SPONSOR: Bank of Cyprus Oncology Centre

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TITLE: A Phase II study of SWItch Maintenance PEmbrolizumab in patients with non small cell lung cancer who do not progress after first line platinum doublet chemotherapy (SWIPE).

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TRIAL SUMMARY

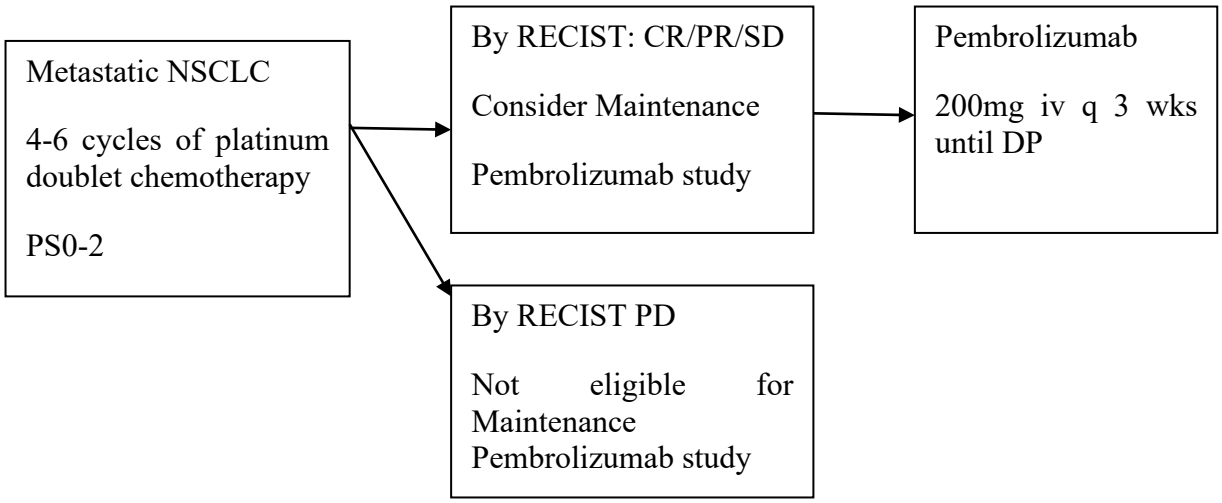
Abbreviated Title	Maintenance Pembrolizumab in patients with Non Small Cell Lung Cancer (NSCLC)
Trial Phase	Phase II
Clinical Indication	For patients with no disease progression after first line chemotherapy
Trial Type	Single arm, one stage, Phase II trial
Type of control	Non randomized
Route of administration	Intravenous
Trial Blinding	Not applicable
Treatment Groups	Single group
Number of trial subjects	Forty eight (48)
Estimated enrollment period	April 2016- October 2017
Estimated duration of trial	Three and a half (3 ½) years
Duration of Participation	Two (2) years
Estimated average length of treatment per patient	6 cycles

1.0 TRIAL DESIGN

1.1 Trial Design

Single arm one stage Phase II study: post 4-6 cycles platinum doublet chemotherapy for patients with metastatic Non Small Cell Lung Cancer (NSCLC) offering Pembrolizumab as maintenance therapy to non-progressors with primary endpoint: Immune Related Progression Free Survival (irPFS) at 1 year. Aim to show that this is at least 25% (compared to an expected 12% 1 year PFS based on the Pemetrexed and Erlotinib maintenance trials).

1.2 Trial Diagram



2.0 OBJECTIVE(S) & HYPOTHESIS(ES)

2.1 Primary Objective(s) & Hypothesis(es)

Objective: The main objective of this trial is to provide efficacy data for Pembrolizumab as maintenance therapy after first line therapy for NSCLC. Especially relevant would be evidence of a higher percentage of patients being progression free at 1 year (primary endpoint), increased response rates, increased Progression free and Overall Survival (OS) compared to the results from other chemotherapy maintenance studies.

Hypothesis: Pembrolizumab can provide superior outcomes in terms of disease control (% of patients Progression Free at 1 year using Immune Related response criteria) compared to other maintenance treatments (specifically pemetrexed continuation maintenance for non-squamous NSCLC and erlotinib switch maintenance for squamous NSCLC).

2.2 Secondary Objective(s) & Hypothesis

Objective: Pembrolizumab can provide superior outcomes in terms of disease control / survival compared to its use in other lines of therapy.

Hypothesis: The secondary study hypothesis is that Pembrolizumab is going to have its biggest impact in patients with metastatic NSCLC, if used in the maintenance setting, i.e. potentially superior outcomes to being used either as first line or last line therapy (as has been tested until now).

2.3 Exploratory Objective

Objective: Document change in PDL1 expression on CTCs, plasma and histology, prior and during first line chemotherapy as well as during immunotherapy with Pembrolizumab, in patients with non progressive disease, and determine patterns of change suggestive of benefit to Pembrolizumab.

3.0 BACKGROUND & RATIONALE

3.1 Background

Based on the GLOBOCAN data, Lung Cancer is the commonest cancer worldwide with 1.8 million cases being diagnosed in 2012, as well as the most common cause of cancer death with 1.6 million deaths worldwide[1]. There are two main subdivisions of Lung Cancer; small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). This study is focused in the treatment of NSCLC, which accounts for approximately 80% of all lung cancers. Although over the last few years there have been a number of new drugs (EGFR / ALK Tyrosine Kinase Inhibitors) and technology developments (e.g. stereotactic ablative radiotherapy and intensity modulated and image guided radiotherapy) in the treatment of NSCLC and there are now a wide range of different treatments available to patients with

NSCLC, survival still remains very poor with only approximately about 10% of patients being alive five year after the initial diagnosis[1]. There is therefore an urgent need to introduce new innovative treatments for patients with NSCLC in order to improve outcomes in this disease.

3.1.1 Therapeutic Background

Information for metastatic Non Small Cell Lung Cancer (NSCLC)

Routine molecular testing is currently being carried out for patients with metastatic NSCLC: predominantly checking for EGFR mutations and ALK translocations. Patients with such genetic alterations are candidates to receive either EGFR Tyrosine Kinase Inbitors (TKIs) i.e. Erlotinib, Gefitinib or Afatinib, if they harbour an EGFR mutation or Crizotinib if they have an ALK translocation[2].

