COMBINATION OF MK3475 AND METRONOMIC CYCLOPHOSPHAMIDE IN PATIENTS WITH ADVANCED SARCOMAS : MULTICENTRE PHASE II TRIAL

Protocol *PEMBROSARC*

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Scientific responsive

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SPONSOR **INSTITUT BERGONIE**

TABLE OF CONTENT

APPROVAL AND SIGNATURES OF PROTOCOL

Titre du protocole : Combination of MK3475 and Metronomic Cyclophosphamide in patients with Advanced Sarcomas: Multicentre Phase II trial.

Competent authority	Name : ANSM	Date de l'autorisation initiale	18/02/2015
		Autorisation de la modification substantielle 1	24/07/2015
		Autorisation de la modification substantielle 2	09/09/2015
		Autorisation de la modification substantielle 3	10/03/2016
		Autorisation de la modification substantielle 4	09/03/2017
		Autorisation de la modification substantielle 4.1	27/04/2017
		Autorisation de la modification substantielle 5	20/12/2017
		Autorisation de la modification substantielle 6.1	30/07/2018
		Autorisation de la modification substantielle 7	29/01/2019
		Autorisation de la modification substantielle 8	07/06/2019
		Autorisation de la modification substantielle 9	18/02/2020
		Autorisation de la modification substantielle 10	NA
		Autorisation de la modification substantielle 11	NA
		Autorisation de la modification substantielle 12	12/08/2020
		Autorisation de la modification substantielle 13	03/11/2020
		Autorisation de la modification substantielle 14	10/02/2021
		Autorisation de la modification substantielle 15	28/07/2021
		Référence :	141573A-12
Ethic Committee	Name : CPP du Sud-Ouest et d'Outre-Mer III	Date de l'avis favorable initial	17/12/2014
		Avis favorable de la modification substantielle 1	27/05/2015
		Avis favorable de la modification substantielle 2	26/08/2015
		Avis favorable de la modification substantielle 3	24/02/2016
		Avis favorable de la modification substantielle 4	26/09/2016
		Avis favorable de la modification substantielle 4.1	29/03/2017
		Autorisation de la modification substantielle 6.1	29/08/2018
		Autorisation de la modification substantielle 7	30/01/2019
		Avis favorable de la modification substantielle 8	29/05/2019
		Avis favorable de la modification substantielle 9	19/02/2020
		Avis favorable de la modification substantielle 10	NA
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		Avis favorable de la modification substantielle 13	25/11/2020
		Avis favorable de la modification substantielle 14	24/02/2021
		Avis favorable de la modification substantielle 15	25/08/2021
		Référence :	2014/106

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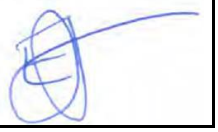
Pharmacist	Emilie TOULZA Institut Bergonié – Bordeaux Tél:05.47.30.60.53/Fax: 05.24.07.19.08 Mail : e.toulza@bordeaux.unicancer.fr	07/07/2021	

I acknowledge having read the whole protocol, and I pledge to lead this protocol in accordance with the Good Clinical Practice (decision of 24 November 2006), the Public Health Law No. 2006-806 of August 09, 2004 and the implementing Decree n° 2006-477 of April 26, 2006 and as described in this document.

I assume my responsibilities as referent investigator including:
- Collection of informed consent, dated and signed by patients before any selection procedure in the protocol,
- Validation of case report forms, completed for each patient included in the study,
- Direct access to source documents for verification by the clinical research assistant (CRA) commissioned by the sponsor,
- Archiving of critical documents of the study for a 15 year-period.

Name and address of the hospital

Name of the Coordinating Investigator :

Date : |__|__| |__|__| |__|__|__|__| Signature :

SYNOPSIS

Title of the study	**Combination of MK3475 and Metronomic Cyclophosphamide in patients with Advanced Sarcomas : Multicentre Phase II trial**
Abbreviation of the trial	**PEMBROSARC**
Sponsor Identification	**Institut Bergonié, Regional Comprehensive Cancer Center**
Coordinating Investigator	**Doctor Antoine ITALIANO** **Department of Medical Oncology**
Number of investigational sites planned	8 centres: - Institut Bergonié, Pr Italiano - Centre Léon Bérard, Pr Blay - Institut Gustave Roussy, Dr Le Cesne - Centre Oscar Lambret, Dr Penel - Institut Curie, Dr Piperno-Neumann - Institut Paoli Calmette, Pr Bertucci - Institut Claudius Regaud, Dr Chevreau - Institut de Cancérologie de l'Ouest – Site René Gauducheau, Dr Bompas Note : for treatment strategy B, only 3 recruiting centers: - Institut Bergonié, Pr Italiano - Centre Léon Bérard, Pr Blay - Institut Gustave Roussy, Dr Le Cesne
Number of patients	**Phase II,** treatment by PEMBROLIZUMAB and Metronomic Cyclophosphamide (treatment strategy A)**, for each stratum:** - Leiomyosarcoma : 33 patients - Undifferentiated sarcoma : 33 patients - Sarcomas others : 33 patients - Osteosarcoma : 33 patients - GIST : 31 patients - Advanced soft-tissue sarcomas with immune signature: 32 patients **Phase II,** treatment by PEMBROLIZUMAB, Metronomic Cyclophosphamide and G100 (treatment strategy B): - Metastatic soft-tissue sarcoma: 32 patients
Duration of the study	Planned enrollment period : 72 months Treatment duration : 2-years maximum Follow-up : 12 months Duration of study : 7 years
Medical conditions	**Advanced /metastatic sarcomas: leiomyosarcoma, undifferentiated sarcoma, other sarcoma, GIST and osteosarcoma.**
Objectives	**Primary objective** **FOR TREATMENT STRATEGY A (STRATA 1 TO 6)** Assessment of the efficacy of PEMBROLIZUMAB and Metronomic Cyclophosphamide (CP) independently for 6 strata as per RECIST v1.1 criteria : • Advanced leiomyosarcoma (in terms of 6-month objective response and 6-month non-progression) • Advanced undifferentiated sarcoma (in terms of 6-month objective response and 6-month non-progression) • Advanced other sarcoma (in terms of 6-month objective response and 6-month non-progression) • Advanced osteosarcoma (in terms of 6-month objective response and 6-month non-progression)

	• Advanced GIST (in terms of 6-month non-progression) • Advanced soft-tissue sarcomas with immune signature (in terms of 6-month non-progression) **FOR TREATMENT STRATEGY B (STRATUM 7)** Assessment of the efficacy of PEMBROLIZUMAB and Metronomic Cyclophosphamide (CP) + G100 in terms of 6-month non-progression (as per RECIST v1.1 criteria) in patients with metastatic soft-tissue sarcoma. **Secondary objectives** For each stratum 1 to 7: • Assessment of the efficacy of the treatment strategy in terms of best overall response (as per RECIST v1.1 criteria), 1-year Progression-free survival (PFS, as per RECIST v1.1 criteria), 6-month immune-related response (Wolchok 2009; central radiological review data), and 1-year overall survival (OS). • Assessment of the safety profile of the treatment strategy using the Common Terminology Criteria for Adverse Events (CTCAE) from the NCI v4.0. • Assessment of the Growth modulation index (GMI), defined for each patient as the ratio of the PFS on the current treatment strategy to the PFS on the previous line of therapy (Von Hoff 1998), in patients with documented progression at inclusion. For each stratum 1 to 5: • Translational research : pharmacodynamic (PD)/mechanism of action (MOA) biomarkers analysis as well as predictive biomarkers analysis (levels of angiogenic and immunologic biomarkers in blood at baseline and different study time points). • Prospective determination of the proportion of STS that express PDL1. • Identification of prognostic biomarkers of treatment response. For strata 6 and 7 : • Translational research on blood and tumor tissue samples obtained at baseline and several time points during treatment for: - pharmacodynamic (PD)/mechanism of action (MOA) analysis assessing angiogenic and immunologic biomarkers, - identification of biomarkers predictive of treatment response.
Study design	This is a phase II trial with seven independent strata: **FOR TREATMENT STRATEGY A (STRATA 1 TO 6):** • **Advanced leiomyosarcoma (stratum 1)** o Single-arm phase 2 trial o Treatment : PEMBROLIZUMAB + Metronomic CP at standard doses. o 2-stage dual endpoint design (Goffin et al. 2008) • **Advanced undifferentiated sarcoma (stratum 2)** o Single-arm phase 2 trial o Treatment : PEMBROLIZUMAB + Metronomic CP at standard doses. o 2-stage dual endpoint design (Goffin et al. 2008) • **Advanced other sarcoma (stratum 3)** o Single-arm phase 2 trial o Treatment : PEMBROLIZUMAB + Metronomic CP at standard doses. o 2-stage dual endpoint design (Goffin et al. 2008)

	• **Advanced osteosarcoma (stratum 4)** o Single-arm phase 2 trial o Treatment : PEMBROLIZUMAB + Metronomic CP at standard doses. o 2-stage dual endpoint design (Goffin et al. 2008) • **Advanced GIST (stratum 5)** o Single-arm phase 2 trial o Treatment : PEMBROLIZUMAB + Metronomic CP at standard doses. o 2-stage optimal Simon's design (Simon, 1989) • **Advanced soft-tissue sarcomas with immune signature (stratum 6)** o Single-arm phase 2 trial o Treatment : PEMBROLIZUMAB + Metronomic CP at standard doses. o 2-stage optimal Simon's design (Simon, 1989) **FOR TREATMENT STRATEGY B (STRATUM 7):** • **Metastatic soft-tissue sarcoma** o Single-arm phase 2 trial o Treatment : PEMBROLIZUMAB + Metronomic CP at standard doses + G100. o 2-stage optimal Simon's design (Simon 1989)
Inclusion criteria	For strata 1 to 5: 1. Histology : Leiomyosarcoma, or UPS (undifferentiated pleomorphic sarcoma), or other sarcoma, or GIST (gastro intestinal stromal tumor) or osteosarcoma, histologically confirmed by central review (Pr Coindre team), except if the diagnosis was already confirmed by the RRePS Network, 2. Advanced non resectable / metastatic disease 3. Documented progression according to RECIST criteria. Progression on the last line of treatment should be confirmed by central review with two radiological assessments identical (CT scans or MRI) obtained at less than 6 months interval within the 12 months before inclusion. 4. For stratum 5, documented disease progression according to RECIST criteria after the first line imatinib and second line sunitinib, 5. Have provided tissue from an archival tissue sample obtained on metastasis or on locally advanced disease, or newly obtained core or excisional biopsy of a tumor lesion, 6. For strata 1, 2 and 3: no more of four previous lines of systemic therapy for metastatic disease 7. Age ≥ 18 years, 8. Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1, 9. Measurable disease according to RECIST v1.1 outside any previously irradiated field. At least one site of disease must be uni-dimensionally ≥ 10 mm, 10. Life expectancy > 3 months, 11. For strata 1, 2 and 3 at least 1 previous line(s) of chemotherapy in the palliative setting 12. No symptomatic central nervous system disease, 13. No chronic use of glucocorticoids. 14. Adequate hematological, renal, metabolic and hepatic function: a. Hemoglobin ≥ 9 g/dl (patients may have received prior red blood cell [RBC] transfusion, if clinically indicated); absolute neutrophil count (ANC) ≥ 1.5 x 10^9/l and platelet count ≥ 100 x 10^9/l,Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2.5 x upper limit of normality (ULN) (≤ 5 in case of liver metastasis). b. Total bilirubin ≤ 1.5 x ULN OR Direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 x ULN. c. Albumin ≥ 25g/l.

d. Serum creatinine ≤ 1.5 x ULN OR Calculated creatinine clearance (CrCl) ≥ 60 ml/min (calculated per institutional standard) for subject with creatinine levels > 1.5 x ULN.
e. Creatine phosphokinase (CPK) ≤ 2.5 x ULN
f. INR ≤ 1.5 x ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
g. aPTT ≤ 1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants,
h. Thyroid functions (T3, T4 and TSH) ≤ 1.5 x ULN and ≥ LLN.
15. No prior or concurrent malignant disease diagnosed or treated in the last 2 years except for adequately treated in situ carcinoma of the cervix, basal or squamous skin cell carcinoma, or in situ transitional bladder cell carcinoma,
16. At least three weeks since last chemotherapy, immunotherapyor any other pharmacological treatment and/or radiotherapy,
17. Recovery to grade ≤ 1 from any adverse event (AE) derived from previous treatment (excluding alopecia of any grade and non-painful peripheral neuropathy grade ≤ 2 (according to the National Cancer Institute Common Terminology Criteria for Adverse Event (NCI-CTCAE, version 4.0),
18. Women of childbearing potential must have a negative serum pregnancy test within 72 hours prior to receiving the first dose of study medication. Both women and men must agree to use a medically acceptable method of contraception throughout the treatment period and for four months after discontinuation of treatment. Acceptable methods for contraception include intrauterine device (IUD), oral contraceptive, subdermal implant and double barrier. Subjects of childbearing potential are those who have not been surgically sterilized or have not been free from menses for ≥ 1 year.
19. Voluntary signed and dated written informed consents prior to any specific study procedure,
20. Patients with a French social security in compliance with the Law relating to biomedical research (Article 1121-11 of French Public Health Code).

