A PHASE I/IB TRIAL OF MK-3475 (PEMBROLIZUMAB) AND AFATINIB IN EGFR-MUTANT NON-SMALL CELL LUNG CANCER WITH RESISTANCE TO ERLOTINIB

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I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated, in accordance with all stipulations of the protocol and in accordance with Good Clinical Practices, local regulatory requirements, and the Declaration of Helsinki.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study agent(s) and the conduct of the study.

_____
Investigator Name (print)

_____
Investigator Signature

_____
Date

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1.0 TRIAL SUMMARY

Abbreviated Title	MK-3475 and Afatinib in EGFR-Mutant Non-Small Cell Lung Cancer
Trial Phase	Phase I
Clinical Indication	The treatment of subjects with incurable, advanced, metastatic or recurrent non-small cell lung cancer with EGFR activating mutations who have progressive disease either clinically or radiographically on erlotinib.
Trial Type	Interventional
Type of control	N/A
Test product(s)/Route of administration	Afatinib (Oral Tablets) MK-3475 (Intravenous)
Trial Blinding	Unblinded Open-label
Treatment Groups	• Dose De-Escalation of Concurrent afatinib + MK-3475 Dose Expansion: (Cohort A) • Concurrent afatinib + MK-3475 (Cohort B) • Lead in MK-3475 for 2 cycles followed by Concurrent afatinib + MK-3475
Number of trial subjects	A minimum of 9 patients, if trial is terminated early due to unacceptable toxicity and a maximum of 38 patients (18 patients in dose de-escalation cohort plus 20 in the expansion cohorts).
Estimated duration of trial	Approximately 36 months from the time the first subject signs the informed consent until the last subject's last visit.
Duration of Participation	• Patients will be followed through 30 days (+/- 5 days) after the last dose of study drugs. • All new drug related events will be reported for 30 days after the last study drug administration. • AEs will be followed until resolution, return to baseline, or it is deemed that further recovery is unlikely. • Patients 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. • Each subject may receive treatment with MK-3475 for up to 2 years from the time of first dose of MK-3475.

2.0 TRIAL DESIGN

2.1 Trial Design

This is a prospective, non-randomized, open label Phase I clinical trial of intravenous (IV) MK-3475 (pembrolizumab, Keytruda®) and afatinib (oral tablets) in subjects with advanced or metastatic NSCLC with EGFR activating mutations (exon 19 deletion, exon 21 L858R, G719X, L861Q) who have experienced disease progression on erlotinib, gefitinib or osimertinib. It is a phase I dose de-escalation study followed by a phase Ib expansion with two cohorts for further safety evaluation and correlative studies of immune modulation with repeat biopsy and peripheral blood collection.

For the dose de-escalated phase, patients will receive MK-3475 and afatinib as outlined in Table 1 and Section 5.1.5 with escalation of MK-3475 to the maximum tolerated dose (MTD). A fixed dose of MK-3475 (200 mg q3 weeks) will be tested in combination with afatinib starting at the FDA approved dose for EGFR-mutated NSCLC (40 mg PO daily). The dose de-escalation phase will establish the MTD of MK-3475 in combination with afatinib.

Once the MTD is reached, patients will initially be allocated to one of two different arms at this dose: concurrent afatinib + MK-3475 (Arm A) or lead in MK-3475 followed by afatinib + MK-3475 (Arm B). For Arm A, there is no lead-in phase. For Arm B, MK-3475 will be given for 2 cycles (6 weeks) as a lead in followed by combination afatinib and MK-3475. Ten patients will be enrolled for each cohort (20 patients total). These two expansion cohorts will further define toxicities at the MTD in order to determine the recommended phase II dose (RP2D) and to assess initial estimates of efficacy and examine correlative studies-particularly regarding immune modulation of afatinib and MK-3475 between the differing cohorts.

Subjects will be evaluated every 6 weeks with radiographic imaging to assess response to treatment per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1. Adverse events will be monitored throughout the trial and graded in severity according to the guidelines outlined in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Treatment with MK-3475 and afatinib will continue until documented disease progression, 2 years from first cycle of MK-3475 (afatinib may continue past 2 years), unacceptable adverse event(s), intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw the subject, subject withdraws consent, pregnancy of the subject, noncompliance with trial treatment or procedure requirements, or administrative reasons.

After the end of treatment, each subject will be followed for a minimum of 30 days for safety monitoring. Subjects will have post-treatment follow-up for disease status until disease progression, initiating a non-study cancer treatment (such as chemotherapy, other targeted therapy, other treatment for lung cancer), withdrawing consent, or becoming lost to follow-up (progression free survival).

2.2 Trial Diagram

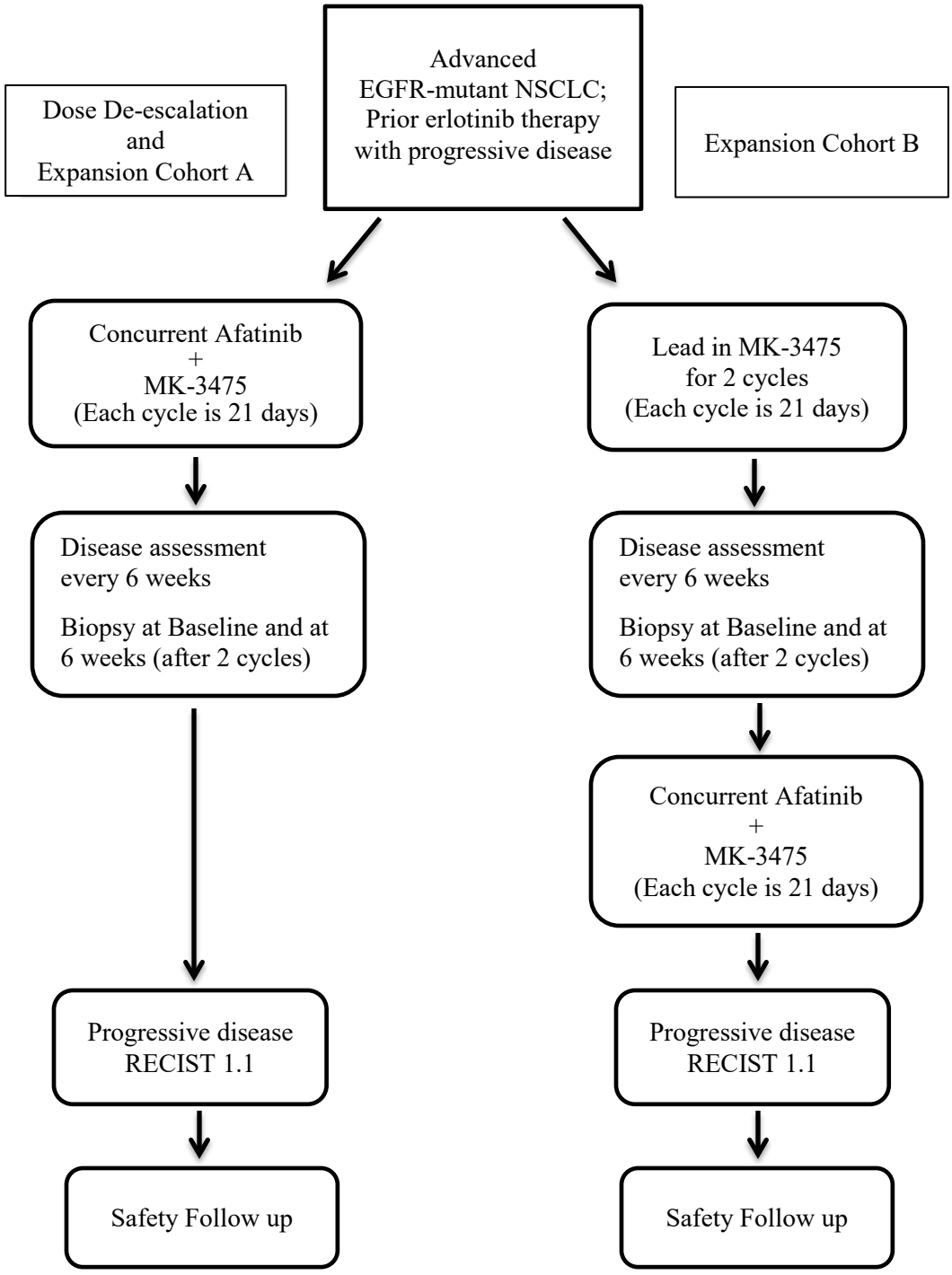


Table 1: Dose De-Escalation Schema

Dose Level	Number of Patients	Afatinib (Daily)	MK-3475 (q3 weeks)
0	**3+**	**40 mg D1**	**200 mg D1**
-1	3+	30 mg D1	200 mg D1
-2	3+	20 mg D1	200 mg D1

Dose Level 0 is the starting combination dose level (in bold). If ≥ 2 patients experience a DLT at dose level 0, the next dose level will be dose level -1. If ≥ 2 patients experience a DLT at dose level -1, the next dose level will be dose level -2.

The phase I dose de-escalation portion of the trial will be closed when the MTD or dose level 0 is reached and six patients have been treated at that dose level.

Please see section 5.1.5 for further details of the dose de-escalation schema.

3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

3.1 Primary Objective & Hypothesis

Objective: To evaluate the safety and tolerability of MK-3475 when given in combination with afatinib in patients with advanced or metastatic non-small cell lung cancer with EGFR activating mutations who have progressive disease on erlotinib.

Hypothesis: We hypothesize that MK-3475 and afatinib will be tolerable and that we can reach an effective maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D).

3.2 Secondary Objective & Hypothesis

Objective: To assess in a preliminary manner the efficacy of this combination (response rate, disease control rate and progression free survival)

Hypothesis: We hypothesize that MK-3475 and afatinib in combination will be efficacious.

3.3 Exploratory Objectives

Objective 1: To determine in an exploratory manner changes in PD-L1 expression in the tumor microenvironment and other immune correlates in blood and in the tumor microenvironment induced by afatinib with concurrent MK-3475 versus MK-3475 preceding combination afatinib/MK-3475.

Objective 2: To determine in an exploratory manner changes in EGFR-mutant plasma DNA in response to treatment with MK-3475 and afatinib.

4.0 BACKGROUND & RATIONALE

4.1 Study Disease

Lung cancer is the leading cause of cancer deaths worldwide due to the majority of patients presenting with metastatic disease for which there is no cure. In recent years, advances in the systemic treatment of non-small cell lung cancer (NSCLC) have increased survival by several months and subsets of patients enjoy prolonged survival beyond two years (Subramanian J, et al. J Thorac Oncol 7:260-5, 2012). More efficacious therapies have been a direct result of our increased understanding and exploitation of the molecular basis of lung cancer. The development of inhibitors to the epidermal growth factor receptor (EGFR) and the resultant blockade of its signaling pathway were the first molecularly targeted agents to improve outcome in this disease (Shepherd FA et al. N Engl J Med 353:123-32, 2005). Patients whose tumors harbor a sensitizing mutation in EGFR derive the most benefit from EGFR tyrosine kinase inhibitor (TKI) therapy (Mok TS et al. N Engl J Med 361:947-57, 2009, Maemondo M. et al. N Engl J Med 362:2380-8, 2010). However, despite impressive responses and significantly prolonged survival in this specialized patient population, all patients develop resistance to EGFR TKIs resulting in tumor progression and death. Concentrated efforts to understand the mechanisms of resistance to EGFR-TKIs are underway. The development of treatment combinations to overcome or delay resistance to erlotinib represents a major unmet need.

4.2 MK-3475

4.2.1 Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades [1]. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies [2; 3; 4; 5; 6]. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells / FoxP3+ regulatory T-cells seems to correlate with improved prognosis and long-term survival in many solid tumors.

The PD-1 receptor-ligand interaction is a major pathway 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) [7; 8]. The structure of murine PD-1 has been resolved [9]. PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable-type (V-type) domain responsible for ligand binding and a cytoplasmic tail which is responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif (ITIM) and an immunoreceptor tyrosine- based switch motif (ITSM). Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3ζ, PKCθ and ZAP70 which are involved in the CD3 T-cell signaling cascade [7; 10; 11; 12]. 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 [13; 14]. 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 [15; 16]. Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells [17]. 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 [18; 19; 20; 13]. 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 [13]. 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) [21]. 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.

MK-3475 (Keytruda®, pembrolizumab, and previously known as SCH 900475) 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. MK-3475 has recently been approved in the United Stated for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilumumab and, if BRAF V600 mutation positive, a BRAF inhibitor. It has also been approved for NSCLC positive for PD-L1 by the DAK 22C3 antibody after progression on platinum-based chemotherapy, as well as for first-line treatment of patients with metastatic (NSCLC whose tumors have high PD-L1 expression [Tumor Proportion Score (TPS) ≥50%)] as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations.

4.2.2 Preclinical and Clinical Trial Data

Refer to the Investigator's Brochure for MK-3475 Preclinical and Clinical data.

4.3 Afatinib

4.3.1 Pharmaceutical and Therapeutic

Afatinib (BIBW2992) is a small molecule, selective and irreversible erbB family blocker. In preclinical models it effectively inhibits EGFR, HER2 and HER4 phosphorylation resulting in tumour growth inhibition and regression of established subcutaneous tumors derived from four human cell-lines known to co-express ErbB receptors.

For the latest information on the drug profile of afatinib, please refer to the current Investigator's Brochure (IB) (U03-3218). All references in this protocol concerning afatinib refer to the free base compound afatinib BI which is used as the oral formulation.

Afatinib is moderately fast absorbed after oral administration. Maximum plasma concentrations of afatinib were achieved mainly at 2 to 5 hours after oral drug administration. Afatinib maximum plasma concentrations and area under the curve increased slightly over- proportional with increasing doses in the therapeutic range of 20-50mg. Moderate to high inter- and intra-individual differences in plasma concentration were seen. Afatinib is highly distributed out of the blood and has a moderate to high clearance. The overall gMean terminal half-life at steady state was 37.2 hours in cancer patients. Steady state was reached no later than 8 days after the first administration. The major route of elimination of afatinib was via feces. After food intake, a decreased systemic exposure was observed compared to administration under fasted conditions. Therefore, afatinib should be taken without food (i.e. food should not be consumed for at least 1 hour before and at least 2 hours after meal). The PK characteristics in Caucasian cancer patients were comparable to those observed in Japanese cancer patients.

Afatinib is bound covalently to proteins to a variable extent and covalent protein adducts were the major circulating metabolites in the plasma. Afatinib did not show relevant inhibition or induction of cytochrome P450 isoenzymes, and it appears unlikely that drug- drug interactions based on this mechanism will occur.

Afatinib is a substrate of the P-gp transporter. Concomitant administration of the potent P-gp inhibitor ritonavir did not relevantly change the exposure to 40 mg afatinib when taken simultaneously with or 6 h after afatinib but increased the bioavailability of afatinib (single dose of 20 mg) by 48% and 39% for $AUC_{0-\infty}$ and C_{max} when given 1 h before afatinib, respectively. Pretreatment with the potent P-gp inducer rifampicin decreased the plasma exposure of 40 mg afatinib by 34 % afatinib ($AUC_{0-\infty}$) and 22 % (C_{max}), respectively. Caution should be exercised when combining afatinib with potent P-gp modulators. In pre-clinical studies, afatinib is not an irritant to intact skin but an ocular irritant. Afatinib is mutagenic in a single bacteria strain, but did not show genotoxic potential in vivo when tested up to overt toxic/lethal doses. Studies on embryo-fetal development in rats and rabbits up to life- threatening doses have revealed no indication of teratogenicity.

Two phase I open label dose-escalation studies determined the MTD with continuous dosing of afatinib in patients with advanced solid tumors at 40mg and 50mg daily, respectively (Ould-Kaci M. Investigator's brochure. Afatinib (BIBW 2992). Version 14, 1200.P1 1200. P10. 2013, Temple G, et al. A Phase I open-label dose escalation study of continuous once-daily oral treatment with BIBW 2992 in patients with advanced solid tumours. Trial 1200.3. 2010.). Adverse events (AE) observed with afatinib are consistent with those reported for other EGFR and dual EGFR/HER2 inhibitors. The most frequent investigator defined drug-related AEs were associated with gastrointestinal disorders (including diarrhoea, and stomatitis), skin and subcutaneous tissue disorders (rash, dry skin, pruritus, acneiform rash, acne), nail effects, epistaxis, fatigue and decreased appetite. Early and proactive management of diarrhea, mucositis/stomatitis and skin rash together with treatment interruptions and dose reductions is recommended in line with recent guidelines in the management of common toxicities of EGFR and EGFR/HER2 TKIs and monoclonal antibodies (Lynch TJ, Jr. et al. Oncologist. 2007 May;12(5):610-21. PubMed PMID: 17522250. Lacouture ME et al. Expert Rev Anticancer Ther. 2013 Jun;13(6):721-8. PubMed PMID: 23506519. Yang JC et al. Expert Rev Anticancer Ther. 2013 Jun;13(6):729-36. PubMed PMID: 23506556. Moy B, Goss P. Oncologist 1007;12(7):756-65. Giaccone G et al. A consensus position from the EGFRI dermatologic toxicity forum. ECCO; Barcelona 2007).

Refer to the Investigator's Brochure for Afatinib Preclinical and Clinical data.

4.4 Rationale

4.4.1 Rationale for the Trial and Selected Subject Population

The discovery of EGFR activating mutations in NSCLC and the targeting of these mutations with EGFR-TKIs represents a substantial advance in the treatment of metastatic NSCLC. EGFR is a member of the ERBB family of receptor tyrosine kinases. Mutations that render EGFR constitutively active in NSCLC are sensitive to inhibition with EGFR tyrosine kinase inhibitors. Invariably, acquired resistance to erlotinib develops; more than 60% of patients experience progression within a year (Rosell R et al Lancet Oncol 2012; 13:239-46). New strategies to overcome or circumvent acquired resistance to EGFR-TKIs represent a major unmet need.

Afatinib, an irreversible inhibitor of EGFR and other complexes formed by the ErbB family of hetero- and homo-dimers, represents a good first step in addressing acquired resistance to first generation EGFR-TKIs. Of note, afatinib is FDA approved as frontline therapy for use in patients with EGFR-activating mutations based on a significant PFS benefit compared to platinum based chemotherapy in patients whose tumors harbor EGFR activating mutations (Sequist, LV et al. JCO 2013 31:27 3327-34). Additionally, in patients with EGFR-mutated cancers and established acquired resistance to erlotinib, afatinib prolongs progression-free survival, with a disease control rate of 57% and a 7% response rate (Miller VA et al. Lancet Oncol 2012; 13:528-38). Combination approaches with afatinib appear more promising. For example, the combination of

afatinib and cetuximab has substantially higher response rates (29% RR) and activity (100% DCR) (Y. Y. Janjigian et al. Cancer Discovery 2014 4:9; 1036-45**)**. This combination activity of afatinib/cetuximab in patients with acquired resistance is in contrast to erlotinib/cetuximab in this setting, where very little activity is seen. Thus afatinib (as an irreversible EGFR inhibitor with activity against mechanisms such as T790M) is a more promising EGFR-TKI to pair with other therapeutics such as MK-3475. MK-3475 is a potent and highly selective humanized mAb of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2.

In preclinical cell lines and genetically engineered (GEMM) mouse models EGFR driven tumors expressed higher levels of PD-L1 with a more immunosuppressive tumor microenvironment (increased FoxP3+ T-cells, decreased CD8+/CD4+ ratio) (Akbay EA et al. Cancer discovery 2013; 3:1355-63). Increased PD-L1 expression was shown across a range of EGFR activating mutations and the EGFR T790M resistance mutation. Addition of an EGFR-TKI that decreased EGFR pathway activity also decreased PD-L1 expression. The irreversible EGFR-TKI WZ004 was more effective in this regard than the reversible EGFR- TKI gefitinib in preclinical models with EGFR T790M (the most common (~60%) EGFR- TKI resistance mutation). Thus, EGFR mutated NSCLC may be particularly sensitive to PD1 antibodies such as MK-3475. An irreversible EGFR inhibitor such as afatinib may be more effective than the reversible EGFR-TKI erlotinib in this setting.

4.4.2 Rationale for Dose Selection/Regimen/Modification

The dose regimen of 200 mg Q3W of MK-3475 (pembrolizumab) is planned for all urothelial cancer trials. Available PK results in subjects with melanoma, NSCLC, and other solid tumor types support a lack of meaningful difference in PK exposures obtained at a given dose among tumor types. An open-label Phase I trial (PN001) in melanoma subjects is being 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.

In KEYNOTE-001, two randomized cohort evaluations of melanoma subjects receiving pembrolizumab at a dose of 2 mg/kg versus 10 mg/kg Q3W have been completed. The clinical efficacy and safety data demonstrate a lack of clinically important differences in efficacy response or safety profile at these doses. For example, in Cohort B2, advanced melanoma subjects who had received prior ipilimumab therapy were randomized to receive pembrolizumab at 2 mg/kg versus 10 mg/kg Q3W. The overall response rate (ORR) was 26% (21/81) in the 2mg/kg group and 26% (25/79) in the 10 mg/kg group (full analysis set (FAS)). The proportion of subjects with drug-related adverse events (AEs), grade 3-5 drug-related AEs, serious drug-related AEs, death or discontinuation due to an AE was comparable between groups or lower in the 10 mg/kg group.

Available pharmacokinetic results in subjects with melanoma, NSCLC, and other solid tumor types support a lack of meaningful difference in pharmacokinetic exposures obtained at a given dose among tumor types. Population PK analysis has been performed and has confirmed the expectation that intrinsic factors do not affect exposure to pembrolizumab to a clinically meaningful extent. Taken together, these data support the use of lower doses (with similar exposure to 2 mg/kg Q3W) in all solid tumor indications. 2 mg/kg Q3W is being evaluated in NSCLC in PN001, Cohort F30 and PN010, and 200 mg Q3W is being evaluated in head and neck cancer in PN012, which are expected to provide additional data supporting the dose selection.

Selection of 200 mg as the appropriate dose for a switch to fixed dosing is based on simulation results indicating that 200 mg will provide exposures that are reasonably consistent with those obtained with 2 mg/kg dose and importantly will maintain individual patient exposures within the exposure range established in melanoma as associated with maximal clinical response. A population PK model, which characterized the influence of body weight and other patient covariates on exposure, has been developed using available data from 476 subjects from PN001. The distribution of exposures from the 200 mg fixed dose are predicted to considerably overlap those obtained with the 2 mg/kg dose, with some tendency for individual values to range slightly higher with the 200 mg fixed dose. The slight increase in PK variability predicted for the fixed dose relative to weight-based dosing is not expected to be clinically important given that the range of individual exposures is well contained within the range of exposures shown in the melanoma studies of 2 and 10 mg/kg to provide similar efficacy and safety. 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 tumor types and 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.