For patients with metastatic NSCLC and good performance status (WHO PS 0-2), without EGFR mutations or ALK translocations, the ESMO guidelines recommend first line treatment with a platinum doublet[2]. A phase III trial suggested superior outcomes for the combination of pemetrexed cisplatin versus gemcitabine cisplatin in patients with non-squamous NSCLC, whilst for patients with squamous cancers gemcitabine cisplatin provided better outcomes[3]. More specifically overall survival was statistically superior for cisplatin/pemetrexed versus cisplatin/gemcitabine in patients with adenocarcinoma (n = 847; 12.6 v 10.9 months, respectively) and large-cell carcinoma histology (n = 153; 10.4 v 6.7 months, respectively), whilst in patients with squamous cell histology, there was a significant improvement in survival with cisplatin/gemcitabine versus cisplatin/pemetrexed (n = 473; 10.8 v 9.4 months, respectively). Equally in the ECOG 4599 trial[4], the addition of Bevacizumab (Avastin) in combination with carboplatin and paclitaxel showed a significant improvement in overall survival to 12.3 months compared to 10.3 months with the same regimen without Bevacizumab (hazard ratio for death, 0.79; P=0.003) in patients with non squamous NSCLC (also excluding patients with significant haemoptysis and brain metastases). Other large phase III trials comparing different platinum based regimens in the first line setting or non platinum versus platinum doublets, or addition of molecularly targeted drugs , e.g. the EGFR inhibitors such as Iressa (gefitinib) in the INTACT1 and 2 trials and Tarceva (erlotinib) in the TALENT and TRIBUTE trials to chemotherapy failed to show an improvement in overall survival compared to cytotoxic chemotherapy alone[2].

As a result of these studies, first line chemotherapy for patients with non-squamous metastatic NSCLC without EGFR mutations or ALK translocations is either pemetrexed platinum chemotherapy (preferred in Europe) or Carboplatin Paclitaxel and Bevacizumab (preferred in the USA). For squamous cancers a non- pemetrexed / non- bevacizumab platinum doublet, often platinum gemcitabine, is used worldwide.

In the second line setting Docetaxel was the first drug to be approved following a landmark randomized control study versus best supportive care showing an improvement in median survival from 4.6 to 7 months[5]. However this was at considerable toxicity especially in terms of severe neutropaenia and malaise. The next step to second line therapy was the randomized

controlled study of Docetaxel versus pemetrexed, which showed similar response rates and overall survival for the two agents[6]. It was also noted that pemetrexed had significantly less toxicity than Docetaxel, especially in terms of severe neutropaenia, febrile neutropaenia, deaths due to neutropaenia and hospitalization rates.

The next agent to gain approval both for second and third line use was Erlotinib (Tarceva) based on the BR21 trial; a randomized controlled versus placebo study showing an improvement in survival from 4.7 to 6.7 months[7]. In this trial eligible patients were those that had either already received first and second line therapy, or had received only first line therapy but were not deemed fit to receive further palliative chemotherapy.

More recently in the last two years, data have supported the use of two novel anti-angiogenic agents, nintedanib and ramucirumab, both in conjunction with docetaxel, as second line treatment for metastatic NSCLC. In the LUME-Lung I trial[8], 1314 patients were randomized to docetaxel with or without nintedanib, with the combination improving overall survival in adenocarcinoma patients with a median of 12.6 versus 10.3 months respectively. In the REVEL trial[9], 1253 patients were randomized to docetaxel with or without ramucirumab, with the combination improving overall survival from a median of 9.1 months to 10.5 months. In this study with ramucirumab the benefit was also seen in patients with squamous histology; this is the first evidence of benefit of an antiangiogenic monoclonal antibody for patients with squamous Lung Cancer.

3.1.2 Background data: Maintenance Chemotherapy in NSCLC:

With the understanding that we have reached a therapeutic plateau with platinum doublet first line chemotherapy in NSCLC, there has been renewed interest in "maintenance" therapy in metastatic NSCLC in the last few years [10] [11]. Maintenance therapy is applied after 4-6 cycles of chemotherapy to patients who have not progressed after the initial chemotherapy. Distinction needs to be made between continuation and switch maintenance. According to the NCCN (National Comprehensive Cancer Network) guidelines, continuation maintenance refers to the use of at least one of the agents used in first line, whilst switch maintenance refers to the initiation of a different agent, not included as part of the first line regimen.

Given that the main toxicity from platinum doublet chemotherapy is due to the platinum agent (especially cisplatin), a number of investigators have looked at the possibility of continuing with the non platinum agent[10]. Such trials include continuation of Paclitaxel (Belani 2003[12]), Gemcitabine (Brodowicz 2006[13], Belani 2010[14] and Perol 2010[15]), and Pemetrexed (Paz Arez 2011[16]). The design of all these trials is that they randomized non progressors after 4 cycles (or 16 weeks in the case of the paclitaxel trial) of chemotherapy to continuing with the non platinum agent until progression. From these trials only the continuation maintenance Pemetrexed trial by Paz Ares showed a statistically significant overall survival difference (from 11.0 to 13.9 months; 22% reduction of risk of death with HR=0.78 and 95% Cl: 0.64 to 0.96; P=.0195) for patients with non-squamous NSCLC.

In terms of continuation maintenance of targeted agents, the licensing studies for both Bevacizumab (ECOG 4599 by Sandler[4]) and Cetuximab (the FLEX trial by Pirker[17]) specified continuation of both agents until progression, and beyond the initial chemotherapy doublet treatment period, hence both cetuximab and bevacizumab if used with the initial chemotherapy doublet, need to be continued until disease progression (although no randomization to a continuation versus no continuation Bevacizumab or Cetuximab was tested in these trials).

In terms of switch maintenance, there have been six (6) randomized trials in the last five years. The common theme in these trials, is that they randomized non progressors after four cycles of first line platinum doublet chemotherapy to immediate treatment with one of four agents already licensed for use as second line therapies in NSCLC, i.e. pemetrexed[18], docetaxel[19], gefitinib[20], erlotinib alone[21] and erlotinib in combination with bevacizumab[22] in patients receiving bevacizumab as part of their first line treatment, versus treatment at progression, and also to vinorelbine[23]. From the chemotherapy switch maintenance trials, there was only one positive trial for overall survival with pemetrexed. In the Pemetrexed / JMEN trial[18], Ciuleanu et al, randomized 663 patients with advanced NSCLC who had not progressed after four cycles of platinum-based chemotherapy (which did not include pemetrexed) to Pemetrexed versus placebo, showing an improvement in PFS (4 vs. 2 months; $p < .00001$) and OS (median 13.4 versus 10.6 months, $p = .012$). As the trial was enacted prior to the understanding of the treatment interaction by histology for pemetrexed, squamous cell cancers were also included. Patients with squamous histology however derived no benefit from pemetrexed, and subset analysis looking at patients with nonsquamous histology showed a large, 5.2 month survival benefit for maintenance Pemetrexed versus placebo. The main criticism about this trial was that 33% of the patients in the observation arm did not receive second-line chemotherapy, whilst only 19% of the patients who received chemotherapy received pemetrexed at the time of progression.

