

**Winship Cancer Institute  
Emory University**

**Phase Ib trial of pembrolizumab and XL888 in patients with  
advanced gastrointestinal malignancies**

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## 1.0 TRIAL SUMMARY

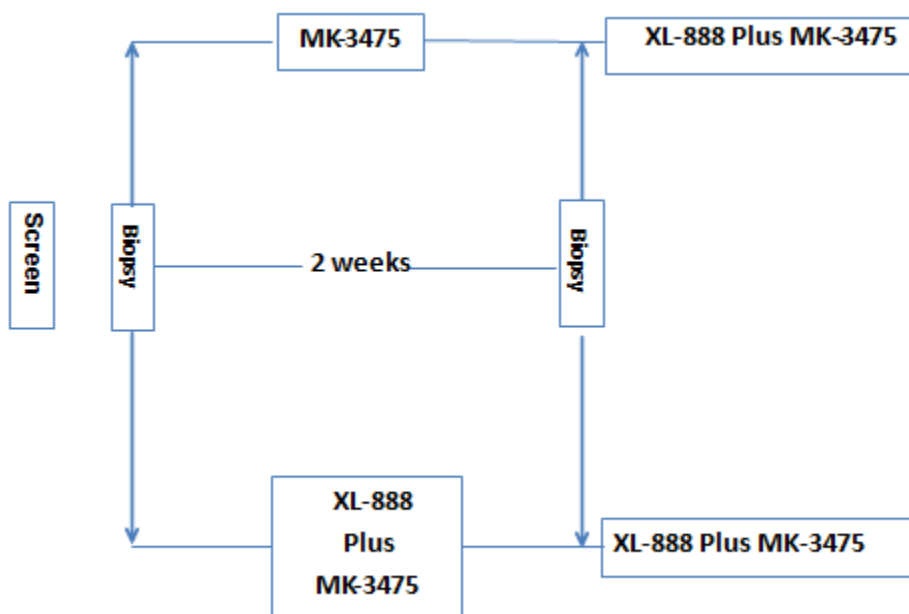
Abbreviated Title	Pembro-XL888
Trial Phase	<i>Phase I</i>
Clinical Indication	GI Malignancies
Trial Type	Single arm dose escalation
Type of control	None
Route of administration	IV and PO
Trial Blinding	None
Treatment Groups	Pembrolizumab and XL888
Number of trial subjects	38-50
Estimated enrollment period	<i>12 Months</i>
Estimated duration of trial	<i>14 months</i>
Duration of Participation	6 months
Estimated average length of treatment per patient	6 months

## 2.0 TRIAL DESIGN

Open label phase I trial. Primary objective is to determine the recommended phase 2 dose (RP2D) of the combination of XL888 and pembrolizumab. The design is 3+3 with 3 dose levels of XL888 (X). MTD is defined as the dose at which less than one-third of the subjects experience a DLT in the first 4 weeks of treatment.

After determining the RP2D, an additional 16 patients with pancreatic cancer (Arm A) and 16 patients with colorectal cancer (Arm B) will be enrolled in an expansion phase to confirm toxicity profile and obtain paired biopsies. Paired biopsy performed on 8 patients in each group. Patient selected for biopsy must have a primary or metastatic non-bone site that is amenable to safe biopsy. Bone only lesions are not suitable for biopsy. Patients undergoing paired biopsies will be assigned into two treatment cohorts (8 in each) and treated according to the schema below.

## 2.1 Trial Diagram



## 3.0 OBJECTIVE(S) & HYPOTHESES

### 3.1 Primary Objective & Hypothesis

- (1) **Objective: Determine the recommended phase II dose for the combination of XL888 and pembrolizumab**

**Hypothesis:** The combination of a PD-1 inhibitor with HSP90 inhibitor is safe with no added toxicity.

### 3.2 Secondary Objectives & Hypotheses

- (1) **Objective:**

**A. Define the toxicity profile of the combination of XL888 and pembrolizumab.** The additional patients enrolled on the expansion cohorts will help confirm the toxicity profile.

- B. Evaluate the activity of the combination of XL888 and pembrolizumab in previously treated patients with gastrointestinal tumors. Specifically, we will measure response rate, response duration and progression free survival. This will only be preliminary data since this is a secondary objective.**

### **3.3 Exploratory Objective**

**Objective: Evaluate the effect of the combination on the immune profile in the serum and in tumor biopsies.**

**Hypothesis:** The HSP90 inhibitor will change the micro-environment to favor an immune response to the PD-1 inhibitor.

## **4.0 BACKGROUND & RATIONALE**

### **4.1 Background**

Refer to the Investigator's Brochure (IB)/approved labeling for detailed background information on MK-3475 and XL888.

#### **4.1.1 Pharmaceutical and Therapeutic Background- Pembrolizumab**

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. In particular, the presence of CD8<sup>+</sup> T-cells and the ratio of CD8<sup>+</sup> effector T-cells / FoxP3<sup>+</sup> 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 hijacked by tumors to suppress immune control. 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 reactions. PD-1 (encoded by the gene *Pdcd1*) is an Ig superfamily member related to CD28 and CTLA-4 which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2). The structure of murine PD-1 has been resolved. 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 CD3 $\zeta$ , PKC $\theta$  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. 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) are constitutively expressed or can be induced in a variety of cell types, including non-hematopoietic tissues as well as in various tumors. Both ligands are type I transmembrane receptors containing both IgV- and IgC-like domains in the extracellular region and contain short cytoplasmic regions with no known signaling motifs. Binding of either PD-1 ligand to PD-1 inhibits T-cell activation triggered through the T-cell receptor. PD-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments. PD-L2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell function in peripheral tissues. Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. PD-1 has been suggested to regulate tumor-specific T-cell expansion in subjects with melanoma (MEL). This suggests that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention.

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. Keytruda™ (pembrolizumab) has recently been approved in the United States for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor.

### **Rationale for pembrolizumab dose selection/regimen/modification**

An open-label Phase I trial (Protocol 001) was conducted to evaluate 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, the highest dose tested in PN001, was the dose and schedule utilized in Cohorts A, B, C and D of this protocol to test for initial tumor activity. Recent data from other clinical studies within the MK-3475 program has shown that a lower dose of MK-3475 and a less frequent schedule may be sufficient for target engagement and clinical activity.

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 rationale for further exploration of 2 mg/kg and comparable doses of pembrolizumab in solid tumors is based on: 1) similar efficacy and safety of pembrolizumab when dosed at either 2 mg/kg or 10 mg/kg Q3W in melanoma patients, 2) the flat exposure-response relationships of pembrolizumab for both efficacy and safety in the dose ranges of 2 mg/kg Q3W to 10 mg/kg Q3W, 3) the lack of effect of tumor burden or indication on distribution behavior of pembrolizumab (as assessed by the population PK model) and 4) the assumption that the dynamics of pembrolizumab target engagement will not vary meaningfully with tumor type.

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.

#### **4.1.2 Pharmaceutical and Therapeutic Background- XL888**

Hsp90 belongs to a class of molecular chaperone proteins that help modulate cellular responses to environmental stress.<sup>1</sup> In particular, Hsp90 regulates the folding, stability, and function of many so-called Hsp90 “client” proteins. Inhibition of Hsp90 is believed to cause these client proteins to adopt aberrant conformations, which are then targeted for ubiquitination and degradation by the proteasome.<sup>2,3</sup> Hsp90 clients include wild-type and or activated forms of many important signaling proteins, such as B-Raf, c-KIT, c-MET, EGFR, human epidermal growth factor receptor 2 (HER2) and platelet-derived growth factor receptor, alpha polypeptide

(PDGFRA).<sup>4,5</sup> Given the diversity of currently identified Hsp90 client proteins, many of which are known to be critical regulators of the immune system, the cancer microenvironment as well as cancer cell proliferation and survival,<sup>1,6</sup> XL888 would be expected to show activity against a wide variety of human tumor types. Although human cancers are typically characterized by a wide variety of genetic alterations that collectively contribute to the transformed state, a subset of cancers appears to be particularly dependent upon single oncoproteins for their genesis, sustained proliferation, and survival. In such cancers, inactivation of the critical oncoprotein can cause rapid cell growth arrest, differentiation, or apoptosis. This phenomenon has been termed “oncogene addiction”.<sup>7</sup> Importantly, a number of such “addicting” oncoproteins are also Hsp90 client proteins,<sup>1</sup> and therefore cancers involving these oncoproteins are particularly promising indications for treatment by Hsp90 inhibition.

XL888 is a synthetic small molecule that binds to the ATP pocket in the N-terminus of Hsp90. It demonstrates significant activity for down-regulating Hsp90 client protein levels. These proteins include EGFR, HER2, MET, insulin-like growth factor-I receptor (IGF-IR) and other signaling kinases. Inhibitors of HSP90 have been shown in preclinical studies and in patient samples to exert anti-tumor effects as well as modulation of signaling pathways.

### **XL888 dose selection/regimen/modification<sup>8</sup>**

Clinical data are available for two clinical studies with XL888. Clinical Study XL888-001 enrolled a total of 33 subjects (study completion date/database lock 22 November 2010). In the ongoing investigator sponsored Study XL888-IST1 a total of 21 subjects have received at least one dose of XL888. Safety information on SAEs is provided to 7 April 2016.

#### **XL888-001**

XL888-001 was a non-randomized, open-label, dose-escalation Phase 1 study conducted in 33 subjects to determine the MTD of XL888 in subjects with refractory solid tumors and to explore the compound’s safety, PK, and pharmacodynamics. XL888 was administered orally on an intermittent schedule. This study evaluated both a PIB formulation and a capsule formulation twice weekly, in 28-day cycles.

The age of the 33 subjects enrolled ranged from 46 to 80 years. Mean age was 64.3 years (standard deviation [SD] 9.32). Sixteen subjects (48.5%) were male, and 17 subjects (51.5%) were female. Sixteen subjects (48.5%) were aged between 45 and 65, and 17 subjects (51.5%) were aged 65 and over. The ECOG performance status (PS) of subjects at baseline was as follows: 16 subjects (48.5%) had a PS of 0; 15 subjects (45.5%) had a PS of 1; and two subjects (6.1%) had a PS of 2.

The primary disease sites for subjects in this study were 10 subjects (30.3%) with colon cancer; 3 subjects each (9.1%) each with prostate, breast, skin, or rectal cancer; 2 subjects (6.1%) each with endometrial cancer, pancreatic, or liver cancer; and 1 subject each (3.0%) with lung, parotid, submandibular, ovarian, or unknown primary cancers.

At the MTD of 135 mg capsule, the number of doses per subject ranged from eight to 31 (mean 18.7, SD 8.94). The number of days of exposure ranged from 25 to 116 (mean 65.2, SD 33.63). The mean number of cycles was 2.5 (SD 1.22). Of the six subjects in this cohort, two subjects (33.3%) completed four cycles, three subjects (50.0%) completed 2 cycles, and one subject (16.7%) completed one cycle.

The most frequently observed AEs ( $\geq 10\%$  of subjects), regardless of the relationship to XL888 are diarrhea, fatigue, nausea, decreased appetite, vomiting, abdominal pain, vision blurred, AST increased, and alkaline phosphatase increased. Most reported AEs were mild, Grade 1 to 2 severity except for four (12.1%) reports of AST elevation, 3 (9.1%) of blood alkaline phosphatase increased, and 1 (3.0%) of fatigue, all of which were Grade 3.