Afatinib will be combined with MK-3475 at the FDA approved single-agent starting dose for afatinib. Dose de-escalation is permitted per protocol.

4.4.3 Rationale for Endpoints

This is a phase I dose 3+3 dose de-escalation study followed by expansion cohorts for safety and correlative studies. Therefore, the endpoints include determination of MTD, and recommended phase II dose (RP2D) correlative and pharmacokinetic endpoints and secondary efficacy endpoints. MTD and RP2D are standard endpoints for phase I dose de-escalation studies.

- The MTD is defined in section 5.1.5.
- The recommended dose expansion and recommended phase II dose (RP2D) will be determined by the overall assessment of the MTD and toxicities observed in the dose de-escalation portion of this study.

4.4.3.1 Efficacy Endpoints

- Overall response rate (ORR). ORR is an acceptable measure of clinical benefit in early phase clinical trials to provide a preliminary signal of activity to consider later phase trials.
- Progression-free survival (PFS). PFS is an acceptable measure of assessing benefit in NSCLC clinical trials.

As this is a phase I study, our goal is a preliminary assessment of a signal of efficacy as defined in the statistical plan.

4.4.3.2 Biomarker Research

The investigator will conduct biomarker research on biopsy and blood collected on trial patients. These studies will focus on mechanisms EGFR-TKI resistance and immune correlates.

1. Immunology Correlates

Immunology correlates will be performed by collaborators at the Translational Immuno-Oncology Laboratory Yale University and/or by the Human Immune Monitoring Core at UC Davis as defined in the protocol. The Human Immune Monitoring Core at UC Davis is under the supervision of Emanual Maverakis, MD. Dr. Maverakis' laboratory is a world renowned immunology laboratory and has the equipment and expertise to conduct the proposed studies. The Translational Immuno-Oncology Laboratory at Yale University is under the direction of David Rimm MD, Ph.D and Kurt Schalper, MD, Ph.D and has been a leader in the translational immuno-oncology of immune checkpoint inhibitors.

a. Biopsy (Biopsy at Baseline and prior to Cycle #3):

- PD-L1 expression by immunohistochemistry at baseline and in repeat biopsy specimens to assess for changes in PD-L1 expression in response to treatment will be conducted by Yale Immuno-Oncology under the direction of Kurt Schalper using the approved DAKO 22C3 antibody and in addition quantitative IHC assays for PD-L1 if tissue permits. UC Davis may also perform IHC for PD-L1 using the standard DAKO 22C3 antibody.

- Enumeration and changes in immune cell subsets by immunohistochemistry in repeat biopsy specimens in response to treatment will be conducted by Yale Translational Immuno-Oncology.

- Whole exome DNA/RNA next generation sequencing and assessment of mutational load will be performed by the Broad Institute in Boston. The Broad Institute is a world leader in genomic sequencing and analysis.

- RPPA (Reverse Phase Protein Assays) for on-target EGFR pathway inhibition will be performed by Theranostics in collaboration with the Mack lab at UC Davis.

b. Peripheral blood will be collected at relevant time points for enumeration of immune cell subsets and changes in cytokine expression in response to treatment with methods including Flow Cytometry and Luminex Cytokine Assays by the Human Immune Monitoring Core at UC Davis.

Plasma PD-L1 DNA/RNA levels will be assayed by Liquid Genomics in a CLIA certified laboratory.

2. EGFR Correlates

a. Biopsy

The type of EGFR activating mutation and the presence of EGFR T790M resistance mutation will be performed per standard of care in a CLIA certified laboratory at the investigators discretion (if previous EGFR T790M mutation negative or not performed).

Whole exome DNA/RNA next generation sequencing and assessment of mutational load will be performed by the Broad Institute in Boston. The Broad Institute is a world leader in genomic sequencing and analysis.

b. Plasma EGFR-mutant DNA/RNA Levels

Changes in plasma EGFR-mutant DNA/RNA in patients with EGFR-mutant NSCLC may be prognostic for recurrence, the development of resistance to existing therapies and may track response or lack of benefit to existing treatment (T. Mok, WCLC 2013). Determination of plasma EGFR-mutant DNA levels will be conducted at Liquid Genomics in a CLIA certified laboratory.

c. If tissue permits, analysis for pharmacodynamic markers of on-target EGFR- inhibition with RPPA will be performed by Theranostics and the Mack lab at UC Davis.

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

Incurable, Advanced and/or Metastatic/Recurrent Non-Small Cell Lung Cancer with EGFR Activating Mutations (Exon 19 del, Exon 21 L858R, L861Q, G719X). Who Have Radiologic and/or Clinically Progressive Disease on Erlotinib or Gefitinib or Osimertinib at any point during the patient's cancer treatment as determined by the Investigator.

5.1.2 Subject Inclusion Criteria

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

1. Be willing and able to provide written informed consent for the trial.
2. Be ≥ 18 years of age on day of signing informed consent.
3. Have a life expectancy of at least 3 months.
4. Have measurable disease based on RECIST 1.1.
5. Adequate archival tissue for determination of EGFR-mutation status and PD-L1 status with a leftover cell block (or equivalent) for additional immune correlates from a tumor lesion biopsied in the last 60 days (prior to signed consent) that has not been previously irradiated occurring: 1) after progression on erlotinib and no intervening systemic treatment between biopsy and initiation of MK-3475 and afatinib or amenable to repeat biopsy.

   If inadequate archival tissue as above, patients must be willing to consent for biopsy at baseline and an on treatment biopsy. Patients must also have a tumor in a location that in the opinion of the investigator that is amenable to biopsy or have provided tissue for PD-L1 and other biomarker analysis from a newly obtained formalin fixed tumor tissue from a recent biopsy of a tumor lesion not previously irradiated. No systemic antineoplastic therapy may be administered between the PD- L1 biopsy and initiating study medication. Fine needle aspirates are not acceptable. Core needle or excisional biopsies, or resected tissue is required.
6. Have a performance status of 0 or 1 on the ECOG (Zubrod) Performance Scale.
7. There is no limit to the number of prior treatments for this phase I trial.
8. Demonstrate adequate organ function as defined in Table 2, all screening labs should be

performed within 10 days of treatment initiation.

Table 2 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	>1,500 /mcL
Platelets	>100,000 / mcL
Hemoglobin	>9 g/dL or >5.6 mmol/L
Renal	
Serum creatinine **OR** Measured or calculated[a] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 X upper limit of normal (ULN) **OR** ≥60 mL/min for subject with creatinine levels > 1.5 X institutional ULN
Hepatic	
Serum total bilirubin	< 1.5 X ULN
	Direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 X ULN **OR** < 5 X ULN for subjects with liver metastases
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT) Activated Partial Thromboplastin Time (aPTT)	≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants ≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
[a]Creatinine clearance should be calculated per institutional standard.	

9. 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.

10. 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 (Section 5.7.2).

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

11. 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 – Contraction, 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 any of its excipients.

5. Has had a prior anti-cancer monoclonal antibody (mAb) within 3 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to agents administered more than 4 weeks earlier. Denosumab is allowed as long as not < 1 week prior to study day 1 and not administered on day of MK-3475 infusion.

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

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

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

7. 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.

8. 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 two 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.

9. Has an active autoimmune disease requiring systemic treatment within the past 3 months or

a documented history of clinically severe autoimmune disease, or a syndrome that requires systemic steroids or immunosuppressive agents. Subjects with vitiligo or resolved childhood asthma/atopy would be an exception to this rule. Subjects that require intermittent use of bronchodilators or local steroid injections would not be excluded from the study. Subjects with hypothyroidism stable on hormone replacement or Sjorgen's syndrome will not be excluded from the study.

10. Has a history of (non-infectious) pneumonitis that required steroids or current pneumonitis. Lymphangitic spread of the NSCLC is not exclusionary.

11. Has an active infection requiring intravenous systemic therapy.

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

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

14. History or presence of clinically relevant cardiovascular abnormalities such as uncontrolled hypertension, congestive heart failure NYHA classification of 3 (Refer to APPENDIX 12.4), unstable angina or poorly controlled arrhythmia as determined by the investigator. Myocardial infarction within 6 months prior to enrollment.

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

16. Has received prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2.

17. Known hypersensitivity to afatinib or the excipients of any of the trial drugs

18. Prior history of receiving afatinib.

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

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

21. Has received a live vaccine within 30 days of planned start of study therapy (See Section 5.5.2). *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.*

22. The presence of poorly controlled gastrointestinal disorders that could affect the absorption of the afatinib (e.g. Crohn's disease, ulcerative colitis, chronic diarrhea,

malabsorption).

23. Receiving drugs known to be strong inducers or inhibitors of P-glycoprotein that are known to interact with afatinib including, but not limited to: ritonavir, cyclosporine A, ketoconazole, itraconazole, erythromycin, verapamil, quinidine, tacrolimus, nelfinavir, saquinavir, and amiodarone. Because the lists of these agents are constantly changing, it is important to regularly consult a frequently-updated list such as http://medicine.iupui.edu/clinpharm/ddis/table.aspx; medical reference texts such as the Physicians' Desk Reference may also provide this information. As part of the enrollment/informed consent procedures, the patient will be counseled on the risk of interactions with other agents, and what to do if new medications need to be prescribed or if the patient is considering a new over-the-counter medicine or herbal product. The subject must stop the strong inducer or inhibitor of P-glycoprotein 7 days before or 5 half lives before study drug administration (whichever timepoint is longer).

24. Major surgery within 4 weeks before starting study treatment or scheduled for surgery during the projected course of the study.

25. Radiotherapy within 4 weeks prior to enrollment, except as follows:

    i.) Palliative radiation to target organs other than chest may be allowed up to 2 weeks prior to enrollment, and

    ii.) Single dose palliative treatment for symptomatic metastasis outside above allowance to be discussed with sponsor-investigator prior to enrolling.

26. Meningeal carcinomatosis.
27. Prior participation in an afatinib clinical study, even if not assigned to afatinib treatment.
28. Any history of or concomitant condition that, in the opinion of the Investigator, would compromise the patient's ability to comply with the study or interfere with the evaluation of the efficacy and safety of the test drug.

5.1.4 Trial Treatments

The treatment to be used in this trial is outlined below in Table 3. Each cycle is 21 days in length.

Table 3 Trial Treatments

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period	Use
MK-3475	200 mg	Q3W	IV infusion	Day 1 of each cycle	Experimental

Afatinib*	20 mg, 30 mg, or 40 mg	Once daily	Oral	Day 1-21 of each cycle	Experimental
The MK-3475 dosing interval may be increased due to toxicity as described in Section 5.1.5.3. *Cohort B begins in Cycle 3					

Table 4: Dose De- Escalation Schema

Dose Level	Number of Patients	Afatinib (Daily)	MK-3475 (q3 weeks)
0	**3+**	**40 mg D1**	**200 mg D1**
-1	3+	30 mg D1	200 mg D1
-2	3+	20 mg D1	200 mg D1
Each cycle is 21 days in length.			

Dose De-Escalation

This treatment will start at dose level 0 (Bold). Afatinib is an oral agent that will be given once daily for 21 days per cycle starting on day 1 of each cycle before administration of MK-3475. It should be taken in the morning with 200 mL of water. Tablets should be taken 1 hour before or 2 hours after meals. MK-3475 will be given once every 3 weeks at a fixed dose of 200 mg. Treatment will be administered until progression or toxicity or withdrawal of consent as defined in this protocol.

Cohort A (Arm A): Dose Expansion

This treatment will start at the MTD determined in the dose de-escalation portion of this trial. Afatinib is an oral agent that will be given once daily for 21 days per cycle starting on day 1 of each cycle before administration of MK-3475. It should be taken in the morning with 200 mL of water. Tablets should be taken 1 hour before or 2 hours after meals. MK-3475 will be given once every 3 weeks. Treatment will be administered until progression or toxicity or withdrawal of consent as defined in this protocol.

Cohort B (Arm B): Dose Expansion

This treatment will start at the MTD determined in the dose de-escalation portion of this trial. MK-3475 will be administered on Day 1 of each cycle, which is q21d in length. Afatinib is an oral agent that will be given once daily for 21 days per cycle starting on Cycle 3 Day 1 of each cycle starting prior to administration of MK-3475 on day 1. It should be taken in the morning with 200 mL of water. Tablets should be taken 1 hour before or 2 hours after meals. MK-3475 will be given once every 3 weeks. Treatment will be administered until progression or toxicity or withdrawal of consent as defined in this protocol.

After the MTD is reached, Cohort A will complete first to further assess toxicity at the MTD of the combination, followed by enrollment in Cohort B. Cohort Assignment is further defined in

Section 5.2.

5.1.5 Dose Selection/Modification

5.1.5.1 Dose Selection

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

MK-3475 will be provided by Merck at no cost to the patient.

Afatinib will be provided by Boehringer Ingelheim at no cost to the patient.

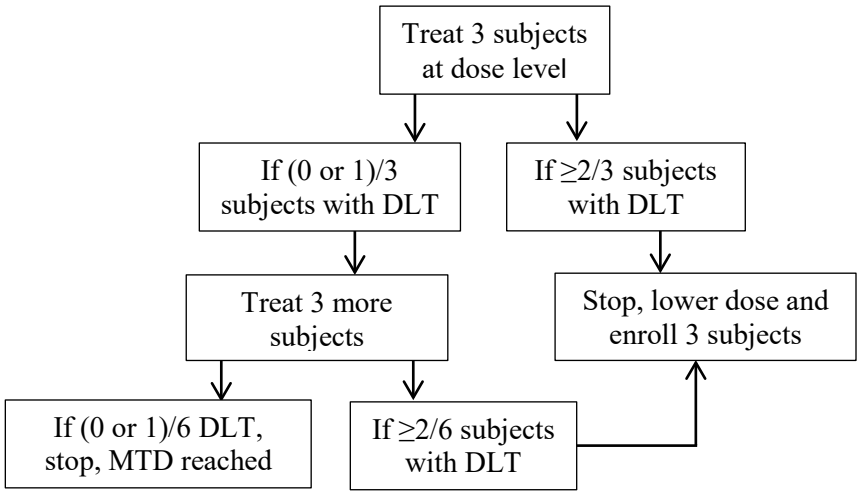
Subjects will take a single oral dose of afatinib daily starting on Day 1 of each cycle, until the development of progressive disease or unacceptable adverse events.

See section 5.1.5 for Dose Modifications for afatinib and MK-3475. See Table 6 for dose reduction for afatinib.

5.1.5.2 Dose De-Escalation

Dose Level	Number of Patients	Afatinib (Daily)	MK-3475 (q3 weeks)
0	**3+**	**40 mg D1**	**200 mg D1**
-1	3+	30 mg D1	200 mg D1
-2	3+	20 mg D1	200 mg D1

Figure 1: Dose De-Escalation Schema



This is a phase I study. A minimum of 9 patients (if trial is terminated early due to unacceptable toxicity and a maximum of 38 patients (18 patients in the dose- de-escalation cohort plus 10 in each of the two expansion cohorts) are anticipated for this trial. Analysis of safety and biomarkers will be limited to patients who receive active treatment.

The dose-de-escalation phase will establish a MTD recommended dose of MK-3475 in expansion cohorts (A +B).

We plan to enter 3 patients at Dose Level 0. If 0/3 or 1/3 patients experience a DLT on level 0, an additional 3 patients will be accrued to Level 0, where 2 or more DLTs will terminate that study arm and we will proceed to dose level -1.

If 2 or more patients have DLTs at level 0, patients will be accrued at level -1. If 1/3 patients experience a DLT on level -1, an additional 3 patients will be accrued to Level -1, where 2 or more DLTs will require termination of that study arm while 1 DLT out of 6 will result in proceeding with dose level -1 as the MTD for the dose expansion cohorts.

If 2 or more patients have DLTs at level -1, patients will be accrued at level -2. If 1/3 patients experience a DLT on level -2, an additional 3 patients will be accrued to Level -2, where 2 or more DLTs will require termination of the study while 1 DLT out of 6 will result in proceeding with dose level -2 as the MTD for the dose expansion cohorts.

The phase I dose de-escalation portion of the trial will be closed when the maximum tolerated dose level (MTD) or dose level 0 is reached and six patients have been treated at that dose level.

Dose modifications for patients that experience DLT is described in section 5.1.5.3. Once the dose is decreased, there will be no dose re-escalation allowed for an individual patient.

The recommended phase II dose (RP2D) will be determined by the overall assessment of the MTD and toxicities observed in the de-dose escalation and dose expansion portion of this study.

5.1.5.3 Dose Modification

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. MK-3475 will be withheld for MK-3475-related toxicities and severe or life- threatening AEs as per Table 5. See Section 5.6.1 and Events of Clinical Interest Guidance Document for supportive care, including use of corticosteroids.

Table 5: Dose modification guidelines for MK-3475 related adverse events.

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Treatment Discontinuation
Diarrhea/Colitis	2-3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	4	Permanently discontinue	Permanently discontinue
AST, ALT, or Increased Bilirubin	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose
	3-4	Permanently discontinue (see exception below)[a]	Permanently discontinue
Type 1 diabetes mellitus (if new onset) or Hyperglycemia	T1DM or 3-4	Hold pembrolizumab for new onset Type 1 diabetes mellitus or Grade 3-4 hyperglycemia associated with evidence of beta cell failure	Resume pembrolizumab when patients are clinically and metabolically stable
Hypophysitis	2-4	Toxicity resolves to Grade 0-1. Therapy with pembrolizumab can be continued while endocrine replacement therapy is instituted	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
Hyperthyroidism	3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	4	Permanently discontinue	Permanently discontinue
Hypothyroidism		Therapy with pembrolizumab	Therapy with pembrolizumab can be continued

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Treatment Discontinuation
		can be continued while thyroid replacement therapy is instituted	while thyroid replacement therapy is instituted
Infusion Reaction	2[b]	Toxicity resolves to Grade 0-1	Permanently discontinue if toxicity develops despite adequate premedication
	3-4	Permanently discontinue	Permanently discontinue
Pneumonitis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	3-4	Permanently discontinue	Permanently discontinue
Renal Failure or Nephritis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	3-4	Permanently discontinue	Permanently discontinue
All Other Drug-Related Toxicity[c]	3 or Severe	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	4	Permanently discontinue	Permanently discontinue

Note: Permanently discontinue for any severe or Grade 3 drug-related AE that recurs or any life-threatening event.
[a] For patients with liver metastasis who begin treatment with Grade 2 AST or ALT, if AST or ALT increases by greater than or equal to 50% relative to baseline and lasts for at least 1 week then patients should be discontinued.
[b] If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose; Refer to Infusion Treatment Guidelines for further management details.
[c] Patients with intolerable or persistent Grade 2 drug-related AE may hold study medication at physician discretion. Permanently discontinue study drug for persistent Grade 2 adverse reactions for which treatment with study drug has been held, that do not recover to Grade 0-1 within 12 weeks of the last dose.

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

Treatment related toxicities will be managed by treatment interruptions and subsequent dose reductions of afatinib according to the schedule described in Table 6. Dose reductions will apply to individual patients only. Once the dose has been reduced, it cannot be increased later.

To prevent the development of more severe adverse events, treatment related diarrhea, nausea and vomiting or rash should be managed early and proactive as described in Section 5.6.

Table 6. Dose reduction scheme for Afatinib

AE Type and CTCAE Grade	Action	Dose Reduction Scheme
Events related to study drug (afatinib): • Diarrhea Grade 2 persisting for 2 or more consecutive days (48 hours) despite adequate anti-diarrheal medication/hydration • Reduced renal function to ≥ Grade 2 as measured by serum creatinine, proteinuria or decrease in glomerular filtration rate of more than 50% from baseline • Any drug related AE Grade ≥3	• Pause treatment until patient has recovered to Grade ≤1 or baseline.[1] • Resume treatment at reduced dose according to schedule opposite. • If patient has not recovered to Grade ≤1 or baseline[1] within 14 days study treatment must be permanently discontinued.[2]	• If patient was receiving 40 mg, resume treatment at a dose of 30 mg. • If patient was receiving 30 mg, resume treatment at a dose of 20 mg. • If patient was receiving 20 mg, discontinue afatinib.
Acute onset and/or unexplained worsening of pulmonary systems (dyspnea, cough, fever)	Pause afatinib while clinical assessment to exclude ILD is completed.	If ILD is ruled out as a cause of symptoms, grade symptoms and relatedness and report as AEs. If AEs are not related, resume afatinib at current dose. If AEs are drug related, follow directions in row above. If ILD is confirmed, discontinue afatinib

[1] Baseline is defined as the CTCAE Grade at the start of treatment.

[2] In the event that the patient is deriving obvious clinical benefit according to the investigator's judgment, further treatment with afatinib will be decided by the investigator.

In the event of any unrelated adverse events, the investigator may choose to interrupt the afatinib for up to 14 days, but no dose reduction should occur. If afatinib is interrupted for more than 14 days, the decision to continue with afatinib will be made by the investigator.

5.1.6 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 may be administered on an outpatient basis.

MK-3475 200 mg will be administered as a 30 minute IV infusion every 3 weeks. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min).

Afatinib is an oral agent that will be given once daily for 21 days per cycle starting on day 1 of each cycle before administration of MK-3475. It should be taken in the morning with 200 mL of water.

The medication should be taken at the same time each day (± 2 hours) without food (at least one hour before or at least 2 hours after a meal).

Missed doses of afatinib can be made up during the same day. Otherwise, the dose must be skipped and patients should take the next scheduled dose at the usual time. Patients with emesis must not take a replacement dose. A missed dose of afatinib should not be taken within 12 hours of the next dose.

5.1.7 Trial Blinding/Masking

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

5.2 Treatment Allocation

Patients will be enrolled into the dose de-escalation protocol until the MTD is reached. Then patients will be enrolled into 2 cohorts for the dose expansion at the recommended expansion dose and RP2D. Cohort (Arm) A: will be concurrent MK-3475 + afatinib at initiation of treatment and Cohort (Arm) B: will be lead in MK-3475 for 2 cycles followed by concurrent MK-3475 and afatinib. The recommended dose for the dose expansion cohorts and RP2D dose will be informed by the MTD determined in the de-dose escalation phase and assessment of the overall toxicity at the treated dose levels.

After the expansion dose (MTD) is determined, for the expansion phase we will enroll and complete Cohort A: Afatinib + MK-3475 (Concurrent) to further define toxicities at the MTD in the dose expansion. After completion of Cohort A, we will enroll patients into Cohort B (lead-in MK-3475 followed by combination afatinib and MK-3475 commencing at cycle #3).

