Title: Phase II Study of Atezolizumab + Bevacizumab in Patients with Advanced Non-Clear Cell Renal Cell Carcinoma

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Atezolizumab (MPDL3280A), Supplied by Genentech, Inc.

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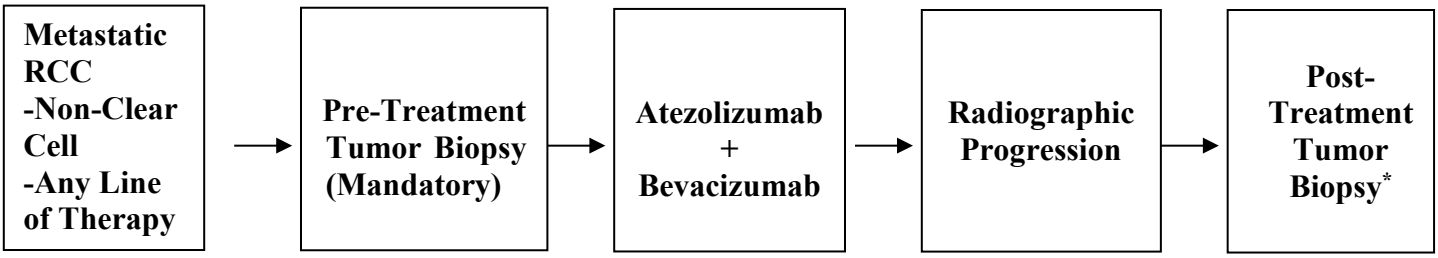
SCHEMA



After progression/treatment discontinuation, participation will be followed for survival and receipt of next line therapies every 6 months until death or 2 years after treatment discontinuation.

*Post-Treatment Tumor Biopsy is only required for a subset of patients who have a tumor response and subsequently progress.

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1. OBJECTIVES

1.1 Study Design

This is an open, single-arm, phase II multi-center study designed to investigate the efficacy and safety of bevacizumab and atezolizumab in patients with advanced non-clear cell renal cell carcinoma (nccRCC). Eligible patients will be enrolled and will be treated with bevacizumab 15 mg/kg intravenously (IV) every 3 weeks and atezolizumab 1200 mg IV every 3 weeks. Patients will be required to undergo a mandatory baseline fresh tumor biopsy if deemed medically feasible and safe. Patients will remain on therapy until radiographic progression, unacceptable adverse events, or other reason. Each cycle will be 3 weeks in duration. Patients who experience relapse after an initial response will be required to undergo a fresh tumor biopsy if medically safe. Patients will be evaluated clinically every 3 weeks and will undergo disease assessments with imaging every 6 weeks. Expected enrollment is 60 patients with an accrual rate of 3 patients per month.

1.2 Primary Objectives

To assess the overall response rate (ORR) by Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1 in patients with advanced nccRCC treated with bevacizumab and atezolizumab.

1.3 Secondary Objectives

- To assess duration of ORR in patients with advanced nccRCC treated with bevacizumab and atezolizumab
- To estimate the ORR according to histology subtypes
- To assess the safety in patients with advanced nccRCC treated with bevacizumab and atezolizumab.
- To assess the immune-related ORR in patients with advanced nccRCC treated with bevacizumab and atezolizumab by immune-related response criteria (irRC).
- To assess progression-free survival (PFS) in patients with advanced nccRCC treated with bevacizumab and atezolizumab.
- To assess overall survival (OS) in patients with advanced nccRCC treated with bevacizumab and atezolizumab.
- To summarize ORR, PFS, and OS in patients with advanced nccRCC treated with bevacizumab and atezolizumab according to subgroups:
    - International mRCC Database Consortium (IMDC) risk groups.
    - Untreated versus previously treated patients.
    - According to histologic subtype (papillary vs. other nccRCC subtypes; sarcomatoid components present vs. absent)
- To evaluate the effect of therapy on quality of life as assessed by the Functional Assessment of Cancer Therapy-Kidney Symptom Index (FKSI)-19 and the Brief Fatigue Inventory (BFI)

1.4 Exploratory Objectives

- To assess the immunomodulatory properties of atezolizumab in combination with bevacizumab via assessment of archival and/or fresh tumor tissue and blood and correlate with ORR, PFS, and OS
- To evaluate the relationship between programmed death-ligand 1 (PD-L1) tumor expression (and other prognostic and predictive tissue biomarkers) and efficacy outcomes (ORR, PFS, OS)
- To evaluate the relationship between PD-L1 status in archival tissue and in fresh tumor specimens
- To evaluate mechanisms of acquired resistance to atezolizumab in combination with bevacizumab in fresh tumor specimens obtained at time of radiographic progression
- To assess molecular mechanisms of resistance to treatment via cfDNA assessment and to correlate cfDNA molecular profile with metastasis biopsy molecular profile.
- Assess mechanisms of response and resistance to treatment via single cell molecular assessment (exome, genome, and transcriptome assessment)
- Correlate single cell molecular profile with metastasis biopsy molecular profile

2. BACKGROUND

2.1 Renal Cell Carcinoma

RCC is the most common cancer of the kidney (>85%) and represents a heterogeneous disease divided generally into two major groups: clear-cell RCC (ccRCC), which comprises approximately 80% of renal epithelial tumors, and nccRCC, which encompasses the remaining percentage of tumors. Non-clear cell RCC includes different histologic and genetic subtypes to include: papillary, chromophobe, collecting duct, unclassified, translocation, and medullary carcinoma. Papillary and chromophobe histologies account for 80% of all nccRCC.

Although many advances have been made in the treatment of metastatic RCC, the majority of studies to date have been limited to patients with a component of clear-cell disease. Three randomized clinical trials included patients with nccRCC. The Global ARCC trial phase III trial randomized 626 patients with previously untreated poor-risk metastatic RCC, including 73 patients with nccRCC, to receive temsirolimus versus interferon-α (IFNα) or the combination. Post hoc subgroup analysis of this study suggested that mTOR inhibition could be a valid option in nccRCC (PFS 7.0 versus 1.8 months, hazard ratio (HR) 0.38, 95% confidence interval (CI) 0.29-0.85; PS 11.6 versus 4.3 months, HR 0.49, 95% CI 0.29-0.85).[1] RECORD-3, a phase II study evaluating sequential therapy with sunitinib followed by everolimus or vice versa included 66 patients with nccRCC. Furthermore, the INTORSECT trial evaluating temsirolimus versus soarfenib included 90 patients with nccRCC. In a single arm phase II study, sunitinib was examined as a treatment for patients with non-clear cell histology.[2] The ORR was 5% and the median PFS was 2.7 months.

Though the general approach to treatment of nccRCC mirrors that of ccRCC, studies have indicated that the standard treatments for patients with clear cell histology are not as effective in patients with non-ccRCC.[3] A recently published study investigated the nccRCC population in the IMDC. This large report assessed the first-, second, and third-line PFS in nccRCC in comparison with ccRCC and revealed a dismal prognosis in this population with an OS of 12.8 months compared to 22.8 months.

Due to the poor prognosis of these heterogeneous populations, there is an urgent need for better treatment paradigms to improve outcomes for these patients.

2.2 Bevacizumab

2.2.1 Clinical Activity in RCC

Bevacizumab is a monoclonal antibody that binds circulating (vascular endothelial growth factor) VEGF and prevents its interaction with the VEGF receptor. Bevacizumab has been studied in a multitude of Phase I, II, and III clinical trials in more than 22,000 patients and in multiple tumor types. Approximately 1,720, 000 patients have been exposed to bevacizumab as a marketed product or in clinical trials. Please refer to the bevacizumab Investigator Brochure for descriptions of all completed Phase I, II, and III trials reported to date.

For patients with metastatic clear cell RCC, two phase III trials have demonstrated improved PFS with bevacizumab plus IFNα compared with IFNα alone. In the AVOREN trial, 649

previously untreated patients were randomly assigned to IFNα (9 million units three times per week for one year) plus either bevacizumab (10 mg/kg IV every two weeks) or placebo[4-6]. Bevacizumab (or placebo) was continued until there was evidence of progressive disease. IFNα plus bevacizumab resulted in the following compared with IFNα plus placebo: 1) an increase in PFS (median 10.2 versus 5.5 months HR 0.63, 95% confidence interval (CI) 0.45-0.72), 2) a significantly higher ORR (31 versus 13%), and 3) a trend toward improved OS (median survival 23.3 versus 21.3 months, HR 0.86, 95% CI 0.72-1.04). Approximately 60% of patients received second-line therapy, potentially obscuring a survival difference between the two treatment arms. There were more common serious adverse events (SAEs) in patients treatment with bevacizumab (29 versus 16%). Grade 3 or 4 adverse events that were more common in patients treated with bevacizumab included thromboembolic events (3 versus 1%) and gastrointestinal (GI) perforation (1 versus 0%).

In the Cancer and Leukemia Group B (CALBG) 90206 trial, 732 previously untreated patients with metastatic RCC were randomly assigned to IFNα plus bevacizumab (10 mg/kg IV every 2 weeks) or IFNα plus placebo on schedules similar to that used in the AVOREN trial.[7] Treatment with bevacizumab plus IFNα resulted in: 1) an improvement in PFS (median 8.5 versus 5.2 months; HR 0.71, 0.61-0.83) and a significant improvement in the ORR (25.5 versus 13.1%). There was a trend toward improved OS favoring the use of combination therapy (median 18.3 versus 17.4 months, HR 0.86, $p = 0.07$).[8] However, this analysis was complicated by the fact that more than one-half of patients on both arms received second-line therapy, including VEGF-targeted therapy in 46% of those originally treated with IFNα alone.

There is data to support the use of bevacizumab in patients with metastatic nccRCC. A phase II study evaluated the efficacy of bevacizumab (15 mg/kg IV every 3 weeks) alone in patient with advanced papillary RCC.[9] Five patients were accrued to the study before the protocol was closed due to slow accrual. Three patients had undergone a prior nephrectomy, one patient underwent resection of a liver metastasis, and one patient had received prior temsirolimus. The PFS for these patients was 25, 15, 11, 10 and 6 months.

These results supported the Food and Drug Administration (FDA) approval of bevacizumab with IFNα in metastatic RCC in July 2009.

2.2.2 Safety Profile

Hypertension: An increased incidence of hypertension (all grades) of up to 42.1% has been observed in patients treated with bevacizumab compared to up to 14% in the comparator arm. In clinical trials across all indications the overall incidence of National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) Grade 3 and 4 hypertension in patients receiving bevacizumab ranged from 0.4% to 17.9%. Grade 4 hypertension (hypertensive crisis) occurred in up to 1.0% of bevacizumab-treated patients, compared to up to 0.2% of patients treated with the same chemotherapy alone. Very rare cases of hypertensive encephalopathy have been reported, some of which were fatal. The risk of bevacizumab-associated hypertension did not correlate with the patients' baseline characteristics, underlying disease or concomitant therapy. Analyses of the clinical safety data suggest that the occurrence of hypertension with bevacizumab therapy is likely to be dose-dependent.

Proteinuria: In clinical trials, proteinuria has been reported within the range of 0.7% to 38% of patients receiving bevacizumab. Proteinuria ranged in severity from clinically asymptomatic, transient, trace proteinuria to nephrotic syndrome. Grade 3 proteinuria was reported in up to 8.1% of treated patients. Grade 4 proteinuria (nephrotic syndrome) was seen in up to 1.4% of treated patients. The proteinuria seen in bevacizumab clinical trials was not associated with renal impairment and rarely required permanent discontinuation of bevacizumab therapy. Analyses of the clinical safety data suggest that the occurrence of proteinuria with bevacizumab therapy is likely to be dose-dependent. Patients with a history of hypertension may be at increased risk for the development of proteinuria when treated with bevacizumab. There is evidence suggesting that Grade 1 proteinuria may be related to bevacizumab dose.

Venous thromboembolism (VTE, including deep venous thrombosis, pulmonary embolism, and thrombophlebitis): Patients may be at risk of developing VTEs, including pulmonary embolism under bevacizumab treatment. In clinical trials across all indications the overall incidence of VTE events was 2.8%-17.3% in the bevacizumab-containing arms compared with 3.2%-15.6% in the chemotherapy control arms. Grade 3-5 VTEs have been reported in up to 7.8% of patients treated with chemotherapy plus bevacizumab compared with up to 4.9% in patients with chemotherapy alone. Patients who have experienced a VTE may be at higher risk for a recurrence if they receive bevacizumab in combination with chemotherapy versus chemotherapy alone.

From a clinical trial in patients with persistent, recurrent, or metastatic cervical cancer (study GOG-0240), grade 3-5 VTEs have been reported in up to 10.6% of patients treated with chemotherapy and bevacizumab compared with up to 5.4% in patients with chemotherapy alone. In clinical trial BO21990, Grade 3-5 VTEs were observed in 7.6% of patients with newly diagnosed glioblastoma treated with bevacizumab in combination with chemotherapy and radiotherapy, compared to 8.0 % of patients treated with chemotherapy and radiotherapy alone.

Arterial Thromboembolism (ATE): An increased incidence of ATE events was observed in patients treated with bevacizumab across indications including cerebrovascular accidents, myocardial infarction, transient ischemic attacks, and other ATEs. In clinical trials, the overall incidence ranged up to 5.9% in the bevacizumab- containing arms compared up to 1.7% in the chemotherapy control arms. Fatal outcome was reported in 0.8% of patients receiving bevacizumab in combination with chemotherapy compared to 0.5% of patients receiving chemotherapy alone. Cerebrovascular accidents (including transient ischemic attacks) were reported in up to 2.3% of bevacizumab treated patients versus 0.5% of patients in the control group. Myocardial infarction was reported in 1.4% of bevacizumab treated versus 0.7% of patients in the observed control group.

In one clinical trial, AVF2192g, patients with metastatic colorectal cancer who were not candidates for treatment with irinotecan were included. In this trial ATEs were observed in 11% (11/100) of bevacizumab patients compared to 5.8% (6/104) in the chemotherapy control group. In an uncontrolled clinical trial, AVF3708g, in patients with relapsed glioblastoma, ATEs were observed in 6.3% (5/79) of patients who received bevacizumab in combination with irinotecan compared to 4.8% (4/84) of patients who received bevacizumab alone.

Patients receiving bevacizumab plus chemotherapy with a history of ATE, diabetes or age greater than 65 years have an increased risk of developing ATEs during bevacizumab therapy. Aspirin is a standard therapy for primary and secondary prophylaxis of ATEs in patients at high risk of such events, and the use of aspirin ≤ 325 mg daily was allowed in the five randomized studies discussed above. Use of aspirin was assessed routinely as a baseline or concomitant medication in these trials, though safety analyses specifically regarding aspirin use were not preplanned. Due to the relatively small numbers of aspirin users and ATEs, retrospective analyses of the ability of aspirin to affect the risk of such events were inconclusive. However, similarly retrospective analyses suggested that the use of up to 325 mg of aspirin daily does not increase the risk of grade 1-2 or grade 3-4 bleeding events.

Gastrointestinal perforation: Bevacizumab has been associated with serious cases of GI perforation. GI perforations have been reported in clinical trials with an incidence of <1% in patients with metastatic breast cancer or non-squamous NSCLC, up to 2% in metastatic RCC, newly diagnosed glioblastoma, or in patients with ovarian cancer receiving front-line treatment, and up to 2.7% (including GI fistula and abscess) in patients with metastatic colorectal cancer. Cases of GI perforations have also been observed in patients with relapsed glioblastoma. Fatal outcome was reported in approximately a third of serious cases of GI perforations, which represents between 0.2-1.0% of all bevacizumab treated patients.

In bevacizumab clinical trials, GI fistulae (all grade) have been reported with an incidence of up to 2% in patients with metastatic colorectal cancer and ovarian cancer, but were also reported less commonly in patients with other types of cancer. From a clinical trial in patients with persistent, recurrent, or metastatic cervical cancer (study GOG-0240), GI perforations, including GI fistulae and abscess (all grade) were reported in 10.1% of bevacizumab treated patients, all of whom had a history of prior pelvic radiation. Fatal outcome was reported in 0.9% of bevacizumab -treated patients. Most patients reported as having GI perforations in this study (15 out of 22) had GI-vaginal fistulae. The presentation of these events varied in type and severity, ranging from free air seen on the plain abdominal X-ray, which resolved without treatment, to intestinal perforation with abdominal abscess and fatal outcome. In some cases underlying intra-abdominal inflammation was present, either from gastric ulcer disease, tumor necrosis, diverticulitis or chemotherapy-associated colitis. A causal association of intra-abdominal inflammatory process and GI perforation to bevacizumab has not been established. Patients may be at increased risk for the development of GI perforation and gallbladder perforation when treated with bevacizumab.

Fistula: Bevacizumab use has been associated with serious cases of fistulae including events resulting in death. From a clinical trial in patients with persistent, recurrent, or metastatic cervical cancer (study GOG-0240), 4.1% of bevacizumab-treated patients and 2.3% of control patients were reported to have had vaginal, vesical or female genital tract fistulae (all grade), some of which were GI vaginal fistulae. The overall rate of GI-vaginal fistulae (all grade), combining both those reported as GI perforations and those reported as fistulae and abscess (as stated above) was 8.2% in bevacizumab-treated patients and 0.9% in control patients. Uncommon (≥0.1% to <1%) reports of other types of fistulae that involve areas of the body other than the GI tract (e.g., bronchopleural, urogenital, biliary fistulae) were observed across various indications. Fistulae have also been reported in post-marketing experience. Events were reported

at various time points during treatment ranging from one week to greater than 1 year from initiation of bevacizumab, with most events occurring within the first 6 months of therapy.

Wound healing complications: Bevacizumab may adversely affect the wound healing process. Serious wound healing complications with a fatal outcome have been reported. Necrotizing fasciitis including fatal cases, has rarely been reported in patients treated with bevacizumab; usually secondary to wound healing complications, GI perforation or fistula formation.

As bevacizumab may adversely impact wound healing, patients who had major surgery within the last 28 days prior to starting bevacizumab treatment were excluded from participation in Phase III trials. Across metastatic colorectal cancer clinical trials there was no increased risk of post-operative bleeding or wound healing complications observed in patients who underwent major surgery between 28-60 days prior to starting bevacizumab therapy. An increased incidence of post-operative bleeding or wound healing complications occurring within 60 days of major surgery was observed if the patient was being treated with bevacizumab at the time of surgery. The incidence varied between 10% (4/40) and 20% (3/15).

In locally recurrent and metastatic breast and ovarian cancer trials, Grade 3-5 wound healing complications were observed in up to 1.1% of patients receiving bevacizumab compared with up to 0.9 % of patients in the control arms. In the study of patients with relapsed glioblastoma (study AVF3708g), the incidence of post-operative wound healing complications (craniotomy site wound dehiscence and cerebrospinal fluid leak) was 3.6% in patients treated with single-agent bevacizumab and 1.3% in patients treated with bevacizumab plus irinotecan. In patients with newly diagnosed glioblastoma (study BO21990) the incidence of Grade 3-5 post-operative wound healing complications (including complications following craniotomy) was 3.3% when treated with bevacizumab in combination with chemotherapy and radiotherapy, compared with 1.6 % when treated with chemotherapy and radiotherapy alone.

Hemorrhage: In clinical trials across all indications the overall incidence of NCI-CTC Grade 3-5 bleeding events ranged from 0.4% to 6.9% in bevacizumab-treated patients, compared to 0 to 4.5% of patients in the chemotherapy control group. The hemorrhagic events that have been observed in bevacizumab clinical studies were predominantly tumor- associated hemorrhage (see below) and minor mucocutaneous hemorrhage (e.g. epistaxis).

Tumor-Associated Hemorrhage: Major or massive pulmonary hemorrhage or hemoptysis has been observed primarily in patients with NSCLC. Possible risk factors include squamous cell histology, treatment with anti-rheumatic/anti-inflammatory drugs, treatment with anticoagulants, prior radiotherapy, bevacizumab therapy, previous medical history of atherosclerosis, central tumor location and cavitation of tumors prior to or during therapy. The only variables that showed statistically significant correlations with bleeding were bevacizumab therapy and squamous cell histology. Patients with NSCLC of known squamous cell histology or mixed cell type with predominant squamous cell histology were excluded from subsequent studies, while patients with unknown tumor histology were included.

In patients with NSCLC excluding predominant squamous histology, all Grade events were seen with a frequency of up to 9% when treated with bevacizumab plus chemotherapy compared with

5% in the patients treated with chemotherapy alone. Grade 3-5 events have been observed in up to 2.3% of patients treated with bevacizumab plus chemotherapy as compared with <1% with chemotherapy alone. Major or massive pulmonary hemorrhage/hemoptysis can occur suddenly and up to two thirds of the serious pulmonary hemorrhages resulted in a fatal outcome.

Mucocutaneus Hemorrage: Across all bevacizumab clinical trials, mucocutaneous hemorrhage has been seen in 50% of patients treated with bevacizumab. These were most commonly NCI-CTC Grade 1 epistaxis that lasted less than 5 minutes, resolved without medical intervention and did not require any changes in bevacizumab treatment regimen. Clinical safety data suggest that the incidence of minor mucocutaneous hemorrhage (e.g. epistaxis) may be dose-dependent. There have also been less common events of minor mucocutaneous hemorrhage in other locations, such as gingival bleeding and vaginal bleeding.

Posterior Reversible Encephalopathy Syndrome (PRES): PRES is a rare neurologic disorder that can present with the following signs and symptoms (among others): seizures, headache, altered mental status, visual disturbance, or cortical blindness, with or without associated hypertension. Brain imaging is mandatory to confirm the diagnosis of PRES. Two confirmed cases (0.8%) of PRES have been reported in one clinical study. Symptoms usually resolve or improve within days, although some patients have experienced neurologic sequelae.

Congestive heart failure (CHF): In clinical trials, CHF was observed in all cancer indications studied to date, but predominantly in patients with metastatic breast cancer. In five Phase III studies (AVF2119g, E2100, BO17708, AVF3694g and AVF3693g) in patients with metastatic breast cancer, Grade ≥ 3 CHF was reported in up to 3.5% of patients treated with bevacizumab in combination with chemotherapy compared with up to 0.9% in the control arms. For patients in study AVF3694g who received anthracyclines concomitantly with bevacizumab, the incidences of Grade ≥ 3 CHF for the respective bevacizumab and control arms were similar to those in the other studies in metastatic breast cancer: 2.9% in the anthracycline + bevacizumab arm and 0% in the anthracycline + placebo arm. In addition, in study AVF3694g the incidence of any grade CHF was similar between the anthracycline + bevacizumab (6.2%) and the anthracycline + placebo arms (6.0%). Most patients who developed CHF during metastatic breast cancer trials showed improved symptoms and/or left ventricular function following appropriate medical therapy.

In most clinical trials of bevacizumab, patients with pre-existing CHF of New York Heart Association (NYHA) II – IV were excluded, therefore, no information is available on the risk of CHF in this population. Prior anthracyclines exposure and/or prior radiotherapy to the chest wall may be possible risk factors for the development of CHF.

An increased incidence of CHF has been observed in a clinical trial of patients with diffuse large B-cell lymphoma (BO20603) when receiving bevacizumab with a cumulative doxorubicin dose greater than 300 mg/m2. This phase III clinical trial compared rituximab/cyclophosphamide/doxorubicin/vincristine/prednisone (R-CHOP) plus bevacizumab to R-CHOP without bevacizumab. While the incidence of CHF in both arms was above that previously observed for doxorubicin therapy the rate was higher in the R-CHOP plus bevacizumab arm.

Events consistent with CHF were reported in clinical trials. The findings ranged from asymptomatic declines in left ventricular ejection fraction to symptomatic CHF, requiring treatment or hospitalization.

Ovarian Failure/Fertility: The incidence of new cases of ovarian failure, defined as amenorrhoea lasting 3 or more months, follicle stimulating hormone (FSH) level ≥ 30mIU/ml and a negative serum β-HCG pregnancy test, has been evaluated. New cases of ovarian failure were reported more frequently in patients receiving bevacizumab. After discontinuation of bevacizumab treatment, ovarian function recovered in the majority of women. Long term effects of treatment with bevacizumab on fertility are unknown.

