2014-111: Phase II study of MK-3475 as Maintenance Therapy in Extensive Stage Small Cell Lung Cancer (SCLC) Patients

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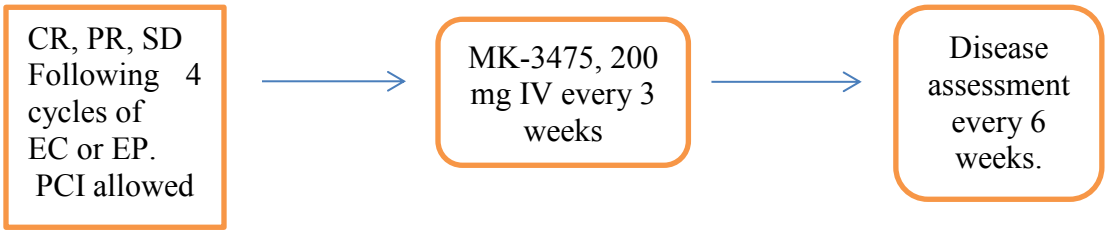
1.0 TRIAL SUMMARY

Abbreviated Title	Maintenance Therapy of MK-3475 in SCLC patients.
Trial Phase	*II*
Clinical Indication	Small Cell Lung Cancer
Trial Type	Single Arm Open Label Phase II
Route of administration	Intravenous
Trial Blinding	N/A
Treatment Groups	N/A
Number of trial subjects	45
Estimated duration of trial	*18 months*

2.0 TRIAL DESIGN

2.1 Trial Diagram



The primary end point of the study is to assess Progression Free Survival (PFS) by RECIST 1.1. However it is well recognized that patients on immune check point inhibitors may experience pseudo-progression or can have delayed response. Therefore patients who do not have development of significant signs or symptoms of progression or significant decline in performance status or the patient/the treating physician feel the need to start next treatment, will require evidence of progression on 2 scans more than 4 weeks apart. Both RECIST defined PFS and **this modified PFS** will be reported for all patients enrolled on the trial.

3.0 OBJECTIVE(S) & HYPOTHESIS

3.1 Primary Objective(s) & Hypothesis

Objective: To assess RECIST 1.1 defined PFS in extensive stage SCLC patients, who have CR, PR or stable disease following minimum of 4 cycles of platinum (cisplatin or carboplatin) and etoposide.

Hypothesis: Maintenance therapy with MK-3475 will increase progression free survival (PFS) in extensive stage SCLC patients, who have non-progressing disease following completion of combination chemotherapy with a platinum analogue and etoposide.

3.2 Secondary Objective(s) & Hypothesis(es)

1. To assess modified PFS in all patients enrolled (**see section 10.2 for definition)**.
2. To assess overall survival of patients enrolled on the trial.
3. To assess PD-L1 expression in archival tumor tissues and in circulating tumor cells (CTCs) and correlate the expression to RECIST defined PFS.

4.0 BACKGROUND & RATIONALE

4.1 Background

Small Cell Lung Cancer (SCLC)

Of the over 225,000 patients diagnosed with lung cancer each year, 13% or about 30,000 patients have SCLC (1). Approximately 66% of the patients have advanced stage disease at the time of diagnosis. The current standard of care treatment for these patients is the chemotherapy combination of a platinum agent and etoposide (2). The median survival with this therapy is only about 10 months, with a progression free survival (PFS) of about 5 months. Despite multiple clinical trials, no therapy has improved outcomes of these patients compared to the current standard of care treatment for the last 20 years. Also very few agents are effective in patients with recurrent SCLC and of the agents that are considered effective the efficacy is very modest. Another challenging aspect of managing SCLC patients is that most of these patients are very symptomatic at the time of diagnosis and require prompt initiation of systemic therapy. The short PFS with initial chemotherapy and the limited number of agents that have benefit in recurrent SCLC, makes this an ideal clinical situation to explore maintenance therapy. Previous trials exploring maintenance therapy have shown only modest benefit in improving PFS with no improvement in overall survival and therefore maintenance therapy is not part of the standard therapy for SCLC patients (3,4,5). **It is important to note that in these maintenance trials the median PFS following disease stabilization with initial chemotherapy is consistently about 2 months in patients who received chemotherapy without maintenance therapy.**

4.2 Immune Surveillance and PD-1

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades (6). Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies (7,8,9). In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells / FoxP3+ regulatory T-cells seems to correlate with improved prognosis and long-term survival in many solid tumors.

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control (10,11,12,13). 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) (10,11). PD-1 was shown to be expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B-cells, T regs and Natural Killer cells. Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells (14). 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 (12, 13). Binding of either PD-1 ligand to PD-1 inhibits T-cell activation triggered through the T-cell receptor. PD-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments. PD-L2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell function in peripheral tissues. Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. 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.

4.2.1 MK-3475 (Pembrolizumab)

MK-3475 (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 (15). This blockade enhances functional activity of the target lymphocytes to facilitate tumor regression and ultimately immune rejection.

Merck is studying MK-3475 for various oncology indications. Protocol 001 (PN001), an open-label Phase I study is being conducted to evaluate the safety and clinical activity of MK-3475 when administered as monotherapy (Investigator's Brochure). The dose escalation portion of this study evaluated three dose levels of single agent MK-3475 (1 mg/kg, 3 mg/kg, and 10 mg/kg), in patients with advanced solid tumors. All three dose levels were well tolerated and no dose-limiting toxicities (DLTs) were observed, therefore the maximum tolerated dose (MTD) has not been determined. Many other trials are ongoing in various tumors types. In addition trials are evaluating the addition of MK-3475 to chemotherapy, ipilimumab and tyrosine kinase inhibitors.

MK-3475 strongly enhances T-lymphocyte immune responses in cultured blood cells from healthy human donors, cancer patients, and primates (Investigator's Brochure). In T-cell activation assays using human donor blood cells, the EC50 (concentration where 50% of the maximum effect is achieved) has been ~0.1 to 0.3 nM. In addition to interleukin-2 (IL-2), tumor necrosis factor alpha (TNFα), interferon gamma (IFNγ), and levels of other cytokines were found to be modulated by MK-3475. The antibody potentiates existing immune responses only in the presence of antigen and does not nonspecifically activate T-cells. Using an anti-murine PD-1 analog antibody, PD-1 blockade has been shown to significantly inhibit tumor growth in a variety of syngeneic murine tumor models. In these experiments in mice, anti-PD-1 therapy is synergistic

with chemotherapeutic agents such as gemcitabine and 5-fluorouracil (5-FU) and combination therapy results in increased complete tumor regression rates in vivo.

As of 26-Jul-2013, there have been 789 patients treated in a phase I trial (PN001) with MK-3475 as a 30-minute IV infusion. Of these 789 patients, preliminary data are available from 479 patients. Based upon this safety database consisting of patients treated up to 10 mg/kg once every two to three weeks, MK-3475 has been generally well-tolerated at doses up to 10 mg/kg every other week without DLTs. One (0.002%) patient assayed to date had samples confirmed positive for ADA, but no impact on safety has been observed. Five other clinical studies (PN002, PN006, PN010, PN011, and PN012) are ongoing however preliminary data analyses are not yet available.

MK-3475 PK results have been obtained from phase I trial following the first dose at 1, 3 and 10 mg/kg IV of MK-3475 administered to 17 patients with solid tumors. Exposure to MK-3475 is approximately linear in the dose range of clinical relevance (1-10 mg/kg).The observed pharmacokinetic profile of MK-3475 was typical of other IgG mAbs with a half-life (t½) of approximately 2 to 3 weeks. There was no indication of dose dependency of half-life in the 3 dose groups and a dose related increase in exposure was observed from 1 to 10 mg/kg. The long half-life supports a dosing interval of every 2 or 3 weeks. Exposure obtained with sparse sampling after dosing melanoma and non-small cell lung cancer (NSCLC) patients at 2 and 10 mg/kg, every 2 or 3 weeks, is consistent with this profile.

Durable objective responses have been reported in patients with melanoma and NSCLC (15, 16). Adverse events have generally been manageable and infrequently require discontinuation of MK-3475 treatment. MK-3475 phase I trial enrolled 207 patients with NSCLC who experienced progression of cancer after previous systemic therapy. The preliminary objective response rate (ORR) by RECIST v1.1 is 23% (95% CI 16%, 30%) in patients with tumors deemed to be PD-L1 positive and 9% (95% CI 2%, 23%) in patients with tumors that were PD-L1 negative, for an overall response rate of about 17%. The median response duration is 31 weeks.

Patients were required to submit a newly obtained tumor biopsy prior to initiating therapy with MK-3475 to evaluate the tumors for expression of PD-L1, the presumptive predictive biomarker of MK-3475, using an immunohistochemistry assay. A modified H-score scoring system of PD-L1 expression was established for NSCLC by analyzing tumor specimens from resected NSCLC specimens. This scoring system was then applied to the samples from these NSCLC patients. A receiver-operating characteristics curve was constructed from the data and the Youden Index identified from that analysis to help determine a preliminary cut point. A stated above, preliminary data suggest higher levels of PD-L1 expression are associated with increased activity. Additional data are required to define the optimal PD-L1 cut point.

The safety of MK-3475 was characterized in the 1-month repeat-dose toxicity study in cynomolgus monkeys when administered as IV doses of 6, 40 or 200 mg/kg once a week (a total of five doses) and in the 6-month repeat-dose toxicity study in cynomolgus monkeys when administered as IV doses of 6, 40 or 200 mg/kg every other week (a total of 12 doses). MK-3475 was well-tolerated in cynomolgus monkeys with a

systemic exposure (AUC) of up to approximately 170,000 µg.day/mL over the course of the 1-month study, and with a systemic exposure (AUC) of up to approximately 67,500 µg.day/mL over the course of the 6-month study. No findings of toxicological significance were observed in either 1-month or 6-month toxicity study with MK-3475 and the NOAEL was ≥200 mg/kg. In addition, no findings of toxicological relevance were observed in the in vitro tissue cross-reactivity study using human and cynomolgus monkey tissues. There were no nonclinical findings that would preclude testing of MK-3475 in clinical trials.