5.3 Definition of Dose Limiting Toxicities (DLT)

All toxicities will be graded using National Cancer Institute (NCI) CTCAE Version 4.0. The occurrence of any of the following toxicities during Cycle 1 will be considered a DLT, if judged by the Investigator to be possibly, probably or definitely related to study drug (either afatinib or MK-3475) administration:

1. Grade 4 non-hematologic toxicity (not laboratory).

2. Grade 4 hematologic toxicity lasting ≥14 days.

3. Grade 3 non-hematologic toxicity (not laboratory) lasting > 3 days despite optimal supportive care with maximal supportive care for diarrhea and rash. See description of maximal supportive care for diarrhea and rash attributed to afatinib below.

4. Any Grade 3 or Grade 4 non-hematologic laboratory value if:

    - Medical intervention is required to treat the patient, or
    - The abnormality leads to hospitalization, or
    - The abnormality persists as ≥ grade 3 for >1 week.

5. Febrile neutropenia Grade 3 or Grade 4:

    - Grade 3 is defined as ANC <1000/mm3 with a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of ≥38 degrees C (100.4 degrees F) for more than one hour
    - Grade 4 is defined as ANC <1000/mm3 with a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of ≥38 degrees C (100.4 degrees F) for more than one hour, with life-threatening consequences and urgent intervention indicated.

6. Thrombocytopenia <25,000/mm3 if associated with:

    - A bleeding event which does not result in hemodynamic instability but requires an elective platelet transfusion, or
    - A life-threatening bleeding event which results in urgent intervention and admission to an Intensive Care Unit
    - Grade 5 toxicity (i.e. death).

7. Diarrhea is an expected adverse event from afatinib. Diarrhea attributed to afatinib will be considered a DLT if grade 3 despite maximal medical management for > 72 hours. Maximal medical management will be defined as anti-diarrheal management that includes: loperamide, diphenoxylate and atropine, and tincture of opium. Grade 4 diarrhea will be considered a DLT.

8. Acneiform rash is an expected adverse event from afatinib. Acneiform rash attributed to afatinib will be considered a DLT if grade 3 despite maximal medical management for > 72 hours. Maximal medical management will be defined as oral antibiotic, preferably doxycycline, cleocin solution or cream and topical steroids. In addition an asymptomatic/minimally symptomatic classic acneiform rash will only be considered a DLT if it covers ≥ 50% BSA. Grade 4 rash will be considered a DLT.

9. To be evaluable for a DLT, 80% of dose must have been administered in cycle 1 unless a DLT occurred.

10. Delay in starting cycle 2 of ≥ 14 days due to toxicity related to afatinib and/or MK-3475

5.4 Attribution of Adverse Events

Investigators are required to assess whether there is a reasonable possibility that afatinib and/or MK-3475 caused or contributed to the adverse event. The following general guidance may be used.

- Definite – The AE *is clearly related* to the study treatment.
- Probable – The AE *is likely related* to the study treatment.
- Possible – The AE *may be related* to the study treatment.
- Unlikely – The AE *is doubtfully related* to the study treatment.
- Unrelated – The AE *is clearly NOT related* to the study treatment.

If an adverse event is attributable (either definite, probable or possible) to MK-3475 and/or afatinib that requires the drug be held the other drug may be continued if it the adverse event is not attributable to that drug (either unlikely or unrelated) with approval of the treating physician and primary investigator. Exceptions include pneumonitis and grade 2 and above enterocolitis (as defined in this protocol) where both MK-3475 and afatinib must be held.

5.5 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 Merck and/or Boehringer Ingelheim. The final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician.

5.5.1 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 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 Event(s) of clinical interest. ECIs guidance document attached within the appendices.

5.5.2 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 or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than MK-3475 and afatinib
- Radiation therapy
  - Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed at the Investigator's discretion.
- Live vaccines within 30 days prior to the first dose of trial treatment 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-Investigator.
- Strong inducers or inhibitors of P-glycoprotein that are known to interact with afatinib including, but not limited to: ritonavir, cyclosporine A, ketoconazole, itraconazole, erythromycin, verapamil, quinidine, tacrolimus, nelfinavir, saquinavir, and amiodarone. Because the lists of these agents are constantly changing, it is important to regularly consult a frequently-updated list such as http://medicine.iupui.edu/clinpharm/ddis/table.aspx; medical reference texts such as the Physicians' Desk Reference may also provide this information.

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

The Exclusion Criteria describes other medications which are prohibited in this trial. There are no prohibited therapies during the Post-Treatment Follow-up Phase.

In case of major surgery (as judged by the investigator), it is recommended to stop treatment with afatinib around one week prior to the surgery, and to restart treatment after complete wound healing. If afatinib is interrupted for more than 14 days, the decision to continue will be made by the Sponsor-Investigator.

5.6 Rescue Medications & Supportive Care

5.6.1 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**:
  Both afatinib and MK-3475 can cause diarrhea. Subjects should additionally 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. Diarrhea

should be managed aggressively with anti-diarrheal agents such as: loperamide, diphenoxylate/atropine and tincture of opium if necessary.For **Grade 2 diarrhea/colitis** that persists greater than 3 days, administer oral corticosteroids.

- For **Grade 3 or 4 diarrhea/colitis** that persists > 1 week, 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.

- **Management of Acneiform Rash** – Afatinib as with other EGFR-inhibitors can cause a classic acneiform rash. Acneiform rash attributed to afatinib ≥ grade 2 should be managed aggressively with cleocin solution and appropriate anti-biotics such as doxycycline. Management for grade 1 acneiform rash per investigator's discretion.

- **Type 1 diabetes mellitus (if new onset, including diabetic ketoacidosis [DKA]) or ≥ Grade 3 Hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA)**
  - For T1DM or Grade 3-4 Hyperglycemia
    - 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 liothyroinine, 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 7 shows treatment guidelines for subjects who experience an infusion reaction associated with administration of MK-3475. Please also see Events of Clinical Interest Appendix attached at end of protocol for further details.

Table 7. Infusion Reaction Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs	**Stop Infusion and monitor symptoms.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g. from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. **Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.**	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of MK-3475 with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **Subject is permanently discontinued from further trial treatment administration**	No subsequent dosing
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration. For Further information, please refer to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE) at http://ctep.cancer.gov		

5.6.2 Rescue medication for Afatinib

Rescue medications to reverse the actions of afatinib are not available. There is no specific antidote for overdosage with afatinib. Potential adverse events should be treated symptomatically. Common adverse events of treatment with afatinib with specified management recommendations and/or requirements include diarrhea, and rash/acne, paronychia. To improve tolerability and the probability of clinical benefit, patients should receive prompt and appropriate supportive care at the first signs of symptoms. Suggested treatments for AEs are described below.

5.6.3 Management of Eye Complications of Afatinib

Patients who present with symptoms of keratitis, such as acute or worsening eye inflammation, lacrimation, light sensitivity, blurred vision, eye pain and/or red eye should be referred promptly to an ophthalmic specialist. If a diagnosis of ulcerative keratitis is confirmed, treatment with afatinib should be interrupted or discontinued. If keratitis is diagnosed, the benefits and risks of continuing treatment with afatinib should be carefully considered. Afatinib should be used with caution in patients with a history of keratitis, ulcerative keratitis or severe dry eye. Contact lens use is a risk factor for keratitis and ulceration.

5.6.4 Management of expected adverse events

Dermatologic adverse events, mucositis/stomatitis and diarrhea are the most common side-effects associated with treatment with afatinib. Treatment of these side-effects should be proactive and should be started as early as possible after onset of symptoms.

5.6.5 Management of diarrhea and hydration status following treatment with afatinib

Diarrhea occurs at a high frequency and generally begins within 2 weeks of exposure to afatinib. Although usually mild to moderate, diarrhea may lead to dehydration and compel treatment modification or discontinuation, so early management is essential (Table 10). At the time of initiation of treatment with afatinib patients should be given a supply of loperamide to keep with them at all times or access to afatinib should be confirmed; and patients should be counselled on the appropriate use.

Patients must be advised to drink an adequate amount of fluids to make up for the fluid lost through diarrhea. (5)

Table 10: Grade specific treatment recommendations for afatinib related diarrhea

Severity (CTCAE Grading)	Description	Intervention Concerning Afatinib Treatment	Specific Intervention
Mild (Grade 1)	Increase of < 4 stools per day over baseline; mild increase in ostomy output compared with baseline	Continue same dose	Stop laxatives and advise patient to drink at least 8-10 glasses of water of clear fluids per day; 4 mg (2 tablets) of loperamide to be taken immediately, followed by 2 mg (1 tablet) after each loose stool until bowel movements cease for 12 hours
Moderate (Grade 2)	Increase of 4-6 stools per day over baseline; IV fluids indicated < 24 hours; moderate increase in ostomy output compared with baseline; not interfering with ADL	Continue same dose unless Grade 2 diarrhea continues for ≥ 2 days (48 hours) in which case treatment must be interrupted until recovered to ≤ Grade 1 followed by dose reduction	Continue loperamide; assess for dehydration and electrolyte imbalance; consider IV fluids and electrolyte replacement
Severe (Grade 3)	Increase of ≥ 7 stools per day over baseline; incontinence; IV fluids >24 hours; hospitalization; severe increase in ostomy output compared with baseline; interfering with ADL	Dose interruption until recovered to ≤Grade 1 followed by dose reduction*	See Grade 2; plus: an infectious process should be ruled out with stool cultures; aggressive iv fluid replacement ≥ 24 hours; hospitalization to monitor progress; consider prophylactic antibiotics if patient is also neutropenic;
Life threatening (Grade 4)	Life-threatening consequences (e.g. hemodynamic collapse)	Dose interruption until recovered to ≤Grade 1 followed by dose reduction*	See Grade 3

* If despite optimal supportive care and a treatment interruption, diarrhea does not resolve to CTC AE Grade ≤1 within 14 days, treatment with afatinib must be permanently discontinued. In the event that the patient is deriving obvious clinical benefit according to the investigator's judgment, further treatment with afatinib will be decided in agreement between the company supporter and the investigator.

5.6.6 Management recommendations for dermatological AEs following treatment with afatinib

Dermatologic AEs of afatinib include rash, acne, dermatitis acneiform, and dry skin. General recommendations for prophylaxis are summarized in Table 11 and grade-specific treatment recommendations are summarized in Table 12 and 13. For dose adjustment of afatinib refer to Table 6.

Specific interventions should be reassessed at least after 2 weeks or at any worsening of

symptoms, in which case the specific intervention should be adjusted and, depending on own clinical experience, early involvement of a dermatologist should be considered. (4).

Table 11: General recommendations for prophylaxis while receiving afatinib

Personal hygiene	• Use of gentle soaps and shampoos for the body, e.g. pH5 neutral bath and shower formulations and tepid water. • Use of very mild shampoos for hair wash. • Only clean and smooth towels are recommended because of potential risk of infection. The skin should be patted dry after a shower, whereas rubbing the skin dry should be avoided. • Fine cotton clothes should be worn instead of synthetic material. Shaving has to be done very carefully. • Manicure, i.e. cutting of nails, should be done straight across until the nails no longer extend over the fingers or toes. Cuticles are not allowed to be trimmed because this procedure increases the risk of nail bed infections
Sun protection	• Sunscreen should be applied daily to exposed skin areas regardless of season. Hypoallergenic sunscreen with a high SPF (at least SPF30, PAPA free, UVA/UVB protection), preferably broad spectrum containing zinc oxide or titanium dioxide are recommended • Patients should be encouraged to consequently stay out of the sun. • Protective clothing for sun protection and wearing a hat should be recommended.
Moisturizer treatment	• It is important to moisturize the skin as soon as anti-EGFR therapy is started. • Hypoallergenic moisturizing creams, ointments and emollients should be used once daily to smooth the skin and to prevent and alleviate skin dryness. • Note: avoid greasy creams (e.g. petrolatum, soft paraffin, mineral oil based) and topical acne medications
Prevention of paronychia	• Patients should keep their hands dry and out of water if ever possible. • They should avoid friction and pressure on the nail fold as well as picking or manipulating the nail. • Topical application of petrolatum is recommended around the nails due to its lubricant and smoothing effect on the skin.

Table 12: Grade specific treatment recommendations of skin reactions to afatinib

Severity	Description	Specific intervention
ACNEIFORM RASH		
Mild (Grade 1)	Macular or papular eruptions or erythema without associated symptoms	Consider topical antibiotics, e.g. clindamycin 2% or topical erythromycin 1% cream of metronidazole 0.75% or topical nadifloxacin 1%; Isolated scattered lesion: cream preferred Multiple scattered areas: lotion preferred
Moderate (Grade 2)	Macular or papular eruptions with pruritus or other associated symptoms; localized desquamation or other lesions covering <30% of BSA	Topical treatment as for Grade 1 plus short term topical steroids, e.g., prednicarbate cream 0.02% plus an oral antibiotic (for at least 2 weeks) e.g. Doxycycline 100mg b.i.d. or Minocycline hydrochloride 100mg b.i.d
Severe (Grade 3)	Severe, generalized erythroderma or macular, popular or vesicular eruption; desquamation covering ≥30% of BSA; associated with pain, disfigurement, ulceration or desquamation	Topical and systemic treatment as for Grade 2. Consider referral to dermatologist Consider systemic steroids
Life threatening (Grade 4)	Generalized exfoliative, ulcerative, or bullous dermatitis	See Grade 3 Systemic steroids are recommended
EARLY AND LATE XEROTIC SKIN REACTIONS - PRURITUS		
Mild (Grade 1)	Mild or localized	Topical polidocanol cream. Consider oral antihistamines, e.g. diphenhydramine, dimethindene, cetirizine, levocetirizine, desloratidine, fexofenadine or clemastine)
Moderate (Grade 2)	Intense or widespread	See Grade 1 plus oral antihistamines; Consider topical steroids, e.g., topical hydrocortisone
Severe (Grade 3)	Intense or widespread and interfering with activities of daily living (ADL)	See Grade 2.
XEROSIS (DRY SKIN)		
Mild (Grade 1)	Asymptomatic	Soap-free shower gel and/or bath oil. Avoid alcoholic solutions and soaps. Urea- or glycerin-based moisturizer. In inflammatory lesions consider topical steroids (e.g., hydrocortisone cream)
Moderate (Grade 2)	Symptomatic, not interfering with ADL	See Grade 1. In inflammatory lesions consider topical steroids (e.g., hydrocortisone cream)
Severe (Grade 3)	Symptomatic, interfering with ADL	See Grade 2. Topical steroids of higher potency (e.g., prednicarbate, mometasone furoate) Consider oral antibiotics

FISSURES		
Mild (Grade 1)	Asymptomatic	Petroleum jelly, Vaseline® or Aquaphor for 30 minutes under plastic occlusion every night, followed by application of hydrocolloid dressing; antiseptic baths (e.g. potassium permanganate therapeutic baths, final concentration of 1:10,000, or povidone-iodine baths) Topical application of aqueous silver nitrate solutions to fissures
Moderate (Grade 2)	Symptomatic, not interfering with	See Grade 1. Consider oral antibiotics.
Severe (Grade 3)	Symptomatic, Interfering with ADL	See Grade 2.
[1] If Grade 2 rash persists for ≥7 days despite treatment and is poorly tolerated by the patient, the investigator may choose to pause treatment up to 14 days followed by a reduction in the dose of afatinib according to the dose reduction scheme in Table 6.		

5.6.7 Management of mucositis/stomatitis

General and grade specific recommendations are described inTable 13. For dose adjustment refer to Section 5,2 and for restrictions on concomitant therapies refer to Section 5.6.

Treatment is supportive and aimed at symptom control. These may include atraumatic cleansing and rinsing with non-alcoholic solutions such as normal saline, diluted salt and baking soda solution (e.g. one-half teaspoonful of salt and one teaspoon of baking soda in one quart of water every four hours); avoidance of agents containing iodine, thyme derivatives and prolonged use of hydrogen peroxide; dietary maneuvers such as promotion of soft, non irritating foods like ice-creams, mashed/cooked vegetables, potatoes and avoidance of spicy, acidic or irritating foods such as peppers, curries, chillies, nuts and alcohol. If the patient is unable to swallow foods or liquids, parenteral fluid and/or nutritional support may be needed. Examples of some of the agents suggested in Table 13 include: topical analgesics –viscous lidocaine 2%; mucosal coating agents - topical kaolin/pectin; oral antacids, maltodextrin, sucralfate; topical antifungals – nystatin suspension. (adapted from (8)).

Table 13: Grade specific treatment recommendations of study-drug related mucositis/stomatitis

Severity (CTCAE Grading)	Description	Treatment Recommendations	Intervention Concerning Afatinib Treatment/Dose Modification
Mild (Grade 1)	Minimal symptoms; normal diet	Oral rinses with agents such as non-alcoholic mouthwash,normal saline, diluted salt and baking soda solution.	No change.
Moderate (Grade 2)	Symptomatic, but can eat and swallow modified diet	Addition of topical analgesic mouth treatments, topical corticosteroids, antiviral therapy if herpetic infection confirmed, antifungal therapy preferably topical on a case by case basis.	Maintain dose if tolerable; Hold dose if intolerable until recovery to grade ≤1, then restart at the same dose.
Severe (Grade 3)	Symptomatic and unable to adequately aliment or hydrate orally	Same as for Grade 2; institute additional symptomatic therapy (topical or systemic) as clinically indicated .	Hold dose until recovery to grade ≤1 or baseline, then restart at the reduced dose according to Section 5.2.
Life threatening (Grade 4)	Symptoms associated with life-threatening consequences	Same as for Grade 2; institute additional symptomatic therapy (topical or systemic) as clinically indicated	Hold dose until recovery to grade ≤1 or baseline, then restart at the reduced dose according to Section 5.2

5.7 Diet/Activity/Other Considerations

5.7.1 Diet

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

Patients should be advised to avoid any foods known to aggravate diarrhea.

5.7.2 Contraception

MK-3475 and afatinib may have adverse effects on a fetus in utero. Furthermore, it is not known if MK-3475 has transient adverse effects on the composition of sperm.

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

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 true abstinence[†] from heterosexual activity, if this is the preferred and usual lifestyle

OR

(2) use (or have their partner use) highly effective methods of contraception during heterosexual activity.

Highly effective methods of contraception for men and women are[‡]:

- Male sterilization (vasectomy). For female patients, the vasectomized male partner should be the only partner
- Female sterilization
- intrauterine device (IUD) (copper or hormonal)
- vasectomy of a female subject's male partner
- Contraceptive subdermal implant (Nexplanon)
- Hormonal birth control (i.e., contraceptive pill, patch, ring or injection) for subject or for male patient's female partner

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

Unacceptable methods for men and women:

- Abstinence at certain times of the cycle only, such as during the days of ovulation, after ovulation (based on symptoms or temperature)
- Pre-ejaculatory withdrawal
- Condom with spermicidal foam/gel /film/cream/suppository
- Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository

†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.

‡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 they must adhere to the contraception requirement (described above) for the duration of the study and during the follow-up period defined in section 7.2.2-Reporting of Pregnancy and Lactation to the Sponsor-Investigator, Merck and Boehringer Ingelheim. If there is any question that a subject will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

5.7.3 Use in Pregnancy

If a subject inadvertently becomes pregnant while on treatment with MK-3475 and afatinib, 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 company supporters and Investigator to Merck and Boehringer Ingelheim without delay and within 24 hours to the Sponsor and within 2 working days to Merck if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The 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 company supporters. If a male subject impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to the Sponsor-Investigator and to Merck and followed as described above and in Section 7.2.2.

5.7.4 Use in Nursing Women

It is unknown whether MK-3475 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.

5.8 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 company supporter 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 by RECIST 1.1

Note: A subject may be granted an exception to continue on treatment with confirmed radiographic progression if clinically stable or clinically improved by the primary investigator in consultation with the sponsor.

- 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 MK-3475 or 35 administrations of study medication, whichever is later
  Note: 24 months of study medication is calculated from the date of first dose.
- 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. 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.

5.8.1 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 had at least two treatments with pembrolizumab beyond the date when the initial CR was declared. Subjects who then experience radiographic disease progression may be eligible for up to one year of additional treatment with pembrolizumab via the Second Course Phase at the discretion of the investigator if no cancer treatment was administered since the last dose of pembrolizumab, the subject meets the safety parameters listed in the Inclusion/Exclusion criteria, and the trial is open. Subjects will resume therapy at the same dose and schedule at the time of initial discontinuation. Additional details are provided in Section 7.1.5.5.

5.9 Subject Replacement Strategy

Patients who consent for the study and do not receive MK-3474 or afatinib on study will be replaced.

Patients who receive <80% of the MK-3475 and afatinib infusion in Cycle 1 (e.g., because the infusion had to be discontinued due to an infusion reaction) and did not experience a DLT will not be taken into account in the assessment of the overall DLT rate for the particular dose level cohort and will need to be replaced.

5.10 Clinical Criteria for Early Trial Termination

Early trial termination will be the result of the criteria specified below:

1. Quality or quantity of data recording is inaccurate or incomplete

2. Poor adherence to protocol and regulatory requirements

3. Incidence or severity of adverse drug reaction in this or other studies indicates a potential health hazard to subjects

4. Plans to modify or discontinue the development of the study drug

In the event of Merck and Boehringer Ingelheim decision to no longer supply study drug, ample notification will be provided so that appropriate adjustments to subject treatment can be made.