For stratum 6:
1. Histology : soft-tissue sarcoma histologically confirmed by central review (Pr Coindre team), except if the diagnosis was already confirmed by the RRePS Network,
2. Advanced non resectable / metastatic disease
3. Documented progression according to RECIST criteria. Progression on the last line of treatment should be confirmed by central review with two radiological assessments identical (CT scans or MRI) obtained at less than 6 months interval within the 12 months before inclusion, except for patients with metastatic disease diagnosed less than 6 months before inclusion.
4. Have provided tissue of a tumor lesion from an archival tissue sample obtained on metastasis or on locally advanced disease, or newly obtained core or excisional biopsy. Tissue < 3 months old and with no subsequent treatment since or from a newly obtained core or excisional biopsy,
5. Presence of tertiary lymphoid structures on freshly obtained tumor biopsy or archival tumor material collected before any systemic treatment or radiation therapy,
6. No more of four previous lines of systemic therapy for metastatic disease
7. Age ≥ 18 years,
8. Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1,
9. Measurable disease according to RECIST v1.1 outside any previously irradiated field. At least one site of disease must be uni-dimensionally ≥ 10 mm,
10. Life expectancy > 3 months,
11. Participant must have advanced disease and must not be a candidate for other approved therapeutic regimen known to provide significant clinical benefit based on investigator judgement,
12. No symptomatic central nervous system disease,

13. No chronic use of glucocorticoids.
14. Adequate hematological, renal, metabolic and hepatic function:
    a. Hemoglobin ≥ 9 g/dl (patients may have received prior red blood cell [RBC] transfusion, if clinically indicated); absolute neutrophil count (ANC) ≥ 1.5 x 10^9/l and platelet count ≥ 100 x 10^9/l,
    b. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2.5 x upper limit of normality (ULN) (≤ 5 in case of liver metastasis).
    c. Total bilirubin ≤ 1.5 x ULN OR Direct bilirubin ≤ ULN for subjects with total bilirubin levels ≥ 1.5 x ULN.
    d. Albumin ≥ 25g/l.
    e. Serum creatinine ≤ 1.5 x ULN OR Calculated creatinine clearance (CrCl) ≥ 60 ml/min (calculated per institutional standard) for subject with creatinine levels ≥ 1.5 x ULN.
    f. Creatine phosphokinase (CPK) ≤ 2.5 x ULN
    g. INR ≤ 1.5 x ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
    h. aPTT ≤ 1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants,
    i. Thyroid functions (T3, T4 and TSH) ≤ 1.5 x ULN and ≥ LLN.
15. No prior or concurrent malignant disease diagnosed or treated in the last 2 years except for adequately treated in situ carcinoma of the cervix, basal or squamous skin cell carcinoma, or in situ transitional bladder cell carcinoma,
16. At least three weeks since last chemotherapy, immunotherapyor any other pharmacological treatment and/or radiotherapy,
17. Recovery to grade ≤ 1 from any adverse event (AE) derived from previous treatment (excluding alopecia of any grade, non-painful peripheral neuropathy grade ≤ 2 and endocrine-related grade ≤ 2 requiring treatment or hormone replacement) (according to the National Cancer Institute Common Terminology Criteria for Adverse Event (NCI-CTCAE, version 4.0),
18. Women of childbearing potential must have a negative serum pregnancy test within 72 hours prior to receiving the first dose of study medication. Both women and men must agree to use 2 medically acceptable methods of contraception throughout the treatment period and for 180 days after discontinuation of treatment. Subjects of childbearing potential are those who have not been surgically sterilized or have not been free from menses for ≥ 1 year,
19. Voluntary signed and dated written informed consents prior to any specific study procedure,
20. Patients with a social security in compliance with the French Law.

For stratum 7:

1. Histology : soft-tissue sarcoma histologically confirmed by central review (Pr Coindre team), except if the diagnosis was already confirmed by the RRePS Network,
2. Locally advanced or metastatic disease with at least one injectable lesion. Note that lesion must be cutaneous, subcutaneous or intramuscular. Nethertheless, it would be allowed to inject deeper lesion, either if patient is not on anticoagulation or per the guidelines in the protocol, the lesion is compressible; either if patient is on ASA or anti-platelet agent and the lesion is not compressing or involving organs or vessels,
3. Documented progression according to RECIST criteria. Progression on the last line of treatment should be confirmed by central review with two radiological assessments identical (CT scans or MRI) obtained at less than 6 months interval within the 12 months before inclusion, except for patients with metastatic disease diagnosed less than 6 months before inclusion.
4. Patients whose disease has progressed despite standard therapy and for whom no standard therapy exists,
5. Have provided tissue of a tumor lesion from an archival tissue sample obtained

	on metastasis or on locally advanced disease, or newly obtained core or excisional biopsy. Tissue < 3 months old and with no subsequent treatment since or from a newly obtained core or excisional biopsy 6. No more than 2 previous lines of systemic therapy in the palliative setting, 7. Age ≥ 18 years, 8. Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1, 9. Measurable disease according to RECIST v1.1 outside any previously irradiated field. At least one site of disease must be uni-dimensionally ≥ 10 mm, 10. Life expectancy > 6 months, 11. At least 1 previous line(s) of chemotherapy in the palliative setting 12. No symptomatic central nervous system disease, 13. No chronic use of glucocorticoids. 14. Adequate hematological, renal, metabolic and hepatic function: a. Hemoglobin ≥ 9 g/dl (patients may have received prior red blood cell [RBC] transfusion, if clinically indicated); absolute neutrophil count (ANC) ≥ 1.5 x 10^9/l, leukocyte count ≥ 2.5 x 10^9/l and platelet count ≥ 100 x 10^9/l, and lymphocyte count ≥ 0.5 x 10^9/l. b. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2.5 x upper limit of normality (ULN) (≤ 5 in case of liver metastasis). c. Total bilirubin ≤ 1.5 x ULN OR Direct bilirubin ≤ ULN for subjects with total bilirubin levels ≥ 1.5 x ULN. d. Albumin ≥ 25g/l. e. Serum creatinine ≤ 1.5 x ULN OR Calculated creatinine clearance (CrCl) ≥ 60 ml/min (calculated per institutional standard) for subject with creatinine levels ≥ 1.5 x ULN. f. Creatine phosphokinase (CPK) ≤ 2.5 x ULN g. INR ≤ 1.5 x ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants h. aPTT ≤ 1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants, i. Thyroid functions (T3, T4 and TSH) ≤ 1.5 x ULN and ≥ LLN. 15. No prior or concurrent malignant disease diagnosed or treated in the last 2 years except for adequately treated in situ carcinoma of the cervix, basal or squamous skin cell carcinoma, or in situ transitional bladder cell carcinoma, 16. At least three weeks since last chemotherapy, and 14 days since last immunotherapy or any other pharmacological treatment and/or radiotherapy, 17. Recovery to grade ≤ 1 from any adverse event (AE) derived from previous treatment (excluding alopecia of any grade and non-painful peripheral neuropathy grade ≤ 2 (according to the National Cancer Institute Common Terminology Criteria for Adverse Event (NCI-CTCAE, version 4.0), 18. Women of childbearing potential must have a negative serum pregnancy test within 72 hours prior to receiving the first dose of study medication. Both women and men must agree to use 2 medically acceptable methods of contraception throughout the treatment period and for 180 days after discontinuation of treatment. Subjects of childbearing potential are those who have not been surgically sterilized or have not been free from menses for ≥ 1 year. 19. Voluntary signed and dated written informed consents prior to any specific study procedure, 20. Patients with a social security in compliance with the French Law .
Exclusion criteria	For strate 1 to 5: 1. Previous treatment with MK3475 or CP, 2. Has received prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways),

	3. Evidence of progressive or symptomatic central nervous system (CNS) or leptomeningeal metastases, 4. Men or women of childbearing potential who are not using an effective method of contraception as previously described; women who are pregnant or breast feeding, 5. Participation to a study involving a medical or therapeutic intervention in the last 30 days, 6. Previous enrolment in the present study, 7. Patient unable to follow and comply with the study procedures because of any geographical, familial, social or psychological reasons, 8. Known hypersensitivity to any involved study drug or of its formulation components, 9. Has an active autoimmune disease requiring systemic treatment within the past 3 months or a documented history of clinically severe autoimmune disease, or a syndrome that requires systemic steroids or immunosuppressive agents. Subjects with vitiligo or resolved childhood asthma/atopy would be an exception to this rule. Subjects that require intermittent use of bronchodilators or local steroid injections would not be excluded from the study. Subjects with hypothyroidism stable on hormone replacement or Sjorgen's syndrome will not be excluded from the study, 10. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment, 11. History of idiopathic pulmonary fibrosis, history of non-infectious pneumonitis that required steroids, drug-induced pneumonitis, organizing pneumonia, or evidence of active pneumonitis on screening chest CT scan. History of radiation pneumonitis in the radiation field (fibrosis) is permitted, 12. Has known active hepatitis B or hepatitis C, 13. Has a known history of Human Immunodeficiency Virus (HIV) (HIV1/2 antibodies), 14. Has received a live vaccine within 30 days prior to the first dose of trial treatment. For stratum 6: 1. Previous treatment with PEMBROLIZUMAB 2. Has received prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody (including ipilimumabor any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways), 3. Evidence of progressive or symptomatic central nervous system (CNS) or leptomeningeal metastases, 4. Men or women of childbearing potential who are not using an effective method of contraception; women who are pregnant or breast feeding, 5. Participation to a study involving a medical or therapeutic intervention in the last 30 days, 6. Previous enrolment in the present study, 7. Patient unable to follow and comply with the study procedures because of any geographical, familial, social or psychological reasons, 8. Known hypersensitivity to any involved study drug or of its formulation components, 9. Has an active autoimmune disease requiring systemic treatment within the

	past 3 months or a documented history of clinically severe autoimmune disease, or a syndrome that requires systemic steroids or immunosuppressive agents. Subjects with vitiligo or resolved childhood asthma/atopy would be an exception to this rule. Subjects that require intermittent use of bronchodilators or local steroid injections would not be excluded from the study. Subjects with hypothyroidism stable on hormone replacement or Sjorgen's syndrome will not be excluded from the study, 10. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment, 11. History of idiopathic pulmonary fibrosis, history of non-infectious pneumonitis that required steroids, drug-induced pneumonitis, organizing pneumonia, or evidence of active pneumonitis on screening chest CT scan. History of radiation pneumonitis in the radiation field (fibrosis) is permitted, 12. Has known history of or is positive for Hepatitis B (HBsAg reactive) or Hepatitis C. 13. Has a known history of Human Immunodeficiency Virus (HIV) infection (HIV1/2 antibodies), 14. Has received a live vaccine within 30 days prior to the first dose of trial treatment. 15. Patients with oral anticoagulation therapy, 16. Known urinary tract obstruction 17. Previous allogenic bone marrow transplant or solid organ transplantation, 18. Has an active infection requiring systemic treatment within 14 days prior to study entry. For stratum 7: 1. Previous treatment with PEMBROLIZUMAB or G100 2. Has received prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody (including ipilimumabor any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways), 3. Evidence of progressive or symptomatic central nervous system (CNS) or leptomeningeal metastases, 4. Men or women of childbearing potential who are not using an effective method of contraception; women who are pregnant or breast feeding, 5. Participation to a study involving a medical or therapeutic intervention in the last 30 days, 6. Previous enrolment in the present study, 7. Patient unable to follow and comply with the study procedures because of any geographical, familial, social or psychological reasons, 8. Known hypersensitivity to any involved study drug or of its formulation components, 9. Has an active autoimmune disease requiring systemic treatment within the past 3 months or a documented history of clinically severe autoimmune disease, or a syndrome that requires systemic steroids or immunosuppressive agents. Subjects with vitiligo or resolved childhood asthma/atopy would be an exception to this rule. Subjects that require intermittent use of bronchodilators or local steroid injections would not be excluded from the study. Subjects with hypothyroidism stable on hormone replacement or Sjorgen's syndrome will not be excluded from the study,

<table>
<tr><td></td><td>10. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment,
11. History of idiopathic pulmonary fibrosis, history of non-infectious pneumonitis that required steroids, drug-induced pneumonitis, organizing pneumonia, or evidence of active pneumonitis on screening chest CT scan. History of radiation pneumonitis in the radiation field (fibrosis) is permitted,
12. Has known history of or is positive for Hepatitis B (HBsAg reactive) or Hepatitis C.
13. Has a known history of Human Immunodeficiency Virus (HIV) infection (HIV1/2 antibodies),
14. Has received a live vaccine within 30 days prior to the first dose of trial treatment.
15. Patients with oral anticoagulation therapy,
16. Known urinary tract obstruction.
17. Previous allogenic bone marrow transplant or solid organ transplantation,
18. Has an active infection requiring systemic treatment within 14 days prior to study.</td></tr>
<tr><td>Route of administration</td><td>Cyclophosphamide will be administered per os bi-daily (50 mg x 2), and given on a week on/ week off schedule.

PEMBROLIZUMAB will be administered intraveinously, and given every 3 weeks on day 8.

G100 will be administered by intra-tumoral injection (20µg), one weekly injection for at least 6 weeks and for a maximum of 12 weeks. Note that only one lesion can be treated.</td></tr>
<tr><td>Treatment schedule</td><td>TREATMENT STRATEGY A
<table>
<tr><th colspan="5">Regimen description</th></tr>
<tr><th>Agent</th><th>Dose</th><th>Route</th><th>Schedule</th><th>Cycle length</th></tr>
<tr><td>CP</td><td>50mg x 2</td><td>Per os</td><td>Daily, 1 week on/1 week off</td><td rowspan="2">3 weeks</td></tr>
<tr><td>PEMBROLIZUMAB</td><td>200 mg</td><td>IV</td><td>On day 8, every 3 weeks</td></tr>
</table>
TREATMENT STRATEGY B
<table>
<tr><th colspan="5">Regimen description</th></tr>
<tr><th>Agent</th><th>Dose</th><th>Route</th><th>Schedule</th><th>Cycle length</th></tr>
<tr><td>CP</td><td>50mg x 2</td><td>Per os</td><td>Daily, 1 week on/1 week off</td><td rowspan="3">3 weeks</td></tr>
<tr><td>PEMBROLIZUMAB</td><td>200 mg</td><td>IV</td><td>On day 8, every 3 weeks</td></tr>
<tr><td>G100</td><td>20µg</td><td>ITum</td><td>One weekly for at least 6 weeks and for a maximum of 12 weeks

Start one week before CP administration, ie. Day -7 (“impregnation phase”)</td></tr>
</table></td></tr>
</table>

	A treatment cycle consists of 3 weeks. Treatment may continue until disease progression or study discontinuation (withdrawal of consent, intercurrent illness, unacceptable adverse event or any other changes rendering further treatment unacceptable, etc. see section 5.2).
Endpoints	**Primary endpoint** • The primary efficacy endpoint for advanced **leiomyosarcoma** (stratum 1), advanced **undifferentiated sarcoma** (stratum 2), advanced **other sarcoma** (stratum 3), advanced **osteosarcoma** (stratum 4) is a dual endpoint encompassing non-progression and objective response at 6 months (as per RECIST evaluation criteria v1.1). • The primary efficacy endpoint for advanced **GIST** (stratum 5), **Advanced soft-tissue sarcomas with immune signature** (stratum 6) and **metastatic STS** (stratum 7) is 6-month non-progression (as per RECIST evaluation criteria v1.1). • Non-progression: complete response, partial response or stable disease more than 24 weeks as per RECIST evaluation criteria v1.1. • Objective response: complete response or partial response as per RECIST evaluation criteria v1.1. • Following RECIST v1.1 recommendations: o claimed responses (complete or partial response) will have to be confirmed at least 4 weeks later; o 6-month radiological data will be reviewed by an independent expert radiologist. o Primary efficacy analysis will be based on the central radiological review data. o Each patient will be assigned one of the following categories: Complete response, Partial response, Stable disease, Progression,not evaluated for response. **Other endpoints** **For each stratum:** • Best overall response defined as per RECIST v1.1 criteria. • 1-year progression-free survival (PFS): PFS is defined as the time from study treatment initiation to the first occurrence of disease progression or death (of any cause), whichever occurs first. • 1-year overall survival (OS): OS is defined as the time from study treatment initiation to death (of any cause). • Growth modulation index (GMI), defined for each patient as the ratio of the PFS on the current treatment strategy to the PFS on the previous line of therapy (Von Hoff, 1998), in patients with documented progression at inclusion. • Immune-related response is defined following Wolchok et al. (Clinical Cancer Research 2009). Analysis will be based on data centrally reviewed by an expert radiologist. • Toxicity will be graded using the Common Terminology Criteria for Adverse Events (CTCAE) from the NCI v4.0. • **For each stratum 1 to 5:**Performance of pharmacodynamic (PD)/mechanism of action (MOA) biomarkers analysis as well as predictive biomarkers analysis (levels of angiogenic and immunologic biomarkers in blood at baseline and different study time points. Blood samples will be collected at predefined time points:

