

**A Phase II, Single Arm, Open label, Simon Two-Stage Study of  
pembrolizumab in metastatic HER2-negative breast cancer patients:  
evaluation of impact of germline variants in APOBEC3B**

**Protocol Number:**

**IIT-UM2018001**

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**1.0 TRIAL SUMMARY**

Abbreviated Title	Pembrolizumab in metastatic HER2-negative breast cancer patients with APOBEC3B germline deletion polymorphism
Trial Phase	Phase II
Clinical Indication	Breast cancer
Trial Type	Intervention
Type of control	Single arm (no control/placebo group)
Route of administration	IV
Trial Blinding	Not applicable
Treatment Groups	Pembrolizumab: 200 mg intravenously every 3 weeks (Q3W)
Number of trial participants	Approximately 44 subjects will be enrolled
Estimated enrollment period	Mar 2019 - Apr 2021
Estimated duration of trial	4 years
Duration of Participation	2 years
Estimated average length of treatment per patient	<p>Each participate in the study from the time the subject signed the informed consent form through the final protocol specific contact. After screening phase of up to 28 days, eligible subjects will receive assigned treatment. Study treatment will continue for 35 administrations of pembrolizumab until any of the following occurs:</p> <ul style="list-style-type: none"> <li>• disease progression, as defined by Response Evaluation Criteria in Solid Tumour version 1.1 (RECIST 1.1) (or progressive disease [PD] is confirmed, subject may be further followed up using consensus guideline of modified RECIST 1.1 [iRECIST] criteria);</li> <li>• unacceptable toxicity;</li> <li>• intercurrent illness that necessitates discontinuation of study treatment;</li> <li>• Investigator’s decision to withdraw the subject,</li> <li>• pregnancy,</li> <li>• non-compliance with study treatment or procedure requirements;</li> <li>• withdrawal of consent to treatment;</li> <li>• death;</li> <li>• end of the study, or</li> <li>• other administrative reasons requiring cessation of study treatment.</li> </ul> <p>After discontinuation of all study treatments, each subject will be followed for 30 days for AE and for 90 days for serious adverse events (SAEs) monitoring, as well as 12 weekly survival follow up using telephone call till end of study period.</p>

## 2.0 TRIAL DESIGN

This is an open label investigator initiated Phase II study of single agent pembrolizumab (Keytruda®) in metastatic HER2-receptive negative breast cancer patients with germline deletion in the cytosine deaminase (APOBEC3B) gene. Approximately 44 subjects will be enrolled in this study to examine the efficacy of pembrolizumab when given 200 mg intravenously (IV) every 3 weeks (Q3W) for up to 35 administrations (2 years). ER+ patients need to have failed at least one line of prior hormonal treatment. All patients need to have failed at least one line, but no more than 3 lines, of prior chemotherapy in the metastatic setting.

Disease status will be followed by imaging studies at 9 weekly interval ( $\pm$  7 days) during the first year, independent of any treatment delays, and every 12 weeks ( $\pm$ 7 days) after the first year, until disease progression, start of non-study treatment, withdrawal of consent to study participation, death or end of the study. RECIST 1.1 will be used as the primary efficacy endpoint of response rate. Safety will be monitored according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0.

Study treatment will continue until any of the following occurs:

1. Disease progression, as defined by Response Evaluation Criteria in Solid Tumour (RECIST version 1.1) (when progressive disease [PD] is confirmed, subject may be further followed up using consensus guideline of modified RECIST 1.1 [iRECIST] criteria);
2. Unacceptable toxicity;
3. Intercurrent illness that necessitates discontinuation of study treatment;
4. Investigator's decision to withdraw the subject,
5. Pregnancy;
6. Non-compliance with study treatment or procedure requirements;
7. Withdrawal of consent to treatment;
8. Death;
9. End of the study;
10. Other administrative reasons requiring cessation of study treatment.

This study will be conducted in conformance with Good Clinical Practices.

Specific procedures to be performed during the trial, as well as their prescribed times and associated visit windows, are outlined in the Trial Flow Chart - Section 6.0. Details of each procedure are provided in Section 7.0 – Trial Procedures.

Subject will be given a pre-screening informed consent form to participate in the genetic testing to determine their APOBEC3B germline mutation status.

Subject with confirmed APOBEC3B germline mutation will be given another informed consent form to participate in the main study.

The primary objective of the trial is to determine the efficacy of pembrolizumab in metastatic HER2-negative breast cancer subjects with APOBEC3B germline deletion polymorphism. Secondary objectives include progression-free survival (PFS), overall survival (OS) and response duration in this subject populations. The relationships of the germline variation, the associated molecular signatures, as well as other potential prognostic biomarkers with the study treatment will be explored as the exploratory objectives.



### **3.0 OBJECTIVE(S) & HYPOTHESIS**

#### **3.1 Hypothesis**

Metastatic HER2-negative breast cancer patients with germline APOBEC3B deletion polymorphism have improved response in PD-1 checkpoint immunotherapy using pembrolizumab (Keytruda®, Merck).

#### **3.2 Primary Objective**

To determine the overall response rate (ORR) to the pembrolizumab treatment in metastatic HER2-negative breast cancer patients with germline APOBEC3B deletion polymorphisms using RECIST 1.1.

#### **3.3 Secondary Objectives**

- 1) To estimate the disease control rate (DCR) i.e. complete response (CR), partial response (PR) or stable disease (SD) to the pembrolizumab treatment in metastatic HER2-negative breast cancer patients with germline APOBEC3B deletion polymorphism.
- 2) To estimate the progression free survival (PFS) to the pembrolizumab treatment in metastatic HER2-negative breast cancer patients with germline APOBEC3B deletion polymorphisms.
- 3) To estimate overall survival (OS) to the pembrolizumab treatment in metastatic HER2-negative breast cancer patients with germline APOBEC3B deletion polymorphisms.

#### **3.4 Exploratory Objectives**

- 1) To evaluate whether genetic variation correlates with clinical response to the pembrolizumab treatment in HER2-negative breast cancer patients
- 2) To perform genomic analyses on tumour samples and to derive molecular signatures that correlate with clinical response to pembrolizumab treatment in HER2-negative breast cancer patients
- 3) To explore other biomarkers (e.g. tumour infiltrating lymphocytes, TIL) potentially be prognostic and predictive indicator to the clinical response of pembrolizumab treatment in HER2-negative breast cancer patients.

### **4.0 BACKGROUND & RATIONALE**

#### **4.1 Background**

Advances in immunotherapy have enabled the development of cell-based, small molecule and monoclonal antibody approaches to treat cancer and some of these, including monoclonal antibodies targeting immune checkpoint regulators such as PD-1, have already resulted in long term remission of melanoma, lung and other cancers. Notably, not all patients respond to therapy and it is thought that tumours with high tumour neoantigens (driven by a high underlying mutational load, such as in lung cancer [Rizvi et al., Science 2015], melanoma [Herbst et al., Nature 2014] and mismatch-repair deficient colorectal cancer [Le et al., NEJM 2015]) are more likely to respond to anti-PD1 treatment. Taken together, the available evidence suggests that neoantigens and neoantigen-specific T cells are strongly associated with tumour regression after checkpoint blockade therapy.

To date, although the mutational burden of breast cancers is higher than that of other cancers [Alexandrov et al., Nature 2013], there have been limited biomarkers to predict potential utility of immunotherapy in breast cancer patients. Notably, breast cancers comprise of many different subtypes [Curtis et al., Nature 2012] and mutational analysis has demonstrated that oestrogen-receptor-positive (ER-positive) breast cancer, generally have low mutations and correspondingly, few neoantigens [Haricharan et al., Breast Cancer Res Treat et al., 2014]. By contrast, triple-negative breast cancers (TNBC), which are negative for ER, progesterone-receptor (PR) and the human epidermal growth factor receptor (HER2), appear to be more likely to have higher mutational load and for a subset of these, an enriched immune signature [Lehmann et al., JNCI 2011]. Indeed, a number of clinical trials are ongoing to test the efficacy of checkpoint blockade therapy on patients with TNBC (see 4.2.1.1). Interestingly, an analysis of the mutational load and immune signature in a cohort of Korean breast cancer patients recently demonstrated that the immune score is higher in Asian patients compared to the predominantly Caucasian dataset in TCGA [Kan et al., Nat Comms 2018], but the underlying basis for this immune enrichment has not been determined.

Notably, a proportion of DNA mutations in human cancers have recently been shown to arise from intrinsic enzymatic activity. In particular, the APOBEC DNA cytosine deaminase have been identified recently as a source of DNA damage and mutagenesis in breast, head/neck, cervical, bladder, lung, ovarian cancers and to lesser extents additional cancer types [Burns et al., Nat Genet 2013, Roberts et al., Nat Genet 2013]. This enzyme is normally an effector protein in the innate immune response to virus infection but upregulation in these cancer types causes elevated levels of genomic C-to-U deamination events, which manifest as C-to-T transitions and C-to-G transversions within distinct DNA trinucleotide contexts (preferentially 5'-TCA and 5'-TCT). Genomic deamination events lead to cytosine mutation clusters (Kataegis) and may precipitate visible chromosomal aberrations such as translocations [Nik-Zainal et al., Cell 2012].