The SAEs observed in the XL888-001 included 9 SAEs (2/9 were assessed as related to study treatment) in 6 subjects (18.2%). Five of these subjects (15.2%) reported at least one Grade 3 SAE. Three subjects (9.1%) discontinued from the study following SAEs: one subject experienced Grade 2 bile duct obstruction and Escherichia bacteremia (both assessed as unrelated in the same subject), one subject experienced Grade 3 pneumonia (assessed as unrelated), and one (the only subject to have been assessed with related SAEs) experienced Grade 2 radiation skin injury and Grade 3 visual impairment (both assessed as related). One subject (3.0%) each also experienced ileus, intestinal obstruction, and pain (all Grade 3). One subject (3.0%) experienced Grade 5 disease progression (metastatic pancreatic carcinoma).

In addition, two SAEs occurred in the XL888-001 Study after clinical database lock. Both were assessed as unrelated and recorded within 30 days of final dose: an 80-year-old female with pancreatic cancer had Grade 3 bacteremia, and a 59-year-old male with prostate cancer had Grade 2 pneumonia.

Pharmacodynamics findings: Pharmacodynamic biomarker analysis in PBMC samples serially collected from 32 subjects in Cohorts 1 through 8 demonstrated an overall trend of progressively increased HSP70 in PBMCs, starting on the first day of XL888 administration, with no obvious dose-dependence. The maximum induction evident was 12-fold in Cohort 7 at the Day 15 time-point. Pharmacodynamic analyses of paired tumor biopsy samples from a subject with metastatic, HER2+ breast cancer and of paired normal skin biopsy samples from five subjects indicated that levels of phosphorylated HER2, MET, AKT, ERK, and S6 proteins, as measured by immunofluorescence, were decreased from baseline by at least 30% within 22 or 57 days of treatment in each of these sets of samples.

### **XL888-IST1**

The primary objectives of the study were to determine the MTD and recommended Phase 2 dose (RP2D) of XL888 when administered orally with vemurafenib in subjects with advanced BRAFV600 mutated melanoma and to evaluate the safety and tolerability of this combination. SixXL888 month progression-free survival (PFS), 1-year overall survival (OS) and overall response rate (ORR) by Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) were also to be assessed as secondary endpoints.

The XL888 MTD and R2PD were therefore established as 90 mg BIW (in combination with 960 mg vemurafenib BID). Ten (48%) subjects reported SAEs. Three subjects had SAEs associated with progressive disease (melanoma in situ, metastatic melanoma excision, and metastatic malignant melanoma) and two subjects each had SAEs of diarrhea, pleural effusion, pneumonia, and vomiting. All other SAE preferred terms (PTs) occurred in one subject. There were two subjects with Grade 5 events (pneumonia and metastatic malignant melanoma), both of which were assessed by the investigator as not related to study treatment.

In data presented for Study XL888-IST1 to the American Society of Clinical Oncology (ASCO) in June 2016 (Eroglu et al 2016), out of 19 evaluable subjects confirmed objective response was observed in 14 subjects (74%; 95% confidence interval [CI]: 54, 94), including two complete responses. Two subjects with PR who underwent surgical resection had a pathological CR. Median PFS was 7.4 months (95% CI: 3.7, 16.2). Estimated 1-year PFS was 40%. Median OS was 33.1 months (95% CI: 5.75, not reached).

## 4.2 Rationale

HSP90 has several effects on the immune system, cancer cells, and tumor microenvironment. **Our overall hypothesis is that the inhibition of HSP90 can modulate multiple facets of the interactions between cancer cells and immune system leading to potentiation of the immunologic response triggered by PD-1 inhibition.** This is based on the following preliminary data.

### A. Inhibition of HSP90 can promote expression of tumor antigens

A known mechanism of tumor evasion of the immune system is through loss of antigen expression and downregulation of MHC expression. Inhibition of HSP90 using different pharmacologic compounds has been shown to improve antigen in melanoma and glioma cell lines.<sup>9,10</sup> Similarly, pharmacologic inhibition of HSP90 has been shown to improve epha2+ tumor cell recognition and T-lymphocyte recruitment through several mechanisms including increased MHC expression by tumor cells.<sup>11,12</sup>

### B. Inhibition of HSP90 can modulate expression of PD-L1

The activation of HIF-1 $\alpha$  and JAK-STAT pathway leads to transcription and overexpression of immune suppressive proteins including PD-L1.<sup>13-15</sup> Our group has demonstrated in vivo and in patient samples that inhibition of HSP90 results in downregulation of HIF-1 $\alpha$  and JAK-STAT in colorectal and pancreatic cancer (not published).<sup>16</sup> Therefore, targeting HSP90 may modulate the expression of immune inhibitory pathways including PD-L1.

### C. Inhibition of HSP90 can affect tumor microenvironment

One of the main challenges in tumor immune therapy is the immune suppressive tumor microenvironment. The immune suppressive effects associated with the tumor microenvironment include:

1. Hypoxia, acidity and high interstitial pressures: the abnormal tumor vasculature impairs dendritic cell function<sup>17,18</sup>, inhibits proliferation and function of T-cells<sup>18-20</sup> and promotes accumulation of alternative activated macrophages (TAM-M2)<sup>21,22</sup>. Anti-angiogenic therapy has been shown to normalize tumor vasculature leading to improved oxygenation and reversal of hypoxia.<sup>23</sup> Furthermore, normalization of tissue vasculature has been shown to improve immune function and as such would be a rational strategy to combine with immune modulators.<sup>24</sup>
2. Circulating VEGF inhibits immune cell proliferation and function.<sup>25,26</sup>
3. T cell exhaustion through chronic stimulation of tumor infiltrating lymphocytes through cytokines.<sup>27</sup> Exhausted T cells have persistent and unopposed activation of proteins like PD-1, Tim-3 and LAG3. Tim3 and LAG3 have been shown to signal through activation of PI3K, Akt and NF- $\kappa$ B signaling pathways.<sup>28</sup> Inhibition of these signaling pathways may potentiate the effects of PD-1 inhibitors.
4. Macrophage migration inhibitory factor (MIF) is a pro-inflammatory cytokine that has been shown to be overexpressed in the tumor micro-environment. MIF has been associated with immune suppressive effects.<sup>29-31</sup>

**Our group has previously shown that the inhibition of HSP90 using ganetespib can modulate angiogenesis, inhibit tumor invasion, and activation of cytokines and inflammatory pathways such as NF- $\kappa$ B.<sup>16,32,33</sup> In addition, we have demonstrated that HSP90 inhibition can result in downregulation of VEGF expression. MIF is a HSP90 client protein and inhibition of HSP90 has been shown to downregulate MIF.<sup>34</sup>**

Furthermore, recent data reported by Proia *et.al.* demonstrate that the combination of ganetespib potentiates the antitumor effects of PD-L1 antibody (STI-A1015) in syngeneic mouse models of colorectal cancer and melanoma.<sup>35</sup>

Heat shock protein 90 has a central role in modulating angiogenesis, tumor microenvironment, inflammatory signaling pathways (NF- $\kappa$ B, HIF-1 $\alpha$  and Jak-STAT), tumor antigen presentation and expression, PD-L1 expression and MIF as well as cytokine production. Inhibition of HSP90 may provide an approach to modulate the microenvironment to improve immune function and potentiate the effects of PD-1 inhibitors in patients with solid tumors. The purpose of this trial is to evaluate the safety of combining an HSP90 inhibitor with a PD-1 inhibitor and to obtain preliminary data regarding the activity of such a combination.

#### **4.2.1 Rationale for Endpoints**

- 4.2.1.1 Efficacy Endpoints:** This is a phase I trial. The primary endpoint is still toxicity. The plan is to evaluate the response rate, response duration, and progression free

survival of the patients on the trial. These endpoints will provide preliminary data in two patient subsets: patients with pancreatobiliary and other GI malignancies.

- 4.2.1.2 **Biomarker Research:** We intend in all patients to evaluate the effects of the combination on T-cell population in peripheral blood. In addition, we plan to evaluate the effects of the combination versus pembrolizumab alone in paired biopsy samples in 16 patients. These samples will be analyzed for tumor infiltrating lymphocytes, stromal/tumor markers and expression immune inhibitory molecules (PD-L1, PD-L2, PD1, etc). We anticipate to see a difference between the group treated with the combination versus the group treated with pembrolizumab alone.

## 5.0 METHODOLOGY

### 5.1 Entry Criteria

#### 5.1.1 Diagnosis/Condition for Entry into the Trial

- a. In the dose escalation phase, the trial will be open for patients with stage IV or locally advanced unresectable gastrointestinal adenocarcinomas (gastric, GEJ, cholangiocarcinoma, hepatocellular, pancreas, small intestinal tumors) who have failed at least one prior therapy. Patients with colorectal cancer must have previously received oxaliplatin, irinotecan, and a fluoropyrimidine.
- b. In the dose expansion phase, Arm A will be open for 16 patients with pancreatic adenocarcinoma. Patients must have histologic diagnosis and either locally advanced unresectable or metastatic disease that has failed at least one standard regimen. Eight patients will participate in the paired biopsy studies. Patient selected for biopsy must have a primary or metastatic non-bone site that is amenable to safe biopsy. Bone only lesions are not suitable for biopsy. These patients will provide informed consent for the paired biopsy study.
- c. In dose expansion phase, Arm B will be open for 16 patients with colorectal adenocarcinoma. Patients must have histologic diagnosis and either locally advanced unresectable or metastatic disease and have previously received oxaliplatin, irinotecan, and a fluoropyrimidine. Eight patients will participate in the paired biopsy studies. Patient selected for biopsy must have a primary or metastatic non-bone site that is amenable to safe biopsy. Bone only lesions are not suitable for biopsy. These patients will provide informed consent for the paired biopsy study.

#### 5.1.2 Subject Inclusion Criteria

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

- Be willing and able to provide written informed consent/assent for the trial.
- Be  $\geq 18$  years of age on day of signing informed consent.

- Have measurable disease based on RECIST 1.1.
- Have a performance status of 0 or 1 on the ECOG Performance Scale.
- Demonstrate adequate organ function as defined in Table 1.

Table 1 Adequate Organ Function Laboratory Values

System	Laboratory Value
<b>Hematological</b>	
Absolute neutrophil count (ANC)	$\geq 1,500$ /mcL
Platelets	$\geq 100,000$ / mcL
Hemoglobin	$\geq 9$ g/dL or $\geq 5.6$ mmol/L without transfusion or EPO dependency (within 7 days of assessment)
<b>Renal</b>	
Serum creatinine <b>OR</b> Measured or calculated <sup>a</sup> creatinine clearance (GFR can also be used in place of creatinine or CrCl)	$\leq 1.5$ X upper limit of normal (ULN) <b>OR</b> $\geq 60$ mL/min for subject with creatinine levels $> 1.5$ X institutional ULN
<b>Hepatic</b>	
Serum total bilirubin	$\leq 1.5$ X ULN <b>OR</b> Direct bilirubin $\leq$ ULN for subjects with total bilirubin levels $> 1.5$ X ULN
AST (SGOT) and ALT (SGPT)	$\leq 2.5$ X ULN <b>OR</b> $\leq 5$ X ULN for subjects with liver metastases (only in the phase II portion)
Albumin	$\geq 2.5$ mg/dL
<b>Coagulation</b>	
International Normalized Ratio (INR) or Prothrombin Time (PT)	$\leq 1.5$ 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)	$\leq 1.5$ X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
<sup>a</sup> Creatinine clearance should be calculated per institutional standard.	