6.0 TRIAL FLOW CHART

6.1 Study Flow Chart

Trial Period:	**Screening Phase**	**Treatment Cycles[1,9]**								**End of Treatment**
	Main Study Screening (Visit 1)	1	2	3	4	To be repeated beyond 8 cycles				Discontinuation Visit/Safety Follow Up Visit/PFS follow up
						5	6	7	8	
Scheduling Window (Days)[2]:	-30 to -1	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	
Informed Consent	X									
Inclusion/Exclusion Criteria	X									
Demographics and Medical History	X									
Prior and Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X
Trial Treatment Administration		X	X	X	X	X	X	X	X	
NSCLC Disease Details and Prior Treatment	X									
Review Adverse Events		X	X	X	X	X	X	X	X	X
Full Physical Examination	X									
Directed Physical Examination		X	X	X	X	X	X	X	X	
Vital Signs and Weight[12]	X	X	X	X	X	X	X	X	X	
Zubrod Performance Status	X	X	X	X	X	X	X	X	X	X
Pregnancy Test – Urine or Serum β-HCG[3,6]	X									
PT/INR and aPTT[4,6]	X[5]									
CBC with Differential[6]	X[5]	X	X	X	X	X	X	X	X	X
Comprehensive Serum Chemistry Panel (see	X[5]	X	X	X	X	X	X	X	X	X
Urinalysis[6]	X[5]									
T3, FT4 and TSH[6]	X[5]		X		X		X		X	X

Trial Period:	**Screening Phase**	**Treatment Cycles[1,9]**								**End of Treatment**
Treatment Cycle/Title:	Main Study Screening (Visit 1)	1	2	3	4	To be repeated beyond 8 cycles				Discontinuation Visit/Safety Follow Up Visit
						5	6	7	8	
Scheduling Window (Days)[2]	-30 to -1		± 3	± 3	± 3	± 3	± 3	± 3	± 3	
Efficacy Measurements										
Tumor Imaging[7]	X			X			X			
Brain Imaging (MRI or CT Scan)[13]	X									
Tumor Biopsies/Archival Tissue Collection/Correlative Studies Blood										
Tissue Collection[10]	X (must be within 60 days)			X						
EGFR Mutation Testing[8]	X									
Correlative Studies Blood Collection[11]	X			X			X			X

1. In general, assessments/procedures are to be performed on Day 1 and prior to the first dose of trial treatment for each cycle unless otherwise specified. Treatment cycles are 3 weeks (21-days); however the MK-3475 treatment cycle interval may be increased due to toxicity according to the dose modification guidelines provided. If treatment cycles are increased all procedures except imaging will be completed according to the Cycle number and not weeks on treatment, imaging will be performed every 6 weeks (± 3 days) from the first dose of trial treatment regardless of any treatment delays. Weekly (D8 and D15 +/- 3 days) follow up visits for the first cycle when starting afatinib is recommended (when afatinib is added (Cohort A C1D1 and Cohort B C3D1).
2. In general, the window for each visit is ± 3 days unless otherwise specified.
3. For women of reproductive potential, a urine or serum pregnancy test will be performed within 72 hours prior to first dose of trial treatment. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test, performed by the local study site laboratory, will be required. Pregnancy tests (serum and/or urine tests) should be repeated if required by local guidelines.
4. Coagulation factors (PT/INR and aPTT) should be monitored closely throughout the trial for any subject receiving anticoagulant therapy.
5. Laboratory tests for screening are to be performed within 10 days prior to the first dose of trial treatment.
6. After Cycle 1, lab samples can be collected up to 72 hours prior to the scheduled time point. Laboratory results must be known and acceptable prior to dosing.
7. The initial tumor imaging will be performed within 30 days prior to the first dose of trial treatment. Scans performed as part of routine clinical management are acceptable for use as the screening scan if they are of diagnostic quality and performed within 30 days prior to the first dose of trial treatment. On-study imaging will be performed every 6 weeks (42 -7 days) after the first dose of trial treatment or more frequently if clinically indicated. The timing for imaging studies should follow calendar days and should not be adjusted for delays in cycle starts or extension of MK-3475/afatinib cycle frequencies. The same imaging technique should be used in a subject throughout the trial. CT including the chest, abdomen and pelvis or PET-CT is required for the baseline assessment.
8. Provide documentation of the subject's tumor EGFR mutation from a CLIA certified laboratory.
9. MK-3475 can be administered for up to 2 years. For the dose de-escalation and Cohort (Arm) A (concurrent afatinib and MK-3475) both drugs will be administered as outlined in this protocol starting with cycle #1. For cohort B. MK-3475 will be initiated with cycle #1 and afatinib will commence in combination with MK-3475 starting with cycle #3.
10. Tumor biopsy for immune and EGFR biomarker analysis will be performed prior to Cycle 1 of treatment either on archival tissue or fresh biopsy (within 60 days). Repeat biopsy will be performed prior to initiation of cycle 3 (42 days (-7 days))
11. Correlative blood draws for immune correlates will be performed prior to cycle 1 (- 3 days), prior to cycle 3 (-3 days), prior to cycle 6 (-3 days) and at progression (+/- 5 days). Correlative blood draws for plasma tumor cfDNA will be performed at baseline, every 2 cycles (+/- 3 days) and at progression (+/- 5 days).
12. Vital signs to include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at screening only.
13. Contrast enhanced MRI brain or CT head is recommended. If contrast is contraindicated, a non-contrast enhanced study may be performed.

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.

Furthermore, additional evaluations/testing may be deemed necessary by the Sponsor-Investigator and/or Merck and/or Boehringer-Ingelheim for reasons related to subject safety. In some cases, such evaluation/testing may be potentially sensitive in nature (e.g., HIV, Hepatitis C, etc.), and thus local regulations may require that additional informed consent be obtained from the subject. In these cases, such evaluations/testing will be performed in accordance with those regulations.

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.

7.1.1.1.1 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.

Specifics about a trial and the trial population will be added to the consent form template at the protocol level.

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

7.1.1.4.1 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.

7.1.1.4.2 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

7.1.1.5.1 Disease Details

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

7.1.1.5.2 Prior Treatment Details

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

7.1.1.5.3 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)

The study medication will be given in accordance with the protocol and the instructions of a site investigator.

The appropriate number of afatinib tablets for 3 weeks of treatment will be provided to patients to be self-administered at home.

Patients will be asked to bring the remaining trial medication at the end of each 3 week to the investigator site for a compliance check. The remaining film-coated tablets will be counted by the investigator/site staff and recorded at the investigator site. Discrepancies between the number of tablets remaining and the calculated number of tablets the patients should have taken must be documented and explained. At the end of each 3 week, any remaining medication will be collected. If the patient is eligible for further treatment, a new bottle of study medication must be dispensed.

The investigator can withdraw a patient from the study in the event of serious and persistent non-compliance which jeopardizes the patient's safety or render study results for this patient unacceptable. Patients who do not attend a minimum of 75% of scheduled study visits, unless due to exceptional circumstances, should be discussed with the company supporter and be evaluated for compliance.

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 12.2). Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

For subjects receiving treatment with MK-3475 all AEs of unknown etiology associated with MK-3475 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). See the separate ECI guidance document in the appendix (Section 12.9) regarding the identification, evaluation and management of potential irAEs.

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

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 (on day 1 prior to MK-3475) 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/Zubrod) Performance Scale

The investigator or qualified designee will assess ECOG status (see Section 12.1) at screening, 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

For the purposes of this study, patients should be re-evaluated for response after cycle 2 (6 weeks) and then every 2 cycles (6 weeks). In addition to a baseline scan, confirmatory scans should also be obtained at least 4 weeks following initial documentation of objective response.

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:

- PET-CT At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

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

Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with *MK-3475 and afatinib.*

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

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

Disease Parameters

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

Note: Tumor lesions that are situated in a previously irradiated area are measurable if there is evidence of growth post-radiation such as increase in size on CT or increase in FDG avidity on PET.

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

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

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

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

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

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

Response Criteria

Evaluation of Target Lesions

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

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

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

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Evaluation of Non-Target Lesions

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

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

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

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

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

Evaluation of Best Overall Response

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

For Patients with Measurable Disease (i.e., Target Disease)

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

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.
Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration."* Every effort should be made to document the objective progression even after discontinuation of treatment.

For Patients with Non-Measurable Disease (*i.e.*, Non-Target Disease)

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

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

Duration of Response

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

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

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

Progression-Free Survival

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

Response Review

Response review will be done by the investigator.

7.1.3 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below.

7.1.3.1 Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

Laboratory tests for hematology, chemistry, urinalysis, and others are specified in the trial flow chart (Section 6) and section 12.7. The total amount of blood/tissue to be drawn/collected over the course of the trial (from pre- trial to post-trial visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per subject.

Laboratory tests for screening or entry into the Second Course Phase should be performed within 10 days prior to the first dose of treatment. After Cycle 1, pre-dose laboratory procedures can be conducted up to 72 hours prior to dosing. Results must be reviewed by the investigator or qualified designee and found to be acceptable prior to each dose of trial treatment.

7.2 Correlative Studies

Correlative Studies

Study-specific correlatives are outlined below. Remaining extra plasma and tissue after these studies are performed may be used for additional research studies focusing on molecular pathways of resistance to EGFR-directed therapy and additional immune markers.

A Study ID number will be assigned to each patient and will be used in sample coding instead of the name. The key linking the number with the patient identity and clinical outcomes will be kept by Dr. Riess and his research staff. This will be kept in a locked location.

7.2.1 EGFR-directed Correlative Studies

7.2.1.1 Plasma EGFR-mutant DNA

Molecular Studies: Blood

- Plasma DNA/RNA detection of EGFR and PD-L1

Prior to each cycle of treatment, two tubes of blood (1 for RNA and 1 for DNA) will be collected for EGFR and PD-L1 DNA and RNA quantification. Tubes will be provided in a collection kit from Liquid Genomics. The assay will be performed by Liquid Genomics, which has validated DNA and RNA assays for EGFR mutations and PD-L1 RNA levels. Please see Appendix 12.6 for tube collection and shipping instructions.

Please be sure to order kits from Liquid Genomics at the time of study activation (if not already available at the site).

7.2.1.2 EGFR-Activating Mutations and Mechanisms of Resistance to EGFR-TKIs on Biopsied Tumor Specimens

7.2.1.3 Standard-of-Care Baseline Biopsy

Biopsy of a patient's tumor upon progression with erlotinib to examine EGFR-resistance mechanisms such as EGFR T790M and rule out small cell histologic transformation is considered standard-of-care. The biopsied tissue performed at baseline will be sent to Foundation Medicine (for patients at UC Davis) or equivalent CLIA-certified assay for confirmation of EGFR-mutation status and determination of EGFR-T790M resistance mutation, following usual clinical procedures. If tissue permits, other mechanisms of resistance will be examined, prioritizing MET amplification, HER2 amplification, PIK3CA specific and pathway mutations, and MEK pathway mutations. (Biopsy must be performed within 60 days of consent).

7.2.2 Repeat Biopsies for EGFR-mutation Status and Immune Correlates

In all patients following consent, two biopsies will be attempted on study: one prior to initiation of study treatment and one after cycle #2 of treatment before initiation of cycle 3. This will be approximately week 5-6 on study (see study calendar). Patient consent for biopsies will be a study requirement.

Biopsies will be performed by a qualified professional and will be tailored to the available disease targets. Potential biopsies could include image-guided core biopsy, or limited surgical or pulmonary interventional biopsy. Image-guided tumor biopsies will be obtained with the help of the Interventional Radiology or Radiology team by a percutaneous approach or by the assistance of our surgical or pulmonary colleagues. Alternative biopsy techniques (e.g. transbronchial, skin punch biopsy) will be considered if indicated after discussion with the principal investigator. When a core biopsy is performed, it is preferred that a core biopsy system be used to obtain at least 3 core biopsies not less than 22 gauge in diameter and 1 cm in length (6 core biopsies is ideal).

If a site is deemed appropriate for biopsy with minimal risk to the participant by agreement between the investigators and biopsy team, a biopsy will be attempted. The use of imaging to facilitate biopsies will be decided by members of the Interventional Radiology or Radiology team and may include an ultrasound (US), a computer tomography (CT) scan, or a magnetic resonance imaging (MRI) scan. Should a CT scan be needed for biopsy, the number of scans for each procedure will be limited to the minimum number needed to safely obtain a biopsy. Tumor biopsies and local anesthesia will be administered only if they are considered to be of low risk to the participant, as determined by the investigators and/or the interventionist.

Tissue Study Requirements on Treatment Listed in Order of Priority

Test	Institution or commercial entity	Baseline Biopsy (slides)	On Treatment Biopsy (Prior to Cycle 3)
Standard-of-Care Genomic Testing in CLIA Certified Lab	Investigator Choice	Per SOC Guidelines	X
PD-L1 and QIF	Yale Translational Immuno-Oncology	5 slides minimum, 10 slides optimal	5 slides minimum, 10 slides optimal
Next Generation Sequencing with Mutational Load*	Broad Institute	10 slides minimum 20 slides optimal. (RNA later processing if available)	10 slides minimum, 20 slides optimal.

RPPA for on target EGFR-inhibition (EGFR, p-EGFR, pERK, ERK, pAKT, AKT), caspase 3 cleavage	Theranostics	3-5 unstained slides	3-5 unstained slides
* Companion blood draw in kit for germline DNA comparison			

7.2.2.1 Standard-of-Care Genomic Testing

Tumor biopsy at baseline will be sent for standard molecular testing at a CLIA-certified lab for confirmation of EGFR activating mutation and to detect the presence or absence of an EGFR-T790M mutation as well as other resistance mechanisms to EGFR-TKI. When possible, the post-TKI specimen will be compared to the diagnostic block to identify treatment-induced differences in molecular profiles.

7.2.2.2 PD-L1 and Evaluation of TILS

The PD-L1 immunohistochemistry will be performed in 3-5 μm-thick histology preparations obtained from conventional biopsy formalin-fixed, paraffin-embedded (FFPE) tissue samples. The tumor PD-L1 protein will be tested using the FDA-approved Dako 22C3 assay using chromogenic immunohistochemistry in the Yale Pathology Labs or UC Davis under CLIA laboratory conditions. The scoring procedure will include the determination of the percentage of positive cells in the tumor by a surgical pathologist using bright field microscopy. The score will be semi-quantitative and determined based on the percentage of positive cells.

The level of major TIL subtypes, TIL activation/proliferation and expression of major immune inhibitory receptors will be evaluated using multiplexed quantitative immunofluorescence (QIF) performed in 3-5 μm-thick histology preparations obtained from formalin-fixed, paraffin-embedded (FFPE) tissue samples, as previously reported (Schalper KA, Brown J, Carvajal-Hausdorf D, McLaughlin J, Velcheti V, Syrigos KN, et al. Objective measurement and clinical significance of TILs in non-small cell lung cancer. J Natl Cancer Inst. 2015;107.). We will perform three multiplexed QIF panels containing the following markers: Panel #1: DAPI/CD4/CD8/CD20; Panel #2: DAPI/CD3/Granzyme-B/Ki-67; and Panel #3: DAPI/CD3/PD-1/TIM-3/LAG-3. The Yale group has already performed validation of the antibodies and combined these markers into multiplexed QIF panels. Simultaneous measurements of the targets will be performed using multispectral imaging and the AQUA® method providing continuous fluorescence marker scores. Eventually, quantification of positive cells for each marker will also be performed using the Vectra multispectral imaging platform with the cell phenotyping tool of the InForm® software; and reported as cell density (number of cells/area unit).See section 7.2.4 for processing and shipping information for the PD-L1 and QIF samples.

7.2.2.3 Next-Generation Sequencing with Mutational Load and Reverse-phase protein arrays (RPPA)

Next-Generation Sequencing (DNA and RNA - if sufficient tissue available) of the Stand Up 2 Cancer (SU2C) Customized Gene Panel which is the standard for the Lung Cancer dream team with a focus on resistance mechanisms to EGFR-TKI and quantifying mutational load will be performed at the Broad Institute. This will be performed at baseline biopsy unless tissue amount is inadequate where it will be performed on the on-treatment biopsy. When requested, the Broad Institute Samples lab will ship sample collection kits to research site. A companion blood collection tube will also be provided and should be collected at baseline for germline mutation testing.

Kits are specific for Material Type collected

i. Labels – FFPE or Frozen Tumors
ii. Labels – Blood or Buffy Coat Samples
iii. Matrix Kits – DNA or RNA analytes

1. Researcher fill kit & provides Sample Kit Metadata spreadsheet (example provided).
2. Kits are shipped back to the Broad Institute Samples lab per instructions provided in the kits. (See Attached Documents). Specimens should be coded with a unique identifier (ie., Institution, Clinical Trial Number, patient number and biopsy number in sequence (ie. for patient 1, UCD250-001-01 (baseline biopsy), UCD250-001-02 (on-treatment biopsy), UCD250-001-03 (post progression biopsy).

Sample Processing & Data Generation will proceed. (Turnaround Time is expected to be 5-6 weeks for Exome runs). RNA sequencing will be batched so timeline will be more variable.

7.2.3 Immunology Correlates

Immune correlates will be performed by Yale University Translational Immuno-Oncology or the Human Immune Monitoring Core (HIMC) at UC Davis as outlined below.

PD-L1 expression will be assayed using Merck's proprietary 22C3 antibody that is FDA approved as a companion diagnostic for pembrolizumab for quantifying PD-L1 expression for MK-3475 trials in NSCLC and melanoma including Garon, Edward B. Naiyer A. Rizvi. "**Pembrolizumab for the Treatment of Non–Small-Cell Lung Cancer.**" nejm.org. The New England Journal of Medicine. April 19, 2015.

7.2.3.1 Biopsied tumor for PD-L1 Quantification

PD-L1 expression by immunohistochemistry at baseline and in repeat biopsy specimens to assess for changes in PD-L1 expression in response to treatment will be conducted by UC Davis or Yale Translational Immuno-Oncology using the FDA approved DAKO 22C3

antibody and by quantitative IHC.

7.2.3.2 Biopsied tumor for Tumor Infiltrating Lymphocytes and Subsets and RT-PCR for Immune Markers

In baseline and on treatment biopsies, the HIMC at UC Davis or Yale University Immunology Core will quantify changes in tumor infiltrating lymphocytes and immune subsets using IHC for T-cell subsets that include CD4, CD8, and Foxp3. Real time-PCR for immune markers (if tissue size permits) including CD3, PD-1, GranzB, Perforin, IL-2, IFNg, Tim3, LAG3, CTLA-4, Foxp3 will be performed if adequate tissue is available.

7.2.4 EGFR & Immunology Biopsy Processing

Tumor tissue obtained at each biopsy time point will be collected by a representative of the study team. At the first biopsy, one of the cores will be submitted directly to Pathology for clinical interpretation and report as well as standard of care molecular studies. The remaining cores will be delivered to UC Davis Research Pathology, Pavilion Room 2P524 (*or corresponding local research lab at other trial sites*) and divided into 2 components.

At least two core biopsies not less than 22 gauge in diameter and 1cm in length or tissue the equivalent of core biopsies sufficient to generate at least 20 cut slides should be paraffin embedded and stored in research pathology until ready for processing and shipping. Ideally, 6 cores per biopsy timepoint should be obtained. At the first timepoint 2 cores should be used for histologic confirmation and standard molecular testing. 2 cores should be paraffin embedded for IHC of PD-L1 and other markers of the tumor immune microenvironment. At UC Davis, this FFPE specimen may also be stored in the laboratory of Dr. Philip Mack or the UC Davis HIMC for storage until sent for further testing.

If available, two additional cores should be immediately stored in 2ml of RNAlater solution (Life Technologies) (the tissue portion should be processed into pieces, each less than 0.5cm^3) for comprehensive DNA/RNA sequencing at the Broad Institute. The Samples in RNAlater solution should be kept refrigerated until processed at HIMC. This should be delivered to the Human Immune Monitoring Core with the contact information listed below. If not enough cores are obtained DNA/RNA sequencing can be sent of the initial FFPE tissue

Specimens in RNA Later should be shipped on cool packs (Monday – Thursday only) to:

Human Immune Monitoring Core (Maverakis Laboratory)
Department of Dermatology
UC Davis School of Medicine
IRC Bldg., Room 1630
2921 Stockton Blvd.
Sacramento CA 95817

LAB: 916-734-2156

Tissue from the second biopsy timepoint will be divided into the 2 research components with the procedures outlined above. Component 1: at least 2 cores or enough tissue for 20 cut slides as specified for initial biopsy for FFPE for PD-L1 and additional IHC quantification by UC Davis or Yale and 2: remaining cores in RNA later solution then FFPE for DNA/RNA sequencing. **(If no cores were available for processing with RNA later in the initial biopsy, the repeat biopsy should all go through FFPE and not through an RNA later step).** A research H&E slide will also be generated and reviewed by a research pathologist to confirm presence of tumor.

If there is limited tissue for the baseline biopsy priority should be given to pathologic assessment and molecular testing at Response Genetics per standard of care and then PD-L1 testing by the central vendor. For the repeat biopsy priority should be given for PD-L1 and additional IHC testing by the central vendor and UC Davis HIMC.

RPPA will be performed at Theranostics using their established procedures for FFPE samples under their CAP-accredited CLIA laboratory. Our previous experience with this resource is that, for phosphorylation states of intracellular signaling molecules, the assay is highly quantitative and correlates with Western blotting analysis conducted at UC Davis. The following analytes will be performed, listed in order of priority (although measured simultaneously): pEGFR, totalEGFR, pERK, totalERK, pAKT, totalAKT, caspase 3 cleavage.

7.2.4.1 Immunohistochemistry and Quantitative Immunofluorescence

Immunohistochemistry and Quantitative Immunofluorescence: Staining for PD-L1, relevant immunoproteins and tumor infiltrating immune cells will be performed by the SU2C Immune Core at Yale University as outlined below. Tissue samples will be collected from participants who have been properly consented and who have agreed to participate in the research study. Tumor tissues are optimally suitable for IHC/QIF studies if fixed in 10% neutral buffered formalin (NBF) for 16-24 hours and processed into paraffin blocks using clinical-grade pathology laboratory conditions.

1. Select the tumor block and obtain one Hematoxylin & Eosin (H&E) stained slide for review by site pathologist to confirm diagnosis and ensure presence of tumor cells. For in situ analyses, there is no lower limit in the amount of tumor cell content.

    a. Samples with few tumor cells (<100-200 cells) may be insufficient for PD-L1 immunostaining but should still be submitted for the QIF studies of TILs and other stromal markers.

3. If pathologist review is not possible or available at the site, the H&E slides or a digital version may be sent directly to Yale Pathology for initial assessment.

3. Obtain 5 additional serial 4-5µm thick sections from the reviewed paraffin block and place each section in a positively-charged glass histology slide. Tissues should be cut and

processed using conventional, clinical-grade in-house histology protocols. Paraffin dipping of slides after sectioning is not recommended.

4. Collect 5 freshly cut (<5 days) unstained serial section slides from each case, label each preparation using the SU2C coding system and place them in a conventional plastic histology slidebox. Make sure slides are in a firm position to avoid damage during transportation and cover with paper towel prior to packing to prevent movement within the box. If possible, also include the sectioning order on the label for each slide.

   a. Whenever feasible, blocks should be processed in batches, and shipped together within a 5-day period after sectioning.

5. Include H&E stained preparation together with the 5 unstained sections in the slidebox. This slide will be digitalized and become available for review within the SU2C group. Specimens should be coded with a unique identifier (ie. institution, trial number, patient number and biopsy number in sequence (ie. for UC Davis patient 1, UCD250-001-01 (baseline biopsy), UCD250-001-02 (on-treatment biopsy), UCD250-001-03 (post progression biopsy).

6. Seal the slidebox using Parafilm and/or a plastic envelope and wrap with bubble wrap prior to shipping. Include detailed sender information (with email) and ship using overnight service to:

   Attention to: Nikita Mani (nikita.mani@yale.edu).
   Backup contact should Nikita be out is Ila Datar (ila.datar@yale.edu)
   Address: BML112/BML113
   Department of Pathology
   Yale School of Medicine
   310 Cedar Street
   New Haven, CT 06510
   Phone 1: 203-737-4205
   Phone 2: 203-785-3588

   A confirmation of sample reception will be sent via email to the sender within 72 hours.

