CLINICAL RESEARCH PROTOCOL

Study Title:	**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**
Protocol Number:	**B-701-U22 (FIERCE-22)**
Investigational Product:	**Vofatamab (B-701) (anti-FGFR3 fully human monoclonal antibody)**
IND Number:	**123185**
Eudra CT Number:	**2017-001292-23**
Amendment 5 (USA)	**01 July 2019**
Amendment 4.2	**20 June 2019**
Amendment 4.1	**07 June 2018**
Amendment 4	**16 May 2018**
Amendment 3.1	**14 March 2018**
Amendment 3	**05 January 2018**
Amendment 2	**11 July 2017**
Amendment 1	**16 December 2016**
Original Date of Issue:	**03 October 2016**
Indication:	**Locally Advanced or Metastatic Urothelial Cell Carcinoma**
Sponsor:	**Rainier Therapeutics, Inc.** **1040 Davis Street, Ste. 202** **San Leandro, CA 94577**

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Development Phase:	**Phase 1b/2**

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PROTOCOL SYNOPSIS

Title of Study:	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
Protocol Number:	B-701-U22 (FIERCE-22)
Location:	Global
Study Centers:	Approximately 50-75 sites will participate in this study.
Study Period:	The study period will include a 4-week screening period, a 2 week treatment period of vofatamab monotherapy, followed by a treatment period of vofatamab plus pembrolizumab to complete 2 years of combination vofatamab and pembrolizumab therapy (21-days per cycle for combination treatment), End of Treatment visit, and telephone follow-up to monitor survival.
Phase of Development:	1b/2

Study Rationale:

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. Non-clinical 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 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 Objectives:

Phase 1b

Primary Objective:

- To establish the initial safety and determine a recommended Phase 2 dose (RP2D) of vofatamab in combination with pembrolizumab

Phase 2 and Phase 2 Expansion

Primary Objectives:

- To evaluate the safety and tolerability of vofatamab plus pembrolizumab in subjects with UCC
- 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 (Cohorts 1, 2 and 3):

- 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) by RECIST 1.1, and overall survival (OS)
- To describe the impact of FGFR3 status at enrollment [wildtype (WT), mutation and/or fusion (Mut/Fus)] on the safety and efficacy after one cycle of B-701 alone, followed by B-701 in combination with pembrolizumab in subjects with advanced UCC
- To evaluate the change in patient reported outcome (PRO) using quality of life measurements over time by the European Organization for Research and Treatment Quality of Life Questionnaire (EORTC QLQ-C30)
- 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.(Cohorts 1 and 2).
- To evaluate the change in expression of markers associated with luminal tumor subtype, immune cell infiltrate, and immune response after start of the combination treatment using a later timepoint for the 2nd biopsy only for Cohort 3 (at the end Cycle 1, Week 5)

1. Exploratory Objectives (Cohorts 1, 2 and 3):
   - To evaluate the pharmacokinetics (PK) of vofatamab in subjects with UCC
   - To assess the immunogenicity of vofatamab in subjects with UCC
   - To determine if other molecular markers predict treatment response
   - To evaluate the efficacy of vofatamab in combination with pembrolizumab in the treatment of subjects with UCC as measured by ORR, DOR, PFS, and DCR per iRECIST

   Secondary Objectives (Cohort 4):
   - To evaluate the efficacy of vofatamab in combination with pembrolizumab in the treatment of unselected subjects with UCC as measured by duration of objective response (DOR), progression free survival (PFS), and disease control rate (DCR) by RECIST 1.1, and overall survival (OS)
   - To evaluate the change in patient reported outcome (PRO) using quality of life measurements over time by the European Organization for Research and Treatment Quality of Life Questionnaire (EORTC QLQ-C30)
2. Exploratory objective (Cohort 4):
   - To evaluate the efficacy of vofatamab in combination with pembrolizumab in the treatment of unselected subjects with UCC as measured by ORR, DOR, PFS, and DCR per iRECIST

Study Design and Methodology:

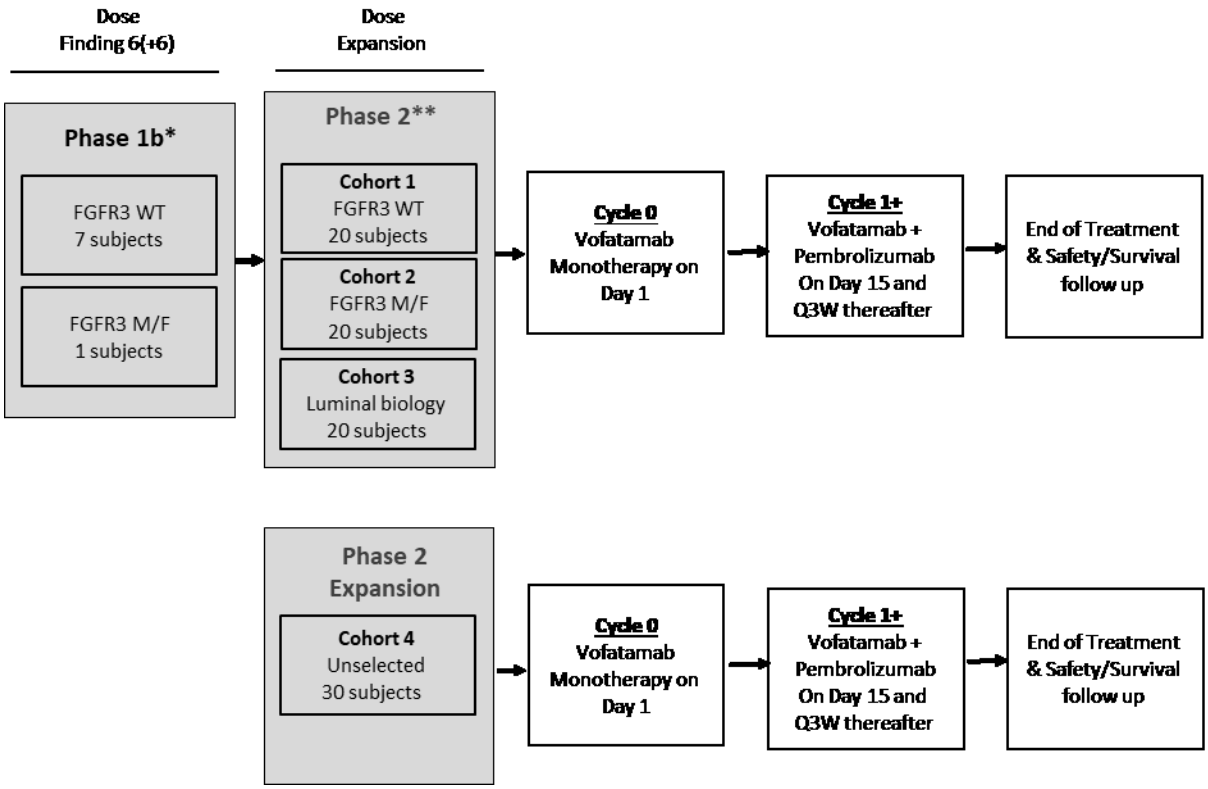
This is a Phase 1b/2, multi-center, open-label study to determine the safety, tolerability, and efficacy of vofatamab plus pembrolizumab in the treatment of subjects with locally advanced or metastatic UCC, who have progressed following platinum-based chemotherapy, and who have not received prior immune checkpoint inhibitor or FGFR inhibitor-targeted therapy. The study consists of 3 parts:

1. A **Phase 1b** which planned to enroll up to 18 patients in a 6+6 design. 8 subjects, 7 WT and 1 Mut/Fus were enrolled (study completed).
2. A **Phase 2** enrolling 60 subjects in 3 seperate cohorts: 20 WT (Cohort 1), 20 Mut/Fus (Cohort 2), and 20 with luminal biology sub-type (Cohort 3).
3. A **Phase 2 expansion** enrolling 30 unselected subjects (independent of their FGFR3 genetic status) (Cohort 4)

Prior to study enrollment, the availability of an archival tumor sample must be requested from participants and availability must be confirmed during screening. A blood sample may be substituted to determine FGFR3 genetic status archival tumor is not available. If an archival biopsy is not available, during the screening window a pre-treatment diagnostic biopsy within 56 days of first study treatment may be obtained to satisfy this requirement, if submitted for additonal required studies. A second biopsy will be taken during treatment for cohorts 1, 2 and 3 or if an expansion phase patient opts in. Study biopsies may not be obtained from lung, bone, or brain.

For the Phase 2 expansion (Cohort 4), the paired biopsies are optional, but if they are taken, the second biospy will be taken at the end of cycle 1, Week 5. Subjects will be required to sign a separate consent form and must confirm their decision to opt-in.

Study Schema



FGFR3 = fibroblast growth factor receptor 3; Mut/Fus = mutant/fusion; Q3W = once every 3 weeks; WT = wild type.

*As of April 03 2018, Phase 1b of the study is complete.

**As of Dec 31 2018, 28 subjects (20 WT and 8 Mut/Fus) have already been enrolled in Phase 2. A total of 32 subjects will be added, 12 Mut/Fus (Cohort 2) and 20 with luminal biology (Cohort 3)

In Phase 2, Cohort 1 and Cohort 2 of the study, subjects will be assigned to a cohort by baseline FGFR3 genetic status of 1) WT or 2) Mut/Fus; in Phase 2, Cohort 3, at selected sites, the patient's bladder cancer sub-type will be luminal enriched as determined by IHC testing for GATA3 and post enrollment by the Decipher Bladder test or acceptable comparable test on samples that were obtained at or after the time when the subject was found to have muscle invasive / metastatic disease.

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.

Dosing for Dose De-escalation

	Dose Level 0	Dose Level -1	Dose Level -2
Vofatamab	25 mg/kg IV q 3 weeks (n=6)	20 mg/kg IV q 3 weeks (n=6)	15 mg/kg IV q 3 weeks (n=6)

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 and Phase 2 expansion:

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 RP2D as no subjects met the study DLT definition of a Grade 3 or higher AE attributed to vofatamab and/or pembrolizumab. After the 1st planned interim analysis which was conducted in April of 2019, the decision to open the expansion phase was made based on initial efficacy and safety (reported ASCO 2019) to unselected subjects based on the ORR seen in both cohorts. Additionally, the exclusion criteria for existing anticoagulation use was removed following a review of the existing safety data by the data safety steering committee that was accepted on review by the FDA.

For Phase 2, subjects will be assigned to one of three cohorts by either baseline FGFR3 genetic status of WT (Cohort 1) or Mut/Fus (Cohort 2), or by bladder cancer molecular subtype (Cohort 3). For Cohort 2, Mut/Fus status must be confirmed prior to initiation of treatment.

Any subject whose biopsy or circulating tumor specimen results in indeterminate or failed result will be considered WT in the analysis

As of December 31, 2018, Cohort 1 has been fully enrolled and is closed.

Cohort 3 will be enrolled at selected sites enrolling patients enriched with tumors showing luminal biology as determined by IHC (GATA 3 positive with the absence of KRT14) and post enrollment by the Decipher Bladder test or acceptable comparable test on samples that were obtained at or after the time when the subject was found to have muscle invasive / metastatic disease. Cohort 3 will be used to study the molecular changes in the tumor after the first dose of combination treatment of vofatamab and pembrolizumab.

All subjects in Phase 2 (Cohorts 1, 2 and 3) 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. A second biopsy will be taken during treatment.

Subjects will be treated in Cycle 0 with an IV infusion of vofatamab alone (without pembrolizumab).

For Phase 2, Cohort 1 and Cohort 2, 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 and prior to the first dose of vofatamab plus pembrolizumab. For patients enrolled in Cohort 3, the second tumor biopsy will occur at the end of cycle 1 of the combination (Week 5), within 3 days before Cycle 2, Day 1 and prior to the administration of the second combination dose of vofatamab and pembrolizumab. Disease re-staging will occur following Cycle 1 for biomarker correlation for all subjects whom underwent paired biopsies but will not be utilized for RECIST evaluation. Subjects whom do not get paired biopsies would not be required to get a scan at the end of Cycle 1. Paired Biopsies will be optional for any patient enrolled in Phase 2 expansion, Cohort 4. If biopsies are performed, the second biospy will be taken at end of cycle 1, Week 5.

On Cycle 1 Day 1, subjects will receive combined treatment of vofatamab (25 mg/kg) plus pembrolizumab (200 mg). Subjects will continue to receive vofatamab plus pembrolizumab Q3W until disease progression, death, decision to discontinue treatment, investigator discretion, or study termination or the completion of 2 years of vofatamab and pembrolizumab therapy.

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. It is highly encouraged that prior to discontinuation of any subject whom is receiving clinical benefit that a consultation occur with the study PI or medical monitor.

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, or the completion of 2 years of pembrolizumab therapy.

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.

Number of Subjects Planned:

This study will enroll approximately 100 subjects in total.

1. A **Phase 1b** which planned to enroll up to 18 patients in a 6+6 design. 8 subjects, 7 WT and 1 Mut/Fus were enrolled (study completed 8 subjects enrolled).
2. A **Phase 2** enrolling 60 subjects: 20 WT(Cohort 1), 20 Mut/Fus (Cohort 2), and 20 with tumors showing luminal biology (Cohort 3). Of these, 20 WT and 8 Mut/Fus subjects have already been enrolled. No further WT patients will be enrolled; a further 12 Mut/Fus and 20 with luminal biology will be enrolled
3. **Phase 2 expansion** enrolling 30 unselected patients (independent of their FGFR3 genetic status) (Cohort 4)

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, Cohort 2 (Mut/Fus), 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 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.

Subjects in Phase 2, Cohort 3 (luminal biology) must have a tumor that appears to have luminal biology as determined by IHC markers (GATA3 positive with the absence of KRT14) or acceptable comparable test on samples that were obtained at or after the time when the subject was found to have muscle invasive / metastatic disease, as evaluated by local pathology interpretation.

Subjects in the phase 2 expansion cohort (Cohort 4) will have FGFR3 genetic status determined but this will not be used to assign treatment.

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
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 1.1).
5. Male and female subjects, age ≥ 18 years.
6. Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤ 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 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 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:

$$\frac{(140 - age) \times (weight\ in\ kg) \times (0.85\ if\ female)}{72 \times (serum\ creatinine\ in\ mg/dL)}$$

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 (past or current).
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 [HBcAb]), Hepatitis C (Hepatitis C virus antibody serology testing [HCV Ab]), human immunodeficiency virus (HIV1/2 antibody +), and /or evidence of active tuberculosis (history and/or radiology findings).

    Note: Subjects positive for Hepatitis core antibody [HBcAb] 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 Drug, Dose, and Mode of Administration:

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. Additional instructions on vofatamab preparation and administration are provided in the Pharmacy Manual.

The study drug dosing regimen is as follows:

Subjects will receive one IV infusion of vofatamab (25 mg/kg) monotherapy over 90 (± 15) minutes. 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 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 treatment of vofatamab plus pembrolizumab will be administered Q3W (Day 1 of each cycle ± 7 days) until disease progression, death, decision to discontinue treatment, investigator discretion, or study termination, or the completion of 2 years of vofatamab and pembrolizumab therapy.

Control Arm, Dose, and Mode of Administration:

Not applicable. There is no control arm in study design.

Endpoints:

Phase 1b:

- DLTs within the 35-day observation period.

Phase 2 (Cohorts 1, 2, 3 and 4):

- **Primary Endpoints:**
- Safety and tolerability measurements of AEs, physical examination findings, laboratory test results, and vital signs over time.
- 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 defined by RECIST 1.1)
- **Secondary Endpoints:**
- Efficacy Endpoints:

Assessed by the investigator using RECIST 1.1 criteria (for progression)

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

- DCR defined as the percentage of subjects who achieve either CR or PR or stable disease (SD).
  - DCR (90), defined as the absence of disease progression and death 90 days from the time of first study drug administration.
  - DCR (180), defined as the absence of disease progression and death 180 days from the time of first study drug administration.
- PFS defined as the time from a first study treatment dose to first occurrence of disease progression (per RECIST 1.1) or death from any cause, whichever occurs first.
- OS defined as the time from first study drug administration to death from any cause.

- The change over time in subject reported quality of life as measured by the European Organization for Research and Treatment Quality of Life Questionnaire (EORTC QLQ-C30)
- The change following vofatamab 14-day lead-in period (Cohort 1 and Cohort 2) and after combination treatment with vofatamab and pembrolizumab (Cohort 3 and in Cohort 4 if biopsy material is available) 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
- The impact of FGFR3 status at enrollment (WT or Mut/Fus) on the safety and efficacy of vofatamab alone and in combination with pembrolizumab in subjects with advanced UCC.

- **Exploratory Endpoints**
- The PK of vofatamab
- The immunogenicity of vofatamab as measured by ATA levels
- The safety and efficacy of vofatamab in combination with pembrolizumab by bladder cancer subtype
- The impact of molecular markers on treatment response
- The efficacy of vofatamab in combination with pembrolizumab in the treatment of subjects with UCC as measured by ORR, DOR, PFS, and DCR per iRECIST

Statistical Methods:
Phase 1b:
Phase 1b endpoint will be number of events of dose limiting toxicity (DLT) observed over the safety observation period.

Phase 2 (Cohorts 1, 2, 3 and 4):
Primary Efficacy and Safety Analysis:

- The safety data will be summarized descriptively for AEs, laboratory test results, ECGs, prior and concomitant medication, and vital signs.

- The ORR will be calculated as the percentage of subjects who have a best overall response of either CR or PR and its 95% CIs at two interim analyses and the primary analysis.

Secondary Efficacy Analyses:

- The time-to-event (OS, PFS, DOR) endpoints will be summarized with descriptive statistics, including median time and its 95% confidence intervals (CIs).
- The categorical response (DCR) endpoint will be summarized with the frequency count, percentage, and 95% CIs.
- PRO EORTC QLQ-C30 endpoints and time to deterioration will be summarized descriptively.
- An evaluation of biomarkers, cytokines, immunogenicity, and predictive biomarker analysis pre and post treatment will be summarized descriptively.

Exploratory Endpoint Analyses:

- Pharmacokinetic parameters will be summarized at baseline and over time.
- ATA levels will be summarized at baseline and over time
- The safety and efficacy of vofatamab in combination with pembrolizumab by FGFR3 status at enrollment will be summarized
- The safety and efficacy of vofatamab in combination with pembrolizumab by bladder cancer subtype at enrollment will be summarized.

Interim Analyses:
There will be two pre-specified interim analyses during Phase 2, one has already been completed on the first 28 subjects (20 WT and 8 Mut/Fus). The second planned interim will occur when a minimum of 52 subjects have been enrolled and have data available to determine ORR.

All tumor assessments scans used in the interim analysis will be evaluated. Analysis will then be conducted using RECIST 1.1 and iRECIST.

The primary efficacy analysis will be performed when approximately 90 subjects (including expansion) in Phase 2 have been followed with sufficient duration to evaluate the primary efficacy endpoint, at the discretion of the sponsor. The number and proportion of responders along with DOR (duration of response) will be reported. The final analysis will be when all OS endpoint has been met or 3 years after the last subject enrolled, at the discretion of the sponsor.

Sample Size Calculations:

Given the expected π=0.343 with Type I error (alpha) at 0.05 (one-sided), 90 subjects will give a power of approximately 87.5% to reject the null hypothesis of $\pi \leq 0.211$. With the expected π=0.343, the 95% CI half width is around 0.098 for the sample size of 90 subjects.

Table 1 Schedule of Assessments for Phase 1b and Phase 2

	Screening	Treatment Phase			End of Treatment/ ET Visit [a,c]	Survival, End of Study Telephone Contact [a]
		Cycle 0[a,b,w]	Cycle 1[w]	Cycles 2+ (until progression) [a,b]		
	Days -28 to -1	14-day cycle	21-day cycle (± 3 days)	21-day cycles (± 7 days)		
Written informed consent [d]	X					
Confirm availability and request archival tumor tissue, blood sample, or perform diagnostic tumor biopsy [e]	X					
Review inclusion/exclusion criteria	X					
Medical history and demographics	X					
Complete physical examination [f]	X					
Targeted physical examination [f]		X	X	X	X	
Biomarker tumor biopsy [g]		X [g]	X [g]			
Height (screening only) and weight	X	X	X	X	X	
Vital signs [h]	X	X [h]	X [h]	X [h]	X	
ECOG performance status	X	X	X	X	X	
Adverse events [i,j]		X [i]	X	X	X [j]	
Concomitant medications and therapies	X	X	X	X	X	
Tumor assessment [k,l]	X [k]		X [l]	X [l]	X [l]	
Hematology [m]	X	X	X	X	X	
Viral serology (HIV -1/2, HBsAg, HBcAb and HCVAb)[x]	X					
Serum chemistry and urinalysis [n]	X	X	X	X	X	

	Screening	Treatment Phase			End of Treatment/ ET Visit [a,c]	Survival, End of Study Telephone Contact [a]
		Cycle 0[a,b,w]	Cycle 1[w]	Cycles 2+ (until progression) [a,b]		
	Days -28 to -1	14-day cycle	21-day cycle (± 3 days)	21-day cycles (± 7 days)		
Electrocardiogram [o]	X	X	X	X	X	
Coagulation (aPTT, PT/INR, and fibrinogen) [p]	X	X	X	X	X	
Urine or serum pregnancy test [q]	X	X	X	X	X	
Pharmacokinetic measurements [r]		X	X	X	X	
Anti-therapeutics antibody assessment [s]		X	X[s]	X[s]	X	
Biomarker assessment [t]		X	X	X	X	
Survival (via visits or telephone contact) [u]						X [u]
EORTC QLQ-C30[w]	X	X	X	X	X	
Study drug infusion [v]		X	X	X		

aPTT = activated partial thromboplastin time; ECOG = Eastern Cooperative Oncology Group; ET = early termination; FGFR3 = fibroblast growth factor receptor 3; IHC = immunohistochemistry; INR = international normalized ratio; PT = prothrombin time; EORTC QLQ-C30 = quality of life questionnaire.