- Female subject of childbearing potential should 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.
- Female subjects of childbearing potential (Section 5.7.2) must be willing to use an adequate method of contraception as outlined in Section 5.7.2 – 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.

- Male subjects of childbearing potential (Section 5.7.1) must agree to use an adequate method of contraception as outlined in Section 5.7.1- 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.

### **5.1.3 Subject Exclusion Criteria**

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

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.
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. Has a known history of active TB (Bacillus Tuberculosis)
4. Hypersensitivity to pembrolizumab or history of severe allergic or hypersensitivity reactions to excipients (e.g., Polyethylene glycol [PEG] 300 and Polysorbate 80)
5. Clinically significant cardiovascular disease or peripheral vascular (e.g. myocardial infarction, unstable angina within 6 months of study entry), symptomatic congestive heart failure, serious uncontrolled cardiac arrhythmia requiring medications, baseline QTc > 450 msec or previous history of QT prolongation while taking other medications
6. Other medications, or severe acute/chronic medical or psychiatric condition, or laboratory abnormality that may increase the risk associated with study participation or study drug administration, or may interfere with the interpretation of study results, and in the judgment of the investigator would make the subject inappropriate for entry into this study
7. Has had a prior anti-cancer monoclonal antibody (mAb) within 4 weeks prior to study Day 1 or who has not recovered (i.e.,  $\leq$  Grade 1 or at baseline) from adverse events due to agents administered more than 4 weeks earlier.
8. 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.,  $\leq$  Grade 1 or at baseline) from adverse events due to a previously administered agent.
  - Note: Subjects with  $\leq$  Grade 2 neuropathy are an exception to this criterion and may qualify for the study.

- Note: Major surgical procedure, or significant traumatic injury within 28 days of registration or incompletely healed surgical wounds are exclusions. Minor surgical procedures such as placement of central venous device (excluding PICC line) are allowed 7 days prior to enrollment to the study.
9. 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.
  10. 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.
  11. 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 (eg., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.
  12. Has known history of, or any evidence of active, non-infectious pneumonitis.
  13. Has an active infection requiring systemic therapy.
  14. Has known substance abuse disorders that would interfere with cooperation with the requirements of the trial.
  15. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the screening visit through 120 days after the last dose of trial treatment.
  16. Has received prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, or HSP inhibitor.
  17. Has a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).
  18. Has known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected).
  19. History of malabsorption or other condition that would interfere with absorption of study drugs.

20. History of or evidence of retinal pathology on ophthalmologic examination that is considered a risk factor for neurosensory retinal detachment, RVO (retinal vein occlusion), or neovascular macular degeneration. The risk factors for RVO are listed below. Patients should be excluded if they have the following current conditions:

- a. Uncontrolled glaucoma with intra-ocular pressures > 21mmHg
- b. Serum cholesterol > Grade 2
- c. Hypertriglyceridemia > Grade 2
- d. Hyperglycemia (fasting) > Grade 2

21. 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.*

#### 5.1.4 Screen Failures

Minimal data for subjects who fail screening will be collected such as demographic information and the reason for screen failure. Such subjects may be re-screened at the discretion of the investigator after approval by the Data and Safety Monitoring Committee (DSMC). The reason for the need to re-screen a subject will be documented in the subject's source documents.

## 5.2 Trial Treatments

The treatment to be used in this trial is outlined below in Table 2

Table 2 Trial Treatment

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period
Pembrolizumab	200 mg	Q3W	IV infusion	Day 1 of each 3 week cycle
XL888	As Below	Twice weekly (Days 1 and 4)	Oral	Twice weekly (days 1 and 4) cycle is 3 weeks

### 5.2.1 XL888 dose levels

Open label phase I trial. Primary objective is to determine the recommended phase 2 dose (RP2D) of the combination of XL-888 and Pembrolizumab in a broad spectrum of GI tumors. The design is 3+3 with 3 dose levels of XL888 (X).

<u>Dose level</u>	<u>XL-888</u>	<u>Pembrolizumab</u>
1 days	45 mg PO twice weekly (Days 1 and 4)	200 mg IV every 21
2 days	90 mg PO twice weekly (Days 1 and 4)	200 mg IV every 21
3 every 21 days	60 mg PO twice weekly (Days 1 and 4)	200 mg IV

**Dose level 3 will only be tested if we observe 2 DLT's on dose level 2.**

### 5.2.2 Dose Escalation

Starting dose of 45mg; if  $\geq 2$  patients with DLTs in 3 ( $\geq 2/3$ ) or 6 ( $\geq 2/6$ ) subjects; stop and consider reduced dose of XL888. If not, increase dose to 90 mg and test 3-6 patients. If  $\geq 2$  patients with DLTs in 3 or 6 subjects, reduce dose to 60 mg and try again. If an acceptable dose is identified, treat 16 more patients at the MTD. Prior to dose escalation, we will obtain approval from the Data Safety and Monitoring Committee (DSMC).

**5.2.3 Dose limiting toxicity (DLT)** will be defined as any of the following definitely treatment related adverse events during the first 21 days of therapy:

- Grade IV neutropenia lasting more than 8 days; any neutropenic fever or sepsis;
- Grade III with clinically significant bleeding or any grade IV thrombocytopenia;
- Grade III nausea, vomiting, or diarrhea, lasting  $>72$  hours despite adequate supportive care;
- Other non-hematologic treatment-related toxicity at Grade III or higher
- Grade 4 asymptomatic laboratory abnormalities that last for more than 24 hours or Grade 3 asymptomatic laboratory abnormalities lasting more than 21 days is a DLT.
- Grade IV or higher diarrhea, nausea, vomiting
- In ability to take more than 75% of XL888 due to toxicity.

### **5.3 Dose Modification:**

XL 888 and pembrolizumab have class-specific safety profiles based on their mechanism of action but may also cause AEs that overlap. For management of AEs which can be clearly attributed to XL 888 or pembrolizumab, independent dose modification for either agent is allowed. For AEs without clear attribution to either study treatment, management of toxicity should include dose modifications of both agents.

#### **5.3.1 Pembrolizumab**

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.

Toxicities unrelated to pembrolizumab will not ordinarily result in the modification of pembrolizumab dose. AEs will be defined based on the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.

Table 3 Dose Modification Guidelines for Drug-Related Adverse Events

<b>General instructions:</b>				
<ol style="list-style-type: none"> <li>1. Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks.</li> <li>2. For situations where pembrolizumab has been withheld, pembrolizumab can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered. Pembrolizumab should be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to <math>\leq 10</math> mg prednisone or equivalent per day within 12 weeks.</li> <li>3. For severe and life-threatening irAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.</li> </ol>				
<b>Immune-related AEs</b>	<b>Toxicity grade or conditions (CTCAEv4.0)</b>	<b>Action taken to pembrolizumab</b>	<b>irAE management with corticosteroid and/or other therapies</b>	<b>Monitor and follow-up</b>
Pneumonitis	Grade 2	Withhold	<ul style="list-style-type: none"> <li>• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper</li> </ul>	<ul style="list-style-type: none"> <li>• Monitor participants for signs and symptoms of pneumonitis</li> <li>• Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment</li> <li>• Add prophylactic antibiotics for opportunistic infections</li> </ul>
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold	<ul style="list-style-type: none"> <li>• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper</li> </ul>	<ul style="list-style-type: none"> <li>• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus).</li> <li>• Participants with <math>\geq</math> Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis.</li> <li>• Participants with 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.</li> </ul>
	Grade 4	Permanently discontinue		

AST / ALT elevation or Increased bilirubin	Grade 2	Withhold	<ul style="list-style-type: none"> <li>Administer corticosteroids (initial dose of 0.5- 1 mg/kg prednisone or equivalent) followed by taper</li> </ul>	<ul style="list-style-type: none"> <li>Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable)</li> </ul>
	Grade 3 or 4	Permanently discontinue	<ul style="list-style-type: none"> <li>Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper</li> </ul>	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of $\beta$ -cell failure	Withhold	<ul style="list-style-type: none"> <li>Initiate insulin replacement therapy for participants with T1DM</li> <li>Administer anti-hyperglycemic in participants with hyperglycemia</li> </ul>	<ul style="list-style-type: none"> <li>Monitor participants for hyperglycemia or other signs and symptoms of diabetes.</li> </ul>
Hypophysitis	Grade 2	Withhold	<ul style="list-style-type: none"> <li>Administer corticosteroids and initiate hormonal replacements as clinically indicated.</li> </ul>	<ul style="list-style-type: none"> <li>Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)</li> </ul>
	Grade 3 or 4	Withhold or permanently discontinue <sup>1</sup>		
Hyperthyroidism	Grade 2	Continue	<ul style="list-style-type: none"> <li>Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate</li> </ul>	<ul style="list-style-type: none"> <li>Monitor for signs and symptoms of thyroid disorders.</li> </ul>
	Grade 3 or 4	Withhold or permanently discontinue <sup>1</sup>		
Hypothyroidism	Grade 2-4	Continue	<ul style="list-style-type: none"> <li>Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care</li> </ul>	<ul style="list-style-type: none"> <li>Monitor for signs and symptoms of thyroid disorders.</li> </ul>
Nephritis and Renal dysfunction	Grade 2	Withhold	<ul style="list-style-type: none"> <li>Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper.</li> </ul>	<ul style="list-style-type: none"> <li>Monitor changes of renal function</li> </ul>
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1 or 2	Withhold	<ul style="list-style-type: none"> <li>Based on severity of AE administer corticosteroids</li> </ul>	<ul style="list-style-type: none"> <li>Ensure adequate evaluation to confirm etiology and/or exclude other causes</li> </ul>

	Grade 3 or 4	Permanently discontinue		
All other immune-related AEs	Intolerable/ persistent Grade 2	Withhold	<ul style="list-style-type: none"><li>Based on type and severity of AE administer corticosteroids</li></ul>	<ul style="list-style-type: none"><li>Ensure adequate evaluation to confirm etiology and/or exclude other causes</li></ul>
	Grade 3	Withhold or discontinue based on the type of event. Events that require discontinuation include and not limited to: Guillain-Barre Syndrome, encephalitis		
	Grade 4 or recurrent Grade 3	Permanently discontinue		
1. Withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician. <b>NOTE:</b> For participants with Grade 3 or 4 immune-related endocrinopathy where withhold of pembrolizumab is required, pembrolizumab may be resumed when AE resolves to $\leq$ Grade 2 and is controlled with hormonal replacement therapy or achieved metabolic control (in case of T1DM).				

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 Sponsor. The reason for interruption should be documented in the patient's study record.

### 5.3.2 XL888

The following guidelines are provided for the modification of the dose of XL888 in the event of toxicities attributed by the investigator to this study drug. Toxicities unrelated to XL888 will not ordinarily result in the modification of dose. AEs will be defined based on the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.

In general, subjects experiencing **Grade 1 and 2** drug related toxicities should not have the dose of XL888 modified. However, appropriate supportive care should be provided for the management of drug related toxicities. Grade 2 toxicities may require dose or schedule modifications (delaying or omitting individual doses) due to potentially greater clinical significance; however, this should occur after discussion with study PI. .