From the switch maintenance trials with targeted agents, there was only one positive trial; the SATURN trial[21] by Capuzzo, which tested the benefit of immediate Erlotinib for patients who had not progressed after four cycles of platinum-based first-line chemotherapy. Erlotinib maintenance therapy significantly improved progression free and overall survival although the absolute difference in median OS was modest of only one month from 11 to 12 months. Both patients with EGFR mutations and wild type patients appeared to benefit. Further analysis of this trial, showed that the main benefit was seen in patients with stable disease (SD) after first line chemotherapy, who had a 2.3 month improvement in median survival. These results led to the approval for Erlotinib for switch maintenance to be limited to patients with SD after induction treatment[2]. Similar to the Pemetrexed trial, there is criticism that only 21% of patients on the placebo arm ever got an EGFR inhibitor like Erlotinib.

As a result of these studies recently there is more interest in providing maintenance therapy to patients with advanced NSCLC, especially for patients with non-squamous histology (where both Pemetrexed as continuation and switch maintenance can be used). For patients with squamous histology, this approach is less commonly applied given the limited benefit seen in the randomized studies (small benefit found for patients with stable disease after first line chemotherapy, by using erlotinib in the SATURN trial[21]). The most common clinical practice pattern in Europe regarding maintenance therapy is the use of continuation maintenance therapy for patients with non-squamous histology with Pemetrexed trial (Paz Ares et al[16]). Equally clinically meaningful improvement in survival has been seen with the switch maintenance trial for Pemetrexed (starting with a non-Pemetrexed containing regimen) again for patients with non-squamous cancers (Ciulianu T et al[18]), however this approach is not commonly used.

Despite the use of various lines of chemotherapy, including maintenance chemotherapy, the benefit seen with these treatments is modest, with median survival for patients with metastatic NSCLC remaining approximately 1 year[24]. There is therefore an urgent unmet need to provide new / innovative therapies to patients with metastatic NSCLC, that are going to have a bigger impact and more specifically that are going to be able to provide them with more durable responses and lasting disease control. **Immunotherapy checkpoint inhibitors have shown very promising results in a number of different cancer types, including Non Small Cell Lung Cancer, and are coming to the forefront to address this need, which is the reason for this study.**

3.1.3 Immune surveillance and the PD1 pathway

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ 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[25]. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an Ig superfamily member related to CD28 and CTLA-4 which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2). The structure of murine PD-1 has been resolved. PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable-type (V-type) domain responsible

for ligand binding and a cytoplasmic tail which is responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM). Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3ζ, PKCθ and ZAP70 which are involved in the CD3 T-cell signaling cascade. The mechanism by which PD-1 down modulates T-cell responses is similar to, but distinct from that of CTLA-4 as both molecules regulate an overlapping set of signaling proteins. PD-1 was shown to be expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B-cells, T regs and Natural Killer cells. Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells. The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types, including non-hematopoietic tissues as well as in various tumors. Both ligands are type I transmembrane receptors containing both IgV- and IgC-like domains in the extracellular region and contain short cytoplasmic regions with no known signaling motifs. Binding of either PD-1 ligand to PD-1 inhibits T-cell activation triggered through the T-cell receptor. PD-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments. PD-L2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell function in peripheral tissues. Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. PD-1 has been suggested to regulate tumor-specific T-cell expansion in subjects with melanoma (MEL). This suggests that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention.

3.1.4 Pembrolizumab: Preclinical and Clinical Trial Data

Keytruda™ Pembrolizumab is a potent and highly selective humanized monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. By blocking the binding of PDL-1 and 2 with the PD- 1 receptor on the surface of activated T-cells, and consequently increase T-cell activation by removing the inhibitory signaling of PD-1[25].

Keytruda™ (pembrolizumab) has been approved in the United Stated for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilumumab and, if BRAF V600 mutation positive, a BRAF inhibitor, and has also received accelerated approval to treat patients with advanced (metastatic) non-small cell lung cancer

(NSCLC) whose disease has progressed after other treatments and with tumors that express PD-L1.

In the recent publication of the KEYNOTE-001 trial[26], including 495 patients, both treatment-naïve and previously treated advanced NSCLC patients, the overall response rate (ORR) was 19.4% and the median duration of response was 12.5 months. The median duration of progression-free survival was 3.7 months, and the median duration of overall survival was 12.0 months. Patients who were treatment naïve had better response rates (RRs): 24.8% compared to 18.0% for the previously treated paients. Equally median PFS was higher in untreated patients: 6 months versus 3 months for the previously treated patients. Finally for patients with greater than 50% PDL1 expression on immunohistochemistry the RR was 42.5%, median progression-free survival was 6.3 months, whilst median overall survival was not reached.

Similar to the KEYNOTE -001 data with Pembrolizumab, clinical trials with other anti-PD-1 and anti-PD-L1antibodies show similar efficacy producing durable responses in approximately 20% of unselected patients with advance NSCLC[26].

Refer to the Investigator's Brochure for further Preclinical and Clinical data[27].

3.2 Rationale

3.2.1 Rationale for the Trial and Selected Subject Population

There are currently no data on maintenance therapy with PD1/PDL1 inhibitors in NSCLC. After an initial response / stable disease to first line chemotherapy, non progressors / candidates for maintenance treatment, represent an ideal setting / patient group to test the efficacy of Pembrolizumab for the following reasons:

1. Chemotherapy results in antigen release, which results in T-cell activation hence facilitates immune system activation, hence it has the potential to augment immune checkpoint blockade [28] [29], thus PD1 inhibition is more likely to be active immediately after chemotherapy compared to using this prior to first line chemotherapy.

2. Equally there is evidence from a randomized phase II study with Ipilimumab that phased / sequential administration of a checkpoint inhibitor compared to concurrent use is more effective[30].

3. Immune responses with PD1 inhibitors occur faster compared with CTLA-4 inhibitors, however about half occur around two (2) months for Nivolumab and Pembrolizumab, and some may occur as late as 8 months from initiation of treatment[31]. Hence there are potential

concerns that for some patients that progress quickly, there may not be enough time to receive the full benefit of this treatment. In the maintenance setting, given that there is already disease response or stabilization of disease following the first line chemotherapy, there is a time window for the immune response to occur, compared to using PD1 inhibition in patients after 2nd - 3rd line therapy, where there is usually rapidly progressing disease, which may not allow the time for this approach to work.

4. Equally after the initial disease response / cytoreduction of the disease, this represents a lower disease burden setting, that again may suit checkpoint inhibition better given the recent studies in Prostate cancer with Ipilimumab and Melanoma with Pembrolizumaba[32] [33], suggesting better outcomes for patients with less extensive disease.

With this study, looking at efficacy and tolerability of Pembrolizumab as maintenance therapy after first line therapy for NSCLC, it is hoped that evidence of better efficacy is going to be generated compared to other chemotherapy maintenance studies and compared to the use of Pembrolizumab in other lines of therapy. This should lead to further studies to establish the role of Pembrolizumab as maintenance therapy in NSCLC, potentially providing better treatments and outcomes for patients with advanced NSCLC.

