UNICANCER Immunotherapy Group

Protocol n° UC-0105/1612

EudraCT n°: 2016-002260-14

Secured access to pembrolizumab for patients with selected rare cancer types

Abbreviated title: **AcSé Pembrolizumab**

Version n°10.0, November 22, 2021

PROTOCOL	VERSION N° - DATE	CPP Approval	ANSM Approval
INITIAL	1.1 – March 21, 2017	March 14, 2017	April 03, 2017
AMENDMENT 1	2.1 – November 30, 2017	October 13, 2017	December 07, 2017
AMENDMENT 2	3.1 – February 21, 2018	February 16, 2018	February 28, 2018
AMENDMENT 3	4.0 - May 24, 2018	September 14, 2018	July 17, 2018
AMENDMENT 4	5.0 –October 09, 2018	November 19, 2018	November 22, 2018
AMENDMENT 5	6.0 - December 20, 2018	June 11, 2019	February 19, 2019
AMENDMENT 6	7.0 - April 23, 2020	June 12, 2020	June 3, 2020
AMENDMENT 7	8.0 - September 07, 2020	November 18, 2020	October 20, 2020
AMENDMENT 8	9.0 - January 19, 2021	March 24, 2021	March 25, 2021
AMENDMENT 9	10.0 - November 22, 2021	March 8, 2022	January 21, 2022

COORDINATING INVESTIGATOR	**Dr Caroline Even** Gustave Roussy Cancer Campus Department Head and Neck Cancer 114 rue Edouard Vaillant - 94805 Villejuif Cedex Phone: +33(0)142116537 Fax: +33(0)142115273Email: caroline.even@gustaveroussy.fr

SPONSOR	**UNICANCER** 101, rue de Tolbiac 75654 Paris Cedex 13 (France) Phone: + 33 (0)1 44 23 04 04 – Fax: + 33 (0)1 44 23 55 69

CLINICAL TRIAL AUTHORIZATION FOR PROTOCOL N° UC-0105/1612

Trial Title: *Secured access to pembrolizumab for patients with selected rare cancer types*

WRITING COMMITTEE	Jean-Charles Soria (Gustave Roussy Cancer Campus, Villejuif), Sylvie Chevret (Université Paris VII-Jussieu, Paris), Aurelien Marabelle (Gustave Roussy Cancer Campus, Villejuif), Stephane Champiat (Gustave Roussy Cancer Campus, Villejuif), Marta Jimenez (R&D UNICANCER, Paris), Daniel Couch (R&D UNICANCER, Paris), Jean-Yves Blay (Centre Léon Bérard, Lyon), Isabelle Ray-Coquard (Centre Léon Bérard, Lyon), Khe Hoang-Xuan (Hôpital de la Pitié-Salpêtrière, Paris), Martin Schlumberger (Gustave Roussy Cancer Campus, Villejuif), Patricia Niccoli (IPC, Marseille), Christophe Massard (Gustave Roussy Cancer Campus, Villejuif), Dr François Janot (Gustave Roussy Cancer Campus, Villejuif), Linda Mahjoubi (Gustave Roussy Cancer Campus, Villejuif)

CONTACT DETAILS AND USEFUL INFORMATION	
Dr Caroline EVEN **Coordinating Investigator**	Gustave Roussy Cancer Campus Department Head and Neck Cancer 114 rue Edouard Vaillant - 94805 Villejuif Cedex Phone: +33(0)142116537 Fax: +33(0)142115273 Email: caroline.even@gustaveroussy.fr
Pr Sylvie Chevret **Biostatistician**	UMR1153, ECSTRA Team, Inserm, Paris Diderot-Paris 7 Service de Biostatistique et Information Médicale 1, avenue Claude Vellefaux - 75475 PARIS CEDEX 10 Tel : +33 (0) 1 42 49 97 42 Fax : +33 (0) 1 42 49 97 45 sylvie.chevret@paris7.jussieu.fr
Clotilde Simon **Project manager** **Immunotherapy Group**	R&D UNICANCER Département d'Immunothérapie 101 rue de Tolbiac – 75654 PARIS cedex 13 Phone: +33 (0)1 73 79 79 11 Fax: +33 (0)1 71 93 61 67 Email: c-simon@unicancer.fr
Pharmacovigilance **Notification**	R&D UNICANCER Pharmacovigilance Unit Phone: + 33 (0)1 44 23 04 16 Fax: + 33 (0)1 44 23 55 70 Email: pv-rd@unicancer.fr

APPROVAL AND SIGNATURE FOR PROTOCOL N° UC-0105/1612

Trial Title: *Secured access to pembrolizumab for patients with selected rare cancer types*

Name Responsibility	**Address**	**Date** (dd-mm-yyyy)	**Signature**
Dr Caroline Even Coordinating Investigator	**Gustave Roussy Cancer Campus** Department Head and Neck Cancer 114 rue Edouard Vaillant - 94805 Villejuif Phone: +33(0)142116537 Fax: +33(0)142115273		
Pr Sylvie Chevret Biostatistician	**UMR1153, ECSTRA Team, Inserm, Paris Diderot-Paris 7** Service de Biostatistique et Information Médicale 1, avenue Claude Vellefaux - 75475 PARIS 10 Tel : +33 (0) 1 42 49 97 42 Fax : +33 (0) 1 42 49 97 45		
Beata Juzyna Director Clinical Programs	**R&D UNICANCER** 101 rue de Tolbiac – 75654 Paris Tél : + 33 (0) 1 44 23 04 19 Fax : + 33 (0) 1 44 23 55 69		
Clotilde Simon Project manager Immunotherapy Group	**R&D UNICANCER** 101 rue de Tolbiac – 75654 Paris Tél. : +33 (0) 1 73 79 79 11 Fax : +33 (0) 1 71 93 61 67		

SYNOPSIS – PROTOCOL N° UC-0105/1612

A) TRIAL IDENTIFICATION

SPONSOR – PROTOCOL CODE NUMBER: UC-0105/1612

VERSION (NR & DATE): Version 10.0. November 22, 2021

TRIAL TITLE: Secured access to pembrolizumab for patients with selected rare cancer types

ABBREVIATED TITLE: AcSé pembrolizumab

COORDINATING INVESTIGATOR: Dr Caroline Even

NUMBER OF PARTICIPATING CENTRES (ESTIMATE): 20-50	**NUMBER OF PATIENTS:** 350

B) SPONSOR IDENTIFICATION

NAME:	**UNICANCER** 101, rue de Tolbiac 75654 Paris Cedex 13 (France)
CONTACT PERSON:	**Clotilde SIMON** PROJECT MANAGER IMMUNOTHERAPY GROUP **R&D UNICANCER** Phone: +33 (0)1 73 79 79 11 Fax: +33 (0)1 71 93 61 67 Email: c-simon@unicancer.fr

C) TRIAL GENERAL INFORMATION

INDICATION:
Patients with unresectable locally advanced or metastatic, rare sarcoma, rare ovarian cancer, primary central nervous system lymphomas (PCNSL), rare thyroid cancer, rare malignant neuroendocrine cancer, germ-cell cancer, or natural killer (NK)-/T-cell lymphoma, which is resistant or refractory to standard therapy, or for which standard therapy does not exist, or is not considered appropriate, and for which no other experimental treatment options are available.

METHODOLOGY:
This is a Phase 2, non-randomised, open-label, multicentric study to investigate the efficacy and safety of pembrolizumab monotherapy in patients with specific rare cancers who have unresectable locally advanced or metastatic disease, which is resistant or refractory to standard therapy, or for which standard therapy does not exist, or is not considered appropriate, and for which no other experimental treatment options are available, in order to identify subsets of patients that may benefit from treatment.

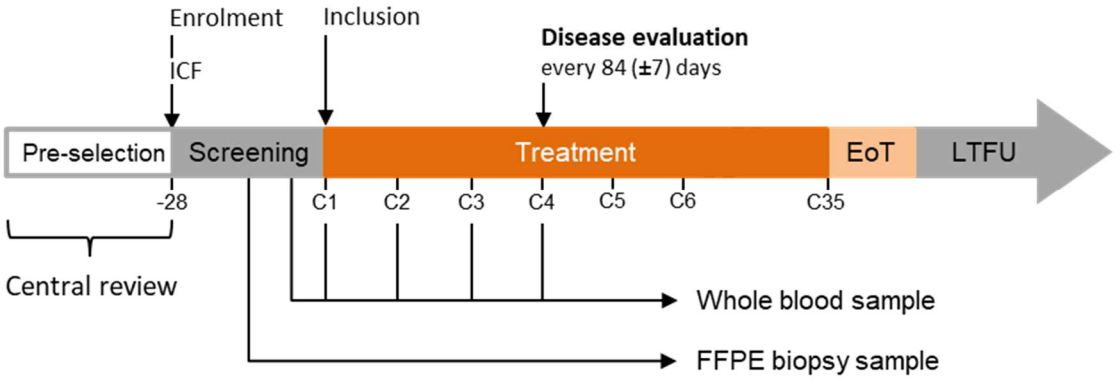
The study plans to enrol up to 350 patients in total. Eligible patients who have provided their written informed consent for study participation will be assigned to one of 7 cohorts determined by indication:

- Cohort 1: Rare sarcoma
- Cohort 2: Rare ovarian cancer
- Cohort 3: Primary central nervous system lymphomas
- Cohort 4: Rare thyroid cancer
- Cohort 5: Rare malignant neuroendocrine cancer
- Cohort 6: Germ-cell cancer
- Cohort 7: NK/T-cell lymphoma

Between 20 and 50 patients will be enrolled in each cohort with the exception of the cohort 1 for which up to 80 patients may be enrolled (extension introduced under amendment 5 of this protocol). Following the amendment 6, up to a maximum of 50 additional patients may be included in the Sarcoma (cohort 1), Rare ovarian cancer (cohort 2) or Primary central nervous system lymphoma (cohort 3) cohorts, within the limit of 350 patients to be included in total.

The study will use a two-stage Bayesian enrichment design. The first stage treats all patients with the investigational product and identifies possibly sensitive cohorts (Berry 2013). The subsequent stage compares outcomes among subsets of patients in the identified cohorts to distinguish between patients who may benefit from the treatment and patients for whom there is no evidence of efficacy; possibly resulting in a halt to inclusion of the latter (Trippa 2012).

Patient participation is divided into 5 phases: Pre-selection, Screening, Treatment, End of Treatment (EoT), and Long-Term Follow-up (LTFU).



C= cycle, EoT= End of treatment visit, FFPE= Formalin-fixed, paraffin-embedded, ICF= Informed consent form, LTFU= Long-term follow-up.

Prospective patients will be subject to a mandatory pre-selection process. Available (anonymised) diagnostic and disease history data will be reviewed centrally by a designated pathology expert to confirm that the patient meets the inclusion criteria concerning disease indication and that no other approved or experimental treatment options are available. Informed consent for study participation may be obtained only after approval of this pre-selection request.

***Note**: No study-specific examinations are required or should be performed as part of the pre-selection process.*

Following signature of the informed consent form patients will enter the Screening period (max. 28 days prior to start of treatment) during which all examinations required to assess their eligibility will be performed, including demographic data collection, tumour evaluation and clinical and laboratory evaluations. Eligible patients will be enrolled and registered through the R&D UNICANCER online electronic case report form and subject to a mandatory central review process prior to inclusion.

The availability of a suitable formalin-fixed, paraffin-embedded (FFPE) biopsy sample of a metastatic site, or primitive tumour tissue will be verified during the screening period. If suitable archived biopsy material is not available, a fresh biopsy of a tumour lesion may be performed, unless this is medically contraindicated.

All included patients will receive the investigational product (IP, pembrolizumab). Adult patients will receive pembrolizumab as a 200 mg intravenous (IV) infusion over 30 minutes every 21 days. Patients under 18 years old will receive pembrolizumab 2mg/kg (maximum dose 200mg) IV over 30 minutes every 21 days. Patients will be asked to attend clinical visits on the first day of each cycle to perform safety and efficacy assessments. Disease assessments will be performed by radiologic imaging every 84 (± 7) days (approx. every 4 cycles). For patients with germ-cell cancer, disease assessments will also include measurement of biomarkers (alpha-fetoprotein [AFP] and human chorionic gonadotropin [hCG] and lactate dehydrogenase [LDH]) performed on Day 1 of each cycle.

Blood samples will be collected prior to the first dose of IP (during the screening period) and following IP administration on Day 1 of Cycles 1, 2, 3 and 4 for comprehensive blood phenotyping and retrospective dosage of auto-antibodies and anti-tumour antibodies in serum, dosage of circulating cytokines, chemokines and receptor/ligand complexes in plasma, and analysis of ctDNA. Additional blood samples may also be collected if the patient experiences a suspected immune-related toxicity for exploratory research.

A table summarizing the examination/visit schedule is provided in the Section H of the Protocol Synopsis.

Patients will continue treatment for a maximum of 24 months (or 35 cycles, whichever is longer), or until disease progression. Treatment may also be terminated early at the initiative of either the patient or the investigator for any reason that would be beneficial to the patient, including: unacceptable toxicity, intercurrent conditions that preclude continuation of treatment, or patient request.

An EoT visit will be performed 30 (± 3) days after discontinuation of study treatment for any reason. After the EoT visit, patients will enter the LTFU period and will be followed for an additional 12 months. During this time information will be collected every 90 (± 14) days concerning survival status, subsequent antineoplastic treatments and the status of ongoing AEs and/or new treatment related AEs. Patients who discontinue treatment for reasons other than disease progression (e.g. due to toxicity, patient or investigator decision) will continue to be assessed by radiologic imaging every 84 (± 7) days throughout the LTFU period, until disease progression or initiation of a new antineoplastic treatment.

All participants who reach the maximum treatment duration per protocol and stop the pembrolizumab with a clinical benefit (prolonged stable disease, partial or complete response), may be eligible for up to an additional 1 year (approximately 17 cycles) of pembrolizumab treatment if they progress during the follow-up period. This retreatment is termed the Second course or Re-challenge.
The second pembrolizumab course will continue until 12 months of retreatment, progression or until the end of the study, whichever occurs first.
An objective response or disease progression that occurs during the Second course of pembrolizumab for a participant will not be taken into account in the primary analysis in this study.

Efficacy of treatment will be assessed according to ; (i) Response Evaluation Criteria In Solid Tumours version 1.1 (RECIST v.1.1, Eisenhauer, 2009) for solid tumours, (ii) RECIST v1.1 combined with biomarker assessment (Fizazi, 2014) for patients with germ-cell cancer, (iii) International PCNSL Cooperative Group (IPCG) response criteria (Abrey, 2005) for patients with PCNSL, (iv) For NK/T-cell lymphoma, disease burden will be assessed using the five-point scale (or 'Deauville criteria'; Meignan, 2009) of focal uptake of FDG measured via PET-CT scan. Evolution of disease will be evaluated using the 'Lugano' classification system (Cheson, 2014). NK/T-cell lymphoma patients with complete response will be further categorised as being in remission or not according to the detectable level of EBV in the blood. In addition to the Investigators' assessment of response, a central disease response evaluation will be performed by an Independent Review Committee (IRC). Efficacy will be analysed separately for each cohort using a two-stage Bayesian enrichment design. Interim analyses will be performed using the Investigators' assessment of response measured at the first scheduled disease assessment following study treatment initiation (Day 84, ± 7 days) to assess the efficacy of treatment and determine if enrolment should continue. Interim analyses will be performed independently for each cohort after the 10 first patients have been enrolled in the cohort and completed at least one disease assessment. Subsequent analysis will be performed in each cohort after every 5 additional patients. Enrolment in a particular cohort may be stopped for futility if the rate of response is below a pre-defined threshold of 0.10. Final analysis of efficacy endpoints will be performed using both the Investigator and IRC assessment of response once recruitment is complete and all patients have completed at

least one post-baseline disease assessment. Comparisons between Investigator and IRC response assessments will also be reported.

PRIMARY OBJECTIVE:

The primary objective of the trial is to evaluate the response to pembrolizumab monotherapy in cohorts of patients with unresectable locally advanced or metastatic, rare sarcoma, rare ovarian cancer, PCNSL, rare thyroid cancer, rare malignant neuroendocrine cancer, germ-cell cancer, or NK/T-cell lymphoma which is resistant or refractory to standard therapy, and for which no other treatment options are available.

SECONDARY OBJECTIVE(S):

- To identify populations, for which the IP is expected to have a clinical benefit.
- To assess the efficacy of pembrolizumab monotherapy in each cohort in terms of survival, progression occurrence and quality of response.
- To assess the safety profile of pembrolizumab monotherapy.

ANCILLARY RESEARCH OBJECTIVES:

- To identify the discriminant molecular mechanisms in patients with tumour response versus patients without tumour response within the same cohort.

DIAGNOSIS AND INCLUSION CRITERIA:

Patients must meet all of the following criteria to be included in the study:

1. Patient information sheet and written informed consent form signed.
2. Histologically confirmed diagnosis of a pathology corresponding to one of the following selected cancer types:
    - Rare sarcoma: Alveolar soft part sarcoma, Chordoma, Dedifferentiated chondrosarcoma, epithelioid sarcoma, sarcoma with loss of INI1, malignant rhabdoid tumours, myxoid liposarcoma, angiosarcoma of the scalp, radiation induced sarcomas. From the 51st patient included in this cohort, only the following histological types will be selected: Alveolar soft part sarcoma, Chordoma, SMARCA4-malignant rhabdoid tumours and Desmoplastic small-round-cell tumor.
    - Rare ovarian cancer: recurrent or relapsed; sex cord tumour, germ cell tumour (immature teratoma, non seminomatous germ cell & dysgerminoma), low-grade serous carcinoma, mucinous carcinoma, clear cell adenocarcinoma, small cell carcinoma, and carcinosarcoma – with histological confirmation following review by members of the Tumeurs Malignes Rares Gynécologiques (TMRG) network (French rare gynaecological tumour group). From the 51st patient included in this cohort, only the following histological types will be selected: teratoma, low-grade serous carcinoma and ovarian small cell carcinoma hypercalcemic type (SCOOHT).
    - Primary central nervous system lymphoma: refractory primary intraocular and CNS lymphoma. From the 51st patient included in this cohort, only CNS lymphoma will be selected.
    - Rare thyroid cancer: differentiated thyroid carcinoma (Papillary, follicular, Hurthle cell (oncocytic), poorly differentiated thyroid carcinoma), medullary thyroid carcinoma, anaplastic thyroid carcinoma.
    - Rare malignant neuroendocrine cancer: poorly differentiated digestive tumours refractory after 2 lines of chemotherapy including cisplatin/carboplatin-etoposide (CDDP/carbo-VP16) and 5-Fluoro-uracile/irinotecan (FOLFIRI), poorly differentiated non digestive tumours refractory after 2 lines of chemotherapy including cisplatin/carboplatin-etoposide (CDDP/carbo-VP16) and any second line of chemotherapy, well differentiated tumours refractory after 4 lines of treatment including 2 lines of chemotherapy, everolimus and sunitinib, carcinoid tumours after 2 lines of treatment including Peptide Receptor Radionuclide Therapy (PRRT) or chemotherapy and everolimus.
    - Trophoblastic germ-cell tumours progressing after standard therapy.

- Natural killer T-cell lymphoma: extranodal NK/T-cell lymphoma regardless of localization that is resistant or refractory to prior L-asparaginase therapy.

3. Metastatic disease or unresectable locally advanced malignancy that is resistant or refractory to standard therapy or for which standard therapy does not exist or is not considered appropriate by the Investigator.
4. Aged ≥ 18 years old for cohort 2 to 7 and aged ≥ 15 years old for patients included in cohort 1 (rare sarcoma).
5. Measurable disease defined:
   - according to RECIST v1.1 guidelines (Eisenhauer, 2009) for patients with solid tumours;
   - according to RECIST v1.1 and / or abnormal levels of AFP, hCG and LDH for patients with germ-cell cancer;
   - according to IPCG response criteria (Abrey, 2005) for patients with PCNSL;
   - as focal uptake in at least one nodal or extra-nodal site with a Lugano 5-PS score of 4 or 5 (Cheson, 2014) for patients with NK/T-cell lymphoma,
6. Able to provide a FFPE biopsy sample of a metastatic site or primitive tumour tissue.

   ***Note**: Patients for whom suitable archived biopsy material is not available must be willing to undergo a biopsy of a tumour lesion prior to study entry, unless this is medically contraindicated (e.g. site inaccessible or patient safety concerns).*
7. Patients must have a mandatory treatment-free interval of at least 21 days following previous systemic anti-cancer treatments.
8. Patients who have received previous systemic anticancer treatment and/or radiotherapy should have recovered from any treatment related toxicity, to a level of ≤ grade 1 (according to National Cancer Institute [NCI] common terminology criteria for adverse events, version 4 (CTCAE v4) with the exception of Grade 2 alopecia.
9. Adequate hematologic function (absolute neutrophil count ≥ 1.0 $x10^9$/L, platelets ≥ 100 $x10^9$/L, haemoglobin ≥ 9 g/dL) measured within 14 days of treatment initiation unless due to lymphoma associated haemophagocytic lymphohistiocytosis (HLH).
10. Adequate renal function (creatinine clearance ≥ 50 mL/min using the MDRD or CKD EPI method) measured within 14 days of treatment initiation.
11. Adequate hepatic function (serum bilirubin ≤ 1.5 xULN unless due to Gilbert's syndrome; aspartate aminotransferase [ASAT] and alanine aminotransferase [ALAT] ≤ 3 xULN) measured within 14 days of treatment initiation unless due to lymphoma associated HLH. For patients with documented liver metastasis ASAT/ALAT ≤ 5x ULN is acceptable.
12. Strictly normal blood levels of calcium and magnesium, measured within 14 days of treatment initiation.
13. Eastern Cooperative Oncology Group Performance Status of ≤ 1.
14. Estimated life expectancy ≥ 90 days.
15. Patients who are sexually active must agree to use a medically accepted method of contraception (e.g. implants, injectables, combined oral contraceptives, some intrauterine devices or vasectomized partner, for participating women; condoms for participating men) or practice complete abstinence, beginning 14 days before the first administration of IP, while on treatment and for at least 5 months after the last administration of IP for female patients, and 7 months after the last administration of IP for male patients.
16. Women of childbearing potential must have a negative urine or serum pregnancy test within 72 hours prior to the first administration of IP. If urine test results are positive or cannot be confirmed as negative, a serum pregnancy test will be required.
17. Women who are breastfeeding should discontinue nursing prior to the first administration of IP and for at least 120 days after the last administration of IP.

18. Patients must be affiliated to a Social Security System or equivalent.

EXCLUSION CRITERIA:

Patients meeting **any** of the following criteria will be excluded from participation in the study:

1. Prior treatment with an anti-PD1 or anti-PD-L1 antibody.
2. Eligible to participate in a clinical trial of an alternative anticancer therapy targeting their disease, which is open to accrual in France.
3. Concurrent steroid medication at a dose greater than prednisone 10 mg/day or equivalent. For patients with germ-cell cancer, PCNSL concurrent steroid medication at a dose greater than prednisone 20 mg/day or equivalent.
4. 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.
5. History of (non-infectious) pneumonitis that required steroids, or current pneumonitis.
6. History of severe hypersensitivity reaction to any monoclonal antibody therapy
7. Radiotherapy (except for brain and extremities) within 21 days prior to the first administration of IP.
8. Treatment with other investigational drugs or participation in another clinical trial within 21 days prior to the first administration of IP or concomitantly with the trial.
9. Has known symptomatic central nervous system (CNS) metastases. Patients with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least four weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to trial treatment.
10. Has known carcinomatous meningitis or a history of leptomeningeal disease except for patients with primary CNS lymphoma.
11. Serum creatinine > 1.5 xULN or glomerular filtration rate < 50 ml/min.
12. Other malignancies within the past 5 years other than basal cell skin cancer or *in situ* carcinoma of the cervix.
13. Active serious infections in particular if requiring systemic antibiotic or antimicrobial therapy.
14. Active or chronic hepatitis B, hepatitis C and/or human immunodeficiency virus infection (HIV 1/2 antibodies), or a known history of active *Tuberculosis bacillus.*
15. Live vaccine received within 30 days of planned start of study treatment.
16. ***Note:*** *Seasonal influenza vaccines for injection are generally inactivated vaccines and are allowed* Active alcohol or drug abuse.
17. Psychological, familial, sociological or geographical factors potentially hampering compliance with the study protocol and follow-up schedule.
18. Any condition which in the Investigator's opinion makes it undesirable for the subject to participate in the trial or which would jeopardize compliance with the protocol.

PRIMARY ENDPOINT:
Objective response rate (ORR) per cohort, defined as the percentage of patients in each cohort with a complete response (CR) or partial response (PR), measured at the first scheduled disease assessment following study treatment initiation (Day 84, ± 7 days) as assessed by an IRC according to; (i) RECIST v1.1 for patients with solid tumours, (ii) RECIST v1.1 combined with biomarker assessment for patients with germ-cell cancer, (iii) IPCG response criteria for patients with PCNSL, (iv) the 'Lugano' criteria for response assessment using the FDG-PET-CT 5-PS and assessment of EBV load for patients with NK/T-cell lymphoma

Patients who withdraw from the study prior to this time point and patients with non-evaluable disease will be considered as 'non-responders'.

SECONDARY ENDPOINT(S):

- Progression-free survival, defined as the time from inclusion until documented disease progression (PD) according to RECIST v1.1, or RECIST v1.1 combined with biomarker assessment, or IPCG response criteria, or Lugano 5-PS criteria, or death, whichever occurs first.
- Overall survival, defined as the time from inclusion until death due to any cause.
- Best response to treatment according to RECIST v1.1, or RECIST v1.1 combined with biomarker assessment, or IPCG response criteria, or Lugano 5-PS criteria, measured at any disease assessment during the course of the study.
- Response duration, defined as the time from first observation of objective response (i.e. PR or CR) according to RECIST v.1.1, or RECIST v1.1 combined with biomarker assessment, or IPCG response criteria, or Lugano 5-PS criteria, until PD or death, whichever occurs first.
- Time to response, defined as the time from inclusion until observation of objective response (i.e. PR or CR) according to RECIST v1.1, or RECIST v1.1 combined with biomarker assessment, or IPCG response criteria, or Lugano 5-PS criteria, during the course of the study.
- Frequency and severity of adverse events assessed according to the NCI CTCAE v4.

D) INVESTIGATIONAL MEDICINAL PRODUCTS

PRODUCT NAMES AND ADMINISTRATION:

Drug name (INN)	Registered name	Pharmaceutical form	Administration route	Posology
Pembrolizumab (MK-3475)	N/A	100mg/4ml solution for infusion in single-use vials	IV	**Adults** ≥ 18 years old : 200 mg **Adolescents** 15-17 years old : 2 mg/kg (maximum dose 200 mg)

THERAPEUTIC REGIMENS:
Pembrolizumab IV as a 30 minute infusion on Day 1 of every 21-day cycle

TREATMENT DURATION:
Treatment will be continued for a maximum of 24 months (or 35 cycles, whichever is longer), or until disease progression. Treatment may also be terminated early at the initiative of either the patient or the investigator for any reason that would be beneficial to the patient, including: unacceptable toxicity, intercurrent conditions that preclude continuation of treatment, or patient request.

For the second course of pembrolizumab:
Treatment will be continued for a maximum of 12 months (approximately 17 cycles) or until disease progression or until the end of the study, whichever occurs first.

DOSE ESCALATION (IF APPLICABLE):
Not applicable

E) STATISTICAL ANALYSIS PLAN

REQUIRED NUMBER OF PATIENTS TO BE INCLUDED:
The study plans to enrol up to 350 patients in total in to one of 7 cohorts , based on disease indication:

- Cohort 1: Rare sarcoma
- Cohort 2: Rare ovarian cancer
- Cohort 3: Primary central nervous system lymphomas
- Cohort 4: Rare thyroid cancer
- Cohort 5: Rare malignant neuroendocrine cancer
- Cohort 6: Germ-cell cancer
- Cohort 7: NK/T-cell lymphoma

In total between 20 and 50 patients will be enrolled in each cohort, with the exception of the cohort 1 for which up to 80 patients may be enrolled (extension introduced under amendment 5 of this protocol). Following the amendment 6, up to a maximum of 50 additional patients may be included in the Sarcoma, Rare ovarian cancer or Primary central nervous system lymphoma cohorts, within the limit of 350 patients to be included in total.

Patient enrolment to individual cohorts will continue until the stopping rules applied at each interim analysis are met, or until the maximum sample size is reached.

STATISTICAL ANALYSIS:
The trial will use a two-stage Bayesian enrichment design, allowing for a smaller more informative trial that is specifically tied to decision making within a drug development program. This process allows for incremental changes to each cohort based on current data, rather than restricting revisions in a trial design using fixed sample sizes.

The first stage treats all patients from the different cohorts with the investigational product and identifies possibly sensitive subpopulations (Berry 2013). The second stage will compare response rates across subsets within the selected cohorts (Trippa 2012).

The first stage will analyse data in each cohort independently of each other. Interim analysis of the ORR according to investigators' assessment is planned after 10 first patients eligible enrolled in the cohort have completed the first scheduled disease evaluation. Based on the estimated response rate and its posterior distribution in each cohort, cohorts that do not reach a minimal ORR of 0.1 (85% confidence) will be potentially closed to further recruitment. In addition, individual cohorts may also be closed during stage 1 if a minimal level of accrual (10 patients in the 2 years after activation of the first site) is not achieved.

In the second stage, intra-cohort analyses will be performed after every 5 additional patients accrued (Berry 2013). These analyses will use all data accumulated up to that point, and will consider potential predictive markers of efficacy; such subset analyses will result in potentially sub-cohorts of poor outcomes that may be proposed for enrolment discontinuation while those of good outcomes will enrich the design (Mandrekar 2009; Zang 2016). In the absence of a decision to halt enrolment, accrual in each cohort will continue until the end of the planned recruitment period (3 years after activation of the first site) or a maximal size by cohort of 50 patients (whatever occurs first) except for the cohorts that were amended where the maximal number of patients may be increased.

