SPONSOR: Michael Overman, MD Anderson Cancer Center

TITLE: Neoadjuvant Pembrolizumab for Patients with Mismatch Repair Deficient Locally Advanced Solid Cancers

IND exempt

NCT number: NCT04082572

Coordinating Center: *University of Texas MD Anderson Cancer Center*

PI: Michael Overman (moverman@mdanderson.org)
Co-PI: Kaysia Ludford

1.0 TRIAL SUMMARY

Abbreviated Title	Neoadjuvant Pembrolizumab for Patients with Mismatch Repair Deficient Locally Advanced Solid Cancers
Trial Phase	*II*
Clinical Indication	Treatment of MSI high locally advanced solid tumors in the neoadjuvant setting
Trial Type	Interventional
Type of control	None
Route of administration	Intravenous
Trial Blinding	Unblinded, open-label
Treatment Groups	All patients will receive pembrolizumab 200mg every 3 weeks
Number of trial participants	35 patients
Estimated enrollment period	We estimate that the trial will require approximately 17 months from the first patient enrolling until the final patient signs informed consent.
Estimated duration of trial	We estimate that the trial will require approximately 24 months to allow full accrual and at least the first 6 cycles of pembrolizumab.
Duration of Participation	Until disease progression, drug intolerance, or 24 months of pembrolizumab therapy.
Estimated average length of treatment per patient	One year

2.0 TRIAL DESIGN

2.1 Trial Design

This study is a Phase II open-label, single center trial assessing the safety and efficacy of pembrolizumab given pre-operatively for 6 months in patients with locally advanced (unresectable primary cancer or a resectable primary cancer with a high chance of recurrence) dMMR solid organ tumors. High risk will be defined by the treating physician as patients with an estimated risk of recurrence of greater than or equal to 20%. Given the variety of cancer types and variety of factors within each tumor type this decision will be based on an expert treating physician estimation for that specific disease type. As an example, for colon cancer, clinoco-radiographic factors have been incorporated into risk recurrence estimation include: age, CEA level, MRI identified perineural or lymphovascular invasion, radiographic T stage, presence of enlarged lymph nodes on radiographic imaging, and involvement of neighboring structures[34]. Unresectable versus resectable status will be defined at the time of study enrollment, as patients with resectable cancers will be monitored to ensure an adequate rate of surgical resection. All tumor types are eligible and prior radiation or chemotherapy is allowed. Based on epidemiological distribution of dMMR we anticipate 70% of tumors will be colorectal, endometrial, gastric and adrenocortical carcinomas.

To ensure safety, interim safety monitoring will be conducted to ensure the consequent resection in resectable patients who do not respond to therapy. In addition, Bayesian toxicity stopping boundaries will be applied using the approach of Thall, Simon, Estey (1995, 1996) for the total of 35 patients throughout

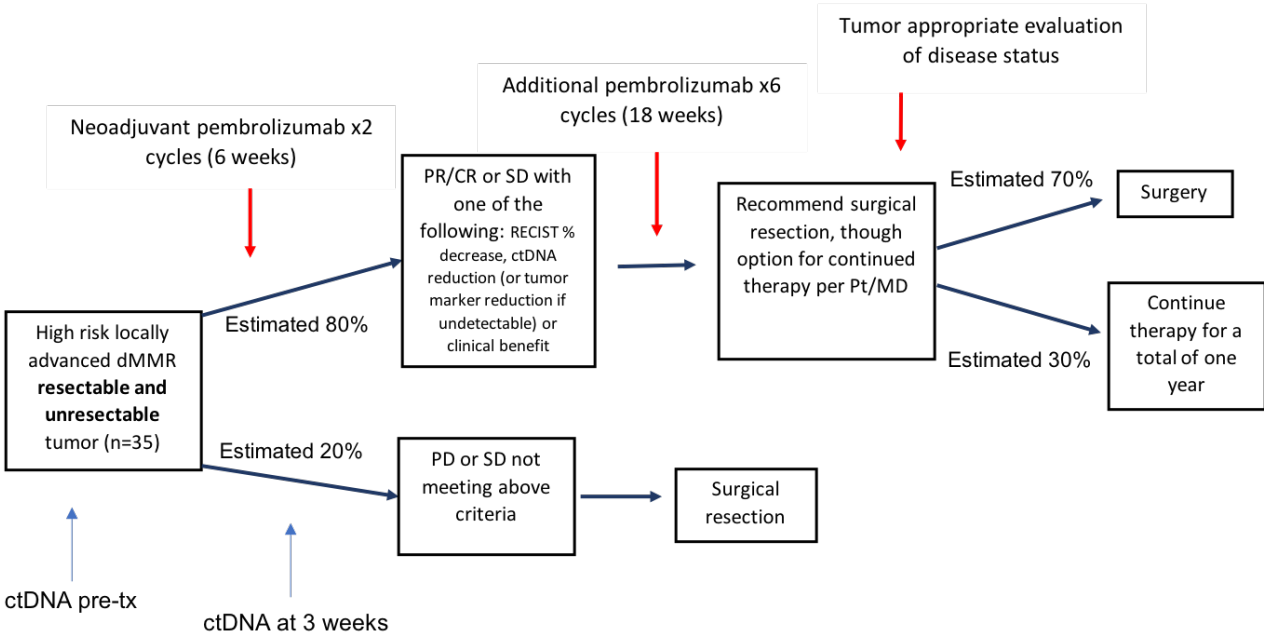
the study. In addition early use of ctDNA will be utilized in addition to radiographic RECIST v1.1 data to help determine treatment benefit at the early time point of 6 weeks. Patients will have pre-treatment and cycle 2 day 1 (3weeks) ctDNA sampling via an MD Anderson CLIA certified 70 gene liquid biopsy panel. After two cycles of pembrolizumab (6weeks) patients will be assessed for a benefit from therapy. Patients with clinical benefit will continue therapy on clinical trial and those that are not benefiting will discontinue the clinical trial. Clinical benefit will be defined if a patient meets any of the following criteria:

(i) Patients with PR/CR per RECIST v1.1
(ii) SD per RECISTv1.1 with either a decrease in total tumor measurement (-1% to -19%), or a stable or decreases in ctDNA tumor mutation from baseline. If there are no mutations on baseline ctDNA then elevated tumor marker can be utilized, such as CEA, CA 19-9, or PSA for example.
(iii) Patients who are felt to have clinical benefit (such as improvement in pain, reduction in bleeding, improved bowel function…).

Patients meeting these criteria will continue therapy with per protocol restaging imaging studies. Stable or decrease in ctDNA tumor mutation will be defined as ctDNA that is declining or the same as pretreatment and if multiple mutations exist then dominant clone will be utilized. Patients with PR/CR/SD will continue therapy for a total of 6 months. At the 6-month time point all participants are recommended to proceed to surgery. However, due to the potential for extremely high risk surgeries to be needed on this clinical trial (for example brain resection for dMMR glioblastoma multiforme) the patient and physician can opt to forego surgery and continue pembrolizumab for a total of one year. Post-operatively after surgical resection following pembrolizumab patients will be monitored for complications (Clavien-Dindo classification for severity[1]) for up to 30 days.

Prior radiation, surgery, or chemotherapy is allowed. Locally recurrent disease is allowed. Disease that is not RECIST measurable maybe allowed after discussions with study PI as long as disease is evaluable by another modality or blood tumor marker/ctDNA is measurable.

2.2 Trial Diagram



OBJECTIVES & ENDPOINTS & HYPOTHESISES

2.3 Primary Objective & Endpoints & Hypothesis

(1) Hypothesis

We hypothesize that neoadjuvant pembrolizumab will be safe and result in a high pathological complete response rate.

(2) Primary Objectives

(i) To assess the safety of neo-adjuvant pembrolizumab in patients with locally advanced (unresectable primary cancer or resectable primary cancer with a high chance of recurrence)) dMMR solid organ tumors by CTCAE assessed toxicity and post-surgical complication assessment by the Clavien-Dindo classification[1]

(ii) To assess the rate of complete pathological response for patients who undergo surgical resection following at least 3 doses of neoadjuvant pembrolizumab. The primary endpoint is pCR after 3 doses.

2.4 Secondary Objective

(i) To quantify the rate of organ sparing at 1 year for all patients treated with one dose of pembrolizumab (intent to treat) and those patients who receive at least 3 doses of neoadjuvant pembrolizumab and decline to undergo surgical resection and opt to continue receiving pembrolizumab for a total of 1 year.

(ii) To assess radiographic tumor response to neoadjuvant pembrolizumab

(iii) To estimate the relapse-free survival and overall survival in all enrolled participants

(iv) To determine the overall rates of pathological response to neoadjuvant pembrolizumab

(v) To assess the rate of complete pathological response (intent to treat) for patients who undergo surgical resection following at least 1 dose of neoadjuvant pembrolizumab.

2.5 Exploratory Objective:

(i) To explore the predictive ability of changes in ctDNA for efficacy endpoints.

(ii) To determine if total mutational burden correlate with response and extent of benefit from pembrolizumab

(iii) To correlate pre-treatment tumor samples tumor-immune microenvironment (for example T-effector cell populations; CD4 subsets; T-regulatory populations; B cell populations; dendritic and macrophage populations) with efficacy endpoints.

(iv) To compare targeted gene expression profiles of immune related genes and genes pertaining to common cancer signaling pathways in pre-treatment samples and also the change in these factors for cases with both pre and on-treatment (i.e. at time of resection) tumor samples of responders (stable disease or radiographic response prior to resection) versus non-responders (progression prior to resection).

3.0 BACKGROUND & RATIONALE

3.1 Background

PEMBROLIZUMAB

Pembrolizumab is a potent humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) with high specificity of binding to the programmed cell death 1 (PD-1) receptor, thus inhibiting its interaction with programmed cell death ligand 1 (PD-L1) and programmed cell death ligand 2 (PD-L2). Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an intravenous (IV) immunotherapy for advanced malignancies. Keytruda® (pembrolizumab) is indicated

for the treatment of patients across a number of indications because of its mechanism of action to bind the PD-1 receptor on the T cell. For more details on specific indications refer to the Investigator brochure.

MSI-HIGH CANCER

Microsatellites are short tracts of DNA in which there are multiple repeats (on the order of 5-50) of 1 to 5 base pair motifs. They occur at thousands of locations within the genome. Many microsatellites are located in non-coding DNA regions and thus are biologically silent. Others are located in regulatory or coding DNA – which can affect biological activity and lead to disease. The mismatch repair (MMR) system is one of several cellular DNA repair mechanisms that functions to maintain the count and integrity of microsatellites during cell division. Deficiencies in the MMR system lead to cells being unable to regulate the length of their microsatellites during cell division, a term called microsatellite instability (MSI). This leads to hypermutability and disease states such as cancers[2]. Mismatch repair deficiencies typically occur through inherited germline mutations in mismatch repair genes such as the case in Lynch syndrome or through somatic hypermutation of mismatch repair genes such as MLH1. The most common tumor types harboring defects in MMR and thus MSI are colorectal, endometrial and gastric adenocarcinomas. MSI is routinely tested in all colorectal cancer patients in accordance with the National Comprehensive Cancer Network (NCCN) guidelines and in selected patients with endometrial and gastric tumors. Little is known about the true prevalence in other cancer types. In order to perform a more comprehensive surveillance of the landscape of MSI across a wide range of tumors, Bonneville and Crook et al[3] examined paired whole-exome sequencing data primarily from the The Cancer Genome Atlas (TCGA) database in 39 distinct cancer types representing 11,139 tumors in 11,080 patients. As shown in figure 1 below, MSI was detected in 27 distinct tumor types with approximately 30% prevalence in endometrial carcinomas and just over 15% in colon and gastric adenocarcinomas consistent with previously published data by Hause[4] which had examined MSI prevalence in 17 distinct tumor types. Interestingly, this study by Bonneville et al.[3] showed significant MSI representation in other tumor types not previously associated with microsatellite instability including adrenocortical carcinoma (~4%), uterine carcino-sarcoma cervical squamous cell carcinoma, Wilms tumor and mesothelioma. MSI status has been shown to be predictive of response to chemotherapy and immunotherapy in colorectal cancers in addition to having prognostic value. Less is known about its predictive and prognostic value in non-colorectal cancers.