Neutropenia: Increased rates of severe neutropenia, febrile neutropenia, or infection with severe neutropenia (including some fatalities) have been observed in patients treated with some myelotoxic chemotherapy regimens plus bevacizumab in comparison to chemotherapy alone.

Hypersensitivity reactions, infusion reactions: Patients may be at risk of developing infusion/ hypersensitivity reactions. In some clinical trials anaphylactic and anaphylactoid-type reactions were reported more frequently in patients receiving bevacizumab in combination with chemotherapies than with chemotherapy alone. The incidence of these reactions in some clinical trials of bevacizumab is common (up to 5% in bevacizumab-treated patients).

Laboratory Abnormalities: Decreased absolute neutrophil count (ANC), decreased white blood count (WBC) and presence of urine protein may be associated with bevacizumab treatment. Across clinical trials, the following Grade 3 and 4 laboratory abnormalities were seen with an increased (≥2%) incidence in patients treated with bevacizumab compared to those in the control groups: hyperglycemia, decreased hemoglobin, hypokalemia, hyponatremia, decreased white blood cell count, increased prothrombin time (PT), normalized ratio.

Additional Adverse Events: See the bevacizumab drug package insert for additional details regarding the safety experience with bevacizumab.

2.3 Atezolizumab (MPDL3280A)

Atezolizumab is a human immunoglobulin (Ig) G1 monoclonal antibody consisting of two heavy chains (448 amino acids) and two light chains (214 amino acids) and is produced in Chinese hamster ovary cells. Atezolizumab was engineered to eliminate Fc-effector function via a single amino acid substitution (asparagine to alanine) at position 298 on the heavy chain, which results in a non-glycosylated antibody that has minimal binding to Fc receptors and prevents Fc-effector function at expected concentrations in humans. Atezolizumab targets human PD-L1 and inhibits its interaction with its receptor, programmed death-1 (PD-1). Atezolizumab also blocks the binding of PD-L1 to B7.1, an interaction that is reported to provide additional inhibitory signals to T cells. Atezolizumab is being investigated as a potential therapy against solid tumors and hematologic malignancies in humans.

2.3.1 Summary of Non-Clinical Experience

The nonclinical strategy of the atezolizumab program was to demonstrate in vitro and in vivo

activity, to determine in vivo pharmacokinetic (PK) behavior, to demonstrate an acceptable safety profile, and to identify a Phase I starting dose. Comprehensive pharmacology, PK, and toxicology evaluations were thus undertaken with atezolizumab.

The safety, pharmacokinetics, and toxicokinetics of atezolizumab were investigated in mice and cynomolgus monkeys to support IV administration and to aid in projecting the appropriate starting dose in humans. Given the similar binding of atezolizumab for cynomolgus monkey and human PD-L1, the cynomolgus monkey was selected as the primary and relevant nonclinical model for understanding the safety, pharmacokinetics, and toxicokinetics of atezolizumab.

Overall, the nonclinical pharmacokinetics and toxicokinetics observed for atezolizumab supported entry into clinical studies, including providing adequate safety factors for the proposed Phase I starting doses. The results of the toxicology program were consistent with the anticipated pharmacologic activity of down-modulating the PD-L1/PD-1 pathway and supported entry into clinical trials in patients. Refer to the atezolizumab Investigator's Brochure for details on the nonclinical studies.

2.3.2 Clinical Experience in RCC and Clinical Activity

Ongoing Phase II Study WO29074 is evaluating the safety and efficacy of atezolizumab monotherapy or the combination of atezolizumab and bevacizumab versus sunitinib in treatment-naïve patients with RCC. Safety and efficacy data are not yet available for this study.

As of the data cutoff of 1 January 2014, efficacy analyses were performed on 386 efficacy evaluable patients who were defined as those patients, with measurable disease at baseline, treated by 1 July 2013 in Study PCD4989g (to ensure that each patient had a minimum of 6 months follow-up). Patients with multiple tumor types were included in the study, with the largest cohorts consisting of patients with non-small cell lung cancer (NSCLC), RCC, and bladder cancer. Objective responses with atezolizumab monotherapy were observed in a broad range of malignancies, including NSCLC, RCC, melanoma, bladder cancer, colorectal cancer, head and neck cancer, gastric cancer, breast cancer and sarcoma. Altogether, there were 47 patients with responses with a median duration of response of 75.7 weeks (range: 11.7+ to 85.9+ weeks, where "+" denotes censored value). The majority of these responses have been durable, with 72.3% (34/47) of responses ongoing as of the clinical cutoff date.

Analyses of tumor-infiltrating immune cells for PD-L1 expression on baseline tumor tissue have been performed for Study PCD4989g. Preliminary results from Study PCD4989g suggest that PD-L1 expression in tumor infiltrating immune cells is likely to be associated with response to atezolizumab.

2.3.3 Clinical Pharmacokinetics and Immunogenicity

The fixed dose of 1200 mg (equivalent to an average body weight-based dose of 15 mg/kg) was selected on the basis of both nonclinical studies and available clinical data. On the basis of available preliminary PK data (0.03-20 mg/kg), atezolizumab appeared to show linear pharmacokinetics at doses ≥1 mg/kg. For the 1-mg/kg and 20-mg/kg dose groups, the mean clearance (CL) and the mean volume at steady state (Vss) had a range of 3.20-4.43 mL/kg and 48.1-64.1 mL/kg, respectively, which is consistent with the expected profile of an IgG1 antibody

in humans.

The development of anti-therapeutic antibodies (ATAs) has been observed in patients in all dose cohorts and was associated with changes in pharmacokinetics for some patients in the lower dose cohorts (0.3, 1, and 3 mg/kg). The development of detectable ATAs has not had a significant impact on pharmacokinetics for doses from 10-20 mg/kg. Patients dosed at the 10-, 15-, and 20-mg/kg dose levels have maintained the expected target trough levels of drug despite the detection of ATAs. To date, no clear relationship between detection of ATAs and adverse events (AEs) or infusion related reactions (IRRs) has been observed.

2.3.4 Clinical Safety

The presented safety data for atezolizumab have been derived mainly from the treatment of patients in Phase Ia Study PCD4989g. As of 10 May 2014, atezolizumab has been administered to approximately 775 patients with solid and hematologic malignancies. No dose-limiting toxicities (DLTs) have been observed at any dose level, and no maximum tolerated dose (MTD) was established. Fatigue was the most frequently reported AE.

The following safety data are from PCD4989g, in which atezolizumab is being used as single-agent therapy in patients with locally advanced or metastatic solid tumors or hematologic malignancies. In 412 treated patients, 97.1% reported an AE while on study. Of these AEs, 48.8% were Grade 1 or 2 in maximum severity on the basis of NCI-CTCAE version 4.0. The most frequently observed AEs (occurring in ≥10% of treated patients) included fatigue, nausea, decreased appetite, pyrexia, dyspnea, diarrhea, constipation, cough, headache, back pain, vomiting, anemia, arthralgia, rash, insomnia, asthenia, abdominal pain, chills, pruritus, and upper respiratory tract infection.

Grade ≥3 AEs were reported by 199 of 412 patients (48.3%). There were 51 patients (12.4%) who reported Grade ≥3 AEs that were assessed as related to study drug by the investigators. The most frequently reported related Grade ≥3 AEs included fatigue (5 patients [1.2%]), increased alanine aminotransferase (ALT) and increased aspartate aminotransferase (AST) (each reported in 4 patients [1.0%]); and asthenia, autoimmune hepatitis, and hypoxia (each reported in 3 patients [0.7%]).

Given the mechanism of action of atezolizumab, events associated with inflammation and/or immune-mediated AEs have been closely monitored during the atezolizumab clinical program. These include potential dermatologic, hepatic, endocrine, and respiratory events as well as events of hepatitis/elevated liver function tests (LFTs) and influenza-like illness.Expected adverse drug reactions associated with atezolizumab include the following: hepatitis/transaminitis, hypothyroidism, IRRs, pneumonitis, influenza-like illness, and dermatologic reactions. Potential adverse drug reactions include the following: ATAs, colitis, endocrine disorders, hypersensitivity, neurologic disorders, and pericardial effusion. For further details, see the atezolizumab Investigator's Brochure.

2.4 Rationale

There is no established high-level evidence for a standard of care for patients with nccRCC. Current approved agents in RCC have limited activity in nccRCC compared to ccRCC and there

is a need to actively investigate new therapies in this setting.

VEGF blocking agents including bevacizumab have been investigated for the treatment of patient with nccRCC. A phase II trial investigating the efficacy of bevacizumab, specifically in patients with papillary RCC was conducted, however was closed to slow accrual, demonstrated safety, and modest activity. For patients who were on this study, individual PFS ranged from 6-25 months.[9]

The rationale for including all nccRCC patients stems from historic and currently ongoing trials in nccRCC which include all non-clear cell histologies. A phase II trial (ESPN) investigated outcomes of first-line everolimus compared to sunitinib in nccRCC patients.[10] Patients were stratified by histology (papillary vs. others), MSKCC risk groups, and Kaplan-Meier curves were used to estimate unadjusted TTE distributions between groups. Accrual was terminated due to futility analysis of PFS and inferior OS with everolimus compared to sunitinib in first-line (median OS with everolimus was 10.5 months (95% CI), and median OS with sunitinib was not reached). Another phase II trial investigated the efficacy of everolumus versus sunitinib in the first-line setting in patients with metastatic nccRCC, with papillary, chromophobe, or any unclassified histology (ASPEN).[11] Patients were stratified by histology and risk group, with the primary endpoint as radiographic PFS. Sunitinib was found to prolong PFS as compared with everolimus in patients with nccRCC. This trial is the largest trial to date in nccRCC and first to demonstrate an mTOR-sensitive subgroup of nccRCC patients as compared with VEGF inhibition in the first-line setting, including chromophobe and poor risk RCC patients.

Given the small size of this study and the limited nccRCC patient population of only 20%, we will allow patients have received both first and second line therapies as this is an exploratory study evaluating for a signal of efficacy in this patient population. If a signal of efficacy is observed, a larger study in a more homogenous patient population can be considered in the future.

Immunotherapy strategies have been used for decades in patients with advanced RCC with prolonged survival being seen in a very small proportion of patients treated with IFN-α or high-dose interleukin-2 therapy. The past several years has witnessed a resurgence in interest in immunotherapy with the developed of blocking antibodies against the inhibitory PD-1 pathway. PD-L1 is broadly expressed on tumor cells and tumor infiltrating mononuclear cells (TIMC). We have previously demonstrated that PD-L1 expression in tumor (10.9%) and TIMC (56.4%) occurs in patients with nccRCC and PD-L1 positivity on tumor cell membrane was associated with aggressive clinicopathological features.[12] Single agent atezolizumab, a monoclonal anti-PD-L1 antibody, has been investigated in metastatic ccRCC as detailed in section 2.3.2.

There is rationale for combining VEGF inhibition with immunotherapy. VEGF has profound effects on immune regulatory cell function, specifically inhibiting dendritic cell maturation and antigen presentation.[13,14] Additionally, there is increasing evidence for the role angiogenic factors play in influencing lymphocyte trafficking across endothelia in tumor deposits.[15]

The combination of bevacizumab (15 mg/kg every 3 weeks) and ipilimumab has been investigated in melanoma.[16] Therapy with these agents revealed that VEFG blockade influences

inflammation, lymphocyte trafficking, and immune regulation based on data from on treatment tumor biopsies and peripheral blood analysis. Clinically, 8 patients had a partial response (PR) and 22 patients stable disease (SD) for disease control rate of 67.4%. Median survival was 25.1 months.

There is precedence to combining VEGF inhibition with immunotherapy in RCC, however this data mainly exits for ccRCC. Two large phase III trials combine bevacizumab with IFN-α.[4,5] A phase II study explored the immunomodulatory effects of bevacizumab and low-dose interleukin-2 in patients with metastatic RCC.[17] In this study, the combination demonstrated modest activity with PFS 9.6 months and ORR 15%. Biological data indicated that inhibition of VEGF levels increased immunosuppressive regulatory T cells. Furthermore, the combination of nivolumab with sunitinib or pazopanib in patients with metastatic RCC is being explored in a phase 1 study.[18] Preliminary data demonstrated that the ORR was 52% (17/33) in patients treated with sunitinib and 45% (9/20) in patients treated with pazopanib. SD rate was 33% in the sunitinib arm and 35% in the pazopanib arm. 24 week PFS was 78% in the sunitinib arm and 55% in the pazopanib arm.

A phase 1b study evaluated atezolizumab in combination with bevacizumab in patients with metastatic ccRCC.[19] Patients were treated with bevacizumab 15 mg/kg alone on cycle 1/day 1 and atezolizumab 20 mg/kg every 3 weeks thereafter. Preliminary data demonstrated that among first-line metastatic RCC patients with one tumor assessment (n = 10), the ORR was 40%. An additional 4/5 patients with best response as SD had prolonged AD at ≥ 24 weeks. On treatment tumor biopsies demonstrated increases in tumor-infiltrating CD8+ cells.

A phase II study evaluating atezolizumab as monotherapy or in combination with bevacizumab compared to sunitinib is currently ongoing but closed to accrual. Patients with previously untreated locally advanced or metastatic renal cell carcinoma with a component of clear cell and/or sarcomatoid histology were enrolled. In this study, patients receive either 1200 mg of atezolizumab every 3 weeks until disease progression, atezolizumab in combination with 15 mg/kg of bevacizumab every 3 weeks until disease progression, or the active comparator, sunitinib administered as 50 mg each day orally, followed by 2 weeks of rest, until disease progression. Patients starting on atezolizumab alone or sunitinib may crossover to the combination arm following disease progression. The primary objective is progression-free survival per RECIST v1.1 via central IRC assessment.

Lastly, a phase III study of atezolizumab in combination with bevacizumab versus sunitinib in patients with untreated inoperable locally advanced or metastatic renal cell carcinoma who have not received prior systemic active or experimental therapy, either in the adjuvant or metastatic setting, is currently ongoing and recruiting patients. Patients must have a definitive diagnosis of unresectable advanced or metastatic RCC with clear-cell histology and/or sarcomatoid carcinoma in order to be eligible. Patients assigned to the experimental dual regimen of atezolizumab plus bevacizumab receive a fixed-dose of 1200 mg of atezolizumab on days 1 and 22 of 42-day cycles until loss of clinical benefit, unacceptable toxicity, symptomatic deterioration attributed to disease progression, or death. Participants assigned to receive single-agent sunitinib are administered 50 mg of sunitinib orally once daily on days 1 through 28. The primary outcome measure, like the phase II, is progression-free survival as determined by RECIST v1.1.

Given the immunomodulatory properties of VEGF, we hypothesize that the combination of atezolizumab and bevacizumab will be synergistic and result in improved response in patients with metastatic nccRCC. In this study, we propose to evaluate the efficacy and safety of the combination of bevacizumab and atezolizumab in patients with non-ccRCC.

2.5 Correlative Studies Background

Immunotherapy has historically had a significant role in the management of metastatic RCC. Treatment using IFNα and interleukin-2 (IL-2) results in objective responses in approximately 5% of patients with RCC and 10% of patients treated with IL-2 exhibit durable disease stabilization. Atezolizumab blocks the inhibitor receptors expressed on tumor cells called PD-L1, resulting in enhanced tumor activity. Studies suggest that this compound derives effect from enhancement of immune function by targeting the PD-L1 axis which may be of critical importance in RCC.

PD-L1 is an extracellular protein that downregulates immune responses primarily in peripheral tissues through binding to its two receptors: PD-1 and B7-1. Many human tumors have been found to overexpress PD-L1, which acts to suppress anti-tumor immunity. PD-1 is an inhibitor receptor expressed on T-cells following T-cell activation, which is sustained in states of chronic stimulation, such as chronic infection or chance.[20] Ligation of PD-L1 and PD-1 inhibits T-cell proliferation, cytokine production, and cytolytic activity, leading to the function inactivation or exhaustion of T-cells. B7-1 is a molecular expressed on antigen-presenting cells (APC) and activated T-cells. PD-L1 binding to B7-1 on T cells and APCs can mediate the downregulation of immune response, including inhibition of T-cell activation and cytokine production.[21,22]

Aberrant expression of PD-L1 on tumor cells has been reported to impede anti-tumor immunity, resulting in immune evasion.[23] Therefore the interruption of the PD-L1/PD-1 pathway represents an attractive strategy to reinvigorate tumor-specific T-Cell immunity. In addition, VEGF is known to play a significant role in the pathogenesis of RCC and recent data suggests that VEGF may have an effect on immune function including antigen presentation and T-cell activation.

In this study, we will evaluate the immunomodulatory properties of atezolizumab in combination with bevacizumab and correlate findings with outcomes. In addition, we will evaluate tumor tissue and TIMC for expression of PD-L1 and correlates with outcomes.

2.5.1 Rationale for Collection of Blood Biomarkers

Changes in biomarkers in the blood may provide evidence for the biological activity of atezolizumab in humans and may allow for the developed of a blood based biomarker to help predict which patients may benefit from atezolizumab. A secondary objective is to assess the immunomodulatory properties of atezolizumab in combination with bevacizumab by evaluating baseline levels and changes in levels upon treatment of surrogate pharmacodynamic markers in the blood. In addition, we will correlate levels with the anti-tumor activity of the combination of these agents.

2.5.2 Rationale for Collection of Archival and Fresh Tumor Specimens

PD-L1/PD-1 pathway activation in tumors, as determined by PD-L1 levels, may be an important

predictive diagnostic for atezolizumab. Published results suggest that expression of PD-L1 in tumors correlates with response to anti-PD-1 therapy.[24] This correlation is also observed with atezolizumab in preliminary data from Study PCD4989g such that patients with PD-L expression appear to derive he most benefit from atezolizumab. Tumor specimens (collected from baseline fresh tumor specimens) from patients meeting eligibility criteria will be tested for PD-L1 expression and other markers of immunogenicity and angiogenesis. In addition, PD-L1 status (as defined by expression of PD-L1 on tumor cells or TIMC) will be correlated with outcomes. Because the expression of PD-L1 on the surface of both tumor cells and TIMC can be a dynamic process and because PD-L1 expression on these cells may vary between primary and metastatic sites, mandatory fresh tumor specimens will be collected. Additionally, to investigate mechanisms of acquired resistance to therapy, patients who experience relapse after an initial response will be required to undergo a mandatory fresh tumor biopsy if medically safe.

3. PARTICIPANT SELECTION

3.1 Eligibility Criteria

- Age ≥ 18 years.

- Unresectable advanced or metastatic non-clear cell RCC to include but not limited to:
    - Papillary RCC, any type
    - Unclassified RCC
    - Translocation RCC
    - Chromophobe RCC
    - Collecting duct RCC
    - Medullary RCC
    - Clear cell RCC or any histology with ≥ 20% sarcomatoid features will be eligible
        - If a patient has not had a nephrectomy, then a patient that has a metastatic biopsy showing sarcomatoid will still be eligible.
    - Other non-clear cell histologies that are not included above need to be discussed with the PI.

- Request for formalin-fixed, paraffin-embedded (FFPE) archival tumor specimens if available **and** willingness of the participant to undergo mandatory fresh tumor biopsy unless determined medically unsafe or not feasible. A note from the study team should be provided documenting availability of tissue. If a target lesion is biopsied at screening, this lesion must be followed as non-target lesion after the biopsy unless it is the patient's only target lesion. If there is only one target lesion, it should be followed as a target lesion regardless.
    - The archival specimen should contain adequate viable tumor tissue.
    - The specimen may consist of a tissue block (preferred and should contain the highest grade of tumor) or at least 30 unstained serial sections. Fine-needle aspiration, brushings, cell pellet from pleural effusion, bone marrow aspirate/biopsy are not acceptable.
    - Fresh tumor biopsy at progression will be required in cases where patients experience relapse after an initial response if medically safe.

- Measurable disease as defined by Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1.

- ECOG performance status ≤ 2 (See Appendix A).

- Adequate hematologic and end-organ function as defined by the following laboratory results obtained within 28 days prior to the first study treatment:
    - Absolute neutrophil count (ANC) ≥ 1500 cells/uL.
    - Platelet count ≥ 100,000/uL.
    - Hemoglobin ≥ 9 g/dL (patients may be transfused to meet this criterion).
    - Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 x upper limit of normal (ULN) with the following exceptions: Patients with documented liver metastases should have AST and ALT ≤ 5 x ULN.
    - Serum bilirubin ≤ 2.0 x ULN with the following exception: Patients with known Gilbert's disease should have a serum bilirubin ≤ 3 x ULN.
    - Creatinine clearance ≥ 30 mL/min as calculated by Cockcroft-Gault equation.

- For female patients of childbearing potential and male patients with partners of childbearing potential, agreement (by patient and/or partner) to use highly effective forms of contraception and to continue its use 6 months after the last dose of atezolizumab or bevacizumab.

- Signed informed consent form.

- Ability and capacity to comply with study and follow-up procedures.

3.2 Exclusion Criteria

- Prior treatment with CD137 agonists, anti- cytotoxic T-lymphocyte-associated protein 4, anti-PD-1, or anti-PDL1 therapeutic antibody or pathway targeting agents. Prior IFNα or IL-2 is allowed following 4 week washout from treatment end date.

- Receipt of any type of small molecule kinase inhibitor (including investigational kinase inhibitors) within 2 weeks of enrollment or receipt of any anti-cancer therapy (including investigational therapy, monoclonal antibodies, cytokine therapy) within 4 weeks of enrollment.

- Prior therapy with bevacizumab.

- Thrombologic event within 3 weeks of treatment start date, unless stable on anticoagulation with LMWH or Factor Xa inhibitor for at least 2 weeks.

- Treatment with systemic immunosuppressive medications including but not limited to: prednisone, dexamethasone, cyclosporin, azathioprine, methotrexate, thalidomide, anti-tumor necrosis factor (TNF) agents, hydroxychloroquine within 2 weeks of first study dose.
    - Patients who have received acute, low-dose systemic immunosuppressant medications may be enrolled.
    - Patients with adrenal insufficiency on physiologic replacement doses of steroids may be enrolled.
    - The use of inhaled, topical intraocular, or intra articular corticosteroids or,

mineralocorticoids are allowed.

- Radiotherapy for RCC within 14 days of first study treatment with the exception of a single fraction of radiation administered for palliation of symptoms.

- Known brain metastases or cranial epidural disease unless adequately treated with radiotherapy, radiosurgery, or surgery and stable for at least 4 weeks prior to the initiation of study treatment. Stability must be confirmed by magnetic resonance imaging (MRI) or computed tomography (CT) imaging and/or treating investigator determination.

- Malignancies other than RCC within 2 years of first study treatment with the exception of those with negligible risk of metastases or death (included but not limited to carcinoma in situ of the cervix, basal or squamous cell skin cancer, localized prostate cancer, ductal carcinoma in situ of the breast, non-muscle invasive urothelial carcinoma, or other malignancy not deemed to impact that patients 5-year life expectancy).

- History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion protein.

- Known hypersensitivity to any component of the atezolizumab product.

- History of autoimmune disease including: myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with anti-phospholipid syndrome, Wegner's granulomatosis, Sjogren's syndrome, Guillain-Barre syndrome, multiple sclerosis, type I diabetes mellitus, vasculitis, or glomerulonephritis. Patients with a history of autoimmune-related hypothyroidism on thyroid replacement hormone or those with autoimmune dermatologic conditions not requiring the use of prednisone > 10 mg or equivalent are eligible.

- History of idiopathic pulmonary fibrosis, organized pneumonia, or evidence of active pneumonitis on screening imaging CT of the chest. History of radiation pneumonitis in the radiation field is permitted.

- Positive test for HIV (test to be performed within 28 days of first treatment start).

- Patients with active or chronic hepatitis B (defined as having a positive hepatitis B surface antigen [HBsAg] test at screening). Patients with past/resolved HBV infection (defined as having negative HBsAg test and a positive antibody to hepatitis B core antigen [anti-HBc] antibody test) are eligible. A negative HBA DNA test must be obtained in patients with positive hepatitis B core antibody prior to Cycle 1 Day 1.
- Active hepatitis C infection. Patients positive hepatitis C antibody test are eligible if PCR is negative for hepatitis C viral DNA.