Finally, it is worth reflecting on the reality of access to innovative new drugs for Lung Cancer patients in Cyprus, whilst maintenance Pemetrexed is also not available due to funding restrictions. As a result, this study provides access to Pembrolizumab, a very important checkpoint inhibitor in NSCLC, as a maintenance treatment, where no other treatment options are available for patients with advanced NSCLC, in Cyprus.

3.2.2 Rationale for Dose Selection/Regimen/Modification

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

PK data analysis of MK-3475 administered Q2W and Q3W showed slow systemic clearance, limited volume of distribution, and a long half-life (refer to IB). Pharmacodynamic data (IL-2 release assay) suggested that peripheral target engagement is durable (>21 days). This early PK and pharmacodynamic data provides scientific rationale for testing a Q2W and Q3W dosing schedule.

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

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

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

3.2.3 Rationale for Endpoints

3.2.3.1 Efficacy Endpoints

Primary endpoint: percentage of patients that have not progressed at 1 year using immune related radiological criteria (see section 11.3). The 1 year timing relates to the time from trial enrollement and initiation of pembrolizumab as maintenance therapy. This is the most clinically relevant endpoint in a maintenance study. Prolongation of disease control is a very worthwhile endpoint, towards the realization of the goal to obtain long term disease control for patients with metastatic NSCLC, similar to the results seen with checkpoint inhibition for patients with melanoma. The timing of assessment at 1 year is based on the durable nature of responses seen with Pembrolizumab so far, suggesting that at 1 year there is going to be a large difference in disease progression between patients on Pembrolizumab compared to the historical data from the maintenance studies.

Secondary Endpoints: These would include

- Response rates (RECIST)
- Response Rates with immune related Response Criteria (irRC)
- Radiological Progression Free Survival (PFS) using RECIST criteria
- Immune-related PFS using irRC: irPFS is the progression free survival (PFS) measured applying immune related radiological criteria. PFS (RECIST) at 6 months and 1 year from initiation of Pembrolizumab.
- Overall survival
- 1, 2 and 3 year OS rate.
- Best overall response rate and disease control rate using both RECIST and irRC in patients with squamous and non-squamous NSCLC and
- Immune-related toxicities (IRAEs)

3.2.3.2 Biomarker Research

From the recent publication of the KEYNOTE-001 trial[28], including 495 treatment-naïve and previously treated advanced NSCLC patients, PDL1 status emerges as a potential predictive factor for response to Pembrolizumab based on the fact that the ORR (irRC) was 45.2% in

patients with strong PD-L1 expression (≥50% staining) statistically higher than for patients with expression of 1-49%, or for those less than 1% ($p<0.0001$).

In this study we propose to undertake PDL1 testing from the histological sample available at diagnosis of metastatic disease (pre- first line chemotherapy sample) and to compare this from a new biopsy after first line chemotherapy and prior to study entry with the aim to undertake PDL1 status again and compare with pre-chemotherapy initial Bx. PDL1 testing is going to be undertaken by QualTek Molecular Laboratories in the United States (http://www.qmlabs.com/About-QualTek.html).

In this study, we aim to investigate the prognostic and predictive value of PD-L1 and Ki67 on CTCs and plasma, to patients receiving first line platinum doublet chemotherapy and patients receiving Pembrolizumab.

Aims are:

1. 1. To investigate the spatial change in PDL1 status with Immunohistochemistry on tumour biopsy pre and after chemotherapy and to correlate responses / clinical benefit to Pembrolizumab with PDL1 status (from initial biopsy prior to chemotherapy and from biopsy after first line chemotherapy).

2. To ascertain whether pre-chemo or post-chemo PDL-1 status is the better predictor of response to Pembrolizumab and whether the pre-chemo Bx is still reliable as a predictive marker, making unnecessary a new Bx after 4-6 cycles of first line chemotherapy.

3. Investigate the differences between membranous, cytoplasmic and nuclear expression of PD-L1 on CTCs using the two different antibodies.

4. Investigate the concordance between the PD-L1 expression analysed with IHC on the initial tumour biopsy compared to PD-L1 expression on CTCs and plasma at baseline prior to starting platinum based chemotherapy.

5. Investigate the prognostic and predictive role of Ki67 expression and PD-L1 expression on CTCs and plasma at baseline to platinum based chemotherapy and Pembrolizumab immunotherapy.

6. Investigate the temporal change of these biomarkers during chemotherapy and immunotherapy, and how this relates to outcomes (e.g. change of CTC number during treatment relating to response to chemotherapy and whether the change in expression has predictive function: comparing patients with PD-L1(+) and PD-L1(-) CTCs, plus change in soluble PD-L1).

7. Finally investigate of all the different methods of assessing PD-L1 (e.g. tissue biopsy immunohistochemistry, soluble PD-L1 and PD-L1 on CTCs) which one, is the most accurate predictive factor to Pembrolizumab immunotherapy.

4.0 METHODOLOGY

4.1 Entry Criteria

4.1.1 Diagnosis/Condition for Entry into the Trial

In order to be eligible for trial entry, patients must have a diagnosis of metastatic Non Small Cell Lung Cancer, and should not have progressed after first line palliative chemotherapy with a platinum doublet. They should have received no more than six (6) cycles of a platinum doublet chemotherapy, and should be able to receive treatment within three (3) to six (6) weeks from the last chemotherapy administration.

4.1.2 Subject Inclusion Criteria

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

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

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

3. Have measurable disease based on RECIST 1.1.

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

5. Have a performance status of **0 to 2** on the ECOG Performance Scale.

6. Demonstrate adequate organ function as defined in Table 1, all screening labs should be performed within 10 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 without transfusion or EPO dependency (within 7 days of assessment)
Renal	
Serum creatinine **OR** Measured or calculated[a] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 X upper limit of normal (ULN) **OR** ≥60 mL/min for subject with creatinine levels > 1.5 X institutional ULN
Hepatic	
Serum total bilirubin	≤ 1.5 X ULN **OR**
	Direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 X ULN **OR** ≤ 5 X ULN for subjects with liver metastases
Albumin	≥2.5 g/L
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT) Activated Partial Thromboplastin Time (aPTT)	≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants ≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
[a]Creatinine clearance should be calculated per institutional standard.	

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

8. Female subjects of childbearing potential (Section 5.7.2) must be willing to use an adequate method of contraception as outlined in Section 5.7.2 – Contraception, for the course of the study through 120 days after the last dose of study medication.

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

9. Male subjects of childbearing potential (Section 5.7.1) must agree to use an adequate method of contraception as outlined in Section 5.7.1- Contraception, starting with the first dose of study therapy through 120 days after the last dose of study therapy.