Germline deletion in *A3B* occurs more frequently in Asian women (45% heterozygous deletion (hetD) and 15% homozygous deletion (homD)) compared to Caucasian women (15% hetDhetD and 4% homD) [Long et al., JNCI 2013, Xuan et al., Carcinogenesis 2013, Wen et al., Breast Cancer Res 2016]. Carriers of *A3B* germline deletion are more likely to develop cancer and early studies with small numbers of samples show that the resultant cancers are more likely to have a hypermutator phenotype [Nik-Zainal et al., Nat Genet 2014], with C>T transitions. In addition, cancers in *A3B* germline deletion carriers are enriched for immune activation [Cescon et al., PNAS 2015], which taken together with the hypermutator phenotype, suggests that an increase in hypermutation generates a higher neoantigen burden which in turn increases immune activation. Indeed, we recently have shown that germline *A3B* deletion is associated with tumour-infiltrating immune cells in The Cancer Genome Atlas (TCGA) and Molecular Taxonomy of Breast Cancer International Consortium (METABRIC) datasets [Wen et al., Breast Cancer Res 2016].

However, because of the limited number of samples which have germline deletion in *A3B* in the predominantly Caucasian cohort of patients analysed in large international consortia to date (for example, only 13 of 707 samples in TCGA and 18 of 1,988 samples in the METABRIC [Cescon et al., PNAS 2015]) studies had a 2-copy deletion of *A3B*, it remains unknown whether women with germline deletions in *A3B* develop tumours with a higher neoantigen burden and whether for these women, there is an opportunity to improve treatment using immunotherapy.

In this clinical trial, we plan to evaluate the utility of immunotherapy for the treatment of Asian breast cancer patients, focusing on the carriers of common *A3B* germline deletions. This will allow us to take into account the unique genetic background of Asian breast cancer patients, which is different from the Caucasian population. We plan to study potential biomarkers which could predict response to immunotherapy in terms of objective response, disease control rate, and survival. This will lead to better standard of care for Asian breast cancer patients and will bring us a step closer to personalized medicine.

#### 4.1.1 Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance function in controlling outgrowth of neoplastic transformations has been known for decades [Disis, 2010]. Accumulating evidence shows a correlation between tumour-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. Tumour-infiltrating lymphocytes can be expanded ex vivo and reinfused, inducing durable objective tumour responses in cancers such as melanoma [Dudley et al., 2005; Hunder et al., 2008].

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumours 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) [Greenwald et al., 2005; Okazaki et al., 2001].

The structure of murine PD-1 has been resolved [Zhang et al., 2004]. 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 (CD3 $\zeta$ ), protein kinase C-theta (PKC $\theta$ ), and zeta-chain-associated protein kinase (ZAP70), which are involved in the CD3 T-cell signaling cascade [Okazaki et al., 2001; Chemnitz et al., 2004; Sheppard et al., 2004; and Riley, 2009]. 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 [Parry et al., 2005; Francisco, 2010]. As a consequence, the PD-1/PD-L1 pathway is an attractive target for therapeutic intervention in breast cancer.

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<sup>®</sup> (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.

#### 4.1.2 Preclinical and Clinical Trial Data

Refer to the Investigator's Brochure for the relevant preclinical and clinical data of pembrolizumab.

## 4.2 Rationale

### 4.2.1 Rationale for the Trial and Selected Population

#### 4.2.1.1 Pembrolizumab in triple negative breast cancer [TNBC]

Pembrolizumab was the first anti PD-1 therapy to receive regulatory approval in US (September 2014). In recent years, pembrolizumab has shown promise in metastatic triple negative breast cancer (TNBC). The first report of clinical activity of an immune checkpoint inhibitor in TNBC, a Merck-sponsored multi centre, non-randomised Phase 1b study (KEYNOTE-012, KN012) showed that single agent Pembrolizumab given at 10mg/kg every 2 week (Q2W) is a well-tolerated and effective treatment with significant anticancer activity in subset of heavily pre-treated subject with mTNBC (18.5% ORR in patients with measurable disease at baseline as assessed by RECIST 1.1 and central radiology review; 6-months PFS rate, 24%; 12-months OS rate, 43.1%; data cutoff date, March 23, 2015).

Among 111 patients with TNBC whose tumour samples were screened for PD-L1 expression, 58.6% had PD-L1–positive tumours. Thirty-two women (median age, 50.5 years; range, 29 to 72 years) were enrolled and assessed for safety and antitumour activity. The median number of doses administered was five (range, 1 to 36 doses). Common toxicities were mild and similar to those observed in other tumour cohorts (eg, arthralgia, fatigue, myalgia, and nausea), and included five (15.6%) patients with grade  $\geq 3$  toxicity and one treatment-related death. Among the 27 patients who were evaluable for antitumour activity, the overall response rate was 18.5%, the median time to response was 17.9 weeks (range, 7.3 to 32.4 weeks), and the median duration of response was not yet reached when the last update was presented at the 2016 San Antonio Breast Cancer Symposium (range, 15.0 to  $\geq 58$  weeks). The median overall survival (OS) was 11.3 months (95% CI [5.3-18.2]). Notably, this length of durable benefit is not typically seen from chemotherapy in patients with pre-treated metastatic TNBC, in whom tumour responses often are short lived.

In the two-arm Phase II Trial (KEYNOTE-086) to evaluate the activity of single-agent Pembrolizumab in metastatic TNBC, cohort A enrolled 170 patients who had centrally confirmed metastatic TNBC regardless of PD-L1 tumour expression. Approximately 44% of patients received three or more lines of prior chemotherapy for advanced disease. The ORR was 4.7% (95% CI [2.3%- 9.2%]), which included one CR and seven PRs. The median duration of response was 6.3 months. Patients in the TNBC subset who had PD-L1–positive tumours had a response rate of 4.8% (five of 105 patients), which was similar to the response of 4.7% (three of 64 patients) in the patients who had PD-L1–negative tumours. Cohort B enrolled patients who had centrally confirmed PD-L1–positive metastatic TNBC and who had no prior systemic therapy for advanced disease. A total of 167 patients were screened for PD-L1 expression, which was measured with a combined positive score, defined as the number of PD-L1–positive cells (tumour cells, lymphocytes, macrophages) out of the total number of tumour cells, multiplied by 100. Among the patients who were screened, 79 (47%) had a positive PD-L1 expression of 1% or greater, and 52 were enrolled and treated with Pembrolizumab. The ORR by RECIST 1.1 was 23% (95% CI [14%-36%]), which included two CRs and 10 PRs. The median duration of response was 8.4 months. This data set demonstrated greater activity of immune checkpoint inhibitors in the first-line metastatic setting, and that response did not depend on PD-L1 expression. As a result of these promising early results, large phase III trials are accruing in TNBC:

1. **KEYNOTE-119** (NCT02555657): A Randomized Open-Label Phase III Study of Single Agent Pembrolizumab Versus Single Agent Chemotherapy per Physician's Choice for Metastatic Triple Negative Breast Cancer (mTNBC).

2. **KEYNOTE-355** (NCT02819518): Study of pembrolizumab plus chemotherapy vs. placebo plus chemotherapy for previously untreated metastatic TNBC
3. **KEYNOTE-522** (NCT03036488): Study of pembrolizumab plus chemotherapy vs. placebo plus chemotherapy as neoadjuvant therapy and pembrolizumab vs. placebo as adjuvant therapy in TNBC

#### 4.2.1.2 Pembrolizumab in ER-positive HER2-negative breast cancer

In another phase Ib trial (KEYNOTE-028), Pembrolizumab was evaluated in patients with estrogen receptor-positive, HER2-negative tumours who had PD-L1-overexpressing mBC and who were previously treated with chemotherapy. Positive PD-L1 expression was defined as a combined positive score of 1 or greater. Approximately 44% of patients received five or more lines of therapy for metastatic disease, including endocrine agents. The ORR was 12% (95% CI [2.5%- 31.2%]) in 25 evaluable patients and included three PRs. The median duration of response was 12 months. The median OS was 8.6 months (95% CI [7.3-11.6]). Interestingly, two of the three responders had invasive lobular cancer, which highlights the possibility that lobular breast cancers may be more responsive to immune checkpoint inhibitors. Larger sample sizes are needed to better characterize this observation.

Hence, pembrolizumab is selected in this study to examine the efficacy of checkpoint immunotherapy in the metastatic HER2-negative breast cancer populations with APOBEC3B germline polymorphism.

#### 4.2.2 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 tumour 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 tumour (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 tumour 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 tumour 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 tumour PD-1 saturation over a wide range of tumour penetration and PD-1 expression. This evaluation concluded that pembrolizumab at 200 mg Q3W achieves full PD-1 saturation in both blood and tumour.

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.

### 4.2.3 Rationale for Endpoints

#### 4.2.3.1 Efficacy Endpoints

**Primary Endpoint:** Overall response rate (ORR) at each treatment cycle 1 – 35 (each cycle is 3 weeks) based on RECIST 1.1. It is commonly used in clinical trials to evaluate cancer treatments for objective response in solid tumours. The observed effect is attributable directly to the drug, not the natural history of the disease. Its application in tumour progression measurement is well accepted by regulatory authorities.

**Secondary Endpoint:** Disease control rate (DCR, i.e. complete response (CR), partial response (PR) or stable disease (SD)) at 6, 12 and 24 months based on RECIST 1.1. For subjects who demonstrate CR, PR or SD, duration of response (DOR) is defined as the time from the start of study medication until the first sign of disease progression.

Progression Free Survival (PFS) measures the time from start of study medication until the first sign of disease progression based on RECIST 1.1 or death from any cause, whichever occurs first. It is a widely accepted endpoint in breast cancer Phase II clinical trials.

