TITLE: MEL1486 - A Multicenter Phase II Study to Evaluate the Safety and Efficacy of Pembrolizumab (MK-3475) in Patients with Advanced Uveal Melanoma

IND NUMBER: 124395

EudraCT NUMBER:

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[redacted]

1.0 TRIAL SUMMARY

Abbreviated Title	Pembrolizumab (MK-3475) in uveal melanoma
Trial Phase	II
Clinical Indication	Advanced uveal melanoma
Trial Type	Two-stage, single arm trial
Type of control	None
Route of administration	Intravenous
Trial Blinding	None
Treatment Groups	Pembrolizumab 200mg every 3 weeks
Number of trial subjects	10-29
Maximum Duration of Therapy	24 months

1.1 SUMMARY OF RATIONALE

The programmed cell death 1 (PD-1) pathway represents a major immune control switch which may be engaged by tumor cells to overcome active T-cell immune surveillance (1). The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in various tumors (2-5). High expression of PD-L1 on tumor cells (and to a lesser extent of PD-L2) has been found to correlate with poor prognosis and survival in various cancer types, including renal cell carcinoma (RCC) (6), pancreatic carcinoma (7), and ovarian carcinoma (8). Furthermore, PD-1 has been suggested to regulate tumor-specific T-cell expansion and function in patients with malignant melanoma (9, 10). Preclinical in vitro and in vivo experiments have shown that PD-1 and/or PD-L1 blockade using monoclonal antibodies (mAb) enhances tumor-cell specific T-cell activation, cytokine production, anti-tumor effector mechanisms, and clearance of tumor cells by the immune system (7, 9, 11-15).

Recent data with nivolumab (BMS-936558), an IgG4 antibody against PD-1, have validated PD-1 as an attractive target for clinical therapeutic intervention (16). In a recent report of the clinical trial data with nivolumab a total of 296 patients with advanced melanoma, non-small cell lung cancer (NSCLC), castration-resistant prostate cancer, renal-cell carcinoma or colorectal cancer were treated at a dose of 0.1, 0.3, 1, 3, or 10 mg/kg every 2 weeks. Among 236 evaluable patients, cumulative response rates (all doses and defined by the Response Evaluation Criteria in Solid Tumors [RECIST] were 18% among patients with NSCLC, 28% among patients with melanoma, and 27% among patients with renal-cell cancer. Responses were reported to be durable: 20 of 31 responses lasted 1 year or more in patients with 1 year or more of follow-up. Grade 3 or 4 adverse events were observed in 49% of patients, while 14% of patients had treatment related Grade 3 or 4 adverse events. Drug-related adverse events of special interest (e.g., those with potential immune-related causes) occurred in 41% of patients and included pneumonitis, vitiligo, colitis, hepatitis, hypophysitis, and thyroiditis (16).

Pembrolizumab (MK-3475, previously known as SCH 900475) is a potent and highly-selective humanized mAb of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Pembrolizumab strongly enhances T lymphocyte immune responses in cultured blood cells from healthy human donors, cancer patients, and primates. In T-cell activation assays using human donor blood cells, the EC50 was in the range of 0.1 to 0.3 nM. Pembrolizumab also modulates the level of interleukin-2 (IL-2), tumor necrosis factor alpha (TNFα), interferon gamma (IFNγ), and other cytokines. The antibody potentiates existing immune responses only in the presence of antigen and does not nonspecifically activate T-cells (for details see the Pembrolizumab Investigator's Brochure).

Despite the recent advances in the treatment of melanoma patients, overall outlook for patients with metastatic disease remains dismal and the development of new effective therapy is still needed. Particularly, the outlook for uveal melanoma remains especially grim. Anti-PD1 mAb nivolumab has reported a response rate of 28% in cutaneous melanoma patients (16). Pembrolizumab has shown a very promising early response rate of 42% in patients who have not received prior ipilimumab treatment, which is much higher than the 11 or 15% response rate observed in ipilimumab registration trials (17).

Uveal melanoma is an uncommon cancer occurring in 3000 patients per year in the United States. At the onset of advanced/metastatic disease, however, this condition has an especially poor prognosis without clearly effective treatment options. Preclinical rationale for use of pembrolizumab in this population is strong. Uveal melanoma cell lines express PD-L1, which predicts for response to therapy in cutaneous melanoma and in NSCLC (18). Uveal melanomas are heavily infiltrated with leukocytes, including CD8+ T cells, potentially indicating functional exhaustion of the immune response (19-21). Finally, although responses occur less frequently than in cutaneous melanoma, objective responses have been reported with ipilimumab in uveal melanoma (22, 23). Taken together, the existing data support the evaluation of the safety and efficacy of pembrolizumab in patients with uveal MEL for whom additional treatment options are needed.

1.2 SUMMARY OF TRIAL DESIGN

Patients will receive pembrolizumab at 200mg IV Q3W at a fixed dose. All patients with advanced uveal melanoma enrolled in the study will receive up to 24 months of pembrolizumab treatment until disease progression, unacceptable toxicity, the withdrawal of consent, confirmed complete response or they require another form of antineoplastic therapy as determined by the Investigator. In the event of a confirmed complete response (CR), it is at the discretion of the investigator to keep a patient on study treatment or to suspend study treatment based on the criteria outlined in section 5.2.3. Patients will continue to be monitored with scheduled disease assessments as described in the protocol (as if the patient were continuing on study treatment), and in the event of a disease recurrence, pembrolizumab may be resumed (Second Course treatment) upon disease recurrence in these patients. Second Course treatment with pembrolizumab may be given for up to 12 additional months. See Section 7.1.6.2 for details regarding second course treatment.

After receiving 24 months of treatment with pembrolizumab, patients with CR, PR or SD will no longer receive treatment with pembrolizumab and will complete the 30-Day Safety Follow Up visit and then proceed to the Post Treatment Follow up visits for up to an additional 48 months per the Flow Chart Section 6.1. At any point in the Post treatment follow up period, if a patient experiences disease progression they are eligible to receive the 12 month Second Course Treatment with pembrolizumab.

Patients who discontinue study treatment for reasons other than documented progression should continue to have CT imaging assessments per schedule as indicated in the Post-Treatment Discontinuation Follow-up per Section 6.0 of the Flow Chart. Patients will enter the survival follow-up phase after confirmed disease progression is documented.

2.0 TRIAL DESIGN

2.1 Trial Diagram

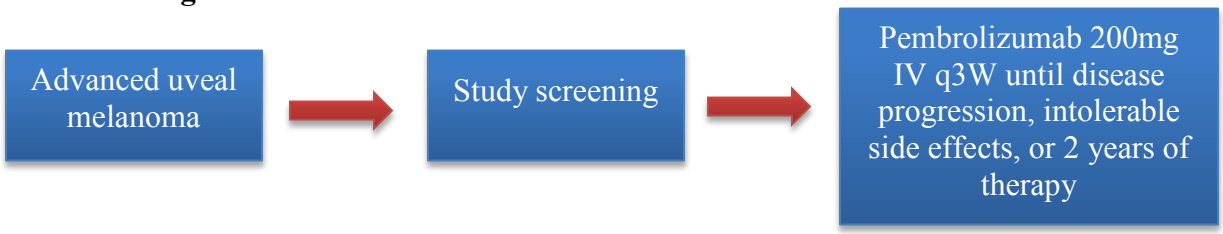

Figure 1: Study schema

2.2 Trial Design

2.2.1 Summary of Trial Design

This is an open-label, two stage, single arm pivotal study of intravenous (IV) pembrolizumab in patients with advanced or metastatic uveal melanoma. The primary endpoint of the study will be objective response rate (ORR). Other endpoints include progression-free survival (PFS), overall survival (OS), response duration, safety, and correlation of response rate with biomarkers (GNAQ/GNA11 mutational status, PD-L1 expression).

The study will enroll 10 patients in stage I of this two stage design; if one or more responses occur, an additional 19 patients will be enrolled. The sample size was designed to test whether pembrolizumab has a ≥20% response rate in uveal melanoma with a clinically uninteresting response rate of 5%. In addition, if ≥2 patients experience stable disease (SD) for >24 weeks, then the study may proceed to stage 2 if the sponsor and PIs are in agreement.

The primary objective of the study is to evaluate the activity of pembrolizumab in terms of ORR. The overall type I error rate for this study is strictly controlled at 5% (two-sided) and the study has a power of 80%. The study is considered to be positive if at least 4 patients treated with pembrolizumab have an objective response (of 29 subjects enrolled). All patients receiving pembrolizumab will receive pembrolizumab as IV infusion at a dose of 200mg every 3 weeks. until disease progression, intolerable toxicity, confirmed complete response,

withdrawal of consent, or they require another form of antineoplastic therapy as determined by the Investigator.

We anticipate an accrual rate of 1 to 2 patients per month from 3 participating centers.

After the baseline tumor evaluation, tumor assessment during the study will be performed by radiological scans every 6 weeks starting from Week 12 until Week 24. At the discretion of investigators, patients who remain on study after 24 weeks and are clinically stable may decrease imaging frequency to every 12 weeks in the following schedule:

• First scheduled disease assessment: week 12

• Disease assessments every 6 weeks from week 18-24

• Disease assessments every 12 weeks from week 36-96

Patients will be evaluated for tumor response and patient management by sites based on the Immune Related RECIST [irRECIST] criteria (Section 7.1.3.3) by the investigator with site radiology reading. Guidelines for irRECIST as described in section 7.1.3.3. On-study assessments by irRECIST take into account the observation that some patients with melanoma can have a transient tumor flare in the first few months after start of immunotherapy with subsequent disease response. Clinical decisions will be based on the interpretation of the investigator at the site treating the patient in real time using the irRECIST criteria.

All patients must have at least one baseline measurable lesion by RECIST 1.1 definition on CT or MRI (as assessed by investigators) (24). The timing for tumor assessments should be based on the calendar and not adjusted for delays or variation in cycle starts.

Patients will be monitored regularly for safety and efficacy throughout the study, as per Section 6.0, Study Flow Chart. Fresh tumor tissue or archived tumor tissue is required for biomarker analysis prior to randomization, then optional at specific timepoints during the study (see Sections 6.1).

2.2.2 DOSAGE/DOSAGE FORM, ROUTE, AND DOSE REGIMEN

All patients will receive pembrolizumab as an IV infusion at 200mg every 3 weeks for a total of 24 months or, until disease progression, intolerable toxicity, confirmed complete response, or withdrawal of the consent. Treatment must be administered within a window of (+/- 2 days) of the scheduled infusion. Patients who have a confirmed complete response by two scans ≥4 weeks apart and who have been on pembrolizumab treatment for at least 6 months may discontinue pembrolizumab treatment at the discretion of the investigator after receiving at least two doses beyond the initial determination of CR. Patients who stop study treatment in CR should continue to undergo disease evaluations with imaging studies as otherwise scheduled in the protocol, and in the event of disease recurrence, pembrolizumab may be resumed in these patients.

The second-course treatment is fully described in Sections 6.2 and 7.1.6.2.2, but in brief, patients should follow the same schedule of pembrolizumab treatment to which they were initially allocated and should be followed with study visits and disease assessments as if they were starting study therapy anew (first scheduled disease assessment at week 12 and then every 6 weeks until week 24). Patients who discontinue study therapy in the second course treatment phase for any reason (progression of disease, AEs, or any other reason) should have a post-study visit within 30 days and then undergo survival follow-up.

3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

3.1 Primary Objective(s) & Hypothesis(es)

(1) **Objective:** To evaluate objective response rate (ORR) in patients with advanced uveal melanoma receiving pembrolizumab.

Hypothesis: Pembrolizumab has a response rate of 20% (and >5%)

3.2 Secondary Objective(s) & Hypothesis(es)

(1) To evaluate progression-free survival (PFS) in patients with advanced uveal melanoma receiving pembrolizumab.

(2) To evaluate safety, tolerability and adverse experience profile of pembrolizumab in uveal melanoma.

(3) To evaluate overall survival (OS) in patients with advanced uveal melanoma receiving pembrolizumab.

3.3 Exploratory Objectives

(1) To evaluate objective response rate (ORR; complete response + partial response)) in patients with advanced uveal melanoma receiving pembrolizumab as stratified by PD-L1 expression and GNAQ/GNA11 mutation status.

(2) To evaluate ORR in patients previously treated with ipilimumab or with MEK inhibitors.

4.0 BACKGROUND & RATIONALE

4.1 Background

4.1.1 Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades [1]. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies (25-29). In particular, the presence of CD8+ T-cells and the ratio of

CD8+ effector T-cells / FoxP3+ regulatory T-cells seems to correlate with improved prognosis and long-term survival in many solid tumors.

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an Ig superfamily member related to CD28 and CTLA-4 which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) (7, 30). The structure of murine PD-1 has been resolved (31). 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 (31-35). 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 (5, 36). 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 (37, 38). Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells (39). 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 (1-5). 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 (5). 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) (9). This suggests that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention.

Pembrolizumab (MK-3475; previously known as SCH 900475) is a potent and highly selective humanized monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Both pembrolizumab and MDX-1106 contain the S228P stabilizing mutation and have no antibody-dependent cell-mediated cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC) activity. Pembrolizumab strongly enhances T lymphocyte immune

responses in cultured blood cells from healthy human donors, cancer patients, and primates. In T- cell activation assays using human donor blood cells, the EC50 was in the range of 0.1 to 0.3 nM. Pembrolizumab also modulates the level of interleukin-2 (IL-2), tumor necrosis factor alpha (TNFα), interferon gamma (IFNγ), and other cytokines. The antibody potentiates existing immune responses only in the presence of antigen and does not nonspecifically activate T- cells. A one-month repeat dose GLP-toxicity study with four months observation post dosing revealed no major safety findings. The no observed adverse event level (NOAEL) was ≥200 mg/kg. (For details on the pre-clinical data of pembrolizumab, see the IB).

4.1.2 Preclinical and Clinical Trial D

Therapeutic studies in mouse models have shown that administration of antibodies blocking PD-1/PD-L1 interaction enhances infiltration of tumor-specific CD8+ T-cells and leads ultimately to tumor rejection, either as a mono-therapy or in combination with other treatment modalities. Anti-mouse PD-1 or anti-mouse PD-L1 antibodies have demonstrated anti-tumor responses as a mono-therapy in models of squamous cell carcinoma, pancreatic carcinoma, MEL and colorectal carcinoma. Blockade of the PD-1 pathway effectively promoted CD8+ T-cell infiltration into the tumor and the presence of IFN-γ, granzyme B and perforin, indicating that the mechanism of action involved local infiltration and activation of effector T-cell function in vivo (7, 11, 12, 14, 15). In addition, the combination of gemcitabine and anti-PD-L1 mAb demonstrated synergy in the rejection of pancreatic mouse tumors (7). In-house experiments have confirmed the in vivo efficacy of PD-1 blockade as a mono-therapy as well as in combination with chemotherapy in syngeneic mouse tumor models (see the investigator's brochure).

Melanoma is the sixth most common malignancy in men and the seventh most common malignancy in women (40). The incidence of melanoma is increasing worldwide, with a growing fraction of patients with advanced disease for which prognosis remains poor. The median survival for patients with metastatic melanoma has traditionally been under 1 year; the 5-year survival rate of patients with visceral involvement has been under 10% (41). Treatment options for metastatic melanoma have been limited to chemotherapeutic agents such as dacarbazine and high-dose interleukin-2 immunotherapy in a small percentage of patients. In the past few years there has been steady progress in the development of targeted therapy and immunotherapy for metastatic melanoma. Vemurafenib, a BRAF inhibitor, was approved in 2011 for the treatment of patients with unresectable or metastatic melanoma with $BRAF^{V600E}$ mutation (42). Ipilimumab, an anti-CTLA4 monoclonal antibody, was also approved in 2011 for the treatment of patients with unresectable or metastatic melanoma (43). In spite of these newly approved therapies, overall outlook for patients with metastatic melanoma remains dismal and the development of new effective therapy is still needed. Of note, the recently developed therapeutics for cutaneous melanoma have largely not translated to benefits for patients with uveal melanoma; effective therapies for this cohort are urgently needed.

4.1.2.1 Clinical Efficacy

4.1.2.1.1 Clinical Efficacy in Melanoma

For more details, please see investigator's brochure for pembrolizumab. In trial PN001, patients with non-uveal melanoma were treated with pembrolizumab. Preliminary analysis was stratified by whether patients had previously received ipilimumab. The overall response rate using IRO by RECIST v1.1 is very similar to the overall response rate using Investigator Assessment by irRC in the IPI-exposed melanoma patients, 24.9% and 27.1 % respectively (17). In the ipilimumab-naïve melanoma patients the overall response rate using an IRO assessment by RECIST was 38.7% (95% CI 31.3%, 46.5%). The response rates were similar in the 2 mg/kg Q3W (35.4%: 95% CI 23.9%, 48.2%) and 10 mg/kg Q3W (36.4%; 95% CI 24.9%, 49.1%) dose schedules in sample sizes of 65 and 66 patients, respectively. A higher overall response rate was noted in the 10 mg/kg Q2W dose schedule (48.6%; 95% CI 31.9%, 65.6%) in a smaller sample of 37 patients.