Final analysis of efficacy endpoints will be performed using both the Investigator and IRC assessment of response according to: (i) RECIST v1.1, (ii) RECIST v1.1 combined with biomarker assessment (iii) IPCG response criteria, or (iv) Lugano 5-PS criteria. Comparisons between Investigator and IRC results will also be reported. Point estimates will be provided with 95% confidence intervals. Predictive analyses of response will be performed.

All analyses will be performed for the primary cohort and the Re-challenge cohort, separately.

F) SAMPLES COLLECTED FOR TRANSLATIONAL RESEARCH

SAMPLE TYPES:
Archived FFPE biopsy material obtained as part of the standard medical care (e.g. collected at time of diagnosis or relapse or prior surgical intervention) will be collected at study entry and shipped to the R&D UNICANCER Biological Resources Centre, at the Centre Leon Berard, Lyon, France. These tumour samples will be used to perform retrospective immunohistochemical staining to identify biomarkers related to the efficacy of pembrolizumab therapy.

Note: *if suitable archived biopsy material is not available, a fresh biopsy of a tumour lesion may be requested, unless this is medically contraindicated.*

In selected cases where exceptional responses or unexpected toxicities are observed additional biopsy samples of the tumour could be collected during the trial treatment for exploratory studies.

Blood samples will be collected prior to the first dose of IP (during the screening period) and following IP administration on Day 1 of Cycles 1, 2, 3 and 4. Additional samples may also be collected if the patient experiences a suspected immune-related toxicity.

SAMPLE QUANTITIES:
Forty-five millilitres (45 mL) of blood will be collected at each sampling time point.

G) TRIAL DURATIONS

INCLUSION PERIOD :
42 months

TREATMENT PERIOD:
Treatment will be continued for a maximum of 24 months (or 35 cycles, whichever is longer), or until disease progression. Treatment may also be terminated early at the initiative of either the patient or the investigator for any reason that would be beneficial to the patient, including: unacceptable toxicity, intercurrent conditions that preclude continuation of treatment, or patient request.

FOLLOW-UP:
12 months after the EoT visit of each patient.

For the patients rechallenged with pembrolizumab, the follow-up period may be extended of 1 year maximum.

DURATION UNTIL PRIMARY ENDPOINT EVALUATION:
The first stage will analyse data in each cohort independently of each other. Interim analysis of the ORR is planned after the 10 first patients eligible have been enrolled in the cohort and completed the first scheduled disease evaluation.

OVERALL TRIAL DURATION (INCLUDING FOLLOW-UP):
Approximately 6,5 years

H) TRIAL FLOW-CHART

VISIT	PRE	SCR	C1D1	C2D1	C3D1	C4D1	C5D1	CnD1…	EoT[1]	LTFU
Days		-28 - 0	D1	D22 (±2)	D43 (±2)	D64 (±2)	D85 (±2)	+Q 21 d (±2)		Q 90 d (±14)
Written informed consent		X								X[30]
Inclusion / exclusion criteria		X								X[30]
DEMOGRAPHY										
Demographic data		X								
Cancer history (diagnosis, prior therapies, etc…)	X[2]	X								
Other relevant medical history	X[2]	X								
Concomitant treatments	X[2]	X								
SAFETY ASSESSMENTS										
Clinical examinations										
Weight and height		X								
Complete clinical examination & vital signs[3]		X	X	X	X	X		X	X	
ECOG performance status		X	X	X	X	X		X	X	
Collection of toxicities / adverse events / signs and symptoms		X	X	X	X	X		X	X[4]	X[4-30]
Laboratory examinations										
Haematology[5]		X[6]	X	X[7]	X[7]	X[7]	X[7]	X[7]	X[8]	
Serum chemistry[9]		X[6]	X	X[7]	X[7]	X[7]	X[7]	X[7]	X[8]	
Coagulation: PT/INR, PTT		X[6]								
Thyroid function (TSH, T3 and FT4)		X[6]		X[7]		X[7]		X[7,10]	X[8]	
Urinalysis: Blood, glucose, protein, specific gravity, microscopic examination of urinary sediment with concomitant dosing of creatinine		X[6]				X		X[11]		
Quantiferon tuberculosis or TST in case of anterior exposure		X[6]								
Virology: HIV, HCV and HBV serology		X[6]								
Antibody: ANA, TPO Ab, Tg Ab		X[6]								
Contraception[12]		X	X							
β-HCG pregnancy test or urine test for women of reproductive potential[13]		X	X							X[30]
Paraclinical examinations										
Electrocardiogram (12-lead)		X[6]								
EFFICACY ASSESSMENTS										
Disease evaluation – Patients with solid tumours										
Clinical assessment		X					X[14]	X[14]	X[15]	
Radiologic assessments[16]		X					X[14,17]	X[14,17]	X[15,17,18]	
Biological assessments[19]		X[20]		X[20]	X[20]		X[14]	X[20]	X[15]	
Assessment of disease status according to RECIST v1.1[21]		X					X[14]	X[14]	X[15]	X[30]
Disease evaluation – Patients with PCNSL										

VISIT	PRE	SCR	C1D1	C2D1	C3D1	C4D1	C5D1	CnD1…	EoT[1]	LTFU
Days		-28 - 0	D1	D22 (±2)	D43 (±2)	D64 (±2)	D85 (±2)	+Q 21 d (±2)		Q 90 d (±14)
Gadolinium-enhanced MRI of the brain[22]		X					X[14]	X[14]	X[15,18]	
CT scan of the chest, abdomen and pelvis		X					X[14]	X[14]	X[15,18]	
Ophthalmologic examination[23]		X					X[14, 24]	X[14, 24]	X[15, 24]	
Lumbar puncture for CSF cytology		X					X[14, 24]	X[14, 24]	X[15, 24]	
Verification of on-going corticosteroid treatment		X					X[14]	X[14]	X[15]	
Assessment of disease status according to IPCG response criteria[25]		X					X[14]	X[14]	X[15]	X[30]
Disease evaluation – Patients with NK/T-cell lymphoma										
Clinical assessment		X					X[14]	X[14]	X[15]	
FDG-PET-CT scan		X					X[14,17]	X[14,17]	X[15,17,18]	
Lumbar puncture for CSF cytology		X					X[14, 24]	X[14, 24]	X[15, 24]	
Bone marrow biopsy or bone marrow aspiration		X					X[14, 24]	X[14, 24]	X[15, 24]	
PCR analysis of EBV load		X					X[14]	X	X[15]	
Assessment of disease status according to the Lugano 5-PS criteria[26]		X					X[14]	X[14]	X[15]	X[30]
RESEARCH ASSESSMENTS										
Tumour Biopsy sample [27]		X								
Blood samples [28]		X	X	X	X	X				
STUDY TREATMENT										
IP administration			X	X	X	X	X	X		X[30]
SURVIVAL STATUS										
Survival status										X[29-30]
Subsequent antineoplastic therapy										X[29]

ANA= antinuclear antibodies; β-hCG= Beta-human chorionic gonadotropin; C= Cycle; CT= Computed tomograpghy; D= Day; d= days; EBV= *Epstein-Barr* virus; ECOG=Eastern cooperative oncology group; EoS= end of study; EoT= end of treatment; FDG= Fluorodeoxyglucose; HBV= hepatitis B; HCV= hepatitis C; HIV= human immune deficiency virus; IP= Investigational product; LTFU= Long-term follow-up; PCR= polymerase chain reaction; PET= Positron emission tomography; PNCSL= Primary central nervous system lymphoma response assessment; PRE= Pre-selection request; PT/INR= prothrombin time /International normalized ratio; PTT= partial thromboplastin time; Q= every; RECIST v1.1= Response Evaluation Criteria In Solid Tumours version 1.1 SCR= screening period; T3= total triiodothyronine; T4= free thyroxine; TgAb= thyroglobulin antibodies; TPO Ab= thyroperoxidase antibodies; TSH= thyroid stimulating hormone; TST= tuberculosis skin test

(1) To be performed 30 (± 3) days after last dose of IP.
(2) Patient is to be informed that information from their medical file will be shared anonymously with the study Sponsor and medical experts in order to assess eligibility for trial participation
(3) Vital signs: blood pressure, seated heart rate, body temperature
(4) All AEs that occur from the time the informed consent form is signed until 30 days after the last dose of IP must be reported; AEs ongoing at the end of this period have to be monitored until resolution or returned to baseline level. All serious adverse events should be reported up to 100 days after the last dose of IP. Any late Serious Adverse Drug Reaction (SAE related to the study drug), occurring at any time after this 100-day period must also be reported to the R&D UNICANCER Safety Office.
(5) Haematological analysis includes: Haemoglobin, haematocrit, red blood cell count, white blood cell count with differential, absolute neutrophil count, absolute lymphocyte count, platelet count, CD4+ count
(6) To be performed within 14 days prior to first administration of IP
(7) Blood draw for laboratory analysis may be performed up to 3 days prior to IP administration
(8) If laboratory examinations were performed less than 14 days after last dose of study treatment, they do not need to be repeated, unless clinically indicated (i.e. ongoing toxicity surveillance).
(9) Serum chemistry analysis includes: Calcium, Chloride, Magnesium, Phosphorus, Potassium, Sodium, Glucose, Albumin, Creatinine (with estimated glomerular filtration rate [MDRD or CKI EPI method]), Uric Acid, Total protein, Blood urea nitrogen, Urea, Total Bilirubin, Direct Bilirubin (only if total bilirubin is elevated above the upper limit of normal), Amylase, Lipase, Alkaline phosphatase, ALAT, ASAT, GGT, LDH, C-reactive protein, Carbon Dioxide (if considered standard of care)
(10) To be performed every 2 cycles.
(11) To be performed every 4 cycles.
(12) Verification that a medically acceptable form of contraception (e.g. implants, injectables, combined oral contraceptives, some intrauterine devices or vasectomized partner, for participating women; condoms for participating men) is being used by all sexually active patients or that complete abstinence is practiced
(13) Pregnancy test for women of childbearing potential: Urine or serum β-HCG test to be performed within 72 hours prior to the first administration of IP. If urine test results are positive or cannot be confirmed as negative, a serum pregnancy test will be required. In all cases, results must be reviewed prior to initiating study treatment.
(14) To be performed every 84 days (±7 days) (i.e. after every 4 cycles) and in case of disease progression.

(15) For patients who were withdrawn from the study for reasons other than disease progression, tumour assessments should be continued and documented every 84 days (±7 days) until disease progression or initiation of a new antineoplastic treatment.
(16) CT scan or MRI is mandatory for each disease assessment. Any other appropriate radiologic assessments (e.g. PET-FDG, PET-CT, mIBG scintigraphy, bone scan, ultrasonography, etc.) may be performed at the Investigator's discretion. Note that the same diagnostic method(s) must be used for each tumour evaluation throughout the study. The results of all radiological assessment (DICOM format) must be provided on CD-ROM for central review by the Independent Review Committee
(17) Radiographic scans that were negative at screening do not have to be repeated unless clinically indicated (i.e new or worsening symptoms). To be repeated 28 days after assessment of a PR or CR for solid tumours.
(18) If the last radiographic assessments were obtained less than 28 days prior to withdrawal of therapy, they do not need to be repeated.
(19) Appropriate biological assessments to be performed at the Investigator's discretion.
(20) For patients with germ-cell cancer only: measurements of alpha-fetoprotein (AFP) and human chorionic gonadotropin (hCG) and lactate dehydrogenase (LDH) will be performed prior to the first dose of IP (during the screening period) and within 72 hours prior to IP administration on Day 1 of each cycle of treatment (after Cycle 1).
(21) Disease response in solid tumours to be assessed according to RECIST v1.1 (Appendix 1) (including documentation of size/status of each measurable and non-measurable lesion). For patients with germ-cell cancer response will be assessed using RECIST v1.1 combined with biomarker assessment (AFP, hCG, LDH, Appendix 2).
(22) Gadolinium-enhanced MRI may be substituted with contrast-enhanced CT scans in patients for whom MRI is medically contraindicated
(23) Detailed ophthalmologic examination including: dilated fundus examination, slit-lamp examination and colour photography of the posterior pole.
(24) Tests that were negative at screening do not have to be repeated unless clinically indicated by new symptoms.
(25) For patients with PCNSL response assessment is to be made according to IPCG response criteria (Appendix 3).
(26) For patients with NK/T-cell lymphoma response assessment is to be made according to the Lugano 5-point scale response criteria (Appendix 4)
(27) Verification of availability of a suitable FFPE biopsy sample of a metastatic site, or primitive tumour tissue. If suitable archived biopsy material is not available, a fresh biopsy of a tumour lesion may be performed following signature of the informed consent form and prior to the first administration of IP, unless this is medically contraindicated.
(28) Blood samples to be collected prior to the first dose of IP (during the screening period) and following IP administration on C1D1, C2D1, C3D1 & C4D1 and when an immune related toxicity event is suspected.
(29) This information may be collected during onsite visits (as part of patients continued treatment at the site), via communication with the patients treating physician or via telephone contact with the patient.
(30) For only the patients rechallenged with pembrolizumab: before restarting pembrolizumab treatment written informed consent has to be obtained and the following parameters have to be checked by the investigator: a) inclusion/non-inclusion safety criteria, b) radiographic disease progression assessed by RECIST 1.1 for patients with solid tumours, RECIST v1.1 combined with biomarker assessment for patients with germ-cell cancer, the IPCG response criteria for patients with PCNSL, the 'Lugano' criteria for response assessment using the FDG-PET-CT 5-PS and assessment of EBV load for patients with NK/T Lymphoma and c) negative urine or serum pregnancy test for women of childbearing potential. Patients' survival status, disease status and status of ongoing AEs and/or new treatment-related AEs will be collected during the 2nd course phase.

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

Abbreviation	Definition
AcSé	Accès Sécurisé – *Secured Access*
ADL	Active daily living
AE	Adverse event
ALAT	Alanine aminotransferase
ANC	Absolute neutrophile count
ANSM	Agence nationale de sécurité du médicament et des produits de santé - *French Competent Authority*
ASAT	Aspartate aminotransferase
β-hCG	Beta-human chorionic gonadotropin
CD	Cluster of differentiation
CI	Confidence interval
CLB	Centre Leon Berard
CNS	Central nervous system
CR	Complete response
CRA	Clinical research assistant
CRB-CLB	Centre des Resources Biologiques - *Biological Resource Center*
CRC	Colorectal cancer
CSF	Central spinal fluid
CT	Computed tomography
CTCAE	Common terminology criteria for adverse events
ctDNA	Circulating tumour DNA
CTL	Cytotoxic T-lymphocytes
CV	Curriculum vitae
DCF	Data clarification form
DCR	Disease control rate
DSUR	Development safety update report
DTC	Differentiated thyroid cancer
EBV	Epstein-Barr virus
EC	Ethic committee
ECG	Electrocardiogram
ECI	Event of clinical interest
ECOG	Eastern cooperative oncology group
eCRF	Electronic case report form
EoT	End of treatment
EudraCT	European Drug Regulatory Authorities Clinical Trials
FDA	Food and Drug Administration (United States of America)
FDG	Fluorodeoxyglucose
FFPE	Formalin-fixed paraffin-embedded
GFR	Glomerular filtration rate
GIST	Gastrointestinal stromal tumour
HNSCC	Head and neck squamous cell carcinoma
HIV	Human immunodeficiency virus
HLH	Haemophagocytic lymphohistiocytosis
HR	Hazard ratio
IAPC	Institutional AsCé Programme Committee
IB	Investigator's brochure
ICH-GCP	International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use Efficacy guideline E6 - Good Clinical Practice
IDMC	Independent data monitoring committee
Ig	Immunoglobulin
IPCG	International primary central nervous system lymphoma cooperative group
INCa	Institut National de Cancer – *French National Cancer Institute*
INR	International normalized ratio
IP	Investigational product
irAE	Immune related adverse event
IRC	Independent Review Committee
ITT	Intent-to-treat
IV	Intravenous
Kg	Kilogram

KI	Kinase inhibitor
LBCL	Large B-cell lymphoma
LTFU	Long-term follow-up
mAb	Monoclonal antibody
MDR	Multi-drug resistance
mg	milligram(s)
mIBG	Metaiodobenzylguanidine
ml	milliliter(s)
MRI	Magnetic resonance imaging
NCI	National cancer institute
NK	Natural killer (cell)
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival
PBMC	peripheral blood mononuclear cells
PCNSL	Primary central nervous system lymphoma
PET	Positron emission tomography
PD	Disease progression
PD-1	Programmed death-1
PD-L	Programmed death ligand
PFS	Progression-free survival
PIS/ICF	Patient information sheet / Informed consent form
PK	Pharmacokinetic
PR	Partial response
PT	Prothrombin time
PTT	Partial thromboplastin time
Q	every
RECIST	Response evaluation criteria in solid tumors
RNA	Ribonucleic acid
SAE	Serious adverse event
SAP	Statistical analysis plan
SUSAR	Suspected unexpected serious adverse event
T3	Triiodothyronine
T4	Thyroxine
TAA	Tumour associated antigen
T-cell	T lymphocyte
TIL	Tumour infiltrating lymphocyte
TMF	Trial master file
TMRG	Tumeurs Malignes Rares Gynécologiques (French rare gynaecological tumour group)
Tregs	Regulatory T cells
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
W	Week(s)

UNICANCER, the trial sponsor, certifies that the trial UC-0105/1612 will be conducted in compliance with the protocol described in this document, and in accordance with the French national regulatory requirements:

- Loi Huriet (n°88-1138) du 20 décembre 1988 relative à la Protection des Personnes se prêtant à la Recherche Biomédicale et modifiée par la loi d'orientation de Santé Publique (n° 2004-806) du 9 août 2004,
- Loi Informatique et Libertés n°78-17 du 6 janvier 1978 modifiée,
- Loi de Bioéthique n°2011-814 du 08 Juillet 2011,
- Décision portant sur les Bonnes Pratiques Cliniques du 24 novembre 2006,
- Bonnes Pratiques de Fabrication en vigueur, notamment la ligne directrice particulière relative aux médicaments expérimentaux.

INTRODUCTION AND RATIONALE OF THE TRIAL

1.1 Justification of the Trial

1.1.1 Adaptive Immune Resistance

Human cancers contain a number of genetic and epigenetic changes, which can result in the expression of neoantigens capable of eliciting an immune response (Sjöblom, 2006). In such cases, the body's immune system recognizes the cancer cells as abnormal and generates a population of cytotoxic T lymphocytes (CTLs) able to traffic to and infiltrate the site of cancer, and specifically bind to and kill the cancer cells. Effective protective immunity against cancer depends on the coordination of CTLs (Mosmann, 1996). Under normal physiological conditions, there are a number of immune checkpoint mechanisms which minimize the damage to surrounding normal tissue and prevent autoimmune reactions.

There is increasing evidence that the development and progression of a tumour is often accompanied by the formation of a tumour immune microenvironment. Numerous cancers have been shown to develop "adaptive immune resistance" via the up-regulation of cell surface molecules which act as immune checkpoint inhibitors, thus inhibiting T-cell action and promoting growth and metastatic progression (Zou, 2005).

1.1.2 Programmed Death-1

Programmed death-1 (PD-1) is a member of the extended CD28/CTLA-4 immunoglobulin family and one of the most important inhibitory co-receptors expressed by T-Cells. Programmed death-1 is expressed on activated lymphocytes including peripheral cluster of differentiation (CD)4+ and CD8+ cells, T cells, B cells, natural killer cells, and regulatory T cells (Tregs) (Keir, 2008; Fransisco, 2009, Yao, 2014). The normal function of PD-1 is to down-modulate unwanted or excessive immune responses, including autoimmune reactions via interaction with one of two ligands, programmed death-ligand 1 (PD-L1), and PD-L2, which are both co-inhibitory. PD-L1 is expressed on resting T cells, B cells, dendritic cells, macrophage, vascular endothelial cells and pancreatic islet cells. PD-L2 expression is seen on macrophages and dendritic cells. PD-L2 is thought to control immune T cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T cell function in peripheral tissues.

Although healthy tissue expresses little (if any) PD-L1, high levels of expression have been demonstrated in a variety of cancer types including non-small cell lung cancer (NSCLC), melanoma, renal cell carcinoma, gastric cancer, hepatocellular cancer, cutaneous cancers, various leukaemia's and multiple myeloma (Velcheti, 2013; Boland, 2013, Spranger, 2013; Thompson, 2005; Bernstein, 2014). Studies relating PD-L1 expression on tumours to disease outcome show that PD-L1 expression strongly correlates with unfavourable prognosis in kidney, bladder, gastric and pancreatic cancer (Inman, 2007; Konishi, 2004; Nomi, 2007).

Zhang *et al* (Zhang, 2010) showed that PD-1 is expressed at much higher levels on CD8+ tumour infiltrating lymphocytes (TILs) in patients with NSCLC, compared with CD8+ T cells collected from peripheral blood samples from NSCLC patients, or health subjects. The CD8+ TILs expressed a significant reduction in cytokine (IFN-γ and IL-2) production and showed a lower rate of proliferation in response to stimulation by anti-CD3 and anti-CD28 antibodies. Furthermore, they demonstrated that incubation with an anti PD-L1 antibody was able restore cytokine secretion and T-cell proliferation in CD8+ TILs from NSCLC patients (Zhang, 2010)

This upregulated expression of PD-L1, via its interaction with the PD-1 receptor on tumour specific T-cells, plays a critical role in tumour immune escape and the formation of the tumour immune microenvironment (Karim, 2009; Taube, 2012). As a consequence the PD-1/PD-L1 pathway is an attractive target for therapeutic intervention in cancer (Topalian; 2012)

1.1.3 Pembrolizumab

Pembrolizumab (Keytruda®, MK-3475) is a potent humanized immunoglobulin (Ig) G4 monoclonal antibody (mAb) with high specificity of binding to the PD-1 receptor, thus inhibiting its interaction with its ligands PD-L1 and 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 being developed clinically as an intravenous (IV) immunotherapy for advanced malignancies.

Refer to the Investigator's Brochure (IB) for full pre-clinical and clinical data.

1.1.3.1 Efficacy Data

An initial first-in-man, Phase I study was conducted to test the safety and efficacy single agent pembrolizumab in patients with progressive, locally advanced or metastatic carcinoma, melanoma or non-small cell lung carcinoma (NSCLC) at doses of 1 mg/kg, 3 mg/kg, and 10 mg/kg in 2-3 week cycles. Through a series of amendments, this study evolved into 4 Phase II-like melanoma substudies, known as Parts B1, B2, B3, and D. The 4 parts include ipilimumab-refractory and ipilimumab-naïve melanoma, as well as 3 different pembrolizumab dose regimens (2 mg/kg every 3 weeks [Q3W], 10 mg/kg Q3W, and 10 mg/kg Q2W). The primary efficacy endpoint was overall response rate (ORR). A secondary efficacy endpoint was disease control rate (DCR). The ORR and DCR was analysed for 655 melanoma patients who received pembrolizumab, regardless of prior exposure to ipilimumab and across all dose levels tested. Overall there were 44 complete responses and 159 partial responses. The ORR was 31% (95% confidence interval [CI]: 28% to 35%). Disease control was achieved in 51% of all patients.

A second, Phase II, partially blinded, randomized study in ipilumamab-refractory advanced melanoma patients tested treatment with pembrolizumab 2 mg/kg Q3W and 10 mg/kg Q3W versus investigator-choice (standard-of-care) chemotherapy in a 1:1:1 ratio. Progression-free survival (PFS) was superior for the 361 patients who received pembrolizumab compared with the 179 patients who received chemotherapy (control arm) The hazard ratio (HR) was 0.57 and 0.50 in favour of the the pembrolizumab 2 mg/kg Q3W arm and 10 mg/kg Q3W arm respectively ($p < 0.0001$ in both comparisons). This met prespecified criteria for a positive study. The PFS rate at 6 months was 34.3% (95% CI: 27.4 to 41.3%) and 37.7% (95% CI: 30.6% to 44.8%) for pembrolizumab 2 mg/kg and 10 mg/kg, respectively, versus 15.6% (95% CI: 10.5% to 21.5%) for the control arm. The median PFS was 2.9 months in both pembrolizumab arms and 2.7 months in the control arm. The ORR was 21% in the pembrolizumab 2 mg/kg arm, 25% in the 10 mg/kg arm, and 4% in the chemotherapy arm ($p<0.0001$ for each pembrolizumab dose versus chemotherapy). A preliminary analysis of overall survival (OS) indicated that the hazard ratio (HR) was 0.88 in favour of the pembrolizumab 2 mg/kg Q3W arm and 0.78 in the favour of the pembrolizumab 10 mg/kg Q3W arm versus the control arm. The one-sided p-value was 0.229 and 0.066 in 2 mg/kg Q3W and 10 mg/kg Q3W respectively.

1.1.3.2 Clinical Safety Data

Safety data are available for a total of 2461 melanoma or NSCLC patients treated with pembrolizumab in 8 Merck-sponsored clinical trials. In the pembrolizumab monotherapy trials, the overall incidence of adverse events (AE) ranged from 83.0% (73 of 88 patients) to 100% (10 of 10 patients). The most commonly reported AEs included fatigue, diarrhoea, decreased appetite, nausea, dyspnoea, and anaemia. The incidence of treatment-related AEs in the pembrolizumab monotherapy trials ranged from 39.8% (35 of 88 patients) to 80.0% (8 of 10 patients). The most commonly reported treatment-related AEs across all monotherapy studies were nausea, fatigue, and diarrhoea. The incidence of Grade 3-5 treatment-related AEs across monotherapy studies ranged from 6.8% (6 of 88 patients) to 12.0% (187 of 1562 patients). The most commonly reported Grade 3-5 treatment-related AEs were anaemia, increased alanine aminotransferase (ALAT), increased aspartate aminotransferase (ASAT), and colitis. Most patients who experienced an AE continued in the study, with the incidence of AEs leading to discontinuation ranging from 4.2% (18 of 430 patients) to 12.3% (192 of 1562 patients). The majority of AEs leading to discontinuation were not considered drug related. Discontinuations due to a treatment-related AE were infrequent and ranged from 0% to 4.5% (4 of 88 patients). The most commonly reported treatment-related AE leading to discontinuation was pneumonitis.

Immune-Mediated Adverse Reactions

Immune-mediated adverse reactions are presented based on 2117 with melanoma and NSCLC. The safety profile was generally similar for subjects with melanoma and NSCLC. Table 1 presents the incidence of immune-mediated adverse reactions by Grade that occurred in subjects receiving pembrolizumab

Table 1. Immune-Mediated Adverse Reactions

	Pembrolizumab 2 mg/kg Q 3 W or 10 mg/kg Q 2 or Q 3 W n=2117				
Adverse reaction	**All Grades (%)**	**Grade 2 (%)**	**Grade 3 (%)**	**Grade 4 (%)**	**Grade 5 (%)**
Hypothyroidism	7.8	5.9	0.1	0	0
Hyperthyroidism	2.9	0.6	0.1	0	0
Pneumonitis	2.4	0.9	0.6	0.1	< 0.1
Colitis	1.7	0.4	1.7	0.1	0
Hepatitis	0.8	0.1	0.5	0.1	0
Hypophysitis	0.7	0.2	0.3	< 0.1	0
Nephritis	0.3	0.1	0.1	< 0.1	0
Diabetes mellitus	0.1	< 0.1	< 0.1	< 0.1	0

Endocrinopathies

The median time to onset of hypophysitis was 3.5 months (range 1 day to 7.2 months). The median duration was 2.0 months (range 0.4 months to 12.7 months). Hypophysitis led to discontinuation of pembrolizumab in 4 (0.2%) patients. Hypophysitis resolved in 7 patients.

The median time to onset of hyperthyroidism was 1.4 months (range 1 day to 21.9 months). The median duration was 1.8 months (range 1 day to 12.8 months). Hyperthyroidism led to discontinuation of pembrolizumab in 2 (0.1%) patients. Hyperthyroidism resolved in 42 subjects.

The median time to onset of hypothyroidism was 3.5 months (range 0.7 weeks to 18.9 months). The median duration was 5.5 months (range 0.9 weeks to 24.3 months). No patients discontinued pembrolizumab due to hypothyroidism.

Pneumonitis

The median time to onset of pneumonitis was 3.1 months (range 2 days to 19.3 months). The median duration was 1.6 months (range 0.3 weeks to 15.1 months). Pneumonitis led to discontinuation of pembrolizumab in 21 (1.0%) patients. Pneumonitis resolved in 32 patients.

Colitis

The median time to onset of colitis was 3.0 months (range 1.3 weeks to 9.7 months). The median duration was 1.2 months (range 1 day to 7.2 months). Colitis led to discontinuation of pembrolizumab in 15 (0.7%) patients. Colitis resolved in 31 patients.

Hepatitis

The median time to onset of hepatitis was 0.8 months (range 1.1 weeks to 21.4 months). The median duration was 1.2 months (range 1.1 weeks to 4.7 months). Hepatitis led to discontinuation of pembrolizumab in 6 (0.3%) patients. Hepatitis resolved in 14 patients.

Nephritis

The median time to onset of nephritis was 5.1 months (range 1.7 weeks to 12.8 months). The median duration was 1.1 months (range 0.4 months to 3.3 months). Nephritis led to discontinuation of pembrolizumab in 2 (0.1%) patients. Nephritis resolved in 4 patients.