Overall Survival (OS) measures the date from study commencement to the date death from any cause. Patients alive or lost to follow up are censored. Overall survival as an endpoint is easily measured, unambiguous, objective and unaffected by the timing of assessment.

#### 4.2.3.2 Biomarker Research

**Planned Biomarker Research:** The specimens collected during clinical trial will be analysed to further investigate the association of genetic variants to the pembrolizumab, the molecular signatures correlate to the response of pembrolizumab and other biomarkers potentially be prognostic indicators to the response of pembrolizumab:

- Germline analyses (blood) which include single nucleotide polymorphism, whole exome sequencing or whole genome sequencing.
- Genetic analyses (tumour biopsy) which include Genome wide and targeted mutational analysis, mRNA expression and microRNA analysis may be performed.

- Other biomarkers: Tumour infiltrating lymphocytes (TILs) have been shown to provide prognostic and potentially predictive value. Hematoxylin and eosin-stained breast tumour sections will be evaluated for TILs, according to published and standardised methodology.

**Future Biomedical Research:** The specimens collected during clinical trial and not analysed will be stored and used for future biomedical research. This research may include genetic analyses DNA, RNA, metabolomics (serum/plasma) and/or the measurement of other analyses. Such research is for biomarker testing to address emergent not described elsewhere in the protocol (as part of the main trial) and will only be conducted on specimens collected from appropriately consented subjects within this study.

## 5.0 METHODOLOGY

### 5.1 Study Population

Written informed consent must be obtained before any study specific procedures are performed. Subjects must meet all the inclusion/exclusion criteria listed below.

#### 5.1.1 Inclusion Criteria

As this is a small Phase II study, only female patients will be included in order to reduce heterogeneity. Participants are eligible to be included in the study only if all of the following criteria apply:

1. Female participants who are at least 18 years of age on the day of signing informed consent with histologically confirmed HER2-negative breast cancer (infiltrating ductal or lobular breast carcinoma) with measurable metastatic disease.
2. Must have received at least one but not more than three (3) prior lines of palliative chemotherapy for metastatic breast cancer.
3. Have received at least one line of hormonal therapy in the metastatic setting, for patients with ER+ (positive) breast cancer.
4. Documented germline *APOBEC3B* mutation (i.e. germline deletion).
5. Can provide archival tumour tissue sample or willing to provide tissues from a newly obtained core or excisional biopsy of a tumour lesion not previously irradiated. Note: Formalin-fixed, paraffin embedded (FFPE) tissue blocks or slides allowed (10 unstained slides are needed);
6. Have measurable disease based on RECIST 1.1 as determined by local radiology review. Lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions.
7. Have Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (assessed within 10 days prior to the start of study treatment).
8. Have life expectancy of at least 3 months.
9. Have adequate organ function, within 10 days prior to the start of study treatment, as defined in the following:
  - a. Absolute neutrophil count (ANC)  $\geq 1,500/\mu\text{l}$ .
  - b. Hemoglobin (Hb)  $\geq 9$  g/dL or 5.6mmol/L<sup>a</sup>.
  - c. Platelets  $> 100,000/\mu\text{l}$ .
  - d. Creatinine  $\leq 1.5$  times ULN.
  - e. ALT (SGPT) and AST (SGOT)  $\leq 2.5$  times the ULN ( $\leq 5$  times for patients with liver metastases).
  - f. Total bilirubin  $\leq 1.5$  mg/dL.
10. LDH  $\leq 2.0$  times the ULN. Women of child-bearing potential must have a negative urine or serum pregnancy test within 72 hours prior to receiving the first dose of study treatment.

11. Women of child-bearing potential prepared to use adequate contraceptive measures if sexually active for the course of the study through 120 days after the last dose of treatment.
12. Have signed informed consent and able to comply with scheduled visits, treatment plan and other study procedures.

### 5.1.2 Exclusion Criteria

Participant is excluded from the study if any of the following criteria apply:

1. Has HER2-positive breast cancer (FISH/CISH confirmed status, or 3+ IHC status)
2. Has use of any investigational agent or participation in another therapeutic clinical trial concurrently or in the 30 days prior to inclusion.
3. Has not recovered (e.g. to  $\leq$ Grade 1 or to baseline) from AEs due to a previously administered therapy. Note: Participants with  $\leq$ Grade 2 neuropathy may be eligible.
4. Has an active autoimmune disease that has required systemic treatment in the past 2 years (e.g. with the 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) is not considered a form of systematic treatment.
5. Has a diagnosis of immunodeficiency or is receiving systematic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to study treatment.
6. Has a concurrently active second malignancy, other than adequately treated non-melanoma skin cancers, in situ melanoma or in situ cervical cancer. Subjects with other non-mammary malignancies must have been disease-free for at least 5 years.
7. Has known active CNS metastases and/or carcinomatous meningitis. Previously treated brain metastases may participate provided these remain stable.
8. Has received prior therapy with an anti-PD1, anti-PDL1 or anti-PDL2 agent or with an agent directed to another co-inhibitory T cell receptor (such as CTLA-4, OX-40, and CD137) or has previously participated in pembrolizumab clinical studies.
9. Patient who has received a live vaccine within 30 days of the first dose of study drug.
10. Known hypersensitive or allergy to pembrolizumab and any of its components.
11. Patient who is pregnant or breastfeeding.
12. Patient with an expected life expectancy of less than 3 months.
13. History of significant comorbidities that, in the opinion of the investigator, may interfere with the conduct of the study, the evaluation of response, or with informed consent.
14. Active uncontrolled infection at the time of inclusion.
15. Has a history of class II-IV congestive heart failure or myocardial infraction.
16. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of this study
17. Has evidence of active pneumonitis, or non-infectious pneumonitis requiring treatment with steroids.
18. Has a known history of Human Immunodeficiency Virus (HIV).
19. 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.



### 5.1.3 Lifestyle Restrictions

#### 5.1.3.1 Meals and Dietary Restrictions

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

#### 5.1.3.2 Contraception

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

### 5.1.4 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 (eg, 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.

### 5.1.5 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.

## 5.2 Trial Treatments

The treatment to be used in this trial is outlined below in Table 1.

**Table 1 Trial Treatment**

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

Trial treatment should begin on the day of treatment allocation or within 3 days of treatment allocation.

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

### **5.2.2 Dose Modification and toxicity management for immune-related AEs associated with pembrolizumab**

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 one 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 2).

**Table 2 Dose modification and toxicity management guidelines for immune-related AEs associated with pembrolizumab**

<b>General instructions:</b>				
<ol style="list-style-type: none"> <li>1. Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks.</li> <li>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 <math>\leq 10</math> mg prednisone or equivalent per day within 12 weeks.</li> <li>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.</li> </ol>				
<b>Immune-related AEs</b>	<b>Toxicity grade or conditions (CTCAEv4.0)</b>	<b>Action taken to pembrolizumab</b>	<b>irAE management with corticosteroid and/or other therapies</b>	<b>Monitor and follow-up</b>
Pneumonitis	Grade 2	Withhold	<ul style="list-style-type: none"> <li>• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper</li> </ul>	<ul style="list-style-type: none"> <li>• Monitor participants for signs and symptoms of pneumonitis</li> <li>• Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment</li> <li>• Add prophylactic antibiotics for opportunistic infections</li> </ul>
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold	<ul style="list-style-type: none"> <li>• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper</li> </ul>	<ul style="list-style-type: none"> <li>• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel</li> </ul>

	Grade 4	Permanently discontinue		<p>perforation (ie, peritoneal signs and ileus).</p> <ul style="list-style-type: none"> <li>• Participants with <math>\geq</math> Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis.</li> <li>• 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.</li> </ul>
AST / ALT elevation or Increased bilirubin	Grade 2	Withhold	<ul style="list-style-type: none"> <li>• Administer corticosteroids (initial dose of 0.5- 1 mg/kg prednisone or equivalent) followed by taper</li> </ul>	<ul style="list-style-type: none"> <li>• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable)</li> </ul>
	Grade 3 or 4	Permanently discontinue	<ul style="list-style-type: none"> <li>• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper</li> </ul>	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of $\beta$ -cell failure	Withhold	<ul style="list-style-type: none"> <li>• Initiate insulin replacement therapy for participants with T1DM</li> <li>• Administer anti-hyperglycemic in participants with hyperglycemia</li> </ul>	<ul style="list-style-type: none"> <li>• Monitor participants for hyperglycemia or other signs and symptoms of diabetes.</li> </ul>
Hypophysitis	Grade 2	Withhold	<ul style="list-style-type: none"> <li>• Administer corticosteroids and initiate hormonal replacements as clinically indicated.</li> </ul>	<ul style="list-style-type: none"> <li>• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)</li> </ul>
	Grade 3 or 4	Withhold or permanently discontinue <sup>1</sup>		

