A Multi-Center, Open-Label Phase 1b/2 Study of a Novel FGFR3 Inhibitor (B-701) Combined with Pembrolizumab in Subjects with Locally Advanced or Metastatic Urothelial Carcinoma who have Progressed Following Platinum-based Chemotherapy or are not eligible for cisplatin-containing chemotherapy.

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Phase 1b Primary Objective: 1. To establish the initial safety and determine a recommended Phase 2 dose (RP2D) of vofatamab in combination with pembrolizumabPhase 2 Primary Objectives: 1. To evaluate the safety and tolerability of vofatamab plus...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Renal and urinary tract neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON48991

Source
ToetsingOnline

Brief title
FIERCE-22

Condition

- Renal and urinary tract neoplasms malignant and unspecified

Synonym
Bladder cancer, Transitional cell carcinoma

Research involving
Human

Sponsors and support

Primary sponsor: Rainier Therapeutics, Inc.
Source(s) of monetary or material Support: BioClin Therapeutics;Inc.

Intervention

Keyword: B-107, FGFR3 Inhibitor, Pembrolizumab, Urothelial Carcinoma

Outcome measures

Primary outcome

Endpoint Phase 1b:

*DLTs within the 35-day observation period.

Endpoints Phase 2:

Primary Endpoints:

*Determine the relationship between the level of FGFR3 receptor expression and

the expression of markers

of FGFR3 pathway inhibition as measured by gene expression profiling (using a

technique such as whole

transcriptome RNAseq) or immunohistochemistry on biopsies taken pre- and

post-vofatamab treatment.

*Safety and tolerability assessed through summariesmeasurements of AEs,

physical examination findings,

laboratory test results, and vital signs over time.

Secondary outcome

Secondary Endpoints:

*Efficacy endpoints:

o*ORR defined as the percentage of subjects who have baseline measurable

disease and who achieve a best

response of either complete response (CR) or partial response (PR) (as

assesseddefined by the investigator

using RECIST v1.1 criteria)

o PFS defined as the time from a first study treatment dose to first occurrence

of disease progression (per

RECIST v1.1) or death from any cause, whichever occurs first.

o OS defined as the time from first study drug administration to death from any

cause.

Secondary Endpoints:

*Biomarker Endpoint

For subjects who receive Cycle 0: Determine the change following vofatamab

14-day lead-in period on the

immune infiltration of tumors in subjects with UCC by evaluating the expression

of markers associated

with tumor sub-type, immune cell infiltrates and cytokine expression and

describe the impact of FGFR3

status at enrollment (WT or MF) on the safety and efficacy of vofatamab alone

and in combination with

pembrolizumab in subjects with advanced UCC.

*Efficacy Endpoints:

Assessed by the investigator using RECIST v1.1 criteria (for progression)

o*DOR defined as the time from first occurrence of a documented, objective response until the time of relapse or death from any cause.

o*DCR defined as the percentage of subjects who achieve either CR or PR or stable disease (SD), as assessed by the investigator per RECIST v1.1.).

o*DCR (90), defined as the absence of disease progression and death 90 days from the time of first study drug administration as assessed by the investigator using RECIST v1.1.

*DCR (150180), defined as the absence of disease progression and death 150180 days from the time of first study drug administration.

o*PFS defined as assessed by the investigator usingthe time from a first study treatment dose to first occurrence of disease progression (per RECIST v1.1) or death from any cause, whichever occurs first.

*OS defined as the time from first study drug administration to death from any cause.

Patient Reported Outcomes

*Assess the change over time in subject reported quality of life as measured by the European Organization for Research and Treatment Quality of Life Questionaire (EORTC QLQ-C30)

Exploratory Endpoints

*The PK of vofatamab as evaluated using an enzyme-linked immunosorbent assay (ELISA).

*The immunogenicity of vofatamab as measured by anti-vofatamab antibody titers at several time points throughout the study.

*Biomarker endpoints:

o Change in expression of markers associated with tumor sub-type, immune cell infiltrate, and inflammatory response, as identified by gene expression profiling (using a technique such as whole transcriptome RNAseq), immunohistochemistry, ELISA, flow cytometry and/or sequencing of T-cell receptors (TCRs).

o Characterization of cytokine levels and circulating immune cells using an ELISA, flow cytometry, or other appropriate techniques.

