CLINICAL STUDY PROTOCOL

TITLE: Phase II, open label, single arm study of **P**embrolizum**A**b combi**N**e**D** with cisplatin or carb**O**platin and etoposide in treatment naïve advanced me**R**kel cell c**A**rcinoma (MCC) (**PANDORA Trial**).

Acronym	PANDORA Trial
EudraCT number	EudraCT 2022-500988-12-00
Version Number	**3.0**
Sponsor	Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy
Phase:	II
Indication:	Advanced, naïve, Merkel cell carcinomas

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1.0 TRIAL SUMMARY

TITLE	Phase II, open label, single arm study of PembrolizumAb combiNeD with cisplatin or carbOplatin and etoposide in treatment naïve advanced meRkel cell cArcinoma (MCC) (PANDORA Trial)
SPONSOR	Fondazione IRCCS Istituto Nazionale dei Tumori- Via G. Venezian 1 20133 Milano
PRINCIPAL INVESTIGATOR:	Dott.ssa Sara Pusceddu
PHASE:	II
BACKGROUND AND RATIONALE	Merkel cell carcinoma (MCC) is a rare neuroendocrine tumor of the skin with a very aggressive clinical course and high propensity for locoregional recurrence and metastasis. Although still relatively rare the incidence of MCC has tripled over the past 20 years. The Surveillance of Rare Cancers in Europe (RARECARE) project reported an incidence rate of 0.13 MCC cases per 100,000 between 1995 and 2002. The incidence of MCC increases with age. The mean age at diagnosis is approximately 75 years. The development of MCC can be associated with integrated Merkel cell polyomavirus (MCPyV) and/or with ultraviolet light (UV) exposure or immunosuppression. The natural evolution of MCC is usually poor with a reported 5-year overall survival (OS) for metastatic disease of 14%. For these patients, the therapeutic options are scant, mainly based on immunotherapy or chemotherapy. MCC is generally considered a chemosensitive tumor. The great part of chemotherapy regimens used in MCC are also used in small cell lung cancer (SCLC), and comprise multiple agents such as cyclophosphamide, doxorubicin, vincristine, etoposide, cisplatin, and carboplatin. However, current literature regarding the management of MCC are poor. Due to the rarity of this disease, there are no randomized trials comparing different chemotherapy regimens, and the available data are still insufficient to completely assess the effect of chemotherapy on patient survival. Overall, response to chemotherapy in metastatic disease ranges from 20 to 61%, but the duration of the response is short, and most patients experience relapse within 8 months. In addition to the unclear benefit in OS, chemotherapy is associated with numerous toxicities (i.e., fatigue, gastrointestinal diseases and renal toxicity, hematological toxicity). Immunotherapy is the most important new approach in advanced/metastatic MCC. A recent study with the PD-L1 inhibitor, avelumab, showed an ORR of 62% in chemotherapy-naive

	participants and 32% in participants with chemotherapy-refractory metastatic disease. Responses occurred in patients with both PD-L1 positive and negative tumors and were independent of Merkel cell polyomavirus status. Furthermore, a phase 2 trial with pembrolizumab, a PD-1 inhibitor, showed objective response rate of 56% in participants with metastatic or recurrent MCC not amenable to definitive surgery or radiation therapy. Based on these results, NCCN guidelines recommend pembrolizumab and avelumab as possible treatment option for patients with recurrent or advanced disease. Chemotherapy has always been seen as immunosuppressive due to its direct cytotoxicity, however emerging data suggest that some chemotherapies may induce immunogenic cell death, eliminate immune-suppressive cells or sensitize tumor cells to immune effector cells. Some chemotherapy agents can impact both on the tumor and on the host immune system, which provides strong rationale for their combination with immunotherapeutic agents. In particular, platinum agents have demonstrated immunogenic effects. Therefore, based on all this rationale, to test this hypothesis in vivo, we propose a phase II study for naïve advanced/metastatic MCC patients, that will include the administration of pembrolizumab plus platinum-based chemotherapy, followed by maintenance with immunotherapy alone.
PATIENT POPULATION	Advanced/metastatic MCC
OBJECTIVES AND ENDPOINTS	To assess the safety and antitumor activity of pembrolizumab combined with cisplatin/carboplatin and etoposide as first line treatment in MCC. **Primary objective** - To assess efficacy of pembrolizumab combined with chemotherapy as first line treatment in patients with MCC **Primary endpoint** - ORR, that will be defined as the percentage of patients achieving complete response (CR) or partial response (PR) according to RECIST 1.1 criteria **Secondary objectives** - To assess safety and efficacy of pembrolizumab combined with chemotherapy as first line treatment in patients with MCC **Secondary endpoints** - Incidence of Serious Adverse Events (SAE) - Incidence and severity of Immune-mediated Adverse Events (imAE)

		- Incidence and severity of Adverse Events (AEs) according to NCI Common Terminology criteria Adverse Event (CTCAE), version 5.0 - Overall Survival (OS) that will be measured from the date of starting therapy to the date of death by any cause - Progression Free Survival (PFS) that will be measured from the date of starting therapy to the date of disease progression or death. - Duration of Response (DOR) that will be measured from the date of the first response to disease progression or death in those patients who achieved a CR o PR during study treatment
	Exploratory objectives - To identify immune and molecular biomarkers that may be indicative of clinical response/resistance, safety, and/or the mechanism of action of pembrolizumab and other treatments. - To assess efficacy of pembrolizumab plus cisplatin/carboplatin and etoposide according to iRECIST. - To assess Health-Related Quality of Life of	**Exploratory Endpoints** - Molecular determinants of response or resistance to treatments, using blood and tumor tissue - Efficacy parameters such as OS and PFS will be evaluated according to iRECIST using investigator response assessments. - Evaluations will included, changes in EQ-5D and FACT-M scores and

	pembrolizumab plus cisplatin/carboplatin and etoposide in participants with advanced/metastatic MCC. correlation of the HR-PRO scores to tumor responses during the treatment period.
STUDY DESIGN	This is an open label, multicenter, phase II study evaluating the activity and safety of pembrolizumab combined with cisplatin/carboplatin and etoposide as first line treatment in patients with advanced MCC. The induction treatment will consist of four cycles of pembrolizumab plus chemotherapy. Each cycle will be administered every 21 days (3 weeks). On Day 1 of each cycle, all eligible patients will receive drug infusions in the following order: • pembrolizumab (200 mg flat dose, administered intravenously) • carboplatin (AUC 5 mg per milliliter per minute, administered intravenously) or cisplatin (75 mg per square meter of body-surface area, administered intravenously) • etoposide (100 mg per square meter of body-surface area, administered intravenously on days 1 through 3 of each cycle). On days 2 and 3 of each cycle, patients will receive etoposide alone at the same dosage. After the induction phase, patients will start maintenance therapy with pembrolizumab 400 mg flat dose intravenously every 6 weeks. Overall, treatment with pembrolizumab will be continued until disease progression, unacceptable toxicity, Investigator's decision or consent withdrawal, for a maximum of 24 months. Palliative radiation will be also allowed as per clinical practice. Subjects will attend clinic visits at regular intervals to receive trial treatment and for efficacy and safety assessments. All subjects will be continuously monitored for any adverse event (AE) according to NCI Common Terminology Criteria for Adverse Event (CTCAE), version 5.0 while on study treatment. Treatment will be continued until disease progression, unacceptable toxicity, Investigator's decision or consent withdrawal. Radiological assessment will be performed by CT scan every 6 weeks (± 7 days) for the first year and every 12 weeks (± 7 days) thereafter. Disease response to treatment will be assessed by the Investigator using RECIST v1.1 and irRECIST. Treatment should be discontinued in all patients who exhibit evidence of disease progression per RECIST v1.1. However, if there is a clinical benefit patient may be considered for treatment beyond radiologic disease progression per RECIST v1.1, at discretion of the investigator and after appropriate discussion with the patient and the Sponsor. Patients who continue treatment after radiographic disease progression

	according to RECIST v 1.1 criteria should undergo careful clinical monitoring and radiographic re-evaluation after 4-6 weeks (investigator choice), or sooner in case of symptomatic worsening.
NUMBER OF PATIENTS	35 patients in 3 National Cancer Centers
INCLUSION CRITERIA	Patients must meet all of the following criteria to be eligible for study entry: • Patients must be capable of giving signed informed consent • Ability to comply with protocol requirements • Patients must be ≥18 years of age at the time of signing the ICF • Locally advanced, relapsed or metastatic MCC stage IIIB-IV according to American Joint Committee on Cancer (AJCC) TNM Staging Classification for Merkel Cell Carcinoma (8th ed. 2017) • Histologically confirmed diagnosis of MCC. • Availability of tumor sample (obtained from core biopsy or surgical specimen) is mandatory for PD L1 expression assessment and biomolecular characterization. • Life expectancy ≥ 3 months • Measurable disease per Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST v1.1) • Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to 1 • No previous systemic therapy for advanced disease • Patients with treated or asymptomatic brain metastases may be enrolled. • Women of childbearing potential must use 2 effective methods of contraception with a failure rate of less than 1% per year, during the entire study treatment period and for a period of 5 months after the last dose of study drug, or agree to practice true abstinence, when this is in line with the preferred and us usual lifestyle of the subject. They must have a negative serum pregnancy test during the screening period. • Adequate haematological function defined by white blood cell (WBC) count ≥2,500/mm 3 with absolute neutrophil count (ANC) ≥1,500/mm 3, platelet count ≥ 100,000/mm 3 and haemoglobin ≥9 g/dL • Adequate hepatic function defined by a total bilirubin ≤ 1.5 x the upper limit of normal (ULN) range (except subjects with Gilbert Syndrome), serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2.5 x ULN (≤ 5 if liver function test elevations are due to liver metastases)

	• Adequate renal function defined by a serum creatinine ≤ 1.5 x ULN or an estimated creatinine clearance of ≥ 30 mL/minute for patients with creatinine levels above institutional limits (if using the Cockcroft Gault formula) • Stable medical condition, including the absence of acute exacerbations of chronic illnesses, serious infections, or major surgery within 4 weeks before registration, and otherwise noted in other inclusion/exclusion criteria
EXCLUSION CRITERIA	Patients who meet any of the following criteria will be excluded from study entry: • Prior treatment with pembrolizumab or any other immunotherapy agents (anti PD 1, anti PD L1, anti PD L2, anti CD137, anti CTLA 4 antibodies, or any other antibody or drug specifically targeting T cell costimulatory immune checkpoint pathways) • Prior treatment with chemotherapy for advanced MCC, with the exception for subjects who received adjuvant or neoadjuvant therapy. They are eligible if the adjuvant/neoadjuvant therapy was completed at least 12 months prior to the onset of metastatic disease. • Adjuvant radiotherapy is permitted if ended ≥ 6 months before trial enrollment • Known hypersensitivity to pembrolizumab, carboplatin, cisplatin and/or etoposide • Concurrent anticancer treatment, immune therapy, or cytokine therapy, except for erythropoietin • Major surgery for any reason within 4 weeks from registration and/or if the subject has not fully recovery from the surgery within 4 weeks of treatment start • Subjects receiving immunosuppressive agents such as steroids for any reason should be tapered of these drugs before initiation of the trial treatment. Low dose corticosteroid therapy will be allowed. • Known severe hypersensitivity reactions to chimeric or monoclonal antibodies, fusion proteins • Patients with untreated, symptomatic and/or progressive brain metastases, or with carcinomatous meningitis. Subjects with brain metastases are eligible if metastases have been treated and there is no clinical evidence of progression • History of active autoimmune diseases. Subjects with diabetes mellitus type I, hypothyroidism only requiring hormone replacement or controlled hyperthyroidism, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.

	• Other concurrent neoplasms requiring active treatment • Prior organ transplantation, including allogenic stem cell transplantation • Any medical condition, within 6 months before receiving the first dose of study drug, considered relevant by Investigator. • Known human immunodeficiency virus (HIV) infection or acquired immunodeficiency syndrome (AIDS) • Serious infection within 14 days before the first dose of study drug • History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug induced pneumonitis, idiopathic pneumonitis, or evidence of active pneumonitis on screening chest computed tomography (CT) scan • Active tuberculosis • Pregnancy or breastfeeding • Vaccination within 4 weeks of the first dose and while on trial is prohibited except for administration of inactivated vaccines • Unwilling or unable to comply with the protocol or cooperate fully with the investigator and site personnel
STUDY DURATION	• Estimated enrollment period: 24 monts • Estimated duration of trial: 48 monts
STATISTICAL METHODS, DATA ANALYSIS	A minimax Simon two-stage design will be applied. Assuming an unsatisfactory ORR of 56%, a valuable ORR of 71%, 24 and 11 patients will be enrolled in the first and second stage, respectively (total number of patients: 35, one-sided alpha: 0.15, power: 0.78). If complete or partial response is assessed in at least 15 patients in the first stage, the second stage will be performed, otherwise the study will be closed, and study failure declared. If complete or partial response is assessed in at least 23 patients at the end of the second stage, the experimental treatment will be considered promising and worthy of further investigation. Only eligible patients who receive at least one dose of experimental treatment will be considered for the primary analysis. Objective response and disease control will be evaluated with point estimates and 95% CIs on the basis of the exact binomial method. DOR, PFS, and OS will be estimated using the Kaplan-Meier method for censored data. In order to detect selection bias, the number of eligible and consecutive patients participating or not to the study will be collected by center. Reasons of participation failure will be collected too. Participant flow through the trial, baseline characteristics, and adverse events will be summarized by descriptive statistics. Data will be analyzed using SAS version 9.4 (SAS Institute, Cary, NC).

2.0 LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
aPTT	activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
CT	Computerised Tomography
CTCAE	(NCI) Common Terminology Criteria for Adverse Events
CTLA-4	Cytotoxic T-Lymphocyte Antigen 4
CR	Complete Response
CrCl	Creatinine Clearance
CV	Cardiovascular Disease
CTCAE	Common Terminology Criteria for Adverse Events
DNA	Deoxyribonucleic Acid
DOR	Duration Of Responce
EC	Ethics Committees
ECG	Electrocardiogram
ECI	Events of Clinical Interest
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EGFR	Epidermal Growth Factor Receptor
EOT	End of treatment
EUDRACT	European Clinical Trials Database
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
GLP	Good Laboratory Practice
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HLA	Human Leukocyte Antigen
IB	Investigator brochure
ICH	International Conference on Harmonisation
IEC	Independent ethics committee
IHC	Immunohistochemistry
IL	Interleukin
INR	International normalized ratio
irAE	Immun-mediated Adverse Event
IRB	Institutional review board

Abbreviation	Definition
iRECIST	immune-mediate Response evaluation criteria in solid tumors
IV	Intravenous
Kg	Kilogram
LDH	Lactate Dehydrogenase
m^2	square meters
Mb	Megabase
MCC	Merkel Cell Carcinoma
mcL	microliter
MCPyV	Merkel cell polyomavirus
mg	Milligram
MHC	Major Histocompatibility Complex
MDSC	myeloid-derived suppressor cells
min	minute
mL	milliliter
mmol	millimole
MRI	magnetic resonance imaging
NCCN	National Comprensive Cancer Network
NCI	National Cancer Institute
NK	natural killer
NSCLC	Non-small Cell Lung Cancer
ORR	Objective Response Rate
OS	Overall Survival
PBMCs	Peripheral blood mononuclear cells
PD-1	Programmed-death 1
PD-L1	Programmed Death-ligand 1
PE	Platinum and Etoposide
PFS	Progression-free Survival
PK	Pharmacokinetic
PS	Performance Status
PT	Prothrombin Time
Q3W	every 3 weeks
Q6W	every 6 weeks
RECIST	Response Evaluation Criteria In Solid Tumors
RNA	Ribonucleic Acid
Treg	regulatory T
SAE	Serious adverse event
SCLC	Small Cell Lung Cancer
SNVs	Single Nucleotide Variants
SD	Stable Disease
SUSAR	Suspected unexpected serious adverse reaction
TAM	tumor-associated macrophages

Abbreviation	Definition
TGF-b	Transforming Growth Factor-b
TMB	Tumor Mutational Burden
TNFa	Tumor Necrosis Factor-a
ULN	Upper Limit of Normal
UV	Ultraviolet
WOCBP	Woman Of Childbearing Potential

3.0 BACKGROUND & RATIONALE

3.1 Background

Pembrolizumab is a potent humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) with high specificity of binding to the programmed cell death 1 (PD-1) receptor, thus inhibiting its interaction with programmed cell death ligand 1 (PD-L1) and programmed cell death ligand 2 (PD-L2). Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an intravenous (IV) immunotherapy for advanced malignancies. Keytruda® (pembrolizumab) is indicated for the treatment of patients across a number of indications because of its mechanism of action to bind the PD-1 receptor on the T cell. For more details on specific indications refer to the Investigator brochure (IB).