Out of a total of 479 patients treated on the phase I trial, 466 (97.3%) experienced treatment emergent AEs of which 368 (76.8%) were considered drug-related. SAEs were reported in 30.1% of patients, but SAEs that were attributed as potentially (possibly, probably, or definitely) drug-related by Investigators were reported in 6.7% of patients overall. Five patients died within 30 days of the last dose of MK-3475; none of the deaths were considered drug-related. Some of the common adverse events were fatigue, pruritus, nausea, diarrhea, cough, dyspnea, skin rash, muscle cramps, fever, hypo or hyperthyroidism, flu like symptoms, neutropenia.

An important concern with a drug like MK-3475 is that patients may experience immune mediated adverse events. Though it is not completely clear that all the listed events were definitely immune related, the following AEs were considered to have an immune etiology. These include rash, vitiligo, hypothyroidism, colitis, hepatitis, adrenal insufficiency and pneumonitis. All these AEs were observed in less than 5% of the patients.

The most common drug related ≥ grade 3 AEs were fatigue, diarrhea, liver enzyme elevation. All these AEs were observed in less than 2 % of the patients. Some of the other ≥ grade 3 AEs included renal failure, pancreatitis, pneumonitis, anemia, pancytopenia.

4.2.2 Targeting PD-1 in SCLC

The role of anti-tumor immunity is not well defined in SCLC. However several studies suggest that anti-tumor immunity may play a role in controlling SCLC. SCLC patients can have a variety of paraneoplastic syndromes, some of which are immune mediated. Certain datasets suggest that patients with immune mediated paraneoplastic disorders may have a longer survival (17,18,19). In addition, it has been observed that patients, with tumors that have a higher ratio of effector T cells to regulatory T cells, have better outcomes and are more likely to have limited stage disease (20). Recent data also shows that lung cancer, both small cell and non-small cell lung cancers have a high rate of mutations (21). This high rate of mutations raises the possibility that there are many neo-antigens expressed on tumor cells, that are not expressed on normal cells and these antigens could serve as targets for the immune cells. All these observations raise the strong possibility that activation of an anti-tumor immune response may control and even shrink small cell lung cancer.

Multiple different immune based strategies have been evaluated in SCLC patients. These include vaccines, immune response modifiers and immune check point

inhibitors. An anti-idiotypic antibody BEC2 administered with BCG as an adjuvant has been tested in SCLC patients (22). This antibody mimics the ganglisoide GD3 expressed in a large proportion of SCLCs and therefore can induce anti-tumor immunity targeting GD-3. In a 15 patient exploratory study administration of BEC2 induced anti-GD-3 antibodies in 5 patients, who had the longest relapse free survival. A subsequent phase III study in limited stage SCLC patients following completion of therapy failed to show clinical benefit (23). However the study showed that there was a trend towards improved survival in one-third of the patients who developed a humoral response. These data suggest that effective immune therapy could provide clinical benefit in SCLC patients when administered as maintenance therapy.

Recently, Reck, et al, published the results of a randomized three arm phase II trial evaluating the addition of ipilimumab to chemotherapy in patients with extensive stage SCLC (24). Iplimumab is a monoclonal antibody targeting CTLA-4, a negative regulator of T-cell activation. Patients in this study received ipilimumab either starting with the first cycle of chemotherapy or was started after the first 2 cycles. Patients on the control arm received placebo with chemotherapy. In this study the patients who received Ipilimumab in a phased in fashion (after the first 2 cycles) had a significantly higher ir (immune related) PFS compared to patients on the control arm. It is well recognized that patients on immune check point inhibitors may experience 'pseudo' progression probably due to inflammation in the region of the cancer and can have a delayed response to therapy. Therefore in many immune therapy trials modified response criteria are utilized to assess progression free survival (ir response criteria). Significant improvement in irPFS was not observed in the patients who received ipilimumab starting with the first cycle of chemotherapy. Also improvement in RECIST defined PFS was not observed. Interestingly, patients who received ipilimumab in a phased in fashion had improved survival, with a median of 12.9 months compared to patients who received chemotherapy alone, with a median of 9.9 month. Similar results were observed with this agent in NSCLC patients (25). It is unclear why clinical benefit was only observed in patients who received ipilimumab in a phased in fashion. The possible reasons are that the cytotoxic effect of chemotherapy may release tumor antigens into the general system priming the effect of ipilimumab and that the concomitant administration of steroids during chemotherapy may limit the efficacy of the ipilimumab. A randomized phase III study evaluating phased in iplimumab in combination with chemotherapy has completed enrollment.

In preliminary clinical studies utilizing anti-PD-1 antibodies promising anti-tumor activity has been observed in patients with different tumor types including non-small cell lung cancer (16, 26). In addition, initial trials suggest that these drugs maybe better tolerated than anti-CTLA4 antibodies since anti-CTL4 antibodies generate more systemic activation of T cells and anti-PD-1 generate more tissue based activation of immune T cells (27).

Currently there is no data available regarding the use of anti-PD-1 or anti-PD-L1 antibodies in SCLC patients. There is indirect evidence to suggest that targeting PD-1 will be beneficial in SCLC patients. Promising activity with both anti-PD-1 and anti-PD-L1 therapies has been observed in NSCLC. In addition, recent data suggests that benefits from anti-PD-L1 antibody MPDL3280A are more likely in NSCLC patients

who are smokers (28). This is possibly related to higher rate of genetic alterations in smoking related NSCLCs and therefore higher expression of antigens on these tumors (21). Almost all patients with SCLC are smokers and generally have a prolonged history of smoking, making it likely that patients with these tumors will benefit from targeting PD-1 pathway.

4.3 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

The outcomes of SCLC patients have not changed from over 20 years. The characteristic features of this cancer are high initial response rate followed by rapid progression/relapse of the tumor. Therefore this is an ideal tumor to consider maintenance therapy. It is challenging to continue therapy with currently available chemotherapy drugs. Therefore it is imperative to evaluate other agents as maintenance therapy with the goal of prolonging disease control and possibly survival. There is indirect evidence that immune therapy may be beneficial in SCLC patients.

Based on all the discussed data, we **hypothesize that maintenance MK-3475 following completion of initial chemotherapy in patients with extensive stage SCLC will result in improved progression free survival.** To test our hypothesis we propose to conduct a single arm phase II study evaluating the efficacy of MK-3475 as maintenance therapy in extensive stage SCLC patients following completion of first line chemotherapy. We believe that immune based therapy is most likely to be beneficial in SCLC patients following 'debulking' of the tumor with chemotherapy and improvement of patient's performance status with disease shrinkage and control. Patients who have complete or partial response or stable disease will be eligible for the trial and will receive MK-3475. We believe that in this setting a single arm phase II study is appropriate since the duration of progression free survival following initial chemotherapy is very well established in this clinical setting over a long period of time and over several trials.

4.2.2 Rationale for Dose Selection/Regimen/Modification

An open-label Phase I trial (Protocol 001) 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). Recent data from other clinical studies within the MK-3475 program has shown that a lower dose of MK-3475 and a less frequent schedule may be sufficient for target engagement and clinical activity.

PK data analysis of MK-3475 administered Q2W and Q3W showed slow systemic clearance, limited volume of distribution, and a long half-life (refer to IB). Pharmacodynamic data (IL-2 release assay) suggested that peripheral target

engagement is durable (>21 days). This early PK and pharmacodynamic data provides scientific rationale for testing a Q2W and Q3W dosing schedule.

A population pharmacokinetic analysis has been performed using serum concentration time data from 476 patients. Within the resulting population PK model, clearance and volume parameters of MK-3475 were found to be dependent on body weight. The relationship between clearance and body weight, with an allometric exponent of 0.59, is within the range observed for other antibodies and would support both body weight normalized dosing or a fixed dose across all body weights. MK-3475 has been found to have a wide therapeutic range based on the melanoma indication. The differences in exposure for a 200 mg fixed dose regimen relative to a 2 mg/kg Q3W body weight based regimen are anticipated to remain well within the established exposure margins of 0.5 – 5.0 for MK-3475 in the melanoma indication. The exposure margins are based on the notion of similar efficacy and safety in melanoma at 10 mg/kg Q3W vs. the proposed dose regimen of 2 mg/kg Q3W (i.e. 5-fold higher dose and exposure). The population PK evaluation revealed that there was no significant impact of tumor burden on exposure. In addition, exposure was similar between the NSCLC and melanoma indications. Therefore, there are no anticipated changes in exposure between different indication settings. Based on all these data MK-3475 will be administered at a **standard flat dose of 200 mg every 3 weeks**.

4.2.3 Rationale for Efficacy Endpoints

We have selected progression free survival as defined by RECIST criteria as the primary endpoint. This was the primary endpoint in most maintenance trials conducted in SCLC patients to date. Consistently the median PFS in these maintenance trials following induction therapy in responding or stable disease patients is about 2 months in the control arm. Therefore it will be possible to assess if the results with maintenance MK-3475 are better than this historical data and thus encouraging enough to continue further evaluation of this drug in this setting.

It is well recognized that patients treated with immune therapy may have pseudo progression or can have delayed response. Therefore many trials of immune therapy assess not only PFS as defined by RECIST criteria but also a modified PFS. The modified criteria require progression on 2 sequential scans, at least 4 weeks apart for definition of progression. The patients will continue on study therapy until these criteria are met, unless there is a decline in patient's performance status or symptoms that is considered not acceptable by the patient or the treating physician, or the patient wants to discontinue therapy for any reason.

In this trial we will not only assess PFS by RECIST criteria but will also assess PFS by this modified criteria as well. In addition we will assess response to MK-3475 by RECIST and overall survival.

4.2.3.1 Biomarker Research

Emerging data suggests that expression of PD-L1 on the tumor may predict for benefit from the MK-3475 and other anti-PD-1. Benefit has also been observed in patients whose tumors don't express PD-L1 but the percentage of such patients who benefit is far less. This difference in efficacy with anti- PD-1 drugs has been observed across tumor types. The rate of PD-L1 expression in SCLC is not well defined. We therefore plan to assess the expression of PD-L1 in tumors of patients enrolled on the trial and correlate the presence of PD-L1 with efficacy end points.