*Genetic characterization of FGFR3, other cancer related genes, TCRs, and mutational burden

by a technique such as next generation sequencing (NGS); and

immunohistochemistry and/or RNA

analyses for FGFR3, cancer-related genes, PD-L1 and markers of immune cell

infiltration performed

on archival samples, study-associated biopsies, and blood samples.

Study description

Background summary

To date, several FDA-approved second-line therapies for the treatment of bladder cancer are available, including immune checkpoint inhibitors such as atezolizumab, avelumab, durvalumab, nivolumab, and pembrolizumab. While immune checkpoint inhibitors (CPIs) are highly effective in a small subset of patients, the majority of patients have disease which progresses while receiving CPI therapy. A significant unmet medical need exists for patients with relapsed or refractory urothelial cell carcinoma (UCC) who have failed first or second line therapy.
The inhibition of programmed cell death protein (PD-1) pathway by CPIs relies on a host immune response against tumor cells for efficacy. Consequently, emerging clinical and nonclinical data suggest that tumors with a non-inflamed phenotype are less likely to respond to immune CPI therapy. Research has found that mutations in fibroblast growth factor receptor 3 (FGFR3) and FGFR3 expression are associated with the non-inflamed bladder cancer phenotype (Sweis 2015). Furthermore, luminal type I bladder cancers, which have the highest expression of FGFR3 when compared across bladder cancer subtypes, have been reported to have the poorest response rate to CPI treatment (Rosenberg 2016).
Vofatamab is a novel fully human monoclonal antibody specific for FGFR3 that is being developed to target FGFR3-positive tumors. Nonclinical studies have also shown that vofatamab suppresses FGFR3 mediated cell proliferation and exerts strong anti-tumor activity in mouse xenograft models of bladder cancer.
Clinical data demonstrate that the majority of patients with UCC express FGFR3 on the tumor cell surface (Cancer Genome Atlas Research Network 2014; Carneiro 2015).
This study is evaluating the safety, tolerability and efficacy of combining vofatamab with pembrolizumab. It is designed to assess whether blockade of the FGFR3 pathway with a highly selective monoclonal antibody, vofatamab, enhances the efficacy of pembrolizumab and whether response to the combination is enhanced in any particular sub-class of disease. In addition it will explore

the impact of the combination on the tumor cell microenvironment

Study objective

Phase 1b
Primary Objective:
1. To establish the initial safety and determine a recommended Phase 2 dose (RP2D) of vofatamab in combination with pembrolizumab
Phase 2
Primary Objectives:
1. To evaluate the safety and tolerability of vofatamab plus pembrolizumab in subjects with UCC
2. To evaluate the efficacy of vofatamab in combination with pembrolizumab in the treatment of subjects with UCC as measured by objective response rate (ORR) by Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1)
Secondary Objectives:
3. To evaluate the change in expression of markers associated with tumor subtype, immune cell infiltrate, and immune response when vofatamab is administered alone during the 14-day lead-in period
4. To evaluate the efficacy of vofatamab in combination with pembrolizumab in the treatment of subjects with UCC as measured by duration of objective response (DOR), progression free survival (PFS), and disease control rate (DCR), and overall survival (OS) by RECIST 1.1
5. To describe the impact of FGFR3 status at enrollment [wildtype (WT), mutation and/or fusion (MF)] on the safety and efficacy after one cycle of vofatamab alone, followed by vofatamab in combination with pembrolizumab in subjects with advanced UCC
6. To evaluate the change in patient reported outcome (PRO) quality of life measurements over time by the European Organization for Research and Treatment Quality of Life Questionnaire (EORTC QLQ-C30)
Exploratory Objectives
7. To evaluate the pharmacokinetics (PK) of vofatamab in subjects with UCC
8. To assess the immunogenic ity of vofatamab in subjects with UCC
9. To determine if other molecular markers predict treatment response

Study design

Study Design and Methodology:
This is a Phase 1b/2 multi-center, open-label study to determine the safety, tolerability, and efficacy of vofatamab plus pembrolizumab in the treatment of subjects with locally advanced or metastatic UCC, who have progressed following platinum-based chemotherapy or are not eligible for cisplatin-containing chemotherapy and who have not received prior immune checkpoint inhibitor or FGFR inhibitor-targeted therapy. The study consists of 2 parts: a Phase 1b lead-in phase enrolling 6 to 18 subjects and a Phase 2 dose expansion phase enrolling up to 74 subjects.

