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TITLE: PHASE 2 STUDY OF PEMBROLIZUMAB AND BAVITUXIMAB FOR PROGRESSIVE RECURRENT/METASTATIC SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK

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The goal of this study is to assess whether treatment with bavituximab shifts the cellular balance to favor an effective T-cell mediated antitumor response resulting to an enhanced response in conjunction with pembrolizumab. Bavituximab is a chimeric (human/mouse) monoclonal antibody that targets phosphatidylserine (PS). PS facilitates the recognition and clearance of dying cells, triggering the release of immunosuppressive cytokines and inhibiting the production of proinflammatory cytokines. Within the tumor microenvironment, PS polarizes macrophages toward an immunosuppressive phenotype. Bavituximab upregulates the adaptive T cell-mediated response through crosslinking FCRγ and dampening of signaling between PS and PS receptors on immunosuppressive myeloid-derived suppressor cells.

Thus, we are doing this phase II single arm study to determine if bavituximab could potentially synergize with PD-1 inhibitor therapy to generate an effective anti-tumor immune response in patients with recurrent/metastatic squamous cell head and neck cancer (HNSCC) who progressed on a PD-1 inhibitor.

Schema:

Pembrolizumab 200mg IV every 21 days for a maximum of 24 months.
Bavituximab 3mg/kg IV weekly

Progression on PD1 inhibitor (if on pembrolizumab, can continue until enrollment)

P P P P P (Q3 week)

B B B B B B B B B B B B B (weekly)

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1. HYPOTHESIS AND OBJECTIVES

1.1 Hypothesis

The addition of bavituximab to pembrolizumab will result in an enhanced anti-tumor response among SCCHN tumors that progressed on immune checkpoint inhibitor therapy.

1.2 Primary Endpoint

The primary outcome of this study will be objective overall response rate (CR+PR via RECIST 1.1).

1.3 Secondary Endpoints

1.1.1 Progression free survival

Progression-free survival will be measured from the time of study enrollment until radiologic, clinical progression or death.

1.1.2 Duration of response

Time (time of first response until progression).

1.1.3 Overall survival

Overall survival will be measured from the time of enrollment until death.

1.1.4 Safety and tolerability

Toxicities observed in the study will be assessed by CTCAE 5.0 criteria.

1.1.5 Laboratory correlates of response

1.1.5.1 PD-L1 expression pre and post treatment

1.1.5.2 Presence of TILs (tumor infiltrating lymphocytes) pre and post treatment

1.1.5.3 Assessment of immune markers in pre-treatment fresh and post-treatment biopsies and blood.

1.1.5.4 Assessment of genomics and tumor mutation burden in select patients.

2. BACKGROUND

2.1 Squamous Cell Head and Neck Cancer

Recurrent/metastatic (R/M) squamous cell head and neck cancer (SCCHN) is a uniformly fatal disease with limited treatment options. Platinum doublet therapy with cetuximab has resulted in a median survival of 10 months and options have been limited for patients with platinum refractory disease.[1] PD-1 inhibitors have activity in a subset of patients, with the response rate of pembrolizumab being about 18%.[2] Similarly, nivolumab has also resulted in a survival benefit compared to standard therapies in the platinum refractory setting.[3] These agents are now FDA approved for patients who have progressed on or after platinum therapy. A majority of patients, though, do not have a response to PD-1 inhibitors and even nivolumab had a modest response rate of 13%. Primary and acquired resistance is a concern and treatment

options are limited in this setting. Strategies are needed to salvage the response in patients who progress on PD-1 inhibitor therapy.

2.2 PD-1 Inhibitor Rationale

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies.[4-9] In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells / FoxP3+ regulatory T-cells seems to correlate with improved prognosis and long-term survival in many solid tumors.

The PD-1 receptor-ligand interaction is a major pathway used to suppress immune control.[10] The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune conditions. PD-1 (encoded by the gene Pdcd1) is an Ig superfamily member related to CD28 and CTLA-4 which negatively regulates antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2).[11] PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable-type (V-type) domain responsible for ligand binding and a cytoplasmic tail which is responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM). Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3ζ, PKCθ and ZAP70 which are involved in the CD3 T-cell signaling cascade. The mechanism by which PD-1 down modulates T-cell responses is similar to, but distinct from that of CTLA-4 as both molecules regulate an overlapping set of signaling proteins PD-1 was shown to be expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B-cells, T regs and Natural Killer cells.[12] [13],[14] Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells. The ligands for PD-1 (PD-L1 and PD-L2) can be induced in a variety of cell types, including non-hematopoietic tissues as well as in various tumors. Binding of either PD-1 ligand to PD-1 inhibits T-cell activation triggered through the T-cell receptor. A variety of head and neck cancers were demonstrated to express elevated levels of this T-cell inhibitor.[15] Inhibition of PD-1 has already been demonstrated to provide significant anti-tumor effect for the treatment of melanoma and NSCLC, in addition to head and neck cancer. Thus, the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion.

Pembrolizumab is a potent and highly selective humanized monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. KeytrudaTM (pembrolizumab) has been approved by the FDA in the United Stated for the treatment of patients with unresectable or metastatic melanoma, metastatic non-small cell lung cancer and recurrent/metastatic squamous cell

carcinoma of the head and neck with disease progression on or after platinum-containing chemotherapy.

2.3 Phosphatidylserine (PS and PS Targeting) Therapy

Bavituximab is a chimeric (human/mouse) monoclonal antibody (mAb) derived from murine mAb 3G4 that targets phosphatidylserine (PS) after binding to β2-glycoprotein 1 (β2-GP1).[16] This highly immunosuppressive membrane phospholipid, PS, acts as an upstream immune checkpoint. In normal non-tumorigenic cells, PS is segregated to the inner leaflet of the plasma membrane but becomes externalized to the outer leaflet of the plasma membrane in cells in the tumor microenvironment (tumor cells, exosomes, and vascular endothelial cells).[17] Phosphatidylserine is recognized and bound by PS receptors on immune cells where it induces and maintains immune suppression. In the absence of a tumor microenvironment and PS-exosome mediated signaling, this process occurs under conditions of normal cell death and immune phagocytic cell clearance[18].

Phosphatidylserine-targeting agents block PS-mediated immunosuppression via reprogramming of the immune cells in the tumor microenvironment to support immune activation.[19] Antibody-mediated PS blockade reduces the levels of myeloid-derived suppressor cells (MDSC), transforming growth factor-beta (TGF-β), and interleukin (IL) -10, and increases the levels of tumor necrosis factor-alpha (TNF-α) and IL-12. Phosphatidylserine blockade also repolarizes tumor-associated macrophages (TAMs) from predominant M2 to predominant M1 phenotype, promotes the maturation of dendritic cells (DCs), and induces potent adaptive antitumor T-cell immunity.[20,21]

Experimental studies have shown that bavituximab binds to PS in the presence of β2-GP1 as a high affinity complex, modulating β2-GP1 binding to PS from 1 μM to 1 nM. In experimental cancer models, bavituximab treatment reduced tumor growth and prolonged survival, where the anti-tumor effects are enhanced by co-administration of chemotherapy or radiation (conditions that increase expression of PS).

2.4 Rationale for the combination of bavituximab and pembrolizumab

Within the tumor microenvironment, phosphatidylserine polarizes macrophages toward an immunosuppressive phenotype. While under normal circumstances it is on the internal surface of the plasma membrane, PS becomes externalized in tumors where it is recognized by macrophages and dendritic cells. Cell damage from anti-cancer therapy such as chemotherapy and radiation further increases external PS exposure. Bavituximab blocks the immunosuppressive signaling of myeloid-derived cells (eg, MDSCs, M2 macrophages) and sends an alternate immune activation signal (FcR-ɣ) leading to an adaptive T-cell mediated anti-tumor response. Thus, treatment with bavituximab shifts the cellular balance to favor an effective T-cell mediated antitumor response. In addition, in vivo studies have shown that inhibition of phosphatidylserine results in differentiation of myeloid derived suppressor cells (MDSC) into M1-like macrophages and dendritic cells.[22] [19]

MDSCs are known to inhibit T cell production and function.[23-25] In squamous cell head and neck tumors, MDSC's have been identified to occur in higher levels in tumor, compared to peripheral blood.26 Horinaka et al. showed increased levels of CD15+ granulocytic MDSC (G-MDSC) and CD14+ monocytic MDSC (M-MDSC) in HNSCC patients. This was inversely related to the percentage of T cells in the peripheral blood.[27]

Thus, bavituximab could potentially synergize with PD-1 inhibitor therapy to generate an effective anti-tumor immune response, by stimulation of a T cell response and abrogation of the inhibitory effects of MDSCs. In preclinical studies of melanoma and breast cancer models, the combination of bavituximab and PD-1 inhibitor therapy resulted in immune stimulation with an increase in CD8+ TILs, in particular compared to PD-1 inhibitor monotherapy.[28] This has been reproduced in breast cancer mouse models, with increased anti-tumor activity noted with the combination compared to monotherapy with either agent. Therefore, there is a rationale for the combination and in particular as a mechanism to stimulate anti-tumor activity in the checkpoint inhibitor resistance setting.

2.5 Agents under Investigation

2.5.1 *Bavituximab*

Bavituximab is a chimeric (human/mouse) monoclonal antibody (mAb) derived from murine mAb 3G4 that targets phosphatidylserine (PS) after binding to β2-glycoprotein 1 (β2-GP1). This highly immunosuppressive membrane phospholipid, PS, acts as an upstream immune checkpoint. In normal non-tumorigenic cells, PS is segregated to the inner leaflet of the plasma membrane but becomes externalized to the outer leaflet of the plasma membrane in cells in the tumor microenvironment (tumor cells, exosomes, and vascular endothelial cells). Phosphatidylserine is recognized and bound by PS receptors on immune cells where it induces and maintains immune suppression. In the absence of a tumor microenvironment and PS-exosome mediated signaling, this process occurs under conditions of normal cell death and immune phagocytic cell clearance.[18]

Bavituximab is a viable immunotherapeutic approach because its primary mechanism of action involves modulating the tumor microenvironment from a primarily immunosuppressive, angiogenesis-promoting state (with infiltrating myeloid-derived suppressor cells [MDSCs] and m2-macrophages) to an immune-activating state (with long term tumor-specific immunity facilitated by m1 macrophages, mature dendritic cells, and activated t lymphocytes). This process occurs via fc-mediated signaling and direct cell killing (antibody-dependent cellular cytotoxicity). In essence, expression of PS on the external surface of the cell acts as an immunosuppressive signal in normal cell death and immune phagocytic clearance. Tumor PS exposure in the microenvironment is immunosuppressive in malignant transformation and progression. Thus bavituximab has been shown to overcome immune suppression and stimulate antitumor immunity in nonclinical models.[19,21]

2.5.2.1 Nonclinical Experience

Data suggest that PS is primarily responsible for expansion of MDSCs and M2-like tumor-associated macrophages (TAMs) in tumors, and that bavituximab could reverse this process and reactivate antitumor immunity. Treatment of tumor-bearing mice with docetaxel in combination with 2aG4 (a PS-targeting antibody and the murine precursor to bavituximab), has been shown to potently suppress the growth and progression of prostate tumors and increase the presence of M1-like TAMs and mature dendritic cells in the tumor microenvironment.[29]