Tumor content in diagnostic biopsies is likely to be limited in SCLC patients. In addition, biopsy of residual tumor following initial chemotherapy may be challenging. Circulating tumor cells (CTCs) hold great promise as a readily available source material that can offer real-time insight into a tumor's genomic architecture. CTCs can be detected in small cell lung cancer patients and appear to have prognostic importance (20, 21). We propose to collect CTCs and assess PD-L1 expression in CTCs an attempt to correlate PD-L1 expression in CTCs with patient's primary tumor and with efficacy parameters.

5.0 ELIGIBILITY

5.1 Inclusion Criteria

1. Patients with extensive stage SCLC who have completed at least 4 cycles of platinum (carboplatin/cisplatin) and etoposide chemotherapy as their first line therapy and have responding or stable disease to this therapy are eligible for this study. Patients who received platinum/etoposide previously for SCLC and it was repeated for recurrence will not be eligible.

2. Patients should be willing and able to provide written informed consent for the trial.

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

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

5. Demonstrate adequate organ function as defined in Table 1, all screening labs should be performed within 14 days of treatment initiation.

Table 1 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** ≥45 mL/min for subject with creatinine levels > 1.5 X institutional ULN
Hepatic	
Serum total bilirubin	≤ 1.5 X ULN **OR**
	Direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 X ULN **OR** ≤ 5 X ULN for subjects with liver metastases
[a]Creatinine clearance should be calculated per institutional standard.	

6. Female subject of childbearing potential should have a negative urine or serum pregnancy within 1 week 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.

7. Female subjects of childbearing potential should be willing to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study medication (Reference Section 5.7.2). Subjects of childbearing potential are those who have not been surgically sterilized or have not been free from menses for > 1 year.

8. Male subjects should agree to use an adequate method of contraception starting with the first dose of study therapy through 120 days after the last dose of study therapy.

5.2 Exclusion Criteria

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

1. Is currently participating in or has participated in a study of an investigational agent within 4 weeks of the first dose of treatment.

2. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy greater than 10 mg/day prednisone equivalent or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment.

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

4. Has had prior chemotherapy, targeted small molecule therapy, or **definitive** radiation therapy within 2 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to a previously administered agent. **Patients who received palliative radiation to any site or prophylactic cranial radiation (≤ 30 Gy) or thoracic RT can start therapy with the study drug 7 days after the last day of radiation therapy as long as they have recovered from any adverse effects (i.e., ≤ Grade 1 or at baseline) of such radiation therapy.**

    - Note: Subjects with ≤ Grade 2 neuropathy or adverse events that are not considered clinically meaningful such as alopecia 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.

5. Has a known additional malignancy that is progressing or requires active treatment. Patient will be eligible if other malignancy is controlled and the treating physician determines that the patient's outcome is unlikely to be affected by the other tumor.

6. Has symptomatic central nervous system (CNS) metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are **clinically** stable and any neurologic symptoms have returned to baseline, have no **clinical** evidence of new or enlarging brain metastases, and are not using steroids greater than prednisone 10mg/day or equivalent dose of another steroid, prior to start of trial treatment.

7. Has an active automimmune disease, including a paraneoplastic syndrome of autoimmune nature, requiring systemic treatment other than chemotherapy for SCLC, within the past 3 months or a documented history of clinically severe autoimmune disease, or a syndrome that requires or required 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.

8. Has evidence of active, non-infectious pneumonitis.

9. Has an active infection requiring therapy.

10. 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.

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

12. 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.

13. Has received prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways).

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

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

16. Has received a live vaccine within 30 days prior to the first dose of trial treatment.

6.0 TRIAL TREATMENTS/PROCEDURE

All patients deemed eligible and registered with Study Coordinator, the Clinical Trials Office at Karmanos Cancer Institute, will initiate study therapy within 5 days of registration. Please see section 7.0 for all required tests and assessments prior to registration. This is a single arm study so all eligible patients will receive the study treatment MK-3475.

Patients will start therapy no **earlier than 3 weeks** from the first day of the last cycle of platinum/etoposide chemotherapy and **no later than 8 weeks** from the first day of the last cycle of chemotherapy. Due to logistical and administrative issues therapy maybe started within 48 hours before the 3 weeks from the first day of the last cycle of chemotherapy or within 48 hours after 8 weeks of the first day of the last cycle of chemotherapy, **after consultation with the Principal Investigator.**

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

Table 2 Trial Treatment

Drug	Dose/Potency	Dose Frequency	Route of Administration
MK-3475	**200 mg**	Every 3 weeks	IV infusion

Treatment will continue for 24 months unless patient experiences intolerable adverse events or disease progression or patient desires to discontinue therapy.

6.1.1 Dose Modification

6.1.1.1 Dose Modification

There is no dose reduction allowed on the protocol. However the dosing frequency can be increased from 3 weeks to every 4 weeks. MK-3475 will be withheld for drug-related Grade 4 hematologic toxicities, non-hematological toxicity ≥ Grade 3 including laboratory abnormalities, and severe or life-threatening AEs as per Table 3 below. **In addition, the drug can be held for any grade of toxicity by the treating physician if it is felt that it is in the best interest of the patient**

Table 3: Dose modification guidelines for drug-related adverse events.

Toxicity	Grade	Hold Treatment (Y/N)	Timing for restarting treatment	Dose/Schedule for restarting treatment	Discontinue Subject (after consultation with Sponsor)
Hematological Toxicity	1, 2, 3* * Patient should not have febrile neutropenia or thrombocytopenia associated with hemorrhage. For grade 2 and 3 neutropenia and thrombocytopenia patients should undergo at least weekly blood counts	No	N/A	N/A	N/A
	4	Yes	Toxicity resolves to Grade 0-1 or baseline	May increase the dosing interval by 1 week	Toxicity does not resolve within 12 weeks of last infusion Permanent discontinuation should be considered for any severe or life-threatening event
Non-hematological toxicity Note: Exception to be treated similar to grade 1 toxicity • Grade 2 alopecia • Grade 2 fatigue For additional information regarding Adverse Events with a potential Immune-Etiology reference Section 6.3.1.1	1	No	N/A	N/A	N/A
	2	Consider withholding for persistent symptoms	Toxicity resolves to Grade 0-1 or baseline	*Clinical AE resolves within 4 weeks*: Same dose and schedule (reference Section 5.6.1.2 for recommendations regarding pneumonitis) *Clinical AE does not resolve within 4 weeks:* May increase the dosing interval by 1 week	Toxicity does not resolve within 12 weeks of last infusion

Toxicity	Grade	Hold Treatment (Y/N)	Timing for restarting treatment	Dose/Schedule for restarting treatment	Discontinue Subject (after consultation with Sponsor)
	3, 4	Yes	Toxicity resolves to Grade 0-1 or baseline	May increase the dosing interval by 1 week	Toxicity does not resolve within 12 weeks of last infusion *Permanent discontinuation should be considered for any severe or life-threatening event*

With investigator and Principal Investigator agreement, subjects with a laboratory adverse event still at Grade 2 after 12 weeks may continue treatment in the trial only if asymptomatic and controlled. **A patient who requires longer than 12 weeks but less than 24 weeks to recover from an adverse event that led to the withholding of the drug could be restarted on the drug IF the treating physician believes that it is in the best interest of the patient to restart the drug and the patient is agreeable. This has to be discussed with the Principal Investigator before restarting the drug.**

Subjects who experience a recurrence of the same severe or life-threatening event at the same grade or greater with re-challenge of MK-3475 should be discontinued from trial treatment.

6.1.2 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 7.0). Trial treatment may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons, including patient's desire.

All trial treatments will be administered on an outpatient basis.

MK-3475 will be administered as a 30 minute IV infusion (treatment cycle intervals may be increased due to toxicity as described in Section 5.2.1.2). Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min).

Merck will provide Pharmacy Manual which contains specific instructions for MK-3475 dose calculation, reconstitution, preparation of the infusion fluid, and administration.

6.2 Concomitant Medications/Vaccinations (allowed & prohibited)

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for one of these or other medications or vaccinations specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The investigator should discuss any questions regarding this with the Principal Investigator. The final decision on any supportive therapy or vaccination rests with the investigator. However, the decision to continue the subject on trial therapy or vaccination schedule requires the mutual agreement of the Investigator, and the subject.

6.2.1 Acceptable Concomitant Medications

All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the case report form (CRF). All concomitant medications at the time of study enrollment and study therapy discontinuation should be recorded.

6.2.2 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:

- Anti-cancer systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Investigational agents other than MK-3475
- Radiation therapy
    - Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed after consultation with the Principal Investigator
- 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, chicken pox, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however intranasal influenza vaccines (e.g. Flu-Mist®) are live attenuated vaccines, and are not allowed.
- 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 Principal Investigator.
- **Patients CAN continue on bone modifying agents such as zolendronic acid or densumomab if deemed necessary by the treating physician.**

6.3 Rescue Medications & AE Mangement

6.3.1 Supportive Care Guidelines

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator including but not limited to the items outlined below:

- Diarrhea: Subjects should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus). In symptomatic subjects, infectious etiologies should be ruled out, and if symptoms are persistent and/or severe, endoscopic evaluation should be considered.

    - In subjects with severe enterocolitis (Grade 3 or greater), MK-3475 will be permanently discontinued and treatment with systemic corticosteroids should be initiated at a dose of 1 to 2 mg/kg/day of prednisone or equivalent. When symptoms improve to Grade 1 or less, corticosteroid taper should be started and continued over at least 1 month. **If the treating physician believes that the patient is deriving clinical benefit from the study drug, then the treating physician after consultation with the Principal Investigator may discuss with the patient regarding continuing therapy with MK-3475**

    - In subjects with moderate enterocolitis (Grade 2), MK-3475 should be withheld and anti-diarrheal treatment should be started. If symptoms are persistent for more than one week, systemic corticosteroids should be initiated (e.g., 0.5 mg/kg/day of prednisone or equivalent). When symptoms improve to Grade 1 or less, corticosteroid taper should be started and continued over at least 1 month. Regarding guidelines for continuing treatment with MK-3475, see Section 5.2.

    - All subjects who experience diarrhea 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.

- Nausea/vomiting: Nausea and vomiting should be treated aggressively, and consideration should be given in subsequent cycles to the administration of prophylactic antiemetic therapy according to standard institutional practice. Subjects should be strongly encouraged to maintain liberal oral fluid intake.