Prior to study enrollment, the availability of an archival tumor sample must be requested and confirmed for all participants. A blood sample may be used to determine FGFR3 genetic status. If archival biopsy is not available, during screening window a pre-treatment diagnostic biopsy within 56 days of first study treatment may be obtained to satisfy this requirement; this allowance is only applicable for subjects in Phase 1b, and Phase 2 when the WT cohort is open for enrollment. This biopsy may also be used in place of the first biomarker biopsy sample (if there is adequate material) for subjects in Phase 1b and the initial 26 subjects in each of the Phase 2 WT and MF cohorts. Biopsies may not be obtained from lung, bone, or brain to satisfy other study-required biopsies.

Phase 1b
Enrolled subjects in Phase 1b will have a biomarker tumor biopsy taken prior to Cycle 0 (lead-in cycle)
· Within 7 days prior if an archival sample is available for screening
· If an archival sample is not available, a biopsy should be obtained within the 28-days screening window. If the sample is adequate, it may be substituted for the initial (pre-treatment) Cycle 0 biomarker biopsy.
After this first biomarker tumor biopsy, subjects will be treated in Cycle 0 with an intravenous (IV) infusion of vofatamab alone. The second biomarker tumor biopsy should be obtained within 3 days of Cycle 1 Day 1 infusion of vofatamab plus pembrolizumab. If the biopsy occurs on Cycle 1 Day 1, it should be obtained prior to the start of the infusion of vofatamab and pembrolizumab. The first cohort of 6 subjects will be treated with vofatamab 25 mg/kg IV monotherapy as a 2-week cycle (Cycle 0) and vofatamab 25mg/kg IV in combination with pembrolizumab as a 3-week cycle (Cycle 1). Subjects will be followed for at least a 35-day dose-limiting toxicity (DLT) window from first dose of vofatamab (14 days of vofatamab monotherapy and 21 days of combination therapy). If * 1 subject experiences a DLT (a Grade 3 or higher AE attributed to vofatamab and/or pembrolizumab), then 25 mg/kg will be declared the RP2D. If 2 or more subjects experience a DLT, then the dose of vofatamab will be de-escalated as outlined in the table below [please refer to the Protocol Synopsis for the table].

On Cycle 1 Day 1, Phase 1b subjects will receive treatment of vofatamab (25 mg/kg [or the RP2D if different than 25 mg/kg]) plus pembrolizumab (200 mg) once every 3 weeks (Q3W) until disease progression, death, decision to discontinue treatment, investigator discretion, or study termination. Subjects who do not experience a study defined DLT, but do not complete the 35-day observation window may be replaced. As of April 03 2018, Phase 1b of the study is complete.

Phase 2
Phase 2 opened on April 04, 2018 following review of the aggregate adverse event (AE) and serious adverse event (SAE) by the vofatamab program Safety Steering Committee (SSC) after the 35-day DLT observation period in the Phase

1b subjects. The dose of vofatamab selected was dose level 0 (25 mg/kg given every 3 weeks) for the RP2Daas no subjects meet the study DLT definition of a Grade 3 or higher AE attributed to vofatamab and/or pembrolizumab.

Subjects will be assigned to one of two cohorts by baseline FGFR3 status of 1) WT or 2) MF. If the sample to assess MF status is non-informative, then any subjects who have initiated treatment will be assigned to the WT cohort for the purpose of analysis. Once the WT cohort has fully enrolled, MF status must be confirmed prior to initiation of treatment.
The first 26 subjects in each Phase 2 cohort will have a biomarker tumor biopsy taken within 14 days prior to Cycle 0 (lead-in cycle). If the subject has undergone a diagnostic tumor biopsy procedure within 56 days of enrolling in the study, and the biopsy has adequate material, this sample may be used in place of the first biomarker biopsy sample. After this first biopsy, subjects will be treated in Cycle 0 with an IV infusion of vofatamab alone (without pembrolizumab). A second tumor biopsy will be obtained 14 days after Cycle 0 Day 1 of vofatamab. The second tumor biopsy should always occur within 3 days before Cycle 1 Day 1 infusion of vofatamab plus pembrolizumab. Disease re-staging will occur following Cycle 1 for biomarker correlation but will not be utilized for RECIST evaluation.
On Cycle 1 Day 1, subjects will receive combined treatment of vofatamab (25 mg/kg1) plus pembrolizumab (200 mg) Q3W. Subjects will continue to receive vofatamab plus pembrolizumab until disease progression, death, decision to discontinue treatment, investigator discretion, or study termination.
If the Phase 2 study expands beyond the initial 26 subjects per cohort, the Cycle 0 and baseline biopsy will become optional. Subjects who do not opt to take part in the biomarker tumor biopsy study will initiate treatment with Cycle 1 Day 1. All post-treatment assessments required on vofatamab monotherapy will not be required for these patients including tumor scans.