The tumor and tumor vasculature localization of PS-targeting antibodies is followed by tumor immunity enhancing effects, tumor vessel damage, tumor vascularity

reduction, tumor necrosis, and tumor growth retardation in multiple models.[20] The synergistic antitumor activity of antibodies targeting PS in combination with cytotoxic chemotherapy has been demonstrated in animal models, including but not limited to the Pan02 pancreatic adenocarcinoma cell line with gemcitabine and the MDA MB 435 breast cancer cell line with docetaxel.[29,30]

In toxicology studies, no target organs of toxicity were identified in rats (up to 20 mg/kg) and monkeys (up to 10 mg/kg) receiving weekly doses for 8 weeks of bavituximab, and minimal histological findings in heart and lung were noted when administered to monkeys at 100 mg/kg. Detailed information about comprehensive nonclinical safety, immunology, and pharmacokinetics (PK) is provided in the current Investigator's Brochure for bavituximab. (IB)

2.5.2.2 Clinical Experience

Bavituximab has been evaluated by Peregrine in clinical studies in over 800 patients (as of July 2016), most of whom were treated with combination therapy. These clinical trials have included patients with a number of tumor types, including pancreatic, breast, lung, and hepatocellular carcinoma, and in chronic HCV. A dose of 3 mg/kg bavituximab given intravenously (IV) was determined and selected for further clinical study based on Phase 1 single-agent and combination therapy studies.[31]

In a Phase II, multicenter, breast cancer trial (PPHM 0702), bavituximab (3 mg/kg), given weekly until progression, was combined with paclitaxel (100 mg/m2) and carboplatin (area under the concentration-time curve = 2), given on Days 1, 8 and 15 of planned 4 week cycles for up to 6 cycles, to 46 patients with metastatic disease, unrestricted by hormone or HER2 status. Objective response per Response Evaluation Criteria in Solid Tumors (RECIST) occurred in 34 of 46 patients (73.9%) with a median duration of response (DOR) of 3.7 months (95% confidence interval [CI]: 3.1, 5.8) and median PFS of 6.9 months (95% CI: 5.6, 7.7)12. The most common Grade 4 treatment-emergent adverse event (TEAE) was neutropenia (12 patients, 26.1%), and the most common Grade 3 TEAEs were leukopenia (11 patients, 23.9%), neutropenia (9 patients, 19.6%), and anemia (5 patients, 10.9%).[32]

In another Phase II, multicenter, breast cancer trial (PPHM 0704), bavituximab (3 mg/kg), given weekly until progression, was combined with docetaxel (35 mg/m2), given on Days 1, 8, and 15 of planned 4-week cycles for up to 6 cycles, to 46 patients with MBC (with any hormone or HER2 status). Objective response occurred in 28 of 46 patients (60.9%) with median DOR of 6.1 months (95% CI: 5.7, 7.5) and median PFS of 7.4 (95% CI: 6.1, 9.1) months. Of the most common TEAEs reported, only fatigue, headache, back pain, and hypertension were Grade ≥3.[33]

In a single-center, investigator sponsored study, breast cancer patients received bavituximab 3 mg/kg weekly in combination with paclitaxel (80 mg/m2) given on Days 1, 8, and 15 in 4-week cycles to 14 patients with HER2-negative MBC. Treatment resulted in an ORR of 85% (2 patients had complete responses) and a median PFS of 7.3 months (95% CI: 2.8, 10.8)14. Bone pain, fatigue, headache, and neutropenia were the most common AEs. Infusion-related reactions were the most common AE related to bavituximab. (IB)

A Phase II, single institution study of bavituximab and sorafenib in advanced hepatocellular carcinoma (HCC) was also conducted. Patients received 3 mg/kg IV weekly of bavituximab and 400 mg PO BID of sorafenib until radiologic progression. Secondary endpoints included overall survival, disease specific survival, 4-month progression free survival, safety, and response rate. The study accrued 38 patients. Median OS was 6.2 months. Two patients achieved partial response and four moth PFS was 61%. There were no grade 4 or 5 adverse events recorded. Most common all grade events were diarrhea (32%), fatigue (26%), and anorexia (24%)15. These results demonstrated that bavituximab and sorafenib were well tolerated in patients with advanced HCC.[34]

Overall, results from Phase I and Phase II studies have demonstrated a clinically meaningful treatment effect of bavituximab, and results were consistent among the studies. The overall safety profile of bavituximab was acceptable, and the safety data were consistent with those observed in other clinical studies. Combination therapy did not substantially increase the risks of side effects. Thus the potential additional benefits of combination therapy are likely to outweigh the risk of AEs experienced during bavituximab treatment.

2.5.2 Pembrolizumab

Pembrolizumab is a highly selective humanized mAb designed to block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Pembrolizumab is an IgG4/kappa isotype with a stabilizing sequence alteration in the Fc region.

2.5.2.1 Head and Neck Squamous Cell Carcinoma

Keynote-012 (KN012) was a Phase 1b trial of pembrolizumab in subjects with advanced solid tumors, including subjects with human papillomavirus (HPV)-negative and HPV-positive squamous cell carcinomas of the head and neck.36, 37 The primary population for analysis included HNSCC subjects who previously progressed on prior platinum therapy, regardless of prior cetuximab exposure. Two dose levels were studied in two cohorts. ORR in KN012 for the platinum-progressed population was 16.7%. The durability of responses to pembrolizumab ranged from ≥2.4 to ≥18.7 months.

2.5.2.2 Rationale for Dose Selection/Regimen/Modification

An open-label Phase I trial (Protocol 001) evaluated the safety and clinical activity of single agent MK-3475. The dose escalation portion of this trial evaluated three dose levels, 1 mg/kg, 3 mg/kg, and 10 mg/kg, administered every 2 weeks (Q2W) in subjects with advanced solid tumors. All three dose levels were well tolerated and no dose-limiting toxicities were observed. This first in human study of MK-3475 showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels (1 mg/kg, 3 mg/kg and 10 mg/kg Q2W). No MTD has been identified to date. 10.0 mg/kg Q2W, was the highest dose tested in PN001. Recent data from other clinical studies within the MK-3475 program has shown that a lower dose of MK-3475 with a fixed schedule of 200mg Q3weeks may be sufficient for target engagement and clinical activity.[35,36]

PK data analysis of MK-3475 administered Q2W and Q3W showed slow systemic clearance, limited volume of distribution, and a long half-life (refer to IB).

Pharmacodynamic data (IL-2 release assay) suggested that peripheral target engagement is durable (>21 days). This early PK and pharmacodynamic data provides scientific rationale for testing a Q2W and Q3W dosing schedule.

A population pharmacokinetic analysis has been performed using serum concentration time data from 476 patients. Within the resulting population PK model, clearance and volume parameters of MK-3475 were found to be dependent on body weight. The relationship between clearance and body weight, with an allometric exponent of 0.59, is within the range observed for other antibodies and would support both body weight normalized dosing or a fixed dose across all body weights. MK-3475 has been found to have a wide therapeutic range based on the melanoma indication. The differences in exposure for a 200 mg fixed dose regimen relative to a 2 mg/kg Q3W body weight based regimen are anticipated to remain well within the established exposure margins of 0.5 – 5.0 for MK-3475 in the melanoma indication. The exposure margins are based on the notion of similar efficacy and safety in melanoma at 10 mg/kg Q3W vs. the proposed dose regimen of 2 mg/kg Q3W (i.e. 5-fold higher dose and exposure). The population PK evaluation revealed that there was no significant impact of tumor burden on exposure. In addition, exposure was similar between the NSCLC and melanoma indications. Therefore, there are no anticipated changes in exposure between different indication settings.

The choice of the 200 mg Q3W as an appropriate dose for the switch to fixed dosing is based on simulations performed using the population PK model of pembrolizumab showing that the fixed dose of 200 mg every 3 weeks will provide exposures that 1) are optimally consistent with those obtained with the 2 mg/kg dose every 3 weeks, 2) will maintain individual patient exposures in the exposure range established in melanoma as associated with maximal efficacy response and 3) will maintain individual patients exposure in the exposure range established in melanoma that are well tolerated and safe.

A fixed dose regimen will simplify the dosing regimen to be more convenient for physicians and to reduce potential for dosing errors. A fixed dosing scheme will also reduce complexity in the logistical chain at treatment facilities and reduce wastage.

3. PATIENT SELECTION

3.1 Eligibility Criteria

In order to be eligible for participation in this trial, the subject must:

3.1.1 Patients will have recurrent/metastatic head and neck cancer and will have radiographic evidence of progression on prior immune checkpoint inhibitor therapy, including nivolumab, pembrolizumab, durvalumab and atezolizumab. Patients must have progressed on prior platinum therapy either in the recurrent setting or within 6 months of treatment with cisplatin and radiation in the potentially curative setting.

3.1.2 Be willing and able to provide written informed consent/assent for the trial.

3.1.3 Be ≥ 18 years of age on day of signing informed consent.

3.1.4 Have measurable disease based on RECIST 1.1.

3.1.5 Be willing to provide tissue from a newly obtained core or excisional biopsy of a tumor lesion. Newly-obtained is defined as a specimen obtained up to 6 weeks (42 days) prior to initiation of treatment on Day 1. Subjects for whom newly-obtained samples cannot be provided (e.g. inaccessible or subject safety concern) may submit an archived specimen only upon agreement from the PI.

3.1.6 Have a performance status of 0 or 1 on the ECOG Performance Scale.

3.1.7 Demonstrate adequate organ function as defined in Table 1, all screening labs should be performed within 10 days of treatment initiation.

Table 1

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1,500 /mcL
Platelets	≥100,000 / mcL
Hemoglobin	≥9 g/dL or ≥5.6 mmol/L without transfusion or EPO dependency (within 7 days of assessment)
Renal	
Serum creatinine **OR** Measured or calculated[a] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 X upper limit of normal (ULN) **OR** ≥60 mL/min for subject with creatinine levels > 1.5 X institutional ULN
Hepatic	
Serum total bilirubin	≤ 1.5 X ULN **OR**
	Direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 X ULN **OR** ≤ 5 X ULN for subjects with liver metastases
Albumin	≥2.5 mg/dL
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT)	≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
Activated Partial Thromboplastin Time (aPTT)	≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants

[a]Creatinine clearance should be calculated per institutional standard.

3.1.8 ***Female subject of childbearing potential must have a negative urine or serum pregnancy within 72 hours prior to receiving the first dose of study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.***

3.1.9 ***Female subjects of childbearing potential (Section 6.2) must be willing to use an adequate method of contraception as outlined in Section 6.2 – Contraception, for the course of the study through 120 days after the last dose of study medication.***

Note: *Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject.*

3.1.10 ***Male subjects of childbearing potential (Section 6.2) must agree to use an adequate method of contraception as outlined in Section 6.2- Contraception, starting with the*** first dose of study therapy through 120 days after the last dose of study therapy.

Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject.