- Anti-infectives: Subjects with a documented infectious complication should receive oral or IV antibiotics or other anti-infective agents as considered appropriate by the treating investigator for a given infectious condition, according to standard institutional practice.

- Immune-related adverse events: Please see Section 6.3.1.1 below regarding diagnosis and management of adverse experiences of a potential immunologic etiology.

- Management of Infusion Reactions: Acute infusion reactions (which can include cytokine release syndrome, angioedema, or anaphylaxis) are different from allergic/hypersensitive reactions, although some of the manifestations are common to both AEs. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Signs/symptoms may include: Allergic reaction/hypersensitivity (including drug fever); Arthralgia (joint pain); Bronchospasm; Cough; Dizziness; Dyspnea (shortness of breath); Fatigue (asthenia, lethargy, malaise); Headache; Hypertension; Hypotension; Myalgia (muscle pain); Nausea; Pruritis/itching; Rash/desquamation; Rigors/chills; Sweating (diaphoresis); Tachycardia; Tumor pain (onset or exacerbation of tumor pain due to treatment); Urticaria (hives, welts, wheals); Vomiting.

Table 4 below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of MK-3475.

Table 4 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).

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
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		

6.3.1.1 Supportive Care Guidelines for Events of Clinical Interest and Immune-related Adverse Events (irAEs)

Events of clinical interest of a potential immunologic etiology (irECIs) may be defined as an adverse event of unknown etiology, associated with drug exposure and is consistent with an immune phenomenon. irAEs may be predicted based on the nature of the MK-3475 compound, its mechanism of action, and reported experience with immunotherapies that have a similar mechanism of action. Special attention should be paid to AEs that may be suggestive of potential irAEs. An irAE can occur shortly after the first dose or **several months after the last dose of treatment**. Examples of such events include pneumonitis, pancreatitis, thyroid disorders.

If an irAE is suspected, efforts should be made to rule out neoplastic, infectious, metabolic, toxin or other etiologic causes prior to labeling an adverse event as an irAE. Information on possible irAEs is included in the Appendix in Section 15.4. Subjects who develop a Grade 2 or higher irAE should be discussed immediately with the Principal Investigator.

Recommendations to managing irAEs not detailed elsewhere in the protocol are detailed in Table 5.

Table 5. General Approach to Handling irAEs

irAE	Withhold/Discontinue MK-3475?	Supportive Care
Grade 1	No action	Provide symptomatic treatment
Grade 2	May withhold MK-3475	Consider systemic corticosteroids in addition to appropriate symptomatic treatment
Grade 3 and Grade 4	Withhold MK-3475 Discontinue if unable to reduce corticosteroid dose to < 10 mg per day prednisone equivalent within 12 weeks of toxicity	Systemic corticosteroids are indicated in addition to appropriate symptomatic treatment. May utilize 1 to 2 mg/kg prednisone or equivalent per day. Steroid taper should be considered once symptoms improve to Grade 1 or less and tapered over at least 4 weeks.

6.3.1.1.1 Management of Possible immune related Adverse Events (irAEs) (see also Appendix, Section 15.4)

Each of the clinical conditions listed below can have causes other than immune related. Appropriate evaluation to determine the cause of the events is necessary and only after other possible causes have been determined to be less likely should the Principal Investigator be contacted within 72 hours. **Please note if the ECI meets the SAE reporting guidelines then the SAE reporting guidelines should be followed**.

6.3.1.1.1a 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, and a Clostridium difficile titer.

Course of Action

Grade 1 diarrhea:

- Treat symptomatically (loperamide, oral hydration, electrolyte substitution and ADA colitis diet).
- Endoscopy is recommended if symptoms persist.

Grade 2 diarrhea (or persistent Grade 1):

- Hold MK-3475.
- GI consultation and endoscopy is recommended to confirm or rule out colitis for Grade 2 diarrhea that persists >1 week or Grade 1-2 diarrhea with rectal bleeding (additional guidelines for the treatment of persistent colitis are provided below).

- Grade 1 events that persist for >1 week or Grade 2 events should be treated with the addition of oral diphenoxylate hydrochloride and atropine sulfate four times daily and budesonide 9 mg daily.

- Grade 2 diarrhea with diffuse ulceration and bleeding seen on endoscopy may require oral steroids with prolonged taper and represent an increased risk for the development of bowel perforation.

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

Grade 3-4 diarrhea (or Grade 2 diarrhea that persist after initial steroid treatment):

- Hold/Discontinue MK-3475.

- Rule out bowel perforation. Imaging with plain films or CT can be useful.

- Consider 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.

- If IV steroids followed by high dose oral steroids does not reduce initial symptoms within 48 to 72 hours, consider treatment with infliximab at 5 mg/kg once every 2 weeks. Discontinue infliximab upon symptom relief and initiate a prolonged steroid taper over 45 to 60 days. If symptoms worsening 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 infliximab. CAUTION: infliximab is contraindicated in patients with bowel perforation or sepsis [12].

- If symptoms persist despite the above treatment a surgical consult should be obtained.

After patient has recovered the treating physician may consider restarting therapy with the study drug after consultation with the Principal Investigator.

6.3.1.1.1b Endocrine Abnormalities

Possible endocrine disorders that could arise include- Adrenal Insufficiency, Hypothyroidism, Hyperthyroidism, Thyroditis, Hypophysitis, Hypopituitarism.

Course of Action

Grade 1-2 events:

- Monitor thyroid function or other hormonal level tests and serum chemistries more frequently until returned to baseline values.
- If hypophysitis is considered, pituitary gland imaging should be considered (MRIs with gadolinium and selective cuts of the pituitary can show enlargement or heterogeneity and confirm the diagnosis).
- Thyroid hormone and/or steroid replacement therapy should be considered in appropriate patients.

Symptomatic pan-hypopituitarism and any Grade 3-4 events

- Hold/discontinue MK-3475.
- Consider Endocrine consultation.
- 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.
- Hypophysitis with clinically significant adrenal insufficiency and hypotension, dehydration, and electrolyte abnormalities (such as hyponatremia and hyperkalemia) constitutes adrenal crisis. Hospitalization and intravenous methylprednisolone should be initiated.

After patient has recovered the treating physician may consider restarting therapy with the study drug after consultation with the Principal Investigator.

6.3.1.1.1c Ocular Events

The following AE term, if considered Grade ≥2, is considered an ECI and should be reported to the Principal Investigator within 72 hours of the event:

- Uveitis

Course of Action for Ocular Events

Grade 1-2 events:

- Evaluation by an ophthalmologist is strongly recommended.
- Treat with topical steroids such as 1% prednisolone acetate suspension and iridocyclitics.
- Discontinue MK-3475 if symptoms persist despite treatment with topical immunosuppressive therapy.

Grade 3-4 events:

- Discontinue MK-3475.
- 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.

After patient has recovered the treating physician may consider restarting therapy with the study drug after consultation with the Principal Investigator.

6.3.1.1.1d Hepatic

The following AE terms, if considered ≥ Grade 2, are considered ECIs and should be reported to the Principal Investigator within 72 hours of the event.

Symptoms may include (but not limited to):

- Elevations in: AST >2.5 times upper limit of normal (ULN), ALT >2.5 times ULN, Total bilirubin >1.5 times ULN, Fever, Malaise, Upper quadrant abdominal pain.

Course of Action

Grade 1 events: Monitor liver function tests more frequently until returned to baseline values.

Grade 2 events: Monitor liver function tests more frequently until returned to baseline values.

Grade 3-4 events: Discontinue MK-3475 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 [12].

- Several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased.

After patient has recovered the treating physician may consider restarting therapy with the study drug after consultation with the Principal Investigator.

6.3.1.1.1e 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

Course of Action

Grade 1 events:

- Mild (Grade 1) irAEs – provide symptomatic treatment.

Grade 2 events:

- Moderate (Grade 2) or Grade 1 irAEs that do not improve with symptomatic treatment – consider withholding MK-3475. Systemic corticosteroids may be indicated.

Grade 3-4 events:

- Clinically significant or severe (≥ Grade 3) irAEs
- Discontinue MK-3475
- 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 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.

Discontinue MK-3475 if unable to reduce corticosteroid dose for irAEs to ≤10 mg.

After patient has recovered the treating physician may consider restarting therapy with the study drug after consultation with the Principal Investigator.

6.3.1.1.1f Dermatologic

The following AEs should always be reported as ECIs, regardless of CTCAE grade, and should be reported to the Principal Investigator within 72 hours of the event:

- Dermatitis Exfoliative
- Erythema Multiforme
- Stevens-Johnson Syndrome
- Toxic Epidermal Necrolysis

The following AE terms should only be reported as an ECI if they are considered to be immune related, ≥ Grade 3 or result in dose modification or discontinuation:

- Pruritus
- Rash
- Rash generalized
- Rash maculo-papular
- Vitiligo

Course of Action with MK-3475

Grade 1-2 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 antipruritics (e.g., diphenhydramine HCl or hydroxyzine HCl).
- Treatment with oral steroids is at investigator discretion for Grade 2 events.

Grade 3 events:

- Hold MK-3475.
- 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.

Grade 4 events:

– Permanently discontinue MK-3475.

– 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.

6.3.1.1.1g Pneumonitis

Subjects with symptomatic pneumonitis should immediately stop receiving MK-3475 and have an evaluation. The evaluation may include bronchoscopy and pulmonary function tests to rule out other causes such as infection. If the subject is determined to have study drug associated pneumonitis, the suggested treatment plan is detailed in Table 6.

Table 6 Recommended Approach to Handling Pneumonitis

Study drug associated pneumonitis	Withhold/Discontinue MK-3475?	Supportive Care
Grade 1 (asymptomatic)	No action	Intervention not indicated
Grade 2	Withhold MK-3475, may return to treatment if improves to Grade 1 or resolves within 12 weeks	Systemic corticosteroids are indicated. Taper if necessary.
Grade 3 and Grade 4	Discontinue MK-3475	Systemic corticosteroids are indicated. The use of infliximab may be indicated as appropriate. Refer to the Event of Clinical Interest and Immune-related Adverse Event Guidance Document for additional recommendations.