The median PFS and the PFS rate at 24-Weeks based on IRO Assessment per RECIST across all doses were 17.9 weeks (95% CI 13.3 weeks, 24.0 weeks) and 41.7 %, respectively. The median PFS and the PFS rates at 24-Weeks are similar in the 2 mg/kg Q3W (median PFS 22.1 weeks (95% CI 12.1 weeks, 31.0 weeks) and 43.7%) and 10 mg/kg Q3W (median PFS 14.4 weeks (95% CI 12.1 weeks, 23.9 weeks) and 36.4%) dose schedules in samples of 89 and 116 patients, respectively. A higher median PFS and PFS rate at 24-Weeks were noted in the 10 mg/kg Q2W dose schedule (median PFS not reached (95% CI 11.6 weeks, -) and 66.7%) in a smaller sample of 16 patients. The median PFS and the PFS rate at 24-Weeks based on Investigator Assessment per irRC across all doses were 29.7 weeks (95% CI 23.6 weeks, 54.0 weeks) and 54.7%, which are slightly higher than the rates using IRO per RECIST.

4.1.2.1.2 Clinical Efficacy in NSCLC

MK-3475 PN001 Part C enrolled 38 patients with NSCLC who experienced progression of cancer after initiation of their second line of systemic therapy to receive pembrolizumab monotherapy. The preliminary objective response rate (ORR) by investigator assessed irRC was 24% (95% CI 11%, 40%); by RECIST v1.1; the objective response rate was 21% (95% CI 9%, 39%). Preliminary median overall survival was 51 weeks (95% CI 14 weeks, -). Preliminary median progression free survival amongst responders has not yet been reached with a minimum of 62 weeks, with most patients remaining on treatment.

Patients were required to submit a newly obtained tumor biopsy prior to initiating therapy with MK-3475 to evaluate the tumors for expression of PD-L1, the presumptive predictive biomarker of MK-3475, using an immunohistochemistry assay. A modified H-score scoring system of PD-L1 expression was established for NSCLC by analyzing tumor specimens from resected NSCLC specimens. This scoring system was then applied to the samples from PN001 Part C. A receiver-operating characteristics curve was constructed from the data and the Youden Index identified from that analysis to help determine a preliminary cut point. Preliminary data suggest higher levels of PD-L1 expression are associated with increased

activity (ORR in patients with tumor PD-L1 expression above a preliminary cutoff was 67% (95% CI 30%, 93%)); additional data are required to define the optimal PD-L1 cut point.

4.1.2.2 Clinical Safety

Among all melanoma patients treated in study PN001, adverse events were reported in 400 (97.3%) out of 411 patients. The most commonly reported treatment emergent AEs experieced in this population across the dose regimens are fatigue (43.6%), nausea (27.5%), cough (26.0%), pruritus (25.1%), diarrhea (24.1%) and rash (22.4%). There was not a significant difference in the most common terms reported across dose schedules.

Among 135 melanoma patients with published efficacy and safety data from PN001, pneumonitis was observed in 4% of patients; none were grade 3-4 (17). In contrast to ipilimumab, only one case of grade 3 diarrhea was observed which resolved with corticosteroids. Other grade 3-4 events included aminotransferase elevations (1%), renal failure (2%), and rash (2%). Eight percent developed hypothyroidism which was managed with thyroid replacement; one patient developed grade 2 adrenal insufficiency. Vitiligo occurred in 9% of patients. Other low-grade toxicities included fatigue, asthenia, myalgias, rash, headaches, and fevers.

See section 5.6 for management of adverse events.

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

Uveal melanoma is the most common primary intraocular malignancy in adults, and arises from melanocytes within the choroid plexus of the eye (44). Melanomas of the ocular and adnexal structures comprise approximately 5% of all melanomas and are biologically and prognostically distinct from cutaneous melanoma (45). In the United States, an estimated 3000 patients are diagnosed with this disease each year. Although uveal melanoma is an uncommon disease, the lack of effective treatment options and poor prognosis makes this condition ideal for developing novel therapeutic strategies. Selumetinib, a selective MEK1/2 inhibitor, demonstrated improved PFS compared to cytotoxic chemotherapy although median survival remained less than one year. Additionally, ipilimumab and chemotherapy may be used although outcomes remain poor. More effective therapies are urgently needed.

In addition to the high response rate of pembrolizumab in non-uveal melanoma, other preclinical and clinical rationale suggests that anti-PD-1 therapy is a promising strategy in uveal melanoma. First, uveal melanoma is associated with an inflammatory phenotype. The majority of uveal melanoma have high levels of tumor infiltrating lymphocytes (TILs) present that co-occur with unfavorable prognostic markers (46). A wide array of leukocytes are present in the tumor microenvironment, including $CD8^+$, $CD4^+$, and regulatory T cells, natural killer cells, and macrophages, potentially indicating functional exhaustion of the antitumor immune response (19-21). This inflammatory infiltrate in the tumor microenvironment may be exploited with immune stimulation as an effective therapeutic

strategy in uveal melanoma. Second, uveal melanoma cell lines demonstrate PD-L1 expression. In a group of metastasis cultures of uveal melanoma cell lines, nearly all lines demonstrated PD-L1 expression which was further augmented with interferon-γ stimulation (11). Although very few patients with uveal melanoma have been treated with anti-PD-1 therapies or have been assessed for PD-L1 expression, this suggests that the PD-1/PD-L1 axis may be a functionally relevant mechanism of immune evasion in uveal melanoma. Third, to evaluate the functional consequences of PD-1 blockade, uveal melanoma cell lines were grown in culture with CD3+ T cells (12). In IFN-γ stimulated cell lines, the addition of anti-PD-1 caused a T cell activation and significant increase in IL-2 production by the CD3+ T cells. Additionally, T-cell activation was found to be promoted by RNA interference of PD-L1 in a co-cultured uveal melanoma cell line with CD3+ T cells (13). Fourth, early phase studies have suggested that PD-L1 expression correlates with response to anti-PD-1/PD-L1, even in cancers other than melanoma, lung cancer, and renal cell carcinoma. (16, 47, 48). Based on cell line experiments, at least a subset of uveal melanomas would be predicted to express PD-L1, potentially predicting benefit from pembrolizumab. Finally, ipilimumab has demonstrated benefit in patients with uveal melanoma. In a retrospective review 39 patients with metastatic uveal melanoma were treated with ipilimumab. ORR by IrRC was 5.4% with one complete response and one partial response. An additional 28% of patients demonstrated stable disease at 23 weeks demonstrating that immune checkpoint inhibition may be an effective therapeutic strategy in uveal melanoma (16).

4.2.2 Rationale for Dose Selection/Regimen/Modification

In the first-in-human study (PN001, refer to IB), pembrolizumab 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). PK data analysis of pembrolizumab administered in Q2W 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 Q2W and Q3W dosing schedules. As such, Phase I expansion cohorts of PN001 enrolled patients at Q2W and Q3W dosing schedules. A recent interim analysis from PN001 was conducted to inform the dose decision for this protocol. PN001 enrolled expansion cohorts with advanced melanoma that are naïve to ipilimumab or previously treated with ipilimumab and treated patients on three different dosing regimens of pembrolizumab: 2 mg/kg every 3 weeks, 10 mg/kg every 3 weeks, and 10 mg/kg every 2 weeks. One of the key clinical findings from this analysis suggests that there are not major differences in the AE profile or overall objective response rate from pembrolizumab when given on an every 3 week schedule at doses of 2 mg/kg or 10 mg/kg. In cohorts of patients who had follow-up of at least 6 months duration (n=46 ipi-naïve patients), the objective response rate was 36% on the Q3W schedules, based on independent central review of imaging studies (confirmed and unconfirmed responses) in the patients who had at least one measurable lesion at baseline. The treatment was well tolerated on the Q3W doses with few SAEs or AEs leading to discontinuation that were attributed to study treatment.

Another key clinical finding of this analysis was a suggestion that a more frequent schedule of pembrolizumab administration may lead to higher efficacy, but at the expense of more AEs. Patients who received pembrolizumab at a Q2W schedule, regardless of prior treatment with IPI (n=57) had an overall objective response rate of 56% based on independent central review of imaging studies (confirmed and unconfirmed responses) in patients who had at least one measurable lesion at baseline. In addition, 9 patients (17%) were reported to have achieved an (unconfirmed) complete remission. Furthermore, progression free survival for patients treated with 10 mg/kg given every 2 or every 3 weeks was evaluated, and showed an overall median PFS of 61 weeks for patients who received pembrolizumab on an every 2 week schedule and 29 weeks for patients who received pembrolizumab on an every 3 week schedule (pooled ipi-naïve and ipi-treated cohorts). However, it is important to note that these were not randomized cohorts of patients which precludes drawing firm conclusions about the differences in response rate between the two doses. In addition, AEs were somewhat more frequent and more severe on the more frequent dosing schedule. For example, grade 3 or higher AEs were reported in 44% of patients receiving 10 mg/kg Q2W and 30% of patients receiving 10 mg/kg Q3W, SAEs were reported in 49% and 39% (Q2W and Q3W respectively), and AEs leading to treatment discontinuation attributed to study treatment were reported in 14% and 7% (Q2W and Q3W, respectively). Thus, while both pembrolizumab schedules are generally tolerable, there may be a higher frequency of clinically important AEs as well as a higher objective response rate when pembrolizumab is given every 2 weeks compared to every 3 weeks.

An open-label Phase I trial (Protocol 001) is being conducted to evaluate the safety and clinical activity of single agent MK-3475. The dose escalation portion of this trial evaluated three dose levels, 1 mg/kg, 3 mg/kg, and 10 mg/kg, administered every 2 weeks (Q2W) in subjects with advanced solid tumors. All three dose levels were well tolerated and no dose-limiting toxicities were observed. This first in human study of MK-3475 showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels (1 mg/kg, 3 mg/kg and 10 mg/kg Q2W). 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 [43].

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.

4.2.3 Rationale for Endpoints

4.2.3.1 Efficacy Endpoints

The primary endpoint for this study is ORR, with the hypothesis that the ORR will be approximately 20% (and >5%) in patients with uveal melanoma. This ORR was chosen in that currently no effective therapies are approved for uveal melanoma and therefore an ORR in the 20% range would be highly desirable clinically. In addition, for the immune therapies, including anti-PD-1, patients who experience objective responses often have durable benefit and superior PFS and OS. Particularly for a phase II trial, therefore, ORR is an appropriate primary endpoint.

PFS and OS will also be assessed as secondary endpoints. These metrics are clearly clinically relevant although the study is not powered to assess these endpoints.

4.2.3.2 Biomarker Research

To assess whether common genetic and protein expression characteristics in uveal melanoma correlate with ORR, we will assess *GNAQ*/*GNA11* mutation status on each patient per institutional protocol. We will furthermore evaluate PD-L1 expression status on archival or fresh tissue from all patients and correlate with ORR.

This study will also investigate other molecular characteristics of uveal melanoma when treated with pembrolizumab. Analysis will focus on tumor and blood markers prior to therapy and early-on-treatment (at the time of the second dose).

Strongly encouraged tumor biopsies may also be performed to allow for assessment of the pharmacodynamics effects of pembrolizumab treatment. Such biopsies may be performed within 21 days of the start of treatment, and on Cycle 2 Day 1 (+/- 3 days). Assessment of these samples will include, but are not limited to, changes in lymphocyte profile in the tumor and blood.

Blood samples (2X 10 ml) will be collected as indicted in the Time and Events Table (see Section 7.1). Blood will be processed to isolate both PBMCs and serum for future biomarker analyses at the conclusion of the study, as to be determined by the investigators based on the

state of knowledge at that time, and available molecular analysis platforms. Possible analyses include, but are not limited to, immune cell populations, circulating free DNA (cfDNA), circulating miRNA, and proteins/cytokines.

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

Histologic confirmation of advanced (metastatic or unresectable) uveal melanoma. If uveal melanoma has been diagnosed clinically and/or by gene expression profiling, patients may be included following discussion with the principal investigator.

5.1.2 Enrollment Procedures

All patients MUST be registered with the [redacted] rior to the start of protocol treatment. Each participating site must also be registered with their own institution according to their institutional guidelines prior to start of protocol treatment. Prior to the first patient registration, a copy of IRB approval at the respective sites will be requested and on file at the VICC Coordinating Center.

[redacted]

- Copy of the patient's signed and dated Informed Consent
- Eligibility Checklist

5.1.3 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. Histologic confirmation of advanced (metastatic or unresectable) uveal melanoma. If uveal melanoma has been diagnosed clinically and/or by gene expression profiling, patients may be included following discussion with the principal investigator.
5. Have provided tissue from an archival tissue sample or newly obtained core or excisional biopsy of a tumor lesion.

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

7. 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
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
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.	

8. 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.

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

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

5.1.4 Subject Exclusion Criteria

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

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

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

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

4. Has had prior chemotherapy, targeted small molecule therapy, or 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.

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

6. 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), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to trial treatment.

7. Has an active automimmune disease requiring systemic treatment within the past 3 months or a documented history of clinically severe autoimmune disease, or a syndrome that requires systemic steroids or immunosuppressive agents. Subjects with vitiligo or resolved childhood asthma/atopy would be an exception to this rule. Subjects that require intermittent use of bronchodilators or local steroid injections would not be excluded from the study. Subjects with hypothyroidism stable on hormone replacement or Sjorgen's syndrome will not be excluded from the study.

8. Has evidence of interstitial lung disease or active, non-infectious pneumonitis.

9. Has an active infection requiring systemic therapy.

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

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

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

13. Has received prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, or anti-CD137. Patients who received anti-CTLA4 (ipilimumab, tremelimumab) will NOT be excluded and are eligible for inclusion.

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

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

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

5.2 Trial Treatments

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

Table 2 Trial Treatment

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period	Use
MK-3475	200mg	Q3 weeks	IV infusion	2 years	Experimental
The MK-3475 dosing interval may be increased due to toxicity as described in Section 5.2.1.2.					

5.2.1 Dose Selection/Modification

5.2.1.1 Dose Selection

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

The dose amount will be 200mg given intravenously every 3 weeks.

5.2.1.2 Dose Modification

Pembrolizumab will be withheld for drug-related Grade 4 hematologic toxicities, non-hematological toxicity ≥ Grade 3 including laboratory abnormalities, and severe or life-threatening AEs as per Table 3 below.

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

Toxicity	Grade	Hold Treatment (Y/N)	Timing for restarting treatment	Dose/Schedule for restarting treatment	Discontinue Subject (after consultation with Sponsor)
Hematological Toxicity	1, 2, 3	No	N/A	N/A	N/A
	4	Yes	Toxicity resolves to Grade 0-1 or baseline	May increase the dosing interval by 1 week	Toxicity does not resolve within 12 weeks of last infusion *Permanent discontinuation should be considered for any severe or life-threatening event*
Non-hematological toxicity Note: Exception to be treated similar to grade 1 toxicity • Grade 2 alopecia • Grade 2 fatigue For additional information regarding Adverse Events with a potential Immune-Etiology reference Section **5.6.1.1**.	1	No	N/A	N/A	N/A
	2	Consider withholding for persistent symptoms	Toxicity resolves to Grade 0-1 or baseline	*Clinical AE resolves within 4 weeks*: Same dose and schedule (reference **Section 5.6.1.2** for recommendations regarding pneumonitis) *Clinical AE does not resolve within 4 weeks:* May increase the dosing interval by 1 week for each occurrence	Toxicity does not resolve within 12 weeks of last infusion

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

In case toxicity does not resolve to Grade 0-1 within 12 weeks after last infusion, trial treatment should be discontinued after consultation with the Sponsor. With investigator and Sponsor agreement, subjects with a laboratory adverse event still at Grade 2 after 12 weeks may continue treatment in the trial only if asymptomatic and controlled. For information on the management of adverse events, see Section 5.6.1.

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

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

5.2.3 Duration of Therapy

Pembrolizumab will be administered every 3 weeks until one of the following occurs:

- Confirmed radiographic disease progression

- Indications for subject discontinuation from the trial as outlined in section 5.8
- Treatment for 24 months
- Confirmed complete response (CR)

In the event of a confirmed complete response (CR), it is at the discretion of the investigator to keep a patient on study treatment or to suspend study treatment based on the criteria.

- Radiographic CR as defined by RECIST criteria
- Confirmation with repeat imaging at least 4 weeks after the initial imaging

Patients will continue to be monitored with scheduled disease assessments as described in the protocol (as if the patient were continuing on study treatment), and in the event of a disease recurrence, pembrolizumab may be resumed (Second Course treatment) upon disease recurrence in these patients. Second Course treatment with pembrolizumab may be given for up to 12 additional months.

5.2.4 Trial Blinding/Masking

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

5.3 Randomization or Treatment Allocation

All patients will receive pembrolizumab 200mg IV q3W. There is no randomization in this study.

5.4 Stratification

No treatment stratification will be performed. Pre-planned analyses will evaluate response rate and PFS by expression of PD-L1 by immunohistochemistry (positive vs. negative) and by *GNAQ*/*GNA11* mutation status.

5.5 Concomitant Medications/Vaccinations (allowed & prohibited)

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

5.5.1 Acceptable Concomitant Medications

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

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

5.5.2 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:

- Anti-cancer 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 after consultation with Sponsor.
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however intranasal influenza vaccines (e.g. Flu-Mist®) are live attenuated vaccines, and are not allowed.