3.2 Subject Exclusion Criteria

The subject must be excluded from participating in the trial if the subject:

3.2.1 ***Is currently participating and receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigational device within 4 weeks of the first dose of treatment.***

3.2.2 ***Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment.***

3.2.3 ***Has a known history of active TB (Bacillus Tuberculosis).***

3.2.4 ***Hypersensitivity to pembrolizumab or any of its excipients. History of hypersensitivity to other antibodies can be discussed with the PI to determine eligibility.***

3.2.5 ***Has had a prior anti-cancer monoclonal antibody (mAb) within 4 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to agents administered more than 4 weeks earlier.***

3.2.6 ***Has had prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to a previously administered agent.***

Note: Subjects with ≤ Grade 2 neuropathy are an exception to this criterion and may qualify for the study.

Note: If subject received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.

3.2.7 Has experienced an immune-related adverse event requiring discontinuation of a prior checkpoint inhibitor.

3.2.8 Has a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin or squamous cell carcinoma of the skin that has undergone potentially curative therapy or in situ cervical cancer.

3.2.9 Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least four weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to trial treatment. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability.

3.2.10 Has active autoimmune disease that has required systemic treatment in the past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement (such as prednisone 10mg daily or its equivalent) for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.

3.2.11 Has known history of, or any evidence of active, non-infectious pneumonitis.

3.2.12 Has an active infection requiring systemic therapy.

3.2.13 Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.

3.2.14 Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.

3.2.15 Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the pre-screening or screening visit through 120 days after the last dose of trial treatment.

3.2.16 Has a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).

3.2.17 Has known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected).

3.2.18 Has received a live vaccine within 30 days of planned start of study therapy.

Note: Seasonal influenza vaccines for injection are generally inactivated flu vaccines and are allowed; however intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines, and are not allowed.

Patients with a condition requiring systemic treatment with either corticosteroids (>10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of randomization. Inhaled or topical steroids and adrenal replacement steroid doses ≤ 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.

3.3 Inclusion of Women and Minorities

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

4. STUDY VISIT SCHEDULE AND PROCEDURES

4.1 Screening

See study table in Section 9 for screening procedures.

4.2 Treatment period

One cycle is 21 days. Patient will remain on treatment as long as they are obtaining clinical benefit with a PR, CR or SD as per RECIST 1.1 criteria, and are without significant toxicity requiring treatment discontinuation.

4.3 Post-Treatment Tumor Follow-up – Once treatment on protocol has discontinued, no further tumor assessments are necessary. The last obtained CT on protocol will be utilized for response assessments.

4.4 End-of-Treatment Visit – This will be planned if feasible within 2 weeks of discontinuation of therapy.

4.5 Long-Term Survival Follow-Up – patients will be followed for survival for 1 year after discontinuation of treatment. Review of medical records or phone calls would be sufficient.

4.6 Early Discontinuation of Patients

Bavituximab and/or pembrolizumab should be discontinued due to significant toxicities if, in the opinion of the investigator, they are related to these agents, and continued treatment poses a significant risk to the patient. Examples of such toxicities include:

4.6.1 *Grade 4 immune-mediated toxicities*

4.6.2 *Grade 4 hypersensitivity*

4.6.3 *Grade ≥3 toxicity that recurs or persists > 21 days.*

4.6.4 *Intolerable adverse effects, laboratory abnormality or intercurrent illness that is judged by the investigator to be either physically or psychologically detrimental to the patient.*

4.6.5 ***Pregnancy.***

4.6.6 ***Patient non-compliance.***

4.6.7 ***Treatment with other anti-cancer drugs.***

4.6.8 ***Confirmed disease progression on therapy.***

4.6.9 ***Withdrawal of informed consent (subject's decision to withdraw for any reason).***

4.6.10 ***Loss of ability to freely provide consent through imprisonment or involuntary incarceration for treatment of either a psychiatric or physical (e.g., infectious disease) illness.***

4.6.11 ***All subjects who discontinue study treatment should comply with protocol specified follow-up and survival procedures as outline in section 4. The ONLY exception to this requirement is when a*** *subject withdraws consent* ***for all study procedures in writing*** *or loses the ability to consent freely* ***(i.e., is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness); in this case they will be deemed off study and no further follow up will be performed.***

4.7 Study Termination

The study will be terminated once all patients have been removed from treatment and no further follow up for toxicity and survival data is needed. All data should be collected and reviewed for completion prior to study termination.

5. TREATMENT PLAN

This phase II study will enroll patients who are eligible and those who sign consent will undergo screening, including acquisition of fresh tissue for correlative analyses, updated imaging and labs. Eligible patients will be enrolled and treated with bavituximab 3 mg/kg IV weekly and pembrolizumab 200mg IV every 3 weeks. One cycle is defined to be 21 days. Patients will be seen for assessments on day 1 of each cycle. Blood will be collected for PK and PD analyses at baseline and during cycles 1 and 2. Patients will be re-staged every 3 cycles and treatment will continue until progression, or significant toxicity up to 24 months. Fresh baseline tissue will be collected and repeat tumor biopsy will be obtained (if feasible) at a time-point week 4-6 after treatment start for correlative analyses. This on study biopsy should not proceed if tumor is inaccessible or if biopsy is not thought to be in the patient's best interest.

5.1 Bavituximab

Bavituximab is manufactured by Oncologie, in Waltham, MA.

Bavituximab is supplied as 5 mL of a sterile solution in borosilicate type I glass vials and contains 120 mg bavituximab (24 mg/mL), 10 mM acetate at pH 5.0, and Water for Injection, United States Pharmacopeia.

Bavituximab will be administered weekly (±2 days) as an IV infusion. Scheduled treatment should not be given outside the ±2-day window; such doses will be skipped, and dosing will resume at the next scheduled dosing visit. Bavituximab will be administered at 3 mg/kg body weight and diluted with normal saline to a volume no less than 100 mL. The total dose is only

required to be recalculated if there is a ≥10% change in weight from Day 1. Prior to each bavituximab infusion, the patient may be premedicated with an antihistamine to decrease the risk of an infusion reaction. There will otherwise be no modification of dose level or schedule of bavituximab treatment at investigator's discretion.

DO NOT ADMINISTER TREATMENT AS AN IV PUSH OR BOLUS.

A pharmacist or designee at the study site will prepare bavituximab to be administered by study personnel to patients in accordance with the scheme. Infusion preparation and administration are to be performed as follows:

Using aseptic technique, withdraw the calculated dose volume of bavituximab from the vials using a sterile non-siliconized needle and syringe and inject contents of syringe into the normal saline container. Thoroughly mix the infusion container by gentle manual rotation. Avoid shaking or vigorous agitation during preparation and prior to administration.

The IV normal saline container admixed with IP may contain a small amount of intrinsic, translucent to white proteinaceous particles. Administer through a low protein binding 0.2-micrometer in-line filter (placed as proximal to the patient as practical). Affix the infusion line and prime it with infusate before starting the infusion. The first IV infusion must be administered over approximately 90 (±10) minutes. If the first IV infusion is tolerated, subsequent infusions may be administered over 60 minutes. Flush the main infusion line with normal saline after infusion.

NOTE: Bavituximab should only be administered in settings in which emergency resuscitative equipment and personnel trained in the management of anaphylaxis are immediately available to treat systemic hypersensitivity reactions. Systemic hypersensitivity

5.1.1 *Bavituximab Treatment Dose Adjustment and Dose Delay*

The total dose is only required to be recalculated if there is a ≥10% change in weight from Day 1. If a patient experiences an AE due to bavituximab requiring treatment interruption, a treatment delay of up to one cycle is permitted. If the patient experiences an AE that is clearly related to other therapy requiring its delay or discontinuation, bavituximab treatment should continue weekly as scheduled in patients receiving

combination therapy. In the absence of toxicity, no scheduled treatment should be given more than 2 days late; such doses will be skipped, and dosing will resume at the next scheduled dosing visit. If there are bavituximab related adverse events which are limiting to further therapy, at investigator's discretion patients may be treated at a -1 dose level of 1mg/kg.

5.1.2 *Storage of Study Treatments*

Bavituximab is stored at 2°C to 8°C. Sites should monitor temperature conditions and report any temperature excursions. Once diluted, bavituximab should be stored at room temperature and infused within 8 hours. The infusion must be completed within 8 hours of dilution.

Bavituximab must be stored in a secure area and administered only to patients entered into the clinical study in accordance with the conditions specified in the protocol. Bavituximab will be managed by a pharmacist or designee at the site.

The pharmacist or designee must keep an accurate accounting of the number of investigational units received from Oncologie, dispensed to patients, and returned to the Oncologie or representative (or destroyed at the site) during and at the completion of the study. Standard operating procedures (SOPs) must be in place to control the use of the study drug. Bavituximab must be dispensed only by an appropriately qualified person and is to be used in accordance with the protocol in patients who are under the direct supervision of the investigator.

All used vials may be stored under ambient conditions for accountability purposes. All unused study treatments should be saved, accounted for, and processed after consulting with Oncologie.

The treatment to be used in this trial is outlined below in Table 1.

Table 1 Trial Treatment

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period	Use
Pembrolizumab	200 mg	Q3W	IV infusion	Day 1 of each 3 week cycle	Experimental
Bavituximab	3 mg/kg	weekly	IV infusion	Weekly of a 21 day cycle	Experimental

Trial treatment must begin within 2 weeks (14 days) to the date of registration.

Dose Selection/Modification

5.2.1 Pembrolizumab Dose Selection

The rationale for selection of doses to be used in this trial is provided in Section 2.5.2.

Details on preparation and administration of pembrolizumab (MK-3475) are provided in the Pharmacy Manual.

5.2.2 Dose Modification (Escalation/Titration/Other)

Adverse events (both non-serious and serious) associated with pembrolizumab exposure may represent an immunologic etiology. These adverse events may occur shortly after the first dose or several months after the last dose of treatment. Pembrolizumab must be withheld for drug-related toxicities and severe or life-threatening AEs as per 3 below. See Section 5.6 for supportive care guidelines, including use of corticosteroids.

Table 3. Pembrolizumab Dose Modification Guidelines for Drug-Related Adverse Events

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Treatment Discontinuation
Diarrhea/Colitis	2-3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	4	Permanently discontinue	Permanently discontinue
AST, ALT, or Increased Bilirubin	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose
	3-4	Permanently discontinue (see exception below)[a]	Permanently discontinue
Type 1 diabetes mellitus (if new	T1DM or 3-4	Hold pembrolizumab for new onset Type 1 diabetes mellitus or Grade 3-4 hyperglycemia	Resume pembrolizumab when patients are clinically and metabolically stable

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Treatment Discontinuation
onset) or Hyperglycemia		associated with evidence of beta cell failure	
Hypophysitis	2-4	Toxicity resolves to Grade 0-1. Therapy with pembrolizumab can be continued while endocrine replacement therapy is instituted	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
Hyperthyroidism	3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	4	Permanently discontinue	Permanently discontinue
Hypothyroidism		Therapy with pembrolizumab can be continued while thyroid replacement therapy is instituted	Therapy with pembrolizumab can be continued while thyroid replacement therapy is instituted
Infusion Reaction	2[b]	Toxicity resolves to Grade 0-1	Permanently discontinue if toxicity develops despite adequate premedication
	3-4	Permanently discontinue	Permanently discontinue
Pneumonitis	2	Permanently discontinue	Permanently discontinue
	3-4	Permanently discontinue	Permanently discontinue
Renal Failure or Nephritis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	3-4	Permanently discontinue	Permanently discontinue

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Treatment Discontinuation
All Other Drug-Related Toxicity[c]	3 or Severe	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	4	Permanently discontinue	Permanently discontinue

Note: Permanently discontinue for any severe or Grade 3 drug-related AE that recurs or any life-threatening event.