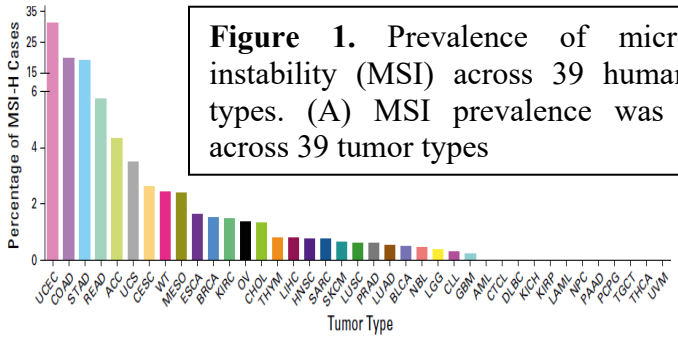


Figure 1. Prevalence of microsatellite instability (MSI) across 39 human cancer types. (A) MSI prevalence was detected across 39 tumor types

LIMITATION OF STANDARD CHEMOTHERAPY IN dMMR CANCER

In colorectal cancer (CRC) the standard treatment for Stage III and high risk Stage II disease is adjuvant 5-fluorouracil (5-FU) based chemotherapy which confers survival advantage of 10%[5]. However, pre-clinical and clinical studies have demonstrated that this advantage does not apply to patients whose tumors express microsatellite instability (MSI-H). Several in vitro studies have shown that MSI-H tumors are resistant to many commonly used chemotherapeutic agents including 5-FU[6-8]. Meyers et al[8] found that MSI-H CRC cell lines with mismatch repair (MMR) deficiency secondary to hMLH1 dysfunction were two-fold more resistant to 5-FU compared to the same cell line with a mismatch repair (MMR) proficient system (restored by chromosome 3 transfer) as shown in figure 2 below. 5-FU is cytotoxic to cancer cells via its active metabolites: fluorodeoxyuridine triphosphate (FdUTP) and fluoridine triphosphate (FUTP) which disrupt DNA and RNA synthesis and disrupt the action of thymidylate synthase leading to nucleotide pool imbalance. The mechanism of 5-FU resistance in MSI-H tumors is thought to be secondary to inability of MMR deficient genes to bind DNA modified by incorporation of 5-FU and its metabolites and by reduced thymidylate synthase activity in MSI-H tumors[9-10]. Similarly, clinical studies have shown that the clinical benefit derived from adjuvant 5-FU based therapies is observed only in MSS patients but not MSI-H patients[11-12]. In an analysis of 570 tissue specimens of patients with Stage II and III CRC from pooled randomized control trials in which patients were randomized either to adjuvant 5-FU or no 5-FU, Ribic et al[11] highlighted two important findings: 1) there was a trend towards reduced survival in patients with MSI-H CRCs receiving 5-FU chemotherapy compared to patients with MSI-H CRCs who did not and 2) patients with MSI-H tumors who did not receive 5-FU had increased 5 year survival rate compared to patients with MSS tumors who did not receive adjuvant 5-FU. Like CRC 5-FU is used in neoadjuvant and adjuvant therapy for gastric cancer. Data for chemotherapy resistance in other solid tumors with microsatellite instability is limited, however preclinical data suggests this effect is also observed with alkylating agents in endometrial carcinoma cell lines known to have mismatch repair deficiency[13]. For Stage II and III endometrial carcinomas with high risk features, the standard of care is systemic adjuvant therapy which includes chemotherapeutic agents such as platinum. There are no clinical studies outlining whether patients with MSI-H endometrial carcinomas respond equivalently to adjuvant chemotherapy as patients with MSS endometrial carcinomas. Given the pre-clinical and clinical data demonstrating that standard chemotherapy may have limited role in the adjuvant treatment of resectable MSI-H tumors, there is a need to explore alternative therapeutic options.

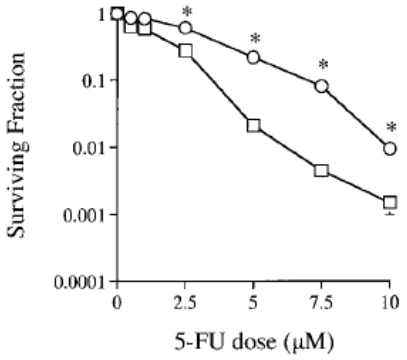


Figure 2. Cytotoxicity of MMR-deficient HCT116 (circle) and MMR-proficient HCT116 3-6 (square) colon cell lines caused by 5-FU. The cell lines were treated with various concentrations of 5-FU continuously for 10 days and colony forming ability was assessed.

IMMUNOTHERAPY IN METASTATIC dMMR CANCER

Mismatch-repair deficiency (dMMR) occurs in a number of solid cancers including colorectal, endometrial, gastric, uterine, biliary tract, pancreatic, ovarian and small intestinal cancer, with 70% of cases occurring among the first three. Key studies have shown that mismatch-repair status predicts clinical

benefit of immune checkpoint blockade. In a landmark trial to assess the clinical activity of pembrolizumab in patients with progressive metastatic carcinoma with and without mismatch-repair deficiency, Le et al[14] showed immune-related objective response rate and immune-related progression free survival rate of 71% and 67% in patients with mismatch-repair deficient non-colorectal cancers. The immune-related objective response rate and immune-related progression free survival rates for mismatch deficient colorectal cancers were 40% and 78% respectively compared to 0% and 11% respectively for mismatch-repair proficient colorectal cancers (see figures 2 and 3 below) [14-15].

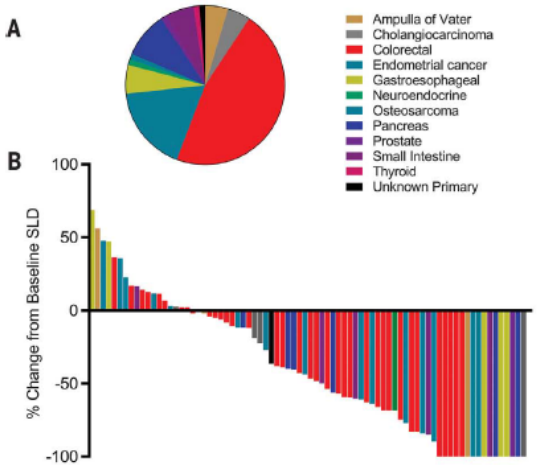


Figure 3. Radiographic responses to treatment with pembrolizumab based on RECIST criteria.

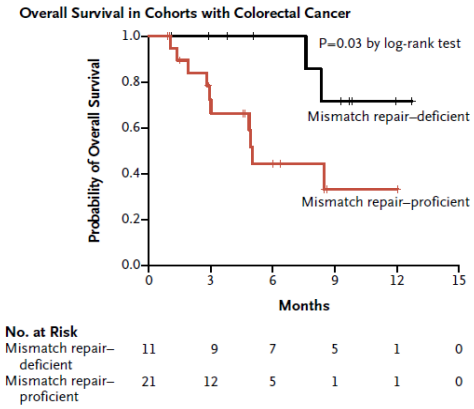


Figure 4. Overall survival among patients with patients with mismatch repair deficient and proficient CRC after pembrolizumab.

Our group has similarly shown high response rates of 31% and progression free survival of 69% at 12 weeks or more in patients with metastatic colorectal cancer with dMMR, treated with nivolumab. Median duration of response was not yet reached at median follow up of one year[16].

This activity level has also been demonstrated by Le et al[14] as the pembrolizumab study for dMMR solid tumors provided therapy for a maximum of 2 years. At the time of the publication 18 patients had reached 2 years and stopped therapy. At a median follow-up of 8 months, none of these 18 patients has had disease progression/recurrence.

NEOADJUVANT AND ADJUVANT IMMUNOHERAPY

Treatment with PD1 inhibitors represents a major advancement in the treatment of Stage IV MSI-H colorectal and non-colorectal cancers. For patients with resectable MSI-H colorectal cancer, surgical resection ± chemotherapy is the standard of care. Despite treatment with curative intent many patients subsequently relapse and develop distant disease. Given that immune checkpoint blockade against programmed cell death-1 (PD-1) is associated with significant improvement in progression free survival in stage IV disease and given that MSI-H tumors do not respond well to standard chemotherapy, there is a need to evaluate PD1 inhibitors in earlier-stage disease. Neoadjuvant immunotherapy is appealing since the primary tumor can serve as a source of antigens against which expanded and activated tumor-specific T-cells are produced by the host to effect systemic surveillance of micrometastases. In addition, neoadjuvant utilization of PD1 blockade offers the opportunity to investigate the in vivo effects of PD1 inhibition on the tumor micro environment and how that correlates with the periphery such as release of ctDNA.

Recently presented data from the NICHE trial at ESMO 2018[35] highlights the impressive response neoadjuvant immune checkpoint inhibition can elicit in early stage dMMR colon adenocarcinomas. In this study, combination checkpoint inhibition with ipilimumab 1mg/kg (day 1) and nivolumab 3mg/kg (days 1 and 15) was administered neoadjuvantly to a cohort of 19 patients stages I-III colon adenocarcinoma, 15 of whom were evaluated for response. Of those, 7 patients had dMMR while 8 harbored pMMR tumors. 4 of the 7 patients with dMMR tumors has complete pathological response at time of definitive resection after 1 cycle of combination checkpoint inhibition. The remaining 3 had 1-2% viable residual tumor. In contrast, among the 8 patients with pMMR, 2 had 100% viable residual tumor at resection and the remaining 6 had 85-95% viable residual tumor. Importantly, there were only 5 cases of grade 3 toxicity and these did not result in delays in surgery.This data confirms that neoadjuvant immune checkpoint inhibition can be safely given and significantly, can generate complete pathological response in early stage dMMR colon cancers.

Likelwise, preliminary data from ongoing trials in other checkpoint sensitive tumor types such as non-small cell lung cancer (NSCLC) have demonstrated that the integration of checkpoint blockage into the treatment of early-stage and locally advanced NSCLC is safe, tolerable, and has the potential to improve outcomes without adding substantial toxicity[17]. As an example, Forde et al[18] performed a pilot study to examine the safety and feasibility of the use of neoadjuvant nivolumab in 21 Stage I-IIIA resectable NSCLC. The study was designed such that treatment would not be considered feasible if the probability that surgery would be delayed was 90% or more for more than 25% of the patient. Of 21 planned resections, 20 were completed and there were no surgical delays thus feasibility endpoint was met. Similarly safety end point was satisfied with minor grade 3-4 events.