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

4.1.3 Subject Exclusion Criteria

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

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

2. Have completed more than six (6) cycles of first line platinum doublet chemotherapy or more than six (6) have elapsed from the last chemotherapy administration of the first line chemotherapy with platinum doublet.

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

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

5. Hypersensitivity to pembrolizumab or any of its excipients.

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

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

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

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

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

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

10. Has active autoimmune disease that has required systemic treatment in the past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (eg., thyroxine, insulin, or

physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.

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

12. Has an active infection requiring systemic therapy.

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

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

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

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

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

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

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

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

4.2 Trial Treatments

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

Table 2 Trial Treatment

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period	Use
Pembrolizumab	200 mg	Q3W	IV infusion	Day 1 of each 3 week cycle	Experimental

Trial treatment should begin on the day of randomization or as close as possible to the date on which treatment is allocated/assigned.

4.2.1 Dose Selection/Modification

4.2.1.1 Dose Selection

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

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

4.2.1.2 Dose Modification (Escalation/Titration/Other)

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

Table 3 Dose Modification Guidelines for Drug-Related Adverse Events

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

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Treatment Discontinuation
Pneumonitis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	3-4	Permanently discontinue	Permanently discontinue
Renal Failure or Nephritis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	3-4	Permanently discontinue	Permanently discontinue
All Other Drug-Related Toxicity[c]	3 or Severe	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	4	Permanently discontinue	Permanently discontinue

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

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

[b] If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose;

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

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

4.2.2 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 6.0). Trial treatment may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons.

All trial treatments will be administered on an outpatient basis.

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

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

4.2.3 Trial Blinding/Masking

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

4.3 Randomization or Treatment Allocation

Not applicable

4.4 Stratification

Not applicable

4.5 Concomitant Medications/Vaccinations (allowed & prohibited)

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

4.5.1 Acceptable Concomitant Medications

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

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

4.5.2 Prohibited Concomitant Medications

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

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab
- Radiation therapy
    - Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed at the investigator's discretion.

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

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

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

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

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

4.6 Rescue Medications & Supportive Care

4.6.1 Supportive Care Guidelines

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of adverse events with potential immunologic etiology are outlined below. Where appropriate, these guidelines include the use of oral or intravenous treatment with corticosteroids as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab.

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

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

- **Pneumonitis**:
    - For **Grade 2 events**, treat with systemic corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
    - For **Grade 3-4 events**, immediately treat with intravenous steroids. Administer additional anti-inflammatory measures, as needed.

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

- **Diarrhea/Colitis**:

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

  - All subjects who experience diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion. For Grade 2 or higher diarrhea, consider GI consultation and endoscopy to confirm or rule out colitis.
  - For **Grade 2 diarrhea/colitis,** administer oral corticosteroids.
  - For **Grade 3 or 4 diarrhea/colitis,** treat with intravenous steroids followed by high dose oral steroids.
  - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

- **Type 1 diabetes mellitus (if new onset, including diabetic ketoacidosis [DKA]) or ≥ Grade 3 Hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA)**
  - For **T1DM** or **Grade 3-4** Hyperglycemia
    - Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria.
    - Evaluate patients with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.

- **Hypophysitis**:
  - For **Grade 2** events, treat with corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
  - For **Grade 3-4** events, treat with an initial dose of IV corticosteroids followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

- **Hyperthyroidism or Hypothyroidism**:

  Thyroid disorders can occur at any time during treatment. Monitor patients for changes in thyroid function (at the start of treatment, periodically during treatment,

and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders.

- **Grade 2** hyperthyroidism events (and **Grade 2-4** hypothyroidism):
  - In hyperthyroidism, non-selective beta-blockers (e.g. propranolol) are suggested as initial therapy.
  - In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyroinine, is indicated per standard of care.
- **Grade 3-4** hyperthyroidism
  - Treat with an initial dose of IV corticosteroid followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

- **Hepatic**:
  - For **Grade 2** events, monitor liver function tests more frequently until returned to baseline values (consider weekly).
    - Treat with IV or oral corticosteroids
  - For **Grade 3-4** events, treat with intravenous corticosteroids for 24 to 48 hours.
  - When symptoms improve to Grade 1 or less, a steroid taper should be started and continued over no less than 4 weeks.
- **Renal Failure or Nephritis**:
  - For **Grade 2** events, treat with corticosteroids.
  - For **Grade 3-4** events, treat with systemic corticosteroids.
  - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
- **Management of Infusion Reactions**: Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion.

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

Table 4 Infusion Reaction Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 1	Increase monitoring of vital signs as medically	None

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Mild reaction; infusion interruption not indicated; intervention not indicated	indicated until the subject is deemed medically stable in the opinion of the investigator.	
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 pembrolizumab (MK-3475) with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **Subject is permanently discontinued from further trial treatment administration.**	No subsequent dosing
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.		

4.7 Diet/Activity/Other Considerations

4.7.1 Diet

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

4.7.2 Contraception

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

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

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

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

OR

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

OR

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

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

(1) practice abstinence[†] from heterosexual activity;

OR

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

Acceptable methods of contraception are[‡]:

Single method (one of the following is acceptable):

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

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

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

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

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

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

4.7.3 Use in Pregnancy

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

The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the 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.

4.7.4 Use in Nursing Women

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

4.8 Subject Withdrawal/Discontinuation Criteria

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

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

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

  Note: A subject may be granted an exception to continue on treatment with confirmed radiographic progression if clinically stable or clinically improved, please see Section 11.3
- Unacceptable adverse experiences as described in Section 5.2.1.2
- Intercurrent illness that prevents further administration of treatment
- Investigator's decision to withdraw the subject
- The subject has a confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements
- The subject is lost to follow-up
- Completed 24 months of uninterrupted treatment with pembrolizumab or 35 administrations of study medication, whichever is later.

  Note: 24 months of study medication is calculated from the date of first dose. Subjects who stop pembrolizumab after 24 months may be eligible for up to one year of

additional study treatment if they progress after stopping study treatment provided they meet the requirements detailed in Section 7.1.5.5

- Administrative reasons

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

4.8.1 Discontinuation of Study Therapy after CR

Discontinuation of treatment may be considered for subjects who have attained a confirmed CR that have been treated for at least 24 weeks with pembrolizumab and had at least two treatments with pembrolizumab beyond the date when the initial CR was declared. Subjects who then experience radiographic disease progression may be eligible for up to one year of additional treatment with pembrolizumab via the Second Course Phase at the discretion of the investigator if no cancer treatment was administered since the last dose of pembrolizumab, the subject meets the safety parameters listed in the Inclusion/Exclusion criteria, and the trial is open. Subjects will resume therapy at the same dose and schedule at the time of initial discontinuation. Additional details are provided in Section 7.1.5.5.