1.1.3.3 Pharmacokinetic and Pharmacodynamic Data

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

A population PK analysis has been performed using serum concentration time data from 476 patients. Within the resulting population PK model, clearance and volume parameters of pembrolizumab were found to be dependent on body weight. The relationship between clearance and body weight, with an

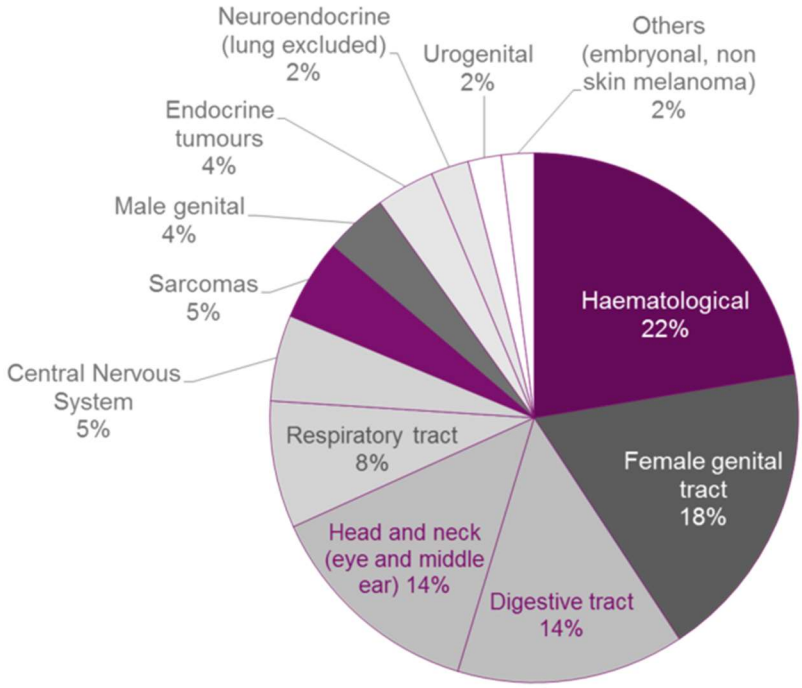
allometric exponent of 0.59, is within the range observed for other antibodies and would support both body weight normalized dosing or a fixed dose across all body weights. Pembrolizumab has been found to have a wide therapeutic range based on the melanoma indication. The differences in exposure for a 200 mg fixed dose regimen relative to a 2 mg/kg Q3W body weight based regimen are anticipated to remain well within the established exposure margins of 0.5 – 5.0 for pembrolizumab in the melanoma indication. The exposure margins are based on the notion of similar efficacy and safety in melanoma at 10 mg/kg Q3W vs. the proposed dose regimen of 2 mg/kg Q3W (i.e. 5-fold higher dose and exposure). The population PK evaluation revealed that there was no significant impact of tumour burden on exposure. In addition, exposure was similar between the NSCLC and melanoma indications. Therefore, there are no anticipated changes in exposure between different indication settings.

1.1.4 Epidemiology of the Pathology

Rare cancers are generally classified in the group of rare diseases, which is defined in the European Union as diseases with a prevalence of fewer than 5 cases out of a population of 10,000. Given that prevalence – the number of patients with the same diagnosis at a given time – is affected by mortality however, the Surveillance of Rare Cancers in Europe (RARECARE) project proposes to define rare cancers based on incidence, i.e. the number of newly-diagnosed cases per year. Using this definition minimizes the risk of mistaking a rare cancer (such as testicular cancer), which is frequently cured and thus has a rather high prevalence, for a common cancer, or a frequent cancer (such as small-cell lung cancer), which has a short life expectancy and thus a low prevalence, for a rare cancer. According to the RARECARE definition, rare cancers are identified as those with an incidence of less than 6 per 100,000 persons per year.

Based on the RARECARE definition, the estimated annual incidence rate of all rare cancers in Europe was estimated at 108 per 100,000, corresponding to 541,000 new diagnoses annually or 22% of all cancer diagnoses (Gatta, 2011). About 4,300,000 patients are living today in the European Union with a diagnosis of a rare cancer, 24% of the total cancer prevalence. Thus rare cancers as a group represent a sizable public health burden. A break-down of the types of rare cancer observed (incidence rate as a percentage of all rare-cancers) is illustrated in Figure 1.

Figure 1. Incidence of Rare Cancer Types in Europe



In France, according to a review conducted by the French National Cancer Institute (Institute National du Cancer, INCa), in 2013 over 12,800 patients with a rare cancer benefited from expert care. The INCa data is based on information obtained from the registries of various national networks. Not all rare cancer patients are reported in these networks however, thus the incidence rate remains an estimate. The

number of new patients who received care in 2013 and estimated incidence rates are summarised by type of cancer in Table 2.

Table 2. Rare Cancer Patients Who Received Care in France in 2013

Type of rare cancer	N new patients in 2013	Estimated incidence
Soft tissue and visceral sarcomas – Clinical	3526	4000
Rare sporadic and hereditary malignant neuroendocrine tumours – Clinical	1592	1200
Rare ovarian cancers	951	500
Cutaneous lymphomas	919	700
Osteosarcomas	512	630
Rare ear, nose and throat cancers	486	900
Uveal melanomas	380	600
Primary ocular and brain lymphomas	287	350
Adrenal cancers	284	125
Malignant pleural mesotheliomas	267	900
Refractory thyroid cancer	255	400
High-grade oligodendrogliomas	285	600
Rare brain tumours	202	1800
Rare skin cancers (other than cutaneous sarcomas)	131	950
Von Hippel-Lindau disease and other hereditary predispositions to renal cancer	120	200
Gestational trophoblastic tumours	118	180
Thymomas and thymic carcinomas	113	250
Gestational cancers	99	500
Rare peritoneal tumours	74	150
Lymphomas associated with coeliac disease	52	350
Rare renal cancers	31	1000
Virally induced cancers in transplant recipianients	31	110
Cancers in HIV+subjects	0	700

1.1.5 Prognosis

According to the RARECARE study, 5-year relative survival was on average worse for rare cancers (47%) than common cancers (65%) (Gatta, 2011).

1.2 International Non-Proprietary Name and Description of Investigational Products

This trial protocol intends to evaluate the efficacy and safety of pembrolizumab (MK-3475).

Pembrolizumab is a potent humanized IgG4 mAb with high specificity of binding to the PD-1 receptor, thus inhibiting its interaction with its ligands PD-L1 and PD-L2.

Pembrolizumab is approved for use by the European Medicines Agency for treatment of the following indications:

- Advanced (unresectable or metastatic) melanoma in adults.
- Locally advanced or metastatic NSCLC in adults whose tumours express PD-L1 and who have received at least one prior chemotherapy regimen. Patients with EGFR or ALK positive tumour mutations should also have received approved therapy for these mutations prior to receiving pembrolizumab.

In the United States of America pembrolizumab has received accelerated approval from the Food and Drug Administration (FDA) for use the following indications:

- Patients with unresectable or metastatic melanoma.

- Patients with metastatic NSCLC whose tumours have high PD-L1 expression [(Tumour Proportion Score (TPS) ≥50%)] as determined by an FDA-approved test, with no EGFR or ALK genomic tumour aberrations, and no prior systemic chemotherapy treatment for metastatic NSCLC.
- Patients with metastatic NSCLC whose tumours express PD-L1 (TPS ≥1%) as determined by an FDA-approved test, with disease progression on or after platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumour aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving pembrolizumab.
- Patients with recurrent or metastatic Head and Neck squamous cell carcinoma (HNSCC) with disease progression on or after platinum-containing chemotherapy.

Posology

The recommended dose of pembrolizumab is 200 mg administered intravenously over 30 minutes every 3 weeks. Treatment should be continued as long as clinical benefit is observed or until treatment is no longer tolerated by the patient.

Dose escalation or reduction is not recommended. Dosing delay or discontinuation may be required based on individual safety and tolerability.

1.3 Trial Rationale

In the last 10 years the treatment and prognosis of certain cancers has been revolutionised by the introduction of therapies which target a molecular abnormality found within a specific a tumour type. Developments in our understanding of tumour biology have allowed identification of pertinent targets and the molecules capable of interacting with these targets. The number of such targeted therapies is constantly increasing. In 2013, over 800 targeted therapies were in early clinical development with at least 15 that had obtained marketing authorization for use in specific cancer pathologies.

The targets of these therapies, initially developed for one pathology, are also present in other pathologies for which therapeutic development has not been pursued and/or marketing authorization not requested. The “Accès Sécurisé” (secured access, AcSé) program launched by INCa aims to offer patients likely to benefit a controlled access to targeted therapies outside of the context of the marketing authorization obtained or envisaged by the pharmaceutical laboratories.

Pembrolizumab is approved for use in the European Union in the treatment of advanced melanoma, it’s mode of action as an inhibitor of the PD-1/PD-L1 interaction makes it an attractive prospect for other cancer indications where an overexpression of PD-L1 has been documented and no therapeutic alternatives exist.

The aim of this study is to provide a secured access to pembrolizumab therapy for rare cancer indications where the literature suggests a potential benefit for patients, but the difficulties of development render individual experimental studies unattractive to the pharmaceutical industry.

Patients with one of 7 rare cancer types have been selected for inclusion in this study: rare sarcoma, rare ovarian cancer, primary central nervous system lymphomas (PCNSL), rare thyroid cancer, rare malignant neuroendocrine cancer, germ-cell cancer, or Natural killer (NK)/T-cell lymphoma.

Due to their low incidence and extreme diversity, there is very limited data available concerning the immune characteristics of these cancers. Nevertheless, information is available for some of them which suggest a potential of tumours within the selected categories to response to pembrolizumab therapy.

Soft Tissue Sarcomas

Expression of PD-L1 has been reported in 58% of soft-tissue sarcomas. The infiltration of PD1-positive lymphocytes and the expression of PD-L1 in sarcomas correlate with reduced overall survival and event-free survival according to univariate analysis. Interestingly, high PD-L1 expression in gastrointestinal stromal tumour (GIST) seems to be an independent favourable prognostic factor for metastatic relapse (Bertucci, 2015).

Osteosarcomas

Data show that the loss of Class I human leukocyte antigen (HLA) expression in osteosarcoma tumours is related to worse overall survival (Tsukahara, 2006). Cytotoxic T lymphocytes have been reported to

be critical effectors of tumour cell killing in osteosarcoma animal models, and intense CTL infiltration correlates with good prognosis in sarcomas (Fritzsching, 2015; Fujii, 2014).

Interestingly, osteosarcoma is notable among paediatric cancers for having a high mutational burden, with median nonsynonymous mutations per genome in the range of 22 to 37 (Chen, 2014). Single nucleotide polymorphism analysis reveals more severe loss of heterozygocity in osteosarcoma than in myxoid liposarcoma or synovial sarcoma (Joseph, 2014). In addition, osteosarcoma has one of the highest rates of structural variation of any paediatric cancer sequenced to date, with 50% to 85% of tumours exhibiting the hypermutation phenomenon termed kataegis. Similar genomic complexity is present in adult sarcomas such as undifferentiated pleomorphic sarcoma and leiomyosarcoma (Silveira, 2013).

Expression of PD-L1 in osteosarcoma has been evaluated using a ribonucleic acid (RNA)-based assay: 74% of tested patients (28/38) presented high or intermediated expression compared to 26% (10/38 with low or now PD-L1 expression (Shen, 2014). Patients with high PD-L1 expression have a trend toward lower median OS (28 months) compared to 89 months for PD-L1 low patients (p= 0,054). PD-L1 expression has been shown to be correlated with tumour lymphocytes infiltration. Finally, blockade of PD-1/PD-L1 interactions dramatically improves the function of osteosarcoma-reactive CTLs in vitro and in vivo, and results in decreased tumour burden and increased survival in the K7M2 mouse model of metastatic osteosarcoma (Lussier, 2015).

Ovarian Cancers

Approximately half of ovarian cancer patients display a spontaneous antitumour immune response by antibodies (Stone, 2003, Reuschenbach, 2009) and oligoclonal T-cells (Schlienger, 2003) which recognize autologous tumor-associated antigens (TAAs). Ovarian cancerexhibits an extreme degree of heterogeneity of TAAs, with an average of 60 private nonsynonymous mutations per tumour. These mutations are rarely shared among different tumours. Within the tumour, a spontaneous antitumor immune response has been demonstrated in approximately 55% of the patients with ovarian cancer in the form of intraepithelial TILs (Zhang, 2003) which has been repeatedly associated with a prolonged survival among ovarian cancer patients (Hwang, 2012).

Though data remains scarce, high immunohistochemical PD-L1 expression (score 2 & 3) has been detected in 68% of ovarian cancer patients (n=70) and that expression of PD-L1 had a strong prognostic value (Hamanashi, 2007). The authors found also that the density of intraepithelial CD8+ T cells was inversely correlated to tumour expression of PD-L1, suggesting that the expression of PD-L1 on tumour cells may inhibit invasion of tumour epithelium by CD8+ T cells. In addition, PD-1 expression at the surface of intra-tumoural CD4+ FOXP3+ Tregs was found to show the highest levels in ovarian cancer (around 20% of the cells) compared to other tumour types, including melanoma, renal cell cancer or hepatoma (Kryczek, 2009). Together with the aforementioned data on immune infiltration, these data provide the rationale for a therapeutic PD-1/PD-L1 pathway blockade in ovarian cancer. In ovarian carcinoma patients, the anti-PD1 compound nivolumab has been reported to achieve 3 objective responses out of 13 (23%) in heavily pre-treated patients (Hamanishi, 2014). Response was maintained over 1 year in 2 out of the 3 responders (Hamanishi, 2015). Similarly, treatment with pembrozilumab achieved 3 confirmed responses (11.5% [(95% CI, 2.4-30.2]) in 26 patients treated in a phase Ib study and 3 additional patients had a tumour reduction of at least 30%. Most common AEs were fatigue (42.3%), anemia (30.8%), and decreased appetite (30.8%). Drug-related AEs occurred in 69.2% of pts (grade ≥ 3, 1/26 pts) (Varga, 2015).

It has been documented that CD8 cells are the dominant lymphocytic cell type in cervical carcinoma and that CD8 cells may have a role in viral clearance in regressing cervical intra-epithelial neoplasia (Monnier-Benoit, 2006; Trimble, 2010). Infection by human papillomavirus in the cervix is indeed strongly associated with PD-L1/PD-1 expression in both the dysplastic/neoplastic squamous cells, which suggest that the CD8 activity may be reduced due to the high expression of PD-L1 (Mezache, 2015; Yang, 2013).

Primary Central Nervous System Lymphomas

The majority of PCNSLs express PD-1/PD-L1 (Berghoff, 2014) and present frequent PD-L1 and PD-L2 copy number alterations and additional translocations of these loci (Chapuy, 2016). In a phase Ib study of the anti-PD-1 mAb nivolumab in patients with relapsed or refractory hematologic malignancies, 4/11 patients (36%) with diffuse large B-cell lymphomas (LBCL) reported an objective response (Lesokhin, 2016). Over 90% of PCNSLs are in fact diffuse LBCLs making this indication a good candidate for treatment with pembrolizumab.

Thyroid Cancers

Patients with advanced radioiodine refractory thyroid cancer have benefited during the last decade from treatment with kinase inhibitors (KI). Following positive phase III trials on PFS, two KIs (sorafenib and lenvatinib) have been labeled for advanced differentiated thyroid cancer (DTC) that is refractory to radioiodine and with documented tumor progression.

Despite the relative rarity of the disease (4-5 advanced radio-iodine refractory DTC cases/million), the 2 phase III trials were conducted in 392 and 417 patients, respectively.

Kinase inhibitors are effective in a fraction of these patients. Mostly partial responses were achieved and all patients who initially responded, later developed resistance. Furthermore, it has been suggested that two lines of anti-angiogenic KIs should be considered, as no cross-resistance has been demonstrated, but there is little rationale to use several more lines of anti-angiogenic drugs.

The scientific rationale for the use of immunotherapy remains limited at present in these patients, and includes:

- The presence of an inflammatory infiltrate in a large percentage of tumours
- The thyroid gland is frequently involved in auto-immune reactions either in the frame of an auto-immune disease or during treatment with antibodies directed against immune checkpoints
- The presence of a driver mutation in many DTCs. The number of mutations per tumor is rather low in classical thyroid cancers but may be higher in radioiodine refractory thyroid cancers. Different driver mutations may lead to immunogenicity.
- Radioiodine resistance may induce neoantigens which may lead to a T-cell response.
- Preclinical, clinical and epidemiological studies have demonstrated a clear relationship between dedifferentiation and tumor progression, autophagy and inflammation.
- A retrospective immunohistochemical analysis of tumour samples from patients with papillary thyroid carcinoma showed that PD-L1 overexpression is a prognostic marker for aggressive papillary thyroid cancer and its variants (Chowdhury, 2016)
- In a recent phase Ib study 22 patients with advanced DTC (15 papillary vs 7 follicular carcinoma) where treated with pembrolizumab. Two patients (9%) achieved a PR in response to treatment. The stable disease rate was 54.5% (n = 12, 95% CI, 32.2-75.6). The 6-month OS rate was 100%; and the 6-month PFS rate was 58.7% (Mehnert, 2016).

Obviously, there is a need for preliminary or translational studies, to better define the inflammatory infiltrate, expression of PD1 and PDL1 in tumor and stromal cells, and to understand the relationships with the mutational status (it has been shown *in vitro* that the presence of BRAF mutation increases the expression of PDL1). These studies can be performed on samples from the primary tumor and from metastases.

Malignant Neuroendocrine Cancer

Past studies have demonstrated relevant clinical activity for interferon and subcutaneous interleukin-2 in neuroendocrine tumours (Lissoni, 1995). The expression of multiple cancer-testis antigens provides additional rationale. Promising results observed with pembrolizumab in small-cell lung cancer, the most aggressive type of neuroendocrine tumours, may suggest that rare neuroendocrine tumours may show a similar activity profile (Ott, 2015).

Germ-Cell Cancer

PD-L1 is highly expressed in both seminomas and non-seminomas and is associated with poor prognosis in testicular germ cell tumours (Frankhauser, 2015; Cierna, 2015)

Natural Killer/T-cell Lymphomas

Extranodal NK/T-cell lymphoma is a rare type of non-Hodgkin lymphoma that develops from NK cells or T lymphocytes (T-cells). Natural killer/T-cell lymphomas develop almost exclusively in non-nodal sites. About 80% of cases, collectively referred to as nasal NK/T-cell lymphomas, occur in the nose, nasopharynx, oropharynx, the Waldeyer's ring, and parts of the upper aerodigestive tract (Tse, 2013).

Natural killer/T-cell lymphomas occur worldwide, with a strong geographic predilection for Asian populations from China, Japan, Korea, and Southeast Asia (Kwong, 2005) and for Central and South American populations from Mexico, Peru, Argentina, and Brazil, constituting 5% to 15% of lymphomas in these countries (Tse, 2013). It is rare in people from other parts of the world, including France, but occasional case series have also been reported from Europe (Jaccard, 2011) and North America (Li, 2013). It usually occurs in adults, at an average age of around 50. It affects more men than women.

Extranodal NK/T-cell lymphoma, nasal type, is a rare and highly aggressive disease with a grim prognosis.

Localized NK/T-cell lymphomas often respond to radiotherapy (Li, 2006; Isobe, 2006) or to concurrent radiation and chemotherapy (Kim, 2009), but relapse is common. Chemotherapy protocols used for lymphomas of other histologic subtypes are poorly effective, at least in part, because of frequent multidrug resistance (MDR) gene expression by tumour cells (Yamaguchi, 1995).

Treatment regimens containing L-asparaginase (a drug with an original anti-tumour mechanism not affected by MDR), particularly SMILE (dexamethasone, methotrexate, ifosfamide, L-asparaginase, and etoposide), have significantly improved the outlook of NK/T-cell lymphomas (Yammaguchi, 2011; Kwong, 2012) and are now the most commonly employed initial therapy (Tse, 2013; Tse, 2016). However, SMILE or SMILE-like regimens still fail in 20% to 40% of cases (Yammaguchi, 2011; Kwong, 2012; Tse, 2013). There is no known effective salvage, and outcome is virtually always fatal.

NK/T-cell lymphomas are invariably infected by Epstein-Barr virus (EBV), which exists in a latency II state, expressing immunogenic antigens EBNA1, LMP1, and LMP2 (Tse, 2015). Furthermore, an upregulation of PD-L1 protein expression has been demonstrated in tumour cells from two nasal-type NK/T cell lymphoma cell lines (SNK-6 and YTS) and in biopsy tissue samples (Chen, 2013; Han, 2014; Jo, 2017). This upregulation of PD-L1 was correlated with a reduction of PD-1 expressing TILs in tissue samples and a reduction in the level of TH1 cytokines (IL-2 and IFN-γ) in serum. Co-culturing CD8+ T-cells for 72 hours with SNK-6 cells led to a significant inhibition of cytokine secretion by the CD8+ cells, which was reversed by the introduction of an antiPD-1 antibody. The PDL1/PD1 axis is therefore a potential mechanism for NK/T-cell lymphomas to avert effector T-cell targeting. Indeed several recently published case studys report impressive responses of NK/T-cell lymphoma to antiPD-1 treatment.

Lai and co-workers (Lai, 2017) reported on the treatment of a patient with relapsed NK/T-cell lymphoma which was refractory to multiple lines of treatment and complicated by extensive ulceration of the skin on the lower members. The patient received pembrolizuman 2 mg/kg Q2W for 11 cycles after which the ulceration was almost healed and EBV DNA was undetectable (PET-CT assessment was not performed). Similarly, in a recent study of 7 patients treated with pembrolizumab after failure of L-asparaginase, all seven responded to treatment, including five complete responses, two of which had metabolic complete response (undetectable levels of EBV DNA)(Kwong, 2017).

1.3.1 Biological Sampling

Beyond tumor mutational landscape and the “antigenome”, several biomarkers are currently being developed for predicting response to anti-PD-1/PD-L1 therapies. Among them, the most promising and best validated one is probably PD-L1 expression assessment by immunohistochemistry staining on tumor and/or tumor-infiltrating immune cells. In this study, tumour samples will be collected from all patients prior to the start of treatment in order to measure the immunohistochemical expression of PD-L1 and other immune markers and investigate the correlation between expression and response to pembrolizumab therapy.

In order to better understand the molecular profile of patients who respond to pembrolizumab therapy, blood samples will also be collected prior to treatment and at various times during the study for retrospective dosage of auto-antibodies and anti-tumour antibodies in serum, dosage of circulating cytokines, chemokines and receptor/ligand complexes in plasma, and analysis of circulating tumour DNA (ctDNA), RNA and peripheral blood mononuclear cells (PBMC).

1.4 Patient Benefits(s) and Foreseeable Risk(s)

This study plans to enrol patients with specific rare cancers which have been selected based on reports in the literature of increased levels of PD-L1 expression in these cancer types, and/or potential for favourable responses to anti-PD1 antibodies. Potential patients are to have unresectable locally advanced or metastatic disease, which is resistant or refractory to standard therapy, or for which

standard therapy does not exist, or is not considered appropriate, and for which no other experimental treatment options are available. The benefit of participation therefore is access to a potentially efficacious experimental therapy where no other treatment options exist.

Foreseeable risks of pembrolizumab therapy include a lack of response to treatment, and potential side effects as outlines in Section 1.1.3.2 and the pembrolizumab IB.

1.5 Justification for the Therapeutic Regimens and Treatment Durations

Pembrolizumab has been approved for commercialization in a number of different indications. The recommended dose of nivolumab in Europe is 2 mg/kg administered intravenously over 30 minutes every 3 weeks (Q3W).

In the United States of America, the FDA recommends two posologies: 2 mg/kg Q3W for melanoma patients and a fixed dose of 200 mg IV Q3W for the approved indications of NSCLC and HNSCC.

The dose of pembrolizumab 2 mg/kg was selected for further exploration in experimental trials in solid tumours based on: i) similar efficacy and safety of pembrolizumab when dosed at either 2 mg/kg or 10 mg/kg Q3W in melanoma patients, ii) the flat exposure-response relationships of pembrolizumab for both efficacy and safety in the dose ranges of 2 mg/kg Q3W to 10 mg/kg Q3W, iii) the lack of effect of tumour burden or indication on distribution behaviour of pembrolizumab (as assessed by the population PK model) and iv) the assumption that the dynamics of pembrolizumab target engagement will not vary meaningfully with tumour type.

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

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

A model-based PK bridging analysis, which included available paediatric PK data from the pembrolizumab paediatric study KN051, was conducted to determine the paediatric dose based on the approach of exposure matching with adults. This analysis showed that a dose of 2 mg/kg (up to 200 mg) Q3W in paediatric participants provided PK exposures similar to those achieved at 2 mg/kg (or 200 mg) Q3W in adults, and served as the basis for approval of a paediatric indication in cHL as well as MSI-H cancers in the US at a dose of 2 mg/kg (up to 200 mg) Q3W. In addition, the safety of this dose in paediatric participants is established based on data from KN051 (see IB). The incidence of positive immunogenicity status after pembrolizumab treatment in paediatric participants (2.8%) was comparable with that in adults (2.1%, see IB Section. 5.2.5) and had no impact on pembrolizumab exposure. Accordingly, the dose of 2 mg/kg (up to 200 mg) Q3W is proposed for use in paediatric subjects.

The regimen for adults included in this study therefore is pembrolizumab 200 mg IV administered every 21 days. The regimen for patients under 18 years old is 2mg/kg (maximum dose 200 mg) IV of pembrolizumab administered every 21 days.

1.6 Trial Population

The trial population is composed of men and women who have developed unresectable locally advanced or metastatic, rare sarcoma, rare ovarian cancer, PCNSL, rare thyroid cancer, rare malignant neuroendocrine cancer,germ-cell cancer, or NK/T-cell lymphoma, which is resistant or refractory to standard therapy, or for which standard therapy does not exist, or is not considered appropriate, and for which no other experimental treatment options are available.

2 TRIAL OBJECTIVES

2.1 Primary Objective

The primary objective of the trial is to evaluate the response to pembrolizumab monotherapy in cohorts of patients with unresectable locally advanced or metastatic, rare sarcoma, rare ovarian cancer, PCNSL, rare thyroid cancer, rare malignant neuroendocrine cancer, germ-cell cancer, or NK/T-cell lymphoma which is resistant or refractory to standard therapy, and for which no other treatment options are available.

2.2 Secondary Objective(s)

- To identify populations, for which the IP is expected to have a clinical benefit.
- To assess the efficacy of pembrolizumab monotherapy in each cohort in terms of survival, progression occurrence and quality of response.
- To assess the safety profile of pembrolizumab monotherapy.

2.3 Ancillary Research Objectives

To identify the discriminant molecular mechanisms in patients with tumour response versus patients without tumour response within the same cohort.

To identify the discriminant molecular mechanisms in patients with tumour response versus patients without tumour response within the same cohort.

3 TRIAL DESIGN

3.1 Evaluation Criteria

3.1.1 Primary Endpoint

Objective response rate per cohort, defined as the percentage of patients in each cohort with a complete response (CR) or partial response (PR) measured at the first scheduled disease assessment following study treatment initiation (Day 84, ± 7 days) as assessed by an Independent Review Committee (IRC) according to (i) the Response Evaluation Criteria in Solid Tumours version 1.1. (RECIST v1.1; Eisenhauer, 2009; Appendix 1) for patients with solid tumours, (ii) RECIST v1.1 combined with biomarker assessment (Fizazi, 2014; Appendix 2) for patients with germ-cell cancer, (iii) the International PCNSL cooperative group (IPCG) response criteria (Abrey, 2005; Appendix 3), (iv) the 'Lugano' criteria for response assessment using the fluorodeoxyglucose-positron emission tomography-computed tomography (FDG-PET-CT) five-point scale (5-PS; Barrington, 2014; Cheson, 2014; Appendix 4) and assessment of *Epstein-Barr* virus (EBV) load.

Patients who withdraw from the study prior to this time point and patients with non-evaluable disease will be considered as 'non-responders'in the analysis.

3.1.2 Secondary Endpoint(s)

- Progression-free survival, defined as the time from inclusion until documented disease progression (PD) according to RECIST v1.1, or RECIST v1.1 combined with biomarker assessment, or IPCG response criteria, or Lugano 5-PS criteria, or death, whichever occurs first.
- Overall survival, defined as the time from inclusion until death due to any cause.
- Best response to treatment according to RECIST v1.1, or RECIST v1.1 combined with biomarker assessment or IPCG response criteria, or Lugano 5-PS criteria, measured at any disease assessment during the course of the study.
- Response duration, defined as the time from first observation of objective response (i.e. PR or CR) according to RECIST v.1.1, or RECIST v1.1 combined with biomarker assessment, or IPCG response criteria, or Lugano 5-PS criteria, until PD or death, whichever occurs first.
- Time to response, defined as the time from inclusion until observation of objective response (i.e. PR or CR) according to RECIST v1.1, or RECIST v1.1 combined with biomarker assessment, or IPCG response criteria or Lugano 5-PS criteria, during the course of the study.
- Frequency and severity of adverse events assessed according to the National Cancer Institute (NCI) Common terminology criteria for adverse events, version 4 (CTCAE v4, Appendix 5).

3.2 Trial Methodology

This is a Phase 2, non-randomised, open-label, multicentric study to investigate the efficacy and safety of pembrolizumab monotherapy in patients with specific rare cancers who have unresectable locally advanced or metastatic disease, which is resistant or refractory to standard therapy, or for which standard therapy does not exist, or is not considered appropriate, and for which no other experimental treatment options are available, in order to identify subsets of patients that may benefit from treatment.