- Infection requiring receipt of therapeutic oral or IV anti-microbials within 2 weeks of first study treatment. Patients receiving routine anti-microbial prophylaxis (for dental extractions/procedures) are eligible.

- Significant cardiovascular disease such as New York Heart Association (NYHA) class II or greater, myocardial infarction within the previous 3 months of first study treatment, unstable arrhythmias, unstable angina. Patients with known coronary artery disease, congestive heart failure not meeting the above criteria, or left ventricular ejection fraction < 50% must be on a stable regimen that is optimized in the opinion of the treating physician, in consultation with a cardiologist when appropriate.

- Inadequately controlled hypertension (defined as systolic blood pressure > 150 mmHg and/or diastolic blood pressure > 100 mmHg). Anti-hypertensive therapy to achieve these parameters is allowed.

- Prior history of hypertensive crisis or hypertensive encephalopathy within the previous 3 months of first study treatment.

- History of stroke or transient ischemic attack within 3 months of first study dose.

- Significant vascular disease (such as aortic aneurysm requiring surgical repair or recent peripheral arterial thrombosis) within 6 months of first study dose. Evidence of bleeding diathesis or significant coagulopathy (in the absence of therapeutic anticoagulation).

- Current or recent use of dipyramidole, ticlopidine, clopidogrel, cilostazol is excluded. Aspirin (≤ 325 mg per day) is allowed. Prophylactic anticoagulation with oral or parenteral anticoagulants for the patency of venous access devices or other indications is allowed. Therapeutic use of low-molecular weight heparin (such as enoxaparin), and factor Xa inhibitors are allowed. Use of warfarin is prohibited.

- Use of plaquenil must be discontinued two weeks prior to first study treatment.

- History of abdominal or tracheoesophageal fistula or GI perforation within 6 months of first study treatment.

- Clinical signs or symptoms of active GI obstruction or requirement of routine parenteral nutrition or tube feedings.

- Evidence of abdominal free air not explained by paracentesis or recent surgical procedure.

- Serious, non-healing or dehiscing wound or active ulcer.

- Proteinuria, as demonstrated by > 1.5 gram of protein in a 24-hour urine collection. All patients with ≥ 2+ protein on dipstick urinalysis at baseline must undergo 24-hour urine collection for protein.

- Major surgical procedure within 21 days of first study treatment.

- Prior allogenic stem cell or solid organ transplant.

- Administration of a live, attenuated vaccine within 4 weeks for first study treatment.

- Pregnant or lactating women.

3.3 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial.

4. REGISTRATION PROCEDURES

4.1 General Guidelines for Dana-Farber/Harvard Cancer Center (DF/HCC) and Dana-Farber/Partners Cancer Care (DF/PCC) Institutions

Institutions will register eligible participants with the DF/HCC Office of Data Quality (ODQ) central registration system. Registrations must occur prior to the initiation of protocol therapy. Any participant not registered to the protocol before protocol therapy begins will be considered ineligible and registration will be denied.

An investigator will confirm eligibility criteria and a member of the study team will complete the ODQ protocol-specific eligibility checklist.

Following registration, participants may begin protocol therapy. Issues that would cause treatment delays should be discussed with the Overall Principal Investigator (PI). If a participant does not receive protocol therapy following registration, the participant's registration on the study must be canceled. Notify the ODQ Registrar of registration cancellations as soon as possible.

4.2 Registration Process for DF/HCC and DF/PCC Institutions

The ODQ registration staff is accessible on Monday through Friday, from 8:00 AM to 5:00 PM Eastern Standard Time. In emergency situations when a participant must begin protocol therapy during off-hours or holidays, call the ODQ registration line [redacted] and follow the instructions for registering participants after hours.

The registration procedures are as follows:

- Obtain written informed consent from the participant prior to the performance of any protocol specific procedures or assessments.

- Complete the ODQ protocol-specific eligibility checklist using the eligibility assessment documented in the participant's medical record and/or research chart. **To be eligible for registration to the protocol, the participant must meet all inclusion and exclusion criterion as described in the protocol and reflected on the eligibility checklist.**

  Reminder: Confirm eligibility for ancillary studies at the same time as eligibility for a treatment protocol. Registration to both treatment and ancillary protocols will not be completed if eligibility requirements are not met for all studies.

- Fax the eligibility checklist(s) and all pages of the consent form(s) to the ODQ [redacted] For Phase I protocols, attach participant dose level assignment confirmation from the sponsor.

- The ODQ Registrar will (a) review the eligibility checklist, (b) register the participant on the protocol, and (c) randomize the participant when applicable.

- An email confirmation of the registration and/or randomization will be sent to the Overall PI, study coordinator(s) from the Lead Site, treating investigator and registering person immediately following the registration and/or randomization.

4.3 General Guidelines for Other Investigative Sites

Eligible participants will be entered on study centrally at the Dana-Farber Cancer Institute (DFCI) by the Study Coordinator. All sites should call the Study Coordinator [redacted] to verify dose level availabilities. The required forms will be provided to all participating institutions by the DFCI study coordination.

Following registration, participants should begin protocol therapy within 7 days or as soon as possible. Issues that would cause treatment delays should be discussed with the Overall PI. If a participant does not receive protocol therapy following registration, the participant's registration on the study must be canceled. The Study Coordinator should be notified of cancellations as soon as possible.

4.4 Registration Process for Other Investigative Sites

To register a participant, the documents listed in Appendix B should be completed by the research nurse or data manager and faxed [redacted] or emailed to the DFCI study coordination.

The research nurse or data manager at the participating site will then call [redacted] or email the DFCI Study Coordinator to verify eligibility. To complete the registration process, the Coordinator will:

- Register the participant on the protocol with the ODQ.
- Fax or e-mail the participant study number, and if applicable the dose treatment level to the participating site.
- Call the research nurse or data manager at the participating site and verbally confirm registration.

NOTE: Registration and randomization with the ODQ can only be conducted during the business hours of 8:00 AM and 5:00 PM Eastern Standard Time Monday through Friday. Same day treatment registrations will only be accepted with prior notice and discussion with the DF/HCC Lead Institution.

5. TREATMENT PLAN

5.1 Treatment Regimen

The participant will then undergo screening procedures and will enter the trial after successful screening. The participant must be willing to undergo a mandatory fresh tumor biopsy at baseline unless the investigator deems the procedure medically unsafe. Participants with no available archival tumor tissue will be required to undergo a fresh tumor biopsy at baseline.

Eligible patients will be enrolled and will treatment with bevacizumab 15 mg/kg IV every 3

weeks and atezolizumab 1200 mg IV every 3 weeks. Each cycle will be 3 weeks in duration. Patients will be evaluated clinically every 3 weeks and will undergo disease assessments with imaging every 6 weeks.

Participants will be continued on therapy until radiographic progression or withdrawal for some other reason as detailed in section 5.6. Participants who experience a response to therapy and then subsequently progress will be required to undergo a mandatory tumor biopsy at the time of progression if medically safe. Reported adverse events, potential risks, and dose modifications are described in Section 6. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the participant's malignancy.

Regimen Description					
Agent	**Premedications; Precautions****	**Dose**	**Route**	**Schedule**	**Cycle Length**
Atezolizumab*	None (may be administered for Cycles ≥2 at the discretion of the treating physician)	1200 mg	IV **before** bevacizumab ***	Every 3 weeks (21 [+/-3] days)	3 weeks (21 [+/-3] days)
Bevacizumab	None (See Section 5.4)	15 mg/kg****	IV*****	Every 3 weeks (21 [+/-3] days)	

* Atezolizumab will be administered first followed by bevacizumab, with a minimum of 5 minutes between dosing.
**Observation should be for at least 2 hours after the first administration of the combination.
*** The initial dose of atezolizumab will be delivered over 60 (+/-15) minutes. If the first infusion is tolerated without infusion associated AEs, the second infusion may be delivered over 30 (+/-10) minutes. If the 30 minute infusion is well tolerated, all subsequent infusions may be delivered over 30 (+/-10) minutes.
****Bevacizumab doses will be calculated based on C1D1 weight unless there is a >5% weight change in subsequent cycles. If a patient has a change of weight that is >5% from C1D1 weight, this value will become the new baseline.
*****The initial dose will be delivered over 90 (+/-15) minutes. If the first infusion is tolerated without infusion associated adverse events (fever and/or chills), the second infusion may be delivered over 60 (+/-10) minutes. If the 60 minute infusion is well tolerated, all subsequent infusions may be delivered over 30 (+/-10) minutes.

5.2 Pre-Treatment Criteria

5.2.1 Cycle 1, Day 1

Prior to cycle 1, day 1, the following parameters must be met:

- ANC ≥ 1500/mm^3.
- Platelet count ≥ 100,000/uL.
- Hemoglobin ≥ 9 g/dL (transfusions allowed).

Cycle 1, day 1 laboratory assessments do not need to re-meet eligibility criteria. For subsequent cycles, labs should be reviewed and CTC grading for toxicities should be done prior to treatment. Dose modifications should be followed per the protocol as necessary.

5.3 Atezolizumab

The dose level of atezolizumab to be tested in this study is 1200 mg (equivalent to an average body weight-based dose of 15 mg/kg) administered by IV infusion every 3 weeks (21 [+/-3] days). Atezolizumab will be delivered in infusion bags with IV infusion lines that have product contacting surfaces of polyvinyl chloride (PVC) or polyolefin and 0.2 um in-line filters (filter membrane of polyethersulfone [PES]). No incompatibilities have been observed between atezolizumab and PVC or polyolefin infusion materials (bags or infusion lines).

Atezolizumab dose preparation will be done on the day atezolizumab is administered. Atezolizumab should be allowed to reach room temperature prior to removal from the vials. The product should be administered only using 250 mL 0.9% sodium chloride saline IV bags. The required volume of atezolizumab for the patient is 20 mL. Dose solutions are prepared by removing 20 mL of saline solution from the IV bag prior to the addition of 20 mL of atezolizumab. The total volume of NS for the final product isThe IV bags containing atezolizumab should be mixed and handled gently. The study drug must be diluted under appropriate aseptic conditions, as it does not contain antimicrobial preservatives. Once the atezolizumab dose solution is prepared, it may be stored at 2°C–8°C (36°F–46°F) and/or at room temperature for up to 8 hours prior to the start of infusion. However, if the infusion is interrupted and the combined storage and dose hold time of the diluted IV bags exceeds the 8-hour limit, prepare a new dose solution to resume the infusion.
If the dose solution is stored at 2°C–8°C (36°F–46°F), it should be removed from refrigeration and allowed to reach room temperature prior to administration. Protect dose solutions from intense light and heat.

Administration of atezolizumab will be performed in a setting with emergency medical facilities and staff who are trained to monitor for and respond to medical emergencies.

Atezolizumab will be administered first, followed by bevacizumab, with a minimum of 5 minutes between dosing. The initial dose of atezolizumab will be delivered over 60 (+/-15) minutes. If the first infusion is tolerated without infusion associated AEs, the second infusion may be delivered over 30 (+/-10) minutes. If the 30 minute infusion is well tolerated, all subsequent infusions may be delivered over 30 (+/-10) minutes. For the first infusion, the patient's vital signs (heart rate, respiratory rate, blood pressure, and temperature) should be determined within 60 minutes before, during (every 15 [+/-5] minutes), and 30 (+/-10) minutes after the infusion. For subsequent infusions, vital signs will be collected within 60 minutes before and within 30 minutes after the infusion. Vital signs should be collected during the infusion only if clinically indicated. Patients will be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such

symptoms. Observation should be for at least 2 hours after the first administration of the combination.

No premedication will be allowed for the first dose of atezolizumab. Premedication may be administered for Cycles ≥2 at the discretion of the treating physician. The management of IRRs will be according to severity as follows:

- In the event that a patient experiences a mild (NCI CTCAE Grade 1) IRR, the infusion rate should be reduced to half the rate being given at the time of event onset. Once the event has resolved, the investigator should wait for 30 minutes while delivering the infusion at the reduced rate. If tolerated, the infusion rate may then be increased to the original rate.
- In the event that a patient experiences a moderate IRR (NCI CTCAE Grade 2) or flushing, fever, or throat pain, the infusion should be immediately interrupted and the patient should receive aggressive symptomatic treatment. The infusion should be restarted only after the symptoms have adequately resolved to baseline grade. The infusion rate at restart should be half of the infusion rate that was in progress at the time of the onset of the IRR.
- For severe or life-threatening IRRs (NCI CTCAE Grade 3 or 4), the infusion should be stopped immediately, and aggressive resuscitation and supportive measures should be initiated. Patients experiencing severe or life threatening IRRs will not receive further infusion and will be further managed as clinically indicated until the event resolves.

If bevacizumab is being held atezolizumab can still be administered unless the participant is experiencing treatment-emergent toxicities for which the etiology could be related to both agents. In this case, both drugs should be held. If one or both study agents are being held, study assessments (e.g. scans, laboratory assessments, etc.) will remain on schedule as per the study calendar.

5.4 Bevacizumab

Bevacizumab should be prepared using aseptic technique. Withdraw the necessary amount of bevacizumab and dilute to the required administration volume with 0.9% Sodium Chloride Injection, USP. Bevacizumab preparation should be conducted as per the USPI. Administration will be as a continuous IV infusion. Anaphylaxis precautions should be observed during study drug administration.

The initial dose will be delivered over 90 (+/-15) minutes. If the first infusion is tolerated without infusion associated adverse events (fever and/or chills), the second infusion may be delivered over 60 (+/-10) minutes. If the 60 minute infusion is well tolerated, all subsequent infusions may be delivered over 30 (+/-10) minutes.

If a subject experiences an infusion–associated AE, he or she may be premedicated for the next study drug infusion; however, the infusion time may not be decreased for the subsequent infusion. If the next infusion is well tolerated with premedication, the subsequent infusion time may then be decreased by 30 (+/-10) minutes as long as the subject continues to be premedicated. If a subject experiences an infusion associated adverse event with the 60 minute infusion, all subsequent doses should be given over 90 (+/-15) minutes. Similarly, if a subject

experiences an infusion associated adverse event with the 30 minute infusion, all subsequent doses should be given over 60 (+/-10) minutes.

If atezolizumab is being held bevacizumab can still be administered unless the participant is experiencing treatment-emergent toxicities for which the etiology could be related to both agents. In this case, both drugs should be held. If one or both study agents are being held, study assessments (e.g. scans, laboratory assessments, etc.) will remain on schedule as per the study calendar.

5.5 General Concomitant Medication and Supportive Care Guidelines

5.5.1 Permitted Therapy

Concomitant therapy includes any prescription medications or over-the-counter preparations used by a patient after 7 days preceding the screening evaluation and prior to the end of treatment visit or the date of RECIST version 1.1 progression, whichever is later. All concomitant medications administered within 14 days preceding Cycle 1, Day 1 and throughout the study until the treatment termination visit will be collected on study-specific electronic Case-Report Forms (eCRFs). The reason(s) for treatment and dates of treatment should be reported to the investigator and recorded as instructed on the study-specific eCRFs.

Patients should receive full supportive care, including transfusions of blood and blood products, antibiotics, anti-emetics, etc., when appropriate. Prophylactic anticoagulation for patency of device with oral or parenteral anticoagulants is allowed. Patients who require therapeutic anticoagulation can be maintained on low molecular weight heparin (LMWH) (e.g., enoxaparin and tinzaparin) or fondaparinux. In addition, patients requiring therapeutic anticoagulation with LMWH during study participation will be allowed to remain on study therapy. Therapeutic warfarin is not allowed on study.

Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or famotidine or another H2 receptor antagonist, as per standard practice. Serious infusion-associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated.

Systemic corticosteroids, TNF-α inhibitors, and hydroxychloroquinemay attenuate potential beneficial immunologic effects of treatment with atezolizumab but may be administered at the discretion of the treating physician after consultation with the PI. If feasible, alternatives to corticosteroids should be considered. Premedication may be administered for Cycles ≥ 2 at the discretion of the treating physician after consultation with the PI. The use of inhaled, topical intraocular or intraarticular corticosteroids, or mineralocorticoids are allowed. Megestrol administered as an appetite stimulant is acceptable while the patient is enrolled in the study. Mineralocorticoids for orthostatic hypotension or adrenalcortical insufficiency are acceptable.

Influenza vaccination should be given during influenza season only (approximately October to March). Patients must not receive live attenuated influenza vaccine within 4 weeks prior to Cycle 1, Day 1 or at any time during the study but may receive inactivated influenza vaccines.

Patients who use hormonal therapy with GnRH agonists or antagonists for prostate cancer, oral contraceptives, hormone-replacement therapyshould continue their use.

Males and females of reproductive potential should use highly effective means of contraception.

All concomitant medications should be reported to the investigator and recorded on the appropriate eCRF.

5.5.2 Prohibited Therapy

Any concomitant therapy intended for the treatment of kidney cancer, whether health authority−approved or experimental, is prohibited. This includes but is not limited to the following:

- Chemotherapy, hormonal therapy, immunotherapy, radiotherapy, investigational agents, or herbal therapy. After Cycle 2, certain forms of radiotherapy may be considered for pain palliation if patients are deriving benefit (such as treatment of known bony metastases).
- Patients experiencing a mixed response requiring local therapy (such as surgery, stereotactic radiosurgery, radiotherapy, radiofrequency ablation) for control of three or fewer lesions may still be eligible to continue study treatment. Patients who receive local therapy directed at a target lesion will no longer be evaluable for radiographic response but will remain evaluable for progression. Such cases must be discussed with and approved by the PI.

Traditional herbal medicines should not be administered because the ingredients of many herbal medicines are not fully studied and their use may result in unanticipated drug-drug interactions that may cause or confound assessment of toxicity.

Patients who are receiving a RANKL inhibitor (denosumab) prior to enrollment must be willing and eligible to receive a bisphosphonate instead while on study; denosumab could potentially alter the activity and the safety of atezolizumab.

Initiation or increased dose of granulocyte colony-stimulating factors (such as granulocyte colony-stimulating factor, granulocyte/macrophage colony-stimulating factor, and/or pegfilgrastim) is prohibited.

Patients are not allowed to receive immunostimulatory agents, including but not limited to IFNα or IL-2, during the entire study. These agents, in combination with atezolizumab, could potentially increase the risk for autoimmune conditions.

Patients should also not receive immunosuppressive medications, including but not limited to cyclophosphamide, azathioprine, methotrexate, and thalidomide. These agents could potentially alter the activity and the safety of atezolizumab. Systemic corticosteroids and anti-TNF-α agents may attenuate potential beneficial immunologic effects of treatment with atezolizumab but may be administered at the discretion of the treating physician after consultation with the PI. If feasible, alternatives to these agents should be considered. In addition, all patients (including

those who discontinue the study early) should not receive other immunostimulatory agents for 10 weeks after the last dose of atezolizumab.

Use of full-dose warfarin will not be allowed during the study. Because bevacizumab has a half-life of approximately 21 days, elective major surgery should be delayed whenever possible. No data are available to define a safe interval. Re-initiation of bevacizumab following surgery requires documented approval from the PI.

5.6 Treatment Beyond Disease Progression

Accumulating evidence indicates a minority of subjects treated with immunotherapy may derive clinical benefit despite initial evidence of disease progression. Subjects will be permitted to continue treatment beyond site investigator assessed progression as long as they meet the following criteria:

- Site investigator-assessed clinical benefit

AND

- Subject is tolerating study drug(s).

The assessment of clinical benefit should take into account whether the subject is clinically deteriorating and unlikely to receive further benefit from continued treatment. All decisions to continue treatment beyond progression should be discussed with the sponsor-investigator and documented in the study records.

Subjects should discontinue study therapy upon evidence of further progression, defined as an additional 10% or greater increase in tumor burden volume from time of initial progression (including all target lesions and new measurable lesions).

New lesions are considered measurable at the time of progression if the longest diameter is at least 10 mm (except for pathological lymph nodes, which must have a short axis of at least 15 mm). Any new lesion considered non-measurable at the time of initial progression may become measurable and therefore included in the tumor burden measurement if the longest diameter increases to at least 10 mm (except for pathological lymph nodes, which must have an increase in short axis to at least 15 mm).

5.7 Criteria for Taking a Participant off Protocol Therapy

Duration of therapy will depend on individual response, evidence of disease progression and tolerance. In the absence of treatment delays due to adverse event(s), treatment may continue until one of the following criteria applies:

- Disease progression.
- Intercurrent illness that prevents further administration of treatment.
- Unacceptable AE(s) requiring discontinuation of both agents.
- Participant demonstrates an inability or unwillingness to comply with the oral medication regimen and/or documentation requirements.

- Participant decides to withdraw from the protocol therapy.
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the judgment of the treating investigator.
- Pregnancy.

Participants will be removed from the protocol therapy when any of these criteria apply but continue to be followed according to protocol. The reason for removal from protocol therapy, and the date the participant was removed, must be documented in the eCRF. Alternative care options will be discussed with the participant.

Participants will be permitted to continue study treatment with atezolizumab and bevacizumab after RECIST v1.1 criteria for investigator-assessed progressive disease are met, at the discretion of the investigator, if they meet all of the following criteria:

- Evidence of clinical benefit as assessed by the investigator
- Absence of symptoms and signs (including worsening of laboratory values [e.g., new or worsening hypercalcemia]) indicating unequivocal progression of disease
- No decline in KPS
- Absence of tumor progression at critical anatomical sites (e.g., leptomeningeal disease) that cannot be readily managed and stabilized by protocol-allowed medical interventions prior to repeat dosing
- Patients must provide written consent to acknowledge deferring any standard treatment options that may exist in favor of continuing atezolizumab treatment at the time of initial progression.
- Patients who demonstrate confirmed radiographic disease progression may be considered for continued study treatment at the discretion of the investigator, provided they continue to meet all the criteria above.

An ODQ Treatment Ended/Off Study Form will be filled out when a participant is removed from protocol therapy. This form can be found on the ODQ website or obtained from the ODQ registration staff.

In the event of unusual or life-threatening complications, treating investigators must immediately notify the Overall PI.

5.8 Duration of Follow Up

Patients will be followed for safety for 90 days following the last dose of study treatment or until receipt of another anticancer therapy, whichever comes first. Patients who have an ongoing study treatment-related AE upon study completion or at discontinuation from the study will be followed until the event has resolved to baseline grade, the event is assessed by the investigator as stable, new anticancer treatment is initiated, the patient is lost to follow-up, the patient withdraws consent, or until it has been determined that study treatment or participation is not the

cause of the AE.

After progression/treatment discontinuation, participants will be followed for survival and receipt of next line therapies every 6 months until death or 2 years after treatment discontinuation Follow-up will be via phone calls and through review of medical records.

5.9 Criteria for Taking a Participant off Study

Participants will be removed from study when any of the following criteria apply:

- Lost to follow-up
- Withdrawal of consent for data submission
- Death

The reason for taking a participant off study, and the date the participant was removed, must be documented in the eCRF.

An ODQ Treatment Ended/Off Study Form will be filled out when a participant comes off study. This form can be found on the ODQ website or obtained from the ODQ registration staff.

5.10 Replacement

A subject who discontinues study participation prematurely for any reason is defined as a "dropout" if the subject has already been assigned to treatment or administered at least one dose of the study drug. Subjects who have dropped out but have not received at least one dose of treatment will be replaced. Subjects that have not received at least one dose of treatment will not be included in data analysis and thus will not require data entry.

5.11 Study and Site Discontinuation

The PI 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 patients.
- Patient enrollment is unsatisfactory.

The PI will notify the investigators if the PI decides to discontinue the study.
The PI has the right to close a site at any time. Reasons for closing a site may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Conference on Harmonisation (ICH) guideline for Good Clinical Practice (GCP)
- No study activity (i.e., all patients have completed and all obligations have been fulfilled)

6. DOSING DELAYS/DOSE MODIFICATIONS

Measures will be taken to ensure the safety of patients participating in this trial, including the use of stringent inclusion and exclusion criteria and close monitoring. Eligibility criteria were selected to guard the safety of patients in this trial. Safety will be evaluated in this study through the monitoring of all serious and non-serious AEs, defined and graded according to NCI CTCAE v4.0. Patients will be assessed for safety (including laboratory values). General safety assessments will include serial interval histories, physical examinations, and specific laboratory studies, including serum chemistries and blood counts all serious adverse events (SAEs) and protocol-defined events of special interest will be reported in an expedited fashion. In addition, the investigators will review and evaluate observed AEs on a regular basis.