Dosing of XL888 must be delayed if a subject experiences a **Grade 3 non-hematologic** toxicity. If the toxicity resolves (returned to baseline or decreased to Grade  $\leq 1$ ) within 14 days, dosing of XL888 may be resumed one lower dose level (See section 5.3.2.1). Exceptions to this rule are as follows:

- Grade 3 fatigue: dose modification are left to the PI's discretion;
- Grade 3 nausea, vomiting and diarrhea: dose modification only after optimal prophylactic measures have failed to control the symptoms adequately;

In the case of Grade 4 **non-hematologic** toxicity, **or persistent Grade 3** toxicity despite one dose level reduction, XL888 will be discontinued.

No dose adjustment of XL888 will be performed for anemia.

No dose adjustment for XL888 will be performed for grade 1, 2, or 3 neutropenia or grade 1, 2, or 3(without bleeding) thrombocytopenia.

Dosing of XL888 will be delayed if subjects develop grade 4 neutropenia or grade 3 thrombocytopenia complicated by bleeding or grade 4 thrombocytopenia. If the toxicity resolves (returned to baseline or decreased to Grade  $\leq 1$ ) within 14 days, dosing of XL888 may be resumed one lower dose level (See section 5.3.2.1).

Dose escalation back to the starting dose will not be allowed.

#### 5.3.2.1 Dose reduction

	Dose	Tablet	Frequency
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Dose level 1	90 mg	2 capsule (45 mg)	Twice weekly (D 1 and 4)
Dose level -1	60 mg	1 capsule (45 mg) 1 capsule (15 mg)	Twice weekly (D 1 and 4)
Dose level -2	45 mg	1 capsule (45 mg)	Twice weekly (d 1 and 4)

### 5.3.2.2 XL888 Specific Toxicities

#### **A. Visual disturbances**

A variety of visual disturbances have been reported in clinical studies of other HSP90 inhibitors including the following descriptive terms: blurred vision, visual impairment, night blindness, photopsia, flashing, delayed dark/light accommodation, dry eyes, keratitis, conjunctivitis, and ocular surface disease <sup>36,37</sup>. In a retinal toxicity study of HSP90 inhibitors in beagle dogs<sup>38</sup>, described findings of loss of pupillary light reflex and abnormal wave forms on electroretinography. Histopathologic changes in the photoreceptor cell layer and outer nuclear layer of the retina were described.

Visual disturbances have been reported in subjects on XL888-001 and XL888IST1. On XL888-001, grade 1 – 2 blurred vision was the most common visual disorder reported (5 of 33 subjects (15.2%) with 2 subjects experiencing visual impairment (one Grade 2, one Grade 3/SAE). One subject on XL888-001 was reported to have Grade 2 iritis.

**All patients will have baseline ophthalmologic exam. Repeat ophthalmologic exam will be performed in patients with symptoms. Low grade toxicity (grade 1 or 2) will be managed symptomatically without drug interruption. Grade 3 or persistent grade 2 will require holding the dose and if treatment resumed should be at lower dose level.**

#### **B. Hepatotoxicity**

Liver Function Test Abnormalities Transaminase elevations have been reported in study XL888-001. Four subjects (12.1%) experienced AEs of AST increased (all Grade 3) and two subjects (6.1%) with ALT increased (both Grade 2). Bilirubin elevation (one Grade 3, one Grade 2) were also seen. Increases in ALP, ALT, AST, SDH, and GGT present in both rat and dog preclinical studies following XL888 administration, consistent with potential hepatotoxicity of this agent. Subjects on XL888 should have liver function tests at baseline and at regular intervals while on treatment.

XL888 will be interrupted for rising transaminases as follows:

1. Transaminase increase to  $> 5 \times \text{ULN}$  [upper limit of normal] in subjects with levels less than  $2.5 \times \text{ULN}$  at baseline
2. Doubling of transaminase level for those subjects with elevated baseline transaminases (levels equal or greater than  $2.5 \times \text{ULN}$ )
3. Isolated elevations of total bilirubin ( $>2\text{XULN}$ ) without other explanation.

Subjects with XL888-related transaminase elevations will have weekly monitoring of transaminases. XL888 will be resumed after transaminases return to baseline and patients will have a dose reduction.

XL888 should be discontinued if hepatic dysfunction is not reversed despite interruption of study treatment for 3 weeks.

Elevations  $>3 \times$  ULN of ALT or AST concurrent with  $>2 \times$  ULN total bilirubin without other explanation can indicate drug induced liver injury and drug should be permanently discontinued.

### **C. Gastrointestinal Disturbance**

Gastrointestinal disturbances (nausea, diarrhea, anorexia, vomiting, constipation, and abdominal pain) have been reported in the subjects treated with XL888, but especially with the subjects who received the PIB formulation. Some of this may be attributed to the effects of the polyethylene glycol in the vehicle; however, multiple histopathological findings were present in multiple tissues of the GI tract (esophagus, glandular and nonglandular stomach, duodenum, jejunum, ileum, cecum, colon, and rectum) in the preclinical studies as well. Gastrointestinal tract histopathologic changes correlated with increases in peripheral neutrophil counts in both rats and dogs and were suggestive of a generalized inflammatory reaction in response to tissue injury.

Diarrhea was the most frequent gastrointestinal disturbance on Study XL888-001. Subjects should be instructed to notify their physician immediately at the first signs of poorly formed or loose stool or an increased frequency of bowel movements.

1. Administration of antidiarrheal agents (example Imodium or Lomotil) is recommended as initial management. Dietary modifications may be helpful. Some subjects may require concomitant treatment with more than one antidiarrheal agent. General supportive measures should be implemented including monitoring for and correction of fluid and electrolyte abnormalities.
2. It is also recommended that nausea and vomiting be treated as indicated with supportive care and anti-emetics.

### **D. QTc Interval Prolongation**

In vitro evaluation of XL888 using manual patch-clamp electrophysiology showed that XL888 inhibits HERG channel activity with an IC<sub>50</sub> value of 5.6  $\mu$ M, which translates to a safety factor of  $\sim 298$  (Redfern et al. 2003) assuming a plasma C<sub>max</sub> of 474 ng/mL (0.94  $\mu$ M) and approximately 98% plasma protein binding. This estimated safety factor is substantially higher than the threshold for concern recommended by Redfern et al (ie, 30-fold), suggesting a low risk of risk of developing QTc interval prolongation at current dose levels. The potential for EXEL-4633 (ie, the primary metabolite of XL888) to prolong the QTc interval has not been evaluated in vitro. Guidelines for management of corrected QT prolongation are as follows:

If a subject on study has a QTc interval increase by  $\geq 60$  ms to an absolute value  $> 470$  ms or an increase to an absolute value of  $> 500$  ms at any evaluation, and if the subject is

asymptomatic (does not have palpitations, dizziness, syncope, orthostatic hypotension, a significant ventricular arrhythmia on electrocardiogram (ECG), or a change in vital signs), the following actions should be taken:

- Hold XL888 dosing
- Check electrolytes, especially magnesium and potassium; correct abnormalities as clinically indicated
- Repeat ECGs hourly until the QTc is < 30 ms increased over the average baseline value

Subjects with QTc prolongation and symptoms should be monitored closely. Cardiology consultation is recommended for evaluation and subject management.

No additional XL888 should be given to the subject until after the event has resolved. If any additional XL888 is given, it should be at a reduced dose.

### **5.3.3 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 6.0). 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.

**Pembrolizumab** 200 mg will be administered as a 30 minute IV infusion every 3 weeks. Given the variability of infusion pumps, 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.

**XL888** will be administered twice weekly (days 1 and 4) orally starting on day 1 of every 3-week cycle.

### **5.3.4 Trial Blinding/Masking**

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

## **5.4 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.

#### **5.4.1 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.

#### **5.4.2 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:

- Antineoplastic systemic chemotherapy, monoclonal antibody or biological therapy (including HSP90 inhibitors)
- Immunotherapy not specified in this protocol
- Investigational agents other than pembrolizumab and XL888
- Radiation therapy
  - Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed at the investigator's discretion. XL888 will be held will be held for 2 weeks before, during and 2 weeks after radiation.
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. 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 the Sponsor.
- Inhibitors of CYP3A4 and/or PgP

Co-administration with strong inhibitors of CYP3A4 (e.g., ketoconazole, itraconazole, ritonavir) is prohibited.

- Co-administration with moderate CYP3A4 inhibitors (e.g., erythromycin, fluconazole) or PgP inhibitors should be avoided in the phase I portion. Co-administration with moderate CYP3A4 in the expansion portion can be done with caution and only if other alternatives are not available.
- Lists of CYP3A4 inducers and inhibitors can be found on: <http://medicine.iupui.edu/clinpharm/ddis/table.aspx> and <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm> ).
- Seville orange, star fruit, grapefruit and their juices affect P450 and PgP activity and concomitant use with XL888 should be prohibited.
- Drugs that alter the gastric pH (eg, antacids, H2 receptor antagonists, and proton pump inhibitors) could reduce the solubility of XL888 in the GI tract and lower systemic exposure to XL888. Concomitant administration of these pH-altering drugs with XL888 should be avoided where possible and carefully documented otherwise.
- XL888 is highly protein bound in human plasma; thus, other drugs that are also highly protein bound should be avoided by subjects unless deemed clinically necessary, and the subject can be monitored for the desired drug effect or level and potential adverse effects. Examples of common medications that are also highly protein bound include warfarin, diazepam, furosemide, dicloxacillin, propranolol, and phenytoin.
- Inducers of CYP3A4 and/or PgP

Strong CYP3A4 inducers (i.e., phenytoin, carbamazepine, rifampin, rifabutin, phenobarbital, St. John's wort) are not allowed during the phase I portion. During the expansion phase, strong CYP3A4 inducers should only be used if alternatives are not available. Moderate inducers of CYP3A4 are allowed if alternatives are not available.

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.

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

## **5.5 Rescue Medications & Supportive Care**

### **5.5.1 Supportive Care Guidelines**

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.

- **Pneumonitis:**

- 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.
- For **Grade 3-4 events**, immediately treat with intravenous steroids. Administer additional anti-inflammatory measures, as needed.
- Add prophylactic antibiotics for opportunistic infections in the case of prolonged steroid administration.

- **Diarrhea/Colitis:**

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).

- 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.
  - For **Grade 2 diarrhea/colitis**, administer oral corticosteroids.
  - For **Grade 3 or 4 diarrhea/colitis**, treat with intravenous steroids followed by high dose oral steroids.
  - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
- **Type 1 diabetes mellitus (if new onset, including diabetic ketoacidosis [DKA]) or  $\geq$  Grade 3 Hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA)**

- For **T1DM** or **Grade 3-4** Hyperglycemia
  - Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria.
  - Evaluate patients with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.
- **Hypophysitis:**
  - 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.
  - 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.
- **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.

  - **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 liothyronine, is indicated per standard of care.
  - **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.
- **Hepatic:**
  - For **Grade 2** events, monitor liver function tests more frequently until returned to baseline values (consider weekly).
    - Treat with IV or oral corticosteroids
  - For **Grade 3-4** events, treat with intravenous corticosteroids for 24 to 48 hours.

- When symptoms improve to Grade 1 or less, a steroid taper should be started and continued over no less than 4 weeks.
- **Renal Failure or Nephritis:**
  - For **Grade 2** events, treat with corticosteroids.
  - For **Grade 3-4** 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.
- **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.