4.9 Subject Replacement Strategy

No patients are going to be replaced in the event of patient withdrawal.

4.10 Clinical Criteria for Early Trial Termination

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

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

2. Poor adherence to protocol and regulatory requirements

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

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

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

5.0 TRIAL FLOW CHART

5.1 Study Flow Chart

Trial Period:	**Screening Phase**		**Treatment Cycles[a]**								**End of Treatment**	**Post-Treatment**		
							To be repeated beyond 8 cycles							
Treatment Cycle/Title:	Pre-screening (Visit 1)	Main Study Screening (Visit 2)	1	2	3	4	5	6	7	8	Discon	Safety Follow-up	Follow Up Visits[b]	Survival Follow-Up
Scheduling Window (Days):		-28 to -1		± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days post discon	Every 9 weeks post discon	Every 12 weeks
Administrative Procedures														
Pre-screening Consent	√													
Informed Consent		√												
Inclusion/Exclusion Criteria	√	√												
Demographics and Medical History	√	√												
Prior and Concomitant Medication Review	√	√	√	√	√	√	√	√	√	√	√			
Trial Treatment Administration			√	√	√	√	√	√	√	√				
Post-study anticancer therapy status												√	√	√
Survival Status			√	√	√	√	√	√	√	√	√	√	√	√
Clinical Procedures/Assessments														
Review Adverse Events				√	√	√	√	√	√	√	√	√		
Full Physical Examination	√	√	√		√		√		√		√	√		
Directed Physical Examination				√		√		√		√	√	√		

Trial Period:	**Screening Phase**		**Treatment Cycles[a]**								**End of Treatment**	**Post-Treatment**		
Treatment Cycle/Title:	Pre-screening (Visit 1)	Main Study Screening (Visit 2)	1	2	3	4	To be repeated beyond 8 cycles: 5	6	7	8	Discon	Safety Follow-up	Follow Up Visits[b]	Survival Follow-Up
Scheduling Window (Days):		-28 to -1		± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days post discon	Every 9 weeks post discon	Every 12 weeks
Vital Signs and Weight		√	√	√	√	√	√	√	√	√	√	√		
ECOG Performance Status	√	√	√	√	√	√	√	√	√	√	√	√		
Laboratory Procedures/Assessments: analysis performed by LOCAL laboratory														
Pregnancy Test – Urine or Serum β-HCG	√	√	√	√	√	√	√	√	√	√	√			
PT/INR and aPTT	√		√	√	√	√	√	√	√	√	√			
CBC with Differential	√	√	√	√	√	√	√	√	√	√	√			
Comprehensive Serum Chemistry Panel	√	√	√	√	√	√	√	√	√	√	√			
Urinalysis	√													
T3, FT4 and TSH	√		√	√	√	√	√	√	√	√	√			
Efficacy Measurements														
Tumor Imaging		√			√			√			√		√	
Tumor Biopsies/Archival Tissue Collection/Correlative Studies Blood														
Newly Obtained Tissue Collection		√												

6.0 TRIAL PROCEDURES

6.1 Trial Procedures

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

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

6.1.1 Administrative Procedures

6.1.1.1 Informed Consent

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

7.1.1.1.1 General Informed Consent

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

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

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

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

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

6.1.1.2 Inclusion/Exclusion Criteria

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

6.1.1.3 Medical History

A medical history will be obtained by the investigator or qualified designee. Medical history will include all active conditions, and any condition diagnosed within the prior 10 years that are considered to be clinically significant by the Investigator. Details regarding the disease for which the subject has enrolled in this study will be recorded separately and not listed as medical history.

6.1.1.4 Prior and Concomitant Medications Review

6.1.1.4.1 Prior Medications

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

6.1.1.4.2 Concomitant Medications

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

6.1.1.5 Disease Details and Treatments

6.1.1.5.1 Disease Details

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

6.1.1.5.2 Prior Treatment Details

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

6.1.1.5.3 Subsequent Anti-Cancer Therapy Status

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

6.1.1.6 Assignment of Screening Number

Register of all patients invited to participate and screened is going to be held.

6.1.1.7 Assignment of Trial Identification Number

Each patient is going to be registered with a number for confidentiality purposes. No randomization is going to take place.

6.1.1.8 Trial Compliance (Medication/Diet/Activity/Other)

Trial compliance is going to be monitored via scheduled visits.

6.1.2 Clinical Procedures/Assessments

See trial flow chart (section 6.0).

6.1.2.1 Adverse Event (AE) Monitoring

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

For subjects receiving treatment with pembrolizumab all AEs of unknown etiology associated with pembrolizumab exposure should be evaluated to determine if it is possibly an event of clinical interest (ECI) of a potentially immunologic etiology (termed immune-related adverse events, or irAEs); see the separate ECI guidance document in Appendix 4 regarding the identification, evaluation and management of potential irAEs.

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

6.1.2.2 Full Physical Exam

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

6.1.2.3 Directed Physical Exam

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

6.1.2.4 Vital Signs

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

6.1.2.5 Eastern Cooperative Oncology Group (ECOG) Performance Scale

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

6.1.2.6 Tumor Imaging and Assessment of Disease

CT scan imaging to be undertaken every 9 weeks (3 cycles of treatment) for the first year and every 12 weeks (4 cycles) from the second year onwards for patients whilst on treatment, or for patients who discontinue trial treatment for reasons other than disease progression.

6.1.2.7 Tumor Tissue Collection and Correlative Studies Blood Sampling

PDL1 status to be undertaken from histological sample available at diagnosis of metastatic disease (pre- first line chemotherapy sample) and also from a new biopsy after first line chemotherapy and prior to study entry.

6.1.3 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

Laboratory tests for hematology, chemistry, urinalysis, and others are specified in Table 5.

Table 5 Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
FBC	Albumin	Blood	Serum β-human chorionic gonadotropin†
Hemoglobin	Alkaline phosphatase	Glucose	(β-hCG)†
Platelet count	Alanine aminotransferase (ALT)	Protein	PT (INR)
WBC (total and differential)	Aspartate aminotransferase (AST)	Specific gravity	aPTT
Absolute Neutrophil Count	Lactate dehydrogenase (LDH)	Microscopic exam *(If abnormal)*	Free thyroxine (T4)
Absolute Lymphocyte Count	Uric Acid	results are noted	Thyroid stimulating hormone (TSH)
	Calcium	Urine pregnancy test †	ACTH
	Chloride		Cortisol (morning sample)
	Glucose		
	Phosphorus		
	Potassium		
	Sodium		
	Magnesium		
	Total Bilirubin		
	Direct Bilirubin *(If total bilirubin is elevated above the upper limit of normal)*		

† Perform on women of childbearing potential only. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required.

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

6.1.3.1 Pharmacokinetic/Pharmacodynamic Evaluations

No pharmacokinetic or pharmacodynamic evaluations are going to be carried out.