Hyperthyroidism	Grade 2	Continue	<ul style="list-style-type: none"> <li>Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate</li> </ul>	<ul style="list-style-type: none"> <li>Monitor for signs and symptoms of thyroid disorders.</li> </ul>
	Grade 3 or 4	Withhold or permanently discontinue <sup>1</sup>		
Hypothyroidism	Grade 2-4	Continue	<ul style="list-style-type: none"> <li>Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care</li> </ul>	<ul style="list-style-type: none"> <li>Monitor for signs and symptoms of thyroid disorders.</li> </ul>
Nephritis and Renal dysfunction	Grade 2	Withhold	<ul style="list-style-type: none"> <li>Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper.</li> </ul>	<ul style="list-style-type: none"> <li>Monitor changes of renal function</li> </ul>
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1 or 2	Withhold	<ul style="list-style-type: none"> <li>Based on severity of AE administer corticosteroids</li> </ul>	<ul style="list-style-type: none"> <li>Ensure adequate evaluation to confirm etiology and/or exclude other causes</li> </ul>
	Grade 3 or 4	Permanently discontinue		
All other immune-related AEs	Intolerable/persistent Grade 2	Withhold	<ul style="list-style-type: none"> <li>Based on type and severity of AE administer corticosteroids</li> </ul>	<ul style="list-style-type: none"> <li>Ensure adequate evaluation to confirm etiology and/or exclude other causes</li> </ul>
	Grade 3	Withhold or discontinue based on the type of event. Events that require discontinuation include and not limited to: Guillain-Barre Syndrome, encephalitis		

	Grade 4 or recurrent Grade 3	Permanently discontinue		
<p>1. Withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician.</p> <p><b>NOTE:</b>                      For participants with Grade 3 or 4 immune-related endocrinopathy where withhold of pembrolizumab is required, pembrolizumab may be resumed when AE resolves to <math>\leq</math> Grade 2 and is controlled with hormonal replacement therapy or achieved metabolic control (in case of T1DM).</p>				

**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 3.

**Table 3 Pembrolizumab Infusion Reaction Dose modification and Treatment Guidelines**

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
<p><b>Grade 1</b> Mild reaction; infusion interruption not indicated; intervention not indicated</p>	<p>Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator.</p>	<p>None</p>
<p><b>Grade 2</b> Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs</p>	<p><b>Stop Infusion.</b> 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. <b>Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment</b></p>	<p>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).</p>



<p><b>Grades 3 or 4</b> 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</p>	<p><b>Stop Infusion.</b> 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. <b>Participant is permanently discontinued from further study drug treatment.</b></p>	<p>No subsequent dosing</p>
<p>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 <a href="http://ctep.cancer.gov">http://ctep.cancer.gov</a></p>		

**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.

**5.2.3 Second Course\***

All participants who top study treatment with stable disease (SD) or better may be eligible for up to an additional 17 cycles (approximately 1 year) of pembrolizumab treatment if they progress after stopping study treatment from the initial treatment phase. This retreatment is termed the Second Course Phase of this study and is only available if the study remains open and the participant meets the following conditions:

**Either**

- Stopped initial treatment with study treatment after attaining an investigator-determined confirmed CR based on RECIST 1.1, and
  - Was treated with at least 8 cycles of study treatment before discontinuing treatment, and

- Received at least 2 treatments with pembrolizumab beyond the date when the initial CR was declared

**OR**

- Had SD, PR, or CR and stopped study treatment after completion of 35 administrations (approximately 2 years) of study treatment for reasons other than disease progression or intolerability

**AND**

- Experienced an investigator-determined radiographic disease progression by RECIST 1.1 after stopping initial treatment, and
  - Upon unblinding at the time of centrally verified disease progression were found to have received pembrolizumab, and
  - No new anticancer treatment was administered after the last dose of study treatment, and
  - The participant meets all of the safety parameters listed in the inclusion criteria and none of the safety parameters listed in the exclusion criteria, and
  - The study is ongoing

An objective response or disease progression that occurs during the Second Course Phase for a participant will not be counted as an event for the primary analysis of either endpoint in this study.

*\*Note: patients must have measurable disease at the start of protocol treatment to be eligible for this provision.*

**5.3 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's primary physician.

**5.3.1 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.

### 5.3.2 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 (eg, 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.

### 5.3.3 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 2]. 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 2 in 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.

#### **5.4 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 8 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 5.2.5.
- The participant is lost to follow-up
- Completion of 35 treatments (approximately 2 years) with pembrolizumab

Note: The number of treatments is calculated starting with the first dose. Participants who stop the combination or pembrolizumab after receiving 35 doses may be eligible for retreatment if they progress after stopping study treatment provided they meet the requirements detailed in Section 5.2.3. Participants may be retreated in the Second Course Phase (Retreatment) for up to an additional 17 cycles (approximately 1 year).

- Administrative reasons

### **5.5 Participant Replacement Strategy**

Additional patients will be recruited to meet the samples size required

### **5.6 Clinical Criteria for Early Trial Termination**

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

1. Unacceptably high incidence of toxicities among subjects enrolled in this or other studies, as assessed by an internal safety monitoring committee
2. Objective evidence of progressive disease as determined by CT scan and/or X-ray and/or ultrasound and/or clinical examination
3. Clinical decision by the investigator that continued participation in the trial is contrary to the patient's best interests
4. Quality or quantity of data recording is inaccurate or incomplete
5. Poor adherence to protocol and regulatory requirements
6. 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.

**6.0 TRIAL FLOW CHART**

**6.1 Initial Treatment with Study Drug**

Trial Period:	Screening Phase	Treatment Cycles (3-week Cycles)								End of Treatment	Post-Treatment			
Treatment Cycle/Title:	Screening	1	2	3	4	To be repeated beyond 8 cycles				Discon	Safety Follow-up	Follow Up Visits	Survival Follow-Up <sup>a</sup>	
Scheduling Window (Days) <sup>b</sup> :	-28 to -1		± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days post last dose	Every 8 weeks post	Every 12 weeks
<b>Administrative Procedures</b>														
Informed Consent	X													
Inclusion/Exclusion Criteria	X													
Demographics and Medical History	X													
Prior and Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	X	X		
Trial Treatment Administration		X	X	X	X	X	X	X	X					
Post-study anticancer therapy status												X		
Survival Status <sup>a</sup>														X
<b>Clinical Procedures/Assessments</b>														

Trial Period:	Screening Phase	Treatment Cycles (3-week Cycles)								End of Treatment	Post-Treatment		
Treatment Cycle/Title:	Screening	1	2	3	4	To be repeated beyond 8 cycles				Discon	Safety Follow-up	Follow Up Visits	Survival Follow-Up <sup>a</sup>
Scheduling Window (Days) <sup>b</sup> :	-28 to -1		± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days post last dose	Every 8 weeks post discon	Every 12 weeks
Review Adverse Events <sup>c</sup>	X	X	X	X	X	X	X	X	X	X	X	X <sup>c</sup>	
Full Physical Examination	X									X			
Directed Physical Examination		X	X	X	X	X	X	X	X				
Height <sup>d</sup> , Weight and Vital Signs (T, P, RR, BP)	X	X	X	X	X	X	X	X	X	X			
ECOG Performance Status <sup>e</sup>	X	X	X	X	X	X	X	X	X	X			
<b>Laboratory Procedures/Assessments: analysis performed by LOCAL laboratory<sup>m</sup></b>													
Pregnancy Test – Urine or Serum β-HCG <sup>f</sup>	X												
PT/INR and aPTT <sup>g,h</sup>	X <sup>e</sup>		X		X		X		X	X			
CBC with Differential <sup>g</sup>	X <sup>e</sup>		X	X	X	X	X	X	X	X	X		
Chemistry and Liver Panel <sup>g</sup>	X <sup>e</sup>		X	X	X	X	X	X	X	X	X		
Urinalysis <sup>g,h</sup>	X <sup>e</sup>		X		X		X		X	X			
T3, FT4 and TSH <sup>g,h</sup>	X <sup>e</sup>		X		X		X		X	X			
<b>Efficacy Assessment</b>													
CT Chest/Abdomen/Pelvis <sup>i</sup>	X					X <sup>i</sup>				X <sup>j</sup>			
Bone Scan <sup>k</sup>	X					X <sup>k</sup>							
Brain Imaging <sup>l</sup>	X					X <sup>l</sup>							

<b>Trial Period:</b>	<b>Screening Phase</b>	<b>Treatment Cycles (3-week Cycles)</b>								<b>End of Treatment</b>	<b>Post-Treatment</b>			
<b>Treatment Cycle/Title:</b>	<b>Screening</b>	<b>1</b>	<b>2</b>	<b>3</b>	<b>4</b>	<b>To be repeated beyond 8 cycles</b>				<b>Discon</b>	<b>Safety Follow-up</b>	<b>Follow Up Visits</b>	<b>Survival Follow-Up<sup>a</sup></b>	
<b>Scheduling Window (Days)<sup>b</sup>:</b>	-28 to -1		± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days post last dose	Every 8 weeks post discon	Every 12 weeks
<b>CENTRAL Laboratory Assessments</b>														
Archival or Newly Obtained Tissue Collection	X										X <sup>n</sup>			
Correlative Studies Blood Collection <sup>m</sup>	X			X				X			X			