3.1.1 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 tumor-infiltrating lymphocytes in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells/FoxP3+ regulatory T-cells (T-regs) correlates with improved prognosis and long-term survival in solid malignancies, such as ovarian, colorectal, and pancreatic cancer; hepatocellular carcinoma; malignant melanoma; and renal cell carcinoma. Tumor-infiltrating lymphocytes can be expanded ex vivo and reinfused, inducing durable objective tumor responses in cancers such as melanoma [Dudley et al., 2005; Hunder et al., 2008].

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene *Pdcd1*) is an immunoglobulin (Ig) superfamily member related to cluster of differentiation 28 (CD28) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) that has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) [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 (CD3ζ), protein kinase C-theta (PKCθ), 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 MCC.

3.1.2 Preclinical and Clinical Trial Data

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

3.2 Rationale

3.2.1 Rationale for the Trial and Selected Population

Merkel cell carcinoma (MCC) is a rare neuroendocrine tumor of the skin with a very aggressive clinical course and high propensity for locoregional recurrence and metastasis [Lemos BD et al., 2010]. Although still relatively rare the incidence of MCC has tripled over the past 20 years [Hodgson NC, 2005]. The Surveillance of Rare Cancers in Europe (RARECARE) project reported an incidence rate of 0.13 MCC cases per 100,000 between 1995 and 2002 [van der Zwan JM et al., 2013]. The incidence of MCC increases with age [Banks PD et al., 2016; Schadendorf D et al., 2017]. The mean age at diagnosis is approximately 75 years [Albores-Saavedra J et al., 2010]. The development of MCC can be associated with integrated Merkel cell polyomavirus (MCPyV) [Feng H et al., 2008] and/or with ultraviolet light (UV) exposure [Agelli M et al., 2003] or immunosuppression [Lanoy E et., 2009; Lanoy E et al., 2010]. The prognosis of MCC is extremely poor with lower survival rates compared with melanoma or other skin malignancies. The 5-year survival rates for patients with MCC are 75% for primary localized tumors, 59% for tumors with regional lymph node metastases (or local recurrence) and 25% for the metastatic disease [Becker et al., 2010].
Surgery potentially followed by radiation therapy represents the standard of care for local-regional disease however relapse is common [Fields et al., 2011]. For the metastatic disease, the therapeutic options are scant, mainly based on immunotherapy or chemotherapy.
Historically, metastatic MCC has been treated with platinum-based chemotherapy regimens that provided high initial response rates but no survival advantage [Lebbe et al., 2015]. Overall, response to chemotherapy in metastatic disease ranges from 20 to 61%, but the duration of the response is short, and most patients experience relapse within 8 months [Nghiem P et al., 2017]. In recent years, immunotherapic agents, such as pembrolizumab and avelumab, showed promising results both in chemotherapy-naïve and chemotherapy-refractory metastatic patients [Nghiem et al., 2016; Kaufamn et al., 2016; D'Angelo et al., 2018]. In these phase 2 trials, objective response rate was 56% for pembrolizumab and 62.1% for avelumab in previously untreated patients and it was independent from PD-L1 expression or MCPyP status. Based on these results, NCCN guidelines recommend pembrolizumab and avelumab as a treatment option for patients with advanced disease [NCCN 2021].
Although the results obtained with checkpoint inhibitors are encouraging, there is still a group of patients not responsive to this treatment.
Currently a single-arm, open-label, multicenter, efficacy, and safety study of pembrolizumab in adult and pediatric participants with previously untreated advanced MCC KEYNOTE-913 trial (NCT03783078) is still ongoing. As with other systemic cancer therapies, resistance to immunotherapy may lead to therapeutic failure. Tumor cells are known to evade immune surveillance by a variety of mechanisms [Mittal D et al., 2014] (i.e. downregulation of tumor antigens, MHC class I and II proteins, and other molecules involved in antigen processing and presentation; intratumoral accumulation of immune suppressive cells, including regulatory T cells (Treg), interleukin (IL)- 17–secreting T cells, myeloid-

derived suppressor cells (MDSC), and tumor-associated macrophages (TAM); expression of PD-L1 by tumor cells and high levels of immune-suppressive cytokines within the tumor microenvironment, including transforming growth factor-b (TGFb), tumor necrosis factor-a (TNFa), and IL10 with the consequent block of the tumor-specific immune responses [Mittal D et al., 2014; 23. Pardoll DM, 2012].
Moreover, recently the immunosuppressive characteristic of tumor microenvironments has been identified as one mechanism for the low therapeutic efficacy of targeted chemotherapy in clinical evaluations. These recent findings have not only initiated a new era of intelligently designed immunotherapies but have also demonstrated a direct or indirect immunostimulatory effect of chemotherapeutic drugs [Motz GT et al., 2013], contrary to their current use, which involves a one-dimensional, cytotoxic interaction with cancer cells. Various chemotherapies can indirectly activate the immune system by inducing immunogenic cell death, which allows dying tumor cells to initiate an immune response [Krysko DV et al., 2012; Galluzzi L et al., 2017]. Furthermore, several chemotherapeutic drugs have been reported to directly affect various immune cells, such as dendritic cells (DCs), macrophages, myeloid-derived suppressor cells (MDSCs), T-cells and natural killer (NK) cells [Galluzzi L et al., 2012]. Consequentially, successful clinical translation of immunotherapy and findings about the immune-modulatory effects of chemotherapeutic drugs have fostered investigations into the combination of chemo- and immunotherapies for the treatment of cancer [Gomez GG et al., 2001]. In particular, platinum agents have demonstrated immunogenic effects [Hato et al., 2014].

We believe that the combination of pembrolizumab plus cisplatin or carboplatin and etoposide may improve the clinical outcome of patients with MCC compared to monotherapy.
Studies that have evaluated the combination of these drugs in other cancers (especially NSCLC and SCLC) showed a safety profile consistent with the defined toxic effects of the individual agents and an improvement in PFS and OS.

Pembrolizumab is being studied as a single agent in the advanced cancer, as well as in combination with chemotherapy. Pembrolizumab has been generally well tolerated.
Safety and anti-tumoral activity of pembrolizumab in association with platinum-based chemotherapy have been evaluated in several clinical trials.
The phase 3 KEYNOTE-189 study evaluated efficacy (OS and PFS) and safety of the combination treatment with pemetrexed and platinum-based chemotherapy plus pembrolizumab for 4 cycles followed by pembrolizumab plus pemetrexed as maintenance therapy (arm 1, n= 410) vs pemetrexed and platinum-based chemotherapy plus placebo for 4 cycles followed by placebo plus pemetrexed maintenance therapy (arm 2, n=206) in naïve metastatic nonsquamous NSCLC without sensitizing EGFR or ALK mutations. The 12-month OS was 69.2% in arm1 vs 49.4% in arm2 (P<0.001).
Median PFS was 8.8 months arm1 vs in arm2 (P<0.001). Adverse events of grade 3 or higher occurred in 67.2% of the patients in the pembrolizumab-combination group and in 65.8% of those in the placebo-combination group [Gandhi L et al., 2018].
In phase 3 KEYNOTE-604 study the investigator evaluated the safety and efficacy of pembrolizumab plus platinum and etoposide (PE) *vs* placebo + PE, in patients with naïve, extensive-stage SCLC. Overall, 453 patients were included in the study and of these, 228 patients were randomly assigned to the pembrolizumab group. The two primary end points were PFS and OS.
The 12-month PFS was 13.6% with pembrolizumab plus EP and 3.1% with placebo plus EP. The 24-month OS was 22.5% with pembrolizumab plus EP and 11.2% with placebo plus EP (significance

threshold was not met). ORR was 70.6% in the pembrolizumab plus EP group and 61.8% in the placebo plus EP group; the estimated proportion of responders remaining in response at 12 months was 19.3% and 3.3%, respectively [Rudin CM et al., 2020].

Based on these observations, the benefit/risk for pembrolizumab in combination with cisplatin or carboplatin plus etoposide, as derived from the participation to the present study, should also be safe and potentially effective.

3.2.2 Justification for Dose

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

- Clinical data from 8 randomized studies in melanoma and NSCLC indications demonstrating flat dose- and exposure-efficacy relationships from 2 mg/kg Q3W to 10 mg/kg Q2W, representing an approximate 5- to 7.5-fold exposure range (refer to IB, Section 5.2.2)
- Population PK analysis showing that both fixed dosing and weight-based dosing provides similar control of PK variability with considerable overlap in the distributions of exposures, supporting suitability of 200 mg Q3W
- Clinical data showing meaningful improvement in benefit-risk including overall survival at 200 mg Q3W across multiple indications, and
- Pharmacology data showing full target saturation in both systemic circulation (inferred from pharmacokinetic [PK] data) and tumor (inferred from physiologically-based PK [PBPK] analysis) at 200 mg Q3W.

In the maintenance phase, the planned dose of pembrolizumab for this study is 400 mg every 6 weeks (Q3W). A 400 mg Q6W dosing regimen of pembrolizumab is expected to have a similar benefit-risk profile as 200 mg Q3W, in all treatment settings where 200 mg Q3W pembrolizumab is currently approved. Specifically, the dosing regimen of 400 mg Q6W is considered adequate, given the following rationale:

- PK simulations demonstrated that in terms of pembrolizumab exposures

- Cavg (or AUC) over the dosing interval at 400 mg Q6W are similar to those at the approved 200 mg Q3W dose, thus bridging efficacy between dosing regimens.

- Ctrough at 400 mg Q6W is ~12% lower at a mean level compared with that at the lowest clinically tested dose of 2 mg/kg Q3W, at steady state. In most (>99%) patients, however, Ctrough at 400 mg Q6W is generally within the range of clinical experience of Ctrough achieved with 2 mg/kg or 200 mg Q3W.

- Cmax and concentrations over the entire dosing interval at 400 mg Q6W are well below those for the highest clinically tested dose of 10 mg/kg Q2W. Clinically, the observed safety profiles were similar among 2 mg/kg Q3W, 10 mg/kg Q3W, and 10 mg/kg Q2W dosing regimens in multiple tumor types based on randomized dose comparisons. Since the Cmax, and Cavg (or AUC) over the dosing

interval expected at 400 mg Q6W lies within the range of those achieved at these clinically tested doses, the safety profile is expected to be comparable to the established safety profile of pembrolizumab.

- The exposure-response relationship for pembrolizumab has been shown to be flat across multiple indications, in the dose/exposure range of 2 mg/kg Q3W or 200 mg Q3W to 10 mg/kg Q2W. Since the Ctrough and Cavg exposures over the dosing interval at 400 mg Q6W lie within the range of those achieved at the Q3W doses with established clinical efficacy, the dosing regimen of 400 mg Q6W is expected to be efficacious across indications where 200 mg (or 2 mg/kg) Q3W has demonstrated efficacy, given the generally similar PK and flat exposure-response relationship for pembrolizumab across tumor types.

The observed PK data from the analysis of Cohort B of KN555 in subjects treated with pembrolizumab at 400 mg Q6W showed that in terms of pembrolizumab exposures through Cycle 1 (ie, the first 6 weeks of treatment) and steady state (Cycle 4, post 18 weeks of treatment):

The observed concentrations for 400 mg Q6W were well within the 90% prediction interval of simulated concentrations using the model.

- The geometric mean of the observed Ctrough, at Week 6 at 400 mg Q6W is ~18% lower than the geometric mean of Ctrough, at Week 6 at 200 mg Q3W and ~10% higher than the geometric mean of Ctrough at Week 6 at 2 mg/kg Q3W, ie, the lowest clinically tested dose shown to be efficacious.

- The geometric mean of the observed Cmax at Week 6 at 400 mg Q6W is ~42% lower than the geometric mean of Cmax at Week 6 at 10 mg/kg Q2W, ie, the highest clinically tested dose shown to be safe.

- The geometric mean of the observed Ctrough, at steady state at 400 mg Q6W is ~22% lower than the geometric mean of Ctrough, at steady state at 200 mg Q3W and ~4% higher than the geometric mean of Ctrough at steady state 6 at 2 mg/kg Q3W.

- The geometric mean of the observed Cmax at steady state at 400 mg Q6W is ~65% lower than the geometric mean of Cmax at steady state at 10 mg/kg Q2W, ie, the highest clinically tested dose shown to be safe.

3.2.3 Rationale for Endpoints

3.2.3.1 Endpoints

Primary

ORR, defined as the percentage of patients achieving complete response (CR) or partial response (PR) according to RECIST 1.1 criteria, is an endpoint commonly accepted for phase II trials.

Secondary

Safety will be assessed by the number, frequency, duration and severity of AEs /irAE /SAEs and changes in vital signs and laboratory values. Adverse events will be assessed as defined by CTCAE, Version 5.0.

OS, defined as the time from the date of enrolment to the date of death by any cause or last follow-up for alive patients, has been recognized as the gold standard for the demonstration of superiority of a new antineoplastic therapy in randomized clinical studies.

PFS, defined as the time from the date of enrolment until disease progression, or death due to any cause, will be assessed per RECIST 1.1.

DOR, defined as the time from an initial objective response (CR or PR) according to RECIST 1.1 until disease progression, or death due to any cause, is a common endpoint in oncology trials.

3.2.3.2 Exploratory Endpoints

Translational assessments

Translational assessments have been included in the Protocol to explore the relationships between tumor and host factors and clinical outcomes. These studies will also help to further understanding of the pathogenesis and drug resistance mechanisms. Investigations may include but are not limited to:

Merkel Cell Polyomavirus (MCPyV) and tumor microenvironment immunophenotypic characterization: for each patient, will be performed direct assessment of MCPyV in tumor tissue sections by immunohistochemistry (IHC) on FFPE samples. In addition, in order to evaluate content and quality of tumor microenvironment the inhibitory receptors and ligands (PD-1, PD-L1), the HLA molecules antigens (HLA-DR and HLA-Class I), the T cell markers (CD3, CD4, CD8), the myeloid markers (CD33 and CD163), the fibroblast phenotypes (with morphology and α-SMA) and the vascularity (with morphology and CD31) will be evaluate. PD-L1 will be assessed by 22C3 (DAKO) pharm DX. The evaluations will be carried out in the malignant cells and, importantly, in the stroma cells near and distant from the tumor.

Mutational analysis and determination of Tumor Mutational Burden (TMB): The IonTorrent technology will be used to screen major alterations for 500 genes in all FFPE samples enrolled. A custom-built bioinformatics pipeline will be used to identify putative somatic mutations and copy number variations. TMB will be estimated and mutational spectrum for each sample was evaluated using the Oncomine TML 5.10 plugin available on IonReporter software. TML is calculated using a specific algorithm of the Ion Reporter software and is expressed as the number of mutations per megabase (muts/Mb), where the number of mutations include nonsynonymous (missense and nonsense single nucleotide variants (SNVs), plus insertion and deletion variants (InDels) detected per megabase (Mb) of exonic sequences.

Gene expression profile and identification of transcriptional networks: the expression of about 20800 genes (canonical transcript) will be evaluated for all samples using IonTorrent platform. Data obtained will be compared to expression profiles of non-neoplastic samples (N).

Fusion transcript identification on tumor tissue**:** Fifty fusion genes with unknown partner will be investigated using Archer FusionPlex Technologies able to identified de-novo fusion transcript starting fromFFPEsample.