There will be no dose reductions for either atezolizumab or bevacizumab on this study however dose delays will be permitted as detailed below for each agent. The descriptions and grading scales found in the revised NCI CTCAE version 4.0 will be utilized for dose delays. A copy of the CTCAE version 4.0 can be downloaded from the Cancer Therapy Evaluation Program (CTEP) website [redacted]

6.1 Atezolizumab Dose Modifications

There will be no dose reduction for atezolizumab in this study. Patients may temporarily suspend study treatment for up to 42 days beyond the scheduled date of delayed infusion if study drug-related toxicity requiring dose suspension is experienced. The decision to temporarily suspend treatment beyond 42 days will be based on a discussion between the treating investigator and Sponsor-Investigator. If atezolizumab is held because of AEs for >42 days beyond the scheduled date of infusion, the patient will be discontinued from atezolizumab and will be followed for safety and efficacy as previously defined in Section 5.7. If, in judgment of the treating investigator, the patient is likely to derive clinical benefit from resuming atezolizumab after >42 days, the study drug may be restarted with the approval of the Sponsor-Investigator.

If a patient must be tapered off steroids used to treat AEs, atezolizumab may be held for additional time beyond 42 days from the scheduled dose until steroids are discontinued or reduced to a prednisone dose (or dose equivalent) of ≤10 mg/day. The acceptable length of interruption will be at the discretion of the investigator.

Dose interruptions for reasons other than toxicity, such as surgical procedures, may be allowed. The acceptable length of interruption will be at the discretion of the Sponsor.

Any toxicities associated or possibly associated with atezolizumab treatment should be managed according to standard medical practice. Additional tests, such as autoimmune serology or biopsies, may be used to determine a possible immunogenic etiology. Although most irAEs observed with immunomodulatory agents have been mild and self limiting, such events should be recognized early and treated promptly to avoid potential major complications. Discontinuation of atezolizumab may not have an immediate therapeutic effect, and there is no available antidote for atezolizumab. In severe cases, immune related toxicities may be acutely

managed with topical corticosteroids, systemic corticosteroids, mycophenolate, or TNF-α inhibitors.

Patients should be assessed clinically (including review of laboratory values) for toxicity prior to, during, and after each infusion. If unmanageable toxicity due to atezolizumab occurs at any time during the study, treatment with atezolizumab should be discontinued.

Management of hepatitis/transaminitis, colitis, rash, and hypothyroidism are presented in this section as they have been observed in this study and are potentially immune related.

Toxicities associated or possibly associated with atezolizumab treatment should be managed according to standard medical practice.

6.1.1 Immune-Related Adverse Event (irAEs)

Although most irAEs observed with immunomodulatory agents have been mild and self-limiting, such events should be recognized early and treated promptly to avoid potential major complications. Discontinuation of atezolizumab may not have an immediate therapeutic effect, and there is no available antidote for atezolizumab. In severe cases, immune-related toxicities may be acutely managed with topical corticosteroids, systemic corticosteroids, mycophenolate, or TNF-α inhibitors.

The primary approach to Grade 1 to 2 irAEs is supportive and symptomatic care with continued treatment with atezolizumab; for higher-grade irAEs, atezolizumab should be withheld and oral and/or parenteral steroids administered. Recurrent Grade 2 irAEs may also mandate withholding atezolizumab or the use of steroids. Assessment of the benefit risk balance should be made by the investigator, with consideration of the totality of information as it pertains to the nature of the toxicity and the degree of clinical benefit a given patient may be experiencing prior to further administration of atezolizumab. Atezolizumab should be permanently discontinued in patients with life threatening irAEs.

6.1.2 Gastrointestinal Toxicity

Immune-mediated colitis has been associated with the administration of atezolizumab.

Patients should be advised to inform the investigator if any diarrhea occurs, even if it is mild.

If the event is of significant duration or magnitude, or is associated with signs of systemic inflammation or acute phase reactants (e.g., increased c-reactive protein or platelet count or bandemia), it is recommended that sigmoidoscopy (or colonoscopy, if appropriate) with colonic biopsy with three to five specimens for standard paraffin block be performed. If possible, one or two biopsy specimens should be snap frozen and stored.

Treatment may be restarted following the resolution of colitis. In addition, if the patient is being managed with corticosteroids, treatment should not be restarted until the steroids have been tapered down to a prednisone dose ≤10 mg/day. Patients who resume treatment should be monitored closely for signs of renewed diarrhea. Table 1 provides a summary of dose modification guidelines for GI toxicities.

Table 1. Dose Modification Guidelines for Gastrointestinal Toxicity

Toxicity	Description	Management
Diarrhea	Grade 2 (4-6 stools per day over baseline) < 5 days	Hold atezolizumab and discontinue NSAIDS (or other medications known to exacerbate colitis). Investigate for etiology. Restart atezolizumab once at baseline stool frequency.
	Grade 2(4-6 stools per day over baseline) > 5 days	Hold atezolizumab and discontinue NSAIDS (or other medications known to exacerbate colitis) while etiology is being investigated. Consider referral to a gastroenterologist. Administer anti-diarrheal agent (e.g., Imodium®). Consider oral budesonide, mesalamine, or 10 mg oral prednisone equivalent per day. Restart atezolizumab once at baseline stool frequency.
	Abdominal pain Blood or mucus in stool OR Grade ≥3 (≥7 stools/day over baseline) with peritoneal signs, ileus, or fever	Hold atezolizumab and discontinue NSAIDS (or other medications known to exacerbate colitis). Rule out bowel perforation. Consider administering prednisone 60 mg/day or equivalent. Taper steroids over 1 month. Restart atezolizumab if diarrhea is resolved and systemic steroid dose is ≤ 10 mg oral prednisone equivalent per day. Permanently discontinue atezolizumab for life-threatening, immune-related diarrhea or colitis.

NSAID = nonsteroidal anti-inflammatory drug.

6.1.3 Hepatotoxicity

Immune-mediated hepatitis has been associated with the administration of atezolizumab.

While in this study, patients presenting with right upper-quadrant abdominal pain and/or unexplained nausea or vomiting should have LFTs performed immediately, and LFTs should be reviewed before administration of the next dose of study drug.

If LFTs increase, neoplastic, concurrent medications, viral hepatitis, and toxic etiologies should be considered and addressed, as appropriate. Imaging of the liver, gall bladder, and biliary tree should be performed to rule out neoplastic or other causes of increased LFTs. Anti nuclear antibody, perinuclear anti-neutrophil cytoplasmic antibody, anti-liver kidney microsomal, and anti-smooth muscle antibody tests should be performed if an autoimmune etiology is considered. Patients with LFT abnormalities should be managed according to the guidelines in Table 2.

Table 2. Dose Modification Guidelines for Hepatoxicity

Toxicity	Description	Management
LFT abnormalities	AST/ALT (> ULN to 3 × ULN) with total bilirubin < 2 × ULN	Continue with the standard monitoring plan (e.g., LFTs every 3 weeks before dosing).
	AST/ALT (> 3 × ULN to < 10 × ULN) with total bilirubin < 2 × ULN	Continue atezolizumab. Monitor LFTs at least weekly. Consider referral to a hepatologist.
	AST/ALT > 10 × ULN	Hold atezolizumab. Consider administering IV steroids for 24-48 hours (prednisone 60 mg/day equivalent) followed by an oral prednisone (or equivalent) taper over 2-4 weeks. If LFT results do not decrease within 48 hours after initiation of systemic steroids, addition of an alternative immunosuppressive agent (e.g., mycophenolate or TNF-α antagonist) to the corticosteroid regimen may be considered. Monitor LFTs every 48-72 hours until decreasing and then follow weekly. Restart atezolizumab if

		AST/ALT ≤3 x ULN with bilirubin <2 x ULN and steroid dose is ≤10 mg oral prednisone equivalent per day. Permanently discontinue atezolizumab for life-threatening, immune-related hepatic events.
	AST/ALT ≥ 3 × ULN with bilirubin > 2 × ULN	Hold atezolizumab. Consult a hepatologist. Consider administering IV steroids for 24-48 hours (prednisone 60 mg/day equivalent) followed by oral taper over 1 month. If LFTs results do not decrease within 48 hours after initiation of systemic steroids, addition of an alternative immunosuppressive agent (e.g., mycophenolate or TNFα antagonist) to the corticosteroid regimen may be considered. Monitor LFTs every 48-72 hours until decreasing and then follow weekly. Restart atezolizumab if AST/ALT ≤ 3 x ULN with bilirubin < 2 x ULN and steroid dose is ≤10 mg oral prednisone equivalent per day.

IV = intravenous; LFT = liver function test; TNF-α = tumor necrosis factor alpha; ULN = upper limit of normal.

6.1.4 Dermatologic Toxicity

Treatment-emergent rash has been associated with atezolizumab. The majority of cases of rash were mild in severity and self-limited, with or without pruritus.

A dermatologist should evaluate persistent and/or severe rash or pruritus. A biopsy should be performed unless contraindicated. Low-grade rash and pruritus irAEs have been treated with symptomatic therapy (e.g., antihistamines). Topical or parenteral corticosteroids may be required for more severe symptoms.

Dermatologic toxicity and rash should be managed according to the guidelines in Table 3.

Table 3. Dose Modification Guidelines for Dermatologic Toxicity

Toxicity	Description	Management
Dermatologic toxicity/rash (e.g., maculopapular or purpura)	Grade 1: Mild < 10% BSA	Continue atezolizumab symptomatic therapy with antihistamine PRN. Consider topical steroids and/or other symptomatic therapy (e.g., antihistamines).
	Grade 2: Moderate 10%–30% BSA	Continue atezolizumab. Consider dermatologist referral. Administer topical steroids. Consider higher potency topical steroids if rash is unresolved.
	Grade 3: Severe >30% BSA	Hold atezolizumab. Consult dermatologist. Administer oral prednisone 10 mg or equivalent. If the rash is unresolved after 48-72 hours, administer oral prednisone 60 mg or equivalent. Restart MPDL3280A if rash is resolved and systemic dose is ≤10 mg oral prednisone equivalent per day. Permanently discontinue atezolizumab for life-threatening, immune-related dermatologic toxicity.

BSA = body surface area; PRN = as needed.

6.1.5 Endocrine Toxicity

Hypothyroidism has been associated with the administration of atezolizumab.

Patients with unexplained symptoms such as fatigue, myalgias, impotence, mental status changes, or constipation should be investigated for the presence of thyroid, pituitary, or adrenal endocrinopathies, as well as for hyponatremia or hyperkalemia. An endocrinologist should be consulted if an endocrinopathy is suspected. Thyroid stimulating hormone (TSH) and free T4 levels should be obtained to determine whether thyroid abnormalities are present. TSH, prolactin, and a morning cortisol level will help to differentiate primary adrenal insufficiency

from primary pituitary insufficiency.

Hypothyroidism should be managed according to the guidelines in Table 4.

Table 4. Dose Modification Guidelines for Endocrine Toxicity

Toxicity	Description	Management
Hypothyroidism	TSH <10, asymptomatic	Continue atezolizumab. Monitor according to Sponsor-Investigator discretion.
	TSH >10, asymptomatic	Continue atezolizumab. Start thyroid-replacement hormone. Monitor according to Sponsor-Investigator discretion.
	TSH >10, symptomatic	Hold atezolizumab. Consider referral to an endocrinologist. Restart atezolizumab when symptoms are controlled by thyroid replacement and TSH levels are decreasing. Monitor according to Sponsor-Investigator discretion.

6.1.6 Pulmonary Toxicity

Dyspnea, cough, fatigue, hypoxia, pneumonitis, and pulmonary infiltrates have been associated with the administration of atezolizumab and have primarily been observed in patients with underlying NSCLC.

Mild-to-moderate events of pneumonitis have been reported with atezolizumab. All pulmonary events should be thoroughly evaluated for other commonly reported etiologies such as pneumonia/infection, lymphangitic carcinomatosis, pulmonary embolism, heart failure, chronic obstructive pulmonary disease (COPD), or pulmonary hypertension and the following should be performed:

- Measurement of oxygen saturation (i.e., arterial blood gas)
- High-resolution CT scan of the chest
- Bronchoscopy with bronchoalveolar lavage and biopsy
- Pulmonary function tests (with diffusion capacity of the lung for carbon monoxide [DLCO])

Patients will be assessed for pulmonary signs and symptoms throughout the study. Patients will also have CT scans of the chest at every tumor assessment.

Pulmonary toxicity should be managed according to the guidelines in Table 5.

Table 5. Dose Modification Guidelines for Pulmonary Toxicity

Toxicity	Description	Management
Pulmonary Toxicity	GGO or non-infectious infiltrate in absence of hypoxia, or dyspnea	Hold treatment with atezolizumab. Re-evaluate after 1 week. If no worsening in GGO/infiltrates and patient still asymptomatic, resume treatment with atezolizumab. If GGO/infiltrates worsen and patient is still asymptomatic, continue to hold atezolizumab and refer for bronchoscopy. Consider starting low-dose oral prednisone 10 mg or equivalent. Re-evaluate after 1 week. Resume atezolizumab if GGO/infiltrates improving.
	Hypoxia or dyspnea in presence of GGO or infiltrate without alternative etiology	Hold atezolizumab. Consult a pulmonologist. Investigate for other etiologies and consider bronchoscopy. If bronchoscopy is consistent with immune-related etiology, start 60 mg prednisone equivalent per day followed by taper over 2 weeks. Restart atezolizumab if symptomatically improved, infiltrates are resolved, and steroid use is ≤10 mg prednisone equivalent per day. Permanently discontinue atezolizumab for life-threatening, immune-related pulmonary events.

GGO = ground glass opacities.

6.1.7 Pancreatic Toxicity

Symptoms of abdominal pain associated with elevations of amylase and lipase, suggestive of pancreatitis, have been associated with administration of other immunomodulatory agents. The differential diagnosis of acute abdominal pain should include pancreatitis. Appropriate workup should include an evaluation for obstruction, as well as serum amylase and lipase tests.

6.1.8 Eye Toxicity

An ophthalmologist should evaluate visual complaints. Uveitis or episcleritis may be treated with topical corticosteroid eye drops. Atezolizumab should be permanently discontinued for immune-mediated ocular disease that is unresponsive to local immunosuppressive therapy.

Ocular toxicity should be managed according to the guidelines in Table 6.

Table 6. Dose Modification Guidelines for Eye Toxicity

Toxicity	Description	Management
Eye toxicity (autoimmune uveitis, iritis, or episcleritis)	Symptomatic	Hold atezolizumab. Consult ophthalmologist and start topical corticosteroid eye drops. Atezolizumab may be restarted following resolution of the events. Permanently discontinue atezolizumab for immune-mediated ocular disease that is unresponsive to local immunosuppressive therapy.

6.2 Bevacizumab Dose Modifications

Bevacizumab dose will not be reduced for reasons other than a >5% change in weight from baseline. Bevacizumab treatment may be either temporarily or permanently suspended in the case of bevacizumab-related events such as fistulae, GI perforation, hypertension, proteinuria, thrombosis/embolism, hemorrhage, CHF, wound healing complications, PRES and hypersensitivity/allergic reactions in addition to any other serious bevacizumab-related toxicity (grade 3 or 4). If bevacizumab is held because of related adverse events for >42 days beyond when the next dose would have been given, then the patient will be discontinued from bevacizumab and be followed for safety according to Section 5.7. If, in judgment of the treating investigator, the patient is likely to derive clinical benefit from resuming bevacizumab after >42 days, the study drug may be restarted with the approval of the Sponsor-Investigator.

In addition, bevacizumab should be temporarily withheld in the event of febrile grade 4 neutropenia and/or grade 4 thrombocytopenia (regardless of the relationship to treatment), since

these conditions are predisposing factors for an increased bleeding tendency.

To summarize, bevacizumab should be held temporarily or permanently discontinued in patients (as per the clinical judgment of the treating physician) experiencing any of the following events:

- Febrile grade 4 neutropenia and/or grade 4 thrombocytopenia regardless of the relationship to treatment (hold treatment temporarily)
- Grade ≥2 fistula (hold temporarily or permanently discontinue)
- GI perforation (permanently discontinue)
- Major surgery or wound healing complications (hold temporarily or permanently discontinue)
- Medically significant hypertension not controlled with antihypertensive therapy, hypertensive crisis or hypertensive encephalopathy (permanently discontinue)
- Grade ≥3 left ventricular dysfunction (CHF) (permanently discontinue)
- Nephrotic syndrome (permanently discontinue)
- Arterial thrombosis/embolism (any grade) (permanently discontinue)
- Grade ≥3 venous thrombosis/embolism (hold temporarily or permanently discontinue for grade 4)
- CNS bleeding (any grade) or ≥grade 3 bleeding of any kind (permanently discontinue)
- Grade ≥2 hemoptysis (hold temporarily or permanently discontinue)
- Hypersensitivity/allergic reactions related to bevacizumab (permanently discontinue)
- PRES (permanently discontinue)

6.2.1 Posterior Reversible Encephalopathy Syndrome (PRES)

There have been rare reports of patients treated with bevacizumab developing signs and symptoms that are consistent with PRES, a rare neurological disorder. PRES is also known as reversible posterior leukoencephalopathy syndrome or RPLS. PRES can present with following signs and symptoms among others: seizures, headache, altered mental status, visual disturbance or cortical blindness, with or without associated hypertension. A diagnosis of PRES requires confirmation by brain imaging. In patients developing PRES, treatment of specific symptoms including control of hypertension is recommended along with discontinuation of bevacizumab. The safety of reinitiating bevacizumab therapy in patients previously experiencing PRES is not known. Adequate brain imaging using MRI must be performed as a follow-up measurement for patients with PRES.

6.2.2 Gastrointestinal Perforation and Fistula

Bevacizumab has been associated with serious cases of gastrointestinal perforation in patients with metastatic colorectal cancer and a few reports of gallbladder perforation have been reported from the post-marketing experience. The presentation of these events has varied in type and severity, ranging from free air seen only on the plain abdominal X-ray, which resolved without treatment, to a colonic perforation with abdominal abscess and fatal outcome. The common feature among these cases was intra abdominal inflammation, either from gastric ulcer disease, tumor necrosis, diverticulitis or chemotherapy-associated colitis. Nevertheless, a causal association of an intra-abdominal inflammatory process and GI perforation to treatment with bevacizumab has not been established. However, caution should be exercised when treating patients with intra-abdominal inflammatory process with bevacizumab.

Bevacizumab should be permanently discontinued in patients who develop GI perforation.

Bevacizumab use has been associated with serious cases of fistulae including events resulting in death. Fistulae within the GI tract or GI tract and skin are common in patients with metastatic colorectal cancer and ovarian cancer, but are uncommon or rare in other indications. Other fistulae (e.g. tracheoesophageal, bronchopleural, urogenital, biliary) have been reported uncommonly in bevacizumab clinical trials patients and in post-marketing reports.

Temporarily discontinue bevacizumab in patients with grade 2 or 3 non- tracheoesophageal fistula until resolution to ≤ grade 1.

Permanently discontinue bevacizumab in patients with tracheoesophageal fistula or any grade 4 fistula. Limited information is available on the continued use of bevacizumab in patients with other fistulae. In cases of internal fistula not arising in the GI tract, discontinuation of bevacizumab should be considered.

6.2.3 Wound Healing Complications

Increased incidences of post-operative bleeding or wound healing complications have been observed in clinical trials of bevacizumab in relapsed glioma and metastatic colorectal and breast cancer.

Bevacizumab therapy should not be initiated for at least 28 days following major surgery or until the surgical wound is fully healed as bevacizumab may adversely impact wound healing.

In patients who experience wound healing complications during bevacizumab treatment, bevacizumab should be withheld until the wound is fully healed. If the wound does not fully heal despite withholding treatment, should be permanently discontinued.

Bevacizumab therapy should be withheld for an interval of at least two half-lives (approximately six weeks) before conducting major elective surgery. Emergency surgery should be performed as appropriate without delay after a careful risk-benefit assessment.

6.2.4 Hypertension

An increased incidence of hypertension has been observed in patients treated with bevacizumab. Clinical safety data suggest the incidence of hypertension is likely to be dose-dependent.

Pre-existing hypertension should be adequately controlled before starting bevacizumab treatment. There is no information on the effect of bevacizumab in patients with uncontrolled hypertension at the time of initiating therapy.

Blood pressure must be assessed before each bevacizumab administration.

In most cases hypertension is controlled adequately using standard antihypertensive treatment appropriate for the individual situation of the affected patient. Bevacizumab should be permanently discontinued if medically significant hypertension cannot be adequately controlled

with antihypertensive therapy, or if the patient develops hypertensive crisis or hypertensive encephalopathy.

6.2.5 Congestive Heart Failure (CHF)

Events consistent with CHF were reported in clinical trials. The findings ranged from asymptomatic declines in left ventricular ejection fraction to symptomatic CHF, requiring treatment or hospitalization. Most of the patients who experienced CHF had metastatic breast cancer and had received previous treatment with anthracyclines, prior radiotherapy to the left chest wall or other risk factors for CHF were present.

Caution should be exercised when treating patients with clinically significant cardiovascular disease such as pre-existing coronary artery disease, concomitant cardiotoxic therapy or CHF with bevacizumab.
Bevacizumab should be permanently discontinued in patients with ≥ grade 3 CHF.

6.2.6 Proteinuria

In clinical studies, the incidence of proteinuria was higher in patients receiving bevacizumab in combination with chemotherapy compared to those who received chemotherapy alone. Proteinuria reported as an AE with bevacizumab treatment has ranged in severity from clinically asymptomatic, transient, trace proteinuria to nephrotic syndrome with the great majority as grade 1 proteinuria. The proteinuria seen in bevacizumab clinical trials was not associated with renal dysfunction and rarely required permanent discontinuation of bevacizumab therapy. Patients with a history of hypertension may be at increased risk for the development of proteinuria when treated with bevacizumab.

Proteinuria must be assessed by dipstick before each bevacizumab administration unless proteinuria has been determined by 24-hour urine collection.

Table 7. Bevacizumab Treatment Management for Proteinuria.

Grade	Urinalysis	Treatment Actions
Grade 1	1+ proteinuria OR urinary protein < 1.0 g/24 hrs	No bevacizumab dose modification
Grade 2	2+ proteinuria OR urinary protein 1.0-3.4 g/24 hrs	For 2+ dipstick: may administer bevacizumab without dose modification and collect 24-hour urine prior to subsequent bevacizumab administration. For 3+ dipstick: must obtain 24-hour urine prior to administering bevacizumab Suspend bevacizumab for urinary protein ≥2 g/24 hrs. Resume bevacizumab when proteinuria is < 2 g/24 hrs.
Grade 3	urinary protein ≥3.5 g/24 hrs	Suspend bevacizumab.

		Resume bevacizumab when proteinuria is < 2 g/24 hrs.
Nephrotic syndrome		Permanently discontinue bevacizumab.

6.2.7 Arterial thrombosis/embolism

Bevacizumab should be discontinued in patients who develop arterial thromboembolic events. A history of arterial thromboembolic events or age greater than 65 years has been associated with an increased risk of arterial thromboembolic events during bevacizumab therapy. Patients receiving bevacizumab plus chemotherapy with a history of arterial thromboembolism and age greater than 65 years have a higher risk. Caution should be taken when treating these patients with bevacizumab.

6.2.8 Venous thrombosis/embolism

Bevacizumab should be held in patients developing a grade 3 thrombosis/embolism. Bevacizumab may be resumed once the patient is adequately anti-coagulated and on a stable level of anticoagulation for at least 2 weeks prior to restarting study drug treatment. Patients on full dose low molecular weight heparins should receive the appropriate dose based on the weight of the patient according to package insert.

An increased risk of venous thromboembolic events and bleeding in patients receiving anti-coagulation therapy after first venous thromboembolic event while receiving bevacizumab has been observed.