Phase 1b and Phase 2:
Subjects may continue vofatamab and/or pembrolizumab treatment beyond radiological disease progression following discussion with the medical monitor and based on clinical judgement of the investigator that the subject is experiencing clinical benefit.
Subjects who discontinue vofatamab may continue on study and receive pembrolizumab alone until disease progression, death, withdrawal of patient consent, investigator discretion, or study termination. Subjects who discontinue pembrolizumab may continue on study and receive vofatamab alone (25 mg/kg Q3W [or RP2D if different than 25 mg/kg]) until disease progression, death, withdrawal of patient consent, investigator discretion, or study termination.

Intervention

Vofatamab will be provided as a sterile lyophilized powder in single-use vials. Vofatamab will be reconstituted with sterile water for injection, and

the drug product will be delivered at a final concentration of * 3 mg/mL.
The study drug dosing regimen is as follows:
* Subjects will receive one IV infusion of vofatamab (25 mg/kg)^2 monotherapy over 90 (± 15) minutes.
· If Phase 2 of the study expands beyond the initial 26 subjects per cohort, the Cycle 0 and baseline biopsy will become optional and patients must opt in for Cycle 0 and related biopsies. All subjects who do not opt in will initiate treatment with Cycle 1 Day 1.
· *Subjects will begin combination treatment with vofatamab plus pembrolizumab on approximately Day 15 (i.e., Cycle 1 Day 1). Subjects will receive pembrolizumab (200 mg) by IV infusion over 30 (-5/+10) minutes followed by vofatamab (25 mg/kg) by IV infusion over 90 (± 15) minutes. If Cycle 0 (if applicable) and Cycle 1 vofatamab infusions have been well-tolerated, subsequent doses of vofatamab may be administered over 30 (± 10) minutes, followed by a 30-minute observation period. The vofatamab infusion will begin approximately 30 minutes after completion of the pembrolizumab infusion. Thereafter, combination vofatamab plus pembrolizumab treatment will be administered Q3W (Day 1 of each cycle ± 7 days) until disease progression, death, decision to discontinue treatment, investigator discretion, or study termination.

Study burden and risks

Vofatamab
Vofatamab has been tested alone and in combination with docetaxel (a chemotherapy), as well as in combination with pembrolizumab. Vofatamab has generally been well-tolerated in clinical studies.

The most common side effects seen in greater than 30% of study subjects treated with vofatamab are:
* Fatigue
* Diarrhea

The most common side effects seen in 10 * 30% of study subjects treated with vofatamab are
* Nausea
* Fever
* Anemia (a decrease in the number of red blood cells in your body)
* Decreased appetite
* Vomiting
* Constipation
* Back pain
* Dyspnea (shortness of breath)

Rare (2%) severe side effects from treatment with vofatamab:
Blood clotting disorder called disseminated intravascular coagulation (DIC), a condition in which blood clots form in small blood vessels throughout the body

which can lead to a serious bleeding problem, organ damage, and even death. Decreased platelets which can lead to bleeding problems have been observed in combination with docetaxel.
Internal bleeding resulting in significant blood loss (severe hemorrhage) that could lead to death. Examples of internal bleeding side effects include intracranial hemorrhage (bleeding with the brain); hemoptysis (coughing up blood); bleeding from stomach or intestines which may look like coffee grounds or black sticky bowel movements; rectal bleeding; and bleeding hemorrhoids.