Table 3 Infusion Reaction Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
<u>Grade 1</u> 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
<u>Grade 2</u> Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs	<b>Stop Infusion and monitor symptoms.</b> Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen 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. <b>Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.</b>	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).  Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).
<u>Grades 3 or 4</u>  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., renal impairment, pulmonary infiltrates)  Grade 4:	<b>Stop Infusion.</b> Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine	No subsequent dosing

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Life-threatening; pressor or ventilatory support indicated	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. <b>Subject is permanently discontinued from further trial treatment administration.</b>	
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.		

## 5.6 Diet/Activity/Other Considerations

### 5.6.1 Diet

Subjects should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea or vomiting. Seville orange, star fruit, grapefruit and their juices affect P450 and PgP activity and concomitant use with XL888 should be avoided.

### 5.6.2 Contraception

Pembrolizumab and XL888 may have adverse effects on a fetus in utero. Furthermore, it is not known if pembrolizumab and XL888 have 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).

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

- (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

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

OR

- (3) has a congenital or acquired condition that prevents childbearing.

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:

(1) practice abstinence<sup>†</sup> from heterosexual activity;

OR

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

Acceptable methods of contraception are<sup>‡</sup>:

Single method (one of the following is acceptable):

- intrauterine device (IUD)
- vasectomy of a female subject's male partner
- contraceptive rod implanted into the skin

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

- diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide)
- cervical cap with spermicide (nulliparous women only)
- contraceptive sponge (nulliparous women only)
- male condom or female condom (cannot be used together)
- hormonal contraceptive: oral contraceptive pill (estrogen/progestin pill or progestin-only pill), contraceptive skin patch, vaginal contraceptive ring, or subcutaneous contraceptive injection

<sup>†</sup>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.

<sup>‡</sup>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.

### **5.6.3 Use in Pregnancy**

If a subject inadvertently becomes pregnant while on treatment with pembrolizumab and XL888, 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 and to Merck and Exelixis without delay and within 24 hours to the Sponsor and within 2 working days to Merck and Exelixis 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 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 be informed immediately and the pregnancy reported to Merck and Exelixis as described above and in Section 7.2.2.

### **5.6.4 Use in Nursing Women**

It is unknown whether pembrolizumab is 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. Patients should be advised not to breastfeed while on XL888 or for at least 3 months after discontinuation.

## **5.7 Subject Withdrawal/Discontinuation Criteria**

Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the investigator or the Sponsor if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding discontinuation or withdrawal are provided in Section 7.1.4 – Other Procedures.

A subject must be discontinued from the trial for any of the following reasons:

- The subject or legal representative (such as a parent or legal guardian) withdraws consent.
- Confirmed radiographic disease progression

*Note:* For unconfirmed radiographic disease progression, please see Section 5.2.2

*Note: A subject may be granted an exception to continue on treatment with confirmed radiographic progression if clinically stable or clinically improved, please see Section 7.1.2.7.1*

- Unacceptable adverse experiences as described in Section 5.2.1.2
- Intercurrent illness that prevents further administration of treatment
- Investigator's decision to withdraw the subject
- The subject has a confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements
- The subject is lost to follow-up
- Completed 24 months of uninterrupted treatment with pembrolizumab or 35 administrations of study medication, whichever is later.

*Note: 24 months of study medication is calculated from the date of first dose. Subjects who stop pembrolizumab/XL888 after 24 months may be eligible for up to one year of additional study treatment if they progress after stopping study treatment provided they meet the requirements detailed in Section 7.1.5.5*

- Administrative reasons

The End of Treatment and Follow-up visit procedures are listed in Section 6 (Protocol Flow Chart) and Section 7.1.5 (Visit Requirements). After the end of treatment, each subject will be followed for 30 days for adverse event monitoring (serious adverse events will be collected for 90 days after the end of treatment as described in Section 7.2.3.1). Subjects who discontinue for reasons other than progressive disease will have post-treatment follow-up for disease status until disease progression, initiating a non-study cancer treatment, withdrawing consent or becoming lost to follow-up. After documented disease progression each subject will be followed by telephone for overall survival until death, withdrawal of consent, or the end of the study, whichever occurs first.

### **5.7.1 Discontinuation of Study Therapy after CR**

Discontinuation of treatment may be considered for subjects who have attained a confirmed CR that have been treated for at least 24 weeks with pembrolizumab and XL888 and had at least two treatments with pembrolizumab and XL888 beyond the date when the initial CR was declared. Subjects who then experience radiographic disease progression may be eligible for additional treatment with pembrolizumab and XL888 via the Second Course Phase at the discretion of the investigator as detailed in Section 7.1.6.2.

### **5.7.2 Subject Replacement Strategy**

Patients who do not complete the intended course of chemotherapy due to reasons other than toxicity will be considered as in-evaluable for the primary endpoint and will be replaced.

[illegible]

Trial Period:	Treatment Cycles <sup>a</sup>									End of Treatment	Post-Treatment		
Treatment Cycle/Title:	Main Study Screening (Visit 2)	1	2	3	4	5	To be repeated beyond 8 cycles			Discon	Safety Follow-up	Follow Up Visits <sup>b</sup>	Survival Follow-Up
Scheduling Window (Days):	-28 to -1	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days post discon ± 7 days	Every 8 weeks post discon	Every 12 weeks
Comprehensive Serum Chemistry Panel	X	X	X	X	X	X	X	X	X	X	X	X	
Fasting triglyceride, cholesterol and glucose	X			X				X					
Urinalysis	X			X				X		X			
T3, FT4 and TSH	X		X			X			X	X	X		
ECG <sup>g</sup>	X	X	X		X		X <sup>g</sup>		X <sup>g</sup>				
Tumor Imaging	X <sup>f</sup>			X <sup>h</sup>			X <sup>h</sup>						
Archival or Newly Obtained Tissue Collection <sup>i</sup>	X	X											
Correlative Studies Blood Collection <sup>j</sup>	X	X	X	X						X			

- Treatment cycles are 3 weeks
- Only for patients with ongoing treatment related toxicities
- Pembrolizumab will be given day 1, XL888 twice weekly orally
- ECOG performance status should be done within 10 days or less from day 1 of cycle 1
- Ophthalmologic exam done at baseline and repeated only if there are symptoms
- Baseline imaging with 8 weeks of day 1 is acceptable
- ECG day1 2 to 3 hours after administration of XL888 every other cycle after C2 (C1, C2, C4, C6 etc)
- Scans will be done every 3 cycles between day 15 and day 21
- Paired biopsies will only be obtained from 16 patients on the dose expansion cohort
- Samples will be collected at baseline, day 15, and every cycle for the first 9 weeks. Analysis will include proportion of T, B, NK, memory and effector T cell subsets and expression of PD-1, PD-L1 and B7 family members. Samples will be collected at baseline and on weeks 6 and 9. This will be performed using interferon- gamma and CD107.

## **7.0 TRIAL PROCEDURES**

### **7.1 Trial Procedures**

The Trial Flow Chart - Section 6.0 summarizes the trial procedures to be performed at each visit. Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator.

#### **7.1.1 Administrative Procedures**

##### **7.1.1.1 Informed Consent**

The Investigator must obtain documented consent from each potential subject prior to participating in a clinical trial.

##### **General Informed Consent**

Consent must be documented by the subject's dated signature or by the subject's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent form should be given to the subject before participation in the trial.

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the subject must receive the IRB/ERC's approval/favorable opinion in advance of use. The subject or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the subject's dated signature or by the subject's legally acceptable representative's dated signature.

The informed consent will adhere to IRB/ERC requirements, applicable laws and regulations and Sponsor requirements.

##### **7.1.1.2 Inclusion/Exclusion Criteria**

All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the subject qualifies for the trial.

##### **7.1.1.3 Medical History**

A medical history will be obtained by the investigator or qualified designee. Medical history will include all active conditions, and any condition diagnosed within the prior 10 years that are considered to be clinically significant by the Investigator. Details regarding the disease for

which the subject has enrolled in this study will be recorded separately and not listed as medical history.

#### **7.1.1.4 Prior and Concomitant Medications Review**

##### **Prior Medications**

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the subject within 28 days before starting the trial. Treatment for the disease for which the subject has enrolled in this study will be recorded separately and not listed as a prior medication.

##### **Concomitant Medications**

The investigator or qualified designee will record medication, if any, taken by the subject during the trial. All medications related to reportable SAEs and ECIs should be recorded as defined in Section 7.2.

#### **7.1.1.5 Disease Details and Treatments**

##### **Disease Details**

The investigator or qualified designee will obtain prior and current details regarding disease status.

##### **Prior Treatment Details**

The investigator or qualified designee will review all prior cancer treatments including systemic treatments, radiation and surgeries.

##### **Subsequent Anti-Cancer Therapy Status**

The investigator or qualified designee will review all new anti-neoplastic therapy initiated after the last dose of trial treatment. If a subject initiates a new anti-cancer therapy within 30 days after the last dose of trial treatment, the 30 day Safety Follow-up visit must occur before the first dose of the new therapy. Once new anti-cancer therapy has been initiated the subject will move into survival follow-up.

#### **7.1.1.6 Trial Compliance (Medication/Diet/Activity/Other)**

Compliance with XL888 will be determined using drug diary and pill counts performed on day 1 of each cycle. Patients who take less than 80% of their prescribed dose of pembrolizumab and/or XL888 due to reasons other than toxicity will be considered inevaluable for the primary endpoint of toxicity and will be replaced.

## **7.1.2 Clinical Procedures/Assessments**

### **7.1.2.1 Adverse Event (AE) Monitoring**

The investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs as specified in the Trial Flow Chart and more frequently if clinically indicated. Adverse experiences will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 4.0 (see Section 11.2). Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

For subjects receiving treatment with pembrolizumab all AEs of unknown etiology associated with pembrolizumab exposure should be evaluated to determine if it is possibly an event of clinical interest (ECI) of a potentially immunologic etiology (termed immune-related adverse events, or irAEs). .

Please refer to section 7.2 for detailed information regarding the assessment and recording of AEs.

Winship Cancer Institute's Clinical Trials Office will perform the quality assurance and quality control checks on this clinical trial. Before enrollment of any subject in this study, CTO personnel and the Investigator will review the protocol; the Investigator's Brochure; the CRFs/electronic CRFs and instructions for completion; the informed consent process; and the procedure for reporting AEs and SAEs.

### **7.1.2.2 Full Physical Exam**

The investigator or qualified designee will perform a complete physical exam during the screening period. Clinically significant abnormal findings should be recorded as medical history. A full physical exam should be performed during screening,

### **7.1.2.3 Directed Physical Exam**

For cycles that do not require a full physical exam per the Trial Flow Chart, the investigator or qualified designee will perform a directed physical exam as clinically indicated prior to trial treatment administration.

### **7.1.2.4 Vital Signs**

The investigator or qualified designee will take vital signs at screening, prior to the administration of each dose of trial treatment and at treatment discontinuation as specified in the Trial Flow Chart (Section 6.0). Vital signs should include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at screening only.

#### **7.1.2.5 Eastern Cooperative Oncology Group (ECOG) Performance Scale**

The investigator or qualified designee will assess ECOG status (see Section 11.1) at screening (within 10 days of day 1 cycle 1), prior to the administration of each dose of trial treatment and discontinuation of trial treatment as specified in the Trial Flow Chart.

#### **7.1.2.6 Tumor Imaging and Assessment of Disease: Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 Criteria for Evaluating Response in Solid Tumors**

RECIST version 1.1\* will be used in this study for assessment of tumor response. While either CT or MRI may be utilized, as per RECIST 1.1, CT is the preferred imaging technique in this study.

