Academic and Community Cancer Research United (ACCRU)

BACCI: A Phase II Randomized, Double-Blind, Placebo-Controlled Study of Capecitabine Bevacizumab plus Atezolizumab versus Capecitabine Bevacizumab plus Placebo in Patients with Refractory Metastatic Colorectal Cancer

For any communications regarding this protocol, please contact the person indicated on the Protocol Resource page. This is a stand-alone document found on the ACCRU web site (www.ACCRU.org).

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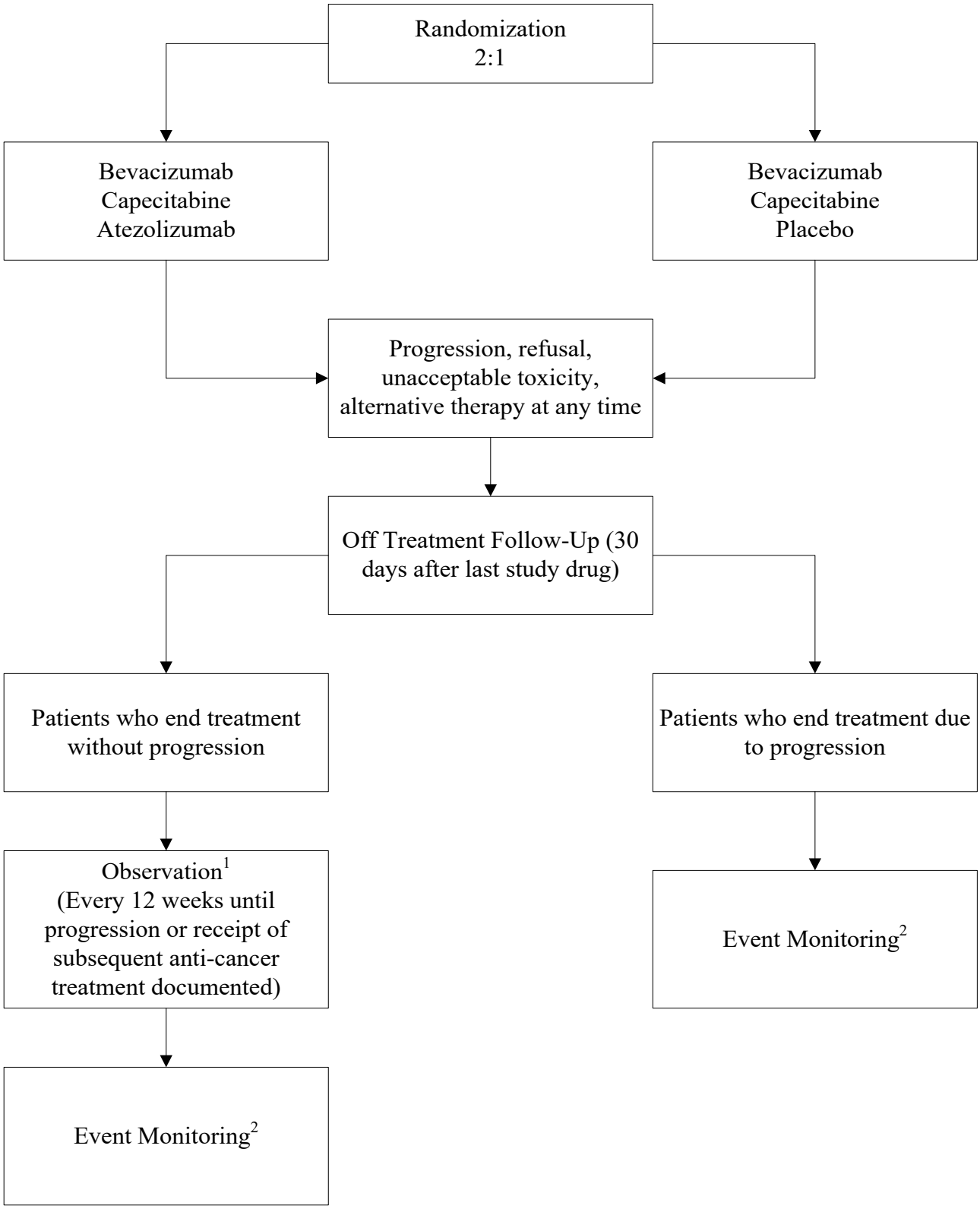

*Cycle= 21 days

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Definitions

1. **Observation:** Part of the Active Monitoring phase of a study. The time period following the active treatment phase when the participant continues to receive cycles of evaluation in compliance with the Test Schedule and may be required to return to the consenting site for protocol tests.
2. **Event Monitoring:** Not part of the Active Monitoring phase of a study. The time period when the participant is no longer following the protocol test schedule. During Event Monitoring, the data collection schedule is dictated by the protocol but the visit schedule is determined by clinical practice at each participating site. During the Event Monitoring Phase of the study, the participant is being monitored for key study events such as progression, new primaries, and death. Participants may not be required to return to the consenting site for study-related reasons or be required to have research-related tests performed. Samples from biospecimens collected in the course of clinical care may be requested but cannot be required of the participant.

1.0 Background

1.1 Introduction

Colorectal cancer and anti-VEGF therapy
Initial treatment of metastatic colorectal cancer (mCRC) involves a 5-fluorouracil (5-FU) based chemotherapy backbone with anti-VEGF therapy, and upon disease progression, multiple studies have suggested a benefit for continued anti-VEGF therapy across lines of therapy in metastatic colorectal cancer. The BRiTE registry demonstrated that the use of bevacizumab beyond progression was associated with a doubling of overall survival (OS, hazard ratio [HR] 0.49, median 19.9 vs 31.8 months) (Grothey, Sugrue et al. 2008). The ARIES registry demonstrated that bevacizumab beyond progression was independently associated with improved post progression survival (HR 0.51; 95% CI, 0.42–0.61) (Bendell, Bekaii-Saab et al. 2012). In the VELOUR study for second line metastatic colorectal cancer, the addition of aflibercept to FOLFIRI chemotherapy was associated with an improvement in overall survival (HR 0.81; median 12.1 vs 13.5 months), progression free survival (PFS, HR 0.76; median 4.7 vs 6.9 months), and objective response rate (ORR 19.8% vs 11.1%), and there was also a benefit in patients who had progressed on bevacizumab, both for PFS (HR 0.66) and OS (HR 0.86) (Van Cutsem, Tabernero et al. 2012). The ML18147 study of second line chemotherapy +/- bevacizumab in patients who had progressed on a first line bevacizumab containing regimen, was found a significant improvement in overall survival for continued bevacizumab therapy (Bennouna, Sastre et al. 2013). In addition, the TRC-0301 study, a phase II multicenter trial that evaluated the response to bevacizumab combined with 5-FU and leucovorin, was associated with rare objective responses (ORR 4%; 95% CI, 1.1% to 9.9%) and had a PFS of 3.5 months and a median OS of 9.0 months (Chen, Mooney et al. 2006). Lastly, regorafenib was recently FDA approved based upon an improvement in overall survival in the CORRECT study, but due to significant toxicities, its clinical use is limited despite its regulatory approvals (Grothey, Van Cutsem et al. 2013). Taken together, these data support the potential value of ongoing VEGF inhibition in mCRC. Given the contribution of inflammation and immune escape to colon cancer progression, targeting of inflammatory and immune check point pathways are attractive approaches to enhance the benefits of VEGF therapy in order to improve outcomes of patients with mCRC.

PD-1/PD-L1 targeted therapies
Programmed death ligand 1 (PD-L1) is a ligand for programmed death 1 (PD-1), a T-cell co-inhibitory receptor, and these molecules contribute to the ability of tumor cells to evade the host's immune system (Brahmer, Tykodi et al. 2012). Therapies targeting the PD-1/PD-L1 axis have made a dramatic impact on the treatment of several cancer types. The PD-1 inhibitors nivolumab and pembrolizumab are currently FDA approved for the treatment of melanoma and non-small cell lung cancer (Squibb ; 2015). Positive phase II and/or phase III data for the PD-1 inhibitors nivolumab and pembrolizumab and/or the PD-L1 inhibitor atezolizumab have been reported in multiple other tumor types, including renal cell (Motzer, Escudier et al. 2015; Motzer, Rini et al. 2015; Sznol, McDermott et al. 2015; Weinstock and McDermott 2015), bladder (Bajorin, Plimack et al. 2015; Bellmunt, Sonpavde et al. 2015; Kates, Sopko et al. 2015; Rosenberg, Petrylak et al. 2015), gastric (Muro, Bang et al. 2014; Fuchs, Denker et al. 2015), small cell lung (Antonia, Bendell et al. 2015; Ott, Elez Fernandez et al. 2015), ovarian (Hamanishi, Mandai et al. 2015), triple negative breast (Callahan, Bendell et al. 2014; Disis and Stanton 2015), hepatocellular (El-Khoueiry, Melero et al. 2015), glioblastoma (Sampson,

Vlahovic et al. 2015), and microsatellite instability high (MSI high) colorectal cancers. Numerous studies with these agents in these and other indications are currently ongoing.

PD-L1 therapy with bevacizumab
In addition to promoting tumor angiogenesis, there is increasing evidence that VEGF plays a role in cancer immune evasion through several different mechanisms. For example, experiments with activated endothelial cells suggested that in the tumor microenvironment, VEGF may reduce lymphocyte adhesion to vessel walls, thus contributing to decreased immune cell recruitment to the tumor site. Some immunosuppressive activities of VEFG can be reversed by inhibition of VEGF signaling. Thus, mice exposed to pathophysiologic levels of VEGF exhibited impaired dendritic cell function, which could be restored by blockade of VEGFR-2. In a murine melanoma model, VEGF blockade synergized with adoptive immunotherapy, as evidenced by improved anti-tumor activity, prolonged survival, and increased trafficking of T cells into tumors.

In patients, bevacizumab treatment has been shown to increase dendritic cell maturation, a finding also seen in preclinical models. Synergistic effects have also been observed in a clinical study combining an immunomodulatory antibody (anti-CTLA-4; ipilimumab) and bevacizumab. Hodi et al. described increased T-cell trafficking in post-treatment biopsies, as well as marked increases in central memory cells in peripheral blood in the majority of patients (Hodi, O'Day et al. 2010).

Therefore, combined treatment with PD-L1 and bevacizumab may augment the anti-tumor immune response, resulting in improved and more durable clinical benefit.

PD-L1 therapy with bevacizumab in colorectal cancer
The safety and activity of atezolizumab in combination with bevacizumab and in combination with FOLFOX chemotherapy and bevacizumab have also recently been reported. Of the 13 patients who received atezolizumab plus bevacizumab, one patient had a partial response that was durable for 10 months; in addition, two patients had minor responses and stable disease lasting more than 12 and 18 months, respectively. Eight of these 13 patients had stable disease for at least 4 months, one of whom also had an unconfirmed partial response. In the first line FOLFOX and bevacizumab plus atezolizumab group the data are immature with a preliminary response rate of 44% and median PFS that is expected to exceed 12 months. Treatment in all groups was well tolerated, and there no unexpected safety signals. Biomarker studies noted increase in the frequency of activated CD8+ T cells in the periphery in patients treated with atezolizumab plus bevacizumab with or without FOLFOX; biomarker studies also suggested a potential signature to distinguish immunogenic versus non-immunogenic colorectal cancers (CD8, IFNγ, granzyme A, granzyme B, perforin and EOMES). Taken together, these data suggest that bevacizumab may increase the immunogenicity of colorectal cancers, the combination of atezolizumab plus bevacizumab may be associated with clinically meaningful response rates and disease control, and there are candidate biomarkers that may help identify those patients most likely to benefit from this combination regimen. The proposed randomized phase II study is meant to follow up these promising but preliminary findings.

1.2 Study Agents

1.21 Capecitabine

Capecitabine (5'-deoxy-5-fluoro-N-[(pentyloxy) carbonyl]-cytidine, Xeloda®) is a fluoropyrimidine carbamate with antineoplastic activity (van Kuijk, Nijdam et al. 2011). Capecitabine is an orally administered precursor of 5'-DFUR which is preferentially converted to the active compound 5-FU in malignant tissues via thymidine phosphorylase (dThdPase). After oral administration, capecitabine is rapidly and extensively absorbed, metabolized in the liver to 5'-DFCR, and then converted to 5'–DFUR by cytidine deaminase, which is principally located in hepatic and tumor tissue. The final step (metabolism of 5'-DFUR to 5-FU by dThdPase) exploits the higher concentrations of dThdPase in tumor tissues compared with adjacent healthy tissues. This enzymatic cascade potentially reduces systemic exposure to 5-FU and allows for a more dose intensive regimen.

As of February 2007, capecitabine has received regulatory approval for the following therapeutic indications (van Kuijk, Nijdam et al. 2011):

Capecitabine monotherapy is approved for:

a. First-line treatment of patients with mCRC when treatment with fluoropyrimidine therapy alone is preferred. Approval has been granted in over 70 countries including the US, EU, Canada, Switzerland, and Australia.

b. Adjuvant treatment of patients following surgery of stage III colon cancer. Approval has been granted in over 70 countries including the US, EU, Canada, Switzerland, and Australia.

c. Treatment of patients with metastatic breast cancer that is either (i) resistant to both paclitaxel and anthracycline-containing regimens (or patients resistant to paclitaxel and for whom further anthracycline therapy is not indicated (e.g., patients who have received cumulative doses of 400 mg/m2 of doxorubicin or doxorubicin equivalents) or (ii) in combination with docetaxel after failure of prior anthracycline-containing therapy.

In more than 50 countries including the US, Switzerland, and Canada, approval has been granted for:

d. Treatment of patients with locally advanced or metastatic breast cancer after failure of taxanes and an anthracycline-containing chemotherapy regimen or for who further anthracycline therapy is not indicated. Approval has been granted in the EU.

e. First-line treatment of patients with inoperable advanced gastric cancer. Approval has been granted in South Korea.

Combination therapy is approved for capecitabine (van Kuijk, Nijdam et al. 2011) in:

f. Combination with docetaxel for treatment of patients with metastatic

breast cancer after failure of prior anthracycline containing chemotherapy. Approval has been granted in the US and the EU.

g. Combination with a platinum-based regimen in the treatment of patients with inoperable advanced gastric cancer. Approval has been granted in EU.

NCCN guidelines in mCRC for the use of capecitabine in:

- Monotherapy in patients intolerant of additional chemotherapy or when bevacizumab is contraindicated.
- Combination with bevacizumab in patients intolerant of additional chemotherapy or as part of maintenance regimen.
- Combination with oxaliplatin in patients in whom bevacizumab is contraindicated.
- Combination with oxaliplatin and bevacizumab.

1.211 Safety Summary for Combination Therapies in mCRC

Capecitabine in combination with oxaliplatin (XELOX): the most frequently occurring AEs in patients with mCRC who received first-line or second-line treatment with XELOX were GI disorders, of which the most common were nausea and diarrhea. Nervous system disorders were also frequently reported, of which the most common were paresthesia and peripheral neuropathy. Diarrhea was the most common grade 3/4 AE (unrelated and related to treatment) as well as the most common treatment-related SAE. In colorectal cancer patients who received XELOX in an adjuvant setting, a similar safety profile was seen.

Xeloda in combination with oxaliplatin and bevacizumab (XELOX+BV): the safety profile of patients with mCRC who received first-line treatment with XELOX+BV was similar to that of XELOX. The most common AEs were nausea, vomiting and paresthesia. There was a moderate increase in the incidence of vomiting and PPE. Diarrhea was the most common grade 3/4 AE (unrelated and related to treatment) as well as the most common treatment-related SAE. An increase in the incidence of vascular disorders was observed, mainly due to the incidence of deep vein thrombosis.

See the capecitabine package insert for additional safety information.

1.22 Bevacizumab

Bevacizumab (Avastin®) is a recombinant humanized monoclonal IgG1 antibody that binds to and inhibits the biologic activity of human vascular endothelial growth factor (VEGF) in in vitro and in vivo assay systems41. Bevacizumab contains human framework regions and the complementarity-determining regions of a murine antibody that binds to VEGF. Bevacizumab has an approximate molecular weight of 149 kD. Bevacizumab is produced in a

mammalian cell (Chinese Hamster Ovary, CHO) expression system in a nutrient medium containing the antibiotic gentamicin. Gentamicin is not detectable in the final product.

Bevacizumab binds VEGF and prevents the interaction of VEGF to its receptors (Flt-1 and KDR) on the surface of endothelial cells. The interaction of VEGF with its receptors leads to endothelial cell proliferation and new blood vessel formation in in vitro models of angiogenesis. Administration of bevacizumab to xenotransplant models of colon cancer in nude (athymic) mice caused reduction of microvascular growth and inhibition of metastatic disease progression.

In the United States, bevacizumab is indicated for the following:

Metastatic Colorectal Cancer (mCRC):
Bevacizumab in combination with fluoropyrimidine-based chemotherapy is indicated for treatment of patients with metastatic carcinoma of the colon or rectum.

Advanced, metastatic or recurrent Non-Small Cell Lung Cancer (NSCLC):
Bevacizumab, in addition to platinum-based chemotherapy, is indicated for first-line treatment of patients with unresectable, advanced, metastatic or recurrent, non-squamous, non-small cell lung cancer.

Advanced and/or metastatic Renal Cell Cancer (mRCC):
Bevacizumab in combination with interferon alfa-2a is indicated for first-line treatment of patients with advanced and/or metastatic renal cell cancer.

Malignant Glioma (WHO Grade IV) - Glioblastoma:
Bevacizumab, as a single agent, is indicated for the treatment of patients with glioblastoma after relapse or disease progression.

Epithelial Ovarian, Fallopian Tube and Primary Peritoneal Cancer:
Bevacizumab, in combination with carboplatin and paclitaxel is indicated for the front-line treatment of epithelial ovarian, fallopian tube, or primary peritoneal cancer.

Bevacizumab, in combination with carboplatin and gemcitabine is indicated for the treatment of patients with recurrent, platinum-sensitive, epithelial ovarian, fallopian tube, or primary peritoneal cancer.

Bevacizumab in combination with paclitaxel, topotecan or pegylated liposomal doxorubicin is indicated for the treatment of patients with recurrent, platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer who received no more than two prior chemotherapy regimens.

Cervical Cancer:
Bevacizumab in combination with paclitaxel and cisplatin or paclitaxel and topotecan is indicated for the treatment of persistent, recurrent, or metastatic carcinoma of the cervix.

1.221 Safety

A number of phase I, II, and III clinical trials have established the clinical safety and bevacizumab-associated adverse events.

Most common adverse reactions (incidence >10% and at least twice the control arm rate) are epistaxis, headache, hypertension, rhinitis, proteinuria, taste alteration, dry skin, rectal hemorrhage, lacrimation disorder, back pain and exfoliative dermatitis (Roche 2013).

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 NCI-CTC 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. Monitor blood pressure every two to three weeks during treatment with bevacizumab. Treat with appropriate anti-hypertensives such as angiotensin-converting enzyme inhibitors, diuretics and calcium-channel blockers and monitor blood pressure regularly. Continue to monitor blood pressure at regular intervals in patients with bevacizumab -induced or –exacerbated hypertension after discontinuation of bevacizumab.

Temporary interruption of bevacizumab therapy is recommended in patients with hypertension requiring medical therapy until adequate control is achieved. Bevacizumab should be permanently discontinued if medically significant hypertension cannot be adequately controlled with antihypertensive therapy. Bevacizumab should be permanently discontinued in patients who develop hypertensive crisis or hypertensive encephalopathy.

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. In the event of Grade 4 proteinuria bevacizumab treatment should be permanently

discontinued. 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. Testing for proteinuria is recommended prior to start of bevacizumab therapy. In most clinical studies urine protein levels of ≥2g/24h led to the holding of bevacizumab until recovery to <2g/24h.

Venous thromboembolism (including deep venous thrombosis, pulmonary embolism, and thrombophlebitis:
Patients may be at risk of developing venous thromboembolic events, 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. Venous thromboembolic events include deep venous thrombosis and pulmonary embolism.

Grade 3-5 venous thromboembolic events 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 venous thromboembolic event 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 venous thromboembolic events 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 venous thromboembolic events 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.

Bevacizumab should be discontinued in patients with life-threatening (Grade 4) venous thromboembolic events, including pulmonary embolism. Patients with thromboembolic events ≤ Grade 3 need to be closely monitored.

Arterial Thromboembolism:
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 arterial thromboembolic events. Bevacizumab should be permanently discontinued in patients who develop arterial thromboembolic events.

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 arterial thromboembolic events 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, arterial thromboembolic events 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 arterial thromboembolism, diabetes or age greater than 65 years have an increased risk of developing arterial thromboembolic events during bevacizumab therapy. Caution should be taken when treating such patients with bevacizumab.

Aspirin is a standard therapy for primary and secondary prophylaxis of arterial thromboembolic events 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 arterial thromboembolic events, 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, and similar data with respect to metastatic colorectal cancer patients were presented at ASCO 2005 (Hambleton, Skillings et al. 2005).

Gastrointestinal perforation:
Bevacizumab has been associated with serious cases of gastrointestinal perforation. Gastrointestinal 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 renal cell cancer, newly diagnosed glioblastoma, or in patients with ovarian cancer receiving front-line treatment, and up to 2.7% (including gastrointestinal 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 gastrointestinal perforations, which represents between 0.2-1.0% of all bevacizumab treated patients.

In bevacizumab clinical trials, gastrointestinal 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 gastrointestinal 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 gastrointestinal perforation to bevacizumab has not been established.

Patients may be at increased risk for the development of gastrointestinal perforation and gallbladder perforation when treated with bevacizumab. Bevacizumab should be permanently discontinued in patients who develop gastrointestinal perforation.

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 <1.0%) reports of other types of fistulae that involve areas of the body other than the gastrointestinal 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.

Permanently discontinue bevacizumab in patients with tracheoesophageal fistulae 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.

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, gastrointestinal perforation or fistula formation. Bevacizumab therapy should be discontinued in patients who develop necrotizing fasciitis, and appropriate treatment should be promptly initiated.

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 mCRC 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.

Bevacizumab should not be initiated for at least 28 days following surgery and until the surgical wound is fully healed. In patients who experience wound healing complications during bevacizumab treatment, bevacizumab should be withheld until the wound is fully healed. Bevacizumab therapy should be withheld for elective surgery. The appropriate interval between the last dose of bevacizumab and elective surgery is unknown; however, the half-life of bevacizumab is estimated to be 20 days. Suspend bevacizumab for at least 28 days prior to elective surgery. Do no administer bevacizumab until the wound is fully healed.

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). Bevacizumab should be permanently discontinued in patients who experience Grade 3 or 4 bleeding during bevacizumab therapy.

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 9.0% when treated with bevacizumab plus chemotherapy compared with 5.0% 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 <1.0% 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.

Patients with non–small cell lung cancer treated with bevacizumab may be at risk for serious, and in some cases fatal, pulmonary hemorrhage/hemoptysis. Patients with recent pulmonary hemorrhage/ hemoptysis (>1/2 teaspoon red blood) should not be treated with bevacizumab.

Lung cancer trials:
Of patients experiencing pulmonary hemorrhages requiring medical intervention, many had cavitation and/or necrosis of the tumor, either preexisting or developing during bevacizumab therapy. Patients developing lung cavitation on treatment should be assessed by the treating physician for risk-benefit.

In Study E4599, in which squamous cell carcinoma was excluded, the rate of any type of Grade ≥3 hemorrhage was 1.0% in the control arm (carboplatin and paclitaxel) versus 4.1% in the carboplatin and paclitaxel + bevacizumab arm (Sandler, Gray et al. 2006).

GI hemorrhages, including rectal bleeding and melena have been reported in patients with CRC, and have been assessed as tumor-associated hemorrhages.

Tumor-associated hemorrhages were also seen rarely in other tumor types and locations and included cases of CNS bleeding in patients with CNS metastases and in patients with glioblastoma.

The incidence of CNS bleeding in patients with untreated CNS metastases receiving bevacizumab has not been prospectively evaluated in randomized clinical studies. In an exploratory retrospective analysis of data from 13 completed randomized trials in patients with various tumor types, 3 patients out of 91 (3.3%) with brain metastases experienced CNS bleeding (all Grade 4) when treated with bevacizumab, compared to 1 case (Grade 5) out of 96 patients (1.0%) that were not exposed to bevacizumab. In two subsequent studies in patients with treated brain metastases (which included around 800 patients), one case of Grade 2 CNS hemorrhage was reported.

Intracranial hemorrhage can occur in patients with relapsed glioblastoma. In study AVF3708g, CNS hemorrhage was reported in 2.4% (2/84) of patients in the bevacizumab alone arm (Grade 1); and in 3.8% (3/79) of patients treated with bevacizumab and irinotecan (Grades 1, 2 and 4).

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. Patients should be monitored for signs and symptoms of CNS bleeding, and bevacizumab treatment

discontinued in cases of intracranial bleeding.

Mucocutaneous Hemorrhage:
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.

In patients who develop 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 (Glusker, Recht et al. 2006; Ozcan, Wong et al. 2006)

Congestive Heart Failure:
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 mBC: 2.9% in the anthracycline + Bv arm and 0% in the anthracycline + placebo arm. In addition, in study AVF3694g the incidence of any grade CHF was similar between the anthracycline + Bv (6.2%) and the anthracycline + placebo arms (6.0%). Most patients who developed CHF during mBC 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 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. Caution should be exercised before initiating bevacizumab therapy in patients with these risk factors.

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 congestive heart failure (CHF) were reported in clinical trials. The findings ranged from asymptomatic declines in left ventricular ejection fraction to symptomatic CHF, requiring treatment or hospitalization.

Caution should be exercised when treating patients with clinically significant cardiovascular disease such as pre-existing coronary artery disease, or congestive heart failure with bevacizumab. Patients receiving concomitant anthracyclines or with prior exposure to anthracyclines should have a baseline MUGA scans or echocardiograms (ECHOs) with a normal LVEF.

Ovarian Failure/Fertility:
The incidence of new cases of ovarian failure, defined as amenorrhea lasting 3 or more months, 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. 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 a reaction occurs, the infusion should be discontinued and appropriate

medical therapies should be administered. A systematic premedication is not warranted.