Additional data suggests there may be superior efficacy of neoadjuvant compared to adjuvant immune checkpoint blockade in immune responsive disease such as non-small cell lung cancer[19]. Preclinical models of resectable NSCLC were generated and immune response after neoadjuvant or adjuvant immunotherapy investigated. Mice with established tumor were randomized to either 3 doses of neoadjuvant anti-PD1, anti-CTLA4, the combination of both or to observation followed by resection of primary tumor 2 days after immunotherapy. On post-operative day 2, mice in the observation group were treated with 3 doses of anti-PD1, anti-CTLA-4 or both and survival and subsequent lung metastases quantified. Notably, combined therapy in the neoadjuvant setting significantly prolonged survival compared to adjuvant combined treatment with more profound reduction in lung metastases compared to adjuvant combined treatment.

Anecdotally at MD Anderson Cancer Center, we have treated two patients with locally advanced dMMR colon adenocarcinoma with anti-PD1 therapy prior to surgical resection of the primary and observed near pathological response in 1 and complete pathological response in the other. As an example patient YH is a 34-year-old man with dMMR locally advanced colorectal adenocarcinoma with abdominal lymphadenopathy who was treated initially with capecitabine/oxliplatin/bevacizumab with stable disease. He subsequently received 3 cycles of pembrolizumab followed by right colectomy one month later. Pathology of the surgical specimen revealed near pathological complete response with "residual adenocarcinoma almost exclusively acellular mucin with rare cluster of well-differentiated adenocarcinoma cells". Eighty of eighty resected lymph nodes were negative for adenocarcinoma. The second patient, a 71-year-old woman with dMMR locally advanced cecal adenocarcinoma with invasion of right lower quadrant mesentery and abdominal lymphadenopathy received 4 cycles of FOLFOX terminated prematurely secondary to poor tolerance. She subsequently received 5 cycles of nivolumab followed by resection of primary 3 months later. Pathology of resected specimen revealed complete pathological response. Though anecdotal in nature this experience appears to demonstrate activity similar to what is seen in metastatic patients and suggests this approach is safe in the locally advanced setting.

NEOADJUVANT CHEMOTHERAPY AS A STANDARD CANCER APPROACH

Neoadjuvant therapy represents a standard of care for multiple cancer types due to the ability to downstage cancer to enhance surgical resection and the ability to provide earlier therapy to micrometastatic disease, which represents the site of greatest post-surgical failure for most cancer types. In particular neoadjuvant therapy is standard for locally advanced gastroesophageal cancers, rectal cancer, T4b colon cancers, and endometrial cancers with cervical involvement. In particular for colon cancer in 2016, the NCCN guidelines included neoadjuvant chemotherapy as a treatment option for patients with clinical T4b colon cancer. The FOxTROT Collaborative Group[20] examined the feasibility, safety and efficacy of preoperative chemotherapy for colon cancer in a pilot randomized controlled trial comparing neoadjuvant chemotherapy followed by surgery and adjuvant chemotherapy to standard of care treatment: surgery followed by adjuvant chemotherapy. The results demonstrated that neoadjuvant chemotherapy resulted in significant TNM downstaging, reduction in resection margin involvement and reduction in tumor regression grading. The Phase III trial to assess long term oncological outcome is ongoing. Retrospective analysis of 921 patients, 3% of adult patients with non-metastatic T3 or T4 colon cancer identified in the National Cancer Database between 2006 and 2014, who received neoadjuvant chemotherapy prior to surgical resection of their colon cancer showed patients with T4b colon cancer treated with neoadjuvant chemotherapy had a 23% lower risk of death at 3 years compared to patients that had adjuvant chemotherapy[21].

3.1.1 Pembrolizumab Background

The importance of intact immune surveillance function in controlling outgrowth of neoplastic transformations has been known for decades[22]. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells/FoxP3+ regulatory T-cells (T-regs) correlates with improved prognosis and long-term survival in solid malignancies, such as ovarian, colorectal, and pancreatic cancer; hepatocellular carcinoma; malignant melanoma; and renal

cell carcinoma. Tumor-infiltrating lymphocytes can be expanded ex vivo and reinfused, inducing durable objective tumor responses in cancers such as melanoma [23-24].

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 immunoglobulin (Ig) superfamily member related to cluster of differentiation 28 (CD28) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) that has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) [25-26].

The structure of murine PD-1 has been resolved[27]. PD-1 and its family members are type I transmembrane glycoproteins containing an Ig-variable–type (IgV-type) domain responsible for ligand binding and a cytoplasmic tail 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, and an immunoreceptor tyrosine-based switch motif. Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases, SHP-1 and SHP-2, to the immunoreceptor tyrosine-based switch motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3 zeta (CD3ζ), protein kinase C-theta (PKCθ), and zeta-chain-associated protein kinase (ZAP70), which are involved in the CD3 T-cell signaling cascade[26,28-30]. The mechanism by which PD-1 down-modulates T-cell responses is similar to, but distinct from, that of CTLA-4, because both molecules regulate an overlapping set of signaling proteins[31-32]. As a consequence, the PD-1/PD-L1 pathway is an attractive target for therapeutic intervention in mismatch repair deficient solid organ tumors.

3.1.2 Preclinical and Clinical Trial Data for Pembrolizumab

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

3.2 Rationale

3.2.1 Rationale for the Trial

While several studies have shown outstanding efficacy of immune checkpoint blockade in metastatic dMMR cancers, there is a dearth of data in a key clinical setting. There are no reports to date testing this mechanism in the preoperative setting for resectable dMMR solid organ cancers. In both metastatic melanoma and dMMR solid cancers, pembrolizumab has demonstrated the ability to eradicate all areas of disease suggesting the potential for a high rate of pathological complete responses and possibly cure from this therapy[33].

Neoadjuvant treatment in the presence of an intact primary tumor maximizes antigen availability for immune priming and could potentially lead to complete pathologic response reducing risk of recurrence post resection of involved organ and ultimately leading to the possibility of organ sparing. As these examples, highlight this study has the potential to bring about a paradigm shift in the treatment of patients with dMMR solid organ tumor through harnessing the immune response through checkpoint blockade in the frontline curative intent setting. This could possibly obviate the need for adjuvant therapy as well as potentiate the possibility of organ sparing while maintaining curative intent.

3.2.2 Justification for Dose

The planned dose of pembrolizumab for this study is 200 mg every 3 weeks (Q3W). Based on the totality of data generated in the Keytruda development program, 200 mg Q3W is the appropriate dose of pembrolizumab for adults across all indications and regardless of tumor type. As outlined below, this dose is justified by:

- Clinical data from 8 randomized studies demonstrating flat dose- and exposure-efficacy relationships from 2 mg/kg Q3W to 10 mg/kg every 2 weeks (Q2W),
- Clinical data showing meaningful improvement in benefit-risk including overall survival at 200 mg Q3W across multiple indications, and
- Pharmacology data showing full target saturation in both systemic circulation (inferred from pharmacokinetic [PK] data) and tumor (inferred from physiologically-based PK [PBPK] analysis) at 200 mg Q3W

Among the 8 randomized dose-comparison studies, a total of 2262 participants were enrolled with melanoma and non-small cell lung cancer (NSCLC), covering different disease settings (treatment naïve, previously treated, PD-L1 enriched, and all-comers) and different treatment settings (monotherapy and in combination with chemotherapy). Five studies compared 2 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B2, KN001 Cohort D, KN002, KN010, and KN021), and 3 studies compared 10 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B3, KN001 Cohort F2 and KN006). All of these studies demonstrated flat dose- and exposure-response relationships across the doses studied representing an approximate 5- to 7.5-fold difference in exposure. The 2 mg/kg (or 200 mg fixed-dose) Q3W provided similar responses to the highest doses studied. Subsequently, flat dose-exposure-response relationships were also observed in other tumor types including head and neck cancer, bladder cancer, gastric cancer and classical Hodgkin Lymphoma, confirming 200 mg Q3W as the appropriate dose independent of the tumor type. These findings are consistent with the mechanism of action of pembrolizumab, which acts by interaction with immune cells, and not via direct binding to cancer cells.

Additionally, pharmacology data clearly show target saturation at 200 mg Q3W. First, PK data in KN001 evaluating target-mediated drug disposition (TMDD) conclusively demonstrated saturation of PD-1 in systemic circulation at doses much lower than 200 mg Q3W. Second, a PBPK analysis was conducted to predict tumor PD-1 saturation over a wide range of tumor penetration and PD-1 expression. This evaluation concluded that pembrolizumab at 200 mg Q3W achieves full PD-1 saturation in both blood and tumor.

Finally, population PK analysis of pembrolizumab, which characterized the influence of body weight and other participant covariates on exposure, has shown that the fixed-dosing provides similar control of PK variability as weight based dosing, with considerable overlap in the distribution of exposures from the 200 mg Q3W fixed dose and 2 mg/kg Q3W dose. Supported by these PK characteristics, and given that fixed-dose has advantages of reduced dosing complexity and reduced potential of dosing errors, the 200 mg Q3W fixed-dose was selected for evaluation across all pembrolizumab protocols.

To date, pembrolizumab (2 mg/kg Q3W) has been evaluated in 85 pediatric participants (aged 1 to 18 years) with advanced melanoma, PD-L1 positive advanced, relapsed, or refractory solid tumors, or lymphoma. The exposures in pediatric participants following the 2 mg/kg Q3W regimen were found to be similar to that observed in adult participants. Pediatric data has also been incorporated in an integrated population PK analysis, which confirmed that a pembrolizumab dose of 2 mg/kg Q3W (up to a maximum of 200 mg Q3W) in pediatric participants renders exposures similar to adults. Based on these results, the pediatric dose for evaluation in this trial is 2 mg/kg Q3W (up to a maximum of 200 mg Q3W).

4.0 METHODOLOGY

4.1 Study Population

4.1.1 Participant Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

1. Male/female participants who are at least 18 years of age on the day of signing informed consent with histologically confirmed diagnosis of solid cancer

2. Solid cancer that is deficient in mismatch repair (dMMR) or microsatellite instability high (MSI-H) as determined by one of three methods:
    a. Immunohistochemistry determined dMMR by complete loss of MLH1, PMS2, MSH2 or MSH6
    b. PCR determined microsatellite instability at >30% of tested microsatellites
    c. Next-generation determined MSI-H based upon instability at multiple microsatellites as determined by the specific next generation sequencing panel
3. Locally advanced cancer defined as either an unresectable primary cancer or a resectable primary cancer with a high chance of recurrence (defined as an estimated greater or equal to 20% chance of recurrence by the treating physician). A resectable primary may include locoregional disease, as long as all disease is felt by the treating physician to be in a resectable distribution.

4. The participant (or legally acceptable representative if applicable) provides written informed consent for the trial.

5. Have measurable disease based on RECIST v1.1 (unless discussed and approved by study PI).

6. Have available archival tumor tissue. Availability will be met as long as a request to obtain formalin-fixed, paraffin embedded (FFPE) tissue blocks (preferred) or slides has been made (unless discussed and approved by study PI).

7. Have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1. Evaluation of ECOG is to be performed within 7 days prior to the date of signing study consent.

8. A female participant is eligible to participate if she is not pregnant (see Appendix 3), not breastfeeding, and at least one of the following conditions applies:
   a.) Not a woman of childbearing potential (WOCBP) as defined in Appendix 3
   OR
   b.) A WOCBP who agrees to follow the contraceptive guidance in Appendix 3 during the treatment period and for at least [120 days (corresponding to time needed to eliminate any study treatment(s) plus 30 days (a menstruation cycle) for risk of genotoxicity] after the last dose of study treatment.
9. Have adequate organ function as defined in the following table (Table 1). Specimens must be collected within 14 days prior to the start of study treatment.