[a] Study visits for Cycle 2+ may occur ± 7 days from the date scheduled if required for logistical/scheduling reasons.

[b] Local laboratory assessments (i.e., hematology, coagulation, serum chemistry, viral serology, urine/serum pregnancy testing, and urinalysis) may be performed within 72 hours preceding study drug administration unless otherwise specified. If an institution performs an equivalent test (e.g., urine albumin rather than urine protein), this may be acceptable and must be approved by the sponsor prior to subject enrollment

[c] Perform within 30 days after the last infusion of study drug.

[d] Informed consent form(s) must be signed by the subject before any study-specific procedures are performed.

[e] For Phase 1b, archival tumor tissue will be tested retrospectively, but the availability of samples of suitable quality and quantity should be determined and requested prior to study enrollment. For Phase 2, Cohort 1 and Cohort 2, subjects will be assigned based on FGFR3 genetic status 1) wild type (WT) or 2) mutant and/or fusion (Mut/Fus). An archival biopsy should be submitted for confirmation of genetic status. If archival biopsy is not (readily) available, a pre-treatment diagnostic biopsy within 56 days of first study treatment, or a blood sample may be used to determine genetic status. This biopsy may also be used in place of the first biomarker biopsy sample (if there is adequate material). A pre-treatment diagnostic biopsy will only be accepted while the WT cohort is open for enrollment. If the archival tumor tissue sample(s) and blood sample used to assess FGFR3 genetic status are non-informative, then any subject who has initiated treatment will be assigned to the WT cohort for the purpose of analysis.

[f] Complete physical exam includes all systems described in the body of the protocol. The targeted physical exam should only include systems of primary clinical relevance (i.e., cardiovascular, respiratory, and those associated with symptoms, and any system that might be associated with tumor assessment).

[g] All subjects enrolled in Phase 1b and Phase 2, Cohort 1, 2 and 3 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. Subsequent biopsies will only be required for subjects in Phase 2, Cohorts 1, 2 , and 3 (luminal biology). For Phase 1b and Phase 2, Cohort 1 and Cohort 2, 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 and prior to the first dose of vofatamab plus pembrolizumab. For patients enrolled in Cohort 3, the second tumor biopsy will occur at the end of cycle 1, Week 5, within 3 days before Cycle 2, Day 1 and prior to the administration of the second combination dose of vofatamab and pembrolizumab. For the Phase 2 expansion (Cohort 4), biopsies are optional. If a second biopsy is performed, it will be at end of cycle 1, Week 5. Subjects will be required to sign a separate consent form and must confirm their decision to opt-in.

[h] Blood pressure, pulse rate, and temperature. On Day 1 of Cycle 0 (if applicable) and Cycle 1, vital signs for vofatamab should be assessed pre-infusion, every 15 (± 5) minutes during the infusion, at the end of the infusion, and 30 (± 10) minutes, 60 (± 10) minutes, and 90 (± 10) minutes post-infusion. On subsequent cycles, vital signs for vofatamab should be assessed pre-infusion and as clinical indicated. For infusions with pembrolizumab, vital signs should be assessed per institutional guidelines, or regional label.

[i] Subjects will be monitored for any untoward effects during study drug infusion, for 90 minutes following completion of the infusion on Day 1 of Cycle 0 (if applicable) and Cycle 1 and then at least 30 minutes for all subsequent cycles in the absence of infusion-related adverse events (AEs). All AEs will be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause.

[j] Follow-up for AEs will occur for 30 days after the subject's last dose of study drug or until initiation of another anti-tumor therapy, whichever occurs first.

[k] All evaluable and measurable disease must be documented at screening and re-assessed at each subsequent tumor evaluation. A documented standard-of-care tumor assessment performed within 28 days prior to first study treatment may be used for the screening assessment. For subjects with measurable disease, response will be assessed by investigator per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1). Screening assessments must include: (1) computerized tomography (CT) scans of the chest, abdomen, and pelvis and all known or suspected sites of disease, and (2) brain scans (CT or magnetic resonance imaging [MRI]). At the investigator's discretion, additional methods of assessment of measurable disease per RECIST 1.1 may be used in addition to those listed above (e.g., bone scan by MRI). For subsequent tumor assessments, a CT scan of the chest, abdomen, and pelvis, and all known or suspected sites of disease must be obtained each time. The same imaging methods used at screening should be used throughout the study for each subject.

[l] For Phase 2, Cohort 1, Cohort 2, and Cohort 3, perform tumor assessments at end of Cycle 1, and every 9 weeks (± 7 days) thereafter (i.e., every third cycle beginning after Cycle 1) until disease progression or lack of tolerability. Disease re-staging will occur following Cycle 1 for biomarker correlation but will not be utilized for RECIST evaluation. Subjects in Cohort 4 who did not have the second biopsy will not need to have the scan following Cycle 1. Additional tumor assessments may be conducted as clinically indicated during the study. Results must be reviewed prior to study drug infusion at next cycle and continuation in the study will be based on the tumor assessment results. A tumor assessment scan should be performed if the subject is discontinuing the study early. At the End of Treatment/ET visit, subjects will be asked to provide any optional metastatic tumor tissue sample collected during the study or at autopsy.

[m] Includes complete blood count (red blood cell [RBC] count, hemoglobin, hematocrit, white blood cell [WBC] count), platelet count, and percent and absolute differential counts. For the Screening visit, testing should be done within 14 days of Day 1 of Cycle 0. If an institution performs an equivalent test to those listed above, for study purposes, this may be acceptable as long as it is noted with institutional normal(s) and approved by the sponsor prior to subject enrollment.

[n] Serum chemistry includes sodium, potassium, chloride, bicarbonate, non-fasting glucose, blood urea nitrogen (or urea concentration), creatinine, calcium, phosphate, magnesium, total and direct bilirubin, total protein, albumin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, lactate dehydrogenase, and uric acid. Urinalysis includes macroscopic analysis (specific gravity, pH, protein, glucose, ketones, blood, bilirubin, leukocyte esterase, urobilinogen, and nitrite) and microscopic urinalysis (RBCs, WBCs, epithelial cells, casts, crystals, bacteria, and yeast). For the Screening visit, testing should be done within 14 days of Day 1 of Cycle 0. If an institution performs an equivalent test to those listed above, for study purposes, this may be acceptable as long as it is noted with institutional normal(s) and approved by the sponsor prior to subject enrollment.

[o] Subjects should be resting for ≥ 10 minutes prior to electrocardiogram (ECG) collection. One ECG reading should be obtained at each of the following time points: Screening, Cycle 0 Day 1 pre-treatment, Cycle 1 Day 1 pre-treatment, Cycle 2 Day 1 pre-treatment, and at the End of Treatment/ET visit.

[p] Coagulation assessments (activated partial thromboplastin time [aPTT] or partial thromboplastin time (PTT) and prothrombin time [PT]/international normalization ratio [INR] and fibrinogen). For the Screening visit, testing should be done within 14 days of Day 1 of Cycle 0.

[q] For women of childbearing potential, a serum or urine pregnancy test must be performed during Screening (within 14 days prior to first vofatamab administration), prior to administration of study drug on Day 1 of each cycle, and the End of Treatment/ET visit.

[r] Blood samples for PK will be obtained prior to the administration of vofatamab and within 30 (± 15) minutes after the completion of the administration of vofatamab on Day 1 of Cycle 0. Blood samples will be obtained prior to the administration of pembrolizumab and within 30 (± 15) minutes after the completion of the administration of vofatamab on Day 1 of Cycles 1 and 4, and once at the End of Treatment/ET visit.

[s] Blood samples for ATA assessments will be obtained prior to infusion of vofatamab on Day 1 of Cycles 0, 1 and 4, and at the End of Treatment/ET Visit.

[t] Blood, serum, and plasma samples for biomarkers will be obtained prior to infusion of vofatamab on Day 1 of Cycles 0, 1, 3, and 5, and at the End of Treatment/ET Visit. Blood for circulating tumor DNA will be collected at the time of progression.

[u] Upon discontinuation of study treatment (vofatamab and pembrolizumab), subjects will be followed for survival every 3 months via telephone until death or full withdrawal of consent. The End of Study visit assessment should be performed by telephone call.

[v] For Cycle 0, the initial infusion of vofatamab should be administered over 90 (± 15) minutes to well-hydrated subjects, followed by a 90-minute observation period post-infusion. On Day 1 of Cycle 1 and beyond, subjects will receive an infusion of pembrolizumab (200 mg) over 30 (-5/+10) minutes followed by an infusion of vofatamab (25 mg/kg). If prior vofatamab infusions have been well-tolerated, subsequent doses of vofatamab may be administered over 30 (± 10) minutes, followed by a 30-minute observation period post-infusion. Vofatamab infusion will begin approximately 30 minutes after completion of the pembrolizumab infusion. Combination treatment will be administered once every 21-days. Doses for Cycle 2 and beyond may be given ± 7 days from the date scheduled if required for logistical/scheduling reasons. Doses may also be delayed up to 21 days for recovery from reversible toxicity. (Note: Subjects who discontinue vofatamab may continue on study and receive pembrolizumab alone [200 mg Q3W] until disease progression, death, withdrawal of patient consent, or study termination. Subjects who discontinue pembrolizumab may continue on study and receive vofatamab alone (25 mg/kg Q3W) until disease progression, death, withdrawal of patient consent, or study termination.)

[w] The EORTC QLQ-C30 instrument is administered at Screening and at Cycles 0, 1 and 2 (prior to administration of study drug), then every 2 cycles and 30 days after discontinuation.

[x] 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 anti-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.

GLOSSARY OF TERMS

Abbreviation/Acronym	Definition
95% CI	95% confidence interval
ADCC	antibody-dependent cell-mediated cytotoxicity
ADL	activities of daily living
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
ATA	anti-therapeutic antibody
ATC	anatomical therapeutic chemical
AUC	area under the concentration curve
BUN	blood urea nitrogen
CBC	complete blood count
CL	Clearance
CNS	central nervous system
CPI	checkpoint inhibitor
CR	complete response
CRF	case report form
CT	computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP3A4	cytochrome 3A4
DCR	disease control rate
DLT	dose-limiting toxicity
DOR	duration of objective response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EE	efficacy evaluable
ELISA	enzyme-linked immunosorbent assay
EORTC	European Organisation for Research and Treatment of Cancer
ET	early termination
FDA	Food and Drug Administration
FGFR3	fibroblast growth factor receptor 3
GCP	Good Clinical Practice
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen

Abbreviation/Acronym	Definition
HBV	hepatitis B virus
HCV	hepatitis C virus
HEENT	head, eye, ear, nose, and throat
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
Ig	immunoglobulin
IgG_1	immunoglobulin G_1
IHC	Immunohistochemistry
INR	international normalized ratio
IRB	Institutional Review Board
IRR	infusion-related reaction
IV	Intravenous
MedDRA	Medical Dictionary for Regulatory Activities
Mut/Fus	mutant fusion
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCI	National Cancer Institute
NGS	Next generation sequencing
ORR	objective response rate
OS	overall survival
PCR	polymerase chain reaction
PD	progressive disease
PD-1	programmed death protein 1
PD-L1	programmed death ligand 1
PK	Pharmacokinetic
PFS	progression-free survival
PR	partial response
PRO	patient reported outcome
PS	performance status
PT	prothrombin time or preferred term
QLQ	quality of life questionnaire
QW	Weekly
Q3W	once every 3 weeks

Abbreviation/Acronym	Definition
RECIST 1.1	Response Evaluation Criteria in Solid Tumors Version 1.1
RBC	red blood cell
RNA	ribonucleic acid
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SD	stable disease
SDV	source data verification
SOC	System Organ Class
SSC	Safety Steering Committee
TCC	transitional cell carcinoma
TCR	T-cell receptors
UCB	urothelial cell carcinoma of the bladder
UCC	urothelial cell carcinoma
ULN	upper limit of normal
US	United States
WBC	white blood cell
WHO	World Health Organization
WT	wild-type

1 INTRODUCTION

1.1 Background on Urothelial Cell Carcinoma

Urothelial cell carcinoma (UCC; also known as transitional cell carcinoma [TCC]) occurs in the urinary system (i.e., kidneys, urinary bladder, and accessory organs) and is the most common type of bladder cancer, accounting for 90% of all bladder tumors (Eble 2004). It is the fifth most common cancer in the United States (US) (Costantini 2011) and fourth most common cancer in Europe (Jemal 2011); with an estimated 74,690 new cases and 15,580 deaths occurring in the US in 2014 (Cancer.org), and an estimated 136,000 new cases and 49,000 deaths occurring in Europe in 2009 (Bellmunt 2009).

Clinical and pathological studies have identified two variants of urothelial cell carcinoma of the bladder (UCB) which arise via distinct mechanisms, a low-grade papillary variant and an invasive tumor variant (Wu 2005, Vallot 2011). The low-grade papillary variant accounts for 80% of all UCBs and arises from urothelial hyperplasia. The five-year survival for this tumor type, when treated with surgery and intravesical immunotherapy, is greater than 90% (Cancer.org). The invasive tumor variant represents 20% of UCBs and has a poor prognosis. Cisplatin-based chemotherapy with either a dose dense MVAC (Sternberg 2001) or gemcitabine cisplatin (von der Maase 2000) remains the standard treatment for invasive UCC. Despite initial response rates on the order of 50 to 70%, this cancer typically progresses rapidly with a median survival of around 13 to 15 months (von der Maase 2000; Siefker-Radtke 2002).

1.1.1 FGFR3 in Bladder Cancer

Recent studies have shown that UCC tumors often have genetic alterations in fibroblast growth factor receptor 3 (FGFR3) or amplification/overexpression of FGFR3 (Cancer Genome Atlas Research Network 2013, Tomlinson 2007a, Gust 2013). FGFR3 belongs to a family of structurally-related tyrosine kinase receptors encoded by four different genes (FGFR1-4). These receptors regulate various biological processes, including proliferation, differentiation, migration and apoptosis. Inappropriate FGFR3 signaling is implicated in the pathogenesis of the majority of muscle invasive UCC tumors with a notable percentage (approximately 20%) caused by activating FGFR3 mutations or gene fusions, and a significant percentage (50% or greater) expressing the receptor (Gomez-Roman 2005, Tomlinson 2007a, Gust 2013, Rainier unpublished data). Preclinical data from several lines of investigation, including short hairpin ribonucleic acid knockdown (Tomlinson 2007b, Qing 2009), antibody targeting (Martinez-Torrecuadrada 2005, Qing 2009), and small molecule inhibition (Lamont 2011) of FGFR3 in bladder cancer cell lines, also demonstrate that FGFR3 is essential for UCC cell growth *in vitro* and *in vivo*.

Additional studies have shown that FGFR3 mutations and expression are associated with the non-inflamed bladder cancer phenotype (Sweis 2015; Rosenberg 2016). Blockade of the FGFR3 pathway could enhance immune cell infiltrate into tumors that express FGFR3 or in which the FGFR3 pathway is activated. Luminal sub-type I bladder cancers are predicted to be highest in FGFR3 expression, have the highest prevalence of FGFR3 mutations (Choi 2014, Robertson 2017), and have the poorest response rate to CPI treatment

(Rosenberg 2016). There is pre-clinical data suggesting that treatment of luminal cell lines with FGFR inhibition may enhance response including immune markers (McConkey/Hahn unpublished data), making these tumors more susceptible to immunotherapy and providing the rationale for sequential treatment with FGFR3 and programmed death ligand 1 (PD-L1) inhibition. A single case report by Nassar et al. reported a complete response in an FGFR3-TACC3 fusion patient who received B-701 followed by a checkpoint inhibitor (Nassar 2018).

1.2 Background on Vofatamab

Vofatamab is a phage-derived, affinity-matured, human monoclonal antibody specific for FGFR3. It is based on a human immunoglobulin G1 (IgG_1) framework containing heavy chain V_HIII and light chain VκI subgroup sequences.

Vofatamab can be used to target FGFR3-positive tumors via three possible modes of action: (1) the blocking of ligand binding, receptor dimerization and activation, and downstream receptor signaling, (2) eliciting effector function such as antibody-dependent cell-mediated cytotoxicity (ADCC), and/or (3) antagonizing ligand-independent activating mutations (Qing 2009).

1.2.1 Non-clinical Data with Vofatamab

In *in vivo* studies, vofatamab demonstrated binding to FGFR3 from multiple species, including mouse, rat, cynomolgus monkey, and human. Vofatamab also inhibited ligand binding to FGFR3, prevented receptor−receptor association, blocked receptor dimerization, and blocked downstream signaling from both wild-type (WT) and common mutant variants of FGFR3, as well as FGFR3-TACC3 fusions linked with bladder cancer.--- Vofatamab suppressed FGFR3mediated cell proliferation and exerted strong antitumor activity in mouse xenograft models of both bladder carcinoma and t(4;14)positive multiple myeloma. Anti-tumor activity was due to direct inhibition of FGFR3 signaling and/or engagement of ADCC.

Vofatamab was well-tolerated and resulted in no severe toxicities when administered intravenously weekly for 8 weeks (total of nine doses) in either rats or cynomolgus monkeys and weekly for 26 weeks in juvenile monkeys, at doses up to the maximum feasible dose of 50 mg/kg. Vofatamab-related effects in the repeat-dose toxicity study in rats were limited to microscopic findings of minimal to slight focal tubular hypospermatogenesis/atrophy in male rats at the recovery necropsy. These observations were limited in distribution and severity, and therefore considered unlikely to result in a detectable impact on fertility. Vofatamab-related effects that were observed in the 8-week cynomolgus monkey study included increased spleen weight and minimal/moderate splenic lymphoid hyperplasia at terminal necropsy. These effects were reversible and not considered adverse. Similarly, administration of vofatamab weekly for 26 weeks was well-tolerated in juvenile monkeys. Changes considered related to vofatamab treatment were limited to moderate increases in white blood cell counts at the 50 mg/kg dose (i.e., increases in lymphocytes, monocytes, basophils and large unstained cells). These changes were no longer present during the recovery period and in the absence of other correlating changes were not considered toxicologically significant.

Pharmacokinetic (PK) studies of vofatamab in mice, Sprague-Dawley rats, and cynomolgus monkeys demonstrated both non-linear and linear PK characteristics, suggesting that the total clearance (CL) of vofatamab consists of contributions of a specific (target-mediated) CL component and a non-specific CL component, with the specific CL component having a greater contribution at lower doses. In repeat-dose toxicology studies in rats and cynomolgus monkeys, drug exposure increased proportionally with weekly (qw) intravenous (IV) doses of 5, 15, and 50 mg/kg, suggesting limited contribution of saturable target-mediated CL to the overall CL at these dose levels. Overall, the PK assessment indicates that vofatamab behaves like a typical IgG1, with some contribution of target-mediated clearance indicated by higher total CL estimates at the lower doses.

Additional non-clinical study information is provided in the Investigator's Brochure.

1.2.2 Clinical Data with Vofatamab

Vofatamab (i.e. B-701 or MFGR1877S) has been administered to 149 subjects in 4 Genentech and Rainier-sponsored clinical trials.

- Study MFG4809g (N = 14): a Phase 1 trial in patients with relapsed/refractory t(4;14)-positive multiple myeloma (NCT01122875). This study is completed.
- Study MFG4991g (N = 26): a Phase 1 trial in patients with advanced solid tumors (NCT01363024). This study is completed.
- Study B-701-U21 (N = 72) is an ongoing Phase 1b/2b trial in patients with locally advanced or metastatic UCC who have relapsed after or are refractory to standard therapy. Total enrollment as of the data cut off of 25 April 2019 is 71 subjects. The Phase 1b (Cohort 1) is complete N = 20 (19 treated). The Phase 2 cohort 2 (N=22, 21 treated) and cohort 3 (N=21), as well as Phase 2b (Monotherapy expansion phase, N=9) have completed enrollment and patients remain on treatment or re in study follow-up.This study is ongoing.
- Study B-701-U22 (adaptive design planned to enroll up to 74 subjects) is an ongoing Phase 1b/2 trial in subjects with locally advanced or metastatic UCC who have progressed following platinum-based chemotherapy. Enrollment as of the data cut off of 25 April 2019: Phase 1b complete n = 8; Phase 2 n = 28. Cohort WT is fully enrolled (as of 14 August 2018) and Cohort Mut/Fus is currently enrolling. This study is ongoing.

In addition, 1 subject was treated with vofatamab in an investigator-sponsored trial (IST).

Causality of AEs assessed by the investigator as possibly related and probably related are categorized as "related", and unlikely related and not related AEs are categorized as "not related". Evaluable patients were those who received at least one dose of vofatamab.