Infusion reactions have been reported with the use of vofatamab alone or in combination with chemotherapy. The majority of these infusion reactions have been mild, however severe allergic reactions have been observed. Allergic reactions may be mild (such as skin rash or hives) to severe (such as breathing difficulties or shock). A severe allergic reaction would require immediate medical treatment and could result in permanent disability or death.

There is a small chance that your immune system might develop special antibodies to vofatamab. If you develop these special antibodies, it may affect your body*s ability to respond to similar drugs made with antibodies.

Vofatamab may cause side effects while it is being given or immediately afterwards. These side effects are called infusion-related reactions. These reactions could include symptoms, such as fever, chills, skin rash, nausea, vomiting, headache, cold-like symptoms, difficulty breathing, or shortness of breath. If you experience these symptoms, your study doctor may slow down, interrupt, or even stop the infusion. Your study doctor may also give you some drugs to treat these symptoms.

Pembrolizumab
If you have any of the following conditions, call or see your doctor right away:
* Inflammation of the lungs, which may include shortness of breath, chest pain or coughing
* Inflammation of the intestines, which may include diarrhea or more bowel movements than usual, black, tarry, sticky stools or stools with blood or mucus, severe stomach pain or tenderness, nausea, vomiting
* Inflammation of the liver, which may include nausea or vomiting, feeling less hungry, pain on the right side of stomach, yellowing of skin or whites of eyes, dark urine or bleeding or bruising more easily than normal
* Inflammation of the kidneys, which may include changes in the amount or color of your urine
* Inflammation of hormone glands (especially the thyroid, pituitary and adrenal glands), which may include rapid heartbeat, weight loss, increased sweating, weight gain, hair loss, feeling cold, constipation, deeper voice, muscle aches, dizziness or fainting, headaches that will not go away or unusual headache
* Type 1 diabetes, which may include feeling more hungry or thirsty than usual, need to urinate more often or weight loss

* Inflammation of the eyes, which may include changes in eyesight
* Inflammation in the muscles, which may include muscle pain or weakness
* Inflammation of the pancreas, which may include abdominal pain, nausea and vomiting
* Inflammation of the skin, which may include rash
* Infusion reactions, which may include shortness of breath, itching or rash, dizziness or fever

Your doctor may withhold the next dose of pembrolizumab or stop your treatment with pembrolizumab.

The most common side effects of Pembrolizumab include:
* Fatigue
* Decreased appetite
* Nausea
* Urinary tract infection
* Pyrexia (fever)
* Constipation

Pembrolizumab
Less frequent side effects of Pembrolizumab are (2 to 5% of the patients):
* Inflammation of the intestine
* Changes in liver function values in the blood
* Pigmentation loss in the skin
* Dry mouth
* Weight loss
* Thyroid anomaly
* Changed blood values
* Low concentration of phosphates, magnesium and potassium in the blood
* High concentration of urine acid in the blood
* Pneumonia
* Coughing
* Dizziness
* Headache
* Low concentration of white blood cells in the blood, leading to a higher risk of fever and infections
* Chills
* Muscle ache, muscle weakness, stiffness, cramps or paralysis
* Pain in arms and legs
* Tingling, burning feeling or numbness in the hands and feet
* Shortness of breath
* Changed taste
* Blush
* High or low blood pressure
* Allergic reaction to the infusion
* Sensitivity of the skin for sunlight. Cover your skin against sunlight.
* Obstipation

* Difficulty with swallowing
* Heartburn
* Low concentration of platelets in the blood (leading to an increased risk of bleeding)

