syndromes XML File Identifier: fLjMlVGtQpIe/E0445DzoEMLnCU= Page 13/23 (including unstable angina pectoris), coronary angioplasty, stenting or bypass grafting c. Congestive heart failure (Class II, III, or IV) as defined by the New York Heart Association functional classification system d. Symptomatic pericarditis

16. Participants with history of bleeding diathesis or recent major bleeding events considered by the Investigator as high risk for investigational drug treatment are also excluded.
17. Any other serious or uncontrolled medical disorder that, in the opinion of the investigator, may increase the risk associated with study participation or study drug administration, impair the ability of the participant to receive protocol therapy, or interfere with the interpretation of study results.
Prior/Concomitant Therapy
18. Received prior systemic anti-cancer therapy within 2 weeks prior to study treatment.
19. Received prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-Cytotoxic T-lymphocyte-associated antigen-4 (CTLA4) antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways).
20. Received prior therapy targeting TGF-* (e.g., Galunistertib, etc.).
21. Received radiation therapy (or other non-systemic disease therapy) within 2 weeks prior to study treatment.
22. Undergone major surgery within 4 weeks prior to administration of study treatment.

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	14-07-2020
Enrollment:	6
Type:	Actual

Medical products/devices used

Product type:	Medicine
Generic name:	Bintrafusp alfa

Ethics review

Approved WMO Date:	03-07-2020
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	14-07-2020
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	29-07-2021
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
EudraCT	EUCTR2020-000416-29-NL
CCMO	NL73512.056.20