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

5.6 Rescue Medications & Supportive Care

5.6.1 Supportive Care Guidelines

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

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

    - In subjects with severe enterocolitis (Grade 3), pembrolizumab will be permanently discontinued and treatment with systemic corticosteroids should be initiated at a dose of 1 to 2 mg/kg/day of prednisone or equivalent. When symptoms improve to Grade 1 or less, corticosteroid taper should be started and continued over at least 1 month.

    - In subjects with moderate enterocolitis (Grade 2), pembrolizumab should be withheld and anti-diarrheal treatment should be started. If symptoms are persistent for more than one week, systemic corticosteroids should be initiated (e.g., 0.5 mg/kg/day of prednisone or equivalent). When symptoms improve to Grade 1 or less, corticosteroid taper should be started and continued over at least 1 month. Regarding guidelines for continuing treatment with pembrolizumab see Section 5.2.1.2.

    - All subjects who experience diarrhea should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.

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

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

- Immune-related adverse events: Please see Section 5.6.1.1 below and the separate guidance document in the administrative binder regarding diagnosis and management of adverse experiences of a potential immunologic etiology.

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

Table 5 below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of pembrolizumab.

Table 5 Infusion Reaction Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs	**Stop Infusion and monitor symptoms.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g. from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. **Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.**	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of MK-3475 with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids	No subsequent dosing

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
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	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.**	
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration. For Further information, please refer to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE) at http://ctep.cancer.gov		

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

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

If an irAE is suspected, efforts should be made to rule out neoplastic, infectious, metabolic, toxin or other etiologic causes prior to labeling an adverse event as an irAE.

Recommendations to managing irAEs not detailed elsewhere in the protocol are detailed in Table 6.

Table 6 General Approach to Handling irAEs

irAE	Withhold/Discontinue pembrolizumab?	Supportive Care
Grade 1	No action	Provide symptomatic treatment
Grade 2	May withhold pembrolizumab	Consider systemic corticosteroids in addition to appropriate symptomatic treatment
Grade 3 and Grade 4	Withhold pembrolizumab Discontinue if unable to reduce corticosteroid dose to <	Systemic corticosteroids are indicated in addition to appropriate symptomatic treatment. May utilize 1 to 2 mg/kg prednisone or equivalent per day.

	10 mg per day prednisone equivalent within 12 weeks of toxicity	Steroid taper should be considered once symptoms improve to Grade 1 or less and tapered over at least 4 weeks.

5.6.1.2 Supportive Care Guidelines for Pneumonitis

Subjects with symptomatic pneumonitis should immediately stop receiving pembrolizumab and have an evaluation. The evaluation may include bronchoscopy and pulmonary function tests to rule out other causes such as infection. If the subject is determined to have study drug associated pneumonitis, the suggested treatment plan is detailed in Table 7.

Table 7 Recommended Approach to Handling Pneumonitis

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

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

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

5.7 Diet/Activity/Other Considerations

5.7.1 Diet

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

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

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

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study they must adhere to the contraception requirement (described above) for the duration of the study and during the follow-up period defined in section 7.2.2-Reporting of Pregnancy and Lactation to the Sponsor and to Merck. If there is any question that a subject will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

5.7.3 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 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.

5.7.4 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.

5.8 Subject Withdrawal/Discontinuation Criteria

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

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

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

  Note: For unconfirmed radiographic disease progression in the absence of clinical deterioration, patients may continue on study.
- 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 treatment with pembrolizumab

  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 7.1.2.6.
- Administrative reasons

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

each subject will be followed by telephone for overall survival until death, withdrawal of consent, or the end of the study, whichever occurs first.

5.9 Subject Replacement Strategy

If a patient withdraws consent or dies prior to receiving the first dose of pembrolizumab, an additional patient will be enrolled.

5.10 Clinical Criteria for Early Trial Termination

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

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

2. Poor adherence to protocol and regulatory requirements

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

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

5. Lack of efficacy as defined by no responses in the first 10 patients AND <2 patients with stable disease at 24 weeks.

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.

6.0 TRIAL FLOW CHART

6.1 Study Flow Chart

Trial Period:	**Screening Phase**	**Treatment Cycles**									**End of Treatment**	**Post-Treatment**		
							Repeat every 12 weeks							
Treatment Cycle/Title:	Screening Visit	1	2	3	4	5	6	7	8	9	Discontinuation	Safety Follow-up[16]	Follow Up Visits[17]	Survival Follow-Up[18]
Week (approximate)		0	3	6	9	12	15	18	21	24				
Scheduling Window (Days)[2]:	-28 to -1 days		± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days post discon	Every 12 weeks post discon	Every 12 weeks
Administrative Procedures														
Informed Consent[2]	X													
Inclusion/Exclusion Criteria	X													
Demographics and Medical History and Prior Medications[3]	X													
Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	X			
Post-study anticancer therapy status												X	X	X
Survival Status												X	X	X
Clinical Procedures/Assessments														
Review Adverse Events[4]		X	X	X	X	X	X	X	X	X	X	X	X	
Physical Examination	X	X	X	X	X	X	X	X	X	X	X	X	X	

Trial Period:	**Screening Phase**	**Treatment Cycles**									**End of Treatment**	**Post-Treatment**		
							Repeat every 12 weeks							
Treatment Cycle/Title:	Screening Visit	1	2	3	4	5	6	7	8	9	Discontinuation	Safety Follow-up[16]	Follow Up Visits[17]	Survival Follow-Up[18]
Optional Eye Exam[19]	X					X					X			
Vital Signs and Weight[5]	X	X	X	X	X	X	X	X	X	X	X	X	X	
ECOG Performance Status	X	X	X	X	X	X	X	X	X	X	X	X	X	
12-Lead EKG	X													
Pembrolizumab Administration (30 Minute Infusion)		X	X	X	X	X	X	X	X	X				
Laboratory Procedures/Assessments: analysis performed by LOCAL laboratory														
Pregnancy Test – Urine or Serum β-HCG[8]	X													
Hepatitis B/C Screening[7]	X													
PT/INR and aPTT[9]	X											X		
CBC with Differential[10]	X[10]		X	X	X	X	X	X	X	X	X	X	X	
Comprehensive Serum Chemistry Panel	X[10]		X	X	X	X	X	X	X	X	X	X	X	
T3, FT4 and TSH	X[11]		X	X	X	X		X		X	X		X	
Efficacy Measurements														
Tumor Imaging[12]	X					X		X[15]		X			X	

Trial Period:	Screening Phase	Treatment Cycles									End of Treatment	Post-Treatment		
							Repeat every 12 weeks							
Treatment Cycle/Title:	Screening Visit	1	2	3	4	5	6	7	8	9	Discontinuation	Safety Follow-up[16]	Follow Up Visits[17]	Survival Follow-Up[18]
Tumor Biopsies/Archival Tissue Collection/Correlative Studies Blood														
Archival or Newly Obtained Tissue Collection[13]	X		X								X			
Correlative Studies Blood Collection[14]	X		X								X			

1 Routine laboratory tests (serum chemistry; hematology) for screening should be performed within 10 days of enrollment.
2 Written consent must be obtained prior to performing any protocol specific procedure. Results of a test performed as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame (e.g. within 28 days prior to Cycle 1, Day 1). Assign Baseline number when the study informed consent is signed.
3 Includes history of treatment for the primary diagnosis, including prior systemic, radiation treatment and surgical treatment, and best response to prior systemic treatments. Date of last prior cancer treatment must be documented. Radiographic studies performed prior to study entry may be collected for review by the investigator. Report complete medication history for 30 days prior to the screening visit (Visit 1).
4 Adverse experiences and laboratory safety measurements will be graded per NCI CTCAE version 4.0. All adverse experiences, whether gradable by CTCAE or not, will also be evaluated for seriousness.
5 Vital signs to include temperature, pulse, respiratory rate and blood pressure. If a patient's baseline weight does not fluctuate by more than 10%, this weight can be used to calculate dose.
6 Electrocardiogram (12-lead ECG) should be performed at Screening.
7 Testing will be performed by the local laboratory at Screening: Hepatitis B and C serologies should be obtained for patients without a known history of hepatitis B or C. Those with a known history are ineligible. Include HCV RNA (qualitative), HBsAg. See Appendix 6.3 for list of laboratory tests.
8 For women of reproductive potential, a urine pregnancy test will be performed within 72 hours of the first dose. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required.
9 PT/INR and aPTT should be collected at Screening and at the mandatory Safety Follow-up Visit after discontinuation of study therapy. Coagulation parameters should be determined throughout the study if clinically indicated. PT/INR and aPTT will be analyzed by the local study site laboratory.
10 Routine laboratory tests (e.g., CBC with differential; comprehensive serum chemistry panel) will be performed by the local study site laboratory or their contract laboratory.
11 Following Cycle 4, TSH, T3, and T4 testing will be performed every other cycle.
12 Tumor imaging will be performed within 30 days prior to enrollment. CT scans are the required modality for measureable disease unless a patient has a clinical condition e.g. severe contrast allergy, or the lesions are significantly better visualized through the use of an MRI. The same imaging technique has to be used in a patient throughout the study. Patients with an objective response should have repeat imaging at least 4 weeks later to confirm the objective

Trial Period:	**Screening Phase**	**Treatment Cycles**									**End of Treatment**	**Post-Treatment**		
							Repeat every 12 weeks							
Treatment Cycle/Title:	Screening Visit	1	2	3	4	5	6	7	8	9	Discontinuation	Safety Follow-up[16]	Follow Up Visits[17]	Survival Follow-Up[18]

response. In addition, patients with progressive disease should undergo a second scan at least 4 weeks later to confirm progression and exclude the possibility of a tumor flare reaction, according to irRECIST guidelines (see Section 7.1.3.3). Response status will be assessed by the investigator. Tumor imaging will be performed every 6 weeks starting at Week 12 through Week 24. Following Week 24, tumor imaging may be performed approximately every 12 weeks (or whenever clinically indicated) while the patient remains on study therapy at the discretion of the investigator (Weeks 36, 48, 60, 72, 84, 96). Timing of imaging scans should follow the calendar and not be adjusted for treatment delays.

13 A newly obtained biopsy sample of at least one tumor lesion or acceptable archival tissue prior to therapy start is required in all patients for PD-L1 evaluation. PD-L1 status must be assessed, and if the tumor biopsy submitted is inadequate for determination of PD-L1 status by immunohistochemistry at a central pathology laboratory, a repeat biopsy is encouraged. If a biopsy at baseline is not judged to be safe by the investigator, this requirement will be waived. Additional biopsy samples approximately at Week 3 and at disease progression are highly desirable when it is feasible. The tissue sample should have proper size to enable multiple planned biomarker analyses, and fine needle aspiration will not be acceptable. The biopsy techniques allowed in the study include core needle biopsies or surgical biopsies. Study sites should use the same biopsy techniques in this study as they routinely use for a given tumor lesion/location. Detailed instructions for tissue collection, processing and shipment are provided in section 8.2.1.

14 Informed consent for future biomedical research samples must be obtained before the DNA sample. DNA sample for analysis should be obtained predose, on Day 1 (or with the next scheduled blood draw), as the last sample drawn, on randomized subjects only, or at a later date as soon as the informed consent is obtained. 20mL in two 10mL sodium heparin tubes will be collected at each time point.

15 Tumor imaging should be performed at week 18 and week 24 but should be repeated only every 12 weeks thereafter or as clinically indicated.

16 **PLEASE NOTE-** This visit is to be completed within 3 weeks of a patient experiencing disease progression, intolerable toxicity or withdrawal of consent. **For Imaging Only-** If a scan has been performed within 6 weeks of this visit, the site does not need to repeat the scan.

17 If subjects discontinue therapy for reasons other than disease progression, they should be followed in the clinic every 3 months with surveillance studies as indicated until completion of the study. At the time of subsequent progression, if Second Cycle Treatment is not pursued, then subjects should be followed by phone contact every 3 months

18 If subjects discontinue therapy for disease progression, they should be followed by for overall survival by phone contact every 3 months until completion of the study

19 On-treatment eye exam may be performed up to 3 weeks after cycle 5.

6.2 Second Course Treatment Flow Chart

Second Course Treatment Pembrolizumab									
Trial Period:	**Treatment Cycles**								
						To be repeated every 12 weeks			
Treatment Cycle/Title:	1	2	3	4	5	6	7	8	9
Week (approximate)	0	3	6	9	12	15	18	21	24
Scheduling Window (Days)[2]:		± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3
Eligibility Criteria[1]	X								
Concomitant Medication Review	X	X	X	X	X	X	X	X	X
Survival Status	X	X	X	X	X	X	X	X	X
Review Adverse Events[3]	X	X	X	X	X	X	X	X	X
Physical Examination	X	X	X	X	X	X	X	X	X

Second Course Treatment Pembrolizumab									
Trial Period:	**Treatment Cycles**								
						To be repeated every 12 weeks			
Treatment Cycle/Title:	1	2	3	4	5	6	7	8	9
Vital Signs and Weight[2]	X	X	X	X	X	X	X	X	X
ECOG Performance Status	X	X	X	X	X	X	X	X	X
Pembrolizumab Administration (30 Minute Infusion)	X	X	X	X	X	X	X	X	X
Pregnancy Test – Urine or Serum β-HCG[8]	X								
PT/INR and aPTT[5]	X								
CBC with Differential[10]	X	X	X	X	X	X	X	X	X
Comprehensive Serum Chemistry Panel[4]	X	X	X	X	X	X	X	X	X
T3, FT4 and TSH[7]	X	X	X	X				X	X
Tumor Imaging[8]	X				X			X[9]	X
Correlative Studies Blood Collection	X	X							
1 Patients who attain a CR, PR or SD at 24 months and discontinue treatment may restart trial treatment if they meet									

Second Course Treatment Pembrolizumab									
Trial Period:	**Treatment Cycles**								
						To be repeated every 12 weeks			
Treatment Cycle/Title:	1	2	3	4	5	6	7	8	9

the criteria specified in Section 7.1.2.5
2 Vital signs to include temperature, pulse, respiratory rate and blood pressure.
3 Adverse experiences and laboratory safety measurements will be graded per NCI CTCAE version 4.0. All adverse experiences, whether gradable by CTCAE or not, will also be evaluated for seriousness.
4 Laboratory tests for screening or entry into the Second Course Phase should be performed within 10 days prior to the first dose of treatment. Routine laboratory tests (e.g., CBC with differential; comprehensive serum chemistry panel; urinalysis) will be performed by the local study site laboratory or their contract laboratory.
5 PT/INR and aPTT should be collected at Cycle 1 and at the mandatory Safety Follow-up Visit after discontinuation of study therapy. Coagulation parameters should be determined throughout the study when clinically indicated. PT/INR and aPTT will be analyzed by the local study site laboratory.
6 For women of reproductive potential, a urine pregnancy test will be performed within 72 hours of the first dose. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required. .
7 Following Cycle 4, testing will be performed every third cycle.
8 Tumor imaging will be performed within 28 days prior to restarting with pembrolizumab after relapse from CR, PR or SD. The same imaging technique has to be used in a patient throughout the study. If a retreated patient has a response or progression, repeat imaging is required approximately 4 weeks later for confirmation, as per immune related response criteria (irRECIST) guidelines (see Section 7.1.3.3). Response status will be assessed by the study site. Following Week 24, tumor imaging will be performed approximately every 12 weeks (or whenever clinically indicated) while the patient remains on study therapy
9 Tumor imaging should be performed at week 18 and week 24 but should be repeated only every 12 weeks thereafter or as clinically indicated.

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

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

Furthermore, additional evaluations/testing may be deemed necessary by the Sponsor 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.

7.1.1 Administrative Procedures

7.1.1.1 Informed Consent

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

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.

If the patient is illiterate, an impartial witness should be present during the entire informed consent reading and discussion. Afterward, the patient should sign and date the informed consent, if capable. The impartial witness should also sign and date the informed consent along with the individual who read and discussed the informed consent (i.e. study staff personnel).

If the patient is legally incompetent (i.e., a minor or mentally incapacitated), the written consent of a parent, legal guardian or legal representative must be obtained. Depending on

local law or review committee requirements such consent may also need to be signed by an impartial witness.

A copy of the signed and dated consent form should be given to the patient before participation in the study. Patients may undergo study screening tests prior to giving written informed consent provided that these tests are considered part of standard care.

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

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.

7.1.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the subject qualifies for the trial. See section 5.1.2 and 5.1.3 for full list of inclusion and exclusion criteria.

7.1.1.3 Medical History

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

7.1.1.4 Prior and Concomitant Medications Review

7.1.1.4.1 Prior Medications

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

7.1.1.4.2 Concomitant Medications

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

7.1.1.5 Disease Details and Treatments

7.1.1.5.1 Disease Details

The investigator or qualified designee will obtain prior and current details regarding disease status. These may be recorded at screening for some aspects (e.g. sites of disease). This will include the following:

- Prior treatments including response
- Date of diagnosis of primary tumor and advanced disease
- Sites of organ involvement

7.1.1.5.2 Prior Treatment Details

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

7.1.1.5.3 Subsequent Anti-Cancer Therapy Status

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

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

A representative from the coordinating institution will review records to ensure compliance. Data will be collected via CRFs and entered into the database per Sponsor guidelines. The Sponsor will check data accuracy by performing source data verification. Source data verification is a direct comparison of the entries made on the CRFs against the appropriate source documentation. Discrepancies in the data will be brought to the attention of the Investigator and/or the Investigator's staff. Any necessary corrections will be made directly to the CRFs or via queries by the Investigator and/or the Investigator's staff.