- a. In subjects who experience PD or starts a new anti-cancer therapy, contact should be made (example: by telephone) approximately Q12W to assess for survival status. Updated survival status may be requested by the Sponsor at any time during the course of study. Upon Sponsor notification, all participants who do not/will not have a scheduled study visit or study contact during the Sponsor defined time period will be contacted for their survival status (excluding participants that have a death event previously recorded).
- b. Cycle 1 treatment must be given within 3 days of treatment allocation. The window for each visit is  $\pm 3$  days unless otherwise noted. If dosing is delayed due to administrative reasons, the subsequent dosing visit should be re-calculated to account for the every 3 week dosing visit.
- c. SAEs will be followed through 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates a new anticancer therapy, whichever is earlier. All protocol specific ECIs will be collected throughout the study as listed in Section 7.2.3.2. If any of the ECI criteria are met, collect the details until the ECIs resolve.
- d. Height will be measured at screening only.
- e. ECOG Performance Status and laboratory test for screening and determining eligibility are to be performed within 10days prior of the first dose of trial treatment except thyroid test, which may performed within 28days.
- f. For women of reproductive potential, a serum pregnancy test should be performed within 72 hours prior to receiving the first dose of study medication (Cycle 1 Day 1). Subject must be excluded/discontinued in the event of a positive results.
- g. After Cycle 1, laboratory samples can be collected up to 72 hours prior to the scheduled time point. CBC with differential, chemistry panel and liver panel to be performed every cycle. Details can be found in Section 7.1.3 Laboratory Procedure/Assessments. Liver panel to include albumin, ALT, AST, total bilirubin, alkaline phosphatase and total protein.
- h. While on treatment, PT/INR and aPTT, UA and thyroid function tests will be performed every other cycle.
- i. Screening tumour imaging will be performed within 28 days prior to treatment allocation. Imaging at screening should include chest, abdomen, and pelvis. The first on-study imaging time point will be performed at 9 week ( $\pm 7$  days) calculated from the date of treatment allocation and will be continue to be performed Q9W ( $63\pm 7$  days) in the first year, Q12W ( $84\pm 7$ days) in the second year of therapy.
- j. If previous imaging was obtained within 4 weeks prior to the date of discontinuation, then imaging at treatment discontinuation is not mandatory.
- k. Only for those with a history of bone metastases, to be repeated Q9W ( $63\pm 7$  days) from treatment allocation in first year, Q12W ( $84\pm 7$ days) in second year of therapy.
- l. Only for those with known brain metastases, CT or MRI brain to be repeated Q9W ( $63\pm 7$  days) from treatment allocation in first year, Q12W ( $84\pm 7$ days) in second year of therapy.
- m. Blood for correlative studies should be collected at Cycle 3, at Cycle 6 and again at discontinuation (end of treatment).
- n. Tissue collection through core needle biopsy (CNB) or excisional biopsy (EB) may be performed when progressive disease is confirmed.

## 6.2 Second Course Treatment

Trial Period:	Screening Phase	Treatment Cycles (3-week Cycles)								End of Treatment	Post-Treatment		
Treatment Cycle/Title:	Screening	1	2	3	4	To be repeated beyond 8 cycles				Discon	Safety Follow-up	Follow Up Visits	Survival Follow-Up <sup>a</sup>
						5	6	7	8				
<b>Scheduling Window (Days)<sup>b</sup>:</b>	-28 to -1		± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days post last dose	Every 8 weeks post discon	Every 12 weeks
<b>Administrative Procedures</b>													
Eligibility Criteria	X												
Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	X		
<b>Clinical Procedures/Assessments</b>													
Review Adverse Events <sup>c</sup>	X	X	X	X	X	X	X	X	X	X	X <sup>c</sup>		
Full Physical Examination	X									X			
Directed Physical Examination		X	X	X	X	X	X	X	X				
Weight and Vital Signs (T, P, RR, BP)	X	X	X	X	X	X	X	X	X	X			
ECOG Performance Status <sup>e</sup>	X	X	X	X	X	X	X	X	X	X			
Post-study Anticancer Therapy Status											X	X	X
Survival Status <sup>a</sup>													X
<b>Laboratory Procedures/Assessments: analysis performed by LOCAL laboratory<sup>m</sup></b>													
Pregnancy Test – Urine or Serum β-HCG <sup>f</sup>	X												

Trial Period:	Screening Phase	Treatment Cycles (3-week Cycles)								End of Treatment	Post-Treatment			
Treatment Cycle/Title:	Screening	1	2	3	4	To be repeated beyond 8 cycles				Discon	Safety Follow-up	Follow Up Visits	Survival Follow-Up <sup>a</sup>	
Scheduling Window (Days) <sup>b</sup> :	-28 to -1		± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days post last dose	Every 8 weeks post discon	Every 12 weeks
PT/INR and aPTT <sup>g,h</sup>	X <sup>e</sup>		X		X		X		X	X				
CBC with Differential <sup>g</sup>	X <sup>e</sup>		X	X	X	X	X	X	X	X		X		
Chemistry and Liver Panel <sup>g</sup>	X <sup>e</sup>		X	X	X	X	X	X	X	X		X		
Urinalysis <sup>g,h</sup>	X <sup>e</sup>		X		X		X		X	X				
T3, FT4 and TSH <sup>g,h</sup>	X <sup>e</sup>		X		X		X		X	X				
<b>Efficacy Assessment</b>														
CT Chest/Abdomen/Pelvis <sup>i</sup>	X								X <sup>i</sup>	X <sup>j</sup>			X	
Bone Scan <sup>k</sup>	X								X <sup>k</sup>					
Brain Imaging <sup>l</sup>	X								X <sup>l</sup>					
<b>CENTRAL Laboratory Assessments</b>														
Archival or Newly Obtained Tissue Collection	X									X <sup>n</sup>				
Correlative Studies Blood Collection <sup>m</sup>	X			X					X	X				

- a. In subjects who experience PD or starts a new anti-cancer therapy contact should be made (example: by telephone) approximately Q12W to assess for survival status. Updated survival status may be requested by the Sponsor at any time during the course of study. Upon Sponsor notification, all participants who do not/will not have a scheduled study visit or study contact during the Sponsor defined time period will be contacted for their survival status (excluding participants that have a death event previously recorded).
- b. Cycle 1 treatment must be given within 3 days of treatment allocation. The window for each visit is  $\pm 3$  days unless otherwise noted. If dosing is delayed due to administrative reasons, the subsequent dosing visit should be re-calculated to account for the every 3 week dosing visit.
- c. SAEs will be followed through 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates a new anticancer therapy, whichever is earlier. All protocol specific ECIs will be collected throughout the study as listed in Section 7.2.3.2. If any of the ECI criteria are met, collect the details until the ECIs resolve.
- d. Height will be measured at screening only.
- e. ECOG Performance Status and laboratory test for screening and determining eligibility are to be performed within 10days prior of the first dose of trial treatment except thyroid test, which may performed within 28days.
- f. For women of reproductive potential, a serum pregnancy test should be performed within 72 hours prior to receiving the first dose of study medication (Cycle 1 Day 1). Subject must be excluded/discontinued in the event of a positive results.
- g. After Cycle 1, laboratory samples can be collected up to 72 hours prior to the scheduled time point. CBC with differential, chemistry panel and liver panel to be performed every cycle. Details can be found in Section 7.1.3 Laboratory Procedure/Assessments. Liver panel to include albumin, ALT, AST, total bilirubin, alkaline phosphatase and total protein.
- h. While on treatment, PT/INR and aPTT, UA and thyroid function tests will be performed every other cycle.
- i. Screening tumour imaging will be performed within 28 days prior to treatment allocation. Imaging at screening should include chest, abdomen, and pelvis. The first on-study imaging time point will be performed at 9 week ( $\pm 7$  days) calculated from the date of treatment allocation and will be continue to be performed Q9W ( $63\pm 7$  days) in the first year, Q12W ( $84\pm 7$ days) in the second year of therapy.
- j. If previous imaging was obtained within 4 weeks prior to the date of discontinuation, then imaging at treatment discontinuation is not mandatory.
- k. Only for those with a history of bone metastases, to be repeated Q9W ( $63\pm 7$  days) from treatment allocation in first year, Q12W ( $84\pm 7$ days) in second year of therapy.
- l. Only for those with known brain metastases, CT or MRI brain to be repeated Q9W ( $63\pm 7$  days) from treatment allocation in first year, Q12W ( $84\pm 7$ days) in second year of therapy.
- m. Blood for correlative studies should be collected at Cycle 3, at Cycle 6 and again at discontinuation (end of treatment).
- n. Tissue collection through core needle biopsy (CNB) or excisional biopsy (EB) may be performed when progressive disease is confirmed.

## **7.0 TRIAL PROCEDURES**

### **7.1 Trial Procedures**

This study has a pre-screening genetic testing to confirm the participant's APOBEC3B germline mutation status. Participant with a confirmed APOBEC3B germline mutation will proceed to the main screening of the study. The Trial Flow Chart - Section 6.0 summarizes the trial procedures to be performed at each visit (including screening 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.

#### **7.1.1 Administrative Procedures**

##### **7.1.1.1 Informed Consent**

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

###### **7.1.1.1.1 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.

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

There are two sets of informed consents forms to be used in this study. The first informed consent form will be provided to all participants to participant in genetic testing to confirm their APOBEC3B germline mutation status at pre-screening. Participants with confirmed APOBEC3B germline mutation will then be provided the second informed consent form to participant in the main study.

### **7.1.1.2 Inclusion/Exclusion Criteria**

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

### **7.1.1.3 Medical History**

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

### **7.1.1.4 Prior and Concomitant Medications Review**

#### **7.1.1.4.1 Prior Medications**

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the 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.

#### **7.1.1.4.2 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.

### **7.1.1.5 Disease Details and Treatments**

#### **7.1.1.5.1 Disease Details**

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

#### **7.1.1.5.2 Prior Treatment Details**

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

#### **7.1.1.5.3 Subsequent Anti-Cancer Therapy Status**

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

#### **7.1.1.6 Assignment of Allocation Number**

All consented subjects will be given a unique allocation number that will be used to identify the subject for all procedures that occurring prior and after treatment allocation. Each subject will be assigned only one allocation number. Allocation numbers must not be re-used for different subjects.