The study plans to enrol up to 350 patients in total. Eligible patients who have provided their written informed consent for study participation will be assigned to one of 7 cohorts determined by indication:

- Cohort 1: Rare sarcoma
- Cohort 2: Rare ovarian cancer
- Cohort 3: Primary central nervous system lymphomas
- Cohort 4: Rare thyroid cancer
- Cohort 5: Rare malignant neuroendocrine cancer
- Cohort 6: Germ-cell cancer
- Cohort 7: NK/T-cell lymphoma

Between 20 and 50 patients will be enrolled in each cohort, with the exception of the cohort 1 for which up to 80 patients may be enrolled (extension introduced under amendment 5 of this protocol). Following the amendment 6, up to a maximum of 50 additional patients may be included in the Sarcoma (cohort 1), Rare ovarian cancer (cohort 2) or Primary central nervous system lymphoma (cohort 3) cohorts, within the limit of 350 patients to be included in total.

Additional, pathology specific cohorts may be added during the conduct of the study as a result of new data concerning response to anti-PD-1 antibody therapies and/or changes to the treatment landscape. The decision to open new cohorts to the study will be made by the Steering Committee (Section 11.3) and subject to ethics committee (EC) approval.

The study uses a two-stage Bayesian enrichment design. The first stage treats all patients from the different cohorts with IP and identifies possibly sensitive subpopulations (Berry 2013). The subsequent stage compares outcomes among subsets of patients in the previously identified cohorts to distinguish between patients who may benefit from the treatment and patients for whom there is no evidence of efficacy; possibly resulting in a halt to inclusion of the latter (Trippa 2012).

Patient participation is divided into 5 phases: Pre-selection, Screening, Treatment, End of Treatment (EoT), and Long-Term Follow-up (LTFU).

Prospective patients will be subject to a mandatory pre-selection process. Available (anonymised) diagnostic and disease history data will be reviewed centrally by a designated pathology expert to confirm that the patient meets the inclusion criteria concerning disease indication and that no other approved or experimental treatment options are available. Informed consent for study participation may be obtained only after approval of this pre-selection request.

***Note**: No study-specific examinations are required or should be performed as part of the pre-selection process.*

Approved candidates who consent to study participation will provide written informed consent and be enrolled in the trial via he R&D UNICANCER online electronic case report form (eCRF; https://ecrf.icm.unicancer.fr/csonline). All enrolled patients will be assigned a unique identification number. This number must be used as the sole patient identifier throughout the study. Enrolled patients will enter the Screening period (max. 28 days prior to start of treatment) during which all examinations required to assess eligibility for inclusion in the study will be performed, including demographic data collection, tumour evaluation and clinical and laboratory evaluations.

***Note:** clinical and laboratory examinations are to be performed within 14 days prior to initiation of study treatment*.

The availability of a suitable formalin-fixed, paraffin-embedded (FFPE) biopsy sample of a metastatic site, or primitive tumour tissue will be verified during the screening period. If suitable archived biopsy material is not available, a fresh biopsy of a tumour lesion may be performed, unless this is medically contraindicated (Section 9.1.1)

Eligible patients will be included in the study (reported via the eCRF) and administered with study treatment. All included patients will be considered in the intent-to-treat (ITT) population for statistical analysis.

Day 1 of the treatment period is defined as the date on which the patient receives a first dose of the investigational product (IP, pembrolizumab). Included adult patients will receive pembrolizumab 200 mg IV over 30 minutes every 21 days. Patients under 18 years old will receive 2mg/kg of pembrolizumab (maximum dose 200mg) by intravenous over 30 minutes every 21 days. Patients will be asked to attend clinical visits on the first day of each cycle to perform safety and efficacy assessments. Disease assessments will be performed by radiologic imaging every 84 (± 7) days (approx. every 4 cycles). For patients with germ-cell cancer, disease assessments will also include measurement of biomarkers (alpha-fetoprotein [AFP] and human chorionic gonadotropin [hCG] and lactate dehydrogenase [LDH]) performed on Day 1 of each cycle.

Blood samples will be collected prior to the first dose of IP (during the screening period) and following IP administration on Day 1 of Cycles 1, 2, 3 and 4 for comprehensive blood phenotyping and retrospective dosage of auto-antibodies and anti-tumour antibodies in serum, dosage of circulating cytokines, chemokines and receptor/ligand complexes in plasma, and analysis of ctDNA. Additional blood samples are to be collected if the patient experiences a suspected immune-related toxicity for

exploratory research. In selected cases where exceptional responses or unexpected toxicities are observed additional biopsy samples of the tumour could also be collected during the trial treatment.

A table summarizing the examination/visit schedule is provided in the Section H of the Protocol Synopsis and Figure 2.

Patients will continue treatment for a maximum of 24 months (or 35 cycles, whichever is longer), or until disease progression, Treatment may also be terminated early at the initiative of either the patient or the investigator for any reason that would be beneficial to the patient, including: unacceptable toxicity, intercurrent conditions that preclude continuation of treatment, or patient request. The decision to discontinue a subject, is the responsibility of the treating physician and will not be delayed or refused by the Sponsor. The Investigator may contact the Sponsor/Coordinating Investigator prior to discontinuing a subject however, and forward appropriate supporting documents for review and discussion.

An EoT visit will be performed 30 (± 3) days after discontinuation of study treatment for any reason. After the EoT visit, patients will enter the LTFU period and will be followed for an additional 12 months. During this time information will be collected every 90 (± 14) days concerning survival status, subsequent antineoplastic treatments and the status of ongoing AEs and/or new IP related AEs. Patients who discontinue treatment for reasons other than disease progression, or consent withdrawal will continue to be assessed by radiologic imaging every 84 (± 7) days throughout the LTFU period, until disease progression or initiation of a new antineoplastic treatment, or death.

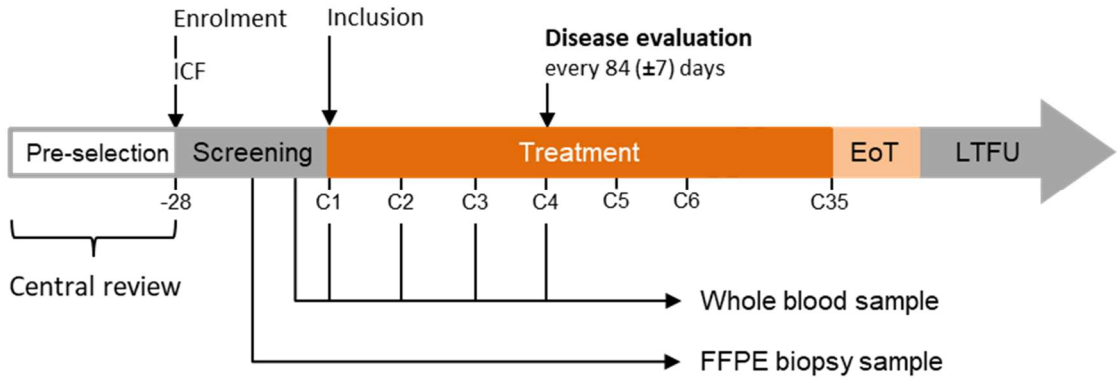
All participants who reach the maximum treatment duration per protocol and stop the pembrolizumab with a clinical benefit (prolonged stable disease, partial or complete response), may be eligible for up to an additional 1 year (approximately 17 cycles) of pembrolizumab treatment if they progress during the follow-up period. This retreatment is termed the Second course or Rechallenge (see sections 5.5 & 7.4.3).
The second pembrolizumab course will continue until 12 months of retreatment, progression or until the end of the study, whichever occurs first.

Efficacy of treatment will be assessed according to: (i) RECIST v1.1 for solid tumours, (ii) RECIST v1.1 combined with biomarker assessment for patients with germ-cell cancer, (iii) or IPCG response criteria for patients with PCNSL. (iv) For NK/T-cell lymphoma, disease burden will be assessed using the five-point scale (or 'Deauville criteria'; Meignan, 2009) of focal uptake of FDG measured via PET-CT scan. Evolution of disease will be evaluated using the 'Lugano' classification system (Cheson, 2014). NK/T-cell lymphoma patients with complete response will be further categorised as being in remission or not according to the detectable level of EBV in the blood. In addition to the Investigators' assessment of response, a central disease response evaluation will be performed by an IRC. Efficacy will be analysed separately for each cohort using a two-stage Bayesian enrichment design. Interim analyses will be performed using the Investigators' assessment of response measured at the first scheduled disease assessment following study treatment initiation (Day 84, ± 7 days) to assess the efficacy of treatment and determine if enrolment should continue. Interim analyses will be performed independently for each cohort after the 10 first patients have been enrolled in the cohort and completed at least one disease assessment. Subsequent analysis will be performed for each cohort after every 5 additional patients. Enrolment in a particular cohort may be stopped for futility if the rate of response is below a pre-defined threshold of 0.10. Final analysis of efficacy endpoints will be performed using both the Investigator and IRC assessment of response according to RECIST v1.1 once recruitment is complete and all patients have completed at least one post-baseline disease assessment. Comparisons between Investigator and IRC response assessments will also be reported.

A Steering Committee will review the safety and efficacy data accumulated throughout the study, including the results of interim analyses, collated safety reports, as well as published data and information provided by the IP license holder concerning concurrent studies. The Steering Committee, based on this information, will assist the Sponsor in resolving issues and/or questions encountered during the conduct of the trial and will make recommendations regarding changes to the protocol conduct as necessary. In addition, an Independent Data Monitoring Committee (IDMC) will be set up at the beginning of the trial, specifically to guarantee effective protection of patients, insure the ethical conduct of the trial, benefit/risk ratio of the trial, and to ensure the independent review of the scientific results during the trial and at the end of the trial. The Steering Committee/Sponsor may seek additional guidance from the IDMC as required during the conduct of the trial.

The study will be conducted in compliance with the International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use Efficacy guideline E6 - Good Clinical Practice (ICH-GCP) and applicable regulatory requirements.

Figure 2. Study Design



C= cycle, EoT= End of treatment visit, FFPE= Formalin-fixed, paraffin-embedded, ICF= Informed consent form, LTFU= Long-term follow-up.

3.3 Progression of the Trial

An overview of the different stages of the trial is provided in Figure 2.

Patients participating in the trial will comply with the protocol and receive treatment for a maximum of 24 months (or 52 cycles, whichever is longer), or until disease progression. Treatment may also be terminated early at the initiative of either the patient or the investigator for any reason that would be beneficial to the patient, including: unacceptable toxicity, intercurrent conditions that preclude continuation of treatment, or patient request. Follow-up information (survival, subsequent therapies) will be collected from all patients for 12 months following treatment discontinuation.

A table summarizing the examination/visit schedule is provided in the Section H of the Protocol Synopsis.

3.4 Inclusion Procedure(s)

3.4.1 Pre-selection

A key characteristic of the AcSé programme of clinical trials is to provide access to experimental therapies for patients with no alternative treatment options, be these drugs or regimens approved or recommended for use in the indication in question or clinical trials of alternative experimental therapies for which the patient is eligible. This trial in particular also has very specific inclusion criteria regarding the subtypes of cancers that are eligible for inclusion.

In order to ensure that these two elements are respected, prospective patients will be subject to a following mandatory pre-selection process.

Investigators will submit a request for pre-selection via completion of a specific selection request form, according to the information available in the patient's medical file. Patients should be informed that the following information will be shared in an anonymous manner with medical experts and the Sponsor study team:

- Anonymised copies of pathology reports confirming diagnosis of the indication in question, including histological confirmation.
- Details of the patient's disease history and current status (i.e. progression, stability …), and relevant concomitant pathologies.
- Details of previous treatments received for the disease under study,
- The conclusions of any local or national clinical review meetings concerning the patient's treatment options.

***Note**: No study-specific examinations are required or should be performed as part of the pre-selection process.*

Preselection requests will be systematically reviewed by the designated pathology expert identified for the concerned cohort who will determine whether or not the patient meets the required disease indication criteria, and if there are any alternative treatment options that should be considered.

The designated pathology expert may request additional information if this is necessary to enable their decision.

If, in the opinion of the designated pathology expert alternative treatment options are available to the patient, best efforts should be made to discuss these with the Investigator. In case of disagreement concerning patient selection, the case is to be referred to the Coordinating Investigator who will make the final decision as to the patient's eligibility.

Following approval of the preselection request by the designated pathology expert, the Investigator may proceed with the enrolment of the patient in the trial.

***Note**: A patient's informed consent for study participation may be obtained only after approval of this pre-selection request.*

3.4.2 Screening and Inclusion

Patients written informed consent is to be obtained before any study related procedures are performed.

Approved candidates who consent to study participation will be considered as enrolled in the trial and are to be registered through the R&D UNICANCER eCRF (https://ecrf.icm.unicancer.fr/csonline). All enrolled patients will be assigned a unique identification number consisting of the letter P (for pembrolizumab) followed by 8 digits. The first 5 digits will identify the participating site and the next 3 the order in which the patient was included at the site (e.g. the third patient included at site 01001 will be assigned the number P01001-003). This number must be used as the sole patient identifier throughout the study especially for the identification of biological samples.

Baseline assessments are to be performed as described in Section 7.1. It is the responsibility of the Investigator to verify and confirm that and all inclusion and non-inclusion criteria are met prior to initiating study treatment.

Once patient eligibility is confirmed Investigators should submit a request for IP via completion of (at a minimum) the inclusion/exclusion criteria pages and registration form available on the R&D UNICANCER eCRF website (https://ecrf.icm.unicancer.fr/csonline/).

Investigators should also complete the remaining CRF pages pertaining to patient screening and baseline disease assessment prior to treatment initiation.

Confirmation of patient inclusion and dispatch of the IP will be transmitted by e-mail to both the investigator and the pharmacist within 24 hours of receipt of the required information. A delay of 72 hours (from time of request) should be anticipated for IP delivery to avoid inappropriate visit scheduling for the patient.

3.5 Procedure for Breaking the Randomization Code (Unblinding)

Not applicable

3.6 Trial Early Terminations/Stopping Rules and Patient Premature Discontinuation

3.6.1 Temporary Discontinuation and Definitive Termination of the Trial

The end of the trial is defined as the last follow-up visit of the last patient.

The trial can be suspended or stopped by the Sponsor after consultation with the Coordinating Investigator and Steering Committee or following a request by the respective Regulatory Authority and/or the responsible EC for the following reasons:

- High frequency and/or unexpected severity of toxicity.

- Insufficient patient recruitment.
- Insufficient quality of data collection.

3.6.2 Premature Trial/Patient Discontinuation Criteria

Patient treatment is planned to continue for a maximum of 24 months (or 35 cycles, whichever is longer), or until failure (i.e. disease progression, or death). Treatment may also be terminated early at the initiative of either the patient or the investigator for any reason that would be beneficial to the patient, including: unacceptable toxicity, intercurrent conditions that preclude continuation of treatment, or patient request.

The decision to discontinue a subject, is the responsibility of the treating physician and will not be delayed or refused by the Sponsor. The Investigator may contact the Sponsor/Coordinating Investigator prior to discontinuing a subject however, and forward appropriate supporting documents for review and discussion.

Patients participating in this trial protocol may withdraw their consent and exit the trial at any time without justification irrespective of their reason(s). Withdrawal of consent does not preclude the patient's right to receive alternative treatment (see Section 14.4).

4 PATIENT SELECTION

4.1 Inclusion Criteria

Patients must meet all of the following criteria to be included in the study:

1. Patient information sheet and written informed consent form (PIS/ICF) signed.
2. Histologically confirmed diagnosis of a pathology corresponding to one of the following selected cancer types:
    - Rare sarcoma: Alveolar soft part sarcoma, Chordoma, Dedifferentiated chondrosarcoma, epithelioid sarcoma, sarcoma with loss of INI1, malignant rhabdoid tumours, myxoid liposarcoma, angiosarcoma of the scalp, radiation induced sarcomas. From the 51st patient included in this cohort, only the following histological types will be selected: Alveolar soft part sarcoma, Chordoma, SMARCA4-malignant rhabdoid tumours and Desmoplastic small-round-cell tumor.
    - Rare ovarian cancer: recurrent or relapsed; sex cord tumour, germ cell tumour (immature teratoma, non seminomatous germ cell & dysgerminoma), low-grade serous carcinoma, mucinous carcinoma, clear cell adenocarcinoma, small cell carcinoma, and carcinosarcoma – with histological confirmation following review by members of the Tumeurs Malignes Rares Gynécologiques (TMRG) network (French rare gynaecological tumour group).From the 51st patient included in this cohort, only the following histological types will be selected: immature teratoma, low-grade serous carcinoma and ovarian small cell carcinoma hypercalcemic type (SCOOHT).
    - Primary central nervous system lymphoma: refractory primary intraocular and CNS lymphoma. From the 51st patient included in this cohort, only CNS lymphoma will be selected.
    - Rare thyroid cancer: differentiated thyroid carcinoma (Papillary, follicular, Hurthle cell (oncocytic), poorly differentiated thyroid carcinoma), medullary thyroid carcinoma, anaplastic thyroid carcinoma.
    - Rare malignant neuroendocrine tumour: poorly differentiated digestive tumours refractory after 2 lines of chemotherapy including cisplatin/carboplatin-etoposide (CDDP/carbo-VP16) and 5-Fluoro-uracile/irinotecan (FOLFIRI), poorly differentiated non digestive tumours refractory after 2 lines of chemotherapy including cisplatin/carboplatin-etoposide (CDDP/carbo-VP16) and any second line of chemotherapy, well differentiated tumours refractory after 4 lines of treatment including 2 lines of chemotherapy, everolimus and sunitinib, carcinoid tumours after 2 lines of treatment including Peptide Receptor Radionuclide Therapy (PRRT) or chemotherapy and everolimus.
    - Trophoblastic germ-cell tumour progressing after standard therapy.
    - Natural killer T-cell lymphoma: extranodal NK/T-cell lymphoma regardless of localization that is resistant or refractory to prior L-asparaginase therapy.
3. Metastatic disease or unresectable locally advanced malignancy that is resistant or refractory to standard therapy or for which standard therapy does not exist or is not considered appropriate by the Investigator.
4. Aged ≥ 18 years old for cohort 2 to 7 and aged ≥ 15 years old for patients included in cohort 1 (rare sarcoma).
5. Measurable disease defined:
    - according to RECIST v1.1 guidelines (Eisenhauer, 2009) for patients with solid tumours;
    - according to IPCG response criteria (Abrey, 2005) for patients with PCNSL;
    - according to RECIST v1.1 and / or abnormal levels of AFP, hCG and LDH for patients with germ-cell cancer;

- as focal uptake in at least one nodal or extra-nodal site with a Lugano 5-PS score of 4 or 5 (Cheson, 2014) for patients with NK/T-cell lymphoma,

6. Able to provide a FFPE biopsy sample of a metastatic site or primitive tumour tissue.

   ***Note**: Patients for whom suitable archived biopsy material is not available must be willing to undergo a biopsy of a tumour lesion prior to study entry, unless this is medically contraindicated (e.g. site inaccessible or patient safety concerns).*

7. Patients must have a mandatory treatment-free interval of at least 21 days following previous systemic anti-cancer treatments.
8. Patients who have received previous systemic anticancer treatment and/or radiotherapy should have recovered from any treatment related toxicity, to a level of ≤ grade 1 (according to NCI-CTCAE criteria, v 4.0, Appendix 5) with the exception of Grade 2 alopecia.
9. Adequate hematologic function (absolute neutrophil count [ANC] ≥ 1.0 $x10^9$/L, platelets ≥ 100 $x10^9$/L, haemoglobin ≥ 9 g/dL) measured within 14 days of treatment initiation unless due to lymphoma associated haemophagocytic lymphohistiocytosis (HLH).
10. Adequate renal function (creatinine clearance ≥ 50 mL/min using the MDRD or CKD EPI method) measured within 14 days of treatment initiation.
11. Adequate hepatic function (serum bilirubin ≤ 1.5 x the reference upper limit of normal (ULN) unless due to Gilbert's syndrome; ASAT and ALAT ≤ 3 xULN) measured within 14 days of treatment initiation unless due to lymphoma associated HLH. For patients with documented liver metastasis ASAT/ALAT ≤ 5x ULN is acceptable.
12. Strictly normal blood levels of calcium and magnesium, measured within 14 days of treatment initiation.
13. Eastern Cooperative Oncology Group (ECOG) Performance Status of ≤ 1 (Oken, 1982; Appendix 6).
14. Estimated life expectancy ≥ 90 days.
15. Patients who are sexually active must agree to use a medically accepted method of contraception (e.g. implants, injectables, combined oral contraceptives, some intrauterine devices or vasectomized partner, for participating women; condoms for participating men) or practice complete abstinence, beginning 14 days before the first administration of IP, while on treatment and for at least 5 months after the last administration of IP for female patients, and 7 months after the last administration of IP for male patients.
16. Women of childbearing potential must have a negative urine or serum pregnancy test within 72 hours prior to the first administration of IP. If urine test results are positive or cannot be confirmed as negative, a serum pregnancy test will be required.
17. Women who are breastfeeding should discontinue nursing prior to the first administration of IP and for at least 120 days after the last administration of IP.
18. Patients must be affiliated to a Social Security System or equivalent.

4.2 Exclusion Criteria

Patients meeting **any** of the following criteria will be excluded from participation in the study:

1. Prior treatment with an anti-PD1 or anti-PD-L1 antibody
2. Eligible, to participate in a clinical trial of an alternative anticancer therapy targeting their disease which is open to accrual in France.
3. Concurrent steroid medication at a dose greater than prednisone 10 mg/day or equivalent (Appendix 7). For patients with germ-cell cancer, PCNSL concurrent steroid medication at a dose greater than prednisone 20 mg/day or equivalent.
4. 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.

5. History of (non-infectious) pneumonitis that required steroids, or current pneumonitis.
6. History of severe hypersensitivity reaction to any monoclonal antibody therapy
7. Radiotherapy (except for brain and extremities) within 21 days prior to the first administration of IP.
8. Treatment with other investigational drugs or participation in another clinical trial within 21 days prior to the first administration of IP or concomitantly with the trial.
9. Has known symptomatic central nervous system (CNS) metastases. Patients with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least four weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to trial treatment.
10. Has known carcinomatous meningitis or a history of leptomeningeal disease, except for patients with primary CNS lymphoma.
11. Serum creatinine > 1.5 xULN or glomerular filtration rate (GFR) < 50 ml/min.
12. Other malignancies within the past 5 years other than basal cell skin cancer or *in situ* carcinoma of the cervix.
13. Active serious infections in particular if requiring systemic antibiotic or antimicrobial therapy.
14. Active or chronic hepatitis B, hepatitis C and/or human immunodeficiency virus (HIV) infection (HIV 1/2 antibodies), or a known history of active *Tuberculosis bacillus.*
15. Has received a live vaccine within 30 days of planned start of study treatment.
16. ***Note:*** *Seasonal influenza vaccines for injection are generally inactivated vaccines and are allowed*Active alcohol or drug abuse.
17. Psychological, familial, sociological or geographical factors potentially hampering compliance with the study protocol and follow-up schedule.
18. Any condition which in the Investigator's opinion makes it undesirable for the subject to participate in the trial or which would jeopardize compliance with the protocol.

5 TRIAL TREATMENTS

5.1 Trial Products and Treatments

The investigational product **pembrolizumab** (MK-3475) is an IV administered human monoclonal antibody manufactured by Merck Sharp & Dohme Corp that blocks the interaction between the PD-1 receptor and its ligands, PD-L1 and PD-L2.

Pembrolizumab solution for infusion is supplied as 4 ml vials of solution for injection (100mg / 4ml). Pembrolizumab Solution for Infusion is a liquid DP (manufactured using the fully formulated IP with L-histidine as a buffering agent, polysorbate 80 as a surfactant, and sucrose as a stabilizer/tonicity modifier).

5.2 Therapeutic Scheme

Pembrolizumab will be administered by intravenous infusion over 30 minutes at a dose of 200 mg in adult patients, or at a dose of 2mg/kg (maximum dose 200 mg) for patients 15-17 years old, on Day 1 of every 21-day cycle. Every effort should be made to target infusion timing to be as close to 30 minutes as possible; given the variability of infusion pumps from site to site however, 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.

Treatment should be continued as long as clinical benefit is observed or until treatment is no longer tolerated by the patient (Section 3.6) up to a maximum of 24 months (or 35 cycles, whichever is longer).

5.3 Dose Adaptation

5.3.1 Dose Reduction

Intrapatient dose reduction is not allowed in this study.

5.3.2 Treatment Interruption

Treatment with pembrolizumab may be interrupted at the Investigators discretion depending on the type and severity of the toxicity encountered. Treatment is to be interrupted in the event of any of the toxicities listed in Table 3.

In the event of treatment interruption due to toxicity of more than 56 days, the decision to restart treatment or not should be discussed and agreed between the Investigator and Sponsor.

Table 3. Dose Modification and Toxicity Management Guidelines for Immune-related Adverse Events Associated with Pembrolizumab

General instructions:

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

Toxicity	Grade*	Action taken with pembrolizumab	Toxicity management	Monitor and follow-up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment • Add prophylactic antibiotics for opportunistic infections
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) 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.
	Grade 4	Permanently discontinue		
AST / ALT elevation or Increased bilirubin	Grade 2	Withhold	• Administer corticosteroids (initial dose of 0.5- 1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable
	Grade 3 or 4	Permanently discontinue	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	

Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold	• Initiate insulin replacement therapy for participants with T1DM • Administer anti-hyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated.	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue(1)		
Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or permanently discontinue(1)		
Hypothyroidism	Grade 2-4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyroinine) per standard of care	• Monitor for signs and symptoms of thyroid disorders.
Nephritis and Renal dysfunction	Grade 2	Withhold	• Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper.	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1 or 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
Severe skin reactions	Grade 1 or 2	Withhold	• Based on the severity of the adverse reaction administer corticosteroids	• Monitor patients for suspected severe skin reactions and exclude other causes • For signs or symptoms of SJS or TEN, refer the patient for specialized care for assessment and treatment. If SJS or TEN is confirmed, permanently discontinue pembrolizumab
	Grade 3 or 4	Permanently discontinue Events that require permanently discontinuation include and not limited to: Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)		
All other immune-related AEs	Intolerable/ persistent Grade 2	Withhold	• Based on type and severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3	Withhold or discontinue based on the type of event.		

		Events that require discontinuation include and not limited to: Gullain-Barre Syndrome, encephalitis		
	Grade 4 or recurrent Grade 3	Permanently discontinue		
***** Grade= NCI CTCAE version 4.0 (1) Withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician. **NOTE:** For participants with Grade 3 or 4 immune-related endocrinopathy where withhold of pembrolizumab is required, pembrolizumab may be resumed when AE resolves to ≤ Grade 2 and is controlled with hormonal replacement therapy or achieved metabolic control (in case of T1DM).				

5.4 Treatment Termination

Treatment will be continued for a maximum of 24 months (or 35 cycles, whichever is longer), or until disease progression. Early treatment discontinuation may also occur at the initiative of either the patient or the investigator for any reason that would be beneficial to the patient. These reasons include, but are not limited to: unacceptable toxicity, intercurrent conditions that preclude continuation of treatment, or patient request. The reasons for treatment discontinuation are to be documented in the patient's medical record and reported in the eCRF.

Except in case of consent withdrawal, patient follow-up will continue for 12-months after discontinuation of IP in compliance with the protocol.

5.5 Second course (Re-challenge)

Recent studies have shown that patients with a clinical benefit (i.e. objective response or prolonged stable disease) from their first anti-PD (L) 1 treatment could benefit from retreatment with the same immunotherapy (Akamatsu, 2018; Giaj Levra, 2019; Gobbini, 2020). This retreatment would be more beneficial in patients who have previously shown prolonged clinical benefit (Akamatsu, 2018; Giaj Levra, 2019; Gobbini, 2020).

Therefore, all participants who reach the maximum treatment duration per protocol (24 months – 35 pembrolizumab cycles) and stop the pembrolizumab with a clinical benefit (prolonged stable disease, partial or complete response), may be eligible for up to an additional 1 year (approximately 17 cycles) of pembrolizumab treatment if they progress during their follow-up phase. This retreatment is termed the Second Course (or Rechallenge) of this study and is only available if the study remains open and the participant meets the following conditions:

- Had SD, PR, or CR and stopped study treatment after completion of 35 administrations (approximately 2 years) of study treatment, and
- Experienced an investigator-determined radiographic disease progression by RECIST 1.1 for solid tumours, RECIST v1.1 combined with biomarker assessment for patients with germ-cell cancer, the IPCG response criteria for patients with PCNSL, the 'Lugano' criteria for response assessment using the FDG-PET-CT 5-PS and assessment of EBV load for patients with NK/T Lymphoma after stopping initial treatment, and
- No new anticancer treatment was administered after the last dose of study treatment, and
- No other approved or experimental treatment options are available 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.

During the second course, pembrolizumab will be administered and managed in the same way as the initial course, according to the Investigator Brochure and all the guidelines outlined above in section 5.

An objective response or disease progression that occurs during the Second course of pembrolizumab for a participant will not be taken into account in the primary analysis.

5.6 Assessment of Treatment Compliance

Study treatment will be administered by intravenous infusion by the Investigator at the Investigational site. Treatment compliance will be assessed via review of patient medical records.

5.7 Drug Packaging and Labelling

Pembrolizumab will be provided by the Sponsor and labelled appropriately as investigational product for this study in accordance with the specific requirements of this study, applicable Good Manufacturing Practices, and national regulations. Packaging will be performed by Merck Sharp & Dohme.

Pembrolizumab for intravenous infusion is formulated as a sterile, preservative-free, concentrate for solution for infusion at a concentration of 25 mg/mL, supplied in single-dose 4 mL vials.

5.8 Shipment, Storage Conditions and Accountability and Destruction

The IP supplies, provided by Merck Sharp & Dohme on behalf of the sponsor, will be distributed to the pharmacy at the investigational centre via a dedicated courier in accordance with the current Good Distribution Practices guidelines.

The pharmacist of the trial site will receive numbered treatment and will acknowledge receipt of each shipment by returning an acknowledgement of receipt form, duly completed, to the distributor.