7. Slides will be stained for IHC and the QIF panels within 5 working days from reception in the lab or stored in appropriately until use and batched to accommodate projects in single experimental runs (whenever possible).

8. Results of the analyzed markers will be provided as continuous scores using fluorescence intensity scores and/or phenotype cell counts. The turnaround time will depend on the amount of slides and project volume.

7.2.5 Immunology Peripheral Blood Processing

7.2.5.1 Peripheral blood Analysis of Changes in Immune Cell Subsets, T-Cell Repertoire, and Cytokines

Flow cytometry for immune cell subsets. (primarily T-cell subsets) will be performed in the Human Immune Monitoring Core (HIMC) at UC Davis. Expression levels determined by MFIs for markers will be compared at baseline and on treatment.

These: subsets will include:

- T cell subset panel: CD4, CD8, CD3, CD25, CD127, Foxp3 (ICS)
- T cell differentiation panel: CD4, CD8, CD3, CD45RA, CCR7 (extras: CD45RO, CD44)
- T cell exhaustion panel: CD4, CD8, CD3, PD-L1, PD-1, TIM3, (extras: LAG3, 2B4, CD160)
- T cell activation panel: CD4, CD8, CD3, HLA-DR, Fas, GranzB (ICS), CD28 (extras: ICOS, CD40L, FasL)

Luminex Assay for measurement of cytokines (25 plea) in plasma and supernatant after activation with CD3+ CD28 or PMA+Ionomycine will also be performed in the HIMC at UC Davis. (http://tools.lifetechnologies.com/content/sfs/manuals/LHC0009_Protocol.pdf).

7.2.5.2 Peripheral Blood Collection for Changes in Immune Subsets

From each patient, at the relevant time points indicated in the study calendar, blood will be withdrawn directly into two 10 mL lavender-topped (EDTA coated) tubes. Samples will be stored and assays run at the Human Immune Monitoring Core (Director: Emanual Maverakis laboratory at UC Davis).

Contact information listed below:

Human Immune Monitoring Core (Maverakis Laboratory)
UC Davis School of Medicine
IRC Bldg., Room 1630
2921 Stockton Blvd. Sacramento CA 95817
LAB: 916-734-2156

The HIMC laboratory (Director: Emanual Maverakis, MD) is a research laboratory at UC Davis with both immunology expertise and the appropriate equipment to carry out the proposed studies. These studies will include: Luminex Cytokine Assays to determine changes

in cytokine profiles in response to treatment and Flow Cytometry to detect changes in immune cell subsets.

The tubes should be centrifuged as soon as possible at approximately 800 x g for 10 minutes. Plasma should be transferred to a 15 mL conical tube and centrifuged a second time at 1000 – 1500 x g for 10 minutes. After the second centrifugation, aliquot plasma in 500 ul aliquots into labeled cryovials. For peripheral blood mononuclear cell (PBMC) preparation, replace the plasma removed with an equal amount of PBS (Ca and Mg free) in the original lavender-top tubes, and then slowly layer it on top of the 15ml of Ficoll in a 50ml conical tube, followed by centrifugation at 800 x g for 20 minutes with the break off. The buffy coat, a whitish layer of cells between the PBS and Ficoll layers above the red blood cell layer, should be collected and transferred into a new 50ml tube, washed once with 50ml of PBS, re-suspended in an appropriate volume of freezing medium and then transferred into labeled cryovials (10^7/ml/vial). All cryovials are then to be frozen as rapidly as possible, and stored in a -70 degree freezer until batch analysis is feasible by the HIMC.

Sites other than UC Davis may store per SOP until ready for shipment to UC Davis HIMC. Please contact Maverakis lab prior to shipment.

7.3 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 5.4 Attribution of adverse events and Section 7.5 - Assessing and Recording Adverse Events. Subjects who a) attain a CR or b) complete 24 months of treatment with MK-3475 may discontinue treatment. After discontinuing treatment following assessment of CR, these subjects should return to the site for a Safety Follow-up Visit and then proceed to the Follow-Up Period of the study.

7.4 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.

7.4.1 Screening

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

Approximately 30 days prior to enrollment, potential subjects will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5.1.Written consent must

be obtained prior to performing any protocol specific procedure. Results of a test performed prior to the subject signing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame. Screening procedures are to be completed within 30 days prior to the first dose of trial treatment except for the following:

Laboratory tests are to be performed within 10 days prior to the first dose of trial treatment. For women of reproductive potential, a urine pregnancy test will be performed within 72 hours prior to first dose of trial treatment. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test, performed by the local study site laboratory, will be required.

Tumor imaging must be performed within 30 days prior to the first dose of trial treatment.

7.4.2 Treatment Period

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

7.4. 3 Post-Treatment Visits

7.4.3.1 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, return to baseline, or it is deemed that further recovery is unlikely, whichever occurs first. SAEs that occur within 30 days of the end of treatment or before initiation of a new anti-cancer treatment should also be followed and recorded.

7.4.3.2 Follow-up Visits

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. Information regarding post-study anti-neoplastic treatment will be collected if new treatment is initiated.

7.4.3.2.1 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.

7.5 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 Merck's and/or BIPI product, is also an adverse event.

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

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

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

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

All adverse events that occur after the consent form is signed but before treatment allocation 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 washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

From the time of treatment allocation 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 7.5. The investigator will make every attempt to follow all subjects with non-serious adverse events for outcome.

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

All adverse events, serious and non-serious, will be collected, documented and reported to the

company supporter by the investigator on the appropriate CRFs / SAE reporting forms (BI and Merck SAE report form).

For each adverse event, the investigator will provide the onset date, end date, CTC AE grade, treatment required, outcome, seriousness, and action taken with the investigational drug. The investigator will determine the relationship of the investigational drug to all AEs as defined below.

Adverse events with onset within first administration of afatinib therapy and 28 days after last administration of afatinib will be considered as on treatment. All AEs, including those persisting after end of study treatment must be followed up until they have resolved or have been sufficiently characterized or the principal investigator decides to not further pursue them. Serious and non-serious adverse events occurring later than 28 days after last administration of trial drugs will only be reported in case they are considered drug-related or trial (procedure) related.

7.5.1 Definition of an Overdose for This Protocol and Reporting of Overdose to Merck

For purposes of this trial, an overdose of pembrolizumab will be defined as any dose of 1,000 mg or greater (>5 times the indicated dose). No specific information is available on the treatment of overdose of MK-3475. Appropriate supportive treatment should be provided if clinically indicated. In the event of overdose, the subject should be observed closely for signs of toxicity.

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

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

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

7.5.2 Reporting of Pregnancy and Lactation to Merck and BIPI

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.

Pregnancy and lactations that occur after the consent form is signed but before treatment allocation 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 through 120 days following cessation of treatment, or 30 days following the 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. Report pregnancy to BIPI only if it is associated with the SAE (including an outcome that meets SAE criteria).

Such events must be reported within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220) as well as Boehringer Ingelheim.

7.5.3 Immediate Reporting of Adverse Events to Merck and BIPI

7.5.3.1 Serious Adverse Events

A serious adverse event is any adverse event occurring at any dose or during any use of Merck's 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 in the same timeframe as SAEs to meet certain local requirements. Therefore, these events are considered serious by Merck for collection purposes.

- Is a new cancer (that is not a condition of the study);
- Is associated with an overdose.

Refer to Table 12.7 for additional details regarding each of the above criteria.

For the time period beginning when the consent form is signed until treatment allocation, any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study (Section 7.2.3.3 for additional details) that occurs to any subject must be reported within 2 working days to Merck Global Safety if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment

or a procedure.

Progression of the cancer under study is not considered an adverse event unless it results in hospitalization or death.

For the time period beginning at treatment allocation, through 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anti-cancer therapy, whichever is earlier, any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of cancer under study (reference Section 7.5.4 for additional details), whether or not related to Merck product, must be reported within 2 working days to Merck Global Safety.

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

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

Assessment of safety laboratory parameters

A copy of all 15 Day Reports and Annual Progress Reports is submitted as required by FDA, European Union (EU), Pharmaceutical and Medical Devices agency (PMDA) or other local regulators. Investigators will cross reference this submission according to local regulations to the Merck Investigational Compound Number (IND, CSA, etc.) at the time of submission. Additionally investigators will submit a copy of these reports to Merck & Co., Inc. (Attn: Worldwide Product Safety; FAX 215 993-1220) at the time of submission to FDA.

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

The investigator shall report all SAEs and non serious AEs relevant to a reported SAE by fax from the time the informed consent is signed until the trial specified observational period (please specify) using BI IIS SAE form to BIPI Unique Entry Point in accordance with the following timelines:

- within five (5) calendar days upon receipt of initial and follow-up SAEs containing at least one fatal or immediately life-threatening event;
- within ten (10) calendar days upon receipt of any other initial and follow-up SAEs.

BI Unique Entry point:
Boehringer Ingleheim Pharmaceuticals, Inc
900 Ridgebury Road
Ridgefield, CT 06877

Fax: 1-203-837-4329

7.5.3.2 Events of Clinical Interest

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

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

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

Events of clinical interest for this trial include:

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

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

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

7.5.4 Protocol-Specific Exceptions to Serious Adverse Event Reporting

Efficacy endpoints as outlined in this section will not be reported to Merck as described in Section 7.5.3 .- Immediate Reporting of Adverse Events to Merck and BIPI, unless there is evidence suggesting a causal relationship between the drug and the event. Any such event will be submitted to Merck Global Safety within 2 working days either by electronic or paper media Specifically, the suspected/actual events covered in this exception include any event that is disease progression of the cancer under study.

The Sponsor will monitor unblinded aggregated efficacy endpoint events and safety data to

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

All the reports specified in this section will also be submitted to BIPI according to SAE reporting timeframe in section 7.5.3.1**.**

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

7.5.5 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.

7.5.6 Sponsor-Investigator Responsibility for Reporting Adverse Events

All Adverse Events will be reported to regulatory authorities, IRB/IECs and investigators in accordance with all applicable laws and regulations.

7.5.7 Safety Reporting Requirements for IND Exempt Studies

For Investigator Sponsored IND Exempt Studies there are some reporting requirements for the FDA in accordance with the guidance set forth in 21 CFR 314.80.

Post-marketing 15-Day 'Alert Report'
The Sponsor-Investigator is required to notify the FDA of each adverse drug experience that is both serious and unexpected and is assessed by the investigator to be possibly related to study treatment as soon as possible but in no case later than 15 calendar days of initial receipt of the information. An unexpected adverse event is one that is not already described in the Investigator Brochure. Such reports (2 copies) are to be submitted to the FDA at the following address: Central Document Room, 5901-B Ammendale Rd., Beltsville, MD 20705-1266.

All 15-Day Alert Reports submitted to the FDA by the Sponsor-Investigator must also be faxed to Merck.

8.0 STATISTICAL ANALYSIS PLAN

8.1 Statistical Analysis Plan Summary

This is a phase I/Ib study. A minimum of 9 patients, if trial is terminated early due to unacceptable toxicity and a maximum of 38 patients (18 patients in the dose de-escalation cohort plus 10 in each of the two expansion cohorts) are anticipated for this trial. Analysis of safety and biomarkers will be limited to patients who receive active treatment.

The dose de-escalation phase will establish a MTD recommended dose of MK-3475 in combination with lead in MK-3475 followed by the combination or concurrent afatinib/MK-3475.

We plan to enter 3 patients at Dose Level 0. If 0/3 or 1/3 patients experience a DLT on level 0, an additional 3 patients will be accrued to Level 0, where 2 or more DLTs will terminate that study arm and we will proceed to dose level -1.

If 2 or more patients have DLTs at level 0, patients will be accrued at level -1. If 1/3 patients experience a DLT on level -1, an additional 3 patients will be accrued to Level -1, where 2 or more DLTs will require termination of that study arm while 1 DLT out of 6 will result in proceeding with dose level -1 as the MTD for the dose expansion cohorts.

If 2 or more patients have DLTs at level -1, patients will be accrued at level -2. If 1/3 patients experience a DLT on level -2, an additional 3 patients will be accrued to Level -2, where 2 or more DLTs will require termination of the study while 1 DLT out of 6 will result in proceeding with dose level -2 as the MTD for the dose expansion cohorts.

The phase I de-dose escalation portion of the trial will be closed when the maximum tolerated dose level (MTD) or dose level 0 is reached and six patients have been treated at that dose level.

Please see section 5.1.4.2 for further details.

All patients at a given dose level who have not experienced DLT, must be observed for a minimum of 21 days or until completion of their first cycle of therapy before the dose level can be escalated. Treatment will continue in an individual patient at the same dose level if no DLT is observed and if benefit is observed. There will be no dose escalation allowed for an individual patient.

The recommended phase II dose (RP2D) will be determined by the overall assessment of the MTD and toxicities observed in the de-dose escalation and dose expansion portion of this study.

The baseline assumption is that single agent afatinib yields a response rate of 10% in this setting, and a response rate of 10% or less would not warrant further study. A response rate of 40% or greater would justify further study with a larger sample size. With 10 patients enrolled in cohort A expansion arm, we will declare this combination lacking promise if fewer than 3 patients respond, and potentially worthy of further study if 3 or more patients respond. If the true response rate is 10%, the chance of having 3 or more patients respond is 7%. If the true response rate is 40%, the

chance of having 3 or more patients respond is 83%.

If 3 or more patients respond, the response rate, toxicity, and progression-free survival will be evaluated to decide if larger randomized studies are warranted in this disease. Descriptive summaries will be provided for each of these summary measures (numbers and proportion responding, number and proportion with specific type and grade of toxicities, Kaplan-Meier plot and life-table summary of progression-free survival.) As stated earlier, a "pick the winner" approach between cohort A and cohort B based on toxicity: RR, PFS and changes in PDL1 expression will decide which dosing scheme to take further. It is assumed that a true RR >40% would be sufficient to recommend such development, provided safety and tolerability are also acceptable.

8.2 Correlative Statistical Analysis Plan

Plasma EGFR-mutant DNA/RNA levels, PDL1 expression by IHC at baseline and in repeat biopsy specimens as well as the other EGFR and immune biomarkers proposed will be evaluated in exploratory manner. A focus is on comparison between changes in PD-L1 expression comparing arm A (concurrent afatinib/MK-3475) and arm B (lead in MK-3475). Descriptive associations with response rate and PFS will be performed. All molecular and other secondary evaluations will be considered for exploratory analyses and in view of the limited sample-size and the exploratory nature of these analyses, any p-values reported will not be adjusted for multiple comparisons, and any such analyses will be stated carefully as being hypothesis-generating.

Standard descriptive methods will be used to summarize the baseline levels and changes in baseline levels will allow us to examine whether observed patterns are consistent with hypothesized patterns. If the combination is not found to have sufficient activity, these patterns may help explain the lack of activity. If sufficient activity is found, then patients who experience an objective response will be compared to those who did not in terms of these correlates.

9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.1 Investigational Product: MK-3475

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 at no cost to subjects as summarized below.

Product Descriptions

Product Name & Potency	Dosage Form
MK-3475 100 mg/ 4mL	Solution for Infusion

Instructions on preparation are provided with Merck pharmacy manual.

9.1.1 Packaging and Labeling Information

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

9.1.2 Clinical Supplies Disclosure

This trial is open-label; therefore, the subject, the trial site personnel, the Sponsor- Investigator 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.

9.1.3 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.

9.1.4 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.

9.2 Investigational Product: Afatinib

9.2.1 Packaging and Labeling Information

Medication numbers will be unique to each bottle and will be used for tracking purposes only.

Afatinib will be supplied as film-coated tablets. Available dosage strengths will be 20, 30 and 40 mg. Tablets will be supplied in HDPE, child-resistant, tamper-evident bottles.

Bottles/boxes will be labelled according to local regulations and will include the following as a minimum;

- Study number [UCDCC#250 + 1200.237]
- Product name (Afatinib)
- Contents of the bottle (number of tablets)
- Tablet strength (mg)
- Batch number
- Medication number
- Use-by date
- Storage information
- Instructions for use
- Sponsor-Investigator name and address
- A statement that the medication is for clinical study use only
- A caution statement

A new bottle of medication will be dispensed on day 1 of each course, regardless of the number of tablets remaining in the bottle from the previous course. The patient will initially receive one bottle of 20, 30 or 40 mg tablets and in the event that dose reduction is necessary the patient will return to the clinic and new medication will be dispensed.

9.2.2 Storage Conditions

Afatinib must be stored in the original package in order to protect from light. Film-coated tablets are humidity-sensitive; therefore, bottles must be kept tightly closed to protect from moisture. Tablets must be stored according to label instructions.

9.2.3 Drug Accountability

Afatinib, which will be provided by Boehringer Ingelheim Pharmaceuticals, Inc, at no cost to subject, will be kept in a secure, limited access storage area under the storage conditions. Where necessary, a temperature log must be maintained to make certain that the drug supplies are stored at the correct temperature.

The responsible person must maintain records of the product's delivery to the study site, the inventory at the site, the use by each patient, and the return to the Boehringer Ingelheim (BIPI) or alternative disposition of unused product(s). Returned or unused study drug will be destroyed at site per site's SOP.

These records will include dates, quantities, batch/serial numbers, expiry ('use by') dates, and the unique code numbers assigned to the investigational product(s) and study patients. The responsible person will maintain records that document adequately that the patients were provided the doses specified by the clinical study protocol and reconcile all investigational product(s) received from Boehringer Ingelheim (BIPI). The responsible person must verify that all unused or partially used drug supplies have been returned by the clinical study patient.

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 Confidentiality

In order to maintain patient privacy, all study reports and communications will identify the patient by initials and the assigned patient number. Data capture records and drug accountability records will be stored in secure cabinets in the UCD Office of Clinical Research. Medical records of patients will be maintained in strict confidence according to legal requirements. The investigator will grant monitor(s) and auditor(s) from Merck/BIPI or its designees and regulatory authority(ies) access to the patient's original medical records for verification of data gathered on the data capture records and to audit the data collection process. The patient's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

10.2 Good Clinical Practice

The study will be conducted in accordance with the International Conference on Harmonization (ICH) for Good Clinical Practice (GCP) and the appropriate regulatory requirement(s). The investigator will be thoroughly familiar with the appropriate use of the drug as described in the protocol and Investigator's Brochure. Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master files should be established at the beginning of the study, maintained for the duration of the study and retained according to the appropriate regulations.

10.3 Patient Information and Informed Consent

After the study has been fully explained, written informed consent will be obtained from

either the patient or his guardian or legal representative prior to study participation. The method of obtaining and documenting the informed consent and the contents of the consent will comply with ICH-GCP and all applicable regulatory requirement(s). In accordance with UCD OCR policy an original signed and dated participant Informed Consent document will reside in a secured location within the UCD OCR. Copies of the signed and dated Informed Consent document will be provided to the study participant and UCD Health System Information Management for inclusion in the participant's UCD Health System Medical Record or per participating site's policies.

10.4 Records and Retention

The investigator will maintain all study records according to ICH-GCP and applicable regulatory requirement(s).

10.5 Data and Safety Monitoring

In addition to the requirements for adverse event reporting as outlined in Section 7.5, this protocol is also subject to the UC Davis Cancer Center's (UCDCC) Data and Safety Monitoring Plan. The UCDCC is committed to pursuing high-quality patient-oriented clinical research and has established mechanisms to ensure both scientific rigor and patient safety in the conduct of clinical research studies. The UCDCC relies on a multi-tiered committee system that reviews and monitors all cancer clinical trials and ensures the safety of its participants, in compliance with institutional and federal requirements on adverse event (AE) reporting, verification of data accuracy, and adherence to protocol eligibility requirements, treatment guidelines, and related matters. The Scientific Review Committee (SRC) assumes overall oversight of cancer studies, with assistance and input from two independent, but interacting, committees: the Quality Assurance Committee and the Data Safety Monitoring Committee. A multi-level review system strengthens the ability of the UCDCC to fulfill its mission in conducting high quality clinical cancer research.

As per University of California Davis Cancer Center (UCDCC) Office of Clinical Research (OCR) SOP AM 506: Protocol Specific Meetings, the principal investigator (PI) and clinical research coordinator (CRC) meet at least monthly for ongoing study information, to discuss patient data and adverse events and to determine if dose escalation is warranted, when applicable. Because this is a phase I study, a meeting and/or conference call will take place when the last subject on each cohort completes DLT (dose-limiting toxicity) assessment. The meeting and/or call will update the attendees of the current status of the study and will include investigators from all participating centers, and, if necessary, representatives from the drug provider or financial supporter. All serious adverse events experienced by study subjects will be discussed and appropriate action taken. If serious adverse events occur between these meetings and/or calls, all investigators will be informed by email.

According to the UCDCC Data and Safety Monitoring Plan (DSMP), any new serious

adverse events related to the drugs being used on this trial are reviewed monthly by the UCDCC Data and Safety Monitoring Committee (DSMC) and any applicable changes to the study are recommended to the PI, if necessary.

The UCDCC Scientific Review Committee (SRC) determines if a UCDCC Data and Safety Monitoring Board (DSMB) is required. If required, the DSMC will appoint a DSMB. The DSMB is responsible for reviewing study accrual logs, adverse event information and dose escalation meeting minutes (where applicable) to ensure subject safety and compliance with protocol defined guidelines.

10.6 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.

10.7 Quality Assurance and Control

Quality assurance audits of select patients and source documents may be conducted by the UC Davis Comprehensive Cancer Center Quality Assurance Committee as outlined in the UC Davis Cancer Center Data and Safety Monitoring plan.

Quality control will be maintained by the OCR Quality Assurance team according to OCR policy.

10.8 Registration Guidelines

A. Before registration, the site study coordinator should check to make sure that the corresponding Investigational Drug Service or equivalent has investigational product(s) in stock.

B. Registrations must be made through the Office of Clinical Research (OCR) of the University of California, Davis Comprehensive Cancer Center between the hours of 9am and 3pm (Pacific Time), Monday through Friday (except holidays). Documentation of current IRB approval of this protocol must be on file prior to registration of patients.

C. Pre-study laboratory tests, scans, and x-rays, must be completed prior to registration, within the time frame specified in the protocol. The eligibility checklist must be completed. Patients must sign an informed consent prior to registration.

D. Patients may be registered up to 72 hours prior to treatment initiation. The signed consent, completed checklist and reports from all pre-study laboratory tests, scans and x-rays must be faxed to UC Davis OCR in order to register the patient. The UC Davis Protocol Coordinator will review these documents and fax a registration confirmation within 3 hours.

E. If the patient is to be registered the same day as the proposed treatment start date, the UC Davis Study Coordinator must be notified by fax 24 hrs prior to proposed treatment start date that the site has a patient to register.