Summaries of the respective studies are provided below, and additional study information is provided in the Investigator's Brochure.

1.2.2.1 Study MFG4991g (Phase 1 study in Patients with Advanced Solid Tumors)

Study MFG4991g was an open-label, multicenter, Phase 1 study in 26 subjects with advanced solid tumors, of which 10 subjects had UCC. The safety and PK of escalating doses of vofatamab were evaluated following IV infusion of vofatamab to subjects once every 28 days (on Day 1 of each cycle), with an additional loading dose on Day 8 of Cycle 1 only. Doses of 2, 4, 8, 15, and 30 mg/kg of vofatamab were evaluated in 26 subjects. The study was terminated early by the Sponsor for reasons unrelated to efficacy or safety. All 26 subjects enrolled were in the dose-escalation stage, and the maximum tolerated dose was not reached. The maximum administered dose was 30 mg/kg on a 28-day schedule, and the median number of doses administered for all subjects was 3 (range 1-16).

Overall, vofatamab administered as an IV infusion at doses up to 30 mg/kg on a 28-day schedule was well-tolerated in subjects with advanced solid tumors. Two deaths due to disease progression were reported, and no deaths due to treatment-related adverse events (AEs) were reported. Only one dose-limiting toxicity (DLT) was observed in the study; and was reported by one subject in the 30 mg/kg cohort (Grade 4 thrombocytopenia which occurred on Day 4 of treatment and was attributed by the investigator as possibly due to concomitant treatment with levofloxacin).

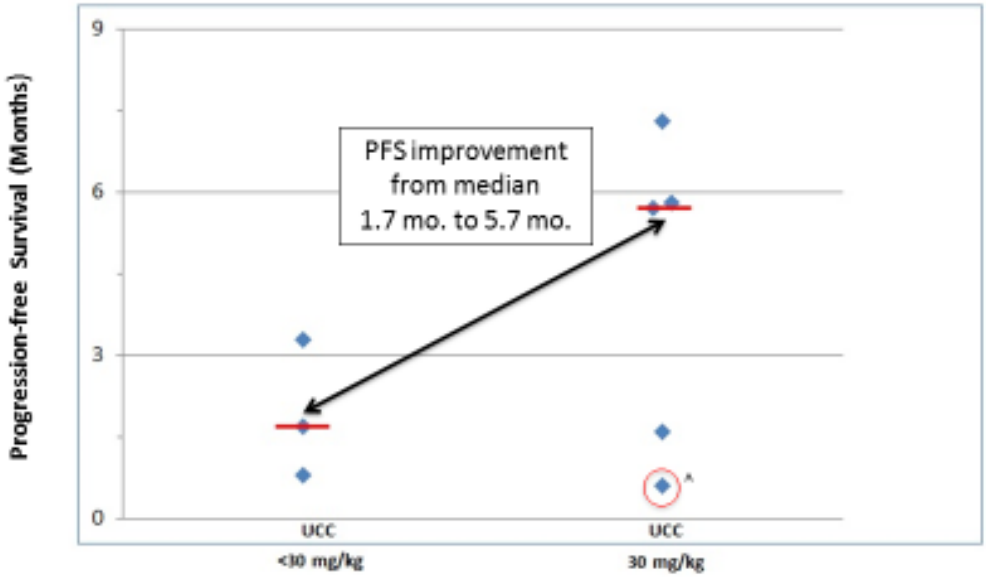
The AEs assessed as related to vofatamab and occurring in ≥ 10% of the subjects were fatigue (19.2%) and mucosal inflammation (11.5%). The majority of vofatamab-related AEs reported were Grade 1 or 2 in severity. Ten (38.5%) subjects experienced Grade ≥ 3 AEs, with 1 (3.8%) having Grade 4 thrombocytopenia and 1 (3.8%) having Grade 3 white blood cell (WBC) count decreased assessed as related to vofatamab. Eleven serious adverse events (SAEs) were reported in 8 (30.8%) subjects, with 1 (3.8%) subject experiencing one SAE assessed as related to vofatamab.

Serum exposure of vofatamab was approximately dose-proportional and increased with dose across the dose range of 2−30 mg/kg.

All 26 subjects enrolled in the study had evaluable anti-vofatamab antibodies (ATA) samples after treatment, and all tested negative for antibodies to vofatamab.

A total of 10 subjects (38%) had stable disease (SD) as their best clinical response on study. Furthermore, a post-hoc analysis comparing progression-free survival (PFS) of high-dose vofatamab (30 mg/kg) vs. low doses of vofatamab (< 30 mg/kg) showed greater PFS in the high-dose subjects (Figure 1). This finding was most notable in the evaluable UCC subpopulation, which had a median PFS of 5.7 months for the high-dose group (n = 5) compared with a median PFS of 1.7 months in the low-dose group (n = 3). Two subjects with UCC were not considered evaluable and were not included in this analysis.

Figure 1: Progression-Free Survival in Subjects with UCC (Study MFG4991g)



Note: This data set excludes one subject who received escalating doses of vofatamab (anti-FGFR3), 4 mg/kg up to 30 mg/kg, and a 2nd subject dosed at 30 mg/kg who died after Day 4 of the study due to disease progression

^ Subject had a single dose of vofatamab (anti-FGFR3) and dropped out of the study due to thrombocytopenia, possibly related to levofloxacin.

1.2.2.2 Study MFG4809g (Phase 1 Study in Patients with Multiple Myeloma)

Study MFG4809g was an open-label, multicenter, Phase 1 study in subjects with relapsed or refractory t(4;14)-positive multiple myeloma. The safety and PK of escalating doses of vofatamab were evaluated following IV infusion of vofatamab to subjects weekly for 3 weeks (Days 1, 8, and 15 of a 28-day cycle), followed by a single infusion of the same dose on Day 1 of the subsequent cycles. Doses of 1, 2, 4, 8, and 15 mg/kg of vofatamab were evaluated in 14 subjects. The median number of cycles administered was 1.5 and the median number of doses administered was 3.5. The study was terminated early by the Sponsor due to unsatisfactory enrollment.

All subjects had discontinued from the study at the time of study termination for the following reasons: 10 (71.4%) subjects due to disease progression, 3 (21.4%) subjects died (including 2 subjects who died due to disease progression and 1 subject who died due to disease progression with Grade 5 intracranial hemorrhage), and 1 (7.1%) subject due to subject/legal guardian decision to withdraw. All 14 subjects experienced at least one AE. The most common AEs irrespective of study drug attribution were fatigue experienced by 6 (42.9%) subjects; anemia and nausea experienced by 4 (28.6%) subjects each; diarrhea, dyspnea, headache, and thrombocytopenia experienced by 3 (21.4%) subjects each; and confusional state, cough, decreased appetite, hypercalcemia, neutropenia, peripheral edema, platelet count decreased, pyrexia, and urinary tract infection experienced by 2 (14.3%)

subjects each. A total of 6 subjects experienced 9 SAEs between Cycle 1 Day 1 and 90 days after the last administration of vofatamab, including one SAE of Grade 5 intracranial hemorrhage and one SAE of Grade 2 pyrexia, which was deemed related to vofatamab. All other SAEs were considered unrelated to vofatamab. There were no AEs of special interest, and there were no additional AEs of interest identified during the conduct of the study. Furthermore, no events were identified as a DLT and the maximum tolerated dose (MTD) was not reached prior to the Sponsor's decision to stop enrollment.

Given the small sample size, no definitive conclusions regarding anti-tumor activity could be drawn. The best overall response achieved was that of SD, which was reported in 7 of 14 subjects.

Exposure to vofatamab increased with increasing dose. Increases in exposure were non-dose proportional in the lower dose groups of 1 and 2 mg/kg, and approximately dose proportional at all other dose groups (i.e., 4, 8, and 15 mg/kg). FGFR3 levels did not appreciably change upon vofatamab treatment, regardless of dose.

1.2.2.3 A Dose Escalation, Expansion Study of Vofatamab (B-701) Alone, Plus Docetaxel, or Versus Docetaxel in Subjects with Locally Advanced or Metastatic Urothelial Cell Carcinoma who have Relapsed After, or are Refractory to Standard Therapy (Study B-701-U21)

Enrollment is complete of the study. In the Phase 1b, 20 subjects have been enrolled of whom 19 subjects have received at least one dose of study drug. No protocol-defined dose limiting toxicities were observed during the safety window in Cohort 1. The dosing regimen of 25 mg/kg of vofatamab and 75 mg/m^2 of docetaxel every 3 weeks has been selected as the recommended dosing regimen for the remaining subjects on study.

Of the 19 evaluable subjects in the Phase 1b safety population, subjects had a mean age of 65 years (range 57-76), were predominately white (95%), and the majority were male (74%) and had an ECOG performance status of 1 (58%).

All subjects received at least 1 line of chemotherapy and most subjects had received 2 or more prior treatments (73.7%), with 42.1% refractory to the last line of therapy. At study enrollment, 10.5% of subjects had liver metastases. Thirteen subjects had FGFR3 WT and 6 subjects had FGFR3 Mut/Fus, with similar pretreatment characteristics between the 2 groups. The median number of days of exposure was 96, with a clear difference in exposure based on Mut/Fus versus WT (147 vs 22 days).

All subjects in Cohort 1 have discontinued study treatment, predominantly due to disease progression (12/19 subjects/63%).

Phase 2 consisted of two cohorts, cohort 2 of subjects who received vofatamab in combination with docetaxel, and cohort 3 of subjects who were treated with vofatamab monotherapy. All subjects had an FGFR3 mutation or fusion. Cohorts 2 and 3 have completed accrual (as of 01 October 2018) and 21 subjects have been enrolled in each cohort. An interim analysis with cut-off data 25 April 2019 was conducted. The study is currently

ongoing. For further information, including safety information, please refer to the Investigator's Brochure.

1.2.2.4 A Phase 1b/2, 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 (Study B-701-U22)

FIERCE-22 is a 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 mUCC, 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 six (6) to 18 subjects and a Phase 2 dose expansion phase enrolling up to 74 subjects. Patients in the Phase 1b were unselected for FGFR3 status, whereas patients in the Phase 2 are assigned to Cohort 1 if their tumor is FGFR3 WT and to Cohort 2 if their tumor is FGFR3 mut/fus. Patients are 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 and following cycles).

The Phase 1b study initiated enrollment on October 2017 with the last subject enrolled in this cohort in February 2018. There was 1 subject enrolled under amendment 1 who received 1 dose of vofatamab and was taken off study after a program wide safety hold. This subject was not included in the DLT analysis as they never received the combination therapy but was included in the safety analysis.

After review of safety data and an amendment to the protocol (amendment 2), the program resumed enrollment. A total of 7 additional subjects were enrolled in Phase 1b. Six subjects were evaluable, and 1 subject was replaced due to disease progression and the need for palliative treatment during the DLT safety window.

Of the 8 subjects in the Phase 1b safety population, subjects had a mean age of 62 years (range 44-78), all (100%) were white and male and the majority (75%) had an ECOG performance status of 1. Among the 7 subjects enrolled after amendment 2, there were 6 subjects with FGFR3 wild-type and 1 with Mut/Fus (pending confirmation by Foundation Medicine, Inc.).

Phase 1b of the study has been completed, Cohort WT was fully enrolled (as of 14 August 2018). The study is currently ongoing. For further information, including safety information, please refer to the Investigator's Brochure.

1.3 Background on Pembrolizumab

Pembrolizumab (Keytruda®) is a programmed death protein 1 (PD-1) blocking antibody that is approved by the FDA for the of treatment of patients with locally advanced or metastatic

UCC who have disease progression during or following platinum -containing chemotherapy or disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy. Pembrolizumab is also approved by the FDA for the treatment of patients with locally advanced or metastatic UCC who are not eligible for cisplatin -containing chemotherapy.

The regular approval for the second-line indication was based on data from Trial KEYNOTE-045, a multicenter, randomized, active-controlled study in patients with locally advanced or metastatic urothelial carcinoma with disease progression on or after platinum containing- chemotherapy. Patients were randomly assigned (1:1) to receive either pembrolizumab 200 mg once every 3 weeks (Q3W; n = 270) or investigator's choice of a chemotherapy regimen (paclitaxel [n = 84], docetaxel [n = 84], or vinflunine [n = 87]) Q3W (n = 272). The study demonstrated statistically significant improvements in overall survival (OS) and objective response rate (ORR) for patients assigned to pembrolizumab compared with chemotherapy. Median OS was 10.3 and 7.4 months in the pembrolizumab and chemotherapy arms, respectively (HR: 0.73; 95% CI: 0.59, 0.91, p = 0.004). ORR was 21% for pembrolizumab and 11% for chemotherapy (p = 0.002). No statistically significant difference in progression-free survival (PFS) between the two arms was observed.

The accelerated approval for the first-line indication was based on data from KEYNOTE--052, a single-arm, open-label study in 370 patients with locally advanced or metastatic urothelial carcinoma who were deemed not eligible for cisplatin-containing chemotherapy. Patients received pembrolizumab 200 mg Q3W. With a median follow-up time of 7.8 months, the ORR was 28.6% (95% CI 24, 34) and the median response duration was not reached (range: 1.4+, 17.8+ months).

The most common adverse reactions reported for at least 20% of pembrolizumab-treated patients in either of the two studies included fatigue, musculoskeletal pain, pruritus, decreased appetite, nausea, diarrhea, constipation, and rash. Discontinuation of pembrolizumab secondary to adverse reactions occurred in 8% of patients in KEYNOTE-045 and in 11% in KEYNOTE-052. Dose interruption of pembrolizumab occurred in approximately 20% of patients in either study. Serious adverse reactions occurred in approximately 40% of pembrolizumab-treated patients. Immune-mediated adverse reactions, including pneumonitis, colitis, hepatitis, endocrinopathies (hypophysitis, hyperthyroidism, hypothyroidism, and Type 1 Diabetes mellitus), and renal dysfunction, were reported in the studies and were managed according to guidelines in Warnings and Precautions of the label for pembrolizumab.

Complete information on dosage and administration, safety information, non-clinical and clinical studies is contained in the FDA approved label for pembrolizumab (available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/125514lbl.pdf).

1.4 Rationale for Combining Vofatamab and Pembrolizumab

To date, several FDA-approved second-line therapies for the treatment of bladder cancer are available, including the immune checkpoint inhibitors (CPIs) such as atezolizumab, avelumab, durvalumab, nivolumab, and pembrolizumab. Although immune CPIs have the

potential to be a major advance in the second-line treatment of UCC, the inhibition of the programmed cell death protein (PD-1) pathway by CPIs depends on an immune response against tumor cells for efficacy. Consequently, emerging clinical and non-clinical data suggest that tumors with a non-inflamed phenotype are less likely to respond to immune CPI therapy. Moreover, while CPIs are highly effective in a small subset of patients whose tumors express PD-1, the majority of patients have disease which will progress while receiving this therapy. Thus, a significant unmet medical need exists for patients with relapsed or refractory metastatic UCC, especially for those tumors that do not have an inflammatory signature.

Recent work using gene expression profiling suggests there are at least two main intrinsic subtypes of UCC, which differ in their response and benefit to systemic chemotherapy (Choi 2014; McConkey 2016; Cancer Genome Atlas Research Network 2014). The basal subtype, which is typically associated with markers associated with stem cells, CK 5/6 positivity, and rapid proliferation, in addition to markers of angiogenesis, and markers of the immune system has a worse prognosis compared with luminal tumors which are typically associated with uroplakin markers, GATA3 positivity on immunohistochemistry (IHC), FGFR3 overexpression and mutations, and lower proliferation with an improved prognosis compared with untreated basal tumors. Using gene expression profiling the basal subtype was found to be predictive of improved survival outcomes when treated with neoadjuvant chemotherapy (McConkey 2016). This is the first clinical data which suggests that bladder cancer is not just one disease, and that with subtyping we may select patients most likely to benefit from specific therapies.

Overexpression of FGFR and FGFR3 mutations are most commonly observed in luminal type I tumors, and are often associated with downstream markers of pathway activation including PPARGamma expression (Choi 2014; Cancer Genome Atlas Research Network 2014). FGFR3 positive luminal tumors also lack immune cell infiltration, and the typical inflammatory markers associated with immune system sensitivity, leading us to predict that this subtype would also be resistant to immune checkpoint inhibition (Sweis 2015). Recent data from Rosenberg et al. support the hypothesis that the luminal subtype 1 is associated with the lack of response and benefit from PD-L1 inhibition (Rosenberg 2016). Therefore, inhibiting the FGFR3 pathway may overcome the immuno-silencing noted in the luminal I subtype.

Vofatamab is a novel fully human monoclonal antibody specific for FGFR3 that is being developed to target FGFR3-positive tumors. Non-clinical 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 vofatamab enhances immune cell infiltration or increase markers of immune system activation in subjects which in turn will enhance the efficacy of pembrolizumab. In addition, it will explore the impact of vofatamab on the tumor cell microenvironment. There is pre-clinical data suggesting that treatment of luminal cell

lines with FGFR inhibition may bring out features that will make tumors more susceptible to immunotherapy, providing the rationale for sequential and or combination treatment with FGFR3 and PD-1 inhibition.

2 OBJECTIVES AND ENDPOINTS

2.1 Objectives

2.1.1 Phase 1b

2.1.1.1 Primary Objective

- To establish the initial safety and to identify the recommended Phase 2 dose (RP2D) of vofatamab and pembrolizumab

2.1.2 Phase 2 and Phase 2 Expansion

2.1.2.1 Primary Objectives (Cohorts 1, 2, and 3)

- To evaluate the safety and tolerability of vofatamab plus pembrolizumab in subjects with UCC.
- 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)

2.1.2.2 Secondary Objectives

- 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) by RECIST 1.1, and overall survival (OS)
- To describe the impact of FGFR3 status at enrollment [wildtype (WT), mutation and/or fusion (Mut/Fus)] on the safety and efficacy after one cycle of B-701 alone, followed by B-701in combination with pembrolizumab in subjects with advanced UCC
- To evaluate the change in patient reported outcome (PRO) using quality of life measurements over time by the European Organization for Research and Treatment Quality of Life Questionnaire (EORTC QLQ-C30)
- To evaluate the change in expression of markers associated with tumor subtype, immune cell infiltrate, and immune response when B-701 is administered alone during the 14-day lead-in period (Cohorts 1 and 2)
- To evaluate the change in expression of markers associated with luminal tumor subtype, immune cell infiltrate, and immune response using a different timepoint for the 2nd biopsy only for Cohort 3 (at the end Cycle 1, Week 5)

2.1.2.3 Exploratory Objectives (Cohorts 1, 2 and 3)

- To evaluate the pharmacokinetics (PK) of vofatamab in subjects with UCC
- To assess the immunogenicity of vofatamab in subjects with UCC

- To determine if other molecular markers predict treatment response
- To evaluate the efficacy of vofatamab in combination with pembrolizumab in the treatment of subjects with UCC as measured by ORR, DOR, OS, PFS, and DCR per iRECIST

2.1.2.4 Secondary Objectives (Cohort 4):

- To evaluate the efficacy of vofatamab in combination with pembrolizumab in the treatment of unselected subjects with UCC as measured by duration of objective response (DOR), progression free survival (PFS), and disease control rate (DCR) by RECIST 1.1, and overall survival (OS)
- To evaluate the change in patient reported outcome (PRO) using quality of life measurements over time by the European Organization for Research and Treatment Quality of Life Questionnaire (EORTC QLQ-C30)

2.1.2.5 Exploratory objective (Cohort 4):

- To evaluate the efficacy of vofatamab in combination with pembrolizumab in the treatment of unselected subjects with UCC as measured by ORR, DOR, PFS, and DCR per iRECIST

2.2 Endpoints

2.2.1 Phase 1b

- DLTs within the 35-day observation period.

2.2.2 Phase 2 (Cohorts 1, 2, 3, and 4)

2.2.2.1 Primary Endpoints

- Safety and tolerability measurements of AEs, physical examination findings, laboratory test results, and vital signs over time.
- 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 defined by RECIST 1.1)

2.2.2.2 Secondary Endpoints:

- **Efficacy Endpoints**

  Assessed by the investigator using RECIST 1.1 criteria (for progression)

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

- DCR defined as the percentage of subjects who achieve either CR or PR or stable disease (SD).
  - DCR (90), defined as the absence of disease progression and death 90 days from the time of first study drug administration.
  - DCR (180), defined as the absence of disease progression and death 180 days from the time of first study drug administration.
- PFS defined as the time from a first study treatment dose to first occurrence of disease progression (per RECIST 1.1) or death from any cause, whichever occurs first.
- OS defined as the time from first study drug administration to death from any cause.
- The change over time in subject-reported quality of life as measured by the EORTC QLQ-C30
- The change following vofatamab 14-day lead-in period (Cohort 1 and Cohort 2) and after combination treatment with vofatamab and pembrolizumab (Cohort 3 and in Cohort 4 if biopsy material is available) 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
- The impact of FGFR3 status at enrollment (WT or Mut/Fus) on the safety and efficacy of vofatamab alone and in combination with pembrolizumab in subjects with advanced UCC.