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 neutrophil count, decreased white blood count, 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 (≥2.0%) incidence in patients treated with bevacizumab compared to those in the control groups: hyperglycemia, decreased hemoglobin, hypokalemia, hyponatremia, decreased white blood cell count, increased PT (prothrombin time), normalized ratio.

Additional Adverse Events:
See the bevacizumab Investigator Brochure for additional details regarding the safety experience with bevacizumab.

1.23 Atezolizumab

TECENTRIQ™ (atezolizumab) is a humanized immunoglobulin (IgG1) monoclonal antibody that is produced in Chinese hamster ovary (CHO) cells. Atezolizumab targets programmed death−ligand 1 (PD-L1) on tumor-infiltrating immune cells (ICs) or tumor cells (TCs) and prevents interaction with the programmed death−1 (PD-1) receptor and B7.1 (CD80), both of which function as inhibitory receptors expressed on T cells and other immune cells. Interference of the PD-L1:PD-1 and PD-L1:B7.1 interactions may enhance the magnitude and quality of the tumor-specific T-cell response through increased T-cell priming, expansion, and/or effector function. Atezolizumab was engineered to eliminate Fc-effector function via a single amino acid substitution at position 298 on the heavy chain, which results in a non-glycosylated antibody that has minimal binding to Fc receptors and, consequently, eliminates detectable Fc-effector function. By eliminating Fc-effector function and antibody-dependent cell-mediated cytotoxicity, antibody-mediated clearance of activated effector T cells is also eliminated.

Expression of PD-L1 is prevalent among many human tumors (Dong et al. 2002), and its overexpression is associated with poor prognosis for patients with certain cancers (Thompson et al. 2006; Hamanashi et al. 2007; Okazaki and Honjo 2007; Hino et al. 2010). Therefore, interruption of the PD-L1/PD-1 pathway represents an attractive strategy to reinvigorate tumor-specific T-cell immunity.

Atezolizumab was approved by the U.S. FDA in May 2016 for the treatment of patients with locally advanced or mUC who 1) have disease progression during or following platinum-containing chemotherapy or 2) have disease progression

within 12 months of neoadjudvant or adjuvant treatment with platinum-containing chemotherapy.

1.231 Toxicology

Toxicology studies consisted of a 2-week, non−Good Laboratory Practice (GLP), repeat-dose pilot study in mice with a 4-week recovery period; 8- and 26-week, GLP, repeat-dose studies in cynomolgus monkeys with 12- and 13-week recovery periods, respectively; a non-GLP in vitro cytokine release assay; a GLP in vitro hemolytic potential and blood compatibility assay; and a GLP tissue cross-reactivity study using human and cynomolgus monkey tissues.

Atezolizumab was well tolerated in C57BL/6 and CD-1 mice at doses of up to 50 mg/kg weekly for 2 weeks (total of three doses). Minimal neuropathy, as evidenced by microscopic findings in the sciatic nerve, was noted in C57BL/6 mice at ≥ 10 mg/kg. This minimal neuropathy was attributed to blockade of PD-L1 by atezolizumab as it is consistent with the observation that female NOD-H2b/b Pdcd1−/− mice (PD-1−deficient) spontaneously develop autoimmune inflammation in multiple tissues, including peripheral nerves, between 20 and 25 weeks of age, while no such lesions were observed in age-matched PD-1−sufficient mice (Yoshida et al. 2008). No clinical observations were noted with this finding. No atezolizumab-related microscopic findings were observed in CD-1 mice.

Atezolizumab was also well tolerated in cynomolgus monkeys following doses of up to 50 mg/kg for up to 26 weeks. Atezolizumab-related arteritis/periarteritis in several organs is consistent with the primary pharmacology of PD-L1 inhibition and the deregulation of peripheral tolerance.

1.232 Clinical Pharmacology

Exposure to atezolizumab increased dose proportionally over the dose range of 1 mg/kg to 20 mg/kg, including the fixed dose of 1200 mg administered every 3 weeks (q3w). On the basis of a population pharmacokinetic (popPK) analysis that included 472 patients in the dose range of 1 mg/kg to 20 mg/kg, the typical population clearance (CL) was 0.20 L/day, the volume of distribution at steady state (Vss) was 6.9 L, and the terminal half-life (t1/2) was 27 days. The popPK analysis suggested that steady state was obtained after 6 to 9 weeks (2 to 3 cycles) of repeated dosing. The systemic accumulation in area under the concentration-time curve (AUC), maximum concentration (Cmax), and trough concentration (Cmin) was 1.91, 1.46, and 2.75-fold, respectively.

Based on an analysis of exposure-safety, and exposure-efficacy data, the following factors had no clinically relevant effect: age (21−89 years), body weight, gender, positive ATA status, albumin levels,

tumor burden, region or ethnicity, renal impairment, mild hepatic impairment, level of PD-L1 expression, or Eastern Cooperative Oncology Group (ECOG) status.

The effect of moderate or severe hepatic impairment (bilirubin > upper limit of normal [ULN] and AST > ULN or bilirubin ≥ 1.0 to 1.5 • ULN and any AST elevation) on the pharmacokinetics of atezolizumab is unknown.

No formal PK drug-drug interaction studies have been conducted with atezolizumab. The drug interaction potential of atezolizumab is unknown.

1.233 Clinical Studies

As of May 10, 2016, clinical data on atezolizumab as a single agent or in combination with chemotherapy or targeted agents are available from 17 studies as follows:

- Monotherapy: Studies JO28944, PCD4989g, GO29293 (hereinafter referred to as IMvigor 210), GO29625 (hereinafter referred to as FIR), GO28753 (hereinafter referred to as POPLAR), GO28754 (hereinafter referred to as BIRCH), and WO29074 (hereinafter referred to as IMmotion 150, where Arm B evaluates atezolizumab as a single agent)

- Combination: Studies GP28328, GP28384, GP28363, GO29383, IMmotion 150 (where Arm A evaluates atezolizumab in combination with bevacizumab), WP29158, GO29322, BP29428, GO29674, BP29435, and BP29392

Refer to atezolizumab (MPDL3280A) Investigator's Brochure Version 8 July 2016 for details of ongoing studies.

1.234 Safety

As of 10 May 2016, an estimated total of 6053 patients with solid tumor and hematologic malignancies have received atezolizumab in clinical trial participation as a single agent or in combination with cytotoxic chemotherapy and/or targeted therapy.

Safety findings of single-agent atezolizumab across multiple tumor types in the clinical development program are consistent with the known mechanism of action of atezolizumab and the underlying disease. Overall, treatment with atezolizumab is well tolerated, with a manageable adverse event profile. Currently, no maximum tolerated dose, no dose-limiting toxicities, and no clear dose-related trends in the incidence of adverse events have been determined. Across all studies and tumor types, the most commonly reported adverse events with single-agent atezolizumab include fatigue,

nausea, decreased appetite, diarrhea, constipation, and cough.

The adverse events observed with atezolizumab in combination with chemotherapy and/or targeted therapies are consistent with the known risks of each study treatment. Systemic immune activation, characterized by an excessive immune response, is a potential risk associated with atezolizumab when used in combination with another immunomodulating compound.

The percentage of patients who discontinued atezolizumab due to any adverse event is consistent when used as a single agent or in combination with chemotherapy (e.g., 5.4% in Study PCD4989g and 5.8% in Study GP28328, respectively). The percentage of patients with any Grade 5 adverse event was similar when used as a single agent or in combination with chemotherapy (e.g., 1.6% in Study PCD4989g and 1.0% in Study GP28328).

Please refer to atezolizumab (MPDL3280A) Investigator's Brochure Version 8 July 2016 for a detailed discussion of available safety data from select studies in the atezolizumab clinical program.

Immune-related adverse events are consistent with the role of the PD-L1/PD-1 pathway in regulating peripheral tolerance. Given the mechanism of action of atezolizumab, events associated with inflammation and/or immune-related adverse events are closely monitored during the atezolizumab clinical program. As of this IB update, immune-related adverse events associated with atezolizumab include hepatitis, pneumonitis, colitis, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism, adrenal insufficiency, Guillain-Barré syndrome, myasthenic syndrome/myasthenia gravis, and meningoencephalitis.

Table 1.234 Serious Adverse Drug Reactions for Atezolizumab in All Indications for Regulatory Reporting Purposes Only

Serious Adverse Drug Reaction Single or Grouped Clinical MedDRA Preferred Term	All SAEs No. of Patients (%) (n = 1978)	Comment
Abdominal pain		
Abdominal pain	22 (1.1%)	—
Abdominal pain lower	1 (<0.1%)	—
Abdominal pain upper	3 (0.2%)	—
Adrenal insufficiency		
Adrenal insufficiency	3 (0.2%)	—
Arthralgia		
Arthralgia	6 (0.3%)	—
Asthenia		
Asthenia	9 (0.5%)	—
Malaise	7 (0.4%)	—
Lethargy [a]	1 (<0.1%)	—

Serious Adverse Drug Reaction Single or Grouped Clinical MedDRA Preferred Term	All SAEs No. of Patients (%) (n = 1978)	Comment
Autoimmune neuropathy		
Neuropathy peripheral	1 (< 0.1%)	—
Peripheral sensory neuropathy	1 (< 0.1%)	—
Autoimmune neuropathy [a]	1 (< 0.1%)	—
Paraesthesia [a]	4 (< 0.1%)	—
Peripheral motor neuropathy [a]	1 (< 0.1%)	—
Peripheral sensorimotor neuropathy [a]	1 (< 0.1%)	—
Back pain		
Back pain	23 (1.2%)	—
Chills		
Chills	2 (0.1%)	—
Colitis		
Colitis	8 (0.4%)	—
Autoimmune colitis [a]	3 (< 0.1%)	—
Colitis ischaemic [a]	2 (< 0.1%)	—
Enterocolitis [a]	2 (< 0.1%)	—
Decreased appetite		
Decreased appetite	2 (0.1%)	—
Dermatitis bullous		
Dermatitis bullous [a]	2 (< 0.1%)	—
Pemphigoid [a]	1 (< 0.1%)	—
Diabetic ketoacidosis		
Diabetic ketoacidosis [a]	1 (< 0.1%)	—
Ketoacidosis [a]	1 (< 0.1%)	—

Serious Adverse Drug Reaction Single or Grouped Clinical MedDRA Preferred Term	All SAEs No. of Patients (%) (n=1978)	Comment
Diabetes mellitus		
Diabetes mellitus	2 (0.1%)	—
Type 1 diabetes mellitus [a]	1 (<0.1%)	—
Hyperglycaemia [a]	11 (0.2%)	—
Diarrhoea		
Diarrhoea	13 (0.7%)	—
Dysphagia		
Dysphagia	5 (0.3%)	—
Dyspnoea		
Dyspnoea	60 (3.0%)	—
Encephalitis		
Encephalitis	1 (<0.1%)	—
Encephalopathy	3 (0.2%)	—
Fatigue		
Fatigue	12 (0.6%)	—
Guillain-Barré syndrome		
Guillain-Barré syndrome	1 (<0.1%)	—
Headache		
Headache [a]	11 (0.2%)	—

Serious Adverse Drug Reaction Single or Grouped Clinical MedDRA Preferred Term	All SAEs No. of Patients (%) (n = 1978)	Comment
Hepatitis		
Autoimmune hepatitis [b]	1 (<0.1%)	Fatal outcome expected for reporting purposes
Hepatitis [b]	1 (<0.1%)	Fatal outcome expected for reporting purposes
Drug-induced liver injury [a]	1 (<0.1%)	—
Hepatitis acute [a]	1 (<0.1%)	—
Hepatocellular injury [a]	2 (<0.1%)	—
Hepatotoxicity [a]	2 (<0.1%)	—
Hypersensitivity		
Hypersensitivity	1 (<0.1%)	—
Anaphylactic reaction [a]	3 (<0.1%)	—
Drug hypersensitivity [a]	5 (<0.1%)	—
Hypokalaemia [a]	4 (<0.1%)	—
Hyponatraemia		
Hyponatraemia	11 (0.6%)	—
Hypotension		
Hypotension	6 (0.3%)	—
Hypothyroidism		
Autoimmune hypothyroidism	1 (<0.1%)	—
Hypothyroidism	4 (0.2%)	—
Thyroiditis acute	1 (<0.1%)	—
Blood thyroid stimulating hormone increased [a]	1 (<0.1%)	—
Hypoxia		
Hypoxia	12 (0.6%)	—

Serious Adverse Drug Reaction Single or Grouped Clinical MedDRA Preferred Term	All SAEs No. of Patients (%) (n = 1978)	Comment
Influenza-like illness		
Influenza-like illness	4 (0.2%)	—
Infusion-related reaction		
Infusion-related reaction	2 (0.1%)	—
Liver function test abnormal		
Alanine aminotransferase increased	5 (0.3%)	—
Aspartate aminotransferase increased	9 (0.5%)	—
Blood alkaline phosphatase increased	1 (<0.1%)	—
Blood bilirubin increased	3 (0.2%)	—
Gamma-glutamyltransferase increased	1 (<0.1%)	—
Hepatic enzyme increased	1 (<0.1%)	—
Liver function test abnormal	1 (<0.1%)	—
Liver function test increased [a]	5 (<0.1%)	—
Transaminases increased [a]	4 (<0.1%)	—
Hepatic function abnormal [a]	2 (<0.1%)	—
Hyperbilirubinaemia [a]	7 (0.1%)	—
Meningitis		
Meningitis	2 (0.1%)	—
Muscular weakness		
Muscular weakness	6 (0.3%)	—
Musculoskeletal pain		
Musculoskeletal pain	3 (0.2%)	—
Myalgia	1 (<0.1%)	—
Myasthenia gravis		
Myasthenia gravis	1 (<0.1%)	—

Serious Adverse Drug Reaction Single or Grouped Clinical MedDRA Preferred Term	All SAEs No. of Patients (%) (n=1978)	Comment
Nausea		
Nausea	16 (0.8%)	—
Pancreatitis		
Pancreatitis	1 (<0.1%)	—
Pancreatitis acute	1 (<0.1%)	—
Autoimmune pancreatitis [a]	1 (<0.1%)	—
Pneumonitis		
Interstitial lung disease	1 (<0.1%)	—
Pneumonitis [b]	24 (1.2%)	Fatal outcome expected for reporting purposes
Lung infiltration [a, c]	1 (<0.1%)	—
Organising pneumonia [a]	1 (<0.1%)	—
Pruritus [a]	5 (<0.1%)	—
Pyrexia		
Hyperthermia	2 (0.1%)	—
Pyrexia	48 (2.4%)	—
Rash		
Rash	3 (0.2%)	—
Rash pruritic	1 (<0.1%)	—
Erythema nodosum [a]	1 (<0.1%)	—
Rash maculo-papular [a]	5 (<0.1%)	—
Thrombocytopenia		
Platelet count decreased	1 (<0.1%)	—
Thrombocytopenia	2 (0.1%)	—

Serious Adverse Drug Reaction Single or Grouped Clinical MedDRA Preferred Term	All SAEs No. of Patients (%) (n=1978)	Comment
Vomiting		
Vomiting	13 (0.7%)	—

SAE=serious adverse event.

[a] Based on cumulative exposure (as of 10 May 2016) of 6053 patients in the clinical development program who received atezolizumab as a single agent or in combination with chemotherapy/targeted therapy.

[b] Fatal outcome(s) reported in either the pooled population or across the clinical development program.

[c] Severity not reported.

Important Identified Risks

The classification of an adverse event as an identified risk/adverse drug reaction (ADR) or a potential risk is based on the data available at the time of assessment. Data obtained at later dates may refute the connection between an adverse event and atezolizumab and lead to an ADR being subsequently reclassified as an adverse event.

As of May 10, 2016, the information below presents a summary of important identified risks for atezolizumab. The safety data presented below is primarily based on pooled single-agent data from 1547 patients with mUC and NSCLC from IMvigor 210, POPLAR, BIRCH, FIR, and Study PCD4989g.

To date, there are no additional identified risks/ADRs specific to the combination of atezolizumab when given with another therapeutic agent. The identified risks/ADRs of other therapeutic agents used in combination with atezolizumab can be found in their respective IBs or Prescribing Information.

A summary of important identified risks is presented below.

Immune-related hepatitis: Cases of hepatitis, some leading to fatal outcomes, have been observed in clinical trials with atezolizumab. Most of the hepatic events identified were non-serious elevations of liver enzymes. Hepatitis occurred in 0.3% (4/1547) of patients who received atezolizumab. The median time to onset was 1.1 months (range: 9 days to 7.9 months). The median duration was 1.2 months (range: 21 days to 1.9 + months; + denotes a censored value). Hepatitis requiring the use of corticosteroids occurred in 0.1% (2/1547) of patients receiving atezolizumab. All of these events resolved with the exception of one case of Grade 1 hepatitis, which was resolving at the time of data cutoff. Additionally, 1 patient (< 0.1%) experienced hepatic failure (with fatal outcome, considered unrelated to study therapy).

Immune-related pneumonitis: Pneumonitis occurred in 3.0% (47/1547) of patients who received atezolizumab. The majority of

patients experienced only mild to moderate events. Of the 47 patients, 66% of the All NSCLC group and 67% of the All UC group experienced events with a maximum severity of Grade 1 or 2. One event was fatal in the All NSCLC group (considered unrelated to atezolizumab), and no events were fatal in the All UC group. The median time to onset was 2.9 months (range: 3 days to 18.7 months). The median duration was 1.4 months (range: 0 days to 12.6 + months; + denotes a censored value). Pneumonitis led to discontinuation of atezolizumab in 6 (0.4%) patients. Pneumonitis requiring the use of corticosteroids occurred in 1.6% (24/1547) of patients receiving atezolizumab. As expected, pneumonitis events occurred more frequently in the NSCLC patient population, most likely due to higher baseline incidence, higher prevalence of other risk factors, and atezolizumab-induced immunologic response to the tumor.

Immune-related colitis: Cases of diarrhea or colitis have been observed in clinical trials with atezolizumab. Colitis occurred in 1.0% (15/1547) of patients who received atezolizumab. The median time to onset was 2.7 months (range: 15 days to 7.3 months). The median duration was 2.5 months (range: 6 days to 8.3 + months; + denotes a censored value). Colitis led to the discontinuation of atezolizumab in 3 (0.2%) patients. Colitis requiring the use of corticosteroids occurred in 0.3% (4/1547) of patients receiving atezolizumab.

Immune-related pancreatitis: Pancreatitis, including amylase increased and lipase increased, occurred in 0.5% (7/1547) of patients who received atezolizumab. Most events identified were non-serious elevations in lipase or amylase. A total of 2 (0.1%) patients experienced pancreatitis, including 1 patient with acute pancreatitis. The median time to onset was 2.6 months (range: 8 days to 10.9 months). The median duration was 1.8 months (range: 3 days to 5.9 + months; + denotes a censored value).

Immune-related diabetes mellitus: Diabetes mellitus occurred in 0.3% (5/1547) of patients who received atezolizumab. Of these, 2 cases were serious and 3 were considered non-serious. The time to onset ranged from 1.6 to 6.5 months. Diabetes mellitus led to the discontinuation of atezolizumab in 1 (< 0.1%) patient.

Immune-related hypothyroidism: Hypothyroidism occurred in 3.6% (56/1547) of patients who received atezolizumab. The median time to onset was 4.8 months (range: 15 days to 11.3 months). Events have generally been mild, and patients who received treatment with thyroid replacement were able to continue on study treatment.

Immune-related hyperthyroidism: Hyperthyroidism occurred in 0.8% (13/1547) of patients who received atezolizumab. The median time to onset was 3.5 months (range: 21 days to 9.1 months). No severe events were identified.

Immune-related adrenal insufficiency: Adrenal insufficiency

occurred in 0.1% (2/1547) of patients who received atezolizumab. The time to onset for the 2 patients (Grade 1−2) was 3 days and 5.2 months. Both patients required the use of corticosteroids.

Immune-related Guillain-Barré syndrome: Guillain-Barré syndrome, which may be life threatening, was observed in a patient receiving atezolizumab. Patients should be monitored for symptoms of motor and sensory neuropathy. Guillain-Barré syndrome occurred in < 0.1% (1/1547) of patients who received atezolizumab. The time to onset for this event was 8.1 months, and the duration was 1.2 months. This patient discontinued atezolizumab due to Guillain-Barré syndrome.

Immune-related myasthenic syndrome/myasthenia gravis: Myasthenic syndrome/myasthenia gravis were observed in patients receiving atezolizumab. Patients should be monitored for symptoms of motor and sensory neuropathy. Two cases of myasthenia gravis or myasthenic syndrome have been reported from across the entire development program as of 25 Febrauary 2016. The first case concerned a 64-year-old male patient receiving atezolizumab monotherapy for RCC in the Study PCD5989g (GO27831). The patient was positive for acetylcholine receptor binding antibodies and acetylcholine receptor modulating antibodies. The event was considered serious and the patient was treated with corticosteroids and discontinued from the study. A second case of myasthenia gravis was received concerning a 64-year-old male patient receiving atezolizumab in combination with ipilimumab in Study GO29322. The event was considered serious, and the patient was treated with corticosteroids and mycophenolate and discontinued from the study.

Immune-related meningoencephalitis: Encephalitis occurred in < 0.1% (1/1547) of patients who received atezolizumab. This patient developed serious Grade 3 encephalitis on Study Day 16 while participating in the BIRCH study and fully recovered (duration 13 days) following treatment with antibiotics and steroids in addition to anti-viral and anti-convulsant medications.

Infusion-related reactions: Infusion-related reactions are known to occur with the administration of monoclonal antibodies. The signs and symptoms of infusion-related reactions share considerable overlap with several very common atezolizumab ADRs including influenza-like illness, pyrexia, and rash. The identified reactions occurred within 24 hours of atezolizumab administration and were generally mild to moderate in severity, and only 8 patients (0.5%) developed serious adverse events. Nineteen (1.2%) of 1547 patients were reported to have experienced the event of infusion reaction (with one serious event). Across all 1547 patients, 12 patients (0.8%) were reported to have hypersensitivity (with one serious event), and none were reported to have experienced anaphylactic or anaphylactoid reactions.

Important Potential Risks

The classification of an adverse event as a potential risk is based on the mechanism of action of atezolizumab, nonclinical findings, and other agents with similar mechanisms of action. Atezolizumab belongs to the class of immune-checkpoint inhibitors that enhance the magnitude and quality of tumor-specific T-cell responses by blocking molecules (such as PD-1, PD-L1, or cytotoxic T-lymphocyte antigen 4) that negatively regulate T-cell activation (Gangadhar and Vonderheide 2014).

A summary of important potential risks is presented below.

Anti-therapeutic antibodies: After a single IV administration to cynomolgus monkeys, anti-atezolizumab antibodies were detected in 12 of 12 animals (100%) at Day 14; 11 of 12 animals remained ATA positive after Day 14 until the end of the study. Fifty of 56 animals (89%) given atezolizumab showed ATAs following nine weekly doses. While ATAs affected the pharmacokinetics of some animals, average exposure for ATA-positive and ATA-negative animals was similar. ATAs have been observed in the clinical trials to date for atezolizumab; however, at doses of 10 mg/kg and above, they do not appear to affect exposure. The incidence of SAEs was increased in ATA-positive patients (40.2%) compared with ATA-negative patients (33.5%), but no specific trend in either MedDRA SOC or individual adverse event preferred term was identified in ATA-positive patients. In all safety-evaluable patients with available post-treatment ATA status (n = 888), the incidence of hypersensitivity events and infusion-related reactions was low and consistent between ATApositive and ATA-negative patients. Hypersensitivity events were reported in 18 patients (1.4%): 8 ATA-negative (1.1%) and 10 ATApositive (1.9%) patients. Infusion-related reactions occurred in 20 patients (1.6%): 11 ATA-negative (1.5%) and 9 ATA-positive (1.7%) patients.

The incidences of all grade adverse events, Grade 5 adverse events, adverse events leading to treatment withdrawal, adverse events leading to dose interruption, and AESIs were similar irrespective of post-baseline ATA status (negative or positive). Differences were observed in Grade 3−4 adverse events (38.4% in ATA-negative vs. 44.3% in ATA-positive patients), driven mainly by more adverse events reported in the gastrointestinal disorders SOC (5.7% vs. 8.5%), but no individual preferred term could be identified to explain this difference.

Embryofetal toxicity: Several nonclinical studies have demonstrated that the PD-L1/PD-1 signaling pathway is critical in establishing and maintaining maternal/fetal tolerance, which is essential for embryo-fetal survival during gestation (Guleria et al. 2005; Habicht et al. 2007; D'Addio et al. 2011). Inhibition of the PD-L1/PD-1 pathway has not been reported to result in teratogenic effects, and syngeneic homozygous knockout fetuses (PD-L1 or PD-1 knockouts) develop normally and have not shown skeletal or visceral defects. Administration of atezolizumab is expected to have an adverse effect

on pregnancy via modulation of maternal/fetal tolerance, and poses a risk to the human fetus, including embryo-lethality via an increased risk of immune-mediated rejection.

No reproductive or teratogenicity studies in animals have been conducted with atezolizumab. There are no clinical studies of atezolizumab in pregnant women. Atezolizumab is not recommended during pregnancy unless the potential benefit for the mother outweighs the potential risk to the fetus.

Other Potential Risks and Class Effects

Other safety events of interest that are currently being monitored in the atezolizumab clinical program include the following: immune-related myositis, immune-related nephritis, immune-related uveitis, immune-related myopathies, and rhabdomyolysis.

Immune-Related Myositis: Three cases in the atezolizumab global safety database were identified, including one case of myasthenia gravis (which is an identified risk for atezolizumab), one case of polymyalgia rheumatic, and one case of dermatomyositis from BIRCH. The dermatomyositis case had features consistent with cancer-associated myositis, and there was insufficient evidence to support the attribution of a causal relationship between myositis and atezolizumab. Myositis is an ADR for other immune-checkpoint inhibitors. Myositis remains a potential risk for atezolizumab and will continue to be monitored by routine pharmacovigilance.

Immune-Related Nephritis: Nephritis is a concern, given the mechanism of action of atezolizumab and findings from other immune-modulating agents. A search of the atezolizumab global safety database retrieved a total of two cases, including one case of nephritis from Study GP28384 and one case of nephrotic syndrome from Study GO29432. Both had clear alternative explanations, and the available evidence did not demonstrate that atezolizumab was causally associated with nephritis. Nephritis remains a potential risk for atezolizumab and will continue to be monitored by routine pharmacovigilance.