Peripheral blood Immunophenotyping: to longitudinally monitor the frequency and the phenotype of circulating immune cells at baseline and during treatment, we will perform multiparametric flow cytometry analysis. PBMCs from pts will be stained with HLA-DR, CD14, CD16, CD15, CD66, c-kit and CD33 antibodies to define the subsets of myeloid-derived suppressor cells. CD8+ and CD4+ T cell frequency will be calculated on the whole CD45+/CD3+ lymphocytes. CD4+ T cell will be characterized with different Abs including CD127, CD25, FOXP3, CTLA-4, OX40, ICOS, PD-1, CD45RA, CCR10, CCR7, CCR4, CCR6, CXCR5, Ki67, IL-17, IFN-g and IL-10. In addition, we will investigate the expression of co-stimulatory and co-inhibitory molecules such as OX40, ICOS, CD69, CTLA-4, PD-1, TIM3 and LAG3.

iRECIST assessment

An exploratory endpoint is to assess efficacy of pembrolizumab plus cisplatin/carboplatin and etoposide according to iRECIST.

Indeed, immunotherapeutic agents may manifest a clinical response after an initial increase in tumor burden or even the appearance of new lesions.

Standard RECIST v1.1 may not provide a fully accurate response assessment of immunotherapeutic agents. Therefore, the general principles of a modified version of RECIST v1.1 for immune-based therapeutics, termed iRECIST, will be used in the evaluation of participant response (Seymour et al 2017) in an exploratory capacity and guide treatment decisions for discontinuation of therapy due to disease progression.

Response per iRECIST should be assessed at each post-baseline imaging timepoint. The use of iRECIST accounts for the response patterns of immunotherapies and includes a requirement for the confirmation of progression to rule out or confirm pseudoprogression.

Health-Related Quality of Life

Health-related PRO assessments are scheduled to align with tumor response assessments. The FACT-M and EQ-5D questionnaires are validated PRO tools that will be used to assess health-related quality-of-life criteria and evaluate correlations between HR-PRO and clinical observations.

The Functional Assessment of Cancer Therapy – Melanoma (FACT-M) is a validated questionnaire specific to melanoma, a disease that shares many similarities with MCC.

The EQ-5D is a self-administered, generic, utility questionnaire. Participants will rate their current health state based on the following criteria: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.

3.2.4 Potential Risks and Benefits

Treatment directed at the PD-1/PD-L1 axis is a promising approach to MCC. Phase 2 results with avelumab and pembrolizumab show efficacy in terms of durable tumor response with preservation of health-related quality of life. MCC is also a chemosensitive tumor with an ORR ranging from 20 to 61% but with a short duration of the response. Preclinical evidence suggests that chemotherapy has immunomodulatory effects, supporting the use of chemotherapy plus immunotherapy combination as a potential effective treatment strategy.
Anti-tumoral activity of pembrolizumab has been demonstrated in both preclinical and clinical trial in a wide variety of malignancies. Pembrolizumab is being studied as a single agent in the advanced cancer, as well as in combination with chemotherapy. Pembrolizumab has been generally well tolerated.
Safety and anti-tumoral activity of pembrolizumab in association with platinum-based chemotherapy have been evaluated in several clinical trials.
In phase 3 KEYNOTE-604 study the investigator evaluated the safety and efficacy of pembrolizumab plus platinum and etoposide (PE) *vs* placebo + PE, in patients with naïve, extensive-stage SCLC. Overall, 453 patients were included in the study and of these, 228 patients were randomly assigned to the pembrolizumab group. The two primary end points were progression-free survival (PFS) and OS.
The 12-month PFS was 13.6% with pembrolizumab plus EP and 3.1% with placebo plus EP. The 24-month OS was 22.5% with pembrolizumab plus EP and 11.2% with placebo plus EP (significance threshold was not met). ORR was 70.6% in the pembrolizumab plus EP group and 61.8% in the placebo plus EP group; the estimated proportion of responders remaining in response at 12 months was 19.3% and 3.3%, respectively [Rudin CM et al 2020].
We believe that the combination of pembrolizumab plus cisplatin/carboplatin and etoposide may improve the clinical outcome of patients with MCC compared to monotherapy.
Studies that have evaluated the combination of these drugs in other cancers (especially SCLC) showed a safety profile consistent with the defined toxic effects of the individual agents and an improvement in PFS and OS.
Based on these observations, the benefit/risk for pembrolizumab in combination with cisplatin/carboplatin plus etoposide, as derived from the participation to the present study, should also be favorable.

3.2.5 GCP Study Conduct Statement

The study will be conducted in compliance with Study Protocol, Declaration of Helsinki, current ICH-GCP and GLP guidelines and other applicable International and National Regulatory Requirements.

3.2.5.1 Clinical Investigator's

Every Clinical Investigator must be a medical doctor qualified according to the regulations in the region where the study is being conducted. The Clinical Investigator agrees to conduct the study as outlined in the approved protocol, and in accordance with all applicable regulations for clinical studies on medicinal products in human beings. The Clinical Investigator agrees that all information provided by Sponsor, including study-related pre-clinical data, protocols, case report forms, verbal and written information, will be kept strictly confidential and will be disclosed only to the personnel involved in conduct of the study. It is recognized this information may be given in confidence to the Institutional Ethics Committee and regulatory authorities.

3.2.5.2 Protocol Amendments

Changes in any part of the protocol must be documented in the Study Protocol Amendment. All amendments that would increase the risk to the subject or may alter the results of the study must be re-submitted to the Ethics Committee and to regulatory authorities and must be approved before their implementation.

If an amendment to Study Protocol substantially alters the study design or the potential risks to the subjects, the Clinical Investigator will decide whether a new subject's consent to continued participation will be needed.

If the changes in Study Protocol involve only logistical or administrative aspects of the trial [e.g. change of monitor(s), telephone number(s)], written approvals are necessary from Sponsor, but not from the Ethics Committee and the Regulatory Authorities before their implementation.

4.0 OBJECTIVE(S), HYPOTHESIS(ES), AND ENDPOINT(S)

This study will evaluate the safety and efficacy of pembrolizumab in combination with cisplatin or carboplatin plus etoposide in patients non-previously treated for unresectable locally advanced or metastatic MCC.
Specific objectives, hypothesis and corresponding endpoints for the study are outlined below.

4.1 Primary Objective(s), Hypothesis(es), and Endpoint(s)

Objectives	Endpoints
Primary objectives: To assess activity of pembrolizumab combined with chemotherapy as first line treatment in patients with MCC. **Hypothesis:** combination of pembrolizumab plus cisplatin/carboplatin and etoposide may improves the ORR in participants with advanced MCC.	• Objective Response Rate (ORR) will be defined as the percentage of patients achieving complete response (CR) or partial response (PR) according to RECIST 1.1 criteria.
Secondary objectives: To assess safety and efficacy of pembrolizumab combined with chemotherapy as first line treatment in patients with MCC. **Hypothesis:** combination of pembrolizumab with cisplatin/carboplatin and etoposide is safe and may improve the PFS and OS in participants with advanced MCC.	• Incidence of Serious Adverse Events (SAE) • Incidence and severity of Immune-related Adverse Events (irAE). • Incidence and severity of Adverse Events (AEs) according to NCI Common Terminology criteria Adverse Event (CTCAE), version 5.0. • Overall Survival (OS) will be measured from the date of starting therapy to the date of death by any cause. • Progression Free Survival (PFS) will be measured from the date of starting therapy to the date of disease progression or death. • Duration of Response (DOR) will be measured from the date of the first response to disease progression or death in those patients who achieved a CR o PR during study treatment.
Exploratory objectives: To identify immune and molecular biomarkers that may be indicative of clinical response/resistance, safety, and/or the mechanism of action of pembrolizumab and other treatments. To assess efficacy of pembrolizumab plus cisplatin/carboplatin and etoposide according to iRECIST. To assess Health-Related Quality of Life of pembrolizumab plus cisplatin/carboplatin and etoposide in participants with advanced/metastatic MCC.	• Molecular determinants of response or resistance to treatments, using blood and tumor tissue. • Efficacy parameters such as OS and PFS will be evaluated according to iRECIST using investigator response assessments. • Evaluations will included, changes in EQ-5D and FACT-M scores and correlation of the HR-PRO scores to tumor responses during the treatment period.

5.0 TRIAL DESIGN

5.1 Trial Design

This is an open label, multicenter, phase II study evaluating the activity and safety of pembrolizumab combined with cisplatin or carboplatin and etoposide as first line treatment in patients with advanced MCC.
The induction treatment will consist of four cycles of pembrolizumab 200 mg flat dose, intravenously every 3 weeks (Q3W) plus cisplatin or carboplatin and etoposide at standard dose (see below). Each cycle will be administered every 21 days (3 weeks). After the induction phase, patients will start maintenance therapy with pembrolizumab 400 mg flat dose intravenously every 6 weeks (Q6W), for a maximum of 16 cycles. Overall, treatment with pembrolizumab (Q3W + Q6W pembrolizumab combined) will be administered for a maximum of 24 months.
Subjects will attend clinic visits at regular intervals to receive trial treatment and for efficacy and safety assessments. All subjects will be continuously monitored for any adverse event (AE) according to NCI Common Terminology Criteria for Adverse Event (CTCAE), version 5.0 while on study treatment. Treatment will be continued until disease progression, unacceptable toxicity, Investigator's decision or consent withdrawal, for a maximum of 24 months.
Radiological assessment will be performed by CT scan every 6 weeks (± 7 days) for the first year, following Cycle 1, Day 1, regardless of treatment dose delays. After completion of the first year, tumor assessments will be required every 12 weeks (± 7 days) thereafter, regardless of treatment dose delays.
Disease response to treatment will be assessed by the Investigator using RECIST 1.1 and irRECIST.
Treatment should be discontinued in all patients who exhibit evidence of disease progression per RECIST 1.1. However, given the limited therapeutic options in MCC patients progressing to a first line of treatment, patients may be considered for treatment beyond radiographic disease progression, at the discretion of the investigator, after appropriate discussion with the patient and after obtaining informed consent if:

- there is a clinical benefit
- there is absence of decline in ECOG Performance Status and/or absence of symptoms and signs (including laboratory values) indicating unequivocal progression of disease

Patients who continue treatment after radiographic disease progression according to RECIST 1.1 criteria should undergo careful clinical monitoring and radiographic re-evaluation after 4-6 weeks (investigator choice), or sooner in case of symptomatic worsening. Treatment should be discontinued if clinical deterioration due to disease progression occurs at any time, or if persistent disease growth (disease progression) is confirmed in a follow-up scan. In addition, patients should be discontinued for unacceptable toxicity or for any other signs or symptoms of deterioration attributed to disease progression as determined by the investigator after an integrated assessment of radiographic data and clinical status.
Patients who discontinue treatment for reasons other than radiographic disease progression per RECIST 1.1 (e.g., toxicity, symptomatic deterioration) will continue scheduled tumor assessments at the same frequency as would have been followed if the patient had remained on study treatment.

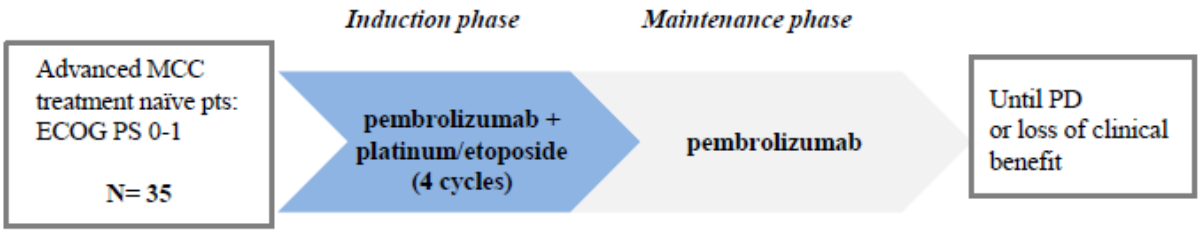
The primary endpoint of the trial is the Objective Response Rate (ORR), defined as the percentage of patients achieving complete response (CR) or partial response (PR) according to RECIST 1.1. Secondary endpoints include Progression Free Survival (PFS), Overall Survival (OS), Duration of Response (DOR)

and safety as assessed by a variety of AE parameters. Exploratory analyses include translational assessments evaluation of effectiveness according to iRECIST and Quality of life assessments.

The duration of the study is expected to be a maximum of 48 months. The study recruitment period is expected to be approximately 24 months. The study will end at the conclusion of additional survival follow-up. The survival follow-up will continue until 6 months after the last subject receives the last dose

5.2 Trial Schema

The trial design is depicted in Figure 1.



Induction phase: Cisplatin (75 mg/sqm on day 1) or carboplatin (AUC 5 on day 1), etoposide (100 mg/sqm on day 1-3), pembrolizumab (200 mg flat dose on day 1). Mainteinance phase: pembrolizumab (400 mg flat dose Q6W).
Overall, pembrolizumab will be administered for a maximum of 24 months.
PD= progression disease.

5.3 Schedule of Activities

5.3.1 Table 1 Study Schedule of Activities

Study Period:	Screening	Treatment cycles							EOT	Notes
Treatment Cycle	Screening (Visit 1)	1	2	3	4	5	6	7 to 24 months	Discon	
Scheduled Window (days)	-28 to -1	+3	±3	±3	±3	±3	±3	±3	At time of discon	
Administrative Procedures										
Informed Consent	X									
Inclusion/Exclusion Criteria	X									
Participant Identification Card	X	.								.
Medical History (includes substance usage and Family history of premature CV disease)	X									
Prior/Concomitant Medication Review	X	X	X	X	X	X	X	X	X	
Tumor tissue collection	X									
Study drug administration										
Treatment • Pembrolizumab + cisplatin/carboplatin + etoposide *(induction phase)*[#]		X	X	X	X					
Treatment • Pembrolizumab *(maintenance phase)*[##]						X	X	X		

Study Period:	Screening	Treatment cycles							EOT	Notes
Treatment Cycle	Screening (Visit 1)	1	2	3	4	5	6	7 to 24 months	Discon	
Scheduled Window (days)	-28 to -1	+3	±3	±3	±3	±3	±3	±3	At time of discon	
Clinical Procedures /assessments										
AE/SAE review	X	X	X	X	X	X	X	X	X	
Full physical examination including, ECOG PS, height and weight	X	X	X	X	X	X	X	X	X	
Vital Signs (heart rate, blood pressure)	X	X	X	X	X	X	X	X	X	
12-lead ECG	X									
Laboratory Procedure / assessments: analysis performed by local laboratory										
Hepatitis B and C screen	X									
Hematology	X	X	X	X	X	X	X	X	X	
Urinalysis	X		X		X				X	
Chemistry	X	X	X	X	X	X	X	X	X	
Thyroid Function Tests (TSH, T3, free T4; periodically)	X		X		X		X		X	
Pregnancy test urine or serum b-HCG*	X	X	X	X	X	X	X	X	X	X**
PT and aPTT (baseline only)	X									
Blood Immunophenotyping	X		X						X	
Patient Reported Outcomes (PRO)										
EuroQoL (EQ)-5D	X		X		X				X	
FACT- M	X		X		X				X	

[#] Cycles every 3 weeks
[##] Clycles every 6 weeks
***** Only for Woman of Childbearing Potential (WOCBP)

** Additional pregnancy testing should be conducted for the time required to eliminate systemic exposure after the last dose of each study intervention (120 days after last dose of pembrolizumab and 180 days after last dose of chemotherapy)

5.3.2 Table 2 Study Schedule of Activities: Survival Status

Study Period	Screening Phase	Treatment Cycles						EOT	Post Treatment Visits			Notes
Treatment Cycle	Screening (Visit 1)	1	2	3	4	5**	6 to 24 months	DC	Safety Follow-up	Efficacy Follow-up	Survival Follow-up[#]	
Scheduling Window (Days):	-28 to -1	+3	±3	±3	±3	±3	±3	Time of DC	30 Days from the last dose (+7 days)	Every 6[*] Weeks (±7 days)	Every 12 Weeks (±7 days)	
Administrative Procedures												
Survival Status		<----------					---------->				X	After investigator determined disease progression or start of new anticancer treatment.

[*] After completion of the first year, tumor assessments will be required every 12 weeks
[#] Telephone contacts are allowed
** From cycle 5, every 6 weeks.