2.2.2.3 Exploratory Endpoints

- The PK of vofatamab
- The immunogenicity of vofatamab as measured by ATA levels
- The safety and efficacy of vofatamab in combination with pembrolizumab by bladder cancer subtype
- The impact of molecular markers on treatment response
- The efficacy of vofatamab in combination with pembrolizumab in the treatment of subjects with UCC as measured by ORR, DOR, PFS, and DCR per iRECIST

3 STUDY DESIGN

3.1 Summary of Study Design

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, and who have not received prior immune checkpoint inhibitor or FGFR inhibitor targeted therapy. The study consists of 3 parts:

4. A **Phase 1b** which planned to enroll up to 18 patients in a 6+6 design. 8 subjects, 7 WT and 1 Mut/Fus were enrolled (study completed).
5. A **Phase 2** enrolling 60 subjects: 20 WT (Cohort 1), 20 Mut/Fus (Cohort 2), and 20 with tumors showing luminal biology (Cohort 3). Of these, 20 WT and 8 Mut/Fus subjects have already been enrolled. No further WT patients will be enrolled; a further 12 Mut/Fus and 20 with luminal biology will be enrolled.
6. A **Phase 2 expansion** enrolling 30 unselected patients (independent of their FGFR3 status) (Cohort 4)

Prior to study enrollment, the availability of an archival tumor sample must be requested from participants and availability must be confirmed during screening. A blood sample may be substituted to determine FGFR3 genetic status archival tumor is not available. If an archival biopsy is not available, during the screening window a pre-treatment diagnostic biopsy within 56 days of first study treatment may be obtained to satisfy this requirement, if submitted for additonal required studies. A second biopsy will be taken during treatment for cohorts 1, 2 and 3 or if an expansion phase patient opts in. Study biopsies may not be obtained from lung, bone, or brain .
For the Phase 2 expansion (Cohort 4), the paired biopsies are optional, but if they are taken, the second biospywill be taken at end of cycle 1, Week 5. Subjects will be required to sign a separate consent form and must confirm their decision to opt-in.

<u>Phase 1b:</u>

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 on-study 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 is on Cycle 1 Day 1, it should be obtained prior to the start of infusion of vofatamab with 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 (200mg) 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 Table 2.

Table 2 Dosing for Dose De-escalation

	Dose Level 0	**Dose Level -1**	**Dose Level -2**
Vofatamab	25 mg/kg IV q 3 weeks (n=6)	20 mg/kg IV q 3 weeks (n=6)	15 mg/kg IV q 3 weeks (n=6)

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, withdrawal of patient consent, investigator discretion, or study termination, or the completion of 2 years of vofatamab and pembrolizumab therapy. 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, the Phase 1b portion of the study was completed with no protocol-defined DLTs reported.

Phase 2 and Phase 2 expansion:

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 RP2D as no subjects met the study DLT definition of a Grade 3 or higher AE attributed to vofatamab and/or pembrolizumab.

For Phase 2, subjects will be assigned to one of three cohorts by either baseline FGFR3 status of WT (Cohort 1) or Mut/Fus (Cohort 2), or by bladder cancer subtype (luminal biology, Cohort 3). As of December 31, 2018, the WT cohort has been fully enrolled and is closed. For Cohort 2, Mut/Fus status must be confirmed prior to initiation of treatment. Cohort 3 will be enrolled at selected limited sites based on their tumor showing luminal biology, to study the molecular changes in the tumor after the first dose of combination treatment of vofatamab and pembrolizumab.

All subjects in Phase 2 (Cohorts 1, 2 and 3) 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. Biopsies will not be required for any patient enrolled in Phase 2 expansion, Cohort 4. If a second biopsy is performed, it will be at end of cycle 1, Week 5.

Subjects will be treated in Cycle 0 with an IV infusion of vofatamab alone (without pembrolizumab).

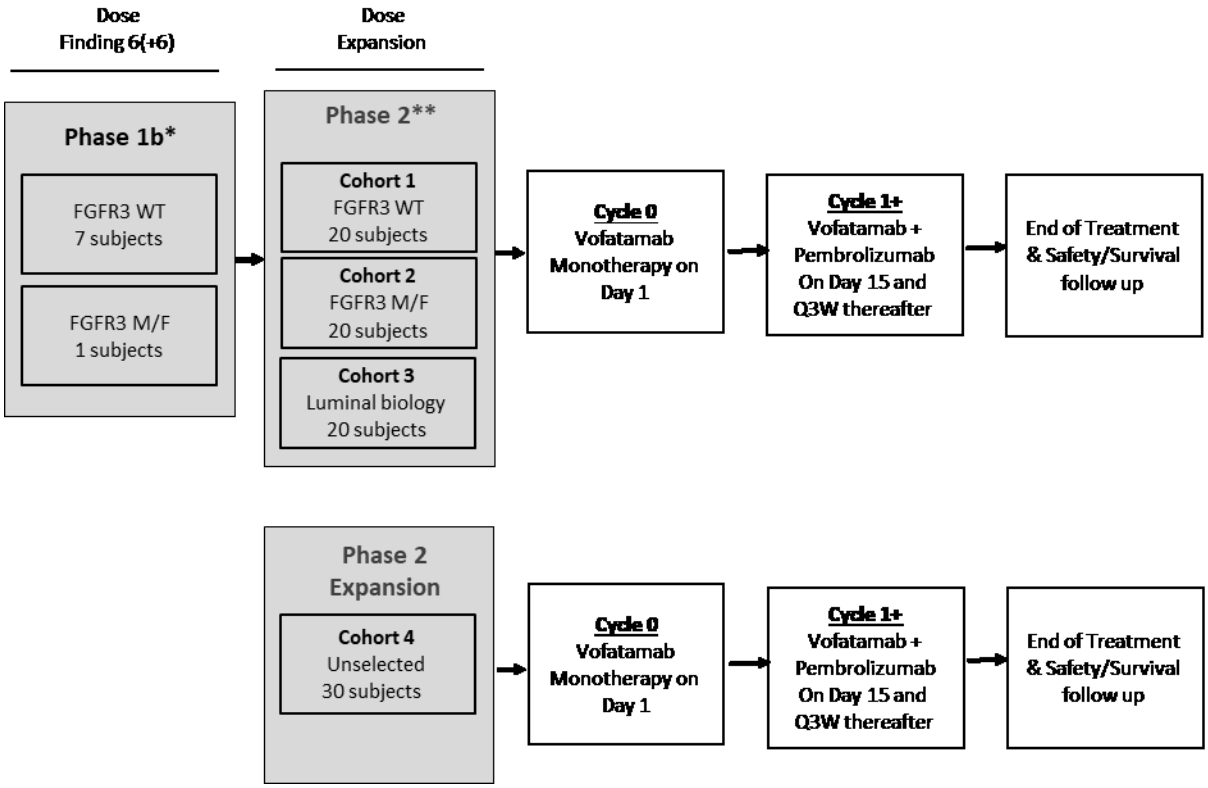
For Phase 2, Cohort 1 and Cohort 2, a second tumor biopsy will be obtained 14 days after Cycle 0 Day 1 of vofatamab. The second tumor biopsy should always occur within 3 days before Cycle 1 Day 1 infusion and prior to the first dose of vofatamab and pembrolizumab. For patients enrolled in Cohort 3, the second tumor biopsy will occur at the end of cycle 1. Week 5, within 3 days before Cycle 2, Day 1 and prior to the administration of the second combination dose of vofatamab and 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/kg) plus pembrolizumab (200 mg) . Subjects will continue to receive vofatamab plus pembrolizumab Q3W until disease progression, death, decision to discontinue treatment, investigator discretion, or study termination.

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. It is highly encouraged that prior to discontinuation of any subject whom is receiving clinical benefit that a consultation occur with the study PI or medical monitor.

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.

Figure 2: Study Design



FGFR3 = fibroblast growth factor receptor 3; Mut/Fus = mutant/fusion; Q3W = once every 3 weeks; WT = wild type.

*As of April 03 2018, Phase 1b of the study is complete.

**As of Dec 31 2018, 28 subjects (20 WT and 8 Mut/Fus) have already been enrolled in Phase 2. A total of 27 subjects will be added, 12 Mut/Fus (Cohort 2) and 15 with luminal biology (Cohort 3). No further WT subjects will be enrolled.

In Phase 2, Cohort 1 and Cohort 2 of the study, subjects will be assigned to a cohort by baseline FGFR3 status of 1) WT or 2) Mut/Fus; in Phase 2, Cohort 3, at selected sites, the patient's bladder cancer sub-type will be luminal enriched as determined by IHC testing for GATA3 and post enrollment by the Decipher Bladder test or acceptable comparable test on samples that were obtained at or after the time when the subject was found to have muscle invasive / metastatic disease.

3.2 Discussion and Rationale for Study Design

3.2.1 Selection of Dose and Dosing Schedule

Pembrolizumab will be used at the dose regimen indicated on its package insert for metastatic UCC. The dose regimen of vofatamab is based on the Phase 1 clinical PK and safety data in advanced solid tumors and should ensure > 90% patients achieve the estimated efficacious exposure. Since each drug has distinct and non-overlapping targets and suppression of each target to the fullest extent possible is desirable, both drugs will be used at full dose from the beginning of the study with the option for de-escalation of vofatamab if unanticipated safety events are observed.

To safeguard the interests of study participants, the toxicity of vofatamab plus pembrolizumab will be monitored closely by a Safety Steering Committee (SSC) (Section 3.2.2).

3.2.1.1 Vofatamab

The vofatamab dose and schedule in this study is consistent with study drug administration in the ongoing Phase 2 study and based on safety and PK data obtained from completed Phase 1 studies. The dosing regimen of vofatamab at 25 mg/kg every 21 days was selected since it is estimated to provide a steady-state area under the concentration curve (AUC) comparable to 30 mg/kg every 28 days, a dose and regimen that was administered and found to be generally safe and well-tolerated in the completed Phase 1 study in advanced solid tumors. The safety of this dose in combination with pembrolizumab will be confirmed in the Phase 1b portion of this protocol.

From an efficacy perspective, this dose is anticipated to be sufficient based on extrapolation from preclinical PK/pharmacodynamic analyses. Furthermore, the 14-day dosing period in phase 1b and initial phase 2 prior to initiating pembrolizumab therapy provides a window for immune cell recruitment without delaying the onset of immune checkpoint therapy for an extended period.

Additional supporting details:

- Murine PK modeling indicated a steady-state AUC of 850 day × µg/mL on a weekly basis, or 3400 day × µg/mL with administration every 4 weeks was needed for efficacy. Using compartmental PK analysis, IV administration of 20 mg/kg and 30 mg/kg of vofatamab every 21 days are expected to have steady state AUC of 3529 day × µg/mL and 5293 day × µg/mL, respectively. Thus, 25 mg/kg every 21 days is predicted to provide adequate doses for efficacy.
- In a Phase 1 study, administration of vofatamab across the dose range of 2 -30 mg/kg every 28-days was well-tolerated in subjects with advanced solid tumors. Serum exposure of vofatamab was approximately dose-proportional and increased with dose across the range tested. Six of the 10 subjects who had SD as their best clinical response on study were treated with 30 mg/kg vofatamab every 28-days.

Based on a population PK analysis, the post-hoc estimate of steady-state AUC for 30 mg/kg every 28-days was 5021 day × µg/mL

3.2.1.2 Pembrolizumab

Binding of the PD-1 ligands, PD-L1 and PD-L2, to the PD-1 receptor found on T cells, inhibits T cell proliferation and cytokine production. Upregulation of PD-1 ligands occurs in some tumors and signaling through this pathway can contribute to inhibition of active T-cell immune surveillance of tumors. Pembrolizumab is a monoclonal antibody that binds to PD-1 and blocks its interaction with PD-L1 and PD-L2, releasing the PD-1 pathway-mediated inhibition of the immune response, including the anti-tumor immune response. In syngeneic mouse tumor models, blocking the PD-1 pathway activity resulted in decreased tumor growth. In clinical studies, blocking the PD-1 pathway resulted in efficacious treatment of melanoma, non-small cell lung cancer, renal cell carcinoma and bladder cancer.

The recommended clinically approved dose of pembrolizumab for the treatment of UCC is 200 mg IV over 30 minutes Q3W. At this dose pembrolizumab has activity in advanced UCC with an ORR of 29% in patients ineligible for platinum therapy and 22% in patients post-platinum therapy.

3.2.2 Safety Monitoring Rules and the Safety Steering Committee

The toxicity of vofatamab plus pembrolizumab will be monitored by an SSC, composed of a Rainier medical representative and three independent UCC specialists. SSC review meetings will be defined in an approved SSC charter.

Standard safety monitoring will be employed for DLT assessment and dose de-escalation decisions. All AEs will be considered during the DLT assessment period (Day 1 through Day 35) unless an event is clearly unrelated to trial treatment. Before dose de-escalation (if applicable) at each dose level of vofatamab and at any other time that safety data warrant review, the Rainier MM will review safety data in consultation with the SSC, as appropriate.

For study monitoring and decisions about treatment, a subject in Phase 1b will be determined to have a DLT defined as follows:

The subject experiences any Grade 3 or higher treatment-emergent AE that is possibly or definitely related to either vofatamab and/or pembrolizumab received on this protocol and occurs up to 35 days after Cycle 0 Day 1. The exception is that a treatment-emergent AE that is potentially treatable with steroids will only count as a DLT if it does not improve to Grade 1 or better within 2 weeks after starting steroids.

3.2.3 Selection of Study Population

This study will be conducted in subjects with locally advanced or metastatic UCC who have progressed following treatment with platinum-based chemotherapy or who are not eligible for cisplatin-containing chemotherapy. This population was chosen on the basis of high unmet need, consistency with the current pembrolizumab label, and preclinical and clinical evidence that vofatamab administered with a PD-1 inhibitor has promising therapeutic

potential in this indication. After the initial safety run (Phase 1b), subjects will be assigned to one of three cohorts in Phase 2 based on either baseline FGFR3 status of WT (Cohort 1) or Mut/Fus (Cohort 2), or by bladder cancer subtype (luminal biology, Cohort 3; at selected limited sites), subjects with unselected tumors will be enrolled into the Phase 2 expansion (Cohort 4).

3.2.4 Blinding

This is an open-label study.

3.2.5 Duration of Subject Participation

The study period will include a 4-week screening period, and may include a 2 -week treatment period of vofatamab, followed by a treatment period of vofatamab plus pembrolizumab to complete 2 years of combination vofatamab and pembrolizumab therapy (21-days per cycle for combination treatment), End of Treatment visit, and telephone follow-up to monitor survival.

3.2.6 Definition of End of Study

The end of the study (i.e., the last visit) will occur due to Sponsor decision or when the last subject experiences disease progression, dies, or is discontinued from study treatment due to withdrawal of consent of investigator discretion.

4 STUDY POPULATION AND WITHDRAWAL

4.1 Inclusion Criteria

Individuals eligible to participate in this study must meet all of the following 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, Cohort 2 (Mut/Fus), 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.

   Subjects in Phase 2, Cohort 3 (luminal biology) must have a tumor that appears to show luminal biology as determined by IHC (GATA3 positive and absence of KRT14), or acceptable comparable test 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.

   Subjects in the Phase 2 expansion cohort (Cohort 4) will have FGFR3 mutation fusion status determined for analysis but this will not be used to assign treatment, but used for analysis purposes

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
3. Have available archival tumor or be willing to undergo diagnostic biopsy at screening
4. Have measurable disease according to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1).
5. Male and female subjects, age ≥ 18 years.
6. Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤ 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 on Cycle 0 Day 1 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 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 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:

$$\frac{(140 - age) \times (weight\ in\ kg) \times (0.85\ if\ female)}{72 \times (serum\ creatinine\ in\ mg/dL)}$$

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.

4.2 Exclusion Criteria

Individuals who meet any of the following exclusion criteria will not be eligible to participate in the study:

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 medication.

   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 the 2 weeks 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 (past or current).
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 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 active infection, 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 [HBcAb]), Hepatitis C (Hepatitis C virus antibody serology testing [HCV Ab]), human immunodeficiency virus (HIV1/2 antibody +), and /or evidence of active tuberculosis (history and/or radiology findings).

    Note: Subjects positive for Hepatitis core antibody [HBcAb] 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.

4.3 Removal of Subjects for Therapy or Assessment

4.3.1 Subject Discontinuation from the Study or Treatment

Subjects must be withdrawn from the study if they experience disease progression (defined using RECIST 1.1 in Appendix 2). Subjects may continue vofatamab and/or pembrolizumab therapy beyond progression following discussion with the medical monitor and based on clinical judgement of the investigator that the subject is experiencing clinical benefit. It is highly encouraged that prior to discontinuation of any subject whom is receiving clinical benefit that a consultation occur with the study PI or medical monitor.

Subjects may discontinue treatment with vofatamab and/or pembrolizumab early (i.e., for reasons other than disease progression) for reasons such as subject/investigator decision or unacceptable toxicity. The reasons for early discontinuation of treatment must be documented on the appropriate case report form (CRF). Subjects who discontinue vofatamab or pembrolizumab should continue on study and receive the other agent alone until disease progression, death, decision to discontinue treatment, investigator discretion, or study termination.

Subjects must be withdrawn from study treatment if they become pregnant.

The investigator has the right to discontinue a subject from the study for any medical condition that the investigator determines may jeopardize the subject's safety, for reasons of noncompliance (e.g., missed doses [≥ 2 doses], visits), or if the investigator determines it is in the best interest of the subject.

The End of Treatment visit assessments should be performed on subjects who prematurely withdraw from the study during the treatment period. Subjects should be followed for safety outcomes for 30 days following the subject's last dose of study drug or until the subject receives another anti-cancer therapy, whichever occurs first.

Upon discontinuation of study treatment (vofatamab and pembrolizumab), subjects will be followed for overall survival every 3 months via telephone until death or full withdrawal of consent.

4.3.1.1 Subject Replacement

Subjects who discontinue the study early will not be replaced with the exception of patients enrolled in the phase 1b portion of the trial whom discontinued for a reason other than DLT.

4.3.2 Study Discontinuation

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of AEs in this or other studies indicates a potential health hazard to subjects.
- Subject enrollment is unsatisfactory
- Evidence that either cohort is providing no potential benefit over current therapies.

5 TREATMENT OF SUBJECTS

5.1 Treatment Regimens

For subjects participating in Cycle 0, vofatamab (25 mg/kg or the RP2D) monotherapy will be administered on Cycle 0 Day 1 by IV infusion over 90 (± 15) minutes.

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 and Cycle 1vofatamab infusions have been well-tolerated, subsequent doses of vofatamab may be administered over 30 (± 10) minutes, followed by a 30-minute observation period post-infusion. 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.

Dosing guidelines for vofatamab and pembrolizumab are summarized in Table 3.

Table 3 Study Drug Dosing Guidelines

Agent	Dose	Route	Schedule
Pembrolizumab	200 mg	IV over 30 (−5/+10) minutes [b]	Day 1 (± 3 days) of Cycle 1 and Day 1 (± 7 days) of Cycles 2+
Vofatamab	25 mg/kg[a]	IV over 90 (± 15) minutes [b]	Day 1 of Cycle 0 (if applicable), Day 1 (± 3 days) of Cycle 1, and Day 1 (± 7 days) of Cycles 2+

Note: Cycle 0 is 14 days and Cycles 1+ are 21 days.

[a.] Or the recommended Phase 2 dose if different than 25 mg/kg.

[b.] If no infusion reactions are observed in Cycles 0 (if applicable) and Cycle 1, subsequent doses of vofatamab may be infused over 30 ± 10 minutes.

The rules for continued dosing are provided in Section 5.1.1, and dose modification instructions are provided in Section 5.1.2. Additional drug administration details are provided in the pembrolizumab package insert.

5.1.1 Guidelines for Continued Dosing

Once enrolled and on study, subjects must meet the following criteria for ongoing clinical benefit and acceptable toxicity to be eligible to receive additional cycles of study treatment:

- Ongoing clinical benefit: Subjects must have no signs or symptoms of progressive disease (PD). Subjects with PD (as defined by RECIST 1.1 in Appendix 2), will be ineligible to receive further treatment with study drug. The end of Cycle 1 scan will be used for biomarker correlation, but will not be used to determine disease progression per RECIST. Limited Exception: Subjects may continue vofatamab and

pembrolizumab treatment beyond progression if the investigator feels they are experiencing benefit. This decision will be made in consultation with the medical monitor.

Acceptable toxicity: All study drug-related AEs from prior infusions must have decreased to Grade 1 or baseline grade on or before the day of the next infusion. Exceptions on the basis of ongoing clinical benefit may be allowed after a careful assessment and discussion of risk versus benefit with the subject by the investigator and approval from the Medical Monitor, with the option of dosing vofatamab at the full dose of 25 mg/kg or reducing the dose of vofatamab to 20 mg/kg (Dose Level -1) or to 15 mg/kg (Dose Level -2). No further dose de-escalation may be done in this study, and the subject should be discontinued for unacceptable toxicity if 15 mg/kg is not tolerated. In addition, delay of therapy due to toxicities not attributed to study drug may not require discontinuation and must be discussed with the Medical Monitor. This may also apply to pembrolizumab with the following caveats: hypothyroidism, adrenal insufficiency, and hypopituitarism which all may require hormone replacement and are likely irreversible. Subjects with asymptomatic elevations of amylase and lipase have been observed, and may continue on pembrolizumab as long as amylase and lipase levels are < Grade 4 using CTCAE.

5.1.2 Dose Modification

There are currently no AEs that are more likely attributed to vofatamab than to pembrolizumab.