F. The Study Coordinator will verify that the patient is eligible, that pre-study tests have been completed, and that the forms are complete. The Study Coordinator will then register the patient and assign a patient accession number. The Study Coordinator will fax back a registration confirmation including the patient accession number within 3 hours.

G. A patient failing to meet all protocol requirements may not be registered. If you have any questions regarding eligibility, contact the coordinating site PI or Study Coordinator.

NOTE: Administration of study medication may not be initiated until the registration confirmation has been received.

10.9 Data Management

All data will be collected using UC Davis data collection forms. Any and all source documentation should be maintained.

☐ SUBMIT WITHIN 24 HOURS OF REGISTRATION:
Patient Registration Form

☐ SUBMIT WITHIN 14 DAYS OF REGISTRATION: In-House Pre-Study Evaluation Form (IH-102)

☐ SUBMIT WITHIN 7 DAYS OF SCREENING FAILURE: Patient Screen Failure Form

☐ SUBMIT WITH 14 DAYS OF CYCLE COMPLETION: Adverse Event/Drug Relationship Form

☐ SUBMIT WITHIN 14 DAYS OF END OF EACH TREATMENT CYCLE: In-House Treatment Cycle Form (IH-201)

☐ SUBMIT WITHIN 14 DAYS OF EACH RESPONSE ASSESSMENT: Tumor Measurement Log

☐ SUBMIT WITHIN 14 DAYS OF OFF TREATMENT:
Off Treatment/In Follow-up/Off Study/Expiration Form (IH-301)

☐ SUBMIT WITHIN 14 DAYS OF KNOWLEDGE OF DEATH IF PATIENT IS STILL ON STUDY OR 30–DAYS IF OFF STUDY:
Off Treatment/In Follow-up/Off Study/Expiration Form (IH-301)

☐ SUBMIT WITHIN 2 DAYS OF KNOWLEDGE OF PROTOCOL DEVIATION: Notice of Protocol Deviation

☐ SUBMIT WITHIN 14 DAYS OF EACH REQUIRED FOLLOW-UP ENCOUNTER:
Follow-Up Form (IH-302)

☐ ALL SERIOUS ADVERSE EVENTS MUST BE REPORTED AS OUTLINED IN THE PROTOCOL.

11.0 LIST OF REFERENCES

1. Disis ML. Immune regulation of cancer. J Clin Oncol 2010; 28(29):4531-8.

2. Dong H, Strome SE, Salomao DR, Tamura H, Hirano F, Flies DB, et al. Tumor-associated B7-H1 promotes T-cell apoptosis: a potential mechanism of immune evasion. Nat Med 2002;8(8):793-800.

3. Sharpe AH, Freeman GJ. The B7-CD28 superfamily. Nature 2002;2:116-26.

4. Brown JA, Dorfman DM, Ma F-R, Sullivan EL, Munoz O, Wood CR, et al. Blockade of programmed death-1 ligands on dendritic cells enhances T cell activation and cytokine production. J Immunol 2003;170:1257-66.

5. Francisco LM, Sage PT, Sharpe AH. The PD-1 pathway in tolerance and autoimmunity. Immunol Rev 2010;236:219-42.

6. Thompson RH, Dong H, Lohse CM, Leibovich BC, Blute ML, Cheville JC, et al. PD-1 expressed by tumor-infiltrating immune cells and is associated with poor outcome for patients with renal cell carcinoma. Clin Caner Res 2007;13(6):1757-61.

7. Talmadge JE, Donkor M, Scholar E. Inflammatory cell infiltration of tumors: Jekyll or Hyde. Cancer Metastasis Rev 2007;26:373-400.

8. Usubütün A, Ayhan A, Uygur MC, zen H, klu C, acan S. Prognostic factors in renal cell carcinoma. J Exp Clin Cancer Res 1998;17(1):77-81.

9. Al-Shibli KI, Donnem T, Al-Saad S, Persson M, Bremnes RM, Busund L-T. Prognostic effect of epithelial and stromal symphocyte infiltration in non-small cell lung cancer. Clin Cancer Res 2008;14(16):5220-7.

10. Deschoolmeester V, Baay M, Van Marck E, Weyler J, Vermeulen p, Lardon F, et al. Tumor infiltrating lymphocytes: an intriguing player in the survival of colorectal cancer patients. BMC Immunol 2010;11:19.

11. Diez M, Pollán M, Enriquez JM, Dominguez P, Santana A, Tobaruela E, et al. Histopathologic prognostic score in colorectal adenocarcinomas. Anticancer Res 1998;18:689-94.

12. Galon J, Costes A, Sanchez-Cabo F, Kirilovsky A, Mlecnik B, Lagorce-Pagès C, et al. Type, density, and location of immune cells within human colorectal tumors predict clinical outcome. Science 2006;313:1960-4.

13. Hiraoka N. Tumor-infiltrating lymphocytes and hepatocellular carcinoma: molecular biology. Int J Clin Oncol 2010;15:544-51.

14. Nobili C, Degrate L, Caprotti R, Franciosi C, Leone BE, Trezzi R, et al. Prolonged survival

of a patient affected by pancreatic adenocarcinoma with massive lymphocyte and dendritic cell infiltration after interleukin-2 immunotherapy. Report of a case. Tumori 2008;94:426-30.

15. Hodi FS, Dranoff G. The biologic importance of tumor-infiltrating lymphocytes. J Cutan Pathol 2010;37(Suppl 1):48-53.

16. Kloor M. Lymphocyte infiltration and prognosis in colorectal cancer. Lancet 2009;10(840):841.

17. Hillen F, Baeten CIM, van de Winkel A, Creytens D, van der Schaft DWJ, Winnepenninckx V, et al. Leukocyte infiltration and tumor cell plasticity are parameters of aggressiveness in primary cutaneous melanoma. Cancer Immunol Immunother 2008;57:97-106.

18. Lee HE, Chae SW, Lee YJ, Kim MA, Lee HS, Lee BL, et al. Prognostic implications of type and density of tumour-infiltrating lymphocytes in gastric cancer. Br J Cancer 2008;99(10):1704-11.

19. Leffers N, Gooden MJM, de Jong RA, Hoogeboom B-N, ten Hoor KA, Hollema H, et al. Prognostic significance of tumor-infiltrating T-lymphocytes in primary and metastatic lesions of advanced stage ovarian cancer. Cancer Immunol Immunother 2009;58:449-59.

20. Nishimura H, Honjo T, Minato N. Facilitation of β selection and modification of positive selection in the thymus of PD-1-deficient mice. J Exp Med 2000;191(5):891-7.

21. Liotta F, Gacci M, Frosali F, Querci V, Vittori G, Lapini A, et al. Frequency of regulatory T cells in peripheral blood and in tumour-infiltrating lymphocytes correlates with poor prognosis in renal cell carcinoma. BJU Intern 2010;107:1500-6.

22. Ropponen KM, Eskelinen MJ, Lipponen PK, Alhava E, Kosma V-M. Prognostic value of tumour-infiltrating lynmphocytes (TILs) in colorectal cancer. J Pathol 1997;182:318-24.

23. Dudley ME, Wunderlich JR, Yang JC, Sherry RM, Topalian SL, Restifo NP, et al. Adoptive cell transfer therapy following non-myeloablative but lymphodepleting chemotherapy for the treatment of patients with refractory metastatic melanoma. J Clin Oncol 2005;23(10):2346-57.

24. Hunder NN, Wallen H, Cao J, Hendricks DW, Reilly JZ, Rodmyre R, et al. Treatment of metastatic melanoma with autologous CD4+ T cells against NY-ESO-1. N Engl J Med 2008;358(25):2698-703.

25. Ölcher M, Braun M, Friedrichs N, Rudlowski C, Bercht E, Fimmers R, et al. Foxp3+ cell infiltration and granzyme B+/Foxp3+ cell ratio are associated with outcome in neoadjuvant chemotherapy-treated ovarian carcinoma. Cancer Immunol Immunother 2010;59:909-19.

26. Okazaki T, Maeda A, Nishimura H, Kurosaki T, Honjo T. PD-1 immunoreceptor inhibits B cell receptor-mediated signaling by recruiting src homology 2-domain-containing tyrosine phosphatase 2 to phosphotyrosine. PNAS 2001;98(24):13866-71

27. Greenwald RJ, Freeman GJ, Sharpe AH. The B7 family revisted. Annu Rev Immunol 2005;23:515-48.

28. Homsi J, Kashani-Sabet M, Messina JL, Daud A. Cutaneous melanoma: prognostic factors. Cancer Control 2005;12(4):223-9.

29. Iannone R, Gergich K, Cong C, Kang P, Daud A, Dronca R, et al. Efficacy and safety of MK-3475 in patients with advanced melanoma. Pigment Cell Melanoma Res 2012;25:836-903.

30. Topalian SL, Hodi FS, Brahmer JR, Gettinger SN, Smith DC, McDermott DF, et al. Safety, activity, and immune correlates of Anti-PD-1 antibody in cancer. N Engl J Med 2012:doi: 10.1056/NEJMoa1200690.

31. Lyford-Pike S, Peng S, Young GD, et al. Evidence for a role of the PD-1:PD-L1 pathway in immune resistance of HPV-associated head and neck squamous cell carcinoma. Cancer Res 2013;73(2): Published online January 3.

32. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent R, Ford R, et al. New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1). Eur J Cancer 2009;45(2):228-47.

33. Wolchok JD, Hoos A, O'Day S, Weber JS, Hamid O, Lebbe C, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clin Cancer Res 2009;15(23):7412-20.

34. Blum JL, Jones SE, Buzdar AU, LoRusso PM, et al. Multicenter Phase II Study of Capecitabine in Paclitaxel-Refractory Metastatic Breast Cancer. J Clin Oncol 17: 485-493, 1999

35. Martin M, Ruiz A, Munoz M, Balil A, Garcia-Mata J, Calvo L, et al. Gemcitabine plus vinorelbine monotherapy in patients with metastatic breast cancer previously treated with anthracyclines and taxanes: final results of the phase III Spanish Breast Cancer Research Group (GEICAM) trial. Lancet Oncol. 2007;8(3):219.

36. Sledge GW, Neuberg D, Bernardo P, Ingle JN, Martino S, et al. Phase III Trial of Doxorubicin, Paclitaxel, and the Combination of Doxorubicin and Paclitaxel as Front-Line Chemotherapy for Metastatic Breast Cancer: An Intergroup Trial (E1193). J Clin Oncol. 2003;21(4):588.

37. Stewart JSW, Ezra E.W. Cohen EEW, Licitra L, Van Herpen CML, et al. Phase III Study of Gefitinib Compared With Intravenous Methotrexate for Recurrent Squamous

Cell Carcinoma of the Head and Neck. J Clin Oncol. 2009;27(11):1864.

38. Vermorken JB, Trigo J, Hitt R, Koralewski P, Diaz-Rubio E, et al. Open-Label, Uncontrolled, Multicenter Phase II Study to Evaluate the Efficacy and Toxicity of Cetuximab As a Single Agent in Patients With Recurrent and/or Metastatic Squamous Cell Carcinoma of the Head and Neck Who Failed to Respond to Platinum-Based Therapy. J Clin Oncol. 2007;25(16):2171.

39. Bellmunt J, Théodore C, Demkov T, Komyakov B, Sengelov L, et al. Phase III Trial of Vinflunine Plus Best Supportive Care Compared With Best Supportive Care Alone After a Platinum-Containing Regimen in Patients With Advanced Transitional Cell Carcinoma of the Urothelial Tract. J Clin Oncol. 2009;27(27):4454

40. Sweeney CJ, Roth BJ, Kabbinavar FF, Vaughn DJ, Arning M, et al. Phase II Study of Pemetrexed for Second-Line Treatment of Transitional Cell Cancer of the Urothelium. J Clin Oncol. 2006;24(21):3451.

41. Clopper C and Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika 1934;26:404-413.

12.0 APPENDICES

12.1 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.	

12.2 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)

12.3 Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 Criteria forEvaluating 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.

12.4 New York Heart Association Classification of Heart Failure

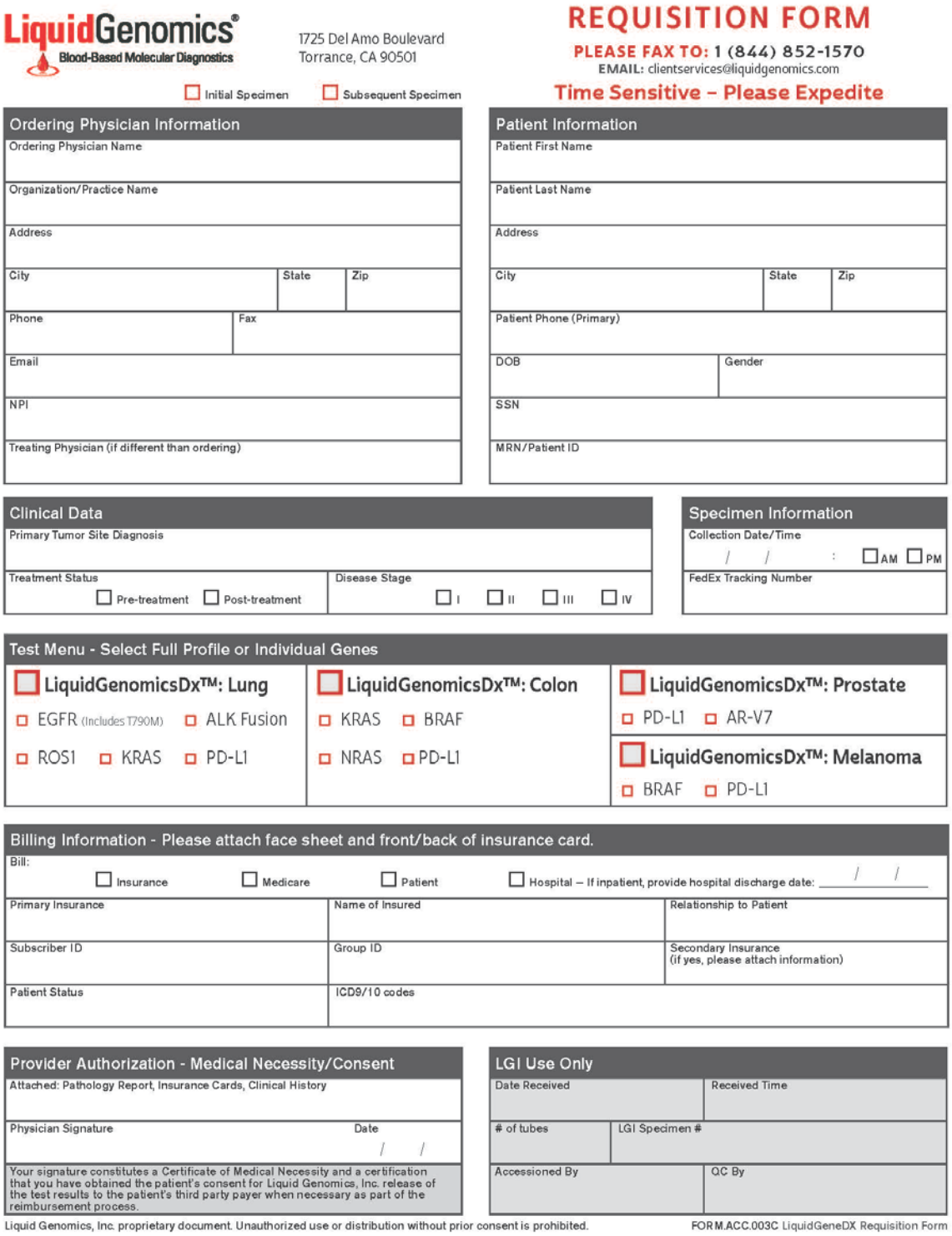
Class	Patient Symptoms
Class I (Mild)	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath)
Class II (Mild)	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea.
Class III (Moderate)	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea.
Class IV (Severe)	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

12.5 List of Potent Inhibitors and Inducers of P-glycoprotein (MDR1)

Inhibitors	**Inducers**
Amiodarone Azithromycin Captopril Carvedilol Clarithromycin Conivaptan Cyclosporine Diltiazem Dronedarone Erythromycin Felodipine Itraconazole Ketoconazole Lopinavir Nelfinavir Ritonavir Quinidine Ranolazine Saquinavir Tacrolimus Ticagrelor Verapamil	Carbamazepine Phenytoin Rifampicin St John's Wort Phenobarbital Salt Tipranavir Ritonavir

The information on potent inhibitors and inducers of P-glycoprotein may evolve, it is important for the investigator to assess such status on concomitant.

12.6. Liquid Genomics Sample Requisition Form



LiquidGenomics®
Blood-Based Molecular Diagnostics

1725 Del Amo Boulevard
Torrance, CA 90501

REQUISITION FORM

PLEASE FAX TO: 1 (844) 852-1570
EMAIL: clientservices@liquidgenomics.com

Time Sensitive – Please Expedite

☐ Initial Specimen ☐ Subsequent Specimen

Ordering Physician Information

Ordering Physician Name
Organization/Practice Name
Address
City | State | Zip
Phone | Fax
Email
NPI
Treating Physician (if different than ordering)

Patient Information

Patient First Name
Patient Last Name
Address
City | State | Zip
Patient Phone (Primary)
DOB | Gender
SSN
MRN/Patient ID

Clinical Data

Primary Tumor Site Diagnosis
Treatment Status: ☐ Pre-treatment ☐ Post-treatment
Disease Stage: ☐ I ☐ II ☐ III ☐ IV

Specimen Information

Collection Date/Time: / / : ☐ AM ☐ PM
FedEx Tracking Number

Test Menu - Select Full Profile or Individual Genes

☐ **LiquidGenomicsDx™: Lung**
☐ EGFR (Includes T790M) ☐ ALK Fusion
☐ ROS1 ☐ KRAS ☐ PD-L1

☐ **LiquidGenomicsDx™: Colon**
☐ KRAS ☐ BRAF
☐ NRAS ☐ PD-L1

☐ **LiquidGenomicsDx™: Prostate**
☐ PD-L1 ☐ AR-V7

☐ **LiquidGenomicsDx™: Melanoma**
☐ BRAF ☐ PD-L1

Billing Information - Please attach face sheet and front/back of insurance card.

Bill: ☐ Insurance ☐ Medicare ☐ Patient ☐ Hospital – If inpatient, provide hospital discharge date: / /

Primary Insurance | Name of Insured | Relationship to Patient
Subscriber ID | Group ID | Secondary Insurance (if yes, please attach information)
Patient Status | ICD9/10 codes

Provider Authorization - Medical Necessity/Consent

Attached: Pathology Report, Insurance Cards, Clinical History
Physician Signature | Date / /
Your signature constitutes a Certificate of Medical Necessity and a certification that you have obtained the patient's consent for Liquid Genomics, Inc. release of the test results to the patient's third party payer when necessary as part of the reimbursement process.

LGI Use Only

Date Received | Received Time
# of tubes | LGI Specimen #
Accessioned By | QC By

Liquid Genomics, Inc. proprietary document. Unauthorized use or distribution without prior consent is prohibited. FORM.ACC.003C LiquidGeneDX Requisition Form

Variants

Gene	Variants
KRAS	G12C
	G12D
	G12A
	G12V
	G12S
	G12R
	G13D
	Q61H

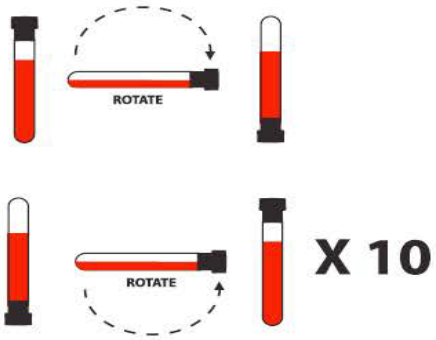
Gene	Variants
EGFR	L858R
	L861Q
	T790M
	G719S
	Ex19Del
BRAF	V600E

Gene	Variants
NRAS	G12D
	Q61K
	Q61L
	Q61R
EML4-ALK	V1
	V2
	V3
	V5a

Gene	Variants
ROS-1	CD74-ROS1 V1
	CD74-ROS1 V2
	CD74-ROS1 V3
	EZR-ROS1 V1
	EZR-ROS1 V2

PD-L1 and AR-V7 are expression assays (AR-V7 is a splice variant of AR)

Specimen Collection



1. Draw one tube of patient blood into the **Cell-Free DNA BCT® tube.**
2. Draw one tube of patient blood into the **Cell-Free RNA BCT® tube.**
3. Use only the tubes provided in the Liquid Genomics collection kit.
4. Draw sufficient blood to fill the tubes provided in the collection kit.
5. Gently invert the tubes 8-10 times to mix the DNA and RNA stabilizer.
6. Label the collection tubes with patient name, draw date and patient date of birth
7. **Do NOT freeze or refrigerate.**
8. Fax completed requisition form to Liquid Genomics at **844-852-1570**
9. Include completed requisition form in the shipment when sending the specimen.
10. Ship via FedEx at ambient temperature to Liquid Genomics, Inc.

Storage Conditions
Store at ambient temperature (18-25° C). Do NOT refrigerate or freeze.

Stability of Specimen
Specimen should be shipped within 24 hours of blood draw (not to exceed 5 days after blood draw).

Shipping Specimens

Mailing Address
Liquid Genomics, Inc.
1725 Del Amo Boulevard
Torrance, CA 90501

FedEx Pick Up
Schedule a FedEx pick up by calling (800) GoFedEx or 1(800) 463-3339 or visiting www.fedex.com. You may also call (844) 282-3363 and our client services team will be happy to schedule a pick up for you.

Tracking Your Package
We are anticipating your package. Please fax the requisition form with the Specimen Information/Tracking Information completed so we can properly track your package and alert you of any delays.

Questions
For more information or to order additional collection kits, please call toll free 844-282-3DNA (3362) or email clientservices@liquidgenomics.com.

Hours of Operation
Monday – Friday, 9 AM-5:30 PM Pacific Time

LiquidGenomics®
Blood-Based Molecular Diagnostics
1725 Del Amo Boulevard
Torrance, CA 90501

FORM.ACC.003C LiquidGeneDX Requisition Form

12.7 Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood	Serum β-human chorionic gonadotropin†
Hemoglobin	Alkaline phosphatase	Glucose	(β-hCG)†
Platelet count	Alanine aminotransferase (ALT)	ProteinCr	PT (INR)
WBC (total and differential)	Aspartate aminotransferase (AST)	Specific gravity	aPTT
Red Blood Cell Count	Lactate dehydrogenase (LDH)	Microscopic exam *(If abnormal)*	Total thriiodothyronine (T3)
Absolute Neutrophil Count	Carbon Dioxide ‡ *(CO_2 or biocarbonate)*	results are noted	Free tyroxine (T4)
	Creatinine	Urine or serum pregnancy test †	Thyroid stimulating hormone (TSH)
	Uric Acid		PK
	Calcium		
	Chloride		Blood for correlative studies
	Glucose		Correlative Biopsies
	Phosphorus		
	Potassium		
	Sodium		
	Magnesium		
	Total Bilirubin		
	Direct Bilirubin *(If total bilirubin is elevated above the upper limit of normal)*		
	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.