[a] For patients with liver metastasis who begin treatment with Grade 2 AST or ALT, if AST or ALT increases by greater than or equal to 50% relative to baseline and lasts for at least 1 week then patients should be discontinued.

[b] If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose; Refer to **Error! Reference source not found.** – Infusion Treatment Guidelines for further management details.

[c] Patients with intolerable or persistent Grade 2 drug-related AE may hold study medication at physician discretion. Permanently discontinue study drug for persistent Grade 2 adverse reactions for which treatment with study drug has been held, that do not recover to Grade 0-1 within 12 weeks of the last dose.

Dosing interruptions are permitted in the case of medical / surgical events or logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events, patient vacation, and/or holidays). Subjects should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the PI. The reason for interruption should be documented in the patient's study record.

5.2.3 Timing of Dose Administration

Trial treatment should be administered on Day 1 of each cycle after all procedures/assessments have been completed as detailed on the Trial Flow Chart (Section 9.0). Trial treatment may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons.

All trial treatments will be administered on an outpatient basis.

On the days both agents are to be administered,, bavituximab will be infused prior to pembrolizumab. Pembrolizumab 200 mg will be administered as a 30 minute IV infusion every 3 weeks. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min).

The Pharmacy Manual contains specific instructions for the preparation of the pembrolizumab infusion fluid and administration of infusion solution.

5.2.4 Trial Blinding/Masking

This is an open-label trial; therefore, the investigator and subject will know the treatment administered.

5.2 Concomitant Medications/Vaccinations (allowed & prohibited)

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for one of these or other medications or vaccinations specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The investigator should discuss any questions regarding this with the PI. The final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician.

5.3.1 Acceptable Concomitant Medications

All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the case report form (CRF) including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF.

All concomitant medications received within 28 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered after 30 days after the last dose of trial treatment should be recorded for SAEs and ECIs as defined in Section 7.2.

5.3.2 Prohibited Concomitant Medications

Subjects are prohibited from receiving the following therapies during the Screening and Treatment Phase (including retreatment for post-complete response relapse) of this trial:

5.3.2.1 Antineoplastic systemic chemotherapy or biological therapy

5.3.2.2 Immunotherapy not specified in this protocol

5.3.2.3 Chemotherapy not specified in this protocol

5.3.2.4 Investigational agents other than pembrolizumab and bavituximab

5.3.2.5 Radiation therapy

Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed at the investigator's discretion.

Live vaccines within 30 days prior to the first dose of trial treatment, while participating in the trial, and 30 days after the last dose of pembrolizumab. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine.

- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with Merck and/or Oncologie.

Subjects who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the trial. Subjects may receive other medications that the investigator deems to be medically necessary.

The Exclusion Criteria describes other medications which are prohibited in this trial.

There are no prohibited therapies during the Post-Treatment Follow-up Phase.

5.3 Rescue Medications & Supportive Care

5.4.1 *Supportive Care Guidelines and Dose Modifications*

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of adverse events with potential immunologic etiology are outlined below. Where appropriate, these guidelines include the use of oral or intravenous treatment with corticosteroids as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is

decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab.

Note: If after the evaluation the event is determined not to be related, the investigator does not need to follow the treatment guidance (as outlined below). Refer to Section 5.2.1 for dose modification.

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event.

5.4.1.1 Pneumonitis

a. For **Grade 2 events,** treat with systemic corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

b. For **Grade 3-4 events**, immediately treat with intravenous steroids. Administer additional anti-inflammatory measures, as needed.

c. Add prophylactic antibiotics for opportunistic infections in the case of prolonged steroid administration.

5.4.1.2 Diarrhea/Colitis

a. Subjects should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus).

b. All subjects who experience diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion. For Grade 2 or higher diarrhea, consider GI consultation and endoscopy to confirm or rule out colitis.

c. For Grade 2 diarrhea/colitis, administer oral corticosteroids.

d. For Grade 3 or 4 diarrhea/colitis, treat with intravenous steroids followed by high dose oral steroids.

e. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

5.4.1.3 Type 1 diabetes mellitus (if new onset, including diabetic ketoacidosis [DKA]) or ≥ Grade 3 Hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA)

For **T1DM** or **Grade 3-4 Hyperglycemia**

a. Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria.

b. Evaluate patients with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.

5.4.1.4 Hypophysitis

a. For **Grade 2 events**, treat with corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

b. For **Grade 3-4 events**, treat with an initial dose of IV corticosteroids followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

5.4.1.5 Hyperthyroidism or Hypothyroidism

Thyroid disorders can occur at any time during treatment. Monitor patients for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders.

a. **Grade 2 hyperthyroidism events** (and Grade 2-4 hypothyroidism):

- In hyperthyroidism, non-selective beta-blockers (e.g. propranolol) are suggested as initial therapy.
- In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyroinine, is indicated per standard of care.

b. Grade 3-4 hyperthyroidism

Treat with an initial dose of IV corticosteroid followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

5.4.1.6 Hepatic

a. For **Grade 2 events**, monitor liver function tests more frequently until returned to baseline values (consider weekly).

Treat with IV or oral corticosteroids

b. For **Grade 3-4 events**, treat with intravenous corticosteroids for 24 to 48 hours.

c. When symptoms improve to Grade 1 or less, a steroid taper should be started and continued over no less than 4 weeks.

5.4.1.7 Renal Failure or Nephritis

a. For **Grade 2 events**, treat with corticosteroids.

b. For **Grade 3-4 events**, treat with systemic corticosteroids.

c. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

5.4.1.8 Management of Infusion Reactions

Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion.

Error! Reference source not found. below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of pembrolizumab (MK-3475).

Table 2 Infusion Reaction Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs	**Stop Infusion and monitor symptoms.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab (MK-3475) with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine).

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
	Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. **Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.**	Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).
Grades 3 or 4 **Grade 3:** Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g.,	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics	No subsequent dosing

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
renal impairment, pulmonary infiltrates) **Grade 4:** Life-threatening; pressor or ventilatory support indicated	Oxygen Pressors Corticosteroids Epinephrine Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **Subject is permanently discontinued from further trial treatment administration.**	
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.		

6. DIET/ACTIVITY/OTHER CONSIDERATIONS

6.1 Diet

Subjects should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea or vomiting.

6.2 Contraception

Pembrolizumab and bavituximab may have adverse effects on a fetus in utero. Furthermore, it is not known if pembrolizumab or bavtuximab has transient adverse effects on the composition of sperm.

For this trial, male subjects will be considered to be of non-reproductive potential if they have azoospermia (whether due to having had a vasectomy or due to an underlying medical condition).

6.2.1 *Female subjects will be considered of non-reproductive potential if they are either:*

6.2.1.1 postmenopausal (defined as at least 12 months with no menses without an alternative medical cause; in women < 45 years of age a high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. In the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.);

OR

6.2.1.2 have had a hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy or bilateral tubal ligation/occlusion, at least 6 weeks prior to screening;

OR

6.2.1.3 has a congenital or acquired condition that prevents childbearing.

6.2.2 *Female and male subjects of reproductive potential must agree to avoid becoming pregnant or impregnating a partner, respectively, while receiving study drug and for 120 days after the last dose of study drug by complying with one of the following:*

6.2.2.1 practice abstinencefrom heterosexual activity;

OR

6.2.2.2 use (or have their partner use) acceptable contraception during heterosexual activity.

6.2.3 ***Acceptable methods of contraception are***

6.2.3.1 Single method (one of the following is acceptable):

a. intrauterine device (IUD)

b. vasectomy of a female subject's male partner

c. contraceptive rod implanted into the skin

d. For men of reproductive potential who may participate in the study, condoms with spermicide, if properly used, are generally considered a reliable form of contraception.

6.2.3.2 Combination method (requires use of two of the following):

a. diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide)

a. cervical cap with spermicide (nulliparous women only)

b. contraceptive sponge (nulliparous women only)

c. male condom or female condom (cannot be used together)

d. hormonal contraceptive: oral contraceptive pill (estrogen/progestin pill or progestin-only pill), contraceptive skin patch, vaginal contraceptive ring, or subcutaneous contraceptive injection

NOTE: Abstinence (relative to heterosexual activity) can be used as the sole method of contraception if it is consistently employed as the subject's preferred and usual lifestyle and if considered acceptable by local regulatory agencies and ERCs/IRBs. Periodic abstinence (e.g., calendar, ovulation, sympto-thermal, post-ovulation methods, etc.) and withdrawal are not acceptable methods of contraception.

NOTE: If a contraceptive method listed above is restricted by local regulations/guidelines, then it does not qualify as an acceptable method of contraception for subjects participating at sites in this country/region.

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study subjects of childbearing potential must adhere to the contraception requirement (described above) from the day of study medication initiation (or 14 days prior to the initiation of study medication for oral contraception) throughout the study period up to 120 days after the last dose of trial therapy. If there is any question that a subject of childbearing potential will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

6.3 Use in Pregnancy

If a subject inadvertently becomes pregnant while on treatment with pembrolizumab and bavituximab, the subject will immediately be removed from the study. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the Sponsor, Oncologie and to Merck without delay and within 24 hours to the Sponsor and within 2 working days to Oncologie and Merck if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn).

The investigator will notify the patient's physician that the patient was participating in a clinical trial and follow the progress of the pregnancy. The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor. If a male subject impregnates his female partner the study personnel at the site must notify the sponsors.

6.4 Use in Nursing Women

It is unknown whether pembrolizumab or bavituximab are excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, subjects who are breast-feeding are not eligible for enrollment.

7. ADVERSE EVENT REPORTING

7.1 Adverse Events

7.1.1 Adverse Event Reporting –

All AEs from first dose (including premedication) until 30 days after the last administration of study treatment will be recorded on CRFs. Whenever possible, medical diagnoses should be captured instead of symptoms to prevent reporting more than one AE for a single event. A medical procedure is not considered an AE. Deaths are not be recorded as an event and are instead to be recorded as the outcome of an event. The condition that resulted in the death is to be recorded as the event.

Abnormal laboratory values that are clinically significant in the investigator's judgment will be recorded as AEs if there is not a related medical diagnosis. Severity (National Cancer Institute Common Terminology Criteria for Adverse Events [CTCAE] Version 50.3), relationship to study therapy, and any treatments given will be noted on the CRF. All related AEs must be followed until resolution or until the event is deemed stable or irreversible. All SAEs, regardless of relationship, should be followed until an outcome of the SAE can be documented. For patients discontinuing the study prematurely, all unrelated AEs are to be followed for 30 days after the last administration of study therapy, and all related AEs and SAEs are be followed as defined above. Cancer progression or cancer-related death will be considered a study endpoint and not an AE. Hospitalization for elective procedures or for protocol compliance is not considered an SAE. Relationship of an AE to the study drug is to be evaluated using the guidelines above.