For Grade 2 pneumonitis that improves to ≤ Grade 1 within 12 weeks, the following rules should apply:

- First episode of pneumonitis
  - May increase dosing interval by one week in subsequent cycles
- Second episode of pneumonitis – permanently discontinue MK-3475 if upon rechallenge subject develops pneumonitis ≥ Grade 2

6.3.1.1.1h Other

The following AEs are considered ECIs and should be reported to the Principal Investigator within 72 hours of the event:

- Autoimmune Neuropathy
- Demyelinating Polyneuropathy
- Guillain-Barre
- Myasthenia Gravis-like Syndrome
- Non-infectious myocarditis
- Non-infectious pericarditis
- Pancreatitis
- Rapid onset of Grade 3 fatigue in the absence of disease progression

Course of Action

- Mild (Grade 1) irAEs – provide symptomatic treatment.

- Moderate (Grade 2) or Grade 1 irAEs that do not improve with symptomatic treatment – consider withholding MK-3475. Systemic corticosteroids may be indicated. Consider biopsy for confirmation of diagnosis.

- Clinically significant or severe (≥Grade 3) irAEs –discontinue MK-3475 and treat with systemic corticosteroids at a dose of 1 to 2 mg/kg prednisone or equivalent once per day. Report as ECI.

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

Discontinue MK-3475 if unable to reduce corticosteroid dose for irAEs to ≤10 mg.
MK-3475 treatment may be restarted and the dose modified as specified in the protocol

6.4 Contraception/Pregnancy/Nursing

6.4.1 Contraception

MK-3475 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. Non-pregnant, non-breast-feeding women may be enrolled if they are willing to use 2 methods of birth control or are considered highly unlikely to conceive. Highly unlikely to conceive is defined as 1) surgically sterilized, or 2) postmenopausal (a woman who is ≥45 years of age and has not had menses for greater than 1 year will be considered postmenopausal), or 3) not heterosexually active for the duration of the study. The two birth control methods can be either two barrier methods or a barrier method plus a hormonal method to prevent pregnancy. Subjects should start using birth control from study Visit 1 throughout the study period up to 120 days after the last dose of study therapy.

The following are considered adequate barrier methods of contraception: diaphragm, condom (by the partner), copper intrauterine device, sponge, or spermicide. Appropriate hormonal contraceptives will include any registered and marketed contraceptive agent that contains an estrogen and/or a progestational agent (including oral, subcutaneous, intrauterine, or intramuscular agents).

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 and to Merck. 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.

6.4.2 Use in Pregnancy

If a subject inadvertently becomes pregnant while on treatment with MK-3475, 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 Principal Investigator and to Merck without delay and within 24 hours if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor. If a male subject impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to the Sponsor and to Merck and followed as described above and in Section 7.2.2.

6.4.3 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.

6.5 Subject 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 Principal Investigator 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 8.1.5.

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 or decides to discontinue study therapy for any reason.

- Confirmed radiographic disease progression according to modified response criteria (see section 10.2).
- Unacceptable adverse experiences
- 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 treatment with MK-3475

  Note: 24 months of study medication is calculated from the date of first dose. Subjects who stop MK-3475 after 24 months may be eligible for up to one year of additional study treatment if they progress after stopping study treatment provided they meet the requirements detailed in Section 8.1.6.1.2

- Administrative reasons

The End of Treatment and Follow-up visit procedures are listed in Section 7 (Protocol Flow Chart) and Section 8.1.6 (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. After documented disease progression each subject will be followed by telephone for overall survival until death, withdrawal of consent, or the end of the study, whichever occurs first.

6.6 Subject Replacement Strategy

Patients will only be replaced if the patient withdraws consent before the first dose of therapy.

7.0 TRIAL FLOW CHART

7.1 Study Flow Chart

Trial Period:	**Treatment Cycles**											
Treatment Cycle/Title:	Main Study Screening (Visit 2)	1	2	3	4	To be repeated beyond 8 cycles				Safety Follow-Up/ EOT	Progression Free Follow-Up Phase [11]	Survival Follow-Up
						5	6	7	8			
Scheduling Window (Days):	-28 to -1		±3	±3	±3	±3	±3	±3	±3	~30 days after last dose/ before initiation of new tx	Every 12 weeks +/- 2weeks	Every 12 weeks +/- 2 weeks
Informed Consent	X											
Inclusion/Exclusion Criteria	X											
Medical History/Physical[1]	X	X	X	X	X	X	X					
Medication Review[2]	X	X	X	X	X	X	X	X	X	X		
Trial Treatment Administration[3]		X	X	X	X	X	X	X	X			
Survival Status												X
Review Adverse Events		X	X	X	X	X	X	X	X	X		
Full Physical Examination[1]	X											
Directed Physical Examination[1]		X	X	X	X	X	X		X	X		
Vital Signs and Weight[3]	X	X	X	X	X	X	X	X	X	X		
ECOG Performance Status[3]	X	X	X	X	X	X	X		X	X		
Pregnancy Test – Urine or Serum β-HCG[4]	X											
CBC with Differential[5]	X	X	X	X	X	X	X	X	X	X		
Comprehensive Serum Chemistry Panel[5]	X	X	X	X	X	X	X	X	X	X		
Urinalysis	X											
T3, FT4 and TSH[6]	X				X				X			
Tumor Imaging[7]	X		X		X		X				X	
Archival Tissue Collection[8]	X											
Correlative Studies Blood Collection[9]		X	X	X								
Retreatment[10]												

1. Patients should undergo a detailed history and physical examination during screening. A full examination, to be performed to determine eligibility, means that based on the patient's medical history and all relevant systems have been examined. All patients should undergo a focused history and physical examination during each treatment day for the first 6 cycles. After the first 6 cycles history and physical examination can be performed every other cycle.

2. All medications need to be reviewed at screening visit. During follow up visits any changes in medications should be documented.

3. MK-3475 will be administered at a dose of 200 mg IV every 3 weeks for a maximum of 2 years. Prior to each administration vital signs- heart rate, blood pressure, temperature, weight, respiratory rate should be documented. Performance status needs to be documented on the day of study drug administration for the first 6 doses. After the first 6 doses it should be documented as deemed appropriate by the treating physician.

4. Pregnancy test should be performed within 1 week of the first dose of MK-3475 in appropriate women.

5. Patients should undergo CBC with differential count, a multiphasic profile consisting of serum electrolytes, BUN, serum creatinine, AST, ALT, serum bilirubin, alkaline phosphatase, and calcium with each treatment. . Baseline labs should be done within 2 weeks of the first dose of MK-3475. During the trial, laboratory tests can be done within 48 hours of the administration of MK-3475.

6. Patients should undergo Thyroid tests within 2 weeks of the first dose. These should be repeated at least every 4 cycles.

7. Patients should undergo appropriate scans, including brain scan, during screening, to document the status of the patient' cancer. The screening scans should be done within 3 weeks before the first dose of MK-3475. Patients should undergo appropriate scans to restage the patient after every 2 cycles for the first 6 cycles. For the first 6 cycles the re-staging scans should be performed within 1 week of the next cycle. After the first 6 cycles, the scans can be done as often as necessary by the treating physician but should be done at least every 4 cycles.

8. Archival tumor tissue will be retrieved to assess tumor PD-L1 status. Any tissue available should be submitted. Patient will be eligible even if tumor tissue cannot be submitted.

9. Patients will undergo blood collection for Circulating Tumor Cells (CTCs). This can be done on the first day of the first cycle prior to dosing MK-3475. This should also

be done on the first day of the second cycle and first day of the third cycle even if the drug is being held.

10. Patients who have completed 24 months on MK-3475 and stop therapy without progression can be retreated if patient has further progression. Patient will have to meet all original eligibility criteria and will be assessed and managed as a new patient starting on therapy. See section 8.1.6.

11. Every 12 weeks until the start of the next treatment for patient's cancer, disease progression, death, end of study.

8.0 TRIAL PROCEDURES

8.1.1 Registration Procedures

Eligible patients will be entered on the study centrally at the clinical trials office of the Karmanos Cancer Center/Wayne State University, by, the Study Coordinator (or a designated study coordinator). All sites should call the Study Coordinator) after initiating screening.

An eligibility check list will be generated by the Study team at Karmanos Cancer Institute. This eligibility check list has to be completed by each site and signed by the responsible investigator. Once this is received by Study Coordinator and confirmed by him/her, the patient will be registered. A registration confirmation will be sent to the site (sites other than Karmanos Cancer Institue).

Once registration has occurred patient has to be treated within 5 days. If patient does not start therapy within 5 days of registration, the reasons for delay should be communicated to the Principal Investigator. He will then decide if the patient can continue on study therapy.

8.1.2 Informed Consent

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

The informed consent will adhere to individual Institutional Review Board requirements, applicable laws and regulations.

8.1.3 Disease Details

The known sites of metastases at the time of diagnosis and study entry will be recorded. The number of cycles of platinum based chemotherapy received and the date of the last cycle of chemotherapy should be recorded.

Details of any radiation administered for the management of SCLC will be recorded. This will include site radiated, dose and dates.

8.1.4 Clinical Procedures/Assessments

8.1.4.1 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 15.2). Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

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 (irAE) (See Section 5.4.1.1)

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

8.1.4.2 Tumor Imaging and Assessment of Disease

Patients will undergo scans to assess the status of the cancer within 3 weeks before the first dose of MK-3475. All known areas of metastases should be imaged. Patients will undergo restaging scans every 2 cycles for the first 6 cycles. Subsequently they can be done as often as necessary, but should be done at least every 4 cycles.

The treating physician will decide which scans need to be done to appropriately assess the status of the cancer.

8.1.4.3 Laboratory Procedures/Assessments

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

Table 8 Laboratory Tests

Hematology	Chemistry	Urinalysis (only at baseline)	Other
Hematocrit	Albumin	Blood	Serum β-human chorionic gonadotropin†
Hemoglobin	Alkaline phosphatase	Glucose	(β-hCG)†
Platelet count	Alanine aminotransferase (ALT)	Protein	Total thriiodothyronine (T3)α
WBC (total and differential)	Aspartate aminotransferase (AST)	Specific gravity	Free tyroxine (T4)α
Red Blood Cell Count	Creatinine	Microscopic exam *(If abnormal)*	Thyroid stimulating hormone (TSH)α
Absolute Neutrophil Count	Carbon Dioxide ‡	results are noted	
	(CO_2 or biocarbonate)	Urine pregnancy test †	
	Calcium		
	Chloride		Blood for correlative studies
	Glucose		
	Potassium		
	Sodium		
	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. This is needed only at baseline

‡ If considered standard of care in your region.