Very rare but possibly severe side effects of Pembrolizumab are (less than 2% of the patients):
* Low oxygen level in the blood
* Acute lung failure
* Fluid accumulation around the lungs
* Appendicitis
* Increase of inflammation proteins in the blood (e.g. lipase)
* Changes in the adrenal gland
* Inflammation of the pituitary
* Decreased sight or impaired sight, inflammation of the eye or bleeding in the eye
* Inflammation of the liver
* Renal failure
* Changed production of blood cells
* Inflammation of the mouth and inflammation of the wall of the digestive system
* Swelling of face, arms and legs
* Inflammation of the pancreas
* Auto-immune disease, including Guillain-Barre syndrome (together with worsening of muscle weakness or muscle paralysis)
* Pressure on the chest
* Palpitations
* Inflammation of the heart or the pericardium
* Fluid accumulation around the hart
* High blood sugar
* Dehydration
* Infections, like sepsis, lung- or skin infections
* Intestine and stomach complaints
* Confusion
* Inflammation of the eye nerve or swelling of the blind spot
* Inflammation or paralysis of the meninges
* Reaction to the treatment with skin rash, changes in blood values, enlarged lymph nodes, kidney-, liver, and lung-impairment, also called DRESS syndrome (Drug Reaction with Eosinophilia and Systemic Symptoms).
* Myastenia Gravis, this is a disease of the nerve system which can lead to muscle weakness of the eye and face and to the muscles used for breathing and swallowing. There is one case known of Myastenia Gravis with a patient that took a combination of pembrolizumab and ipilimumab. This patient has passed away, this is ascribed to myasthenia gravis and a severe inflammation (sepsis).
* Inflammation of the brain causing changed brain function (encephalitis). This is possibly life threatening or can be fatal.
* Toxic epidermal necrolysis, a potential life threatening disease which is characterized by the forming of vesicles on or the let loose of the top skin

layer, this looks similar as severe burning, it has occurred with patients that were treated with pembrolizumab.

Pneumonia: It is possible that Pembrolizumab will cause an inflammation of the long tissue. This side effect is reported with a low frequency for patients that are treated with pembrolizumab. While some patients, which showed changes on the X-rays or CT-scan did not have symptoms, other patients developed mild to severe symptoms. In rare cases their pneumonia was fatal. Signs and symptoms for pneumonia are amongst others: difficulty to breath, pain or discomfort when breathing, chest pain, coughing, shortness of breath, increased breathing frequency, fever, low oxygen level in the blood or fatigue.

Blood Draws
Blood samples will be collected for:
1. Routine blood samples: These blood tests are part of the routine monitoring for subjects. This includes the assessment of complete blood count and the amount of red and white blood cells will be determined per volume. Potassium, sodium, magnesium and proteins in the blood will also be measured among others. Also coagulation, HIV and hepatitis B/C will be tested and iron levels will be measured.
2. Study specific samples:
a. Pharmacokinetics blood samples: these are blood samples to analyze absorption/breakdown of the study drug in your body. Blood samples will be taken at different times to see how long the investigational or control drug stays in your body.
b. Anti-therapeutics antibody assessment (ATA): These blood samples will analyze if your body will produce antibodies against the therapeutic antibody.
3. Biomarker assessment: Blood samples will be used to investigate biomarkers in your blood.
During the complete study, the maximum amount of blood drawn will be about 705 mL, based on 12 cycles.

Electrocardiogram (ECG):
During the ECG test a heart film is made which measures the electrical activity of your heart. With an ECG you can measure the heart rate and heart rhythm and detect changes in the heart.

Eastern Cooperative Oncology Group (ECOG) Performance Status
Your study doctor will assess your ability to perform daily activities using the ECOG grading scale. No physical tests or questionnaires are taken for this.

CT Scans:
A CT scan is a series of detailed pictures of areas inside the body. The images are made by scanning from different angles. A dye is usually used for this, this can be injected into your vein, taken as a capsule or a suppository to improve the pictures.

Magnetic Resonance Imaging (MRI):
An MRI sends a magnetic signal throughout body. The signal is then absorbed again and using this absorbed signal, the soft tissue of your body can be shown. A dye may be injected into your vein to improve the pictures.

Bladder biopsy
A biopsy is a procedure where a small sample of tissue is taken from the inside of your bladder. A small amount of tissue will be taken through a hollow needle.

Contacts

Public
Rainier Therapeutics, Inc.

1040 Davis Street Ste. 202
San Leandro CA 94577
US
Scientific
Rainier Therapeutics, Inc.

1040 Davis Street Ste. 202
San Leandro CA 94577
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Have locally advanced (on TNM staging: T4b and any N, or any T and N2-3) or