7.1.2 Serious Adverse Event Reporting

All SAEs and pregnancies that occur between the first dose of study drug and 30 days after the last dose of study drug, whether or not considered related to the study drug, must be reported. In addition, SAEs occurring at any time that are attributable to study drug must be reported.

7.1.2.1 The SAE report should include

a. date and time of onset
b. description of event
c. severity (CTCAE Version 4.0.3), duration
d. outcome
e. etiology
f. relationship to study drug

g. action taken

h. other relevant details should be documented on these forms as available.

i. SAEs related to other therapy or treatment must be reported as per local requirements.

7.1.2.2 Patients

Patients may be hospitalized for observation following study drug administration. Planned hospitalization (e.g., for observation, protocol compliance, elective procedures, social reasons) will not be considered an SAE; however, any AE that prolongs hospitalization will be considered an SAE.

7.1.2.3 Investigator

a. The investigator must also report SAEs to the IRB in accordance with local requirements.

b. The investigator must maintain documentation of all communications with the IRB.

c. The lead investigator will expedite the reporting of suspected unexpected serious adverse reactions to concerned regulatory authorities, ethics committees, and investigators in accordance with all relevant laws and regulations governing the reporting of adverse drug reactions from clinical trials.

d. Investigators are required to report to Merck and Oncologie Drug Safety any SUSAR (Suspected Unexpected Serious Adverse Reaction) as soon as possible.

7.1.2.4 SUSAR

A SUSAR is any sign, symptom or medical condition that emerges during bavituximab treatment or during a post-treatment follow-up period that (1) was not present at the start of bavituximab treatment and it is not a chronic condition that is part of the patient's medical history, OR (2) was present at the start of bavituximab treatment or as part of the patient's medical history but worsened in severity and/or frequency during therapy, AND that meets any of the following regulatory serious criteria:

a. Results in death

b. Is life-threatening

c. Requires or prolongs inpatient hospitalization

d. Is disabling

e. Is a congenital anomaly/birth defect

f. Is medically significant or requires medical or surgical intervention to prevent one of the outcomes listed above.

All SUSARs are to be recorded on a MedWatch 3500A Form and emailed to:

AND:

AND:

Sites local Institutional Review Boards (IRB); reporting must occur within the timeframe required by the site IRB.

7.1.3 MedWatch 3500A Reporting Guidelines

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

7.1.3.1 **Treatment regimen (dosing frequency, combination therapy)**

7.1.3.2 Protocol description (and number, if assigned)

7.1.3.2 Description of event, severity, treatment, and outcome, if known

7.1.3.3 Supportive laboratory results and diagnostics (as applicable)

7.1.3.4 Investigator's assessment of the relationship of the adverse event to each investigational product and suspect medication

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

7.1.3.5 Adding to the original MedWatch 3500A report and submitting it as follow-up

7.1.3.6 Adding supplemental summary information and submitting it as follow-up with the original MedWatch 3500A form

7.1.3.7 Summarizing new information and faxing it with a cover letter including patient identifiers (i.e. D.O.B. initial, patient number), protocol description and number, if assigned, suspect drug, brief adverse event description, and notation that additional or follow-up information is being submitted (The patient identifiers are important so that the new information is added to the correct initial report)

Occasionally Oncologie may contact the reporter for additional information, clarification, or current status of the patient for whom and adverse event was reported.

7.1.4 Assessing Causality

Investigators are required to assess whether there is a reasonable possibility that bavituximab caused or contributed to an adverse event. The following general guidance may be used.

7.1.4.1 Yes

If the temporal relationship of the clinical event to bavituximab or pembrolizumab administration makes a causal relationship possible, and other drugs, therapeutic interventions or underlying conditions do not provide a sufficient explanation for the observed event.

7.1.4.2 No

If the temporal relationship of the clinical event to bavituximab or pembrolizumab administration makes a causal relationship unlikely, or other drugs, therapeutic interventions or underlying conditions provide a sufficient explanation for the observed event.

7.1.5 Safety Reporting Requirements for IND Holders

In accordance with 21 CFR 212.32, investigator-investigators of studies conducted under an IND must comply with following safety reporting requirements:

7.1.5.1 Expedited IND Safety Reports

a. 7 Calendar-Day Telephone or Fax Report

The Investigators required to notify the FDA of any fatal or life-threatening adverse event that is unexpected and assessed by the investigator to be possibly related to the use of bavituximab. An unexpected adverse event is one that is not already described in the Investigator Brochure. Such reports are to be telephoned or faxed to the FDA and Oncologie within 7 calendar days of first learning of the event. Each telephone call or fax transmission (see fax number below) should be directed to the FDA new drug review division in the Center for Drug Evaluation and Research or in the product review division for the Center for Biologics Evaluation and Research, whichever is responsible for the review of the IND.

b. 15 Calendar-Day Written Report

The Investigators also required to notify the FDA and all participating investigators, in a written IND Safety Report, of any serious, unexpected AE that is considered possibly related to the use

of bavituximab. An unexpected adverse event is one that is not already described in the Investigator Brochure.

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

Written IND safety reports with Analysis of Similar Events are to be submitted to the FDA, Oncologie Drug Safety, and all participating investigators within 15 calendar days of first learning of the event. The FDA prefers these reports on a MedWatch 3500A Form but alternative formats are acceptable (e.g. summary letter).

7.1.5.2 FDA fax number for IND Safety Reports:

a. 1 (800) FDA - 0178

b. All written IND Safety Reports submitted to the FDA by the Investigator must also be emailed to:

Oncologie

	North America
Safety Reporting Email Fax	

AND

AND

Sites local Institutional Review Boards (IRB); reporting must occur within the timeframe required by the site IRB.**For questions related to safety reporting, contact:**

All SAEs, whether related or unrelated to bavituximab, pembrolizumab, and all pregnancies must be reported to the within 24 hours of knowledge of the event for reporting to Peregrine, Merck, and the FDA (as applicable, by the investigator or designee).

7.1.5.3 IND Annual Reports

In accordance with the regulation 21 CFR § 312.32, the Investigatorhall within 60 days of the anniversary date that the IND went into effect submit a brief report of the progress of the investigation. Please refer to Code of Federal Regulations, 21 CFR § 312.32 for a list of the elements required for the annual report. All IND annual reports submitted to the FDA by the Sponsor-Investigator should be copied to Oncologie. Copies of such reports should be mailed to

7.2 Assessing and Recording Adverse Events – Merck

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the Merck's product, is also an adverse event.

Changes resulting from normal growth and development that do not vary significantly in frequency or severity from expected levels are not to be considered adverse events. Examples of this may include, but are not limited to, teething, typical crying in infants and children and onset of menses or menopause occurring at a physiologically appropriate time.

Merck product includes any pharmaceutical product, biological product, device, diagnostic agent or protocol-specified procedure, whether investigational (including placebo or active comparator medication) or marketed, manufactured by, licensed by, provided by or distributed by Merck for human use.

Adverse events may occur during the course of the use of Merck product in clinical trials, or as prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

Progression of the cancer under study is not considered an adverse event.

All adverse events that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the subject to be

excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

From the time of treatment allocation/randomization through 30 days following cessation of treatment, all adverse events must be reported by the investigator. Such events will be recorded at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in section 7.2.3.1. The investigator will make every attempt to follow all subjects with non-serious adverse events for outcome.

Adverse events will not be collected for subjects during the pre-screening period (for determination of archival tissue status) as long as that subject has not undergone any protocol-specified procedure or intervention. If the subject requires a blood draw, fresh tumor biopsy etc., the subject is first required to provide consent to the main study and AEs will be captured according to guidelines for standard AE reporting. [Please delete this section if N/A].

7.2.1 Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor and to Merck

For purposes of this trial, an overdose of pembrolizumab will be defined as any dose of 1,000 mg or greater (≥5 times the indicated dose). No specific information is available on the treatment of overdose of pembrolizumab. Appropriate supportive treatment should be provided if clinically indicated. In the event of overdose, the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

If an adverse event(s) is associated with ("results from") the overdose of a Merck product, the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met.

If a dose of Merck's product meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported as a non-serious Event of Clinical Interest (ECI), using the terminology "accidental or intentional overdose without adverse effect."

All reports of overdose with and without an adverse event must be reported within 24 hours to the Sponsor and within 2 working days hours to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220)

7.2.2 Reporting of Pregnancy and Lactation to the Sponsor and to Merck

Although pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them) that occurs during the trial.

Pregnancies and lactations that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

Pregnancies and lactations that occur from the time of treatment allocation/randomization through 120 days following cessation of Sponsor's product, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, must be reported by the investigator. All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Such events must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220)

7.2.3 Immediate Reporting of Adverse Events to the Sponsor and to Merck

7.2.3.1 Serious Adverse Events

a. A serious adverse event is any adverse event occurring at any dose or during any use of Merck's product that:

b. Results in death;

c. Is life threatening;

d. Results in persistent or significant disability/incapacity;

e. Results in or prolongs an existing inpatient hospitalization;

f. Is a congenital anomaly/birth defect;

g. Is another important medical event;

Note: In addition to the above criteria, adverse events meeting either of the below criteria, although not serious per ICH definition, are reportable to the Merck in the same timeframe as SAEs to meet certain local requirements. Therefore, these events are considered serious by Merck for collection purposes.

h. Is a new cancer (that is not a condition of the study);

i. Is associated with an overdose.

Refer to Table 6 for additional details regarding each of the above criteria.

For the time period beginning when the consent form is signed until treatment allocation/randomization, any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study (reference Section 7.2.3.3 for additional details) [Note: this portion in blue text only applies to trials capturing Disease Progression as primary or secondary endpoint (PFS or ORR) – please delete if N/A]. that occurs to any subject must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study (reference Section 7.2.3.3 for additional details), [Note: this portion in blue text only applies to trials capturing Disease Progression as primary or secondary endpoint (PFS or ORR) – please delete if N/A]. whether or not related to the Merck product, must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety.

Additionally, any serious adverse event, considered by an investigator who is a qualified physician to be related to Merck product that is brought to the attention of the investigator at any time following consent through the end of the specified safety follow-up period specified in the paragraph above, or at any time outside of the time period specified in the previous paragraph also must be reported immediately to the Sponsor and to Merck Global Safety.

All subjects with serious adverse events must be followed up for outcome.

SAE reports and any other relevant safety information are to be forwarded to the Merck Global Safety facsimile number: +1-215-993-1220

A copy of all 15 Day Reports and Annual Progress Reports is submitted as required by FDA, European Union (EU), Pharmaceutical and Medical Devices agency (PMDA) or other local regulators. Investigators will cross reference this submission

according to local regulations to the Merck Investigational Compound Number (IND, CSA, etc.) at the time of submission. Additionally, investigators will submit a copy of these reports to Merck & Co., Inc. (Attn: Worldwide Product Safety; FAX 215 993-1220) at the time of submission to FDA.

7.2.3.2 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220).

For the time period beginning when the consent form is signed until treatment allocation/randomization, any ECI, or follow up to an ECI, that occurs to any subject must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, any ECI, or follow up to an ECI, whether or not related to Merck product, must be reported within 24 hours to the Sponsor and within 24 hours to Merck Global Safety.