In the event of recurrent grade 3 thrombosis/embolism, the patient should be discontinued from bevacizumab.

Bevacizumab should be discontinued in patients with life-threatening (grade 4) pulmonary embolism.

6.2.9 Hemorrhage

An increased incidence of bleeding events was observed in study patients treated with bevacizumab as compared to control treatment arms. The hemorrhagic events observed in bevacizumab studies were predominantly tumor-associated hemorrhage and minor mucocutaneous hemorrhage.

Patients with untreated CNS metastases were routinely excluded from clinical trials with bevacizumab, based on imaging procedures or signs and symptoms. Therefore, the risk of CNS hemorrhage in such patient has not been prospectively evaluated in randomized clinical studies.

Bevacizumab should be permanently discontinued for:

- Grade 3 or 4 bleeding of any kind.
- Any grade of CNS bleeding. Patients should be monitored for signs and symptoms of CNS bleeding.

Bevacizumab should be temporarily held or permanently discontinued for grade ≥ 2 haemoptysis

(defined as ≥ 2.5 mL bright red blood per episode). The safety of re-initiating bevacizumab in patients previously experiencing grade ≥ 2 haemoptysis has not been evaluated.

If hemorrhagic complications occur in patients on full dose anti-coagulation therapy, permanently discontinue bevacizumab treatment and follow guidelines of the treating institution. Standard procedures such as antagonisation with protamin or vitamin K and infusion of vitamin K dependent factors should be considered dependent on the severity of the bleeding.

6.2.10 Hypersensitivity/Allergic Reactions and Infusion-Associated Reactions

Bevacizumab should be permanently discontinued in patients exhibiting hypersensitivity/allergic reactions.

The NCI CTCAE distinguishes between hypersensitivity reactions and acute infusion reactions induced by cytokine release. Despite the different possible mechanisms underlying hypersensitivity and infusion reactions, the clinical signs and symptoms associated with these reactions overlap.

Patients may be at risk of developing infusion reactions to bevacizumab. Close observation of the patient during and following the administration of bevacizumab is recommended as expected for any infusion of a therapeutic humanized monoclonal antibody. If an infusion reaction occurs, the infusion should be discontinued and appropriate medical therapies should be administered. A systematic premedication is not warranted.

6.2.11 Osteonecrosis of the Jaw

Osteonecrosis of the jaw was reported in patients receiving bevacizumab mainly in combination with bisphosphonates in the post-marketing setting. The pathogenesis of the osteonecrosis is unclear. For further information, please refer to the bevacizumab Investigator's Brochure.

6.2.12 Ovarian Failure

Ovarian failure has been reported more frequently in patients receiving bevacizumab. Ovarian function recovered in the majority of women after bevacizumab discontinuation. For further information, please refer to the bevacizumab Investigator's Brochure.

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Safety assessments will consist of monitoring and reporting adverse events (AEs) and serious adverse events (SAEs) per protocol. This includes all events of death, and any study specific issue of concern. AE monitoring and reporting is a routine part of every clinical trial. Adverse events associated with atezolizumab and bevacizumab are detailed in Section 2.

7.1 Adverse Events

An AE is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product (IMP) or other protocol imposed intervention, regardless of attribution.
This includes the following:

- AEs not previously observed in the patient that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with Advanced Non-Clear Cell Renal Cell Carcinoma that were not present prior to the AE reporting period
- Complications that occur as a result of protocol-mandated interventions (e.g., invasive procedures such as cardiac catheterizations)
- If applicable, AEs that occur prior to assignment of study treatment associated with medication washout, no treatment run-in, or other protocol-mandated intervention
- Pre-existing medical conditions (other than the condition being studied) judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period

7.2 Serious Adverse Event

An AE should be classified as an SAE if the following criteria are met:

- It results in death (i.e., the AE actually causes or leads to death)
- It is life threatening (i.e., the AE, in the view of the investigator, places the patient at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.)
- It requires or prolongs inpatient hospitalization
- It results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the patient's ability to conduct normal life functions)
- It results in a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the IMP
- It is considered a significant medical event by the investigator based on medical judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

7.3 Methods and Timing for Assessing and Recording Safety Variables

The investigator is responsible for ensuring that all AEs and SAEs that are observed or reported during the study are collected and reported to the U.S. Food and Drug Administration (FDA), appropriate Institutional Review Boards (IRBs), and Genentech, Inc., in accordance with CFR 312.32 (Investigational New Drug [IND] Safety Reports).

7.3.1 Adverse Event Reporting Period

The study period during which all AEs and SAEs must be reported begins after informed consent is obtained and initiation of study treatment and ends 30 days following the last administration of study treatment or study discontinuation/termination, whichever is earlier. After this period, investigators should only report SAEs that are attributed to prior study treatment.

7.3.2 Assessment of Adverse Events

All AEs and SAEs, whether volunteered by the patient, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means, will be reported appropriately. Each reported AE or SAE will be described by its duration (i.e., start and end dates), regulatory seriousness criteria if applicable, suspected relationship to the study drug (see following guidance), and actions taken.

To ensure consistency of AE and SAE causality assessments, investigators should apply the following general guideline:

- Yes: There is a plausible temporal relationship between the onset of the AE and administration of atezolizumab or bevacizumab, and the AE cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies; and/or the AE follows a known pattern of response to atezolizumab or bevacizumab or with similar treatments; and/or the AE abates or resolves upon discontinuation of atezolizumab or bevacizumab or dose reduction and, if applicable, reappears upon re-challenge.
- No: Evidence exists that the AE has an etiology other than atezolizumab or bevacizumab (e.g., pre existing medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the AE has no plausible temporal relationship to atezolizumab or bevacizumab administration (e.g., cancer diagnosed 2 days after first dose of study drug).

Expected AEs are those AEs that are listed or characterized in the Package Insert (PI) or current Investigator's Brochure.

Unexpected AEs are those not listed in the PI or current Investigator's Brochure or not identified. This includes AEs for which the specificity or severity is not consistent with the description in the PI or Investigator's Brochure. For example, under this definition, hepatic necrosis would be unexpected if the PI or Investigator's Brochure only referred to elevated hepatic enzymes or hepatitis.

For patients receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

7.4 Procedures for Eliciting, Recording, and Reporting Adverse Events

Eliciting Adverse Events
A consistent methodology 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 clinical visit?"
- "Have you had any new or changed health problems since you were last here?"

Specific Instructions for Recording Adverse Events
Investigators should use correct medical terminology/concepts when reporting AEs or SAEs. Avoid colloquialisms and abbreviations.

7.4.1 Diagnosis versus Signs and Symptoms

If known at the time of reporting, a diagnosis should be reported 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, it is acceptable to report the information that is currently available. If a diagnosis is subsequently established, it should be reported as follow-up information.

7.4.2 Deaths

All deaths that occur during the protocol-specified AE reporting period, regardless of attribution, will be reported to the appropriate parties. When recording a death, the event or condition that caused or contributed to the fatal outcome should be reported as the single medical concept. If the cause of death is unknown and cannot be ascertained at the time of reporting, report "Unexplained Death."

7.4.3 Pre-existing Medical Conditions

A pre-existing medical condition is one that is present at the start of the study. Such conditions should be reported as medical and surgical history. A pre-existing medical condition should be re-assessed throughout the trial and reported as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When reporting such events, it is important to convey the concept that the pre existing condition has changed by including applicable descriptors (e.g., "more frequent headaches").

7.4.4 Hospitalizations for Medical or Surgical Procedures

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE. If a patient is hospitalized to undergo a medical or surgical procedure as a result of an AE, the event responsible for the procedure, not the procedure itself, should be reported as the SAE. For example, if a patient is hospitalized to undergo coronary bypass surgery, record the heart condition that necessitated the bypass as the SAE.
Hospitalizations for the following reasons do not require reporting:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for pre-existing conditions,
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study, or
- Hospitalization or prolonged hospitalization for scheduled therapy of the target disease of the study.

7.4.5 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE (V4.0 Update current versions) will be used for assessing adverse event severity. Below Table should be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living [a]
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living [b,c]
4	Life-threatening consequences or urgent intervention indicated d
5	Death related to adverse event [d]

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.
Note: Based on the most recent version of NCI CTCAE (v4.0), which can be found at: [redacted]

a. Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
b. Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by patients who are not bedridden.
c. If an event is assessed as a "significant medical event," it must be reported as a serious adverse event
d. Grade 4 and 5 events must be reported as serious adverse events

7.4.6 Pregnancies

If a female subject or female partner of the male study subject becomes pregnant while receiving the study drug or within 6 months after the last dose of study drugs,a report should be completed and expeditiously submitted to Genentech, Inc. Follow-up to obtain the outcome of the pregnancy should also occur. Abortion, whether accidental, therapeutic, or spontaneous, should always be classified as serious, and expeditiously reported as an SAE. Similarly, any congenital anomaly/birth defect in a child born to a female subject exposed to the atezolizumab and/or bevacizumab should be reported as an SAE.

7.4.7 Case Transmission Verification of Single Case Reports / Reconciliation

The Sponsor-Investigator agrees to conduct reconciliation for the product(s) to ensure that all single case reports have been adequately received by Genentech via sponsor emailing Genentech a Quarterly line-listing documenting single case reports sent by Sponsor to Genentech in the preceding time period. Genentech and the Sponsor will agree to the reconciliation periodicity and format, but agree at minimum to exchange quarterly line listings of cases received by the other party. The periodic line-listing will be exchanged within seven (7) calendar days of the end of the agreed time period. Confirmation of receipt should be received within the time period mutually agreed upon.

If discrepancies are identified, the Sponsor and Genentech will cooperate in resolving the discrepancies. The responsible individuals for each party shall handle the matter on a case-by-case basis until satisfactory resolution. The sponsor shall receive reconciliation guidance documents within the 'Activation Package'.

Following reconciliation, sponsor-investigator shall forward single case reports, which have not been received by Genentech, to Genentech within five (5) calendar days from request by Genentech.

At the end of the study, a final cumulative reconciliation (Case Transmission Verification) report will be sent to Genentech.

7.4.8 Post-Study Adverse Events

The investigator should expeditiously report any SAE occurring after a patient has completed or discontinued study participation if attributed to prior atezolizumab and/or bevacizumab exposure. If the investigator should become aware of the development of cancer or a congenital anomaly in a subsequently conceived offspring of a female patient who participated in the study, this should be reported as an SAE.

7.4.9 Adverse Events of Special Interest

AESIs are a subset of Events to Monitor (EtMs) of scientific and medical concern specific to the product, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor is required. Such an event might require further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the trial Sponsor to other parties (e.g., Regulatory Authorities) may also be warranted.

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law:
    - Treatment-emergent ALT or AST > 3 × ULN in combination with total bilirubin > 2 × ULN
    - Treatment-emergent ALT or AST > 3 × ULN in combination with clinical jaundice

Data related to a suspected transmission of an infectious agent by the study drug (STIAMP), as defined below:

Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected

Atezolizumab specific AESIs:

- Pneumonitis
- Colitis
- Endocrinopathies: diabetes mellitus, pancreatitis, hyperthyroidism, adrenal insufficiency and hypophysitis
- Hepatitis, including AST or ALT > 10 x ULN
- Systemic lupus erythematosus
- Neurological disorders: Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis and meningoencephalitis..
- Events suggestive of hypersensitivity, infusion-related reactions, cytokine release influenza-like illness and systemic inflammatory response syndrome syndrome.
- Nephritis.
- Ocular toxicities (e.g., uveitis, retinitis, optic neuritis).
- Myositis
- Myopathies, including rhabdomyolysis.
- Grade ≥ 2 cardiac disorders (e.g., atrial fibrillation, myocarditis, pericarditis).
- Vasculitis.
- Autoimmune hemolytic anemia.
- Severe cutaneous reactions (e.g., Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis)

Bevacizumab specific AESIs:

- Haemorrhage ≥ grade 3 (any grade CNS bleeding; ≥ grade 2 haemoptysis)
- Hypertension ≥ grade 3
- GI perforation, abscesses and fistulae (any grade)
- Wound healing complication/wound dehiscence ≥ grade 3
- Arterial thromboembolic events (any grade)
- Venous thromboembolic events ≥ grade 3
- Posterior Reversible encephalopathy syndrome (PRES) [or RPLS; any grade]
- Non-GI fistula or abscess ≥ grade 2
- Proteinuria ≥ grade 3
- Congestive heart failure/cardiomyopathy ≥ grade 3

7.4.10 Adverse Event Reporting to Genentech Inc

Investigators will be responsible for collecting all protocol-defined Adverse Events (AEs)/Serious Adverse Events (SAEs), AEs of Special Interest (AESIs), Special Situation Reports (including pregnancy reports) and Product Complaints (with or without an AE) originating from the Study for the Product(s).

Investigators must report all the above-mentioned single case reports adequately to Genentech within the timelines described below. The completed MedWatch forms should be faxed/emailed immediately upon completion to Genentech at the following contacts:

All protocol-defined AEs, SAEs, AESIs, Special Situation Reports (including pregnancy reports) and Product Complaints *with* an AE should be sent to:

[redacted]

All Product Complaints *without* an AE should be sent to:

[redacted]

It is understood and agreed that the Sponsor will be responsible for the evaluation of AEs/SAEs, AESIs, Special Situation Reports (including pregnancy reports) and Product Complaints (with or without an AE) originating from the study.

These single case reports will be exchanged between the parties as outlined below so that regulatory obligations are met.

Serious adverse events (SAEs), AEs of Special Interest (AESIs), pregnancy reports (including pregnancy occurring in the partner of a male study subject), other Special Situation Reports and Product Complaints (with or without an AE), where the patient has been exposed to the Genentech Product, will be sent on a MedWatch form or CIOMS I form or on Genentech approved reporting forms to Genentech Drug Safety. Transmission of these reports (initial and follow-up) will be either electronically or by fax and within the timelines specified below:

Serious Adverse Drug Reactions:

Serious AE reports that are related to the Product shall be transmitted to Genentech within fifteen (15) calendar days of the awareness date.

- **Other SAEs**
  Serious AE reports that are unrelated to the Product shall be transmitted to Genentech within thirty (30) calendar days of the awareness date.

- **AESIs**
  AESIs shall be forwarded to Genentech within fifteen (15) calendar days of the awareness date.

- **Special Situation Reports**
  Pregnancy reports
  While such reports are not serious AEs or Adverse Drug Reactions (ADRs) per se, as defined herein, any reports of pregnancy (including pregnancy occurring in the partner of a male study subject), where the fetus may have been exposed to the Product, shall be transmitted to Genentech within thirty (30) calendar days of the awareness date.

Pregnancies will be followed up until the outcome of the pregnancy is known, whenever possible, based upon due diligence taken to obtain the follow-up information.

Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 30 days after the last dose of study drug. A Clinical Trial Pregnancy Reporting Form should be completed and submitted to Genentech within thirty (30) calendar days of the awareness date.

- **Other Special Situation Reports**

  In addition to all SAEs, pregnancy reports and AESIs, the following other Special Situations Reports should be collected even in the absence of an Adverse Event and transmitted to Genentech within thirty (30) calendar days:
    - Data related to the Product usage during breastfeeding
    - Data related to overdose, abuse, misuse or medication error (including potentially exposed or intercepted medication errors)
    - In addition, reasonable attempts should be made to obtain and submit the age or age group of the patient, in order to be able to identify potential safety signals specific to a particular population
- **Product Complaints**

  All Product Complaints (with or without an AE) shall be forwarded to Genentech within fifteen (15) calendar days of the awareness date.

  A Product Complaint is defined as any written or oral information received from a complainant that alleges deficiencies related to identity, quality, safety, strength, purity, reliability, durability, effectiveness, or performance of a product after it has been released and distributed to the commercial market or clinical trial.

MedWatch 3500A Reporting Guidelines

In addition to completing appropriate patient demographic and suspect medication information, the report should include the following information within the Event Description (Section 5) of the MedWatch 3500A form:

- Protocol description (and number, if assigned)
- Description of event, severity, treatment, and outcome if known
- Supportive laboratory results and diagnostics
- Investigator's assessment of the relationship of the AE to each investigational product and suspect medication

Follow-Up Information

Additional information may be added to a previously submitted report by any of the following methods:

- Adding to the original MedWatch 3500A report and submitting it as follow-up
- Adding supplemental summary information and submitting it as follow-up with the original MedWatch 3500A form
- Summarizing new information and faxing it with a cover letter including patient identifiers (i.e., date of birth, initial, patient number), protocol description and number, if assigned, brief AE description, and notation that additional or follow-up information is being submitted. (The patient identifiers are important so that the new information is

added to the correct initial report.)

Occasionally Genentech may contact the reporter for additional information, clarification, or current status of the patient for whom and AE was reported. For questions regarding SAE reporting, you may contact the Genentech Drug Safety representative noted above or the Medical Science Liaison assigned to the study. Relevant follow-up information should be submitted to Genentech Drug Safety as soon as it becomes available and/or upon request.

[redacted]

7.4.11 Reporting to Regulatory Authorities, Ethics Committees and Investigators

Sponsor-Investigator, will be responsible for the expedited reporting of safety reports originating from the Study to the Regulatory Authorities (FDA) where it has filed a clinical trial approval, in compliance with local regulations.

Sponsor-Investigator will be responsible for the distribution of safety information to its own investigators, where relevant, in accordance with local regulations.

7.4.12 Additional Reporting Requirements for IND

For investigator-sponsored IND studies, some additional reporting requirements for the FDA apply in accordance with the guidance set forth in 21 CFR § 600.80.

Events meeting the following criteria need to be submitted to the FDA as expedited IND Safety Reports according to the following guidance and timelines:

7 Calendar Day Telephone or Fax Report:
The investigator is required to notify the FDA of any fatal or life-threatening AE that is unexpected and assessed by the investigator to be possibly related to the use of atezolizumab and/or bevacizumab. An unexpected AE is one that is not already described in the atezolizumab and/or bevacizumab Investigator's Brochure as applicable. Such reports are to be telephoned or faxed to the FDA and Genentech within 7 calendar days of first learning of the event.

15 Calendar Day Written Report:
The Investigator is also required to notify the FDA and all participating investigators, in a written IND Safety Report, of any serious, unexpected AE that is considered reasonably or possibly related to the use of atezolizumab. An unexpected AE is one that is not already described in the atezolizumab Investigator's Brochure.

Written IND Safety reports should include an Analysis of Similar Events in accordance with regulation 21 CFR § 312.32. All safety reports previously filed by the investigator with the IND concerning similar events should be analyzed and the significance of the new report in light of the previous, similar reports commented on.

Written IND safety reports with analysis of similar events are to be submitted to the FDA, Genentech, and all participating investigators within 15 calendar days of first learning of the event. The FDA prefers these reports on a MedWatch 3500 form, but alternative formats are acceptable (e.g., summary letter).

[redacted]

All written IND safety reports submitted to the FDA by the investigator must also be faxed to the following:

[redacted]

Sponsor will be responsible for the distribution of safety information to Site IRB when an event meets reporting requirements.

[redacted]

For questions related to safety reporting, please contact Genentech Drug Safety:

[redacted]

7.4.13 IND Annual Reports

Copies of all IND annual reports submitted to the FDA by the Sponsor-investigator should be emailed to Genentech[redacted]

7.4.14Other Reports

Sponsor-Investigator will forward a copy of the Final Study Report to Genentech upon completion of the Study.

7.4.15 Study Close Out

Any study report submitted to the FDA by the Sponsor-investigator should be copied to Genentech. This includes all IND annual reports and the Clinical Study Report (final study report). Additionally, any literature articles that are a result of the study should be sent to Genentech. Copies of such reports should be mailed to the assigned Clinical Operations contact for the study:
Atezolizumab Protocols

[redacted]

QUERIES

Queries related to the Study will be answered by Sponsor-Investigator. However, responses to all safety queries from regulatory authorities or for publications will be discussed and coordinated between the Parties. The Parties agree that Genentech shall have the final say and control over safety queries relating to the Product. Sponsor-Investigator agrees that it shall not answer such queries from regulatory authorities and other sources relating to the Product independently but shall redirect such queries to Genentech.

Both Parties will use all reasonable effort to ensure that deadlines for responses to urgent requests for information or review of data are met. The Parties will clearly indicate on the request the reason for urgency and the date by which a response is required.

SAFETY CRISIS MANAGEMENT

In case of a safety crisis, e.g., where safety issues have a potential impact on the indication(s), on the conduct of the Study, may lead to labeling changes or regulatory actions that limit or restrict the way in which the Product is used, or where there is media involvement, the Party where the crisis originates will contact the other Party as soon as possible.

The Parties agree that Genentech shall have the final say and control over safety crisis management issues relating to the Product. Sponsor-Investigator agrees that it shall not answer such queries from media and other sources relating to the Product but shall redirect such queries.

7.5 Expedited Adverse Event Reporting

For multi-institution studies where a DF/HCC investigator is serving as the Overall PI, each participating institution **must** abide by the reporting requirements set by the DF/HCC. This applies to any medical event equivalent to an unexpected grade 2 or 3 with a possible, probable or definite attribution, unexpected grade 4 toxicities, and grade 5 (death) regardless of study phase or attribution.

7.5.1 DF/HCC Expedited Reporting Guidelines

Investigative sites within DF/HCC and DF/PCC will report SAEs directly to the DFCI Office for Human Research Studies (OHRS) per the DFCI IRB reporting policy.

Other investigative sites will report SAEs to their respective IRB according to the local IRB's policies and procedures in reporting adverse events. A copy of the submitted institutional SAE form should be forwarded to the Overall PI within the timeframes detailed in the table below.

Table 8. DF/HCC Reportable AEs

Attribution	DF/HCC Reportable AEs				
	Grade 2 & 3 AE Expected	**Grade 2 & 3 AE Unexpected**	**Grade 4 AE Expected**	**Grade 4 AE Unexpected**	**Grade 5 AE Expected or Unexpected**
Unrelated Unlikely	Not required	Not required	5 calendar days[#]	5 calendar days	24 hours*
Possible Probable Definite	Not required	5 calendar days	5 calendar days[#]	5 calendar days	24 hours*
# If listed in protocol as expected and not requiring expedited reporting, event does not need to be reported.					
* For participants enrolled and actively participating in the study ***or*** for AEs occurring within 30 days of the last intervention, the AE should be reported within 24 business hours of learning of the event.					

The Overall PI will submit SAE reports from outside institutions to the DFCI OHRS according to DFCI IRB policies and procedures in reporting adverse events.

7.6 Expedited Reporting to the FDA

The Overall PI, as study sponsor, will be responsible for all communications with the FDA. The Overall PI will report to the FDA, regardless of the site of occurrence, any serious adverse event that meets the FDA's criteria for expedited reporting following the reporting requirements and timelines set by the FDA.

7.7 Expedited Reporting to Hospital Risk Management

Participating investigators will report to their local Risk Management office any participant safety reports or sentinel events that require reporting according to institutional policy.

7.8 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions to the Overall PI on the toxicity case report forms. **AEs reported through expedited processes (e.g., reported to the IRB, FDA, etc.) must also be reported in routine study data submissions.**

8. PHARMACEUTICAL INFORMATION

8.1 Atezolizumab

8.1.1 Description

Atezolizumab is a human immunoglobulin (Ig) G1 monoclonal antibody consisting of two heavy chains (448 amino acids) and two light chains (214 amino acids) and is produced in Chinese hamster ovary cells. Atezolizumab was engineered to eliminate Fc-effector function via a single amino acid substitution (asparagine to alanine) at position 298 on the heavy chain, which results in a non-glycosylated antibody that has minimal binding to Fc receptors and prevents Fc-effector function at expected concentrations in humans. Atezolizumab targets human programmed death-ligand 1 (PD-L1) and inhibits its interaction with its receptor, programmed death-1 (PD-1). Atezolizumab also blocks the binding of PD-L1 to B7.1, an interaction that is reported to provide additional inhibitory signals to T cells.

8.1.2 Form

The atezolizumab drug product is provided in a single-use, 20 cc USP/Ph. Eur. Type 1 glass vial as a colorless-to-slightly-yellow, sterile, preservative-free clear liquid solution intended for IV administration. The vial is designed to deliver 20 mL (1200 mg) of atezolizumab solution but may contain more than the stated volume to enable delivery of the entire 20 mL volume. The Atezolizumab drug product is formulated as 60 mg/mL atezolizumab in 20 mM histidine acetate, 120 mM sucrose, 0.04% polysorbate 20, pH 5.8.