Table 1 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1500/μL
Platelets	≥100 000/μL
Hemoglobin	≥ 8.0 g/dL or ≥5.6 mmol/L[a]
Renal	
Creatinine OR Measured or calculated[b] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 × ULN OR ≥30 mL/min for participant with creatinine levels >1.5 × institutional ULN
Hepatic	
Total bilirubin	≤1.5 ×ULN OR direct bilirubin ≤ULN for participants with total bilirubin levels >1.5 × ULN
AST (SGOT) and ALT (SGPT)	≤2.5 × ULN (≤5 × ULN for participants with liver metastases)
Coagulation	

International normalized ratio (INR) OR prothrombin time (PT) Activated partial thromboplastin time (aPTT)	≤1.5 × ULN unless participant is receiving anticoagulant therapy as long as PT or aPTT is within therapeutic range of intended use of anticoagulants

ALT (SGPT) =alanine aminotransferase (serum glutamic pyruvic transaminase); AST (SGOT) =aspartate aminotransferase (serum glutamic oxaloacetic transaminase); GFR=glomerular filtration rate; ULN=upper limit of normal.

[a] Criteria must be met without erythropoietin dependency and without packed red blood cell (pRBC) transfusion within last 2 weeks.

[b] Creatinine clearance (CrCl) should be calculated per institutional standard.

Note: This table includes eligibility-defining laboratory value requirements for treatment; laboratory value requirements should be adapted according to local regulations and guidelines for the administration of specific chemotherapies.

4.1.2 Participant Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1. A WOCBP who has a positive urine pregnancy test within 72 hours prior to enrollment (see Appendix 3). If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. Note: in the event that 72 hours have elapsed between the screening pregnancy test and the first dose of study treatment, another pregnancy test (urine or serum) must be performed and must be negative in order for subject to start receiving study medication.
2. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent or with an agent directed to another stimulatory or co-inhibitory T-cell receptor (e.g., CTLA-4, OX-40, CD137).
3. Has received prior systemic anti-cancer therapy including investigational agents within 2 weeks of study treatment. Note: Participants must have recovered from all AEs due to previous therapies to ≤Grade 1 or baseline. Participants with ≤Grade 2 neuropathy may be eligible.
4. If participant received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting study treatment.
5. Has received prior radiotherapy within 2 weeks of start of study treatment. Participants must have recovered from all radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis. A 1-week washout is permitted for palliative radiation (≤2 weeks of radiotherapy) to non-CNS disease.
6. Has received a live vaccine within 30 days prior to the first dose of study drug. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, Bacillus Calmette–Guérin (BCG), and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed;

however, intranasal influenza vaccines (e.g., FluMist®) are live attenuated vaccines and are not allowed.

7. Is currently participating in or has participated in a study of an investigational agent or has used an investigational device within 4 weeks prior to the first dose of study treatment.
   Note: Participants who have entered the follow-up phase of an investigational study may participate as long as it has been 4 weeks after the last dose of the previous investigational agent.

8. Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior to the first dose of study drug.

9. Has a known additional malignancy that is progressing or has required active treatment within the past 1 year. Note: Participants with basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or carcinoma in situ (e.g. breast carcinoma, cervical cancer in situ) or other similar good prognosis cancer with recurrence rates expected to be <10% that have undergone potentially curative therapy are not excluded.

10. Known metastatic sites of disease. Note: locoregional lymph nodes or tumor deposits are not considered metastatic disease.

11. Has severe hypersensitivity (≥Grade 3) to pembrolizumab and/or any of its excipients.

12. Has active autoimmune disease that has required systemic treatment in the past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g.., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.

13. Has a history of (non-infectious) pneumonitis that required steroids or has current pneumonitis.

14. Has an active infection requiring systemic therapy.

15. Has a known history of Human Immunodeficiency Virus (HIV).

16. Has a known history of Hepatitis B (defined as Hepatitis B surface antigen [HBsAg] reactive) or known active Hepatitis C virus (defined as HCV RNA [qualitative] is detected) infection. Note: no testing for Hepatitis B and Hepatitis C is required unless mandated by local health authority.

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

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

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

4.1.3 Lifestyle Restrictions

4.1.3.1 Meals and Dietary Restrictions

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

4.1.3.2 Contraception

Pembrolizumab may have adverse effects on a fetus in utero. Refer to Appendix 3 for approved methods of contraception.

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

4.1.4 Pregnancy

If a participant inadvertently becomes pregnant while on treatment with pembrolizumab, the participant will be immediately discontinued from study treatment. The site will contact the participant at least monthly and document the participant's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to Merck within 2 working days 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 Merck. If a male participant impregnates his female partner, the study personnel at the site must be informed immediately and the pregnancy must be reported to Merck and followed as described in Section 7.2.2.

4.1.5 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, participants who are breast-feeding are not eligible for enrollment.

4.2 Trial Treatments

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

Table 2 Trial Treatment

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

Trial treatment should begin as close as possible to signing study consent considering appropriate time for screening procedures to be completed.

4.2.1 Timing of Dose Administration

Trial treatment should be administered on Day 1 of each cycle after all procedures/assessments have been completed as detailed on the Trial Flow Chart (Section 6.0). Trial treatment may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons.

All trial treatments will be administered on an outpatient basis.

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

The current label for pembrolizumab contains specific instructions for the preparation of the pembrolizumab infusion fluid and administration of infusion solution.

4.2.2 Dose Modification and toxicity management <u>for immune-related AEs associated with pembrolizumab</u>

AEs associated with pembrolizumab exposure may represent an immunologic etiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than on body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab are provided in Table 3.

Table 3 Dose modification and toxicity management guidelines for immune-related AEs associated with pembrolizumab

General instructions:

1. Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks.
2. For situations where pembrolizumab has been withheld, pembrolizumab can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered. Pembrolizumab should be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks.
3. For severe and life-threatening irAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.

Immune-related AEs	Toxicity grade or conditions (CTCAEv4.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment • Add prophylactic antibiotics for opportunistic infections
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (i.e., diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (i.e., peritoneal signs and ileus).

	Grade 4	Permanently discontinue		• Participants with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
AST / ALT elevation or Increased bilirubin	Grade 2	Withhold	• Administer corticosteroids (initial dose of 0.5- 1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable
	Grade 3 or 4	Permanently discontinue	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold	• Initiate insulin replacement therapy for participants with T1DM • Administer anti-hyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated.	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (e.g., propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or permanently discontinue[1]		

Hypothyroidism	Grade 2-4	Continue	• Initiate thyroid replacement hormones (e.g., levothyroxine or liothyroinine) per standard of care	• Monitor for signs and symptoms of thyroid disorders.
Nephritis and Renal dysfunction	Grade 2	Withhold	• Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper.	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1 or 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
All other immune-related AEs	Intolerable/ persistent Grade 2	Withhold	• Based on type and severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3	Withhold or discontinue based on the type of event. Events that require discontinuation include and not limited to: Gullain-Barre Syndrome, encephalitis		
	Grade 4 or recurrent Grade 3	Permanently discontinue		

1. Withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician.

NOTE:

For participants with Grade 3 or 4 immune-related endocrinopathy where withhold of pembrolizumab is required, pembrolizumab may be resumed when AE resolves to ≤ Grade 2 and is controlled with hormonal replacement therapy or achieved metabolic control (in case of T1DM).

Dose modification and toxicity management of infusion-reactions related to pembrolizumab

Pembrolizumab may cause severe or life threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab associated infusion reaction are provided in Table 4.

Table 4 Pembrolizumab Infusion Reaction Dose modification and 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 participant is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 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 participant should be premedicated for the next scheduled dose. **Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment**	Participant may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of analgesic).

Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: Epinephrine** IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Oxygen Pressors Corticosteroids Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. **Participant is permanently discontinued from further study drug treatment.**	No subsequent dosing
Appropriate resuscitation equipment should be available at the bedside 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		

Other allowed dose interruption for pembrolizumab

Pembrolizumab may be interrupted for situations other than treatment-related AEs such as medical / surgical events or logistical reasons not related to study therapy. Participants should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the patient's study record.

4.2.3 Second Course *

4.3 Participants who stop study treatment with SD or better will not be eligible for a second course of pembrolizumab. The intent of the study is to treat with maximum of 1 year of pembrolizumab. 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 final decision on any supportive therapy or vaccination rests with the investigator and/or the participants' primary physician.

4.3.1 Acceptable Concomitant Medications

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

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

4.3.2 Prohibited Concomitant Medications

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

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol

- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab
- Radiation therapy
    - Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed at the investigator's discretion.
- Live vaccines within 30 days prior to the first dose of study treatment and while participating in the study. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g., FluMist®) are live attenuated vaccines and are not allowed.

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

Participants who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the study. All treatments that the Investigator considers necessary for a participant's welfare may be administered at the discretion of the Investigator in keeping with the community standards of medical care.

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing study. If there is a clinical indication for any medication or vaccination specifically prohibited during the study, discontinuation from study therapy or vaccination may be required. The final decision on any supportive therapy or vaccination rests with the investigator and/or the participant's primary physician. However, the decision to continue the participant on study treatment requires the mutual agreement of the investigator, the Sponsor and the participant.

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

4.3.3 Rescue Medications & Supportive Care

Participants should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined along with the dose modification guidelines in Section 5.2.2, [Table 3]. Where appropriate, these guidelines include the use of oral or IV treatment with corticosteroids, as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment

guidelines are intended to be applied when the Investigator determines the events to be related to pembrolizumab.

Note: If after the evaluation of the event, it is determined not to be related to pembrolizumab, the Investigator does not need to follow the treatment guidance. Refer to [Table 3] in Section 5.2.2 for guidelines regarding dose modification and supportive care.

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

4.4 Participant Withdrawal/Discontinuation Criteria

Participants may discontinue study treatment at any time for any reason or be dropped from the study treatment at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study treatment by the investigator or the Sponsor if study treatment is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding procedures to be performed at study treatment discontinuation are provided in Section 7.1.4 – Other Procedures.

A participant must be discontinued from study treatment but continue to be monitored in the study for any of the following reasons:

- The participant or participant's legally acceptable representative requests to discontinue study treatment
- Confirmed radiographic disease progression outlined in Section 7.1.2.6
- Any progression or recurrence of any malignancy, or any occurrence of another malignancy that requires active treatment
- Unacceptable adverse experiences as described in Section 5.2.2.
- The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or sponsor, placed the participant at unnecessary risk from continued administration of study treatment.
- The participant has a confirmed positive serum pregnancy test
- Noncompliance with study treatment or procedure requirements
- Recurrent Grade 2 pneumonitis
- Discontinuation of treatment may be considered for participants who have attained a confirmed complete response (CR) and have been treated for at least 6 cycles (at least 24 weeks), receiving at least 2 doses of pembrolizumab beyond the date when the initial CR was declared. These participants may be eligible for second course treatment described in Section 5.2.3.