Events of clinical interest for this trial include:

a. an overdose of Merck product, as defined in Section 7.2.1 - Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor, that is not associated with clinical symptoms or abnormal laboratory results.

b. 2. an elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

***Note**: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology.

7.2.3.3 Protocol-Specific Exceptions to Serious Adverse Event Reporting

Efficacy endpoints as outlined in this section will not be reported to Merck as described in Section 7.2.3.- Immediate Reporting of Adverse Events to the Sponsor and to Merck, unless there is evidence suggesting a causal relationship between the drug and the event. Any such event will be submitted to the Sponsor within 24 hours and to Merck Global Safety within 2 working days either by electronic or paper media.

Specifically, the suspected/actual events covered in this exception include any event that is disease progression of the cancer under study.

The Sponsor will monitor unblinded aggregated efficacy endpoint events and safety data to ensure the safety of the subjects in the trial. Any suspected endpoint which upon review is not progression of the cancer under study will be forwarded to Merck Global Safety as a SAE within 2 working days of determination that the event is not progression of the cancer under study

Hospitalization related to convenience (e.g.transportation issues etc.) will not be considered a SAE.

7.2.4 Evaluating Adverse Events

An investigator who is a qualified physician will evaluate all adverse events according to the NCI Common Terminology for Adverse Events (CTCAE), version 4.0. Any adverse event which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the adverse event case report forms/worksheets.

All adverse events regardless of CTCAE grade must also be evaluated for seriousness.

Table 6 Evaluating Adverse Events	
An investigator who is a qualified physician, will evaluate all adverse events as to:	
V4.0 CTCAE Grading	
Grade 1	Mild; asymptomatic or mid symptoms; clinical or diagnostic observations only; intervention not indicated

Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation or hospitalization indicated; disabling; limiting self-care ADL.
Grade 4	Life threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE
Seriousness	A serious adverse event is any adverse event occurring at any dose or during any use of Merck or Oncologie product that:
†Results in death; or	
†Is life threatening;	or places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred
Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death; or	
†Results in a persistent or significant disability/incapacity	substantial disruption of one's ability to conduct normal life functions; or
†Results in or prolongs an existing inpatient hospitalization	hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation.
Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not a serious adverse event. **Note**: A pre-existing condition is a clinical condition that is diagnosed prior to the use of a Merck product and is documented in the patient's medical history; or	
†Is a congenital anomaly/birth defect	(in offspring of subject taking the product regardless of time to diagnosis);or

Is a new cancer	(that is not a condition of the study) (although not serious per ICH definition, is reportable to the PI within 24 hours and to Merck and Oncologie within 2 working days to meet certain local requirements); or
Is an overdose (whether accidental or intentional).	Any adverse event associated with an overdose is considered a serious adverse event for collection purposes. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours to the PI and to Merck and Oncologie within 2 working days.
Other important medical events	that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).
Duration Record	the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units
Action Taken	Did the adverse event cause Merck or Oncologie product to be discontinued?

Relationship to Merck/Oncologie Product	Did Merck or Oncologie product cause the adverse event? The determination of the likelihood that the Merck or Oncologie product caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the adverse event based upon the available information.
The following components are to be used to assess the relationship between Merck product and the AE; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely Merck product caused the adverse event (AE):	
Exposure	Is there evidence that the subject was actually exposed to Merck or Oncologie product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
Time Course	Did the AE follow in a reasonable temporal sequence from administration of Merck or Oncologie product?
Time of Onset	Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?

Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors
Relationship	The following components are to be used to assess the relationship between the test drug and the AE: (continued)
	to Merck or Oncologie Product
Dechallenge	Was Merck or Oncologie product discontinued or dose/exposure/frequency reduced?
If yes,	did the AE resolve or improve?
If yes,	this is a positive dechallenge.
If no,	this is a negative dechallenge.
Note: This criterion is not applicable if: **1)** the AE resulted in death or permanent disability; **2)** the AE resolved/improved despite continuation of the Sponsor's product; or **3)** the trial is a single-dose drug trial); or **4)** Sponsor's product(s) is/are only used one time.	
Rechallenge	Was the subject re-exposed to Merck or Oncologie product in this study?
If yes,	did the AE recur or worsen?
If yes,	this is a positive rechallenge.
If no,	this is a negative rechallenge.
Note: This criterion is not applicable if: **1)** the initial AE resulted in death or permanent disability, or **2)** the trial is a single-dose drug trial); or **3)** Sponsor's product(s) is/are used only one time.	

NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY MERCK PRODUCT, OR IF REEXPOSURE TO MERCK PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE SUBJECT, THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL.	
Consistency with Trial Treatment Profile	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding Merck product or drug class pharmacology or toxicology?
Note: The assessment of relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.	
Record one of the following: Use the following scale of criteria as guidance (not all criteria must be present to be indicative of Merck product relationship).	
Yes, there is a reasonable possibility of Merck product relationship.	There is evidence of exposure to Merck or Oncologie product. The temporal sequence of the AE onset relative to the administration of Merck product is reasonable. The AE is more likely explained by Merck product than by another cause.

No, there is not a reasonable possibility of Merck product relationship.	Subject did not receive the Merck or Oncologie product OR temporal sequence of the AE onset relative to administration of Merck or Oncologie product is not reasonable OR the AE is more likely explained by another cause than the Merck or Oncologie product. (Also, entered for a subject with overdose without an associated AE.)

8. LABORATORY EVALUATIONS

8.1 Efficacy Measures

Patients will be re-staged every 3 cycles and treatment will continue until progression, or significant toxicity up to 24 months. Staging assessments will include cross-section imaging with either MRI head and neck or CT head and neck with contrast, and CT chest/abdomen with contrast.

8.2 The Following Laboratory Parameters Will Be Assessed:

Hematology: complete blood count (red blood cell count, white blood cell count, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration) with differentials, and platelets,

Chemistry: AST, ALT, gamma-glutamyl transpeptidase, alkaline phosphatase, lactate dehydrogenase, creatinine, blood urea nitrogen, serum bilirubin (serum total and direct bilirubin at screening, direct bilirubin subsequently only if serum total bilirubin is elevated), total protein, albumin, glucose, uric acid, magnesium, phosphate, amylase, lipase, electrolytes (sodium, potassium, chloride, calcium, and bicarbonate), thyroid function tests (thyroid stimulating hormone [TSH] reflex to free triiodothyronine and free thyronine if abnormal TSH result).

Urinalysis: specific gravity, pH, dipstick for blood, glucose, protein, and microscopy for cells and casts.

Pregnancy testing for women of childbearing potential - See section 3.1.8

Other safety evaluations will be made based on regular vital signs assessments (heart rate, systolic and diastolic blood pressure, oxygenation at rest and walking, weight) and physical examinations.

8.3 Correlative Studies - Please see lab manual for full details regarding collection and processing.

Exploratory correlatives are planned in order to determine biomarkers that may be related to response to therapy. Blood will be collected at baseline, during each cycle and at the end of the study. The blood samples from the baseline, cycles 2, 4, and the end of the study will be used for DNA extraction and biomarker discovery analyses (mutation- and methylation-specific). The blood samples at cycles 1 and 3 will be preserved in case of any issues or with blood samples at cycles 2 and 4. Fresh biopsy tissue will be obtained at the baseline and if feasible at the end of the study. Fresh biopsy tissue will be used for DNA and RNA extraction. The following correlative studies will be performed:

8.3.1 H&E staining will be performed on each tumor samples to define the tumor histology. This will be performed at the University of Maryland Pathology Department under the direction of Dr. John Papadimitriou.

8.3.2 Immunohistochemical analysis of PD-L1 protein expression will be performed on primary tumor samples at the baseline and the end of the study.

8.3.3 HPV status will be obtained as per clinical standard. If this data is available in the medical record repeat testing is not necessary.

8.3.4 The somatic genomic analysis will be performed using AmpliSeq platform on primary tumor tissues collected at the baseline and the end of the study, as well as on the blood samples collected at the baseline, cycles 2, 4, and the end of the study. DNA from plasma will be used for such AmpliSeq analysis. DNA from lymphocytes collected at the baseline will be used as a somatic control for mutation detection. Tumor and blood samples will be compared at the baseline and the end of the study to define the blood-based detection specificity and sensitivity. Overall, 7 samples per patient will be used for AmpliSeq analysis.

8.3.5 DNA methylation analysis of primary samples will be performed on tumor samples at the baseline and the end of the study using DNA methylation array 850K (Illumina) to define DNA methylation-based biomarkers. All DNA samples will be bisulfite-converted before the analysis. For this reason, the extracted DNA from n=15 normal mucosa of non-cancer patients matched by the age, gender and smoking status (available from Otolaryngology tissue bank) will be used as non-cancer controls. The panel of 10 hypermethylated DNA sites (including 4 well-characterized and 6 patient-unique signals) for each patient will be developed for each patient.

8.3.6 Ten hypermethylated DNA sites (developed for each patient) will be used for the design of droplet digital PCR (ddPCR) primers and probes assays. Plasma DNA at the baseline, cycles 2, 4, and the end of the study will be used as a template for ddPCR. All DNA samples will be bisulfite-converted before the analysis. The sensitivity and specificity of the developed ddPCR assay, as well as their ability to trace the treatment response, will be evaluated on this step.

8.3.7 Gene expression analysis landscape of tumors tissues before and after treatment will be evaluated on the primary samples at the baseline and the end of the study using low-throughput RNA-Seq analysis. For this reason, the extracted RNA from n=15 normal mucosa of non-cancer patients matched by the age, gender and smoking status (available from Otolaryngology tissue bank) will be used as non-cancer controls. Pathway analysis will be performed for each patient using the panel of differentially expressed genes relative to controls. This will allow defining the treatment response on the gene expression level. The gene expression will also be correlated with DNA methylation landscape to evaluate which of the cancer-related changes are triggered by epigenetic changes common for cancers.

8.3.8 The analysis of immune cell infiltration and cell repertoire will be performed for each sample using gene expression analysis of immune markers, as well as other immune-related and cell type-specific genes.

8.3.9 Immunohistochemical staining of immune markers (especially one detected on the RNA level) will be performed.

9. STUDY CALENDAR

Baseline laboratory and exam evaluations are to be conducted within 10 days prior to start of protocol therapy. Scans and x-rays must be done $\leq$4 weeks prior to the start of therapy. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.

With the exception of screening evaluations, all time points on study have leeway of plus or minus 3 days.