7.1.2 Clinical Procedures/Assessments

7.1.2.1 Adverse Event (AE) Monitoring

The investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs as specified in the Trial Flow Chart and more frequently if clinically indicated. Adverse experiences will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 4.0 (see Section 12.2). Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

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 (irAE). See Section 5.6.1.1 and the separate guidance document in the administrative binder regarding the identification, evaluation and management of AEs of a potential immunological etiology.

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

7.1.2.2 Physical and Ophthalmologic 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,

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.

Subjects may have an optional standard ophthalmic examination performed by an ophthalmologist at the times described (Section 6) to assess changes in any residual primary tumor (including treated tumors). At certain time points in the trial and if visual changes develop, an eye exam is indicated. The exam will include best corrected visual acuity, color vision (Ishihara color plates), measurement of tear production with Shirmer's strips, tonometry, slit lamp biomicroscopic examination, and dilated indirect fundoscopy with special attention to retinal abnormalities. Fundus photography of both maculas and optic discs, and of the tumor, should be obtained at all visits. Optical coherencetomography is strongly recommended at scheduled visits, and if retinal abnormalities are suspected. Other types of ancillary testing including fluorescein angiography are also recommended if clinically indicated. B scan ultrasonographic measurements of residual tumor height should be obtained at baseline and at follow-up visits. All adverse events should be graded and documented separately for the tumor and for the non-tumor eye. See Appendix 13.5 for Ophthalmology Documentation Form.

7.1.2.3 Vital Signs

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

7.1.2.4 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status (see Section 12.4) at screening, prior to the administration of each dose of trial treatment and discontinuation of trial treatment as specified in the Trial Flow Chart. After Cycle 8 assessment of ECOG status will be performed every other cycle in conjunction with the directed or full physical exam.

7.1.2.5 Eligibility for Second Course of Treatment

Patients who discontinue pembrolizumab with a CR prior to 24 months or with best response of PR or SD may be eligible for a second course of pembrolizumab therapy. Prior to enrollment in a second course, screening tests are required as outlined in section 6.2. Subjects will receive pembrolizumab 200mg IV q3 weeks for up to 12 months. All other on-treatment procedures are the same as in the initial phase and are outlined in section 6.2. Subjects are eligible for retreatment if they meet the following criteria:

- Best response of CR, PR, or SD
- Treatment for 12 months or more if confirmed CR, PR, or SD
- Subsequent progression of disease as defined by irRECIST criteria
- If immune related adverse events occurred on the initial course, they must have not caused treatment discontinuation and must be resolved at the time of consideration
- ECOG performance status of 0-1
- No intervening systemic therapies following initial course of pembrolizumab
- Other inclusion criteria as outlined in section 5.1.2 and 5.1.3.

If extenuating circumstances occur, discussion with the PI can occur and consideration will be given to retreatment.

7.1.2.6 Tumor Tissue and Blood Collection

Collection of tumor tissue is required prior to enrollment in this study to evaluate an important potential biomarker, PD-L1 that may be predictive of treatment benefit from pembrolizumab. A newly obtained tumor biopsy is highly desirable and preferred, but an

archival tumor specimen is acceptable if a new biopsy cannot be obtained. Patients should submit the specimen for central pathology assessment of PD-L1 status. The results of PD-L1 status are not required to initiate pembrolizumab.

Patients who submit an inadequate archival sample may undergo new biopsy and patients who submit an inadequate recent biopsy may undergo a rebiopsy at the discretion of the investigator. Fine needle aspirations are not acceptable specimens. If a patient is unable to provide a newly obtained tumor biopsy, then collection of archival tumor tissue is required. If a patient has multiple archival tumor tissue samples, the most recently obtained tissue sample is preferred. Finally, if an acceptable archival sample or new biopsy specimen is unable to be obtained due to safety reasons, the requirement may be waived and a patient may be enrolled.

If a patient is unable to provide an archival tissue sample, then collection of a newly obtained tumor biopsy is highly encouraged. Tru-cut (or equivalent) core needle biopsies and surgical biopsies are acceptable. Fine needle aspirations are not acceptable. In addition, tumor biopsies while on study therapy at approximately Week 6, Week 12, and Week 24 and at disease progression are also desirable, especially in patients who initially responded but then progressed on pembrolizumab as changes in biomarkers compared to baseline may provide meaningful insights into characteristics associated with sensitivity or resistance to pembrolizumab.

In addition, at the discretion of the investigator, new lesions or fluid collections may require histological or cytological confirmation if progression is suspected, if indicated by the clinical circumstances. If a new lesion or fluid collection is biopsied during the course of the study to document progressive disease or evaluate suspicious new findings, the date of the procedure, type of procedure, and the histological or cytological results of the biopsy should be recorded in the case report forms.

Assessment of peripheral blood lymphocyte profiles may also yield critical insights into response and resistance to pembrolizumab. Blood collection is required on day 1 of pembrolizumab treatment, two weeks into treatment (cycle 2), and at the time of progression. Twenty (20) ml of peripheral blood should be obtained at each timepoint.

7.1.3 Tumor Imaging and Assessment of Disease

The Immune Related RECIST (irRECIST) will be used for assessment of tumor response for the purposes of managing patients on protocol treatment and decision making for discontinuation of study therapy due to disease progression. These disease assessments will be performed by the investigator with site radiology reading. At least one measurable lesion according to RECIST 1.1 criteria must be present on a bi-dimensional imaging study (CT or MRI) at baseline. A measurable lesion is defined as measuring at least 10 mm in longest diameter or twice the slice thickness whichever is greater; the exception being that lymph nodes must measure 15 mm in short axis for lymph nodes.

The irRECIST criteria are described in Section 7.1.3.3. For the purposes of the efficacy endpoints of the study, response assessment based on irRECIST will be applied as the primary measure.

If imaging shows a complete response (CR) or partial response (PR), tumor imaging should be repeated at least 4 weeks later to confirm response, per irRECIST recommendations. Patients will then return to regular scheduled imaging, starting with the next scheduled imaging time point. Patients who obtain a confirmation scan do not need to undergo scheduled imaging assessment 2 weeks later (e.g. If a patient obtains a scan at Week 16 to confirm a Week 12 response, they will not also be required to complete the scheduled Week 18 scan).

If imaging shows PD, it is at the discretion of the investigator to keep a patient on study treatment or to stop study treatment until imaging is repeated approximately 4 weeks later in order to confirm PD, as described in the irRECIST recommendations. Patients that are deemed clinically unstable or who have biopsy proven new metastatic lesions are not required to have repeat imaging for confirmation. This decision will be based on clinical judgment of a patient's overall clinical condition, including performance status, clinical symptoms, and laboratory data. At a minimum, patients must meet the following criteria for continued treatment on study after disease progression is identified at a tumor assessment:

- Absence of symptoms and signs (including worsening of laboratory values) indicating disease progression
- No decline in ECOG performance status
- Absence of rapid progression of disease or of progressive tumor at critical anatomical sites (e.g., cord compression) requiring urgent alternative medical intervention.

If repeat imaging shows an objective response or stable disease relative to baseline, treatment with pembrolizumab will continue/resume and the next imaging studies will be conducted every 6 weeks as previously scheduled. If repeat imaging confirms PD, patients will be discontinued from study therapy.

In patients who discontinue study therapy early without documented disease progression, every effort should be made to continue monitoring their disease status by radiologic imaging following the guidelines described in Section 7.1.6.4.

7.1.3.1 Assessment Guidelines

Please note the following:

- The same diagnostic method, including use of contrast when applicable, must be used throughout the study to evaluate a lesion.

- All measurements should be taken and recorded in millimeters (mm), using a ruler or calipers.

- Ultrasound is not a suitable modality of disease assessment. If new lesions are identified by ultrasound, confirmation by CT or MRI is required.

- FDG-PET is generally not suitable for ongoing assessments of disease. However FDG-PET can be useful in confirming new sites of disease where a positive FDGPET scan correlates with the new site of disease present on CT/MRI or when a baseline FDG-PET was previously negative for the site of the new lesion. FDG-PET may also be used in lieu of a standard bone scan providing coverage allows interrogation of all likely sites of bone disease and FDG-PET is performed at all assessments.

- If PET/CT is performed then the CT component can only be used for standard response assessments if performed to diagnostic quality, which includes the required anatomical coverage and prescribed use of contrast. The method of assessment should be noted as CT on the electronic CRF.

- CT and MRI: Contrast enhanced CT with 5mm contiguous slices is recommended.

Minimum size of a measurable baseline lesion should be twice the slice thickness, with a minimum lesion size of 10 mm when the slice thickness is 5 mm. MRI is acceptable, but when used, the technical specification of the scanning sequences should be optimized for the evaluation of the type and site of disease and lesions must be measured in the same anatomic plane by use of the same imaging examinations. Whenever possible, the same scanner should be used.

X-ray: Should not be used for target lesion measurements owing to poor lesion definition.

Lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung; however chest CT is preferred over chest X-ray.

Brain Scan: If brain scans are required, then contrast enhanced MRI is preferable to contrast enhanced CT.

7.1.3.2 Measurable and Non-measurable Definitions

A measurable lesion is a non-nodal lesion that can be accurately measured in at least one dimension (longest dimension) of:

- ≥10 mm with MRI or CT when the scan slice thickness is no greater than 5mm. If the slice thickness is greater than 5mm, the minimum size of a measurable lesion must be at least double the slice thickness (e.g., if the slice thickness is 10 mm, a measurable lesion must be ≥20 mm).

- ≥10 mm caliper/ruler measurement by clinical exam or medical photography.

- ≥20 mm by chest x-ray.

Additionally, lymph nodes can be considered pathologically enlarged and measurable if:

- ≥15 mm in the short axis when assessed by CT or MRI (slice thickness recommended to be no more than 5 mm). At baseline and follow-up, only the short axis will be measured.

A non-measurable lesion is:

- All other lesions including lesions too small to be considered measurable (longest diameter <10 mm or pathological lymph nodes with ≥10 mm and <15 mm short axis) as well as truly non-measurable lesions, which include: ascites, pleural or pericardial effusions, inflammatory breast disease, lymphangitic involvement of the skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques (Eisenhauer 2009).

Measurable disease: The presence of at least one measurable lesion. Palpable lesions that are not measurable by radiologic or photographic evaluations may not be utilized as the only measurable lesion.

Non-Measurable only disease: The presence of only non-measurable lesions. Note: nonmeasurable only disease is not allowed per protocol.

7.1.3.3 Response Criteria (irRC)

7.1.3.3.1 Immune-related RECIST Criteria (irRECIST) Overview

- All measurements are undimensional

- If a patient is classified as having progressive disease, confirmation by a second scan at least 4 weeks later in the absence of rapid clinical deterioration is required to assess for a late response.

- The presence of new lesions does not constitute disease progression by itself.

- Target lesions and new lesions are incorporated into overall tumor burden which is used to evaluate progression or responses as in the following:

  Tumor Burden = Sum of the Diameter (target) + Sum of the Diameter (new)

7.1.3.3.2 Target Lesions

- Up to 5 lesions may be selected as target lesions (up to 2 per organ).

- Immune-related Complete Response (irCR): Disappearance of all target lesions. Any pathological lymph nodes must be <10 mm in the short axis.

- Immune-related Partial Response (irPR): At least a 30% decrease in the total tumor burden, including target lesions and new lesions, taking as a reference, the baseline sum of the diameters (e.g. percent change from baseline).

- Immune-related Stable Disease (irSD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease.

- Immune-related Progressive Disease (irPD): At least a 20% increase in the tumor burden (defined as the sum of diameters of target lesions and new lesions), taking as a reference, the smallest sum of diameters recorded since the treatment started (e.g. percent change from nadir, where nadir is defined as the smallest sum of diameters recorded since treatment start). In addition, the sum must have an absolute increase from nadir of 5mm.

- Not Applicable (NA): No target lesions at baseline.

- Not Evaluable (NE): Cannot be classified by one of the five preceding definitions.

NOTE:

- If lymph nodes are documented as target lesions the short axis is added into the sum of the diameters (e.g. sum of diameters is the sum of the longest diameters for non-nodal lesions and the short axis for nodal lesions). When lymph nodes decrease to non-pathological size (short axis <10mm) they should still have a measurement reported in order not to overstate progression.

- If at a given assessment time point all target lesions identified at baseline are not assessed, sum of the diameters cannot be calculated for purposes of assessing CR, PR, or SD, or for use as the nadir for future assessments. However, the sum of the diameters of the assessed lesions and the percent change from nadir should be calculated to ensure that progression has not been documented. If an assessment of PD cannot be made, the response assessment should be NE.

- All lesions (nodal and non-nodal) should have their measurements recorded even when very small (e.g., 2 mm). If lesions are present but too small to measure, 5 mm should be recorded and should contribute to the sum of the diameters, unless it is likely that the lesion has disappeared in which case 0 mm should be reported.

- If a lesion disappears and reappears at a subsequent time point it should continue to be measured. The response at the time when the lesion reappears will depend upon the status of the other lesions. For example, if the disease had reached a irCR status then irPD would be documented at the time of reappearance. However, if the response status was irPR or irSD, the diameter of the reappearing lesion should be added to the remaining diameters and response determined based on percent change from baseline and percent change from nadir.

7.1.3.3.3 Non-Target Lesions

Non-target lesions are not incorporated into tumor burden calculations. However, for the diagnosis of CR to be achieved, all non-target lesions must also resolve.

NOTE:

- In the presence of measurable disease, progression on the basis of solely non-target disease requires substantial worsening such that even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy.

- Sites of non-target lesions, which are not assessed at a particular time point based on the assessment schedule, should be excluded from the response determination (e.g. non-target response does not have to be "Not Evaluable").

7.1.3.3.4 New Lesions

New lesions do not automatically qualify as irPD. The diameter of new lesions should be added to the sum of target lesions to assess disease burden.

Any equivocal new lesions should continue to be followed. Treatment can continue at the discretion of the investigator until the next scheduled assessment. If at the next assessment the new lesion is considered to be unequivocal, it should be added to the disease burden.

Table 8 presents the overall response at an individual time point for all possible combinations of tumor responses in target and non-target lesions with or without the appearance of new lesions for subjects with measurable disease at baseline.

7.1.3.3.5 Evaluation of Overall Response

Table 8 Evaluation of Overall Response for Subjects with Measurable Disease at Baseline

Overall Response	**irRECIST (total tumor burden = target lesions + new lesions)**	**Non-target lesions**	**New lesions**
irCR	Disappearance of all lesions	Absence	Absence
irPR	≥ 30% decrease in tumor burden compared with baseline	Any	Any
irSD	<30% decrease to < 20% increase in total tumor burden compared with baseline	Any	Any
irPD	≥ 20% increase in tumor burden compared with nadir or baseline with confirmation of progression by a second scan at least 4 weeks later	Any	Any

ir=immune related, CR=complete response, PR = partial response, SD=stable disease, PD=progressive disease, NA= Not applicable, and NE=Not Evaluable

NOTE:

- Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration." Objective response status is determined by evaluations of disease burden. Every effort should be made to document the objective progression even after discontinuation of treatment.

- In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of CR depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the CR.

- If patients experience irPD and remain clinically stable or improved, an exception may be granted to continue on study after discussion with the PI. If confirmed irPD is documented and an exception is granted, repeat imaging should be performed in 4-6 weeks and if further progression is documented then study treatment should be discontinued. If an isolated lesions progresses and is treated with local therapy (surgical resection or radiation therapy), imaging should be performed to document local stability and overall irRECIST re-evaluation.

7.1.4 Laboratory Procedures/Assessments

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

7.1.4.1 Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

Laboratory tests for hematology, chemistry, urinalysis, and others are specified in Table 9.

Table 9 Laboratory Tests

Hematology	Chemistry	Other
Hematocrit	Albumin	Serum β-human chorionic gonadotropin†
Hemoglobin	Alkaline phosphatase	(β-hCG)†
Platelet count	Alanine aminotransferase (ALT)	PT (INR)
WBC (total and differential)	Aspartate aminotransferase (AST)	aPTT
Red Blood Cell Count	Lactate dehydrogenase (LDH)	Total thriiodothyronine (T3)
Absolute Neutrophil Count	Carbon Dioxide ‡	Free tyroxine (T4)
	(CO_2 or biocarbonate)	Thyroid stimulating hormone (TSH)
	Uric Acid	
	Calcium	
	Chloride	Blood for correlative studies
	Glucose	
	Potassium	
	Sodium	
	Magnesium	
	Total Bilirubin	
	Direct Bilirubin *(If total bilirubin is elevated above the upper limit of normal)*	
	Total protein	
	Blood Urea Nitrogen	

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

‡ If considered standard of care in your region.

Laboratory tests for screening or entry into the Second Course Phase should be performed within 14 days prior to the first dose of treatment. After Cycle 1, pre-dose laboratory procedures can be conducted up to 72 hours prior to dosing. Results must be reviewed by the investigator or qualified designee and found to be acceptable prior to each dose of trial treatment.