α These tests are to be conducted at baseline. Once the patient is on trial therapy tests to be conducted at least every 4 cycles.

Laboratory tests for screening or entry into the Second Course Phase should be performed within 14 days prior to the first dose of treatment. After Cycle 1, pre-dose laboratory procedures can be conducted up to 48 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.

8.1.5 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. Subjects who a) attain a CR or b) complete 24 months of treatment with MK-3475 may discontinue treatment with the option of restarting treatment (see section 8.1.6). After discontinuing treatment following assessment of CR, these subjects should return to the site for a Safety Follow-up Visit (described in Section 8.1.6.1).

8.1.6 Visit Requirements/Safety Follow Up Visit/Retreatment

Visit requirements are outlined in Section 7.0 - Trial Flow Chart. Specific procedure-related details are provided above in Section 8.1 - Trial Procedures.

It is recognized that the safety follow up visit maybe difficult to accomplish in patients with extensive stage small cell lung cancer. However, every effort should be made to conduct a Safety Follow-Up Visit approximately 30 days after the last dose of trial treatment or before the initiation of a new anti-cancer treatment, whichever comes first. All AEs that occur prior to the Safety Follow-Up Visit should be recorded. Subjects with an AE of Grade > 1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new anti-neoplastic therapy, whichever occurs first.

8.1.6.1 Follow-up Visits

Subjects who discontinue trial treatment for a reason other than disease progression will move into the Follow-Up Phase and should be assessed every 12 weeks by radiologic imaging to monitor disease status. Every effort should be made to collect information regarding disease status until the start of new anti-neoplastic therapy, disease progression, death, end of the study or if the subject begins retreatment with MK-3475 as detailed in Section 8.1.6.1.2

Subjects who are eligible to receive retreatment with MK-3475 according to the criteria in Section 8.1.6.1.2 will move from the follow-up phase to the Second Course Phase when they experience disease progression.

8.1.6.1.1 Survival Follow-up

Once a subject experiences confirmed disease progression according to modified response criteria 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.

8.1.6.1.2 Retreatment

Patients who have disease progression following completion of 2 years of therapy with MK-3475 can be re-treated with this drug if the patient meets all eligibility criteria as in Section 5.0 except for the criteria of stable or responding disease following chemotherapy.

The schedule of study activities will be according to the study flow chart Section 6.0.

8.2 Assessing and Recording Adverse Events

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of MK-3475, is also an adverse event.

Adverse events may occur during the course of the use of MK-3475 from overdose (whether accidental or intentional), from abuse and from withdrawal.

All adverse events will be recorded from the time the patient starts therapy with the study drug through 30 days following cessation of treatment and at each examination on the Adverse Event case report forms/worksheets.

Merck or Principal Investigator will also forward to individual sites relevant SAE reports occurring on MK-3475. These should be forwarded to appropriate regulatory authorities according to local rules and regulations.

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

For purposes of this trial, an overdose will be defined as any dose exceeding the prescribed dose for MK-3475 by 20% over the prescribed dose. No specific information is available on the treatment of overdose of MK-3475. In the event of overdose, MK-3475 should be discontinued and the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

If an adverse event(s) is associated with ("results from") the overdose of MK-3475, the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met.

If a dose of MK-3475 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 Principal Investigator and within 2 working days hours to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220)

8.2.2 Reporting of Pregnancy and Lactation to the Principal Investigator and to Merck

Although pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them), including the pregnancy of a male subject's female partner that occurs during the trial or within 120 days of completing the trial completing the trial, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier. All subjects and female partners of male subjects who become pregnant must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

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

8.2.3 Immediate Reporting of Adverse Events

8.2.3.1 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 a new cancer (that is not a condition of the study);
- Is associated with an overdose;
- Is another important medical event

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

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 that occurs to any subject from the time the consent is signed through 90 days following cessation of treatment, or the initiation of new anti-cancer therapy, whichever is earlier, whether or not related to MK-3475, must be reported within 2 working days of learning to the Principal Investigator and to Merck Global Safety.

Additionally, any serious adverse event, considered by an investigator who is a qualified physician to be related to MK-3475 that is brought to the attention of the investigator at any time outside of the time period specified in the previous paragraph also must be reported immediately to the Principal Investigator and to Merck.

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

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

8.2.4 Evaluating Adverse Events

An investigator who is a qualified physician will evaluate all adverse events according to the NCI Common Terminology for Adverse Events (CTCAE), version 4.0. Any adverse event which changes CTCAE grade over the course of a

given episode will have each change of grade recorded on the adverse event case report forms/worksheets.

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

9.0 CORRELATIVE STUDIES

Response rates to PD-1 and PD-L1 targeted agents indicate that a subset of patients derive greater benefit from this treatment strategy, whereas some patients have no benefit. To complement this study and increase its scientific yield, we are proposing several scientific correlates in an attempt to identify potentially predictive biomarkers for MK-3475. While these are unlikely to be definitive, based on the relatively small numbers of patients involved, the data collected will help guide the development of potential biomarkers in future studies as well as identify patients most likely to benefit or not benefit from MK-3475. Some of these studies will be limited to patients randomized to the treatment arm.

Preliminary data suggest that tumor PD-L1 expression may be a predictive marker for MK-3475 (18). In an effort to characterize PD-L1 expression in SCLC, we will collect archived tumor specimens from all participants for PD-L1 expression analyses. PD-L1 expression will be assessed by QualTek Clinical Laboratories, Pennsylvania. Tissue for PD-L1 testing should be sent to QualTek Clinical Laboratories, 300 Pheasant Run, Newton, PA 18940. Tumor tissues by participating sites will be sent to Dr. Julie Boerner, Director of the Biobanking and Correlative Sciences Core at Karmanos Cancer Institute. Address for shipping is the same as shipping blood for CTC assessment as mentioned in section 9.1.

Tumor content in diagnostic biopsies is likely to be limited in SCLC patients. In addition, serial biopsies are challenging in patients with SCLC. Also after completion of chemotherapy, biopsy of residual tumor may be challenging. Circulating tumor cells (CTCs) hold great promise as a readily available source material that can offer real-time insight into a tumor's genomic architecture as well as tumor burden. CTCs can be detected in small cell lung cancer patients and appear to have prognostic importance (20, 21). Dr. Julie Boerner, Director of the Biobanking and Correlative Sciences Core will supervise quantitation of CTCs in patients enrolled on this study. Peripheral blood (8 mL) will be collected into a Cell Search CTC collection tube. Tumor cells are then subject to negative immunomagnetic selection with anti-CD45 antibodies and positive immunomagnetic selection with EpCAM antibodies and fluorescently labeled for quantitation. These fluorescently labeled cells can be stained for PD-L1 for correlation with tumor progression assessment. Alternatively, the immunomagnetic platform allows isolation of EpCAM selected cells from the peripheral blood from which mRNA can be reverse-transcribed for RT-PCR. Using beta-actin as an internal control, mRNA expression levels of target genes can be ascertained. As a correlate to this trial, we will collect blood prior to therapy on the first day of the first cycle, on the first day of second cycle, and first day of the third cycle. After processing, samples will be shipped to the Dr. Boerner's laboratory (see shipping address and conditions below). Both

CTC counts and assessment of PD-L1 protein and mRNA expression in isolated CTCs will be done.

9.1 Shipping of CTC samples to Karmanos Cancer Institute

Blood (min. 7.5 ml) for CTC counting will be collected in a Cell Save purple and yellow marbled topped tube. Blood for CTC isolation needs to be collected in an EDTA tube. Both specimens should remain at room temperature.

Blood for CTC samples should be shipped within 24 hr. to the address below at ambient temperatures. The tubes are glass and special care needs to be taken to ensure the tubes do not break. Bubble wrap pouches with extra cushioning works best.

Ship to:
Biobanking and Correlative Sciences Core
Attn: Julie Boerner
Wayne State University/Karmanos Cancer Institute
816 HWCRC
4100 John R. St.
Detroit, MI 48201
PH: 313-576-8350

10.0 DEFINITIONS OF END POINTS

All patients who are registered and have received at least one dose of the study drug will be eligible to be considered for all the following end points-

10.1 Primary Endpoint- RECIST 1.1 defined Progression Free Survival (PFS)- PFS is defined as the duration of time from registration to time of progression. Patients who die without reported prior progression will be considered to have progressed on the day of their death. Patients who did not progress will be censored at the day of last tumor assessment.

10.2 Secondary Endpoints-

Modified Progression Free Survival- Modified PFS requires that RECIST defined PFS is confirmed by a second scan at least 4 weeks apart. Following issues need to be considered

a. New lesion/lesions are considered as progression in RECIST defined PFS. However for modified PFS the largest unidirectional measurement of new lesion/lesions will be added to the total tumor measurement. If this exceeds 20% on 2 consecutive scans then the patient will be considered to have tumor

progression according to modified PFS criteria. A new lesion or lesions alone will not qualify for this modified PFS definition.

b. If patients who have RECIST defined progression are symptomatic or have decline in performance status or develop unacceptable laboratory abnormalities and the treating physician and/or the patient decide to discontinue therapy or change therapy then the second scan confirming progression is not required.

Overall Survival- Overall survival is defined as the time from registration to time of death. If the patient is lost to follow-up, survival will be censored on the last date the patient was known to be alive.

11.0 STATISTICAL ANALYSIS PLAN

11.1 Study Design and Primary Endpoint

This is a single arm Phase II study to evaluate the efficacy of consolidation MK-3475 in extensive stage SCLC patients following completion of 4 cycles of chemotherapy with cisplatin or carboplatin and etoposide and whose disease has either responded or stabilized following chemotherapy. We propose a single arm study since the standard initial therapy for SCLC is well established for the last 20 years and the median PFS following such induction therapy is well defined, making a randomized study with control arm less necessary.

The primary endpoint is PFS with RECIST criteria defined as duration of time from registration to time of progression. Patients register after the induction chemotherapy is completed and have achieved stable or responding disease. Patients who die without reported prior progression will be considered to have progressed on the day of their death. Patients who did not progress will be censored at the day of last tumor assessment. PFS has been the primary endpoint in most maintenance trials conducted in SCLC patients to date.