	○ Serum/plasma cytokines levels (TNFγ, TNFα, TGFβ, IL2, 4, 6, 10) (ELISA) ○ Serum/plasma VEGF and TPS-1 levels (ELISA) ○ Treg, CD4+ CD8+ and DR lymphocytes subpopulations monitoring, CD8+/Treg ratio (flow cytometry) ○ Plasma levels of Kynurenine and Kynurenine to Tryptophan ratio (ELISA and LC/MS) • Fresh pre-treatment (or archival material obtained from less than 12 weeks before inclusion) will be collected in consenting patients to assess pharmacodynamics biomarkers. • Formalin-fixed, paraffin-embedded biopsy samples will be analysed for (but not limited to) PDL1, CSF-1R, CD68/CD163, CD68/MHC class II, CD31 (microvessel density), Ki67 and other exploratory markers. **<u>For strata 6 and 7:</u>** • Performance of pharmacodynamic (PD)/mechanism of action (MOA) biomarkers analysis as well as predictive biomarkers analysis (levels of angiogenic and immunologic biomarkers) in blood and tumor tissue at baseline and different study time points. ○ Blood samples will be mandatory collected at predefined timepoints for assessment of: – Serum/plasma cytokines levels (TNFγ, TNFα, TGFβ, IL2, 4, 6, 10) (ELISA) – Treg, CD4+ CD8+ and DR lymphocytes subpopulations monitoring, CD8+/Treg ratio (flow cytometry) – Plasma levels of Kynurenine and Kynurenine to Tryptophan ratio (ELISA and LC/MS) • Fresh tumor samples will be mandatorily collected at baseline and during treatment. Formalin-fixed, paraffin-embedded biopsy samples will be analysed for (but not limited to) CD8+ effectors, CD68 and 163 Macrophages and FOXP3+ cells infiltrates as well as PDL1, IDO1, CD31 (microvessel density), Ki67 expression by IHC. Frozen samples will be analysed by (but not limited to) RNA sequencing in search for a predictive signature for response.
Statistical considerations	**NUMBER OF SUBJECTS NEEDED** **<u>Advanced leiomyosarcoma (stratum 1)</u>** • Single-arm phase 2 trial • 2-stage dual endpoint design (Goffin et al. 2008). • PEMBROLIZUMAB + metronomic CP will be considered promising if 6-month non-progression or 6-month objective reponse rate is promising • 30 eligible and assessable patients: PEMBROLIZUMAB + metronomic CP will be considered worthy of further testing in this indication if at least 8 objective responses or at least 20 non-progressions at six months are observed among the 30 evaluable patients. • In order to account for not evaluable patients (+/- 10%), 33 patients with advanced leiomyosarcoma will be recruited. **<u>Advanced undifferentiated sarcoma (stratum 2)</u>** • Single-arm phase 2 trial • 2-stage dual endpoint design (Goffin et al. 2008). • PEMBROLIZUMAB + metronomic CP will be considered promising if 6-month

non-progression or 6-month objective reponse rate is promising
- 30 eligible and assessable patients: PEMBROLIZUMAB + metronomic CP will be considered worthy of further testing in this indication if at least 8 objective responses or at least 20 non-progressions at six months are observed among the 30 evaluable patients.
- In order to account for not evaluable patients (+/- 10%), 33 patients with advanced undifferentiated sarcoma will be recruited.

Advanced other sarcoma (stratum 3)

- Single-arm phase 2 trial
- 2-stage dual endpoint design (Goffin et al. 2008).
- PEMBROLIZUMAB + metronomic CP will be considered promising if 6-month non-progression or 6-month objective reponse rate is promising
- 30 eligible and assessable patients: PEMBROLIZUMAB + metronomic CP will be considered worthy of further testing in this indication if at least 8 objective responses or at least 20 non-progressions at six months are observed among the 30 evaluable patients.
- In order to account for not evaluable patients (+/- 10%), 33 patients with advanced other sarcoma will be recruited.

Advanced osteosarcoma (stratum 4)

- Single-arm phase 2 trial
- 2-stage dual endpoint design (Goffin et al. 2008).
- PEMBROLIZUMAB + metronomic CP will be considered promising if 6-month non-progression or 6-month objective reponse rate is promising
- 30 eligible and assessable patients: PEMBROLIZUMAB + metronomic CP will be considered worthy of further testing in this indication if at least 8 objective responses or at least 20 non-progressions at six months are observed among the 30 evaluable patients.
- In order to account for not evaluable patients (+/- 10%), 33 patients with advanced osteosarcoma will be recruited.

Advanced GIST (stratum 5)

- Single-arm phase 2 trial
- 2-stage Simon's design (Simon 1989).
- PEMBROLIZUMAB + metronomic CP will be considered promising if 6-month non-progression rate is promising
- 28 eligible and assessable patients: PEMBROLIZUMAB + metronomic CP will be considered worthy of further testing in this indication if at least 13 patients are progression-free (out of the 28 evaluable patients).
- Control arm: none
- In order to account for not evaluable patients (+/- 10%), 31 patients with advanced GIST will be recruited.

Advanced soft-tissue sarcomas with immune signature (stratum 6)

- Single-arm phase 2 trial
- 2-stage optimal Simon's design (Simon, 1989).
- PEMBROLIZUMAB + metronomic CP will be considered promising if 6-month non-progression is promising.
- 29 eligible and assessable patients:
    - Stage 1: Following the inclusion of the first 13 assessable patients, if 2 or less patients are progression-free at 6 months (complete response, partial response or stable disease), the study will be terminated early. Otherwise, the second group of 16 subjects will be recruited.
    - PEMBROLIZUMAB + metronomic CP will be considered worthy of further testing in this indication if at least 8 non-progressions at six months are observed among the 29 evaluable patients.

- In order to account for not evaluable patients (+/- 10%), 32 patients with sarcoma with immune signature will be recruited.

<u>Metastatic soft-tissue sarcoma (stratum 7)</u>

- Single-arm phase 2 trial
- 2-stage optimal Simon's design (Simon, 1989).
- PEMBROLIZUMAB + metronomic CP + G100 will be considered promising if 6-month non-progression is promising.
- 29 eligible and assessable patients:
    - Stage 1: Following the inclusion of the first 13 assessable patients, if 2 or less patients are progression-free at 6 months (complete response, partial response or stable disease), the study will be terminated early. Otherwise, the second group of 16 subjects will be recruited.
    - PEMBROLIZUMAB + metronomic CP + G100 will be considered worthy of further testing in this indication if at least 8 non-progressions at six months are observed among the 29 evaluable patients.
- In order to account for not evaluable patients (+/- 10%), 32 patients with metastatic soft-tissue sarcoma will be recruited.

STATISTICAL ANALYSIS

- Each stratum will be analysed independently. No statistical comparison will be performed between strata.
- The primary efficacy endpoint will be analysed based on the eligible and assessable population and based on the central radiological review data.
- Efficacy will be assessed in terms of :
    - 6-month objective response (complete response and partial response) and 6-month non-progression (complete response, partial response or stable disease more than 24 weeks) for leiomyosarcoma (stratum 1), undifferentiated sarcoma (stratum 2), other sarcoma (stratum 3), osteosarcoma (stratum 4) (dual endpoint).
    - 6-month non-progression for GIST (stratum 5), advanced soft-tissue sarcomas with immune signature (stratum 6) and metastatic STS (stratum 7) (single endpoint).
- Objective response and non-progression are defined as per RECIST v1.1 criteria.
- Each patient will be assigned one of the following categories: Complete response, Partial response, Stable disease, Progression, Not evaluated for response.
- The rates of objective response and non-progression at 6 months will be reported
- The safety analysis will be performed on the safety population.
- Interim Statistical Analyses
- Early review of safety data: for each therapeutic strategy (except for stratum 6), safety data will be reviewed following the inclusion of the first 3 treated patient with at least 2-month follow-up data (independently of the stratum), then after 6 and 10 treated patients.

Additionally, for each stratum, an interim statistical analysis will be performed at the end of the 1st stage of recruitment. Results of these interim statistical analyses will be presented to the IDMC members.

Schedule of assessments and procedures for treatment strategy A by the combination of PEMBROLIZUMAB plus metronomic cyclophosphamide

	SCREENING	*CYCLE 1*			*CYCLE 2*			*CYCLE 3*			*CYCLE 4*			*CYCLE N*	*END OF TREATMENT*
		W1	**W2**	**W3**	**W1**	**W2**	**W3**	**W1**	**W2**	**W3**	**W1**	**W2**	**W3**	**W**	
CP 50 mg (per os)		**D1 to D7**		**D15 to D21**		**D8 to D14**		**D1 to D7**		**D15 to D21**		**D8 to D14**		**1 week/2**	
PEMBROLIZUMAB (i.v)			**X**			**X**			**X**			**X**		**D8**	
Consultation	**X**	**D1**		**D15**				**D1**						**D1[f]**	**X**
Day-hospitalization			**X**			**X**			**X**			**X**		**D8**	
Written Informed consent	X														
Demographics data	X														
Medical history/baseline condition	X														
Concomitant treatments	X	X……Throughout the study……X													
Physical examination	X[e]	X	X	X		X		X	X			X		D1[f]-D8	X
Assessment of signs and symptoms	X[e]		X	X		X		X	X			X		D1[f]-D8	X
Performance status (ECOG)	X[e]		X	X		X		X	X			X		D1[f]-D8	X
Vital signs (heart rate, blood pressure, temperature)	X[e]	X	X	X		X		X	X			X		D1[f]-D8	X
Height	X														
Weight	X[e]	X	X	X		X		X	X			X		D1[f]-D8	X
Hematology[a]	X[e]	X	X	X		X		X	X			X		D1[f]-D8	X
Biochemistry[b]	X[e]	X	X	X		X		X	X			X		D1[f]-D8	X
Thyroid test: T3, T4 and TSH	X[e]	X				X			X					Every 3 cycles	
Urinalysis[c]	X[e]	X	X	X		X		X	X			X		D1[f]-D8	X
ECG	X[e]	Repeated if indicated													
Serum pregnancy test (*if indicated*)	X[e]	Repeat if applicable													
Adverse Events		X……Throughout the study……X													X
Tumor measurement	X[d]	Repeated every 6 weeks. Documentation (radiologic) must be provided for patients removed from study for progressive disease, and response must be confirmed ≥ 4 weeks													
PD		**X**	**X**			**X**			**X**			**X**		**C6 and progression**	
biopsy (optional for strata 1 to 5)	**X**					**D8**									

a: NFS, platelets, PT/INR, aPTT
b: albumin, total bilirubin (direct bilirubin in case of abnormality), uric acid, urea, calcium, chloride, creatinine, creatinine clearance, glucose, LDH, phosphorus, potassium, totalprotein, alkaline phosphatase, AST, ALT, GGT, sodium, magnesium, CPK
c: blood, glucose, protein, specific gravity
d: baseline tumor assessment should be performed within 28 days (+/- 1 week) before treatment initiation
e:to be done or repeated in the 7 days before treatment initiation and within the 72 hours for pregnancy test
f: **one** week/2 (CP administration)

Schedule of assessments and procedures for treatment strategy B by the combination of PEMBROLIZUMAB + metronomic CP + G100

	SCREENING	*IMPREGNATION D-7*	*CYCLE 1*			*CYCLE 2*			*CYCLE 3*			*CYCLE 4*			*CYCLE N*	*EOT*
			W1	W2	W3	W1	W2	W3	W1	W2	W3	W1	W2	W3	W	
CP 50 mg (per os)			**D1 to D7**		**D15 to D21**		**D8 to D14**		**D1 to D7**		**D15 to D21**		**D8 to D14**		**1 week/2**	
G100 (ITum)		**X**	**D1**	**D8**	**D15**	**D1**	**D8**	**D15**	**D1**	**D8**	**D15**	**D1**	**D8**			
PEMBROLIZUMAB (i.v)				**D8**			**D8**			**D8**			**D8**		**D8**	
Consultation	**X**	**X**	**D1**		**D15**	**X**			**D1**						**D1[f]**	**X**
Day-hospitalization				**D8**			**D8**			**D8**			**D8**		**D8**	
Written Informed consent	X															
Demographics data	X															
Medical history/baseline condition	X															
Concomitant treatments	X		X.....Throughout the study.....X													
Physical examination	X[e]	X	X	X	X	X	X		X	X			X		D1[f]-D8	X
Assessment of signs and symptoms	X[e]	X	X	X	X	X	X		X	X			X		D1[f]-D8	X
Performance status (ECOG)	X[e]	X	X	X	X	X	X		X	X			X		D1[f]-D8	X
Vital signs (heart rate, blood pressure, temperature)	X[e]	X	X	X	X	X	X		X	X			X		D1[f]-D8	X
Height	X															
Weight	X[e]	X	X	X	X		X		X	X			X		D1[f]-D8	X
Hematology[a]	X[e]	X	X	X	X		X		X	X			X		D1[f]-D8	X
Biochemistry[b]	X[e]	X	X	X	X		X		X	X			X		D1[f]-D8	X
Thyroid test: T3, T4 and TSH	X[e]	X					X			X					Every 3 cycles	
Urinalysis[c]	X[e]	X	X	X	X		X		X	X			X		D1[f]-D8	X
ECG	X[e]		Repeated if indicated													
Serum pregnancy test (*if indicated*)	X[e]	X[e]	Repeat if applicable													
Adverse Events			X.....Throughout the study.....X													X
Tumor measurement	X[d]		Repeated at week#9, week#18 and week#24, and every 6 weeks thereafter. Documentation (radiologic) must be provided for patients removed from study for progressive disease, and response must be confirmed > 4 weeks													
PD		**X**		**X**			**X**			**X**			**X**		**X[h]**	
Biopsy		**X**				**X[i]**										

a: differential WBC, haemoglobin, platelets, PT/INR, aPTT
b: Serum electrolytes (Na^+, Mg^{++}, K^+, Cl^-, Ca^{++} and phosphorus), liver function tests (AST, ALT, AP, GGT and total bilirubin/direct bilirubin), LDH, creatinine, glucose, total proteins, urea, uric acid, CPK, albumin and creatinine clearance
c: blood, glucose, protein, specific gravity
d: baseline tumor assessment should be performed within 28 days (+/- 1 week) before treatment initiation
e:to be done or repeated in the 7 days before treatment initiation and within the 72 hours for pregnancy test
f: **one** week/2 (CP administration)
h: at cycle 6 and at progression
i: At day 8 of cycle 2, except in case of irradiation. In case of irradiation, 1st on-treatment biopsy must be done before RT initiation and an additional biopsy must be performed within 3-4 weeks after RT termination.