Subjects will be closely monitored for platelets and coagulation factors including aPTT, PT/INR, and fibrinogen (see Table 1 for the timing of assessments). If either aPTT or PT/INR exceeds 1.5 × ULN or if fibrinogen falls below the LLN, all study drug treatment should be held until these factors return to baseline levels before re-dosing. Exceptions may be allowed upon discussion with the Medical Monitor and Investigator.

5.1.2.1 Vofatamab Dose Modification

Subjects in whom toxicities have not reversed sufficiently by the scheduled day of infusion (for Cycle 1 and beyond) may have their dose of vofatamab delayed by up to 21 days. If all study drug–related toxicities have reversed sufficiently and the additional criteria described in Section 5.1.1 have been met, then the subject may receive the subsequent dose of vofatamab.

Subjects who do not fulfill the criteria for dosing after 21 days have elapsed will be discontinued from vofatamab, but may continue on study and receive pembrolizumab alone until disease progression, death, withdrawal of patient consent, investigator discretion, or study termination. Exceptions on the basis of ongoing clinical benefit may be allowed following a careful assessment and discussion of risk versus benefit with the subject by the investigator and approval from the Medical Monitor, with the option of dosing vofatamab at the full dose of 25 mg/kg or reducing the dose of vofatamab to 20 mg/kg (Dose Level -1) or to 15 mg/kg (Dose Level -2). No further dose de-escalation may be done in this study, and the subject should be discontinued for unacceptable toxicity if 15 mg/kg is not tolerated. In

addition, delay of therapy because of toxicities not attributed to study drug may not require discontinuation and will be discussed with the Medical Monitor.

The SSC will review the overall safety data from dosed subjects and DLTs, and can make recommendations to stop the study. Safety analyses will be performed by the SSC based on guidelines outlined in the SSC Charter.

5.1.2.2 Pembrolizumab Dose Modification

Pembrolizumab dosing delays or dose modifications will be performed consistent with the pembrolizumab package insert. Refer to Warnings and Precautions sections of the FDA-approved package insert for additional information. Vofatamab may be continued after consultation with the medical monitor.

Subjects who experience any of the following should have pembrolizumab withheld until resolution of the toxicity to Grade 0 or 1:

- Grade 2 pneumonitis
- Grade 2 or 3 colitis
- Grade 3 or 4 endocrinopathies
- Grade 2 nephritis
- Grade ≥ 3 hyperthyroidism
- AST or ALT greater than 3 and up to 5× ULN
- Total bilirubin greater than 1.5 and up to 3× ULN
- Any other severe or Grade ≥3 treatment-related adverse reaction

Pembrolizumab should be permanently discontinued if any of the following are observed and deemed by the investigator to be most likely due to pembrolizumab treatment:

- Any life-threatening adverse reaction (excluding endocrinopathies controlled with hormone replacement therapy)
- Grade 3 or 4 pneumonitis or recurrent pneumonitis of Grade 2 severity
- Grade 3 or 4 nephritis
- AST or ALT greater than 5× ULN or total bilirubin greater than 3× ULN
- Grade 3 or 4 infusion-related reactions
- Inability to reduce corticosteroid dose to 10 mg/day or less of prednisone or equivalent per day within 12 weeks

- Persistent Grade 2 or 3 adverse reactions (excluding endocrinopathies controlled with hormone replacement therapy) that do not recover to Grade 0-1 within 12 weeks after last dose of pembrolizumab
- Any severe or Grade 3 treatment-related adverse reaction that recurs

Pembrolizumab dose modification guidelines for drug-related AEs are summarized in the pembrolizumab package insert.

5.1.3 Post-Study Access to Study Drug

The Sponsor does not have any plans to provide vofatamab, pembrolizumab, or other study interventions to subjects after the end of the study (defined in Section 3.2.6).

5.2 Preparation, Administration, and Storage of Study Drug

5.2.1 Vofatamab

5.2.1.1 Preparation and Administration

Vofatamab is provided as a sterile lyophilized powder and contains no preservatives. After reconstitution with sterile water for injection, the drug product is formulated as 10 mg/mL vofatamab in 200 mM arginine succinate, 0.02% polysorbate 20, pH 5.5. The drug product will be delivered at a final concentration of ≥ 3 mg/mL.

Drug product will be delivered using standard medical syringes and syringe pumps or IV bags. Delivery will be carried out with a 0.22 μm in-line filter on either the syringe-pump extension set or the IV infusion set

The initial dose of vofatamab (Cycle 0 and Cycle 1) will be administered over 90 (± 15) minutes to well-hydrated subjects. The infusion may be slowed or interrupted for subjects experiencing infusion-associated symptoms. Following the initial dose, subjects will be observed for 90 minutes for fever, chills, rigors, hypotension, nausea, or other infusion-associated symptoms. If prior infusions have been well-tolerated, subsequent doses of vofatamab (Cycle 2+) may be administered over 30 (± 10) minutes, followed by a 30-minute observation period post-infusion. Additional instructions on study drug preparation and administration are provided in the Pharmacy Manual.

5.2.1.2 Storage

Vofatamab vials must be refrigerated at 2ºC–8ºC (36ºF-46ºF) upon receipt until use. Vofatamab should not be used beyond the expiration date provided by the manufacturer. The lyophilized vofatamab vials should be reconstituted with sterile water for injection the day of use. Vial contents should not be frozen or shaken and should be protected from direct sunlight. Vofatamab solutions may be stored at refrigerated (2-8ºC) for 24 hours or at room temperatures (25ºC [77ºF]) for up to 8 hours prior to use, total time at both temperatures not to exceed 24 hours.

Additional vofatamab dosage, administration, and storage instructions are provided in the Pharmacy Manual.

5.2.1.3 Precautions

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 life-threatening allergic reactions have been observed. The administration of vofatamab should be performed in a setting with access to emergency equipment and staff who are trained to monitor and respond to medical emergencies. Subjects will be monitored during and after each vofatamab infusion for 90 minutes after the Cycle 0 (if applicable) and Cycle 1 and for 30 minutes after subsequent infusions in the absence of infusion--related AEs. Subjects who experience infusion-related symptoms should be managed as directed in Table 4 below.

Table 4 Management of Infusion-Related Symptoms (e.g., fever, chills/rigors, nausea, vomiting, pruritus, headache, rhinitis, rash, hypotension, hypersensitivity, anaphylaxis, dyspnea, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress)

Infusion-Related Symptoms [a]	Guidance
Grade 1–2	• Slow or hold infusion. • Give supportive treatment [b]. • Upon symptom resolution, may resume infusion rate escalation at the investigator's discretion [c].
Grade 3-4	• Discontinue infusion immediately, treat symptoms aggressively, and do not restart drug.

[a] Refer to National Cancer Institute Common Terminology Criteria for Adverse Events, v4.0, for the grading of symptoms. This table does not refer to management of IgE-mediated allergic reactions, which should be managed as directed in text following this table.

[b] Supportive treatment: Subjects should be treated with acetaminophen/paracetamol and an antihistamine such as diphenhydramine if they have not been received in the last 4 hours. Intravenous saline may be indicated. For bronchospasm, urticaria, or dyspnea, subjects may require antihistamines, oxygen, corticosteroids (e.g., 100 mg IV prednisolone or equivalent), and/or bronchodilators. For hypotension, subjects may require vasopressors.

[c] Infusion rate escalation after re-initiation: Upon complete resolution of symptoms, the infusion may be resumed at 50% of the rate achieved prior to interruption. In the absence of infusion-related symptoms, the rate of infusion may be escalated in increments of 50 mg/h every 30 minutes.

Subjects who experience vofatamab infusion-related temperature elevations of > 38.5°C or other minor infusion-related symptoms may be treated symptomatically with acetaminophen (≥ 500 mg) and/or H_1 and H_2 histamine-receptor antagonists (e.g., diphenhydramine, ranitidine). Serious infusion-related events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with additional supportive therapies (e.g., supplemental oxygen, β_2-agonists, and/or corticosteroids) as clinically indicated according to standard clinical practice.
Infusion-related reaction (IRR) prophylaxis with medications (e.g., acetaminophen, antihistamines, and/or corticosteroids) may be instituted at any point in the study that it is

determined to be in the best interest of subjects due to the observation of IRRs in a significant number of subjects.

In the event of a life-threatening infusion-related reaction (which may include pulmonary or cardiac events) or immunoglobulin (Ig) E-mediated anaphylactic reaction, vofatamab should be discontinued and no additional vofatamab should be administered. Subjects who experience these reactions should receive aggressive symptomatic treatment and should be discontinued from study treatment.

Precautions and procedures for suspected anaphylactic reaction during study drug infusions are provided in Appendix 3. Prophylactic administration with acetaminophen and antihistamine may be used at investigator discretion.

5.2.2 Pembrolizumab

Complete preparation, administration, and storage instructions for pembrolizumab are provided in the Pharmacy Manual.

Subjects should be monitored for signs and symptoms of pembrolizumab-related pneumonitis, colitis, hepatitis, and endocrinopathies; and changes in liver function, renal function, and thyroid function. Subjects who experience any of the above pembrolizumab-related toxicities should have the dose of pembrolizumab modified as described in Section 5.1.2.2.

5.3 Study Drug Accounting

5.3.1 Receipt of Drug Supplies

Upon receipt of the study treatment supplies, an inventory must be performed and a drug receipt log filled out and signed by the person accepting the shipment. It is important that the designated study staff counts and verifies that the shipment contains all the items noted in the shipment inventory. Any damaged or unusable study drug in a given shipment (active drug or comparator) will be documented in the study files. The investigator must notify study sponsor of any damaged or unusable study treatments that were supplied to the investigator's site.

5.3.2 Return or Destruction of Study Drug

At the completion of the study, there will be a final reconciliation of drug shipped, drug consumed, and drug remaining. This reconciliation will be logged on the drug reconciliation form, signed and dated. Any discrepancies noted will be investigated, resolved, and documented prior to return or destruction of unused study drug. Drug destroyed on site will be documented in the study files.

5.4 Concomitant and Prohibited Therapies

5.4.1 Concomitant Therapy

Concomitant therapy includes any prescription medications or over-the-counter preparations used by a subject between the signing of the Informed Consent Form and the end of study visits. All concomitant medications and therapies should be reported to the investigator and recorded on the appropriate CRF.

Subjects who use oral contraceptives, hormone-replacement therapy, or other maintenance therapy should continue their use. Concomitant use of hematopoietic growth factors is allowed in accordance with instructions provided in the package inserts.

5.4.2 Prohibited Therapy

Use of the following therapies is prohibited during the study:

- Cytotoxic chemotherapy
- Radiotherapy (unless for palliative care of a solitary non-target lesion)
- Immunotherapy
- Hormone therapy (other than contraceptives, hormone-replacement therapy, hormone therapy for adjuvant breast cancer therapy or megestrol acetate)
- Biologic agents (other than hematopoietic growth factors, which are allowed if clinically indicated and used in accordance with instructions provided in the package inserts)
- Any therapies intended for the treatment of UCC, whether approved by local regulatory authorities or investigational

Subjects who require the use of any of these agents will be discontinued from treatment with vofatamab and/or pembrolizumab. See Section 6.1.5 for assessments that are to be performed for subjects who discontinue from the study early.

5.5 Treatment Compliance

Subject compliance with treatment is not applicable since study site personnel will administer study drug.

6 STUDY PROCEDURES (PHASE 1B AND 2 INCLUDING EXPANSION COHORT)

The Schedule of Assessments, Screening through End of Study, is presented in Table 1.

All screening evaluations must be completed and reviewed by the Medical Monitor to confirm that subjects meet all eligibility criteria and are approved for enrollment before the first infusion of study drug.

All visits should occur on the scheduled days. However, visits after Cycle 1 may occur ± 7 days from the scheduled date if a change is required for logistical/scheduling reasons. Assessments scheduled on the day of study drug administration (Day 1) of each cycle should be performed prior to study drug infusion, unless otherwise noted.

Local laboratory assessments may be performed within 72 hours preceding study drug administration on Day 1 of each cycle, unless otherwise specified. Results must be reviewed and the review documented prior to study drug administration.

6.1 Assessments by Study Visit

6.1.1 Screening

The following Screening evaluations will be performed within 28 days preceding the first dose of study drug, unless otherwise specified.

- Written informed consent must be signed before any study-specific procedures are performed (described in Section 7.1.1).
- Confirm availability and request archival tumor tissue (described in Section 7.1.3) or undergo diagnostic biopsy during Screening window
- Review inclusion/exclusion criteria (described in Section 7.1.4)
- Medical history and demographics (described in Section 7.1.5)
- Complete physical examination (described in Section 7.2.2)
- Height and weight (described in Section 7.2.2)
- Vital signs (described in Section 7.2.3)
- ECOG PS (see Appendix 1)
- Concomitant medications and therapies
- Tumor assessment: A documented standard-of-care tumor assessment performed within 56 days prior to Cycle 0, Day 1 may be used for the screening assessment (described in Section 7.3.1 and Appendix 2). The same imaging methods used at screening should be used throughout the study for each subject where possible.

- Hematology (described in Section 7.2.4.1)
- Viral serology (HIV -1/2, HBsAg and HBcAb, (HBV DNA by PCR if required) and HCV Ab)
- Serum chemistry (described in Section 7.2.4.1
- Urinalysis (described in Section 7.2.4.1)
- Electrocardiogram (ECG; described in Section 7.2.5)
- Coagulation (i.e., activated partial thromboplastin time [aPTT] or partial thromboplastin time PTT, prothrombin time [PT]/international normalized ratio [INR], and fibrinogen; described in Section 7.2.4.1)
- Urine or serum pregnancy test within 14 days prior to first study treatment (described in Section 7.2.4.1)
- EORTC QLQ-C30

6.1.2 Cycle 0

6.1.2.1 Day 1 of Cycle 0

Note: Study-related biopsies should not be obtained from lung, bone, or brain at any point during the study.

The following assessments should be performed prior to study drug infusion:

- Targeted physical examination (described in Section 7.2.2)
- Biomarker tumor biopsy (optional for Phase 2 expansion, Cohort 4) (described in Section 7.1.2)
- Weight
- Vital signs (described in Section 7.2.3)
- ECOG PS (see Appendix 1)
- Concomitant medications and therapies
- Hematology (described in Section 7.2.4.1)
- Serum chemistry (described in Section 7.2.4.1)
- Urinalysis (described in Section 7.2.4.1)
- Coagulation (i.e., aPTT, PT/INR, and fibrinogen; described in Section 7.2.4.1)
- Urine or serum pregnancy test (described in Section 7.2.4.1)

- ECGs (described in Section 7.2.5)
- PK blood samples collected before vofatamab administration (described in Section 7.4)
- ATA and biomarker blood samples (described in Sections 7.5 and 7.6, respectively)
- For Phase 2 only:
  - Assign subject to a cohort by baseline FGFR3 status (WT or Mut/Fus) (described in Section 7.1.3).

For Phase 2 and Phase 2 expansion:

- Patient reported outcome (PRO) assessment/ EORTC QLQ-C30 (described in Section 7.3.3)

Study drug administration:

- Subjects should be well-hydrated prior to study drug administration. Subjects will receive Cycle 0 and Cycle 1 infusions of vofatamab over 90 (± 15) minutes. The infusion will be followed by a 30-minute observation period (described in Section 5.2)
- Vital signs should be assessed every 15 (± 5) minutes during the vofatamab infusion, and at the end of the vofatamab infusion (described in Section 7.2.3)

AEs should be collected and recorded while the subject is receiving study drug (described in Section 7.2.1)

The following assessment(s) should be performed after study drug infusion has been completed:

- Vital signs should be assessed every 30 (± 10) minutes for 90 minutes post-vofatamab-infusion (i.e., 30 [± 10] minutes, 60 [± 10] minutes, and 90 [± 10] minutes post-infusion; described in Section 7.2.3)
- PK blood samples collected within 30 (± 15) minutes after the completion of vofatamab administration (described in Section 7.4)

AEs: Subjects should be monitored for 90 minutes following completion of the infusion (described in Section 7.2.1)

6.1.3 Day 1 of Cycle 1 (± 3 days)

Biomarker tumor biopsy (described in Section 7.1.2): For subjects in Phase 2, Cohort 1 and Cohort 2, this procedure should occur approximately 2 weeks after the first vofatamab infusion and no more than 3 days before the Cycle 1 Day 1 visit.

The following assessments should be performed prior to study drug infusion:

- Targeted physical examination (described in Section 7.2.2)
- Biomarker tumor biopsy Phase 2, Cohorts 1 and 2 only (described in Section 7.1.2)
- Weight
- Vital signs (described in Section 7.2.3)
- ECOG PS (see Appendix 1)
- AEs since the previous visit (described in Section 7.2.1)
- Concomitant medications and therapies
- Tumor assessments (described in Section 7.3.1)
- Hematology (described in Section 7.2.4.1)
- Serum chemistry (described in Section 7.2.4.1)
- Urinalysis (described in Section 7.2.4.1)
- Coagulation (i.e., aPTT, PT/INR, and fibrinogen; described in Section 7.2.4.1)
- Urine or serum pregnancy test (described in Section 7.2.4.1)
- ECG (Cycles 1 and 2 only; described in Section 7.2.5)
- PK blood samples collected before pembrolizumab administration (described in Section 7.4)
- ATA and biomarker blood samples (described in Sections 7.5 and 7.6, respectively)
- Phase 2 and Phase 2 expansion only: PRO assessment/EORTC QLQ-C30 (described in Section 7.3.3)

  Note: The EORTC QLQ-C30 will be assessed at baseline during screening or prior to Cycle 0 and for Cycles 1 and 2, then every 2 cycles, and 30 days after discontinuation.

Study drug administration:

- Subjects should be well-hydrated prior to study drug administration. Subjects will receive one IV infusion of pembrolizumab over 30 (−5/+10) minutes, followed by one IV infusion of vofatamab. If prior vofatamab infusions have been well-tolerated, subsequent doses of vofatamab may be administered over 30 (± 10) minutes. The vofatamab infusion will begin approximately 30 minutes after completion of the pembrolizumab infusion. Vofatamab infusions will be followed by a 30-minute observation period (described in Section 5.2)

- Vital signs should be assessed every 15 (± 5) minutes during the vofatamab infusion, and at the end of the vofatamab infusion (described in Section 7.2.3). For infusions with pembrolizumab, vital signs should be assessed per institutional guidelines.

AEs should be collected and recorded while the subject is receiving study drug (described in Section 7.2.1)

The following assessment(s) should be performed after study drug infusion has been completed:

- Vital signs should be assessed 30 (± 10) minutes post-vofatamab-infusion (described in Section 7.2.3)
- PK blood samples collected within 30 (± 15) minutes after the completion of vofatamab administration (described in Section 7.4)

AEs: Subjects should be monitored for 90 (± 10) minutes following completion of the infusion (described in Section 7.2.1)

6.1.4 Day 1 of Cycles 2+ (± 7 days) until Disease Progression

All visits should occur on the scheduled days. However, visits may occur ± 7 days from the scheduled date, if a change is required for logistical/scheduling reasons.

The following assessments should be performed prior to study drug infusion:

- Targeted physical examination (described in Section 7.2.2)
- Biomarker tumor biopsy Phase 2, Cohort 3 and Cohort 4 (optional) (described in Section 7.1.2). The biopsy will be taken at end of cycle 1, Week 5.
- Weight
- Vital signs (described in Section 7.2.3)
- ECOG PS (see Appendix 1)
- AEs since the previous visit (described in Section 7.2.1)
- Concomitant medications and therapies
- Tumor assessments (described in Section 7.3.1)
- Hematology (described in Section 7.2.4.1)
- Serum chemistry (described in Section 7.2.4.1)
- Urinalysis (described in Section 7.2.4.1)

- Coagulation (i.e., aPTT, PT/INR, and fibrinogen; described in Section 7.2.4.1)
- Urine or serum pregnancy test (described in Section 7.2.4.1)
- ECG (Cycles 1 and 2 only; described in Section 7.2.5)
- PK blood samples collected before pembrolizumab administration (described in Section 7.4)
- ATA and biomarker blood samples (described in Sections 7.5 and 7.6, respectively)
- Phase 2 and phase 2 expansion only: PRO assessment/EORTC QLQ-C30 (described in Section 7.3.3)

  Note: The EORTC QLQ-C30 will be assessed at baseline during screening or prior to Cycle 0 and for Cycles 1 and 2, then every 2 cycles, and 30 days after discontinuation.

Study drug administration:

- Subjects should be well-hydrated prior to study drug administration. Subjects will receive one IV infusion of pembrolizumab over 30 (−5/+10) minutes, followed by one IV infusion of vofatamab over 90 (± 15) minutes. The vofatamab infusion will begin approximately 30 minutes after completion of the pembrolizumab infusion. (Note: If prior vofatamab infusions have been well-tolerated, doses of vofatamab may be administered over 30 [± 10 minutes]). Infusions will be followed by a 30-minute observation period (described in Section 5.2)
- Vital signs should be assessed prior to vofatamab infusion, and as clinically indicated during the infusion (described in Section 7.2.3). For infusions with pembrolizumab, vital signs should be assessed per institutional guidelines.