5.3.3 Table 3 Study Schedule of Activities: Tumor Imaging

Study Period:	Screening Phase	Treatment Cycles				End of Treatment	Post-Treatment		
Treatment Cycle/Title:	Screening (Visit 1)	1	2	3	4*	Discon	Safety Follow-Up	Follow-Up Visits	Survival Follow-Up
Scheduling Window (Days):	-28 to -1	+3	±3	±3	±3	At time of discon	30 days post discon	Every 12 weeks post discon	Every 12 weeks
Tumor imaging	X		X		X	X			

*Radiological assessment will be performed by CT scan every 6 weeks (± 7 days) for the first year, After completion of the first year, tumor assessments will be required every 12 weeks (± 7 days)

6.0 METHODOLOGY

6.1 Study Population

6.1.1 Participant Inclusion Criteria

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

1. Male/female subjects with histologically confirmed diagnosis of MCC, who have not received prior systemic treatment for their advanced or metastatic MCC, are at least 18 years of age on the day of signing informed consent, will be enrolled in this study.

2. Male participants:
   A male participant must agree to use a contraception as detailed in Appendix 3 of this protocol during the treatment period and for at least 120 days, corresponding to time needed to eliminate any study treatments (e.g. 5 terminal half-lives for pembrolizumab and/or any active comparator/combination) plus an additional 90 days (a spermatogenesis cycle) after the last dose of study treatment and refrain from donating sperm during this period.

   Female participants:
3. A female participant is eligible to participate if she is not pregnant (see Appendix 3), not breastfeeding, and at least one of the following conditions applies:

   a. Not a woman of childbearing potential (WOCBP) as defined in Appendix 3
   OR
   b. A WOCBP who agrees to follow the contraceptive guidance in Appendix 3 during the treatment period and for at least 120 days (corresponding to time needed to eliminate any study treatments (pembrolizumab and/or any active comparator/combination) plus 30 days (a menstruation cycle) after the last dose of study treatment.

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

5. Unresectable and locally advanced, relapsed or metastatic MCC stage IIIB-IV according to American Joint Committee on Cancer (AJCC) TNM Staging Classification for Merkel Cell Carcinoma (8^{th} ed. 2017)

6. No prior systemic treatment for metastic MCC. Subjects who received adjuvant or neoadjuvant therapy are eligible if the adjuvant/neoadjuvant therapy was completed at least 12 months prior to the onset of metastatic disease.

7. Have a life expectancy of at least 3 months.

8. Have measurable disease based on RECIST 1.1. Lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions.

9. Have provided archival tumor tissue sample or newly obtained core or excisional biopsy of a tumor lesion not previously irradiated. Formalin-fixed, paraffin embedded (FFPE) tissue blocks are preferred to slides. Newly obtained biopsies are preferred to archived tissue.

10. Have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1. Evaluation of ECOG is to be performed within 7 days prior to the first dose of study intervention.

11. Have adequate organ function as defined in the following table (Table 4). Specimens must be collected within 10 days prior to the start of study intervention.

Table 4. Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1500/μL
Platelets	≥100 000/μL
Hemoglobin	≥9.0 g/dL or ≥5.6 mmol/L[a]
Renal	
Creatinine OR Measured or calculated[b] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 × ULN OR ≥30 mL/min for participant with creatinine levels >1.5 × institutional ULN
Hepatic	
Total bilirubin	≤1.5 ×ULN OR direct bilirubin ≤ULN for participants with total bilirubin levels >1.5 × ULN
AST (SGOT) and ALT (SGPT)	≤2.5 × ULN (≤5 × ULN for participants with liver metastases)
Coagulation	
International normalized ratio (INR) OR prothrombin time (PT) Activated partial thromboplastin time (aPTT)	≤1.5 × ULN unless participant is receiving anticoagulant therapy as long as PT or aPTT is within therapeutic range of intended use of anticoagulants

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

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

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

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

6.1.2 Participant Exclusion Criteria

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

1. A WOCBP who has a positive urine pregnancy test within 72 hours prior to allocation (see Appendix 3). If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

2. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent or with an agent directed to another stimulatory or co-inhibitory T-cell receptor (eg, CTLA-4, OX-40, CD137).

3. Has received prior systemic anti-cancer therapy, with the exception for subjects who received adjuvant or neoadjuvant therapy. They are eligible if the adjuvant/neoadjuvant therapy was completed at least 12 months prior to the onset of metastatic disease.

4. Has received prior radiotherapy within 2 weeks of start of study intervention. Participants must have recovered from all radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis. A 1-week washout is permitted for palliative radiation (≤2 weeks of radiotherapy) to non-CNS disease.

5. Has received a live vaccine or live-attenuated vaccine within 30 days prior to the first dose of study drug. Administration of killed vaccines is allowed.

6. Is currently participating in or has participated in a study of an investigational agent or has used an investigational device within 4 weeks prior to the first dose of study intervention.

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

8. Has a known additional malignancy that is progressing or has required active treatment within the past 2 years. Participants with basal cell carcinoma of the skin, squamous cell carcinoma of the skin, transitional cell carcinoma of urothelial cancer or carcinoma in situ (eg, breast carcinoma, cervical cancer in situ) that have undergone potentially curative therapy are not excluded.

9. Has known active CNS metastases and/or carcinomatous meningitis. Participants with previously treated brain metastases may participate provided they are radiologically stable, i.e. without evidence of progression for at least 4 weeks by repeat imaging (note that the repeat imaging

should be performed during study screening), clinically stable and without requirement of steroid treatment for at least 14 days prior to first dose of study intervention.

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

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

12. Has a history of (non-infectious) pneumonitis/interstitial lung disease that required steroids or has current pneumonitis/interstitial lung disease.

13. Has an active infection requiring systemic therapy.

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

15. Has a known history of active Hepatitis B (defined as HBV DNA is detected) or known active Hepatitis C virus (defined as HCV RNA quantitative is detected) infection.

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

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

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

19. Has had an allogenic tissue/solid organ transplant.

6.1.3 Lifestyle Considerations

6.1.3.1 Meals and Dietary Restrictions

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

6.1.3.2 Contraception

Study drugs may have adverse effects on a fetus in utero.

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

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

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

OR

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

OR

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

Sexually active fertile subjects and their partners must agree to use medically accepted methods of contraception with a failure rate of < 1% per year during the study and contraception in both males and females should be used until 120 days after last dose of pembrolizumab and 180 days after last dose of chemotherapy that corresponding to time needed to eliminate systemic exposure after the last dose of each study intervention.

- practice abstinence from heterosexual activity;

OR

- use (or have their partner use) acceptable contraception during heterosexual activity. Acceptable methods of contraception are:

  - Single method (one of the following is acceptable):

• intrauterine device (IUD)

• vasectomy of a female subject's male partner

• contraceptive rod implanted into the skin

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

• diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide)

• cervical cap with spermicide (nulliparous women only)

• contraceptive sponge (nulliparous women only)

• male condom or female condom (cannot be used together)

- hormonal contraceptive: oral contraceptive pill (estrogen/progestin pill or progestin-only pill), contraceptive skin patch, vaginal contraceptive ring, or subcutaneous contraceptive injection

In order to participate in the study, subjects (both male and female) of childbearing potential must adhere to the contraception requirement (described above) from the day of study medication initiation (or 14 days prior to the initiation of study medication for oral contraception) throughout the study period up to 120 days after last dose of pembrolizumab and 180 days after last dose of chemotherapy that corresponding to time needed to eliminate systemic exposure after the last dose of each study intervention.

If there is any question that a subject of childbearing potential will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

Refer to Appendix 3 for more details.

6.1.4 Pregnancy

If a participant inadvertently becomes pregnant while on treatment with pembrolizumab, the participant will be immediately discontinued from study intervention(s). 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 the Promoter within 2 working days if the outcome is a serious adverse experience (e.g. death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The study Investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Promoter. If a male participant impregnates his female partner, the study personnel at the site must be informed immediately and the pregnancy must be reported to the Promoter and followed as described in Section 7.2.

6.2 Trial Intervention(s)

6.2.1 Preparation, Handling and Storage of Drug

Refer to the Pharmacy Manual (V. 8.0 28 April 2021) for guidance on preparation, handling and storage information for Pembrolizumab.

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.

At the end of the study, the Promoter will ensure the correct destruction of the remaining drug according to applicable laws and regulations.

Pembrolizumab will be provided by MSD as summarized in Table 10.

Table 10. Product Descriptions

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

All other supplies not indicated in Table 10 above will be used locally.

6.2.2 Packaging and Labeling Information

Supplies will be labeled in accordance with regulatory requirements.

6.2.3 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; 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.

6.2.4 Drug Administration and Dosage Schedule

The intervention(s) to be used in this trial is outlined below in**:**

Table 5 Trial Intervention(s)

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period	Use
Pembrolizumab	200 mg	Q3W	IV infusion	Day 1 of each 3-week cycle	Experimental
Pembrolizumab	400 mg	Q3W	IV infusion	Day 1 of each 6-week cycle	Experimental
Cisplatin	75 mg/m^2	Q3W	IV infusion	Day 1 of each 3-week cycle	Treatment of cancer
Carboplatin	AUC 5	Q3W	IV infusion	Day 1 of each 3-week cycle	Treatment of cancer
Etoposide	100 mg/m^2	Q3W	IV infusion	Day 1-3 of each 3-week cycle	Treatment of cancer

6.2.5 Timing of Dose Administration

Trial interventions should be administered on Day 1 of each cycle after all procedures/assessments have been completed as detailed on the Schedule of Activities, Section 5.3. Trial interventions may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons.

All trial interventions will be administered on an outpatient basis.

On Day 1 of each cycle, all eligible patients will receive drug infusions in the following order:

Induction phase:

Pembrolizumab (200 mg flat dose, administered intravenously) → cisplatin (75 mg/ per square meter of body-surface area, admistered intravenously) or carboplatin (AUC 5 mg per milliliter per minute, administered intravenously) → etoposide (100 mg per square meter of body-surface area, administered intravenously on days 1 through 3 of each cycle).

On Days 2 and 3, patients will receive etoposide alone.

Manteinance phase:

Pembrolizumab (400 mg flat dose, administered intravenously).

Pembrolizumab 200/400 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.

Concomitant standard chemotherapeutic agents will be prepared and administered as per the approved product label at the doses indicated below:

- **Cisplatin:** 75 mg/m^2
- **Carboplatin:** AUC 5 (using Calvert formula). Carboplatin dose not to exceed 750mg
  Calvert Formula
  Total Dose (mg) = (target AUC) x (CrCl + 25)
  The estimated CrCl used in the Calvert formula should not exceed 125 mL/min
  Maximum carboplatin dose (mg) = target AUC 5 (mg•min/mL) x (125 + 25) = 5 x150 mL/min = 750 mg
- **Etoposide:** 100 mg/m^2

6.2.6 Dose Modification and toxicity management for immune-related AEs associated with Pembrolizumab and combination therapy

AEs associated with pembrolizumab exposure, including coadministration with additional compounds, may represent an immunologic aetiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of pembrolizumab/combination 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/combination treatment, 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. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab/combination treatment are provided in Table 6.
Pembrolizumab dose reductions are not permitted. Pembrolizumab treatment may be interrupted or discontinued due to toxicity.
Chemotherapy dose reductions are permitted (Table 5.1). If a dose reduction for toxicity occurs with any agent, the dose may not be re-escalated. Subjects can have a maximum of 2 dose modifications (if applicable) to each of the components of study therapy throughout the course of the study for toxicities. If a subject experiences several toxicities and there are conflicting recommendations, the most conservative dose adjustment recommended should be followed (dose reduction appropriate to the most severe toxicity). Subjects who require a 3rd dose modification to any particular component will have that agent discontinued. Reduction of one chemotherapy agent and not the other agent is appropriate if, in the opinion of the Investigator, the toxicity is clearly related to one of the treatments. If, in the opinion of the Investigator, the toxicity is related to the combination of both chemotherapy agents, both drugs should be reduced according to recommended dose modifications. If the toxicity is related to the combination of three agents, all three agents should be reduced (if applicable), interrupted, or discontinued according to the recommended dose modifications. Subjects may have chemotherapy discontinued and continue on pembrolizumab alone. Similarly subjects may discontinue pembrolizumab and continue on chemotherapy alone if appropriate.

Chemotherapy may be interrupted for a maximum of 6 weeks from last dose; pembrolizumab may be interrupted for a maximum of 12 weeks from last dose. The Common Terminology Criteria for Adverse Events version 5.0 (CTCAE 5.0) must be used to grade the severity of adverse events. All dose modifications should be based on the AE requiring the greatest dose modification.

Table 5.1. Dose Modifications for Trial Medications

	Dose Level 0	**Dose Level -1**	**Dose Level -2**	**Dose Level -3**
Cisplatin	75 mg/m^2	56 mg/ m^2	38 mg/ m^2	Discontinue
Carboplatin	AUC 5 Maximum dose 750mg	AUC 3.75 Maximum dose 562.5mg	AUC 2.5 Maximum dose 375mg	Discontinue
Etoposide	100 mg/m^2	75 mg/m^2	50 mg/m^2	Discontinue
Pembrolizumab	200/400 mg fixed dose	Dose reductions are not permitted	Dose reductions are not permitted	Dose reductions are not permitted

Attribution of Toxicity:

The investigator may attribute a toxicity event-to the combination, to chemotherapy alone or to pembrolizumab alone, for adverse events listed in Table 6. Interventions must be held according to the criteria in Table 6.

Holding Study Interventions:

If the AE is considered immune-related interventions should be held according to recommended dose modifications.

Restarting Study Interventions:

Participants may not have any dose modifications (no change in dose or schedule) of pembrolizumab in this study, as described in Table 6.

- If the toxicity does not resolve or the criteria for resuming treatment are not met, the participant must be discontinued from all study interventions.
- If the toxicities do resolve and conditions are aligned with what is defined in Table 6, the combination of cisplatin or carboplatin and etoposide plus pembrolizumab may be restarted at the discretion of the investigator.In the cases where the toxicity is attributed to the chemotherapy re-initiation of pembrolizumab as a monotherapy may be considered at the principal investigator's discretion.

Table 6. Dose modification and toxicity management guidelines for immune-related AEs associated with pembrolizumab monotherapy and IO Combinations

General instructions:

1. Severe and life-threatening irAEs should be treated with IV corticosteroids followed by oral steroids. Other immunosuppressive treatment should begin if the irAEs are not controlled by corticosteroids.
2. Study intervention must be permanently discontinued if the irAE does not resolve or the corticosteroid dose is not ≤10 mg/day within 12 weeks of the last study intervention treatment.
3. The corticosteroid taper should begin when the irAE is ≤ Grade 1 and continue at least 4 weeks.
4. If study intervention has been withheld, study intervention may resume after the irAE decreased to ≤ Grade 1 after corticosteroid taper.

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper • Add prophylactic antibiotics for opportunistic infections	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment
	Recurrent Grade 2, Grade 3 or 4	Permanently discontinue		
Diarrhea/Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever)

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
	Recurrent Grade 3 or Grade 4	Permanently discontinue		and of bowel perforation (ie, peritoneal signs and ileus) • Participants with ≥Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion
AST or ALT Elevation or Increased Bilirubin	Grade 2 [a]	Withhold	• Administer corticosteroids (initial dose of 0.5 to 1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable)
	Grade 3 [b] or 4 [c]	Permanently discontinue	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	
T1DM or Hyperglycemia	New onset T1DM or Grade 3 or 4 hyperglycemia	Withhold [d]	• Initiate insulin replacement therapy for participants with T1DM	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
	associated with evidence of β-cell failure		• Administer antihyperglycemic in participants with hyperglycemia	
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue [d]		
Hyperthyroidism	Grade 2	Continue	• Treat with nonselective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders
	Grade 3 or 4	Withhold or permanently discontinue [d]		
Hypothyroidism	Grade 2, 3 or 4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care	• Monitor for signs and symptoms of thyroid disorders
Nephritis: grading according to increased creatinine or acute kidney injury	Grade 2	Withhold	• Administer corticosteroids (prednisone 1 to 2 mg/kg or equivalent) followed by taper	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Neurological Toxicities	Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 2, 3 or 4 or clinical suspicion*	Permanently discontinue	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Confirmed SJS, TEN, or DRESS	Permanently discontinue		
All Other irAEs	Persistent Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3	Withhold or discontinue based on the event [e]		
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

*In case of asymptomatic cardiac enzyme elevation with clinical suspicion of Myocarditis the treatment dosing should be withheld

AE(s)=adverse event(s); ALT= alanine aminotransferase; AST=aspartate aminotransferase; CTCAE=Common Terminology Criteria for Adverse Events; DRESS=Drug Rash with Eosinophilia and Systemic Symptom; GI=gastrointestinal; IO=immuno-oncology; ir=immune related; IV=intravenous; SJS=Stevens-Johnson Syndrome; T1DM=type 1 diabetes mellitus; TEN=Toxic Epidermal Necrolysis; ULN=upper limit of normal.