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE (s)	Adverse Event (s)
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
ANSM	Agence Nationale de sécurité du Médicament
AP	Alkaline Phosphatase
aPTT	Activate Partial Prothrombin Time
AST	Aspartate Aminotransferase
BCG	Bacille de Calmette et Guérin
BM	Biomarker
C	Common
CI	Confidence Interval
CNS	Central Nervous System
CP	Cyclophosphamide
CPP	Ethic Committee
CR	Complete Response
CRA	Clinical Research Assistant
CrCL	Creatinine Clearance
CRF	Case Report Form
CT	Computerized Tomography
CTLA	anti-Cytotoxic T-lymphocyte-associated antigen
DNA	Deoxyribonucleic Acid
DQF	Data Query Form
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EMEA	European Medicines Evaluation Agency
FFPE	Formalin-Fixed Paraffin-Embedded
FUP	Follow-Up
GCP	Good Clinical Practice
GGT	Gamma Glutyl-transferase
GIST	Gastro Intestinal Stromal Tumour
GMI	Growth Modulation Index
HCG	Human Chorionic Gonadotropin
HIV	Human Immunodeficiency Virus
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IEC	Institutional Ethics Committee
IHC	Immunohistochemistry
IMP	Investigational Medical Product
INR	International Normalized Ratio
IRB	Institutional Review Board
IrEICS	Events of Clinical Interest Immune-related
ITum	Intratumoral
ITIM	Immunoreceptor Tyrosine-based Inhibition Motif
ITSM	Immunoreceptor Tyrosine-based Switch Motif
IUD	IntraUterine Device
IV	Intravenous
LDH	Lactate Dehydrogenase
mAb	Monoclonal Antibody
MC	Metronomic chemotherapy
MedDRA	Medical Dictionary for Regulatory Activities
MEL	Melanoma
MRI	Magnetic Resonance Imaging
MT	Methotrexate
MTD	Maximum Tolerated Dose

NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NK	Natural Killer
NPR	Non Progression Rate
NSCLC	Non-Small Cell Lung Cancer
ORR	Overall Response Rate
OS	Overall Survival
OSS	Osteosarcoma
OTC	Over The Count
PD	Progressive Disease
PDGFR	Platelet-Derived GrowthFactor Receptor
PFS	Progression Free Survival
PK	Pharmacokinetic
PR	Partial Response
PRE TT	Pre-Treatment
PS	Performance Status
PT	Prothrombin
PTT	Prothrombin Time
Q2W	Every two weeks
RBC	Red Blood Cell
RECIST	Response Evaluation Criteria in Solid Tumors
RRePS	Réseau de Référence en Pathologie des Sarcomes des Tissus mous et des Viscères
RT	Radiotherapy
SAE	Serious Adverse Event
SD	Stable Disease
SIC	Sarcoma Immune Classes
SmPC	Summary Product Characteristic
SPC	Summary of Product Characteristics
STS	Soft Tissue Sarcoma
SUSAR	Suspected Unexpected Serious Adverse Reaction
TIL	Tumor Infiltrating Lymphocyte
U	Uncommon
ULN	Upper Limit of Normality
UPS	Undifferentiated Pleomorphic Sarcoma
US	United States
TNF	Tumor Necrosis Factor
TSH	Thyroid Stimulating Hormon
TT	Treatment
VEGF	Vascular Endothelial Growth Factor

1. RATIONALE OF THE TRIAL

1.1. MANAGEMENT OF SOFT TISSUE SARCOMA, OSTEOSARCOMA AND GASTROINTERTINAL STROMAL TUMORS IN THE ADVANCED SETTING

Well-planned wide surgical excision complemented by adjuvant radiotherapy in cases of large (> 5 cm) and/or deep tumors is the standard loco-regional treatment for soft-tissue sarcoma (STS) patients (1, 2). However, despite optimal local treatment, 40 to 50% of patients will develop metastatic disease (3). Doxorubicin is considered as the standard first-line therapy. Several chemotherapy regimens have been administered to patients with soft tissue sarcomas who have relapsed after being treated with first line chemotherapy. In 2007, the European Medicines Agency (EMA) approved trabectedin (ET-743, Yondelis®, Pharmamar, Madrid, Spain) for the treatment of patients with advanced STS after failure of anthracyclines and ifosfamide, or who are unsuited to receive these agents. This approval was based on phase 2 clinical trials showing a 6-months non-progression rate of about 30% (5-7). Pazopanib was more recently approved in both the US and European Union for the treatment of patients with soft tissue sarcomas (except liposarcomas) who have either not responded or were refractory to a doxorubicin-containing first line treatment regimen. Approval was based on a single phase 3 study comparing pazopanib to placebo in these patients. Neither arm demonstrated a significant ORR; pazopanib patients had a median PFS of 4.6 months (CI 3.7-4.8) compared to placebo (PFS 1.6 months; CI 0.9-1.8). The hazard ratio was 0.31, with a 95% CI of 0.24-0.40 ($p<0.0001$). OS did not differ significantly between the two arms (8) Overall only few drugs have shown activity in the advanced setting (3) and the median overall survival has only slightly improved in the last 20 years from 12 months to 18 months. (1, 3). There is a compelling unmet medical need for effective therapy for patients with recurrent metastatic STS following chemotherapy.

Osteosarcoma (OSS) is the most common primary malignancy of bone in children and adolescents, and the fifth most common malignancy among adolescents and young adults aged 15 to 19 (9). Indeed, OSS incidence rate has two peaks of about 4 per million per year, one in children and young adults ≤ 24 years, and the second after 60 (10). Use of chemotherapy in the neoadjuvant/adjuvant setting has dramatically improved overall survival (OS) in OSS. Most active agents in OSS are anthracyclines, platinum salts, ifosfamide and methotrexate given in combination in different protocols (11). At relapse, combination protocols with the same drugs are favoured when complete surgery of the metastases is considered achievable. However, patients (pts) not amenable to this strategy have a very poor prognosis and there is no standard therapy in this setting (12-14).

Gastrointestinal stromal tumors (GIST) are the most frequent mesenchymal tumors of the gastrointestinal tract. In most cases of GIST, somatic mutations can be found in the gene encoding the KIT protein, typically in exons 11 and 9 (more rarely in exon 13 or exon 17) (15-16). These mutations confer a gain of function to the receptor, which becomes constitutively activated regardless of the presence of its ligand, stemcell factor. In some cases of GIST, no mutation is found in KIT. The search for additional molecular abnormalities led to the discovery that in many KIT-negative GIST there is a somatic mutation in the gene encoding the platelet-derived growthfactor receptor (PDGFR) (17-18). PDGFR is closely related to KIT, and also belongs to the type III family of receptor tyrosine kinases (19). Mutated KIT or PDGFR confer a growth advantage to tumor cells, and have recently become targets for therapeutic intervention. Imatinib is an oral tyrosine-kinase inhibitor that has revolutionized the treatment of GIST, since this drug is able to inhibit the tyrosine-kinase activities of KIT and PDGFR (18, 20, 21). Imatinib was approved in February 2002 for the treatment of patients with metastatic and/or unresectable GIST (22-23).
Among patients with unresectable or metastatic disease at diagnosis, the ESMO guidelines recommend treatment with imatinib until disease progression (ESMO Guidelines, 2010).
When there is disease progression, the ESMO guidelines recommend continuing tyrosine kinase inhibition with increased daily doses of imatinib (800 mg) or with sunitinib. However, resistance to

imatinib may develop and represents a clinical challenge. Sunitinib has been approved in 2009 by the European Commission for patients whose disease has progressed or who are intolerant to imatinib therapy. However, clinical progression and drug resistance to sunitinib subsequently evolve, generally within 1 year of treatment. More recently regorafenib was approved by the FDA for patients refractory to imatinib and sunitinib based on the results of a phase III of regorafenib versus placebo in patients who had progressed during sunitinib therapy. Progression-free survival on regorafenib (4.8 months) was significantly superior to that observed on placebo (0.9 month) but remained modest (24). Therefore, new treatments are needed.
Overall there is a compelling unmet medical need for effective therapy for patients with recurrent metastatic mesenchymal tumors following standard treatment. Immunotherapy could represent a new efficient therapeutic strategy for this group of tumors (79, 80).

1.2. METRONOMIC CYCLOPHOSPHAMIDE

1.2.1. Background

Metronomic chemotherapy (MC) is defined as frequent and regular administration of low dose of a cytotoxic agent (25). Cyclophosphamide (CP) is the cytotoxic the most widely used with a metronomic schedule. Metronomic CP combines both antiangiogenic and immunomodulatory properties that make it a 'niche' multi-targeted therapy interesting to explore both on the clinical and translational level (26-30). Metronomic CP specifically decreases the number of circulating Treg, restores T cell proliferation, stable anti-tumor T–cell response and NK cell effector functions (30, 31). STS is the most frequent indication for routine use of metronomic CP in adult solid tumors, with a very favourable toxicity profile and encouraging results in prospective and retrospective studies (32-35). An EORTC sponsored clinical trial is under development to assess metronomic CP compared to doxorubicin in first line treatment of advanced STS.

1.2.2. Structure and mechanism of action - Pharmacokinetics

Cyclophosphamide (CP) is a nitrogen mustard alkylating agent from the oxazophorines group. CP mustard forms DNA crosslinks between and within DNA strands at guanine N-7 positions.
Cytotoxic effects occur only after activation in the liver, where CP is converted by enzymes of the Cytochrome P450, (namely 2B6 and in a lesser extent 3A4/5) to active metabolites. The main active metabolite, 4-hydroxy-cyclophosphamide (4-OH-CP), exists in equilibrium with its tautomer aldophosphamide. Oral CP biodisponibility is > 75%. Its half-life is 4 to 7 hours. It does not bind to protein (12-14%) but its metabolites do (52-60%). CP is excreted principally (36–99%) in urine within 48 hours, 5–30% as unchanged drug.

1.2.3. Preclinical and clinical data

Several preclinical studies demonstrated that low-dose CP has a selective effect against cycling vascular endothelial cells (26, 28, 27). Metronomic CP not only directly induces apoptosis of endothelial cells but also alters their functionality, inducing modifications in angiogenic signalling (29, 36).
In several tumor-bearing mice models, low-dose CP has also demonstrated an impact on immune dynamics that can be potentiated by administration of immuno-stimulant agents (37-42). Preclinical data showed that low-dose CP decreases levels of immunosuppressive lymphocytes "Treg" (CD4(+), CD25(High) Foxp3(+) regulatory T cells), as well as levels of immunosuppressive cytokines such as TGF-β, IL-10 and IL-2 produced by effector CD4 cells, and triggers T cell and INF-γ producing NK cell effector functions as well as maturation of dendritic cells (40-42).
Oral CP is the most widely studied drug in metronomic regimen, and a large number of retrospective and prospective clinical studies have investigated metronomic CP in various tumors as single-agent or in combination, notably with methotrexate (MT) (35). Metronomic CP is also routinely used in advanced STS (32-35). Protocols include combination of oral CP (50 mg/d continuously) and MT (2.5 mg b.i.d. on days 1 and 2 each week) (32), oral CP alone at 50mg b.i.d. continuously (33, 34, 43) or

at 100mg b.i.d. combined with 20mg of prednisolone both given one week/2 (34). The best efficacy has been demonstrated with the latter dose but 200 mg per day has been associated with loss of immuno-stimulating effect (30). Alternating schedule such as one week on /one week off appears to be the best tolerated and the most interesting in terms of immunological effects (30, 44, 45). Therefore CP given 50mg b.i.d on a one week on /one week off schedule appears to be the best compromise between efficacy and immunomodulatory effect when considering a combination.

1.2.4. Safety

Main toxicities of CP when used at conventional doses are listed below (Table 1). These toxicities are mostly dose-dependent with the most common being myelosuppression. Reported toxicities in published series and clinical trials assessing metronomic CP are very mild. In STS, Penel et al. reported 4% of grade 3/4 toxicities (33). With a higher dose, Mir et al. reported 7.7% grade 3/4 anaemia or thrombocytopenia, no febrile neutropenia, and no organ impairment on treatment (34).

Table 1 CP side effects at usual MTD doses

Blood/bone marrow	Leukocytopenia, thrombocytopenia, anaemia
Gastro-intestinal	C: Nausea, vomiting, anorexia, diarrhea, constipation, stomatitis U: Hemorrhagic colitis, oral ulceration
Renal and urinary	C: Hemorrhagic cystitis, micro/macro-haematuria
Hepato-biliary	U: Increase in SGOT, SGPT, gamma-GT, PAL, bilirubin
Cardiac /respiratory	U: Pneumonitis, interstitial pneumonia, chronic interstitial lung fibrosis
Secondary malignancies	U: carcinoma of urinary tract, myelodysplastic syndrome/acute leukemia
Other side effects	C: Alopecia (reversible), skin inflammation (palm of hand, finger nails, sole of foot), mucositis

C: Common; U: Uncommon

1.3. PEMBROLIZUMAB

1.3.1. Pharmaceutical and therapeutic background

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades (46). Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies (47-51). In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells / FoxP3+ regulatory T-cells seems to correlate with improved prognosis and long-term survival in many solid tumors.

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an Ig superfamily member related to CD28 and CTLA-4 which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD L2) (52, 53). The structure of murine PD-1 has been resolved (54). PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable-type (V-type) domain responsible for ligand binding and a cytoplasmic tail which is responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM). Following T-cell stimulation, PD 1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3ζ, PKCθ and ZAP70 which are involved in the CD3 T-cell signaling cascade (52, 55-57). The mechanism by which PD-1 down modulates T-cell responses is similar to, but distinct from that of

CTLA-4 as both molecules regulate an overlapping set of signaling proteins (58, 59). PD-1 was shown to be expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B-cells, T regs and Natural Killer cells (60, 61). Expression has also been shown during thymic development on CD4- CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells (62). The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types, including non-hematopoietic tissues as well as in various tumors (63-65, 58). Both ligands are type I transmembrane receptors containing both IgV- and IgC-like domains in the extracellular region and contain short cytoplasmic regions with no known signaling motifs. Binding of either PD-1 ligand to PD-1 inhibits T-cell activation triggered through the T-cell receptor. PD-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments. PD-L2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell function in peripheral tissues (58). Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. PD-1 has been suggested to regulate tumor-specific T-cell expansion in subjects with melanoma (MEL) (66). This suggests that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention.