A single subject cannot be assigned more than 1 allocation number.

#### **7.1.1.7 Trial Compliance (Medication/Diet/Activity/Other)**

Interruptions from the protocol specified treatment plan for greater than 12 weeks between doses for non-drug-related or administrative reasons require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on subject management.

The total volume of study treatment infused will be compared to the total volume prepared to determine compliance with each dose administered. The instructions for preparing and administering study treatment are provided in the Pharmacy Manual.

Administration of trial medication will be witnessed by the investigator and/or trial staff or qualified designee per institutional guidelines and procedures.

### **7.1.2 Clinical Procedures/Assessments**

#### **7.1.2.1 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.

#### **7.1.2.2 Full Physical Exam**

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

#### **7.1.2.3 Directed Physical Exam**

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

#### **7.1.2.4 Vital Signs**

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

#### **7.1.2.5 Eastern Cooperative Oncology Group (ECOG) Performance Scale**

The investigator or qualified designee will assess ECOG status (see Appendix 1) at screening, within 10 days prior to the administration of each dose of trial treatment and discontinuation of trial treatment as specified in the Trial Flow Chart.

#### **7.1.2.6 Tumour Imaging and Assessment of Disease**

Tumour 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 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 tumour burden and improve the accuracy of the assessment of response or progression based on imaging.

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.

##### **7.1.2.6.1 Initial Tumour Imaging**

Initial tumour imaging at Screening must be performed within 28 days prior to the date of treatment allocation. The site study team must review screening images to confirm the participant has measurable disease per RECIST 1.1.

The screening images must be reviewed by dedicated trial radiologists for measurable disease per RECIST 1.1 for eligibility prior to allocation.



Brain imaging, if performed to document the stability of existing metastases, should be by MRI if possible. CT with contrast is an acceptable alternative.

#### **7.1.2.6.2 Tumour Imaging During the Study**

The first on-study imaging assessment should be performed at 9 weeks ( $\pm 7$  days) from the date of treatment allocation. Subsequent tumour imaging should be performed every 9 weeks ( $\pm 7$  days) or more frequently if clinically indicated. After 52 weeks ( $\pm 7$  days), participants who remain on treatment will have imaging performed every 12 weeks ( $\pm 7$  days). 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.

Per iRECIST (Section 9.2.1.6), disease progression should be confirmed by the site 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 tumour imaging if it is less than 4 weeks later; tumour 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.

#### **7.1.2.6.3 End of Treatment and Follow-up Tumour Imaging**

In participants who discontinue study treatment, tumour imaging should be performed at the time of treatment discontinuation ( $\pm 4$  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 tumour imaging.

In participants who discontinue study treatment without documented disease progression, every effort should be made to continue monitoring their disease status by tumour imaging using the same imaging schedule used while on treatment (every 9 weeks in Year 1 or every 12 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.

#### **7.1.2.6.4 Second Course (Retreatment) Tumour Imaging**

Tumour 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 9 weeks ( $\pm 7$  days) after the restart of treatment. Subsequent tumour imaging should be performed every 12 weeks ( $\pm 7$  days) or more frequently, if clinically indicated.

Per RECIST 1.1 (Section 9.1.2.6), if tumour imaging shows initial PD, tumour 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 tumour 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 tumour imaging indicating PD, by the Investigator using iRECIST, in clinically stable participants.

In participants who discontinue study treatment, tumour imaging should be performed at the time of treatment discontinuation ( $\pm 4$  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 tumour 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 ( $\pm 7$  days) until either the start of a new anticancer treatment, disease progression, pregnancy, death, or the end of the study, whichever occurs first.

#### **7.1.2.6.5 RECIST 1.1 Assessment of Disease**

RECIST 1.1 will be used as the primary measure for assessment of tumour response, date of disease progression, and as a basis for all protocol guidelines related to disease status (eg, discontinuation of study treatment).

#### **7.1.2.6.6 iRECIST Assessment of Disease**

iRECIST is based on RECIST 1.1, but adapted to account for the unique tumour 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 tumour flare in the first few months after the start of immunotherapy, and then experience subsequent disease response.

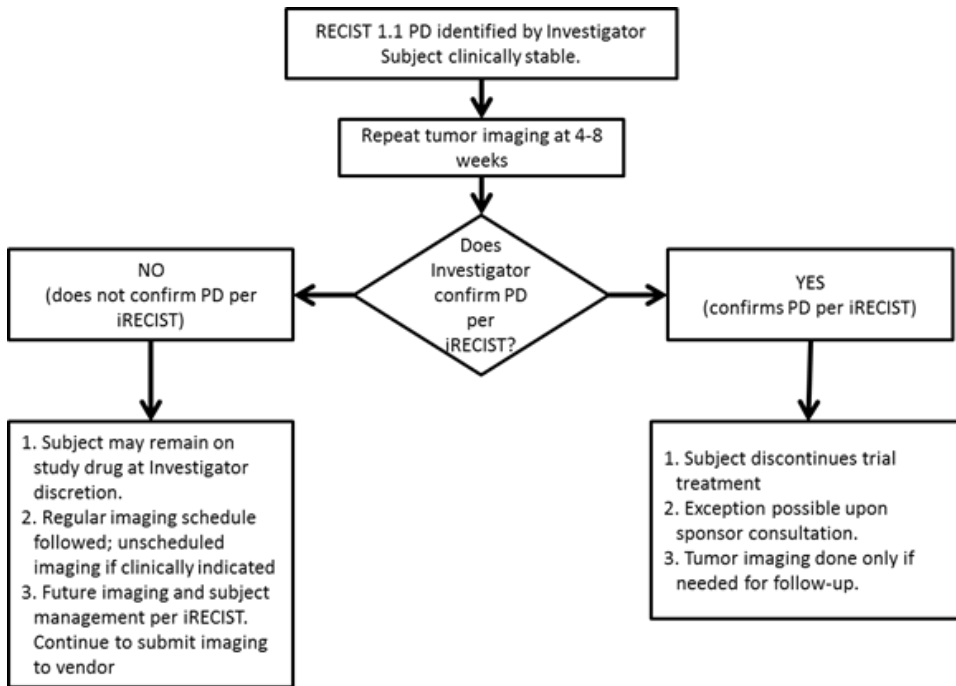
A description of the adaptations and iRECIST process is provided in Appendix 4, with additional detail in the iRECIST publication [Seymour et al, 2017]. iRECIST will be used by the Investigator to assess tumour response and progression, and make treatment decisions.

### **Table 4 Imaging and Treatment after First Radiologic Evidence of Progressive Disease**

	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 tumour imaging by site by iRECIST.	Repeat imaging at 4 to 8 weeks to confirm PD per Investigator’s discretion only.	Discontinue treatment
Repeat tumour 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 tumour 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 tumour 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 tumour 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 Tumours 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 Tumours 1.1..

Figure 1: Imaging and Treatment for Clinically Stable Participants after First Radiologic Evidence of PD Assessed by the Investigator



### **7.1.2.7 Tumour Tissue Collection and Correlative Studies Blood Sampling**

Prior to study treatment, tumour tissues should be collected through core needle biopsy (CNB) or excisional biopsy (EB) from a metastatic tumour site. It should be a recently or newly obtained biopsy. This may be exempted due to site inaccessibility and/or subject safety concerns. Additional tumor tissues may be collected through CNB or EB when progressive disease is confirmed.

Blood for correlative studies should be collected according to the Trial Flow Chart in Section 6.0.

Further investigations will be performed on the collected specimens:

- 7.1.2.7.1** Genetic analyses using tumour tissue: Genome wide and targeted mutational analysis, mRNA expression and microRNA analysis may be performed to define gene expression signatures that correlate to clinical response to treatment with pembrolizumab.
- 7.1.2.7.2** Germline analysis using peripheral white blood cells: Targeted mutational analysis, whole exome sequencing or whole genome sequencing may be performed to evaluate whether genetic variation correlates with response to pembrolizumab.
- 7.1.2.7.3** Hematoxylin and eosin-stained (H&E) breast tumour sections will be evaluated for PD-L1, TILs, according to published and standardised methodology.

### **7.1.3 Laboratory Procedures/Assessments**

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

#### **7.1.3.1 Laboratory APOBEC3B Germline Mutation Evaluation**

After the subject consented to genetic testing (at pre-screening), 20 ml of blood (1.5 tablespoon) will be drawn into two EDTA tubes. Genotyping of APOBEC3B will be done using PCR. Germline DNA extracted from peripheral blood will be genotyped for the APOBEC3B germline polymorphism using a single tube PCR assay as described in Klonowska et al., *Oncotarget* 2017.

In brief, the test takes advantage of nucleotide positions specific for particular duplicated regions and consists of 3 PCR primers, i.e. one forward primer and two distinct reverse primers. The forward primer is located in the border of APOBEC3A intron 3 and exon 4 (upstream of the 5' breakpoint of the APOBEC3B deletion) and the reverse primers R1 and R2 are located at the APOBEC3A exon 5 downstream of the presumed 3' breakpoint of the deletion, or the APOBEC3B exon 8 downstream of the presumed 3' breakpoint of the deletion. The R1 and R2 primers distinguish the A3B+ and A3B- alleles respectively, as the resultant PCR products can be distinguished by agarose gel electrophoresis, where the A3B +/+ genotype produces one smaller band, the A3B -/- genotype produces one larger band, and the A3B +/- genotype produces two bands.