#### **7.1.2.7 Tumor Tissue Collection and Correlative Studies Blood Sampling**

Pre- and post- treatment tumor biopsies will be obtained from 16 patients enrolled on the expansion phase. Patients will sign the optional biopsy consent prior to starting treatment and will be assigned to either start pembrolizumab or pembrolizumab/XL888 for the first cycle. Biopsies will be obtained within 4 weeks prior to the first dose of study therapy (biopsy #1) and then during the third week between Day 14 and Day 20. At least three core biopsies will be obtained at the time of the biopsy (unless limited for technical/safety reasons). The obtained tissues will be handled in the following way:

- 1) RNAlater for RNA stabilization and tissue storage
- 2) Formalin-fixed paraffin block with one cut H&E stained slide
- 3) Liquid nitrogen frozen tissue in cryo-preservation vials

All collected tissues are stabilized and stored in -80°C freezers (RNAlater stabilized, OCT embedded, short term storage) or the vapor phase of a liquid nitrogen freezer (long term storage) in single use aliquots. All FFPE tissue blocks are stored in a climate controlled storage room that is temperature (less than 27°C) and humidity controlled.

Tissue will be evaluated using IHC for CD3, CD4, CD8, CD163, PD-1, PD-2, PDL-1, MIF, TAM and stromal/ vascular markers. Tissue will also be dissociated and flow cytometry will be used to determine the characteristics of macrophages and lymphocytes. Genomic (transcriptome) profiling will be performed on tissue and lymphocytes.

#### **Peripheral blood samples**

Approximately 10 mL of peripheral blood samples will be collected prior to initiation of study therapy, on day 1 of the first 3 cycles. The peripheral blood mononuclear cells will be isolated from these samples and stored in -80°C freezers until analysis. Samples will be evaluated for:

- i. Determine whether there is an increase in expression of T-cell co-stimulatory markers in PBMCs after treatment. Samples will be collected at baseline and every other week for the first 9 weeks. Analysis will include proportion of T, B, NK, memory and effector T cell subsets and expression of PD-1, PD-L1 and B7 family members.
- ii. Determine whether changes in ex vivo functional assays for PBMCs post treatment correlate with response. Samples will be collected at baseline and on weeks 6 and 9. This will be performed using interferon- gamma and CD107.

Shipping and handling instructions

After appropriate processing, the frozen samples will be sent to:

Lesinski Laboratory  
Suite C3054, Bay 17  
1365-C Clifton Rd NE  
Winship Cancer Institute of Emory University  
Atlanta, GA 30322

Table 5 Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood	Serum $\beta$ -human chorionic gonadotropin†
Hemoglobin	Alkaline phosphatase	Glucose	( $\beta$ -hCG)†
Platelet count	Alanine aminotransferase (ALT)	Protein	PT (INR)
WBC (total and differential)	Aspartate aminotransferase (AST)	Specific gravity	aPTT
Red Blood Cell Count	Lactate dehydrogenase (LDH)	Microscopic exam ( <i>If abnormal</i> )	Total triiodothyronine (T3)
Absolute Neutrophil Count	Carbon Dioxide ‡	results are noted	Free tyroxine (T4)
Absolute Lymphocyte Count	( $CO_2$ or biocarbonate)	Urine pregnancy test †	Thyroid stimulating hormone (TSH)
	Calcium		
	Chloride		Blood for correlative studies
	Glucose		
	Phosphorus		
	Potassium		
	Sodium		
	Magnesium		
	Total Bilirubin		
	Direct Bilirubin ( <i>If total bilirubin is elevated above the upper limit of normal</i> )		
	Total protein		
	Blood Urea Nitrogen		
† Perform on women of childbearing potential only. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required.			
‡ If considered standard of care in your region.			

### **7.1.3 Other Procedures**

#### **Withdrawal/Discontinuation**

When a subject discontinues/withdraws prior to trial completion, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.2 - Assessing and Recording Adverse Events. Subjects who a) attain a CR or b) complete 24 months of treatment with pembrolizumab may discontinue treatment with the option of restarting treatment if they meet the criteria specified in Section 7.1.5.5. After discontinuing treatment following assessment of CR, these subjects should return to the site for a Safety Follow-up Visit (described in Section 7.1.5.3.1) and then proceed to the Follow-Up Period of the study (described in Section 7.1.5.4).

### **7.1.4 Visit Requirements**

Visit requirements are outlined in Section 6.0 - Trial Flow Chart. Specific procedure-related details are provided above in Section 7.1 - Trial Procedures.

#### **7.1.4.1 Screening**

##### **7.1.4.1.1 Screening Period**

All subjects must sign an informed consent document prior to the initiation of any study related procedures. The informed consent document must be signed within 28 days of Cycle 1 Day 1. Screening procedures (with the exception of the scans) are to be conducted within 28 days of Cycle 1 Day 1.

- Review of study eligibility criteria
- Medical History
- Record concomitant medications taken up to 28 days prior to day 1 cycle 1
  - Vitals [temperature, heart rate (HR), blood pressure (BP) and respiratory rate (RR)]
  - Physical Examination, including height and weight
  - Ophthalmologic exam- baseline
  - ECOG Performance Status evaluation (within 10 days or less of cycle 1 day 1)
  - Laboratory Assessments
    - Hematology: hemoglobin, hematocrit, red blood cell count, white blood cell count with differential and platelet count

- Serum chemistry: sodium, potassium, chloride, bicarbonate, magnesium, calcium, phosphorus, blood urea nitrogen, creatinine, total bilirubin, LDH, total protein, ALP, ALT, AST, and albumin. Fasting triglycerides, cholesterol and glucose.
- Serum or urine pregnancy test for women of childbearing potential
- Prothrombin time (PT) and activated partial thromboplastin time (aPTT)
- Urinalysis
- Tumor markers(when applicable such as known elevated tumor markers): CEA, CA19-9, or  $\alpha$ -fetoprotein
- T3, FT4, TSH
- HIV, HBsAg, HCV RNA if clinically indicated
- 12-lead ECG
- Ophthalmologic exam
- Radiologic imaging studies to evaluate tumor status. contrast computed tomography (CT) or magnetic resonance imaging (MRI) of the chest and abdomen and pelvis. Additional imaging may be obtained as clinically indicated. Baseline scans may be done within 8 weeks prior to cycle 1 day 1.
- Baseline fresh biopsy (in selected group) will be obtained with 28 days of day1 cycle 1 and after consent is signed.

#### **7.1.4.2 Treatment Period**

##### **7.1.4.1 Day 1 ( $\pm 3$ days) of each cycle**

- Record concomitant medications
  - Vitals (temperature, HR, BP and RR)
  - History and physical exam, pill diary (prior cycle see section 11.4) and pill count (prior cycle)
  - ECOG performance status
  - Toxicity assessment
  - 12 lead ECG after XL888 administration in cycle 1, cycle 2 and every other cycle
    - Laboratory Assessments

- Hematology hemoglobin, hematocrit, red blood cell count, white blood cell count with differential and platelet count
  - Chemistry sodium, potassium, chloride, bicarbonate, magnesium, calcium, phosphorus, blood urea nitrogen, creatinine, glucose (random), total bilirubin, LDH, total protein, ALP, ALT, AST, and albumin
  - Tumor markers - when applicable
  - Fasting Lipid profile every 3 cycles starting Cycle 4 (i.e C4D1, C7D1, C10D1, C13D1 etc)
  - Urinalysis every 3 cycles starting Cycle 4 (i.e C4D1, C7D1, C11D1 etc)
    - T3, FT4, TSH cycle 2 and then after every 3 cycle
    - For the cycle 1 day 1 labs, blood samples from the screening tests maybe used if completed within 1 week of day 1
- Blood sample 20 cc for correlative work (only cycle 1, 2, 3)
  - Pembrolizumab 200 mg will be administered as a 30 minute IV infusion every 3 weeks. Given the variability of infusion pumps, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min).
- XL888 will be administered orally in the infusion center (first dose of each cycle only) prior to pembrolizumab. **(in selected case in patients receiving paired biopsies XL888 will be held in cycle 1)**

#### 7.1.4.2 Days 4, 8, 11, 15 and 18

- XL888 dose administered and diary completed

#### 7.1.4.3 Days 8 and 15 ( $\pm 1$ day) in cycle 1 and 2 ONLY

- Record concomitant medications
- Vitals (temperature, HR, BP and RR)
- History and physical exam
- ECOG performance status
- [Toxicity assessment](#)
- Blood for correlative assays on Day 15 of cycle 1
- Laboratory Assessments

- Chemistry sodium, potassium, chloride, bicarbonate, magnesium, calcium, phosphorus, blood urea nitrogen, creatinine, glucose (random), total bilirubin, LDH, total protein, ALP, ALT, AST, and albumin

#### **7.1.4.3 Between days 14-21 cycle 1**

- Repeat biopsy in selected cases.

#### **7.1.4.4 Every 3 cycles between day 15 and 21 (C3D15-D21, C6D15-21, etc)**

- Repeat cross sectional imaging (CT or MRI)

#### **7.1.4.5 End of treatment visit**

- Record concomitant medications
  - Vitals (temperature, HR, BP and RR)
  - History and physical exam
  - ECOG performance status
  - Toxicity assessment
    - Laboratory Assessments
      - Hematology hemoglobin, hematocrit, red blood cell count, white blood cell count with differential and platelet count
      - Chemistry sodium, potassium, chloride, bicarbonate, magnesium, calcium, phosphorus, blood urea nitrogen, creatinine, glucose (random), total bilirubin, LDH, total protein, ALP, ALT, AST, and albumin
      - Tumor markers - when applicable
      - T3, FT4, TSH cycle 2 and then after every 3 cycle
- Blood sample 20 cc for correlative work

#### **7.1.5 Safety Follow-Up Visit**

The mandatory Safety Follow-Up Visit should be conducted approximately 30 days after the last dose of trial treatment or before the initiation of a new anti-cancer treatment, whichever comes first. All AEs that occur prior to the Safety Follow-Up Visit should be recorded. Subjects with an AE of Grade > 1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new anti-neoplastic therapy, whichever occurs first. SAEs that occur within 90 days of the end of treatment or before initiation of a new anti-cancer treatment should also be followed and recorded. Subjects who are eligible for retreatment with pembrolizumab/XL888 (as described in Section 7.1.6.2) may have up to two safety follow-up visits, one after the Treatment Period and one after the Second Course Phase.

### **7.1.6 Follow-up Visits**

Subjects who discontinue trial treatment for a reason other than disease progression will move into the Follow-Up Phase and should be assessed every 6 weeks ( $42 \pm 7$  days) by radiologic imaging to monitor disease status. After 1 year, the imaging time point will occur every 9 weeks ( $\pm 7$  days). Every effort should be made to collect information regarding disease status until the start of new anti-neoplastic therapy, disease progression, death, end of the study or if the subject begins retreatment with pembrolizumab/ XL888 as detailed in Section 7.1.6.2. Information regarding post-study anti-neoplastic treatment will be collected if new treatment is initiated.

Subjects who are eligible to receive retreatment with pembrolizumab/ XL888 according to the criteria in Section 7.1.6.2 will move from the follow-up phase to the Second Course Phase when they experience disease progression. Details are provided in Section 6.2 – Trial Flow Chart for Retreatment.