AEs should be collected and recorded while the subject is receiving study drug (described in Section 7.2.1)

The following assessment(s) should be performed after study drug infusion has been completed:

- Vital signs should be assessed 30 (± 10) minutes post-vofatamab-infusion (described in Section 7.2.3)
- PK blood samples collected within 30 (± 15) minutes after the completion of vofatamab administration (described in Section 7.4)

AEs: Subjects should be monitored for 30 (± 10) minutes following completion of the infusion (described in Section 7.2.1)

6.1.5 End of Treatment

Subjects who complete the study or discontinue from study treatment early will be asked to return to the clinic within 30 days after the last study drug infusion for an End of Treatment/ET visit. The visit at which response assessment shows progressive disease may be used as the End of Treatment/ET visit.

The following assessments should be performed:

- Targeted physical examination (described in Section 7.2.2)
- Weight
- Vital signs (described in Section 7.2.3)
- ECOG PS (see Appendix 1)
- AEs (described in Section 7.2.1)
- Concomitant medications and therapies
- Tumor assessment; subjects will also be asked to provide any optional metastatic tumor tissue sample collected during end of treatment or at autopsy (described in Section 7.3.1).
- Hematology (described in Section 7.2.4.1)
- Serum chemistry (described in Section 7.2.4.1)
- Urinalysis (described in Section 7.2.4.1)
- Coagulation (i.e., aPTT, PT/INR, and fibrinogen; described in Section 7.2.4.1)
- Urine or serum pregnancy test (described in Section 7.2.4.1)
- ECG (described in Section 7.2.5)
- PK blood sample (described in Section 7.4)
- ATA and biomarker blood samples (described in Section 7.5 and 7.6, respectively), including blood for circulating tumor DNA at the time of progression
- PRO assessment/EORTC QLQ-C30 (described in Section 7.3.3)

6.1.6 End of Study

All subjects will be followed for survival until death or full withdrawal of consent (described in Section 7.3.2). After the end of treatment, subjects will be monitored for survival every 3 months until the End of Study visit via telephone follow-up from the investigator.

7 STUDY ASSESSMENTS

7.1 Screening/Baseline Assessments

7.1.1 Informed Consent

The potential subject or legal guardian of a potential subject will be given a verbal explanation of the study and the procedures involved and will have all questions addressed. The subject or legal guardian must sign and date a consent form that has been approved by the appropriate Institutional Review Board (IRB)/Ethic Committee (IEC) before any study-specific procedures are initiated. The subject or legal guardian will be given a copy of the signed and dated informed consent form.

Informed Consent Forms for subjects who are not subsequently enrolled will be maintained at the study site. Additional details are provided in Section 10.1.

7.1.2 Collection of Biomarker Tumor Biopsy Samples

All 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.
- No study related biopsy may be obtained from lung, bone, or brain (study exclusion CNS disease)
- Biopsies should be obtained using the least invasive procedure feasible (no major surgical procedure are to be done for study purposes)
- If possible biopsies should not be performed in target lessions to allow for accurate ORR evaluations

All subjects in Phase 2 (Cohorts 1, 2 and 3) 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. For the Phase 2 expansion (cohort 4), a biopsy is optional. Subjects will be required to sign a separate consent form and must confirm their decision to opt-in.

For Phase 2, Cohort 1 and Cohort 2, 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 and prior to the first dose of vofatamab plus pembrolizumab.

For patients enrolled in Phase 2, Cohort 3 and Cohort 4 (optional), the second tumor biopsy will occur at the end of cycle 1, Week 5, within 3 days before Cycle 2, Day 1 and prior to the administration of the second combination dose of vofatamab and pembrolizumab.

Biopsies will be used to evaluate how treatment with vofatamab affects the FGFR3 signaling pathway relative to FGFR3 expression, immunological status of the tumor, and to explore what markers are associated with and predictive of response to vofatamab. Sample analysis may include any or all of the following: molecular profiling (RNA analysis), sequencing of cancer related genes, IHC on cancer related proteins and markers of immune cell infiltration. Sample analyses will be performed by a laboratory selected by the Sponsor.

7.1.3 Archival/Diagnostic Tissue Collection

All subjects in this study must consent to submit archival tumor tissue that was obtained at the time or after the subject was found to have muscle invasive or metastatic disease. Availability of archival tumor tissue of suitable quality and quantity should be confirmed prior to study entry. 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 will be verified using archival tissue or the first biomarker tumor biopsy sample. If archival tumor tissue is not available, the subject may undergo a diagnostic tumor biopsy procedure within 56 days of enrolling in the study. For Phase 2, Cohort 1 and Cohort 2, subjects will be assigned based on FGFR3 status of 1) WT or 2) Mut/Fus.

Genetic sequencing of FGFR3, other cancer related genes, immune response related genes, and determination of mutation burden may also be performed by the Sponsor, a laboratory selected by the Sponsor or a participating institution.

Detailed instructions will be provided in the Sample Collection & Processing Manual.

7.1.4 Subject Eligibility

During the Screening visit, all subjects will be assessed for eligibility against the inclusion and exclusion criteria described in Section 4.1 and Section 4.2.

7.1.5 Medical History and Demographics

Complete medical history will be recorded at the Screening visit.

7.2 Safety Assessments

7.2.1 Adverse Events

7.2.1.1 Definitions

7.2.1.1.1 Adverse Event

An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug-related. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) products.

All AEs resulting in discontinuation from the study should be followed until resolution or stabilization. Subjects who are discontinued from study drug will be followed for safety outcomes through the safety follow-up visit after the subject's last dose of study drug or until the subject receives another anti-cancer therapy, whichever occurs first.

Suspected Adverse Reaction is any AE for which there is a reasonable possibility that the drug caused the AE. For the purposes of expedited safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the AE. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug.

A life-threatening AE or life-threatening suspected adverse reaction is an AE or suspected adverse reaction that, in the view of either the investigator or Sponsor, places the subject at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

7.2.1.1.2 Serious Adverse Event

An SAE or serious suspected adverse reaction is an AE or suspected adverse reaction that at any dose, in the view of either the investigator or Sponsor, results in any of the following outcomes:

- Death
- A life-threatening AE
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect

Important medical events that may not result in death, be immediately life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definition.

All AEs that do not meet any of the criteria for serious should be regarded as non-serious AEs.

The definition of an SAE also includes any important medical event. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the previous definition. These should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

It is important to distinguish between serious and severe adverse events. Severity is a measure of intensity; however, an AE of severe intensity need not necessarily be considered serious. For example, nausea, which persists for several hours, may be considered severe nausea, but may not be considered an SAE. On the other hand, a stroke which results in only a limited degree of disability may be considered only a mild stroke, but would be considered an SAE.

All deaths should be reported with the primary cause of death as the AE term, as death is typically the outcome of the event, not the event itself.

7.2.1.1.3 Adverse Event of Special Interest

Bleeding and bleeding-related adverse events will be carefully followed.

7.2.1.2 Severity of Adverse Events

Each AE and SAE should be graded as mild, moderate, severe, life-threatening, or death using the following definitions. The severity of all adverse events will be graded using the National Cancer Institute (NCI) CTCAE v4.0 in Table 5.

Table 5 Adverse Event Severity Grading Scale

Grade	Severity	Alternate Description [a]
1	Mild (apply event-specific NCI CTCAE grading criteria)	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
2	Moderate (apply event-specific NCI CTCAE grading criteria)	Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL[b]
3	Severe (apply event-specific NCI CTCAE grading criteria)	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL[c]
4	Very severe, life threatening, or disabling (apply event-specific NCI CTCAE grading criteria)	Life-threatening consequences; urgent intervention indicated
5	Death related to AE	

ADL = activities of daily living; AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; NCI = National Cancer Institute.

The NCI CTCAE v4.0 can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40.

Note: Regardless of severity, some events may also meet regulatory serious criteria. Refer to definition of an SAE (see Section 7.2.1.1).

[a] Use these alternative definitions for Grade 1, 2, 3, and 4 events when the observed or reported AE is not in the NCI CTCAE listing.

[b] Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[c] Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

To make sure there is no confusion or misunderstanding of the difference between the terms "serious" and "severe," which are not synonymous, the following note of clarification is provided. The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious" which is based on subject/event outcome or action criteria usually associated with events that pose a threat to a subject's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

7.2.1.3 Relationship of Adverse Events to Study Drug

The investigator will assess the potential relationship of each AE and SAE to vofatamab and to pembrolizumab using the following descriptions.

- **Unrelated:** This category applies to an AE or SAE that is clearly not related to the investigational agent/procedure, beyond a reasonable doubt. That is, another cause of the event is most plausible; and/or a clinically plausible temporal sequence is inconsistent

with the onset of the event and the exposure to study drug and/or a causal relationship is considered biologically implausible.

- **Possibly Related:** This category applies to an AE that follows a reasonable temporal sequence from administration of the study drug and that follows a known or expected response pattern to the suspected study drug, but that could readily have been produced by a number of other factors.
- **Related:** This category applies to an AE that is certainly related to the investigational agent/procedure. That is, the AE has a temporal relationship to the administration of the investigational agent(s) or research intervention, which cannot be explained by concurrent disease or other drugs or chemicals; the response to withdrawal of drug is clinically plausible; and the event has been shown to be definitively pharmacologically or phenomenologically related using a satisfactory rechallenge procedure.

Note: The investigator's assessment of causality for individual AE reports is part of the study documentation process. Regardless of the "Yes" or "No" causality assessment for individual AE reports, the Sponsor will promptly evaluate all reported SAEs against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators and applicable regulatory authorities.

7.2.1.4 Eliciting Adverse Events

A consistent methodology of non-directive questioning for eliciting AEs at all subject evaluation time points should be adopted. Examples of non-directive questions include:

"How have you felt since your last clinic visit?"

"Have you had any new or changed health problems since you were last here?"

7.2.1.5 Adverse Event Reporting Period

After informed consent, but prior to initiation of study drug, only SAEs caused by a protocol-mandated intervention will be collected (e.g., SAEs related to invasive procedures such as biopsies, medication washout, or no treatment run-in). All medical occurrences from the time of signing the informed consent that meet this definition should be recorded. Events preceding first study drug administration, however, should be recorded as medical history, not as AEs.

After initiation of study drug, all AEs and SAEs regardless of attribution will be collected until 30 days following the last administration of study drug, 30 days after subject discontinuation, initiation of another anti-tumor therapy, resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. After this period, investigators should report only SAEs that are felt to be related to prior study treatment (see Section 7.2.1.9).

7.2.1.6 Recording of Adverse Events

Information on all AEs should be recorded immediately in the source document, and in the appropriate adverse event module of the CRF. All clearly related signs, symptoms, and abnormal diagnostic procedure results should be recorded in the source document, grouped under one diagnosis.

7.2.1.6.1 Diagnosis versus Signs and Symptoms

If known, a diagnosis should be recorded on the CRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded as an AE or SAE on the CRF. If a diagnosis is subsequently established, it should be reported as follow-up information.

For this study, the NCI CTCAE terms “cytokine release syndrome” should not be used. If multiple signs or symptoms occur with a given event, each sign or symptom should be recorded separately with its level of severity.

7.2.1.6.2 Adverse Events Occurring Secondary to Other Events

In general, AEs occurring secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause. For example, if severe diarrhea is known to have resulted in dehydration, it is sufficient to record only diarrhea as an AE or SAE on the CRF.

However, medically significant AEs occurring secondary to an initiating event that are separated in time should be recorded as independent events on the Adverse Event CRF. For example, if a severe gastrointestinal hemorrhage leads to renal failure, both events should be recorded separately on the Adverse Event CRF.

7.2.1.6.3 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the start of the study. Such conditions should be recorded on the General Medical History and Baseline Conditions CRF.

A preexisting medical condition should be recorded as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When recording such events on an Adverse Event CRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., “more frequent headaches”).

7.2.1.6.4 Persistent or Recurrent Adverse Events

A persistent AE is one that extends continuously, without resolution between subject evaluation time points. Such events should only be recorded once in the CRF unless their severity increases. If a persistent AE becomes more severe, it should be recorded as a new entry on the Adverse Event CRF. If a previously reported SAE increases in severity, it should

be reported on the previously submitted CRF as a follow-up or update and not as a new event.

A recurrent AE is one that occurs and resolves between subject evaluation time points and subsequently recurs. All recurrent AEs should be recorded on an Adverse Event CRF.

7.2.1.6.5 Abnormal Laboratory Values

Only clinically significant laboratory abnormalities that require active management will be recorded as AEs or SAEs on the Adverse Event CRF (e.g., abnormalities that require study drug dose modification, discontinuation of study treatment, more frequent follow-up assessments, further diagnostic investigation, etc.).

If the clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., ALP and bilirubin 5 × the ULN associated with cholecystitis), only the diagnosis (e.g., cholecystitis) needs to be recorded on the Adverse Event CRF.

If the clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded as an AE or SAE on the Adverse Event CRF. If the laboratory abnormality can be characterized by a precise clinical term, the clinical term should be recorded as the AE or SAE. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as “hyperkalemia.”

Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly recorded as AEs or SAEs on the Adverse Event CRF, unless their severity, seriousness, or etiology changes.

7.2.1.6.6 Worsening of Urothelial Cell Carcinoma

Progression of underlying malignancy should not be reported as an AE if it is clearly consistent with the suspected progression of the underlying cancer, as defined by respective disease criterion or other criteria as determined by protocol. Hospitalization due solely to the progression of underlying malignancy should NOT be reported as an SAE. Clinical symptoms of progression may be reported as AEs, if the symptom cannot be determined as exclusively due to the progression of the underlying malignancy, or does not fit the expected pattern of progression for the disease under study.

7.2.1.6.7 Hospitalization, Prolonged Hospitalization, or Surgery

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE unless specifically instructed otherwise in this protocol.

There are some hospitalization scenarios that do not require reporting as an SAE when there is no occurrence of an AE. These scenarios include a planned hospitalization or prolonged hospitalization to:

- Perform an efficacy measurement for the study

- Undergo a diagnostic or elective surgical procedure for a preexisting medical condition that has not changed
- Receive scheduled therapy for the target disease of the study

7.2.1.6.8 Deaths

Deaths that occur during the protocol-specified AE reporting period that are attributed by the investigator solely to progression of UCC will be recorded only on the Study Discontinuation CRF. All other on study deaths, regardless of attribution, will be recorded on an Adverse Event CRF and expeditiously reported to the Sponsor.

7.2.1.6.9 Pregnancy

Conditions of pregnancy and lactation are excluded from study participation. During the study, females of childbearing potential must contact the treating Investigator immediately if they suspect that they may be pregnant (a missed or late menstrual period should be reported to the treating Investigator).

If an investigator suspects that a subject may be pregnant after the subject started study drug, study drug must immediately be withheld until the result of the pregnancy test is confirmed. If a pregnancy is confirmed, the study drug(s) must be immediately and permanently stopped, the subject must be discontinued from the study, and the Investigator must notify the study Sponsor within 24 hours of confirmation.

If a female subject becomes pregnant while receiving investigational therapy or within 120 days after the last dose of the study drug, a Pregnancy Report CRF should be completed. Pregnancy should not be recorded on the Adverse Event CRF.

Abortion, whether therapeutic or spontaneous, should always be classified as serious (as the Sponsor considers these medically significant), recorded on an Adverse Event CRF, and expeditiously reported to the Sponsor. After the study period, such events should still be reported expeditiously to the Sponsor.

Any congenital anomaly/birth defect in a child born to a female subject or female partner of a male subject exposed to the investigational product should be classified as serious, recorded on an Adverse Event CRF, and expeditiously reported to the Sponsor during the study period. After the study period, such events should still be reported expeditiously to the Sponsor recorded and reported as an SAE.

7.2.1.7 Expedited Reporting Requirements for Serious Adverse Events and Serious Drug Reactions

7.2.1.7.1 Reporting Requirements for All SAEs

Investigators will submit reports of all SAEs, regardless of attribution, and all protocol-defined non-serious expedited AEs to the Sponsor within 24 hours of learning of the

events. For initial SAE and protocol-defined non-serious expedited AE reports, investigators should record all case details that can be gathered within 24 hours on an Adverse Event CRF and submit as follows:

- To Parexel Drug Safety group. Complete the SAE report form and fax the documents to PAREXEL GMS using the PAREXEL SAE fax number: **+1 781 434 5957**

Or

- Complete the SAE report form and submit it to PAREXEL GMS via email utilizing the address: **NorthAmerica_Medical@parexel.com**

and/or

- In the event that the site staff is unable to complete the SAE form within 24 hours of their knowledge of the event, the investigators may report the SAE over the telephone and then provide the completed SAE form via **fax or email** within the next 24 hours. If questions arise regarding the reporting procedures or the specifics of the reporting of an event, sites may call utilizing the following number: **+1 781 434 5010**

7.2.1.7.2 IRB/IEC Notification by the Investigator

Reporting of SAEs to the IRB/IEC will be done in compliance with the standard operating procedures and policies of the IRB/IEC and with applicable regulatory requirements. Adequate documentation must be obtained by Rainier showing that the IRB/IEC was properly and promptly notified as required.

7.2.1.7.3 Regulatory Agency Notification by the Sponsor

The study sponsor or designee, shall notify all applicable regulatory agencies by telephone, by facsimile transmission, or registration in EudraVigilance database of any suspected unexpected serious adverse reaction (SUSAR) associated with the use of the drug as soon as possible but no later than 7 calendar days from the Sponsor's original receipt of the information.

If a previous AE that was not initially deemed reportable is later found to fit the criteria for reporting, the study sponsor will submit the AE in a written report to the appropriate regulatory agencies as soon as possible, but no later than 15 calendar days from the time the determination is made.

7.2.1.8 Type and Duration of Follow-Up after Adverse Events

The investigator should follow all unresolved AEs and SAEs until the events are resolved to baseline grade, the event is assessed by the investigator as stable, new anti-cancer treatment is initiated, the subject is lost to follow-up, or it has been determined that the study treatment or participation is not the cause of the AE/SAE. Resolution of AEs and SAEs (with dates) should be documented on the appropriate Adverse Event CRF and in the subject's medical record to facilitate source data verification (SDV) during the study period.

For some SAEs, the Sponsor or its designee may follow-up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details deemed necessary to appropriately evaluate the SAE report (e.g., hospital discharge summary, consultant report, or autopsy report).

7.2.1.9 Post-Study Adverse Events

At the last scheduled visit, the investigator should instruct each subject to report to the investigator any subsequent SAEs that the subject's personal physician believes could be related to prior study treatment.

The investigator should notify the Sponsor of any death or other SAE occurring at any time after a subject has discontinued or terminated study participation if felt to be related to prior study treatment. The Sponsor should also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a subject who participated in this study. The investigator should report these events to the Sponsor on the study Adverse Event CRF.

7.2.2 Physical Examination, Height, and Weight

Complete physical examinations should include the evaluation of head, eye, ear, nose, and throat (HEENT), cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, and neurological systems.

Targeted physical examinations may be limited to systems of primary clinical relevance (i.e., cardiovascular, respiratory, those systems associated with symptoms, and any system that might be associated with tumor assessment).

Changes from baseline for all targeted physical examinations should be recorded at each subsequent physical examination. New or worsened abnormalities should be recorded as AEs if appropriate.

Height should be measured only at the Screening visit and weight should be measured at the Screening visit and on Day 1 of each cycle.

7.2.3 Vital Signs

Vital signs will include measurements of systolic and diastolic blood pressure, pulse rate, and body temperature.

On Day 1 of Cycle 0 and Cycle 1, vital signs for vofatamab should be assessed pre-infusion, every 15 (± 5) minutes during the infusion, at the end of the infusion, and 30 (± 10) minutes, 60 (± 10) minutes, and 90 (± 10) minutes post-infusion. On Day 1 of Cycles 2+, vital signs for vofatamab should be assessed pre-infusion, as clinically indicated during the infusion, and at the end of the vofatamab infusion. For infusions with pembrolizumab, vital signs should be assessed per institutional guidelines.

7.2.4 Laboratory Assessments

For the Screening visit, local laboratory assessments should be done within 14 days of Day 1 of Cycle 0. After Cycle 0, local laboratory assessments may be performed within 72 hours preceding study drug administration on Day 1, unless otherwise specified. Results must be reviewed and the review documented prior to study drug administration.

Detailed sample collection instructions will be provided in the Sample Collection & Processing Manual.

7.2.4.1 Local Laboratory Assessments

Samples for hematology, serum chemistry, and pregnancy will be analyzed at the study site's local laboratory. If an institution performs an equivalent test to those listed below (for example, urine albumin rather than urine protein) for study purposes, this may be acceptable as long as it is noted with institutional normal(s) and approved by the sponsor prior to subject enrollment:

- Hematology: complete blood count (complete blood count [CBC]; including RBC, hemoglobin, hematocrit, WBC), platelet count, and percent and absolute differential count (neutrophils, bands, lymphocytes, eosinophils, monocytes, and basophils)
- Coagulation: aPTT, PT/INR, and fibrinogen
- Serum chemistry: sodium, potassium, chloride, bicarbonate, non-fasting glucose, blood urea nitrogen (BUN), creatinine, calcium, phosphate, magnesium, total and direct bilirubin, total protein, albumin, ALT, AST, ALP, lactate dehydrogenase, and uric acid
- Urinalysis: Urinalysis includes Urinalysis includes macroscopic analysis (specific gravity, pH, protein, glucose, ketones, blood, bilirubin, leukocyte esterase, urobilinogen, and nitrite) and microscopic urinalysis (RBCs, WBCs, epithelial cells, casts, crystals, bacteria, and yeast)

Pregnancy test: For women of childbearing potential, a urine or serum pregnancy test must be performed during Screening (within 14 days prior to first administration of study treatment), prior to administration of study drug on Day 1 of each cycle, and the End of Treatment/ET visit.