- The participant is lost to follow-up
- Completion of 17 treatments (approximately 1 year) with pembrolizumab
- Note: The number of treatments is calculated starting with the first dose. Participants who stop pembrolizumab after receiving 17 doses are not eligible for retreatment if they progress after stopping study treatment. Administrative reasons

4.5 Participant Replacement Strategy

A participant that discontinues from the study after receiving a dose of pembrolizumab will not be replaced. 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 participants
4. Plans to modify or discontinue the development of the study drug

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

5.0 TRIAL FLOW CHART

5.1 Study Flow Chart

Trial Period:	**Screening Phase**		**Treatment Cycles**								**End of Treatment**	**Post-Treatment**		
Treatment Cycle/Title:	Pre-screening (Visit 1)	Main Study Screening (Visit 2)	1 [a]	2	3	4	To be repeated beyond 8 cycles (max 16 cycles, [1yr]) 5	6	7	8	6m (surgery) or 12m (no surgery)	Safety Follow-up	Follow Up Visits[b]	Survival Follow-Up
Scheduling Window (Days):		-14 to C1D1	± 2	± 3	± 3	± 3	± 3	± 3	± 3	± 3	6m (surgery) or 12m (no surgery)	30 days post +/- 7d	Every 4 months +/- 31d	Every 24 weeks +/-56d
Administrative Procedures														
Informed Consent	x													
Inclusion/Exclusion Criteria	x													
Demographics and Medical History	x													
Prior and Concomitant Medication Review	x	x												
Trial Treatment Administration			x	x	x	x	x	x	x	x				
Post-study anticancer therapy status												x	x	
Survival Status												x	x	x
Clinical Procedures/Assessments														
Review Adverse Events			x	x	x	x	x	x	x	x	x	x		
Full Physical Examination	x	x												
Directed Physical Examination			x	x	x	x	x	x	x	x				
Vital Signs and Weight	x	x	x	x	x	x	x	x	x	x				
ECOG Performance Status	x	x	x											
Laboratory Procedures/Assessments: analysis performed by LOCAL laboratory														
Pregnancy Test – Urine or Serum β-HCG		x	x											
PT/INR and aPTT, HIV, hepatitis*		x												
CBC with Differential		x	x	x	x	x	x	x	x	x				

Trial Period:	**Screening Phase**		**Treatment Cycles**								**End of Treatment**	**Post-Treatment**		
Treatment Cycle/Title:	Pre-screening (Visit 1)	Main Study Screening (Visit 2)	1 [a]	2	3	4	To be repeated beyond 8 cycles (max 16 cycles, [1yr]) 5	6	7	8	6m (surgery) or 12m (no surgery)	Safety Follow-up	Follow Up Visits[b]	Survival Follow-Up
Scheduling Window (Days):		-14 to C1D1	± 2	± 3	± 3	± 3	± 3	± 3	± 3	± 3	6m (surgery) or 12m (no surgery)	30 days post +/- 7d	Every 4 months +/- 31d	Every 24 weeks +/-56d
Comprehensive Serum Chemistry Panel		x	x	x	x	x	x	x	x	x				
Urinalysis		x												
FT4 and TSH		x		x		x		x		x				
Tumor marker (e.g. CEA, PSA…)**		x		x	x			x		x			x	
ctDNA--MD Anderson CLIA validated 70-Gene Liquid Biopsy Panel (LBP-70)		x		x										
Optional tumor biopsies		X		X (may be done between weeks 3-9)										
Efficacy Measurements														
Tumor Imaging (on-tx +/-14 days)***		x			x			x		X****			x	
Archival Tissue Collection/Correlative Studies Blood														
Archival Tissue Collection	x										x			
Correlative Studies Blood Collection		x		x	x			x		x	x			

Trial Period:	**Screening Phase**		**Treatment Cycles**								**End of Treatment**	**Post-Treatment**		
Treatment Cycle/Title:	Pre-screening (Visit 1)	Main Study Screening (Visit 2)	1 [a]	2	3	4	To be repeated beyond 8 cycles (max 16 cycles, [1yr]) 5	6	7	8	6m (surgery) or 12m (no surgery)	Safety Follow-up	Follow Up Visits[b]	Survival Follow-Up
Scheduling Window (Days):		-14 to C1D1	± 2	± 3	± 3	± 3	± 3	± 3	± 3	± 3	6m (surgery) or 12m (no surgery)	30 days post +/- 7d	Every 4 months +/- 31d	Every 24 weeks +/-56d

*can be up to 28days prior to first dose

**if standard of care for that tumor type

***baseline tumor imaging may be up to 28d prior (required imaging based on standard of care for that tumor type)

**** = Cycle 9, 12, and 15. Imaging is not needed on Cycle 8.

[a] If screening labs are done within 3 days of Cycle 1, labs for C1D1 do not need to be repeated

[b] The interval is a recommendation. Given the various tumor types, the follow up should be according to the standard of care approach for each tumor type.

Note: For luminal tumors, endoscopic evaluation prior to and at approximately 3 weeks or first restaging should be considered to help guide disease response assessment.

6.0 TRIAL PROCEDURES

6.1 Trial Procedures

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

Furthermore, additional evaluations/testing may be deemed necessary by the Sponsor and/or Merck for reasons related to participant 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 participant. In these cases, such evaluations/testing will be performed in accordance with those regulations.

6.1.1 Administrative Procedures

6.1.1.1 Informed Consent

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

6.1.1.1.1 General Informed Consent

Consent must be documented by the participant's dated signature or by the participant'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 participant before participation in the trial.

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the participant must receive the IRB/ERC's approval/favorable opinion in advance of use. The participant or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the participant'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 participant's dated signature or by the participant's legally acceptable representative's dated signature.

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

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

6.1.1.2 Inclusion/Exclusion Criteria

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

6.1.1.3 Medical History

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

6.1.1.4 Prior and Concomitant Medications Review

6.1.1.4.1 Prior Medications

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

6.1.1.4.2 Concomitant Medications

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

6.1.1.5 Disease Details and Treatments

6.1.1.5.1 Disease Details

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

6.1.1.5.2 Prior Treatment Details

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

6.1.1.5.3 Subsequent Anti-Cancer Therapy Status

The investigator or qualified designee will review all new anti-neoplastic therapy initiated after the last dose of trial treatment. If a participant 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 participant will move into survival follow-up.

6.1.2 Clinical Procedures/Assessments

6.1.2.1 Adverse Event (AE) Monitoring

The investigator or qualified designee will assess each participant 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 Appendix 2). Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

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

6.1.2.2 Full Physical Exam

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

6.1.2.3 Directed Physical Exam

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

6.1.2.4 Vital Signs

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

6.1.2.5 Eastern Cooperative Oncology Group (ECOG) Performance Scale

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

6.1.2.6 Tumor Imaging and Assessment of Disease

This trial will utilize iRECIST upon initial progression at any time point after the first restaging study at 6weeks. At this initial restaging study, iRECIST will not be utilized but the criteria specified in the protocol will be used to guide subsequent treatment at this time point.

Tumor imaging is strongly preferred to be acquired by computed tomography (CT). For the abdomen and pelvis, contrast-enhanced magnetic resonance imaging (MRI) may be used when CT with iodinated contrast is contraindicated, or when local practice mandates it. MRI is the strongly preferred modality for imaging the brain. The same imaging technique regarding modality, ideally the same scanner, and the use of contrast should be used in a participant throughout the study to optimize the reproducibility of the assessment of existing and new tumor burden and improve the accuracy of the assessment of response or progression based on imaging. For participants with primary brain tumor, brain imaging is required at screening. MRI is preferred; however CT imaging will be acceptable, if MRI is medically contraindicated. For luminal tumors, endoscopic evaluation prior to and at first restaging should be considered to help guide disease response assessment. Expedited confirmation of measurable disease based on RECIST 1.1 at screening should be used to determine participant eligibility. Confirmation that the participant's imaging shows at least 1 lesion that is appropriate for selection as a target lesion per RECIST 1.1 is highly recommended prior to participant allocation. Participant eligibility will be determined using local assessment (Investigator assessment) based on RECIST 1.1. In addition, images (including via other modalities) that are obtained at an unscheduled time point to determine disease progression, as well as imaging obtained for other reasons, but which demonstrate radiologic progression, should also be used to determine progression.

When the Investigator identifies radiographic progression per RECIST 1.1, efforts should be made to verify radiologic PD. Treatment should continue until PD has been verified. Regardless of whether PD is verified, if the Investigator considers the participant has progressed, but elects to implement iRECIST, the Investigator will assess for confirmation of progression by iRECIST at subsequent time points.

Expedited confirmation of measurable disease based on RECIST 1.1 at Screening should be used to determine participant eligibility. Confirmation that the participant's imaging shows at least 1 lesion that is appropriate for selection as a target lesion per RECIST 1.1 is highly recommended prior to participant enrollment

7.1.2.6.1 Initial Tumor Imaging

Initial tumor imaging at Screening must be performed within [28] days prior to the date of pembrolizumab. The site study team must review screening images to confirm the participant has measurable disease per RECIST 1.1. Tumor imaging performed as part of routine clinical management is acceptable for use as screening tumor imaging if they are of diagnostic quality and performed within 28 days prior to the date of first pembrolizumab. Need for additional imaging aside from standard cross-sectional imaging will be determined by the standard of care imaging performed for that tumor type.

6.1.2.6.1 Tumor Imaging During the Study

The first on-study imaging assessment should be performed at approximately 6 weeks (42 days ±7 days]) from the date of first pembrolizumab. Subsequent tumor imaging should be performed every 9 weeks (63 days ±7 days) or more frequently if clinically indicated. . It is highly recommended that imaging timing should follow calendar days and should not be adjusted for delays in cycle starts. Imaging should continue to be performed until disease progression is identified by the Investigator or completion of planned treatment duration per protocol.

Objective response should be confirmed by a repeat imaging assessment. Tumor imaging to confirm PR or CR should be performed at least 4 weeks after the first indication of a response is observed. Participants will then return to regular scheduled imaging every 9 weeks, starting with the next scheduled imaging time point. Participants who receive additional imaging for confirmation do not need to undergo the next scheduled tumor imaging if it is less than 4 weeks later; tumor imaging may resume at the subsequent scheduled imaging time point.

Per iRECIST (Section 9.2.1.6), disease progression should be confirmed 4 to 8 weeks after first radiologic evidence of PD in clinically stable participants. Participants who have unconfirmed disease progression may continue on treatment at the discretion of the Investigator until progression is confirmed by the site provided they have met the conditions detailed in Section 9.2.1.6. Participants who receive confirmatory imaging do not need to undergo the next scheduled tumor imaging if it is less than 4 weeks later; tumor imaging may resume at the subsequent scheduled imaging time point, if clinically stable. Participants who have confirmed disease progression by iRECIST, as assessed by the site, will discontinue study treatment. Exceptions are detailed in Section 9.2.1.6.

6.1.2.6.2 End of Treatment and Follow-up Tumor Imaging

In participants who discontinue study treatment, tumor imaging should be performed at the time of treatment discontinuation (±4 week window). If previous imaging was obtained within 4 weeks prior to the date of discontinuation, then imaging at treatment discontinuation is not mandatory. In participants who discontinue study treatment due to documented disease

progression and the Investigator elects not to implement iRECIST, this is the final required tumor imaging.

In participants who discontinue study treatment without documented disease progression, every effort should be made to continue monitoring their disease status by tumor imaging using the same imaging schedule used while on treatment (every 9 weeks in Year 1 or every 16 weeks after Year 1) to monitor disease status until the start of a new anticancer treatment, disease progression, pregnancy, death, withdrawal of consent, or the end of the study, whichever occurs first.

6.1.2.6.3 Second Course (Retreatment) Tumor Imaging

Tumor imaging must be performed within 28 days prior to restarting treatment with pembrolizumab. Local reading (Investigator assessment with site radiology reading) will be used to determine eligibility.

The first on-study imaging assessment should be performed at 6 weeks (24 days ±7 days) after the restart of treatment. Subsequent tumor imaging should be performed every 9 weeks (63 days ±7 days) or more frequently, if clinically indicated.