	Pre-Study	3 week cycles (repeat)					
		Cycle 1	Cycle 2	Cycle 3	Cycle 4	EOS	Follow up
Pembrolizumab [1]		X	X	X	X		
Bavituximab[7]		X	X	X	X		
Informed Consent	X						
History & Physical[2]	X	X	X	X	X		
Concurrent Meds	X	X	X	X	X		
CBC and Chemistry[3]	X	X		X			
Research Bloods [4]	X	X	X	X	X	X	
β-HCG[8]	X						
AE assessment	X	X	X	X	X		X
CT or MRI for Tumor Assessment [5]	X[5]*				X[5]		
Tumor Biopsy[6]	X				X		
Review of medical records, telephone contact for recurrence-free and overall survival							**Every 3 months up to 1 year**

1. 200 mg IV day 1 of each cycle up to 24 months while on study
2. History to be collected only at baseline; physical, includes interval history, prior treatment and radiation exposure, vital signs, (heart rate, systolic and diastolic blood pressure, oxygenation at rest and walking, height, weight, and performance status. Height is only required at baseline.
3. Complete blood count and differential, and comprehensive metabolic panel, NOTE -TSH, Free T4 once every 4 weeks.
4. Amount is detailed in laboratory manual.
5. Tumor assessment includes radiologic assessment for RECISTv1.1 evaluation. Repeat radiologic assessment at week 9 and every 9 weeks thereafter while patient continues to receive study therapy.
6. Tumor biopsy to be obtained after cycle 4 if feasible. Archival tissue will be collected at baseline if pre-study biopsy is not feasible at the discretion of the PI.

[7] Bavituximab is dosed weekly

[8] See section 3.1.8

10. MEASUREMENT OF EFFECT

Antitumor Effect – Solid Tumors

On this study, planned radiologic evaluations will be performed at baseline (within 4 weeks prior to starting study therapy) and then every 3 cycles. Confirmatory scans should be obtained not less than 4 weeks following initial documentation of objective response, and will typically be obtained at the time of the next planned evaluation.

Response and progression will be evaluated in this study using the new international criteria proposed by the Immune-related Response Evaluation Criteria in Solid Tumors (irRECIST) guideline[Clin Cancer Res. 2009 Dec 1;15(23):7412-20] , Changes in the longest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECISTv1.1 criteria.

Accumulating evidence indicates that the emergence of objective responses to agents that activate anti-tumor immune responses may follow delayed kinetics of weeks or months, and can be preceded by initial apparent radiological progression, or the appearance of new lesions or some enlarging lesions while certain target lesions are regressing ("mixed response"). It is thus reasonable, in the absence of clinical deterioration, to continue to treat these subjects until radiologic progression is both confirmed and found to have worsened at a subsequent imaging evaluation. Evidence of PD will be based on a comparison with baseline (or nadir) scans, in which there is either an increase of 20% or more in the sum of the longest diameters (SLD) of target lesions taking as reference the smallest sum of the longest diameters (nadir) recorded since starting pembrolizumab/bavituximab treatment, and/or unequivocal progression of non-target lesions, with or without the development of 1 or more new lesions. PD should be confirmed by repeat scans at the next scheduled imaging evaluation 8 weeks later (but no sooner than 4 weeks).

Subjects with PD should be managed in the study as per Section 4.

10.1 Definitions

10.1.1 Evaluable for toxicity

All patients will be evaluable for toxicity from the time of their first treatment on protocol.

10.1.2 Evaluable for objective response

For each, only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of the first cycle of either therapy will also be considered evaluable.)

10.1.3 Evaluable Non-Target Disease Response

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

10.2 Disease Parameters

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

10.2.1 Measurable disease

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

Note: Tumor lesions that are situated in a previously irradiated area are not considered measurable unless there has been demonstrated progression in the lesion.

10.2.2 Malignant lymph nodes

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

10.2.3 Non-measurable disease

All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitic involvement of the skin or lung, inflammatory breast disease, and abdominal masses/abdominal organomegaly (not followed by CT or MRI), are considered as non-measurable.

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

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

10.2.4 Target lesions

All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

10.2.5 Non-target lesions

All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

10.3 Methods for Evaluation of Measurable Disease

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

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

10.3.1 Clinical lesions

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

10.3.2 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 is preferable.

10.3.3 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. MRI is also acceptable in certain situations (e.g. for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECISTv1.1 guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

10.3.4 PET-CT

At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST v1.1 measurements. However, 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 v1.1 measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT

introduces additional data which may bias an investigator if it is not routinely or serially performed.

10.3.5 Ultrasound

Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

10.3.6 Endoscopy, Laparoscopy

The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

10.3.7 Tumor markers

Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published [JNCI 96:487-488, 2004; J Clin Oncol 17, 3461-3467, 1999; J Clin Oncol 26:1148-1159, 2008]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer [JNCI 92:1534-1535, 2000].

10.3.8 Cytology, Histology

These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

10.3.9 FDG-PET

While FDG-PET response assessments related to NSCLC management and to immunotherapy need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of tumor progression (particularly possible 'new' disease) or regression (evaluation of potential CR). Lesions can be assessed on FDG-PET imaging according to the following algorithm:

Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.

No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

10.4 Response Criteria

10.4.1 Evaluation of Target Lesions

10.4.1.1 Complete Response (CR)

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

10.4.1.2 Partial Response (PR)

At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

10.4.1.3 Progressive Disease (PD):

At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

10.4.1.4 Stable Disease (SD)

Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

10.4.2 Special notes on the assessment of target lesions

10.4.2.1 Lymph nodes

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

10.4.2.2 Target lesions that become 'too small to measure'

All lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (eg, 2mm). If the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5mm. When such a lesion becomes difficult to assign an exact measurement, it is recommended to: If it is in the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned (note: in case of a lymph node believed to be present and faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness).

10.4.2.3 Lesions that split or coalesce on treatment

When non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have

coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

10.4.3 Evaluation of Non-Target Lesions

10.4.3.1 Complete Response (CR):

Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

10.4.3.2 Non-CR/Non-PD:

Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

10.4.3.3 Progressive Disease (PD):

Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator). When the patient also has measurable disease: To achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. When the patients has only non-measurable disease: To achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening such that the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease

is comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e., an increase in tumor burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from 'trace' to 'large', an increase in lymphangitic disease from localized to widespread, or may be described in protocols as 'sufficient to require a change in therapy'. If 'unequivocal progression' is seen, the patient should be considered to have had overall PD at that point.

10.4.4 Evaluation of Best Overall Response

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

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

Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.

** Only for non-randomized trials with response as primary endpoint.

*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration."* Every effort should be made to document the objective progression even after discontinuation of treatment.

10.5 Duration of Response

10.5.1 **Duration of overall response:**

The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

10.5.2 **Duration of stable disease:**

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

10.6 Progression-Free Survival

PFS is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first.

11. STATISTICAL CONSIDERATIONS

The primary outcome of this study is overall response rate (CR+PR via RECIST 1.1). We will use a Simon's optimal 2-stage design with 80% power and 5% one-sided type-I error to compare the null hypothesis of ORR=5% vs. the alternative of ORR=20%. The first stage will enroll 10 patients, and if 1 or more responses are observed an additional 19 patients will be enrolled. If at least 4 responses are observed out of the 29 patients, the null hypothesis will be rejected

Safety Monitoring: We will monitor adverse events (AEs) throughout the study. If it appears that the risk of a serious AE is excessive, we will evaluate the treatment regimen and either modify the treatment plan or consider stopping the study. The risk of a serious AE (or DLT as defined above) is excessive if the risk is greater than 25%. Our stopping criterion corresponds to our determining that there is 75% or greater probability that the risk of a DLT exceeds 25%. Experience with single-agent anti-PD1 therapy suggests that the risk of a serious AE is between 15% and 20% but may be higher with the combination. We characterize this estimate with uncertainty using a beta distribution with parameters 2 and 8. This distribution has mean 0.2 and 90% probability that the risk is between 4% and 43%. The following table shows the stopping boundaries for safety monitoring.

Number of patients experiencing a DLT	4	5	6	7	8	9	10	11
Number of patients treated	4 - 6	7 - 9	10 - 13	14 - 17	18 - 20	21 - 24	25 - 27	28 - 29

Estimates of the operating characteristics for this stopping rule, as estimated from 5,000 simulations for each scenario, are as follows.

Risk of DLT	0.10	0.15	0.20	0.25	0.30	0.35	0.40	0.45	0.50
Chance of declaring the combination too toxic	1.2	4.8	14.2	31.2	51.7	71.5	86.9	94.9	98.3
Average sample size	28.8	28.1	26.6	24.0	20.8	17.2	13.7	11.1	9.1

11.1 Data Analysis

We will summarize the response experience of the patients with percentages and confidence intervals. (We will not adjust for the interim analysis when computing the confidence intervals.) We will define overall survival as the time from the start of treatment until death from any cause. Patients who leave the study and whose survival status we cannot determine will be censored at the last date they were known to be alive. Progression-free survival will be the time from the start of treatment until disease progression or death from any cause. Patients who start non-protocol therapy in the

absence of disease progression will be considered to have progressed on the date the new therapy begins. If the patient is lost to follow up, the patient's time to progression will be censored at the last date they were known to be alive and disease free. Duration of response will be defined as the time from the first known response until disease progression, with death not related to disease censoring this endpoint. All failure-time endpoints will be analyzed with appropriate statistical methods for censored data. We will estimate the distributions of times until the events by the method of Kaplan and Meier. We will fit the proportional hazards model to learn about associations of patient or tumor characteristics with failure-time endpoints. Data displays will include summary statistics and confidence intervals.

Correlative analyses (e.g., laboratory correlates of response, such as PD-L1 expression, presence of TILs, and changes in immune markers) will be exploratory

Safety Analysis

All patients who receive any study treatment will be included in final summaries of safety data. Summaries of AEs and other safety parameters will be provided as appropriate. Summary tables for extent of exposure to study treatment will also be provided.

11.2 Interim Analysis

The first stage will enroll 10 patients, and if 1 or more responses are observed an additional 19 patients will be enrolled. After the first 6 patients are accrued, the regimen will be evaluated for toxicity. If 2 or more patients experience a DLT, the study will be halted for excess toxicity.

12. ADMINISTRATIVE ITEMS

This protocol is to be conducted in accordance with the International Conference on Harmonisation (ICH) Guideline on Good Clinical Practice (GCP) and any other applicable regulatory requirements, such as national legislation, European Union (EU) Directives, and Title 21 of the US Code of Federal Regulations (CFR), as well as with the Investigator's (or designee's) SOPs.

This clinical trial will be registered on the "clinicaltrials.gov" clinical trial registry website and any additional national clinical trial registries, as applicable.

Safety reporting will be conducted by and through the holder of the IND to Oncologie.

Before the start of this study and the shipment of investigational agent to the main site, the following documents must be on file at Oncologie, Inc.

a. U.S. Food and Drug Administration (FDA) Form 1572, signed by the Principal Investigator

b. The names of any sub-investigators must appear on this form. Investigators must also complete all regulatory documentation as required by local regulations

c. Current curricula vitae and license of the Principal Investigator

d. Final Protocol

e. A signed and dated investigator brochure acceptance form

f. Written documentation of IRB approval of protocol (identified by title and date of approval) for each site

g. Written documentation from the FDA assigning an IND number to the trial and the approval to begin the study

h. A signed Confidentiality Agreement

i. A signed Clinical Trial Agreement for each site

j. A letter of cross-reference to the Oncologie Pharmaceuticals IND

The following data and materials are required by Oncologie before a study can be considered complete or terminated:

a. Copies of protocol amendments and IRB approval/notification, if appropriate

b. Copies of the IRB final report, documentation of submission to the IRB and to the FDA.

c. A summary of the study prepared by the Principal Investigator (Study report, manuscript and/or abstract)

d. All regulatory documents (e.g., updated curriculum vitae for each Principal Investigator, updated U.S. FDA Form 1572 for each site)

12.1 Ethics

The trial will be conducted in accordance with the Declaration of Helsinki for biomedical research involving human subjects and with local regulatory requirements.