Investigational product will be supplied to sites on a per-patient basis. An initial supply of IP will be shipped to sites following registration of the patient in the eCRF. Subsequent requests for resupply should be made to the Sponsor as described in the Pharmacy Manual.

The Investigator is responsible for a safe and proper handling and storage of the IP at the investigational centre (this task may be delegated to a qualified pharmacist). The IP must be stored in a locked facility with restricted access to the Investigator and authorized personnel, and under environmental conditions consistent with the drug manufacturer recommendations (Summary of Product Characteristics [SmPC] or IB). Investigational products must be stored in the dark at a temperature between 2°C and 8°C. Do not freeze. Temperature logs should be maintained to document adequate storage during the trial. In the event of temperature excursions outside the labelled storage conditions, affected IP supplies should be placed in quarantine. The Sponsor should be contacted to recommend further action to be taken and/or arrange for resupply.

The Investigator must ensure that IP is administrated only to patients enrolled in this trial. The IP must not to be used outside the context of the trial protocol.

The Investigator or the authorized staff must document the receipt, the dispensation, and the return or destruction of all IP received during this trial. Records of IP delivery to the investigational site, the inventory at the site, the use by each patient, and the return to the Sponsor or destruction by the site of all unused IP must be implemented and maintained by the Investigator or another appropriately trained individual at the investigational site. These records should record, at least; dates, quantities, and batch numbers of IP. Forms will be provided by the sponsor to ensure trial treatment accountability. This process will be monitored by the Sponsor Clinical Research Associate (CRA) during the trial.

All remaining unused IP will be collected and returned for destruction. The destruction will take place in the Investigator centre under the responsibility of the pharmacist in accordance with national regulatory requirements, and with prior formal agreement from the sponsor. A certificate of destruction, identifying concerned products, will be given to the sponsor.

5.9 Concomitant Treatments

All medications and therapies taken by the patients or administered to the patients at the onset of trial and all medication given in addition to the IP during the trial are considered as concomitant medications.

Medications or vaccinations specifically prohibited in the exclusion criteria or Section 5.9.2 are not allowed during the ongoing trial. If there is a clinical indication requiring treatment with one of these medications, discontinuation from trial therapy may be required. The investigator should discuss any questions regarding this with the Sponsor. The final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician.

5.9.1 Authorized Concomitant Treatments

All treatments that the investigator considers necessary for a subject’s welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the eCRF including all prescription, over-the-counter, 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 eCRF.

All medications that may interact with pembrolizumab or may induce or potentiate pembrolizumab related adverse events (see Section 5.9.2 and the Investigator Brochure) should be recorded if received within 14 days before the first dose of IP and 30 days after the last dose of IP.

The investigator should instruct the patient to notify the study site about any new medications (including over-the-counter drugs and herbal/alternative medications) he/she takes after the start of study

treatment. Patients must be instructed not to take any additional medications (including over-the-counter products and herbal/alternative medications) during the trial without prior consultation with the investigator.

Patients may receive any medications that the Investigator deems to be medically necessary, except for those prohibited treatments listed in Section 5.9.2.

5.9.2 Prohibited Concomitant Treatments

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

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab
- Radiation therapy
    - Palliative radiation therapy to a single symptomatic lesion or to the brain may be allowed, provided the lesion is not a target lesion for RECIST v1.1 evaluation and the need for therapy does not equate to progressive disease. Patients with PD must discontinue study treatment.
- Live vaccines within 30 days prior to the first dose of IP and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, Bacillus Calmette–Guérin (BCG), and typhoid vaccine.
- Systemic glucocorticoids at a dose greater than prednisone 10 mg/day or equivalent (Appendix 4). The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.
- Other medications described in the exclusion criteria (Section 4.2)

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

There are no prohibited therapies during the LTFU Phase.

5.10 Rescue Medication

5.10.1 Supportive Care Guidelines

Subjects should receive appropriate supportive care measures as deemed necessary by the treating Investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined in Table 3 (Section 5.3). Where appropriate, these guidelines include the use of oral or intravenous treatment with corticosteroids as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids.

Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event. The treatment guidelines are intended to be applied when the Investigator determines the events to be related to pembrolizumab. If after the evaluation the event is determined not to be related, the Investigator does not need to follow the treatment guidance below.

Management of Infusion Reactions:

Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Table 4 below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of pembrolizumab.

Overdose:

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

Table 4. Infusion Reaction Treatment Guidelines

Grade[1]	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 patient is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs	**Stop Infusion and monitor symptoms.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the investigator. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the patient should be premedicated for the next scheduled dose. **Patients who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.**	Patient may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab (MK-3475) with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates)	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine	No subsequent dosing
Grade 4: Life-threatening; pressor or ventilatory support indicated	Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **Patient is permanently discontinued from further trial treatment.**	

NSAIDS= Nonsteroidal anti-inflammatory drugs
(1) NCI-CTCAE version 4.1
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.

5.11 Diet/Activity/Other Considerations

5.11.1 Diet

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

5.11.2 Contraception

Patients should be informed that pembrolizumab may have adverse effects on a foetus *in utero*. Furthermore, it is not known if pembrolizumab has transient adverse effects on the composition of sperm. All patients of reproductive potential must agree to use (or have their partner use) a medically accepted form of contraception[1] during heterosexual activity, or practice abstinence[2] from heterosexual activity for the period beginning at least 14 days prior to their first IP administration, during the treatment period, and for at least 5 months after their last dose of IP for female patients, and 7 months after the last administration of IP for male patients. If there is any question that a patient of reproductive potential will not reliably comply with the requirements for contraception, that patient should not be entered into the study.

Acceptable methods of contraception[1] are:

- Single method (one of the following is acceptable):
    - intrauterine device
    - 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 (oestrogen/progestin pill or progestin-only pill), contraceptive skin patch, vaginal contraceptive ring, or subcutaneous contraceptive injection

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

1. Postmenopausal (defined as at least 12 months with no menses without an alternative medical cause; in women < 45 years of age a high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. In the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.);
2. OR, have had a hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy or bilateral tubal ligation/occlusion, at least 6 weeks prior to screening;
3. OR, have a congenital or acquired condition that prevents childbearing.

---

[1] If one of the contraceptive methods listed is restricted by local regulations/guidelines, then it does not qualify as an acceptable method of contraception for subjects participating at sites in this country/region.

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

5.11.3 Use in Pregnancy

If a patient inadvertently becomes pregnant while on treatment with pembrolizumab, the patient will immediately be removed from the study. The Investigator will contact the patient at least monthly and document the patient's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the Sponsor and to the IP license holder without delay and within 24 hours to the Sponsor and within 2 working days to the IP license holder 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 Investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the foetus or newborn to the Sponsor. If a male subject impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to the Sponsor and to the IP license holder and followed as described above.

5.11.4 Use in Nursing Women

It is unknown whether pembrolizumab is excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, patients who are breast-feeding should discontinue nursing prior to the first administration of IP and for at least 120 days after the last administration of IP.

6 EVALUATION OF TREATMENT EFFICACY AND SAFETY

6.1 Efficacy Evaluation

Treatment efficacy will be evaluated in solid tumours by measuring changes in tumour size in response to treatment; measured by computed tomography (CT) scan or Magnetic Resonance Imaging (MRI) according to RECIST v1.1 (Appendix 1). Patients with germ-cell cancer will be evaluated via RECIST v1.1 combined with measurement of biomarkers (AFP, hCG, and LDH; Appendix 2). Patients with PCNSL will be evaluated by magnetic resonance imaging (MRI) according to IPCG response criteria (Appendix 3). For patients with NK/T lymphoma response will be assessed via the 'Lugano' criteria for response assessment using the 5-PS classification system of FDG-PET-CT (Appendix 4 NK/T-cell lymphoma patients with complete response will be further categorised as being in remission or not according to the detectable level of EBV in the blood.

Patients disease will be assessed at "baseline" (during the screening period) and then every 84 (± 7) days until documented PD, or death, whichever occurs first. Assessment of biomarkers in germ-cell cancer patients will be performed on Day 1 of each treatment cycle (after Cycle 1). Patients who discontinue IP treatment for reasons other than progression, death or consent withdrawal will continue to perform disease evaluations every 84 (± 7) days during the LTFU period until PD, or new antineoplastic therapy.

The primary evaluation endpoint is the ORR after the first disease assessment at 84 (± 7) days (i.e. following four cycles of therapy). Death or withdrawal of consent before this point will be considered as treatment failure in this analysis.

Secondary evaluation endpoints include PFS, OS, best response to treatment, time to response and duration of response (see Section 3.1)

6.1.1 Independent Review Committee

In addition to the Investigators assessment of response, a central evaluation of disease response will be performed by an IRC for all patients to confirm the response after the first disease assessment at 84 (± 7) days and each reported complete response.

The interim analysis of ORR in each cohort will be performed using the Investigator's assessment of response after the 10 first patients eligible have been enrolled in order to test for futility according to the two-stage Bayesian enrichment design (Section 10.2).

The IRC and Investigators' assessment of response will be used for the analysis of efficacy endpoints in the final study report. Comparisons between Investigator and IRC results will also be reported.

The IRC will comprise of experts in each cohort pathology. The IRC will be provided with recordings of each scheduled CT scan or MRI exam (DICOM format) as well as the results of any other clinical, biological, or radiological disease assessments performed. Disease evaluation will be performed according to the schedule and methods described in a separate IRC charter.

***Note**: Treatment decisions are to be made by the Investigator, based on their assessment of patient response.*

6.2 Safety Evaluation

Evaluation of the safety of pembrolizumab will be based on AE occurrence, the use of concomitant treatments, changes occurring in the course of treatment, observed during physical examination, in the vital signs (artery pressure, pulse, body temperature), in electrocardiogram (ECG) and biological and clinical examinations (biochemistry, haematology). Safety criteria will be assessed according to NCI-CTCAE v4.0 (Appendix 4).

In case of emergency, the patient, a patient's relative or the patient's general practitioner should inform the investigator about the occurrence of an AE. The possible treatment interruption for the investigational product will be considered as well as adequate concomitant treatment if necessary.

7 DESCRIPTION OF VISITS AND INVESTIGATIONS

The study is divided into five phases: a mandatory Pre-selection phase (see Section 3.4), a Screening phase of up to 28 days, a Treatment phase, an EoT visit, and a LTFU phase. During the Treatment phase, patients will be monitored via on site visits on Day 1 of each 21-day treatment cycle. Tumour evaluation will be performed every 84 (± 7) days. Treatment will continue for a maximum of 24 months (or 35 cycles, whichever is longer), or until disease progression. Treatment discontinuation may also occur at the initiative of either the patient or the investigator for any reason that would be beneficial to the patient, including: unacceptable toxicity, intercurrent conditions that preclude continuation of treatment, or patient request. An EoT visit will be performed 30 (± 3) days after discontinuation of study treatment for any reason. After the EoT visit, patients will enter the LTFU period and will be followed for an additional 12 months. During this time they will be contacted every 90 (± 14) days to collected information concerning survival status, subsequent antineoplastic treatments and the status of ongoing AEs and/or new treatment related AEs. Patients who discontinue treatment for reasons other than disease progression, or consent withdrawal will continue to be assessed by radiologic imaging every 84 (± 7) days throughout the LTFU period, until disease progression or initiation of a new antineoplastic treatment, or death.

A table summarizing the examination/visit schedule is provided in the Section H of the Protocol Synopsis.

7.1 Screening

***Note**: Patient inclusion is subject to a mandatory centralised pre-selection process in order to confirm specific eligibility criteria (see Section 3.4). Patient screening procedures may only be initiated after approval of this pre-selection request.*

Written informed consent is to be obtained before any study related procedures are performed. If a protocol required screening procedure or assessment has been performed as part of the routine standard of patient care however, and has been performed within the study timeframe, the procedure or assessment does not need to be repeated, unless clinically indicated.

The following should be performed within **28 days** prior to the first administration of study treatment:

- Patient's written informed consent obtained
- Collection of demographic data: date of birth, gender, height and body weight
- Collection of cancer history (including verification of pathological diagnosis, date of diagnosis, stage at diagnosis, dates and sites of recurrent disease) and prior therapy (including name of agents, date of initiation, setting, date of last dose)
- Collection of other relevant medical history, and concomitant therapies
- Complete clinical examination (major body systems)
- Measurement of vital signs (blood pressure, seated heart rate, body temperature)
- Assessment of ECOG performance status
- Assessment of ongoing toxicities including pre-existing symptoms such as intestinal transit issues, dyspnoea and coughing, rash, nausea, headaches, signs of motor or sensory neuropathy and arthralgia. History of fever or recent infection must be investigated appropriately.
- Disease evaluation, including:

  For patients with solid tumours:

  - Clinical assessment of palpable or visual lesions.
  - Mandatory CT scan or MRI for baseline disease assessment.
  - Other appropriate radiological assessment (e.g. FDG-labelled PET, PET-CT, metaiodobenzylguanidine [mIBG] scintigraphy, bone scan, ultrasonography), to be performed at the Investigator's discretion.
  - Appropriate biological assessments to be performed at the Investigator's discretion.
  - Documentation of baseline tumour status including identification of all measurable and non-measurable lesions as per RECIST v1.1.

  For patients with PCNSL, disease assessment should include:

- Gadolinium-enhanced MRI of the brain (may be substituted with contrast-enhanced CT scans in patients for whom MRI is medically contraindicated).
- CT scan of the chest, abdomen and pelvis.
- Detailed ophthalmologic examination with dilated fundus examination, slit-lamp examination and colour photography of the posterior pole.
- Lumbar puncture for central spinal fluid (CSF) cytology
- Verification of on-going corticosteroid treatment.
- Documentation of baseline tumour status including verification of all measurable (uni-dimensional measurements) and non-measurable lesions as per IPCG response criteria.

For patients with NK/T-cell lymphoma, disease assessment should include:

- Clinical assessment.
- Mandatory FDG-labelled PET-CT scan of the head, chest, abdomen, pelvis and extremities.
- Documentation of baseline tumour status according to the 5-PS (Cheson, 2014)
- Lumbar puncture for central spinal fluid (CSF) cytology
- Bone marrow biopsy or bone marrow aspiration

Note: *same diagnostic method(s) must be used to evaluate disease status throughout the study. The results of all radiological assessment (DICOM format) must be provided on CD-ROM for central review by the IRC (Section 6.1.1).*

- Verification of availability of a suitable FFPE biopsy sample of a metastatic site, or primitive tumour tissue. If suitable archived biopsy material is not available, a fresh biopsy of a tumour lesion may be performed following signature of the informed consent form and prior to the first administration of IP, unless this is medically contraindicated (Section 9.1.1)
- Collection of blood samples (45 mL on heparin) for phenotyping and retrospective analyses (see Section 9.1.2)

The following should be performed within **14 days** prior to the first administration of study treatment:

- Electrocardiogram (12-lead)
- Haematology analysis including CD4+ count (see Table 5).
- Serum chemistry analysis (see Table 5).
- Measurement of coagulation factors: prothrombin time (PT)/International normalized ratio (INR), partial thromboplastin time (PTT) (see Table 5).
- Thyroid function tests: thyroid-stimulating hormone (TSH), total triiodothyronine (T3), free thyroxine (T4) (see Table 5).
- ***Patients with germ-cell cancer only***: Measurement of biomarkers (AFP, hCG and LDH)
- ***Patients with NK/T-cell lymphoma only***: PCR analysis of EBV load.
- Urinalysis (morning sample, fasting if possible): Blood, glucose, protein, specific gravity, microscopic examination of urinary sediment with concomitant dosing of creatinine (see Table 5).
- QuantiFERON-TB Gold (QFT®) test for mycobacterium tuberculosis, or tuberculosis skin test in cases of anterior exposure.
  Virology screening for HIV, hepatitis B and hepatitis C.
- Antibody screening for antinuclear antibodies, thyroperoxidase antibodies and thyroglobulin antibodies.
- Verification that a medically acceptable form of contraception (e.g. implants, injectables, combined oral contraceptives, some interuterine devices or vasectomized partner, for participating women; condoms for participating men) is being used by all sexually active patients, or that complete abstinence is practiced.

The following should be performed within **72 hours** prior to the first administration of study treatment:

- Urine or serum beta-human chorionic gonadotropin (β-hCG) pregnancy test for women of childbearing potential.

  Note: *If urine test results are positive or cannot be confirmed as negative, a serum pregnancy test will be required. In all cases, results must be reviewed prior to initiating study treatment.*

Table 5. Safety Laboratory Analyses to be Performed During the Trial

Haematology[1]	Serum chemistry[1]	Urinalysis[2]	Other
Haemoglobin	Calcium	Blood	Serum β-hCG [3]
Haematocrit	Chloride	Glucose	PT / INR[4]
Red Blood Cell Count	Magnesium	Protein	PTT[4]
WBC (total and differential)	Phosphorus	Specific gravity	T3[5]
ANC	Potassium	Creatinine	T4[5]
Lymphocytes	Sodium	Microscopic examination	TSH[5]
Platelet count	Glucose		
CD4+ count	Albumin		
	Creatinine[6]		
	Uric Acid		
	Total protein		
	Blood urea nitrogen		
	Urea		
	Total Bilirubin		
	Direct Bilirubin[7]		
	Amylase		
	Lipase		
	Alkaline phosphatase		
	ALAT		
	ASAT		
	GGT		
	LDH		
	C-reactive protein		
	Carbon Dioxide[8]		

ALAT= Alanine aminotransferase, ASAT=Aspartate aminotransferase, ANC= Absolute Neutrophil Count, β-hCG= β-human chorionic gonadotropin, GGT= gamma-glutamyl transferase, INR=International normalized ratio, LDH= Lactate dehydrogenase, PT= prothrombin time, PTT= partial thromboplastin time, T3= Total thriiodothyronine, T4= Free tyroxine, TSH= Thyroid stimulating hormone, WBC= White blood cell

(1) To be performed at screening visit (within 14 days prior to the first administration of study treatment) and at the start of each cycle (within 72 hours prior to treatment administration).
(2) To be performed on a morning sample, fasting if possible, at screening visit (within 14 days prior to the first administration of study treatment) and at the start of every sixth cycle (within 72 hours prior to treatment administration).
(3) To be performed at screening visit (within 14 days prior to the first administration of study treatment, and as close to the start of treatment as possible). β-hCG pregnancy test may be replaced by a urine pregnancy test performed within 72 hours of start of study treatment. In all cases, results must be reviewed prior to initiating study treatment.
(4) To be performed at screening visit (within 14 days prior to the first administration of study treatment)
(5) To be performed at screening visit (within 14 days prior to the first administration of study treatment) and at the start of every second cycle (within 72 hours prior to treatment administration).
(6) With estimated GFR (MDRD or CKI EPI method
(7) If total bilirubin is elevated above the upper limit of normal
(8) $C0_2$ or biocarbonate if considered standard of care in your region.

7.2 Assessment During Treatment Period

7.2.1 Visit 1 (Cycle 1 Day 1)

The following should be performed **prior to the first administration** of IP:

- Complete clinical examination (major body systems)
- Measurement of vital signs (blood pressure, seated heart rate, body temperature)
- Assessment of ECOG performance status
- Assessment of ongoing toxicities including pre-existing symptoms.
- Haematology analysis (see Table 5).
- Serum chemistry (see Table 5).

- Verification that a medically acceptable form of contraception (e.g. implants, injectables, combined oral contraceptives, some interuterine devices or vasectomized partner, for participating women; condoms for participating men) is being used by all sexually active patients or that complete abstinence is practiced
- Urine or serum β-hCG pregnancy test for women of childbearing potential

  Note: *Not required if already performed within 72 hours prior to start of treatment. If urine test results are positive or cannot be confirmed as negative, a serum pregnancy test will be required. In all cases, results must be reviewed prior to initiating study treatment.*

The following should be performed **after the first administration** of IP:

- Collection of blood samples (45 mL on heparin) for phenotyping and retrospective analyses (see Section 9.1.2)

7.2.2 Visit 2 (Cycle 2 Day 1)

The following should be performed on **prior to administration** of IP:

- Complete clinical examination (major body systems)
- Measurement of vital signs (blood pressure, seated heart rate, body temperature)
- Assessment of ECOG performance status
- Assessment of new and ongoing toxicities.
- Haematology[3] analysis (see Table 5).
- Serum chemistry[3] (see Table 5).
- Thyroid function tests[3]: TSH, T3, T4 (see Table 5).
- ***Patients with germ-cell cancer only****:* Measurement of biomarkers (AFP, hCG and LDH)[3].

The following should be performed **after administration** of IP:

- Collection of blood samples (45 mL on heparin) for phenotyping and retrospective analyses (see Section 9.1.2)

7.2.3 Visit 3 (Cycle 3 Day 1)

The following should be performed, **prior to administration** of IP:

- Complete clinical examination (major body systems)
- Measurement of vital signs (blood pressure, seated heart rate, body temperature)
- Assessment of ECOG performance status
- Assessment of ongoing toxicities including pre-existing symptoms.
- Haematology[3] analysis (see Table 5).
- Serum chemistry[3] (see Table 5).
- ***Patients with germ-cell cancer only****:* Measurement of biomarkers (AFP, hCG and LDH)[3]

The following should be performed **after administration** of IP:

- Collection of blood samples (45 mL on heparin) for phenotyping and retrospective analyses (see Section 9.1.2)

[3] *Blood draw for laboratory analysis may be performed up to 72 hours prior to IP administration.*

7.2.4 Visit 4 (Cycle 4 Day 1)

The following should be performed **prior to administration** of IP:

- Complete clinical examination (major body systems)
- Measurement of vital signs (blood pressure, seated heart rate, body temperature)
- Assessment of ECOG performance status
- Assessment of new and ongoing toxicities.
- Haematology[4] analysis (see Table 5).
- Serum chemistry[4] (see Table 5).
- Thyroid function tests[4]: TSH, T3, T4 (see Table 5).
- Urinalysis (morning sample, fasting if possible): Blood, glucose, protein, specific gravity, microscopic examination of urinary sediment with concomitant dosing of creatinine (see Table 5).
- ***Patients with germ-cell cancer only****:* Measurement of biomarkers (AFP, hCG and LDH)[4]

The following should be performed **after administration** of IP:

- Collection of blood samples (45 mL on heparin) for phenotyping and retrospective analyses (see Section 9.1.2)

7.2.5 Subsequent Visits – Day 1 of Each Cycle

The following should be performed **prior to administration** of IP on Day 1 of every cycle:

- Complete clinical examination (major body systems)
- Measurement of vital signs (blood pressure, seated heart rate, body temperature)
- Assessment of ECOG performance status
- Assessment of ongoing toxicities.
- Haematology[4] analysis (see Table 5).
- Serum chemistry[4] (see Table 5).
- ***Patients with germ-cell cancer only****:* Measurement of biomarkers (AFP, hCG and LDH)[4]

If the patient experiences a suspected immune-related toxicity a blood sample (45 mL on heparin) should also be collected for phenotyping and retrospective analyses (see Section 9.1.2)

7.2.6 Subsequent Visits – Day 1 of Every Second Cycle

The following additional analysis should be performed **prior to administration** of IP on Day 1 of every second cycle (i.e. Cycle 6, 8, 10, 12….):

- Thyroid function tests[4]: TSH, T3, T4

7.2.7 Subsequent Visits – Day 1 of Every Fourth Cycle

The following additional analysis should be performed **prior to administration** of IP on Day 1 of every Sixth cycle (i.e. Cycle 8, 12, 16, 20….):

- Urinalysis (morning sample, fasting if possible): Blood, glucose, protein, specific gravity, microscopic examination of urinary sediment with concomitant dosing of creatinine (see Table 5).

[4] *Blood draw for laboratory analysis may be performed up to 72 hours prior to administration of study treatment.*

7.2.8 Disease Evaluation

Disease evaluation should be performed **every 84 days (± 7days)** after the initiation of study treatment (i.e. **at the end of** Cycle 4, 8, 12, 16…). Additional radiologic disease evaluations should also be performed if recommended by standard practice for a specific indication, or if clinical symptoms indicate a need for radiologic confirmation of PD.

Note: *In the event of a change in the patient's treatment schedule (e.g. treatment interrupted due to toxicity) time delay between tumour evaluations (84 days [± 7days]) should be maintained.*

The following will be performed at each disease evaluation:

For patients with solid tumours (other than germ-cell cancer):

- Clinical assessment of palpable or visual lesions.
- Mandatory CT scan or MRI.
- Other appropriate radiological assessments to be performed at the Investigator's discretion (e.g. PET-FDG, PET-CT, mIBG scintigraphy, bone scan, ultrasonography).
- Appropriate biological assessments to be performed at the Investigator's discretion.
- Documentation of response assessment according to RECIST v1.1 if solid tumour (including documentation of size/status of each measurable and non-measurable lesion),

For patients with germ-cell cancer:

- Clinical assessment of palpable or visual lesions.
- Mandatory CT scan or MRI.
- Other appropriate radiological assessments to be performed at the Investigator's discretion (e.g. PET-FDG, PET-CT, mIBG scintigraphy, bone scan, ultrasonography).
- Appropriate biological assessments to be performed at the Investigator's discretion.
- Measurement of biomarkers (AFP, hCG and LDH)
- Documentation of response assessment according to RECIST v1.1 (as above) combined with assessment of biomarker response for patients with germ-cell cancer,

For patients with PCNSL:

- Gadolinium-enhanced MRI of the brain (may be substituted with contrast-enhanced CT scans in patients for whom MRI is medically contraindicated).
- CT scan of the chest, abdomen and pelvis.
- Detailed ophthalmologic examination with dilated fundus examination, slit-lamp examination and colour photography of the posterior pole, if results of these studies were positive at screening, or if clinically indicated by new symptoms.
- Lumbar puncture for central spinal fluid (CSF) cytology, if results of these studies were positive at screening, or if clinically indicated by new symptoms.
- Verification of on-going corticosteroid treatment.
- Documentation of disease assessment according to IPCG response criteria (including documentation of size [uni-dimensional measurements] /status of each lesion).

For patients with NK/T-cell lymphoma:

- Clinical assessment.
- Mandatory FDG-labelled PET-CT scan of the chest, abdomen and pelvis and extremities. ***Note***: *repeat scans of regions which were negative for tumour involvement at baseline are not required unless clinically indicated by new symptoms or suspicion of disease progression.*
- CT scan or MRI if clinically indicated
- Lumbar puncture for central spinal fluid (CSF) cytology, if results were positive at screening, or if clinically indicated by new symptoms
- Bone marrow biopsy or bone marrow aspiration, if results were positive at screening, or if clinically indicated by new symptomsPCR analysis of EBV load
- Documentation of disease assessment according to the 'Lugano' criteria for response assessment using the FDG-PET-CT 5-PS classification system

Note: *The same diagnostic method(s) must be used to evaluate disease status throughout the study. Confirmatory radiographic scans should be repeated 28 days after assessment of a PR or CR for solid tumours (RECIST v1.1, Appendix 1). Radiographic scans that were negative at baseline do not have to be repeated unless clinically indicated (i.e new or worsening symptoms).*
The results of all radiological assessment (DICOM format) must be provided on CD-ROM for central review by the IRC (Section 6.1.1).
In case of progression, CT scan or MRI imaging prior to baseline will be collected.

7.2.8.1 Disease Progression: Special Considerations for First Disease Evaluation

In some patients, immune-related response patterns can be characterized by an initial increase in size of tumour lesions before any subsequent decrease in tumour burden. In order to avoid prematurely interrupting the patients' treatment, the following guidelines should be observed.

At the first disease evaluation only (i.e. Day 84, ± 7 days): In the event that the patient shows an increase in lesion size consistent with RECIST v1.1 or IPCG criteria for disease progression, the investigator may also consider the signs of clinical deterioration when deciding how to manage the situation:

- If the patient presents with signs and symptoms that could be related to disease progression: the patient is to be considered as having progressive disease and is to be withdrawn from treatment
- If the patient presents no clinical signs or symptoms associated with disease progression and the investigator suspects an immune-related response: treatment may be continued at the investigators discretion. **In this case a follow-up clinical and radiological assessment performed within 28 days (± 7 days)**. If at this follow-up assessment the disease is evaluated as stable or responding according to RECIST v1.1 or IPCG response criteria, treatment may be continued and the patient will remain on study. If radiological disease progression is confirmed by this second evaluation however, the treatment will be discontinued (regardless of clinical status) and the appropriate end of treatment evaluations performed.

For the purposes of analysis, the results of both the initial (Day 84) disease assessment and follow-up disease assessment should be recorded in the eCRF. In all cases, evaluation of response will be made according to RECIST criteria base on radiological measurement.

For time to event analyses, the date of disease progression will be considered as the date of the initial evaluation at which disease progression was suspected (as per RECIST / IPCG recommendations) regardless of the clinical decision taken.

If the criteria for disease progression are met at a time point later than Day 84, the patient is to be withdrawn from treatment, regardless of clinical status. No confirmation of PD is required in this case.

7.2.8.2 Disease Progression: Special Considerations for Germ-Cell Cancer

For patients with germ-cell cancer, in addition to a radiologic disease assessment every 84 days (± 7days), biomarker measurement (AFP, hCG and LDH) will be performed prior to the first dose of IP (during the screening period) and within 72 hours prior to IP administration on Day 1 of each cycle of treatment (after Cycle 1) in order to assess response to treatment.

In this patient group, disease progression will be defined as any of the following:

- Two consecutive elevations (i.e. consistent increase between 3 consecutive samples) in any of the three biomarkers.
- Disease progression according to RECIST v1.1, except when pathological evidence of a growing teratoma syndrome is provided.

7.2.8.3 Disease Progression: Special Considerations for NK/T-cell lymphoma

For patients with NK/T-cell lymphoma, in addition to a radiologic disease assessment (FDG-labelled PET-CT scan), PCR analysis of EBV load will be performed prior to the first dose of IP (during the screening period) and then every 84 days (± 7days) in order to assess response to treatment.