metastatic transitional cell carcinoma of the urothelium, including the urinary bladder, urethra, ureter, and/or renal pelvis. The diagnosis must be histologically or cytologically confirmed.
For subjects in the Phase 2 MF cohort, tumors must have at least one of the following FGFR3 mutations: R248C, S249C, G370/2C, S371/3C, Y373/5C, G380/82R, F384/6L, K650/2X (X<=E,T or M) or FGFR3- TACC3 fusion, as shown by tests performed by a CAP or CLIA certified laboratory (or equivalent outside of the US) on samples that were obtained at or after the time when the subject was found to have muscle invasive / metastatic disease or high grade papillary non-muscle invasive disease.
In the absence of pre-existing genetic test results, subjects can submit archival tissue (obtained at or after the time subject was found to have muscle invasive / metastatic disease) for genetic testing. If no suitable tissue is available, a blood sample may be used to determine FGFR3 genetic status. Subsequent to subject enrollment, blood samples used to determine FGFR3 status, or previous test results that were not provided by Foundation Medicine will be verified using archival tissue or the first biomarker tumor biopsy sample.
2. Have progression during or following platinum-containing chemotherapy in metastatic setting or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy
OR
Have a PD-L1 positive tumor (per label) at the time of metastatic disease, and are not eligible for cisplatin-containing chemotherapy defined as meeting any of the following criteria:
- Creatinine clearance <60 mL/min (GFR by direct measurement, or using Cockcroft-Gault equation)
- Equal to or greater than grade 2 hearing loss
- Equal to or greater than grade 2 peripheral neuropathy
- New York Heart Association Class III heart failure
3. Have available archival tumor or be willing to undergo diagnostic biopsy during screening.
4. Have measurable disease according to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1).
5. Male and female subjects, age ? 18 years.
6. Eastern Cooperative Oncology Group (ECOG) performance status (PS) < 1 (see Appendix 1).
7. Willingness to avoid pregnancy or fathering children based on the criteria below:
a. Women of non-childbearing potential (i.e., surgically sterile with a hysterectomy and/or bilateral oophorectomy OR chemically sterile OR ? 12 months of amenorrhea in the absence of chemotherapy, anti-estrogens, or ovarian suppression). Women of non-childbearing potential need not undergo pregnancy testing.
b. Women of childbearing potential who have a negative urine or serum pregnancy test at Screening and before the first dose of study drug and who agree to take appropriate precautions to avoid pregnancy (with approximately 99% certainty) from Screening through 120 days after the last dose of study drug. Permitted

methods of contraception that are approximately 99% effective in preventing pregnancy are described in Appendix 4, should be communicated to the subject, and the subject*s understanding confirmed.
c. Men who agree to take appropriate precautions to avoid fathering children (with at least 99% certainty) from Screening through 120 days after the last dose of study drug. Permitted methods of contraception that are approximately 99% effective in preventing pregnancy are described in Appendix 4, should be communicated to the subject, and the subject*s understanding confirmed.
8. Ability to understand and sign informed consent form (ICF) and comply with all study procedures
9. Have adequate hematologic and end organ function defined by the following laboratory results obtained within 14 days prior to the first dose of study treatment:
a. Absolute neutrophil count ? 1,500/µL.
b. Platelet count ? 100,000/µL.
c. Hemoglobin ? 9.0 g/dL without transfusion.
d. Albumin ? 2.5 g/dL.
e. Aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP) < 2.5 × upper limit of normal (ULN), with the following exception: ALP * 5 × ULN for subjects with documented bone metastases
i. Creatinine clearance ? 30 mL/min on the basis of the Cockroft-Gault glomerular filtration rate estimation:
(140 * age) x (weight in kg) x (0.85 if female) 72 x (serum creatinine in mg/dL). Note: Creatine clearance < 30 mL/min may have confirmatory re-testing done using a 24-hour creatinine clearance by Cockroft-Gault estimation or direct measurement
f. Prothrombin time/international normalized ratio (PT/INR) and partial thromboplastin time (PTT) must be < 1.5 × ULN.