Per RECIST 1.1 (Section 9.1.2.6), if tumor imaging shows initial PD, tumor assessment should be repeated 4 to 8 weeks later in order to confirm PD with the option of continuing treatment while awaiting radiologic confirmation of progression. Participants who obtain confirmatory imaging do not need to undergo scheduled tumor imaging if it is less than 4 weeks later and may wait until the next scheduled imaging time point, if clinically stable.

Imaging should continue to be performed until disease progression, the start of a new anticancer treatment, withdrawal of consent, death, or notification by the Sponsor, whichever occurs first. Disease progression may be confirmed 4 to 8 weeks after the first tumor imaging indicating PD, by the Investigator using iRECIST, in clinically stable participants.

In participants who discontinue study treatment, tumor imaging should be performed at the time of treatment discontinuation (±4 week window). If previous imaging was obtained within 4 weeks prior to the date of discontinuation, then imaging at treatment discontinuation is not mandatory. In participants who discontinue study treatment due to documented disease progression, this is the final required tumor imaging.

In participants who discontinue study treatment without documented disease progression, every effort should be made to continue monitoring their disease status by radiologic imaging every 9 weeks (63 days ±7 days) until either the start of a new anticancer treatment, disease progression, pregnancy, death, or the end of the study, whichever occurs first.

6.1.2.6.4 RECIST 1.1 Assessment of Disease

RECIST 1.1 will be used as the primary measure for assessment of tumor response, date of disease progression, and as a basis for all protocol guidelines related to disease status (e.g., discontinuation of study treatment). Although RECIST 1.1 references a maximum of 5 target lesions in total and 2 per organ, the Sponsor allows a maximum of 10 target lesions in total and 5 per organ, if clinically relevant to enable a broader sampling of tumor burden.

6.1.2.6.5 iRECIST Assessment of Disease

iRECIST is based on RECIST 1.1, but adapted to account for the unique tumor response seen with immunotherapeutic drugs. When clinically stable, participants should not be discontinued until progression is confirmed by the Investigator, working with local radiology, according to the rules below. This allowance to continue treatment despite initial radiologic PD takes into account the observation that some participants can have a transient tumor flare in the first few months after the start of immunotherapy, and then experience subsequent disease response.

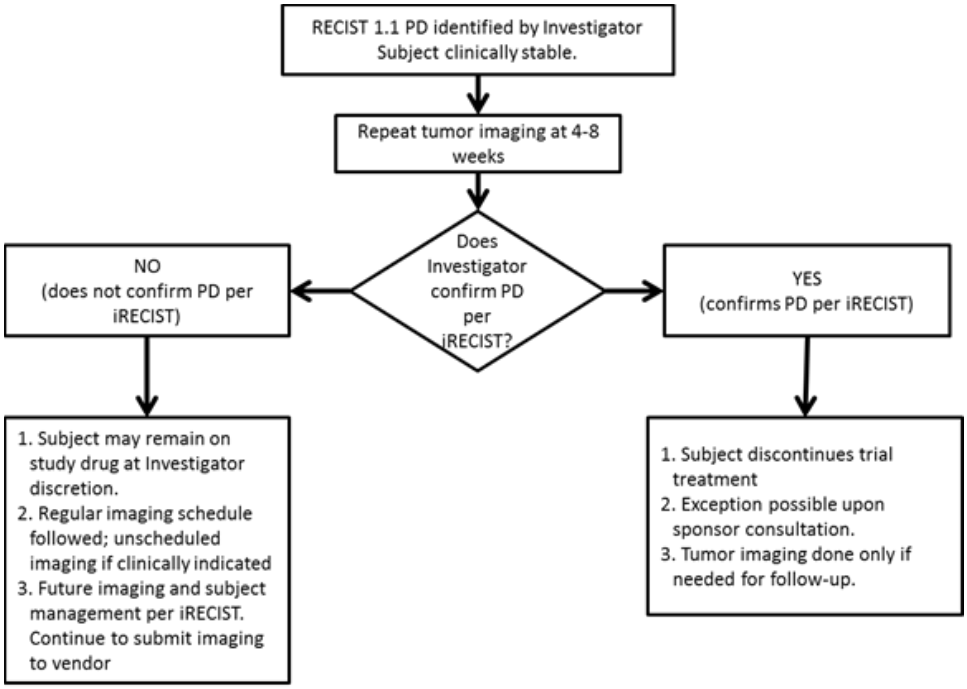
A description of the adaptations and iRECIST process is provided in Appendix 4, with additional detail in the iRECIST publication [Seymour et al, 2017]. iRECIST will be used by the Investigator to assess tumor response and progression, and make treatment decisions.

Table 5 Imaging and Treatment after First Radiologic Evidence of Progressive Disease (first restaging evaluation at approximately 6weeks excluded)

	Clinically Stable		**Clinically Unstable**	
	Imaging	**Treatment**	**Imaging**	**Treatment**
First radiologic evidence of PD by RECIST 1.1	Repeat imaging at 4 to 8 weeks to confirm PD.	May continue study treatment at the Investigator's discretion while awaiting confirmatory tumor imaging by site by iRECIST.	Repeat imaging at 4 to 8 weeks to confirm PD per Investigator's discretion only.	Discontinue treatment
Repeat tumor imaging confirms PD (iCPD) by iRECIST per Investigator assessment	No additional imaging required.	Discontinue treatment (exception is possible upon consultation with Sponsor).	No additional imaging required.	Not applicable
Repeat tumor imaging shows iUPD by iRECIST per Investigator assessment	Repeat imaging at 4 to 8 weeks to confirm PD. May occur at next regularly scheduled imaging visit.	Continue study treatment at the Investigator's discretion.	Repeat imaging at 4 to 8 weeks to confirm PD per Investigator's discretion only.	Discontinue treatment
Repeat tumor imaging shows iSD, iPR, or iCR by iRECIST per Investigator assessment.	Continue regularly scheduled imaging assessments.	Continue study treatment at the Investigator's discretion.	Continue regularly scheduled imaging assessments.	May restart study treatment if condition has improved and/or clinically stable per Investigator's discretion. Next tumor image should occur according to the regular imaging schedule.

iCPD = iRECIST confirmed progressive disease; iCR = iRECIST complete response; iRECIST = modified Response Evaluation Criteria in Solid Tumors 1.1 for immune-based therapeutics; iSD = iRECIST stable disease; iUPD = iRECIST unconfirmed progressive disease; PD = progressive disease; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors 1.1..

Figure 5: Imaging and Treatment for Clinically Stable Participants after First Radiologic Evidence of PD Assessed by the Investigator



6.1.2.7 Tumor Tissue Collection and Correlative Studies Blood Sampling

Submit at least one formalin fixed paraffin-embedded (FFPE) archived tumor tissue block from biopsy of the primary cancer at time of enrollment and from the resected surgical specimen at the time of primary tumor resection. A corresponding H&E slide from the submitted block must be provided to permit quality assessment (QA) of tissue block. If patient has tissue collected for reasons other than the protocol, study will also acquire surplus tissue remaining.

The FFPE tissue block is preferred; however, if unable to provide a tissue block, cut 20 five-micron unstained slides and mount on charged glass slides and 10 ten-micron unstained slides mounted on uncharged slides. Label the slides with the patient ID number, accession number, and order of sections (i.e., 1-11). H&E stain the first cut slide (i.e., slide labeled 1). Please do not re-label over the original label. For samples containing less than 7 square millimeters of tumor tissue, multiple sections should be mounted onto each slide to ensure that the appropriate amount of tumor tissue is available. Ideally, each slide must have a minimum of 75% tumor tissue on the slide to be deemed adequate for study. Do not bake or place cover slips on the slides.

The following materials below are mandatory (unless indicated otherwise), though:

- Paraffin embedded tissue blocks with corresponding H&E (or 30 slides), if limited tissue is available exceptions to the amount of tissue will be made.

- Surgical Pathology Report

Correlative blood sampling will be performed at screening, prior to second cycle of pembrolizumab and subsequently corresponding to restaging frequency

6.1.3 Laboratory Procedures/Assessments

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

Laboratory tests for hematology, chemistry, urinalysis, and others are specified in Table 6.

Table 6 Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood	Serum β-human chorionic gonadotropin†
Hemoglobin	Alkaline phosphatase	Glucose	(β-hCG)†
Platelet count	Alanine aminotransferase (ALT)	Protein	PT (INR)
WBC (total and differential)	Aspartate aminotransferase (AST)	Specific gravity	aPTT
Red Blood Cell Count	Lactate dehydrogenase (LDH)	Microscopic exam *(If abnormal)*	Free thyroxine (T4)
Absolute Neutrophil Count	Carbon Dioxide ‡	results are noted	Thyroid stimulating hormone (TSH)
Absolute Lymphocyte Count	*(CO_2 or bicarbonate)*	Urine pregnancy test †	Blood for correlative studies
	Uric Acid		Tumor markers (per tumor type)
	Calcium		
	Chloride		
	Glucose		
	Phosphorus*		
	Potassium		
	Sodium		
	Magnesium		
	Total Bilirubin		
	Direct Bilirubin *(If total bilirubin is elevated above the upper limit of normal)*		
	Total protein		
	Blood Urea Nitrogen		

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

‡ If considered standard of care in your region.

* Not performed during screening.

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.

6.1.4 Other Procedures

6.1.4.1 Withdrawal/Discontinuation

When a participant 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. Participants 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 5.2.3. After discontinuing treatment following assessment of CR, these participants should return to the site for a Safety Follow-up Visit (described in Section 7.1.5.3.1) and then proceed to the Follow-Up Period of the study (described in Section 7.1.5.3.2).

6.1.4.2 Blinding/Unblinding

This is an open-label unblinded study

6.1.5 Visit Requirements

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

6.1.5.1 Screening

6.1.5.1.1 Screening Period

If a patient is thought to be a potential candidate for the trial then he/she can be offered participation and, if agreeable, will undergo screening procedure outlined below from D-14 to C1D1. Previously conducted HIV, PT/PTT, and hepatitis testing within 30 days does not need to be repeated and will be acceptable for screening purposes (results performed at outside laboratories as standard of care testing will be accepted).

Table 6.1.5.1-1: Screening Procedural Outline		
Procedure	**Screening Visit From D-14 to C1D1***	**Notes**
Eligibility Assessments		
Informed Consent	X	Original IC in screening for protocol participation;
Inclusion/Exclusion Criteria	X	All inclusion/exclusion criteria should be assessed at screening and confirmed prior to first dose.
Determination of resectable or unresectable	X	
Medical History	X	
Tumor Tissue Sample	X	Confirm diagnosis of solid organ cancer
Paraffin Tissue	X	Determine availability and order prior collected tumor tissue
Prior Medications	X	Prior exposure to checkpoint inhibitor therapy excluded
ECOG Performance Status	X	Within 14 days prior to first dose
Safety Assessments		
Physical Examination	X	
Vital Signs & Oxygen Saturation	X	Including BP, HR, temperature and oxygen saturation by pulse oximetry (at rest). Obtain vital signs at the screening visit and within 72 hours prior to first dose.
Physical Measurements	X	Height and Weight. Within 14 days prior to first dose
Assessment of Signs and Symptoms	X	Within 14 days prior to first dose
Concomitant Medication Collection	X	Within 14 days prior to first dose

Table 6.1.5.1-1: Screening Procedural Outline		
Procedure	**Screening Visit From D-14 to C1D1***	**Notes**
Laboratory Tests	X	CBC w/differential and platelet count, Chemistry panel including: LDH, AST, ALT, ALP, T.Bili, BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, Glucose, CEA, amylase, lipase, TSH, Free T4, appropriate tumor markers per primary site (for example CEA, PSA, CA19-9, CA125…),within 14 days prior to first dose
Research Blood Test	x	correlative blood sample (60ml of blood: approximately 3 10ml Streck cell-free DNA BCT gold/black top tubes) within 14 days prior to first dose. (for full details related to blood collection please see laboratory collection manual and note exact tube types may be adjusted during study)
HIV, hepatitis, PT/PTT laboratory tests	X	HIV Ab, Hepatitis B surface antigen (HBV sAg), and hepatitis C antibody (HCV Ab) or Hepatitis C RNA (HCV RNA) or PT/PTT within 28 days prior to first dose
Pregnancy Test (WOCBP only)	X	Serum or urine to be done at screening visit and repeated within 72hours of first dose of study therapy
Efficacy Assessment		
Baseline Tumor Imaging Assessment	X	CT of the C/A/P or or PET/CT or MRI brain or appropriate standard of care imaging per that disease type as indicated within 28 days of first treatment dose.