8.1.3 Storage and Stability

Atezolizumab must be refrigerated at 2°C-8°C (36°F-46°F) upon receipt until use. Atezolizumab vials should not be used beyond the expiration date provided by the manufacturer. No preservative is used in the atezolizumab drug product; therefore, each vial is intended for single use only. Discard any unused portion of drug left in a vial. Vial contents should not be frozen or shaken and should be protected from direct sunlight.

8.1.4 Compatibility

No incompatibilities between the bevacizumab and atezolizumab have been observed.

8.1.5 Handling

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the chemotherapeutic agent in a self-contained and protective environment.

8.1.6 Availability

Genentech/Roche will supply atezolizumab.

8.1.7 Preparation

See section 5.3.

8.1.8 Administration

See section 5.3.

8.1.9 Ordering

Genentech/Roche will supply atezolizumab and ordering will take place through Genentech/Roche. The study team will complete the Drug Request Form, which is kept as separate document. All Drug Request Forms should be sent to the following email [redacted]

8.1.10 Accountability

Accountability for investigational product is the responsibility of the investigator. The research pharmacy will maintain a careful record of the inventory and disposition of the agent using the NCI Drug Accountability Record Form (DARF) or another comparable drug accountability form.

8.1.11 Destruction and Return

Drug should be destroyed at the site, after the investigator approves the drug destruction policy at the site. Drug will not be returned to Genentech/Roche. Destruction will be documented in the Drug Accountability Record Form.

8.2 Bevacizumab

8.2.1 Description

Bevacizumab is a recombinant, humanized monoclonal antibody which binds to, and neutralizes, VEGF.

8.2.2 Form

Bevacizumab is manufactured by recombinant DNA technology, using a genetically engineered Chinese hamster ovary (CHO) cell line. The protein is purified from the cell culture medium by routine methods of column chromatography and filtration. The final product is tested for quality, identity, safety, purity, potency, strength, and excipient/chemical composition according to International Conference on Harmonisation (ICH) guidelines. The purity of bevacizumab is >95%.

Bevacizumab may be supplied in 6-cc (100-mg) and 20-cc (400-mg) glass vials containing 4 mL or 16 mL of bevacizumab, respectively (all at 25 mg/mL). Vials contain bevacizumab with phosphate, trehalose, polysorbate 20, and sterile water for injection (SWFI). Vials contain no preservative and are suitable for single use only.

8.2.3 Storage and Stability

Upon receipt of the study drug, vials are to be refrigerated at 2°C-8°C (36°F-46°F) and should remain refrigerated until just prior to use. DO NOT FREEZE. DO NOT SHAKE. Keep vial in the outer carton due to light sensitivity.

VIALS ARE FOR SINGLE USE ONLY. Vials used for 1 subject may not be used for any other subject. Chemical and physical in-use stability has been demonstrated for 48 hours at 2°C-30°C in 0.9% Sodium Chloride solution. If not used immediately, in-use storage times and conditions are the responsibility of the user and would normally not be longer than 24 hours at 2°C-8°C, unless dilution has taken place in controlled and validated aseptic conditions.

8.2.4 Compatibility

No incompatibilities between the bevacizumab and atezolizumab have been observed.

8.2.5 Handling

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the chemotherapeutic agent in a self-contained and protective environment.

8.2.6 Availability

Genentech/Roche will supply bevacizumab.

8.2.7 Preparation

See section 5.4.

8.2.8 Administration

See section 5.4.

8.2.9 Ordering

Genentech/Roche will supply bevacizumab from its commercial supply. Bevacizumab will be ordered using the Drug Request Form, which is kept as a separate document. All Drug Request Forms should be sent to the following email: [redacted]

8.2.10 Accountability

Accountability for investigational product is the responsibility of the investigator. The investigator, or a responsible party designated by the investigator, should maintain a careful record of the inventory and disposition of the agent using the NCI Drug Accountability Record Form (DARF) or another comparable drug accountability form.

8.2.11 Destruction and Return

Drug should be destroyed at the site, after the investigator approves the drug destruction policy at the site. Drug will not be returned to Genentech/Roche. Destruction will be documented in the Drug Accountability Record Form.

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

Correlative studies will be exploratory in nature. In this study, we will evaluate the immunomodulatory properties of atezolizumab in combination with bevacizumab and correlate findings with outcomes. In addition, we will evaluate tumor tissue and TIMC for expression of PD-L1 in mandatory baseline biopsies and progression biopsies (mandatory in patients who have a response to treatment as per RECIST 1.1 and then subsequently progress) and correlate with outcomes. Lastly, we will evaluate mechanisms of resistance to therapy in progression biopsy specimens.

Whole blood for germline DNA and cfDNA plasma samples will be analyzed by investigators at collaborating institutions, such as the Broad Institute, for all patients enrolled on this trial. From these samples, the data will be submitted to the National Institutes of Health's Database for Genotypes and Phenotypes (dbGaP) and other public databases. Samples and data will be de-identified.

9.1 Blood Studies

Biomarker Analysis
Serum plasma will be collected for flow cytometry studies to analyze peripheral blood mononuclear cells. Additionally, plasma will be collected to analyze soluble biomarkers to include cytokines/chemokines and angiogenic/growth factors.

For DF/HCC participating sites, 30 mL of blood will be collected as per the Laboratory Manual and couriered within 6 hours of collection to The Center of Immunooncology Laboratory.

For non-DF/HCC participating sites, 30 mL of blood will be collected and stored as per the Laboratory Manual and batch shipped at the end of study to The Center of Immunooncology Laboratory.

Germline DNA
Whole blood for Germline DNA for cfDNA will be collected as per the Laboratory Manual and stored until the end of study at which time the sample will be shipped overnight to the Broad Institute.

Whole blood for Germline DNA for tissue will be collected as per the Laboratory Manual and stored until the end of study at which time the sample will be shipped overnight to the Signoretti Laboratory.

cfDNA Plasma
As an exploratory endpoint, plasma will be collected at baseline, every two cycles, and at the end of study for genomic analysis of circulating free DNA (cfDNA).

Blood for cfDNA will be collected as per the Laboratory Manual and shipped at the end of study to the Broad Institute.

9.2 Tissue Studies

Tissue will be collected to assess the immunomodulatory properties of atezolizumab in combination with bevacizumab, assess PD-L1 tumor and TIMC expression, and evaluate mechanisms of acquired resistance to therapy. Mutation profiling will be performed using massively parallel sequencing technology (Oncopanel) and/or whole exome and transcriptome sequencing.

Mutational profiling of molecular mechanisms of response and resistance will be analyzed via whole exome or whole genome sequencing and via RNA-sequencing. If fresh tissue is available, the specimen will be collected, as stated in this protocol and according to institutional guidelines, and put on ice to be transported to the processing laboratory. A portion of fresh tissue will be dissociated into a single cell suspension and frozen for future studies, including single cell transcriptome studies and cell line creation.

Archived Tumor Tissue
Archived tumor tissue will be collected pre-study as per the Laboratory Manual and stored at ambient temperature until the end of study at which time the specimens will be shipped to the Signoretti Laboratory.

Fresh Tumor Tissue
Fresh tumor biopsy will be conducted pre-study as per the Laboratory Manual. Fresh tumor biopsy may be conducted at the end of study on patients who experience a response as per RECIST 1.1 and then subsequently progress if medically safe. Frozen specimens should be stored at -80°C and specimens fixed in formalin should be stored at 4°C until shipping. At the end of study, the tumor specimens will be shipped to the Signoretti Laboratory.

9.3 Radiology Imaging Studies

Images of all radiologic assessments at baseline, on study, and at treatment discontinuation with corresponding imaging reports for non-DFCI patients need to be placed on a CD and sent to the DFCI for central review of exploratory imaging response assessment by irRC. Images and reports should be sent on all patients once they discontinue study treatment. Reference the Laboratory Manual for additional information.

10. STUDY CALENDAR

	Pre- Study[1]	Day 1 of Each Cycle (+/- 3 days)[2]	Every 6 weeks (+/- 7 days)[3]	Treatment Discontinuation Visit (within 30 days of last treatment)[20]	Follow up[4]
Informed Consent	X				
Demographics	X				
History and Physical[5]	X	X		X	
ECOG Performance Status	X	X		X	
Vital Signs[6]	X	X		X	
Weight	X	X		X	
Height	X	X		X	
Hematology[7]	X	X		X	
Serum Chemistry[8]	X	X		X	
Liver Function Tests[9]	X	X		X	
TSH/fT3/fT4	X	X		X	
Urinalysis[10]	X	X		X	
Coagulation Factors[11]	X				
Pregnancy Test[12]	X				
Viral Serologies[13]	X				
C-Reactive Protein	X		X		
EKG	X				
ECHO	X				
MRI or CT Brain[14]	X				
Imaging[15]	X		X		
FKSI-19	X		X	X	
BFI	X		X		
Concomitant Medications	X	X		X	
Adverse Events	X				
Atezolizumab Administration		X[21]			
Bevacizumab Administration		X[21]			
Germline DNA[16]		X			

Plasma cfDNA[17]		X	X	X	
Blood Biomarkers[17]		X	X	X	
Archival Tumor Tissue[18]	X				
Tumor Biopsy[19]	X			X[22]	

1: Baseline evaluations are to be conducted within 28 days prior to registration. Scans must be done within 28 days of registration. All baseline screening should be done prior to registration.
2: A cycle will be defined as 21 days (+/- 3 days).
3: Imaging assessments and quality of life assessments will take place every 6 weeks (2 cycles) for the first 24 weeks (6 months). After 6 months, imaging assessments and quality of life assessments can take place every 12 weeks (+/- 7-10 days)
4: After progression/treatment discontinuation, participants will be followed for survival and receipt of next line therapies every 6 months until death or 2 years after treatment discontinuation.
5: Physical examination should include general description of participant, head, eyes, ears, nose, and throat, chest, abdominal, extremities, neurologic, skin, and lymph node examination. Any other evaluation is up to the discretion of the practitioner. It will not be considered a violation if the exam is not described as outlined here.
6: Vital signs include blood pressure, heart rate, respiratory rate, and body temperature.
7: Hematology testing to include full CBC with WBC, ANC, hemoglobin, and platelet count and differential.
8: Serum chemistry to include full comprehensive metabolic panel with sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, calcium, albumin, magnesium, and LDH.
9: Liver function tests to include AST, ALT, , total bilirubin, and direct bilirubin.
10: Patients with ≥ 2+ protein on dipstick urinalysis at baseline must undergo 24-hour urine collection for protein.
11: Coagulation factors to include PT, aPTT, and INR.
12: Pregnancy test only needs to be obtained in childbearing women.
13: Hepatitis B virus (HBV) serology (HBsAg, , hepatitis B core antibody), and HCV serology (anti-HCV). HBV DNA test is required for patients who have known positive serology for hepatitis B core antibody. HCV RNA test is required for patients who have known positive serology for anti HCV. HIV testing is also required.
14: MRI of the brain with and without contrast is preferred. If a patient is not able to obtain an MRI, CT imaging with contrast is acceptable. If a patient is no able to receive contrast, CT head without contrast is acceptable.
15: Diagnostic CT chest and CT or MRI of the abdomen and pelvis should be obtained at baseline and at every 6 week imaging assessment. All baseline scans used to determine disease burden should be continued during restaging scans. In instances when providers would like to follow with bone scans they can be followed at 6 or 12 weeks by provider discretion. Actual images and imaging reports at all time points including baseline, on study, and at treatment discontinuation must be sent to DFCI for central review once a patient has discontinued treatment.
16: Blood for germline DNA analysis will be collected once at Cycle 1 Day 1.
17: Research plasma cfDNA analysis and blood biomarkers to be collected at baseline, every 6 weeks on treatment for the first 24 weeks (6 months). After 6 months, research plasma if cfDNA and blood biomarkers can be collected every 12 weeks (+/- 7-10 days), and at the time of progression. If off treatment collection is within 2 weeks of prior collection, research samples do not need to be collected.
18: Archival tissue should to be requested and availability confirmed prior to therapy initiation. A note from the study team should be provided documenting availability of tissue.
19: Baseline fresh tumor biopsies are not optional, and must occur at least 7 days prior to the first dose of bevacizumab if medically feasible and safe.
20: Patients who discontinue from treatment will be asked to return to the clinic no more than 30 days after the last treatment for a treatment discontinuation visit. The visit at which a response assessment shows progressive disease may be used as the treatment discontinuation visit.
21: Atezolizumab and bevacizumab are to be administered +/-3 days of Day 1 of each cycle. Each cycle should be calculated from the last dose of study drug or last study visit if both study drugs were skipped (either single agent Atezolizumab or bevacizumab or drug combination).
22: Progression tumor biopsies are mandatory in a subset of participants who demonstrate a tumor response to therapy and then subsequently develop tumor progression if medically safe. The progression tumor biopsy must be at least 2 weeks after the participants' last dose of bevacizumab.

11. MEASUREMENT OF EFFECT

11.1 Antitumor Effect – Solid Tumors

For the purposes of this study, participants should be re-evaluated for response every 6 weeks. Response and progression will be evaluated in this study using the new international criteria proposed by the RECIST guideline (version 1.1).[25] Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

11.1.1 Definitions

Evaluable for Target Disease response. Only those participants who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for target disease response. These participants will have their response classified according to the definitions stated below. (Note: Participants who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Evaluable Non-Target Disease Response. Participants who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

11.1.2 Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm by chest x-ray or ≥10 mm with CT scan, MRI, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area are not considered measurable.

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), are considered non-measurable disease. Leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all considered non-measurable.

Note: Cystic 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 participant, these are preferred for selection as target lesions.

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that 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 which can be measured reproducibly should be selected. 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 diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow up. If a target lesion is biopsied at screening, this lesion must be followed as non-target lesions after the biopsy unless it is the patients only target lesion. If there is only one target lesion, it should be followed as a target lesion regardless.

11.1.3 Methods for Evaluation of Disease

All measurements should be taken and recorded in metric notation using a ruler, calipers, or a digital measurement tool. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

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

Conventional CT and MRI. This guideline has defined measurability of lesions on CT scan based on the assumption that CT thickness is 5mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size of a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (*e.g.* for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

11.1.4 Response Criteria

11.1.4.1 Evaluation of 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 the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: 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 diameters while on study.

11.1.4.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and 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 lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase. For patients who demonstrate PD at the first on-treatment imaging assessment, patients will be allowed to remain on study until confirmatory imaging at the next imaging assessment at the discretion of the treating investigator if it appears that the patients is clinically benefiting from treatment.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the

treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

11.1.4.3 Evaluation of New Lesions

The finding of a new lesion should be unequivocal (i.e. not due to difference in scanning technique, imaging modality, or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). However, a lesion identified on a follow-up scan in an anatomical location that was not scanned at baseline is considered new and will indicate PD. If a new lesion is equivocal (because of small size etc.), follow-up evaluation will clarify if it truly represents new disease and if PD is confirmed, progression should be declared using the date of the initial scan on which the lesion was discovered.

11.1.4.4 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Table 9. For Participants with Measurable Disease (*i.e.*, Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Participants 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 the objective progression even after discontinuation of treatment.

Table 10. For Participants with Non-Measurable Disease (*i.e.*, Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

* 'Non-CR/non-PD' is preferred over 'SD' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised

11.1.5 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started, or death due to any cause. Participants without events reported are censored at the last disease evaluation).

Duration of overall CR: The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented, or death due to any cause. Participants without events reported are censored at the last disease evaluation.

Duration of SD: SD is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

11.1.6 Immune-Related Response Criteria (irRC)

The sum of the products of the two largest perpendicular diameters of lesions (SPD; 5 lesions per organ, up to 10 visceral lesions) at tumor assessment using the immune related response criteria (irRC) for progressive disease incorporates the contribution of new measurable lesions (up to 5 new lesions per organ: 10 new visceral lesions).[26] Each net Percentage Change in Tumor Burden per assessment using irRC criteria accounts for the size and growth kinetics of both old and new lesions as they appear.

11.1.6.1 Definition of IndexLesions Response Using irRC

- irComplete Response (irCR): Complete disappearance of all target lesions in two consecutive observations not less than 4 weeks apart. This category encompasses exactly the same subjects as "CR" by the mWHO criteria.
- irPartial Response (irPR): Decrease, relative to baseline, of 50% or greater in the sum of the products of the two largest perpendicular diameters of all target and all new measurable lesions in two consecutive observations not less than 4 weeks apart.

(i.e., Percentage Change in Tumor Burden). Note: the appearance of new measurable lesions is factored into the overall tumor burden, but does not automatically qualify as progressive disease until the SPD increases by > 25% when compared to SPD at nadir.

- irStable Disease (irSD): Does not meet criteria for irCR or irPR, in the absence of progressive disease.
- irProgressive Disease (irPD): At least 25% increase in the percentage change in tumor burden (i.e., taking SPD of all target lesions and any new lesions) when compared to SPD at nadir, in two consecutive observations at least 4 weeks apart, in the absence of rapid clinical deterioration.

11.1.6.2 Definition of Non-Index Lesions Response Using irRC

- irComplete Response (irCR): Complete disappearance of all non-index lesions. This category encompasses exactly the same subjects as "CR" by the mWHO criteria.
- irPartial Response (irPR): Non-index lesion(s) are not considered in the definition of PR; this term does not apply.
- irStable Disease (irSD): Does not meet the criteria for irCR or irPD.
- irProgressive Disease (irPD): Increases in number or size of non-index lesion(s) does not constitute progressive disease unless/until the Percentage Change in Tumor Burden increases by 25% (i.e., the SPD at nadir of the target lesions increases by the required amount).

11.1.6.3 Impact of New Lesions on irRC

New lesions in and by themselves do not qualify as progressive disease. However their contribution to total tumor burden is included in the SPD which in turn feeds into the irRC criteria for tumor response. Therefore, new non-measurable lesions will not discontinue any subject from the study.

11.1.6.4 Definition of Overall Response Using irRC

Overall response using irRC will be based on these criteria:

- Immune-Related Complete Response (irCR): Complete disappearance of all tumor lesions (index and non-index together with no new measurable/unmeasurable lesions) for at least 4 weeks from the date of documentation of complete response.
- Immune-Related Partial Response (irPR): The sum of the products of the two largest perpendicular diameters of all index lesions is measured and captured as the SPD baseline. At each subsequent tumor assessment, the SPD of the two largest perpendicular diameters of all index lesions and of new measurable lesions are added together to provide the Immune Response Sum of Product Diameters (irSPD). A decrease, relative to baseline of the irSPD compared to the previous SPD baseline, of 50% or greater is considered an immune Partial Response (irPR).
- Immune-Related Stable Disease (irSD): irSD is defined as the failure to meet criteria for immune complete response or immune partial response, in the absence of progressive disease.
- Immune-Related Progressive Disease (irPD): It is recommended to confirm PD by serial imaging. Any of the following will constitute progressive disease:
  - At least 25% increase in the SPD of all target lesions over nadir SPD calculated

for the index lesions.
- At least a 25% increase in the SPD of all index lesions and new measurable lesions (irSPD) over the nadir SPD calculated for the target lesions.

Table 11. Immune-Related Response Criteria Definitions

Target Lesion Definition	Non-Target Lesion Definition	New Measurable Lesions	New Unmeasurable Lesions	Percent Change in Tumor Burden (including measurable new lesions when present)	Overall irRC Response
Complete Response	Complete Response	No	No	-100%	irCR
Partial Response	Any	Any	Any	≥-50%	irPR
				<-50% to <+25%	irSD
				>+25%	irPD
Stable Disease	Any	Any	Any	<-50% to <+25%	irSD
				>+25%	irPD
Progressive Disease	Any	Any	Any	≥+25%	irPD

11.1.6.5 Immune-Related Best Overall Response Using irRC (irBOR)

irBOR is the best confirmed irRC overall response over the study as a whole, recorded between the date of first dose until the last tumor assessment before subsequent therapy (except for local palliative radiotherapy for painful bone lesions) for the individual subject in the study. For the assessment of irBOR, all available assessments per subject are considered. irCR or irPR determinations included in the irBOR assessment must be confirmed by a second (confirmatory) evaluation meeting the criteria for response and performed no less than 4 weeks after the criteria for response are first met.

11.1.7 Response Review

Tumors will be assessed for response and progression by RECIST version 1.1 by central radiology review.

11.1.8 Progression-Free Survival

Overall Survival: Overall Survival (OS) is defined as the time from randomization (or registration) to death due to any cause, or censored at date last known alive.

Progression-Free Survival: Progression-Free Survival (PFS) is defined as the time from randomization (or registration) to the earlier of progression or death due to any cause. Participants alive without disease progression are censored at date of last disease evaluation.

12. DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

12.1 Data Reporting

12.1.1 Method

The ODQ will collect, manage, and perform quality checks on the data for this study.

12.1.2 Responsibility for Data Submission

Investigative sites within DF/HCC or DF/PCC are responsible for submitting data and/or data forms to the ODQ according to the schedule set by the ODQ.

12.2 Data Safety Monitoring

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this study. The committee is composed of clinical specialists with experience in oncology and who have no direct relationship with the study. Information that raises any questions about participant safety will be addressed with the Overall PI and study team.

The DSMC will review each protocol up to four times a year or more often if required to review toxicity and accrual data. Information to be provided to the committee may include: up-to-date participant accrual; all grade 2 or higher unexpected adverse events that have been reported; , summary of all deaths while being treated and during active follow-up; any response information; audit results, and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

12.3 Multicenter Guidelines

This protocol will adhere to the policies and requirements of the DF/HCC Multi-Center Data and Safety Monitoring Plan. The specific responsibilities of the Overall PI, Coordinating Center, and Participating Institutions and the procedures for auditing are presented in Appendix C.

- The Overall PI/Coordinating Center is responsible for distributing all IND Action Letters or Safety Reports to all participating institutions for submission to their individual IRBs for action as required.

- Mechanisms will be in place to ensure quality assurance, protocol compliance, and adverse event reporting at each site.

- Except in very unusual circumstances, each participating institution will order the study agent(s) directly from supplier. A participating site may order the agent(s) only after the initial IRB approval for the site has been forwarded to the Coordinating Center.

13. STATISTICAL CONSIDERATIONS

13.1 Study Design/Endpoints

This is a multi-center, open-label, single-arm phase II study of the combination of the human immunoglobulin (Ig) G1 monoclonal antibody (atezolizumab) with bevacizumab in patients with advanced non-clear cell renal cell carcinoma (nccRCC).

The primary objective is to evaluate the efficacy of the drug combination.

Primary Endpoints:

- Objective Response Rate: Confirmed CR or PR as best overall response according to RECIST version 1.1 as defined in section 11.1.4 by central review.

Secondary/exploratory Endpoints:

- ORR by histologic subtype (papillary, sarcomatoid RCC, and other nccRCC)
- Duration of ORR
- Safety and tolerability according to NCI CTCAE version 4.0.
- Immune Related Objective Response Rate as defined according to Immune-Related Response Criteria[26] and detailed in section 11.1.6.
- PFS defined as the time from trial treatment start to the earlier of progression or death due to any cause. Participants alive without disease progression are censored at date of last disease evaluation.
- OS defined as the time from trial treatment start to death due to any cause, or censored at date last known alive.
- Quality of life assessments include FKSI-19 and BFI. The FKSI-19 is a 19 item questionnaire with each item scored on a scale of 0-4 for a total score of 0-76 with higher scores indicating fewer symptoms (Appendix D).[27] The BFI is a 9 item questionnaire with each item scored on a scale of 0-10.[28] Scores are categorized as mild (1-3), moderate (4-6), or severe (7-10). A global fatigue score can be found by averaging the score obtained on each test item completed (Appendix E).
- Immunomodulatory properties: Blood based biomarkers representing immunomodulatory properties of combination treatment with atezolizumab and bevacizumab at baseline, on treatment and at disease progression

- Tumor expression for PD-L1 at pre-treatment and post treatment/ radiographic progression.
- Resistance to therapy measured by somatic mutation, insertions and deletions, copy number alterations, overexpressed genes, and chimeric transcripts and a complete set of potential driver alterations

13.2 Sample Size, Accrual Rate and Study Duration

A single arm design was used to estimate the sample size for this phase II trial. Evaluable patients who receive at least one combination therapy of bevacizumab and atezolizumab will be included in the sample size.