6.1.3.1.1 Blood Collection for Serum Pembrolizumab

Not applicable

6.1.3.1.2 Blood Collection for Anti-Pembrolizumab Antibodies

Not applicable

6.1.4 Other Procedures

6.1.4.1 Withdrawal/Discontinuation

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

6.1.4.2 Blinding/Unblinding

Not applicable.

6.1.5 Visit Requirements

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

6.1.5.1 Screening

Patients with metastatic NSCLC who have not progressed after first line chemotherapy, are going to be identified by the treating oncologists, Dr Haris Charalambous, Dr Flora Kyriakou

and Dr George Orphanos. Following initial discussion about proposed study, patients are going to be referred to the Clinical Trials Unit staff, to undertake screening for the study.

6.1.5.1.1 Screening Period

Aim to start in January 2016 and finish once all forty-eight (48) patients have been enrolled, with a target date to finish accrual in July 2017.

6.1.5.2 Treatment Period

Aim to start treatment in January 2016. Patients to receive treatment until either progressive disease or until they have received two (2) years of continuous Pembrolizumab treatment.

6.1.5.3 Post-Treatment Visits

See flow chart (section 6.0).

7.1.5.3.1 Safety Follow-Up Visit

The mandatory Safety Follow-Up Visit should be conducted approximately 30 days after the last dose of trial treatment or before the initiation of a new anti-cancer treatment, whichever comes first. All AEs that occur prior to the Safety Follow-Up Visit should be recorded. Subjects with an AE of Grade > 1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new anti-neoplastic therapy, whichever occurs first. SAEs that occur within 90 days of the end of treatment or before initiation of a new anti-cancer treatment should also be followed and recorded. Subjects who are eligible for retreatment with pembrolizumab (as described in Section 7.1.5.5) may have up to two safety follow-up visits, one after the Treatment Period and one after the Second Course Phase.

6.1.5.4 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 9 weeks (63 ± 7 days) by radiologic imaging to monitor disease status. After 1 year, the imaging time point will occur every 12 weeks (84 ± 7 days). Every effort should be made to collect information regarding disease status until the start of new anti-neoplastic therapy, disease progression, death, end of the study or if the subject begins retreatment with pembrolizumab as detailed in Section 7.1.5.5. Information regarding post-study anti-neoplastic treatment will be collected if new treatment is initiated.

Subjects who are eligible to receive retreatment with pembrolizumab according to the criteria in Section 7.1.5.5 will move from the follow-up phase to the Second Course Phase when they experience disease progression.

6.1.5.4.1 Survival Follow-up

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

6.1.5.5 Second Course Phase (Retreatment Period)

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

- Had SD, PR or CR and stopped pembrolizumab treatment after 24 months of study therapy for reasons other than disease progression or intolerability

AND

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

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

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

6.2 Assessing and Recording Adverse Events

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

6.2.3.1 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 another important medical event

- **Note:** In addition to the above criteria, adverse events meeting either of the below criteria, although not serious per ICH definition, are reportable to the Merck in the same timeframe as SAEs to meet certain local requirements. Therefore, these events are considered serious by Merck for collection purposes.
    - Is a new cancer (that is not a condition of the study);
    - Is associated with an overdose.

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

For the time period beginning when the consent form is signed until treatment allocation/randomization, any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study (reference Section 7.2.3.3 for additional details) that occurs to any subject must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study (reference Section 7.2.3.3 for additional details), whether or not related to the Merck product, must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety.

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

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

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

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

6.2.3.2 Events of Clinical Interest

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

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

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

Events of clinical interest for this trial include:

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

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

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

6.2.3.3 Protocol-Specific Exceptions to Serious Adverse Event Reporting

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

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

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

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

6.2.4 Evaluating Adverse Events

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

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

Table 6 Evaluating Adverse Events

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

V4.0 CTCAE Grading	**Grade 1**	**Mild; asymptomatic or mid symptoms; clinical or diagnostic observations only; intervention not indicated.**
	Grade 2	**Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.**
	Grade 3	**Severe or medically significant but not immediately life-threatening; hospitalization or prolongation or hospitalization indicated; disabling; limiting self-care ADL.**
	Grade 4	**Life threatening consequences; urgent intervention indicated.**
	Grade 5	**Death related to AE**
Seriousness	A serious adverse event is any adverse event occurring at any dose or during any use of Merck product that:	
	†**Results in death**; or	
	†**Is life threatening; or** places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred (Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.); or	
	†**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or	
	†**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not a serious adverse event. A pre-existing condition is a clinical condition that is diagnosed prior to the use of a Merck product and is documented in the patient's medical history.); or	
	†**Is a congenital anomaly/birth defect** (in offspring of subject taking the product regardless of time to diagnosis);or	
	Is a new **cancer** (that is not a condition of the study) **(**although not serious per ICH definition, is reportable to the Sponsor within 24 hours and to Merck within 2 working days to meet certain local requirements); **or**	
	Is an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event for collection purposes. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours to the Sponsor and to Merck within 2 working days..	
	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes	

	listed previously (designated above by a †).	
Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the adverse event cause Merck product to be discontinued?	
Relationship to Merck Product	Did Merck product cause the adverse event? The determination of the likelihood that Merck product caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the adverse event based upon the available information. **The following components are to be used to assess the relationship between Merck product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely Merck product caused the adverse event (AE):	
	Exposure	Is there evidence that the subject was actually exposed to Merck product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
	Time Course	Did the AE follow in a reasonable temporal sequence from administration of Merck product? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors

Relationship to Merck Product (continued)	**The following components are to be used to assess the relationship between the test drug and the AE: (continued)**	
	Dechallenge	Was Merck product discontinued or dose/exposure/frequency reduced? If yes, did the AE resolve or improve? If yes, this is a positive dechallenge. If no, this is a negative dechallenge. (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Sponsor's product; or (3) the trial is a single-dose drug trial); or (4) Sponsor's product(s) is/are only used one time.)
	Rechallenge	Was the subject re-exposed to Merck product in this study? If yes, did the AE recur or worsen? If yes, this is a positive rechallenge. If no, this is a negative rechallenge. (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the trial is a single-dose drug trial); or (3) Sponsor's product(s) is/are used only one time). NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY MERCK PRODUCT, OR IF REEXPOSURE TO MERCK PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE SUBJECT, THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL.
	Consistency with Trial Treatment Profile	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding Merck product or drug class pharmacology or toxicology?
The assessment of relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.		
Record one of the following		**Use the following scale of criteria as guidance (not all criteria must be present to be indicative of Merck product relationship).**
Yes, there is a reasonable possibility of Merck product relationship.		There is evidence of exposure to Merck product. The temporal sequence of the AE onset relative to the administration of Merck product is reasonable. The AE is more likely explained by Merck product than by another cause.
No, there is not a reasonable possibility of Merck product relationship		Subject did not receive the Merck product OR temporal sequence of the AE onset relative to administration of Merck product is not reasonable OR the AE is more likely explained by another cause than the Merck product. (Also entered for a subject with overdose without an associated AE.)