Exclusion criteria

1. Participants with a history of idiopathic pulmonary fibrosis, organizing pneumonia, drug-induced pneumonitis, idiopathic pneumonitis, or evidence of active pneumonitis on the Screening chest CT scan.
2. Prior therapy with an anti-programmed cell death 1 (PD-1) or anti-PD-Ligand 1 agent, or with an agent directed to another co-inhibitory T-cell receptor or FGFR inhibitor.
3. Patients with autoimmune disease or medical conditions that required systemic corticosteroids (> 10 mg/day prednisone or its equivalent) or other immunosuppressive medications or any other form of systemic immunosuppressive therapy within 7 days prior to the first dose of study treatment. Note: Replacement therapy (e.g. physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.
4. Prior anti-cancer therapy (e.g. biologic or other targeted therapy,

chemotherapy or hormonal therapy) within 14 days prior to the first dose of study treatment.
A washout of less than 14 days may be allowed after discussion with the Medical Monitor, provided
that the subject has recovered from any clinically relevant toxicity
(Exception: participants with neuropathy of Grade 1 will be allowed study entry).
5. Acute clinical AEs, except for alopecia, from any previous treatments must have resolved to < Grade 1, or chronic defined as present for more than 6 months without worsening and not greater than Grade 2
6. Laboratory AEs from any previous treatments must have resolved to < Grade 1 or to within 10% of baseline prior to the first dose of study treatment.
7. Participants who are receiving or have received any other investigational drugs or devices within 14 days prior to the first dose of study medications.
8. Participants with a diagnosis of immunodeficiency.
9. Primary central nervous system (CNS) malignancy or CNS metastases.
10. Participants with a history of allergic reactions attributed to monoclonal antibody therapy (or recombinant antibody-related fusion proteins).
11. History of major bleeding (requiring a blood transfusion * 2 units) not related to a tumor within the past 12 months.
12. History of clinically significant coagulation or platelet disorder in the past 12 months.
13. Participants who have not recovered adequately from the toxicity and/or complications from the interventions prior to starting therapy.
14. Incomplete healing from wounds from prior surgery (wounds larger than 2 cm in length) within 28 days prior to the first dose of study treatment
15. Participants with an active uncontrolled infection requiring systemic therapy (e.g., IV antibiotics or antifungal therapy).
Note: The use of oral anti-infectious agents for prophylaxis or treatment of resolving infections is not considered exclusionary under this rule.
16. Participants who have received a live vaccine within 30 days of planned start of study therapy.
Note: Seasonal influenza vaccines with inactivated flu vaccines are allowed; however, live
attenuated vaccines such as intranasal influenza vaccines (e.g., Flu-Mist®) are not allowed.
17. Participants with uncontrolled intercurrent illness including, but not limited to, ongoing or symptomatic congestive heart failure, unstable angina pectoris, or psychiatric illness/social situations that would limit compliance with study requirements.
18. Participants with a history of other malignancy which could affect compliance with the protocol or interpretation of results. Individuals with a history of curatively treated basal or squamous cell carcinoma of the skin, in situ carcinoma of the cervix, and definitively treated prostate cancer discovered incidentally at surgery are allowed. Participants with other malignancies that have been treated with curative intent will also be allowed if the malignancy has been in remission without treatment for * 2 years prior

to Cycle 0 Day 1 (prior to first dose of study treatment).
19. Pregnant and breast-feeding women are excluded from this study because the risks with vofatamab and pembrolizumab are unknown. Because there is an unknown but potential risk for AEs in nursing infant(s) secondary to treatment of the mother with vofatamab and pembrolizumab, breastfeeding should be discontinued.
20. Presence of positive test results for Hepatitis B (Hepatitis B surface antigen [HBsAg] and/or total Hepatitis B core antibody [HBc Ab]), Hepatitis C (Hepatitis C virus antibody [HCV Ab] serology testing), human immunodeficiency virus (HIV1/2 antibody +), and /or evidence of active tuberculosis (history and/or radiology findings).
Note: Subjects positive for Hepatitis B core antibody (HBC Ab) are eligible only if confirmatory polymerase chain reaction (PCR) is negative for evidence of Hepatitis B Virus DNA (within the Institution cutoff value) and for study purposes the reported positive antibody testing will be considered to be a false positive test result.

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	2
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	B-701
Generic name:	B-701
Product type:	Medicine
Brand name:	Pembrolizumab
Generic name:	KEYTRUDA®

Ethics review

Approved WMO Date:	26-09-2017
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	08-02-2018
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	28-02-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	08-03-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	09-05-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	26-06-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	28-06-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	16-07-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	02-08-2018

Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	30-08-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	05-09-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	21-12-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	09-01-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	19-08-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	27-08-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

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
Other	2017-001292-23
EudraCT	EUCTR2017-001292-23-NL
CCMO	NL63144.041.17