In this patient group, disease progression will be defined as any of the following:

- Disease progression as determined by FDG-PET-CT scan according to the 5-PS.
- A significant increase in the EBV DNA copy number which in the Investigators opinion is indicative of disease progression

7.3 End-of-Treatment Visit

Patients will continue to receive study treatment, and undergo study procedures as outlined above for a maximum of 24 months (or 35 cycles, whichever is longer), or until disease progression. Treatment may also be terminated early at the initiative of either the patient or the investigator for any reason that would be beneficial to the patient, including: unacceptable toxicity, intercurrent conditions that preclude continuation of treatment, or patient request.

Following treatment discontinuation for any reason, the following examinations are to be performed 30 (± 3) days after last dose of IP, or before initiating a new antineoplastic therapy, whichever comes first:

- Complete clinical examination (major body systems)
- Measurement of vital signs (blood pressure, seated heart rate, body temperature)
- Assessment of ECOG performance status
- Assessment of new and ongoing toxicities.
- Haematology analysis (see Table 5).
- Serum chemistry (see Table 5).
- Thyroid function tests: TSH, T3, T4 (see Table 5).

Note: *Laboratory examinations that were performed less than 14 days prior to the EoT visit do not need to be repeated, unless clinically indicated (i.e. ongoing toxicity surveillance).*

All AEs that occur prior to the EoT visit should be recorded. Subjects with an AE of Grade > 1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new anti-neoplastic therapy, whichever occurs first. Treatment-related SAEs that occur more than 28 days after the end of treatment or before initiation of a new anti-cancer treatment should also be followed and recorded.

7.3.1 End-of-Treatment Disease Evaluation(s)

Disease evaluation is to be performed outlined in Section 7.2.8. within 30 (± 3) days of last dose of IP, or before initiating a new antineoplastic therapy, whichever comes first:

Note: *If the last radiographic assessment was performed less than 28 days prior to last dose of IP it does not need to be repeated.*
For the patients who discontinued treatment for reasons other than disease progression or withdrawal of consent, tumour assessments should be continued and documented every 84 days (± 7 days) until disease progression or initiation of a new antineoplastic treatment (Section 7.4.1).

7.4 Follow-up

7.4.1 Long Term Follow-up

Long-term follow-up assessments will be performed for all patients every 90 (± 14) days for 12 months following the EoT visit.

The following information will be collected at each LTFU assessment:

- Patients survival status.
- Subsequent antineoplastic therapies.
- Status of ongoing AEs and/or new treatment-related AEs.

This information may be collected during onsite visits (as part of patients continued treatment at the site), via communication with the patients treating physician or via telephone contact with the patient.

Long-term follow-up will continue until death, withdrawal of consent, or 12 months after the EoT visit, whichever occurs first.

7.4.2 Efficacy follow-up

All patients who discontinue treatment for reasons other than disease progression, or withdrawal of consent from the entire study should continue to be assessed every 84 (± 7) days during the LTFU period to monitor disease status, until disease progression or initiation of a new antineoplastic treatment or death.

The disease evaluation will be performed according to the methods outlined in Section 7.2.8.

7.4.3 Second Course assessments

Second course assessments will be performed for only the eligible patients rechallenged with pembrolizumab (See Section 5.5) every 90 (± 14) days for 12 months in the same way as for the LTFU.Prior to the first re-administration of pembrolizumab, the following parameters will be checked by the investigator

- Inclusion/non-inclusion safety criteria
- Radiographic disease progression assessed by RECIST 1.1 for patients with solid tumours, RECIST v1.1 combined with biomarker assessment for patients with germ-cell cancer, the IPCG response criteria for patients with PCNSL, the 'Lugano' criteria for response assessment using the FDG-PET-CT 5-PS and assessment of EBV load for patients with NK/T Lymphoma.
- Negative urine or serum pregnancy test for women of childbearing potential.

The following information will be collected:

- Written informed consent,
- Patients' survival status and disease status,
- Status of ongoing AEs and/or new treatment-related AEs.

This information will be collected during onsite visits.

The second pembrolizumab course will continue until 12 months of retreatment, disease progression or until the end of the study, whichever occurs first.

During the second course, pembrolizumab will be administered and managed in the same way as the initial course, according to the Investigator Brochure and all the guidelines outlined above in section 5.

7.5 Provisions in Case of Treatment or Trial Interruption

In cases of patient withdrawal of consent or early trial termination, all efforts should be made to perform the EoT visit assessments (see Section 7.3). The patient's future clinical management will be left to the discretion of the treating physician

8 SAFETY EVALUATION

8.1 Adverse Events

8.1.1 General definition

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

Changes resulting from normal growth and development that do not vary significantly in frequency or severity from expected levels are not to be considered AEs.

Progression of the disease under study is not considered as AE.

All subjects will be monitored for AEs during the study. Assessments may include monitoring of any or all of the following parameters: the subject's clinical symptoms, laboratory, pathological, radiological or surgical findings, physical examination findings, or findings from other tests and/or procedures.

8.1.2 Evaluating Adverse Events

As far as possible, each AE should be evaluated to determine:

- The severity of the event
- Its relationship to the IP (related/ not related)
- Its duration (start and end dates or if continuing at final exam)
- Action taken (corrective treatment, hospitalization/prolonged hospitalization, …)
- The seriousness of the event (Section 8.2).

Severity

The severity (intensity) of AEs must not be confused with the seriousness criterion which is the guide for defining the reporting requirements (Section 8.2). Severity will be assessed by a qualified physician (Investigator) using the NCI CTCAE version 4.0 (Appendix 4). The intensity of adverse events not listed in this classification will be assessed according to the following qualifiers:

- **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 the event.

Relationship

The investigator must do his/her best to explain each adverse event and establish when it exists, the connection with the IP.

Duration

Adverse events must be followed until they have resolved or stabilized.

8.1.3 Adverse Event Reporting

All AEs that occur from the time the informed consent form is signed until 30 days after the last dose of IP must be reported by the Investigator (the reporting timeframe for AEs meeting any serious criteria is described in Section 8.2). All AEs will be recorded on the AE page of the CRF and in the subject's source

documents. The investigator will make every attempt to follow all subjects with non-serious AEs for outcome.

8.2 Serious Adverse Events

8.2.1 General definition

A serious adverse event is defined as any untoward medical occurrence or effect that at any dose:

- results in death,
- is life-threatening,
- requires hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability or incapacity,
- is a congenital anomaly or birth effect,
- or is medically relevant in the context of the pathology and the clinical trial.

These characteristics/consequences have to be considered at the time of the event. For example, regarding a life-threatening event, this refers to an event in which the subject 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 was more severe.

The terms disability and incapacity correspond to any clinically relevant physical or psychic handicap, transient or permanent, with impacts on the physical condition/activity and/or the quality of life of the patient.

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious, such as important medical events that might not be immediately life-threatening or result in death or hospitalization, but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed in the definition above (for example: overdose, second cancer,…).

The following events leading to a hospitalization or prolongation of hospitalization are not considered as Serious Adverse Events:

- Hospitalisation already scheduled before the start of the trial,
- Hospitalisation required as part of the protocol (biopsy, chemotherapy, etc.),

Any SAE, or follow up to a serious adverse event (including death due to any cause other than progression of the cancer under study) that occurs from the time the informed consent form is signed until 28 days after the last dose of IP must be reported to the Sponsor within 24 hours of the Investigator's knowledge.

Additionally, any SAE which is considered to be related to the study treatment by an investigator which occurs at any time outside of the time period specified in the previous paragraph also must be reported immediately to the Sponsor.

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

The assessment of whether there is a reasonable causal relationship is made by the investigator. If the sponsor disagrees with the investigator's causality assessment, the opinion of both the investigator and the sponsor should be provided with the report.

8.2.2 Suspected Unexpected Serious Adverse Reaction

A suspected unexpected serious adverse reaction (SUSAR) is defined as any serious adverse reaction, for which the nature, severity or outcome is not consistent with the applicable drug information (e.g. IB for an unapproved investigational product or package insert/summary of product characteristics for an approved product).

The reference document for assessment of expectedness in this study will be the pembrolizumab IB.

The assessment of expected / unexpected character is the responsibility of the sponsor.

New event: is defined as any new event relating to the conduct of the trial or the development of the investigational medicinal product where that new event is likely to affect the safety of the subjects.

8.2.3 Serious Adverse Event Reporting

The investigator ensures that adequate medical care is provided to the patient. Treatment of the event may require decoding of the IP.

The investigator must immediately and no later than 24 hours following knowledge of the event, notifies the R&D UNICANCER pharmacovigilance unit of any SAE or any new event defined here above, whether or not related to the research, which occurs during the 'trial reporting period'. This reporting period:

- Starts at the date of the signature of the informed consent form,
- covers the entire period during which the patient is receiving the IP or is subject to specific procedures related to the trial,
- covers a period of 100 days after the last administration of the experimental drug.

Any later SAE, i.e. occurring after a period of 100 days, which is considered to be related to the IP or to the research (other treatment used, diagnostic procedures and examinations carried out during the research) must be reported without any limitation in terms of deadline.

Notification must be made immediately by fax to the R&D UNICANCER pharmacovigilance unit by sending the form "notification of an SAE", located in the Investigator Master File, completed as precisely as possible, dated and signed by the physician-investigator:

Notification must be carried out immediately by fax to the R&D UNICANCER pharmacovigilance unit:

R&D UNICANCER
Pharmacovigilance unit, France
Phone: +33 (0)1 44 23 04 16 – Fax: +33 (0)1 44 23 55 70
Email: pv-rd@unicancer.fr

The R & D UNICANCER pharmacovigilance unit will inform Merck Global Safety (facsimile number: +1-215-993-1220) and other appropriate persons about all SAEs, as well as pregnancy and events of clinical interest (see Section 8.3), within 2 working days of knowledge of the event.

Abnormal laboratory results should be reported as SAE if they possibly put at risk the patient or they require medical intervention to prevent an outcome corresponding to one of severity criteria.

Second cancers, whether or not related to the research, must be reported to the R&D UNICANCER pharmacovigilance unit without any limitation in terms of deadline.

The Investigator **shall send additional information to the R&D UNICANCER pharmacovigilance unit** using a SAE declaration form (by ticking the Follow-up X box to specify that it is a follow-up and not an initial report) as soon as he is aware of the event. He shall also submit the last follow-up at the resolution or stabilization of the SAE.

The Investigator is responsible for appropriate medical follow-up of patients until the resolution or stabilization of the event or until the death of the patient. This can sometimes mean that the follow-up continues after the patient has left the trial.

The Investigator must keep the documents concerning the suspected SAE in order to supplement the information previously submitted if necessary.

Requests for clarification and / or additional information may be sent to the Investigator by the R&D UNICANCER pharmacovigilance unit or Sponsor clinical research associate (CRA) of the trial to document and treat the case.

The physician-investigator should also attach to the form « notification of a SAE », whenever possible:

- a copy of the hospital report or extended hospitalization report,
- a copy of all results of additional investigations carried out, including also relevant negative results, and enclosing the normal laboratory values,
- a copy of the autopsy report if necessary,
- any other document deemed to be useful and pertinent.

All these documents must be pseudonymised.

Overdose:

For purposes of this trial, an overdose of pembrolizumab will be defined as any dose of 1,000 mg or greater (≥5 times the indicated dose). If a dose of pembrolizumab meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the event of overdose is to be reported as a SAE, using the terminology "accidental or intentional overdose without adverse effect."

If an adverse event(s) is associated with ("results from") the overdose of IP, the adverse event(s) is to be reported as a SAE, using the terminology "EVENT due to overdose", even if no other seriousness criteria are met (Section 8.2.1).

All reports of overdose with and without an adverse event must be reported to the Sponsor immediately and no later than 24 hours following the Investigator's knowledge of the event.

Events related to disease progression:

Events occurring within the trial reporting period that meet the criteria of a SAE (Section 8.2.1) but which are related to, or occur in the context of disease progression do not require expedited reporting as described above. These events are to be considered as serious however, and should be reported as such in the CRF and followed for outcome.

Second course of pembrolizumab

For patients receiving second course of study product (see section 5.5), SAE occurred after reintroduction of the IP, pembrolizumab, must be notified to the sponsor in the same manner and timelines that the first course of pembrolizumab. SAE must be reported since the first administration of the second course of pembrolizumab, during entire period which the patient is receiving the IP and until a period of 100 days after its last administration.
SAE occurring after this period of 100 days, which is considered to be related to the IP or to the research, must be reported without any limitation in terms of deadline. It is agreed that the second course of pembrolizumab, as part of this clinical trial, will not exceed 12 months.

8.3 Events of Clinical Interest

In addition to the above criteria, AEs meeting the following criteria (although not serious per ICH-GCP definition) are considered events of clinical interest. Any ECI occurring within the time period beginning when the consent form is signed until 100 days after the last dose of study treatment are reportable to the Sponsor in the same timeframe as an SAE, i.e. within 24 hours of the Investigator's knowledge of the event.

Events of clinical interest for this study include:

8.3.1 Hepatic toxicity

Hepatic toxicity of clinical interest is defined as an elevated ASAT or ALAT lab value ≥ 3x ULN and an elevated total bilirubin lab value ≥ 2x ULN and, at the same time, an alkaline phosphatase lab value < 2x the ULN, 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.*

8.3.2 Pregnancy

The occurrence of pregnancy is not considered as an SAE. If, however a female study patient becomes pregnant or is discovered to have been pregnant during the treatment period or within 5 months after the last IP administration the investigator must immediately notify the Sponsor of this event via the Pregnancy Notification Form in accordance with SAE reporting procedures. Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the Pregnancy Notification Form.

Any pregnancy that occurs in a female partner of a male study patient during the treatment period or within 7 months after last IP administration should be reported to the Sponsor via the Pregnancy Notification Form. In order for Sponsor or designee to collect any pregnancy surveillance information from the female partner, the female partner must sign an informed consent form for disclosure of this information. Information on this pregnancy will be collected on the Pregnancy Notification Form.

Note: *While pregnancy itself is not considered to be a SAE, any anomaly detected in the foetus or child, any elective termination of a pregnancy for medical reasons or spontaneous abortion will be reported as a SAE, using SAE reporting procedure (Section 8.2.3).*

9 ANCILLARY STUDY(IES)

9.1 Biological Ancillary Study

The aim of the proposed ancillary studies is to address specific scientific questions related to potential predictive biomarkers of efficacy and the mechanism of action of the antitumour immune response, such as:

- Which biomarkers are specifically associated with tumour response to treatment?
- Which biomarkers are specifically associated with treatment-related toxicity?
- What are the common immune parameters modified by the treatment in all patients?
- Which tumour immune infiltration patterns are seen in responding versus non-responding patients?
- Are identified biomarkers unique to a particular tumour, or universally present across all tumour types

9.1.1 Tumour Biopsy

Formalin-fixed, and paraffin-embedded biopsy samples of a metastatic site, or primitive tumour tissue are required from patients in order to perform retrospective immunohistochemistry analysis.

Archived samples will be collected in preference, however if suitable archived biopsy material is not available, a fresh biopsy of a tumour lesion may be performed following signature of the informed consent form and prior to the first administration of study treatment, unless this is medically contraindicated (e.g. site inaccessible or patient safety concerns).

Such biopsies should be performed by appropriately qualified personnel in accordance with clinical best practice and the local institutions standards of care. In addition, various measures are to be implemented to minimize the risk of the biopsy procedure, notably:

- Blood counts and hemostasis analysis will be performed prior to identify any coagulation abnormality which could prohibit a biopsy.
- Tumour lesions of more than 3 cm will be preferred to smaller lesions
- Non thoracic-lesions will be favored over pulmonary lesions to decrease the risk of biopsy

The site of biopsy will be selected by the Investigator according to accessibility and volume of metastatic tissue available. The choice of biopsy site and sampling conditions are to be reported in the eCRF.

Note: *In the perspective of performing translational studies on biopsied tissue, the samples collected must be* ***core*** *biopsies; fine needle aspirations will not be accepted.*

All biopsy samples will be shipped to the R&D UNICANCER Biological Resources Centre (Centre des Resources Biologiques) at the Centre Leon Berard (CRB-CLB, see Section 14.10).

Depending on the quality of tumour tissue collected, immunohistochemical staining will be performed according to the following order of priority:

1. PD-L1 expression in the tumour microenvironment
2. Tconv / Tregs (CD4+, FOXP3+) and CD8+ T cell infiltration and co-markers (Fas-L, OX40)
3. Tumour vascularization and markers of endothelium & pericytes (stainings for VEGF, CD31; CD34)
4. Macrophages (CD68/CD163 co-staining for M1/M2)
5. Dendritic Cells (DC-lamp, PS100)

In selected cases where exceptional responses or unexpected toxicities are observed additional biopsy samples of the tumour could be collected during the trial treatment for exploratory studies.

All biological specimens not used for genomic profiling will be stored centrally in the Unicancer Biobank located at the CRB-CLB.

9.1.2 Blood Samples

Blood samples (45 mL on heparin) will be collected for biomarker phenotyping and retrospective analyses during the Screening period and following treatment administration on Day 1 of Cycles 1, 2, 3, and 4. Additional samples are to be collected if the patient experiences a suspected immune-related toxicity.

Collected blood will be shipped to the CRB-CLB (see Section 14.10) for the following:

- Comprehensive blood phenotyping, notably costimulatory and co-inhibitory markers (ICOS, OX40, CTLA-4, PD-L1, CD137) and homing receptors (CLA) on T cells (Tregs & Tconv CD4+ T cells, CD8+ T-cells[CD8+/HLA-DR+/Ki-67+]) and NK cells.
- Serum storage for retrospective dosage of autoantibodies and antitumour antibodies.
- Plasma storage for retrospective dosage of circulating cytokines, chemokines and circulating receptors/ligands such as soluble PD-L1, soluble B7.1, soluble CD25, circulating levels of VEGFs, soluble VEGFRs, PDGF, FGF, ITAC, IL18, IL6, and IFNg.
- Plasma storage for subsequent ctDNA analysis and whole exome sequencing.

The procedure for blood processing and shipment are described in greater detail in a separate Laboratory Manual.

10 STATISTICAL ANALYSIS PLAN

10.1 Required Number of Patients

This is a Phase 2, non-randomised, open-label, multicentric study to investigate the efficacy and safety of pembrolizumab monotherapy in patients with specific rare cancers who have unresectable locally advanced or metastatic disease, which is resistant or refractory to standard therapy, or for which standard therapy does not exist, or is not considered appropriate, and for which no other experimental treatment options are available. The trial is designed to identify subsets of patients that may benefit from treatment.

Enrolled patients will be assigned to cohorts based on disease indication. Seven cohorts are defined as follows:

- Cohort 1: Rare sarcoma
- Cohort 2: Rare ovarian cancer
- Cohort 3: Primary central nervous system lymphomas
- Cohort 4: Rare thyroid cancer
- Cohort 5: Rare malignant neuroendocrine cancer
- Cohort 6: Germ-cell cancer
- Cohort 7: NK/T-cell lymphoma

This will be an adaptive design since new cohorts may be defined by the Steering Committee during the course of the trial (see Section 11.3).

The study plans to enrol 350 patients in to one of 7 cohorts. In total between 20 and 50 patients will be enrolled in each cohort, with the exception of the cohort 1 for which up to 80 patients may be enrolled (extension introduced under amendment 5 of this protocol). Following the amendment 6, up to a maximum of 50 additional patients may be included in the Sarcoma (cohort 1), Rare ovarian cancer (cohort 2) or Primary central nervous system lymphoma (cohort 3) cohorts, within the limit of 350 patients to be included in total.

Patient enrolment to individual cohorts will continue until the stopping rules applied at each interim analysis are met, or until the maximum sample size is reached.

Based on the number of investigational centres and the expected accrual rate for patients with the appropriate profile, i.e. 10-15 patients per cohort per year, patient enrolment is expected to be complete in 3.5 years.

The final analysis is scheduled for approximately 4 years after the last patient is enrolled.

10.2 Planned Statistical Analysis

The trial will use a two-stage Bayesian enrichment design, allowing for a smaller more informative trial that is specifically tied to decision making within a drug development program. This process allows for incremental changes to each cohort based on current data, rather than restricting revisions in a trial design using fixed sample sizes.

The first stage treats all patients from the different cohorts with the IP and identifies possibly sensitive subpopulations (Berry 2013). The second stage will compare response rates across subsets within the selected cohorts (Trippa 2012).

Let p0, define the rate of response that is considered uninteresting, and p1 a targeted level of interest. Let k, be the number of initially defined cohorts of patients. Let Y=0,1 define the response of patient I in the cohort k, and nki the total sample size.

We will model the probability of response, $\theta = P(Y = 1)$, and will use a subscript to indicate patient cohort: $\theta_1, \theta_2, \ldots \theta_k$. This allows us to reflect the treatment effects in each group relatively to the targeted values. All inference and stopping rules on futility or efficacy will be based on the probability scale which is clinically interpretable (Berry 2013; Jacob 2016, Zalavsky 2013).

The first stage will analyse data in each cohort independently of the other cohorts. Interim analysis of the primary endpoint (ORR according to Investigator response assessment) is planned after the 10 first patients eligible have been enrolled in the cohort and completed the first scheduled disease evaluation.

Based on the estimated response rate and its posterior distribution in each cohort, cohorts that do not reach a targeted level of confidence in terms of minimal efficacy will be potentially closed to further recruitment.

In the second stage intra-cohort analyses will be performed after every 5 additional patients accrued (Berry 2013). These analyses will use all data accumulated up to that point, and will consider potential predictive markers of efficacy; such subsets analyses will result in potentially sub-cohorts of poor outcomes that may be proposed for enrolment discontinuation while those of good outcomes will enrich the design (Mandrekar 2009; Zang 2016).

In the absence of a decision to halt enrolment, accrual in each cohort will continue until the end of the planned of recruitment period (3 years after activation of the first site) or a maximal accrual of 50 patients is achieved (whatever occurs first). In case of promising subtypes, enrolment could increase possibly above the pre-established limit of 50 patients, unless the maximal sample size of 350 patients has been reached or the termination date of study enrolment. There is no drawback from a statistical point of view that sample size of cohorts will differ from one another, while increased subsamples may allow more accurate estimates of the outcome in those subsets.

Note: *Patient enrolment will be suspended for each cohort following the inclusion of the 10 first patients eligible until the outcome of the interim analysis is known. Enrolment may be reopened prior to the interim analysis upon the decision of the Steering Committee if there is a recognised clinical need and provided that at least one response has been observed and confirmed by a collegiate revue.*

Rare ovarian cancer cohort: due to the aggressively of this disease and the prognostic heterogeneity between ovarian cancer subtypes with the difficulties this poses in the interpretation of response rate, the decision to continue enrolment in this cohort will also take into account the number of patients with stabilisation of their disease. Recruitment to this cohort will continue (up to 50 patients) if ≥ 4/10 patients achieve at least stable disease at their first disease evaluation. Response rate will be subsequently re-evaluated for each histological subset following the inclusion of the 10 first patients of each type with the application of the stopping rule as outlined below. In the subset of promising subtypes (teratoma and low-grade serous carcinoma), enrolment will increase possibly above the pre-established limit of 50 patients.

Final analysis of efficacy endpoints will be performed using both the Investigator and IRC assessment of response according to RECIST v1.1, or RECIST v1.1 combined with biomarker assessment, or IPCG response criteria, or the 'Lugano' response using the FDG-PET-CT 5-PS and assessment of EBV load. Comparisons between Investigator and IRC results will also be reported.

Statistical data will be expressed in the form of:

- Frequencies and Percentages (qualitative variables),
- Mean and standard deviation
- Median and interquartile range (quantitative variables),
- Survival curve estimates calculated with the Kaplan Meier method (survival data) (Kaplan, 1958).

Each primary and secondary evaluation criterion will be reported with a confidence interval of 95%.

Multivariate predictive analyses of each endpoint will be performed with regression models: logistic regression (for the main end point), and Cox (for PFS and OS) models.

Gail and Simon statistics will be used to test if the disease features and the mutational load measured in tumour samples of certain cohorts is correlated with pembrolizumab efficacy on the primary end point.

Data will be analysed with the SAS (SAS Inc, Cary, NC) and R (https://www.R-project.org/) software packages

10.2.1 Analysis of the Primary Endpoint

The primary endpoint in this study is objective response rate per cohort, defined as the percentage of patients in each cohort with a CR or PR, measured at the first scheduled disease assessment following study treatment initiation (Day 84, ± 7 days) as assessed by the IRC according to RECIST v1.1, or

RECIST v1.1 combined with biomarker assessment, or IPCG response criteria or the 'Lugano' response using the FDG-PET-CT 5-PS and assessment of EBV load.

Results will be expressed as a percentage of the analysis population with a 95% exact confidence interval.

Patients who withdraw from the study prior to this time point or who have non-evaluable disease will be considered as 'non-responders' in this analysis.

10.3 Statistical Rules for Trial / Early Trial Termination

The trial as a whole or individual cohorts may be stopped early based on the outcome of scheduled interim analyses (see Section 10.2). Individual cohorts may also be closed if a minimal level of accrual (10 patients in the 2 years after activation of the first site) is not achieved.

Note: Patients who are discovered to have been incorrectly assigned to a cohort (e.g. following re-evaluation of a diagnostic sample) prior to evaluation of their response will be considered as "non-evaluable" in this interim analysis.

Continuation of treatment of incorrectly assigned patients must be discussed and approved by the coordinating Investigator according to the individual benefit-risk ratio.

The same futility rule is applied to all the k cohorts at each interim analysis.

Early stopping for futility is based on the current posterior probability that p is lower than p0

$$P(p_k < p_{0k} | y_{ki}, n_{ki}) > \gamma_k \qquad \text{(equation 1)}$$

where p_{0k} defines the minimal probability of efficacy under which the treatment appears ineffective; it will be fixed at a minimum level of 0.10 in each cohort; the decision threshold $\gamma_k$may also depend on the cohort (Berry 2013). It usually lies in (0.8,0.9).

***Note**: This early stopping for futility rule is applicable for all cohorts except the rare ovarian cancer cohort (see Section 10.2).*

Additionally, we will use a stopping criterion for efficacy if the probability that the response rate, p_k, is greater than p_{1k}, is higher than 90%:

$$P(p_k > p_{1k} | y_{ki}, n_{ki}) > 0.9 \qquad \text{(equation 2)}$$

where p_{1k} defines the minimal probability of efficacy over which the treatment appears effective; it will be fixed at a minimum level of 0.50 in each cohort.

***Note**: if available scientific data warrant, the Steering Committee may modify the minimal probability levels of a given cohort before the first interim analysis.*

The prior parameters will be chosen to insure non informative either Jeffreys' or uniform prior distributions.

The second stage will be based on the comparison of response rates across subsets based on predictive biomarkers in the selected cohorts. It will be based on the comparison of response rates across subsets (any a and b in 1,,…, k) as follows

$$P(p_a - p_b > 0 \ | y_i, n_i) > 85\% \ (2) \qquad \text{(equation 3)}$$

Such subset analyses will result in potentially sub-cohorts of poor outcomes that may be proposed for discontinuation while those of good outcomes will enrich the design (Mandrekar 2009; Zang 2016).

In the absence of a decision to halt enrolment, accrual in each cohort will continue until the end of the planned of recruitment period (3 years after activation of the first site) or a maximal accrual of 50 patients is achieved (whatever occurs first) unless promising results have allowed some cohorts to include more patients.

10.4 Managing Missing and/or Non-Valid Data

Patients lost to follow-up:

Patients lost to follow-up or dead before the evaluation of primary criterion will be considered as treatment failures.

10.5 Selection of Patients to be included in the Statistical Analysis

Statistical analysis will be performed on an intent-to-treat (ITT) basis which means that the entire population of included patients will be included in the statistical analysis taking into account their assigned cohort.

Different populations of patients may be defined for the analysis that will handle the two study cohorts, separately,

First, dealing with the primary cohorts:

- Intent-to-treat population: all included patients.
- Per cohort: all registered/included patients in a particular cohort
- Treated population: all registered/included patients who receive at least one dose of IP.

Secondly, dealing with the Re-Challenge cohort:

- All patients enrolled in the Re-challenge cohort
- If the sample size of the Re-challenge cohort is large enough, some analyses restricted to sub-cohorts will be performed too.

Note that response in the Re-challenge cohort will be only that measured on this cohort.

10.6 Modifications of Statistical Analysis Plan

Any modification/change made to the initial statistical analysis plan (SAP) will be described in detail, well-argued and commented in an updated version of the SAP. These modifications may include complementary/exploratory analyses not envisaged initially.

11 OVERSIGHT COMMITTEES

11.1 Independent Review Committee

An IRC with expertise and experience in the pathology, will be set up at the beginning of the trial to perform retrospective assessment of disease response based on centralized radiographic imaging and other relevant data. The results of this central review will be used in the final analysis of efficacy (Section 6.1.1)

11.2 Independent Data Monitoring Committee

An IDMC, with expertise and experience in the pathology, and without direct involvement in the conduct of the trial, will be set up at the beginning of the trial, specifically to guarantee effective protection of patients, insure the ethical conduct of the trial, benefit/risk ratio of the trial, and to ensure the independent review of the scientific results during the trial and at the end of the trial.

The IDMC will be composed of at least 3 expert members (2 clinicians and 1 statistician). IDMC members must have no financial interest in the outcome of the trial and be independent from the Investigators, Funding bodies, Sponsor, Steering committee and any other institution involved in the trial. Members will be selected according to their expertise in their respective fields by the Institutional AsCé Programme Committee (IAPC, see Section 11.4).