Immune-Related Uveitis: Three cases (representing approximately 0.1% of atezolizumab patients) containing four events were identified, originating from Studies GP28384 and WP29158. All three cases were nonserious and contained compelling alternative explanations. Uveitis is not considered an important risk for atezolizumab, and it will continue to be monitored by routine pharmacovigilance.

Immune-Related Myopathies, Including Rhabdomyolysis: Reports of myopathies, including rhabdomyolysis, have been observed across the clinical development program of atezolizumab. Patients who present with signs or symptoms of muscular pain should be assessed for inflammatory causes for muscle pains. Management of these patients should be along institutional guidelines.

Risk	Notes/ Exclusions
Gastrointestinal Disorders	Includes colitis, diarrhea, dysphagia, nausea, vomiting, abdominal pain and decreased appetite
Dermatologic reactions	Includes rash and pruritus
Endocrine disorders	Includes hyperthyroidism, hypothyroidism and adrenal insufficiency
Hepatitis[a]	Includes ALT increased, AST increased, and hepatic enzymes abnormal
Hypersensitivity reactions/ Infusion-related Reactions	
Influenza-like illness	Includes arthralgia, musculoskeletal pain, asthenia, chills, fever, fatigue, and nasal congestion
Nervous system disorders	Includes meningitis, Guillain-Barre syndrome, myasthenic syndrome
Pneumonitis[a]	Includes dyspnea and hypoxia
General and Metabolic disorders	Includes hyponatremia , hypokalemia, and insomnia
Vascular disorders	Includes hypertension and hypotension

ALT = alanine aminotransferase; AST = aspartate aminotransferase.
Note: Any term covered by the medical concepts presented in this list is considered "expected" for both non-serious and serious reports of suspected unexpected ADRs to Health Authorities, excluding events with fatal outcome unless detailed otherwise in the table.
[a] Includes fatal events.

1.3 Study Rationale

Preclinical and clinical data suggest that anti-VEGF therapy may augment immunotherapy, including anti-PD-L1 treatment. Preliminary data from patients with refractory metastatic colorectal cancer suggest that bevacizumab may increase the immunogenicity of colorectal cancers, that the combination of atezolizumab plus bevacizumab may be associated with clinically meaningful response rates and disease control, and that there are candidate biomarkers that may help identify those patients most likely to benefit from this combination regimen. The proposed randomized phase II study is meant to follow up these promising but preliminary findings.

1.4 Correlative Research

The importance of developing cancer biomarkers offers the potential to identify patients most likely to benefit and/or have toxicity from novel therapies and to define mechanisms of resistance that may potentially improve the clinical outcomes of cancer patients and the cost-effectiveness of cancer therapies. In the last decade, our understanding of tumor angiogenesis, pro-cancer inflammation and anti-tumor immunity have increased dramatically, as have the technologies available to assess these biologies. The VEGF and PD axes are among the most important targets in these areas. The key drivers of cancer biology are the targets of bevacizumab and atezolizumab, respectively.

Archived FFPE tumor samples, plasma, serum, and circulating immune cells will be collected and analyzed with the goal of better understanding the mechanisms of action, sensitivity, resistance, and toxicity for bevacizumab and atezolizumab, and the biology of colorectal cancer. Studies will be performed using optimized assays under the supervision of the Duke Phase I Biomarker Laboratory at Duke University Medical Center, which acts as a molecular profiling laboratory for tissue- and blood-based biomarkers of targeted therapies, and the Duke Immune Profiling Core (DIPC) Laboratory, which acts as a core facility to study the immune correlates of immune directed therapies.

All analyses will be based upon the best science and technology at the time of analysis, sample quantities, and available funding. Patterns of expression will be described, expression among markers will be correlated, and expression will be correlated with clinical outcomes. Details of statistical analyses are described in the statistical section of the protocol.

1.41 Tissue Based Biomarkers: Archival formalin-fixed paraffin-embedded (FFPE) tumor tissue will be analyzed by immunohistochemistry and quantitative polymerase chain reaction (qPCR) assays, although other technologies may be utilized. Candidate markers may include, but are not limited to, VEGF, IL6, and PD axis ligands, receptors, and co-receptors and other markers related to tumor angiogenesis, inflammation, and immunity, and colon cancer biology. MSI status may also be analyzed by IHC or PCR; mutational load may be assessed by NGS. Immune cell populations may also be analyzed including, but not limited to, CD3, CD4, CD8, CD56, CD68, Foxo-P3, Th17 cells.

1.42 Plasma and Serum Biomarkers: Plasma and serum markers will be analyzed by multiplex ELISA approaches, although other technologies may be used. Candidate markers may include, but are not limited to, VEGF-A, -C, -D, VEGFR-1, -2, -3, IL6, IL6R, s-gp130, IL11, IL17A, IL17E, IL17R, IL22, IL22, IL23, and TGFβ. Other markers related to tumor angiogenesis, inflammation, and immunity, and colon cancer biology may also be evaluated. Analyses of cell free DNA in plasma may also be considered to assess genetic alterations, using technologies such as next generation genomic sequencing or digital PCR. Candidate alterations include, but are not limited to, mutations in Ras and Raf.

1.43 Circulating Immune Cell Biomarkers: Immune cell correlates using flow-based assays will be performed in collaboration with the Duke Immune Profiling Core (DIPC) laboratory. Cells to be used in flow-based assays will be obtained from individual patients' acid citrate dextrose (ACD) anti-coagulated fresh whole blood that have been processed to isolate peripheral blood mononuclear cells (PBMC), cryopreserved, and stored in liquid nitrogen (LN2) freezers for batch processing.

It is anticipated that two fifteen color polychromatic flow cytometry panels will be used to analyze changes in the immune cell subtypes that are expected to be altered by treatment. Other technologies approaches may also be considered. The 13-color base panels to identify immune cell types and related markers will be determined based upon the best science available at the time of analysis. The lymphoid panel focuses on T-cell activation, maturation,

regulation, and exhaustion. The myeloid panel focuses on myeloid derived suppressor cells (MDSC), M1/M2 polarization, and dendritic cells (DC, pDC). The markers included in each respective panel have been reported to be of value in the context of prognostic or predictive immune markers in cancer studies (Blank, Gajewski et al. 2005; Blank and Mackensen 2007; Keir, Butte et al. 2008; Brahmer, Tykodi et al. 2012; Sznol, McDermott et al. 2015). While the majority of immune markers reported are associated with the tumor microenvironment, measurement of peripheral MDSCs has been associated with progression free survival in the context of neoadjuvant ipilimumab therapy for melanoma. The two additional markers for each panel are included to enable assaying for novel markers based on literature current at the time of funding as well as scientific data supporting the use for each additional marker. Data will be analyzed using novel computational methods developed at Duke that can be used to identify multi-dimensional populations and evaluate changes in these populations across treatment (Chan, Feng et al. 2008; Frelinger, Ottinger et al. 2010).

1.44 Pharmacogenomic Biomarkers: Germ-line DNA will be isolated from peripheral blood mononuclear cells and stored for potential pharmacogenomics analyses. Candidate gene of interest for analysis include those known to regulate angiogenesis, inflammation, immunity, auto-immunity, and antibody or drug action of clearance, such as VEGF, NOS, IL6, IL17, Fc Receptors, and MHCs.

2.0 Goals

2.1 Primary

2.11 To estimate the efficacy of capecitabine/bevacizumab + atezolizumab, as compared with capecitabine/bevacizumab + placebo in refractory metastatic colorectal cancer (mCRC) as measured by progression-free survival (defined as the time of randomization to the first occurrence of progression based on Response Evaluation Criteria in Solid Tumors version 1.1, clinical progression, or death from any cause on study as determined by the Investigator).

2.2 Secondary

2.21 To estimate the efficacy of capecitabine/bevacizumab + atezolizumab, as compared with capecitabine/bevacizumab + placebo in refractory mCRC as measured by objective response rate (defined as partial response plus complete response) as determined by the Investigator using Response Evaluation Criteria in Solid Tumors version 1.1 and immune-related response criteria (irRC).

2.22 To estimate the efficacy of capecitabine/bevacizumab + atezolizumab as compared with capecitabine/bevacizumab + placebo in refractory mCRC as measured by overall survival (defined as death from any cause from the time of randomization until study completion).

2.23 To evaluate the safety and tolerability of atezolizumab in combination with bevacizumab and capecitabine in refractory mCRC as measured by the serious

adverse events and adverse events ≥ grade 3 according to National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0.

2.3 Correlative Research

2.31 To explore any correlation between tissue and blood based biomarkers and clinical outcomes.

3.0 Patient Eligibility

3.1 Randomization – Inclusion Criteria

3.11 Age ≥18 years.

3.12 Histologically confirmed colorectal cancer that is either clinically or histologically proven to be metastatic and has progressed on regimens containing a fluoropyrimidine (e.g., 5-fluorouracil or capecitabine), oxaliplatin, irinotecan, bevacizumab and an anti-EGFR antibody (if tumor is RAS wild-type), or where the treatment was not tolerated or contraindicated.

3.13 Measurable disease as defined in Section 11.0. Note: Previously irradiated sites can be included if there is documented disease progression in that site.

3.14 Capecitabine and bevacizumab considered appropriate treatment for the patient.

3.15 ECOG Performance Status (PS) 0-1. (Form is available on the ACCRU web site)

3.16 The following laboratory values obtained ≤7 days prior to randomization.

- Absolute neutrophil count ≥ 1,500/μL
- Platelets ≥ 100,000/μL
- Total bilirubin ≤ 1.5 X upper limit of normal (ULN) Patients with known Gilbert's Syndrome who have serum bilirubin ≤ 3 X ULN may enroll.
- AST/ALT ≤ 1.5 X ULN; < 3X ULN if known hepatic metastases
- Hemoglobin ≥ 9 g/dL Continuation of erythropoietin products is permitted. Hemoglobin must be stable ≥ 9 g/dL ≥14 days without blood transfusion to maintain hemoglobin level.
- Calculated creatinine clearance must be ≥50 ml/min using the Cockcroft-Gault formula below or a 24 hour urine:

Cockcroft-Gault Equation:

Creatinine clearance for males = $\frac{\text{(140 - age)(weight in kg)}}{\text{(72)(serum creatinine in mg/dL)}}$

Creatinine clearance for females = $\frac{\text{(140 - age)(weight in kg)(0.85)}}{\text{(72)(serum creatinine in mg/dL)}}$

3.17 The following laboratory values obtained ≤14 days prior to randomization.

- PT/PTT/INR ≤1.5 X ULN if not anticoagulated.
  Within local institutional guidelines per local physician if anticoagulated.

3.18 Negative pregnancy test done ≤7 days prior to randomization, for women of childbearing potential only.

3.19a Provide informed written consent.

3.19b Willingness to return to enrolling institution for follow-up (during the Active Monitoring Phase of the study).

3.19c Willingness to provide tissue and blood samples for correlative research purposes (see Sections 6.0, 14.0 and 17.0).

3.19d Life expectancy of ≥3 months.

3.2 Randomization – Exclusion Criteria

3.21 Any of the following because this study involves an investigational agent whose genotoxic, mutagenic and teratogenic effects on the developing fetus and newborn are unknown:

- Pregnant women
- Nursing women
- Women of child-bearing potential must agree to use two forms of adequate contraception from time of initial consent, for the duration of study participation, and for ≥6 months after the last dose of study drug. Medically acceptable contraceptives include: (1) surgical sterilization (such as a tubal ligation or hysterectomy), (2) approved hormonal contraceptives (such as birth control pills, patches, implants or injections), (3) barrier methods (such as a condom or diaphragm) used with a spermicide, or (4) an intrauterine device (IUD). Contraceptive measures such as Plan B™, sold for emergency use after unprotected sex, are not acceptable methods for routine use. Postmenopausal woman must have been amenorrheic for at least 2 years to be considered of non-childbearing potential. Sexually active men must use at least one form of adequate contraception from time of initial consent, for the duration of study participation, and for ≥ 6 months after the last dose of study drug.

3.22 Chemotherapy, biologic anti-cancer therapy, or central field radiation therapy

≤28 days prior to randomization. Note: Local or stereotactic radiation ≤14 days prior to randomization.

3.23 Any investigational agent ≤28 days or 5 half-lives prior to randomization (whichever is longer).

3.24 Prior treatment with atezolizumab or another PD-L1/PD-1 therapy.

3.25 History of allergic reactions attributed to therapeutic antibodies. Note: Patients with reactions to chimeric antibodies may be permitted on a case by case basis with approval by Study Chair by contacting the Data Manager.

3.26 Known untreated CNS metastases. Note: Patients with radiated or resected lesions are permitted, provided the lesions are fully treated and inactive, patients are asymptomatic, and no steroids have been administered for this purpose ≤30 days prior to randomization.

3.27 Inadequately controlled hypertension (defined as average systolic blood pressure >150 mmHg and/or diastolic blood pressure >100 mmHg).

3.28 History of hypertensive crisis or hypertensive encephalopathy.

3.29a New York Heart Association (NYHA) Grade II or greater congestive heart failure (Form is available on the ACCRU web site https://www.accru.org/accru/forms/NonProtocolSpecificForms/index.html).

3.29b History of myocardial infarction, unstable angina, cardiac or other vascular stenting, angioplasty, or surgery ≤12 months prior to randomization.

3.29c Active coronary heart disease evidenced as angina or requiring medications to prevent angina.

3.29d History of stroke or transient ischemic attack, or other arterial thrombosis ≤12 months prior to randomization.

3.29e Symptomatic peripheral vascular disease.

3.29f Any other significant vascular disease (e.g., aortic aneurysm, aortic dissection, or carotid stenosis that requires medical or surgical intervention, including angioplasty or stenting).

3.29g Any previous NCI CTCAE Grade 4 venous thromboembolism.

3.29h Clinically-significant evidence of bleeding diathesis or coagulopathy as so judged by the treating physician.

3.29i History of active gastrointestinal (GI) bleeding or other major bleeding ≤12 months prior to randomization. Note: Patients who do not have resolution of the predisposing risk factor (e.g., resection of a bleeding tumor, treatment and endoscopic documentation of a resolved ulcer) will also be excluded.

3.29j Major surgical procedure, open biopsy, or significant traumatic injury ≤56 days prior to randomization.

3.29k Anticipation of need for major surgical procedure ≤6 months after randomization.

3.29l Minor surgical procedure ≤7 days prior to randomization. Exception: Insertion of an indwelling catheter or percutaneous needle biopsy ≤48 hours prior to randomization.

3.29m History of intra-abdominal abscess ≤6 months prior to randomization. Note: If the affected area was surgically resected, and there is no further risk to the area, patients may enroll.

3.29n History of abdominal or other significant fistula, gastrointestinal or other organ perforation. Note: If the affected area was surgically resected, and there is no further risk to the area, patients may enroll.

3.29o Serious, non-healing wound, ulcer, or bone fracture as so judged by the treating physician.

3.29p Known proteinuria defined by ≥2+ protein by urinalysis (UA) or ≥1 gram protein by 24 hour urine collection. Note: Subjects that are ≥2+ or greater on dipstick but <1 g protein on 24 hour urine ARE eligible to participate.

3.29q Intolerance to bevacizumab defined as any NCI CTCAE Grade 3 or Grade 4 toxicity attributed to this agent that required discontinuation of bevacizumab (e.g., arterial thromboembolism [ATE], perforation, wound healing difficulty, proteinuria, reversible posterior leukoencephalopathy syndrome [RPLS]). Note: Patients with prior Grade 3 bevacizumab-related hypertension may be permitted if hypertension was manageable with standard oral antihypertensives as so judged by the treating physician.

3.29r Known dihydropyrimidine dehydrogenase (DPD) deficiency.

3.29s Impairment of GI function or GI disease that may significantly alter capecitabine drug absorption.

3.29t Active inflammatory bowel disease.

3.29u History of diverticulitis, chronic ulcerative lower GI disease such as Crohn's disease or ulcerative colitis, or other symptomatic lower GI conditions that might predispose to perforations.

3.29v History of autoimmune disease including, but not limited to, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Bell's palsy, Guillain-Barré syndrome, multiple sclerosis, autoimmune thyroid disease, vasculitis, or glomerulonephritis. Note: Patients with a history of autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone may be

eligible for this study.

3.29w Active current infection or history of recurrent bacterial, viral, fungal, mycobacterial or other infections, including but not limited to tuberculosis and atypical mycobacterial disease, hepatitis B and C, herpes zoster, and HIV, but excluding fungal infections of nail beds.

3.29x Vaccination with a live or attenuated vaccine ≤28 days prior to randomization. Note: Other types of vaccines, including inactivated/killed, toxoid (inactivated toxoid), and subunit/conjugate are all permitted at any time.

3.29y Any reversible treatment-related toxicity that has not resolved to NCI CTCAE Grade ≤1 except neuropathy.

3.29z Other concurrent severe and/or uncontrolled medical disease, psychiatric illness, or social situation, which could compromise safety of treatment as so judged by the treating physician. Note: This includes but is not limited to: severely impaired lung function, uncontrolled diabetes (history of consistent blood glucose readings above 300 mg/dL or less than 50 mg/dL), severe infection, severe malnutrition, ventricular arrhythmias, known active vasculitis of any cause, tumor invasion of any major blood vessel, chronic liver or renal disease, and active upper GI tract ulceration.

3.29aa Unwilling to or unable to comply with the protocol.

3.29bb Current or recent (≤10 days prior to randomization) use of aspirin (>325 mg/day), or clopidogrel (>75 mg/day).

3.29cc Current or recent (≤10 days prior to randomization) use of therapeutic oral or parenteral anticoagulants or thrombolytic agents for therapeutic purposes, unless the patient has been on a stable dose of anticoagulants for at least 2 weeks at the time of randomization. Note: The use of full-dose oral or parenteral anticoagulants is permitted as long as the INR or aPTT is within therapeutic limits (according to the medical standard of the institution) and the patient has been on a stable dose of anticoagulants ≥14 days at the time of randomization. Prophylactic use of anticoagulants is allowed.

3.29dd History or recent diagnosis of demyelinating disease.

3.29ee History of other carcinoma ≤3 years. Exception: If risk of recurrence is known to be under 5% at time of randomization.

3.29ff Current or recent (≤90 days prior to randomization) endoluminal stent in the stomach, bowel, colon or rectum.

3.29gg Colonoscopy, sigmoidoscopy, or proctoscopy ≤7 days prior to randomization.

3.29hh Current or recent (≤28 days prior to randomization) use of sorivudine, brivudine, and St. John's Wort.

3.29ii Primary or secondary immunodeficiency (history of or currently active) unless

related to primary disease under investigation.

3.29jj Prior allogeneic bone marrow transplantation or prior solid organ transplantation.

3.29kk Treatment with systemic immunosuppressive medications (including but not limited to prednisone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor [anti-TNF] agents) ≤14 days prior to randomization. Exception: Patients who have received acute, low-dose, systemic immunosuppressant medications (e.g. a one-time dose of dexamethasone for nausea) are eligible. The use of inhaled corticosteroids and mineralcorticoids (e.g. fludrocortisone) for patients with orthostatic hypotension or adrenocortical insufficiency is allowed.

4.0 Test Schedule

NOTE: Treatments and assessments on schedule are expected to improve patient outcomes. However, it is known that routine scheduling issues may occur. For this reason, +3 day window for day 1 of each cycle is allowed. Special scheduling issues may also arise on occasion for personal reasons. In such cases, cycles may be delayed by up to 2 weeks without the approval of the Study Chair. Scheduling issues occurring outside of this window must be pre-approved by the Study Chair by contacting the Data Manager. If such issues are not approved by the Study Chair, they will be recorded as protocol deviations. In case of toxicity, treatments should be delayed in accordance with dose modifications (Section 8.0). Additional monitoring or interventions beyond those listed below should also be done as deemed clinically appropriate.

Tests and Procedures	Active Monitoring Phase					
	Baseline (prior to Cycle 1 Day 1 treatment)		Cycle (21 days)[20]	Restaging	Off Treatment Follow-up +/- 7 days	Observation +/- 14 days
	≤14 Days	≤7	Day 1	Every 3 Cycles	30 days after Last Study Drug	Every 12 Weeks
Informed Consent[1]	X					
Demographics	X					
Medical History	X					
Physical Exam	X		X		X	
Adverse Event Evaluation[2]	X		**Continuous Assessment**			
Concomitant Medications	X		**Continuous Assessment**			
Vital Signs[3]	X		X		X	
Height	X					
Weight	X		X		X	
ECOG Performance Status	X		X		X	
CBC with differential[4]		X	X		X	
Chemistries with liver function tests[5]		X	X		X	
TSH, free T3 and free T4[21]	X					
ECG[6]	X					
β-HCG[7]		X		X	X	
UA or 24 hour urine for protein[8]	X		X		X	
Coagulation tests[9]	X					
Randomization[10]		X				
Capecitabine[11]			**Days 1-14**			
Bevacizumab[12]			X			
Atezolizumab or Placebo[12]			X			
Blood Biomarkers[15, R]			X[22]	X	X	
Whole Blood[14, R]			X[22]			
Blood Immune Cells[16, R]			X[22]	X		
Archived Paraffin Tumor[13, R]			X			
Radiographic Assessment[17]	X			X		X[19]
Tumor Blood Bio-Markers (CEA)[18]	X			X		X[19]
Anti-cancer Treatment						X[19]

1. Informed consent may occur ≤30 days prior to randomization.
2. Using NCI CTCAE version 4.0.
3. Vital signs include: temperature, heart rate, and blood pressure.
4. CBC with differential includes: hemoglobin, hematocrit, platelets, WBC and ANC. At baseline must be ≤7 days prior to randomization; and Cycle 2 and higher may be drawn up to 3 days prior to day 1 of each cycle.
5. Chemistry with LFTs includes: albumin, BUN, creatinine, calculated creatinine clearance using Cockcroft-Gault (at baseline and as clinically indicated), glucose, potassium, total bilirubin, ALT, AST, and alkaline phosphatase (ALP). At baseline must be ≤7 days prior to randomization on C1D1; and Cycle 2 and higher may be drawn up to 3 days prior to day 1 of each cycle.
6. 12-lead ECG. At baseline ≤14 days prior to randomization; and as clinically indicated.
7. Serum pregnancy test in women of childbearing potential only. At baseline must be serum ≤7 days prior to randomization; serum or urine at every restaging; serum or urine at off-treatment follow-up. Refer to Section 10.0 for pregnancy guidelines.
8. Urine analysis (UA) or 24-hour urine for protein. At baseline must be ≤14 days prior to randomization; day 1 on Cycle 2 and all subsequent cycles; (if result not available prior to treatment on day 1, may use result from previous cycle for current cycle); and off-treatment follow-up. Note: If UA is ≥2+, confirm with 24-hour urine prior to the initiation of the next cycle. Refer to Section 8.63 for procedure to obtain a urine

protein/creatinine (UPC) ration from random urine sample. Protein and creatinine concentrations should be available on standard reports of urinalyses, if protein and creatinine concentrations are not routinely reported at an institution, their measurements and reports may need to be requested.

9. PT/PTT/INR. At baseline must be ≤14 days prior to randomization; and if on anticoagulation should have clinically appropriate monitoring per institutional guidelines and as clinically indicated.
10. Must be ≤7 days of Cycle 1 Day 1.
11. Commercial supply. Days 1-14 of 21-day cycle.
12. Study supply. Day 1 of 21-day cycle.
13. Archived tumor collection may occur outside the screening period and at a timepoint determined by the Study Chair. See Section 17.0 for details.
14. Whole blood collected at baseline only (may be drawn pre-dose on Cycle 1 Day 1). Refer to Section 14.0 for details.
15. Plasma and serum biomarkers will be collected at baseline (may be draw pre-dose on Cycle 1 Day 1); every restaging (prior to Cycle 4 treatment prior to Cycle 7 treatment, etc.); at progression or off-treatment visit (if discontinued from study drug for reason other than progression); and off-treatment follow-up. Refer to Section 14.0 for details.
16. Circulating immune cells will be collected at baseline (may be drawn pre-dose on Cycle 1 Day 1) and at the first restaging (prior to Cycle 4 treatment) and at progression/off-treatment. Refer to Section 14.0 for details.
17. Radiographic assessments (CT and/or MRI) of chest, abdomen, and pelvis using the same method of assessment throughout study. At baseline must be ≤28 days prior to randomization; every restaging (may occur ≤14 days prior to Day 1 of the new cycle); and as clinically indicated. If bone metastasis is present, obtain a baseline bone scan and repeat every 18 weeks and as clinically indicated. Additional modalities to track non-measurable disease, such as bone scan, PET scan, may also be used as clinically indicated.
18. Blood tumor bio-markers (CEA) or other tumor markers. At baseline must be ≤28 days prior to randomization; every restaging (may occur ≤14 days prior to Day 1 of the new cycle); and as clinically indicated. If CEA is not expressed, CEA need not be performed. If another tumor marker is used (e.g., CA19-9), that tumor marker should be assessed.
19. If a subject comes off treatment with no documented disease progression, follow-up is every 12 weeks or as clinically indicated with tumor assessments and blood tumor markers (i.e., CEA or other tumor markers) until disease progression or receipt of subsequent anti-cancer treatment is documented. Note: If subject is not able to return to the consenting institution after the Active Monitoring Phase, subject health records such as medical oncology physician notes, laboratory results, and/or radiology reports with tumor assessments from another institution is permissible for tumor assessment of disease progression or documentation of subsequent anti-cancer treatment.
20. ≤3 day window for day 1 of each cycle is allowed for cycles 2 and up.Baseline (≤14 prior to Cycle 1 Day 1
21. treatment) and then as clinically indicated.
22. To be collected prior to dosing on C1D1

R Research funded (see Section 19.0)

5.0 Stratification Factors:

5.1 Stratification Factors

5.11 ECOG Performance Status: 0 vs. 1.

5.12 RAS Status: Wild-type vs. mutant.

5.121 If mutant and known, site will select the appropriate mutant status from the following: (Note: Mutant RAS status is not utilized in stratification.)