11.2 Sample Size and Accrual Rate:

The median PFS in SCLC patients who have stable or responding disease following initial chemotherapy is approximately 2 months. We expect that the experimental treatment will improve the median PFS 50% to 3 months. Assume an exponential and one-sided alpha 0.05, 40 patients accrued in 18 months with minimum follow-up time 6 months will achieve 80% power to test the null hypothesis that median PFS is 2 months versus the alternative of 3 months.[PASS14.0.7] (29). In this protocol, we assume about 10% of patients will be ineligible. Thus, a total of 45 will be enrolled to study. To assess the efficacy, we will follow each patient to at least 6 months or progression.

It is estimated that approximately 28 patients per year should be accrued once the study is open at all sites (4-5 sites). Thus, the accrual duration will be about 18 months and the study duration is 24 months including the 6 months follow-up. All patients will be followed for PFS and OS to evaluate the clinical benefit of MK-3475.

11.3 Analysis plan for primary and secondary endpoints

The primary endpoint, PFS, will be estimated with the standard Kaplan-Meier method, from which summary statistics of interest (median, 1-year rate, etc.) will be derived. Both point and 95% confidence interval estimates of PFS will be calculated. In this trial we will also assess PFS using modified criteria as well. It is well recognized that patients treated with immune therapy may have pseudo progression or can have delayed response. The modified PFS requires RECIST defined progression on 2 sequential scans at least 4 weeks apart for definition of progression. Overall survival is defined as the time from start of treatment to time of death. If the patient is lost to follow-up, survival will be censored on the last date the patient was known to be alive. All time-to-event endpoints will be estimated using standard Kaplan-Meier methods, from which the median and confidence interval will be calculated. Point and exact confidence interval estimates will be calculated for the toxicities and response rates. Cox model will be used to evaluate the association between time to event outcomes and covariates such as PD-L1 status and CTCs.

PD-L1 (yes/no) in tumor tissue and circulating tumor cells (CTCs) will be measured and their association will be studied with logistic regression. We will explore associations between PD-L1 and PFS, modified PFS, and OS using the Cox model. If biopsy samples are 15 patients or less, statistical analysis will be descriptive.

12.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

12.1 Investigational Product

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.

The investigational product will be provided by Merck

12.2 Packaging and Labeling Information

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

12.3 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.

12.4 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.

13.0 ADMINISTRATIVE AND REGULATORY DETAILS

13.1 Confidentiality

All efforts will be made at each participating site to maintain the confidentiality of patients enrolled on the trial according to institutional, local and federal guidelines.

13.2 Compliance with Financial Disclosure Requirements

All participating staff will disclose any financial conflicts of interest to respective institutional review boards or applicable compliance authorities.

13.3 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 Principal Investigator 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.

13.4 Data and Safety Monitoring

Scheduled meetings will occur monthly or more frequently depending on the activity of the protocol. These meetings will include the Principal Investigator (PI) and research staff involved with the conduct of the protocol, specifically the Study Coordinator and the Statistician. In addition the PI will contact the co-investigators on a regular basis (frequency to be based on the rate of enrollment) and review the clinical outcomes of the patients enrolled on the study.

During these meetings the following points will be reviewed and discussed:

- Safety of protocol participants
- Validity and Integrity of the data
- Enrollment rate and Eligibility of patients enrolled
- Adherence to Protocol Requirements
- Completeness of the Collected Data
- Protocol Amendments if any.

Data and Safety Monitoring Reports (DSMR) will be completed by the study coordinator and will be sent to the Data and Safety Monitoring Committee of the Karmanos Cancer Institute.

The Karmanos Cancer Institute's Data and Safety Monitoring Committee will provide the primary oversight for data and safety monitoring for this investigator initiated trial.

13.5 Oversight of Participating sites

This is a multi-center study with Karmanos Cancer Institute/Wayne State University as the coordinating site.

Each participating site will undergo study training prior to enrollment by the site. This training will only occur once the study is approved by appropriate regulatory authorities at the site. The study training will be conducted either by the Principal Investigator or his designee from the Karmanos Cancer Institute (KCI) Clinical Trials Office (CTO).

This study will utilize Karmanos Oncore (Karmanos Cancer Institute Clinical Trial Management System) eCRFs (electronic Case Report Forms) to capture clinical trial data. Appropriate personnel at all participating sites will be trained in this Oncore system by the Karmanos Informatics department.

Trial data entered in Oncore will be verified by source documentation. CRFs should be completed by participating sites within 10 business days of the availability of clinical documentation of a study visit. Data clarification and queries should be completed within 7 working days of notification.

A monitor specialist from KCI CTO will remotely monitor essential clinical trial data. Frequency of monitoring will be based on accrual at a site but will occur at least once every 2 months if a patient has been enrolled.

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15.0 APPENDICES

15.1 ECOG Performance Status

Table 9

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.	

15.2 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)**Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 Criteria for Evaluating Response in Solid Tumors**

15.3 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.

15.4 Events of Clinical Interest and Immune Related Adverse Event

The purpose of this section is to provide study sites with guidance for the identification of immune-related adverse experiences that are defined as Events of Clinical Interest (ECI) in the protocol, and to provide the documentation and reporting requirements for these events. ECIs are selected adverse experiences that **must be reported to the Principal Investigator and Merck within 72 hours** from the time the Investigator is aware of such an occurrence and require additional detailed information to be collected and entered in the study database.

Based on the available data, and consideration of mechanism of action of MK-3475, potential immune-related adverse events (irAEs) are the primary ECI. Given that immune-related events can involve different organ systems, following section provides information on the major potential target organs that could be affected by MK-3475 and other molecules that function via an immune mechanism. It is possible that irAEs other than those listed in this document may be observed in patients receiving MK-3475; therefore, all adverse events (AEs) of unknown etiology associated with drug exposure should be evaluated to determine if it is possibly immune-related.

Table 10 provides the list of terms and reporting requirements for ECIs for MK-3475 protocols.

Table 10

Colitis (reported as ECI if ≥ Grade 2)		
Bowel Obstruction	Colitis	Colitis microscopic
Enterocolitis	Enterocolitis hemorrhagic	GI Perforation
Necrotizing Colitis		
Diarrhea (report as ECI if ≥ Grade 3 or any grade resulting in dose modification)		
Endocrine (reported as ECI if ≥ Grade 3 or any grade resulting in dose modification)		
Adrenal Insufficiency	Hyperthyroidism	Hypophysitis
Hypopituitarism	Hypothyroidism	Thyroid Disorder
Thyroiditis		
Eye		
Uveitis (report as ECI if ≥ Grade 2 or any grade resulting in dose modification)		
Hepatic (reported as ECI if ≥ Grade 2 or any grade requiring dose modification)		
Hepatitis	Hepatitis, Autoimmune	
Pneumonitis (reported as ECI if ≥ Grade 2)		
Acute Interstitial Pneumonitis	Interstitial Lung Disease	Pneumonitis

Renal (reported as ECI if ≥ Grade 2 or any grade resulting in dose modification)		
Nephritis	Nephritis Autoimmune	Renal Failure
Renal Failure, Acute		
Skin (always reported as ECI regardless of grade)		
Dermatitis Exfoliative	Erythema Multiforme	Stevens-Johnson Syndrome
Toxic Epidermal Necrolysis		
Skin (reported as ECI if ≥ Grade 3 or any grade resulting in dose modification)		
Pruritus	Rash	Rash generalized
Rash maculo-papular	Vitiligo	
Other (The following should always be reported as an ECI, regardless of grade)		
Autoimmune Neuropathy	Demyelinating Polyneuropathy	Guillain-Barre
Myasthenia Gravis like syndrome	Non-infectious myocarditis	Non-infectious pericarditis
Pancreatitis	Rapid onset of Grade 3 fatigue in the absence of disease progression	

See also Section 6.3.1.1 for detailed description of the management of these irAEs.

Dose Modification/Discontinuation

The treatment guidance suggests when to hold and/or discontinue MK-3475

2. ECI REPORTING GUIDELINES

ECIs are selected non-serious and serious adverse experiences that must be reported to Principal Investigator within 72 hours regardless of attribution to trial treatment. Any event that meets the ECI criteria in Table 1 or in the respective protocol (event term and Grade) must be reported regardless of investigator-determined causality with study medication or if considered immune-related (unless otherwise specified). Investigators/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.

3. ECI CATEGORIES AND TERMS

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

3.1 Colitis

The following AE terms, if considered ≥ Grade 2, are considered ECIs and should be reported to the Principal Investigator within 72 hours of the event:

- Bowel obstruction
- Colitis
- Colitis microscopic
- Enterocolitis
- Enterocolitis hemorrhagic
- GI perforation
- Necrotizing colitis

Diarrhea should be reported as an ECI if it is ≥ Grade 3.

The following signs and symptoms may be associated with any of the above diagnosis. The signs and symptoms below may represent one of the included adverse events, but do not need to be reported as an ECI unless the investigator suspects one of the ECI events listed above.

Symptoms

Symptoms may include (but not limited to):

- Abdominal pain, cramping and/or bloating
- Blood and/or mucus in stool with or without fever
- Constipation
- Diarrhea

- Ileus
- Nausea and/or vomiting
- Peritoneal signs consistent with bowel perforation
- Rectal bleeding
- With or without fever

Differential Diagnosis

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, and a Clostridium difficile titer.

Course of Action

Grade 1 diarrhea:

- Treat symptomatically (loperamide, oral hydration, electrolyte substitution and ADA colitis diet).
- Endoscopy is recommended if symptoms persist.