PEMBROLIZUMAB (previously known as SCH 900475) is a potent and highly selective humanized monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2.

As of today, PEMBROLIZUMAB is FDA approved in the treatment of metastatic melanoma, metastatic non-small lung cancer, recurrent or metastatic head and neck squamous cell carcinoma, urothelial bladder carcinoma, cancers molecularly defined as Microsatellite Instability-High (MSI-high) and mismatch repair-deficient (MMR-deficient), and classical Hodgkin lymphoma.

1.3.2. Rational for dose selection/regimen/modification

An open-label Phase I trial (Protocol 001) is being conducted to evaluate the safety and clinical activity of single agent PEMBROLIZUMAB. The dose escalation portion of this trial evaluated three dose levels, 1 mg/kg, 3 mg/kg, and 10 mg/kg, administered every 2 weeks (Q2W) in subjects with advanced solid tumors. All three dose levels were well tolerated and no dose-limiting toxicities were observed. This first in human study of PEMBROLIZUMAB showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels (1 mg/kg, 3 mg/kg and 10 mg/kg Q2W). No MTD has been identified to date. 10.0 mg/kg Q2W, the highest dose tested in PN001, will be the dose and schedule utilized in Cohorts A, B, C and D of this protocol to test for initial tumor activity. Recent data from other clinical studies within the PEMBROLIZUMAB program has shown that a lower dose of PEMBROLIZUMAB and a less frequent schedule may be sufficient for target engagement and clinical activity.

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

A population pharmacokinetic analysis has been performed using serum concentration time data from 476 patients. Within the resulting population PK model, clearance and volume parameters of 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 200 mg Q3W body weight based regimen are anticipated to remain well within the established exposure margins of

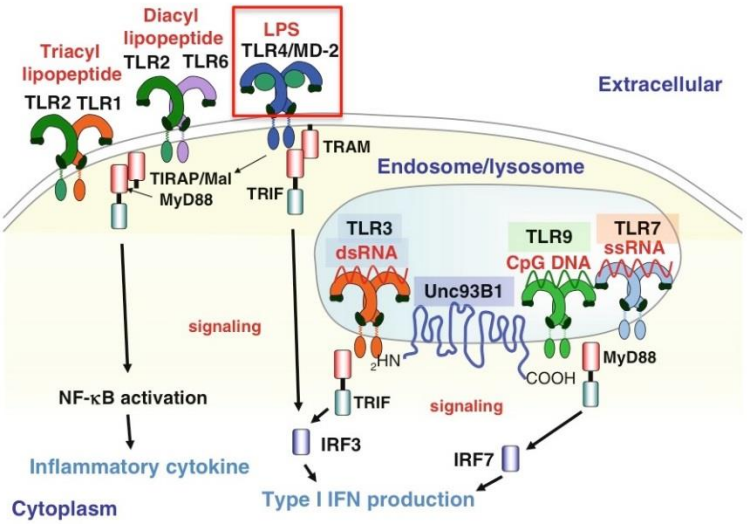
0.5 – 5.0 for PEMBROLIZUMAB in the melanoma indication. The exposure margins are based on the notion of similar efficacy and safety in melanoma at 10 mg/kg Q3W vs. the proposed dose regimen of 200 mg Q3W (i.e. 5-fold higher dose and exposure). The population PK evaluation revealed that there was no significant impact of tumor burden on exposure. In addition, exposure was similar between the NSCLC and melanoma indications. Therefore, there are no anticipated changes in exposure between different indication settings.

1.4. G100

1.4.1. Background

The activation of immune responses in cancer patients has been challenging because DCs at the tumor site are often dysfunctional and unable to prime T cells efficiently. Several biological agents, such as CD40L, 4-1BBL, TNF, oligodeoxynucleotides containing certain unmethylated C-G motifs (CpG) [83] and toll-like receptor-4 (TLR4) agonists activate DCs and B cells by inducing their expression of costimulatory molecules and by triggering cytokine production. TLR4 agonists are particularly suited for this approach. (Figure 1). TLR4 is a cell surface receptor that is critical for the recognition of lipopolysaccharide (LPS), an integral component of gram-negative bacteria. TLR4 reside on the cell surface as opposed to TLR 9, a common target of CpGs, which is mainly expressed in the endosomal compartment. TLR4 agonists activate APCs and induce acute inflammatory responses including production of chemokines and cytokines that mediate inflammatory reactions. Activation of TLR4 induces two distinct signaling pathways controlled by (i) MyD88/MAL which results in activation of nuclear factor (NF)-kB for induction of a number of NF-kB- dependent genes and inflammatory cytokines, and (ii) TRIF/ TRAM which induces production of type I interferons (IFN) [84] TLR4 also plays a non-redundant role in eliciting DC maturation, which is of key importance for effective priming naive T cells and initiating potent immune responses. Recent studies have demonstrated that both MyD88 and TRIF synergize for maximal DC activation.

Figure 1: TLR Ligands and Signaling



Toll-like receptors (TLRs) recognize bacterial and viral components. TLR ligands induce TLRs homodimer or heterodimer to trigger the activation of signaling molecules. TLR4 recognizes LPS to form a homodimer. TLR3, TLR7, and TLR9 localize in intracellular compartment and recognize pathogen-derived nucleotides like double-strand RNA, single- strand RNA, and CpG-containing DNA, respectively. TLR1/TLR2, TLR2/TLR6, and TLR4 activate MyD88 pathway through TIRAP, which is a membrane-association molecule, to induce inflammatory cytokines. In addition, TLR4 activates TRAM and TRIF to induce type I interferon through activating IRF3. (from Saitoh, Chapter 4, Innate Immune Regulation and Cancer Immunotherapy, Springer, Editor Wang).

1.4.2. Structure and mechanism of action of G100 - Glucopyranosyl Lipid A Stable Emulsion, GLA-SE

Immune Design's G100 agent is a fully synthetic toll-like receptor-4 (TLR4) agonist that is a potent stimulator of innate immune responses. G100 consists of a stable emulsion (SE) formulation of GLA,

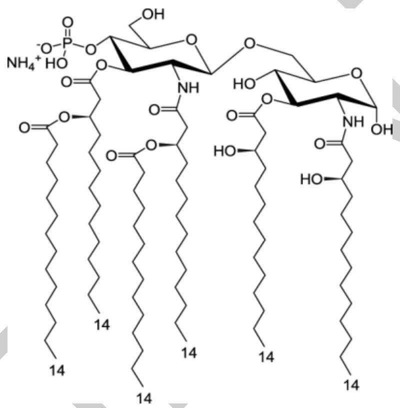
or glucopyranosyl lipid A, a fully synthetic glycolipid acyl component of endotoxin lipid A with the molecular formula of C96H184N3O22P and a molecular weight of 1,762.31 (Figure 2). G100 is manufactured by high-pressure micro-fluidization followed by filter-sterilization. It contains squalene (oil), glycerol, tocopherol (vitamin E), synthetic dimyristoylphosphatidylcholine (DMPC), surfactant (polaxamer) and ammonium phosphate buffer. The emulsion is filled aseptically into vials and appears as a milky-white liquid.

GLA improves the immunogenicity of a wide variety of antigens by increasing the magnitude of the Th1 immune response marked by a high antigen-specific IgG2a:IgG1 ratio and increased production of IFN-γ, TNFα, and IL-12 compared to IL-4, IL-5, and IL-13.

GLA has been extensively evaluated in human subjects formulated in stable oil-in-water emulsion or in an aqueous formulation and has been examined in over 1000 patients as an adjuvant for various infectious agent and cancer vaccines (Investigational Brochure, IB). G100 has been examined in 2 ongoing clinical studies involving patients with Merkel cell carcinoma or sarcoma where it has been administered intratumorally either alone or in combination with local radiation therapy. It has demonstrated the ability to stimulate immune responses with an acceptable safety profile.

In this study, G100 will be administered intratumorally in order to generate an immune response against endogenous tumor antigens.

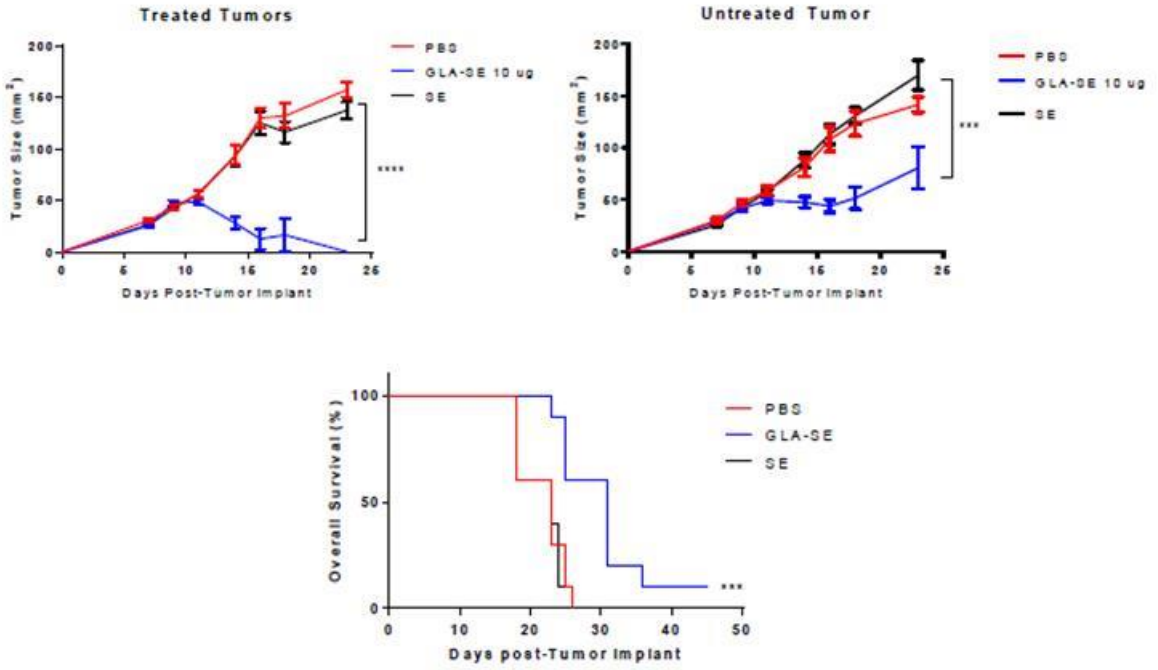
Figure 2: Structure of GLA



1.4.3. Preclinical studies

GLA has demonstrated activity as an intratumoral monotherapy in various preclinical models such as mouse tumor models of melanoma or various lymphoma (IB). GLA has also demonstrated an abscopal effect with intratumoral injection in mice with A20 lymphoma (IAS15-071) (Figure 3).

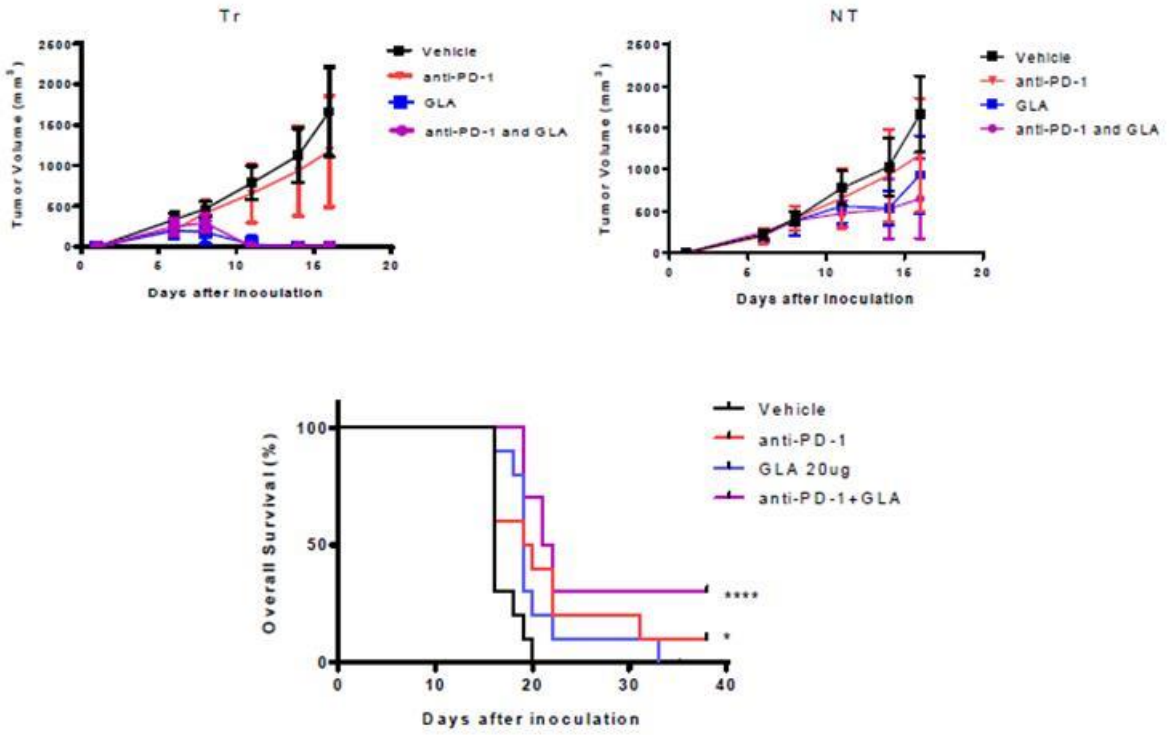
Figure 3: Abscopal Effects of GLA-SE Adminstered Intratumorally in Mouse A20 Lymphoma



GLA-SE = Glucopyranosyl Lipid A stable emulsion; PBS = phosphate buffered saline; SC = subcutaneously; SE = stable emulsion Note: A20 tumor cells (5 × 106) were implanted SC at both the right and left of the flank. GLA-SE (10 µg of GLA in 2% SE) or vehicle control (SE) or PBS was injected to the tumor on the right side (treated tumor) three times a week for a total of three weeks. The graph on the top left shows tumor growth in treated tumors and the graph on the top right shows the tumor growth in the untreated tumors. The graph on the bottom shows the survival of the mice. ***, p<0.001; ****, p<0.0001 from control PBS group.