Note: Non-irAE will be managed as appropriate, following clinical practice recommendations.

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab	Corticosteroid and/or Other Therapies	Monitoring and Follow-up

[a] AST/ALT: >3.0 to5.0 x ULN if baseline normal; >3.0 to 5.0 x baseline, if baseline abnormal; bilirubin:>1.5 to 3.0 x ULN if baseline normal; >1.5 to 3.0 x baseline if baseline abnormal

[b] AST/ALT: >5.0 to 20.0 x ULN, if baseline normal; >5.0 to 20.0 x baseline, if baseline abnormal; bilirubin:>3.0 to 10.0 x ULN if baseline normal; >3.0 to 10.0 x baseline if baseline abnormal

[c] AST/ALT: >20.0 x ULN, if baseline normal; >20.0 x baseline, if baseline abnormal; bilirubin: >10.0 x ULN if baseline normal; >10.0 x baseline if baseline abnormal

[d] The decision to withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician. If control achieved or ≤ Grade 2, pembrolizumab may be resumed.

[e] Events that require discontinuation include, but are not limited to: encephalitis and other clinically important irAEs (eg, vasculitis and sclerosing cholangitis).

6.2.7 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 7.

Table 7. Pembrolizumab Infusion Reaction Dose modification and Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g. from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose. **Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug intervention**	Participant may be premedicated 1.5h (± 30 minutes) prior to infusion of study intervention with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of analgesic).
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4:	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: Epinephrine** IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Oxygen Pressors Corticosteroids Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated.	No subsequent dosing

Life-threatening; pressor or ventilatory support indicated	**In cases of anaphylaxis, epinephrine should be used immediately. **Participant is permanently discontinued from further study drug intervention.**	
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 v5.0 (CTCAE) at http://ctep.cancer.gov		

Other allowed dose interruption for pembrolizumab

Pembrolizumab may be interrupted for situations other than treatment-related AEs such as medical / surgical events and/or unforeseen circumstances not related to study intervention. However, intervention is to be restarted within 3 weeks of the originally scheduled dose and within 42 days of the previously administered dose, unless otherwise discussed with the Sponsor. The reason for study intervention interruption is to be documented in the patient's study record.

Dose Modification for Chemotherapy

Recommended dose modifications for key chemotherapy toxicities are outlined in Table 5.2 and Table 5.3. These serve as a guide and do not replace investigator judgment and applicable local label recommendations if more stringent.

Table 5.2. Recommended Dose Modifications for Chemotherapy Hematological Toxicity

		Etoposide	**Cisplatin/Carboplatin**
Platelets	**ANC**	**Dose level (DL) from Table 5.1**	
≥50,000/mcL AND	≥ 500/mcL	DL 0	DL 0
≥50,000/mcL AND	< 500/mcL	DL -1	DL -1
<50,000/mcL without bleeding AND	ANY	DL -1	DL -1
<50,000/mcL with Grade ≥ 2bleeding AND	ANY	DL -2	DL -2
ANY AND	< 1,000/mcL + fever ≥ 38.5°C (101°F)	DL -1	DL -1

Table 5.3. Recommended Dose Modifications for Chemotherapy Non-Hematological Toxicity

		Etoposide	**Cisplatin**	**Carboplatin**
	CTC Grade	**Dose level (DL) from Table 5.1**		
Nausea or vomiting	Grade 3or 4	DL 0	DL 0	DL 0
Diarrhea	Grade 3or 4	DL -1	DL -1	DL 0
Mucositis	Grade 3or 4	DL -2	DL 0	DL 0
Neurotoxicity	Grade 2	DL 0	DL -2	DL 0
	Grade 3or 4	DL -1	Discontinue	DL -1
Transaminase elevation	Grade 3	DL -1	DL -1	DL -1
	Grade 4	Discontinue	Discontinue	Discontinue
Other non-hematological toxicity	Grade 3 or 4	DL -1	DL -1	DL -1

6.2.8 Second Course

All participants who stop study intervention with 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 study intervention 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 intervention after completion of 35 administrations (approximately 2 years) of study intervention 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
  - 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.

Participants who have experienced an initial disease progression by RECIST 1.1 and have an iSD, iPR,or iCR per iRECIST after completion of 35 administrations of study intervention for reasons other than disease progression or intolerability may be considered for the Second Course Phase after consultation with the Sponsor.

6.3 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 participant's primary physician. However, the decision to continue the participant on study intervention requires the mutual agreement of the investigator, the Sponsor, and the participant.

Below are summarized the most relevant interactions with other drugs and other forms of interactions including drugs that are prohibited or should be used with caution for cisplatin, carboplatin etoposide and pembrolizumab.

CISPLATIN

Nephrotoxic substances

Concomitant administration of nephrotoxic (e.g. cephalosporins, aminoglycosides, amphotericin B or contrast media) or ototoxic (e.g. aminoglycosides) medicinal products potentiates the renal toxic effect of cisplatin. During or after cisplatin therapy caution is advised with the use of predominantly renally eliminated substances, eg cytostatic agents such as bleomycin and methotrexate, due to reduced renal elimination.

The renal toxicity of ifosfamide may be greater when used with cisplatin or in patients previously treated with cisplatin.

In some cases, a reduction in blood lithium values has been observed after treatment with cisplatin in combination with bleomycin and etoposide. It is therefore recommended to monitor lithium levels.

The manifestations of nephrotoxicity caused by cisplatin may be intensified by concomitant therapy with antihypertensives containing furosemide, hydralazine, diazoxide and propranolol. The dosage of allopurinol, colchicine, probenecid or sulfinpyrazone may need to be adjusted when used concomitantly with cisplatin, since cisplatin induces an increase in serum uric acid concentrations.

Forced diuresis with loop diuretics should not be induced with loop diuretics due to possible renal tract damage, except in patients receiving doses of cisplatin greater than 60 mg/m2 and whose urine secretion is less than 1000 ml in 24 hours. . Simultaneous use of ifosfamide causes increased protein excretion.

Ototoxic substances
Concomitant administration of ototoxic medicinal products (e.g. aminoglycosides, loop diuretics) potentiates the toxic effect of cisplatin on hearing function. Forced diuresis with loop diuretics should not be induced with loop diuretics due to possible renal tract damage, except in patients receiving doses of cisplatin greater than 60 mg/m2 and whose urine secretion is less than 1000 ml in 24 hours. and ototoxicity. Ifosfamide may increase hearing loss due to cisplatin.
Live attenuated virus vaccines Yellow fever vaccine is strictly contraindicated due to the risk of a fatal systemic vaccine reaction.
In view of the risk of generalized reaction, it is advisable to use an inactivated vaccine, if available. The use of live virus vaccines is not recommended within three months of stopping cisplatin therapy.

Oral anticoagulants
In case of concomitant administration of oral anticoagulants, it is advisable to check the INR regularly. Antihistamines, phenothiazines and others Simultaneous use of antihistamines, buclizine, cyclizine, loxapine, meclozine, phenothiazines, thioxanthenes or trimethobenzamides may mask the symptoms of ototoxicity (such as dizziness and tinnitus). Anticonvulsant drugs Serum concentrations of anticonvulsant drugs may remain at subtherapeutic levels during treatment with cisplatin. Cisplatin may reduce the absorption of phenytoin, resulting in impaired epilepsy control when phenytoin is given as existing treatment. It is absolutely contraindicated to start a new phenytoin-based anticonvulsant treatment during cisplatin therapy.
Pyridoxine + altretamine combination In a randomized study on the treatment of advanced ovarian cancer, response time to therapy was negatively affected when pyridoxine was used in combination with altretamine (hexamethylmelamine) and cisplatin. Paclitaxel Treatment with cisplatin prior to a paclitaxel infusion can reduce paclitaxel clearance by 33%, thereby enhancing its neurotoxicity.
Other the simultaneous use of myelosuppressive agents or radiotherapy potentiates the effects of the myelosuppressive activity of cisplatin.
Cisplatin given in combination with bleomycin and vinblastine can cause Raynaud's phenomenon. In a study of cancer patients with advanced or metastatic tumors, docetaxel in combination with cisplatin induced more severe neurotoxic effects (dose-dependent and sensory) than either agent taken individually at similar doses.
Chelating agents, such as penicillamine, can reduce the effectiveness of cisplatin. In case of concomitant use of cisplatin and cyclosporine, excessive immunosuppression with risk of lymphoproliferation should be considered.

CARBOPLATIN

Carboplatin is mostly used in combination with antineoplastic drugs having similar cytotoxic effects. Additive toxicity may occur under these circumstances.
Concomitant use of carboplatin and other myelosuppressive agents or radiotherapy may potentiate haematological toxicity.

An increased incidence of emesis has been reported when carboplatin was administered concomitantly with other emesis-inducing drugs, or in patients who had previously received emetic therapy.
Concomitant administration of carboplatin and aminoglycosides carries an increased risk of nephrotoxicity and/or ototoxicity, so these drugs should be used concomitantly with caution.
Use of other nephrotoxic drugs results in potentiation of the renal effects of carboplatin. Carboplatin interacts with aluminum, forming a black precipitate of platinum and decreasing potency. Needles, syringes, catheters, or IV administration sets containing aluminum should not be used for carboplatin administration.
Due to the increased thrombotic risk, in the case of tumor pathologies, the use of anticoagulants is frequent. During diseases, the variability of individual coagulability, and the possibility of interaction between oral anticoagulants and anticancer chemotherapy, require an increase in the frequency of INR (prothrombin time) monitoring monitoring, if it is decided to treat the patient with oral anticoagulants.
Concomitant use contraindicated - Yellow fever vaccine: risk of fatal generalized vaccinal disease.

Concomitant use not recommended
- Live attenuated vaccines (except yellow fever): risk of a systemic, potentially fatal disease. This risk is increased in people who are already immunosuppressed due to the disease. Where it exists it is necessary to use an inactivated vaccine (poliomyelitis).
- Phenytoin, fosphenytoin due to risk of exacerbation of seizures caused by decreased gastric absorption of phenytoin due to cytotoxic drug or due to risk of enhanced toxicity or loss of efficacy of cytotoxic drug due to increased hepatic metabolism by phenytoin. Concomitant use to be considered
- Cyclosporine (and by extrapolation tacrolimus and sirolimus): excessive immunosuppression with risk of lymphoproliferation.
- Aminoglycosides: Concomitant use of carboplatin with aminoglycoside antibiotics should be considered due to cumulative nephrotoxicity and toxicity, particularly in patients with renal insufficiency. - Loop diuretics: Concomitant use of carboplatin with a loop diuretic should be considered due to cumulative nephrotoxicity and ototoxicity.

ETOPOSIDE

Effects of other medicinal products on the pharmacokinetics of etoposide
High doses of cyclosporine, resulting in plasma concentrations above 2,000 ng/mL, co-administered with oral etoposide, resulted in an 80% increase in etoposide exposure (AUC) with a 38% decrease in total body clearance of etoposide versus etoposide monotherapy.
Concomitant cisplatin-based therapy is associated with a reduction in the total body clearance of etoposide.
Concomitant phenytoin therapy is associated with increased etoposide clearance and decreased efficacy, and other enzyme-inducing antiepileptic therapies may be associated with increased etoposide clearance and decreased efficacy. Plasma protein binding in vitro is 97%.
Phenylbutazone, sodium salicylate and acetylsalicylic acid can displace etoposide from plasma protein binding.

Effect of etoposide on the pharmacokinetics of other medicinal products
Co-administration of antiepileptic medicinal products and etoposide and associated names may result in decreased seizure control due to pharmacokinetic medicinal product interactions.

Co-administration of warfarin and etoposide may cause an increase in international normalized ratio (INR). Careful monitoring of INR is recommended.

Pharmacodynamic interactions
There is an increased risk of fatal systemic vaccination disease following administration of yellow fever vaccine. Live vaccines are contraindicated in immunosuppressed patients.
Prior or concomitant use of other medicinal products with myelosuppressive action similar to etoposide may cause additive or synergistic effects.
Cross-resistance between anthracyclines and etoposide has been reported in preclinical studies.

PEMBROLIZUMAB

No formal pharmacokinetic interaction studies have been performed with pembrolizumab.
Since pembrolizumab is cleared from the bloodstream by catabolism, no metabolic drug-drug interactions are expected. The use of systemic corticosteroids or immunosuppressants prior to initiating pembrolizumab therapy should be avoided due to their possible interference with the pharmacodynamic activity and efficacy of pembrolizumab. However, corticosteroids or other systemic immunosuppressants may be used after initiation of pembrolizumab therapy to treat immune-related adverse reactions (see section 6.2.7). Corticosteroids may also be used as premedication, when pembrolizumab is used in combination with chemotherapy, as antiemetic prophylaxis and/or to alleviate chemotherapy-related adverse reactions.

6.3.1 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 prior to the first dose of trial intervention and up to 30 days after the last dose of trial intervention should be recorded. If participants experience an SAE or ECI, concomitant medications administered30 days after the last dose of trial intervention are to be recorded as defined in Section 7.2.

6.3.2 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 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. However, the decision to continue the participant on study intervention requires the mutual agreement of the investigator, the Sponsor, and the participant.

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

6.3.3 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 6.2.6, [Table 6]. 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.

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

6.4 Participant Discontinuation Criteria

Discontinuation of study intervention does not represent withdrawal from the study.

As certain data on clinical events beyond study intervention discontinuation may be important to the study, they must be collected through the participant's last scheduled follow-up, even if the participant has discontinued study intervention. Therefore, all participants who discontinue study intervention prior to completion of the protocol-specified treatment period will still continue to be monitored in this study and participate in the study visits and procedures as specified in Section 5.3 unless the participant has withdrawn from the study (Section 6.6).

Participants may discontinue study intervention at any time for any reason or be discontinued from the study intervention at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study intervention by the investigator or the Sponsor if study intervention is inappropriate, the study plan is violated, or for administrative and/or other safety reasons.

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 intervention
- After prolonged study intervention interruption that prohibits restarting study intervention if agreed upon with the Sponsor
- Radiographic disease progression outlined in Section 7.1.4.
- Any progression or recurrence of any malignancy, or any occurrence of another malignancy that requires active treatment
- Any study intervention-related toxicity specified as a reason for permanent discontinuation as defined in the guidelines for dose modification due to AEs in Section 6.2.6.
- 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

Completion of pembrolizumab Q3W monotherapy consists of 35 treatments (approximately 2 years). Discontinuation of treatment may be considered for participants who have attained a confirmed complete response (CR) and have been treated for at least 24 weeks, receiving beyond the date when the initial CR was declared. These participants may be eligible for second course treatment described in Section 6.2.8

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 intervention provided they meet the requirements detailed in Section 6.2.8. Participants may be retreated in the Second Course Phase (Retreatment) for up to an additional 17 cycles (approximately 1 year).

6.5 Participant withdrawal From Study

A participant must be withdrawn from the study if the participant or the participant's legally acceptable representative withdraws consent from the study.

If a participant withdraws from the study, they will no longer receive study intervention or be followed at scheduled protocol visits.

Specified details regarding procedures to be performed at the time of withdrawal from the study are outlined in Section 7.1.6.1.