Grade 2 diarrhea (or persistent Grade 1):

- Hold MK-3475.
- GI consultation and endoscopy is recommended to confirm or rule out colitis for Grade 2 diarrhea that persists >1 week or Grade 1-2 diarrhea with rectal bleeding (additional guidelines for the treatment of persistent colitis are provided below).
- Grade 1 events that persist for >1 week or Grade 2 events should be treated with the addition of oral diphenoxylate hydrochloride and atropine sulfate four times daily and budesonide 9 mg daily.
- Grade 2 diarrhea with diffuse ulceration and bleeding seen on endoscopy may require oral steroids with prolonged taper and represent an increased risk for the development of bowel perforation.
- When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

Grade 3-4 diarrhea (or Grade 2 diarrhea that persist after initial steroid treatment):

- Hold/Discontinue MK-3475.
- Rule out bowel perforation. Imaging with plain films or CT can be useful.
- Consider 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.
- If IV steroids followed by high dose oral steroids does not reduce initial symptoms within 48 to 72 hours, consider treatment with infliximab at 5 mg/kg once every 2 weeks. Discontinue infliximab upon symptom relief and initiate a prolonged steroid taper over 45 to 60 days. If symptoms worsening 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 infliximab. CAUTION: infliximab is contraindicated in patients with bowel perforation or sepsis [12].
- If symptoms persist despite the above treatment a surgical consult should be obtained.

3.2 Endocrine

The following AE terms, if considered ≥ Grade 3 or if ≥ Grade 2 and require holding/discontinuation of MK-3475, are considered ECIs and should be reported to the Principal Investigator within 72 hours of the event:

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

The following signs and symptoms may be associated with any of the above diagnoses. The occurrence of the signs and symptoms listed below do not require reporting as an ECI unless the investigator suspects one of the ECI events listed above.

Symptoms

Symptoms may include (but not limited to):

- Abdominal pain
- Abnormal thyroid function tests and/or serum chemistries
    - TSH increased (decreased),
    - Free Thyroxine increased,
    - Tri-iodothyronine increased.
- Arrhythmias*
- Cold or heat intolerance
- Fatigue
- Fever
- Headache
- Hypotension*
- Loss of appetite
- Mental status and/or behavior changes
- Nausea and/or vomiting
- Unusual bowel habits
- Vision disturbances
- Weakness

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

Differential Diagnosis

All attempts should be made to rule out other causes such as brain metastases, sepsis and/or infection. An endocrinology consultation is recommended.

Course of Action

Grade 1-2 events:

- Monitor thyroid function or other hormonal level tests and serum chemistries more frequently until returned to baseline values.
- If hypophysitis is considered, pituitary gland imaging should be considered (MRIs with gadolinium and selective cuts of the pituitary can show enlargement or heterogeneity and confirm the diagnosis).
- Thyroid hormone and/or steroid replacement therapy to manage adrenal insufficiency.

Symptomatic pan-hypopituitarism and any Grade 3-4 events

- Hold/discontinue MK-3475.
- Consider Endocrine consultation.
- 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.
- Hypophysitis with clinically significant adrenal insufficiency and hypotension, dehydration, and electrolyte abnormalities (such as hyponatremia and hyperkalemia) constitutes adrenal crisis. Hospitalization and intravenous methylprednisolone should be initiated.

3.3 Eye

The following AE term, if considered Grade ≥2, is considered an ECI and should be reported to the Principal Investigator within 72 hours of the event:

- Uveitis

The following signs and symptoms may be associated with the above diagnosis. The occurrence of the signs and symptoms listed below do not require reporting as an ECI unless the investigator suspects the ECI event listed above.

Symptoms

Symptoms may include (but not limited to):

- Blurred vision
- Diffuse erythema and a prominent blush on the sclerae
- Dryness of the eyes
- Pain
- Photophobia

Differential Diagnosis

All attempts should be made to rule out other causes such as metastatic disease, infection or other ocular disease (e.g. glaucoma or cataracts).

Course of Action

Grade 1-2 events:

- Evaluation by an ophthalmologist is strongly recommended.
- Treat with topical steroids such as 1% prednisolone acetate suspension and iridocyclitics.
- Discontinue MK-3475 if symptoms persist despite treatment with topical immunosuppressive therapy.

Grade 3-4 events:

- Discontinue MK-3475.
- 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.

3.4 Hepatic

The following AE terms, if considered ≥ Grade 2, are considered ECIs and should be reported to the Principal Investigator within 72 hours of the event:

- Hepatitis
- Hepatitis, Autoimmune

The following signs and symptoms may be associated with any of the above diagnoses. The signs and symptoms below may represent one of the included adverse events, but do not need to be reported as an ECI unless the investigator suspects one of the ECI events listed above.

Symptoms

Symptoms may include (but not limited to):

- Elevations in:
  - AST >2.5 times upper limit of normal (ULN)
  - ALT >2.5 times ULN
  - Total bilirubin >1.5 times ULN
- Fever
- Malaise
- Upper quadrant abdominal pain

Differential Diagnosis

All attempts should be made to rule out other causes such as metastatic disease, progressive liver disease, viral hepatitis, alternative drug toxicity, infectious causes and/or myositis.

Course of Action

Grade 1 events:

- Monitor liver function tests more frequently until returned to baseline values.

Grade 2 events:

- Monitor liver function tests more frequently until returned to baseline values.

Grade 3-4 events:

- Discontinue MK-3475 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 [12].
- Several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased.

Note: in the event of a drug-induced liver injury (DILI) adverse event (as outlined in the study protocol), please follow the DILI guidance outlined in the site Administrative Binder.

3.5 Pneumonitis

The following AE terms, if considered ≥ Grade 2, are considered ECIs and should be reported to the Principal Investigator within 72 hours of the event:

- Pneumonitis
- Interstitial lung disease
- Acute interstitial pneumonitis

The following signs and symptoms may be associated with any of the above diagnoses. The signs and symptoms represent one of the included adverse events, but do not need to be reported as an ECI unless the investigator suspects one of the ECI events listed above.

Symptoms

Symptoms may include (but not limited to):

- Abnormal breath sounds
- Chest pain and/or tightness*
- Dyspnea*
- Dry cough
- Fatigue
- Fever
- Hemoptysis

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

Differential Diagnosis

All attempts should be made to rule out other causes such as metastatic disease, bacterial or viral infection.

Course of Action

Grade 1 events: (asymptomatic with radiographic findings only):

- MK-3475 may be continued with close monitoring.
- Radiologic findings should be followed on serial imaging studies.
- Consider pulmonary consultation and/or bronchoscopy if clinically indicated.

Grade 2 events:

- Hold MK-3475 as specified in the protocol.
- Consider pulmonary consultation with bronchoscopy and biopsy/BAL.
- Consider pulmonary function tests.
- 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.
- Treatment with MK-3475 may be resumed if the event improves to grade 0 or 1 within 12 weeks and corticosteroids have been reduced to the equivalent of methylprednisolone 10 mg po daily or less. Repeat chest imaging monthly as clinically indicated.
- Second episode of pneumonitis – discontinue MK-3475 if upon rechallenge the patient develops a second episode of Grade 2 or higher pneumonitis.

Grade 3 and 4 events:

- Permanently Discontinue MK-3475.
- Consider pulmonary function tests with pulmonary consult.
- Bronchoscopy with biopsy and/or BAL is recommended.
- Treat with intravenous steroids (methylprednisolone 125 mg). 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 infliximab at 5 mg/kg once every 2 weeks. Discontinue infliximab upon symptom relief and initiate a prolonged steroid taper over 45 to 60 days. If symptoms worsening 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 infliximab.

3.6 Renal

The following AEs if ≥ Grade 2 are considered ECIs and should be reported to the Principal Investigator within 72 hours of the event:

- Nephritis
- Nephritis autoimmune
- Renal failure
- Renal failure, Acute

The following signs and symptoms may be associated with any of the above diagnosis. The occurrence of the signs and symptoms listed below do not require reporting as an ECI unless the investigator suspects one of the ECI events listed above.

Symptoms

Symptoms may include (but not limited to):

- Fatigue
- High blood pressure
- Increased serum creatinine
- Swelling

Differential Diagnosis

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

Course of Action

Grade 1 events:

- Mild (Grade 1) irAEs – provide symptomatic treatment.

Grade 2 events:

- Moderate (Grade 2) or Grade 1 irAEs that do not improve with symptomatic treatment – consider withholding MK-3475. Systemic corticosteroids may be indicated.

Grade 3-4 events:

- Clinically significant or severe (≥ Grade 3) irAEs
- Discontinue MK-3475
- 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 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.

Discontinue MK-3475 if unable to reduce corticosteroid dose for irAEs to ≤10 mg.

MK-3475 treatment may be restarted and the dose modified as specified in the protocol

3.7 Skin

The following AEs should always be reported as ECIs, regardless of CTCAE grade, and should be reported to the Principal Investigator within 72 hours of the event:

- Dermatitis Exfoliative
- Erythema Multiforme
- Stevens-Johnson Syndrome

- Toxic Epidermal Necrolysis

The following AE terms should only be reported as an ECI if they are considered to be immune related, ≥ Grade 3 or result in dose modification or discontinuation:

- Pruritus
- Rash
- Rash generalized
- Rash maculo-papular
- Vitiligo

Differential Diagnosis

All attempts should be made to rule out other causes such as metastatic disease, infection or allergic dermatitis.

Course of Action with MK-3475

Grade 1-2 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 antipruritics (e.g., diphenhydramine HCl or hydroxyzine HCl).
- Treatment with oral steroids is at investigator discretion for Grade 2 events.

Grade 3 events:

- Hold MK-3475.
- 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.

Grade 4 events:

- Permanently discontinue MK-3475.
- 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.

3.8 Other

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

- Autoimmune Neuropathy
- Demyelinating Polyneuropathy
- Guillain-Barre
- Myasthenia Gravis-like Syndrome
- Non-infectious myocarditis
- Non-infectious pericarditis
- Pancreatitis
- Rapid onset of Grade 3 fatigue in the absence of disease progression

Differential Diagnosis

All attempts should be made to rule out other causes. Therapeutic specialists should be consulted as appropriate.

Course of Action

- Mild (Grade 1) irAEs – provide symptomatic treatment.

- Moderate (Grade 2) or Grade 1 irAEs that do not improve with symptomatic treatment – consider withholding MK-3475. Systemic corticosteroids may be indicated. Consider biopsy for confirmation of diagnosis.
- Clinically significant or severe (≥Grade 3) irAEs –discontinue MK-3475 and treat with systemic corticosteroids at a dose of 1 to 2 mg/kg prednisone or equivalent once per day. Report as ECI.

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

Discontinue MK-3475 if unable to reduce corticosteroid dose for irAEs to ≤10 mg.

MK-3475 treatment may be restarted and the dose modified as specified in the protocol.

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