7.2.5 Electrocardiogram Assessments

ECG measurements must be obtained from subjects who have been resting for at least 10 minutes, either before or after drawing blood samples. One ECG reading should be obtained at each of the following time points: Screening, Cycle 0 Day 1 pre-treatment, Cycle 1 Day 1 pre-treatment, Cycle 2 Day 1 pre-treatment, and at the End of Treatment/ET visit (described in Section 6.1 and Table 1).

7.3 Response/Efficacy Assessments

7.3.1 Tumor and Response Assessments

For subjects with measurable disease, response will be assessed by the investigator per RECIST 1.1 (see Appendix 2).

All evaluable and measurable disease must be documented at the Screening visit, at the end of Cycle 1, and every 9 weeks (± 7 days) thereafter (i.e., every third cycle beginning after Cycle 1) until disease progression or lack of tolerability; and will include the following measures:

- CT scans of the chest, abdomen, and pelvis, and all known or suspected sites of disease
- Brain scan (CT or magnetic resonance imaging [MRI]) at Screening only
- Bone scans (CT or MRI), if clinically indicated

Scans performed at End of Cycle 1 will not be used to determine progression per RECIST 1.1. Progression per RECIST 1.1 will be determined using radiographic assessments taken at end of Cycle 3 onward.

Additional methods of assessment of measurable disease per RECIST 1.1 may be used in addition to those listed above. The same imaging methods used at screening must be used throughout the study for each subject. Additional tumor assessments may be conducted as clinically indicated during the study. Results must be reviewed prior to study drug infusion at the next cycle to assess whether a subject is eligible to continue treatment.

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. It is highly encouraged that prior to discontinuation of any subject whom is receiving clinical benefit that a consultation occur with the study PI or medical monitor.

A tumor assessment scan should be performed if the subject is discontinuing the study early. In addition, confirmation scans are required of any patient exhibiting PR or CR.

At the End of Treatment/ET visit or at autopsy, subjects will be asked to provide any optional metastatic tumor tissue samples collected during the study or at autopsy.

7.3.2 Survival

Upon discontinuation of study treatment (vofatamab and pembrolizumab), subjects will be followed for overall survival every 3 months via telephone until death or full withdrawal of consent.

The End of Study visit assessment should be performed by telephone call.

7.3.3 Patient-Reported Outcome/European Organization for Research and Treatment Quality of Life Questionnaire

In Phase 2 and expansion phase of the study, the EORTC QLQ-C30 assesses the quality of life (disease and treatment-related symptoms, physical, psychological, and social functioning) of cancer patients using a self-reported questionnaire. The EORTC QLQ-C30 will be assessed from baseline for Cycles 0 (if applicable) through Cycle 2, then every 2 cycles, and 30 days after discontinuation.

7.4 Pharmacokinetic Assessments

Blood samples will be obtained prior to the administration of vofatamab and within 30 (± 15) minutes after the completion of the administration of vofatamab on Day 1 of Cycle 0. Blood samples will be obtained prior to the administration of pembrolizumab and within 30 (± 15) minutes after the completion of the administration of vofatamab on Day 1 of Cycles 1 and 4, and once at the End of Treatment/ET visit. Serum samples will be analyzed for the quantitative determination of vofatamab.

7.5 Anti-therapeutic Antibody Assessments

As may occur with any recombinant antibodies, either vofatamab or pembrolizumab may elicit an immune response and subjects may develop antibodies against either agent. Although ATAs directed against either agent are not expected to result in significant clinical consequence, subjects will be monitored for any potential immune response to vofatamab in this clinical study.

Blood samples for ATA assessment will be obtained prior to infusion of vofatamab on Day 1 of Cycles 0 (if applicable), 1 and 4, and once at the End of Treatment/ET visit. Serum samples will be analyzed for the determination of antibodies to vofatamab.

7.6 Biomarker Assessments

Whole blood (PBMCs), serum, and plasma samples for biomarker analyses will be obtained prior to infusion of vofatamab on Day 1 of Cycles 0, 1, 3, and 5, and once at the End of Treatment/ET visit.

Blood for circulating tumor DNA will be collected at the time of progression to assess FGFR3 status.

The effects of vofatamab on the downstream signaling of the FGFR3 pathway, tumor sub-type and on the immune surveillance of UCC tumors will be monitored using a range of techniques that may include but are not limited to gene expression profiling (such as whole transcriptome RNAseq), sequencing of TCRs, flow cytometry, ELISA, and immunohistochemistry. Analyses will be performed on biopsy samples taken pre- and post-vofatamab treatment (as described in Section 7.1.2), archival tissue samples (described in Section 7.1.3), and whole blood, serum and plasma samples, as appropriate.

In order to identify possible predictors or response to therapy, in addition to the techniques described in the preceding paragraph, samples may be analyzed for mutational burden and genetic alterations in genes associated with cancer including FGFR3.

7.7 Appropriateness of Measurements

The efficacy and safety assessments for this study are standard, widely used, and generally recognized as reliable, accurate, and relevant.

8 DATA QUALITY CONTROL AND QUALITY ASSURANCE

8.1 Site Training and Monitoring Procedures

Manuals with instructions for study compliance and CRF completion will be provided. Prior to the enrollment of subjects at the site, the Sponsor or its designated clinical and medical personnel will review the following items with the Investigator and clinic staff:

- The protocol, study objectives, eligibility requirements, study procedures, registration and withdrawal processes
- Current Investigator's brochure/package insert
- Recording and reporting AEs and SAEs
- Enrollment goals and study timelines
- The CRF completion process and source documentation requirements
- Monitoring requirements
- Institutional Review Board/Independent Ethics Committee (IRB/IEC) review and approval process
- Informed consent process
- Good Clinical Practice (GCP) guidelines and related regulatory documentation requirements
- Key study team roles and responsibilities
- Investigational product storage, accountability, labeling, dispensing and record keeping
- Subject coding
- Study samples/specimen collection, handling and shipping
- Protocol compliance
- Clinical study record keeping, document retention, and administrative requirements

Monitoring and auditing procedures developed by the Sponsor and/or its designee will be implemented to ensure compliance with FDA and International Council for Harmonisation (ICH) GCP guidelines. The Sponsor's designated representative (the monitor) will contact the investigator and conduct regular visits to the study site. The monitor will be expected and allowed to verify the investigator's qualifications, to inspect clinical site facilities, and to inspect study records, including proof of IRB review, with the stipulation that subject confidentiality will be maintained in accordance with local and federal regulations, including Health Insurance Portability and Accountability Act (HIPAA) requirements. The monitor will also be responsible for confirming adherence to the study protocol, inspecting CRFs and source documents, and ensuring the integrity of the data. CRFs will be checked for accuracy,

completeness, and clarity and will be cross-checked for consistency with source documents, including laboratory test reports and other subject records. Instances of missing or uninterruptable data will be resolved in coordination with the investigator.

The monitor will also investigate any questions concerning adherence to regulatory requirements. Any administrative concerns will be clarified and followed. The monitor will maintain contact with the site through frequent direct communications with the study site by e-mail, telephone, facsimile, and/or mail. The investigator and all other site personnel agree to cooperate fully with the monitor and will work in good faith with the monitor to resolve any and all questions raised and any and all issues identified by the monitor.

8.2 Data Management Procedures

The Sponsor or its designee will provide CRF Completion Guidelines for electronic CRF (eCRF) data entry. Study specific data management procedures will be maintained in the data management plan. Queries resulting from edit checks and/or data verification procedures will be posted electronically in the eCRF.

8.3 Access to Source Data

The investigator understands that regulatory authorities, the IRB, and/or the Sponsor or its designees have the right to access all CRFs, source documents, and other study documentation for on-site audit or inspection and will retain this right from the start of the study to at least 2 years after the last approval of a marketing application or for at least 2 years after clinical development of the study drug for the indication being studied has been discontinued. The investigator is required to guarantee access to these documents and to cooperate with and support such audits and inspections.

8.4 Accuracy and Reliability of Data

Steps to be taken to assure the accuracy and reliability of data include:

- The selection of qualified investigators and appropriate study centers.
- Review of protocol procedures with the investigators and associated personnel prior to the study.
- Periodic monitoring visits by the designated monitor(s).

CRFs will be reviewed for accuracy and completeness by the designated monitor(s) during monitoring visits to the study centers. Any discrepancies will be resolved with the Investigator or designees as appropriate.

8.5 Quality Assurance Procedures

The Clinical Quality Assurance group or its designee may conduct audits at the clinical site or other study-related facilities and organizations during or at any time after the study. Audit

reports will be retained by the Sponsor's Clinical Quality Assurance group or its designee as part of the written record.

8.6 Data Handling and Record Keeping

8.6.1 Data Handling

The investigator is required to initiate and maintain, for each subject, an adequate and accurate case history that records all observations and other data related to the study for that subject. Data must be recorded on CRFs approved by the Sponsor or its designee. All information recorded on CRFs for this study must be consistent with the subject's source documentation.

Initial data entry and any changes to the data will be made only by authorized users. An explanation of any data change should be recorded in the CRF. All data entered in to the CRF must be verifiable; therefore, CRFs will be routinely checked for accuracy, completeness, and clarity and will be cross-checked for consistency with source documents, including laboratory test reports and other subject records by the Sponsor or its designee. The investigator must allow direct access to all source documents.

8.6.2 Records Retention

All study records must be retained for at least 2 years after the last approval of a marketing application in the US or an ICH region and until (1) there are no pending or contemplated marketing applications in the US or an ICH region or (2) at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product under study. The Investigator/institution should retain subject identifiers for at least 15 years after the completion or discontinuation of the study. Subject files and other source data must be kept for the maximum period of time permitted by the hospital, institution or private practice, but not less than 15 years. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by agreement. The Sponsor must be notified and will assist with retention should the Investigator/institution be unable to continue maintenance of subject files for the full 15 years. All study records must be stored in a secure and safe facility.

9 STATISTICAL METHODS

Complete details of the prospective analyses and procedures for handling missing/spurious data handling will be provided in the Statistical Analysis Plan.

9.1 Sample Size Consideration

In Phase 1b of the study, at least 6 subjects are required for the first dose level and up to 18 subjects may be required for 3 dose levels.

The primary efficacy endpoint for Phase 2 of the study is ORR and will be compared against historical ORR of pembrolizumab (21.1%) (Bellmunt J, et al., 2017).

The total of 90 subjects in Cohort 1,2,3 and 4 will be the primary efficacy analysis set for Phase 2. Given the expected π=0.343 with Type I error (alpha) at 0.05 (one-sided), 90 subjects will give a power of approximately 87.5% to reject the null hypothesis of $\pi \leq 0.211$. With the expected π=0.343, the 95% CI half width is around 0.098 for the sample size of 90 subjects. The sample size calculation for Phase 2 was performed for a 3-look group sequential design. The α-spending formula of Lan and DeMets O'Brian-Fleming stopping boundary was used. EAST® v6.4.1 was used to derive the sample size and efficacy and futility boundary as well as the alpha allocation. Results are shown in Table 6.

Table 6 Three- Look Group Sequential Sample Size, Boundary and Alpha Allocation

Look #	Information Fraction	Sample Size	Efficacy Boundary			Futility Boundary		
			Alpha	N	Proportion (95% CI)	Alpha	N	Proportion (95% CI)
1	28/90=0.311	28	0.0004	14	0.5 (0.307 0.694)	0.890	3	0.107 (0.023 0.282)
2	52/90=0.578	52	0.010	18	0.346 (0.220 0.491)	0.379	11	0.212 (0.111 0.347)
3	1	90	00.47	26	0.289 (0.198 0.394)			

Note: The total sample size has increased from 74 in protocol amendment 4 to 90 in amendment 5; therefore the information fractions for the 1st interim and 2nd interim analysis both changed. These changes lead to changes in alpha spending and subsequent changes in boundaries from protocol amendment 4.

9.2 Interim Analysis

There is no interim analysis planned for Phase 1b.

There will be two pre-specified interim analyses during Phase 2, one has already been conducted on the first 28 subjects (20 WT and 8 Mut/Fus). The second planned interim will occur when a minimum of 52 subjects have been enrolled and have data available to determine ORR.

All tumor assessment scans used in the interim analysis will be assessed by investigator for response per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1). Analysis will then be conducted using RECIST 1.1 and iRECIST. The first interim analysis has been performed for 28 subjects (20 in the WT cohort and 8 in the Mut/Fus cohort). The second interim analysis will be performed for 52 subjects. If the number of responders is below or equal to the futility boundary (N = 11), the study may stop for futility. If the number of responders is above or equal to efficacy boundary (N = 18), the study may stop for efficacy.

The primary efficacy analysis will be performed when approximately 90 subjects (including expansion) in Phase 2 have been followed with sufficient duration to evaluate the primary efficacy endpoint, at the discretion of the sponsor. The number and proportion of responders along with DOR (duration of response) will be reported. The final analysis will be when OS endpoint has been met or 3 years after the last subject enrolled, at the discretion of the sponsor.
Additional informal interim analyses may be performed for presentation at scientific meetings.

If the study is not stopped during the interim analyses, the primary analysis will be conducted with 90 subjects. If the number of responders is above or equal to 26, the null hypothesis of $\pi \leq 0.211$ shall be rejected.

9.3 Analysis Populations

Safety Population: For both Phase 1b and Phase 2, the safety population will consist of all subjects that receive at least one dose of study drug. All subjects receiving a dose of study drug will be included in all safety summaries.

Full Analysis Set (FAS) Population: The efficacy analysis for Phase 2 will be performed on the FAS population, which is defined as all subjects who were enrolled in the study, regardless of whether they received a dose of study drug.

For Phase 2, all efficacy analyses will be presented by overall and by subgroups of FGFR3 status at enrollment. For Cohort 3, subgroup analysis by luminal subtypes may also be performed.

9.4 Planned Analyses

9.4.1 Safety Monitoring Rule

The study will be monitored by the program safety steering as per the charter.

9.4.2 Primary Biomarker Analysis

For primary analysis, descriptive statistics will be used to summarize FGFR3 receptor expression and expressions of markers of FGFR3 pathway. Details of analyses will be provided in a statistical analysis plan.

9.4.3 Subject Disposition

The disposition of subjects will be tabulated for all subjects in Phase 1b and Phase 2 (including Phase 2 expansion). Subjects who received at least one dose of study treatment and the reasons for discontinuation of treatment or withdrawal from the study will be tabulated.

9.4.4 Demographic and Baseline Characteristics

For Phase 1b and Phase 2 (including Phase 2 expansion), demographics (i.e., age, sex, race, ethnicity), baseline characteristics (i.e., ECOG, BMI) and disease history (i.e., cancer stage at time of diagnosis and enrollment, prior anti-cancer therapy) will be summarized descriptively.

9.4.5 Medical History and Physical Examination

For Phase 1b and Phase 2 (including Phase 2 expansion), medical history will be coded with MedDRA and will be presented by system organ class and preferred term.

Descriptive summary statistics for physical examination and their changes from baseline will be presented by visit. Clinically significant abnormalities on physical examination noted at baseline will be presented as preexisting conditions. New clinically significant abnormalities on study will be presented as AEs.

9.4.6 Study Drug Administration

For Phase 1b and Phase 2 (including Phase 2 expansion), the total number of vofatamab and pembrolizumab doses administered and dose modifications, including dose delays, dose omissions, and reasons, will be summarized.

9.4.7 Safety Analyses

Safety will be assessed through summaries of AEs, changes in laboratory test results, ECGs, and changes in vital signs. All subjects who receive any amount of vofatamab or pembrolizumab will be included in the safety analysis.

The safety data will be presented in individual subject listings and summary tables.

For both Phase 1b and Phase 2 (including Phase 2 expansion), all safety endpoints will be summarized in the safety population.

9.4.7.1 Adverse Events

Subject incidence of all AEs occurring on or after first dose will be summarized by Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC), MedDRA preferred term (PT), and NCI CTCAE v4.0 toxicity grade. Each subject will be counted only once within an SOC or a PT by using the AEs with the highest severity (per CTCAE v4.0) within each category.

Subjects who experienced at least one treatment-emergent AE, treatment-related AE, serious AE (SAE), AE with toxicity grade 3 and above, AE leading to treatment discontinuation, and AE leading to death will be summarized by incidence rate.

Number of treatment interruptions or cessations due to an adverse event will be summarized.

9.4.7.2 Laboratory Tests

Descriptive summary statistics for selected chemistry, hematology, and coagulation laboratory test results and their changes from baseline will be presented by visit.

Shift tables will be generated for selected laboratory parameters showing the worst post-baseline toxicity grade per NCI CTCAE v4.0 by baseline categories.

9.4.7.3 Vital Signs

Descriptive summary statistics for vital signs (including temperature, respiratory rate, blood pressure, heart rate, and weight) and their changes from baseline will be presented by visit.

9.4.7.4 12-Lead Electrocardiogram

Descriptive summary statistics for the 12-lead ECG and their changes from baseline will be presented by visit. Clinically significant changes may be summarized.

9.4.7.5 ECOG Performance Status

Descriptive summary statistics for Eastern Cooperative Oncology Group (ECOG) Performance Score and changes from baseline will be presented by visit. A shift table of ECOG may be generated.

9.4.7.6 Prior and Concomitant Medications and Therapies

The World Health Organization (WHO) Drug Dictionary will be used to classify concomitant medications by anatomical therapeutic class (ATC) and preferred term. Concomitant medications include medications that stop at any time after first dose of study treatment or remain ongoing at the end of the entire treatment period. Prior medications include medications that started before the first dose.

The frequency counts and percentages of subjects taking a prior or a concomitant medication will be tabulated by ATC and PT. Although a subject may have taken two or more medications, the subject is counted only once within an ATC classification.

9.5 Efficacy Analysis

Efficacy analysis will only be performed in the FAS population.

9.5.1 Primary Efficacy Endpoint

The primary efficacy outcome measure will be ORR, defined as the percentage of subjects who have baseline measurable disease and who achieve a best response of either CR or PR as assessed by the investigator using RECIST 1.1 criteria. All the responses will be confirmed according to RECIST 1.1. The end of Cycle 1 radiographic assessment will not be used to determine progression per RECIST 1.1. Progression per RECIST 1.1 will be determined using radiographic assessments taken at end of Cycle 3 onward.

The ORR will be summarized descriptively by percentage and its 95% CI.

The comparison of ORR with historical ORR of pembrolizumab (21.1%) (Bellmunt J, et al., 2017) will be performed using one-sample binomial test in interim analyses as well as the primary analysis.

A sensitivity analysis will also be performed on the efficacy evaluable (EE) population. Sensitivity analysis for ORR assessed by iRECIST will also be performed.

9.5.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints are PFS, OS, DOR, Disease Control Rate (DCR), and Patient-Reported Outcome (PRO).

- PFS is defined as the time from first study drug administration to first occurrence of disease progression (per RECIST 1.1) or death, whichever occurs first. If a subject does not experience PD or death, PFS will be censored at the day of the last adequate tumor assessment.
- OS is defined as the time from first study drug administration to death from any cause. For subjects who are alive at the time of analysis data cutoff, OS will be censored at the last date the subject was known to be alive. Survival time for subjects with no post-baseline survival information will be censored on the date of first study drug administration.
- DOR is defined as from the first occurrence of a documented, objective response until the time of disease progression or death from any cause. This will be calculated only for responders. In the absence of confirmation of death or progressive disease, duration of response will be censored at the last adequate disease assessment date.

- DCR is defined as the percentage of subjects who achieve either CR or PR or SD, as assessed by the investigator per RECIST 1.1.

- DCR (90) is defined as 90 days from the time of first study drug administration.

- DCR (180) is defined as the absence of disease progression and/or death in 180 days from the time of first study drug administration.

Distribution of the time-to-event endpoints (OS, PFS, DOR) will be summarized descriptively and plotted as Kaplan-Meier curves. Median time and its 95% confidence intervals will be presented.

The categorical response (DCR) will be summarized as percentage with 95% confidence intervals.

Descriptive summary statistics for PRO EORTC QLQ-C30 questionnaires and changes from baseline will be presented by visit.

Time to Deterioration (TTD), defined as more than 10 points decreases from baseline in QLQ-C30 questionnaires, will be summarized descriptively.

9.6 Exploratory Endpoints

PK and biomarker endpoints will be summarized.

9.6.1 Pharmacokinetic Analyses

Vofatamab Ctrough levels will be summarized over time throughout the study and will be compared to predicted exposure-based levels from data observed in previous studies with vofatamab. The vofatamab Ctrough levels will also be compared to historical data to ensure that the co- administration of pembrolizumab has no impact on vofatamab pharmacokinetics.

9.6.2 Immunogenicity Analyses

The incidence of ATAs to vofatamab will be summarized. The possible effects of ATA on pharmacokinetics, efficacy and safety may be explored.