6.6 Clinical Criteria for Early Trial Termination

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

1. Quality or quantity of data recording is inaccurate or incomplete
2. Poor adherence to protocol and regulatory requirements
3. Incidence or severity of adverse drug reaction in this or other studies indicates a potential health hazard to participants
4. Plans to modify or discontinue the development of the study drug

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

7.0 TRIAL ASSESSMENTS AND PROCEDURES

7.1 Trial Procedures

- Study procedures and their timing are summarized in The Schedule of Activities, Section 5.3.
- Adherence to the study design requirements, including those specified in the Schedule of Activities is essential and required for study conduct.
- The investigator is responsible for ensuring that procedures are conducted by appropriately qualified (by education, training, and experience) staff.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

7.1.1 Administrative and General Procedures

7.1.1.1 Informed Consent

The Investigator must obtain documented consent from each potential participant or each participant's legally acceptable representative prior to participating in a clinical trial. If there are changes to a participant's status during the study (e.g. health requirements) the investigator must ensure appropriate consent is in place.

7.1.1.2 General Informed Consent

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

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

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

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

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

If the investigator recommends continuation of study intervention beyond disease progression, the participant or his/her legally acceptable representative will be asked to sign consent.

7.1.1.3 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.

7.1.1.4 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.

7.1.1.5 Prior and Concomitant Medications Review

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.

Concomitant Medications

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

7.1.1.6 Disease Details and Treatments

Disease Details

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

Prior Treatment Details

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

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.

7.1.1.7 Assignment of Screening Number

All consented subjects will be given a unique screening number that will be used to identify the subject for all procedures that occur prior to treatment allocation. Each subject will be assigned only one screening number. Screening numbers must not be re –used for different subjects. Any subject who is screened multiple times will retain the original screening number assigned at the initial screening visit.

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 5.0 (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

A complete physical examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) as per institutional standard systems . Height and weight will also be measured and recorded. 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. The time points for full physical exams are described in Section 5.3. After the first dose of study intervention, new clinically significant abnormal findings should be recorded as AEs. Investigators should pay special attention to clinical signs related to previous serious illnesses.

7.1.2.3 Vital Signs

The investigator or qualified designee will take vital signs at screening, prior to the administration of each dose of trial treatment and at treatment discontinuation as specified in the Schedule of Activities (Section 5.3). Vital signs should include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at screening only.

7.1.2.4 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status (see Appendix 1) at screening, prior to the administration of each dose of trial treatment and discontinuation of trial treatment as specified in the Schedule of Activities (Section 5.3).

7.1.2.5 Electrocardiograms

A standard 12-lead ECG will be obtained and reviewed by an investigator or medically qualified designee (consistent with local requirements) as outlined in the SoA (see Appendix X) using an ECG machine that automatically calculates the HR.

7.1.3 Clinical Safety Laboratory Assessments

Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.

- The investigator or medically qualified designee (consistent with local requirements) must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.

- If laboratory values from nonprotocol-specified laboratory assessments performed at the institution's local laboratory require a change in study participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the appropriate CRF (eg, SLAB).

- For any laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30 days after the last dose of study intervention, every attempt should be made to perform repeat assessments until the values return to normal or baseline or if a new baseline is established as determined by the investigator.

Details regarding specific laboratory procedures/assessments to be performed in this study are provided below. The total amount of blood/tissue to be drawn/collected over the course of the study (from prestudy to poststudy visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per participant can be found in the Study Procedures Manual. Refer to the Study Flow Chart (Section 5.3) for the timing of laboratory assessments.

7.1.3.2 Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

Laboratory tests for hematology, chemistry, and urinalysis are specified in Appendix 2.

7.1.3.3 Pregnancy Testing

All women who are being considered for participation in the study, and who are not surgically sterilized or postmenopausal, must be tested for pregnancy at each cycle. If a urine test is positive or not evaluable,

a serum test will be required. Participants must be excluded/discontinued from the study in the event of a positive test result.

7.1.4 Tumor Imaging and Assessment of Disease

Tumor imaging is strongly preferred to be acquired by computed tomography (CT). For the abdomen and pelvis, contrast-enhanced magnetic resonance imaging (MRI) may be used when CT with iodinated contrast is contraindicated, or when local practice mandates it. MRI is the strongly preferred modality for imaging the brain. The same imaging technique regarding modality, ideally the same scanner, and the use of contrast should be used in a participant throughout the study to optimize the reproducibility of the assessment of existing and new tumor burden and improve the accuracy of the assessment of response or progression based on imaging. Brain imaging is required for all participants at screening. MRI is preferred; however, CT imaging will be acceptable according to the investigator decision. Local site investigator/radiology 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 participation allocation.

7.1.4.1 Initial Tumor Imaging

Initial tumor imaging at Screening must be performed within 28 days prior to the date of allocation. The site study team must review screening images to confirm the participant has measurable disease per RECIST 1.1. Brain imaging, if performed to document the stability of existing metastases, should be by MRI if possible. If MRI is medically contraindicated, CT with contrast is an acceptable alternative.

7.1.4.2 Tumor Imaging During the Study

The first on-study imaging assessment should be performed at 6 weeks (±7 days) from the date of allocation. Subsequent tumor imaging should be performed every 6 weeks (±7 days) or more frequently if clinically indicated. After the first years, participants who remain on treatment will have imaging performed every 12 weeks (±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 7.1.4.6), 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 7.1.4.6. Participants who receive confirmatory imaging do not need to undergo the next scheduled tumor imaging if it is less than 4 weeks later; tumor imaging may resume at the subsequent scheduled imaging time point, if clinically stable. Participants who have confirmed disease progression by iRECIST, as assessed by the site, will discontinue study treatment. Exceptions are detailed in Section 7.1.4.6.

7.1.4.3 End of Treatment and Follow-up Tumor Imaging

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

For participants who discontinue study treatment without documented disease progression, every effort should be made to continue monitoring their disease status by tumor imaging using the same imaging schedule used while on treatment (every 6 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.

7.1.4.4 Second Course (Retreatment) Tumor Imaging

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

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

Per RECIST 1.1 (Section 7.1.4.5), if tumor imaging shows initial PD, tumor assessment should be repeated 4 to 8 weeks later in order to confirm PD with the option of continuing treatment while awaiting radiologic confirmation of progression with the option of continuing treatment while awaiting radiological confirmation of progression in clinically stable patients. Participants who obtain confirmatory imaging do not need to undergo scheduled tumor imaging if it is less than 4 weeks later and may wait until the next scheduled imaging time point, if clinically stable.

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

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

For participants who discontinue study treatment without documented disease progression, every effort should be made to continue monitoring their disease status by radiologic imaging every 12 weeks (±7 days) until either the start of a new anticancer treatment, disease progression, pregnancy, death, or the end of the study, whichever occurs first.

7.1.4.5 RECIST 1.1 Assessment of Disease

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

7.1.4.6 iRECIST Assessment of Disease

iRECIST is based on RECIST 1.1, but adapted to account for the unique tumor response seen with immunotherapeutic drugs. iRECIST will be used by the investigator to assess tumor response and progression and make treatment decisions. When clinically stable, participants should not be discontinued until progression is confirmed by the investigator, working with local radiology, according to the rules outlined in Appendix 4. This allowance to continue treatment despite initial radiologic disease progression takes into account the observation that some participants can have a transient tumor flare in the first few months after the start of immunotherapy, and then experience subsequent disease response. This data will be captured in the clinical database.

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 intervention at central verification of site-assessed first radiologic evidence of disease progression, and is not required to have repeat tumor imaging for confirmation of disease progression by iRECIST.

If the investigator decides to continue treatment, the participant may continue to receive study intervention and the tumor assessment should be repeated 4 to 8 weeks later to confirm disease progression by iRECIST, per investigator assessment.

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

If a participant has confirmed radiographic progression (iCPD) as defined in Appendix 4, study intervention should be discontinued; however, if the participant is achieving a clinically meaningful benefit, an exception to continue study intervention may be considered. In this case, if study

intervention is continued, tumor imaging should continue to be performed following the intervals as outlined in Section 7.

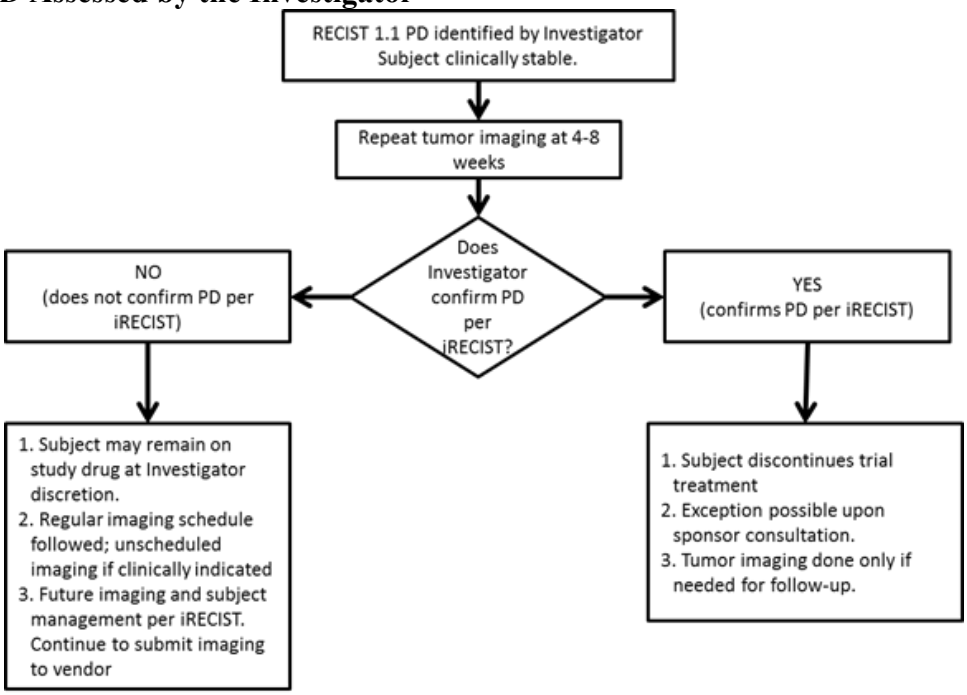
A description of the adaptations and iRECIST process is provided in Appendix 4. A summary of imaging and treatment requirements after first radiologic evidence of progression is provided in Table 8 and illustrated as a flowchart in Figures 2.

Table 8. Imaging and Treatment After First Radiologic Evidence of Progressive Disease

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

	Clinically Stable		Clinically Unstable	
	Imaging	**Treatment**	**Imaging**	**Treatment**
iCPD=iRECIST confirmed progressive disease; iCR=iRECIST complete response; iRECIST=modified Response Evaluation Criteria in Solid Tumors 1.1 for immune-based therapeutics; iSD=iRECIST stable disease; iUPD=iRECIST unconfirmed progressive disease; RECIST 1.1=Response Evaluation Criteria in Solid Tumors 1.1; VOP=verification of progression.				

Figure 2. Imaging and Treatment for Clinically Stable Participants after First Radiologic Evidence of PD Assessed by the Investigator



7.1.5 Tumor Tissue Collection and Correlative Studies Blood Sampling

- **Tissue collection**

As mandatory inclusion criteria, the tissue submitted will be used to assess exploratory biomarkers. The tissue submitted should be a formalin-fixed, paraffin-embedded (FFPE) tumor specimen or 10 serial, freshly cut, unstained slides accompanied by an associated pathology report. Cytological samples are not acceptable. Representative FFPE tissue samples will be collected from the primary tumor and/or any previous metastatic tissue specimens, so that further analysis may be performed on that/those tissue sample(s) as appropriate. The samples will be received, processed and centrally analysed by the Department of Pathology of Fondazione IRCCS Istituto Nazionale dei Tumori.
Analysis on biomarkers is exploratory by nature and will be performed retrospectively after the main study analysis is completed. Tissue received in excess to that required by this study will be returned to the histopathology department from where it was originally requested. Tumor tissue (archival or recently biopsied) obtained at enrollment will be used to explore potentially pathway components or modulators associated with the mechanism of action of the chemo-immunotherapy combination as predictive biomarkers.

- **Blood immunophenotype**

PBMCs and plasma will be obtained from fresh blood of patients at baseline (before treatment initiation), at the first radiological evaluation and at the end of treatment. The samples will be processed locally in each center and subsequently collected and centrally analyzed at Fondazione IRCCS Istituto Nazionale dei Tumori. We will perform multiparametric flow cytometry analysis. PBMCs from patients will be stained with HLA-DR, CD14, CD16, CD15, CD66, c-kit and CD33 antibodies to define the subsets of myeloid-derived suppressor cells. CD8+ and CD4+ T cell frequency will be calculated on the whole CD45+/CD3+ lymphocytes. CD4+ T cell will be characterized with different Abs including CD127, CD25, FOXP3, CTLA-4, OX40, ICOS, PD-1, CD45RA, CCR10, CCR7, CCR4, CCR6, CXCR5, Ki67, IL-17, IFN-g and IL-10. In addition, we will investigate the expression of co-stimulatory and co-inhibitory molecules such as OX40, ICOS, CD69, CTLA-4, PD-1, TIM3 and LAG3.

7.1.6 Other Procedures

7.1.6.1 Discontinuation and withdrawal

Participants who discontinue study intervention prior to completion of the treatment period should be encouraged to continue to be followed for all remaining study visits as outlined in the SoA and Section 7.2.

Participants who withdraw from the study should be encouraged to complete all applicable activities scheduled for the final study visit at the time of withdrawal. Any AEs that are present at the time of withdrawal should be followed in accordance with the safety requirements outlined in Section 7.2.

7.1.7 Visit Requirements

Visit requirements are outlined in Section 5.3 – Schedule of Activities. Specific procedure-related details are provided above in Section 7.1 - Trial Procedures.

7.1.7.1 Screening

7.1.7.1.1 Screening Period

Approximately 28 days prior to allocation, potential subjects will be evaluated to determine that they fulfill the entry requirements as set forth in Section 6.1. Written consent must be obtained prior to performing any protocol specific procedure. Screening procedures (i.e., vital signs and full physical exam) and 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 are to be performed within 10 days prior to the first dose of trial treatment.
- For women of reproductive potential, a urine pregnancy test will be performed within 72 hours prior to first dose of trial treatment. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test, performed by the local study site laboratory, will be required.
- Tumor imaging must be performed within 28 days prior to the first dose of trial treatment.

Subjects may be rescreened after initially failing to meet the inclusion/exclusion criteria. Results from assessments performed during the initial screening period are acceptable in lieu of repeating a screening test if performed within the specified time frame and the results meet the inclusion/exclusion criteria.

7.1.7.2 Treatment Period

Visit requirements are outlined in Section 5.3. Specific procedure-related details are provided above in Section 7 – Trial assessment and procedures.

7.1.7.3 Post-Treatment Visits

Subjects will be followed for up to 2 years. If the subject experienced a CR, PR, or SD during the Treatment Phase on pembrolizumab, and then experiences PD at any time during that two year follow-up period, he/she will be eligible to receive up to 12 months of therapy with pembrolizumab in the Second Course Phase according to the criteria in Section 6.2.8. After the Second Course Phase, subjects should be followed for up to two years, with no option for retreatment with pembrolizumab on study. Subjects who discontinue trial treatment for a reason other than disease progression will still be considered as on study and should continue with regularly scheduled assessments including collecting subject information on the start of new antineoplastic therapy, disease progression, and death.

7.1.7.3.1 Safety Follow-Up Visit

The mandatory Safety Follow-Up Visit should be conducted approximately 30 days after the last dose of study intervention or before the initiation of a new anti-cancer treatment, whichever comes first. Participants who are eligible for retreatment with pembrolizumab (as described in Section 6.2.8) may have up to two safety follow-up visits, one after the Initial Treatment Period and one after the Second Course Treatment.

7.1.7.3.2 Efficacy Follow-up Visits

Participants who complete the protocol-required cycles of study intervention of who discontinue study intervention for a reason other than disease progression will begin the Efficacy Follow-Up Phase and should be assessed every 6 weeks (42 ± 7 days) by radiologic imaging to monitor disease status. After 1 year, the imaging time point will occur every 12 weeks (± 7 days). Every effort should be made to collect information regarding disease status until the start of new anti-cancer therapy, disease progression, death, end of the study or if the participant begins retreatment with pembrolizumab . Information regarding post-study anti-cancer treatment will be collected if new treatment is initiated. Participants who completed all efficacy assessments and/or will not have further efficacy assessments must enter the Survival Follow-up Phase.