The null hypothesis (Ho) of a true objective response rate (ORR) of 6%-10% were seen from reported with sunitinib and data of targeted therapy in patients with nccRCC from the IMDC.[2,3] The following table shows that a corresponding alternative hypothesis (Ha) of objective response rate to be detected under the scenario with the adequate statistical power. Specifically, assuming a hypothesis test of Ho: ORR=0.1 versus Ha: ORR=0.25 (**bold in table**), there is a 90% statistical power with the minimum sample size of 40 for an exact one-sided one-sample binomial test with a type I error rate=0.1 and beta (type II error =0.1) to assess the efficacy (ORR) of the bevacizumab and atezolizumab combination, i.e., if at least 7 responses out of 40 patients are observed, then the treatments are considered to be efficacious or the null hypothesis of 10% ORR is rejected.

Type I error (one-sided)	Ho: ORR (%)	Ha: ORR	Sample size	# of responses required to reject Ho	Corresponding 80% confidence interval (CI)	Power (%)
0.1	6	15	77	>7	(6,16)	91
0.1	**10**	**25**	**40**	**>6**	**(10, 28)**	**90**
0.1	15	30	53	>11	(15,32)	90

The accrual is expected to be 3 patients every month for a duration of 20 months to complete enrollment.

As of April 28, 2017, the sample size will be increased from n=40 to 60 patients. The increased sample size to n=60 patients will allow for better efficacy analysis according to histology subtypes. Specifically, an exploratory objective has been added to estimate the ORR according to histology subtypes.

Justification of sample size increase: It is estimated that among the targeted patient population, 50% would be papillary RCC, 20% would be other nccRCC, and 30% RCC with > 20% sarcomatoid features. With the assumed/expected sample size in each histology subtype and the targeted ORR rate, the following table provides the ORR estimate precision (the width of a confidence interval (CI)) to be achieved based on the unknown targeted ORR rate. The precision of ORR estimate uses 80% CI, to be consistent with the original study design, which was based on 90% power for a one-sided type I error of 10% for a hypothesis test of Ho: ORR=0.05 vs. Ha: ORR=0.25.

For example, if the targeted ORR is 0.25, with a sample size of n=30 with papillary RCC (bold), the width of 80% CI for a ORR estimate would be 0.24 (precision), and with the maximum width of 80% CI to be .26 (corresponding to a ORR of 0.5)

			ORR estimate	
Histology subtypes	N	Targeted ORR	80% CI	Width of 80% CI
Papillary RCC (50%)	30	0.2	(0.11,0.32)	0.21
	30	**0.25**	**(0.16,0.4)**	**0.24**
	30	0.5	(0.37,0.63)	0.26*
RCC with >20% sarcomatoid features (30%)	18	0.2	(0.1,0.4)	0.3
	18	0.25	(0.1,0.4)	0.3
	18	0.5	(0.33,0.67)	0.34*
Other nccRCC (20%)	12	0.2	(0.05,0.39)	0.34
	12	0.25	(0.1,0.48)	0.38
	12	0.5	(0.29,0.71)	0.42*

* The maximum width of a 80%CI for a ORR estimate.

13.3 Definition of Study Population /Stratification Factors

Safety/Evaluable population: All patients receiving at least one dose of bevacizumab and atezolizumab will be included in analyses unless otherwise specified.

No stratification factors are used in enrolling patients.

IMDC risk group (favorable, intermediate, versus poor risk as previously defined),[29] prior systemic treatment for RCC (yes versus no), histology (papillary versus other) will be used in subset analysis. IMDC risk factors include ECOG < 1, time from original diagnosis to treatment less than one year, hemoglobin less than the lower limit of normal, and serum calcium, neutrophil count, or platelet count greater than the upper limit of normal.

13.4 Analysis of Demographics/Baseline Characteristics

Demographic and other baseline characteristics will be summarized for all patients by study population. Demographic and baseline characteristics of patients who are replaced will be summarized in a separate category. Summaries of continuous demographic/baseline variables, including age, weight, and vital signs, will be presented as N, mean, standard deviation, median, quartiles and minimum and maximum values. For categorical variables, such as histology type, the number and percentage of patients will be used.

13.5 Efficacy Analysis

Primary Analysis

Tumor assessment will be performed every 6 weeks (every 2 cycles). At the time of each restaging, patients will be classified as achieving complete response (CR), partial response (PR),

stable disease (SD), progressive disease (PD), or non-evaluable for response according to RECIST (Version 1.1) criteria. Objective response will be determined by the best overall confirmed response designation recorded between the date of first dose of trial therapy and the date of objectively documented disease progression or cessation of trial therapy, whichever occurs first. For patients without documented progression or cessation of trial therapy, all available response designations will contribute to the objective response determination. The proportion of patients with an objective response will be presented with a two-sided 80% confidence interval **(CI)** using exact binominal method. Based on a sample size of 40 patients, the confidence interval will be no wider than 0.22. For the targeted ORR=25%, the estimated ORR precision (two sided 80%CI) would be 0.20.

Secondary Analyses

Safety and Tolerability: All adverse events recorded during the trial will be summarized for the safety population. The incidence of events that are new or worsening from the time of first dose of treatment will be summarized according to system organ class and/or preferred term, severity (based on CTCAE version 4.0 grade), type of adverse event, and relation to study treatment. Deaths reportable as SAEs and non-fatal serious adverse events will be listed by patient and tabulated by primary system organ class, and type of adverse event.

Immune Related Objective Response Rate: The proportion of patients with immune ORR (as defined in section 11.1.6) will be presented with two-sided 90% confidence interval estimated using exact binomial methods.

PFS and OS: PFS and OS will each be summarized using the product-limit method of Kaplan-Meier. Median times for each endpoint will be presented with two-sided 90% confidence intervals estimated using log(-log(survival)) methodology. Kaplan-Meier estimates of PFS at 6 or 12 months after treatment initiation may also be presented with two-sided 90% confidence intervals.

Quality of Life Assessment:

The quality of life assessments use the FKSI-1 comprising of 19 items (each has score range from 0 to 4) with a possible maximum total score of 76. The BFI is a 9 items questionnaire (each score ranging from 0-10) with possible maximum score of 90. Patients will be asked to complete FKSI-19 and BFI Forms at baseline (prior to randomization), at every 6 week visits or time of treatment termination (only FKSI-19).

- The estimated differences in quality of life measurements (total scores) between baseline (pre-treatment) and the subsequent timepoints while patients receiving treatment will be summarized with 90% CI.
- Each of the 19 (FKSI) items will also be summarized descriptively over time as the proportion of patients with “clinically significant” symptoms (those scoring 3 or 4). Two sided 90% CI for the difference in the proportion will also be assessed.
- Missing assessments may be due to stopping treatment, not completing the FKSI or BFI assessments, and other reasons. Information on reasons why the patient did not complete the FKSI or BFI Form will be collected.

13.6 Exploratory/Correlative Analysis

We anticipate that 15-20% of tumors (of the 40s patients) will not be evaluable for the analyses given issue with biopsy/staining/ etc. The evaluable samples for the analysis will be 32 (80% of 40 patients).

We anticipate that 15-20% of tumors (of the 40s patients) will not be evaluable for the analyses given issue with biopsy/staining/ etc. The evaluable samples will be 32 (80% of 40 patients).

Tumor infiltrating lymphocytes (TILs) (biomarkers of immunomodulatory properties)

The relationship between tumor-infiltrating lymphocytes (TILs) and outcomes will be explored according to pre-treatment TIL percentages. It is hypothesized that higher levels of lymphocytic infiltration will be associated with better outcomes. To examine responses according to levels of TILs, the evaluable samples will be divided retrospectively according to objective response or non-response. Pre-treatment percentages of stromal infiltrating lymphocytes will be summarized descriptively for the two response groups and compared using Wilcoxon rank-sum tests. Assume a targeted ORR of 25% (our primary study alternative hypothesis), if there are 8 responses (25% of 32 patients) and 24 non-responses, a Wilcoxon rank-sum test with a two-sided, 10% type I error will have 88% power to detect a difference in baseline TILs between the two response groups that is 1.2 times the common standard deviation.

Kaplan-Meier estimates will be used to visualize the relationship between PFS or OS and lymphocyte predominant breast cancer (LPBC) phenotype or median of the distribution of intratumoral or stromal percentages. The LPBC phenotype is defined as 50% or higher infiltration (baseline TIL) of either stromal or intratumoral lymphocytic infiltration. Medians of the time-to-event endpoints will be calculated with two-sided 90% confidence intervals according to the LPBC groups.

Changes in TILs between baseline and progression/treatment discontinuation will be calculated (post-pre) for each patient and summarized descriptively. In addition, the correlation of TIL changes with measures of peripheral blood markers/cytokines (including a panel of markers IL1, 2, 4, 6, 8, 19, 12, IFN, TNFa, GMCSF) will be explored graphically, or by appropriate statistical methods based on data availability, to assess associations.

PD-L1 Expression Levels

The PD-L1 expression will be evaluated by IHC in both tumor cell membrane and TIMC. The association between pre-treatment PD-L1 expression (percentages) and outcomes will be explored. It is hypothesized that higher expression levels of PD-L1 will be associated with poor outcomes, due to the fact that upregulation of PD-L1 may allow cancers to evade the immune system.

To examine responses according to PD-L1 expression, the evaluable samples will be divided retrospectively according to objective response or non-response. Pre-treatment PD-L1 expression will be summarized descriptively for the two response groups.

In order to assess the association of PD-L1 positivity with objective response, given the limited sample size, the study could only detect large difference. Based on our experience in a cohort of nccRCC patients [ref], the observed PD-L1 positivity is 11% in tumor cell membrane, and 56% in TIMC, respectively. The following table displays the detectable differences in PD-L1 positivity (PD-L1>5%) between the response groups (yes vs. no) with reasonable statistical power in TIMC samples, assuming an overall expected % PD-L1+ of 50%-60%, i.e., only large differences in % of PD-L1 positivity (56% in responder vs. 6% in non-responders) could be detected with 81% power.

[ref]: T.K. Choueiri et al. PD-L1 expression in nonclear-cell renal cell carcinoma. *Annals of Oncology* 25: 2178–2184, 2014

Responder		Non-responder		
% PD-L1 + in TIMC	# samples	% PD-L1 + in TIMC	# samples	Exact Power of Fisher's test
50%	8	3%	24	82%
56%	8	6%	24	81%
60%	8	9%	24	80%

Therefore, no formal inference will be made. The proportion of patients with objective response according to pre-treatment (baseline) PD-L1 positivity (PD-L1 ≥5% tumor cell membrane staining) will be summarized with two-sided 90% exact binomial CI. Kaplan-Meier estimates will be used to describe the distribution of PFS according to baseline PD-L1 expression positivity. Medians of time to event endpoints will be shown with two-sided 90% CIs.

Mechanism of Resistance to Therapy
We will analyze mechanisms of resistance to therapy via serial tumor biopsies (pre-treatment and post treatment/progression). Mutation profiling will be performed using massively parallel sequencing technology (Oncopanel) and/or whole exome and transcriptome sequencing. The sequencing data will be analyzed for somatic mutations, insertions and deletions, copy number alterations, overexpressed genes, and chimeric transcripts and a complete set of potential driver alterations will be compiled at baseline and progression.

Changes in the aforementioned mutation measures of resistance between baseline and progression/treatment discontinuation will be calculated (post-pre) for each patient and summarized descriptively. In addition, the correlation among the resistance (marker changes post-pre) measures will be explored graphically, or by appropriate statistical methods based on data availability, to potentially assess associations.

13.7 Safety Monitoring

No formal stopping rule regarding the primary efficacy endpoints is planned. Adverse event reports are to be submitted within 28 days of each clinic visit. All relevant adverse events will be

reviewed by the DSMC for up to 4 times each year. The DSMC will make recommendation to the study management team if it notes any concerns regarding patient safety or if further action needs to be taken based on the safety monitoring review results. Formal assessment of (targeted) adverse events will also be included in statistical analysis for secondary objectives as detailed in section 13.5.

14. ETHICAL CONSIDERATIONS

14.1 Compliance with Laws and Regulations

Patients who comply with the requirements of the protocol, are tolerating study treatment, and may be receiving benefit will be offered dosing beyond Cycle 1 at the investigator's discretion after a careful assessment and thorough discussion of the potential risks and benefits of continued treatment with the patient. Such patients may have the option to receive atezolizumab treatment as long as they continue to experience clinical benefit in the opinion of the investigator until the earlier of unacceptable toxicity, symptomatic deterioration attributed to disease progression, or any of the other reasons for treatment discontinuation listed in Section 5.6.

14.2 Informed Consent

The informed consent document must be signed by the subject or the subject's legally authorized representative before his or her participation in the study. The case history for each subject shall document that informed consent was obtained prior to participation in the study. A copy of the informed consent document must be provided to the subject or the subject's legally authorized representative. If applicable, it will be provided in a certified translation of the local language. Signed consent forms must remain in each subject's study file and must be available for verification by study monitors at any time.

14.3 Institutional Review Board or Ethics Committee Approval

This protocol, the informed consent document, and relevant supporting information must be submitted to the IRB for review and must be approved before the study is initiated. The study will be conducted in accordance with FDA, applicable national and local health authorities, and IRB requirements.

The Principal Investigator is responsible for keeping the IRB apprised of the progress of the study and of any changes made to the protocol as deemed appropriate, but in any case, the IRB must be updated at least once a year. The Principal Investigator must also keep the IRB informed of any significant AEs.

Investigators are required to promptly notify their respective IRB of all adverse drug reactions that are both serious and unexpected. This generally refers to SAEs that are not already identified in the Investigator's Brochure and that are considered possibly or probably related to the molecule or study drug by the investigator. Some IRBs may have other specific AE requirements to which investigators are expected to adhere. Investigators must immediately forward to their IRB any written safety report or update provided by Genentech (e.g., IND safety report, Investigator's Brochure, safety amendments and updates, etc.).

14.4 Confidentiality

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the ICF (or separate authorization to use and disclose personal health information) signed by the patient or unless permitted or required by law.
Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare for treatment purposes.

Data 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, Genentech representatives and collaborators, and the IRB/Ethics Committee (EC) for each study site, if appropriate.

14.5 Study Medical Monitoring Requirements

This clinical research study will be monitored both internally by the PI and externally by the IRB. In terms of internal review, the PI will continuously monitor and tabulate AEs. Appropriate reporting to the IRB will be made. The PI of this study will also continuously monitor the conduct, data, and safety of this study to ensure that:

- Interim analyses occur as scheduled,
- Stopping rules for toxicity and/or response are met,
- Risk/benefit ratio is not altered to the detriment of the subjects,
- Appropriate internal monitoring of AEs and outcomes is done,
- Over-accrual does not occur,
- Under-accrual is addressed with appropriate amendments or actions, and
- Data are being appropriately collected in a reasonably timely manner.

Routine monitoring will be carried out via a periodic team conference among investigators during which toxicity data, including all SAEs, will be reviewed and other issues relevant to the study such as interim assessment of accrual, outcome, and compliance with study guidelines, will be discussed. Monitoring will be carried out on an ongoing basis. The severity, relatedness, and whether or not the event is expected will be reviewed.

14.6 Study Medication Accountability

If study drug will be provided by Genentech, the recipient will acknowledge receipt of the drug by returning the INDRR 1 form indicating shipment content and condition. Damaged supplies will be replaced.

Accurate records of all study drug dispensed from and returned to the study site should be recorded by using the institution's drug inventory log or the National Cancer Institute drug accountability log.

All partially used or empty containers should be disposed of at the study site according to institutional standard operating procedure. Return unopened, expired, or unused study drug with the Inventory of Returned Clinical Material form as directed by Genentech.

14.7 Data Collection

The study coordinator and investigators are responsible for ensuring that the eligibility checklist is completed in a legible and timely manner for every patient enrolled in the study, and that data are recorded on the appropriate forms and in a timely manner. Any errors on source data should be lined through, but not obliterated, with the correction inserted, initialed, and dated by the study coordinator or PI. All source documents will be available for inspection by the FDA and the DFCI IRB.

Before trial completion, it is possible to report data on a subset of patients for safety reasons or in case a later cohort was added mainly for correlatives purposes or a specific cohort within the trial finished accrual.

14.8 Retention of Records

FDA regulations (21 CFR §312.62[c]) and the ICH Guideline for GCP (see Section 4.9 of the guideline) require that records and documents pertaining to the conduct of clinical trials and the distribution of investigational drug, patient records, consent forms, laboratory test results, and medication inventory records, must be retained for 2 years after the last marketing application approval in an ICH region or after at least 2 years have elapsed since formal discontinuation of clinical development of the investigational product. All state and local laws for retention of records also apply.

15. PUBLICATION PLAN

The data will be collected by the Principal Investigator and analyzed by the Principal Investigator and the statistical team at DFCI. It is anticipated that the results will be made public within 12 months of the end of data collection. A report is planned to be published in a peer-reviewed journal, however initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors.

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17. APPENDIX A: PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

18. APPENDIX B: REQUIRED FORMS FOR REGISTRATION

Please notify the lead clinical research coordinator at the time a participant is identified or consented to the study. The DFCI coordinator will register the participant once the below documentation is finalized using the DFCI OnCore registration system. Non-DF/HCC participating sites will send the documents to the DFCI research coordinator to complete registration. Please allow a one-week turn-a-round time for the DFCI research team to determine participant eligibility. The following documentation is required prior to participant registration:

- Current IRB approved consent form signed by participant and Investigator (MD only)
- HIPAA authorization form (if separate from the informed consent document)
- Signed and dated DFCI eligibility checklist (signed by MD and RN)
- The following source documentation is typically required:
- Please note: Additional documentation may be required by the lead institution.
    - Documentation of prior treatments/procedures performed to treat RCC
    - Reports documenting disease status
        - MRI or CT Brain
        - Chest CT
        - CT or MRI Abdomen and Pelvis
        - Bone Scan if applicable
        - PET/CT
    - Pathology Report
    - Concomitant medication list
    - Progress note or equivalent documentation of consenting visit
    - Progress note documenting medical history and oncologic history
    - Screening Labs
        - Complete blood count with differential
        - Electrolytes
        - Liver Function Tests
        - TSH/fT3/fT4
        - Urinalysis
        - Coagulation factors
        - Pregnancy test
    - Screening visit note with vital signs, weight, height, ECOG performance status, physical examination
    - Screening ECG, ECHO

19. APPENDIX C: MULTICENTER MONTIORING PLAN

DFCI IRB Protocol #: 15-592

Dana-Farber/Harvard Cancer Center
Multi-Center Data and Safety Monitoring Plan

TABLE OF CONTENTS

1. INTRODUCTION

The Dana-Farber/Harvard Cancer Center Multi-Center Data and Safety Monitoring Plan (DF/HCC DSMP) outlines the procedures for conducting a DF/HCC Multi-Center research protocol. The DF/HCC DSMP serves as a reference for any sites external to DF/HCC that are participating in a DF/HCC clinical trial.

1.1 Purpose

To establish standards that will ensure that a Dana-Farber/Harvard Cancer Center Multi-Center protocol will comply with Federal Regulations, Health Insurance Portability and Accountability Act (HIPAA) requirements and applicable DF/HCC Standard Operating Procedures.

1.2 Multi-Center Data and Safety Monitoring Plan Definitions

DF/HCC Multi-Center Protocol: A research protocol in which one or more outside institutions are collaborating with Dana-Farber/Harvard Cancer Center where a DF/HCC investigator is the sponsor. DF/HCC includes Dana-Farber/Partners Cancer Care (DF/PCC) Network Clinical Trial Affiliates.

Lead Institution: One of the Dana-Farber/Harvard Cancer Center consortium members (Dana-Farber Cancer Institute (DFCI), Massachusetts General Hospital (MGH), Beth Israel Deaconess Medical Center (BIDMC), Boston Children's Hospital (BCH), Brigham and Women's Hospital (BWH) responsible for the coordination, development, submission, and approval of a protocol as well as its subsequent amendments per the DFCI IRB and applicable regulatory guidelines (CTEP, Food and Drug Administration (FDA), Office of Biotechnology Activities (OBA) etc.). The Lead Institution is typically the home of the DF/HCC Sponsor. The Lead Institution also typically serves as the Coordinating Center for the DF/HCC Multi-Center Protocol.

DF/HCC Sponsor: The person sponsoring the submitted Multi-Center protocol who takes responsibility for initiation, management and conduct of the protocol at all research locations. In applicable protocols, the DF/HCC Sponsor will serve as the single liaison with any regulatory agencies The DF/HCC Sponsor has ultimate authority over the protocol and is responsible for the conduct of the study at DF/HCC and all Participating Institutions. In most cases the DF/HCC Sponsor is the same person as the DF/HCC Overall Principal Investigator; however, both roles can be filled by two different people.

Participating Institution: An institution that is outside the DF/HCC and DF/PCC consortium that is collaborating with DF/HCC on a protocol where the sponsor is a DF/HCC Investigator. The Participating Institution acknowledges the DF/HCC Sponsor as having the ultimate authority and responsibility for the overall conduct of the study.
Coordinating Center: The entity (i.e. Lead Institution, Medical Monitor, Contract Research Organization (CRO), etc) that provides administrative support to the DF/HCC Sponsor in order that he/she may fulfill the responsibilities outlined in the protocol document and

DSMP, and as specified in applicable regulatory guidelines. In general, the Lead Institution is the Coordinating Center for the DF/HCC Multi-Center Protocol.

DF/HCC Office of Data Quality (ODQ): A group within DF/HCC responsible ensuring high-quality standards are used for data collection and the ongoing management of clinical trials, auditing, and data and safety monitoring. ODQ also coordinates quality assurance efforts related to multi-center clinical research.

DF/HCC Clinical Trials Research Informatics Office (CTRIO): A group within DF/HCC responsible for providing a comprehensive data management platform for managing clinical trial data.

2. GENERAL ROLES AND RESPONSIBILITIES

For DF/HCC Multi-Center Protocols, the DF/HCC Sponsor, the Coordinating Center, and the Participating Institutions are expected to adhere to the following general responsibilities:

2.1 DF/HCC Sponsor

The DF/HCC Sponsor, [redacted] will accept responsibility for all aspects of conducting a DF/HCC Multi-Center protocol which includes but is not limited to:

- Oversee the coordination, development, submission, and approval of the protocol as well as subsequent amendments.
- Ensure that the investigators, study team members, and Participating Institutions are qualified and appropriately resourced to conduct the protocol.
- Include the Multi-Center Data and Safety Monitoring Plan as an appendix to the protocol.
- Ensure all Participating Institutions are using the correct version of the protocol.
- Ensure that each participating investigator and study team member receives adequate protocol training (and/or a Site Initiation Visit prior to enrolling participants) and throughout the trials conduct as needed.
- Ensure the protocol will be provided to each participating site in a language understandable to all applicable site personnel when English is not the primary language.
- Monitor progress and overall conduct of the study at all Participating Institutions.
- Ensure all DFCI Institutional Review Board (IRB), DF/HCC and other applicable (i.e., FDA,) reporting requirements are met.
- Review data and maintain timely submission of data for study analysis.
- Act as the single liaison with the FDA, as applicable.
- Ensure compliance with all requirements as set forth in the Code of Federal Regulations, applicable DF/HCC requirements, HIPAA requirements, and the approved protocol.
- Commit to the provision that the protocol will not be rewritten or modified by anyone other than the DF/HCC Sponsor.
- Identify and qualify Participating Institutions and obtain accrual commitments prior to extending the protocol to that site.

- Monitor accrual and address Participating Institutions that are not meeting their accrual requirements.