6.2.5 Sponsor Responsibility for Reporting Adverse Events

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

6.3 Procedures for filing complaints

Patients will e able to communicate directly with the doctor / researcher or with the research nurses of the study (by phone or by visiting the centre) for any grievance, complaint or any clarification they need, in relation to the study. All patients are going to receive a card with all the necessary contact details for the participating doctors and research nurses. The same information is going to be available on the consent form.

Complaints can also be submitted in person or anonymously to the Chief Executive Officer of the Bank of Cyprus Oncology Centre (BOCOC), Mr. Panos Ergatoudes. Finally, complaints can be posted in a complaints box located in the main entrance of the building at the BOCOC.

7.0 STATISTICAL ANALYSIS PLAN

7.1 Statistical Analysis Plan Summary

The study employs a one stage phase II Fleming's design using irPFS at 1 year as primary endpoint.

Using response hypotheses of H0 < 12 % and Ha> 25% i.e. that the irPFS at 1 year for the maintenance Pembrolizumab arm is 25%, compared to 12% in the normal chemotherapy maintenance arm, with a significance level (i.e., the probability of rejecting H0 when it is true) α=0.05 and the power (i.e. the probability of deciding the regimen is active) is 0.8 when true response rate is 25%, 48 patients are required to be entered into this study.

7.2 Statistical Analysis Plan

Comparator data regarding patients' outcomes receiving maintenance therapy can be obtained from the Pemetrexed continuation and Erlotinib switch maintenance studies.

The best available data for maintenance treatment of non-squamous NSCLC patients come from the continuation Pemetrexed trial (Pas Ares[16]). This trial enrolled good performance status patients (PS 0-1), with non-squamous histology, who did not progress after 4 cycles of Pemetrexed / Cisplatin, and continued Pemetrexed chemotherapy, resulting in a 1-year PFS of 18.6%, whilst in the placebo arm the 1 year PFS was 5%.

For the squamous patients, the best available data come from the switch maintenance Erlotinib trial[21] (SATURN), given that Erlotinib is the only agent approved for maintenance treatment in patients with squamous cancers. The 1-year PFS for the erlotinib arm is slightly above placebo, around 6%.

Hence for the comparator arm by using:

- data from the Pemetrexed continuation study for non squamous histology: 1-year PFS of 18% for non squamous on Pemetrexed maintenance,
- data from the erlotinib arm in the SATURN trial for patients with squamous histology and estimating 1-year PFS of 6% for squamous patients
- whilst assuming a ratio of 1:1 adenocarcinomas to squamous,
- provides us a weighted average of 12% of 1-year PFS

Assume irPFS at 1 year for the maintenance Pembrolizumab arm to be 25%, compared to 12% in the normal chemotherapy maintenance arm.

Sample size for Fleming one stage Phase II trials

Probability of Type I Error (α) = 0.05
Power (1 - β) = 0.8
Lower proportion for rejection (p_0) = 0.12
Higher proportion for acceptance (p_n) = 0.25
Sample size required = 48

8.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

8.1 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.

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

Table 7 Product Descriptions

Product Name & Potency	Dosage Form

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

8.2 Packaging and Labeling Information

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

8.3 Clinical Supplies Disclosure

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

8.4 Storage and Handling Requirements

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

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

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

8.5 Returns and Reconciliation

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

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

9.0 ADMINISTRATIVE AND REGULATORY DETAILS

9.1 Confidentiality

Confidentiality standards are going to be maintained by coding each patient enrolled in the study through assignment of a unique patient identification number. This would mean that

patient names are not going to be included in any data sets that are going to be transferred to the sponsor.

Patient medical information obtained by this study remains confidential and may only be disclosed to a patient's personal physician / or other appropriate medical personnel responsible for the patient, for treatment purposes.

9.2 Compliance with Financial Disclosure Requirements

Investigators are going to be responsible to provide information on financial interests during the course of the study and for 1 year after completion of the study, to the appropriate health authorities and in accordance with local regulations.

9.3 Compliance with Law, Audit and Debarment

This study is going to be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice, the EU Clinical Trial Directive (2001/20/EC) and the principles of the Declaration of Helsinki, as well as the laws and regulations of the republic of Cyprus. Ethics committee approval is going to be sought from the Cyprus National Bioethics committee.

Study data (including patients' medical records and CRFs) are going to be available for inspection and audit from either the sponsor or the Regulatory Bodies.

9.4 Compliance with Trial Registration and Results Posting Requirements

This trial is going to be submitted 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, as well as provide them information regarding the results, when those become available.

9.5 Quality Management System

The primary investigator is going to be responsible for data management of this study, including quality checking of the data. Study monitors should be carried out intermittently to confirm that critical protocol data entered into the CRFs and the Electronic Data Collection (EDC) system by authorized study personnel are accurate, complete and verifiable from source documents.

9.6 Data Management

Data collected manually on CRFs are going to be entered electronically into the Electronic Data Collection (EDC) system. System backups for data stored electronically are going to be carried out, whilst paper records are going to be retained in the Clinical Trials Unit at the BOCOC (as with the conduct of other studies in the centre).

10.0 APPENDICES

10.1 ECOG Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

* As published in Am. J. Clin. Oncol.: *Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.* The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.

10.2 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)

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

Both RECIST version 1.1[34] and immune related Response Criteria[35] (irRC) 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.

The use of irRC is to correct for the possibility of pseudo-progression / deal with the altered patterns of response seen with ipilimumab and potentially other immunotherapies [Wolchok JD al[35], table 8).

The decision to discontinue treatment is going to be based on irRC assessment. The irRC assessment considers the patient's "total tumour burden" and requires confirmation of suspected disease progression with a subsequent CT scan, four weeks later.

Table 8. Immune related response rates:

Immune-related complete response	Complete resolution of all measureable and nonmeasurable lesions, with no new lesions. Complete response must be confirmed by a second, consecutive assessment at least four weeks later.
Immune-related partial response	A decrease in the total tumor burden of 50 percent or more compared to baseline, which must be confirmed by a second, consecutive assessment at least four weeks later. This category allows for the inclusion of progression of some lesions or the appearance of new lesions as long as the total tumor burden meets the response criterion.
Immune-related stable disease	Not meeting the criteria for either a partial or complete response or for progressive disease.
Immune-related progressive disease	An increase in tumor burden of 25 percent or more relative to the minimum recorded tumor burden. This must be confirmed by a second, consecutive assessment no less than four weeks after the initial documentation of an increase in tumor

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