Combination of intratumoral GLA-SE with systemic administration of anti-PD-1 mAb has also shown enhanced anti-tumor effects in various mouse models such as lymphoma (Figure 4). Combination of intratumoral GLA-SE with local irradiation also enhances anti-tumor effects in mouse models of melanoma and lymphoma (Figure 5).

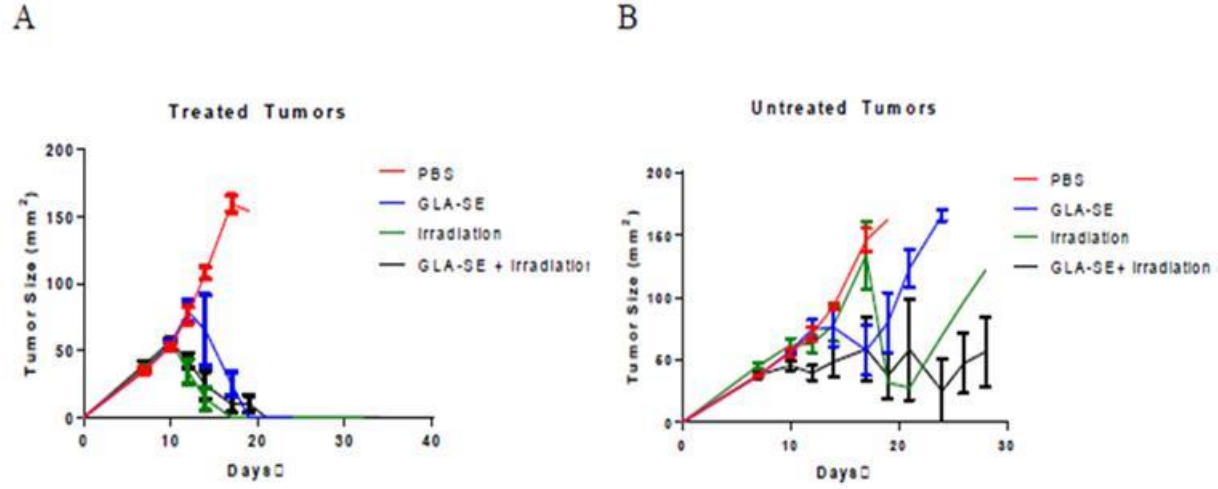
Figure 4: Synergy Between Intratumoral Injection of GLA-SE and Systemic Administration of



Checkpoint Inhibitors in Mouse A20 Lymphoma.

GLA= Glucopyranosyl Lipid A; GLA-SE = Glucopyranosyl Lipid A stable emulsion; PBS = phosphate buffered saline; SE = stable emulsion; SEM = standard error of the means Note: Balb/c mice were inoculated with A20 tumor cells (5 × 106) subcutaneously on both the right and left abdomen. Tumor growth was monitored with a digital caliper. Irradiation (10 Gy) was given on Day 10 to the tumor on the right side. Intratumoral injection of GLA-SE alone (10 µg of GLA in 2% SE) was given 3x/week starting on the day after irradiation, also on the right side. (A) Tumor growth curve of the tumors on the treated side. Shown are the group average (mean±SEM) in each group. (B) Tumor growth curve of the tumors on the untreated side.

Figure 5: Synergy Between Intratumoral Injection of GLA-SE and Local Irradiation in A20 lymphoma



CD= cluster of differentiation; GLA = Glucopyranosyl Lipid A; i.p. = intraperitoneal; IT = intratumoral; mAb = monoclonal antibody; PD-1 = programmed death-1; SC = subcutaneously; SE = stable emulsion
Note: BALB/c mice were inoculated with A20 tumor cells (5 × 106) subcutaneously on both the right and left of the abdomen. Tumor growth was monitored with a digital caliper. Treatment started on Day 6 after tumor inoculation when tumor reached 5-7 mm in the largest diameter. Mice were treated with GLA-SE alone (20 µg of GLA in 2% SE), anti-PD-1 mAb alone (clone RMP1-14, 150 µg), or GLA plus anti-PD-1 mAb. GLA was injected into the right tumor; anti-PD-1 mAb was injected intraperitoneally. Both agents were injected 3 times a week for a total of 5 injections. The graph on the top left shows tumor growth curve in the right tumor (treated, Tr). The graph on the top right shows tumor growth curve in the left tumor (untreated [NT]). The graph on the bottom shows overall survival in each group. *, p<0.05 from vehicle control group; ****, p<0.0001 from vehicle control group.

1.4.4. Clinical studies

G100 (GLA-SE used alone) is being evaluated as an IT immunotherapeutic product in cancer in Merkel cell carcinoma (MCC) and in sarcoma.

In 2013, IMDZ opened a pilot study of IT GLA-SE (G100) in patients with MCC. In this study, patients with metastatic or locoregional MCC were enrolled and treated using 5 µg G100 prior to definitive planned surgery or radiation therapy. IMDZ is currently conducting a randomized study in follicular NHL that will examine up to 3 dose levels of G100 (5 µg, 10 µg, and 20 µg) following low dose local radiation therapy and a group will also receive pembrolizumab. A separate investigator sponsored study was initiated late 2014 in sarcomas. In this ongoing study, 3 G100 IT dose levels are being examined: 5 µg, 10 µg, and 20 µg/dose in combination with radiation therapy.

A Phase 1 Trial of G100 in MCC, Protocol IDC-G100-2013-001
This is a single-arm, open-label, single center pilot trial that assessed the safety of IT G100 injections in 10 patients with MCC and injectable lesions and examined the feasibility of this approach as an anti-cancer immunotherapy. Eligible patients with MCC were enrolled into 2 cohorts, according to their disease status, and received G100 (5 µg total daily dose) intratumorally into MCC tumor(s) on treatment days as specified below:
• COHORT A (Patients with loco-regional disease who were candidates for definitive therapy): Patients received IT G100 injections on Days 1 and 8 (± 2 days) followed by a post-treatment biopsy on Day 22 (± 3 days). After the biopsy, the patients received definitive treatment that included surgery and/or radiation per standard care guidelines as determined by the team of treating physicians. Three patients with loco-regional disease were enrolled into Cohort A.
• COHORT B (Patients with disseminated disease who were not candidates for definitive therapy): Seven patients have received IT G100 injections on Days 1, 8 (± 2 days), and 22 (± 2 days) over a 6-week long cycle. A post-treatment biopsy was obtained on Day 22 (± 3 days) of the first cycle. These patients had their first overall tumor response assessment at week 6 (± 1 week) after the first injection.

In this study, treatment was completed on all 10 planned patients and long-term follow-up continues. An update on the data from the 10 patients was reported at ASCO 2016 (IB). No DLTs or treatment-related SAEs occurred and nearly all reported related AEs were grade 1 or 2. There was 1 possibly

related grade 3 AE consisting of mild skin breakdown at the site of injection and possibly associated with the tumor biopsy site. As of 18-May-2016, of the patients with locoregional disease, 3/3 patients successfully completed G100 followed by surgery plus RT; of these, 2 patients are free of recurrence (27.5+ and 23+ months). One patient (002) had a pathologic CR following two G100 injections alone. Of the 7 patients with metastatic disease, 2 have had ongoing objective responses (17+ and 18+ months) after G100 therapy and are in follow-up; 5/7 had progressive disease (PD). One patient with a partial response (PR) had a 28% regression in the injected tumor following G100 alone in the first cycle, suggesting an anti-tumor response from G100 monotherapy. This response was also associated with increased IT infiltration of CD8+ T cells. The injected lesion regressed completely after the second cycle, which consisted of radiotherapy plus G100. In this pilot study of MCC, IT administration of G100 demonstrated an acceptable safety profile and was associated with encouraging anti-tumor activity.

A Phase 1/2 Trial of G100 in NHL, Protocol IMDZ-G142

The overall goal of this study is to evaluate the safety and immunogenicity of repeat-dose intratumoral G100 administration in patients with NHL following standard local radiation therapy.

In Part 1: Dose Escalation, two dose levels of G100 will be examined, 5 µg and 10 µg, using a standard 3+3 dose escalation design. Treatments consist of weekly intratumoral injections for 6 to 9 doses.

In Part 2, two groups of patients will be examined. In the first group, Patient Expansion With Or Without Pembrolizumab, up to 24 patients will be treated with G100 at the MTD or maximum safe dose determined in Part 1. In this portion of the study, patients will be randomized to receive either intratumoral G100 alone, or intratumoral G100 and sequential anti-PD-1 antibody therapy. This portion of the study is designed to be exploratory. The main goal of Part 2, Patient Expansion With Or Without Pembrolizumab, is to gain safety information regarding these approaches to allow planning for future studies with these agents. The G100 treatment regimen will be identical to that used in Part 1, Dose Escalation. For patients randomized to receive pembrolizumab, the anti-PD-1 antibody begins on day 14 and follows a standard every 3-week schedule. In the second group, Part 2, Large Tumor, a higher dose of G100 (20µg) may be examined. If the G100 dose consisting of 10 µg of the GLA component is determined to be the maximal safe dose and the DMC agrees, an optional treatment group for Large Tumor patients will be treated. In this group, up to 4 patients with injectable lymphoma mass(es) >4 cm in total size (based on the sum of the measurements of the single greatest dimension of each the tumor(s)) will be enrolled and will receive G100 consisting of 20 µg of the GLA component per dose. This will allow greater distribution of the G100 within the large tumor mass(es) and the examination of safety and dose effect. Following the G100 course of treatment, if the patient meets certain eligibility requirements they may be able to receive an optional second course of therapy without radiation as a boost.

Enrollment and safety evaluation of Part 1 (Dose Escalation) was completed in June 2016. On 21 June 2016, an independent DMC reviewed all safety data following the DLT observational period for each cohort and determined that there were no safety issues with the 5 or 10 µg dose levels. The DMC recommended that Part 2 of the study could open and that the 10 µg dose could be used. They also recommended that the Part 2 Large Tumor group be open to use the 20 µg dose.

As of 08-August-2016, Part 1 (Dose Escalation) has been completed and Part 2 is enrolling and treating patients. Three patients in Cohort 1 (5 µg/dose) and 3 patients in Cohort 2 (10 µg/dose) were sequentially enrolled in Part 1 (Dose Escalation) of the study. Two patients have been enrolled in the randomized portion of the study comparing G100 with G100 + pembrolizumab. Therefore, a total of 8 patients have been or are being treated in this study.

A Phase 1 Trial of G100 in Sarcoma

This investigator-sponsored study, ongoing at the Fred Hutchinson Cancer Research Center, is a phase 1, pilot study examining the safety and efficacy of IT G100 in combination with or without radiation in patients with metastatic sarcoma.

Patients requiring therapy and who have planned palliative radiation to a tumor mass that is also accessible for injection are eligible. The primary endpoint is the safety of G100 injected into the tumor. In the original protocol, patients were treated with full dose radiation to their tumor site with doses typically administered over 10-14 days. G100 was then given in 8 weekly injections beginning just prior to radiation. This study was originally designed to examine the 5 µg dose of G100. The protocol was then amended to examine 10 and 20 µg doses of G100 and was further amended to examine the effect of 20 µg/dose when given as a course of G100 intratumorally before radiation. As of November 2016, the study has enrolled 6 subjects in the 5 µg dose cohort and 6 subjects into the

10 µg dose cohort. The 20 µg dose cohort is currently enrolling and at the time of this report at least 3 subjects are being treated at this dose level.

1.4.5. Safety - Summary of Known and Potential Risks to Human Patients

Over 1000 human subjects have been injected with GLA in either the SE formulation (GLA SE) or a second aqueous formulation (AF), with or without antigen. Dosing has ranged from 0.5 to 10 µg with repeat dosing and has primarily been given SC or IM. Eleven patients have received up to 7 doses of 5µg G100 intratumorally with or without local radiation. More than 270 human subjects treated with GLA in different regimens (with or without antigen and via different dosing methods) have had 1 year of systematic post-vaccination follow-up, and there have been no long latency AEs or autoimmune or inflammatory AEs. (Table 1).

Table 1: Total Subjects Treated and Total Doses of GLA Administered to Human Subjects Through August 2014

Study Treatment	**Exposure**	**N**
Any GLA Product	Total doses administered	2299
	Total subjects treated	1065
	GLA 0.5 µg	6
	GLA 1.0 µg	274
	GLA 2.0 µg	332
	GLA 2.5 µg	63
	GLA 5.0 µg	349
	GLA 10.0 µg	41
GLA-AF	Total doses administered	576
	Total subjects treated	255
GLA-SE	Total doses administered	1723
	Total subjects treated	810

The majority of the human experience to date with GLA has been as an adjuvant with infectious agent or cancer associated protein antigens. The most commonly observed AEs have been injection site reactions of mild to moderate severity using the conservative "2007 FDA Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials." The only laboratory abnormalities of note have been transient increases in acute phase reactants (C-reactive protein [CRP] and fibrinogen) and peripheral blood neutrophils.

The safety findings across multiple studies including different formulations of GLA suggest that the dose response for GLA safety will vary with different co-administered antigens. The 5 µg dose of GLA-SE administered with a complex and highly immunogenic influenza (Fluzone®) split virus resulted in 3 of 4 subjects developing Grade 2 AEs (2007 Preventive Vaccine Grading Scale above) of arthralgia, myalgia, fatigue, and chills. However, an investigator-initiated study performed in Brazil has indicated that 50 µg of recombinant hookworm protein administered with a 10 µg dose of GLA-SE 3 times over 2 months was well tolerated. Fewer than 4% of AEs reported in association with GLA containing vaccines have been considered Grade 3 or higher in severity.

The AEs considered expected include injection site reactions, fever, fatigue, chills, myalgia, and arthralgia. There are insufficient data to date to establish that the safety profile is substantially different when GLA-SE is administered by either the IM or subcutaneous route of administration or as the SE or AF formulation.

Twenty-five SAEs have been reported from all GLA-SE clinical trials to date, most temporally dissociated from vaccination and no reports considered possibly, probably or definitely related to GLA treatment. The majority of these events were elective hospitalizations for surgical procedures. One SAE has been reported within 2 weeks of vaccine administration: A 37-year-old female was enrolled and vaccinated, with 3.8 µg investigational recombinant avian influenza protein + 1.0 µg GLA-SE and

eight days later was observed overnight in a hospital setting, where cardiac enzymes and electrocardiogram (ECG) were normal. The patient was discharged with ibuprofen 800 mg, aspirin 325 mg, and omeprazole 40 mg with a discharge diagnosis of costochondritis.