Participants who are eligible to receive retreatment with pembrolizumab according to the criteria in Section 6.2.8 will move from the Efficacy Follow-up Phase to the Second Course Phase when they experience disease progression. Details are provided in the SoA (Section 5.3) for retreatment with pembrolizumab.

7.1.7.3.3 Survival Follow-up Contacts

Participant survival follow-up status will be assessed approximately every 12 weeks by visit or by telephone contact, to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

The first survival follow-up assessment should be scheduled as described below:

- For participants who discontinue treatment intervention and who will not enter the Efficacy Follow-up Phase, the first survival follow-up contact will be scheduled 12 weeks after the discontinuation visit and/or safety follow-up visit (whichever is last).

7.2 Adverse Events (AEs), Serious Adverse Events (SAEs), and Other Reportable Safety Events

The definitions of an AE or SAE, as well as the method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting AE, SAE, and other reportable safety event reports can be found in Appendix 5.

Adverse events, SAEs, and other reportable safety events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE as well as other reportable safety events. Investigators remain responsible for following up AEs, SAEs, and other reportable safety events for outcome, for 90 days after EOT.

The investigator, who is a qualified physician, will assess events that meet the definition of an AE or SAE as well as other reportable safety events with respect to seriousness, intensity/toxicity and causality.

7.2.1 Time Period and Frequency for Collecting AE, SAE, and Other Reportable Safety Event Information

All AEs, SAEs, and other reportable safety events that occur after the consent form is signed but before intervention allocation must be reported by the investigator 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 intervention allocation through 30 days following cessation of study intervention must be reported by the investigator.
- All AEs meeting serious criteria, from the time of intervention allocation through 90 days following cessation of study intervention or 30 days following cessation of study intervention 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 intervention allocation through 120 days following cessation of study intervention, or 30 days following cessation of study intervention 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 if the event is considered drug-related.

All initial and follow-up SAEs and other reportable safety events occurring in all centers participating in the clinical trial, will be recorded and reported to the Promoter's Pharmacovigilance (farmacovigilanza.studispontanei@istitutotumori.mi.it) within the time frames as indicated in Table 9. The Promoter will inform MSD about SAEs that occurred during the study.

Table 9. Reporting Time Periods and Time Frames for Adverse Events and Other Reportable Safety Events

Type of Event	**Reporting Time Period:** **Consent to Allocation**	**Reporting Time Period:** **Allocation through Protocol-specified Follow-up Period**	**Reporting Time Period:** **After the Protocol-specified Follow-up Period**	**Time Frame to Report Event and Follow-up Information to Promoter's Phamacovigilance:**
Serious Adverse Event (SAE)	Report if: - due to protocol-	Report all	Report if: - drug/vaccine related.	Within 2 business days but no longer than 3

Type of Event	Reporting Time Period: Consent to Allocation	Reporting Time Period: Allocation through Protocol-specified Follow-up Period	Reporting Time Period: After the Protocol-specified Follow-up Period	Time Frame to Report Event and Follow-up Information to Promoter's Phamacovigilance:
including Cancer and Overdose	specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment		(Follow ongoing to outcome)	calendar days of learning of event
Pregnancy/Lactation Exposure	Report if: - due to intervention - causes exclusion	Report all	Previously reported – Follow to completion/termination; report outcome	Within 2 business days but no longer than 3 calendar days of learning of event
Event of Clinical Interest (require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - potential drug-induced liver injury (DILI) - require regulatory reporting	Not required	Within 2 business days but no longer than 3 calendar days of learning of event

7.2.2 Method of Detecting AEs, SAEs, and Other Reportable Safety Events

Care will be taken not to introduce bias when detecting AEs and/or SAEs and other reportable safety events. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

7.2.3 Follow-up of AE, SAE, and Other Reportable Safety Event Information

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs, SAEs, and other reportable safety events including pregnancy and exposure during breastfeeding, events of clinical interest (ECIs), cancer, and overdose will be followed until resolution, stabilization, until the event is otherwise explained, or the participant is lost to follow-up.. In addition, the investigator will make every attempt to follow all nonserious AEs that occur in allocated or randomized participants for outcome. Further information on follow-up procedures is given in Appendix 5.

7.2.4 Sponsor Responsibility for Reporting Adverse Events

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

7.2.5 Pregnancy and Exposure During Breastfeeding

Although pregnancy and infant exposure during breastfeeding are not considered AEs, any pregnancy or infant exposure during breastfeeding in a participant (spontaneously reported to the investigator or their designee) that occurs during the study are reportable to the Promoter.

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.

7.2.6 Events of Clinical Interest (ECIs)

Selected nonserious and SAEs are also known as ECIs and must be reported to Promoter's Pharmacovigilance. The Promoter will inform MSD about selected nonserious and SAEs that occurred during the study.

Events of clinical interest for this study include:

1. An overdose of pembrolizumab that is not associated with clinical symptoms or abnormal laboratory results. For purposes of this study, an overdose of pembrolizumab will be defined as any dose of 1,000 mg or greater (≥5 times the indicated dose). No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated. If an adverse event(s) is associated with ("results from") the overdose of a MSD product, the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met.

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.

7.3 Suspected unexpected serious adverse reactions (SUSARs)

Unexpected adverse reactions are SUSARs if the following three conditions are met:

- The event must be serious;

- There must be a certain degree of probability that the event is a harmful and an undesirable reaction to the medicinal product under investigation, regardless of the administered dose;

- The adverse reaction must be unexpected, that is to say, the nature and severity of the adverse reaction are not in agreement with the product information as recorded in the reference safety information.

7.3.1 Reporting of SUSARs by the sponsor to the EudraVigilance database

The sponsor will keep detailed records of all AEs which are reported to him/her by the investigator or investigators (CTR: Article 41(3)).

The sponsor will report electronically and without delay to EudraVigilance database all relevant information about any SUSAR (CTR: Article 42).

The period for the reporting of SUSARs by the sponsor to EudraVigilance will take account of the seriousness of the reaction and will be as follows:

- In the case of fatal or life-threatening SUSARs, as soon as possible and in any event not later than 7 days after the sponsor became aware of the reaction (CTR: Article 42(2(a)));

- In the case of non-fatal or non-life-threatening SUSARs, not later than 15 days after the sponsor became aware of the reaction (CTR: Article 42(2(b)));

- In the case of a SUSARs which was initially considered to be non-fatal or nonlife threatening but which turns out to be fatal or life-threatening, as soon as possible and in any event not later than 7 days after the sponsor became aware of the reaction being fatal or life-threatening (CTR: Article 42(2(c))).

Where necessary to ensure timely reporting, the sponsor may, in accordance with section 2.4 of Annex III, submit an initial incomplete report followed up by a complete report (CTR: Article 42(2)).

8.0 STATISTICAL ANALYSIS PLAN

8.1 Statistical Analysis Plan Summary

Objective Response Rate (ORR) according to RECIST 1.1 will be the primary endpoint. A minimax Simon two-stage design will be applied. Assuming an unsatisfactory ORR of 56%, a valuable ORR of 71%, 24 and 11 patients will be enrolled in the first and second stage, respectively (total number of patients: 35, one-sided alpha: 0.15, power: 0.78). If complete or partial response is assessed in at least 15 patients in the first stage, the second stage will be started, otherwise the study will be closed, and study failure declared. If complete or partial response is assessed in at least 23 patients at the end of the second stage, the experimental treatment will be considered promising and worthy of further investigation. Sample size and minimax thresholds were calculated using R version 4.1.0 (R Core Team, 2021) and the

clinfun version 1.0.15 package [Venkatraman E. Seshan (2018). clinfun: Clinical Trial Design and Data Analysis Functions. R package version 1.0.15. https://CRAN.R-project.org/package=clinfun] in R statistical software.

8.2 Statistical Analysis Plan

Only eligible patients who receive at least one dose of experimental treatment will be considered for the primary analysis. A consecutive enrollment of eligible patients will be performed in order to better control selection bias in this single arm study. Number and reasons of participation failure from consecutive enrollment will be collected by center and reported in a flow-chart. Consecutive enrollment will not be interrupted between the first and second stage. Study enrollment will be interrupted in the following cases:

- study failure could be prematurely declared
- the planned number of patients with an assessed objective tumor response has been enrolled.

In case of success at the end of the second stage, according to the chosen type I error probability (i.e. the probability of incorrectly rejecting the null hypothesis), an exact one-sided 85%CI will be estimated for the primary endpoint. Objective response and disease control rates will be evaluated with point estimates and 95% CIs on the basis of the exact binomial method. Treatment administration will be summarized by starting dose, number of cycles, number, type and reason of dose modification and dose intensity. Protocol violations of treatment administration and reasons for ending treatment will be summarized too. Type of adverse events and SAE will be tabulated using the last updated MedDRA dictionary. For each type of AE and SAE, the maximum grade observed in each patient will be used as summary statistic. For time-to-event endpoints the median and interquartile range of follow-up will be estimated using the reverse Kaplan-Meier estimator. The survival function will be estimated using the Kaplan-Meier estimator. The 95%CI of median survival times will be estimated using the robust non-parametric method due to Brookmeyer and Crowley [Brookmeyer, R. and Crowley, J. (1982), "A Confidence Interval for the Median Survival Time," Biometrics, 38, 29-41]. Participant flow through the trial, baseline characteristics and adverse events will be summarized by non-parametric descriptive statistics (i.e. absolute and percentage frequencies for categorical variables and median and range for continuous variables). Data will be analyzed using SAS version 9.4 (SAS Institute, Cary, NC).

9.0 ETHICAL CONSIDERATIONS

9.1 Compliance with law and regulation

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual.

9.2 Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and Competent Authority (CA)

Before initiating the trial, the Investigators must obtain a written favourable opinion from the IRB/IEC and CA for the study protocol, the written informed consent form, the subject recruitment procedures and any other written information to be provided to subjects. All the correspondence with the IRB/IEC and CA must be retained in the Investigator File.

9.3 Informed consent

The Sponsor's Informed Consent Form (and ancillary sample Informed Consent Forms (if applicable) will be provided to each site. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's Informed Consent Forms or any alternate consent forms proposed by the site before IRB/EC submission. The final IRB/EC–approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements. The investigator or authorized designee will explain to each patient the objectives, methods, and potential risks associated with each optional procedure. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time for any reason.

The Consent Forms must be signed and dated by the patient or the patient's legally authorized representative before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient.

Patients must be re-consented to the most current version of the Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and IRB/EC policy) during their participation in the study. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time

9.4 Confidentiality and Privacy

All information provided to the Investigator by the Sponsor, information produced during the clinical trial including, but not limited to the protocol, e-CRF, IB, and the results obtained during the course of the trial is confidential. The members of the research team agree not to discuss such information in any way

without prior written permission from the Sponsor. Subject names will remain confidential and will not be supplied to the Sponsor. The subject's personal data, i.e. name and contact information and date of birth will be replaced by a code (so called pseudonymized). The Investigator will maintain a personal subject identification list (subject and treatment numbers with the corresponding subject names) to enable records to be identified. The ICF will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation. Patients will give explicit permission for the Sponsor or its designee, regulatory authorities, and the relevant IRB/IEC to inspect their medical records to verify the information collected. Patients will be informed that all personal information made available for inspection will be handled in the strictest confidence and in accordance with local data protection/privacy laws.

9.5 Financial disclosure

Investigators will provide sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities.

9.6 Premature Closure of the Study

This study may be prematurely terminated, if in the opinion of the investigator, there is sufficient reasonable cause. Written notification documenting the reason for study termination will be provided to the investigator by the terminating party.
Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to patients
- Failure to enter patients at an acceptable rate
- Insufficient adherence to protocol requirements
- Insufficient complete and/or evaluable data
- Plans to modify, suspend or discontinue the development of the drug

10.0 DATA MANAGEMENT

10.1 Data Quality Assurance

The Sponsor will be responsible for data management of this study, including quality check of the data.
Data will be collected through use of electronic case report for (e-CRFs). Sites will be responsible for data entry into the e-CRFs.
e-CRFs and correction documentation will be maintained in the CRF system's audit trail.
System backups for data stored by the sponsor and records retention for the study data will be consistent with the sponsor's standard procedures.

10.2 Electronic case report forms

Sites will receive training for appropriate e-CRF use. All e-CRFs should be completed by designated, trained site staff. e-CRFs should be reviewed and electronically signed and dated by the investigator. At

the end of the study, the investigator will receive patient data for his or her site in a readable format that must be kept with the study records. Acknowledgement of receipt of the data is required.

10.3 Source data documentation

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, patient-reported outcomes, checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial. Before study initiation, the types of source documents that are to be generated will be defined.
Source documents that are required to verify the validity and completeness of data entered into the e-CRFs must not be obliterated or destroyed and must be retained per the policy for retention of records.
To facilitate source data verification and review, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The study site must also allow inspection by applicable health authorities.

11.0 QUALITY CONTROL

11.1 Responsibilities of the investigators

The Investigators undertake to perform the study in accordance with Good Clinical Practice. The Investigator is required to ensure his compliance to the procedures required by the protocol with respect to the investigational drug schedule and visit schedule. The Investigator agrees to provide all information requested in the Case Report Form in an accurate and legible manner according to the instructions provided. The Investigator has responsibilities to take all reasonable steps to ensure the proper conduct of the study as regards ethics, protocol adherence, integrity and validity of the data recorded on the case report forms.

11.2 Study Monitoring

Monitoring activities will be done in order to verify that the data are authentic, accurate, and complete; that the safety and rights of the subject are being protected; and that the study is conducted in accordance with the currently approved protocol, GCP, and all applicable regulatory requirements. At regular intervals during the study, the center will be contacted by a representative of the Sponsor (internal and/or external staff authorized and duly appointed by the Sponsor), through site visits and/or remote visit and/ or telephone calls, to review the study progress, the investigators and subjects' adherence to protocol requirements.

The following points will be scrutinized:
- subject informed consent
- subject recruitment and follow-up

- study drug allocation
- subject compliance to the study treatment
- study treatment accountability
- Adverse Event documentation and reporting

According to the guidelines on ICH Good Clinical Practice, the monitor of the study will check the case report form entries against the source documents.

Data will be collected by e-CRF and data will be systematically checked by representative of the Sponsor (internal and/or external staff authorized and duly appointed by the Sponsor) for consistency, completeness and accuracy.

11.3 Retention of Records

Records and documents pertaining to the conduct of this study, including e-CRFs, ICFs, Investigator Site File (ISF) must be retained by the Principal Investigator for at least **25** years after completion or discontinuation of the study, or for the length of time required by relevant national or local health authorities, whichever is longer. After that period, the documents may be destroyed, according to local regulations.

11.4 Site Discontinuation (if applicable):

The Sponsor has the right to close a site at any time.
Reasons for closing a site may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Council for Harmonisation (ICH) guideline for Good Clinical Practice
- No study activity (i.e., all patients have completed the study and all obligations have been fulfilled

12.0 STUDY CONDUCTION

12.1 Administrative Structure

This trial will be sponsored by Fondazione IRCCS Istituto Nazionale dei Tumori di Milano.
The Sponsor will provide clinical operations oversight, data management, and medical monitoring.
3 National Cancer Centers will participate to enroll approximately 35 patients.
Central facilities will be used for certain study assessments throughout the study (e.g., specified laboratory tests, biomarker and PK analyses)..
As mandatory inclusion criteria, the tissue submitted will be used to assess exploratory biomarkers. The tissue submitted should be a formalin-fixed, paraffin-embedded (FFPE) tumor specimen or 20 serial, freshly cut, unstained slides accompanied by an associated pathology report. Cytological samples are not acceptable. Representative FFPE tissue samples will be collected from the primary tumor and/or any previous metastatic tissue specimens, so that further analysis may be performed on that/those tissue

sample(s) as appropriate. The samples will be received, processed and centrally analysed by the Department of Pathology of Fondazione IRCCS Istituto Nazionale dei Tumori under the responsibility of Dr. Massimo Milione, Director of Pathology Division 1. Tissue received in excess to that required by this study will be returned to the histopathology department from where it was originally requested. For information on tumor tissue assessments see the section 3.2.3.2.