* If screening labs are done within 3 days of Cycle 1, labs for C1D1 do not need to be repeated.

6.1.5.2 Treatment Period

Once enrolled on trial, each participant will have the visits/events outlined in the study flow chart in section 5.1. Treatment will not commence until at least 2 weeks from prior systemic

chemotherapy or radiation therapy. Patients may undergo screening during this time or after two weeks. There is no maximum time from prior chemotherapy until pembrolizumab treatment. Any resectable patient confirmed to have disease progression on restaging visit should be evaluated for and proceed to surgical resection. Each clinic visit while on active therapy will include targeted physical examination, vital signs, adverse events assessment and routine labs. Thyroid function testing should be done every 6 weeks.

Post-Treatment Visits

Follow-up will be done as per standard of care guidelines and decision-making by the treating physician

The research team will conduct chart reviews or patient calls approximately every six months to assess survival and disease recurrence status for up to 2 years following surgery or last dose of drug.

7.1.5.3.1 Safety Follow-Up Visit

The mandatory Safety Follow-Up Visit should be conducted approximately 30 days after the last dose of study 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. Participants 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-cancer 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. Participants who are eligible for retreatment with pembrolizumab (as described in Section 5.2.3) may have up to two safety follow-up visits, one after the Initial Treatment Period and one after the Second Course Treatment.

7.1.5.3.2 Follow-up Visits

Participants who discontinue study treatment for a reason other than disease progression will move into the Follow-Up Phase and should be assessed every 6 weeks (42 ± 7 days) by radiologic imaging to monitor disease status. After 1 year, the imaging time point will occur every 9 weeks (± 7 days). Every effort should be made to collect information regarding disease status until the start of new anti-cancer therapy, disease progression, death, end of the study or if the participant begins retreatment with pembrolizumab as detailed in Section 5.2.3. Information regarding post-study anti-cancer treatment will be collected if new treatment is initiated.

Participants who are eligible to receive retreatment with pembrolizumab according to the criteria in Section 5.2.3 will move from the follow-up phase to the Second Course Phase when they experience disease progression.

7.1.5.3.3 Survival Follow-up

Participants who experience confirmed disease progression or start a new anticancer therapy, will move 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 trial, whichever occurs first.

6.2 Assessing and Recording Adverse Events

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

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

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

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

All AEs, SAEs and other reportable safety events that occur after the consent form is signed but before treatment allocation must be reported by the investigator if the participant is receiving placebo run-in or other run-in treatment, if the event cause the participant to be excluded from the study, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, or a procedure.

● All AEs from the time of treatment allocation through 30 days following cessation of study treatment must be reported by the investigator.

● All AEs meeting serious criteria, from the time of treatment allocation through 90 days following cessation of study treatment, or 30 days following cessation of study treatment if the participant initiates new anticancer therapy, whichever is earlier must be reported by the investigator.

● All pregnancies and exposure during breastfeeding, from the time of treatment allocation through 120 days following cessation of study treatment, or 30 days following cessation of

study treatment if the participant initiates new anticancer therapy must be reported by the investigator.

● Additionally, any SAE brought to the attention of an investigator at any time outside of the time period specified above must be reported immediately by the investigator if the event is considered to be drug-related.

Investigators are not obligated to actively seek AE or SAE or other reportable safety events in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify Merck.

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

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

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

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

All reports of overdose with and without an adverse event must be reported within 24 hours to the Sponsor and within 2 working days hours to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215-661-6229)

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

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

Pregnancies and infant exposures during breastfeeding that occur after the consent form is signed but before treatment allocation must be reported by the investigator if they cause the participant to be excluded from the trial, or are the result of a protocol-specified intervention,

including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

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

Such events must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215-661-6229)

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

6.2.3.1 Serious Adverse Events

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

- Results in death;
- Is life threatening;
- Results in persistent or significant disability/incapacity;
- Results in or prolongs an existing inpatient hospitalization;
- Is a congenital anomaly/birth defect;
- Is another important medical event

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

Refer to Table 7 for additional details regarding each of the above criteria.

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

For the time period beginning at treatment allocation through 90 days following cessation of treatment, or 30 days following cessation of treatment if the participant initiates new anticancer therapy, whichever is earlier, any serious adverse event, or follow up to a serious adverse event, including death due to any cause whether or not related to the Merck product, must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety.

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

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

SAE reports and any other relevant safety information are to be forwarded to the Merck Global Safety facsimile number: +1-215-661-6229

A copy of all 15 Day Reports and Annual Progress Reports is submitted as required by FDA, European Union (EU), Pharmaceutical and Medical Devices agency (PMDA) or other local regulators. Investigators will cross reference this submission according to local regulations to the Merck Investigational Compound Number (IND, CSA, etc.) at the time of submission. Additionally investigators will submit a copy of these reports to Merck & Co., Inc. (Attn: Worldwide Product Safety; FAX 215-661-6229) at the time of submission to FDA.

6.2.3.2 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be reported within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215-661-6229).

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

For the time period beginning at treatment allocation through 90 days following cessation of treatment, or 30 days following cessation of treatment if the participant initiates new anticancer therapy, whichever is earlier, any ECI, or follow up to an ECI, whether or not related to Merck product, must be reported within 2 working days to Merck Global Safety.

Events of clinical interest for this trial include:

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

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

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

6.2.4 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 7 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 participant, in the view of the investigator, at immediate risk of death from the event as it occurred (Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.); or	
	†**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or	
	†**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not a serious adverse event. A pre-existing condition is a clinical condition that is diagnosed prior to the use of a Merck product and is documented in the patient's medical history.); or	
	†**Is a congenital anomaly/birth defect** (in offspring of participant taking the product regardless of time to diagnosis);or	
	Is a new **cancer** (that is not a condition of the study) **(**although not serious per ICH definition, is reportable to the Sponsor within 24 hours and to Merck within 2 working days to meet certain local requirements); **or**	
	Is an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event for collection purposes. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours to the Sponsor and to Merck within 2 working days..	

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

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

6.2.5 Sponsor Responsibility for Reporting Adverse Events

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

7.0 STATISTICAL ANALYSIS PLAN

7.1 Statistical Analysis Plan Summary

Statistical Consideration:

Efficacy:

1) The primary endpoint is Pathological complete response (pCR) after 3 doses. Pathological complete response will also be estimated for all patients who receive at least 1 dose of pembrolizumab (intent to treat). Those who do not undergo surgical resection will be classified as non-pCR for the intention to treat analysis. We will estimate the pCR rate among the group of patients who receive at least 3 doses of pembrolizumab and undergo surgical resection (the primary endpoint). Assuming the pCR is 80%, with 20 patients, the 95% confidence interval is (0.56, 0.94).

2) Rate of organ sparing at 1 year (primary tumor control and no metastatic disease) will be assessed for all patients who receive at least 1 doses of neoadjuvant pembrolizumab for the intention to treat analysis. In addition we will estimate the organ sparing rate at 1 year among the group of patients who receive at least 3 doses of neoadjuvant pembrolizumab and do not undergo surgical resection. Assuming the organ sparing rate of 0.7, with 10 patients, the 95% confidence interval is (0.35, 0.93) .

Safety monitoring:

Toxicity will be monitored using the Bayesian approach of Thall, Simon, Estey (1995, 1996) and the extension by Thall and Sung (1998). Multc Lean Desktop (version 2.1) was used to generate the stopping boundaries and the OC tables for toxicity monitoring. Toxicity monitoring will be performed (n=35 patients) throughout the study. Unacceptable toxicities are defined as any Grade 3 or higher probably or definite treatment-related CTCAE toxicity that occurs during the first 6 months of therapy. Denote the probability of toxicity by PT. We assume as a priori, PT ~ beta (0.5, 1.5). Our stopping rule is given by the following probability statement:

Pr (PT > 0.25 | data)>0.85.

That is, we will stop the trial for new patient enrollment if at any time during the study, we determine that there is more than 85% chance that the unacceptable toxicity rate is more than 25%. This toxicity monitoring rule will be applied after the first 5 patients have been enrolled and evaluated, and then will be monitored by cohort of 5. Stopping boundaries corresponding to this stopping rule are listed in Table 8.

Table 8. Early stopping boundaries for toxicity monitoring

# of patients (in cohort size of 5, starting from the 5th patient) Stop this cohort if there are this many patients with toxicities:

# of patients (in cohort size of 5, starting from the 5th patient)	Stop this cohort if there are this many patients with toxicities:
5	3-5
10	5-10
15	6-15
20	8-20
25	9-25
30	11-30
35	Always stop with this many patients

Table 9. Operating characteristic for toxicity monitoring

True toxicity rate	Prob(stop the trial early)	Average number of patients treated
0.15	0.04	33.87
0.25	0.27	29.02
0.35	0.66	20.46
0.45	0.93	12.94

If patients do not respond to pembrolizumab, they would stop the treatment after two doses. In case the patients have resectable tumors, the subsequent surgical resection will be monitored. Patients will be allowed up to 6 months to have surgery. We expect that 80% of these patients with resectable tumors would undergo surgery. After 5 patients falling into this category, the

Bayesian stopping rule: Pr (surgery rate> 0.8|data) < 0.01 will be continuously implemented assuming the surgery rate follows a Beta prior (0.8,0.2). That is, if at any time after enrolling 5 patients who have resectable tumor and don't respond to pembrolizumab, we determine that there is a less than 1% chance that the surgery rate is more than 80%, we will stop enrollment of the study. Assuming there are 20 patients, the surgery rate monitoring rule will be applied after the first 5 patients have been enrolled and evaluated, and then will be monitored by cohort of 5. Stopping boundaries corresponding to this stopping rule are listed in Table 10 (operating characteristic in table 11). For example, if there is none or only 1 patient out of the 1st 5 patients undergo surgery, the study will be stopped. Table 10. Early stopping boundaries for surgery rate monitoring for patients who do not respond to pembrolizumab but with resectable tumor

# of patients (in cohort size of 5, starting from the 5th patient)	Stop the study if there are this many patients with surgery
5	0-1
10	0-4
15	0-7
20	0-11

Table 11. Operating characteristic for surgery rate monitoring for patients who do not respond to pembrolizumab but with resectable tumor

True surgery rate	Prob(stop the trial early)
0.5	0.56
0.6	0.27
0.7	0.08
0.8	0.01

7.2 Statistical Analysis Plan

Analysis Plan:

All patients who received any dose of the study agent, pembrolizumab, will be included in the analysis for efficacy and safety. Demographic/clinical characteristics and safety data of the patients will be summarized using descriptive statistics such as frequency, mean, standard

deviation, median and range. We will follow standard reporting guidelines for adverse events. Safety data will be summarized by category, severity and frequency.