7.1.5 Other Procedures

7.1.5.1 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 7.1.6.2.2. After discontinuing treatment following assessment of CR, these subjects should return to the site for a Safety Follow-up Visit (described in Section 7.1.6.3) and then proceed to the Follow-Up Period of the study (described in Section 7.1.6.4).

7.1.5.2 Blinding/Unblinding

No blinding will be performed in this trial.

7.1.6 Study Visits

Study procedures should be performed as close to the scheduled time as possible. The exact time at which a procedure is performed must be recorded in the patients study records or appropriate worksheet (if applicable). Any nonscheduled procedures required for urgent evaluation of safety concerns take precedence over all routine scheduled procedures.

A detailed outline of all scheduled study procedures is provided in the Study Flow Chart (Section 6.0). Procedures should be performed at the study center where the patient is being treated.

Blood collections for safety evaluation assume priority over other procedures. Whenever possible, blood samples should be obtained by fresh peripheral venipuncture. If a patient does not have peripheral access, the sample may be collected from a central catheter immediately after an initial withdrawal of at least 10 mL of blood; or preferably, after a series of other blood sample collections from the central catheter.

The patient will be assessed for adverse experiences per the Study Flow Chart (Section 6.0) and at all unscheduled visits.

Specific procedure-related details are provided above in Section 7.1 - Trial Procedures.

7.1.6.1 Screening Period

All screening procedures will be performed during the screening period. Screening requirements are outlined in Section 6.0 - Trial Flow Chart.

7.1.6.2 Treatment Period

7.1.6.2.1 Initial Treatment Period

Treatment visits will occur every 3 weeks with symptom evaluation, physical exam, and laboratory studies as documented in Section 6.0. If grade 3-4 adverse events that meet the criteria listed in Table 3, then the treatment interval may be lengthened to every 4 weeks.

7.1.6.2.2 Subsequent Treatment Period

Patients who stop pembrolizumab with SD or better may be eligible for up to one year of additional pembrolizumab therapy if they progress after stopping pembrolizumab. The following criteria must be met to be eligible for second-course treatment:

- Patient had a confirmed CR and stopped pembrolizumab treatment after at least 6 months plus an additional 2 doses of study therapy OR

  Patient had SD, PR or CR and stopped pembrolizumab treatment after at least 12 months of study therapy

- Patient has documented disease progression after stopping pembrolizumab study treatment

- Patient did not discontinue pembrolizumab due to AEs from study treatment

- Patient did not initiate new anti-cancer treatment since stopping pembrolizumab (note – local surgery or radiation therapy with palliative intent may be allowed).

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

- Demonstrate adequate organ function as detailed in Section 5.1.2

- Female patient of childbearing potential should have a negative urine or serum pregnancy test within 72 hours prior to receiving retreatment with study medication.

- Female patients of childbearing potential should be willing to use 2 methods of birth control or be surgically sterile, or a barrier method plus a hormonal method of contraception to prevent pregnancy, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study medication (Reference Section 2.2). Patients of child bearing potential are those who have not been surgically sterilized or have been free from menses for > 18 months (see Section 2.2).

- Male patients 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 patient's participation for the full duration of the trial or is not in the best interest of the patient to participate, in the opinion of the treating investigator.

Patients who restart treatment will be retreated at the dose and dose frequency they received upon initial treatment with pembrolizumab. Treatment will be administered for up to 12 additional months.

See Section 5.1.2.5 for eligibility requirements for reinduction and Section 6.2 for flowchart for induction.

7.1.6.3 Post-Treatment Visits

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.

7.1.6.4 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 12 weeks (84 ± 7 days) by radiologic imaging to monitor disease status. Every effort should be made to collect information regarding disease status until the start of new anti-neoplastic therapy, disease progression, death, end of the study or if the subject begins retreatment with pembrolizumab as detailed in Section 7.1.6.2.2. Information regarding post-study anti-neoplastic treatment will be collected if new treatment is initiated.

Subjects who are eligible to receive retreatment with pembrolizumab will move from the follow-up phase to the Second Course Phase when they experience disease progression. Details are provided in Section 6.0 – Trial Flow Chart.

7.1.6.4.1 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.

7.2 Assessing and Recording Adverse Events

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

Adverse events may also occur in screened subjects during any pre-allocation baseline period as a result of a protocol-specified intervention, including washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

All adverse events will be recorded from the time the consent form is signed through 30 days following cessation of treatment and 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.

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

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

For purposes of this trial, an overdose will be defined as any dose exceeding the prescribed dose for pembrolizumab by 20% over the prescribed dose. No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose,

pembrolizumab should be discontinued and the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

If an adverse event(s) is associated with ("results from") the overdose of 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."

[redacted]

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

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

[redacted]

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

7.2.3.1 Serious Adverse Events

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

- Results in death;
- Is life threatening;
- Results in persistent or significant disability/incapacity;
- Results in or prolongs an existing inpatient hospitalization;
- Is a congenital anomaly/birth defect;
- Is a new cancer (that is not a condition of the study);
- Is associated with an overdose;
- Is another important medical event

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

Any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study that occurs to any subject from the time the consent is signed through 90 days following cessation of treatment, or the initiation of new anti-cancer therapy, whichever is earlier, whether or not related to Merck product, must be reported within 24 hours to the Sponsor and within 2 working days to [redacted]

Non-serious Events of Clinical Interest will be forwarded [redacted] handled in the same manner as SAEs.

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 outside of the time period specified in the previous paragraph also must be reported immediately to the Sponsor and to Merck.

[redacted]

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 [redacted] the time of submission. [redacted]

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

7.2.3.2 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be recorded as such on the Adverse Event case report forms/worksheets and reported within 24 hours to the Sponsor and within 2 working days to [redacted]

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. The trial site guidance for assessment and follow up of these criteria can be found in the Investigator Trial File Binder (or equivalent).

3. In the event a subject develops any of the following AEs, a detailed narrative of the event should be reported as an ECI to the Sponsor within 24 hours and to [redacted] within 2 working days of the event:

a. Grade ≥ 3 diarrhea
b. Grade ≥ 3 colitis
c. Grade ≥ 2 pneumonitis
d. Grade ≥ 3 hypo- or hyperthyroidism

A separate guidance document has been provided entitled "event of Clinical Interest and Immune-Related Adverse Event Guidance Document." This document provides guidance regarding identification, evaluation and management of ECIs and irAEs. Additional ECIs are identified in this guidance document and also need to be reported to the Sponsor within 24 hours and to [redacted] within 2 working days of the event.

Subjects should be assessed for possible ECIs prior to each dose. Lab results should be evaluated and subjects should be asked for signs and symptoms suggestive of an immune-related event. Subjects who develop an ECI thought to be immune-related should have additional testing to rule out other etiologic causes. If lab results or symptoms indicate a possible immune-related ECI, then additional testing should be performed to rule out other etiologic causes. If no other cause is found, then it is assumed to be immune-related.

ECIs that occur in any subject from the date of first dose through 90 days following cessation of treatment, or the initiation of a new anticancer therapy, whichever is earlier, whether or not related to the Merck's product, must be reported within 24 hours to the Sponsor and to [redacted] within 2 working days.

7.2.4 Evaluating Adverse Events

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

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

Table 10 Evaluating Adverse Events

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

V4.0 CTCAE Grading	**Grade 1**	**Mild; asymptomatic or mid symptoms; clinical or diagnostic observations only; intervention not indicated.**
	Grade 2	**Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.**
	Grade 3	**Severe or medically significant but not immediately life-threatening; hospitalization or prolongation or hospitalization indicated; disabling; limiting self-care ADL.**
	Grade 4	**Life threatening consequences; urgent intervention indicated.**
	Grade 5	**Death related to AE**
Seriousness	A serious adverse event is any adverse event occurring at any dose or during any use of Merck product that:	
	†**Results in death**; or	
	†**Is life threatening; or** places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred (Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.); or	
	†**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or	
	†**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization [including hospitalization for an elective procedure] for a preexisting condition which has not worsened does not constitute a serious adverse event.); or	
	†**Is a congenital anomaly/birth defect** (in offspring of subject taking the product regardless of time to diagnosis);or	
	Is a new **cancer;** (that is not a condition of the study) **or**	
	Is an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours.	
	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	
Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the adverse event cause the Merck product to be discontinued?	
Relationship to test drug	Did the Merck product cause the adverse event? The determination of the likelihood that the Merck product caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the adverse event based upon the available information. **The following components are to be used to assess the relationship between the Merck product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Merck product caused the adverse event (AE):	
	Exposure	Is there evidence that the subject was actually exposed to the Merck product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
	Time Course	Did the AE follow in a reasonable temporal sequence from administration of the Merck product? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors

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

7.2.5 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.

7.2.6 Adverse Event Collection

Adverse events forms developed by the sponsor institution will be distributed and collected to document adverse events of interest. The sponsor institution will collect, maintain, and monitor CRFs.

8.0 BIOMARKERS AND CORRELATIVE STUDIES

8.1 Biomarker Study Overview

Tumor *GNAQ* and *GNA11* status will be determined for all patients treated on this study using archived or newly acquired tumor material. PD-L1 expression by IHC will also be performed on all baseline tumor samples (either archival or new biopsies). All patients with safely accessible tumor will undergo pre- and post-treatment (day 14 +/- 3 days) tumor biopsies for biomarker and correlative analysis. The decision to not pursue these biopsies must be made in collaboration with the Principal Investigator. An additional tumor biopsy will be requested from patients at the time of disease progression; however, this biopsy is optional.

In addition to *GNAQ* and *GNA11* mutational status and PD-L1 staining, peripheral blood and tumor will be collected to assess other immune correlates including but not limited to peripheral circulating lymphocytes and tumor infiltrating lymphocytes prior to therapy and at the time of progression by multiplexed mass cytometry. Specific populations of T cells assessed will include (but not limited to) CD8+ cytotoxic T cells, regulatory T cells, and PD-1+ T cells.

8.2 Correlative Studies

8.2.1 Tumor Biopsies

Investigators are highly encouraged to collect tumor biopsies at baseline (in the absence of sufficient archival tissue) and 14 days (+/- 3 days) following initiation of therapy, with an optional tumor biopsy conducted at the time of disease progression. The pre-treatment biopsy will be obtained within 28 days of starting therapy. As noted, archival tissue within one year of starting therapy of sufficient quantity will preclude the need for an initial biopsy. Issues that would cause treatment delays should be discussed with the PI who may grant permission on a case-by-case basis to analyze tissue from a protocol pre-treatment biopsy that has occurred greater than 28 days prior to study treatment. The post-treatment biopsy will be performed at day 14 ± 3 days following the morning dose of the study medications. An optional third tumor biopsy will be requested of these patients at the time of tumor progression, with particular efforts made at obtaining such biopsies in patients who have developed progression after achieving a radiographic response to treatment or after prolonged disease control (i.e., greater than 4 months). Up to eight core samples will be obtained with each biopsy, providing sufficient tissue for the correlative studies.

Tissue will be divided such that a portion (one core in the case of core needle biopsy procedures) is formalin fixed and designated for immunohistochemistry (IHC) and the remainder flash frozen in liquid nitrogen.

Fresh tumor biopsy samples should be snap-frozen using liquid nitrogen or a dry ice slurry as outlined below. The tissue must be frozen as soon as possible after biopsy to minimize any form of degradation and to avoid risking the viability of the tissue.

Snap-Freezing in Liquid Nitrogen:

- Label cryogenic vial(s) with the subject's study identification number (ie. Accession number for MSKCC patients), the date of collection, time point (baseline, day 14, or progression) and the study center performing the biopsy. Ensure that the label adheres to the vial and does not come off when placed in liquid nitrogen. Labels cannot be adequately affixed to the vials after freezing.
- Immediately place the freshly obtained tissue into the labelled cryogenic vial. Place the vial with tissue in liquid nitrogen for 2 minutes or longer to snap-freeze the tissue. Tumor cores should be frozen individually in separate cryovials as collected in order to minimize the time between removal and freezing.
- Remove the crygenic vial from the liquid nitrogen.
- Store the sample in a -80°C freezer (-65°C to -80°C is acceptable) until ready for shipping.

Freezing Procedure with Dry Ice Slurry

- Materials required include: 5 lbs dry ice, alcohol (ethanol or comparable), basin, long forceps
- Place at least 5 lbs of dry ice into a basin and pour one liter of alcohol over the ice.
- Label cryogenic vial(s) with the subject's study identification number, the date of collection, and the study center performing the biopsy. Ensure that the label adheres to the vial and does not come off when placed in liquid nitrogen. Labels cannot be adequately affixed to the vials after freezing.
- Immediately place the freshly obtained tissue into the labelled cryogenic vial. Place the vial with tissue in liquid nitrogen for 2 minutes or longer to snap-freeze the tissue. Tumor cores should be frozen individually in separate cryovials as collected in order to minimize the time between removal and freezing.
- Pace the lower half of the sealed cryotube containing tissue into the solution for at least 2 minutes until frozen solid.
- Store the sample in a -80°C freezer (-65°C to -80°C is acceptable) until ready for shipping.

8.2.2 PD-L1 Staining Assay

Archival or fresh tissue biopsies obtained prior to start of treatment will be subjected to PD-L1 by immunohistochemistry per a proprietary assay. Percentage of tumor cells expressing PD-L1 will be correlated to duration of progression-free survival. Cutoffs of strong PD-L1 staining

(≥50% of cells) and weak PD-L1 staining (1-49% of cells) will be used and correlated with response rate by irRECIST criteria.

Biopsies should be processed in the following manner:

- Formalin fixed paraffin embedded tissue samples are acceptable; a fine needle aspirate, frozen sample, plastic embedded sample, cell block, clot, bone, bone marrow or cytologic specimen will not be acceptable for IHC analysis.

- It is recommended that FFPE blocks be sectioned fresh (within 7 days of sectioning and sending for PD-L1 analysis) onto positively charged slides; slides should be stored and shipped (and stored upon receipt at Qualtek) at 2-8C in the dark.

- Recommended fixation time for samples is 24 hours to 48 hours in 10% neutral buffered formalin.

8.2.3 Blood Collection

Two 10 ml sodium heparin tubes will be collected from patients prior to treatment, at the beginning of cycle 2 (week 3), and at the time of progression. Samples will be subsequently stored for future correlative studies. The samples drawn prior to treatment can be drawn on C1W1 prior to initiation of study drug.

Process samples in the following manner.

- Utilizing the 3 sodium heparin tubes, use your institutions choice of best practices to isolate mononuclear cells (i.e., accuspin system, leucosep system, CPT tubes, general ficoll layering).
- Transfer the cells to a BD Falcon ® tube and wash the cells three times with PBS (ex: aliquot cellular layer to falcon tube and fill with 15 ml of PBS, invert several times to mix. Cap and centrifuge at 300 x *g* for 10 min, pour off PBS and repeat).
- After the third wash, carefully pour off the PBS one last time and freeze the cell pellet at -80°C until shipment to the respective biorepository
- Label tubes with the subject's study identification number, initials, the date of collection, time point and protocol number.

9.0 STATISTICAL ANALYSIS PLAN

9.1 Statistical Analysis Plan Summary

The primary objective is to determine whether pembrolizumab is an effective therapy in uveal melanoma. The null hypothesis is that the objective response rate (ORR; percentage of patients achieving a confirmed CR or PR) is not attractive (defined as ≤5%). The alternative hypothesis is that the response rate is of interest for further development (defined as ≥20%).

The final analysis of the overall response rate will be performed with a power of 80% with one sided α=0.05. It is calculated that at least 4 responses are needed out of a total of 29 patients to reject the null hypothesis.

To allow early termination of the trial due to lack of efficacy, the trial will be conducted in two stages per Simon's Optimal Design. If no responses are demonstrated in the first 10 patients, then the trial will be terminated early for futility. If ≥1 responses are observed, enrollment will continue to 29 patients. Notably, in the absence of ≥1 response, if ≥2 patients experience stable disease (SD) for >24 weeks, then the study may proceed to stage 2 if the sponsor and PIs are in agreement. This provision was added since the probability of early termination was as high as 10% even with a response rate of 20%.

9.2 Statistical Analysis Plan

9.2.1 Sample Size Assumptions

To determine the overall sample size and the interim sample size, a two stage Simon's Optimal design was evaluated. To test the hypotheses (ORR=5% vs. 20%), 1 response from the first 10 subjects would be required to progress to stage 2 and a total of 29 subjects will be needed to achieve the desired type I (<5%) and type II error rate (Power>80%). The risk of prematurely stopping the trial after stage I if the drug is effective is approximately 10%. To reduce this risk, we will include the condition that if 2 or more patients experience stable disease for at least 24 weeks then the trial will proceed to stage 2.

Table 11: Sample Size Calculations

If the True Response Rate to pembrolizumab is: (%)	Probability of Early Termination after Stage I	Probability of Rejecting the Null Hypothesis
5%	0.599	0.047 (type 1 error)
10%	0.349	0.289
15%	0.197	0.589
20%	0.107	0.801
25%	0.056	0.913
30%	0.028	0.963

9.2.2 Efficacy Endpoints

9.2.2.1 Primary Endpoint

Objective response rate (ORR) as defined by immune-related response criteria (irRC) will be the primary endpoint of the study. As mentioned, the primary hypothesis is that ORR of pembrolizumab in uveal melanoma will be 20%. We will enroll 10 patients in stage I to allow for early termination for futility. If no responses are observed the trial will be terminated. However, if ≥1 objective response occurs, OR if ≥2 patients experience stability of disease for ≥24 weeks, the trial will proceed to stage II.