5.1211 KRAS: Exon 2 (codon 12, 13)

5.1212 KRAS: Exon 3 (codon 59, 61)

5.1213 KRAS: Exon 4 (codon 117, 146)

5.1214 NRAS: Exon 2 (codon 12, 13)

5.1215 NRAS: Exon 3 (codon 59, 61)

5.1216 NRAS: Exon 4 (codon 117, 146)

5.1217 Other (Please list)

6.0 Registration/Randomization Procedures

6.1 Randomization Procedures

6.11 To register a patient, access the ACCRU web page at www.accru.org, click on "Training Page" and enter the registration/randomization application.

The registration/randomization application is available 24 hours a day, 7 days a week. Back up and/or system support contact information is available on the Web site. If unable to access the Web site, call the Academic and Community Cancer Research United (ACCRU) Registration Office at (507) 284-4130 between the hours of 8 a.m. and 4:30 p.m. Central Time (Monday through Friday).

The instructions for the registration/randomization application are available by using the Help button. Prior to initiation of protocol study intervention, this process must be completed in its entirety and an ACCRU subject ID number must be available as noted in the instructions. It is the responsibility of the individual and institution registering the patient to confirm the process has been successfully completed prior to release of the study agent. Patient randomization via the registration/randomization application can be confirmed in any of the following ways:

- Contact the ACCRU Registration Office (507)-284-4130. If the patient was fully registered, the ACCRU Registration Office staff can access the information from the centralized database and confirm the randomization.
- Refer to "Instructions for Remote Registration" in section "Finding/Displaying Information about A Registered Subject."

6.2 Correlative Research

A mandatory correlative research component is part of this study. The patient will be automatically registered onto this component (see Sections 3.0, 14.0 and 17.0).

6.21 Prior to accepting the registration/randomization, the registration/randomization application will verify the following:

- IRB approval at the registering institution
- Patient eligibility
- Existence of a signed consent form
- Existence of a signed authorization for use and disclosure of protected health information

6.22 Documentation of IRB approval must be on file in the Registration Office before an investigator may register/randomize any patients.

In addition to submitting initial IRB approval documents, ongoing IRB approval documentation must be on file (no less than annually) at the Registration Office (fax: 507-284-0885). If the necessary documentation is not submitted in advance of attempting patient registration/randomization, the registration/randomization will not be accepted and the patient may not be enrolled in the protocol until the situation is resolved.

When the study has been permanently closed to patient enrollment, submission of annual IRB approvals to the Registration Office is no longer necessary.

6.23 At the time of randomization, the following will be recorded:

- Patient has/has not given permission to store and use his/her sample(s) for future research to learn about, prevent, or treat cancer.
- Patient has/has not given permission to store and use his/her sample(s) for future research to learn, prevent, or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease).
- Patient has/has not given permission for ACCRU to give his/her sample(s) to outside researchers.

6.24 Treatment on this protocol must commence at an ACCRU institution under the supervision of a medical oncologist.

6.25 Treatment cannot begin prior to randomization and must begin ≤7 days after randomization.

6.26 Pretreatment tests/procedures (see Section 4.0) must be completed within the guidelines specified on the test schedule.

6.27 All required baseline symptoms (see Section 10.5) must be documented and graded.

6.28 Study drug is available on site.

6.29a Blood draw kit is available on site. Kits must be used for this study.

6.29b Randomization Procedures

6.29b1 The factors defined in Section 5.0, together with the registering membership, will be used as stratification factors.

6.29b2 After the patient has been registered into the study, the values of the stratification factors will be recorded, and the patient will be assigned to one of the following treatment groups using the Pocock and Simon dynamic allocation procedure which balances the marginal distributions of the stratification factors between the treatment groups. (Pocock, Simon 1975)

- Bevacizumab + Capecitabine + Atezolizumab
- Bevacizumab + Capecitabine + Placebo

6.3 Procedures for Double-Blinding the Treatment Assignment

6.31 After the treatment assignment has been ascertained by the registration/randomization application, the registration specialist will notify the designated data manager/nurse/pharmacist at the patient's institution. The name of this contact person is to be entered in the designated space on the eligibility checklist so the Registration Office personnel have it for each patient at the time of randomization. Make sure this contact person will be available at the time of randomization so he or she can take a call from the registration specialist if necessary. This contact person may not be involved in assessing adverse events or any other outcome measure and should not be the same person listed on page one of the Eligibility Checklist Form as the person completing the form. The last page of the Eligibility Checklist Form should provide the sources of communication, either fax or e-mail, and the appropriate contact information. The registration specialist will then communicate the treatment assignment to the designated contact at the patient's institution.

6.32 The treatment assignment will be to bevacizumab + Capecitabine + Atezolizumab or bevacizumab + Capecitabine + Placebo. Genentech will provide supplies labeled for investigational use to Biologics. Each participating institution will order the drug from Biologics using the protocol-specific Drug Order Request Form. Each participating institution will be responsible for monitoring drug supplies and will use the Drug Order Request Form to order additional supplies as needed. Upon receipt of orders, Biologics will send bulk supply to participating institutions. The atezolizumab/placebo solution will be prepared and labeled by the unblinded pharmacist as "atezolizumab/placebo study drug 1 dose" so that the contents are not discernible to the person administering the treatment.

6.33 The unblinded pharmacist will maintain records that indicate the identity of the patient and their corresponding treatment assignment.

7.0 Protocol Treatment

7.1 Dose Levels

Subjects will be randomized 2:1 to one of the blinded arms described in the table below. Cycles are 21 days in length.

Atezolizumab/placebo will be given before the bevacizumab infusion. Subjects randomized to the Bevacizumab + Capecitabine + Atezolizumab arm will receive atezolizumab at 1200 mg IV on day 1 of each cycle. Subjects randomized to the Bevacizumab + Capecitabine + Placebo arm will receive an equivalent volume of placebo (for atezolizumab) on day 1 of each cycle. All subjects will receive capecitabine orally twice per day on days 1-14 of each cycle.

Dose Levels

Agent	Dose Level	Route	Day(s)	ReRx
Atezolizumab/Placebo[1]	1200 mg	IV	1	Every 21 days
Bevacizumab[2]	7.5 mg/kg	IV	1	
*Capecitabine[3]	850 or 1000 mg/m^2	PO	1-14 BID	

1. Atezolizumab/placebo will be prepared by an unblinded pharmacist. The infusion drug will be prepared and labeled for blinding purposes. Atezolizumab/placebo infusion will be given before the bevacizumab infusion. Do not administer as bolus or push. The initial dose of atezolizumab/placebo will be delivered over 60 (±15) minutes. If the first infusion is tolerated without infusion-associated adverse events, the second infusion may be delivered over 30 (±10) minutes. If the 30-minute infusion is well tolerated, the third and all subsequent infusions may be delivered over 30 (±10) minutes until disease progression or unacceptable toxicity. If a patient has an infusion related reaction during the atezolizumab infusion, vitals should be recorded after the atezolizumab administration if clinically indicated (even up to 1 hour). Bevacizumab administration may be delayed until the patient is clinically stable and appropriate to treat.
2. Bevacizumab will be calculated on the basis of milligrams of drug per kilogram of body weight at baseline and will be recalculated based upon weight per local institutional standards. The initial dose of bevacizumab 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. The IV infusion lines should be properly flushed with 0.9% Sodium Chloride between administrations of other drugs.
3. Capecitabine 850 mg/m^2 or 1000 mg/m^2 may be used based upon local physician and patient preferences. Capecitabine is taken orally twice per day on days 1-14 of 21-day cycle. The dose of capecitabine will be calculated on the basis of milligrams of drug per square meter of body surface area (BSA) at baseline and will be recalculated based upon weight per local institutional standards. The method of dose adjustments for capecitabine should be based upon prescribing information and local institutional standards.
   *Missed capecitabine doses are not to be re-taken.

7.2 Patients can be instructed in administration techniques and granted treatment independence with nursing staff approval.

7.3 For this protocol, the patient must return to the consenting ACCRU institution for evaluation at least every 21 days during treatment (Active Monitoring Phase) and if possible every 12 weeks during observation.

7.4 Treatment by a local medical doctor (LMD) is not allowed.

7.5 Breaking Codes in Double–Blinded Studies

Situations requiring codes to be broken:

Unblinding will not be routinely performed but may be considered on a case-by-case basis as described below.

- In the event of an emergency for an individual patient.
- In the event that it would be helpful for the future clinical care of an individual patient after she/he has completed participation in the trial.
- If a subject is considering enrollment to another study while in the follow up period and prior drug administration information is required for enrollment in new study.

In the event of an emergency, call the [redacted] to break the code on Monday through Friday, 8:00 a.m. to 4:30 p.m. Central Time. If the code must be broken after hours, assume the patient was assigned to active treatment and treat accordingly. Place a call

to the ACCRU Registration Office and leave a message informing them of the need to un-blind a patient. Provide your contact information so that ACCRU Registration Office personnel can return the call the next business day.

On a case by case basis, if in the judgment of the attending physician, it would be helpful for the future clinical care of the individual patient, the code may be broken *after* the patient has completed the study. That is, after the patient has been fully evaluated and all evaluation information has been recorded by the attending physician and the patient (if appropriate), the ACCRU Registration Office may be called to find out which study therapy the patient was receiving.

All Investigators, study personnel and subjects will be blinded to the study treatment assignments. However, each site will have designated pharmacists that will not be blinded to the study treatment assignments.

8.0 Dosage Modification Based on Adverse Events

8.1 Please refer to prescribing information for capecitabine and bevacizumab as well as investigator brochures for capecitabine, bevacizumab, and atezolizumab for further information on toxicities and management information. The following are general guidelines for dose modifications and toxicity management for this study:

- Toxicity will be graded according to the NCI Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0.
- All dose modifications and dose holds along with study drug attributions must be recorded.
- Subjects must be followed at least weekly when any drug is held for any toxicity until the toxicity returns to Grade ≤1 or is determined to be chronic or irreversible.
- If toxicity could be related to either the study drug (atezolizumab/placebo) or to the chemotherapy backbone capecitabine or bevacizumab, dose modifications will be performed on all drugs possibly causing that toxicity.
- Subjects should be managed under the assumption they are on active treatment and unblinding should be reserved for toxicities that cannot be managed otherwise.
- Subjects that are unblinded will be removed from study treatment but will be followed until resolution of toxicity, disease progression and survival as appropriate.
- For toxicity management, the doses of bevacizumab and atezolizumab/placebo can only held. There are no dose reductions or other dose modifications of these agents for toxicity.
- Held doses of drug will not be made up at a later date.
- Aggressive and more conservative dose reductions or holds are permitted if felt to be clinically indicated. The treating physician may elect greater dose reduction based upon the duration of the adverse event or additional circumstance, etc.
- Follow dose modifications or holds for any agent(s) thought to be related to toxicity.
- If several toxicities occur at the same time, the dose modifications or holds should be according to the highest grade observed.
- If a subject experiences a Grade 4 event more than once, retreatment (even with dose modifications) must be approved by the Lead Study Chair prior to re-dosing.
- When treatment is temporarily interrupted because of toxicity, treatment cycles should be restarted such that the atezolizumab/placebo and bevacizumab infusions remain synchronized and aligned with the capecitabine schedule. However, if it is anticipated that capecitabine will be delayed by ≥2 weeks, then atezolizumab/placebo and bevacizumab should be given without capecitabine if there is no contraindication.
- If a subject is deemed to have been benefiting from therapy and the treatment delay was not directly related to study treatment (e.g., scheduling conflicts or intercurrent illness) then subject may continue therapy on a case-by-case basis after consultation with the Study Chair.

- Bevacizumab and atezolizumab/placebo do not need to be held together or given together. For example, if there is a bevacizumab-related adverse effect, the bevacizumab may need to be held, while atezolizumab/placebo may be able to be continued. However, in cases in which the adverse effect may be related to either bevacizumab or atezolizumab/placebo, both drugs may need to be held.
- Dose adjustments for weight-based or BSA-based chemotherapy are per local institutional standards. For most sites, the preferred method is to adjust the dose only if the weight changes by more than 10%. Subsequent dose recalculations (for second or higher occurrences of ≥10% weight change) are based on the most recent baseline weight. Another acceptable method of dose adjustment is to dose on actual weight, even if the subject's weight change is less than 10%.

8.2 Treatment Parameters for Day 1 of Each Cycle

Treatment on **Day 1** of each cycle should be delayed until:

- Absolute neutrophil count (ANC) is ≥1,000/mm^3 **and** platelet count is ≥75,000/mm^3
- Recovery to Grade ≤ 1 from any clinically significant treatment-related non-hematologic toxicity. Subjects may continue drug with Grade 2 toxicity if not considered clinically significant by treating physician.
- Laboratory only abnormalities are permitted but must meet the following criteria. However, caution is needed to ensure re-treatment is considered safe and in the interest of the subject.

  1. Abnormal lab is not considered clinically significant in the treating physician's judgment (with the exception of ANC and platelet count).
  2. Subject has no clinical symptoms.
  3. Abnormal lab does not require treatment modifications or delays or result in a medical intervention.

8.3 Dose Modifications for Capecitabine

Management of capecitabine toxicity should follow the prescribing information and local institutional standards. Dose modification levels for capecitabine are listed in Table 8.31. These dose modification levels are applied to toxicity-specific tables in Section 8.6 of the protocol. The "next lower" dose level is defined as the next dose below what the subject had most recently been taking**.** In the case where a dose reduction is required and there is no lower dose level, capecitabine should be discontinued. If capecitabine is held or discontinued for toxicity or intolerance, subjects may continue on study with the remaining agents as clinically indicated.

Table 8.31 Capecitabine Dose Levels

Dose Modification Level	**Capecitabine (orally, days 1-14, mg/m^2)**	
Initial Dose*	**1000**	**850**
-1	850	680
-2	680	545
-3	545	Discontinue
-4	Discontinue	

**Starting dose level of capecitabine.*

For common capecitabine-related toxicity including, but not limited to diarrhea and nausea/vomiting that are not included in a toxicity-specific table in Section 8.6 of the protocol, the guidelines in Table 7.2 for dose adjustments will be performed on the capecitabine dosing.

Table 8.32 Management of Capecitabine Common Toxicities

Toxicity Grade*	Occurrence	Capecitabine	Dose Modification 1000 mg/m^2 Initial Dose	Dose Modification 850 mg/m^2 Initial Dose
Grade 1	Any	Maintain current dose level	1000	850
Grade 2	1st	Hold until recovery to grade ≤1 -OR- Discontinue after dose level reduction of 545 mg/m^2	1000	850
	2nd		850	680
	3rd		680	545
	4th		545	
Grade 3	1st	Hold until recovery to grade ≤1 -OR- Discontinue after dose level reduction of 545 mg/m^2	850	680
	2nd		680	545
	3rd		545	
Grade 4	1st	If treating physician and Study Chair deems it is in the patient's best interest to continue, hold until recovery to grade ≤ 1-OR- Discontinue after dose level reduction of 545 mg/m^2	680	545
	2nd		545	

**Use National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0.*

For subjects who experience dose reductions due to toxicity, dose re-escalations are permitted as long as the subject tolerates the reduced dose with Grade 1 or lower toxicity for a minimum of 2 consecutive cycles. The treating physician, patient, and Lead Study Chair must agree that escalation is in the best interest of the patient.

8.4 Dose Modifications for bevacizumab

No reductions in bevacizumab dose are allowed in this study.

Infusion of bevacizumab should be interrupted in subjects who develop dyspnea or clinically significant hypotension. Refer to Section 8.661 for management of infusion-related reactions.

If adverse events occur that necessitate holding bevacizumab, the dose will remain unchanged once treatment resumes. Temporary suspension of bevacizumab must occur if a subject experiences a serious adverse event or a Grade 3 or 4 non-serious adverse event assessed by the treating physician as related to bevacizumab. If the event resolves to Grade ≤1, bevacizumab may be restarted at the same dose level. If bevacizumab is delayed due to toxicity for >42 days beyond

when the next dose should have been given, the subject must be permanently discontinued from bevacizumab.

The appropriate interval between the last dose of bevacizumab and major surgery is unknown. Because bevacizumab has a half-life of approximately 21 days, elective surgery should be delayed whenever possible, but if necessary, bevacizumab should be held for ≥28 days prior to the procedure. Re-initiation of bevacizumab following surgery should not occur for ≥28 days and until wounds have fully healed. Re-initiation of bevacizumab after surgery requires documented approval from the Lead Study Chair.

8.5 Dose Modifications for Atezolizumab

No reduction or modification of the atezolizumab dose will be allowed. Any toxicity associated or possibly associated with atezolizumab treatment should be managed according to standard medical practice.

Withhold Atezolizumab for any of the following:

- Grade 2 pulmonary events, including pneumonitis
- Grade 2 aspartate aminotransferase (AST), alanine aminotransferase (ALT), or total bilirubin
- Grade 2 or 3 diarrhea or colitis
- Symptomatic hypothyroidism
- Symptomatic hyperthyroidism
- Symptomatic, Grade 2-4 adrenal insufficiency
- Grade 3 or 4 hyperglycemia
- Grade 2 ocular events
- Grade 2 infusion-related reaction (refer to Section 8.661 for management of infusion-related reactions)
- Grade 3 or 4 amylase and/or lipase elevation
- Grade 2 or 3 immune-related pancreatitis
- Grade 3 dermatologic event
- Grade 2 immune-related neuropathy

Atezolizumab may be resumed in patients whose adverse reactions recover to Grade 0–1.

Permanently discontinue Atezolizumab for any of the following:

- Grade 2 that does not resolve to Grade 1 or better within 12 weeks, Grade 3 or 4 pulmonary events, including pneumonitis
- Grade 2 that does not resolve to Grade 1 or better within 12 weeks, Grade 3 or 4 AST or ALT or total bilirubin greater than 3 times ULN
- Grade 2 or 3 that does not resolve to Grade 1 or better within 12 weeks or Grade 4 diarrhea or colitis
- Symptomatic, Grade 2-4 that does not resolve to Grade 1 or better within 12 weeks adrenal insufficiency
- Grade 2 that does not resolve to Grade 1 or better within 12 weeks, Grade 3 or 4 ocular events
- Grade 3 or 4 infusion-related reaction (refer to Section 8.661 for management of infusion-related reactions)
- Grade 3 or 4 that does not resolve to Grade 1 or better within 12 weeks amylase and/or lipase elevation
- Grade 2 or 3 that does not resolve to Grade 1 or better within 12 weeks, or Grade 4 immune-related pancreatitis

- Grade 3 that does not resolve to Grade 1 or better within 12 weeks, or Grade 4 dermatologic event
- Grade 2 that does not resolve to Grade 1 or better within 12 weeks, Grade 3 or 4 immune-related neuropathy
- Any grade Myasthenia Gravis or Guillain-Barre syndrome
- Any grade immune-related meningoencephalitis

Additional tests, such as autoimmune serology or biopsies, may be used to determine a possible immunogenic etiology. While most immune-related adverse events (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 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, or TNF-α inhibitors.

The primary approach to Grade 1-2 IRAEs is supportive and symptomatic care; for higher grade IRAEs, steroids by mouth or parenteral given, and either skipping a dose or holding therapy is appropriate. Recurrent Grade 2 IRAEs may also mandate skipping a dose of atezolizumab/placebo or the use of steroids.

Patients should be assessed clinically for toxicity prior to, during, and after each infusion. If unmanageable toxicity thought to be due to atezolizumab/placebo occurs at any time during the study, treatment with atezolizumab/placebo should be discontinued. If atezolizumab/placebo is held because of adverse events >42 days beyond when next dose should have been given, the patient will be discontinued from study treatment. If patients must be tapered off steroids used to treat adverse events, study treatment may be held for >42 days. The acceptable length of interruption will depend on agreement between the treating physician and the Lead Study Chair.

Dose interruptions for reason(s) other than toxicity may be allowed with the Lead Study Chair approval. The acceptable length of interruption will depend on agreement between the treating physician and the Lead Study Chair.

Consideration for benefit/risk balance should be made by the treating physician, 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 study drug.

8.6 Toxicity Management

8.61 Hematologic Toxicities

Treating physicians should be vigilant and alert to early and overt signs of myelosuppression, infection, febrile neutropenia and related events, so that these complications can be promptly and appropriately managed. Patients should be made aware of these signs and encouraged to seek medical attention at the earliest opportunity.

Dose Modifications for Thrombocytopenia

Thrombocytopenia Toxicity Grade*	Occurrence	Capecitabine	Bevacizumab	Atezolizumab/ Placebo
Grade 2	Any	Maintain current dose	Maintain current dose	Maintain current dose
Grade 3	1st to 3rd	Hold until recovery to grade ≤1,then resume at one dose level lower	Hold until recovery to grade ≤1, then resume at current dose	Hold until recovery to grade ≤1, then resume at current dose

Thrombocytopenia Toxicity Grade*	Occurrence	Capecitabine	Bevacizumab	Atezolizumab/ Placebo
	4th	Discontinue	Hold until recovery to grade ≤1, then resume at current dose with approval of Study Chair	Hold until recovery to grade ≤1, then resume at current dose with approval of Study Chair
Grade 4	1st	Hold until recovery to grade ≤1, then resume at two dose levels lower	Hold until recovery to grade ≤1, then resume at current dose	Hold until recovery to grade ≤1, then resume at current dose
	2nd	Discontinue	Hold until recovery to grade ≤1, then resume at current dose with approval of Study Chair	Hold until recovery to grade ≤1, then resume at current dose with approval of Study Chair

* Platelet count decreased is the corresponding adverse event term from NCI CTCAE version 4.0 for reporting purposes.

Dose Modifications for Neutropenia

Neutropenia Toxicity Grade*	Occurrence	Capecitabine	Bevacizumab	Atezolizumab/ Placebo
Grade 2	Any	Maintain current dose	Maintain current dose	Maintain current dose
Grade 3	1st to 3rd	Hold until recovery to grade ≤1, then resume at one dose level lower	Maintain current dose	Hold until recovery to grade ≤1, then resume at current dose
	4th	Discontinue	Hold until recovery to grade ≤1, then resume at current dose with approval of Study Chair	Hold until recovery to grade ≤1, then resume at current dose with approval of Study Chair
Grade 4	1st	Hold until recovery to grade ≤1, then resume at two dose levels lower	Hold until recovery to grade ≤1, then resume at current dose	Hold until recovery to grade ≤1, then resume at current dose
	2nd	Discontinue	Hold until recovery to grade ≤1, then resume at current dose with approval of Study Chair	Hold until recovery to grade ≤1, then resume at current dose with approval of Study Chair

* Decreased neutrophil count is the corresponding adverse event term from NCI CTCAE version 4.0 for reporting purposes.

Dose Modifications for Febrile Neutropenia

Febrile Neutropenia Toxicity Grade*	Occurrence	Capecitabine	Bevacizumab	Atezolizumab/ Placebo
Grade 3	1st	Hold until recovery of fever and neutropenia to grade ≤1, then resume at two dose levels lower	Hold until recovery of fever and neutropenia to grade ≤1, then resume at current dose	Hold until recovery of fever and neutropenia to grade ≤1, then resume at current dose
	2nd	Discontinue	Hold until recovery of fever and neutropenia to grade ≤1, then resume at current dose	Hold until recovery of fever and neutropenia to grade ≤1, then resume at current dose

Febrile Neutropenia Toxicity Grade*	Occurrence	Capecitabine	Bevacizumab	Atezolizumab/ Placebo
	3rd	Discontinue	Hold until recovery of fever and neutropenia to grade ≤1, then resume at current dose with approval of Study Chair	Hold until recovery of fever and neutropenia to grade ≤1, then resume at current dose with approval of Study Chair
Grade 4	1st	Hold until recovery of fever and neutropenia to grade ≤1, then resume at two dose levels lower	Hold until recovery of fever and neutropenia to grade ≤1, then resume at current dose	Hold until recovery of fever and neutropenia to grade ≤1, then resume at current dose
	2nd	Discontinue	Hold until recovery of fever and neutropenia to grade ≤1, then resume at current dose with approval of Study Chair	Hold until recovery of fever and neutropenia to grade ≤1, then resume at current dose with approval of Study Chair

* Febrile neutropenia is the corresponding adverse event term from NCI CTCAE version 4.0 for reporting purposes.

8.62 Hypertension

Early and aggressive medical management of hypertension is strongly recommended to minimize the need for dose holding. Addition or adjustment of blood pressure medications should be considered for blood pressure values persistently >150/100. In addition, blood pressure medications should be added or adjusted for blood pressure values requiring dose holding.

Refer to Section 9.92 for hypertension supportive care guidelines.

Dose Modifications for Hypertension

Hypertension Toxicity Grade*	Occurrence	Capecitabine	Bevacizumab	Atezolizumab/ Placebo
Grade 2	Any	Maintain current dose	Maintain current dose	Maintain current dose
Grade 3 Asymptomatic	1st to 3rd	Maintain current dose	Hold until BP is ≤150/100 for at least one week, then resume at current dose	Maintain current dose
	4th	Maintain current dose	Discontinue	Maintain current dose
Grade 3 Symptomatic	1st to 3rd	Maintain current dose	Hold until symptoms have resolved and BP is ≤150/100 for at least two weeks, then resume at current dose	Maintain current dose
	4th	Maintain current dose	Discontinue	Maintain current dose

Hypertension Toxicity Grade*	Occurrence	Capecitabine	Bevacizumab	Atezolizumab/ Placebo
Grade 4 (including RPLS confirmed by MRI or hypertensive encephalopathy)	1st	Hold until recovery to grade ≤1, then resume at current dose with approval of Study Chair	Discontinue	Hold until recovery to grade ≤1, then resume at current dose with approval of Study Chair

* Hypertension is the corresponding adverse event term from NCI CTCAE version 4.0 for reporting purposes. Other applicable adverse event terms to consider may include reversible posterior leukoencephalopathy syndrome.

8.63 Proteinuria

Proteinuria will be monitored by urinalysis (UA) dipstick or 24 hour urine every cycle (every 21 days). UA dipstick values ≥2+ protein should be confirmed by 24 hour collection and management based upon 24 hour protein values.

After Cycle 1, urine protein should be completed on day 1 on each cycle. However, if result is not available prior to treatment on day 1, the urine protein result from the previous cycle may be used for to determine treatment for current cycle.