Safety will be recorded according to CTCAE toxicity and also post-operative complications will be classified according to Clavien-Dindo classification[1].

For the efficacy analysis, we will estimate the pathological complete response and rate of organ sparing at 1 year along with the 95% confidence interval.

For each subject, relapse-free survival and overall survival will be calculated. Relapse-free survival is defined as the number of days from the date of response to the date of documented treatment failure, relapses or death from any cause, whichever occurs first, and will be calculated for all patients. The overall survival is defined as the time from treatment start till death or last follow-up. The distribution of time-to-event endpoints including overall survival (OS) and event free survival (RFS) will be estimated using the method of Kaplan and Meier. Comparisons of time-to-event endpoints by important subgroups will be made using the log-rank tests. The association between response (e.g. pathological complete response) and patient's clinical characteristics, such as changes in ct DNA, mutation burden, T-effector cell populations, gene expression profiles, etc. will be examined by Wilcoxon's rank sum test or Fisher's exact test, as appropriate.

8.0 TRANSLATIONAL PLAN

The following are part of efforts to further exploratory objectives:

Patient ctDNA levels may be tracked at various time-points during the study to identify patterns of change and it association to treatment benefit for patients.

Optional paired tumor biopsies may be performed at baseline and while on treatment. Biomarkers evaluated from the biopsies will include the following: pre-treatment indel mutation score, which is potentially predictive of MSI-H cancer outcomes (Mandal et al., Science. 2019); correlation of CD8 infiltration changes with efficacy; and relationship of protein and RNA expression of immune resistance with tumor response and progression.

9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.1 Investigational Product

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

Pembrolizumab will be provided by Merck as summarized in Table 8.

Table 12 Product Descriptions

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

9.2 Packaging and Labeling Information

Supplies will be labeled in accordance with regulatory requirements.

9.3 Clinical Supplies Disclosure

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

9.4 Storage and Handling Requirements

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

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

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

9.5 Returns and Reconciliation

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

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

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

The investigator's or site's designated investigational product manager is required to maintain accurate investigational product accountability records. Upon completion of the study, copies of investigational product accountability records will be returned to Merck. All unused investigational product will be returned to Merck- authorized depot or disposed of upon authorization by Merck.

10.1 Patient confidentiality

In order to maintain patient confidentiality, we will protect participants' privacy by coding samples and keeping the master list of identifiers accessible to only key project staff. Patient data will be kept on secure computers and Samples will be kept in freezers in locked laboratories and buildings. Additionally in some other cases, samples may be provided from outside collaborators or institutions for discovery and research purposes. In such cases, the samples should be obtained under IRB-approved protocols at these outside collaborators and institutions to allow them for participation in this protocol and under a specific grant/ contract or Material Transfer Agreement (MTA) with MD Anderson Cancer Center.

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37.

12.0 APPENDICES

Appendix 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.

Appendix 2: Common Terminology Criteria for Adverse Events V4.0 (CTCAE)

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

Appendix 3: Contraceptive Guidance and Pregnancy Testing

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below)

Women in the following categories are not considered WOCBP:

- Premenarchal
- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

  Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with two FSH measurements in the postmenopausal range is required.
  - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Requirements

Female Participants:

Female participants of childbearing potential are eligible to participate if they agree to use one of the contraception methods described in Table 11 consistently and correctly during the protocol-defined time frame in Section X.

Table 11 Contraceptive Methods

Acceptable Contraceptive Methods

Failure rate of >1% per year when used consistently and correctly.
● Male or female condom with or without spermicide ● Cervical cap, diaphragm or sponge with spermicide
Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of <1% per year when used consistently and correctly.*
● Combined (estrogen- and progestogen- containing) hormonal contraception [b] ○ Oral ○ Intravaginal ○ Transdermal ○ Injectable
● Progestogen-only hormonal contraception [b] ○ Oral ○ Injectable
Highly Effective Methods That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
● Progestogen- only contraceptive implant [b, c] ● Intrauterine hormone-releasing system (IUS) [b] ● Intrauterine device (IUD) ● Bilateral tubal occlusion
● **Vasectomized partner** A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
● **Sexual abstinence** Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)
Notes: Use should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies. a) Typical use failure rates are lower than perfect-use failure rates (i.e. when used consistently and correctly). b) If hormonal contraception efficacy is potentially decreased due to interaction with study treatment, condoms must be used in addition to the hormonal contraception during the treatment period and for at least [X days, corresponding to time needed to eliminate study treatment plus 30 days for study treatments with genotoxic potential] after the last dose of study treatment . c) If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable hormonal contraceptives are limited to those which inhibit ovulation.

Pregnancy Testing

WOCBP should only be included after a negative highly sensitive urine or serum pregnancy test.

Pregnancy testing will be performed whenever an expected menstrual cycle is missed or when pregnancy is otherwise suspected.

Appendix 4: Description of the iRECIST Process for Assessment of Disease Progression

Assessment at Screening and Prior to RECIST 1.1 Progression

Until radiographic progression based on RECIST 1.1, there is no distinct iRECIST assessment.

Assessment and Decision at RECIST 1.1 Progression

In participants who show evidence of radiological PD by RECIST 1.1 the Investigator will decide whether to continue a participant on study treatment until repeat imaging is obtained (using iRECIST for participant management (see Table 5 and Figures 1 and 3). This decision by the Investigator should be based on the participant's overall clinical condition.

Clinical stability is defined as the following:

- Absence of symptoms and signs indicating clinically significant progression of disease
- No decline in ECOG performance status
- No requirements for intensified management, including increased analgesia, radiation, or other palliative care

Any participant deemed clinically unstable should be discontinued from study treatment at site-assessed first radiologic evidence of PD, and is not required to have repeat tumor imaging for confirmation of PD by iRECIST.

If the Investigator decides to continue treatment, the participant may continue to receive study treatment and the tumor assessment should be repeated 4 to 8 weeks later to confirm PD by iRECIST, per Investigator assessment. I

Tumor flare may manifest as any factor causing radiographic progression per RECIST 1.1, including:

- Increase in the sum of diameters of target lesion(s) identified at baseline to ≥ 20% and ≥ 5 mm from nadir
    - Please note: the iRECIST publication uses the terminology "sum of measurements", but "sum of diameters" will be used in this protocol, consistent with the original RECIST 1.1 terminology.
- Unequivocal progression of non-target lesion(s) identified at baseline
- Development of new lesion(s)

iRECIST defines new response categories, including iUPD (unconfirmed progressive disease) and iCPD (confirmed progressive disease). For purposes of iRECIST assessment,

the first visit showing progression according to RECIST 1.1 will be assigned a visit (overall) response of iUPD, regardless of which factors caused the progression.

At this visit, target and non-target lesions identified at baseline by RECIST 1.1 will be assessed as usual.

New lesions will be classified as measurable or non-measurable, using the same size thresholds and rules as for baseline lesion assessment in RECIST 1.1. From measurable new lesions, up to 5 lesions total (up to 2 per organ), may be selected as New Lesions – Target. The sum of diameters of these lesions will be calculated, and kept distinct from the sum of diameters for target lesions at baseline. All other new lesions will be followed qualitatively as New Lesions – Non-target.

Assessment at the Confirmatory Imaging

On the confirmatory imaging, the participant will be classified as progression confirmed (with an overall response of iCPD), or as showing persistent unconfirmed progression (with an overall response of iUPD), or as showing disease stability or response (iSD/iPR/iCR).

Confirmation of Progression

Progression is considered confirmed, and the overall response will be iCPD, if ANY of the following occurs:

- Any of the factors that were the basis for the initial iUPD show worsening
  - For target lesions, worsening is a further increase in the sum of diameters of ≥ 5 mm, compared to any prior iUPD time point
  - For non-target lesions, worsening is any significant growth in lesions overall, compared to a prior iUPD time point; this does not have to meet the "unequivocal" standard of RECIST 1.1
  - For new lesions, worsening is any of these:
    - An increase in the new lesion sum of diameters by ≥ 5 mm from a prior iUPD time point
    - Visible growth of new non-target lesions
    - The appearance of additional new lesions
- Any new factor appears that would have triggered PD by RECIST 1.1

Persistent iUPD

Progression is considered not confirmed, and the overall response remains iUPD, if:

- None of the progression-confirming factors identified above occurs AND

- The target lesion sum of diameters (initial target lesions) remains above the initial PD threshold (by RECIST 1.1)

Additional imaging for confirmation should be scheduled 4 to 8 weeks from the scan on which iUPD is seen. This may correspond to the next visit in the original visit schedule. The assessment of the subsequent confirmation scan proceeds in an identical manner, with possible outcomes of iCPD, iUPD, and iSD/iPR/iCR.

Resolution of iUPD

Progression is considered not confirmed, and the overall response becomes iSD/iPR/iCR, if:

- None of the progression-confirming factors identified above occurs, AND
- The target lesion sum of diameters (initial target lesions) is not above the initial PD threshold.

The response is classified as iSD or iPR (depending on the sum of diameters of the target lesions), or iCR if all lesions resolve.

In this case, the initial iUPD is considered to be pseudo-progression, and the level of suspicion for progression is "reset". This means that the next visit that shows radiographic progression, whenever it occurs, is again classified as iUPD by iRECIST, and the confirmation process is repeated before a response of iCPD can be assigned.

Management Following the Confirmatory Imaging

If repeat imaging does not confirm PD per iRECIST, as assessed by the Investigator, and the participant continues to be clinically stable, study treatment may continue and follow the regular imaging schedule. If PD is confirmed, participants will be discontinued from study treatment.

NOTE: If a participant has confirmed radiographic progression (iCPD) as defined above, but the participant is achieving a clinically meaningful benefit, an exception to continue study treatment may be considered. In this case, if study treatment is continued, tumor imaging should continue to be performed following the intervals as outlined in Section 6.

Detection of Progression at Visits After Pseudo-progression Resolves

After resolution of pseudo-progression (i.e., achievement of iSD/iPR/iCR), iUPD is indicated by any of the following events:

- Target lesions
    - Sum of diameters reaches the PD threshold ($\geq$ 20% and $\geq$ 5 mm increase from nadir) either for the first time, or after resolution of previous pseudo-progression. The nadir is always the smallest sum of diameters seen during the entire trial, either before or after an instance of pseudo-progression.

- Non-target lesions
    - If non-target lesions have never shown unequivocal progression, their doing so for the first time results in iUPD.
    - If non-target lesions had shown previous unequivocal progression, and this progression has not resolved, iUPD results from any significant further growth of non-target lesions, taken as a whole.
- New lesions
    - New lesions appear for the first time
    - Additional new lesions appear
    - Previously identified new target lesions show an increase of ≥ 5 mm in the new lesion sum of diameters, from the nadir value of that sum
    - Previously identified non-target lesions show any significant growth

If any of the events above occur, the overall response for that visit is iUPD, and the iUPD evaluation process (see Assessment at the Confirmatory Imaging above) is repeated. Progression must be confirmed before iCPD can occur.

The decision process is identical to the iUPD confirmation process for the initial PD, except in one respect. If new lesions occurred at a prior instance of iUPD, and at the confirmatory scan the burden of new lesions has increased from its smallest value (for new target lesions, their sum of diameters is ≥5 mm increased from its nadir), then iUPD cannot resolve to iSD or iPR. It will remain iUPD until either a decrease in the new lesion burden allows resolution to iSD or iPR, or until a confirmatory factor causes iCPD.

Additional details about iRECIST are provided in the iRECIST publication [Seymour et al, 2017].