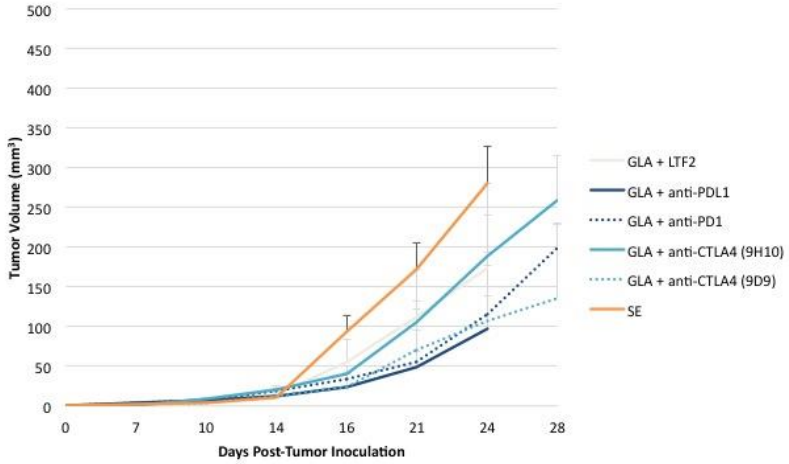
In separate pilot studies, intratumoral injections of 5µg G100 have been administered to patients with Merkel cell carcinoma and to patients with advanced sarcoma. As of February 5, 2015, 11 patients have been enrolled and treated in these ongoing studies. Six patients have received G100 treatment before, during and after radiation therapy. No grade 3 or higher adverse events have been reported and the majority of events have consisted of grade 1 or 2 local reaction, pain and fatigue. In early results, 1 patient with biopsy proven, locoregional Merkel cell carcinoma was found to have a pathologic CR following resection of the treated lesion. Tumor-specific cytotoxic T cells were found in a draining lymph node adjacent to the tumor mass, supporting the concept that clinically meaningful induction of anti-tumor immune activity can be achieved by this approach.

1.4.6. Rationale for G100 Therapy in combination with anti PDL1 and Radiotherapy in sarcoma

Intratumoral administration of TLR4 agonists can activate local DCs and other immune cells to react to local cancer cells despite the immunosuppressive nature of the tumor microenvironment. This approach has the potential to stimulate immune responses against known "specific" as well as previously unrecognized "endogenous" tumor antigens. This locally generated anti-tumor response would be expected to result in a systemic immunity and lead to regression of distal untreated lesions (abscopal response). In preclinical models and in ongoing clinical studies of Merkel cell carcinoma and sarcoma patients, intratumoral G100 has demonstrated early evidence of clinical activity with a reasonable safety profile.

Rationale for anti-PD-1 Therapy and Proposed Schedule
Clinically, anti-PD-1/L1 blocking antibodies are active as a single agent but are limited in their ability to induce objective responses (CR and PR). For this treatment to have a clinical effect, it is hypothesized that tumor-reactive T cells are present, but are being suppressed by this pathway. Blocking this axis would restore anti-tumor immunity. One theory that can explain why anti-PD1/L1 blocking antibodies do not result in higher response rates is that non-responding patients do not have pre-existing effective anti-tumor T cells present that are being suppressed15. As a corollary, if more patients had pre-existing anti-tumor immune responses, then these anti-PD-1/L1 agents could potentially be more effective. In patients with cancer, the PD-1/L1 pathway would be expected to diminish any anti-tumor immune response, and it stands to reason that CD8 T cells generated by the immune response to G100 would eventually be affected by this pathway. Therefore, G100 activity might be enhanced by blocking the PD-1/L1 pathway, especially in the presence of tumor or cells within the tumor microenvironment expressing PD-L1. This effect can be demonstrated in tumor-bearing animals, where blocking PD-1 in combination with active immunization with G100 controlled tumor growth significantly better than animals treated with G100 alone (Figure 6).

Figure 6: Intratumoral G100 plus check point inhibitors in the B16 Melanoma Model



On Day 0, B6 mice were injected with 5 x 105 B16F10 cells, footpad. On Day 4 and every 3-4 days thereafter, G100 (5 µg GLA/2% SE) was administered intratumorally either with or without anti-PD-1, anti-PD-L1, anti-CTLA4 (2 antibody clones) or

control (100ug intraperitoneal injection). The anti-tumor effect of anti-PD-1, anti-PD-L1 and anti-CTLA4 antibodies were additive or synergistic when combined with G100.

There is reasonable rationale that an optimal dose schedule of an active immune approach with an anti-PD-1/L1 may require that a T-cell response be induced before introducing PD-1/L1 blockade.

Rationale for Radiotherapy with Intratumoral G100
Recent studies with CpGs (a TLR9 agonist) administered intratumorally plus local radiation therapy have been associated with tumor responses at local and distant sites, both in mycosis fungoides [85] and B cell lymphoma [86]. Local radiation therapy is thought to increase tumor immunogenicity by inducing tumor cell apoptosis and death and thereby releasing endogenous tumor antigens for cross-presentation by local DCs. In addition, radiation can increase tumor MHC Class I expression and help facilitate DC migration [87].

As discussed, G100 is a very potent TLR4 agonist that can promote the stimulation of DCs and immune effector cells. The combination of intratumoral G100 and radiation would be expected to augment the release of tumor antigens and enhance cross-presentation by DCs and the effective stimulation of anti-tumor immunity. TLR4 agonists may have an advantage over TLR9 agonists such as CpGs in this approach. TLR4 reside and are accessible on the cell surface as opposed to TLR 9, which is mainly expressed in the endosomal compartment. TLR4 agonists also stimulate both the MyD88 and TRIF pathways leading to broad immune stimulation through NF-kB and induction of type I interferon (Figure 1: TLR Ligands And Signaling).

Rationale for use of this approach in sarcoma
Historically, sarcoma represent the first tumor model for which immunotherapy has been suggested as a relevant therapeutic strategy. In 1866, Busch et al. described tumor shrinkage in sarcoma patients suffering from postoperative wound infections. In 1891, Coley et al. reported the first description of immunotherapy of malignant tumors. The highest incidence of sarcoma in immunocompromised people such as allograft transplant recipient or HIV positive individuals supports also the relevance of the immune system in this disease. Approaches currently developed in immunotherapy for sarcoma with anti-PD1 have shown that using antiPD1 alone is not sufficient despite CD8 effectors cells present on site. This suggests other mechanisms imparing efficacious immune response. A synergistic approach with TLR4 agonist could help trigger more efficacious CD8 effectors activity and obtain a better antitumor immune response in these tumors.

1.5. SARCOMA IMMUNE CLASSES

We have recently reported a comprehensive analysis of transcriptomic data of four independent publicly-available complex genomic STS and used these data to propose an immune classification of STS (93). This classification highlighted 5 sarcoma immune classes (SIC) differing in the level of immune infiltration. Tumours of SIC C2 exhibit the largest infiltrate of CD8+ T cells), and expresses the PDCD1 gene (coding for PD-1) more highly than tumours of any other SIC. Thus, we hypothesized that this immune classification can predict response to immunotherapy and that tumours of SIC C may respond better to treatment with PD-1 blockade compared to tumours of SIC A or B. An analysis of 15 pretreatment STS biopsies from the SARC028 clinical trial15 which enrolled patients with advanced, unresectable sarcomas who were treated with the anti-PD-1 monoclonal antibody pembrolizumab was performed. Pretreatment tumours were characterized and classified by SIC. Of these 15 patients, 1 achieved complete response (CR), 3 partial response (PR), 4 stable disease (SD) and 7 had progressive disease (PD) (Fig. 7). All 4 patients who achieved objective clinical response by RECIST (CR or PR) were found to be assigned to SIC C2, and all C2 tumours responded to anti-PD-1 therapy. Of the 4 patients who achieved SD, 3 had tumours assigned to SIC A1 and 1 to SIC B (Fig 7).
Patients with tumours classified as SIC C had a significantly longer PFS compared to SIC A (p=0.0079, log-rank test, Fig. 7) and trended towards longer PFS compared to SIC B (p=0.0574, although only 2 tumours were assigned to SIC B).

Among responders, 2 patients achieving 100% reduction in the target lesions (Fig. 7) (including 1 patient who had non-CR in non-target lesions but -100% change in target lesions and thus did not qualify for CR) (94).

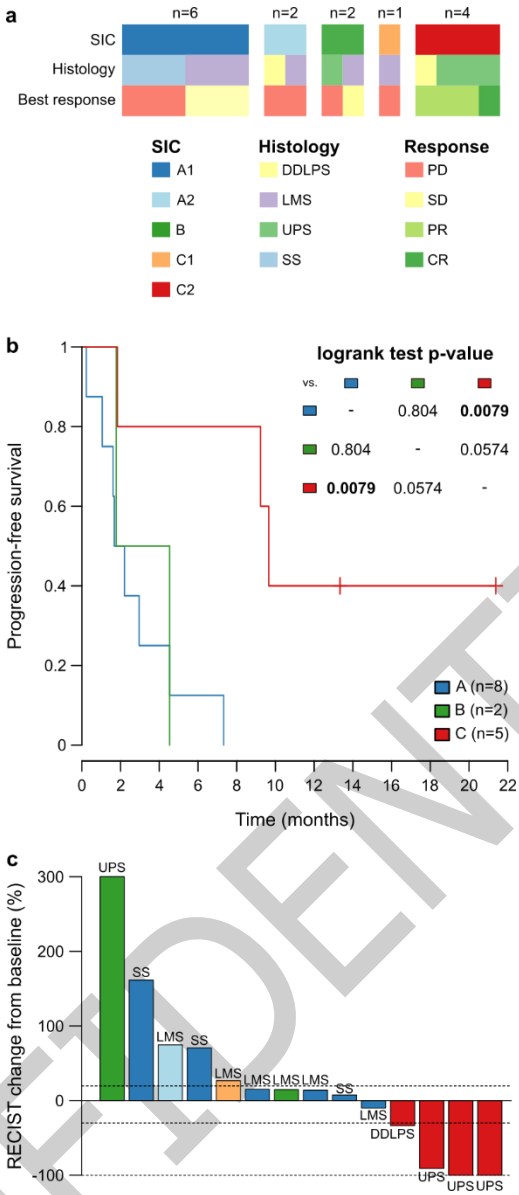


Figure. 7: SIC are accurate predictors of STS response to PD-1 blockade therapy.
This figure refers to the SARC028 cohort (n=15). a Progression-free survival of patients from the SARC028 trial, depending on the SIC group of their tumours. b Relationship between SIC, histology and response to treatment in the SARC028 cohort. c Waterfall plot showing the best response to pembrolizumab as percentage change of target lesions from baseline in size. Tumour sizes were calculated as the sum of target lesion diameters. The colours indicate the SIC to which each tumour was assigned. Dashed lines indicate +20%, -30% and -100% change from baseline levels. DDLPS: dedifferentiated liposarcoma, LMS: leiomyosarcoma, UPS: undifferentiated pleomorphic sarcoma, SS: synovial sarcoma.

These results indicate that SIC is associated with patient outcome and accurately predicts response to PD-1 blockade therapy. The presence of tertiary lymphoid structures (TLS) is an important hallmark of the immune high group that responds to immunotherapy; this enables identification of this population by generic immunohistochemistry. Overall, these findings lay the foundation for a tool to risk-stratify STS patients, identify those who may be more likely to benefit from immunotherapies, inform clinical decision-making, and can guide future immunotherapy drug development in STS.

1.6. HYPOTHESIS

Recent studies have shown that PDL1 is expressed to 58% of cases of STS, osteosarcomas and GIST (67-69). This overexpression has been associated with poor prognosis. Besides, preliminary unpublished data from our lab corroborates the finding that a proportion of STS express PDL1 (Italiano, personal communication), leading to speculate that drugs targeting this immune checkpoint would be of great interest in these tumors and particularly in complex genomics sarcomas (including leiomyosarcomas, undifferentiated sarcomas). Targeting the PD1/DPL1 interaction was associated with impressive anti-tumor activity in a pre-clinical model of osteosarcoma (70). Metronomic CP has

shown a synergistic effect on immuno-stimulation when combined with immunotherapies such as oncolytic adenovirus (44) or survivin HLA-I peptides vaccine (45) and a French NCI sponsored trial is underway with metronomic CP in association with an oncolytic virus in breast cancer and STS. Metronomic CP has also shown synergy with the antitumor effect of an anti- PD1 antibody in a pre-clinical model (71).

We therefore hypothesized that the association of metronomic CP and PEMBROLIZUMAB could have a synergistic antitumor, antiangiogenic and immuno-stimulating activity together with excellent toxicity profile in patients with advanced or metastatic STS, osteosarcoma and GIST.
Preliminary results of ancillary studies from the PEMBROSARC trial on strata 1, 2 , 3 , 5 (Toulmonde et al. Jama Oncol 2017, In Press) demonstrated a moderate and differential expression of PD-L1 in specific subtypes of sarcomas. Importantly there was a high correlation between efficacy and PD-L1 expression on immune cells.

Several studies have recently highlighted the complex relationship between epigenetics and immune checkpoint expression and activity [88-90]. Epigenetic therapy drugs not only boost immune attraction properties of cancer cells, they also exert important Regulation of Host Immune Cells themselves [91].

2. OBJECTIVES

2.1. PRIMARY OBJECTIVE

2.1.1. For treatment strategy A (strata 1 to 6)

Assessment of the efficacy of PEMBROLIZUMAB and Metronomic Cyclophosphamide (CP) independently for 6 strata (as per RECIST v1.1 criteria):

- Advanced leiomyosarcoma (in terms of 6-month objective response and 6-month non-progression),
- Advanced undifferentiated sarcoma (in terms of 6-month objective response and 6-month non-progression),
- Advanced other sarcoma (in terms of 6-month objective response and 6-month non-progression),
- Advanced osteosarcoma (in terms of 6-month objective response and 6-month non-progression),
- Advanced GIST (in terms of 6-month non-progression).
- Advanced soft-tissue sarcomas with immune signature (in terms of 6-month non-progression)

2.1.2. For treatment strategy B (stratum 7)

Assessment of the efficacy of PEMBROLIZUMAB and Metronomic Cyclophosphamide (CP) + G100 in terms of 6-month non-progression (as per RECIST v1.1 criteria) in patients with metastatic soft-tissue sarcoma.

2.2. SECONDARY OBJECTIVES

For each stratum:

- Assessment of the efficacy of the treatment strategy in terms of best overall response (as per RECIST v1.1 criteria), 1-year Progression-free survival (PFS, as per RECIST v1.1 criteria), and 1-year overall survival (OS).
- Assessment of the efficacy of the treatment strategy in terms of 6-month immune-related response (Wolchok et al. Clinical Cancer Research 2009) based on centrally reviewed radiological data.
- Assessment of the safety profile of the treatment strategy using the Common Terminology Criteria for Adverse Events (CTCAE) from the NCI v4.0.
- Growth modulation index (GMI), defined for each patient as the ratio of the PFS on the current treatment strategy to the PFS on the previous line of therapy (Von Hoff 1998), in patients with documented progression at inclusion.