UPC = protein concentration (mg /dL) / creatinine concentration (mg /dL). To obtain urine protein/creatinine (UPC) ratio from random urine sample (i.e., not 24-hour urine):

a. Obtain at least 4 ml of a random urine sample.
b. Determine protein concentration (mg/dL)
c. Determine creatinine concentration (mg/dL)
d. Divide b by c

UPC directly correlates with the amount of protein excreted in the urine per 24 hours (i.e., UPC of 1 should be equivalent to 1g protein in a 24hr urine collection).

Dose modifications are based on urine protein values and nephrotic syndrome versus CTCAE grading scale.

Dose Modifications for Proteinuria

Proteinuria*	Occurrence	Capecitabine	Bevacizumab	Atezolizumab/ Placebo
>2.0g/24 hrs (Note: UA ≥2+ aor UPCR ≥1, 24hr urine protein collection must be performed.)	1st to 3rd	Maintain current dose	Hold until recovery to 24hr urine protein <2g, then resume at current dose	Maintain current dose
	4th	Hold until recovery to 24hr urine protein <2g, then resume at current dose	Discontinue	Maintain current dose
Nephrotic Syndrome	1st	Hold until recovery to 24hr urine protein <2g, then resume current dose with approval of Study Chair	Discontinue	Hold until recovery to 24hr urine protein <2g, then resume current dose with approval of Study Chair

* Proteinuria is the corresponding adverse event term from NCI CTCAE version 4.0 for reporting purposes.

Dose Modifications for Hemorrhage

Hemorrhage Toxicity Grade*	Occurrence	Capecitabine	Bevacizumab	Atezolizumab/ Placebo
Grade 2 non-pulmonary or non-CNS	Any	Maintain current dose	Maintain current dose	Maintain current dose
Grade 2 pulmonary	Any	Hold until recovery to grade ≤1, then resume at current dose	Discontinue	Hold until recovery to grade ≤1, then resume at current dose
Grade 3 or 4	Any	Hold until recovery to grade ≤1, then resume at current dose with approval of Study Chair	Discontinue	Hold until recovery to grade ≤1, then resume at current dose with approval of Study Chair
Any grade CNS hemorrhage	Any	Hold until recovery to grade ≤1, then resume at current dose with approval of Study Chair	Discontinue	Hold until recovery to grade ≤1, then resume at current dose with approval of Study Chair

* The following terms from NCI CTCAE version 4.0 may be considered for reporting purposes: Vitreous hemorrhage, Anal hemorrhage, Cecal hemorrhage, Colonic hemorrhage, Duodenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage, Hemorrhoidal hemorrhage, Ileal hemorrhage, Intra-abdominal hemorrhage, Jejunal hemorrhage, Lower gastrointestinal hemorrhage, Oral hemorrhage, Pancreatic hemorrhage, Rectal hemorrhage, Retroperitoneal hemorrhage, Upper Gastrointestinal hemorrhage, Hepatic hemorrhage, Intraoperative hemorrhage, Postoperative hemorrhage, Tracheal hemorrhage, Intracranial hemorrhage, Renal hemorrhage, Ovarian hemorrhage, Prostatic hemorrhage, Spermatic cord hemorrhage, Testicular hemorrhage, Uterine hemorrhage, Vaginal hemorrhage, Bronchopulmonary hemorrhage, Laryngeal hemorrhage, Mediastinal hemorrhage, Pharyngeal hemorrhage, and Pleural hemorrhage.

Dose Modifications for Venous Thromboembolic Events (VTE)

VTE Toxicity Grade*	Occurrence	Capecitabine	Bevacizumab	Atezolizumab/ Placebo
Grade 2	Any	Maintain current dose	Maintain current dose	Maintain current dose
Grade 3**	Any	Hold until stable full-dose anticoagulation is achieved (at least 48 hours), then resume at current dose if not thrombocytopenic (i.e., platelet count decreased is ≤ grade 1) with approval of Study Chair	Hold until stable full-dose anticoagulation is achieved (at least 48 hours), then resume at current dose if not thrombocytopenic (i.e., platelet count decreased is ≤ grade 1) with approval of Study Chair	Hold until stable full-dose anticoagulation is achieved (at least 48 hours), then resume at current dose if not thrombocytopenic (i.e., platelet count decreased is ≤ grade 1) with approval of Study Chair
Grade 4**	1st	Hold until stable full-dose anticoagulation is achieved (at least 48 hours), then resume at current dose if not thrombocytopenic (i.e., platelet count decreased is ≤ grade 1) with approval of Study Chair	Discontinue	Hold until stable full-dose anticoagulation is achieved (at least 48 hours), then resume at current dose if not thrombocytopenic (i.e., platelet count decreased is ≤ grade 1) with approval of Study Chair

* The following terms from NCI CTCAE version 4.0 may be considered for reporting purposes: Superior vena cava syndrome, Portal vein thrombosis, and Vascular access complication.

** The following criteria must be met by patients who experience a Grade 3 or 4 VTE: (a) No evidence of tumor involving major blood vessels on current CT scan; (b) No use of warfarin; (c) No use of anti-platelet agents during full dose anticoagulation; (d) May use low molecular weight heparin or oral factor Xa inhibitors; (e) No Grade 3 or 4 hemorrhagic event while on anticoagulation; and (f) Clinically stable on a stable dose of low molecular weight heparin or other anticoagulant for at least 48 hours prior to resuming study drug treatment.

Dose Modifications for Arterial Thromboembolic Events (ATE)

ATE Toxicity Grade*	Occurrence	Capecitabine	Bevacizumab	Atezolizumab/ Placebo
Any Grade	1st	Discontinue	Discontinue	Discontinue

* The following terms from NCI CTCAE version 4.0 may be considered for reporting purposes: Stroke, Acute coronary syndrome, Myocardial infarction, Visceral arterial ischemia, Ischemia cerebrovascular.

Dose Modifications for Congestive Heart Failure (CHF)

CHF Toxicity Grade*	Occurrence	Capecitabine	Bevacizumab	Atezolizumab/ Placebo
Grade 2	Any	Maintain current dose	Maintain current dose	Maintain current dose
Grade 3	1st	Hold until recovery to grade ≤1, then resume at current dose	Discontinue	Hold until recovery to grade ≤1, then resume at current dose
	2nd	Hold until recovery to grade ≤1, then resume at current dose with approval of Study Chair	Discontinue	Hold until recovery to grade ≤1, then resume at current dose with approval of Study Chair
	3rd	Discontinue	Discontinue	Hold until recovery to grade ≤1, then resume at current dose with approval of Study Chair
Grade 4	1st	Discontinue	Discontinue	Discontinue

* The following terms from NCI CTCAE version 4.0 may be considered for reporting purposes: Heart failure, Left Ventricular Systolic Dysfunction, Restrictive cardiomyopathy, and Right ventricular dysfunction.

8.64 Hepatotoxicities

Subjects with Grade 3-4 hepatotoxicity should be evaluated for disease progression. If disease progression is found, discontinue study treatment. It is also recommended that subjects with Grade 3-4 hepatotoxicity be evaluated for biliary obstruction. If biliary obstruction is found to be the cause of the elevated bilirubin and is corrected, study treatment may resume at current dose level once bilirubin has resolved to Grade <2. If biliary obstruction is due to progressive disease and cannot be fixed, study treatment should be discontinued.

Dose Modifications for Hepatotoxicities

Hepatic Toxicity Grade*	Occurrence	Capecitabine	Bevacizumab	Atezolizumab/ Placebo
Grade 2**	1st	Maintain current dose	Maintain current dose	Hold until recover to grade ≤1, then resume at current dose
	2nd	Hold until recovery to grade ≤1, then resume one dose lower	Maintain current dose	Hold until recover to grade ≤1, then resume at current dose
	3rd	Hold until recovery to grade ≤1, then resume one dose lower	Maintain current dose	Hold until recovery to grade ≤1, then resume at current dose
	4th	Hold until recovery to grade ≤1, then resume one dose lower	Maintain current dose	Hold until recovery to grade ≤1, then resume at current dose
	5th	Discontinue	Maintain current dose	Hold until recovery to grade ≤1, then resume at current dose
	6th	Discontinue	Maintain current dose	Discontinue
Grade 3***	1st	Hold until recovery to grade ≤2, then restart at one dose level lower	Maintain current dose	Discontinue
	2nd	Hold until recovery to grade ≤2, then restart at one dose level lower	Maintain current dose	Discontinue
	3rd	Hold until recovery to grade ≤2, then restart at one dose level lower	Maintain current dose	Discontinue
	4th	Discontinue	Maintain current dose	Discontinue
	5th	Discontinue	Hold until recovery to grade ≤2, then resume at current dose with approval of Study Chair	Discontinue

Hepatic Toxicity Grade*	Occurrence	Capecitabine	Bevacizumab	Atezolizumab/ Placebo
Grade 4***	1st	Hold until recovery to grade ≤2, then restart at two dose levels lower	Hold until recovery to grade ≤2, then resume at current dose	Discontinue
	2nd	Discontinue	Hold until recovery to grade ≤2, then resume at current dose with approval of Study Chair	Discontinue

* Alanine aminotransferase increased, Aspartate aminotransferase increased, and Blood bilirubin increased are the corresponding adverse event terms from NCI CTCAE version 4.0 for reporting purposes.

** If toxicity has not resolved to Grade ≤ 1 within 12 weeks, permanently discontinue atezolizumab/placebo.

*** If toxicity has not resolved to Grade ≤ 2 within 8 weeks, discontinue study treatment.

8.65 Perforation, Fistula, Abscess, and Obstruction

Timely diagnosis and appropriate treatment may reduce the potential for complications of diverticulitis and thus reduce the risk of GI perforations. Therefore, patients should be made aware of the symptomatology potentially indicative of diverticular disease, and they should be instructed to alert their healthcare provider as soon as possible if these symptoms arise. Patients with a history of diverticulitis, chronic ulcerative lower GI disease such as Crohn's disease or ulcerative colitis, or other symptomatic lower GI conditions that might predispose to perforations are excluded from the current study.

Dose Modifications for Perforation, Fistula or Abscess

Perforation/ Fistula/ Abscess Toxicity Grade*	Occurrence	Capecitabine	Bevacizumab	Atezolizumab/ Placebo
Grade 1	Any	Maintain current dose with caution	Maintain current dose with caution	Maintain current dose with caution
Grade 2 and higher	1st	Discontinue	Discontinue	Discontinue

* The following terms from NCI CTCAE version 4.0 may be considered for reporting purposes: Colonic perforation, Duodenal perforation, Esophageal perforation, Gastric perforation, Ileal perforation, Jejunal perforation, Rectal perforation, Small intestine perforation, Gall bladder perforation, Perforation bile duct, Laryngeal fistula, Pharyngeal fistula, Anal fistula, Colonic fistula, Duodenal fistula, Enterovesical fistula, Esophageal fistula, Gastric fistula, Gastrointestinal fistula, Ileal fistula, Jejunal fistula, Oral cavity fistula, Pancreatic fistula, Rectal fistula, Salivary gland fistula, Biliary fistula, Gallbladder fistula, Abdominal infection, Anorectal infection, Biliary tract infection, Cecal infection, Duodenal infection, Esophageal infection, Gallbladder infection, Hepatic infection, Pancreas infection, Pelvic infection, Peritoneal infection, Small intestine infection, Splenic infection, Stoma site infection, Wound infection, and Infections and infestations - Other.

Dose Modifications for GI Obstruction

GI Obstruction Toxicity Grade*	Occurrence	Capecitabine	Bevacizumab	Atezolizumab/ Placebo
Grade 2	Any	Hold until recovery to grade ≤1, then resume at current dose. Hold for partial obstruction requiring medical intervention. Resume at current dose when obstruction is resolved.	Hold until recovery to grade ≤1, then resume at current dose. Hold for partial obstruction requiring medical intervention. Resume at current dose when obstruction is resolved.	Hold until recovery to grade ≤1, then resume at current dose. Hold for partial obstruction requiring medical intervention. Resume at current dose when obstruction is resolved.
Grade 3	Any	Hold until recovery to grade ≤1, then resume at current dose with approval of Study Chair. Hold for complete obstruction. If surgery is necessary, resume all study drugs at current doses after full recovery from surgery with approval of Study Chair.	Hold until recovery to grade ≤1, then resume at current dose with approval of Study Chair. Hold for complete obstruction. If surgery is necessary, resume all study drugs at current doses after full recovery from surgery with approval of Study Chair.	Hold until recovery to grade ≤1, then resume at current dose with approval of Study Chair. Hold for complete obstruction. If surgery is necessary, resume all study drugs at current doses after full recovery from surgery with approval of Study Chair.
Grade 4	1st	Discontinue	Discontinue	Discontinue

* The following terms from NCI CTCAE version 4.0 may be considered for reporting purposes: Gallbladder obstruction, Intestinal stoma obstruction, Tracheal obstruction, Colonic obstruction, Duodenal obstruction, Esophageal obstruction, Ileal obstruction, Jejunal obstruction, Obstruction gastric, Rectal obstruction, and Small intestine obstruction.

8.66 Hypersensitivity or Anaphylaxis

An infusion reaction is defined as an adverse event occurring during and within 24 hours after the infusion. The most serious of these infusion reactions are hypersensitivity or anaphylactic reactions.

Signs of a possible hypersensitivity or anaphylactic reaction include but are not limited to:

- fever, chills, pruritus, urticaria, angioedema, and skin rash.
- cardiopulmonary reactions, including chest pain, dyspnea, hypotension or hypertension.

Healthcare professionals administering atezolizumab/placebo infusions should be trained in the appropriate administrative procedures, be able to recognize the symptoms associated with potential anaphylactic or hypersensitivity reactions, and have the appropriate medication available for immediate use in case of anaphylaxis or hypersensitivity reaction during or after administration of atezolizumab/placebo. Healthcare professionals should also instruct patients to seek medical attention if they

experience symptoms of a hypersensitivity reaction outside of the clinic. In the event of a serious hypersensitivity or anaphylactic reaction, atezolizumab/placebo should be permanently discontinued.

Acute infusion reactions are to be managed by institutional standards. Use of H1 and H2 blockers are encouraged. The use of IV or PO steroids is permitted. However, since this study is placebo controlled and patients may be receiving atezolizumab therapy, the dose of steroids should be as low as needed to treat the reaction. Prophylactic steroids to prevent infusion reactions are not permitted. For infusions reactions that cannot be managed with prophylactic H1 and H2 blockers, atezolizumab placebo should be discontinued.

8.661 Infusion Reactions

8.6611 Infusion of bevacizumab should be interrupted for subjects who develop dyspnea or clinically significant hypotension during the bevacizumab infusion.

If a subject experiences an infusion-associated adverse event, 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.

Subjects who experience Grade 3 or 4 allergic reaction, adult respiratory distress syndrome, or bronchospasm (regardless of grade) will be discontinued from bevacizumab treatment.

8.6612 No pre-medication will be permitted for the first dose of atezolizumab/placebo. Subjects who experience infusion-related symptoms may be pre-medicated for subsequent infusions with standard of care agents.

The infusion should be slowed to 50% or less or interrupted for subjects who experience Grade 1infusion-associated symptoms. For subjects who experience Grade 2 infusion-related reactions, interrupt the infusion. When the subject's symptoms have completely resolved, the infusion may be continued at no more than 50% of the rate prior to the reaction and increased in 50% increments every 30 minutes if well tolerated. Infusions may be restarted at the full rate during the next cycle.

Subjects who experience Grade 3 or 4 allergic reaction, adult respiratory distress syndrome, or bronchospasm (regardless of grade) will be discontinued from atezolizumab/placebo treatment.

8.67 Opportunistic Infections and Serious Infections

Atezolizumab/placebo should not be administered to patients with active infections including active inflammatory bowel disease, history of diverticulitis, autoimmune diseases, active current infection or history of recurrent bacterial, viral, fungal, mycobacterial, or other infections, including but not limited to tuberculosis and atypical mycobacterial disease, hepatitis B and C, herpes zoster, HIV, EBV, CMV, or those with a recent history of oral or IV antibiotics or prophylactic antibiotics (e.g., for prevention of a urinary tract infection or chronic obstructive pulmonary disease). The effects of atezolizumab/placebo on CRP, neutrophils, and the signs and symptoms of infection should be considered when evaluating a patient for a potential infection.

Vigilance for timely detection of serious infection is recommended as signs and symptoms of acute inflammation may be lessened due to suppression of the acute phase reaction. Patients must be instructed to contact their physician immediately when any symptoms suggesting infection appear, in order to assure rapid evaluation and appropriate treatment.

If a patient develops a serious infection, administration of atezolizumab/placebo is to be interrupted until the infection is controlled. The treating physician should consider the benefit-risk before resuming treatment with atezolizumab/placebo.

8.68 Wound Requiring Intervention

Dose Modifications for Wound Requiring Medical or Surgical Intervention

Wound Toxicity Grade*	Occurrence	Capecitabine	Bevacizumab	Atezolizumab/ Placebo
Grade 1	Any	Continue	Discontinue	Continue
Grade 2	Any	Hold until recovery to grade ≤1, then resume at current dose	Discontinue	Hold until recovery to grade ≤1, then resume at current dose
Grade 3	1st	Hold until recovery to grade ≤1, then resume at current dose with approval of Study Chair	Discontinue	Hold until recovery to grade ≤1, then resume at current dose with approval of Study Chair
Grade 4	1st	Discontinue	Discontinue	Discontinue

* The following terms from NCI CTCAE version 4.0 may be considered for reporting purposes: Wound infection, Wound complication, Wound dehiscence, Abdominal soft tissue necrosis, and Pelvic soft tissue necrosis.

8.69 Other Related Toxicities

Dose Modifications for Posterior Reversible Encephalopathy Syndrome (PRES)

Toxicity Grade*	Occurrence	Capecitabine	Bevacizumab	Atezolizumab/ Placebo
Any Grade (confirmed by MRI)	Any	Hold until recovery to grade ≤1, then resume at current dose with approval of Study Chair	Discontinue	Hold until recovery to grade ≤1, then resume at current dose with approval of Study Chair

* Use National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0.

Dose Modifications for Other Unspecified Study Treatment Related Toxicity

Toxicity Grade*	Occurrence	Capecitabine	Bevacizumab	Atezolizumab/ Placebo
Grade 2	Any	Maintain current dose unless treating physician deems it clinically necessary to hold until recovery to grade ≤1	Maintain current dose unless treating physician deems it clinically necessary to hold until recovery to grade ≤1	Maintain current dose unless treating physician deems it clinically necessary to hold until recovery to grade ≤1
Grade 3	Any	Hold until recovery to grade ≤1, then resume at current or reduced dose with approval of Study Chair	Hold until recovery to grade ≤1, then resume at current dose with approval of Study Chair	Hold until recovery to grade ≤1, then resume at current dose with approval of Study Chair
Grade 4	Any	Hold until recovery to grade ≤1, then resume at current or reduced dose with approval of Study Chair	Hold until recovery to grade ≤1, then resume at current or reduced dose with approval of Study Chair	Hold until recovery to grade ≤1, then resume at current or reduced dose with approval of Study Chair

* Use National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0.

8.7 Surgery

Consultation should occur between the treating physician and surgeon(s) as to timing of surgery and planned treatment interruptions. If subject on treatment require elective major surgery, it is recommended that bevacizumab and atezolizumab/placebo be held for 4-8 weeks prior to the surgical procedure. Holding capecitabine for at least 4 weeks is generally recommended to ensure the subject's performance status is optimal for surgery. Subject undergoing a major surgical procedure should not begin/restart bevacizumab or atezolizumab/placebo until at least 4 weeks after that procedure and provided that adequate wound healing and general recuperation is documented. In the case of high risk procedures such as liver resection, thoracotomy, or neurosurgery, it is recommended that treatment be restarted no earlier than 8 weeks after surgery. Subjects should have re-staging procedures performed before restarting study treatment.

- Minor surgery, such as cataract surgery and placement of central venous catheters, should preferably be scheduled at least 2 weeks after the last dose of bevacizumab and

atezolizumab/placebo. Post-procedure, study drugs should be postponed one week and/or until complete wound healing has taken place.
- Minor procedures, such as tooth extractions, can proceed without any adjustment in bevacizumab and atezolizumab/placebo.
- Very minor procedures, such as dental fillings and cleanings, can proceed without interruption of study drugs.
- In medical circumstances often requiring surgery (e.g., bowel obstruction), due to the possible need for surgery in the setting of bowel obstruction; subjects with bowel obstruction requiring bowel rest should have the study treatment held until the bowel obstruction has resolved.

9.0 Ancillary Treatment/Supportive Care

9.1 Patients may be premedicated with standard-of-care methods to control nausea and vomiting. Since systemic corticosteroids may attenuate potential beneficial immunologic effects of protocol treatments, alternatives to these agents should be considered.

9.2 Blood products and growth factors should be utilized as clinically warranted and following institutional policies and recommendations. The use of growth factors should follow published guidelines of the American Society of Clinical Oncology (ASCO) Update of Recommendation for the Use of White Blood Cell Growth Factors: An Evidence-Based Clinical Practice Guideline (Smith, Khatcheressian et al. 2006).

9.3 Patients should receive full supportive care while on this study. This includes blood product support, antibiotic treatment, and treatment of other newly diagnosed or concurrent medical conditions. All blood products and concomitant medications such as antidiarrheals, analgesics, and/or antiemetics received from the first day of study treatment administration until 30 days after the final dose will be recorded in the medical records.

9.4 General Exclusions

The following therapies are <u>excluded</u> at all times while on study:

- Any non-protocol investigational agent.
- Any non-protocol chemotherapy or targeted anti-cancer therapy.
- Any non-protocol cancer immunotherapy or other biologic therapy.
- Radiotherapy (except for palliative therapy for treatment of known bony metastasis).
- Warfarin.
- Sorivudine and Brivudine (5-bromovinyluracil is a metabolite of these antiviral agents, and is a potent inhibitor of dihydropyrimidine dehydrogenase, the enzyme that catabolizes 5-FU. Subjects should not receive concurrent therapy with either of these antiviral agents while receiving capecitabine. If a subject has received prior sorivudine or brivudine, then at least four weeks must elapse before the subject receives capecitabine therapy.).
- St John's Wort (Due to risk of overlapping toxicities with capecitabine, subjects should not receive concurrent therapy with this agent while receiving capecitabine.).

9.5 Therapies to be used with Caution

The following therapies may only be considered if there is clear medical indication with no alternatives. Permission for use must be obtained from the Lead Study Chair.

- Vitamin B6 (pyridoxine)
- Allopurinol (Oxypurinol, a metabolite of allopurinol, can potentially interfere with 5-FU anabolism via orotate phosphoribosyltransferase. Although this was originally used as a

strategy to protect normal tissues from 5-FU-associated toxicity, further laboratory studies suggested possible antagonism of the anticancer activity of 5-FU in some tumor models. If a subject is receiving allopurinol, allopurinol should be discontinued prior to starting on this regimen, and another agent substituted for it.)

- Phenytoin (Increased phenytoin plasma concentrations have been reported during concomitant use of capecitabine with phenytoin, suggesting a potential interaction. Subjects taking phenytoin concomitantly with capecitabine should be regularly monitored for increased phenytoin plasma concentrations and associated clinical symptoms.)

9.6 Hematopoietic Growth Factors

Growth factors (e.g., G-CSF, GM-CSF, erythropoietin, platelet growth factors, etc.) may be prescribed by the treating physician for rescue from severe hematologic events if clinically appropriate. Therapeutic growth factor usage is permitted per American Society of Clinical Oncology (ASCO) and treating physician guidelines.

Prophylactic use is not permitted (except for erythropoietin stimulating agents) given the potential interaction with continuously dosed chemotherapies in this regimen. Similarly, use of growth factor to meet re-dosing criteria or to avoid dose delays is not permitted.

Dose reduction and/or holding drugs as noted in Section 8.71 are the preferred approach for minimizing hematologic toxicity.

9.7 Anticoagulation

Full dose anti-coagulation is permitted with low molecular weight heparins and factor Xa inhibitors. Due to interactions with diet and with capecitabine, warfarin is prohibited.

Prophylactic use of anticoagulation at baseline and during study treatment for the maintenance of patency of permanent indwelling central venous access devices is permitted. Treating physicians are urged to use caution with patients in the setting of thrombocytopenia while on full-dose anticoagulation.

9.8 Vaccinations

Live/attenuated vaccines should not be given within 4 weeks prior to baseline and during the study as clinical safety has not been established.

9.9 Supportive Care Recommendations

9.91 Stomatitis/Oral Mucositis/Mouth Ulcers

Stomatitis/oral mucositis/mouth ulcers due to capecitabine should be treated using local supportive care. If examination reveals mouth ulcers rather than a more general inflammation of the mouth, please classify the adverse event as such.

The paradigm below is recommended for treatment of stomatitis/oral mucositis/mouth ulcers:

Toxicity Grade*	Recommended Treatment
Grade 1	Non-alcoholic mouth wash or salt water (0.9%) mouth wash several times a day until resolution.

Toxicity Grade*	Recommended Treatment
Grade 2 or 3	Topical analgesic mouth treatments (i.e. local anesthetics such as benzocaine, butyl aminobenzoate, tetracaine hydrochloride, menthol, or phenol) with or without topical corticosteroids, such as triamcinolone oral paste 0.1% (Kenalog in Orabase®).

* *Use National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0.*

If possible, patients avoid agents containing hydrogen peroxide, iodine, and thyme derivatives as they may tend to worsen mouth ulcers. Patients should be reminded to check for these agents in toothpastes and mouthwashes.

9.92 Hypertension

Early and aggressive medical management of hypertension is strongly recommended to minimize the need for dose holding and/or dose reductions. Addition or adjustment of blood pressure medications should be considered for blood pressure values persistently >150/100. In addition, blood pressure medications should be added or adjusted for blood pressure values requiring dose holding or interruptions.

The anti-hypertensive regimen is left to discretion of the treating physician.

Blood pressure should be treated to maintain blood pressure measurements ≤150/100.

Other general recommendations include the following:

- Diuretics should be avoided or used with caution in subjects with volume depletion, anorexia, or diarrhea.
- Beta blockers should be avoided or used with caution in subjects with fatigue.