2.2 Coordinating Center

The general responsibilities of the Coordinating Center may include but are not limited to:

- Assist in protocol development.
- Maintain FDA correspondence, as applicable.
- Review registration materials for eligibility and register participants from Participating Institutions in the DF/HCC clinical trial management system (CTMS).
- Distribute protocol and informed consent document updates to Participating Institutions as needed.
- Oversee the data collection process from Participating Institutions.
- Maintain documentation of Serious Adverse Event (SAE) reports and deviations/violation submitted by Participating Institutions and provide to the DF/HCC Sponsor for timely review and submission to the DFCI IRB, as necessary.
- Distribute serious adverse events reported to the DF/HCC Sponsor that fall under the DFCI IRB Adverse Event Reporting Policy to all Participating Institutions.
- Provide Participating Institutions with information regarding DF/HCC requirements that they will be expected to comply with.
- Carry out plan to monitor Participating Institutions either by on-site or remote monitoring.
- Maintain Regulatory documents of all Participating Institutions which includes but is not limited to the following: local IRB approvals/notifications from all Participating Institutions, confirmation of Federalwide Assurances (FWAs) for all sites, all SAE submissions, Screening Logs for all sites, IRB approved consents for all sites
- Conduct regular communications with all Participating Institutions (conference calls, emails, etc) and maintain documentation all relevant communications.

2.3 Participating Institution

Each Participating Institution is expected to comply with all applicable federal regulations and DF/HCC requirements, the protocol and HIPAA requirements.

The general responsibilities for each Participating Institution may include but are not limited to:

- Document the delegation of research specific activities to study personnel.
- Commit to the accrual of participants to the protocol.
- Submit protocol and/or amendments to their local IRB.
- Maintain regulatory files as per sponsor requirements.
- Provide the Coordinating Center with regulatory documents or source documents as requested.
- Participate in protocol training prior to enrolling participants and throughout the trial as required (i.e. teleconferences).
- Update Coordinating Center with research staff changes on a timely basis.

- Register participants through the Coordinating Center prior to beginning research related activities.
- Submit Serious Adverse Event (SAE) reports to local IRB per institutional requirements and to the Coordinating Center, in accordance with DF/HCC requirements.
- Submit protocol deviations and violations to local IRB per institutional requirements and to the DF/HCC Sponsor in accordance with DF/HCC requirements.
- Order, store and dispense investigational agents and/or other protocol mandated drugs per federal guidelines and protocol requirements.
- Have office space, office equipment, and internet access that meet HIPAA standards.
- Participate in any quality assurance activities and meet with monitors or auditors at the conclusion of a visit to review findings.
- Promptly provide follow-up and/or corrective action plans for any monitoring queries or audit findings.

3. DF/HCC REQUIREMENTS FOR MULTI-CENTER PROTOCOLS

The following section will clarify DF/HCC Requirements and further detail the expectations for participating in a DF/HCC Multi-Center protocol.

3.1 Protocol Distribution

The Coordinating Center will distribute the final DFCI IRB approved protocol and any subsequent amended protocols to all Participating Institutions.

3.2 Protocol Revisions and Closures

The Participating Institutions will receive notification of protocol revisions and closures from the Coordinating Center. It is the individual Participating Institution's responsibility to notify its IRB of these revisions.

- **Non-life-threatening revisions:** Participating Institutions will receive written notification of protocol revisions regarding non-life-threatening events from the Coordinating Center. Non-life-threatening protocol revisions must be IRB approved and implemented within 90 days from receipt of the notification.

- **Revisions for life-threatening causes:** Participating Institutions will receive immediate notification from the Coordinating Center concerning protocol revisions required to protect lives with follow-up by fax, mail, e-mail, etc. Life-threatening protocol revisions will be implemented immediately followed by IRB request for approval.

- **Protocol closures and temporary holds:** Participating Institutions will receive notification of protocol closures and temporary holds from the Coordinating Center. Closures and holds will be effective immediately. In addition, the Coordinating Center,

will update the Participating Institutions on an ongoing basis about protocol accrual data so that they will be aware of imminent protocol closures.

3.3 Informed Consent Requirements

The DF/HCC approved informed consent document will serve as a template for the informed consent for Participating Institutions. The Participating Institution consent form must follow the consent template as closely as possible and should adhere to specifications outlined in the DF/HCC Guidance Document on Model Consent Language for PI-Initiated Multi-Center Protocols. This document will be provided separately to each Participating Institution upon request.

Participating Institutions are to send their version of the informed consent document and HIPAA authorization, if a separate document, to the Coordinating Center for review and approval prior to submission to their local IRB. The approved consent form must also be submitted to the Coordinating Center after approval by the local IRB for all consent versions.

The Principal Investigator (PI) at each Participating Institution will identify the physician members of the study team who will be obtaining consent and signing the consent form for therapeutic protocols. Participating institutions must follow the DF/HCC requirement that only attending physicians obtain informed consent and re-consent for all interventional drug, biologic, or device research.

3.4 IRB Documentation

The following must be on file with the Coordinating Center:

- Initial approval letter of the Participating Institution's IRB.
- Copy of the Informed Consent Form(s) approved by the Participating Institution’s IRB.
- Participating Institution’s IRB approval for all amendments.
- Annual approval letters by the Participating Institution's IRB.

3.5 IRB Re-Approval

Verification of IRB re-approval from the Participating Institutions is required in order to continue research activities. There is no grace period for continuing approvals.

The Coordinating Center will not register participants if a re-approval letter is not received from the Participating Institution on or before the anniversary of the previous approval date.

3.6 Participant Confidentiality and Authorization Statement

In 1996, congress passed the first federal law covering the privacy of health information known as the Health Insurance Portability and Accountability Act (HIPPA). Any information, related to the physical or mental health of an individual is called Protected

Health Information (PHI). HIPAA outlines how and under what circumstances PHI can be used or disclosed.

In order for covered entities to use or disclose protected health information during the course of a study, the study participant must sign an authorization statement. This authorization statement may or may not be separate from the informed consent document. The Coordinating Center, with the approval from the DFCI IRB will provide a consent template, with information regarding authorization for the disclosure of protected health information.

The DF/HCC Sponsor will use all efforts to limit its use of protected health information in its trials. However, because of the nature of these trials, certain protected health information must be collected. DF/HCC has chosen to use authorizations, signed by the participant in the trial, rather than limited data sets with data use agreements.

3.6.1 DF/HCC Multi-Center Protocol Confidentiality

All documents, investigative reports, or information relating to the participant are strictly confidential. Whenever reasonably feasible, any participant specific reports (i.e. Pathology Reports, MRI Reports, Operative Reports, etc.) submitted to the Coordinating Center should be de-identified. It is recommended that the assigned protocol case number (as described below) be used for all participant specific documents. Participant initials may be included or retained for cross verification of identification.

3.7 DF/HCC Multi-Center Protocol Registration Policy

3.7.1 Participant Registration and Randomization

To register a participant, the following documents should be completed by the Participating Institution and faxed or e-mailed to the Coordinating Center at Dana-Farber Cancer Institute at [redacted] or e-mailed to the DFCI Clinical Research Manager and Clinical Research Coordinator. Please notify the DFCI team in advance that a registration packet is to be expected with the following items:

- Current IRB approved informed consent document signed by participant and investigator. Participant name and MRN must be redacted. Please ensure the participant's initials are written on each page of the informed consent document.
- HIPAA authorization form (if separate from the informed consent document)
- Signed and dated DFCI eligibility checklist
- The following source documentation is typically required. Please note additional documentation may be required by the lead institution:
- Lab values used to determine eligibility
- Imaging reports
- Pathology Report
- Concomitant medication list
- Progress note or equivalent documentation of consenting visit
- Progress note documenting medical history and oncologic history
- Screening visit note, with BP, vital signs, ECOG Performance status
- Screening EKG

- ECHO
- Other screening assessments

The Coordinating Center will review the submitted documents in order to verify eligibility and consent. To complete the registration process, the Coordinating Center will:

- Register the participant on the study with the DF/HCC Clinical Trial Management System (CTMS).
- Upon receiving confirmation of registration, the Coordinating Center will inform the Participating Institution and provide the study specific participant case number, and, if applicable, assigned treatment and/or dose level.

Treatment may not begin without confirmation from the Coordinating Center that the participant has been registered.

Randomization can only occur during normal business hours, Monday through Friday from 8:00 AM to 5:00 PM Eastern Standard Time.

3.7.2 Initiation of Therapy

Participants must be registered with the DF/HCC CTMS before the initiation of treatment or other protocol-specific interventions. Treatment and other protocol-specific interventions may not be initiated until the Participating Institution receives confirmation of the participant's registration from the Coordinating Center. The DF/HCC Sponsor and DFCI IRB must be notified of any violations to this policy.

3.7.3 Eligibility Exceptions

No exceptions to the eligibility requirements for a protocol without DFCI IRB approval will be permitted. All Participating Institutions are required to fully comply with this requirement. The process for requesting an eligibility exception is defined below.

3.8 DF/HCC Protocol Case Number

At the time of registration, the following identifiers are required for all subjects: initials, date of birth, gender, race and ethnicity. Once eligibility has been established and the participant successfully registered, the participant is assigned a unique protocol case number. Participating Institutions should submit all de-identified subsequent communication and documents to the Coordinating Center, using this case number to identify the subject.

3.8.1 Protocol Deviations, Exceptions and Violations

Federal Regulations require an IRB to review proposed changes in a research activity to ensure that researchers do not initiate changes in approved research without IRB review and approval, except when necessary to eliminate apparent immediate hazards to the participant. DF/HCC requires all departures from the defined procedures set forth in the IRB approved protocol to be reported to the DF/HCC Sponsor, who in turn is responsible for reporting to the DFCI IRB.

For reporting purposes, DF/HCC uses the terms "violation", "deviation" and "exception" to describe departures from a protocol. All Participating Institutions must adhere to these requirements for reporting to the DF/HCC Sponsor and will follow their institutional policy for reporting to their local IRB.

3.8.2 Definitions

Protocol Deviation: Any departure from the defined procedures set forth in the IRB-approved protocol which is prospectively approved prior to its implementation.

Protocol Exception: Any protocol deviation that relates to the eligibility criteria, e.g. enrollment of a participant who does not meet all inclusion/exclusion criteria.

Protocol Violation: Any protocol departure that was not prospectively approved by the IRB prior to its initiation or implementation.

3.8.3 Reporting Procedures

DF/HCC Sponsor: is responsible for ensuring that clear documentation is available in the medical record and/or regulatory documents to describe all protocol exceptions, deviations and violations. The DF/HCC Sponsor will also be responsible for ensuring that all protocol violations/deviations are promptly reported per DFCI IRB guidelines.

Participating Institutions: Protocol deviations require prospective approval from the DFCI IRB. The Participating Institution must submit the deviation request to the Coordinating Center who will then submit the deviation request to the DFCI IRB. Upon DFCI IRB approval the deviation is submitted to the Participating Institution IRB, per institutional policy. A copy of the Participating Institution's IRB report and determination will be forwarded to the Coordinating Center within 10 business days after the original submission. The deviation may not be implemented without all required approvals.

All protocol violations must be sent to the Coordinating Center in a timely manner. The Coordinating Center will provide training for the requirements for the reporting of violations.

Coordinating Center: Upon receipt of the violation/deviation report from the Participating Institution, the Coordinating Center will submit the report to the DF/HCC Sponsor for review. Subsequently, the Participating Institution's IRB violation/deviation report will be submitted to the DFCI IRB for review per DFCI IRB reporting guidelines. DF/HCC will forward all violation reports to CTEP via an internal DF/HCC process, as applicable.

3.9 Safety Assessments and Toxicity Monitoring

The study teams at all participating institutions are responsible for protecting the safety, rights and well-being of study participants. Recording and reporting of adverse events that occur during the course of a study help ensure the continuing safety of study participants.

All participants receiving investigational agents and/or other protocol mandated therapy will be evaluated for safety. The safety parameters include all laboratory tests and hematological

abnormalities, physical examination findings, and spontaneous reports of adverse events reported by participants. All toxicities encountered during the study will be evaluated according to the NCI criteria specified in the protocol. Life-threatening toxicities must be reported immediately to the DF/HCC Sponsor via the Coordinating Center.

Additional safety assessments and toxicity monitoring will be outlined in the protocol.

3.9.1 Guidelines for Reporting Serious Adverse Events

Guidelines for reporting Adverse Events (AEs) and Serious Adverse Events (SAEs) are detailed in protocol section 7.

Participating Institutions must report the SAEs to the DF/HCC Sponsor and the Coordinating Center following the DFCI IRB Adverse Event Reporting Policy.

The Coordinating Center will maintain documentation of all Participating Institution Adverse Event reports and be responsible for communicating to all participating investigators, any observations reportable under the DFCI IRB Reporting Requirements. Participating Institutions will review and submit to their IRB according to their institutional policies and procedures

3.9.2 Guidelines for Processing IND Safety Reports

The DF/HCC Sponsor will review all IND Safety Reports and ensure that all IND Safety Reports are distributed to the Participating Institutions. Participating Institutions will review/submit to their IRB according to their institutional policies and procedures.

3.10 Data Management

DF/HCC CTRIO develops case report forms (CRF/eCRFs), for use with the protocol. These forms are designed to collect data for each study. DF/HCC CTRIO provides a web based training for all eCRF users.

3.10.1 Data Forms Review

Data submissions are monitored for timeliness and completeness of submission. If study forms are received with missing or questionable data, the submitting institution will receive a written or electronic query from the DF/HCC Office of Data Quality, Coordinating Center, or designee.

Responses to all queries should be completed and submitted within 14 calendar days.

Responses may be returned on the written query or on an amended paper case report form, or in the case of electronic queries, within the electronic data capture (eDC) system. In the case of a written query for data submitted on a paper case report form, the query must be attached to the specific data being re-submitted in response.

If study forms are not submitted on schedule, the Participating Institution will periodically receive a Missing Form Report from the Coordinating Center noting the missing forms.

4. REQUISITIONING INVESTIGATIONAL DRUG

The ordering of investigational agent is specified in the protocol section 8.
Participating Institutions should order their own agent regardless of the supplier. (i.e., pharmaceutical company.)

If the agent is commercially available, check with the local Director of Pharmacy and/or the Research Pharmacy to ensure that the agent is in stock. If the agent is not stocked, ensure that the agent can be ordered once the protocol is approved by the local IRB.

If the agent is investigational, ensure that the pharmacy will be able to receive and store the agent according to state and federal requirements. The local IRB should be kept informed of who will supply the agent (i.e., pharmaceutical company) so that any regulatory responsibilities can be met in a timely fashion.

5. MONITORING: QUALITY CONTROL

The quality control process for a clinical trial requires verification of protocol compliance and data accuracy. The Coordinating Center, with the aid of the DF/HCC Office of Data Quality, provides quality control oversight for the protocol.

5.1 Ongoing Monitoring of Protocol Compliance

The Participating Institutions maybe required to submit participant source documents to the Coordinating Center for monitoring. Participating Institution may also be subject to on-site monitoring conducted by the Coordinating Center.

The Coordinating Center will implement ongoing monitoring activities to ensure that Participating Institutions are complying with regulatory and protocol requirements, data quality, and participant safety. Monitoring practices may include but are not limited to source data verification, and review and analysis of eligibility requirements, informed consent procedures, adverse events and all associated documentation, review of study drug administration/treatment, regulatory files, protocol departures reporting, pharmacy records, response assessments, and data management.

Site visits will generally occur once a year for sites that are actively enrolling participants and have participants in treatment. Additional monitoring activities may occur if incidences of non-compliance are discovered or at the request of the DF/HCC Sponsor. Virtual monitoring (source documents are sent to DFCI for review) may be performed in lieu of a site visit if the study staff and PI determine that virtual monitoring is appropriate for the site. The decision to perform virtual monitoring in lieu of a site visit will be based upon the site's enrollment, study compliance history, history collaborating with DFCI on other multi-center studies, and number of participants in active treatment.

Monitoring will occur before the clinical phase of the protocol begins and will continue during protocol performance through study completion.

Teleconferences between DFCI and the participating sites will be conducted on approximately a monthly basis. Meeting minutes for teleconferences will be issued to all participating sites. Site initiation visits will be conducted via teleconference. Ongoing training will also be conducted via teleconference as needed. The Coordinating Center, Dana Farber Cancer Institute will be available to all participating sites for resolving questions, concerns and facilitating compliance.

5.2 Monitoring Reports

The DF/HCC Sponsor will review all monitoring reports to ensure protocol compliance. The DF/HCC Sponsor may increase the monitoring activities at Participating Institutions that are unable to comply with the protocol, DF/HCC Sponsor requirements or federal and local regulations.

5.3 Accrual Monitoring

Prior to extending a protocol to an external site, the DF/HCC Sponsor will establish accrual requirements for each participating institution. Accrual will be monitored for each participating institution by the DF/HCC Sponsor or designee. Sites that are not meeting their accrual expectations may be subject to termination.

6. AUDITING: QUALITY ASSURANCE

Auditing is a method of Quality Assurance and involves the systematic and independent examination of all trial related activities and documents. Audits determine if evaluated activities were appropriately conducted and whether data was generated, recorded and analyzed, and accurately reported per the protocol, applicable Standard Operating Procedures (SOPs), and the Code of Federal Regulations (CFR).

6.1 DF/HCC Internal Audits

All Participating Institutions are subject to audit by the DF/HCC Office of Data Quality (ODQ). Typically, approximately 3-4 participants would be audited at the site over a 2 day period. If violations which impact participant safety or the integrity of the study are found, more participant records may be audited.

6.2 Audit Notifications

It is the Participating Institution's responsibility to notify the Coordinating Center of all scheduled audit dates (internal or NCI) and re-audit dates (if applicable), which involve this protocol. All institutions will forward a copy of final audit and/or re-audit reports and corrective action plans (if applicable) to the Coordinating Center, within 12 weeks after the audit date.

6.3 Audit Reports

The DF/HCC Sponsor will review all final audit reports and corrective action plans, if applicable. The Coordinating Center, must forward any reports to the DF/HCC ODQ per DF/HCC policy for review by the DF/HCC Audit Committee. For unacceptable audits, the DF/HCC Audit Committee would forward the final audit report and corrective action plan to the DFCI IRB as applicable.

6.4 Participating Institution Performance

The DF/HCC Sponsor and DFCI IRB is charged with considering the totality of an institution's performance in considering institutional participation in the protocol.

Participating Institutions that fail to meet the performance goals of accrual, submission of timely and accurate data, adherence to protocol requirements, and compliance with state and federal regulations, may be recommended for a six-month probation period. Such institutions must respond with a corrective action plan and must demonstrate during the probation period that deficiencies have been corrected, as evidenced by the improved performance measures. Participating Institutions that fail to demonstrate significant improvement will be considered by the DF/HCC Sponsor for revocation of participation. A DF/HCC Sponsor and/or the DFCI IRB may terminate a site's participation if it is determined that a site is not fulfilling its responsibilities as described above.

20. APPENDIX D: FKSI-19

Today's Date: _____ Participant Study ID: _____
Participant Name: _____ Cycle Number: _____

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to <u>the last 7 days</u>.**

			Not at all	A little bit	Some-what	Quite a bit	Very much
DRS-P	GP1	I have a lack of energy	0	1	2	3	4
	GP4	I have pain	0	1	2	3	4
	C2	I am losing weight	0	1	2	3	4
	H17	I feel fatigued	0	1	2	3	4
	B1	I have been short of breath	0	1	2	3	4
	BRM3	I am bothered by fevers (episodes of high body temperature)	0	1	2	3	4
	BP1	I have bone pain	0	1	2	3	4
	L2	I have been coughing	0	1	2	3	4
	H112	I feel weak all over	0	1	2	3	4
	RCC2	I have blood in my urine	0	1	2	3	4
	C6	I have a good appetite	0	1	2	3	4
	GF5	I am sleeping well	0	1	2	3	4
DRS-E	GE6	I worry that my condition will get worse.....	0	1	2	3	4
TSE	GP2	I have nausea	0	1	2	3	4
	C5	I have diarrhea	0	1	2	3	4
	GP5	I am bothered by side effects of treatment...	0	1	2	3	4
FWB	GF1	I am able to work (include work at home)....	0	1	2	3	4
	GF3	I am able to enjoy life	0	1	2	3	4
	GF7	I am content with the quality of my life right now	0	1	2	3	4

DRS-P = Disease-related symptoms subscale – Physical
DRS-E = Disease-related symptoms subscale – Emotional
TSE = Treatment side effects subscale
FWB = Function and well-being subscale

NCCN/FACT Kidney Symptom Index-19 (FKSI-19)
Scoring Guidelines (Version 4)

Instructions:*

1. Record answers in "item response" column. If missing, mark with an X
2. Perform reversals as indicated, and sum individual items to obtain a score.
3. Multiply the sum of the item scores by the number of items in the subscale, then divide by the number of items answered. This produces the symptom index score.
4. As with all FACIT questionnaires, a high score is good. Therefore, a score of "0" is a severely symptomatic patient and the highest possible score is an asymptomatic patient.

*For guidelines on handling missing data and scoring options, please refer to the administration and scoring guidelines online at www.facit.org.

Scale	Item Code	Reverse item		Item response	Item Score
FKSI-19 Total	GP1	4	-	_____	=_____
	GP4	4	-	_____	=_____
	C2	4	-	_____	=_____
	HI7	4	-	_____	=_____
Score range: 0-76	B1	4	-	_____	=_____
	BRM3	4	-	_____	=_____
	BP1	4	-	_____	=_____
	L2	4	-	_____	=_____
	HI12	4	-	_____	=_____
	RCC2	4	-	_____	=_____
	C6	0	+	_____	=_____
	GF5	0	+	_____	=_____
	GE6	4	-	_____	=_____
	GP2	4	-	_____	=_____
	C5	4	-	_____	=_____
	GP5	4	-	_____	=_____
	GF1	0	+	_____	=_____
	GF3	0	+	_____	=_____
	GF7	0	+	_____	=_____

Sum individual item scores: _____
Multiply by 19: _____
Divide by number of items answered: _____ = **FKSI-19 score**

21.APPENDIX E: BRIEF FATIGUE INVENTORY

Brief Fatigue Inventory

STUDY ID# _____ HOSPITAL # _____

Date: ____/____/____ Time: _____

Name _____ _____ _____
Last First Middle Initial

Throughout our lives, most of us have times when we feel very tired or fatigued. Have you felt unusually tired or fatigued in the last week? Yes ☐ No ☐

1. Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your fatigue right NOW.

0 1 2 3 4 5 6 7 8 9 10
No Fatigue — As bad as you can imagine

2. Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your USUAL level of fatigue during past 24 hours.

0 1 2 3 4 5 6 7 8 9 10
No Fatigue — As bad as you can imagine

3. Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your WORST level of fatigue during past 24 hours.

0 1 2 3 4 5 6 7 8 9 10
No Fatigue — As bad as you can imagine

4. Circle the one number that describes how, during the past 24 hours, fatigue has interfered with your:

A. General activity
0 1 2 3 4 5 6 7 8 9 10
Does not interfere — Completely Interferes

B. Mood
0 1 2 3 4 5 6 7 8 9 10
Does not interfere — Completely Interferes

C. Walking ability
0 1 2 3 4 5 6 7 8 9 10
Does not interfere — Completely Interferes

D. Normal work (includes both work outside the home and daily chores)
0 1 2 3 4 5 6 7 8 9 10
Does not interfere — Completely Interferes

E. Relations with other people
0 1 2 3 4 5 6 7 8 9 10
Does not interfere — Completely Interferes

F. Enjoyment of life
0 1 2 3 4 5 6 7 8 9 10
Does not interfere — Completely Interferes

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SAFETY REPORTING FAX COVER SHEET

Genentech Supported Research

[redacted]

[redacted]

Genentech Study Number	
Principal Investigator	
Site Name	
Reporter name	
Reporter Telephone #	
Reporter Fax #	

Initial Report Date	*[DD] / [MON] / [YY]*
Follow-up Report Date	*[DD] / [MON] / [YY]*

Subject Initials (Enter a dash if patient has no middle name)	*[ ] - [ ] - [ ]*

SAE or Safety Reporting questions, contact Genentech Safety: [redacted]

PLEASE PLACE MEDWATCH REPORT or SAFETY REPORT BEHIND THIS COVER SHEET