In stage II, an additional 19 patients will be enrolled. If ≥4 responses occur in all patients treated on stage I and stage II, the trial will be considered positive.

Of note, response rates by RECIST 1.1 criteria will also be assessed although irRC will be used for the primary endpoint.

ORR will be stratified by PD-L1 expression and *GNAQ*/*GNA11* mutation status (see section 8.2.2.3).

9.2.2.2 Secondary Endpoints

9.2.2.2.1 Progression Free Survival

Progression-free survival (PFS) as defined as the time from the first dose of pembrolizumab to progression as defined by RECIST 1.1 criteria. PFS will be summarized in the method of Kaplan and Meier. Median PFS and PFS at one year will be reported with 95% confidence intervals. PFS analysis based on investigator's assessment using irRC will also be carried out.

Since disease progression is assessed periodically, progressive disease (PD) can occur any time in the time interval between the last assessment where PD was not documented and the assessment when PD is documented. For the primary analysis, for the patients who have PD, the true date of disease progression will be approximated by the date of first assessment at which PD is objectively documented using RECIST 1.1 criteria, regardless of discontinuation of study drug. Death is always considered as a confirmed PD event. Patients without documented PD/death will be censored at the last disease assessment date.

9.2.2.2.2 Overall Survival

Overall survival is defined as the interval between the first dose of pembrolizumab and death for any reason. The Kaplan-Meier method will be used to estimate the overall survival. The treatment difference in survival will be assessed by the stratified log-rank test. Median survival and its 95% confidence interval will be estimated and reported.

9.2.2.2.3 Duration of Response

If sample size permits, response duration will be summarized descriptively using Kaplan-Meier medians and quartiles. Only the subset of patients who show a complete response or partial response will be included in this analysis.

9.2.2.3 Subgroup Analyses

To investigate predictors of response to pembrolizumab in uveal melanoma, we will stratify outcomes (ORR, PFS, OS) by clinical and laboratory factors. Clinical factors will include baseline LDH, visceral involvement, ECOG performance status, prior ipilimumab, and prior MEK inhibitor therapy. To investigate for possible genetic biomarkers for response, we will perform $GNAQ^{209}$/$GNA11^{Q209}$ mutation analysis and evaluate outcomes by mutation status. In addition, we will perform stratification by PD-L1 expression status.

Differences in PFS and OS between subgroups will be assessed by the stratified logrank test. Differences in ORR between subgroups will be assessed by the Pearson chi-square test. No adjustments will be made for multiple comparisons.

9.2.3 Safety Endpoints

Adverse events attributed to pembrolizumab will be listed by CTCAE grade and reported in terms of the number of patients who experienced adverse events as a percentage of all treated patients. This endpoint will be reported descriptively without formal statistical analysis.

9.2.4 Baseline Characteristics and Other Analyses

Each relevant clinical characteristic will be recorded by the use of tables and/or graphs. No statistical hypothesis tests will be performed on these characteristics. The number and percentage of patients treated, and the primary reason for discontinuation will be displayed. Demographic variables (such as age) and baseline characteristics will be summarized by descriptive statistics.

Drug accountability data for pembrolizumab will be collected during the study. Compliance with pembrolizumab administration will be measured by patients: 1) receiving unscheduled study agent infusions/injections; 2) missing an infusion/injection. Numbers and percentages of patients and infusion/injection visits with any deviation in these measures will be reported.

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Protocol date: August 30, 2016

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12.0 LIST OF REFERENCES

1. DISIS ML. IMMUNE REGULATION OF CANCER. J CLIN ONCOL. 2010;28:4531-8.
2. DONG H, STROME SE, SALOMAO DR, TAMURA H, HIRANO F, FLIES DB, ET AL. TUMOR-ASSOCIATED B7-H1 PROMOTES T-CELL APOPTOSIS: A POTENTIAL MECHANISM OF IMMUNE EVASION. NAT MED. 2002;8:793-800.
3. SHARPE AH, FREEMAN GJ. THE B7-CD28 SUPERFAMILY. NAT REV IMMUNOL. 2002;2:116-26.
4. BROWN JA, DORFMAN DM, MA FR, SULLIVAN EL, MUNOZ O, WOOD CR, ET AL. BLOCKADE OF PROGRAMMED DEATH-1 LIGANDS ON DENDRITIC CELLS ENHANCES T CELL ACTIVATION AND CYTOKINE PRODUCTION. J IMMUNOL. 2003;170:1257-66.
5. FRANCISCO LM, SAGE PT, SHARPE AH. THE PD-1 PATHWAY IN TOLERANCE AND AUTOIMMUNITY. IMMUNOL REV. 2010;236:219-42.
6. THOMPSON RH, DONG H, LOHSE CM, LEIBOVICH BC, BLUTE ML, CHEVILLE JC, ET AL. PD-1 IS EXPRESSED BY TUMOR-INFILTRATING IMMUNE CELLS AND IS ASSOCIATED WITH POOR OUTCOME FOR PATIENTS WITH RENAL CELL CARCINOMA. CLIN CANCER RES. 2007;13:1757-61.
7. NOMI T, SHO M, AKAHORI T, HAMADA K, KUBO A, KANEHIRO H, ET AL. CLINICAL SIGNIFICANCE AND THERAPEUTIC POTENTIAL OF THE PROGRAMMED DEATH-1 LIGAND/PROGRAMMED DEATH-1 PATHWAY IN HUMAN PANCREATIC CANCER. CLIN CANCER RES. 2007;13:2151-7.
8. HAMANISHI J, MANDAI M, IWASAKI M, OKAZAKI T, TANAKA Y, YAMAGUCHI K, ET AL. PROGRAMMED CELL DEATH 1 LIGAND 1 AND TUMOR-INFILTRATING CD8+ T LYMPHOCYTES ARE PROGNOSTIC FACTORS OF HUMAN OVARIAN CANCER. PROC NATL ACAD SCI U S A. 2007;104:3360-5.
9. FOURCADE J, KUDELA P, SUN Z, SHEN H, LAND SR, LENZNER D, ET AL. PD-1 IS A REGULATOR OF NY-ESO-1-SPECIFIC CD8+ T CELL EXPANSION IN MELANOMA PATIENTS. J IMMUNOL. 2009;182:5240-9.
10. AHMADZADEH M, JOHNSON LA, HEEMSKERK B, WUNDERLICH JR, DUDLEY ME, WHITE DE, ET AL. TUMOR ANTIGEN-SPECIFIC CD8 T CELLS INFILTRATING THE TUMOR EXPRESS HIGH LEVELS OF PD-1 AND ARE FUNCTIONALLY IMPAIRED. BLOOD. 2009;114:1537-44.
11. CAI G, KARNI A, OLIVEIRA EM, WEINER HL, HAFLER DA, FREEMAN GJ. PD-1 LIGANDS, NEGATIVE REGULATORS FOR ACTIVATION OF NAIVE, MEMORY, AND RECENTLY ACTIVATED HUMAN CD4+ T CELLS. CELL IMMUNOL. 2004;230:89-98.
12. IWAI Y, ISHIDA M, TANAKA Y, OKAZAKI T, HONJO T, MINATO N. INVOLVEMENT OF PD-L1 ON TUMOR CELLS IN THE ESCAPE FROM HOST IMMUNE SYSTEM AND TUMOR IMMUNOTHERAPY BY PD-L1 BLOCKADE. PROC NATL ACAD SCI U S A. 2002;99:12293-7.
13. HINO R, KABASHIMA K, KATO Y, YAGI H, NAKAMURA M, HONJO T, ET AL. TUMOR CELL EXPRESSION OF PROGRAMMED CELL DEATH-1 LIGAND 1 IS A PROGNOSTIC FACTOR FOR MALIGNANT MELANOMA. CANCER. 2010;116:1757-66.

14. TSUSHIMA F, TANAKA K, OTSUKI N, YOUNGNAK P, IWAI H, OMURA K, ET AL. PREDOMINANT EXPRESSION OF B7-H1 AND ITS IMMUNOREGULATORY ROLES IN ORAL SQUAMOUS CELL CARCINOMA. ORAL ONCOL. 2006;42:268-74.
15. BLANK C, MACKENSEN A. CONTRIBUTION OF THE PD-L1/PD-1 PATHWAY TO T-CELL EXHAUSTION: AN UPDATE ON IMPLICATIONS FOR CHRONIC INFECTIONS AND TUMOR EVASION. CANCER IMMUNOL IMMUNOTHER. 2007;56:739-45.
16. TOPALIAN SL, HODI FS, BRAHMER JR, GETTINGER SN, SMITH DC, MCDERMOTT DF, ET AL. SAFETY, ACTIVITY, AND IMMUNE CORRELATES OF ANTI-PD-1 ANTIBODY IN CANCER. N ENGL J MED. 2012;366:2443-54.
17. HAMID O, ROBERT C, DAUD A, HODI FS, HWU WJ, KEFFORD R, ET AL. SAFETY AND TUMOR RESPONSES WITH LAMBROLIZUMAB (ANTI-PD-1) IN MELANOMA. N ENGL J MED. 2013.
18. JIA R, JIAO Z, XU X, WANG J, ZHOU Y, SONG X, ET AL. FUNCTIONAL SIGNIFICANCE OF B7-H1 EXPRESSED BY HUMAN UVEAL MELANOMA CELLS. MOL MED REP. 2011;4:163-7.
19. BRONKHORST IH, VU TH, JORDANOVA ES, LUYTEN GP, BURG SH, JAGER MJ. DIFFERENT SUBSETS OF TUMOR-INFILTRATING LYMPHOCYTES CORRELATE WITH MACROPHAGE INFLUX AND MONOSOMY 3 IN UVEAL MELANOMA. INVEST OPHTHALMOL VIS SCI. 2012;53:5370-8.
20. BRONKHORST IH, JAGER MJ. INFLAMMATION IN UVEAL MELANOMA. EYE (LOND). 2013;27:217-23.
21. BRONKHORST IH, LY LV, JORDANOVA ES, VROLIJK J, VERSLUIS M, LUYTEN GP, ET AL. DETECTION OF M2-MACROPHAGES IN UVEAL MELANOMA AND RELATION WITH SURVIVAL. INVEST OPHTHALMOL VIS SCI. 2011;52:643-50.
22. LUKE JJ, CALLAHAN MK, POSTOW MA, ROMANO E, RAMAIYA N, BLUTH M, ET AL. CLINICAL ACTIVITY OF IPILIMUMAB FOR METASTATIC UVEAL MELANOMA: A RETROSPECTIVE REVIEW OF THE DANA-FARBER CANCER INSTITUTE, MASSACHUSETTS GENERAL HOSPITAL, MEMORIAL SLOAN-KETTERING CANCER CENTER, AND UNIVERSITY HOSPITAL OF LAUSANNE EXPERIENCE. CANCER. 2013.
23. MAIO M, DANIELLI R, CHIARION-SILENI V, PIGOZZO J, PARMIANI G, RIDOLFI R, ET AL. EFFICACY AND SAFETY OF IPILIMUMAB IN PATIENTS WITH PRE-TREATED, UVEAL MELANOMA. ANN ONCOL. 2013;24:2911-5.
24. EISENHAUER EA, THERASSE P, BOGAERTS J, SCHWARTZ LH, SARGENT D, FORD R, ET AL. NEW RESPONSE EVALUATION CRITERIA IN SOLID TUMOURS: REVISED RECIST GUIDELINE (VERSION 1.1). EUR J CANCER. 2009;45:228-47.
25. SHIRABE K, MOTOMURA T, MUTO J, TOSHIMA T, MATONO R, MANO Y, ET AL. TUMOR-INFILTRATING LYMPHOCYTES AND HEPATOCELLULAR CARCINOMA: PATHOLOGY AND CLINICAL MANAGEMENT. INT J CLIN ONCOL. 2010;15:552-8.
26. DIEDERICHSEN AC, HJELMBORG J, CHRISTENSEN PB, ZEUTHEN J, FENGER C. PROGNOSTIC VALUE OF THE CD4+/CD8+ RATIO OF TUMOUR INFILTRATING LYMPHOCYTES IN COLORECTAL CANCER AND HLA-DR EXPRESSION ON TUMOUR CELLS. CANCER IMMUNOL IMMUNOTHER. 2003;52:423-8.
27. HILLEN F, BAETEN CI, VAN DE WINKEL A, CREYTENS D, VAN DER SCHAFT DW, WINNEPENNINCKX V, ET AL. LEUKOCYTE INFILTRATION AND TUMOR CELL

PLASTICITY ARE PARAMETERS OF AGGRESSIVENESS IN PRIMARY CUTANEOUS MELANOMA. CANCER IMMUNOL IMMUNOTHER. 2008;57:97-106.
28. GAO Q, QIU SJ, FAN J, ZHOU J, WANG XY, XIAO YS, ET AL. INTRATUMORAL BALANCE OF REGULATORY AND CYTOTOXIC T CELLS IS ASSOCIATED WITH PROGNOSIS OF HEPATOCELLULAR CARCINOMA AFTER RESECTION. J CLIN ONCOL. 2007;25:2586-93.
29. OSHIKIRI T, MIYAMOTO M, SHICHINOHE T, SUZUOKI M, HIRAOKA K, NAKAKUBO Y, ET AL. PROGNOSTIC VALUE OF INTRATUMORAL CD8+ T LYMPHOCYTE IN EXTRAHEPATIC BILE DUCT CARCINOMA AS ESSENTIAL IMMUNE RESPONSE. J SURG ONCOL. 2003;84:224-8.
30. GREENWALD RJ, FREEMAN GJ, SHARPE AH. THE B7 FAMILY REVISITED. ANNU REV IMMUNOL. 2005;23:515-48.
31. ZHANG X, SCHWARTZ JC, GUO X, BHATIA S, CAO E, LORENZ M, ET AL. STRUCTURAL AND FUNCTIONAL ANALYSIS OF THE COSTIMULATORY RECEPTOR PROGRAMMED DEATH-1. IMMUNITY. 2004;20:337-47.
32. OKAZAKI T, MAEDA A, NISHIMURA H, KUROSAKI T, HONJO T. PD-1 IMMUNORECEPTOR INHIBITS B CELL RECEPTOR-MEDIATED SIGNALING BY RECRUITING SRC HOMOLOGY 2-DOMAIN-CONTAINING TYROSINE PHOSPHATASE 2 TO PHOSPHOTYROSINE. PROC NATL ACAD SCI U S A. 2001;98:13866-71.
33. CHEMNITZ JM, PARRY RV, NICHOLS KE, JUNE CH, RILEY JL. SHP-1 AND SHP-2 ASSOCIATE WITH IMMUNORECEPTOR TYROSINE-BASED SWITCH MOTIF OF PROGRAMMED DEATH 1 UPON PRIMARY HUMAN T CELL STIMULATION, BUT ONLY RECEPTOR LIGATION PREVENTS T CELL ACTIVATION. J IMMUNOL. 2004;173:945-54.
34. SHEPPARD KA, FITZ LJ, LEE JM, BENANDER C, GEORGE JA, WOOTERS J, ET AL. PD-1 INHIBITS T-CELL RECEPTOR INDUCED PHOSPHORYLATION OF THE ZAP70/CD3ZETA SIGNALOSOME AND DOWNSTREAM SIGNALING TO PKCTHETA. FEBS LETT. 2004;574:37-41.
35. RILEY JL. PD-1 SIGNALING IN PRIMARY T CELLS. IMMUNOL REV. 2009;229:114-25.
36. PARRY RV, CHEMNITZ JM, FRAUWIRTH KA, LANFRANCO AR, BRAUNSTEIN I, KOBAYASHI SV, ET AL. CTLA-4 AND PD-1 RECEPTORS INHIBIT T-CELL ACTIVATION BY DISTINCT MECHANISMS. MOL CELL BIOL. 2005;25:9543-53.
37. AGATA Y, KAWASAKI A, NISHIMURA H, ISHIDA Y, TSUBATA T, YAGITA H, ET AL. EXPRESSION OF THE PD-1 ANTIGEN ON THE SURFACE OF STIMULATED MOUSE T AND B LYMPHOCYTES. INT IMMUNOL. 1996;8:765-72.
38. VIBHAKAR R, JUAN G, TRAGANOS F, DARZYNKIEWICZ Z, FINGER LR. ACTIVATION-INDUCED EXPRESSION OF HUMAN PROGRAMMED DEATH-1 GENE IN T-LYMPHOCYTES. EXP CELL RES. 1997;232:25-8.
39. NISHIMURA H, HONJO T, MINATO N. FACILITATION OF BETA SELECTION AND MODIFICATION OF POSITIVE SELECTION IN THE THYMUS OF PD-1-DEFICIENT MICE. J EXP MED. 2000;191:891-8.
40. SIEGEL R, MA J, ZOU Z, JEMAL A. CANCER STATISTICS, 2014. CA CANCER J CLIN. 2014;64:9-29.