9.93 Diarrhea, Nausea, or Vomiting

Symptoms of diarrhea and/or abdominal cramping may occur at any time and should be managed according to the prescribing information for capecitabine, atezolizumab, and standard institutional practice. Aggressive support of toxicity and disease symptoms is encouraged.

Anti-emetics and supportive medications are permitted. Aggressive support of toxicity and disease symptoms is encouraged. Loperamide should be used with caution.

Intravenous (IV) hydration and use of loperamide is recommended for diarrhea, as well as close observation. If control takes longer than 2 days, medical evaluation including relevant diagnostic procedures, alternative treatment and possible investigation of dihydropyrimidine dehydrogenase (DPD) deficiency should be considered.

For diarrhea, which could be attributed to either capecitabine or to atezolizumab, treatment should also follow the guidelines for the treatment of autoimmune colitis related to atezolizumab. Treatment of study-related diarrhea will, however, be at the discretion of the treating physician. The following are offered as suggestions for management of study-related diarrhea.

For patients with grade 1 diarrhea, the treating physician may consider conservative treatment with anti-diarrheal medications and intravenous fluids.

For patients with grade 2 diarrhea, the treating physician may consider treatment interruption and conservative treatment with anti-diarrheal medications and intravenous fluids for signs and symptoms of dehydration. If the symptoms do not improve and/or worsen after 72 hours, more aggressive management could be considered including evaluation by a gastroenterologist for consideration of endoscopic examination with biopsy and treatment with oral corticosteroids (prednisone 1-2 mg/kg per day or the equivalent). When the signs and symptoms have improved to grade ≤1, a steroid taper is suggested.

For patients with grade 3 or 4 diarrhea, the treating physician should strongly consider empiric treatment of a presumed autoimmune colitis related to atezolizumab therapy. Suggestions include treatment interruption, evaluation by a gastroenterologist for consideration of endoscopic examination with biopsy, and corticosteroids (methylprednisolone 135 mg IV every 6 hours followed by high-dose oral steroids such as prednisone 1-2 mg/kg by mouth per day or dexamethasone 4 mg by mouth every 4 hours). If intravenous steroids followed by high-dose oral steroids do not reduce the initial symptoms in patients with grade 3 or 4 diarrhea within 48-72 hours, anti-TNF-alpha antibody therapy (e.g., infliximab) should strongly be considered. Once symptoms improve to grade ≤1, a steroid taper is suggested over 6-8 weeks in patients with diffuse and severe ulceration and/or bleeding. If symptoms worsen during the steroid taper, initiating a re-tapering of steroids starting at a higher dose followed by a more prolonged taper and re-administration of anti-TNF-alpha therapy should be considered. Unblinding will not be routinely performed but may be considered on a case-by-case basis as noted above in section 7.5.

Subjects should also be instructed to notify the treating physician or nurse for the occurrence of bloody or black stools, symptoms of dehydration, fever, inability to take liquids by mouth, inability to control diarrhea (return to baseline) within 24 hours. Subjects with diarrhea should be evaluated frequently by a nurse or physician until resolution of diarrhea.

For severe diarrhea (i.e., Grade 3 and 4), hospital admission, I.V. fluids, corticosteroids, and electrolytes should be administered as appropriate. Clostridium Difficile (C. diff) testing is strongly recommended.

9.94 Hand-Foot Syndrome

Hand-Foot Syndrome should be treated according to the prescribing information for capecitabine and standard institutional practice. This may include the use of emollients such as Aveeno®, Lubriderm®, Udder Cream®, and Bag Balm®.

10.0 Adverse Event (AE) Reporting and Monitoring

The site principal investigator is responsible for reporting any/all serious adverse events to the sponsor as described within the protocol, regardless of attribution to study agent or treatment procedure. The sponsor/sponsor-investigator is responsible for notifying FDA and all participating investigators in a written safety report of any of the following:

- Any suspected adverse reaction that is both serious and unexpected.
- Any findings from laboratory animal or *in vitro* testing that suggest a significant risk for human subjects, including reports of mutagenicity, teratogenicity, or carcinogenicity.

- Any findings from epidemiological studies, pooled analysis of multiple studies, or clinical studies, whether or not conducted under an IND and whether or not conducted by the sponsor, that suggest a significant risk in humans exposed to the drug.
- Any clinically important increase in the rate of a serious suspected adverse reaction over the rate stated in the protocol or Investigator's Brochure (IB).

Definitions

Adverse Event
Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

This includes the following:

- AEs not previously observed in the subject that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with metastatic colorectal cancer that were not present prior to the AE reporting period.
- Complications that occur as a result of the 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.
- Preexisting 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.
    - A preexisting medical condition is one that is present at the start of the study. Such conditions should be reported as medical and surgical history. A preexisting 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 preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

Suspected Adverse Reaction
Any adverse event for which there is a reasonable possibility that the drug caused the adverse event.

Expedited Reporting
Events reported to sponsor within 24 hours, 5 days or 10 days of study team becoming aware of the event.

Routine Reporting
Events reported to sponsor via case report forms

Events of Interest
Events that would not typically be considered to meet the criteria for expedited reporting, but that for a specific protocol are being reported via expedited means in order to facilitate the review of safety data (may be requested by the FDA or the sponsor).

10.1 Adverse Event Characteristics

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site: [redacted]

a. Adverse event monitoring and reporting is a routine part of every clinical trial.

b. Identify the grade and severity of the event using the CTCAE version 4.0.
c. Determine whether the event is expected or unexpected (see Section 10.2).
d. Determine if the adverse event is related to the study intervention (agent, treatment or procedure) (see Section 10.3).
e. Determine whether the event must be reported as an expedited report. If yes, determine the timeframe/mechanism (see Section 10.4).
f. Determine if other reporting is required (see Section 10.5).

Note: All AEs reported via expedited mechanisms must also be reported via the routine data reporting mechanisms defined by the protocol (see Sections 10.6 and 18.0).

10.11 Each CTCAE term in the current version is a unique representation of a specific event used for medical documentation and scientific analysis and is a single MedDRA Lowest Level Term (LLT).

NOTE: A severe AE, as defined by the above grading scale, is NOT the same as serious AE which is defined in the table in Section 10.4.

10.2 Expected vs. Unexpected Events

Expected events - are those described within the Section 15.0 of the protocol, the study specific consent form, package insert (if applicable), and/or the investigator brochure, (if an investigator brochure is not required, otherwise described in the general investigational plan).

Unexpected adverse events or suspected adverse reactions are those not listed in Section 15.0 of the protocol, the study specific consent form, package insert (if applicable), or in the investigator brochure (or are not listed at the specificity or severity that has been observed); if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan.

Unexpected also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs but have not been observed with the drug under investigation.

Unanticipated Adverse Device Event (UADE)
Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects

10.3 Assessment of Attribution

All AEs and SAEs, whether volunteered by the subject, discovered by the 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 evaluation date, grade, attribution to any treatment, and actions taken (if applicable).

When assessing whether an adverse event is related to a medical treatment or procedure, the following attribution categories are utilized:

Definite - The adverse event *is clearly related* to the agent(s).
Probable - The adverse event *is likely related* to the agent(s).

Possible - The adverse event *may be related* to the agent(s).
Unlikely - The adverse event *is doubtfully related* to the agent(s).
Unrelated - The adverse event *is clearly NOT related* to the agent(s).

Events determined to be possibly, probably or definitely attributed to a medical treatment suggest there is evidence to indicate a causal relationship between the drug/device and the adverse event.

10.31 **AEs Experienced Utilizing Investigational Agents and Commercial Agent(s) on the SAME (Combination) Arm**

When a commercial agent(s) is (are) used on the same treatment arm as the investigational agent/intervention (also, investigational drug, biologic, cellular product, or other investigational therapy under an IND), the **entire combination (arm) is then considered an investigational intervention for reporting**. These AEs should be assessed as specified in the appropriate **IND/IDE** reporting guidelines in Section 10.4

10.4 Expedited Adverse Event Reporting Requirements for IND/IDE Agents

10.41 **Phase 1 and Early Phase 2 Studies:** Expedited Reporting via the **ACCRU Adverse Event Expedited Report Form** for Adverse Events That Occur Within 30 Days[1] of the Last Dose of the Investigational Agent

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria MUST be immediately reported to the sponsor within the timeframes detailed in the table below.

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	7 Calendar Days	24-Hour 3 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required	

Expedited AE reporting timelines are defined as:

- "24-Hour; 3 Calendar Days" - The AE must initially be reported within 24 hours of learning of the AE, followed by a complete expedited report within 3 calendar days of the initial 24-hour report.
- "7 Calendar Days" - A complete expedited report on the AE must be submitted within 7 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 3 calendar days for:

- All Grade 3, 4, and Grade 5 AEs

Expedited 7 calendar day reports for:

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

[2] For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 5, 2011

Special Instructions:

- Follow site-specific reporting guidelines.
- Submit the [redacted] via fax [redacted] The ACCRU SAE Coordinator will forward a copy of the expedited reports within 1 business day of receipt using the Genentech Fax Coversheet to:

  Genentech Drug Safety at Fax: [redacted]

- The ACCRU SAE Coordinator will forward to [redacted] The ACCRU IND Coordinator will assist the sponsor-investigator in notifying the FDA if required.

- **Genentech AEs of Special Interest (AESI)**: AEs of Special Interest are defined by Genentech as a potential safety problem identified as a result of ongoing safety monitoring of their products. As such, surveillance for the AESIs in Appendix II MUST be undertaken at each treatment evaluation. Development of one of these AESIs (≥ grade 1 unless otherwise noted) MUST be reported in terms of CTCAE v4.0 grade and attribution (please refer to the table below):

Adverse Event	Form(s) Needed	Site timeline to report to ACCRU	ACCRU timeline to report to sponsor
Non-Serious Adverse Event (Sections 10.52-10.53)	Adverse Events form (see CRF packet)	At each evaluation	Quarterly
Adverse Events of Special Interest (Section 10.41 special instructions and Appendix II)*	Adverse Events of Special Interest Form**	At each occurrence	Within 1 business day of receipt
	Adverse Events form (if criteria in 10.5 is met)		Quarterly

Adverse Event	Form(s) Needed	Site timeline to report to ACCRU	ACCRU timeline to report to sponsor
Pregnancy (Sections 10.41 and 10.54)	ACCRU Adverse Event Expedited Report Form**	At each occurrence	Within 1 business day of receipt
	Adverse Events form (if criteria in 10.5 is met)		Quarterly
Serious Adverse Events (Section 10.41)*	ACCRU Adverse Event Expedited Report Form**	At each occurrence	Within 1 business day of receipt
	Adverse Events form (see CRF packet)		Quarterly

*If an adverse event meets the criteria for both an AE of Special Interest and a Serious Adverse Event, please report only as a Serious Adverse Event.
** The Adverse Events of Special Interest Form and ACCRU Adverse Event Expedited Report Form are available on the ACCRU web site [redacted]

10.42 Reporting of re-occurring SAEs

ALL SERIOUS adverse events that meet the criteria outlined in table 10.41 MUST be immediately reported to the sponsor within the timeframes detailed in the corresponding table. This reporting includes, but is not limited to SAEs that re-occur again after resolution.

10.5 Other Required Reporting

10.51 Unanticipated Problems Involving Risks to Subjects or Others (UPIRTSOs) in general, include any incident, experience, or outcome that meets all of the following criteria:

1. Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
2. Related or possibly related to participation in the research (in this guidance document, possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
3. Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Some unanticipated problems involve social or economic harm instead of the physical or psychological harm associated with adverse events. In other cases, unanticipated problems place subjects or others at increased risk of harm, but no harm occurs.

Note: If there is no language in the protocol indicating that pregnancy is not considered an adverse experience for this trial, and if the consent form does not indicate that subjects should not get pregnant/impregnate others, then any pregnancy in a subject/patient or a male patient's partner (spontaneously reported) which occurs during the study or within 120 days of completing the study should be reported as a UPIRTSO.

If the event meets the criteria for an UPIRTSO, submit to your IRB as required by your institutional policies.

10.52 Baseline and Adverse Events Evaluations

Pre-treatment symptoms/conditions to be graded at baseline and adverse events to be graded starting with day 1 treatment and at each evaluation per the CTCAE v4.0 grading unless otherwise stated in the table below: Please note: if an SAE were to occur prior to day 1 treatment, please collect that SAE from the day of consent.

System Organ Class (SOC)	Adverse event/Symptoms	Baseline	Each evaluation
Gastrointestinal Disorders	Diarrhea	# of stools	X
	Nausea	X	X
	Vomiting	X	X
General Disorders and Administration	Fatigue	X	X

10.53 **Case Report Forms** - Academic and Community Cancer Research United (ACCRU)

Submit the following AEs not specified in Section 10.5 (paper or electronic, as applicable):

10.531 Grade 2, 3, 4 and 5 AEs regardless of attribution to the study treatment or procedure.

10.532 Grade 5 AEs (Deaths)

10.5321 Any death within 30 days of the patient's last study treatment or procedure regardless of attribution to the study treatment or procedure.

10.5322 Any death more than 30 days after the patient's last study treatment or procedure that is felt to be at least possibly treatment related must also be submitted as a Grade 5 AE, with a CTCAE type and attribution assigned.

10.54 Pregnancy

- During the course of the trial, all female subjects of childbearing potential should be instructed to contact the treating physician immediately if they suspect they might have conceived a child. In addition, a missed or late menstrual period should be reported to the treating physician. If a female subject, or an investigator, suspects a pregnancy prior to administration of study drugs, the study drugs must be withheld until the results of a pregnancy test are available. If pregnancy is confirmed the subject must not receive study medications and must be withdrawn from the study. All supporters of the study will be informed if a pregnancy occurs.
- Throughout the entire pregnancy, additional contact should be made with the subject and in some cases with the healthcare provider, to identify spontaneous abortions and elective terminations, as well as any medical reasons for elective termination. In addition, the investigator should include perinatal and neonatal outcome. Infants should be followed for a minimum of 8 weeks.
- If a male subject is suspected of having fathered a child while on study drugs, the pregnant female partner must be notified and counseled regarding the possible risk to the fetus. In addition, the treating physician must follow the course of the pregnancy, including prenatal and neonatal outcome. Infants should be followed for a minimum of 8 weeks.
- The subject must be instructed to stop taking capecitabine if she becomes pregnant during the study and immediately inform the investigator. The investigator should counsel the subject, and discuss the risk of continuing with the pregnancy and the possible effect on the fetus. Monitoring of the subject should continue until conclusion of the pregnancy. Pregnancy occurring in the partner of a subject participating in the study must also be treated as describe above.
- If a female subject becomes pregnant while receiving investigational therapy or ≤120 days after the last dose of study drug, a report should be completed and expeditiously submitted to the 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 cancer or congenital anomaly/birth defect in a child born to a female subject exposed to the study drugs should be reported as an SAE.

10.55 Post-Study Adverse Events

The investigator should expeditiously report any SAE occurring after a subject has completed or discontinued study participation if attributed to prior exposure to atezolizumab or bevacizumab.

10.56 Reconciliation: ACCRU agrees to conduct reconciliation for the product. Genentech and ACCRU will agree to the reconciliation periodicity and format, but agree at maximum to exchange quarterly line listings of cases received by the other party. 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.

10.57 IND Annual Reports: All IND annual reports submitted to the FDA by the Sponsor-Investigator should be copied to Genentech. Copies of such reports should be faxed to Genentech Drug Safety:

10.58 All non-serious adverse events originating from the study will be forwarded by ACCRU in a quarterly report to Genentech.

10.59 Study Close-Out: Any study report submitted to the FDA by the Sponsor-Investigator should be copied to Genentech. This includes all Clinical Study Reports (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.

11.0 Treatment Evaluation Using RECIST Guideline

NOTE: This study uses protocol RECIST v1.1 template dated 2/16/2011. See the footnote for the table regarding measureable disease in Section 11.44, as it pertains to data collection and analysis.

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guidelines (version 1.1) (Eisenhauer, Therasse et al. 2009). Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the short axis measurements in the case of lymph nodes are used in the RECIST guideline (Pocock and Simon 1975). However, if the patient is considered to have pseudo-progression by Immune-Related Response Criteria (Wolchok, Hoos et al. 2009), please contact the Study Chair. Pseudo-progression is usually accompanied by improvements in CEA and tumor symptoms. Such patients may be allowed to continue treatment on a case by case basis with permission of the Study Chair by contacting the Data Manager.

11.1 Schedule of Evaluations: For the purposes of this study, patients should be reevaluated at least every 21 days during treatment and if possible every 12 weeks if discontinued from treatment for reasons other than disease progression.

11.2 Definitions of Measurable and Non-Measurable Disease

11.21 Measurable Disease

11.211 A non-nodal lesion is considered measurable if its longest diameter can be accurately measured as ≥2.0 cm with chest x-ray, or as ≥1.0 cm with CT scan, CT component of a PET/CT, or MRI.

11.212 A superficial non-nodal lesion is measurable if its longest diameter is ≥1.0 cm in diameter as assessed using calipers (e.g. skin nodules) or imaging. In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

11.213 A malignant lymph node is considered measurable if its short axis is >1.5 cm when assessed by CT scan (CT scan slice thickness recommended to be no

greater than 5 mm).

NOTE: Tumor lesions in a previously irradiated area are not considered measurable disease.

11.22 Non-Measurable Disease

All other lesions (or sites of disease) are considered non-measurable disease, including pathological nodes (those with a short axis ≥1.0 to <1.5 cm). Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable as well.

Note: "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 patient, these are preferred for selection as target lesions. In addition, lymph nodes that have a short axis <1.0 cm are considered non- pathological (i.e., normal) and should not be recorded or followed.

11.3 Guidelines for Evaluation of Measurable Disease

11.31 Measurement Methods:

- All measurements should be recorded in metric notation (i.e., decimal fractions of centimeters) using a ruler or calipers.
- The same method of assessment and the same technique must be used to characterize each identified and reported lesion at baseline and during follow-up. For patients having only lesions measuring at least 1 cm to less than 2 cm must use CT imaging for both pre- and post-treatment tumor assessments.
- Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used at the same evaluation to assess the antitumor effect of a treatment.

11.32 Acceptable Modalities for Measurable Disease:

- Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness.
- 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. The lesions should be measured on the same pulse sequence. 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.
- PET-CT: If the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time.
- Chest X-ray: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT scans are preferable.

- Physical Examination: For superficial non-nodal lesions, physical examination is acceptable, but imaging is preferable, if both can be done. In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

11.33 Measurement at Follow-up Evaluation:

- In the case of stable disease (SD), follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of 8 weeks (see Section 11.44).

11.4 Measurement of Effect

11.41 Target Lesions & Target Lymph Nodes

- Measurable lesions (as defined in Section 11.21) up to a maximum of 5 lesions, representative of all involved organs, should be identified as "Target Lesions" and recorded and measured at baseline. <u>These lesions can be non-nodal or nodal (as defined in 11.21)</u>, where no more than 2 lesions are from the same organ and no more than 2 malignant nodal lesions are selected.

  Note: If fewer than 5, target lesions and target lymph nodes are identified (as there often will be) there is no reason to perform additional studies beyond those specified in the protocol to discover new lesions.

- Target lesions and target lymph nodes should be selected on the basis of their size, be representative of all involved sites of disease, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion (or malignant lymph node) does not lend itself to reproducible measurements in which circumstance the next largest lesion (or malignant lymph node) which can be measured reproducibly should be selected.
- Baseline Sum of Dimensions (BSD): A sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes will be calculated and reported as the baseline sum of dimensions (BSD). The BSD will be used as reference to further characterize any objective tumor response in the measurable dimension of the disease.
- Post-Baseline Sum of the Dimensions (PBSD): A sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes will be calculated and reported as the post-baseline sum of dimensions (PBSD). If the radiologist is able to provide an actual measure for the target lesion (or target lymph node), that should be recorded, even if it is below 0.5 cm. If the target lesion (or target lymph node) is believed to be present and is faintly seen but too small to measure, a default value of 0.5 cm should be assigned. If it is the opinion of the radiologist that the target lesion or target lymph node has likely disappeared, the measurement should be recorded as 0 cm.
- The minimum sum of the dimensions (MSD) is the minimum of the BSD and the PBSD.

11.42 Non-Target Lesions & Non-Target Lymph Nodes

Non-measurable sites of disease (Section 11.22) are classified as non- target lesions or non-target lymph nodes and should also be recorded at baseline. These lesions and lymph nodes should be followed in accord with 11.433.

11.43 Response Criteria

11.431 All target lesions and target lymph nodes followed by CT/MRI/PET-CT/Chest X-ray/physical examination must be measured on re-evaluation at evaluation times specified in Section 11.1. Specifically, a change in objective status to either a PR or CR cannot be done without re-measuring target lesions and target lymph nodes.

Note: Non-target lesions and non-target lymph nodes should be evaluated at each assessment, especially in the case of first response or confirmation of response. In selected circumstances, certain non-target organs may be evaluated less frequently. For example, bone scans may need to be repeated only when complete response is identified in target disease or when progression in bone is suspected.

11.432 Evaluation of Target Lesions

- Complete Response (CR): All of the following must be true:

  a. Disappearance of all target lesions.
  b. Each target lymph node must have reduction in short axis to <1.0 cm.
  c. Normalization of tumor biomarkers.

- Partial Response (PR): At least a 30% decrease in PBSD (sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes at current evaluation) taking as reference the BSD (*see* Section 11.41).

- Progression (PD): At least one of the following must be true:

  a. At least one new malignant lesion, which also includes any lymph node that was normal at baseline (< 1.0 cm short axis) and increased to ≥ 1.0 cm short axis during follow-up.
  b. At least a 20% increase in PBSD (sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes at current evaluation) taking as reference the MSD (Section 11.41). In addition, the PBSD must also demonstrate an absolute increase of at least 0.5 cm from the MSD.
  c. See Section 11.32 for details in regards to the requirements for PD via FDG-PET imaging.

- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR, nor sufficient increase to qualify for PD taking as reference the MSD.

11.433 Evaluation of Non-Target Lesions & Non-target Lymph Nodes

- Complete Response (CR): All of the following must be true:

  a. Disappearance of all non-target lesions.
  b. Each non-target lymph node must have a reduction in short axis to <1.0 cm.
  c. Normalization of tumor biomarkers

- Non-CR/Non-PD: Persistence of one or more non-target lesions or non-target lymph nodes and/or maintenance of tumor marker level above the normal limits.
- Progression (PD): At least one of the following must be true:

  a. At least one new malignant lesion, which also includes any lymph node that was normal at baseline (<1.0 cm short axis) and increased to ≥1.0 cm short axis during follow-up.
  b. Unequivocal progression of existing non-target lesions and non-target lymph nodes. (NOTE: Unequivocal progression should not normally trump target lesion and target lymph node status. It must be representative of overall disease status change.)
  c. See Section 11.32 for details in regards to the requirements for PD via FDG-PET imaging.

11.44 Overall Objective Status

The overall objective status for an evaluation is determined by combining the patient's status on target lesions, target lymph nodes, non-target lesions, non-target lymph nodes, and new disease as defined in the following tables:

For Patients with Measurable Disease

Target Lesions & Target Lymph Nodes	Non-Target Lesions & Non-Target Lymph Nodes	New Sites of Disease	Overall Objective Status
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
PR	CR Non-CR/Non-PD	No	PR
CR/PR	Not All Evaluated*	No	PR**
SD	CR Non-CR/Non-PD Not All Evaluated*	No	SD
Not all Evaluated	CR Non-CR/Non-PD Not All Evaluated*	No	Not Evaluated (NE)
PD	Unequivocal PD CR Non-CR/Non-PD Not All Evaluated*	Yes or No	PD
CR/PR/SD/PD/Not all Evaluated	Unequivocal PD	Yes or No	PD
CR/PR/SD/PD/Not all Evaluated	CR Non-CR/Non-PD Not All Evaluated*	Yes	PD

* See Section 11.431

** NOTE: This study uses the protocol RECIST v1.1 template dated 2/16/2011. For data collection and analysis purposes the objective status changed from SD to PR in the ACCRU protocol RECIST v1.1 template as of 2/16/2011 and to match RECIST v1.1 requirements.

For Patients with Non-Measurable Disease Only:

Non-Target Lesions & Non-Target Lymph Nodes	New Sites of Disease	Overall Objective Status
CR	No	CR
Non-CR/Non-PD	No	Non-CR/Non-PD
Not All Evaluated*	No	Not Evaluated (NE)
Unequivocal PD	Yes or No	PD
Any	Yes	PD

* See Section 11.431

12.0 Descriptive Factors

12.1 RAF Status: Wild-type vs. mutant.

12.11 If mutant, select appropriate alteration from the following:

12.111 V600E vs. other (please list)

12.2 MSI Status: Microsatellite Stable (MSS) or Mismatch Repair (MMR) Proficient vs. Microsatellite Unstable or Microsatellite Instability present or Mismatch Repair Deficient.

12.21 List test used:

12.221 Immunohistochemistry (IHC)

12.222 Polymerase Chain Reaction (PCR)

12.223 Both IHC and PCR

13.0 Treatment/Follow–up Decision at Evaluation of Patient

13.1 All patients will remain on treatment until progression of disease, unacceptable toxicity, refusal to continue, or other reason for treatment discontinuation.

13.2 Patients who develop PD while receiving therapy will go to the event-monitoring phase.

13.3 Patients who go off protocol treatment for reasons other than PD and receive no subsequent anti-cancer therapy will go to Observation and then event monitoring per Section 18.0.

13.4 A patient is deemed ineligible if after randomization, it is determined that at the time of randomization, the patient did not satisfy each and every eligibility criteria for study entry. The patient may continue treatment off-protocol at the discretion of the physician as long as there are no safety concerns, and the patient was properly registered. The patient will go directly to the event-monitoring phase of the study (or off study, if applicable).

- If the patient received treatment, all data up until the point of confirmation of ineligibility must be submitted. Event monitoring will be required per Section 18.0 of the protocol.
- If the patient never received treatment, on-study material must be submitted. Event monitoring will be required per Section 18.0 of the protocol.
- Up to 14 patients withdrawn prior to treatment or determined to be ineligible will be replaced.