### **7.1.3.2 Laboratory Safety Evaluations**

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

**Table 5 Laboratory Tests**

<b>Hematology</b>	<b>Chemistry</b>	<b>Urinalysis</b>	<b>Other</b>
Hematocrit	Albumin	Blood	Serum $\beta$ -human chorionic gonadotropin ( $\beta$ -hCG)
Hemoglobin	Alkaline phosphatase	Glucose	
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 ( <i>If abnormal</i> )	Total triiodothyronine (T3)
Absolute Neutrophil Count	Calcium	results are noted	Free thyroxine (T4)
Absolute Lymphocyte Count	Chloride	Urine pregnancy test	Thyroid stimulating hormone (TSH)
	Glucose		Blood for correlative studies
	Potassium		
	Sodium		
	Total Bilirubin		
	Direct Bilirubin ( <i>If total bilirubin is elevated above the upper limit of normal</i> )		
	Total protein		
	Urea		

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

### **7.1.3.3 Future Biomedical Research**

The following specimens are to be obtained and stored for future biomedical research:

- Blood for genomics use
- Leftover archival tumour tissue or leftover newly obtained biopsy sample
- Leftover correlative blood samples

### **7.1.4 Other Procedures**

#### **7.1.4.1 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).

#### **7.1.4.2 Blinding/Unblinding**

Not applicable.

### **7.1.5 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.

#### **7.1.5.1 Screening Period**

Approximately 28 days prior to treatment, potential subjects will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5.1. Screening procedures may be repeated.

Subjects may be rescreened after initially failing to meet the inclusion/exclusion criteria.

Subjects who are rescreened will retain their original allocation number. Results of a test performed prior to the subject signing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame.

Screening procedures are to be completed within 28 days prior to the first dose of trial treatment except for the following:

- Laboratory tests and ECOG PS are to be performed within 10 days prior to the first dose of trial treatment.



- For women of reproductive potential, a urine or serum pregnancy test will be performed within 72 hours prior to the first dose of trial treatment.

### **7.1.5.2 Treatment Period**

Visit requirements are outlined in the Trial Flow Chart (Section 6.0). Specific procedure-related details are provided in the Trial Procedures (Section 7.0).

### **7.1.5.3 Post-Treatment Visits**

#### **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/crossover 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 9 weeks ( $63 \pm 7$  days) by radiologic imaging to monitor disease status. After 1 year, the imaging time point will occur every 12 weeks ( $\pm 7$  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.

## **7.2 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/randomization 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/randomization 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/randomization 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/randomization 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.

### **7.2.1 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 ( $\geq 5$  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)

### **7.2.2 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/randomization 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/randomization 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)

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

#### 7.2.3.1 Serious Adverse Events

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

- Results in death;
- Is life threatening;
- Results in persistent or significant disability/incapacity;
- Results in or prolongs an existing inpatient hospitalization;
- Is a congenital anomaly/birth defect;
- Is an other important medical event
  
- **Note:** In addition to the above criteria, adverse events meeting either of the below criteria, although not serious per ICH definition, are reportable to the Merck in the same timeframe as SAEs to meet certain local requirements. Therefore, these events are considered serious by Merck for collection purposes.
- Is a new cancer (that is not a condition of the study);
- Is associated with an overdose.

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

For the time period beginning when the consent form is signed until treatment allocation/randomization, any serious adverse event, or follow up to a serious adverse event, including death due to any cause 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/randomization 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.

#### **7.2.3.2 Events of Clinical Interest**

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be 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/randomization, 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/randomization 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.

#### **7.2.4 Evaluating Adverse Events**

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

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

### **7.2.5 Sponsor Responsibility for Reporting Adverse Events**

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

**Table 6 Evaluating Adverse Events**

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

<b>V4.0 CTCAE Grading</b>	<b>Grade 1</b>	<b>Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.</b>
	<b>Grade 2</b>	<b>Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.</b>
	<b>Grade 3</b>	<b>Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.</b>
	<b>Grade 4</b>	<b>Life threatening consequences; urgent intervention indicated.</b>
	<b>Grade 5</b>	<b>Death related to AE</b>
<b>Seriousness</b>	A serious adverse event is any adverse event occurring at any dose or during any use of Merck product that:	
	† <b>Results in death</b> ; or	
	† <b>Is life threatening</b> ; 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	
	† <b>Results in a persistent or significant disability/incapacity</b> (substantial disruption of one's ability to conduct normal life functions); or	
	† <b>Results in or prolongs an existing inpatient hospitalization</b> (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	
	† <b>Is a congenital anomaly/birth defect</b> (in offspring of participant taking the product regardless of time to diagnosis); or	
	<b>Is a new cancer</b> (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	
	<b>Is an overdose</b> (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..	

	<b>Other important medical events</b> 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 †).
<b>Duration</b>	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units
<b>Action taken</b>	Did the adverse event cause Merck product to be discontinued?
<b>Relationship to Merck Product</b>	<p>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.</p> <p><b>The following components are to be used to assess the relationship between Merck product and the AE;</b> 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):</p>
<b>Exposure</b>	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?
<b>Time Course</b>	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)?
<b>Likely Cause</b>	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors



<b>Relationship to Merck Product (continued)</b>	<b>The following components are to be used to assess the relationship between the test drug and the AE: (continued)</b>	
	<b>Dechallenge</b>	<p>Was Merck product discontinued or dose/exposure/frequency reduced?</p> <p>If yes, did the AE resolve or improve?</p> <p>If yes, this is a positive dechallenge. If no, this is a negative dechallenge.</p> <p>(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.)</p>
	<b>Rechallenge</b>	<p>Was the participant re-exposed to Merck product in this study?</p> <p>If yes, did the AE recur or worsen?</p> <p>If yes, this is a positive rechallenge. If no, this is a negative rechallenge.</p> <p>(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).</p> <p>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.</p>
	<b>Consistency with Trial Treatment Profile</b>	<p>Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding Merck product or drug class pharmacology or toxicology?</p>
<p>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.</p>		
<b>Record one of the following</b>	<b>Use the following scale of criteria as guidance (not all criteria must be present to be indicative of Merck product relationship).</b>	
<b>Yes, there is a reasonable possibility of Merck product relationship.</b>	<p>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.</p>	
<b>No, there is not a reasonable possibility of Merck product relationship</b>	<p>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.)</p>	

## **8.0 STATISTICAL ANALYSIS PLAN**

### **8.1 Hypotheses**

Objectives and hypotheses of the study are stated in the Section 3.0.

### **8.2 Analysis endpoints**

#### **8.2.1 Primary Efficacy Endpoint(s):**

Overall responsive rate (ORR) [Time Frame: at each treatment cycle 1 to 35 (each cycle is 3 weeks)] - ORR is defined as the proportion of subjects in the analysis population who have a complete response (CR) or partial response (PR)

#### **8.2.2 Secondary Efficacy Endpoint(s):**

1. Disease Control Rate (DCR) [Time Frame: up until the first sign of progression through to study completion (2 years)] - DCR will be measured as CR, PR or stable disease (SD) at 6, 12 and 24 months
2. Progression-free Survival (PFS) [Time Frame: up until the first sign of progression through to study completion (2 years)] - PFS will be measured from the date of treatment commencement to the date of first progression at any site or date of death from any cause
3. Overall Survival (OS) [Time Frame: up until the first sign of progression through to study completion (2 years)] - OS will be measured from the date of treatment commencement to the date death from any cause
4. Duration of Response (DOR) [Time Frame: up until the first sign of progression through to study completion (2 years)] - DOR will be assessed on patients who responded to treatment and will be measured from the start of study medication until disease progression or death due to any cause, whichever occurs first, based on assessment per RECIST 1.1.

### **8.3 Study population**

All patients screened and enrolled will be accounted for. All enrolled discontinuations will be summarized by reason for discontinuation. The number of patients screened and enrolled will be presented.

### **8.4 Sample size determination**

The Simon minimax 2 stage design will be used in this study. The response rate to pembrolizumab in unselected breast cancer is estimated to be 10%. We hypothesize that the response rate to pembrolizumab in patients with APOBEC3B germline deletion will be 25%. Assuming power of 80% and one-sided level of significance of 5%, 22 evaluable patients will be required in stage I. If 6 or more patients achieve CR/PR in stage I, the study will proceed to stage II to enroll another 18 patients (total 40 evaluable patients). Taking into account an estimated 10% attrition rate, we plan to enroll 44 patients to have 40 patients evaluable for response.

## 8.5 Analysis population

The Full Analysis Set (FAS) population will serve as the primary population for the analysis of efficacy data in this study. The FAS population consists of all subjects who:

- Receive at least one dose of study treatment, and
- Have a baseline scan with measurable disease per RECIST 1.1

## 8.6 Interim Analysis

There will be one interim analysis at the end of Stage I (Section 8.4). If 6 or more patients out of the 22 evaluable patients achieve CR/PR in stage I, the study will proceed to stage II to enroll another 18 patients (total 40 evaluable patients).

## 8.7 Statistical methods

### 8.7.1 Statistical method for efficacy analysis

For the primary efficacy endpoint, investigator assessed RECIST 1.1 overall response rate (ORR), the point estimate of ORR and its 95% will be provided.