The IDMC will meet at least once every 12 months and additionally if expert advice is sought by the Steering Committee (SC, see Section 11.3). The IDMC will review accumulated data regarding overall safety and efficacy of the study treatment including the results of interim analyses, collected safety reports prepared by the Sponsor as well as published data and information provided by the IP license holder concerning concurrent studies. Data presented to IDMC are strictly confidential.

The IDMC will provide recommendations regarding continued recruitment or termination of enrolment in each cohort, or if new cohorts/indications should be considered as well as any modifications of protocol design which might be necessary.

The IDMC may recommend the early termination of the trial if one of the following conditions is met:

- The results of the interim analysis clearly show that the experimental treatment is ineffective or more effective than expected (see equations 1 and 2 in Section 10.3).
- An unacceptable level of toxicity is reported.
- All available data from the trial or any other source of information are sufficiently convincing to influence the therapeutic practices of the majority of clinicians.

The IDMC has only a consultative role; it will inform the Sponsor and Steering Committee who will decide whether the IDMC recommendation will be followed.

An IDMC charter must be available upon submission of the trial (initial protocol) to the respective Competent Authority.

11.3 Steering Committee

A Steering Committee has been implemented for this trial. The Steering Committee will meet on a quarterly basis. Additional meetings may be set, as required.

The Steering Committee is composed of:

- The Coordinating Investigator
- The Biostatistician
- Project Manager (or delegate)
- Representative(s) of INCa
- Pathology expert(s) designated for each pathology cohort
- Other participants as required depending the meeting agenda.

Representative(s) of the IP license holder (Merck Sharp & Dohme) will also be invited to attend at least once per semester.

The Steering Committee will review the accumulated data regarding overall safety and efficacy of the study treatment, including the results of interim analyses, collated safety reports prepared by the Sponsor, as well as published data and information provided by the IP license holder concerning concurrent studies. The Steering Committee will also review, or may request, recommendations made by the IDMC. The Steering Committee, based on this information, will assist the Sponsor in resolving issues and/or questions encountered during the conduct of the trial and will make recommendations regarding continued recruitment or termination of enrolment in each cohort, or if new cohorts/indications should be considered.

Any recommendations which would result in substantial modifications to the conduct of the study, amendment of the protocol design, or the introduction of new indications must obtain approval from the ANSM and EC prior to implementation (see Section 14.5).

The roles and responsibilities of the Steering Committee are further detailed in the Steering Committee Charter.

The Coordinating Investigator will generate minutes of each meeting and report the outcome of Steering Committee meetings to the IAPC (see Section 11.4).

11.4 Institutional AcSé Programme Committee

The IAPC is responsible for piloting the complete AcSé programme and providing the overall strategic orientation. It is chaired by the President of INCa and composed of:

- INCa representatives
- Coordinating Investigators of active trials and other expert physicians
- Statisticians
- Patient representatives
- Sponsors of active protocols and other potential sponsors
- Representatives of centralised service providers (“platforms”)
- Other participants at the request of INCa.

The roles and responsibilities of the IAPC are fully described in the INCa AcSé Programme Charter.

The responsibility for calling and organising an IAPC meeting lies with INCa.

12 ACCESS TO DATA

It is the responsibility of the Sponsor to obtain the agreement from all parties involved in the research in order to guarantee that the Sponsor has direct access to all investigator sites, original records, source data/document and reports to allow quality control and auditing by the sponsor or on behalf of the Sponsor.

Investigators will make available to the authorized persons the documents and the patients' individual data that are essential to monitor the trial on an ongoing basis, to perform quality control and audit of this research in accordance with national regulatory requirements.

13 QUALITY ASSURANCE

13.1 Data Collection

The Database will be hosted by the Institut du Cancer Montpellier (ICM) – Val d'Aurelle, Unité de Biométrie – CTD INCa, 208 rue des Apothicaires – Parc Euromédecine – 34298 Montpellier cedex 5 – France under the responsibility of Sophie Gourgou. Database management will be provided by an electronic Case Report Form (eCRF) developed using the Ennov Clinical® software. The conditions for data transfer of all or part of the study database will be decided by the study sponsor in accordance with the written consent provided by each patient.

All data necessary to the research must be entered in a timely manner into the trial eCRFs. Case report forms will be completed by the Investigator and other designated members duly designated from his/her staff.

The following data will be collected:

- Demographic information.
- Disease and medical history.
- Clinical examination results, weight, height, vital signs, ECG.
- Blood and biological test results.
- Tumour evaluation results and copies of radiologic images for central review.
- Adverse events and serious adverse events occurring at each cycle.
- IP administration.

During the trial, Data clarification forms (DCFs) may be sent for data consistency validation, by the UNICANCER Central Data Center, under the responsibility of Mrs. Sophie Gourgou, located at the following address:

Institut régional du Cancer Montpellier / Val d'Aurelle, 208 rue des Apothicaires – Parc Euromédecine - 34298 Montpellier cedex 5 - France.

Corrections addressed by these queries should be made by persons authorized to complete the eCRF.

When using eCRF, traceability of access and changes is traced by the software (audit trial).

13.2 Trial Monitoring

To ensure the authenticity and credibility of data in accordance with the "Décision portant sur les Bonnes Pratiques Cliniques, 24 November 2006", the sponsor establishes a system of quality assurance that consists in:

- The management and the monitoring of the trial according to R&D UNICANCER procedures;
- The quality control data of the investigational centres by the monitor involves:
    - verifying that the protocol, as well as the current guidelines ICH-GCP, the national regulatory requirements, are accurately followed,
    - verifying the informed consent and the eligibility of each patient participating in another research,
    - verifying that the eCRF data is consistent and in agreement with the source documents,
    - verifying the notification of each SAE,
    - verifying the drug traceability (dispatching, storage and accountability),
    - verifying *(if applicable)* that patients are not already participating in another research trial which may exclude their inclusion in this protocol. The monitor also verifies that patients have not participate in another trial following which an exclusion period if applicable before they can participate in another protocol,
- The audit of the participating investigational centres when deemed necessary;
- The centralized review of disease response (Section 6.1.1).

The CRAs in charge of trial monitoring will be mandated by the Sponsor. They must have access to all patient data as necessary for their duty in accordance with the national regulatory requirements. The CRAs are bound by professional secrecy under the national regulatory requirements. Written reports must be issued to ensure monitoring visit traceability.

In order to ensure the optimal research quality control, the investigator commits to provide the monitor with direct access to all patient files.

13.3 Audits and Inspection

As part of its audit program, the Sponsor may need to audit some investigational centres. The centre and the Investigator agree that audits are carried out by Sponsor or any person duly authorized for at least fifteen years after the trial.

More generally, the investigator centre and the Investigator undertake to devote the time necessary to audit procedures, control and additional information requested by the sponsor or by a Concerned Competent Authority.

A Competent Authority may also wish to conduct an inspection (during the trial or after its completion). If a Competent Authority requests an inspection, the investigator must inform the sponsor immediately that this request has been made. The investigator must provide a direct access to source documents.

14 ETHICAL AND REGULATORY CONSIDERATIONS

14.1 General Requirements

The trial must be conducted in accordance with the French national regulatory requirements:

- Loi Huriet (n° 88-1138) du 20 décembre 1988 relative à la Protection des Personnes se prêtant à la Recherche Biomédicale et modifiée par la loi d'orientation de Santé Publique (n° 2004-806) du 9 août 2004,
- Loi Informatique et Libertés n° 78-17 du 6 janvier 1978 modifiée,
- Loi de Bioéthique n° 2011-814 du 08 Juillet 2011,
- Décision portant sur les Bonnes Pratiques Cliniques du 24 novembre 2006,
- Bonnes Pratiques de Fabrication en vigueur, notamment la ligne directrice particulière relative aux médicaments expérimentaux.

14.2 Clinical Trial Authorization

Prior to the start of the trial, the sponsor will submit the trial protocol, patient information sheet(s), informed consent form(s), and other trial-related documents as required by French national regulatory requirements, to the competent authority (Agence National de Santé Medical, ANSM) for authorization and to the EC for their written approval.

The sponsor will inform ANSM and the EC, according to French national regulatory requirements, about protocol amendments including any substantial modification that require an ethical/regulatory reconsideration of the trial protocol.

Data recorded during this trial are subject to a computerized treatment by the biostatistical unit of Université Paris VII-Jussieu, Département de Biostatistique et Informatique Médicale under the responsibility of Dr Sylvie Chevret, in compliance with the "Loi Informatique et Libertés n° 78-17, 6 January 1978 modified".

The collection of biological samples implemented within the framework of the trial was declared to ANSM in the same time that the request of Clinical Trial Authorization. After the trial, and in case of storage, the storage of the collection of biological samples will be notified to the Minister of Research (and submitted to the EC to notice if change of purpose of Research).

14.3 Patient Identification

Patient will be identified by a numeric code, the first letter of the last name, the first letter of the first name and the date of birth in case of homonymy.

All patients will receive a unique patient identification number when signing the informed consent form by the patient and before any trial procedure is performed. This number will be used to identify the patient throughout the trial and must be used on all trial documentation related to this patient. The patient identification number must remain constant throughout the entire trial; it must not be changed.

14.4 Patient Information and Consent

Patient information and informed consent from the patient must be handled in accordance with the "French regulation, especially article L.1122-1 and subsequent articles.

Prior to the participation of a patient in the trial, the patient will be informed both verbally and in writing about the objectives of the trial, its methods, anticipated benefits and potential risks and the discomfort to which they may be exposed. All items must be explained by the investigator in a language and in terms that are easy to comprehend by the patient. Patients will also be informed that the participation is voluntary and that they have the right to withdraw from participation in the trial at any time without giving the reasons and without any disadvantages for their subsequent care.

The patients must be given enough time to decide about their participation in the trial.

The PIS/ICF must be associated within the same document to ensure that all the information regarding the trial is provided to the patient. Each patient will confirm their consent in writing prior to trial start and any trial-related procedure. The informed consent form must be personally dated and signed by the

patient and Investigator in two originals. One original of the patient information sheet and the signed informed consent will be provided to the patient; the other will be filed in the Trial Master File (TMF).

The patient may withdraw consent to further study participation at any time. The patient is not obliged to give reason(s) for withdrawing from the trial. However, the Investigator should make a reasonable effort to ascertain the reason(s) while fully respecting the patient's rights. In case of any changes are made to the written PIS/ICF, the Investigator will ensure that all patients still participating in the trial receive the updated patient information in a timely manner and are asked for written consent to the changes.

In the event of withdrawal of consent, the Investigator will ensure that the eCRF is completed up to the date of withdrawal. Further information (with the exception of SAE reporting (see Section 8.2) should not be collected concerning this patient however. All data and samples collected prior to the withdrawal of consent may be kept in the database and exploited in the planned analysis, unless the patient states his/her opposition.

14.5 Changes to the Protocol

The trial will be conducted in strict compliance with this protocol. Changes will be included in an amended version of the trial protocol. The list and tracking of modifications and rationales will be provided in the amended version of the trial protocol. Amended trial protocols with substantial modifications have to be submitted to the ANSM and to the EC by the sponsor, according to the French regulation.

Amendments with substantial modifications to the protocol should be implemented only after approval by the ANSM and the EC.

14.6 Sponsor Responsibilities

UNICANCER, the sponsor of the trial, who has initiated this trial and is therefore accountable for the trial management and for verifying that the financing schedule covers the anticipated expenses.

The main sponsor responsibilities are:

- The protocol writing and amendments, as well as trial-related documents;
- The subscription of a civil-responsibility insurance;
- The obtaining of an EudraCT (European Drug Regulatory Authorities Clinical Trials) identification number;
- The request according to the French regulation the opinion of the EC, and authorization from the ANSM on the initial protocol and possible amendments;
- The notification of any SUSAR, according to the French regulation, to the ANSM, and the notification of this information to the EC and the physician-investigators of the trial;
- The information on the trial to the investigational centres' heads, pharmacists and physician-investigators, according to local regulatory requirements;
- The information of any new event to the ANSM, and the measures taken, and the notification to the EC in the same time, according to the local requirements;
- The recording of the trial in database research accessible to the public
- Also the recording of the trial in the international database ClinicalTrials.gov and the "Register of French cancer clinical trials" of the INCa, before the enrolment of the first patient ;
- The permanent assessment of ongoing safety of the investigational drug and therefore the safety of patients;
- The transmission of the Development Safety Update Reports (DSUR) to the ANSM and to the EC according to the French regulation;
- The notification of the beginning and the end of the trial to the ANSM and to the responsible EC, according to the French regulation;
- The final report writing on the trial and its communication, according to the French regulation, to the ANSM;
- The information on the trial's results, according to the French regulation, to the ANSM, to the EC. The trial's results may also be communicated to the research participant, at their request, by the physician-investigator;

- The archiving of the trial's essential documents for a minimal duration of 15 years after the research has ended.

14.7 Insurance Compensation

R&D UNICANCER, the sponsor of the trial certifies that it has taken out a Civil Liability insurance policy covering its civil liability for this clinical trial under its sponsorship. This insurance policy is in accordance with local laws and requirements. The insurance of the sponsor does not exempt the investigator and its team from maintaining their own liability insurance policy.

14.8 Investigator Responsibilities

The Principal Investigator of each investigator site participating in the trial commits to conduct the trial as specified in this protocol and in accordance with the "Décision portant sur les Bonnes Pratiques Cliniques, 24 November 2006".

It is the responsibility of the Principal Investigator to:

- Provide to the sponsor with her/his own *curriculum vitae* (CV) and those of his/her collaborators, and evidence that the center will be able to conduct the trial. CV must be dated and signed;
- Identify the members of his/her team who participate in the trial and to define their individual responsibilities;
- Start recruiting patients after approval of the sponsor;
- Be available for monitoring visits, audits and investigator meetings.

It is the responsibility of each Principal Investigator and of each investigator team member to:

- Ensure the confidentiality of all data recorded during the trial;
- Collect the informed consent, written, dated and signed personally by each individual research participant before any specific selection procedure to the trial;
- Regularly complete the eCRF for each of the patients included in the trial and allow the CRA mandated by the sponsor to have direct access to the source documents in order to validated the data collected in the eCRF;
- Declare to the sponsor as soon as he aware, any serious adverse event occurring during the trial according to provisions of this protocol;
- Accept regular visits by the CRA and possibly those of auditors as mandated by the sponsor or the inspectors of the respective regulatory authorities;
- Date, correct and sign the corrections made in the eCRF and the requests of the DCFs for each patient included in the trial.

14.9 Federation of the Patient Committees for Clinical Research in Cancerology

The dedicated task of the Committee is to review clinical trial protocols in oncology. The French patient committees' federation is coordinated by the "Ligue Nationale Contre le Cancer" and INCa. The Committee reviews the trial protocol and documentation to suggest improvements in the quality of information given to the patients, the delivery of trial treatment and monitoring plan, to maximize the convenience and comfort of the patients.

14.10 Human Biological Samples Collection

Biological studies are necessary to improve the knowledge of diseases as they allow the development of new and more effective treatments. These studies use human biological samples (blood, tissue tumours) than can be collected from patients either while they receive medical care (examination, surgery) or specifically for the research purpose.

As for research aimed at studying the genetic characteristics of the patients, a consent form must be signed by each participating patient after he has been informed on the research undertaken, irrespective of the type of sample collected (already existing or specifically collected).

Additionally, it must be noted that the results of biological studies may be published under the condition that all the data relative to the patients are made anonymous.

14.10.1 Storage and Use of Disease Assessment Samples (Blood, Biopsy, Tumour Specimens)

At study entry, archived FFPE biopsy material obtained as part of the standard medical care (e.g. confirmation of diagnosis) or prior surgical intervention will be collected and shipped to the R&D UNICANCER Biological Resources Centre (Centre des Resources Biologiques) at the Centre Leon Berard (CRB-CLB) 28 rue Laënnec – 69373 Lyon cedex 08, Bâtiment CHENEY B Rez de Chaussée - France.

Note: *if suitable archived biopsy material is not available, a fresh biopsy of a tumour lesion may be requested, unless this is medically contraindicated.*

These tumour samples will be used to perform retrospective immunohistochemical staining to identify biomarkers related to the efficacy of pembrolizumab therapy.

Any biological specimens not used for genomic profiling will be stored centrally in the Unicancer Biobank located at the CRB-CLB.

The patient will be informed via a patient information sheet that, in the absence of opposition of his part, these biological samples will be prepared, stored and used for this research.

The preparation, storage and use of the biological samples does not modify or imply any change with respect to the diagnosis, cares and treatments that will be administrated to the patient.

14.10.2 Collecting Additional Biological Samples for Research Purposes

One of the objectives of this research is to investigate the molecular profile of patients who respond to pembrolizumab therapy, versus patients without tumour response within the same disease cohort. Analysis will include retrospective dosage of auto-antibodies and anti-tumour antibodies in serum, dosage of circulating cytokines, chemokines and receptor/ligand complexes in plasma, and analysis of ctDNA, RNA and PBMC.

To this end, blood samples will be collected during the Screening period and following treatment administration in Cycles 1, 2, 3 and 4. Additional samples may also be collected if the patient experiences a suspected immune-related toxicity.

In selected cases where exceptional responses or unexpected toxicities are observed additional biopsy samples of the tumour could also be collected during the trial treatment for exploratory studies.

These biological samples will be prepared, stored and used for the purpose of the research.

These additional samples are subject to written consent from the patient which is revocable at any time. Similarly, at any time of the research, the patient has the opportunity to request the destruction of these samples.

15 DATA PROCESSING AND CONSERVATION OF DOCUMENTS AND DATA

15.1 Data Processing

15.1.1 Under the Responsibility of the Sponsor

The statistical data analysis will be transferred to the biostatistical unit of Université Paris VII-Jussieu, Département de Biostatistique et Informatique Médicale under the responsibility of Dr Sylvie Chevret. All data from the trial remain the property of R&D UNICANCER, the research sponsor.

The software Clinsight® will be used for data entry, management and archiving of data. The statistical analysis will be performed using the SAS (SAS Inc, Cary, NC) and R (https://www.R-project.org/) software packages.

15.1.2 In the Investigational Centre, When Computerized Medical Records Are Used

If the case that computerized patient records are used in a participating centre to process or store data related to the trial, the centre must:

- Verify and document that the computer system used to process the data is in conformity with the requirements in terms of data completeness, accuracy and reliability with respect to the expected performances (quality validation);
- Define and follow the standardized procedures related to these systems;
- Ensure that these systems allow modifications of the collected data, that each modification is automatically authenticated, and that the data cannot be removed (i.e. any change or modification of the data must be traceable);
- Set up and maintain a security control to prevent unauthorized access to the data;
- Establish and regularly update the list of persons authorized to have access and modify the data;
- Carry out appropriate backups of the data;
- Ensure confidentiality, whenever it is applicable (e.g. during data input);
- Ensure that the computerized patient individual Data are processed in accordance with the “Loi Informatique et Libertés n° 78-17, 6 January 1978 modified”.

If data are transformed while being processed, it should always be possible to compare them with the original observations/records.

The computerized system used to identify the patients participating in the trial must not be ambiguous and should allow the identification of all data collected for each patient while preserving their confidentiality in accordance with the “Loi Informatique et Libertés n° 78-17, 6 January 1978 modified”.

15.2 Retention of Documents by Investigator Sites

The Investigator must maintain source documents for each trial patient.

All information in case report forms must be traceable and consistent with source documents, which are generally maintained in the patient’s file. The source documents should contain all demographic and medical information, laboratory data, radiology, electrocardiograms, etc…, including a copy of the patient information sheet and signed informed consent form.

The investigator must retain essential documents as listed below, as described below. The Investigator agrees to adhere to the document retention procedures by signing the protocol. Essential documents include:

- Approvals from the EC for the trial protocol and all amendments;
- Authorizations from the ANSM for the trial protocol and all amendments;

- All source documents and laboratory records;
- eCRF copies;
- Patients' informed consent forms;
- Investigator master file and pharmacy file;
- Any other pertinent trial document.

All documents of the trial must be kept in a locked and secured place and considered to be confidential material.

Data will be archived under the responsibility of the principal investigator of each participating centre according to the "Décision portant sur les Bonnes Pratiques Cliniques, 24 November 2006". The archives will be kept as well as a list of patient identifications for a minimum period of 15 years after the end of the trial. R&D UNICANCER will inform the investigational centres when the trial-related records are no longer required.

The investigational centre may destroy the data only after the sponsor has given its written authorization.

16 DATA OWNERSHIP AND CONFIDENTIALITY

By signing the protocol, the investigator agrees to keep all information provided by R&D UNICANCER in strict confidence and to request similar confidentiality from his/her staff. This obligation does not cover information to be provided to the patients nor information already publically available.

Trial documents provided by R&D UNICANCER (protocols, investigators' brochures, CRFs and other material) will be stored appropriately to ensure their confidentiality. The information provided by R&D UNICANCER to the physician-investigator may not be disclosed to others without direct written authorization from R&D UNICANCER.

The physician-investigator commits not to publish, not to spread or use in any manner, directly or indirectly, the scientific and technical information and results related to the trial.

17 PUBLICATION RULES

All information resulting from this trial is considered to be confidential, at least until appropriate analysis and checking has been completed by the sponsor, the principal investigator and the statistician of the trial.

Any publication, abstract or oral presentations including results of the trial must be submitted to the sponsor (R&D UNICANCER) for approval.

Additionally, all communications, manuscripts or oral presentations must include a section mentioning R&D UNICANCER as well as any institution, physician-investigators, collaborative research group, scientific society that has contributed to the trial, including organizations that have provided financial support.

The list of authors of any publication, in French or in English must include the following:

- Coordinating Investigator (first or last author);
- Investigators having included the largest numbers of patients (sorted by decreasing order) irrespective of the collaborative group they belong to;
- A person representing the expert group for each pathology cohort, if not already mentioned among the investigators having included the largest numbers of patients;
- The trial statistician;
- A person representing the sponsor (R&D UNICANCER, e.g. Project Manager)

Similarly, the list of authors of ancillary study (biological study) publications will include the name of the person(s) who carried it out as well as the name of any other person who was involved in it.

It is desirable to include the contributors from weakly recruiting centres and who have not been mentioned in the first article in the later publications.

R&D UNICANCER will arbitrate and rule any dispute that may arise.

18 REFERENCES

AcSé Programme Charter: Available at: http://www.e-cancer.fr/Professionnels-de-la-recherche/Recherche-clinique/Le-programme-AcSe/

Abrey LE, Batchelor TT, Ferreri AJ, Gospodarowicz M, Pulczynski EJ, *et al*. Report of an international workshop to standardize baseline evaluation and response criteria for primary CNS lymphoma. *J Clin Oncol*. 2005; 23(22):5034-5043.

Akamatsu, H., Teraoka, S., Koh, Y., Yamanaka, T., Yamamoto, N., & Nakagawa, K. (2019). A Phase II Study of Nivolumab in Patients With Advanced Non-small-cell Lung Cancer who Responded to Prior PD-1/L1 Inhibitors: West Japan Oncology Group 9616L (WJOG9616L). Clinical Lung Cancer, 20(2), 139–141. https://doi.org/10.1016/j.cllc.2018.12.001

Barrington SF, Mikhaeel NG, Kostakoglu L, Meignan M, Hutchings M, *et al*. Role of imaging in the staging and response assessment of lymphoma: Consensus of the International Conference on Malignant Lymphomas Imaging Working Group. *JCO*. 2014 ; 32(27) :3048-3058

Berghoff AS, Ricken G, Widhalm G, Rajky O, Hainfellner JA, *et al*. PD1 (CD279) and PD-L1 (CD274, B7H1) expression in primary central nervous system lymphomas (PCNSL). *Clin Neuropathol*. 2014; 33(1):42-49.

Bernstein MB, Garnett CT, Zhang H, Velcich A, Wattenberg MM, *et al*. Radiation-induced modulation of costimulatory and coinhibitory T-cell signaling molecules on human prostate carcinoma cells promotes productive antitumor immune interactions. *Cancer Biother Radiopharm*. 2014; 29(4):153-161.

Berry SM, Broglio KR, Groshen S, Berry DA. Bayesian hierarchical modeling of patient subpopulations: efficient designs of Phase II oncology clinical trials. *Clin Trials*. 2013; 10(5):720-734.

Bertucci F, Finetti P, Mamessier E, Pantaleo MA, Astolfi A, *et al*. PDL1 expression is an independent prognostic factor in localized GIST. *Oncoimmunology*. 2015; 4(5):e1002729.

Boland JM, Kwon ED, Harrington SM, Wampfler JA, Tang H, *et al*. Tumor B7-H1 and B7-H3 expression in squamous cell carcinoma of the lung. *Clin Lung Cancer*. 2013; 14(2):157-163.

Chapuy B, Roemer MG, Stewart C, Tan Y, Abo RP, *et al*. Targetable genetic features of primary testicular and primary central nervous system lymphomas. *Blood*. 2016; 127(7):869-881.

Chen BJ, Chapuy B, Ouyang J, *et al*. PD-L1 expression is characteristic of a subset of aggressive B-cell lymphomas and virus associated malignancies. *Clin Cancer Res*. 2013;19(13):3462-3473.

Cheson BD, Fisher RI, Barrington SF, Cavalli F, Schwartz LH, *et al*. Recommendations for initial evaluation, staging and response assessment of Hodgkin and non-Hodgkin lymphoma: The Lugano classification. *Blood*. 2014; 32(27):3059-3068.

Chowdhury S, Veyhl J, Jessa F, Polyakova O, Alenzi A, *et al*. Programmed death-ligand 1 overexpression is a prognostic marker for aggressive papillary thyroid cancer and its variants. *Oncotarget*. 2016; 7(22):32318-32328.

Cierna Z, Mego M, Miskovska V, Machalekova K, Chovanec M, *et al*. Prognostic value of programmed-death-1 receptor (PD-1) and its ligand 1 (PD-L1) in testicular germ cell tumors. *Ann Oncol*. 2015; 27(2):300-305.

Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron*. 1976; 16(1):31-41.

Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, *et al*. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009; 45(2):228-247.

Fankhauser CD, Curioni-Fontecedro A, Allmann V, Beyer J, Tischler V, *et al*. Frequent PD-L1 expression in testicular germ cell tumors. *Br J Cancer*. 2015; 113(3):411–413.

Fizazi K, Pagliaro L, Laplanche A, Fléchon A, Mardiak J, *et al*. Personalised chemotherapy based on tumour marker decline in poor prognosis germ-cell tumours (GETUG 13) : a phase 3, multicentre, randomized trial. *Lancet Oncol.* 2014; 15:1442-1450.

Francisco LM, Salinas VH, Brown KE, Vanguri VK, Freeman GJ, *et al*. PD-L1 regulates the development, maintenance, and function of induced regulatory T cells. *J Exp Med*. 2009; 206(13):3015-3029.

Fritzsching B, Fellenberg J, Moskovszky L, Sápi Z, Krenacs T, *et al*. CD8(+)/FOXP3(+)-ratio in osteosarcoma microenvironment separates survivors from non-survivors: a multicenter validated retrospective study. *Oncoimmunology*. 2015; 4(3):e990800.

Fujii H, Arakawa A, Utsumi D, Sumiyoshi S, Yamamoto Y, *et al*. CD8+ tumor-infiltrating lymphocytes at primary sites as a possible prognostic factor of cutaneous angiosarcoma. *Int J Cancer*. 2014; 134(10):2393–2402.

Gatta G, van der Zwan JM, Casali PG, Siesling S, Dei Tos AP, *et al*. Rare cancers are not so rare: the rare cancer burden in Europe. *Eur J Cancer*. 2011; 47(17):2493–2511.

Giaj Levra, M., Cotté, F.-E., Corre, R., Calvet, C., Gaudin, A.-F., Penrod, J. R., Grumberg, V., Jouaneton, B., Jolivel, R., Assié, J.-B., & Chouaïd, C. (2020). Immunotherapy rechallenge after nivolumab treatment in advanced non-small cell lung cancer in the real-world setting: A national data base analysis. Lung Cancer (Amsterdam, Netherlands), 140, 99–106. https://doi.org/10.1016/j.lungcan.2019.12.017

Gobbini, E., Toffart, A. C., Pérol, M., Assié, J.-B., Duruisseaux, M., Coupez, D., Dubos, C., Westeel, V., Delaunay, M., Guisier, F., Veillon, R., Gounant, V., Giroux Leprieur, E., Vanel, F.-R., Chaabane, N., Dansin, E., Babey, H., Decroisette, C., Barlesi, F., Levra, M. G. (2020). Immune Checkpoint Inhibitors Rechallenge Efficacy in Non-Small-Cell Lung Cancer Patients. Clinical Lung Cancer, 21(5), e497–e510. https://doi.org/10.1016/j.cllc.2020.04.013

Gobbini, E., Charles, J., Toffart, A.-C., Leccia, M.-T., Moro-Sibilot, D., & Levra, M. G. (2020). Literature meta-analysis about the efficacy of re-challenge with PD-1 and PD-L1 inhibitors in cancer patients. Bulletin Du Cancer. https://doi.org/10.1016/j.bulcan.2020.07.009

Hamanishi J, Mandai M, Iwasaki M, Okazaki T, Tanaka Y, *et al*. Programmed cell death 1 ligand 1 and tumor-infiltrating CD8+ T lymphocytes are prognostic factors of human ovarian cancer. *Proc Natl Acad Sci USA*. 2007; 104(9):3360–3365.

Hamanishi J, Mandai M, Ikeda T, Minami M, Kawaguchi A, *et al*. Efficacy and safety of anti-PD-1 antibody (Nivolumab: BMS-936558, ONO-4538) in patients with platinum-resistant ovarian cancer. *J Clin Oncol*. 2014; 32:5s, suppl; abstr 5511.