#### **7.1.6.1 Survival Follow-up**

Once a subject experiences confirmed disease progression or starts a new anti-cancer therapy, the subject moves into the survival follow-up phase and should be contacted by telephone every 12 weeks to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

#### **7.1.6.2 Second Course Phase (Retreatment Period)**

Subjects who stop pembrolizumab/ XL888 with SD or better may be eligible for up to one year of additional pembrolizumab/ XL888 therapy if they progress after stopping study treatment. This retreatment is termed the Second Course Phase of this study and is only available if the study remains open and the subject meets the following conditions:

- **Either**
  - Stopped initial treatment with pembrolizumab/ XL888 after attaining an investigator-determined confirmed CR according to RECIST 1.1, and
    - Was treated for at least 24 weeks with pembrolizumab/ XL888 before discontinuing therapy
    - Received at least two treatments with pembrolizumab/ XL888 beyond the date when the initial CR was declared
- OR**
- Had SD, PR or CR and stopped pembrolizumab/ XL888 treatment after 24 months of study therapy for reasons other than disease progression or intolerability

**AND**

- Experienced an investigator-determined confirmed radiographic disease progression after stopping their initial treatment with pembrolizumab/ XL888
- Did not receive any anti-cancer treatment since the last dose of pembrolizumab/ XL888
- Has a performance status of 0 or 1 on the ECOG Performance Scale
- Demonstrates adequate organ function as detailed in Section 5.1.2
- Female subject of childbearing potential should have a negative serum or urine pregnancy test within 72 hours prior to receiving retreatment with study medication.
- Female subject of childbearing potential should be willing to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study medication (Reference Section 5.7.2). Subjects of child bearing potential are those who have not been surgically sterilized or have been free from menses for > 1 year.
- Male subject should agree to use an adequate method of contraception starting with the first dose of study therapy through 120 days after the last dose of study therapy.
- Does not have a history or current evidence of any condition, therapy, or laboratory abnormality that might 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.

Subjects who restart treatment will be retreated at the same dose and dose interval as when they last received pembrolizumab/ XL888. Treatment will be administered for up to one additional year.

Visit requirements are outlined in Section 6.0 – Trial Flow Chart.

## **7.2 Assessing and Recording Adverse Events**

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 investigational products, 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.

Investigational products include pembrolizumab and XL888.

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

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 7.2.4. The investigator will make every attempt to follow all subjects with non-serious adverse events for outcome.

### **7.2.1 Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor and to Merck/ Exelixis**

For purposes of this trial, an overdose of pembrolizumab will be defined as any dose of 1,000 mg or greater ( $\geq 5$  times the indicated dose). Overdose of XL888 is defined as  $\geq$  double 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 an investigational product, the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met.

If a dose of investigational 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 to Merck Global Safety (Attn: Worldwide Product Safety; FAX 215 993-1220) and Exelixis (FAX 1-650-837-7392).

### 7.2.2 Reporting of Pregnancy and Lactation to the Sponsor and to Merck/ Exelixis

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 investigational products, 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 Exelixis (FAX 1-650-837-7392) and Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220)

### 7.2.3 Serious Adverse Events

A serious adverse event is any adverse event occurring at any dose or during any use of investigational product that:

- Results in death;
- Is life threatening;
- Results in persistent or significant disability/incapacity;
- Results in or prolongs an existing inpatient hospitalization;
- Is a congenital anomaly/birth defect;
- 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 and Exelixis in the same timeframe as SAEs to meet certain local requirements. Therefore, these events are considered serious by Merck/ Exelixis for collection purposes.
  - Is a new cancer (that is not a condition of the study);

- 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 that occurs to any subject must be reported within 24 hours to Sponsor and within 2 working days to Merck Global Safety and Exelixis 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 whether or not related to the Exelixis and Merck product, must be reported within 24 hours to sponsor and within 2 working days to Exelixis and Merck Global Safety.

Serious adverse events related to study treatment or study procedures must be recorded even if the SAE occurs more than 30 days after cessation of treatment and also must be reported immediately to the Sponsor and to Exelixis and Merck Global Safety.

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

#### **7.2.4 Immediate Reporting of Adverse Events to the Sponsor, Merck and Exelixis**

**All SAE must be recorded on a MedWatch 3500 Form. SAE reports and any other relevant safety information are to be forwarded to**

**Merck Global Safety**  
**Facsimile number: +1-215-993-1220**

**Exelixis**  
**Facsimile number: 1-650-837-7392**

MedWatch 3500 Reporting Guidelines:

*Note: MedWatch 3500 forms and other information related to MedWatch reporting are available at <http://www.fda.gov/medwatch/index.html>.*

All 15 Day Reports and Annual Progress Reports will be submitted by the sponsor as required by FDA. 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 Exelixis (FAX 1-650-837-

7392) and Merck & Co., Inc. (Attn: Worldwide Product Safety; FAX 215 993-1220) at the time of submission to FDA.

#### **7.2.4.1 Events of Clinical Interest**

Serious adverse events attributed to investigational agent as detailed in section 5.3.1 and 5.3.2 must be reported within 24 hours to the Sponsor and within 2 working days to Exelixis (FAX 1-650-837-7392) and 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 Exelixis and 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 Exelixis and Merck product, must be reported within 24 hours to the Sponsor and within 24 hours to Exelixis and Merck Global Safety.

#### **7.2.5 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.

### **7.3 Reporting Requirements for IND holders**

For Investigator-sponsored IND studies, reporting requirements for the FDA apply in accordance with the guidance set forth in 21 CFR, Part 312.32. Events meeting the following criteria need to be submitted to the FDA as Expedited IND Safety Reports.

#### **7 Calendar-Day Telephone or Fax Report**

The Sponsor-Investigator is required to notify the FDA of a fatal or life-threatening adverse event that is unexpected and assessed by the investigator to be possibly related to the use of *investigational agents*. An unexpected adverse event is one that is not already described in the most recent Guidance for Investigator section of the Investigator's Brochure. Such reports are

to be telephoned or faxed to the FDA, Merck and Exelixis within 7 calendar days of the first learning of the event.

15 Calendar-Day Written Report

The Sponsor-Investigator is also required to notify the FDA and all participating investigators, in a written IND Safety Report, of any serious unexpected adverse event that is considered reasonably or possibly related to the use of investigational agent.

Written IND Safety Reports with analysis of similar events are to be submitted to the FDA, Exelixis, and Merck within 15 calendar days of first learning of the event. The FDA prefers these reports on a MedWatch 3500 Form but alternative formats (eg, summary letter) are acceptable.

FDA Fax number of IND Safety Reports: 1-(800)-FDA-1078

All written IND Safety Reports submitted to the FDA by the Sponsor-Investigator must also be faxed to:

Exelixis Drug Safety  
Fax number: 1-650-837-7392

Merck Global Safety  
facsimile number: 1-215-993-1220

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 mild 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 of 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 investigational 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. A pre-existing condition is a clinical condition that is diagnosed prior to the use of investigational products 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 Sponsor within 24 hours and to Merck and Exelixis 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 Sponsor and to Merck and Exelixis within 2 working days.	

	<b>Other important medical events</b> 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 †).	
<b>Duration</b>	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
<b>Action taken</b>	Did the adverse event cause investigational products to be discontinued?	
<b>Relationship to investigational Product(s)</b>	<p>Did investigational product(s) cause the adverse event? The determination of the likelihood that investigational product(s) 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.</p> <p><b>The following components are to be used to assess the relationship between investigational product and the AE;</b> 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):</p>	
	<b>Exposure</b>	Is there evidence that the subject was actually exposed to investigational product(s) such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
	<b>Time Course</b>	<p>Did the AE follow in a reasonable temporal sequence from administration of investigational product(s)?</p> <p>Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?</p>
	<b>Likely Cause</b>	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors

<b>Relationship to investigational product (continued)</b>	<b>The following components are to be used to assess the relationship between the test drug and the AE: (continued)</b>	
	<b>Dechallenge</b>	<p>Was investigational product(s) discontinued or dose/exposure/frequency reduced?</p> <p>If yes, did the AE resolve or improve?</p> <p>If yes, this is a positive dechallenge. If no, this is a negative dechallenge.</p> <p>(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.)</p>
	<b>Rechallenge</b>	<p>Was the subject re-exposed to investigational product(s) in this study?</p> <p>If yes, did the AE recur or worsen?</p> <p>If yes, this is a positive rechallenge. If no, this is a negative rechallenge.</p> <p>(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).</p> <p>NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY investigational 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.</p>
	<b>Consistency with Trial Treatment Profile</b>	<p>Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding investigational product(s) or drug class pharmacology or toxicology?</p>
<p>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.</p>		
<b>Record one of the following</b>	<b>Use the following scale of criteria as guidance (not all criteria must be present to be indicative of investigational product(s) relationship).</b>	
<b>Yes, there is a reasonable possibility of investigational product(s) relationship.</b>	<p>There is evidence of exposure to investigational product (s) . The temporal sequence of the AE onset relative to the administration of investigational product(s) is reasonable. The AE is more likely explained by investigational product(s) than by another cause.</p>	
<b>No, there is not a reasonable possibility of investigational product(s) relationship</b>	<p>Subject did not receive the investigational product OR temporal sequence of the AE onset relative to administration of investigational product(s) is not reasonable OR the AE is more likely explained by another cause than the Merck product. (Also entered for a subject with overdose without an associated AE.)</p>	

### **7.3.1 Sponsor Responsibility for Reporting Adverse Events**

Written IND safety reports will be submitted to the FDA by the IND sponsor, for serious, unexpected suspected adverse reactions within 15 calendar days of learning of its occurrence. If the event is fatal or is deemed to be life threatening, the report will be made within 7 calendar days. The IND sponsor will also make an assessment of whether the event constitutes an unanticipated problem posing risks to subjects or others (UP). This assessment will be provided to the Emory University IRB, which, in turn will make a final determination. If the Emory IRB determines an event is a UP it will notify the appropriate regulatory agencies and institutional officials.

## **8.0 STATISTICAL ANALYSIS PLAN**

### **8.1 Determination of Sample Size**

This is a 3+3 standard phase I trial design. The plan is to evaluate two dose cohorts- 45mg and 90 mg. An intermediate dose cohort (60 mg) will be evaluated only if we observe 2 or more DLT's in the 3 or 6 patients enrolled on the 90mg dose. If we observe 2 dose limiting toxicities on dose level 1, then the study will be completed with three patients (minimal number of patients). If we observe two DLT in the first three patients on dose level 1, the study will stop and the principal investigator will discuss at that point whether a lower dose level of XL888 should be tested. If we do not observe any dose limiting toxicities the study will require 9 patients. If we observe one dose limiting toxicity per dose level (maximum number of patient), then the study would require 18 patients. Therefore the phase part sample size can range from 3 to 18 patients. Expansion phase will be started once the recommended phase II dose (RP2D) is determined. Given minimal activity of checkpoint inhibitors in colorectal and pancreatic cancer, an overall response rate of the combination of PD-1 plus HSP90 inhibitor of 20% would be considered clinically significant. With an alpha of 0.1, and power of 80% (relaxed due to the pilot preliminary nature of this proposal) a total of 16 patients should be sufficient to make this determination. We will also obtain biologic endpoints with the paired biopsy samples that can help further develop the combination and understand its role in GI cancers. We plan to enroll 32 patients on the RP2D level with 16 patients per cohort (pancreas and colorectal cancer). Patients in the expansion phase will be assigned to treatment arms by PI (MK-3475 or MK-3475 plus XL-888). After the first 3 weeks all patients will receive the combination therapy. There is no planned comparison between the two arms. The aim of the expansion phase is to confirm the safety profile and tolerability of the regimen in patients with pancreatic and colorectal cancer.