41. KORN EL, LIU PY, LEE SJ, CHAPMAN JA, NIEDZWIECKI D, SUMAN VJ, ET AL. META-ANALYSIS OF PHASE II COOPERATIVE GROUP TRIALS IN METASTATIC STAGE IV MELANOMA TO DETERMINE PROGRESSION-FREE AND OVERALL SURVIVAL BENCHMARKS FOR FUTURE PHASE II TRIALS. J CLIN ONCOL. 2008;26:527-34.
42. CHAPMAN PB, HAUSCHILD A, ROBERT C, HAANEN JB, ASCIERTO P, LARKIN J, ET AL. IMPROVED SURVIVAL WITH VEMURAFENIB IN MELANOMA WITH BRAF V600E MUTATION. N ENGL J MED. 2011;364:2507-16.
43. HODI FS, O'DAY SJ, MCDERMOTT DF, WEBER RW, SOSMAN JA, HAANEN JB, ET AL. IMPROVED SURVIVAL WITH IPILIMUMAB IN PATIENTS WITH METASTATIC MELANOMA. N ENGL J MED. 2010;363:711-23.
44. STRICKLAND D, LEE JA. MELANOMAS OF EYE: STABILITY OF RATES. AM J EPIDEMIOL. 1981;113:700-2.
45. CHANG AE, KARNELL LH, MENCK HR. THE NATIONAL CANCER DATA BASE REPORT ON CUTANEOUS AND NONCUTANEOUS MELANOMA: A SUMMARY OF 84,836 CASES FROM THE PAST DECADE. THE AMERICAN COLLEGE OF SURGEONS COMMISSION ON CANCER AND THE AMERICAN CANCER SOCIETY. CANCER. 1998;83:1664-78.
46. MAAT W, LY LV, JORDANOVA ES, DE WOLFF-ROUENDAAL D, SCHALIJ-DELFOS NE, JAGER MJ. MONOSOMY OF CHROMOSOME 3 AND AN INFLAMMATORY PHENOTYPE OCCUR TOGETHER IN UVEAL MELANOMA. INVEST OPHTHALMOL VIS SCI. 2008;49:505-10.
47. WEBER JS, KUDCHADKAR RR, GIBNEY GT, DE CONTI RC, YU B, ET AL. PHASE I/II TRIAL OF PD-1 ANTIBODY NIVOLUMAB WITH PEPTIDE VACCINE IN PATIENTS NAIVE TO OR THAT FAILED IPILIMUMAB. J CLIN ONCOL. 2013;31:9011.
48. TABERNERO J, POWERDERLY JD, HAMID, O, ET AL. . CLINICAL ACTIVITY, SAFETY, AND BIOMARKERS OF MPDL3280A, AN ENGINEERED PD-L1 ANTIBODY IN PATIENTS WITH LOCALLY ADVANCED OR METASTATIC CRC, GASTRIC CANCER (GC), SCCHN, OR OTHER TUMORS. . J CLIN ONCOL. 2013;31:3622.

13.0 APPENDICES

13.1 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.

Product: MK-3475
Protocol/Amendment No. 03

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Protocol date: August 30, 2016

Product: MK-3475
Protocol/Amendment No. 03

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Protocol date: August 30, 2016

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Supplementary Table 3: Events of Clinical Interest

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higher dose of 80 or 100 mg followed by a more prolonged taper and administer additional anti-

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Grade 3 events:

- Report as ECI

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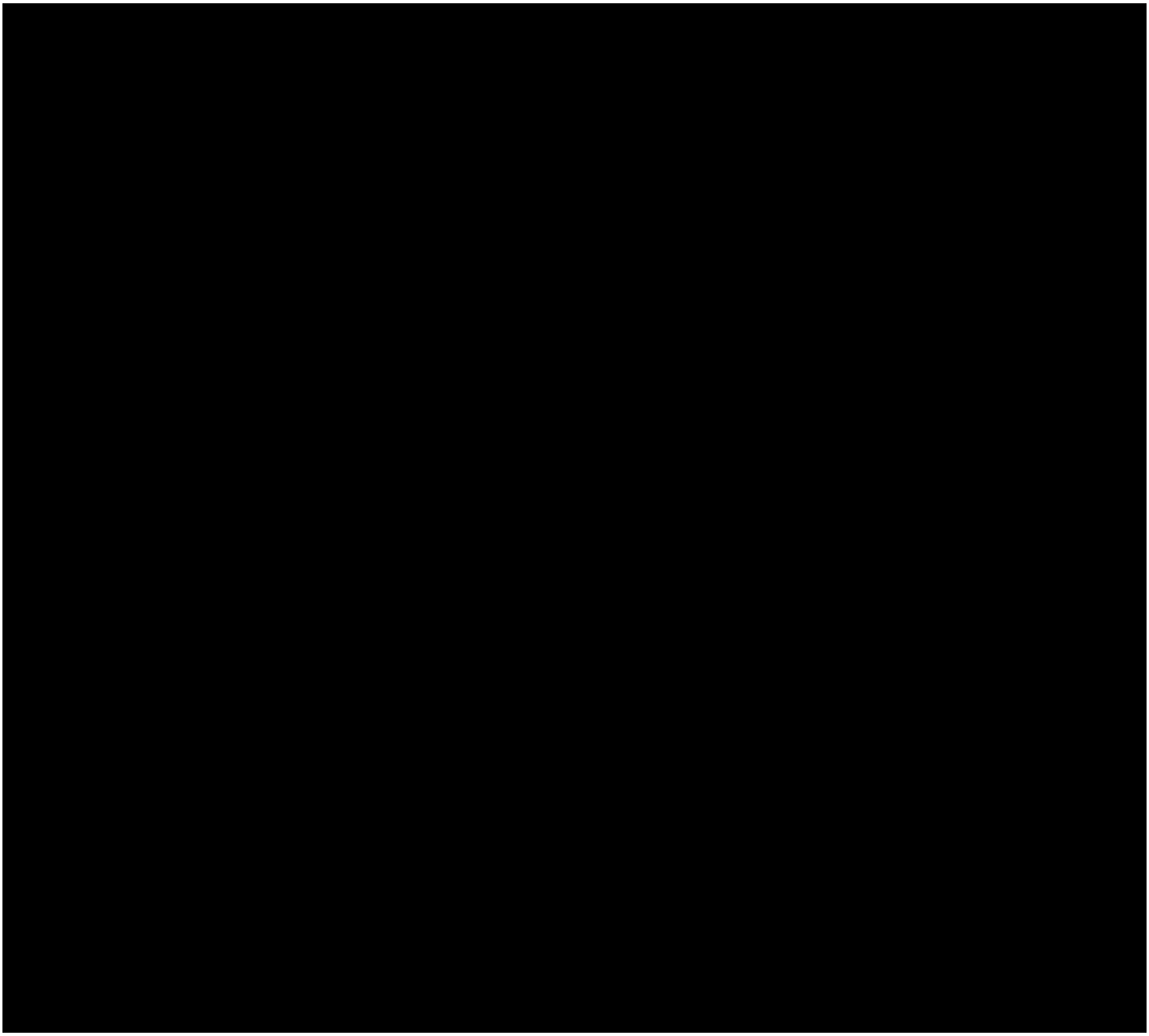

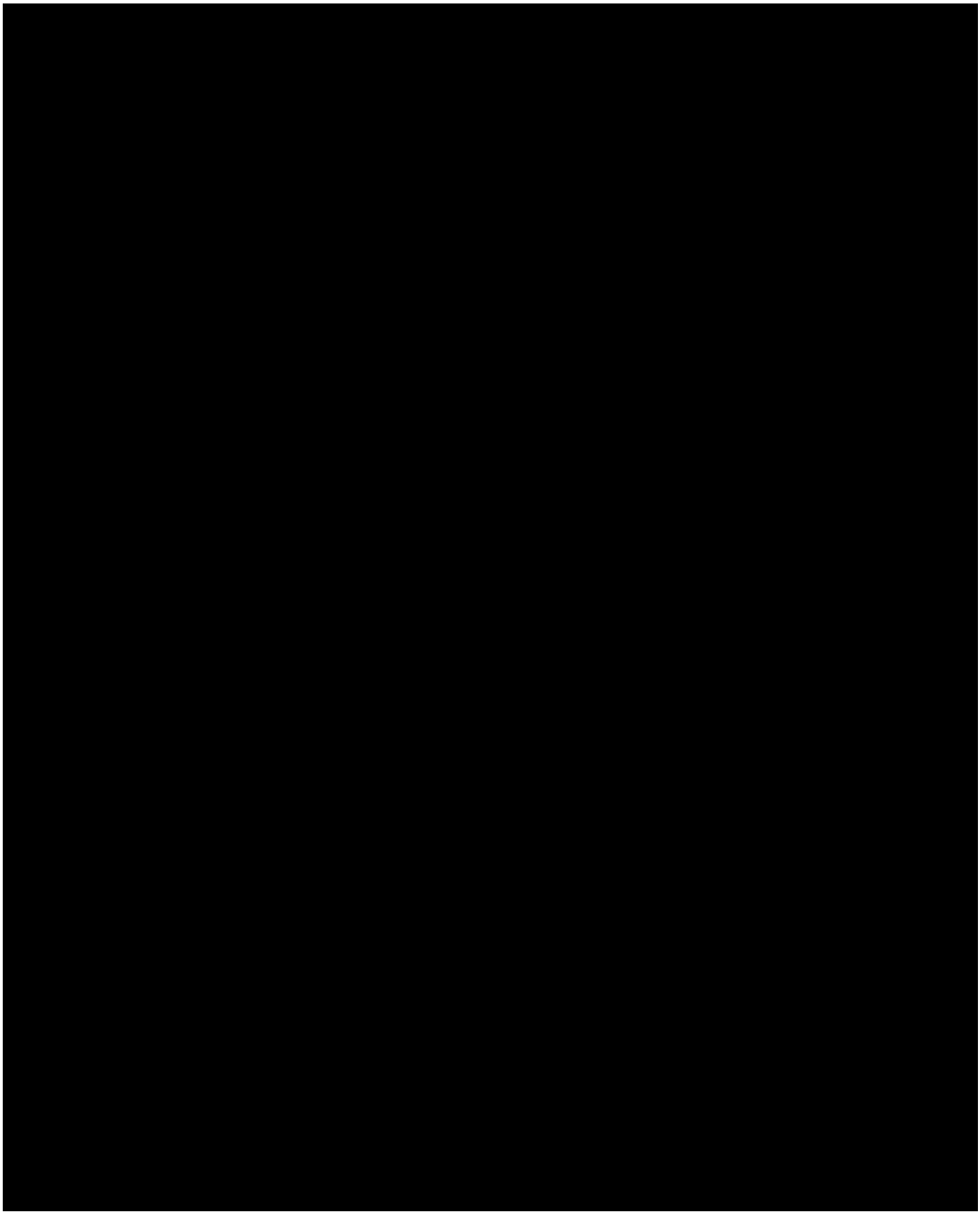

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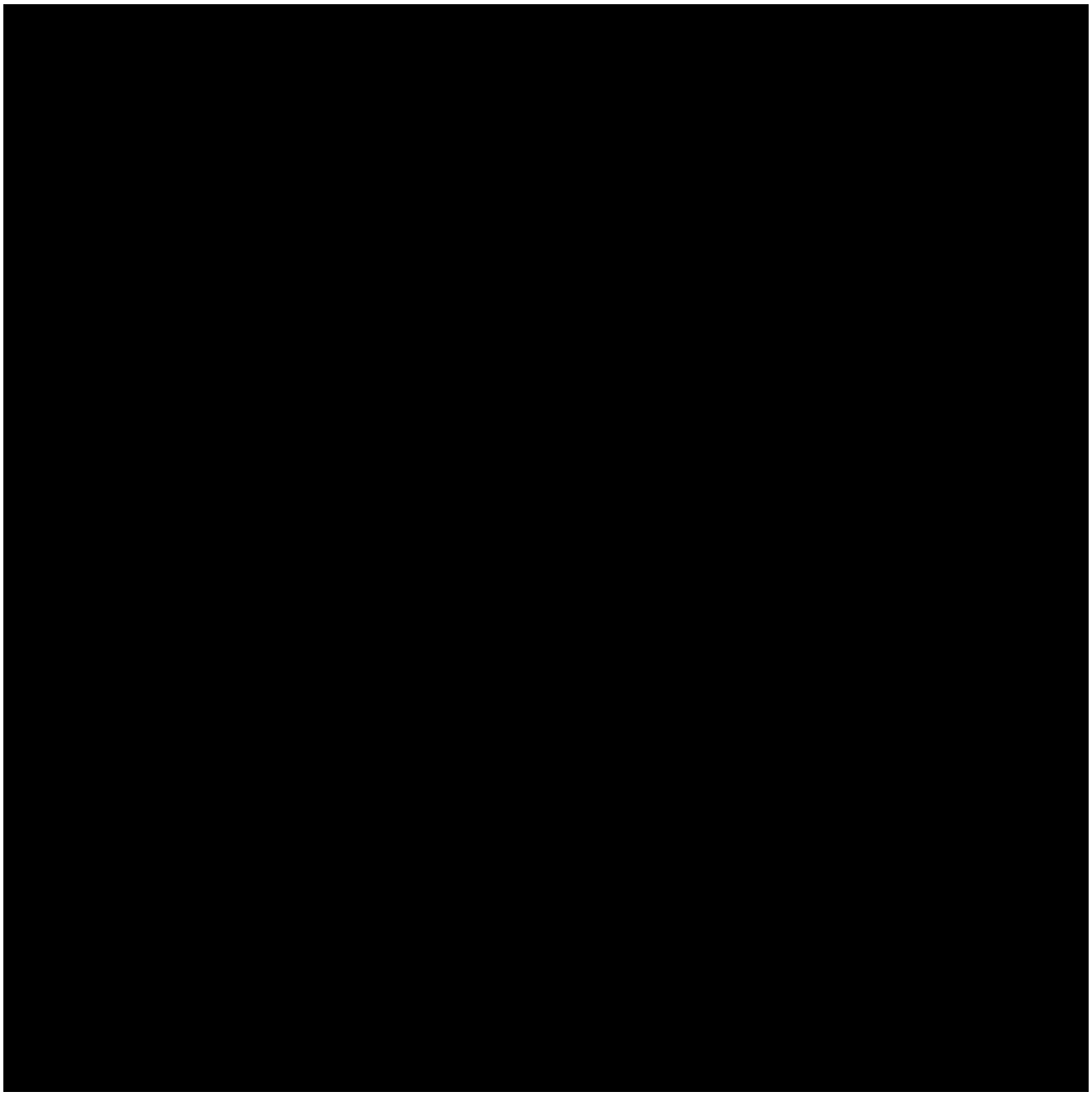

Infusion Reactions

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4. REFERENCES

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

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

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

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

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

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

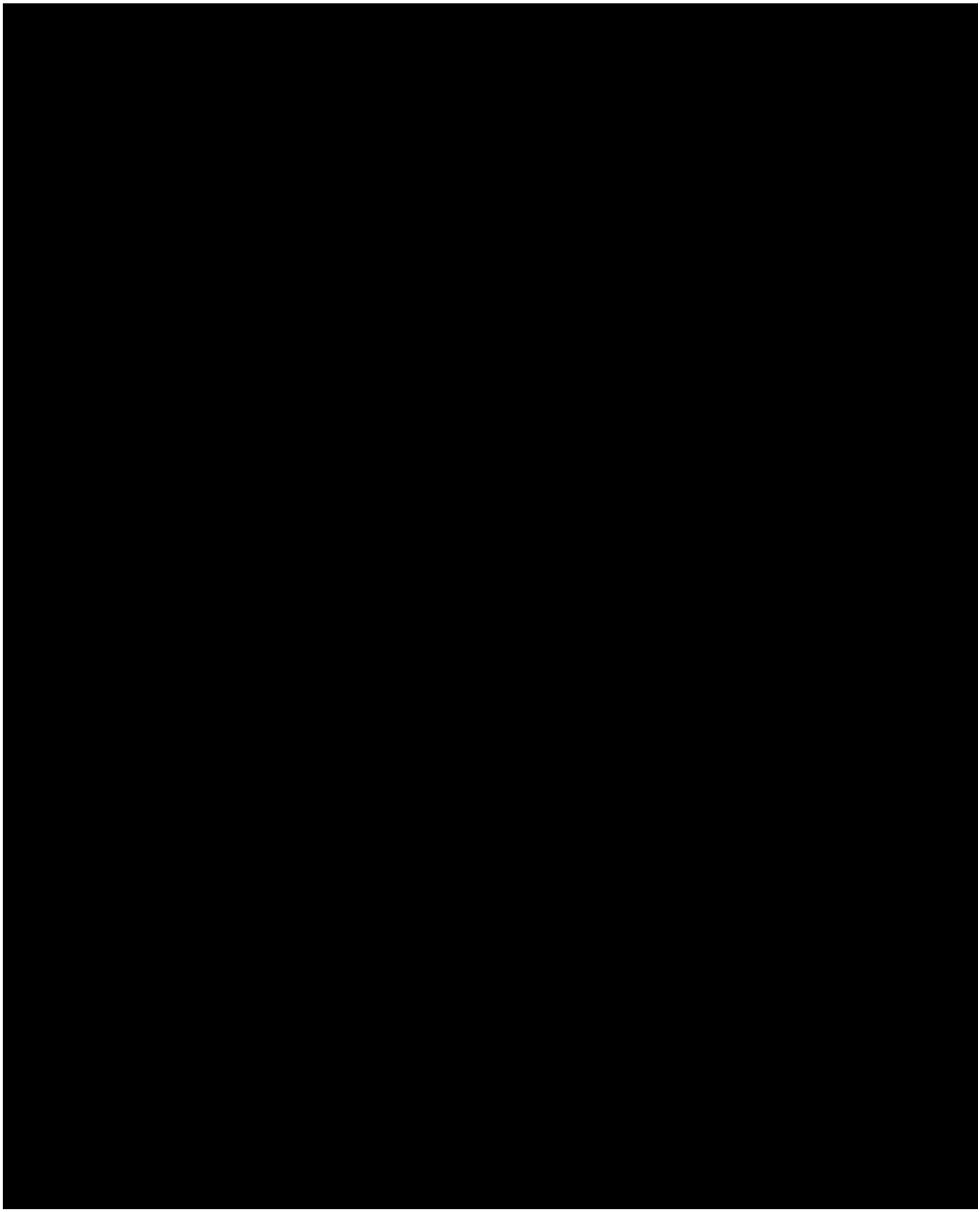
7. Weber J, Thompson JA, Hamid O, et al: A randomized, double-blind, placebo-controlled, phase II study comparing the tolerability and efficacy of ipilimumab administered with or without prophylactic budesonide in patients with unresectable stage III or IV melanoma. Clin Cancer Res 15:5591-5598, 2009.