12.2 Ethical Principles

The study is based on adequately performed laboratory and animal experimentation. The study will be conducted under a protocol reviewed by an IRB. The study is to be conducted by scientifically and medically qualified persons. The benefits of the study are in proportion to the risks. The rights and welfare of the patients will be respected. The physicians conducting the study will ensure that the hazards do not outweigh the potential benefits. The results to be reported will be accurate. Patients will give their informed consent and will be competent to do so and not under duress. The study will comply with the ethical principles in Title 21 of the US CFR and other country-specific requirements.

12.3 Compliance with Informed Consent Regulations

This study will be conducted in full compliance with informed consent regulations in US 21 CFR Part 50 or with other applicable regulations. The ICF must be reviewed and approved by the Investigator prior to initiation of the study. The ICF must contain a full explanation of the possible advantages, risks, alternate treatment options, and availability of treatment in the case of injury, in accordance with the applicable regulations. The ICF should also indicate that, by signature, the patient (or legal guardian where appropriate) permits access to relevant medical records by the Investigator and by representatives of the agency.

The investigator is responsible for obtaining written consent from potential patients prior to performing any screening tests or assessments required by the protocol. A copy of the signed ICF will be given to the patient and the original retained by the investigator with other study documentation maintained at the site.

No investigator may involve a human being as a subject in research unless the investigator has obtained the legally effective informed consent of the patient or the patient's legally authorized representative. An investigator may seek such consent only under circumstances that provide the prospective patient or the representative sufficient opportunity to consider whether to participate and that minimize the possibility of coercion or undue influence. The information given to the patient or the representative must be in a language understandable to the patient or the representative. No informed consent, whether oral or written, may include any exculpatory language through which the patient or the representative is made to waive or appear to waive any of the patient's legal rights, or releases or appears to release the investigator, the institution, the Investigator, or its agents from liability for negligence.

Each patient must sign the ICF before any screening assessments specific to this study can be initiated. The signed ICF must remain in the patient's file and must be available for verification by a representative of the Investigator.

12.4 Compliance with IRB Regulations

This study will be conducted in full compliance with the IRB regulations in 21 CFR Part 56 and other applicable regulations. This protocol will not be initiated unless it and the ICF have been reviewed and approved by, and remains open to continuing review by, an appropriate IRB. The IRB shall review and have the authority to approve, require modification in (to secure approval), or disapprove the protocol. The IRB shall notify the investigator and the institution in writing of its decision, and the Letter of Approval from the IEC/IRB must contain specific identification of the documents approved. The IRB shall require that the information given to patients as part of the informed consent is in accordance with 21 CFR Part 50.25 and/or other applicable regulations. Copies of all reports to and correspondence between the investigator and

the IRB must be provided to the Investigator. At the completion or early termination of the trial, a final report should be made to the IRB by the investigator within the legal timelines.

The investigator is obligated to maintain an IRB correspondence file and to make this file available for review by the Investigator's representatives as part of the trial monitoring process.

12.5 Patient Confidentiality and Privacy

The investigator must ensure that patient confidentiality is maintained. Patients should not be identified by name on any documents submitted to the Investigator or during verbal communications. Patients will be identified only by an appropriate identifier and a patient number assigned as specified in the protocol.

Permission for direct access to patient data will be sought in writing for the patient by the investigator as part of the informed consent procedure. The patient will be informed that all clinical information is confidential, but that the Investigator or designee, the IRB, and regulatory authorities may need to inspect the portion of these records that is related to the study. The Investigator may review the records for monitoring and audit purposes.

Written authorization (US sites) and other documentation in accordance with the relevant country and local privacy requirements (where applicable) is to be obtained from each patient prior to enrollment into the study, and/or from the patient's legally authorized representative in accordance with the applicable privacy requirements (e.g., the Health Insurance Portability and Accountability Act Standards for Privacy of Individually Identifiable Health Information ("HIPAA").

In accordance with HIPAA requirements, additional purposes of this study include the following:

a. to publish anonymous patient data from the study; and
b. to create and maintain a data repository

12.6 Trial Conduct

This trial will be conducted in compliance with the protocol approved by the IRB and by the Competent Authorities (CA), as applicable, and according to GCP standards. No modification to the protocol will be implemented without the prior review and approval of the IRB and/or CA except where it may be necessary to eliminate an immediate hazard to a research subject. In such case, the modification will be reported to the IRB and/or CA as soon as possible.

All study drug of bavituximab required for completion of this study will be provided by Oncologie. and (other compound company if needed) (unless otherwise noted). The recipient

will acknowledge receipt of the study drug by returning the drug receipt form indicating shipment content and condition. Damaged supplies will be replaced.

Study drug accountability records should be maintained by the site in accordance with the FDA regulations.

The original drug supply request will be submitted to Peregrine along with the form "Approval for Drug Re-Supply", indicating which personnel will be able to submit drug re-supply requests.

Drug re-supply requests for Bavituximab will be directly submitted to Oncologie from the site.

Drug re-supply requests for (other compound) will be directly submitted to (other pharmaceutical company) from the site.

At the time of study closure, unused, used and expired study drug will be destroyed at the site per Institutional SOPs. For bavituximab, if site SOPs are not available, drug may be returned using the Agent Return Form.

12.7 Changes to the Protocol

The investigator must not implement any modifications or changes to the protocol without approval by the Investigator and prior review and documented approval/favorable opinion from the IRB of a protocol amendment, except where necessary to eliminate immediate hazards to study patients, or when the changes involve only logistical or administrative aspects of the study (e.g., change in monitors, change of telephone numbers).

Agreement from the investigator must be obtained for all protocol amendments and amendments to the ICF. The IRB must be informed of all substantial amendments and give approval. The investigator must send a copy of the approval letter from the IRB to the Investigator.

If applicable, approval of the CA must also be obtained prior to implementing a protocol amendment. Other local approvals may also be required.

12.8 Study Documentation

Documents that must be provided to the Investigator prior to study initiation are as follows:

Medical license, signed and dated current curriculum vitae, and financial disclosure forms for investigators; Food and Drug Administration Form 1572; and any other forms required by local authorities.

Signed and dated Investigator Agreement.

Assurance that an IRB that complies with applicable regulatory requirements has reviewed and approved the protocol. The required documentation will consist of the name and address of the IRB and a current list of IRB members.

A copy of the formal written notification to the investigator regarding approval of the protocol and ICF by the IRB. The written notification is to be signed by the chairman or authorized designee and must identify the specific protocol. In cases where an IRB member has a known conflict of interest, abstention of that individual from voting should be documented; an investigator (or sub-investigator) may be a member of the IRB, but may not vote on any research in which he or she is involved.

A copy of the IRB-approved ICF and other adjunctive materials (e.g., advertising) to be used for the study, including written documentation of IRB approval of these items. The IRB will determine if the ICF requires revision. The investigator should also comply with the IRB procedures for reporting any other safety information.

In addition to the documents required prior to the study, other documentation may be required during the course of the study.

The investigator will promptly report to the IRB all changes in research activity and all unanticipated problems involving risks and will not make any changes in the research without IRB approval, except where necessary to eliminate immediate hazards to human subjects. Those amendments that involve no more than minimal risk or minor changes in previously approved research only require submission to the IRB. Protocol modifications will be reported as required by the IRB. Major amendments require approval of the full IRB committee and must be submitted to the agency/licensing authority by the Investigator before implementation, except in an emergency situation. Documentation of all study amendment activity should be forwarded to the Investigator. The investigator must also provide updates to the IRB at least yearly on the progress of the investigation.

Continuing IRB review should be documented by a letter from the IRB, which should be forwarded to the Investigator. Notification to the IRB by the investigator within 3 months after completion, termination, or discontinuation of the study at the specific study center must be documented.

12.9 Case Report Forms

Patient medical information obtained by this study is confidential, and disclosure to third parties other than those noted below is prohibited.

Upon the patient's permission, medical information may be given to his or her personal physician or other appropriate medical personnel responsible for his or her welfare. This medical information must be made available to Oncologie and authorized representatives of Oncologie, upon request, for source verification of study documentation.

Data generated by this study must be available for inspection upon request by representatives of the U.S. FDA, local health authorities, Oncologie, Inc., and their authorized representative(s), collaborators and licensees, and the IRB for each study site, if appropriate.

All information will be collected on study-specific case report forms in CRMS by the study staff.

The completed forms will be forwarded for central review and inclusion in the study dataset with relevant source documentation as outlined in the case report forms. The data submission schedule is as follows:

At the time of registration:

a. Registration Form
b. Informed Consent Form (signed by the subject)
c. Eligibility Checklist
d. Source documents related to eligibility and randomization

Within 2 weeks after registration:

a. Baseline study case report forms
b. Pertinent source documents

Within 2 weeks after final dose of study medication:

a. On study case report forms
b. Pertinent source documents

The investigator will permit study-related monitoring, audits, and inspections by the IRB, government regulatory bodies, and University compliance and quality assurance groups of all study related documents. The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

12.10 Quality Management and Data Management

Data monitoring of this protocol will occur on a regular basis with the frequency dependent on the rate of subject accrual and the progress of the study. The protocol will be monitored internally (University of Maryland Greenebaum Comprehensive Cancer Center) by the

Principal Investigator. Clinical data will be entered into the Oncore® database by the designated data manager at the University of Maryland Marlene and Stewart Greenebaum Cancer Center (UMGCC). CRSS implemented Oncore® as its clinical research database in FY2006. Oncore is equipped for HIPAA-compliant internet-based entry of protocol tracking and review information, houses accrual and demographic information for patients enrolled in clinical trials, offers customizable study calendars and case report forms, and contains invoicing data for clinical trials and summaries of external and internal adverse events. Oncore® easily generates accrual information for IRB annual reports, NCI-required Summary 4 reports, agendas for scientific review and DSMB meetings, and reports about adverse events. Using the internet, physicians and nursing staff can access Oncore® to download current versions of protocols, consents, and other protocol-related documents. Such access eliminates the need to maintain and track paper copies when a patient is waiting in a clinic. Oncore's® study calendars are linked to an invoice-generating financial module, allowing for seamless communication between research and billing staff. One-half of an FTE in the Cancer Center is dedicated to the overall management, quality control, and staff education in relation to Oncore®. Opening and accruing protocols at UMGCC are listed on the UMGCC website on the Internet via an Oncore interface, along with summaries for referring physicians and patients.

All study data will be collected by the Research team at each and every study visit and recorded in the research record. This data will then be entered in to the study database in a timely fashion.All source documents will be obtained and retained along with any study forms, and placed into the patient's research folder.

13. DATA SAFETY AND MONITORING BOARD (DSMB)

Local DSMB oversight will be conducted in accordance with performance site guidelines. The Greenebaum Comprehensive Cancer Center DSMB will also provide trial oversight per its standard operating procedures.

References:

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