10 ETHICAL AND REGULATORY CONSIDERATIONS

This study will be conducted in accordance with the Protocol; ICH Guidance E6 (R1); FDA CFR [21 CFR Parts 50, 56, 312]); Declaration of Helsinki World Medical Association Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects, as it may be amended; applicable data protection laws and regulations; and all laws, rules and regulations applicable to the study or the study drug in jurisdictions in which the Investigator conducts the study.

10.1 Informed Consent

Appropriate forms for documenting written informed consent will be provided by the investigator, and reviewed and approved by the Sponsor or its designee before submission to the IRB/IEC. The Sponsor or its designee must receive a copy of the IRB's approval of the Informed Consent Form (ICF) before the shipment of Investigational Product to the study site.

It is the investigator's responsibility to obtain signed written informed consent from each potential study subject prior to the conduct of any study procedures. This written informed consent will be obtained after the methods, objectives, requirements, and potential risks of the study have been fully explained to each potential subject. The investigator must explain to each subject that the subject is completely free to refuse to enter the study or to withdraw from it at any time.

The method of obtaining and documenting informed consent and the contents of the ICF will comply with ICH GCP guidelines, the requirements of 21 CFR Part 50, "Protection of Human Subjects," the HIPAA regulations, and all other applicable regulatory requirements. Subjects will be given a copy of the signed ICF and will be provided any new information during the course of the study that might affect their continued participation in the study. The investigator or a qualified designee will be available to answer each subject's questions throughout the study, and all of the subject's questions must be answered to the subject's satisfaction. If the protocol is amended and the ICF is revised, each subject will be required to provide written informed consent again using the revised ICF.

Receipt of written informed consent will be documented in each potential subject's CRF. The signed ICF will remain in each subject's study file and must be available to the study monitor(s) at all times.

10.2 Confidentiality of Personal Subject Information

The investigator must ensure that each subject's anonymity is maintained as described below. On the CRFs or other documents submitted to the Sponsor, subjects must be identified by no more than their initials, date of birth, and a subject number. Signed ICFs and other documents should be kept in strict confidence by the investigator in compliance with applicable regulations and ICH GCP Guidelines. As described in Section 8.3, the investigator and institution must permit authorized representatives of the Sponsor, of regulatory agencies, and the IRB direct access to review the subject's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying,

and reproducing any records and reports that are needed for the evaluation of the study. The investigator is obligated to inform the subject in the ICF that the above named representatives may review study-related records from subjects.

10.3 Biospecimens

Clinical samples donated by subjects in the study (blood, urine, tissue, etc.) comprise study results of the Sponsor and will be collected and processed in accordance with this protocol and delivered to the Sponsor or Sponsor's designee, as instructed by the Sponsor. Clinical samples shall not be retained or used by the Investigator or institution except as expressly permitted by the Sponsor in writing. The ICF will contain information on the treatment of subject personal information relating to clinical samples including, if applicable, the labeling of clinical samples

10.4 Ethical Conduct of the Study

This protocol is written in accordance with the principles established by the 18th World Medical Assembly General Assembly (Helsinki, 1964) and subsequent amendments and clarifications adopted by the General Assemblies. The investigator will make every effort that the study described in this protocol is conducted in full conformance with those principles, current FDA regulations, ICH GCP guidelines, and local ethical and regulatory requirements. Should a conflict arise, the investigator will follow whichever law or guideline affords the greater protection to the individual subject. The investigator will also make sure he or she is thoroughly familiar with the appropriate administration and potential risks of administration of the Investigational Product, as described in this protocol and the Investigator's Brochure, prior to the initiation of the study.

10.5 Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

This protocol, any protocol amendments, the associated informed consent forms, and the informed consent procedures must be submitted to the IRB/IEC for review and must be approved before the enrollment of any subject into the study. Investigational Product may not be shipped to the investigator until the Sponsor or its designee has received a copy of the letter or certificate of approval from the IRB for the protocol and any protocol amendments, as applicable.

All subject recruitment and/or advertising information must be submitted to the IRB/IEC and the Sponsor or its designee for review and approval prior to implementation. IRB/IEC approval of any protocol amendments must be received before any of the changes outlined in the amendments are put into effect, except when the amendment has been enacted to protect subject safety. In such cases, the chair of the IRB/IEC should be notified immediately and the amendment forwarded to the IRB/IEC for review and approval.

10.6 Regulatory Requirements

This study will be submitted to the local regulatory authority for approval or notification whichever is applicable. The study will only be undertaken in compliance with the local regulatory requirements.

In accordance with Directive 2001/20/EC, the Sponsor will notify the relevant (European) regulatory authority(ies) and IRBs/ECs within 90 days of the end of the study. If the study terminates early, the Sponsor will notify the relevant (European) regulatory authority(ies) and IRBs/ECs within 15 days and will provide the reasons for early termination.

Safety updates for vofatamab will be prepared by the Sponsor as required, for submission to the relevant regulatory authority(ies).

10.7 Investigators and Administrative Structure

Each investigator must provide the Sponsor and/or its designee a completed and signed Form FDA 1572 and a Financial Disclosure Form. All sub-investigators must be listed on Form FDA 1572 and Financial Disclosure Forms must be completed for all sub-investigators listed on Form FDA 1572.

The Sponsor and/or its designee will be responsible for managing and monitoring the clinical study to ensure compliance with FDA and ICH GCP guidelines. A trained designated representative (the monitor) will conduct regular visits to the clinical site, to perform SDV. The monitor will verify the investigator's ongoing qualifications, to inspect clinical site facilities, and to inspect study records, including proof of IRB review, with the stipulation that subject confidentiality will be maintained in accordance with local and federal regulations, including HIPAA requirements.

10.8 Protocol Amendments and Study Termination

Any changes to the study, which arise after approval of the protocol, must be documented as protocol amendments. Protocol amendments that are deemed substantial (e.g. affecting the safety of the subject, the scope of the study and/or the scientific quality) will be submitted to regulatory authorities and/or to the IEC/IRB as appropriate. For substantial amendment, the changes will become effective only after approval by the Sponsor, the responsible Investigator, IEC/IRB and competent authorities. All other amendments (i.e. non-substantial or administrative amendments) will be documented in the Trial Master File (TMF).

The Investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to study subjects without prior IRB/IEC approval/favorable opinion. As soon as possible, the implemented deviation or change, the reasons for it, and, if appropriate, the proposed protocol amendment(s) should be submitted to the following:

- IRB/IEC for review and approval/favorable opinion
- Sponsor for agreement
- Regulatory authority(ies), if required

10.9 Clinical Study Report

At the conclusion of the study (but within 1 year after study closure), when the data are analyzed, the Sponsor will prepare an integrated Clinical Study Report in compliance with ICH E3. A draft copy of the report will be available for review by the coordinating investigator. The final version will be signed by the Sponsor and the coordinating investigator.

At the conclusion of the study (but within 1 year after study closure), when the data are analyzed, the Sponsor will also post the study results on the European database referred (EudraCT) per Article 11(1) of Directive 2001/20/EC.

10.10 Disclosure of Source Data and Documents

Subject medical information obtained by this study is confidential and may only be disclosed to third parties as permitted by the Informed Consent Form (or separate authorization to use and disclose personal health information) signed by the subject or unless permitted or required by law.

Medical information may be given to a subject's personal physician or other appropriate medical personnel responsible for the subject's welfare for treatment purposes.

Source data/documents generated by this study must be available for inspection upon request by representatives of the FDA and other regulatory agencies, national and local health authorities, Sponsor monitors/representatives and collaborators, and the IRB for each study site, if appropriate.

10.11 Publication Policy

The investigator shall not prepare and/or submit any manuscripts or slide shows based on the Sponsor data for publication or oral presentation prior to the publication of the primary manuscript of the study. The Sponsor shall acknowledge the investigator's contribution to the study in any Sponsor publications regarding the study.

The Sponsor shall comply with the requirements for publication of study results and determination of authorship in accordance with standard editorial and ethical practice and with the International Committee of Medical Journal Editors (ICMJE) requirements.

11 REFERENCES

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12 SIGNATURE PAGE

Protocol Title:	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
Protocol Number:	B-701-U22 (FIERCE-22)
Date of Amendment 5 (USA)	July 01, 2019
Date of Amendment 4.2	June 20, 2019
Date of Amendment 4.1	June 07, 2018
Date of Amendment 4:	May 16, 2018
Date of Amendment 3.1	March 14, 2018
Date of Amendment 3:	January 05, 2018
Date of Amendment 2:	July 11, 2017
Date of Amendment 1:	December 16, 2016
Date of Original Protocol	October 3, 2016

By signing below, I agree to the conditions relating to this study as set out in this protocol (Study B-701-U22 Protocol Amendment 5 (USA), dated July 01, 2019). I agree to conduct this clinical study according to the International Conference of Harmonisation Guideline on Good Clinical Practice (ICH GCP E6). I fully understand that any changes instituted by me without previous discussion with the Sponsor or their designated representative constitute a violation of the protocol. I agree to adhere to the protocol in all circumstances other than where necessary to protect the well-being of the subject. I will ensure that the study products supplied by Rainier will be used only for administration to subjects included in this study protocol and for no other purpose.

_____ _____

Investigator Signature Date

_____

Print Name

Accepted by the Sponsor

As the Sponsor representative, I confirm the Sponsor will comply with all obligations as detailed in all applicable regulations and guidelines. I will ensure that the Investigator is informed of all relevant information that becomes available during the conduct of this study.

Steve Abella M.D.
Chief Medical Officer

Date

APPENDIX 1 EASTERN COOPERATIVE ONCOLOGY GROUP PERFORMANCE STATUS SCALE

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework or office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about > 50% of waking hours
3	Capable of only limited self-care, confined to a bed or chair > 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Source: Oken 1982.

APPENDIX 2 RESPONSE EVALUATION CRITERIA IN SOLID TUMORS VERSION 1.1 (RECIST 1.1)

Selected sections from the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1 (Eisenhauer 2009) are presented below, with slight modifications and the addition of explanatory text as needed for clarity.

Measurability of Tumor at Baseline

Definitions

At baseline, tumor lesions/lymph nodes will be categorized as measurable or non-measurable as described below.

a. Measurable Tumor Lesions

Tumor Lesions. Tumor lesions must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size as follows:

- 10 mm by computed tomography (CT) or magnetic resonance imaging (MRI) scan (CT/MRI scan slice thickness/interval no greater than 5 mm)
- 10 mm caliper measurement by clinical examination (lesions that cannot be accurately measured with calipers should be recorded as non-measurable)

20 mm by chest X-ray.

Malignant Lymph Nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in the short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and follow-up, only the short axis will be measured and followed. See also notes below on “Baseline Documentation of Target and Non-Target Lesions” for information on lymph node measurement.

b. Non-Measurable Tumor Lesions

Non-measurable tumor lesions encompass small lesions (longest diameter < 10 mm or pathological lymph nodes with short axis ≥ 10 but < 15 mm), as well as truly non-measurable lesions. Lesions considered truly non-measurable include leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, and abdominal mass/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques.

c. Special Considerations Regarding Lesion Measurability

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment, as outlined below.

Bone Lesions:

- Bone scan, positron emission tomography (PET) scan, or plain films are not considered adequate imaging techniques for measuring bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic–blastic lesions, with identifiable soft tissue components, that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.

Blastic bone lesions are non-measurable.

Cystic Lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

Cystic lesions thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same subject, these are preferred for selection as target lesions.

Lesions with Prior Local Treatment:

Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.

Target Lesions: Specifications by Methods of Measurements

a. Measurement of Lesions

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

b. Method of Assessment

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during the study. Imaging-based evaluation should always be the preferred option.

Clinical Lesions. Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm in diameter as assessed using calipers (e.g., skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested.

Chest X-Ray. Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new

lesions. However, lesions on a chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT, MRI. CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thicknesses greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable. If prior to enrollment it is known that a subject is unable to undergo CT scans with intravenous (IV) contrast because of allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI (without IV contrast) will be used to evaluate the subject at baseline and during the study should be guided by the tumor type under investigation and the anatomic location of the disease. For subjects who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) will be performed should also be based on the tumor type and the anatomic location of the disease and should be optimized to allow for comparison with the prior studies if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, if not, the subject should be considered not evaluable from that point forward. Care must be taken in measurement of target lesions on a different modality and interpretation of non-target disease or new lesions since the same lesion may appear to have a different size using a new modality.

Ultrasound. Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement.

Endoscopy, Laparoscopy, Tumor Markers, Cytology, Histology. The utilization of these techniques for objective tumor evaluation cannot generally be advised.

Tumor Response Evaluation

Assessment of Overall Tumor Burden and Measurable Disease

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements. Measurable disease is defined by the presence of at least one measurable lesion, as detailed above.

Baseline Documentation of Target and Non-Target Lesions

When more than one measurable lesion is present at baseline, all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. This means that, for instances in which subjects have only one or two organ sites involved, a maximum of two lesions (one site) and four lesions (two sites), respectively, will be recorded. Other lesions (albeit measurable) in those organs will be recorded as non-measurable lesions (even if the size is > 10 mm by CT scan).

Target lesions should be selected based on their size (lesions with the longest diameter) and be representative of all involved organs, but in addition, should lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement, in which circumstance, the next largest lesion that can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal anatomical structures that may be visible by imaging even if not involved by tumor. As noted above, pathological nodes that are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT, this is almost always the axial plane; for MRI, the plane of acquisition may be axial, sagittal, or coronal). The smaller of these measures is the short axis. For example, an abdominal node that is reported as being 20 mm × 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis of < 10 mm are considered non-pathological and should not be recorded or followed.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum of diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum of diameters will be used as a reference to further characterize any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease), including pathological lymph nodes, should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as “present,” “absent,” or in rare cases “unequivocal progression.”

In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the Case Report Form (CRF) (e.g., “multiple enlarged pelvic lymph nodes” or “multiple liver metastases”).

Response Criteria

a. Evaluation of Target Lesions

This section provides the definitions of the criteria used to determine objective tumor response for target lesions.

- Complete response (CR): disappearance of all target lesions

  Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.

- Partial response (PR): at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters
- Progressive disease (PD): at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (nadir), including baseline

  In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

  The appearance of one or more new lesions is also considered progression.

Stable disease (SD): neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum on study

b. Special Notes on the Assessment of Target Lesions

Lymph Nodes. Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to < 10 mm on study. This means that when lymph nodes are included as target lesions, the sum of lesions may not be zero even if CR criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm.

Target Lesions that Become Too Small to Measure. During the study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2 mm). However, sometimes lesions or lymph nodes that are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being too small to measure. When this occurs, it is important that a value be recorded on the CRF as follows:

- If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm.
- If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned and below measurable limit (BML) should be ticked. (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well and BML should also be ticked.)

To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm, and in that case, BML should not be ticked.

Lesions that Split or Coalesce on Treatment. When non-nodal lesions fragment, the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that

would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximum longest diameter for the coalesced lesion.

c. Evaluation of Non-Target Lesions

This section provides the definitions of the criteria used to determine the tumor response for the group of non-target lesions. While some non-target lesions may actually be measurable, they need not be measured and, instead, should be assessed only qualitatively at the time points specified in the protocol.

- CR: disappearance of all non-target lesions and (if applicable) normalization of tumor marker level

  All lymph nodes must be non-pathological in size (< 10 mm short axis).

- Non-CR/Non-PD: persistence of one or more non-target lesions and/or (if applicable) maintenance of tumor marker level above the normal limits

- PD: unequivocal progression of existing non-target lesions. The appearance of one or more new lesions is also considered progression.

d. Special Notes on Assessment of Progression of Non-Target Disease

When the Subject Also Has Measurable Disease. In this setting, to achieve unequivocal progression on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease in a magnitude that, even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest increase in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely based on change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the Subject Has Only Non-Measurable Disease. This circumstance arises in some Phase III studies when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above; however, in this instance, there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable), a useful test that can be applied when assessing subjects for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease, that is, an increase in tumor burden representing an additional 73% increase in volume (which is equivalent to a 20% increase in diameter in a measurable lesion). Examples include an increase in a pleural effusion from “trace” to “large” or an increase in lymphangitic disease from localized to widespread or may be described in protocols as “sufficient to require a change in therapy.” If unequivocal progression is seen, the subject should be considered to have had overall PD at that point. While it would be ideal to have objective criteria apply to

non-measurable disease, the very nature of that disease makes it impossible to do so; therefore, the increase must be substantial.

e. New Lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal, that is, not attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumor (for example, some "new" bone lesions may be simply healing or flare of preexisting lesions). This is particularly important when the subject's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a "new" cystic lesion, which it is not.

A lesion identified during the study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

Evaluation of Response

a. Time Point Response (Overall Response)

It is assumed that at each protocol-specified time point, a response assessment occurs. Table 6 provides a summary of the overall response status calculation at each time point for subjects who have measurable disease at baseline. When subjects have non-measurable (therefore non-target) disease only, Table 7 is to be used.

Table 6 Time Point Response: Subjects with Target Disease (With or Without Non-Target Lesions)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or no	PD
Any	PD	Yes or no	PD
Any	Any	Yes	PD

CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.

Table 7 Time Point Response: Subjects with Non-Target Disease Only

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD [a]
Not all evaluated	No	NE
Unequivocal PD	Yes or no	PD
Any	Yes	PD

CR = complete response; NE = not evaluable; PD = progressive disease.

[a] "Non-CR/non-PD" is preferred over "stable disease" for non-target disease since stable disease is increasingly used as an endpoint for assessment of efficacy in some studies; thus, assigning "stable disease" when no lesions can be measured is not advised.

b. Missing Assessments and Not-Evaluable Designation

When no imaging/measurement is done at all at a particular time point, the subject is not evaluable at that time point. If only a subset of lesion measurements is made at an assessment, usually the case is also considered not evaluable at that time point unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD. For example, if a subject had a baseline sum of 50 mm with three measured lesions, and during the study, only two lesions were assessed but those gave a sum of 80 mm, the subject will have achieved PD status, regardless of the contribution of the missing lesion.

If one or more target lesions were not assessed either because the scan was not done or the scan could not be assessed because of poor image quality or obstructed view, the response for target lesions should be "unable to assess" since the subject is not evaluable. Similarly, if one or more non-target lesions are not assessed, the response for non-target lesions should be "unable to assess" except where there is clear progression. Overall response would be "unable to assess," if either the target response or the non-target response is "unable to assess" except where this is clear evidence of progression, as this equates with the case being not evaluable at that time point.

c. Best Overall Response: All Time Points

The best overall response is determined once all the data for the subject is known.

Best response determination in studies where confirmation of complete or partial response IS NOT required: Best response in these trials is defined as the best response across all time points (for example, a subject who has SD at first assessment, PR at second assessment, and PD on last assessment has a best overall response of PR). When SD is believed to be best response, it must also meet the protocol specified minimum time from baseline. If the minimum time is not met when SD is otherwise the best time point response, the patient's best response depends on the subsequent assessments. For example, a subject who has SD at first assessment, PD at second and does not meet minimum duration for SD, will have a best response of PD. The same subject lost to follow-up after the first SD assessment would be considered unevaluable at a subsequent time point as specified in the protocol (generally

4 weeks later). In this circumstance, the best overall response can be interpreted as in Table 8.

Table 8 Best Overall Response when Confirmation of CR and PR Required

Overall Response First Time Point	Overall Response Subsequent Time Point	Best Overall Response
CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE
NE	NE	NE

CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.

[a] If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

d. Special Notes of Response Assessment

When nodal disease is included in the sum of target lesions and the nodes decrease to "normal" size (< 10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that subjects with CR may not have a total sum of "zero" on the CRF.

Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response; it is a reason for stopping study therapy. The objective response status of such subjects is to be determined by evaluation of target and non-target disease.

For equivocal findings of progression (e.g., very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

In studies for which subjects with advanced disease are eligible (i.e., primary disease still or partially present), the primary tumor should also be captured as a target or non-target lesion, as appropriate. This is to avoid an incorrect assessment of CR if the primary tumor is still present but not evaluated as a target or non-target lesion.

APPENDIX 3 ANAPHYLAXIS PRECAUTIONS AND PROCEDURES

The following equipment is needed in the event of a suspected anaphylactic reaction during study drug infusion:

- Tourniquet
- Oxygen
- Epinephrine for subcutaneous, intravenous, and/or endotracheal use in accordance with standard practice as needed
- Antihistamines
- Corticosteroids
- Intravenous infusion solutions, tubing, catheters, and tape.

The following are the procedures to follow in the event of a suspected anaphylactic reaction during study drug infusion:

1. Stop the study drug infusion.
2. Apply a tourniquet proximal to the injection site to slow systemic absorption of study drug. Do not obstruct arterial flow in the limb.
3. Maintain an adequate airway.
4. Administer antihistamines, epinephrine, or other medications, as required by subject status and directed by the physician in charge.
5. Continue to observe the subject and document observations.

APPENDIX 4 INFORMATION REGARDING EFFECTIVENESS OF CONTRACEPTIVE METHODS

The following methods of contraception can achieve a failure rate of less than 1% per year when used consistently and correctly, and are considered highly effective birth control methods:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation[1]
  - oral
  - intravaginal
  - transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation[1]
  - oral
  - injectable
  - implantable[2]
- Intrauterine device (IUD)[2]
- Intrauterine hormone-releasing system (IUS)[2]
- Bilateral tubal occlusion[2]
- Vasectomized partner[2,3]
- Sexual abstinence[4]

Source: CTFG 2014.