For secondary efficacy endpoints, summary statistics using Kaplan-Meier (KM) method will be provided as appropriate.

### 8.7.2 Summaries of Baseline characteristics, demographics and others

Baseline characteristics will be assessed by the use of tables and/or graphs. No statistical hypothesis tests will be performed on these characteristics. The number and percentage of subjects screened, allocated, the primary reasons for screening failure, and the primary reason for discontinuation will be displayed. Demographic variables (e.g., age, gender), baseline characteristics, and prior and concomitant therapies will be summarized by treatment either by descriptive statistics or categorical tables. Safety data (i.e. AEs, serious adverse events (SAEs) and events of clinical interest (ECIs) will be summarized by descriptive statistics.

## 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 7.

Table 7 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 REFERENCES

1. Alexandrov LB, Nik-Zainal S, Wedge DC, Aparicio SA, Behjati S, Biankin AV, Bignell GR, Bolli N, Borg A, Borresen-Dale AL *et al*: **Signatures of mutational processes in human cancer**. *Nature* 2013, **500**(7463):415-421.
2. Burns MB, Temiz NA, Harris RS: **Evidence for APOBEC3B mutagenesis in multiple human cancers**. *Nature genetics* 2013, **45**(9):977-983
3. Cescon DW, Haibe-Kains B, Mak TW: **APOBEC3B expression in breast cancer reflects cellular proliferation, while a deletion polymorphism is associated with immune activation**. *Proceedings of the National Academy of Sciences of the United States of America* 2015, **112**(9):2841-2846
4. Chemnitz JM, Parry RV, Nichols KE, June CH, Riley JL. SHP-1 and SHP-2 associate with immunoreceptor tyrosine-based switch motif of programmed death 1 upon primary human T cell stimulation, but only receptor ligation prevents T cell activation. *J Immunol* 2004;173:945-54.

5. Curtis C, Shah SP, Chin SF, Turashvili G, Rueda OM, Dunning MJ, Speed D, Lynch AG, Samarajiwa S, Yuan Y *et al*: **The genomic and transcriptomic architecture of 2,000 breast tumours reveals novel subgroups**. *Nature* 2012, **486**(7403):346-352.
6. Disis ML. Immune regulation of cancer. *J Clin Oncol* 2010;28(29):4531-8.
7. Dudley ME, Wunderlich JR, Yang JC, Sherry RM, Topalian SL, Restifo NP, et al. Adoptive cell transfer therapy following non-myeloablative but lymphodepleting chemotherapy for the treatment of patients with refractory metastatic melanoma. *J Clin Oncol* 2005;23(10):2346-57.
8. Francisco LM, Sage PT, Sharpe AH. The PD-1 pathway in tolerance and autoimmunity. *Immunol Rev* 2010;236:219-42
9. Greenwald RJ, Freeman GJ, Sharpe AH. The B7 family revisited. *Annu Rev Immunol* 2005;23:515-48.
10. Haricharan S, Bainbridge MN, Scheet P, Brown PH: **Somatic mutation load of estrogen receptor-positive breast tumours predicts overall survival: an analysis of genome sequence data**. *Breast cancer research and treatment* 2014, **146**(1):211-220
11. Herbst RS, Soria JC, Kowanetz M, Fine GD, Hamid O, Gordon MS, Sosman JA, McDermott DF, Powderly JD, Gettinger SN *et al*: **Predictive correlates of response to the anti-PD-L1 antibody MPDL3280A in cancer patients**. *Nature* 2014, **515**(7528):563-567.
12. Hunder NN, Wallen H, Cao J, Hendricks DW, Reilly JZ, Rodmyre R, et al. Treatment of metastatic melanoma with autologous CD4+ T cells against NY-ESO-1. *N Engl J Med* 2008;358(25):2698-703.
13. Le DT, Uram JN, Wang H, Bartlett BR, Kemberling H, Eyring AD, Skora AD, Lubner BS, Azad NS, Laheru D *et al*: **PD-1 Blockade in Tumours with Mismatch-Repair Deficiency**. *The New England journal of medicine* 2015, **372**(26):2509-2520.
14. Lehmann BD, Bauer JA, Chen X, Sanders ME, Chakravarthy AB, Shyr Y, Pietenpol JA: **Identification of human triple-negative breast cancer subtypes and preclinical models for selection of targeted therapies**. *The Journal of clinical investigation* 2011, **121**(7):2750-2767
15. Long J, Delahanty RJ, Li G, Gao YT, Lu W, Cai Q, Xiang YB, Li C, Ji BT, Zheng Y *et al*: **A common deletion in the APOBEC3 genes and breast cancer risk**. *Journal of the National Cancer Institute* 2013, **105**(8):573-579
16. Nik-Zainal S, Alexandrov LB, Wedge DC, Van Loo P, Greenman CD, Raine K, Jones D, Hinton J, Marshall J, Stebbings LA *et al*: **Mutational processes molding the genomes of 21 breast cancers**. *Cell* 2012, **149**(5):979-993
17. Nik-Zainal S, Wedge DC, Alexandrov LB, Petljak M, Butler AP, Bolli N, Davies HR, Knappskog S, Martin S, Papaemmanuil E *et al*: **Association of a germline copy number polymorphism of APOBEC3A and APOBEC3B with burden of putative APOBEC-dependent mutations in breast cancer**. *Nature genetics* 2014, **46**(5):487-491

18. Okazaki T, Maeda A, Nishimura H, Kurosaki T, Honjo T. PD-1 immunoreceptor inhibits B cell receptor-mediated signaling by recruiting src homology 2-domain-containing tyrosine phosphatase 2 to phosphotyrosine. *Proc Natl Acad Sci U S A* 2001;98(24):13866-71.
19. Parry RV, Chemnitz JM, Frauwirth KA, Lanfranco AR, Braunstein I, Kobayashi SV, et al. CTLA-4 and PD-1 receptors inhibit T-cell activation by distinct mechanisms. *Mol Cell Biol* 2005;25(21):9543-53.
20. Riley JL. PD-1 signaling in primary T cells. *Immunol Rev* 2009;229:114-25.
21. Rizvi NA, Hellmann MD, Snyder A, Kvistborg P, Makarov V, Havel JJ, Lee W, Yuan J, Wong P, Ho TS *et al*: **Cancer immunology. Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer.** *Science* 2015, **348**(6230):124-128
22. Roberts SA, Lawrence MS, Klimczak LJ, Grimm SA, Fargo D, Stojanov P, Kiezun A, Kryukov GV, Carter SL, Saksena G *et al*: **An APOBEC cytidine deaminase mutagenesis pattern is widespread in human cancers.** *Nature genetics* 2013, **45**(9):970-976
23. Seymour L, Bogaerts J, Perrone A, Ford R, Schwartz LH, Mandrekar S, et al. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. *Lancet Oncol.* 2017;18(3):e143-e152. Epub 2017 Mar 2.
24. Sheppard K-A, Fitz LJ, Lee JM, Benander C, George JA, Wooters J, et al. PD-1 inhibits T-cell receptor induced phosphorylation of the ZAP70/CD3zeta signalosome and downstream signaling to PKCtheta. *FEBS Lett.* 2004;574:37-41
25. Wen WX, Soo JS, Kwan PY, Hong E, Khang TF, Mariapun S, Lee CS, Hasan SN, Rajadurai P, Yip CH *et al*: **Germline APOBEC3B deletion is associated with breast cancer risk in an Asian multi-ethnic cohort and with immune cell presentation.** *Breast cancer research : BCR* 2016, **18**(1):56
26. Xuan D, Li G, Cai Q, Deming-Halverson S, Shrubsole MJ, Shu XO, Kelley MC, Zheng W, Long J: **APOBEC3 deletion polymorphism is associated with breast cancer risk among women of European ancestry.** *Carcinogenesis* 2013, **34**(10):2240-2243.
27. Zhang X, Schwartz J-CD, Guo X, Bhatia S, Cao E, Chen L, et al. Structural and functional analysis of the costimulatory receptor programmed death-1. *Immunity* 2004;20:337-47.
28. Romeu, JL. Understanding Binomial Sequential Testing. Statistical Confidence, Reliability Information Analysis Center (RIAC START). Department of Defense United States of America, 2013.

## 11.0 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.: <i>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.</i>	

**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 of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception that has a low user dependency consistently and correctly as described in Table 8 during the protocol-defined time frame in Section X.

Table 8 Highly Effective Contraceptive Methods That Have Low User Dependency

<b>Highly Effective Methods That Have Low User Dependency</b>
<i>Failure rate of &lt;1% per year when used consistently and correctly.</i>
<ul style="list-style-type: none"> <li>● Intrauterine device (IUD)</li> <li>● Bilateral tubal occlusion</li> </ul>
<ul style="list-style-type: none"> <li>● <b>Vasectomized partner</b> 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.</li> </ul>
<ul style="list-style-type: none"> <li>● <b>Sexual abstinence</b> 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</li> </ul>

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.
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**Pregnancy Testing**

WOCBP should only be included after a negative highly sensitive urine or serum pregnancy test and in accordance with local requirements. When applicable this test should be repeated a maximum of 24-hours before the first dose/vaccination.

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 4 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 tumour imaging for confirmation of PD by iRECIST.

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

Tumour 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  $\geq 20\%$  and  $\geq 5$  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  $\geq 5$  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  $\geq 5$  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, tumour 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 (ie, 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  $\geq 5$  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  $\geq 5$  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].