13.5 A patient is deemed a major violation, if protocol requirements regarding treatment in cycle 1 of the initial therapy are severely violated that evaluability for primary end point is questionable. All data up until the point of confirmation of a major violation must be submitted. The patient will go directly to the event-monitoring phase of the study. The patient may continue treatment off-protocol at the discretion of the physician as long as there are no safety concerns, and the patient was properly registered. Event monitoring will be required per Section 18.0 of the protocol.

13.6 A patient is deemed a cancel if he/she is removed from the study for any reason before any study treatment is given. On-study material and the End of Active Treatment/Cancel Notification Form must be submitted. The patient will go directly to the event-monitoring phase of the study, and event monitoring will be required per Section 18.0 of the protocol. Up to 14 patients withdrawn prior to treatment or determined to be ineligible will be replaced.

14.0 Body Fluid Biospecimens

14.1 Summary Table of Research Blood/Blood Products to Be Collected for This Protocol

Indicate if specimen is mandatory or optional	Collection tube description and/or additive (color of tube top)	Volume to collect per tube (number of tubes to be collected)	Blood product being processed and submitted by participating site	When to submit?	Reason for Submission
Mandatory	EDTA K_2 (Pink)	6 mL (1)	Whole Blood	Baseline	Genotyping
Mandatory	EDTA K_2 (Purple)	6 mL (2)	Plasma	Multiple timepoints	Blood Biomarkers
Mandatory	SST (Gold)	5 mL (1)	Serum	Multiple timepoints	Blood Biomarkers
Mandatory	ACD (Yellow)	8.5 mL (3)	Whole Blood	Multiple timepoints	Blood Biomarkers

14.11 **Kits are required for this study.**

14.111 The kit contains supplies and instructions for collecting, processing, and shipping specimens.

14.112 Participating institutions may obtain kits by completing and faxing the Supply Order Form (found in the Forms Packet) to the number listed on the form. Fill out the site address to where the kits will be shipped on the Fax Supply form. Because we are now being charged for all outgoing kits, a small, but sufficient, supply of the specimen collection kits should be ordered prior to patient entry. Do not send the unused kits back to BAP.

14.113 Kits will be sent via FedEx® Ground at no additional cost to the participating institutions. Allow up to two weeks to receive the kits. Kits will arrive inside the shipping boxes.

14.114 Kits will not be sent via rush delivery service unless the participating institution provides their own FedEx® account number or alternate billing number for express service. ACCRU will not cover the cost for rush delivery of kits.

14.115 Summary Table of Research Blood to Be Collected for This Protocol

Collection container description	Volume to collect (number of containers to be collected)	Baseline[1]	Restaging[2]	Off Treatment[3]	Off Treatment Follow up[4]	Site to process	Storage/ shipping conditions[5]
EDTA K_2 (Pink)	6mL (1)	X				No	Freeze (Brown shipper)
EDTA K_2 (Purple)	6 mL (2)	X	X	X	X	Yes	Freeze (Brown shipper)
SST (Gold)	5 mL (1)	X	X	X	X	Yes	Freeze (Brown shipper)
ACD (Yellow)[6]	8.5 mL (3)	X	X[7]	X		No	Ambient (White shipper)

1. May occur prior to treatment on Cycle 1 Day 1.
2. At time of radiographic assessments (i.e., prior to Cycle 4, prior to Cycle 7, etc.) which may occur ≤14 days prior to day 1 of new cycle.
3. Discontinuation of study treatment.
4. 30 days from last dose of study drug.
5. After all samples have been processed according to kit instructions, ship all specimens according to shipping instructions (see Section 14.12 for detailed shipping instructions).
6. Samples only viable for 1 overnight shipment. Email [redacted] prior to shipping.
7. At first restaging only (i.e., prior to Cycle 4 only).

14.12 Shipping

14.121 Verify ALL sections of the Blood Specimen Submission Form (see CRF Packet), BAP Requisition Form (provided in kit), and specimen collection labels are completed and filled in correctly.

14.122 Specimens must be shipped the same day they are drawn.

14.123 Ship ACD whole blood specimens in the White shipping box Priority Overnight service **Monday – Thursday ONLY Ambient Temp to Duke University** according to kit instructions. ATTN: [redacted]

14.124 Ship EDTA whole blood, plasma and serum specimens in the Brown shipping box via Priority Overnight service, Monday – Thursday on Dry Ice, to BAP Freezer according to kit instructions. Do not send samples on Fridays, weekends, or just prior to federal holidays. Brown shippers will arrive at BAP Freezer and specimens will be immediately forwarded to the [redacted]

14.125 The BAP kits will include a smart shipper label (3x5 white barcoded label) affixed to the boxes. The smart shipper label is a pre-addressed which replaces the need for airbills. Shipping costs will be covered by ACCRU only if the provided shippers are used. ATTENTION: Brown shippers will be sent to BAP Freezer and White shippers will be sent to Duke University. Use extra caution to ensure the correct samples go in the different shippers.

14.2 Study Methodology and Storage Information

14.21 Blood/blood product samples will be collected for the following research

14.211 DNA will be extracted from whole blood and stored for future pharmacogenetic assays (e.g., genetic polymorphisms such as those known to regulate angiogenesis, inflammation, immunity, auto-immunity, and antibody or drug action of clearance) that may correlate with efficacy and tolerability. The Duke Phase I Biomarker Laboratory located at Duke University may analyze the DNA for the presence of markers of interest including, but not limited to VEGF, NOS, IL6, IL17, Fc Receptors, and MHCs, using standard laboratory protocols.

14.212 Plasma and serum will be analyzed for the presence of markers related to tumor angiogenesis, inflammation, immunity, colon cancer biology, and other factors that may correlate with efficacy and tolerability. The Duke Phase I Biomarker Laboratory located at Duke University Medical Center may analyze the plasma and serum for the presence of markers of interest including, but not limited to VEGF-A, -C, -D, VEGFR-1, -2, -3, IL6, IL6R, s-gp130, IL11, IL17A, IL17E, IL17R, IL22, IL23, and TGFβ, using standard laboratory protocols.

14.213 Circulating immune cells will be analyzed for lymphoid focus on T-cell activation, maturation, regulation, and exhaustion and myeloid focus on myeloid derived suppressor cells (MDSC), M1/M2 polarization, and dendritic cells (DC, pDC). The Duke Immune Profiling Core Laboratory located at Duke University Medical Center may analyze the circulating immune cells for the presence of markers of interest including, but not limited to Amine, CD3, CD4, CD45RO, CD38, CD278-ICOS, FoxP3, CD25, Tim3, CD152-CTLA4, IDO, CD223-LAG3, CD279-PD1, CD11b, CD33, HLA-DR, CD123, CD11c, CD304-BDCA4, CD86, CD163, CD206, CD16, CD68, using standard laboratory protocols.

14.214 As part of ongoing research of Dr. Herbert Hurwitz and other ACCRU investigators, any DNA, immune cell, plasma and/or serum samples left over from the analysis of this study will be stored for future research studies on molecular determinants of efficacy and tolerability, according to patient consent information. Leftover samples will be stored frozen at -70ºC by Duke University until specific analyses are identified. As protocols are developed, they will be presented for IRB review and approval.

14.3 Return of Genetic Testing Research Results

Because the results generated by the genetic testing included in this section are not currently anticipated to have clinical relevance to the patient or their family members, the genetic results will not be disclosed to the patients or their physicians.

If at any time, genetic results are obtained that may have clinical relevance, IRB review and approval will be sought regarding the most appropriate manner of disclosure and whether or not validation in a CLIA-certified setting will be required. Sharing of research data with individual patients should only occur when data have been validated by multiple studies and testing has been done in CLIA-approved laboratories.

15.0 Drug Information

IND #130760

15.1 Bevacizumab (Avastin®)

- Investigator brochure: Available on the ACCRU website.

15.11 **Background**: Bevacizumab is classified as an Anti-VEGF Monoclonal Antibody and a Vascular Endothelial Growth Factor (VEGF) Inhibitor. Bevacizumab is a recombinant, humanized monoclonal immunoglobulin G1 (IgG1) antibody which binds to, and neutralizes, vascular endothelial growth factor (VEGF), preventing its association with endothelial receptors, Flt-1 and KDR. VEGF binding initiates angiogenesis (endothelial proliferation and the formation of new blood vessels). The inhibition of microvascular growth is believed to retard the growth of all tissues (including metastatic tissue).

15.12 **Formulation**: 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 is supplied in 100 mg (4 mL) and 400 mg (16 mL) glass vials, each with a concentration of 25 mg/mL. Vials contain bevacizumab with phosphate, trehalose, polysorbate 20, and sterile water for injection (SWFI), USP. Vials contain no preservative and are suitable for single use only.

15.13 **Preparation and storage**: Bevacizumab vials should be stored in a refrigerator at 2°C-8°C. Keep vial in the outer carton due to light sensitivity. DO NOT FREEZE. DO NOT SHAKE.

Chemical and physical in-use stability has been demonstrated for 48 hours at 2°C-30°C in 0.9% sodium chloride solution. **Do not administer or mix with dextrose solution.** From a microbiological point of view, the product should be used immediately. 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 to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

Withdraw the necessary amount of bevacizumab and dilute to the required administration volume with 0.9% sodium chloride solution. The concentration of the final bevacizumab solution should be kept within the range of 1.4 - 16.5 mg/mL. Discard any unused portion left in a vial, as the product contains no preservatives. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

15.14 **Administration**: Do not administer as an intravenous push or bolus. Administer only as an intravenous (IV) infusion. Do not initiate bevacizumab for 28 days following major surgery and until surgical wound is fully healed.

Refer to Section 7 for protocol-specific administration instructions. Guidelines recommended by the manufacturer are included for reference.

First infusion: Administer infusion over 90 minutes.
Subsequent infusions: Administer second infusion over 60 minutes if first infusion is tolerated; administer all subsequent infusions over 30 minutes if infusion over 60 minutes is tolerated.

15.15 **Pharmacokinetic information**:
Distribution: V_d: 3.28L
Half-life elimination: 3-4 weeks
Clearance: 0.22L/day. A low serum albumin and high tumor burden increase clearance by 30% and 7% respectively. Clearance increases with increasing body weight, and is 15% slower in women than men.
Time to steady state: 100 days

15.16 **Potential Drug Interactions**:

No clinically relevant pharmacokinetic interaction of co-administered chemotherapy on bevacizumab pharmacokinetics has been observed based on the results of a population PK analysis. There was neither statistical significance nor clinically relevant difference in clearance of bevacizumab in patients receiving bevacizumab monotherapy compared with patients receiving bevacizumab in combination with Interferon alpha 2a or other chemotherapies (IFL, 5-FU/LV, carboplatin/paclitaxel, capecitabine, doxorubicin or cisplatin/gemcitabine).

No clinically relevant interaction of bevacizumab was observed on the pharmacokinetics of co-administered interferon alpha 2a, erlotinib (and its active metabolite OSI-420), or the chemotherapies irinotecan (and its active metabolite SN38), capecitabine, oxaliplatin (as determined by measurement of free and total platinum), and cisplatin. Conclusions on the impact of bevacizumab on gemcitabine pharmacokinetics cannot be drawn.

Combination of bevacizumab and sunitinib malate: In two clinical trials studies of metastatic renal cell carcinoma, microangiopathic hemolytic anemia (MAHA) was reported in 7 of 19 patients' treated with bevacizumab (10 mg/kg every two weeks) and sunitinib malate (50 mg daily) combination. MAHA is a hemolytic disorder which can present with red cell fragmentation, anemia, and thrombocytopenia. In addition, hypertension (including hypertensive crisis), elevated creatinine, and neurological symptoms were observed in some of these patients. All of these findings were reversible upon discontinuation of bevacizumab and sunitinib malate.

15.17 **Known potential adverse events:** Consult the investigator's brochure and package insert for the most current and complete information. U.S. Boxed Warnings report that severe or fatal hemorrhage, including hemoptysis, GI bleeding, hematemesis, CNS hemorrhage, epistaxis, and vaginal bleeding, occurs up to 5-fold more frequently in patients receiving bevacizumab products. Do not administer bevacizumab products to patients with a recent history of hemoptysis. Discontinue in patients who develop grade 3 to 4 hemorrhage.Percentages reported as Monotherapy and as part of combination chemotherapy regimens.

Very Common (≥ 1/10) Infections and infestations: paronychia
Blood and lymphatic system disorders: febrile neutropenia, leucopenia, neutropenia, thrombocytopenia
Metabolism and nutrition disorders: anorexia, hypomagnesemia, hyponatremia
Nervous system disorders: peripheral sensory neuropathy, dysgeusia, headache, dysarthria
Eye disorders: eye disorder, increased lacrimation

Vascular disorders: hypertension
Respiratory, thoracic and mediastinal disorders: dyspnea, epistaxis, rhinitis, cough
Gastrointestinal disorders: diarrhea, nausea, vomiting, abdominal pain, constipation, stomatitis, rectal hemorrhage
Endocrine disorders: ovarian failure
Skin and subcutaneous tissue disorders: exfoliative dermatitis, dry skin, skin discoloration
Musculoskeletal, connective tissue, and bone disorders: arthralgia
Renal and urinary disorders: proteinuria
General disorders and administration site conditions: asthenia, fatigue, pyrexia, pain, mucosal inflammation
Investigations: weight decreased

Common (≥ 1/100 to < 1/10) Infections and infestations: sepsis, abscess, cellulitis, infection
Blood and lymphatic system disorders: anemia, lymphopenia
Metabolism and nutrition disorders: dehydration
Cardiac disorders: cardiac failure congestive, supraventricular tachycardia
Vascular disorders: arterial thromboembolism, deep vein thrombosis, hemorrhage
Respiratory, thoracic and mediastinal disorders: pulmonary embolism, hypoxia
Gastrointestinal disorders: intestinal perforation, ileus, intestinal obstruction, recto-vaginal fistula, gastrointestinal disorder, proctalgia
Skin and subcutaneous tissue disorders: palmar-plantar erythrodysesthesia syndrome
Musculoskeletal, connective tissue, and bone disorders: muscular weakness, myalgia, arthralgia, back pain
Renal and urinary disorders: urinary tract infection
General disorders and administration site conditions: lethargy
Reproductive system and breast: pelvic pain**Rare (≥ 1/10,000 to < 1/1,000)**
Infections and infestations: necrotizing fasciitis
Nervous system disorders: posterior reversible encephalopathy syndrome

15.18**Drug procurement:** Genentech, Inc. will supply the drug to Clinical Research Services, a division of Rx Crossroads by McKesson. Each participating ACCRU treating location will order the drug from Clinical Research Services, a division of Rx Crossroads by McKesson. Fax the Drug Order Request Form (found in the forms packet) to:

[redacted]

Each participating ACCRU treating location will be responsible for monitoring the supply of bevacizumab and will use the Drug Order Request Form to order additional supplies as needed.

Outdated or remaining drug is to be destroyed on-site as per procedures in place at each institution.

Temperature excursions that occur at the site should be reported by the site using the IMP Deviation Form found on the ACCRU web site for this study and emailed to: [redacted] Any shipment deviations (those not occurring at the site) should be reported to Clinical Research Services, a division of Rx Crossroads by McKesson via email to: [redacted] Clinical Research Services, a division of Rx Crossroads by McKesson will complete the IMP Deviation

Form and report shipment deviations to Genentech via email to: [redacted] (those not occurring at the site).

15.19 **Nursing guidelines:**

15.191 Monitor patients closely for infusion type reactions, including fever, chills, myalgias, rigors, or other allergic reactions. While this is less likely given that bevacizumab is a humanized antibody, there still exists the potential for severe allergic reactions. If these signs or symptoms occur stop the infusion immediately and contact MD. Have emergency equipment nearby and be prepared to administer emergency treatment as ordered by MD.

15.192 Monitor urine dipstick or UPC as required by the test schedule.

15.193 Evaluate IV site regularly for signs of infiltration.

15.194 Bleeding in the absence of thrombocytopenia is a dose limiting toxicity. Monitor patient closely for hemorrhagic events, including CNS hemorrhage, epistaxis, hematemesis and hemoptysis. Most cases of bleeding have occurred at the tumor site. Advise patient about the potential for bleeding or thrombosis.

15.195 In patients receiving treatment for lung cancer, hemoptysis and pulmonary hemorrhage occurred in up to 10% of patients in one study. Monitor these patients especially closely.

15.196 Patient may experience Grade 1-2 nausea, however vomiting is uncommon. Medicate as ordered and monitor for effectiveness.

15.197 Monitor for skin rash, instruct patient to report to MD.

15.198 Monitor blood pressure. Administer antihypertensives as ordered by MD.

15.199a Monitor for signs and symptoms of deep vein thrombosis (DVT) or pulmonary embolism (PE), or myocardial infarction (MI) including new or worsening angina. These have been reported with therapy. Instruct patient to report any calf pain, chest pain or shortness of breath to MD immediately.

15.199b Asthenia and headache were reported commonly during therapy (in up to 70% and 50% of patients respectively). Administer acetaminophen as needed. Monitor for its effectiveness. Avoid the use of aspirin, or ibuprofen as this may interfere with the coagulation cascade and further add to the risk of bleeding.

15.199c Monitor CBC, including platelets. Instruct patient to report signs and symptoms of infection, unusual bruising or bleeding to the MD.

15.199d Patients receiving warfarin therapy for thrombosis should have their PT or INR monitored weekly until two stable therapeutic levels are attained. For patients on warfarin for venous access prophylaxis, routine monitoring is satisfactory.

15.199e A rare but serious complication of bevacizumab is wound dehiscence. Patients who have had recent surgery or have other open wounds should be monitored carefully.

15.199f Gastrointestinal perforation with or without abdominal abscess is rare but

possible. This may present itself as vague abdominal pain associated with constipation and vomiting. Instruct patient to report abdominal pain to the MD.

15.199g Reversible Posterior Leukoencephalopathy Syndrome (RPLS) is a rare (<1%) but serious condition. Presenting symptoms may include changes in mental status, visual disturbance, seizure, or other CNS changes. Patients with this syndrome generally had HTN as well, therefore BP monitoring is important. Instruct patient to report any mental status changes, visual changes, seizures, or other CNS changes to the MD immediately. These may be a sign of RPLS or more serious condition, such as hemorrhagic event in the CNS.

15.199h Warn female patients of the possibility of ovarian failure and subsequent infertility. Vaginal hemorrhage is also possible. Instruct patients to report any heavy or unusual vaginal bleeding to health care team.

15.199i Warn female patients of the risk of recto-vaginal fistula.

15.199j Agent may cause increased cardiotoxic effects of anthracyclines as well as toxic effects of irinotecan, sorafenib, and sunitinib. Patients who on are on dual therapy with these agents should be monitored closely.

15.2 Capecitabine (Xeloda)

15.21 **Background**: Capecitabine is classified as an antineoplastic agent, Antimetabolite (Pyrimidine Analog). Capecitabine is a prodrug of fluorouracil. It undergoes hydrolysis in the liver and tissues to form fluorouracil which is the active moiety. Fluorouracil is a fluorinated Pyrimidine Antimetabolite that inhibits thymidylate synthetase, blocking the methylation of deoxyuridylic acid to thymidylic acid, interfering with DNA, and to a lesser degree, RNA synthesis. Fluorouracil appears to be phase specific for the G1 and S phases of the cell cycle.

15.22 **Formulation**: Commercially available in 150 mg and 500 mg tablets for oral administration.

15.23 **Preparation, storage, and stability**: Store at room temperature of 25ºC, with excursions between 15ºC and 30ºC permitted.

15.24 **Administration**: Usually administered in 2 divided doses taken 12 hours apart. Doses should be taken with water within 30 minutes after a meal (Because current safety and efficacy data are based upon administration with food, it is recommended that capecitabine be administered with food. In all clinical trials, patients are instructed to take with water within 30 minutes after a meal).

Since capecitabine tablets cannot be split, subjects may take different numbers of pills in the morning and evening in order to achieve the appropriate dose. Use of only 500mg tablets is encouraged to minimize the risk of dosing or compliance errors. If the local institutional standard is to use 150 mg size tablet, this is permissible.

15.25 **Pharmacokinetic information**:
Absorption: Rapid and extensive
Protein Binding: <60%; ~35% to albumin

Metabolism:
Hepatic: Inactive metabolites

Tissue, Active metabolite, Fluorouracil
Distribution: V_d: 46 mL/kg
Half-life elimination: 0.5-1 hour
Time to peak: 1.5 hours; Fluorouracil, 2 hours
Excretion: Urine (96%), Feces (<3%)

15.26 **Potential Drug Interactions**:
Increased Effect/Toxicity: Phenytoin and warfarin levels or effects may be increased. [U.S. Boxed Warning] Capecitabine may increase the anticoagulant effects of warfarin; monitor closely.

Nutrition Interactions: Food reduced the rate and extent of absorption of capecitabine.

15.27 **Known potential adverse events:** Consult the package insert for the most current and complete information. Frequency listed derived from Monotherapy trials.

Common known potential toxicities, >10%:
Cardiovascular: Edema
Central nervous system: Fatigue, fever, pain
Dermatologic: Palmar-plantar erythrodysesthesia (hand-and-foot syndrome), dermatitis.
Gastrointestinal: Diarrhea may be dose limiting, nausea, vomiting, abdominal pain, stomatitis, appetite decreased, anorexia, constipation.
Hematologic: Lymphopenia, anemia, neutropenia, thrombocytopenia.
Hepatic: Bilirubin increased.
Neuromuscular & skeletal: Paresthesia.
Ocular: Eye irritation.
Respiratory: Dyspnea.

Less common known potential toxicities, 5% - 10%:
Cardiovascular: Venous thrombosis, chest pain.
Central Nervous System: Headache, lethargy, dizziness, insomnia, mood alteration, depression.
Dermatologic: Nail disorder, rash, skin discoloration, alopecia, Erythema.
Endocrine& metabolic: Dehydration.
Gastrointestinal: Motility disorder, oral discomfort, dyspepsia, upper GI inflammatory disorders, hemorrhage, ileus, taste perversion.
Neuromuscular & skeletal: Back pain, weakness, neuropathy, myalgia, arthralgia, limb pain
Ocular: Abnormal vision, conjunctivitis.
Respiratory: Cough.
Miscellaneous: Viral infection.

Rare known potential toxicities, <5% (Limited to important or life-threatening):
Angina, ascites, asthma, atrial fibrillation, Bradycardia, bronchitis, bronchopneumonia, bronchospasm, cachexia, cardiac arrest, cardiac failure, cardiomyopathy, cerebral vascular accident, cholestasis, coagulation disorder, colitis, deep vein thrombosis, diaphoresis, duodenitis, dysphagia, dysrhythmia, ECG changes, encephalopathy, epistaxis, fungal infection, gastric ulcer, gastroenteritis, hematemesis, hemoptysis, hepatic failure, hepatic fibrosis, hepatitis, hypokalemia, hypomagnesemia, hyper-/hypotension, hypersensitivity, hypertriglyceridemia, idiopathic thrombocytopenia purpura, ileus, infection, intestinal obstruction, keratoconjunctivitis, lacrimal duct stenosis, leukopenia, loss

of consciousness, lymphedema, MI, multifocal leukoencephalopathy, myocardial ischemia, myocarditis, necrotizing enterocolitis (typhlitis), oral candidiasis, pericardial effusion, thrombocytopenic purpura, pancytopenia, photosensitivity reaction, pneumonia, pruritus, pulmonary embolism, radiation recall syndrome, renal impairment, respiratory distress, sedation, sepsis, skin ulceration, tachycardia, thrombophlebitis, toxic megacolon, tremor, ventricular extrasystoles.

15.28 **Drug procurement:** Commercial supplies. Pharmacies or clinics shall obtain supplies from normal commercial supply chain or wholesaler.

15.29 **Nursing guidelines:**

15.291 Instruct patients to take the tablets within 30 minutes of a meal (breakfast and dinner). Tablets should be swallowed with 6 8 oz. of water.

15.292 Instruct patient to avoid taking a missed dose, to never double up on a dose, and to notify the health care team if a dose has been missed.

15.293 Diarrhea can be severe and dose-limiting. Instruct patient to contact the health care team immediately if they experience >4 BMs/day and/or nocturnal diarrhea above baseline. Monitor carefully for dehydration and need for fluid and electrolyte replacement. Standard antidiarrheal treatment, e.g., loperamide is recommended.

15.294 Nausea and vomiting can be severe and dose-limiting. Instruct patient to report nausea and vomiting to the health care team if they experience >2 episodes of emesis in a 24-hour period. Initiate symptomatic treatment.

15.295 Hand and Foot Syndrome is common and dose-limiting (redness, swelling, pain, numbness, tingling, blistering, and moist desquamation).Instruct patient to notify health care team immediately if symptoms appear. Chemotherapy may have to be discontinued until symptoms subside with future dose reduction initiated. The syndrome may recur with a rechallenge.

- Advise patient to apply cool compress for comfort.
- Advise patient to avoid harsh soaps and to use alcohol-free emollients.
- Administer analgesics as prescribed.
- Administer systemic steroids and pyridoxine as prescribed.

15.296 Treat stomatitis symptomatically -- may try dabbing vitamin E oil on lesions. Do not swallow oil. Advise frequent and careful oral hygiene.

15.297 Assess for warfarin use. Patients taking Coumadin-derivative anticoagulants concomitantly with capecitabine should be monitored regularly for alterations in their coagulation parameters (PT or INR).

15.298 Carefully assess patient’s understanding and need of instruction in adequate birth control measures. Discuss importance of avoiding pregnancy. Periodically re-assess.

15.299a Renal impairment: Check creatinine values weekly and calculate creatinine clearance weekly for signs of renal impairment. Follow dose modifications.

15.299b The use of Sorivudine or its analogue, Brivudine, is contraindicated for this

study due to a possible, even fatal, drug reaction. Assess patient's drug use. Impress on patients the importance of avoiding these drugs while on study.

15.299c Cardiotoxicity (including MI, angina, dysrhythmias, and cardiac arrest) has been seen with capecitabine. Observe patients closely for signs of cardiac dysfunction. Instruct patient to report any chest pain or palpitations to the health care team immediately or seek emergency medical attention.

15.299d Monitor patient closely who are taking concomitant phenytoin therapy. There have been reports of increased levels of phenytoin in patients who are also taking capecitabine. These patients may require more frequent monitoring of their phenytoin levels and dose adjustments as necessary.