12.8 Evaluating Adverse Events

An investigator who is a qualified physician, will evaluate all adverse events as to:

V4.0 CTCAE Grading	**Grade 1**	**Mild; asymptomatic or mid symptoms; clinical or diagnostic observations only; intervention not indicated.**
	Grade 2	**Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.**
	Grade 3	**Severe or medically significant but not immediately life-threatening; hospitalization or prolongation or hospitalization indicated; disabling; limiting self-care ADL.**
	Grade 4	**Life threatening consequences; urgent intervention indicated.**
	Grade 5	**Death related to AE**
Seriousness	A serious adverse event is any adverse event occurring at any dose or during any use of Merck 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 [including hospitalization for an elective procedure] for a preexisting condition which has not worsened does not constitute a serious adverse event.); 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) **or**	
	(For Merck Only. BIPI does not list criteria for overdose)Is an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported	
	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	
Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the adverse event cause the Merck product to be discontinued?	
Relationship to test drug	Did the Merck product cause the adverse event? The determination of the likelihood that the Merck product caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the adverse event based upon the available information. **The following components are to be used to assess the relationship between the Merck product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Merck product caused the adverse event (AE):	
	Exposure	Is there evidence that the subject was actually exposed to the Merck product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
	Time Course	Did the AE follow in a reasonable temporal sequence from administration of the Merck product? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors

Relationship to Merck product (continued)	**The following components are to be used to assess the relationship between the test drug and the AE: (continued)**	
	Dechallenge	Was the Merck product discontinued or dose/exposure/frequency reduced? If yes, did the AE resolve or improve? If yes, this is a positive dechallenge. If no, this is a negative dechallenge. (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Merck product; or (3) the trial is a single-dose drug trial); or (4) Merck product(s) is/are only used one time.)
	Rechallenge	Was the subject re-exposed to the Merck product in this study? If yes, did the AE recur or worsen? If yes, this is a positive rechallenge. If no, this is a negative rechallenge. (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the trial is a single-dose drug trial); or (3) Merck product(s) is/are used only one time). NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY THE MERCK PRODUCT, OR IF REEXPOSURE TO THE MERCK PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE SUBJECT, THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE U.S. CLINICAL MONITOR AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL.
	Consistency with Trial Treatment Profile	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Merck product or drug class pharmacology or toxicology?
The assessment of relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.		
Record one of the following	**Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Merck product relationship).**	
Yes, there is a reasonable possibility of Merck product relationship.	There is evidence of exposure to the Merck product. The temporal sequence of the AE onset relative to the administration of the Merck product is reasonable. The AE is more likely explained by the Merck product than by another cause.	
No, there is not a reasonable possibility Merck product relationship	Subject did not receive the Merck product OR temporal sequence of the AE onset relative to administration of the Merck product 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.)	

12.9 Event of Clinical Interest Guidance Document

PEMBROLIZUMAB PROGRAM (MK-3475)

EVENT OF CLINICAL INTEREST

GUIDANCE DOCUMENT

Version 5.0

For Instructional Purpose Only

*Ensure that you are using the most current version of this document.

REVISION HISTORY LOG

Version	Effective Date*	Revision Author	Action
1	08-Aug-2012	Kevin Gergich	Initial Release of guidance document for MK-3475
2	07-June-2013	Marty Huber, Kevin Gergich, Holly Brown	Revised title, formerly was "MK-3475 Immune-Related Adverse Event Identification, Evaluation and Management Guidance Document for Investigators" Revised the format of irAE Guidance document, including layout, font, sectioning, etc. for consistency with Sponsor Events of Clinical Interest guidance documents. Modified Categories for irAEs: – Replaced GI with Colitis category. – Removed Neurologic category. – Added Renal category. Removed detail in the irAE Guidance document that can be located in the Investigator's Brochure for MK-3475. Removed details regarding non-MK-3475 compounds. Added ECI reporting guidelines. Included a Table Events of Clinical Interest: Immune-Related Adverse Events that includes the key terms. – Also placed a pull-out quick-review sheet in the Appendix. Updated background, diagnosis and course of treatment details for irAEs.

3	10-Sep-2014	Marty Huber, Kevin Gergich, Holly Brown	Renamed the document: "Pembrolizumab Program (MK-3475) - Events of Clinical Interest Guidance Document". Introduced generic name: pembrolizumab (MK-3475) and inserted throughout the document. Updated Overview – Section 1 - Clarified the scope of the document and the reporting window for ECIs - Updated Table 1 with medDRA Preferred Terms for adverse events to correspond with reporting of terms to clinical database, rearranged the order, and updated the reporting criteria. - Updated the dose modification/discontinuation section to clarify discontinuation and hold terminology. Updated Section 2 – ECI Reporting Guidelines

			– Clarified that ECIs must be reported to Merck **within 24 hours** regardless of attribution to study treatment or etiology. Updated Section 3 – For All Sections, removed the Course of Action for Grade 1 events. - Section 3.1 Pneumonitis – Moved Pneumonitis to beginning of ECI Section – Updated management guidelines for Grade 2 and Grade 3-4 events - Section 3.2 Colitis: - Updated AE terms and ECI criteria, updated course of action language for clarity - Section 3.3 Endocrine: - Updated ECI criteria and updated course of action language for clarity. - Added subsections for hypophysitis, hyperthyroidism and hypothyroidism to clarify management guidelines. - Section 3.4 Hematologic: - New section added. - Section 3.5: Hepatic: - Updated terms and added additional guidance for reporting of DILI ECI; updated course of action for clarity - Section 3.6 Neurologic: - New section added. - Section 3.7 Ocular: - Changed the name of this section from Eye to Ocular - Added the term “iritis”, updated ECI guidance, and updated course of action language for clarity

			- Section 3.11 Infusion Reactions: - New section added. - Section 3.12: Follow-up to Resolution: - New section added. - Section 4: - References updated. - Section 5: - ECI table updated for consistency with Table 1. - Section 6: Appendix 2 – Past Medical History Related to Dermatologic Event: New section added.
4	04-Dec-2014	Scot Ebbinghaus, Oswaldo Bracco, Holly Brown, Kevin Gergich	- Table 1 - Updated Endocrine (reported as ECI if ≥ Grade 3 or ≥ Grade 2 and resulting in dose modification or use of systemic steroids to treat the AE) Section to include: - Hyperglycemia, if ≥Grade 3 and associated with ketosis or metabolic acidosis (DKA) - Created new section in Table 1 – Endocrine (reported as ECI) and added: - Type 1 diabetes mellitus (if new onset) - Hepatic: Clarified Transaminase elevations as: - Transaminase elevations (ALT and/or AST) - Section 3.2 Colitis - Updated the duration of diarrhea requirments under the Course of Action for Grade 2 and Grade 3 - Section 3.3 Endocrine - Clarified Course of Action for hyperthyroidism and hypothyroidism
5	18-Dec-2014	Holly Brown Kevin Gergich	- Section 3.3 Endocrine - Updated the Course of Action for Hypophysitis

*Ensure that you are using the most current version of this document.

TABLE OF CONTENTS

1. OVERVIEW

The purpose of this document is to provide study sites with guidance on the identification and management of
Events of Clinical Interest for the MK-3475 (also known as pembrolizumab) program.

Based on the literature review [1-11], and consideration of mechanism of action of pembrolizumab, potential immune-related adverse events (irAEs) are the primary Event of Clinical Interest (ECI). Immune-related AEs are adverse events associated with the treatment of patients with immunotherapy treatments that appear to be associated with the immune therapy's mechanism of action. Based on these potential irAEs, the sponsor has defined a list of specific adverse event terms (ECIs) that are selected adverse experiences that **must be reported to Merck within 24 hours** from the time the Investigator/physician is aware of such an occurrence, regardless of whether or not the investigator/physician considers the event to be related to study drug(s). In addition, these ECIs require additional detailed information to be collected and entered in the study database. ECIs may be identified through spontaneous patient report and / or upon review of subject data. **Table 1** provides the list of terms and reporting requirements for AEs that must be reported as ECIs for MK-3475 protocols. Of note, the requirement for reporting of ECIs applies to all arms, including comparators, of MK-3475 clinical trials

Given that our current list of events of clinical interest is not comprehensive for all potential immune-related events, it is possible that AEs other than those listed in this document may be observed in patients receiving pembrolizumab. Therefore any Grade 3 or higher event that the investigator/physician considers to be immune-related should be reported as an ECI regardless of whether the specific event term is in Table 1 **and reported to Merck within 24 hours** from the time the Investigator/physician is aware of such an occurrence. Adverse events that are both an SAE and an ECI should be reported one time as an SAE only, however the event must be appropriately identified as an ECI as well in in the database.

Table 1: Events of Clinical Interest

Pneumonitis (reported as ECI if ≥ Grade 2)		
Acute interstitial pneumonitis	Interstitial lung disease	Pneumonitis
Colitis (reported as ECI if ≥ Grade 2 or any grade resulting in dose modification or use of systemic steroids to		
Intestinal Obstruction	Colitis	Colitis microscopic
Enterocolitis	Enterocolitis hemorrhagic	Gastrointestinal perforation
Necrotizing colitis	Diarrhea	
Endocrine (reported as ECI if ≥ Grade 3 or ≥ Grade 2 and resulting in dose modification or use of systemic steroids to treat		
Adrenal Insufficiency	Hyperthyroidism	Hypophysitis
Hypopituitarism	Hypothyroidism	Thyroid disorder
Thyroiditis	Hyperglycemia, if ≥Grade 3 and associated with ketosis or metabolic acidosis (DKA)	
Endocrine (reported as ECI)		
Type 1 diabetes mellitus (if new onset)		
Hematologic (reported as ECI if ≥ Grade 3 or any grade resulting in dose modification or use of systemic steroids to treat the		
Autoimmune hemolytic anemia	Aplastic anemia	Thrombotic Thrombocytopenic Purpura (TTP)
Idiopathic (or immune) Thrombocytopenia Purpura (ITP)	Disseminated Intravascular Coagulation (DIC)	Haemolytic Uraemic Syndrome (HUS)
Any Grade 4 anemia regardless of underlying mechanism		
Hepatic (reported as ECI if ≥ Grade 2, or any grade resulting in dose modification or use of systemic steroids to treat		
Hepatitis	Autoimmune hepatitis	Transaminase elevations (ALT and/or
Infusion Reactions (reported as ECI for any grade)		
Allergic reaction	Anaphylaxis	Cytokine release syndrome
Serum sickness	Infusion reactions	Infusion-like reactions
Neurologic (reported as ECI for any grade)		
Autoimmune neuropathy	Guillain-Barre syndrome	Demyelinating polyneuropathy
Myasthenic syndrome		
Ocular (report as ECI if ≥ Grade 2 or any grade resulting in dose modification or use of systemic steroids to treat		
Uveitis	Iritis	
Renal (reported as ECI if ≥ Grade 2)		
Nephritis	Nephritis autoimmune	Renal Failure
Renal failure acute	Creatinine elevations (report as ECI if ≥Grade 3 or any grade resulting in dose modification or use of systemic steroids to treat the AE)	

Skin (reported as ECI for any grade)		
Dermatitis exfoliative	Erythema multiforme	Stevens-Johnson syndrome
Toxic epidermal necrolysis		
Skin (reported as ECI if ≥ Grade 3)		
Pruritus	Rash	Rash generalized
Rash maculo-papular		
Any rash considered clinically significant in the physician's judgment		
Other (reported as ECI for any grade)		
Myocarditis	Pancreatitis	Pericarditis
Any other Grade 3 event which is considered immune-related by the physician		

Each of the events above is described within this guidance document, along with site requirements for reporting these events to the Sponsor. The information collected should be entered into the narrative field(s) of the Adverse Event module in the database (please note, if narrative entry into the database is not available, please use the narrative text box on the 1727/AER Form). If additional Medical History or Concomitant Medications are reported, the Medical History and Concomitant Medication modules in the database must be updated.

In addition, the guidelines include recommendations on the management of these ECIs. These guidelines are intended to be applied when the physician determines the events to be related to pembrolizumab. Note: if after the evaluation the event is determined not to be related, the physician is instructed to follow the ECI reporting guidance but does not need to follow the treatment guidance (below). Therefore, these recommendations should be seen as guidelines and the treating physician should exercise individual clinical judgment based on the patient. For any question of dose modification or other treatment options, the specific language in the protocol should be followed. Any questions pertaining to the collection of this information or management of ECIs should be directed to your local Sponsor contact.

Dose Modification/Discontinuation

The treatment guidance provides specific direction when to hold and/or discontinue pembrolizumab for each immune related adverse event. Of note, when the guidance states to "discontinue" pembrolizumab this is the permanent discontinuation of treatment with pembrolizumab. "Hold" means to stop treating with pembrolizumab but resumption of treatment may be considered assuming the patient meets the criteria for resumption of treatment.

2. ECI REPORTING GUIDELINES

ECIs are selected non-serious and serious adverse experiences that must be reported to Merck **within 24 hours** regardless of attribution to study treatment. The AEs listed in this document and any event that meets the ECI criteria (as noted) in Table 1 or in the respective protocol

(event term and Grade) must be reported regardless of physician-determined causality with study medication and whether or not considered immune-related by the physician (unless otherwise specified). Physicians/study coordinators/designated site personnel are required to record these experiences as ECIs on the Adverse Experience electronic Case Report Forms (eCRFs) (or on paper) and to provide supplemental information (such as medical history, concomitant medications, investigations, etc.) about the event.

– Please refer to the Data Entry Guidelines (DEGs) for your protocol.
– Please refer to protocol for details on reporting timelines and reporting of Overdose and Drug Induced
Liver Injury (DILI).

3. ECI CATEGORIES AND TERMS

This section describes the ECI categories and outlines subject management guidelines when an ECI is reported.

3.1 Pneumonitis

The following AE terms, if considered ≥ Grade 2, are considered ECIs and should be reported to the Sponsor within 24 hours of the event:

– Pneumonitis
– Interstitial lung disease
– Acute interstitial pneumonitis

If symptoms indicate possible new or worsening cardiac abnormalities additional testing and/or a cardiology consultation should be considered.

All attempts should be made to rule out other causes such as metastatic disease, bacterial or viral infection**. It is important that patients with a suspected diagnosis of pneumonitis be managed as per the guidance below until treatment-related pneumonitis is excluded. Treatment of both a potential infectious etiology and pneumonitis in parallel may be warranted. Management of the treatment of suspected pneumonitis with steroid treatment should not be delayed for a therapeutic trial of antibiotics.** If an alternative diagnosis is established, the patient does not require management as below; however the AE should be reported regardless of etiology.

Course of Action

Grade 2 events:
– Report as ECI
– Hold pembrolizumab.
– Consider pulmonary consultation with bronchoscopy and biopsy/BAL.
– Consider ID consult

– Conduct an in person evaluation approximately twice per week
– Consider frequent Chest X-ray as part of monitoring
– Treat with systemic corticosteroids at a dose of 1 to 2 mg/kg/day prednisone or equivalent. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
– Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.
– Second episode of pneumonitis – discontinue pembrolizumab if upon re-challenge the patient develops a second episode of Grade 2 or higher pneumonitis.

Grade 3 and 4 events:
– Report as ECI
– Discontinue pembrolizumab.
– Hospitalize patient
– Bronchoscopy with biopsy and/or BAL is recommended.
– Immediately treat with intravenous steroids (methylprednisolone 125 mg IV). When symptoms improve to Grade 1 or less, a high dose oral steroid (prednisone 1 to 2 mg/kg once per day or dexamethasone 4 mg every 4 hours) taper should be started and continued over no less than 4 weeks.
– If IV steroids followed by high dose oral steroids does not reduce initial symptoms within 48 to 72 hours, treat with additional anti-inflammatory measures. Discontinue additional anti-inflammatory measures upon symptom relief and initiate a prolonged steroid taper over 45 to 60 days. If symptoms worsen during steroid reduction, initiate a retapering of steroids starting at a higher dose of 80 or 100 mg followed by a more prolonged taper and administer additional anti-inflammatory measures, as needed
– Add prophylactic antibiotics for opportunistic infections.

3.2 Colitis

The following AE terms, if considered ≥ Grade 2 or resulting in dose modification or use of systemic steroids to treat the AE, are considered ECIs and should be reported to the Sponsor within 24 hours of the event:

– Colitis
– Colitis microscopic
– Enterocolitis
– Enterocolitis hemorrhagic
– Gastrointestinal perforation
– Intestinal obstruction
– Necrotizing colitis
– Diarrhea

All attempts should be made to rule out other causes such as metastatic disease, bacterial or parasitic infection, viral gastroenteritis, or the first manifestation of an inflammatory bowel

disease by examination for stool leukocytes, stool cultures, a Clostridium difficile titer and endoscopy. However the AE should be reported regardless of etiology.

Course of Action

Grade 2 Diarrhea/Colitis (4-6 stools/day over baseline, dehydration requiring IV fluids < 24 hours, abdominal pain, mucus or blood in stool):

– Report as ECI
– Hold pembrolizumab.
– Symptomatic Treatment
– For Grade 2 diarrhea that persists for greater than 3 days, and for diarrhea with blood and/or mucus,
o Consider GI consultation and endoscopy to confirm or rule out colitis
o Administer oral corticosteroids (prednisone 1-2 mg/kg QD or equivalent)
– When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
– Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.
– If symptoms worsen or persist > 3 days treat as Grade 3

Grade 3 Diarrhea/Colitis (or Grade 2 diarrhea that persists for > 1 week):

– Report as ECI
– Hold pembrolizumab.
– Rule out bowel perforation. Imaging with plain films or CT can be useful.
– Recommend consultation with Gastroenterologist and confirmation biopsy with endoscopy.
– Treat with intravenous steroids (methylprednisolone 125 mg) followed by high dose oral steroids (prednisone 1 to 2 mg/kg once per day or dexamethasone 4 mg every 4 hours) When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Taper over 6 to 8 weeks in patients with diffuse and severe ulceration and/or bleeding.
– Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.
– If IV steroids followed by high dose oral steroids does not reduce initial symptoms within 48 to 72 hours, consider treatment with additional anti-inflammatory measures as described in the literature [5]. Discontinue additional anti-inflammatory measures upon symptom relief and initiate a prolonged steroid taper over 45 to 60 days. If symptoms worsen during steroid reduction, initiate a retapering of steroids starting at a higher dose of 80 or 100 mg followed by a more prolonged taper and administer additional anti-inflammatory measures as needed.

Grade 4 events:

– Report as ECI
– Permanently discontinue pembrolizumab.
– Manage as per Grade 3.

3.3 Endocrine

The following AE terms, if considered ≥Grade 3 or if ≥Grade 2 and require holding/discontinuation/ modification of pembrolizumab dosing, are considered ECIs and should be reported to the Sponsor within 24 hours of the event:

– Adrenal insufficiency
– Hyperthyroidism
– Hypophysitis
– Hypopituitarism
– Hypothyroidism
– Thyroid disorder
– Thyroiditis

All attempts should be made to rule out other causes such as brain metastases, sepsis and/or infection. However the AE should be reported regardless of etiology.

Hypophysitis or other symptomatic endocrinopathy other than hypo- or hyperthyroidism

Grade 2-4 events:
– Report as ECI if appropriate
– Hold pembrolizumab
– Rule out infection and sepsis with appropriate cultures and imaging.
– Monitor thyroid function or other hormonal level tests and serum chemistries more frequently until returned to baseline values.
– Pituitary gland imaging should be considered (MRIs with gadolinium and selective cuts of the pituitary can show enlargement or heterogeneity and confirm the diagnosis).
– Treat with prednisone 40 mg p.o. or equivalent per day. 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.
– Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.
– Hypophysitis with clinically significant adrenal insufficiency and hypotension, dehydration, and electrolyte abnormalities (such as hyponatremia and hyperkalemia) constitutes adrenal crisis.
– Consultation with an endocrinologist may be considered.

Hyperthyroidism and 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, Grade 2-4 hypothyroidism events:
– Report as ECI if appropriate (see Table 1)
– Monitor thyroid function or other hormonal level tests and serum chemistries more frequently until returned to baseline values.
– Thyroid hormone and/or steroid replacement therapy to manage adrenal insufficiency.
– Therapy with pembrolizumab can be continued while treatment for the thyroid disorder is instituted.
– In hyperthyroidism, non-selective beta-blockers (e.g. propranolol) are suggested as initial therapy.
– In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyroinine, is indicated per standard of care.
– Consultation with an endocrinologist may be considered.

Grade 3 hyperthyroidism events:
– Report as ECI
– Hold pembrolizumab.
– Rule out infection and sepsis with appropriate cultures and imaging.
– Treat with an initial dose of methylprednisolone 1 to 2 mg/kg intravenously followed by oral prednisone 1 to 2 mg/kg per day. 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.
– Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.

Grade 4 hyperthyroidism events:
– Report as ECI
– Discontinue pembrolizumab.
– Manage as per Grade 3

Type 1 diabetes mellitus (if new onset) and ≥ Grade 3 Hyperglycemia

The following AE terms are considered ECIs and should be reported to the Sponsor within 24 hours of the event:

– Type I diabetes mellitus (T1DM), if new onset, including diabetic ketoacidosis (DKA)
– Grade 3 or higher hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA).

Immune-mediated diabetes may present as new onset of Type 1 diabetes or an abrupt worsening of pre- existing diabetes associated with laboratorial evidence of beta cell failure. All attempts should be made to rule out other causes such as type 2 diabetes mellitus (T2DM), T2DM decompensation, steroid-induced diabetes, physiologic stress-induced diabetes, or poorly controlled pre-existing diabetes (either T1DM or T2DM), but events meeting the above criteria should be reported as ECIs regardless of etiology. The patients may present with hyperglycemia (abrupt onset or abrupt decompensation) with clinical evidence of diabetic ketoacidosis or laboratory evidence of insulin deficiency, such as ketonuria, laboratory evidence of metabolic acidosis, or low or undetected c-peptide.

Course of Action

T1DM should be immediately treated with insulin.

T1DM or Grade 3-4 Hyperglycemia events:
- Report as ECI if appropriate (see Table 1)
- Hold pembrolizumab for new onset Type 1 diabetes mellitus or Grade 3-4 hyperglycemia associated with evidence of beta cell failure, and resume pembrolizumab when patients are clinically and metabolically stable.
- 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.
- Consultation with an Endocrinologist is recommended.
- Consider local testing for islet cell antibodies and antibodies to GAD, IA-2, ZnT8, and insulin may be obtained.