The total number of patients will range from 38 to 50 patients.

### **8.2 Stopping Rules**

Not Applicable

### **8.3 Statistical and Analytical Plans**

Summary statistics will be presented for all safety, efficacy and biomarker parameter analyses. The purpose of these analyses is hypothesis generating and therefore, formal statistical testing will not be performed. Various exploratory statistical tests may be applied to data generated from this trial to generate hypotheses to be tested in subsequent trials. In general, data for continuous parameters will be presented using descriptive statistics including sample size, mean, and median; standard deviation; and minimum and maximum. Categorical parameters (such as pathologic response rate) will be displayed using counts and percentages. Toxicities will be presented as worst toxicity per patient and will be reported as percent toxicity.

### **8.4 Analysis Sets**

All subjects who receive any amount of study drug will be included in the evaluation of safety and efficacy, except for patients who take less than 80% of their prescribed dose of pembrolizumab and/or XL888 since they will be considered inevaluable for the primary endpoint of toxicity.

### **8.5 Subject Disposition and Baseline Characteristics**

The number and percentage of subjects who enrolled, were treated, and who discontinued will be tabulated. The reasons for treatment and study discontinuation will be presented. Demographic and other baseline characteristics will be summarized using descriptive statistics or counts and percentages, as appropriate.

### **8.6 Safety Analysis**

#### **8.6.1.1 Adverse Events**

Adverse events will be classified using MedDRA System Organ Classes and Preferred Terms. Furthermore, SAEs, AEs with a severity grade of 3 or above using NCI CTCAE version 4.0, AEs deemed related to study drug, AEs leading to discontinuation of study drug, and AEs leading to death will also be summarized in preferred term by system organ class and listed on an individual subject basis.

#### **8.6.1.2 Laboratory Data**

Descriptive statistics for worst grade of each laboratory parameter by the NCI CTCAE scale version 4.0 at baseline and follow-up will be presented along with change from Baseline. Additionally, laboratory values  $\geq$  Grade 3 severity will be tabulated and listed on an individual subject basis.

#### **8.6.1.3 Dose Modifications and Reasons**

The number of subjects with skipped doses, dose delays and dose reductions as well as major reasons for dose modifications will be summarized.

## 9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

### 9.1 Investigational Product

#### 9.1.1 Pembrolizumab

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

Clinical Supplies will be provided by Merck as summarized in Table 7.

Table 7 Product Descriptions

Product Name & Potency	Dosage Form
Pembrolizumab 50 mg	Lyophilized Powder for Injection
Pembrolizumab 100 mg/ 4mL	Solution for Injection

#### 9.1.2 Packaging and Labeling Information

Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

#### 9.1.3 Clinical Supplies Disclosure

This trial is open-label; therefore, the subject, the trial site personnel, the Sponsor and/or designee are not blinded to treatment. Drug identity (name, strength) is included in the label text; random code/disclosure envelopes or lists are not provided.

#### 9.1.4 Storage and Handling Requirements

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label.

Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site.

Clinical supplies may not be used for any purpose other than that stated in the protocol.

### **9.1.5 Returns and Reconciliation**

The investigator is responsible for keeping accurate records of the clinical supplies received from Merck or designee, the amount dispensed to and returned by the subjects and the amount remaining at the conclusion of the trial.

Upon completion or termination of the study, all unused and/or partially used investigational product will be destroyed at the site per institutional policy. It is the Investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

### **9.1.6 Dose Selection**

#### **9.1.6.1 Dose Selection**

The rationale for selection of doses to be used in this trial is provided in Section 4.0 – Background and Rationale.

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

## **9.2 XL888**

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of investigational product in accordance with the protocol and any applicable laws and regulations

**9.2.1 Storage and Handling:** XL888 will be supplied as an amorphous spray-dried solid dispersion (SDSD) capsule formulation. The XL888 drug product is available in capsule strengths of 15 mg (Opaque White) and 45 mg (Swedish Orange) in Size 0 hard gelatin capsules. Both the 15 mg and 45 mg capsules are packaged in high-density polyethylene (HDPE) bottles with child-resistant caps.

The storage conditions are room temperature 15-30 °C for XL888 powder, suspension vehicle, and capsules. Clinical supplies will be stored in a secure, limited-access location under the storage conditions specified on the label in the Investigational Drug Pharmacy (IDS).

Eligible subjects will receive XL888 under the direction of a physician identified on the US Food and Drug Administration (FDA) form 1572. Receipt and dispensing of trial medication must be recorded by an authorized person in IDS.

Clinical supplies will not be used for any purpose other than that stated in the protocol.

### **9.1.2 Returns and Reconciliation**

The investigator is responsible for keeping accurate records of the clinical supplies received from Exelixis, the amount dispensed to and returned by the subjects and the amount remaining at the conclusion of the trial.

Upon completion or termination of the study, all unused and/or partially used investigational product will be destroyed at the site per institutional policy. It is the Investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

## **10.0 ADMINISTRATIVE AND REGULATORY DETAILS**

### **10.1 Compliance with Trial Registration and Results Posting Requirements**

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the Sponsor of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to the Clinical Trials Data Bank, <http://www.clinicaltrials.gov>. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

### **10.2           Prestudy Documentation**

The Sponsor-Investigator must provide Merck/ Exelixis with the following documents prior to the enrollment of any subjects:

- Copy of the IRB/IEC approval letter for protocol, informed consent, Investigator and site
- Signed and dated current curricula vitae of the investigator
- Copy of approved informed consent document
- Copy of the FDA letter and IND receipt and number assignment
- Signed Clinical Trial Agreement

### **10.3           Protocol Adherence**

By signing the Form FDA 1572, the Investigator agrees to conduct the study according to the protocol and the FDA regulations set forth in 21 CFR Parts 50, 54, 56, and 312.

### **10.4           Retention of Study Documents**

All documentation of adverse events, records of study drug receipt and dispensation, and all IRB correspondence will be maintained for at least 2 years after the investigation is completed.

## **10.5 Data Management**

The Data and Safety Monitoring Committee (DSMC) of the Winship Cancer Institute will provide oversight for the conduct of this study. The DSMC functions independently within Winship Cancer Institute to conduct internal monitoring functions to ensure that research being conducted by Winship Cancer Institute Investigators produces high-quality scientific data in a manner consistent with good clinical practice (GCP) and appropriate regulations that govern clinical research. Depending on the risk level of the protocol, the DSMC review may occur every 6 months or annually. For studies deemed High Risk, initial study monitoring will occur within 6 months from the date of the first subject accrued, with 2 of the first 5 subjects being reviewed. For studies deemed Moderate Risk, initial study monitoring will occur within 1 year from the date of the first subject accrued, with 2 of the first 5 subjects being reviewed. Subsequent monitoring will occur in routine intervals per the Winship Data and Safety Monitoring Plan (DSMP).

The DSMC will review pertinent aspects of the study to assess subject safety, compliance with the protocol, data collection, and risk-benefit ratio. Specifically, the Winship Cancer Institute Internal Monitors assigned to the DSMC may verify informed consent, eligibility, data entry, accuracy and availability of source documents, AEs/SAEs, and essential regulatory documents. Following the monitoring review, monitors will provide a preliminary report of monitoring findings to the PI and other pertinent individuals involved in the conduct of the study. The PI is required to address and respond to all the deficiencies noted in the preliminary report. Prior to the completion of the final summary report, monitors will discuss the preliminary report responses with the PI and other team members (when appropriate). A final monitoring summary report will then be prepared by the monitor. Final DSMC review will include the final monitoring summary report with corresponding PI response, submitted CAPA (when applicable), PI Summary statement, and available aggregate toxicity and safety data.

The DSMC will render a recommendation and rating based on the overall trial conduct. The PI is responsible for ensuring that instances of egregious data insufficiencies are reported to the IRB. Continuing Review submissions will include the DSMC recommendation letter. Should any revisions be made to the protocol-specific monitoring plan after initial DSMC approval, the PI will be responsible for notifying the DSMC of such changes. The Committee reserves the right to conduct additional audits if necessary.

Dose escalation decisions will be done at the GI working group. The PI or designee must obtain approval from the DSMC for dose escalation. The PI will provide an update on all relevant safety data of patients entered to a dose level to the DSMC when dose escalation is planned.

Dr. Alese and the investigators, the clinical research coordinator and the regulatory affairs coordinator will meet to review and discuss study data to ensure subject safety. During the meetings the PI or co-I will review the eligibility criteria for each new patient. In addition, during these meeting the group will review all the toxicity (AE/SAE) logs, random checks of case report form completion and roadmap for each patient on the trial. All study personnel will be trained on the protocol by the PI or co-I. Study personnel will sign training log prior to being

included on delegation of authority log. All AE and SAE will be handled according to Section 7.2 which provides detailed instructions on reporting requirements.

## 11.0 APPENDICES

### 11.1 ECOG Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.
* As published in Am. J. Clin. Oncol.: Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982. The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.	

### 11.2 Common Terminology Criteria for Adverse Events V4.0 (CTCAE)

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for adverse event reporting. (<http://ctep.cancer.gov/reporting/ctc.html>)

### 11.3 Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 Criteria for Evaluating Response in Solid Tumors

RECIST version 1.1\* will be used in this study for assessment of tumor response. While either CT or MRI may be utilized, as per RECIST 1.1, CT is the preferred imaging technique in this study.

\* As published in the European Journal of Cancer:

E.A. Eisenhauer, P. Therasse, J. Bogaerts, L.H. Schwartz, D. Sargent, R. Ford, J. Dancey, S. Arbuck, S. Gwyther, M. Mooney, L. Rubinstein, L. Shankar, L. Dodd, R. Kaplan, D. Lacombe, J. Verweij. New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1). Eur J Cancer. 2009 Jan;45(2):228-47.

In addition, volumetric analysis will be explored by central review for response assessment.

# 11.4 Pill Diary

Protocol	Subject Number	Subject Initials	Visit
WCI	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/>	Cycle <input type="text"/>

## Patient Diary

Please use this diary to record your daily protocol medication.

### XL888 Dose

Please take \_\_\_\_\_ capsules of \_\_\_\_\_ mg

<b>Week 1</b> <b>Date</b>	<b>Day 1</b>	<b>Day 4</b>
Record Time Taken	Time:	Time:

<b>Week 2</b> <b>Date</b>	<b>Day 1</b>	<b>Day 4</b>
Record Time Taken	Time:	Time:

<b>Week 3</b> <b>Date</b>	<b>Day 1</b>	<b>Day 4</b>
Record Time Taken	Time:	Time:

Please sign at the completion of this cycle and **return with pill bottle** to the study team.

Patient's

Signature \_\_\_\_\_ Date \_\_\_\_\_

**Please record all health/medical complaints you may have experienced below.**

Please describe what you experienced	Date Started	Date Stopped

## Other Medications

**Record all medications taken during this cycle for example prescriptions and over the counter including vitamins.**

<b>Name of Medication</b>	<b>Why did you take the medication?</b>	<b>Date Medication Started</b>	<b>Date Medication Stopped</b>

***If you have any questions, please call: \_\_\_\_\_***

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