15.299e Cimetidine may alter the clearance of capecitabine and cause toxic levels. Cimetidine should be avoided while taking capecitabine.

15.3 Atezolizumab (RO5541267) for IV administration

- Investigator brochure: Available on the ACCRU website.

15.31 **Background:** Atezolizumab is a human immunoglobulin (IgG1) monoclonal antibody that is produced in Chinese hamster ovary (CHO) cells. Atezolizumab targets programmed death-ligand 1 (PD-L1) on immune cells or tumor cells and prevents interaction with either programmed death−1 (PD-1) receptor or B7.1 (CD80), both of which function as inhibitory receptors expressed on T cells. Interference of the PD-L1:PD-1 and PD-L1:B7.1 interactions may enhance the magnitude and quality of the tumor-specific T-cell response through increased T-cell priming, expansion, and/or effector function. Atezolizumab shows anti-tumor activity in various nonclinical models and is being investigated as a potential therapy for cancer patients with locally advanced or metastatic malignancies.

15.32 **Formulation:** Atezolizumab is supplied in a single use 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.

15.33 **Preparation and storage:** Atezolizumab must be refrigerated at 2°C−8°C (36°F−46°F) upon receipt until use. No preservative is used in atezolizumab drug product; therefore, the 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. Atezolizumab is administered only using 0.9% sodium chloride 250mL Atezolizumab IV bags and infusion lines equipped with 0.2 micron in-line filters (filter membrane of polyethersulfone [PES]). Bags may be constructed of polyvinyl chloride (PVC), polyethylene, or polyolefin (PO). The final diluted concentration must be between 2.4 mg/mL and 9.6 mg/mL. For flat or fixed dosing (e.g. 800 mg, 840 mg, or 1200 mg) in 250 mL IV infusion bags, the prepared solution of atezolizumab may be stored at 2°C−8°C (36°F−46°F) for 24 hours or at ambient temperature ≤ 25°C (77°F) for 8 hours. For weight-based dosing using a 250-mL IV bag or smaller, the dose solution may be stored for 24 hours at 2°C−8°C (36°F−46°F) including no more than 4 hours at room temperature prior to administration. 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. Do not shake or freeze infusion bags

containing the dose solution.

15.34 **Administration:** The initial dose of atezolizumab will be delivered over 60 (± 15) minutes. Do not administer as bolus or push. If the first infusion is tolerated without infusion-associated adverse effects, the second infusion may be delivered over 30 (± 10) minutes. If the 30-minute infusion is well tolerated, the third and all subsequent infusions may be delivered over 30 (± 10) minutes. Atezolizumab will be administered with tubing and an in-line filter. The bag would read "Atezolizumab/placebo.

15.35 **Pharmacokinetic information:**

Distibution: V_{dss}: 6.9 L
Half-life elimination: 27 days
Hepatic Impairment: No clinically relevant effect with mild hepatic impairment. The effect of moderate or severe hepatic impairment on the pharmacokinetics of atezolizumab is unknown.
Renal Impairment: No clinically relevant effect with renal impairment.

15.36 **Potential Drug Interactions:** No formal PK drug-drug interaction studies have been conducted with atezolizumab. The drug interaction potential of atezolizumab is unknown.

15.37 **Known potential toxicities:** The most commonly (>10%) reported AEs include fatigue, decreased appetite, cough, nausea, dyspnea, constipation, diarrhea pyrexia, vomiting, arthralgia, back pain, asthenia, anemia, pruritus, rash, headache, and peripheral edema. Consult the package insert and investigator's brochure for the most current and complete information.

15.38 **Drug procurement:** Genentech Inc. will supply the atezolizumab to Biologics, Inc. Each participating ACCRU treating location will order the drug from Biologics, Inc. Fax the Drug Order Request Form (found in the forms packet) to:

[redacted]

Each participating ACCRU treating location will be responsible for monitoring the supply of atezolizumab and will use the Drug Order Request Form to order additional supplies as needed.

Outdated or remaining drug is to be destroyed on-site as per procedures in place at each institution.

Temperature excursions that occur at the site should be reported by the site using the IMP Deviation Form found on the ACCRU web site for this study and emailed to: [redacted]. Please include the Genentech protocol number: ML29034 on your form. Any shipment deviations (those not occurring at the site) should be reported to Biologics, Inc. via email to: [redacted] Biologics, Inc. will complete the IMP Deviation Form and report shipment deviations (those not occurring at the site).

15.39 **Nursing Guidelines**

15.391 Anti PD-L1 side effects vary greatly from those of traditional chemotherapy

and can vary in severity from mild to life threatening. Instruct patients to report any side effects to the study team immediately. Side effects may be immediate or delayed up to months after discontinuation of therapy. Most side effects are reversible with prompt intervention of corticosteroids.

15.392 Diarrhea can be common and can be very severe, leading to colonic perforation. Instruct patients to report ANY increase in the number of stools and/or change in baseline, blood in the stool, abdominal pain to the study team immediately.

15.393 Rash/pruritus/dermatitis is seen. Patients should report any rash to the study team. Treat per section 8.0 and monitor for effectiveness.

15.394 Monitor LFT's closely as elevations in these levels could indicate early onset autoimmune hepatitis. Patients should also be instructed to report any jaundice, or right upper quadrant pain to the study team immediately.

15.395 Pneumonitis can be seen and may be mild (only seen on imaging) to severe. Patients should be instructed to report any SOB, dyspnea, cough, chest pain, etc. to the study team immediately. Patients reporting these symptoms should have a pulse ox checked and consider immediate imaging per the treating MD.

15.396 Endocrinopathies (including hypopituitarism, hypothyroidism, hypophysistis, and adrenal insufficiency) are a concern given the mechanism of action of this agent. Patients may present only with the vague sense of fatigue and "not feeling well". Additional symptoms may be that of nausea, sweating and decreased activity tolerance. Instruct patients to report these signs or symptoms immediately and obtain appropriate labs as ordered by MD.

15.397 Pancreatitis is possible with anti PD-L1 therapy based on mechanism of action. Instruct patients to report abdominal pain, nausea and vomiting to the study team.

15.398 Patients who are started on steroid therapy for any side effects of anti PD-L1 toxicity should be instructed to take the steroids as ordered, and not to discontinue abruptly as symptoms may return and be severe. Patients may be on steroid therapy for weeks. Instruct patients to report any increase or change in side effects with any dosage decrease as patients may need a slower taper.

15.4 Placebo for Atezolizumab

The placebo will be normal saline (NS, 0.9% sodium chloride).

15.41 **Administration:** To protect the blinding, the initial dose of placebo will be delivered over 60 (±15) minutes. Do not administer as bolus or push. If the first infusion is tolerated without infusion-associated adverse effects, the second infusion may be delivered over 30 (±10) minutes. If the 30-minute infusion is well tolerated, the third and all subsequent infusions may be delivered over 30 (±10) minutes. Placebo will be administered with tubing and an in-line filter. The bag would read "Atezolizumab/placebo .

16.0 Statistical Considerations and Methodology

16.1 Study Design

16.11 This is a randomized, double-blind, placebo-controlled, phase II study for patients with refractory mCRC. One hundred and thirty five (135) subjects will be randomized 2:1 to bevacizumab and capecitabine plus atezolizumab or bevacizumab and capecitabine plus placebo.

16.12 Study Populations

Primary and secondary efficacy analyses will include all eligible, randomized patients, with patients allocated to the treatment arm to which they were randomized regardless of the treatment received (modified ITT).

Safety analyses will include all randomized patients who received at least one dose of study treatment, with patients allocated to the treatment arm associated with the regimen actually received.

16.2 Statistical Design and Analysis for Primary Endpoint

16.21 Progression free survival (PFS) is the primary endpoint in this study. PFS is defined as the time from randomization to the first documentation of disease progression by RECIST (v1.1) or death from any cause. Patients without documentation of disease progression or death on study will be censored at the time of last tumor assessment. Patients who are alive and have no tumor measurement post-baseline will be censored for PFS at Day 1 post-randomization.

16.22 Statistical Design

To ensure one hundred twenty (120) eligible (meeting the inclusion and exclusion criteria), 135 total subjects will be randomized in a 2:1 ratio to receive capecitabine/bevacizumab/atezolizumab or capecitabine/bevacizumab/placebo. The median PFS in the capecitabine/bevacizumab/placebo arm is assumed to be approximately 2 months (8.7 weeks) based on results of published studies of patients with refractory colorectal cancer.

The primary comparisons will be superiority of the active treatment for the PFS endpoint, atezolizumab versus placebo testing at 1-sided α=0.1. A PFS hazard ratio of 0.65 (active treatment versus placebo) is detectable with 80% power (1-sided α=0.1). Assumptions include exponential survival, a 52-week accrual period with uniform patient entry, and a 52-week follow-up period.

No interim analyses for futility or efficacy will be conducted. At the time of final analysis, a total of 110 events are required. Assuming 12% of subjects will be ineligible or withdraw from the trial, the target of 120 eligible subjects will require approximately 135 randomized subjects.

16.23 Study Operating Characteristics

The table below shows the operating characteristics assuming the PFS follows exponential survival functions. The percent of times that 1) the study would stop early due to futility and 2) the study would conclude that bevacizumab + capecitabine + ateloziumab is superior to bevacizumab + capecitabine + placebo at the final analysis are tabulated by true medians of PFS and the true hazard ratio. Proportions are based on 10,000 replicates in the simulation study.

True Median PFS (Weeks)		True hazard ratio	% of times that bevacizumab + capecitabine + atezolizumab is superior at the final analysis
Bevacizumab + Capecitabine + Placebo	Bevacizumab + Capecitabine + Atezolizumab		
8.7	13.4	0.65	81.4
8.7	12.3	0.71	67.1
8.7	11.1	0.78	47.3
8.7	9.9	0.88	27.1
8.7	8.7	1	11

16.24 Analysis Plan

Final Analysis Decision Rules

The primary efficacy analysis will be performed at the time when 110 PFS events have occurred. The specific hazard ratio and critical p-values for declaring superiority or futility are specified in the table below. Specifically, at the final analysis, if p-value is less than or equal to 0.10, the bevacizumab + capecitabine + atezolizumab regimen will be deemed effective; otherwise, bevacizumab + capecitabine + atezolizumab regimen will be considered to have not met the criteria for efficacy. Brookmeyer, R. and J. Crowley, *A Confidence Interval for the Median Survival Time.* Biometrics, 1982. **38**(1): p. 29-41.

Analysis time point (% events)	Number of PFS events	Critical p-value for efficacy	HR for efficacy	Critical p-value for futility	HR for futility
100% (Final)	110	0.10	0.772	0.10	0.772

Analysis Plan Final Analyses: PFS will be compared between treatment arms using the un-stratified log-rank test at one-sided level of 0.10 and the p-value will be used for decision making. The HR for PFS will be estimated using a Cox proportional hazards model and the 95% CI for the HR will be provided. Results from a stratified analysis will also be provided. Kaplan-Meier methodology will be used to estimate the median PFS for each treatment arm, and Kaplan-Meier curves will be produced. Brookmeyer-Crowley methodology will be used to construct the 95% CI for the median PFS for each treatment arm [28].

16.3 Sample Size, Accrual Time and Study Duration

Accounting for approximately 12% ineligibility and dropout, the total sample size is 135 patients to be enrolled over 52 weeks (2-3 patients per week) with 52 weeks of follow-up. Patients will be randomized 2:1 to active or placebo.

For purpose of ClinicalTrials.gov reporting, the primary endpoint completion date (PECD) for this study is the time the 110th PFS event occurs. Per design, the maximum study duration is estimated to be 104 months (52-month accrual time + 52-month follow-up) from the first patient randomized.

16.4 Supplementary Analysis Plans

16.41 Secondary Endpoints

- Overall Survival (OS): OS time is defined as the time from randomization to death due to any cause. Patients who are alive will be censored at last follow-up for OS. The distribution of survival time will be estimated using the method of Kaplan-Meier. OS will be compared between treatment arms using the log-rank test. OS medians, survival rates and HR will be estimated along with 95% confidence intervals.
- Objective Response: Objective response by RECIST v1.1 criteria will be estimated using objective response rate (ORR) where ORR is defined as the number of evaluable patients achieving a response (PR or CR per RECIST v1.1) during treatment with study therapy divided by the total number of evaluable patients. Rates of response will be compared across arms using a Chi-Square Test for Proportion. Point estimates will be generated for objective response rates within each arm along with 95% binomial confidence intervals XX. ”CJ Clopper and ES Pearson, “The use of confidence or fiducial limits illustrated in the case of the binomial.” Biometrika 26:404-413, 1934.”
-
- Toxicity Profile: As per NCI CTCAE v4.0, the term toxicity is defined as adverse events that are classified as possibly, probably, or definitely related to study treatment. Toxicities will be evaluated via the ordinal CTCAE standard toxicity grading. The analyses will be conducted according the safety population as defined in Section 16.12.

16.42 Subset Analysis

Approximately 5% of patients’ tumors (4 on atezolizumab and 2 on placebo) are expected to exhibit MSI high and approximately 95% (76 on atezolizumab and 38 on placebo) are expected to be MSI stable. Potential differences in PFS and OS will also be investigated in the subset of patients with known MSI stable tumors (n=114). These analyses will be considered exploratory.

16.5 Monitoring the Study

16.51 Adverse Event Stopping Rule

This trial will be monitored for safety by the Mayo Clinic Cancer Center (MCCC) Data and Safety Monitoring Board (DSMB). According to the MCCC Directive: DSMB, the DSMB will review safety data on this trial every six months. Data on all Grade 3 or greater adverse events regardless of attribution will be provided by treatment arm. Study investigators will comply with DSMB requests and follow their recommendations.

The proportions of patients experiencing treatment-related Grade 4 and 5 adverse events will be monitored on each treatment arm. The rate of these events is expected to be low among patients treated with placebo.

If at any time after at least 20 patients have been randomized to the experimental arm (total of 30 patients randomized), the proportion of patients in that arm experiencing treatment-related Grade 5 events exceeds 10%, or the proportion of patients in the experimental arm experiencing Grade 4 or 5 non-hematological events exceeds 20%, accrual to the study will be suspended and a detailed review of all Grade 4 and Grade 5 events and SAEs will be promptly conducted to better assess causality with respect to treatment, disease, and inter-current illness. The study may then be closed or amended as appropriate.

16.52 Accrual Monitoring Stopping Rule

There is no formal plan to monitor for slow accrual.

16.6 Study Reporting

This study will be monitored by the Mayo Clinic Data Safety Monitoring Board (DSMB). Reports containing patient characteristics, toxicity, and administrative information will be provided to the DSMB every 3 or six months, with the first report due at the first reporting period after study initiation. Reporting time points are: January 31, April 30, July 31, and October 31.

17.0 Pathology Considerations/Tissue Biospecimens

17.1 Tissue Biospecimen Submission

17.11 Summary Table of Tissue Biospecimens for This Protocol

	Mandatory or optional**	**When to submit**	**Reason for submission (background/ methodology section)**	**Where to find specific details for biospecimen submission**
Ten (10) 4-micron, unstained slides and two (2) corresponding H&E slides from primary tumors (if available)	Mandatory	≤30 days from randomization	Correlative studies (Section 17.4)	Section 17.2
Ten (10) 4-micron, unstained slides and two (2) corresponding H&E slides from metastatic tumors (if available)	Mandatory	≤30 days from randomization	Correlative studies (Section 17.4)	Section 17.2
Up to fifteen (15) 4-micron, unstained slides and two (2) corresponding H&E slides from primary tumors (if available)	Mandatory	Within 12 months of the analysis of the primary endpoint when requested by study chair	Correlative studies (Section 17.4)	Section 17.2
Up to fifteen (15) 4-micron, unstained slides and two (2) corresponding H&E slides from metastatic tumors (if available)	Mandatory	Within 12 months of the analysis of the primary endpoint when requested by study chair	Correlative studies (Section 17.4)	Section 17.2

* *If an institution is not able to provide the tissue, it does not cause the patient to be ineligible; however the collection of these tissues is* ***strongly recommended****.*

***Note that sites can collect EITHER primary or metastatic tumor. It is not required to collect both.*

17.2 Tissue Slides Collection and Preparation

17.21 Tissue submitted ≤30 days from randomization

17.211 Submit from both primary and metastatic tumors, 10 unstained, uncharged slides cut at 4 microns and 2 corresponding H&E slides cut at 4 microns on charged slides. Label the slides with patient Id, study number, accession number, order of sections (i.e., 1-12) and date of preparation. If institutional

labeling method for clinical slides does not include all required information, DO NOT use sticky labels to cover the original label. Please add label to the back top of slide.

17.212 The following materials are mandatory for shipment with the slides:

- Surgical Pathology Report
- Specimen Submission: Tissue
- Please fill out the Specimen Submission Tissue form found on the ACCRU website; [redacted]

17.213 Follow the cutting instructions provided below:

- Ensure good preparation practices to avoid contamination.
    - A clean microtome blade should be used for each paraffin block to avoid genetic contamination.
    - Blade and tweezers should be wiped with an RNaseZap wipe.
- Request pathologist review of tissue by H&E to confirm the presence of tumor tissue within the sample.
- Obtain slides and ship to ACCRU within 30 days after randomization.

For each available primary and metastatic paraffin tumor block:

1. Face the block (i.e. cut 1-2 microns of the top section) and discard the cut tissue.
2. Cut 4 microns of the top section.
3. Place top cut section on a slide and H&E stain.
4. Cut up to (10) 4 micron sections and place on unstained slides.
5. Cut 4 microns of the bottom section (i.e. after the 10^{th} or last unstained slide).
6. Place bottom cut section on a slide and H&E stain.
7. Affix label on each side.
8. Store slides at ambient temperature.
9. Insert slides into container for shipment to ACCRU.

NOTE: ACCRU will batch ship slides to Duke Lab on a quarterly basis.

17.22 Tissue submitted within 12 months of the analysis of the primary endpoint (upon request)

17.221 Submit if available from both primary and metastatic tumors, 15 unstained, charged slides cut at 4 microns and 2 corresponding H&E slides cut at 4 microns on charged slides. Label the slides with patient Id, study number, accession number, order of sections (i.e., 1-17) and date of preparation. Please do NOT use sticky labels on slides.

17.222 The following materials are mandatory for shipment with the slides:

- Surgical Pathology Report
- Specimen Submission: Tissue
- Please fill out the Specimen Submission Tissue form found on the

ACCRU website; [redacted] under the Case Report Form tab and send in with the Pathology Report and Tissue.

17.223 Follow the cutting instructions provided below:

- Ensure good preparation practices to avoid contamination.
    - A clean microtome blade should be used for each paraffin block to avoid genetic contamination.
    - Blade and tweezers should be wiped with an RNaseZap wipe.
- Request pathologist review of tissue by H&E to confirm the presence of tumor tissue within the sample.
- Obtain slides and ship to ACCRU within 30 days of receipt of study memo requesting 2nd collection of archived tumor tissue.

For each available primary and/or metastatic paraffin tumor block:

1. Face the block (i.e. cut 1-2 microns of the top section) and discard the cut tissue.
2. Cut 4 microns of the top section.
3. Place top cut section on a slide and H&E stain.
4. Cut up to (15) 4 micron sections and place on unstained slides.
5. Cut 4 microns of the bottom section (i.e. after the 15th or last unstained slide).
6. Place bottom cut section on a slide and H&E stain.
7. Affix label on each side.
8. Store slides at ambient temperature.
9. Insert slides into container for shipment to ACCRU.

NOTE: ACCRU will batch ship slides to Duke Lab on a quarterly basis.

17.3 Ship all slides and accompanying materials to the ACCRU Research Coordinating Center at the following address:

[redacted]

17.4 Study Methodology and Storage Information

17.41 The correlative research goal of this study is to explore any correlation between tissue and blood based biomarkers and clinical outcomes. In the current study, we will collect pre-treatment tumor samples to evaluate specific protein biomarkers associated with sensitivity or resistance to the agents under study by immunohistochemistry (IHC). Once these samples have been selected for analysis and the slides cut, the tissue will be macrodissected, RNA/DNA isolated, and assessment of gene expression, mutational analyses, and/or sequencing approaches that include both standard and Next Gen sequencing platforms may be performed.

Submitted tissue samples will be analyzed as follows:

17.411 Available pre-treatment FFPE tumor tissue slides will be collected and processed for each subject. H&E slides will be reviewed by a cytotechnologist to assess tumor content of the specimen. Appropriately identified tumor sections will then be used to isolate RNA and DNA. RNA and DNA isolation will be performed by the Duke Phase I Biomarker Laboratory.

FFPE tumor tissue slides will also be collected to assess correlation of specific protein biomarkers and responses to treatment in each of the treatment arms by immunohistochemistry (IHC). The specific protein biomarkers will be determined at a later date. IHC stains will be performed in the Duke University Medical Center Department of Pathology. Analyses of the stained slides will be performed in a blinded fashion without knowledge of the patient outcome or treatment of study by a board certified pathologist at Duke University Medical Center.

17.42 At the completion of the study, any unused/remaining material will be stored in the ACCRU Central Operations Office or Duke Phase I Biomarker Lab (Attn: Pathology Coordinator) for future research according to the patient consent permission (see Section 6.0). Potential future research may include immunohistochemistry (IHC) analyses and DNA extraction. When a protocol is developed, it will be presented for IRB review and approval.

17.5 Return of Genetic Testing Research Results

Because the results generated by the genetic testing included in this section are not currently anticipated to have clinical relevance to the patient or their family members, the genetic results will not be disclosed to the patients or their physicians.

If, at any time, genetic results are obtained that may have clinical relevance, IRB review and approval will be sought regarding the most appropriate manner of disclosure and whether or not validation in a CLIA certified setting will be required. Sharing of research data with individual patients should only occur when data have been validated by multiple studies and testing has been done in CLIA-approved laboratories.

18.0 Records and Data Collection Procedures

Access the RAVE system through the iMedidata portal at https://login.imedidata.com. All data must be entered by Remote Date Entry (RDE) and completed by qualified and authorized personnel. All data on the CRF must reflect the corresponding source document. Please refer to the ACCRU website for instructions https://www.accru.org/main/member/standard.xhtml?path=%2FMember%2FTraining

18.1 Submission Timetable

Initial Material(s)

CRF	**Active-Monitoring Phase** (Compliance with Test Schedule Section 4.0)
Institutional Contacts	≤2 weeks after randomization
On-Study	
On-Study: Prior Surgery[2]	
On-Study: Prior Systemic Therapy[2]	
On-Study: Prior Radiation[2]	
Adverse Events: Baseline	
RECIST Measurements: Baseline	
Op and Pathology Reports (See Section 17.0)[1]	
Supporting Documentation: Baseline	
Specimen Submission: Blood - Baseline (see Section 14.0)	
Specimen Submission: Tissue - Baseline (see Section 17.0)	
Patient Status: Baseline	
Concomitant Medications	
Off Treatment	Submit ≤2 weeks after randomization if withdrawal/refusal occurs prior to beginning protocol therapy

1. Upload Op and Path Reports via the Supporting Documentation: Baseline form. This is in addition to the pathology material requirements for tissue submission (Section 17.0).

2. Submit only if applicable.

Test Schedule Material(s)

CRF	**Active-Monitoring Phase** (Compliance with Test Schedule Section 4.0)		
	At each evaluation during treatment	At end of treatment	Observation
Treatment (Intervention)	X		
Treatment (Intervention): Dose Modifications, Omissions and	X[2]		
Adverse Events: Solicited	X	X	

CRF	Active-Monitoring Phase (Compliance with Test Schedule Section 4.0)		
	At each evaluation during treatment	At end of treatment	Observation
Adverse Events: Other	X	X	
RECIST Measurements	X[1]	X[1]	X[1]
Supporting Documentation	X[1]	X[1]	X[1]
Laboratory Tests and Results	X	X	
Specimen Submission: Blood	X (see Section 14.0)		
Specimen Submission: Tissue[3]	X (see Section 17.0)		
Patient Status: Treatment (Intervention)	X	X	
Concomitant Medications	X	X	
Off Treatment		X	
Patient Status: Clinical Follow-Up/Observation			X
Notice of New Primary[2]	X	X	X
Consent Withdrawal (choose appropriate form)[2] • Consent Withdrawal: Specimen Only • Consent Withdrawal: Clinical Follow-Up Only • Consent Withdrawal: All Follow-Up	X	X	X
Lost to Follow-Up[2]	X	X	X
Deviation Form[2]	X	X	X
Non Protocol Treatment[2]			X

1. Upload a copy of documentation of progression in RAVE on the Supporting Documentation Form.
2. Submit only if applicable.
3. 2nd submission will be upon request from the study chair.

Follow-up Material(s)

CRF	Event Monitoring Phase[1]				
	q. 3 months until PD	At PD	After PD q. 6 mos.	Death	At Each Event Occurrence
Patient Status: Survival and Disease Status Follow-Up/Event Monitoring	X[2]	X[2]	X	X	
Non Protocol Treatment [3]					At each occurrence
Adverse Events: Late[3]					At each occurrence
Lost to Follow-Up[3]					At each occurrence
Notice of New Primary[3]					At each occurrence
Consent Withdrawal (choose appropriate form)[3] • Consent Withdrawal: Specimen Only • Consent Withdrawal: Clinical Follow-Up					At each occurrence

CRF	Event Monitoring Phase[1]				
	q. 3 months until PD	At PD	After PD q. 6 mos.	Death	At Each Event Occurrence
Only • Consent Withdrawal: All Follow-Up					
Specimen Submission: Tissue					X[4]

1. If a patient is still alive 5 years after randomization, no further follow-up is required.
2. Upload a copy of documentation of progression in RAVE on the Supporting Documentation Form.
3. Submit only if applicable.
4. 2nd submission will be upon request from the study chair.

19.0 Budget

19.1 Each site should review the test schedule (Section 4.0), taking into account local and regional coverage policies, to determine which items are standard of care and which are research at their site. Refer to the payment synopsis for funding provided per accrual for covering study costs, as well as any additional invoiceables that may be allowed.

19.2 Tests to be research funded: Mandatory blood and tissue sample collection for correlative research.

19.3 Other budget concerns: Bevacizumab and Atezolizumab will be provided by Genentech. Capecitabine and placebo agents will not be supplied, but are commercially available.

20.0 References

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