3.4 Hematologic

The following AE term, if considered Grade ≥3 or requiring dose modification or use of systemic steroids to treat the AE, are considered an ECI and should be reported to the Sponsor within 24 hours of the event:

– Autoimmune hemolytic anemia
– Aplastic anemia
– Disseminated Intravascular Coagulation (DIC)
– Haemolytic Uraemic Syndrome (HUS)
– Idiopathic (or immune) Thrombocytopenia Purpura (ITP)
– Thrombotic Thrombocytopenic Purpura (TTP)
– Any Grade 4 anemia regardless of underlying mechanism

All attempts should be made to rule out other causes such as metastases, sepsis and/or infection. Relevant diagnostic studies such as peripheral blood smear, reticulocyte count, LDH, haptoglobin, bone marrow biopsy or Coomb's test, etc., should be considered to confirm the diagnosis. However the AE should be reported regardless of etiology.

Course of Action

Grade 2 events:
– Report as ECI
– Hold pembrolizumab
– Prednisone 1-2 mg/kg daily may be indicated
– Consider Hematology consultation.

Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.

Grade 3 events:
– Report as ECI
– Hematology consultation.
– Hold pembrolizumab Discontinuation should be considered as per specific protocol guidance.
– Treat with methylprednisolone 125 mg iv or prednisone 1-2 mg/kg p.o. (or equivalent) as appropriate
– Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.

Grade 4 events:
– Report as ECI
– Hematology consultation
– Discontinue pembrolizumab for all solid tumor indications; refer to protocol for hematologic malignancies.
– Treat with methylprednisolone 125 mg iv or prednisone 1-2 mg/kg p.o. (or equivalent) as appropriate

3.5 Hepatic

The following AE terms, if considered ≥ Grade 2 or greater (or any grade with dose modification or use of systemic steroids to treat the AE), are considered ECIs and should be reported to the Sponsor within 24 hours of the event:

– Autoimmune hepatitis
– Hepatitis
– Transaminase elevations

All attempts should be made to rule out other causes such as metastatic disease, infection or other hepatic diseases. However the AE should be reported regardless of etiology.

Drug Induced Liver Injury (DILI)

In addition, the event must be reported as a Drug Induced Liver Injury (DILI) ECI, if the patient meets the laboratory criteria for potential DILI defined as:

☐ An elevated alanine transaminase (ALT) or aspartate transaminase (AST) lab value that is greater than or equal to three times (3X) the upper limit of normal (ULN) and

☐ An elevated total bilirubin lab value that is greater than or equal to two times (2X) ULN and

☐ At the same time, an alkaline phosphatase (ALP) lab value that is less than 2X ULN,

☐ As a result of within-protocol-specific testing or unscheduled testing.

Note that any hepatic immune ECI meeting DILI criteria should only be reported once as a DILI event.

Course of Action

Grade 2 events:

– Report as ECI

– Hold pembrolizumab when AST or ALT >3.0 to 5.0 times ULN and/or total bilirubin >1.5 to 3.0 times ULN.

– Monitor liver function tests more frequently until returned to baseline values (consider weekly).

o Treat with 0.5-1 mg/kg/day methylprednisolone or oral equivalent and when LFT returns to grade 1 or baseline, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume pembrolizumab per protocol

– Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.

– Permanently discontinue pembrolizumab for patients with liver metastasis who begin treatment with Grade 2 elevation of AST or ALT, and AST or ALT increases ≥50% relative to baseline and lasts ≥1 week.

Grade 3 events:

– Report as ECI

– Discontinue pembrolizumab when AST or ALT >5.0 times ULN and/or total bilirubin >3.0 times ULN.

– Consider appropriate consultation and liver biopsy to establish etiology of hepatic injury, if necessary

– Treat with high-dose intravenous glucocorticosteroids for 24 to 48 hours. When symptoms improve to Grade 1 or less, a steroid taper with dexamethasone 4 mg every 4 hours or prednisone at 1 to 2 mg/kg should be started and continued over no less than 4 weeks.
– If serum transaminase levels do not decrease 48 hours after initiation of systemic steroids, oral mycophenolate mofetil 500 mg every 12 hours may be given. Infliximab is not recommended due to its potential for hepatotoxicity.

– Several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased.
– Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.

Grade 4 events:
– Report as ECI
– Permanently discontinue pembrolizumab
– Manage patient as per Grade 3 above

3.6 Neurologic

The following AE terms, regardless of grade, are considered ECIs and should be reported to the Sponsor within 24 hours of the event:

– Autoimmune neuropathy
– Demyelinating polyneuropathy
– Guillain-Barre syndrome
– Myasthenic syndrome

All attempts should be made to rule out other causes such as metastatic disease, other medications or infectious causes. However the AE should be reported regardless of etiology.

Course of Action

Grade 2 events:
– Report as ECI
– Moderate (Grade 2) – consider withholding pembrolizumab.
– Consider treatment with prednisone 1-2 mg/kg p.o. daily as appropriate
– Consider Neurology consultation. Consider biopsy for confirmation of diagnosis.
– Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.

Grade 3 and 4 events:
– Report as ECI

– Discontinue pembrolizumab
– Obtain neurology consultation. Consider biopsy for confirmation of diagnosis
– Treat with systemic corticosteroids at a dose of 1 to 2 mg/kg prednisone or equivalent once per day. If condition worsens consider IVIG or other immunosuppressive therapies as per local guidelines

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

3.7 Ocular

The following AE terms, if considered Grade ≥2 or requiring dose modification or use of systemic steroids to treat the AE, is considered an ECI and should be reported to the Sponsor within 24 hours of the event:

– Uveitis
– Iritis

All attempts should be made to rule out other causes such as metastatic disease, infection or other ocular disease (e.g. glaucoma or cataracts). However the AE should be reported regardless of etiology.

Course of Action

Grade 2 events:
– Evaluation by an ophthalmologist is strongly recommended.
– Treat with topical steroids such as 1% prednisolone acetate suspension and iridocyclitics.
– Discontinue pembrolizumab as per protocol if symptoms persist despite treatment with topical immunosuppressive therapy.

Grade 3 events:
– Evaluation by an ophthalmologist is strongly recommended
– Hold pembrolizumab and consider permanent discontinuation as per specific protocol guidance.
– Treat with systemic corticosteroids such as prednisone at a dose of 1 to 2 mg/kg per day. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
– Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.

Grade 4 events:
– Evaluation by an ophthalmologist is strongly recommended
– Permanently discontinue pembrolizumab.
– Treat with corticosteroids as per Grade 3 above

3.8 Renal

The following AEs if ≥ Grade 2 are considered ECIs and should be reported to the Sponsor within 24 hours of the event:

– Nephritis
– Nephritis autoimmune
– Renal failure
– Renal failure acute

Creatinine elevations ≥ Grade 3 or any grade with dose modification or use of systemic steroids to treat the AE.

All attempts should be made to rule out other causes such as obstructive uropathy, progression of disease, or injury due to other chemotherapy agents. A renal consultation is recommended. However the AE should be reported regardless of etiology.

Course of Action

Grade 2 events:
– Hold pembrolizumab
– Treatment with prednisone 1-2 mg/kg p.o. daily.
– Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.

Grade 3-4 events:
– Discontinue pembrolizumab
– Renal consultation with consideration of ultrasound and/or biopsy as appropriate
– Treat with systemic corticosteroids at a dose of 1 to 2 mg/kg prednisone IV or equivalent once per day.

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

3.9 Skin

Rash and Pruritus

The following AEs should be considered as ECIs, if ≥ Grade 3 and should be reported to the Sponsor within 24 hours of the event:

– Pruritus
– Rash
– Rash generalized
– Rash maculo-papular
– In addition to CTCAE Grade 3 rash, any rash that is considered clinically significant, in the physician's judgment, should be treated as an ECI. Clinical significance is left to the physician to determine, and could possibly include rashes such as the following:
o rash with a duration >2 weeks; OR
o rash that is >10% body surface area; OR
o rash that causes significant discomfort not relieved by topical medication or temporary cessation
of study drug.

Classic acneiform rash from afatinib < grade 3 need not be reported to sponsor.

Other Skin ECIs

The following AEs should **always** be reported as ECIs, regardless of grade, and should be reported to the
Sponsor within 24 hours of the event:

– Dermatitis exfoliative
– Erythema multiforme
– Steven's Johnson syndrome
– Toxic epidermal necrolysis

Please note, the AE should be reported regardless of etiology.

Course of Action

Grade 2 events:
– Symptomatic treatment should be given such as topical glucocorticosteroids (e.g., betamethasone
0.1% cream or hydrocortisone 1%) or urea-containing creams in combination with oral anti-pruritics
(e.g., diphenhydramine HCl or hydroxyzine HCl).
– Treatment with oral steroids is at physician's discretion for Grade 2 events.

Grade 3 events:
– Hold pembrolizumab.
– Consider Dermatology Consultation and biopsy for confirmation of diagnosis.
– Treatment with oral steroids is recommended, starting with 1 mg/kg prednisone or equivalent once per day or dexamethasone 4 mg four times orally daily. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
– Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.

Grade 4 events:
– Permanently discontinue pembrolizumab.
– Dermatology consultation and consideration of biopsy and clinical dermatology photograph.
– Initiate steroids at 1 to 2 mg/kg prednisone or equivalent. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

3.9.1. Immediate Evaluation for Potential Skin ECIs

A. <u>Photographs</u>:

Every attempt should be made to get a photograph of the actual ECI skin lesion or rash as soon as possible**. Obtain appropriate consent for subject photographs if a consent form addendum is required by your IRB/ERC.**

– Take digital photographs of:
o the head (to assess mucosal or eye involvement),
o the trunk and extremities, and
o a close-up of the skin lesion/rash.
– If possible, a ruler should be placed alongside the site of a skin occurrence as a fixed marker of distance.
– The time/date stamp should be set in the 'ON' position for documentation purposes.
– Photographs should be stored with the subject's study records.
– The Sponsor may request copies of photographs. The local study contact (e.g., CRA) will provide guidance to the site, if needed.

B. <u>Past Medical History</u>:

Collect past medical history relevant to the event, using the questions in Appendix 2 (Past Medical History Related to Dermatologic Event) as a guide. Any preexisting conditions not previously reported (e.g., drug allergy) should be entered into the Medical History eCRF.

C. <u>Presentation of the Event:</u>

Collect information on clinical presentation and potential contributing factors using the questions in Appendix
3 (Presentation of the Dermatologic Event) as a guide. This information should be summarized and entered in narrative format in the AE eCRF. Please use the available free-text fields, such as Signs and Symptoms. Note pertinent negatives where applicable to reflect that the information

was collected. Any treatments administered should be entered on the Concomitant Medication eCRF.

D. <u>Vitals Signs and Standard Laboratory Tests:</u>

Measure vital signs (pulse, sitting BP, oral temperature, and respiratory rate) and record on the Vital Signs eCRF. Perform standard laboratory tests (CBC with manual differential and serum chemistry panel, including LFTs).

E. <u>Focused Skin Examination:</u>

Perform a focused skin examination using the questions in Appendix 4 (Focused Skin Examination) as a guide. Information should be summarized and entered on the Adverse Experience eCRF as part of the narrative.

F. <u>Dermatology Consult</u>

Refer the subject to a dermatologist as soon as possible.

– For a **"severe rash"**, the subject must be seen within **1-2 days** of reporting the event.
– For **clinically significant rash**, the subject should be seen within **3-5 days**.

The dermatologist should submit a biopsy sample to a certified dermatopathology laboratory or to a pathologist experienced in reviewing skin specimens.

The site should provide the dermatologist with all relevant case history, including copies of clinical photographs and laboratory test results.

3.10 Other

The following AEs, regardless of grade, are considered ECIs and should be reported to the Sponsor within 24 hours of the event:

– Myocarditis
– Pericarditis
– Pancreatitis
– Any additional Grade 3 or higher event which the physician considers to be immune related

All attempts should be made to rule out other causes. Therapeutic specialists should be consulted as appropriate. However the AE should be reported regardless of etiology.

Course of Action

Grade 2 events or Grade 1 events that do not improve with symptomatic treatment:

– Withhold pembrolizumab.
– Systemic corticosteroids may be indicated.
– Consider biopsy for confirmation of diagnosis.
– If pembrolizumab held and corticosteroid required, manage as per grade 3 below.

Grade 3 events:

– Hold pembrolizumab

– Treat with systemic corticosteroids at a dose of 1 to 2 mg/kg prednisone or equivalent once per day.
– When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
– Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks. Otherwise, pembrolizumab treatment may be restarted and the dose modified as specified in the protocol

Grade 4 events:
– Treat with systemic corticosteroids at a dose of 1 to 2 mg/kg prednisone or equivalent once per day.
– Discontinue pembrolizumab

3.11 Infusion Reactions

The following AE terms, regardless of grade, are considered ECIs and should be reported to the Sponsor within 24 hours of the event:
– Allergic reaction
– Anaphylaxis
– Cytokine release syndrome
– Serum sickness
– Infusion reactions
– Infusion-like reactions

Please note, the AE should be reported regardless of etiology.

Course of Action

Refer to infusion reaction table in the protocol and below.

Infusion Reactions

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 1 Mild reaction; infusion interruption not indicated;	Increase monitoring of vital signs as medically indicated until the	None
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs	**Stop Infusion.** 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	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab with: Diphenhydramine 50 mg p.o. (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg p.o. (or equivalent dose of antipyretic).
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated.	No subsequent dosing
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration. For Further information, please refer to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE) at http://ctep.cancer.gov		

3.12 Follow-up to Resolution

Subjects should be followed to resolution. The Adverse Experience eCRF should be updated with information regarding duration and clinical course of the event. Information obtained from the consulting specialist, including diagnosis, should be recorded in the appropriate AE fields. Free-text fields should be used to record narrative information:

– Clinical course of the event
– Course of treatment
– Evidence supporting recovery
– Follow-up to the clinical course

Any treatments administered for the event should also be entered in the Concomitant Medication eCRF.

4. REFERENCES

1. Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. Nature Reviews Cancer 2012; 12:252-264.

2. Weber JS Practical Management of Immune-Related Adverse Events from Immune Checkpoint Protein Antibodies for the Oncologist. American Society of Clinical Oncology 2012; 1092-9118/10/1-10.

3. Weber JS, Ka¨hler KC, and Hauschild A. Management of Immune-Related Adverse Events and Kinetics of Response With Ipilimumab. J Clin Oncol 30. 2012. http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2012.41.6750.

4. Hodi FS, O'Day SJ, McDermott DF, Weber RW, Sosman JA, et al. Improved Survival with Ipilimumab in Patients with Metastatic Melanoma. N Engl J Med 363:711-723, 2010.

5. Topalian SL, Hodi FS, Brahmer JR, Gettinger SN, Smith DC, McDermott DF, et al. Safety, Activity, and Immune Correlates of Anti-PD-1 Antibody in Cancer. N Engl J Med 2012; 366:2443-2454.

6. Brahmer JR, Tykodi SS, Chow LQM, Hwu WJ, et al. Safety and Activity of Anti–PD-L1 Antibody in Patients with Advanced Cancer. N Engl J Med 2012; 366:2455-2465.

7. Weber J, Thompson JA, Hamid O, et al: A randomized, double-blind, placebo-controlled, phase II study comparing the tolerability and efficacy of ipilimumab administered with or without prophylactic budesonide in patients with unresectable stage III or IV melanoma. Clin Cancer Res 15:5591-5598, 2009.

8. Lemech C and Arkenau HT. Novel Treatments for Metastatic Cutaneous Melanoma and the Management of Emergent Toxicities. Clinical Medicine Insights: Oncology 2012:6 53–66.

9. Phan GQ, Weber JS, and Sondak VK. CTLA-4 Blockade with Monoclonal Antibodies in Patients with Metastatic Cancer: Surgical Issues. Annals of Surgical Oncology 15(11):3014–3021.

10. Bristol-Myers Squibb: YERVOY (ipilimumab): Serious and fatal immune-mediated adverse reactions— YERVOY Risk Evaluation and Mitigation Strategy (REMS). http://www.yervoy.com/hcp/rems.aspx

11. Bristol-Myers Squibb: YERVOY (ipilimumab) prescribing information revised March 2011. http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/125377s0000lbl.pdf

5. APPENDIX 1 –Events of Clinical Interest (ECI) – Reference Table

Pneumonitis (reported as ECI if ≥ Grade 2)		
Acute interstitial pneumonitis	Interstitial lung disease	Pneumonitis
Colitis (reported as ECI if ≥ Grade 2 or any grade resulting in dose modification or use of systemic steroids to treat		
Intestinal Obstruction	Colitis	Colitis microscopic
Enterocolitis	Enterocolitis hemorrhagic	Gastrointestinal perforation
Necrotizing colitis	Diarrhea	
Endocrine (reported as ECI if ≥ Grade 3 or ≥ Grade 2 and resulting in dose modification or use of systemic steroids to treat		
Adrenal Insufficiency	Hyperthyroidism	Hypophysitis
Hypopituitarism	Hypothyroidism	Thyroid disorder
Thyroiditis	Hyperglycemia, if ≥Grade 3 and associated with ketosis or metabolic acidosis	
Endocrine (reported as ECI)		
Type 1 diabetes mellitus (if new onset)		
Hematologic (reported as ECI if ≥ Grade 3 or any grade resulting in dose modification or use of systemic steroids to treat the		
Autoimmune hemolytic anemia	Aplastic anemia	Thrombotic Thrombocytopenic Purpura (TTP)
Idiopathic (or immune) Thrombocytopenia Purpura (ITP)	Disseminated Intravascular Coagulation (DIC)	Haemolytic Uraemic Syndrome (HUS)
Any Grade 4 anemia regardless of underlying mechanism		
Hepatic (reported as ECI if ≥ Grade 2, or any grade resulting in dose modification or use of systemic steroids to treat		
Hepatitis	Autoimmune hepatitis	Transaminase elevations (ALT and/or
Infusion Reactions (reported as ECI for any grade)		
Allergic reaction	Anaphylaxis	Cytokine release syndrome
Serum sickness	Infusion reactions	Infusion-like reactions
Neurologic (reported as ECI for any grade)		
Autoimmune neuropathy	Guillain-Barre syndrome	Demyelinating polyneuropathy
Myasthenic syndrome		
Ocular (report as ECI if ≥ Grade 2 or any grade resulting in dose modification or use of systemic steroids to treat		
Uveitis	Iritis	
Renal (reported as ECI if ≥ Grade 2)		
Nephritis	Nephritis autoimmune	Renal Failure
Renal failure acute	Creatinine elevations (report as ECI if ≥Grade 3 or any grade resulting in dose modification or use of systemic steroids to treat the AE)	
Skin (reported as ECI for any grade)		
Dermatitis exfoliative	Erythema multiforme	Stevens-Johnson syndrome
Toxic epidermal necrolysis		

Skin (reported as ECI if ≥ Grade 3)		
Pruritus	Rash	Rash generalized
Rash maculo-papular		
Any rash considered clinically significant in the physician's judgment		
Other (reported as ECI for any grade)		
Myocarditis	Pancreatitis	Pericarditis
Any other Grade 3 event which is considered immune-related by the physician		

6. APPENDIX 2 – Past Medical History Related to Dermatologic Event

Past Medical History:
Any preexisting conditions not previously reported (e.g., drug allergy) should be entered into the Medical History eCRF.

1. Does the subject have any allergies? □ Yes □ No

If yes, please obtain the following information:

a. Any allergy to drugs (including topical or ophthalmic drugs)? □ Yes □ No

List the drug name(s) and describe the type of allergic response (e.g. rash, anaphylaxis, etc): ____
_____

b. Any allergy to external agents, such as laundry detergents, soaps, poison ivy, nickel, etc.?
□ Yes □ No

Describe the agent and type of allergic response: _____
_____

c. Any allergy to food? □ Yes □ No

Describe the food and type of allergic response:_____
_____

d. Any allergy to animals, insects? □ Yes □ No

Describe the allergen and type of allergic response: _____
_____

e. Any other allergy? □ Yes □ No

Describe the allergen and type of allergic response: _____

2. Does the subject have any other history of skin reactions, skin eruptions, or rashes? □ Yes □ No

If so what kind? _____

3. Has the subject ever been treated for a skin condition? □ Yes □ No

If so what kind? _____

4. Is the current finding similar to a past experience? □ Yes □ No

7. APPENDIX 3 – Presentation of the Dermatologic Event

Presentation of the event:
Collect information on clinical presentation and potential contributing factors. Key information should be summarized and entered on the Adverse Experience eCRF. Any treatments administered should be entered on the Concomitant Medication eCRF.

1. What is the onset time of the skin reaction, skin eruption, or rash relative to dose of study drug?
_____

2. Has the subject contacted any known allergens? □ Yes □ No

If so what kind? _____

3. Has the subject contacted new, special, or unusual substances (e.g., new laundry detergents, soap, personal care product, poison ivy, etc.)? □ Yes □ No

If so what kind? _____

4. Has the subject taken any other medication (over the counter, prescription, vitamins, and supplement)?
□ Yes □ No

If so what kind? _____

5. Has the subject consumed unaccustomed, special or unusual foods? □ Yes □ No

If so what kind? _____

6. Does the subject have or had in the last few days any illness? □ Yes □ No

If so what kind? _____

7. Has the subject come into contact with any family or house members who are ill? □ Yes □ No

If so who and what? _____

8. Has the subject recently been near children who have a skin reaction, skin eruption, or rash (e.g., *Molluscum Contagiosum*)? □ Yes □ No

9. Has the subject had recent sun exposure? □ Yes □ No

10. For the current rash, have there been any systemic clinical signs? □ Yes □ No

If so what kind? _____

i. Anaphylaxis? □ Yes □ No
ii. Signs of hypotension? □ Yes □ No iii. Signs of dyspnea? □ Yes □ No
iv. Fever, night sweats, chills? □ Yes □ No

11. For the current rash, has the subject needed subcutaneous epinephrine or other systemic catecholamine therapy? □ Yes □ No

If so what kind? _____

12. For the current rash, has the subject used any other medication, such as inhaled bronchodilators, antihistaminic medication, topical corticosteroid, and/or systemic corticosteroid? □ Yes □ No

List medication(s) and dose(s): _____
_____

13. Is the rash pruritic (itchy)? □ Yes □ No

8. APPENDIX 4 – Focused Skin Examination

Focused Skin Examination:
Key information should be summarized and entered on the Adverse Experience eCRF.

Primary Skin Lesions Description
Color: ____

General description:

_____

_____

Describe the distribution of skin reaction, skin eruption, or rash on the body:

_____

_____

Is skin reaction, skin eruption, or rash resolving or continuing to spread?

_____

_____

Any associated signs on physical

_____