To longitudinally monitor the frequency and the phenotype of circulating immune cells at baseline and during treatment, we will perform multiparametric flow cytometry analysis on peripheral blood.
The blood samples collected will be sent to the Promoter and processed and centrally analysed by the Experimental Oncology And Molecular Medicine Department of Fondazione IRCCS Istituto Nazionale dei Tumori under the responsibility of Dr.ssa Roberta Mortarini.

12.2 Training of study site personnel

The Principal Investigator will ensure that appropriate training relevant to the study is given to all investigational staff, and that any new information relevant to the performance of this study is forwarded to the staff involved.

12.3 Study timetable and end of study

The duration of the study is expected to be a maximum of 48 months. The study recruitment period is expected to be approximately 24 months. The end of the study is defined as the conclusion of survival follow-up. The survival follow-up will continue until 6 months after the last subject receives the last dose.

The study is expected to start in Oct 2023 and patient enrollment should be completed by September 2027 . The study may terminate prematurely if concerns for safety arise. All patients will receive follow-up care in accordance with standard local clinical practice.
Any SAE or non-serious AE that is ongoing at the time of this data cut-off must be followed up to resolution unless the event is considered unlikely to resolve by the investigator, or the patient is lost to follow-up.

12.4 Data Handling

According to the ICH Guidelines on Good Clinical Practice the sponsor of a study is the owner of the data resulting there from. All centers and investigators participating in the study should be made aware of such circumstance and invited not to disseminate information or data without the Institution's prior express consent. Source documents are where data is first recorded. These include, but are not limited to, hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence. Direct access to source data will be granted to authorized representatives to permit trial-related monitoring, audits and inspections. Data Management will be carried out by Clinical Trial Center of Fondazione IRCCS Istituto Nazionale dei Tumori, Via Venezian 1, 20133, Milan, Italy.

12.5 Data Breach Management

In case of a data breach, the Data Protection Officer (DPO) and the legal team of the National Cancer Institute must be informed of all personal data breaches as soon as possible.

12.5.1 Management of data breaches occurring within the Promoter or Data Owner's facility.

To manage a personal data breach, the following six steps, two of which are optional, need to be followed:

- Reporting;
- Preliminary investigation, risk assessment, response & recovery;
- Notification to the Supervisory Authority (if applicable);
- Communication to the affected parties (if applicable);
- Documentation of the breach.

The Data Protection Officer (DPO) must record the breaches and collaborate with the responsible clinical data member (the "data owner") to assess the likely impact of the breach. A breach is considered notifiable unless it is unlikely to result in a risk to the rights and freedoms of individuals.
The notification should include the nature of the personal data breach, including, where possible: the approximate number of data subjects affected, and the approximate number of personal data records involved.

12.5.2 Data breach at third-party data processors acting on behalf of the Foundation.

During the contractual phase of acquiring services and/or technologies involving data processing on behalf of the Data Owner, the Foundation has appointed suppliers, individuals, or legal entities as data processors (Article 28 GDPR). As soon as the Data Processor becomes aware of a data breach within its organization, or the Data Processor becomes aware of a potential breach involving personal data for which the Foundation is the data controller, the breach must be reported following the instructions specified in the appointment agreement. The communication includes the relevant documentation to enable the Foundation to report the breach to the Supervisory Authority, if necessary, and to inform the affected parties if required.
If the Foundation is the data controller for sensitive data and becomes aware of a breach, it must inform the Data Owner without undue delay, through the Data Protection Officer (DPO), in accordance with the instructions received in the appointment agreement. If precise instructions have not been provided, INT undertakes to inform the Data Owner of the data breach, providing all necessary information for evaluation, within 24 hours of becoming aware of the breach.
In the event of difficulties with computer systems or computer crashes, internal procedures within the Foundation may also be conducted in writing. The notification to the Supervisory Authority is exclusively carried out online; therefore, in the event of email service issues, an alternative email address will be used by INT to minimize communication delays.
Written communication with the affected individual may be conducted via postal mail.

12.6 Publication of Data

The protocol will be registered in a publicly accessible database such as clinicaltrials.gov and as required in EudraCT.
This trial is intended for publication, even if terminated prematurely. Publication may include any or all of the following: posting of a synopsis online, abstract and/or presentation at a scientific conference, or publication of a full manuscript. In addition, after study completion and finalization of the study report, results of this trial will be submitted for publication and posted in a publicly accessible database of clinical trial results, as well as in Health Authority websites (e.g. Clinicaltrials.gov, EudraCT etc.)

12.7 FINANCING AND INSURANCE

Financing is addressed in a separate agreement.
Sponsor as a holder of the insurance policy will cover the liability to all subjects in the case of any study related injury or death and provide indemnity for the Clinical Investigators, except for claims resulting from malpractice and/or negligence.

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45. ICH Gudeline for Good Clinical Practice E6 (R2) 14.06.2017

46. REGOLAMENTO (UE) N. 536/2014 DEL PARLAMENTO EUROPEO E DEL CONSIGLIO del 16 aprile 2014 sulla sperimentazione clinica di medicinali per uso umano e che abroga la direttiva 2001/20/CE

47. Regolamento generale per la protezione dei dati personali n. 2016/679 (General Data Protection Regulation o GDPR)

14.0 APPENDICES

14.1 Appendix 1: ECOG Performance Status

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

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

14.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 11 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 6.1 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 11. Protocol-required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	RBC Indices: MCV MCH %Reticulocytes	WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Chemistry	BUN	Potassium	AST/SGOT	Total bilirubin (and direct bilirubin, if total bilirubin is elevated above the ULN)
	Albumin	Bicarbonate	Chloride	Phosphorous
	Creatinine	Sodium	ALT/SGPT	Total Protein
	Glucose fasting	Calcium	Alkaline phosphatase	
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, [bilirubin, urobilinogen, nitrite, leukocyte esterase] by dipstick • Microscopic examination (if blood or protein is abnormal)			
Pregnancy Testing	• Highly sensitive serum or urine hCG pregnancy test (needed only for WOCBP)			
Other Screening Tests	• HBsAg, and hepatitis C virus antibody			

ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; FSH=follicle-stimulating hormone; hCG=human chorionic gonadotropin; MCH=mean corpuscular hemoglobin; MCV=mean corpuscular volume; RBC=red blood cell; SGOT=serum glutamic-oxaloacetic transaminase; SGPT=serum glutamic-pyruvic transaminase; ULN=upper limit of normal; WOCBP=women of childbearing potential; WONCBP=women of nonchildbearing potential

The investigator (or medically qualified designee) must document their review of each laboratory safety report.

14.3 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

Male Participants:

Male participants with female partners of childbearing potential are eligible to participate if they agree to one of the following during the protocol defined time frame in section 6.1.1:

- Be abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent
- Use a male condom plus partner use of a contraceptive method with a failure rate of <1% per year as described in Table 12 when having penile-vaginal intercourse with a woman of childbearing potential who is not currently pregnant.
  - Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration.

Female Participants:

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in Table 12 during the protocol-defined time frame in Section 6.1.1.

Table 12. Highly Effective Contraception Methods

Highly Effective Contraceptive Methods That Are User Dependent [a]
● Combined (estrogen- and progestogen- containing) hormonal contraception [b, c] ○ Oral ○ Intravaginal ○ Transdermal ○ Injectable
● Progestogen-only hormonal contraception [b, c] ○ Oral ○ Injectable
Highly Effective Methods That Have Low User Dependency .
● Progestogen- only contraceptive implant [b, c] ● Intrauterine hormone-releasing system (IUS) [b] ● Intrauterine device (IUD) ● Bilateral tubal occlusion
● **Vasectomized partner** A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
● **Sexual abstinence** Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)
Notes: Use should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies.

a) Typical use failure rates are lower than perfect-use failure rates (i.e. when used consistently and correctly).

b) If hormonal contraception efficacy is potentially decreased due to interaction with study treatment, condoms must be used in addition to the hormonal contraception during the treatment period and for at least (120 days after last dose of pembrolizumab and 180 days after last dose of chemotherapy) corresponding to time needed to eliminate systemic exposure after the last dose of each study intervention.
c) If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable hormonal contraceptives are limited to those which inhibit ovulation.

Female Participants:

Female participants of childbearing potential are eligible to participate if they agree to use one of the contraception methods described in Table 14 consistently and correctly during the protocol-defined time frame in Section 6.1.1.

Table 13 . Contraceptive Methods

Acceptable Contraceptive Methods
● Male or female condom with or without spermicide ● Cervical cap, diaphragm or sponge with spermicide
Highly Effective Contraceptive Methods That Are User Dependent [a]
● Combined (estrogen- and progestogen- containing) hormonal contraception [b] ○ Oral ○ Intravaginal ○ Transdermal ○ Injectable
● Progestogen-only hormonal contraception [b] ○ Oral ○ Injectable
Highly Effective Methods That Have Low User Dependency
● Progestogen- only contraceptive implant [b, c] ● Intrauterine hormone-releasing system (IUS) [b] ● Intrauterine device (IUD) ● Bilateral tubal occlusion
● **Vasectomized partner** A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
● **Sexual abstinence**

Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)
Notes: Use should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies. a) Typical use failure rates are lower than perfect-use failure rates (i.e. when used consistently and correctly). b) If hormonal contraception efficacy is potentially decreased due to interaction with study treatment, condoms must be used in addition to the hormonal contraception during the treatment period and for at least (120 days after last dose of pembrolizumab and 180 days after last dose of chemotherapy) corresponding to time needed to eliminate systemic exposure after the last dose of each study intervention. c) If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable hormonal contraceptives are limited to those which inhibit ovulation.

Pregnancy Testing

WOCBP should only be included after a negative highly sensitive urine or serum pregnancy test and in accordance with local requirements. When applicable this test should be repeated a maximum of 24-hours before the first dose/vaccination. Following initiation of treatment additional pregnancy testing will be performed at each cycle during the treatment period and should be conducted for the time required to eliminate systemic exposure after the last dose of each study intervention (120 days after last dose of pembrolizumab and 180 days after last dose of chemotherapy) and as required locally.

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

Until radiographic progression based on RECIST 1.1, there is no distinct iRECIST assessment. 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 4 to 8 weeks later is obtained (using iRECIST for participant management (see Table 8 and Figures 2). This decision by the Investigator should be based on the participant's overall clinical condition.

Clinical stability is defined as the following:

- Absence of symptoms and signs indicating clinically significant progression of disease
- No decline in ECOG performance status

- No requirements for intensified management, including increased analgesia, radiation, or other palliative care

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

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

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

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

iRECIST defines new response categories, including iUPD (unconfirmed progressive disease) and iCPD (confirmed progressive disease). For purposes of iRECIST assessment, the first visit showing progression according to RECIST 1.1 will be assigned a visit (overall) response of iUPD, regardless of which factors caused the progression.

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

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

Assessment at the Confirmatory Imaging

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

Confirmation of Progression

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

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

Persistent iUPD

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

- None of the progression-confirming factors identified above occurs AND
- The target lesion sum of diameters (initial target lesions) remains above the initial PD threshold (by RECIST 1.1)

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

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.

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

NOTE: If a participant has confirmed radiographic progression (iCPD) as defined above, but the participant is achieving a clinically meaningful benefit, an exception to continue study treatment may be considered. In this case, if study treatment is continued, tumor imaging should continue to be performed following the intervals as outlined in Section 7.

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 (≥ 20% and ≥ 5 mm increase from nadir) either for the first time, or after resolution of previous pseudo-progression. The nadir is always the smallest sum of diameters seen during the entire trial, either before or after an instance of pseudo-progression.
- Non-target lesions
  - If non-target lesions have never shown unequivocal progression, their doing so for the first time results in iUPD.
  - If non-target lesions had shown previous unequivocal progression, and this progression has not resolved, iUPD results from any significant further growth of non-target lesions, taken as a whole.
- New lesions
  - New lesions appear for the first time
  - Additional new lesions appear
  - Previously identified new target lesions show an increase of ≥ 5 mm in the new lesion sum of diameters, from the nadir value of that sum
  - Previously identified non-target lesions show any significant growth

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

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

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

14.5 Appendix 5: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definition of AE

- An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.
- For all reports of overdose (whether accidental or intentional) with an associated AE, the AE term should reflect the clinical symptoms or abnormal test result. An overdose without any associated clinical symptoms or abnormal laboratory results is reported using the terminology “accidental or intentional overdose without adverse effect.”

Events NOT meeting the AE definition

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

- Surgery planned prior to informed consent to treat a pre-existing condition that has not worsened.

Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met.

An SAE is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

- The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

d. 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 an SAE.

e. Results in persistent or significant disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated he**adache, nausea, vomiting, diarrhea, influenza, and accident**al trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

f. Is a congenital anomaly/birth defect

- In offspring of participant taking the product regardless of time to diagnosis.

g. Other important medical events

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious.

- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Recording AE and SAE

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will record all relevant AE/SAE information on the AE CRFs/worksheets at each examination.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of intensity/toxicity

- An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, not when it is rated as severe.

1. The investigator will make an assessment of intensity for each AE and SAE (and other reportable safety event) according to the NCI Common Terminology for Adverse Events (CTCAE), version 5. Any AE that changes CTCAE grade over the course of a given episode will have each change of grade recorded on the AE CRFs/worksheets.
    - Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
    - Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL).
    - Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
    - Grade 4: Life threatening consequences; urgent intervention indicated.
    - Grade 5: Death related to AE.

Assessment of causality

1. Did a product cause the AE?

2. The determination of the likelihood that a product caused the AE 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 product and the AE based upon the available information.

3. The following components are to be used to assess the relationship between a product and the AE; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely product caused the AE:

    - **Exposure:** Is there evidence that the participant was actually exposed to a product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?

    - **Time Course:** Did the AE follow in a reasonable temporal sequence from administration of the product? Is the time of onset of the AE compatible with a drug-induced effect (applies to studies with investigational medicinal product)?

    - **Likely Cause:** Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors.

    - **Dechallenge:** Was the product discontinued or dose/exposure/frequency reduced?

    - If yes, did the AE resolve or improve?

    - If yes, this is a positive dechallenge.

    - If no, this is a negative dechallenge.

    - **Rechallenge:** Was the participant re-exposed to the product in this study?

    - If yes, did the AE recur or worsen?

    - If yes, this is a positive rechallenge.

    - If no, this is a negative rechallenge.

4. **Consistency with study intervention profile:** Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the product or drug class pharmacology or toxicology?

5. 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.

6. Use the following scale of criteria as guidance (not all criteria must be present to be indicative of the product relationship).

    - Yes, there is a reasonable possibility of the product relationship:

    - There is evidence of exposure to the product. The temporal sequence of the AE onset relative to the administration of the product is reasonable. The AE is more likely explained by the product than by another cause.

    - No, there is not a reasonable possibility of the product relationship:

    - Participant did not receive the product OR temporal sequence of the AE onset relative to administration of the product is not reasonable OR the AE is more likely explained by another cause than the product. (Also entered for a participant with overdose without an associated AE.)

7. For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

8. There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to Promoter's Pharmacovigilance . However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to Promoter's Pharmacovigilance .The Promoter will inform MSD about SAEs that occurred during the study.

9. The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

10. The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

11. For studies in which multiple agents are administered as part of a combination regimen, the investigator may attribute each AE causality to the combination regimen or to a single agent of the combination. In general, causality attribution should be assigned to the combination regimen (ie, to all agents in the regimen). However, causality attribution may be assigned to a single agent if in the investigator’s opinion, there is sufficient data to support full attribution of the AE to the single agent.

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- New or updated information will be recorded in the CRF.

Reporting of AEs, SAEs, and Other Reportable Safety Events to the Promoter's Pharmacovigilance

All serious adverse events occurring during the clinical study, in all centers participating, will be reported to the Pharmacovigilance Unit of the study sponsor Institution (Fondazione IRCCS Istituto Nazionale dei Tumori) by the Investigator or a delegate member of investigational staff, using the Serious Adverse Event Form, which must be signed by a member of the investigational staff, within the time frames as indicated in Table 9, section 7.2.1.

Pharmacovigilance e-mail: farmacovigilanza.studispontanei@istitutotumori.mi.it.

The Promoter will inform MSD about SAEs that occurred during the study, according to the established deadlines.