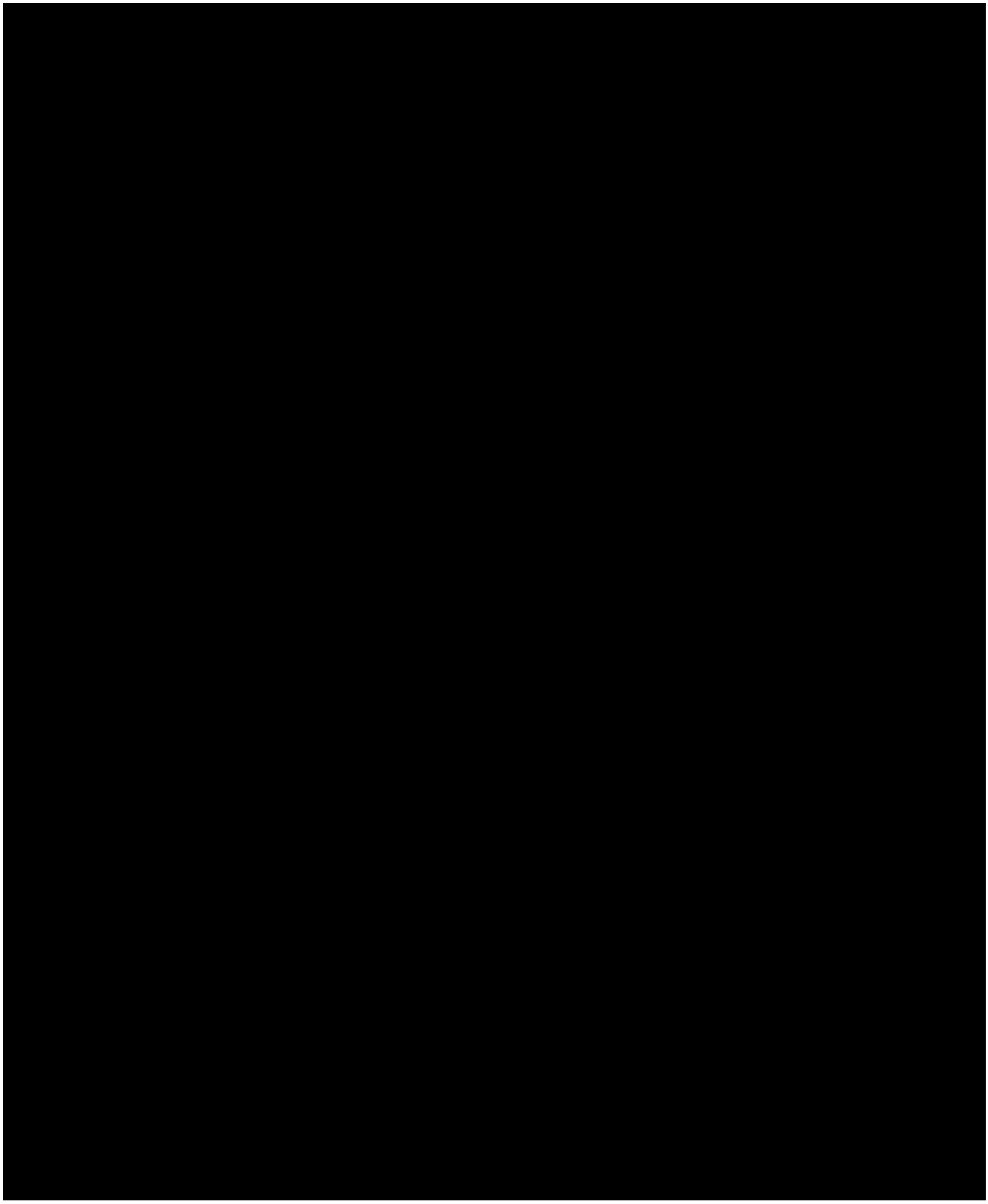
8. Lemech C and Arkenau HT. Novel Treatments for Metastatic Cutaneous Melanoma and the Management of Emergent Toxicities. Clinical Medicine Insights: Oncology 2012:6 53–66.

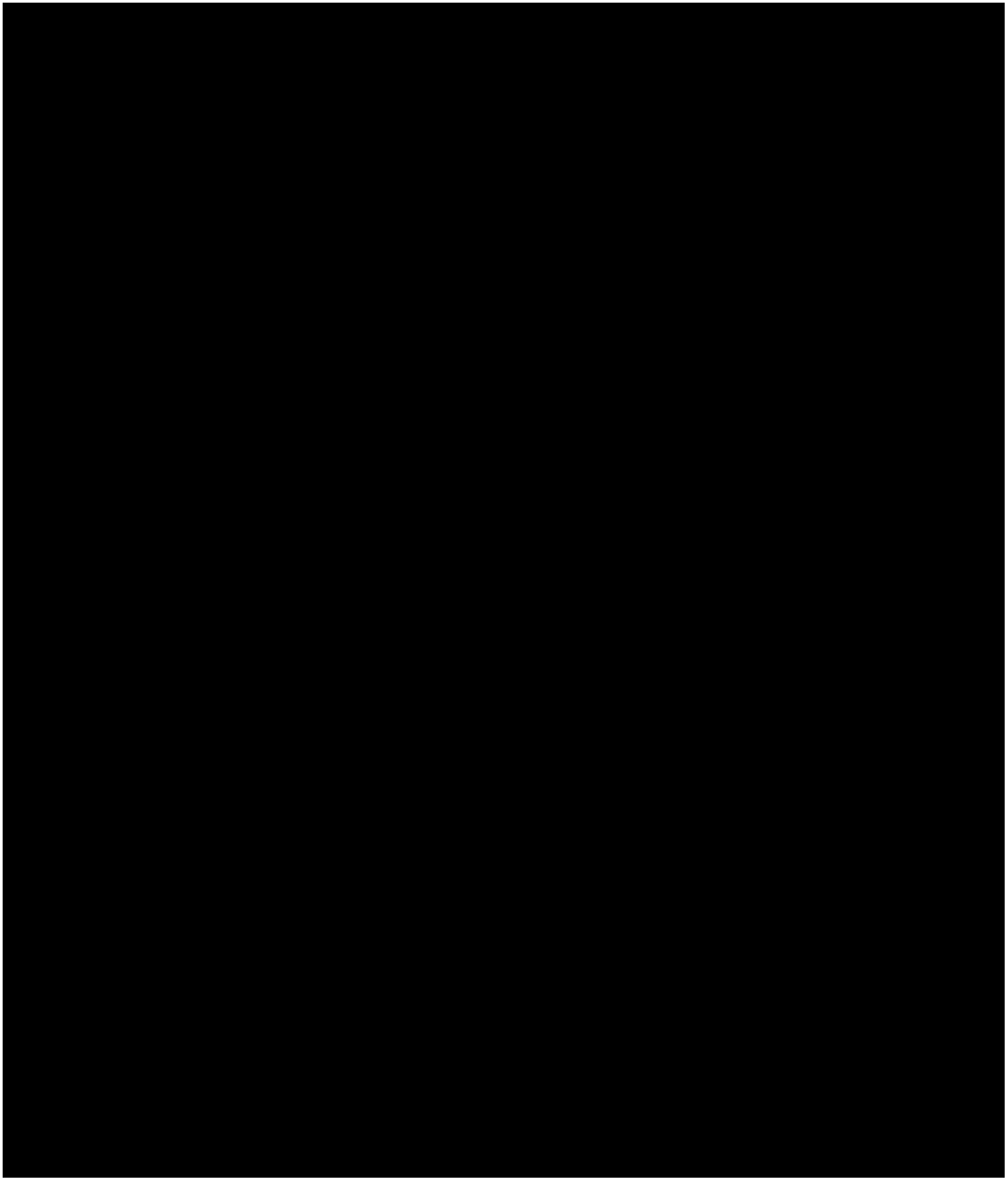
9. Phan GQ, Weber JS, and Sondak VK. CTLA-4 Blockade with Monoclonal Antibodies in Patients with Metastatic Cancer: Surgical Issues. Annals of Surgical Oncology 15(11):3014–3021.

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

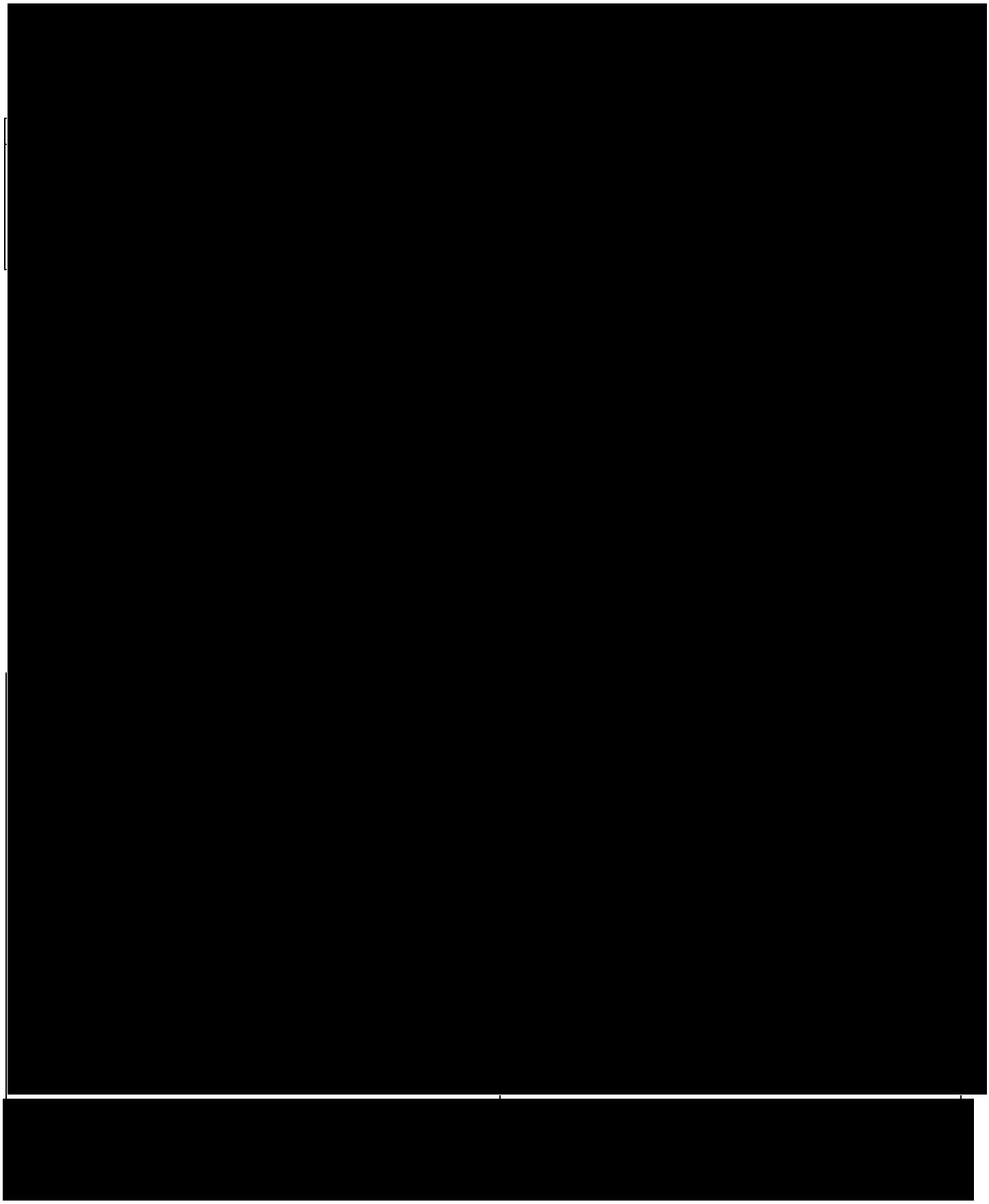
11. Bristol-Myers Squibb: YERVOY (ipilimumab) prescribing information revised March 2011. http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/125377s0000lbl.pdf

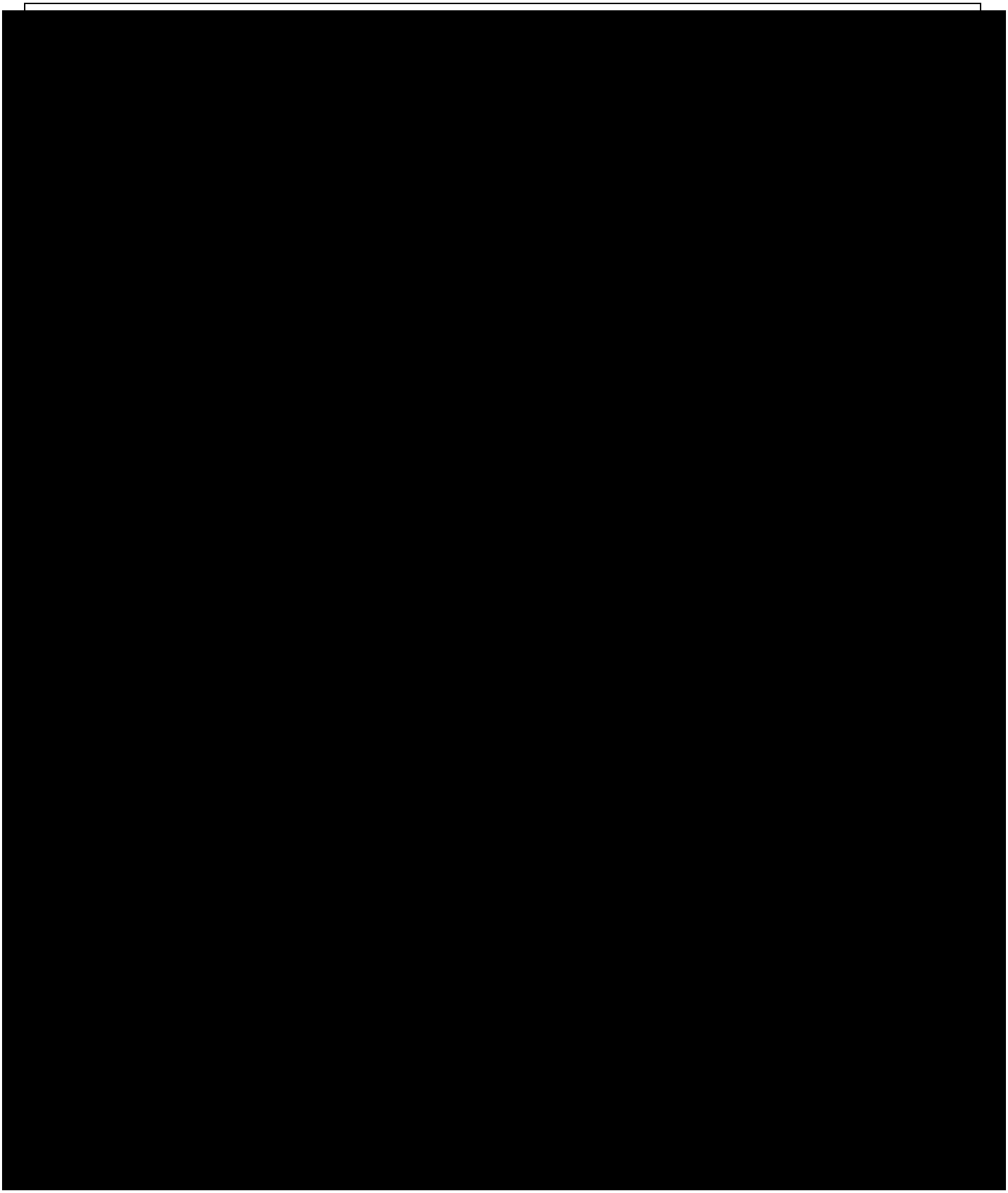






Appendix 13.5 – PD1 Eye Exam Source Document





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MD Signature: _____ Date: _____