Hamanishi J, Mandai M, Ikeda T, Minami M, Kawaguchi A, *et al*. Durable tumor remission in patients with platinum-resistant ovarian cancer receiving nivolumab. *J Clin Oncol*. 2015; 33,suppl; abstr 5570

Hwang WT, Adams SF, Tahirovic E, Hagemann IS, Coukos G. Prognostic significance of tumor-infiltrating T cells in ovarian cancer: a meta-analysis. *Gynecol Oncol*. 2012; 124(2):192-198.

Inman BA, Sebo TJ, Frigola X, Dong H, Bergstralh EJ, *et al*. PD-L1 (B7-H1) expression by urothelial carcinoma of the bladder and BCG-induced granulomata: associations with localized stage progression. *Cancer*. 2007; 109(8):1499-1505.

Isobe K, Uno T, Tamaru J, *et al*. Extranodal natural killer/T-cell lymphoma, nasal type: the significance of radiotherapeutic parameters. *Cancer* 2006;106(3):609-615.

Jaccard A, Gachard N, Marin B, *et al*; GELA and GOELAMS Intergroup. Efficacy of L-asparaginase with methotrexate and dexamethasone (AspaMetDex regimen) in patients with refractory or relapsing extranodal NK/T-cell lymphoma, a phase 2 study. *Blood* 2011;117(6):1834-1839.

Jacob L, Uvarova M, Boulet S, Begaj I, Chevret S. Evaluation of a Multi-arm Multi-stage Bayesian Design for Phase II Drug Selection Trials – An example in Hemato-oncology. *BMC Med Res Methodol*. 2016; 16(1):67.

Joseph CG, Hwang H, Jiao Y, Wood LD, Kinde I, *et al*. Exomic analysis of myxoid liposarcomas, synovial sarcomas, and osteosarcomas. *Genes Chromosomes Cancer*. 2014; 53(1):15-24.

Kaplan EL, Meier P: Nonparametric estimation from incomplete observations. *J Amer Statist Assn*. 1958; 53:457–481.

Karim R, Jordanova ES, Piersma SJ, Kenter GG, Chen L, *et al*. Tumor-expressed B7-H1 and B7-DC in relation to PD-1+ T-cell infiltration and survival of patients with cervical carcinoma. *Clin Cancer Res*. 2009; 15(20):6341–6347.

Keir ME, Butte MJ, Freeman GJ, Sharpe AH. PD-1 and its ligands in tolerance and immunity. *Annu Rev Immunol*. 2008;26:677-704.

Kim SJ, Kim K, Kim BS, *et al*. Phase II trial of concurrent radiation and weekly cisplatin followed by VIPD chemotherapy in newly diagnosed, stage IE to IIE, nasal, extranodal NK/T-Cell Lymphoma: Consortium for Improving Survival of Lymphoma study. *J Clin Oncol* 2009;27(35):6027-6032.

Konishi J, Yamazaki K, Azuma M, Kinoshita I, Dosaka-Akita H, *et al*. B7-H1 expression on non-small cell lung cancer cells and its relationship with tumor-infiltrating lymphocytes and their PD-1 expression. *Clin Cancer Res*. 2004; 10(15):5094-5100.

Kryczek I, Liu R, Wang G, Wu K, Shu X, *et al*. FOXP3 defines regulatory T cells in human tumor and autoimmune disease. *Cancer Res*. 2009; 69(9):3995-4000.

Kwong YL. Natural killer-cell malignancies: diagnosis and treatment. *Leukemia* 2005;19(12):2186-2194.

Kwong YL, Kim WS, Lim ST, *et al*. SMILE for natural killer/T-cell lymphoma: analysis of safety and efficacy from the Asia Lymphoma Study Group. *Blood*. 2012;120(15):2973-2980.

Kwong YL, Chan TSY, Tan D, Kim SJ, Poon LM, *et al*. PD1 blockade with pembrolizumab is highly effective in relapsed or refractory NK/T-cell lymphoma failing L-asparaginase. *Blood*. 2017;129(17):2437-2442

Lesokhin AM, Ansell SM, Armand P, Scott EC, Halwani A, *et al*. Nivolumab in Patients With Relapsed or Refractory Hematologic Malignancy: Preliminary Results of a Phase Ib Study. *J Clin Oncol*. 2016; 34(23):2698-2704.

Li S, Feng X, Li T, *et al*. Extranodal NK/T-cell lymphoma, nasal type: a report of 73 cases at MD Anderson Cancer Center. *Am J Surg Pathol* 2013;37(1):14-23.

Li YX, Yao B, Jin J, *et al*. Radiotherapy as primary treatment for stage IE and IIE nasal natural killer/T cell lymphoma. *J Clin Oncol* 2006;24(1):181-189.

Lissoni P, Barni S, Tancini G, Mainini E, Piglia F, *et al*. Immunoendocrine therapy with low-dose subcutaneous interleukin-2 plus melatonin of locally advanced or metastatic endocrine tumors. *Oncology*. 1995; 52(2):163–166.

Lussier DM, O'Neill L, Nieves LM, McAfee MS, Holechek SA, *et al*. Enhanced T-cell immunity to osteosarcoma through antibody blockade of PD-1/PD-L1 interactions. *J Immunother*. 2015; 38(3):96–106.

Mandrekar SJ, Sargent DJ. Clinical trial designs for predictive biomarker validation: theoretical considerations and practical challenges. *J Clin Oncol*. 2009; 27(24):4027-4034.

Mehnert JM, Varga A, Brose M, Aggarwal RR, Lin CC, *et al*. Pembrolizumab for advanced papillary or follicular thyroid cancer: preliminary results from the phase 1b KEYNOTE-028 study. *J Clin Oncol*. 2016; 34, suppl; abstr 6091

Mezache L, Paniccia B, Nyinawabera A, Nuovo GJ. Enhanced expression of PD L1 in cervical intraepithelial neoplasia and cervical cancers. *Mod Pathol*. 2015; 28(12):1594–1602.

Monnier-Benoit S, Mauny F, Riethmuller D, Guerrini J-S, Căpîlna M, *et al*. Immunohistochemical analysis of CD4+ and CD8+ T-cell subsets in high risk human papillomavirus-associated pre-malignant and malignant lesions of the uterine cervix. *Gynecol Oncol*. 2006; 102(1):22–31.

Mosmann TR, Sad S. The expanding universe of T-cell subsets: Th1, Th2 and more. *Immunol Today*. 1996; 17(3):138-146.

Nomi T, Sho M, Akahori T, Hamada K, Kubo A, *et al*. Clinical significance and therapeutic potential of the programmed death-1 ligand/programmed death-1 pathway in human pancreatic cancer. *Clin Cancer Res*. 2007; 13(7):2151-2157.

Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, *et al*. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol*. 1982 Dec;5(6):649-655.

Ott PA, Fernandez MEE, Hiret S, Kim DW, Moss RA, *et al*. Pembrolizumab (MK-3475) in patients (pts) with extensive-stage small cell lung cancer (SCLC): Preliminary safety and efficacy results from KEYNOTE-028. *J Clin Oncol*. 2015; 33(suppl):abstr 7502

Reuschenbach M, von Knebel Doeberitz M, Wentzensen N. A systematic review of humoral immune responses against tumor antigens. *Cancer Immunol Immunother*. 2009; 58(10):1535-1544.

Schlienger K, Chu CS, Woo EY, Rivers PM, Toll AJ, *et al*. TRANCE- and CD40 ligand-matured dendritic cells reveal MHC class I-restricted T cells specific for autologous tumor in late-stage ovarian cancer patients. *Clin Cancer Res*. 2003; 9(4):1517-1527

Shen JK, Cote GM, Choy E, Yang P, Harmon D, *et al*. Programmed cell death ligand 1 expression in osteosarcoma. *Cancer Immunol Res*. 2014; 2(7):690–698.

Silveira SM, Villacis RAR, Marchi FA, Barros Filho M de C, Drigo SA, *et al*. Genomic signatures predict poor outcome in undifferentiated pleomorphic sarcomas and leiomyosarcomas. *PloS One*. 2013; 8(6):e67643.

Sjöblom T, Jones S, Wood LD, Parsons DW, Lin J, *et al*. The consensus coding sequences of human breast and colorectal cancers. *Science*. 2006; 314(5797):268-274.

Spranger S, Spaapen RM, Zha Y, Williams J, Meng Y, *et al*. Up-regulation of PD-L1, IDO, and T(regs) in the melanoma tumor microenvironment is driven by CD8(+) T cells. *Sci Transl Med*. 2013; 5(200):200ra116.

Stone B, Schummer M, Paley PJ, Thompson L, Stewart J, *et al*. Serologic analysis of ovarian tumor antigens reveals a bias toward antigens encoded on 17q. *Int J Cancer*. 2003; 104(1):73-84.

Taube JM, Anders RA, Young GD, Xu H, Sharma R, *et al*. Colocalization of inflammatory response with B7-h1 expression in human melanocytic lesions supports an adaptive resistance mechanism of immune escape. *Sci Transl Med*. 2012; 4(127):127ra37.

Thompson RH, Gillett MD, Cheville JC, Lohse CM, Dong H, *et al*. Costimulatory molecule B7-H1 in primary and metastatic clear cell renal cell carcinoma. *Cancer*. 2005; 104(10):2084-2091.

Topalian SL, Hodi FS, Brahmer JR, Gettinger SN, Smith DC, *et al*. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. *N Engl J Med*. 2012 ;366(26):2443–2454.

Trimble CL, Clark RA, Thoburn C, Hanson NC, Tassello J, *et al*. Human papillomavirus 16-associated cervical intraepithelial neoplasia in humans excludes CD8 T cells from dysplastic epithelium. *J Immunol*. 2010; 185(11):7107–7114.

Trippa L, Rosner GL, Müller P. Bayesian enrichment strategies for randomized discontinuation trials. *Biometrics*. 2012; 68(1):203-211.

Tse E, Kwong YL. How I treat NK/T-cell lymphomas. *Blood*. 2013;121(25):4997-5005.

Tse E, Kwong YL. Epstein Barr virus-associated lymphoproliferative diseases: the virus as a therapeutic target. *Exp Mol Med*. 2015;47:e136.

Tse E, Kwong YL. Diagnosis and management of extranodal NK/T cell lymphoma nasal type. *Expert Rev Hematol*. 2016;9(9):861-871.

Tsukahara T, Kawaguchi S, Torigoe T, Asanuma H, Nakazawa E, *et al*. Prognostic significance of HLA class I expression in osteosarcoma defined by anti-pan HLA class I monoclonal antibody, EMR8-5. *Cancer Sci*. 2006; 97(12):1374–1380.

Varga A, Piha-Paul SA, Ott PA, Mehnert JM, Berton-Rigaud D, *et al*. Antitumor activity and safety of pembrolizumab in patients (pts) with PD-L1 positive advanced ovarian cancer: Interim results from a phase Ib study. *J Clin Oncol*. 2015; 33(suppl):abstr 5510.

Velcheti V, Schalper KA, Carvajal DE, Anagnostou VK, Syrigos KN, *et al*. Programmed death ligand-1 expression in non-small cell lung cancer. *Lab Invest*. 2014;94(1):107-116.

Yamaguchi M, Kita K, Miwa H, *et al*. Frequent expression of P-glycoprotein/MDR1 by nasal T-cell lymphoma cells. *Cancer* 1995;76(11):2351-1256.

Yamaguchi M, Kwong YL, Kim WS, *et al*. Phase II study of SMILE chemotherapy for newly diagnosed stage IV, relapsed, or refractory extranodal natural killer (NK)/T-cell lymphoma, nasal type: the NK-Cell Tumor Study Group study. *J Clin Oncol*. 2011;29(33):4410-4416.

Yang W, Song Y, Lu Y-L, Sun J-Z, Wang H-W. Increased expression of programmed death (PD)-1 and its ligand PD-L1 correlates with impaired cell-mediated immunity in high-risk human papillomavirus-related cervical intraepithelial neoplasia. *Immunology*. 2013; 139(4):513–522.

Yao S, Chen L. PD-1 as an immune modulatory receptor. *Cancer J*. 2014; 20(4):262–264.

Zalavsky BG. Bayesian hypothesis testing in two-arm trials with dichotomous outcomes. *Biometrics* 2013; 69(1):157-163.

Zang Y, Yuan Y. Optimal sequential enrichment designs for phase II clinical trials. Stat Med. 2016 Sep 19. doi: 10.1002/sim.7128. [Epub ahead of print]

Zhang L, Conejo-Garcia JR, Katsaros D, Gimotty PA, Massobrio M, *et al*. Intratumoral T cells, recurrence, and survival in epithelial ovarian cancer. *N Engl J Med*. 2003; 348(3):203-213.

Zhang Y, Huang S, Gong D, Qin Y, Shen Q. Programmed death-1 upregulation is correlated with dysfunction of tumor-infiltrating CD8+ T lymphocytes in human non-small cell lung cancer. *Cell Mol Immunol*. 2010; 7(5):389-395.

Zou W. Immunosuppressive networks in the tumour environment and their therapeutic relevance. *Nat Rev Cancer*. 2005; 5(4):263-274.

19 APPENDICES

Appendix 1: Summary of Response Evaluation Criteria in Solid Tumours v1.1

Appendix 2: Response Criteria for Germ-Cell Cancer

Appendix 3: Primary Central Nervous System Lymphoma Response Criteria

Appendix 4: Lugano Classification of Response For NK/T-cell Lymphoma

Appendix 5: Common Terminology Criteria for Adverse Events

Appendix 6: Eastern Cooperative Oncology Group Performance Status Scale

Appendix 7: Corticosteroid Dose Equivalents

Appendix 1: Summary of Response Evaluation Criteria in Solid Tumours v1.1

Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer. 2009; 45(2):228-247.

Full article available at: http://ctep.cancer.gov/

1. Measurability of Tumour at Baseline:

At baseline, tumour lesions/lymph nodes will be categorized measurable or non-measurable as follows:

a) Measurable

Tumour lesions: Must be accurately measured in a least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- ≥ 10 mm by CT scan (CT scan slice thickness no greater than 5 mm);
- ≥ 10 mm calliper measurement by clinical exam;
- 20 mm by chest (=X-ray);

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

b) Non-measurable

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

Note: Bone lesions, cystic lesions, and lesions previously treated with local therapy require special considerations regarding lesion measurability (see below):

c) Bone lesions

Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.

Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.

Blastic bone lesions are non-measurable.

2. Target lesions

When more than one measurable lesion is present at baseline all lesions up to a **maximum of five lesions total (and a maximum of two lesions per organ)** representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. Pathological nodes which are defined as measurable and may be identi- fied as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan.

The baseline sum diameters will be used as reference to further characterise any objective tumour regression in the measurable dimension of the disease.

3. Non-target lesions

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression' during the trial.

4. Response criteria:

a) Target lesions

- **Complete Response (CR):** Disappearance of all target lesions.Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm

  ***Warning**: lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on trial.This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of <10 mm. In order to qualify for CR, each node must achieve a short axis <10 mm.*

- **Partial Response (PR):** At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

- **Progressive Disease (PD):** At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on trial (this includes the baseline sum if that is the smallest on trial). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

  ***Warning**: when a progression is recorded with respect to the Nadir but there is a response with respect to baseline, progression must be considered.*

- **Stable Disease (SD):** Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on trial.

b) Non-target lesions

- **Complete Response (CR):** Disappearance of all non-target lesions. All lymph nodes must be non-pathological in size (<10 mm short axis).

- **Non-CR/Non-PD:** Persistence of one or more non-target lesion(s).

- **Progressive Disease (PD):** Unequivocal progression (see comments below) of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).

5. Overall response:

Target lesions	Non-target lesions	New lesions		Overall response
CR	CR	No	=	**CR**
CR	Non CR/Non PD	No	=	**PR**
CR	Not evaluated	No	=	**PR**
PR	Non PD or not all evaluated	No	=	**PR**
SD	Non PD or not all evaluated	No	=	**SD**
Not all evaluated	Non PD	No	=	**Not-evaluable**
PD	No change	Yes or No	=	**PD**
No change	PD	Yes or No	=	**PD**
No change	No change	Yes	=	**PD**

Special considerations regarding baseline lesion measurability

Bone lesions:

Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.

Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.

Cystic lesions:

Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if noncystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment:

Tumour lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Trial protocols should detail the conditions under which such lesions would be considered measurable.

Appendix 2: Response Criteria for Germ-Cell Cancer

Response will be assed via a combination of RECIST v1.1 and assessment of evolution of biomarker levels (alpha-fetoprotein [AFP] and human chorionic gonadotropin [hCG] and lactate dehydrogenase [LDH]) in the blood, as follows:

Response criteria:

a) **Target lesions (according to RECIST v1.1, see Appendix 1)**

- **Complete Response (CR):** Disappearance of all target lesions.Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm

  ***Warning**: lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on trial.This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of <10 mm. In order to qualify for CR, each node must achieve a short axis <10 mm.*

- **Partial Response (PR):** At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
- **Progressive Disease (PD):** At least a 20% increase in the sum of diameters of target lesions[5], taking as reference the smallest sum on trial (this includes the baseline sum if that is the smallest on trial). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

  ***Warning**: when a progression is recorded with respect to the Nadir but there is a response with respect to baseline, progression must be considered.*

- **Stable Disease (SD):** Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on trial.

b) **Non-target lesions (according to RECIST v1.1, see Appendix 1)**

- **Complete Response (CR):** Disappearance of all non-target lesions. All lymph nodes must be non-pathological in size (<10 mm short axis).
- **Non-CR/Non-PD:** Persistence of one or more non-target lesion(s)
- **Progressive Disease (PD):** Unequivocal progression (see comments below) of existing non-target lesions[6]. (Note: the appearance of one or more new lesions is also considered progression).

c) **Biomarkers**

- **Complete Response (CR):** Normalisation of all 3 tumour markers to within expected ranges.
- **Non-CR/Non-PD:** Maintenance of at least one tumour marker level above the normal limits.
- **Progressive Disease (PD):** Two consecutive elevations of any of the tumour markers (i.e. consistent increase in the level measured between 3 consecutive samples)

[5] *Except when pathological evidence of a growing teratoma syndrome is provided*

Overall response:

Target lesions	Non-target lesions	New lesions	Biomarkers	Overall response
CR	CR	No	CR	**CR**
CR	CR	No	Non CR/Non PD	**PR**
CR	CR	No	Not evaluated	**PR**
CR	Non CR/Non PD	No	CR	**PR**
CR	Non CR/Non PD	No	Non CR/Non PD	**PR**
CR	Non CR/Non PD	No	Not evaluated	**PR**
CR	Not evaluated	No	CR	**PR**
CR	Not evaluated	No	Non CR/Non PD	**PR**
CR	Not evaluated	No	Not evaluated	**PR**
PR	Non PD or NE	No	Non PD or NE	**PR**
SD	Non PD or NE	No	Non PD or NE	**SD**
Not evaluated	Non PD	No	Non-PD	**Not-evaluable**
PD	No change	Yes or No	No change	**PD**
No change	PD	Yes or No	No change	**PD**
No change	No change	Yes or No	PD	**PD**
No change	No change	Yes	No change	**PD**

Appendix 3: Primary Central Nervous System Lymphoma Response Criteria

Abrey LE, Batchelor TT, Ferreri AJ, Gospodarowicz M, Pulczynski EJ, *et al*. Report of an international workshop to standardize baseline evaluation and response criteria for primary CNS lymphoma. *J Clin Oncol*. 2005; 23(22):5034-5043.

Full article available at: http://jco.ascopubs.org/

1. Baseline tumour status:

Baseline tumour status will be assessed via:

a) Radiological examination of tumour lesions including gadolinium-enhanced MRI of the brain (may be substituted with contrast-enhanced CT scans in patients for whom MRI is medically contraindicated) and CT scan of the chest, abdomen and pelvis. Bulky parenchymal disease must be accurately measured in a least one dimension (longest diameter in the plane of measurement is to be recorded).

b) Detailed ophthalmologic examination should be performed, including dilated fundus examination, slit-lamp examination and colour photography of the posterior pole.

c) Lumbar puncture for central spinal fluid (CSF) cytology (positive or negative)

d) Verification of on-going corticosteroid treatment.

2. Response criteria

Complete response (CR) requires the following:

- Complete disappearance of all enhancing abnormalities on gadolinium-enhanced MRI.
- No evidence of active ocular lymphoma as defined by absence of cells in the vitreous and resolution of any previously documented retinal or optic nerve infiltrates. Chronic changes of the retinal pigment epithelium in the setting of a prior retinal or optic nerve infiltrate does not preclude the definition of a CR. All patients with initial involvement of the eyes on baseline evaluation should have a detailed follow-up evaluation including dilated fundus examination and color photographs of the posterior pole of the eye. Repeat ophthalmologic evaluation is not required for patients without evidence of ocular lymphoma at baseline or interval development of ocular symptoms.
- Negative CSF cytology. Given the reported disparity between cytologic specimens obtained from the ventricular system as opposed to lumbar puncture, it is recommended that a negative CSF cytology be confirmed from both spaces in patients with an Ommaya reservoir.[30] Patients without significant CSF abnormalities at baseline do not require repeat CSF evaluation provided they have not developed interval symptoms that suggest leptomeningeal dissemination. Although baseline CSF total protein may have prognostic importance, the value of CSF total protein after therapy is unknown.
- At the time a CR is determined, the patient should have discontinued use of all corticosteroids for at least 2 weeks. Rare exceptions may be made for those patients receiving corticosteroids for another diagnosis (eg, panhypopituitarism).

Unconfirmed complete response (CRu) includes those patients who fulfill the criteria for CR with the following features/limitations:

- Any patient who fulfills all criteria for CR but continues to require corticosteroid therapy at any dose should be considered an unconfirmed CR. This is critical because corticosteroids may be oncolytic in treating occult tumor. In addition, corticosteroids may decrease gadolinium enhancement on MRI.
- Some patients will have a small but persistent enhancing abnormality on MRI related to biopsy or focal hemorrhage. It is often difficult to ascertain whether this represents a residual nidus of tumor or scar tissue. Adjunctive radiologic studies such as single-photon emission computed tomography or positron emission tomography may be helpful, but often the nature of these abnormalities may only be determined by observing the patient with serial scans. If the type of abnormality does not change

or slowly involutes over time without therapy and corticosteroids, it is reasonable to categorize it as a CR.

- Patients with a persistent minor abnormality on follow-up ophthalmologic examination (persistent nonmalignant cells in the vitreous, alteration of the retina/optic nerve that is not consistent with tumor infiltration) may be considered a CRu if this abnormality is unlikely to represent ocular lymphoma.

Partial response (PR) requires all of the following:

- A ≥ 50% decrease in the contrast-enhancing lesion seen on MRI as compared with baseline imaging.
- Corticosteroid dose is irrelevant to the determination of PR.
- Ophthalmologic examination should show a decrease in the vitreous cell count or retinal/optic nerve cellular infiltrate but may continue to show persistent malignant or suspicious cells. Color photos of the posterior pole of the eye should be obtained to document improvement in retinal/optic nerve infiltrates.
- CSF cytologic examination may be negative or continue to show persistent malignant or suspicious cells in patients with a ≥ 50% decrease in the primary brain lesion. In the setting of primary leptomeningeal lymphoma, PR is not recognized; all patients should be categorized as CR, CRu, stable disease, or progressive disease.
- No new sites of disease.

Stable disease (SD) is defined as less than a PR but is not progressive disease.

Progressive disease (PD) requires the following:

- A more than 25% increase in the contrast-enhancing lesion seen on MRI as compared with baseline or best response (comparison should be made to the smallest of multiple lesions).
- Progression of ocular disease as indicated by an increase in the vitreous cell count or progressive retinal or optic nerve infiltration.
- Appearance of any new lesion or site of disease (ocular, leptomeningeal or systemic) during or at the end of therapy.

Relapsed disease (only applicable to patients with a prior CR, CRu) requires the following:

- Appearance of any new lesion.

Response	Brain imaging	Corticosteroid dose	Eye examination	CSF cytology
CR	No contrast enhancement	None	Normal	Negative
CRu	No contrast enhancement / Minimal abnormality	Any	Normal / Minor RPE abnormality	Negative
PR	50% decrease in enhancing tumour	Any	Normal / Minor RPE abnormality Decrease in vitreous cell or retinal infiltrate	Negative, persistent or suspicious
PD	25% increase in leasion size Any new site of disease: CNS or systemic	Any	Recurrent or new ocular disease	Recurrent or positive

CR= complete response; CRu= unconfirmed complete response; RPE= retinal pigment epithelium; PR= partial response; PD= progressive disease

Appendix 4: Lugano Classification of Response For NK/T-cell Lymphoma

Cheson BD, Fisher RI, Barrington SF, Cavalli F, Schwartz LH, *et al*. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and Non-Hodgkin lymphoma: The Lugano classification. *JCO*. 2014; 32(27):3059-3067

Full article available at: http://jco.ascopubs.org/

Five-point scale of fluorodeoxyglucose (FDG) uptake measured by PET-CT[6].

The 5-PS scores the most intense uptake in a site of initial disease, if present, as follows:

Score	Description
1	No uptake
2	Uptake ≤ mediastinum
3	Uptake> mediastinum but ≤ liver
4	Uptake moderately higher than liver
5	Uptake markedly higher than liver and/or new lesions
X	New areas of uptake unlikely to be related to lymphoma

Criteria for FDG-PET-CT based response assessment

Response	Site	Criteria
Complete metabolic response	Lymph nodes and extra lymphatic sites	Score 1, 2, or 3* with or without a residual mass on 5PS† It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (eg, with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake
	New lesions	None
	Bone marrow	No evidence of FDG-avid disease in marrow
Partial metabolic response	Lymph nodes and extra lymphatic sites	Score 4 or 5† with reduced uptake compared with baseline and residual mass(es) of any size
		At interim, these findings suggest responding disease
		At end of treatment, these findings indicate residual disease
	New lesions	None
	Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan
No metabolic response	Target nodes/nodal masses, extranodal lesions	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment
	New lesions	None
	Bone marrow	No change from baseline

[6] Barrington SF, Mikhaeel NG, Kostakoglu L, Meignan M, Hutchings M, *et al*. Role of imaging in the staging and response assessment of lymphoma: Consensus of the International Conference on Malignant Lymphomas Imaging Working Group. *JCO*. 2014 ; 32(27) :3048-3058

Response	Site	Criteria
Progressive disease (any)	Individual target nodes/nodal masses, extranodal lesions	Score 4 or 5 with an increase in intensity of uptake from baseline and/or
		New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment
	New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered
	Bone marrow	New or recurrent FDG-avid foci

5PS= 5-point scale; CT= computed tomography; FDG= fluorodeoxyglucose; PET, positron emission tomography

*A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid undertreatment). Measured dominant lesions: Up to six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (eg, liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation. Nonmeasured lesions: Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (eg, GI tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response, but should be no higher than surrounding normal physiologic uptake (eg, with marrow activation as a result of chemotherapy or myeloid growth factors).

†PET 5PS: 1, no uptake above background; 2, uptake ≤ mediastinum; 3, uptake > mediastinum but ≤ liver; 4, uptake moderately > liver; 5, uptake markedly higher than liver and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma.

Appendix 5: Common Terminology Criteria for Adverse Events

In the present trial, adverse events will be recorded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.0, *(Published Date October 1, 2009)*

A copy of the toxicity evaluation scale can be obtained from the NCI website: http://ctep.cancer.gov/

Cancer Therapy Evaluation Program

The intensity of adverse events not listed in the CTCAE v4.0 classification will be assessed according to the following qualifiers:

- **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 the event.

Appendix 6: Eastern Cooperative Oncology Group Performance Status Scale

Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, *et al*. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol*. 1982 Dec;5(6):649-655.

GRADE	ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

Comparing the ECOG Performance Status to the Karnofsky* Performance Status

The ECOG Performance Status and the Karnofsky* Performance Status are two widely used methods to assess the functional status of a patient. Both scales have been in the public domain for many years

as ways to classify a patient according to their functional impairment, compare the effectiveness of therapies, and assess the prognosis of a patient.

The table below displays one a comparison of the two systems.

ECOG PERFORMANCE STATUS	KARNOFSKY* PERFORMANCE STATUS
0 Fully active, able to carry on all pre-disease performance without restriction	100 Normal, no complaints; no evidence of disease 90 Able to carry on normal activity; minor signs or symptoms of disease
1 Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work	80 Normal activity with effort, some signs or symptoms of disease 70 Cares for self but unable to carry on normal activity or to do active work
2 Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours	60 Requires occasional assistance but is able to care for most of personal needs 50 Requires considerable assistance and frequent medical care
3 Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours	40 Disabled; requires special care and assistance 30 Severely disabled; hospitalization is indicated although death not imminent
4 Completely disabled; cannot carry on any selfcare; totally confined to bed or chair	20 Very ill; hospitalization and active supportive care necessary 10 Moribund
5 Dead	0 Dead

*Karnofsky D, Burchenal J, The clinical evaluation of chemotherapeutic agents in cancer. In: MacLeod C, ed. Evaluation of Chemotherapeutic Agents. New York, NY: Columbia University Press; 1949:191–205.

Appendix 7: Corticosteroid Dose Equivalents

Equivalent Dose	Steroid
1.2 mg	Betamethasone (long-acting)
1.5 mg	Dexamethasone (long-acting)
8 mg	Methylprednisolone (intermediate-acting)
8 mg	Triamcinolone (intermediate-acting)
10 mg	Prednisone (intermediate-acting)
10 mg	Prednisolone (intermediate-acting)
40 mg	Hydrocortisone (short-acting)
50 mg	Cortisone (short-acting)

Mager DE, Lin SX, Blum RA, Lates CD, Jusko WJ. Dose equivalency evaluation of major corticosteroids: pharmacokinetics and cell trafficking and cortisol dynamics. *J Clin Pharmacol*. 2003 Nov. 43(11):1216-27..

Webb R, Singer M. Oxford Handbook of Critical Care. Oxford University Press. 2005.