For each stratum 1 to 5:

- Translational research: pharmacodynamic (PD)/mechanism of action (MOA) biomarkers analysis as well as predictive biomarkers analysis (levels of angiogenic and immunologic biomarkers in blood at baseline and different study time points).
- Prospective determination of the proportion of STS that express PDL1.
- Identification of prognostic biomarkers of treatment response.

For strata 6 to 7:

- Translational research on blood and tumor tissue samples obtained at baseline and several time points during treatment for:
  - pharmacodynamic (PD)/mechanism of action (MOA) analysis assessing angiogenic and immunologic biomarkers,

identification of biomarkers predictive of treatment response.

3. STUDY DESIGN

This is a phase II trial with seven independent strata:

FOR TREATMENT STRATEGY A (STRATA 1 TO 6):

- **Advanced leiomyosarcoma (stratum 1)**
  - Single-arm phase 2 trial
  - Treatment: PEMBROLIZUMAB + Metronomic CP at standard doses.
  - 2-stage dual endpoint design (72)
- **Advanced undifferentiated sarcoma (stratum 2)**
  - Same design/treatment as for leiomyosarcoma
- **Advanced other sarcoma (stratum 3)**
  - Same design/treatment as for leiomyosarcoma
- **Advanced osteosarcoma (stratum 4)**
  - Single-arm phase 2 trial
  - Treatment: PEMBROLIZUMAB + Metronomic CP at standard doses.
  - 2-stage dual endpoint design (72)
- **Advanced GIST (stratum 5)**
  - Single-arm phase 2 trial
  - Treatment: PEMBROLIZUMAB + Metronomic CP at standard doses.
  - 2-stage optimal Simon's design (73)
- **Advanced soft-tissue sarcomas with immune signature (stratum 6)**
  - Single-arm phase 2 trial
  - Treatment: PEMBROLIZUMAB + Metronomic CP at standard doses.
  - 2-stage optimal Simon's design (73)

FOR TREATMENT STRATEGY B (STRATUM 7):

- **Metastatic soft-tissue sarcoma**
  - Single-arm phase 2 trial
  - Treatment : PEMBROLIZUMAB + Metronomic CP at standard dose + G100
  - 2-stage optimal Simon's design (73)

4. SELECTION OF PATIENTS

4.1. INCLUSION CRITERIA

4.1.1. For strata 1 to 5

1. Histology: Leiomyosarcoma, or UPS (undifferentiated pleomorphic sarcoma), or other sarcoma, or GIST (gastro intestinal stromal tumor, or osteosarcoma, histologically confirmed by central review (Pr Coindre team), except if the diagnosis was already confirmed by the RRePS Network,
2. Advanced non resectable / metastatic disease,
3. Documented progression according to RECIST criteria. Progression on the last line of treatment should be confirmed by central review with two radiological assessments identical (CT scans or MRI) obtained at less from 6 months interval within the 12 months before inclusion,
4. For strata 5, documented disease progression according to RECIST criteria after the first line imatinib and second line sunitinib,
5. Have provided tissue from an archival tissue sample obtained on metastasis or on locally advanced disease, or newly obtained core or excisional biopsy of a tumor lesion
6. For strata 1, 2 and 3: no more of four previous lines of systemic therapy for metastatic disease,
7. Age ≥ 18 years,
8. Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1,
9. Measurable disease according to RECIST v1.1 outside any previously irradiated field. At least one site of disease must be uni-dimensionally ≥ 10 mm,
10. Life expectancy > 3 months,
11. For strata 1, 2 and 3 at least 1 previous line(s) of chemotherapy in the palliative setting,
12. No symptomatic central nervous system disease,
13. No chronic use of glucocorticoids14. Adequate hematological, renal, metabolic and hepatic function:
    a. Hemoglobin $\geq$ 9 g/dl (patients may have received prior red blood cell [RBC] transfusion, if clinically indicated); absolute neutrophil count (ANC) $\geq$ 1.5 x 10^9/l and platelet count $\geq$ 100 x 10^9/l,
    b. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) $\leq$ 2.5 x upper limit of normality (ULN) ($\leq$ 5 in case of liver metastasis).
    c. Total bilirubin $\leq$ 1.5 x ULN OR Direct bilirubin $\leq$ ULN for subjects with total bilirubin levels > 1.5 x ULN.
    d. Albumin $\geq$ 25g/l.
    e. Serum creatinine $\leq$ 1.5 x ULN OR Calculated creatinine clearance (CrCl) $\geq$ 60 ml/min (calculated per institutional standard) for subject with creatinine levels $\geq$ 1.5 x ULN.
    f. Creatine phosphokinase (CPK) $\leq$ 2.5 x ULN
    g. INR $\leq$ 1.5 x ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
    h. aPTT ≤ 1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants,
    i. Thyroid function (T3, T4 and TSH) ≤ 1.5 x ULN and ≥ LLN.
15. No prior or concurrent malignant disease diagnosed or treated in the last 2 years except for adequately treated in situ carcinoma of the cervix, basal or squamous skin cell carcinoma, or in situ transitional bladder cell carcinoma,
16. At least three weeks since last chemotherapy, immunotherapy or any other pharmacological treatment and/or radiotherapy,
17. Recovery to grade < 1 from any adverse event (AE) derived from previous treatment (excluding alopecia of any grade and non-painful peripheral neuropathy grade < 2 (according to the National Cancer Institute Common Terminology Criteria for Adverse Event (NCI-CTCAE, version 4.0),
18. Women of childbearing potential must have a negative serum pregnancy test within 72 hours prior to receiving the first dose of study medication. Both women and men must agree to use a medically acceptable method of contraception throughout the treatment period days and for four months after discontinuation of treatment. Acceptable methods for contraception include intrauterine device (IUD), oral contraceptive, subdermal implant and double barrier. Subjects of childbearing potential are those who have not been surgically sterilized or have not been free from menses for > 1 year.
19. Voluntary signed and dated written informed consents prior to any specific study procedure,

20. Patients with a French social security in compliance with the Law relating to biomedical research (Article 1121-11 of French Public Health Code).

4.1.2. For stratum 6

1. Histology : soft-tissue sarcoma histologically confirmed by central review (Pr Coindre team), except if the diagnosis was already confirmed by the RRePS Network,
2. Advanced non resectable / metastatic disease
3. Documented progression according to RECIST criteria. Progression on the last line of treatment should be confirmed by central review with two radiological assessments identical (CT scans or MRI) obtained at less than 6 months interval within the 12 months before inclusion, except for patients with metastatic disease diagnosed less than 6 months before inclusion.
4. Have provided tissue of a tumor lesion from an archival tissue sample obtained on metastasis or on locally advanced disease, or newly obtained core or excisional biopsy. Tissue < 3 months old and with no subsequent treatment since or from a newly obtained core or excisional biopsy,
5. Presence of tertiary lymphoid structures on freshly obtained tumor biopsy or archival tumor material collected before any systemic treatment or radiation therapy,
6. No more of four previous lines of systemic therapy for metastatic disease
7. Age ≥ 18 years,
8. Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1,
9. Measurable disease according to RECIST v1.1 outside any previously irradiated field. At least one site of disease must be uni-dimensionally ≥ 10 mm,
10. Life expectancy > 3 months,
11. Participant must have advanced disease and must not be a candidate for other approved therapeutic regimen known to provide significant clinical benefit based on investigator judgement,
12. No symptomatic central nervous system disease,
13. No chronic use of glucocorticoids.
14. Adequate hematological, renal, metabolic and hepatic function:

a. Hemoglobin ≥ 9 g/dl (patients may have received prior red blood cell [RBC] transfusion, if clinically indicated); absolute neutrophil count (ANC) ≥ 1.5 x 10^9/l and platelet count ≥ 100 x 10^9/l,
b. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2.5 x upper limit of normality (ULN) (≤ 5 in case of liver metastasis).
c. Total bilirubin ≤ 1.5 x ULN OR Direct bilirubin ≤ ULN for subjects with total bilirubin levels ≥ 1.5 x ULN.
d. Albumin ≥ 25g/l.
e. Serum creatinine ≤ 1.5 x ULN OR Calculated creatinine clearance (CrCl) ≥ 60 ml/min (calculated per institutional standard) for subject with creatinine levels ≥ 1.5 x ULN.
f. Creatine phosphokinase (CPK) ≤ 2.5 x ULN
g. INR ≤ 1.5 x ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
h. aPTT ≤ 1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants,
i. Thyroid functions (T3, T4 and TSH) ≤ 1.5 x ULN and ≥ LLN.

15. No prior or concurrent malignant disease diagnosed or treated in the last 2 years except for adequately treated in situ carcinoma of the cervix, basal or squamous skin cell carcinoma, or in situ transitional bladder cell carcinoma,
16. At least three weeks since last chemotherapy, immunotherapyor any other pharmacological treatment and/or radiotherapy,
17. Recovery to grade ≤ 1 from any adverse event (AE) derived from previous treatment (excluding alopecia of any grade and non-painful peripheral neuropathy grade ≤ 2 (according to the National Cancer Institute Common Terminology Criteria for Adverse Event (NCI-CTCAE, version 4.0),
18. Women of childbearing potential must have a negative serum pregnancy test within 72 hours prior to receiving the first dose of study medication. Both women and men must agree to use 2 medically acceptable methods of contraception throughout the treatment period and for 180 days after discontinuation of treatment. Subjects of childbearing potential are those who have not been surgically sterilized or have not been free from menses for ≥ 1 year,
19. Voluntary signed and dated written informed consents prior to any specific study procedure,
20. Patients with a social security in compliance with the french Law.

4.1.3. For stratum 7

1. Histology: soft-tissue sarcoma histologically confirmed by central review (Pr Coindre team), except if the diagnosis was already confirmed by the RRePS Network,
2. Locally advanced or metastatic disease with at least one injectable lesion. Note that lesion must be cutaneous, subcutaneous or intramuscular. Nethertheless, it would be allowed to inject deeper lesion, either if patient is not on anticoagulation or per the guidelines in the protocol, the lesion is compressible; either if patient is on ASA or anti-platelet agent and the lesion is not compressing or involving organs or vessels
3. Documented progression according to RECIST criteria. Progression on the last line of treatment should be confirmed by central review with two radiological assessments identical (CT scans or MRI) obtained at less from 6 months interval within the 12 months before inclusion, except for patients with metastatic disease diagnosed less than 6 months before inclusion,
4. Patients whose disease has progressed despite standard therapy and for whom no standard therapy exists,
5. Have provided tissue of a tumor lesion from an archival tissue sample obtained on metastasis or on locally advanced disease, or newly obtained core or excisional biopsy. Tissue < 3 months old and with no subsequent treatment since or from a newly obtained core or excisional biopsy
6. No more than 2 previous lines of systemic therapy in the palliative setting,
7. Age ≥ 18 years,
8. Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1,
9. Measurable disease according to RECIST v1.1 outside any previously irradiated field. At least one site of disease must be uni-dimensionally ≥ 10 mm,
10. Life expectancy > 6 months,
11. At least 1 previous line(s) of chemotherapy in the palliative setting,
12. No symptomatic central nervous system disease,
13. No chronic use of glucocorticoids
14. Adequate hematological, renal, metabolic and hepatic function:
    a. Hemoglobin ≥ 9 g/dl (patients may have received prior red blood cell [RBC] transfusion, if clinically indicated); absolute neutrophil count (ANC) ≥ 1.5 x 10^9/l, leukocyte count ≥ 2.5 x 10^9/l and platelet count ≥ 100 x 10^9/l, and lymphocyte count ≥ 0.5 x 10^9/l.
    b. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2.5 x upper limit of normality (ULN) (≤ 5 in case of liver metastasis).
    c. Total bilirubin ≤ 1.5 x ULN OR Direct bilirubin ≤ ULN for subjects with total bilirubin levels ≥ 1.5 x ULN.
    d. Albumin ≥ 25g/l.
    e. Serum creatinine ≤ 1.5 x ULN OR Calculated creatinine clearance (CrCl) ≥ 60 ml/min (calculated per institutional standard) for subject with creatinine levels ≥ 1.5 x ULN.
    f. Creatine phosphokinase (CPK) ≤ 2.5 x ULN
    g. INR ≤ 1.5 x ULN unless subject is receiving anticoagulant therapy
    as long as PT or PTT is within therapeutic range of intended use of anticoagulants
    h. aPTT ≤ 1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants,
    i. Thyroid function (T3, T4 and TSH) ≤ 1.5 x ULN and ≥ LLN.
15. No prior or concurrent malignant disease diagnosed or treated in the last 2 years except for adequately treated in situ carcinoma of the cervix, basal or squamous skin cell carcinoma, or in situ transitional bladder cell carcinoma,
16. At least three weeks since last chemotherapy, and 14 days since last immunotherapy or any other pharmacological treatment and/or radiotherapy,
17. Recovery to grade < 1 from any adverse event (AE) derived from previous treatment (excluding alopecia of any grade and non-painful peripheral neuropathy grade ≤ 2 (according to the National Cancer Institute Common Terminology Criteria for Adverse Event (NCI-CTCAE, version 4.0),
18. Women of childbearing potential must have a negative serum pregnancy test within 72 hours prior to receiving the first dose of study medication. Both women and men must agree to use 2 medically acceptable methods of contraception throughout the treatment period and for 180 days after discontinuation of treatment. Subjects of childbearing potential are those who have not been surgically sterilized or have not been free from menses for ≥ 1 year.
19. Voluntary signed and dated written informed consents prior to any specific study procedure,
20. Patients with a social security in compliance with the French Law.

4.2. EXCLUSION CRITERIA

4.2.1. For strata 1 to 5

1. Previous treatment with PEMBROLIZUMAB or CP,
2. Has received prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody (including ipilimumabor any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways),
3. Evidence of progressive or symptomatic central nervous system (CNS) or leptomeningeal metastases,
4. Men or women of childbearing potential who are not using an effective method of contraception as previously described; women who are pregnant or breast feeding,
5. Participation to a study involving a medical or therapeutic intervention in the last 30 days,
6. Previous enrolment in the present study,
7. Patient unable to follow and comply with the study procedures because of any geographical, familial, social or psychological reasons,
8. Known hypersensitivity to any involved study drug or of its formulation components,
9. Has an active autoimmune disease requiring systemic treatment within the past 3 months or a documented history of clinically severe autoimmune disease, or a syndrome that requires systemic steroids or immunosuppressive agents. Subjects with vitiligo or resolved childhood asthma/atopy would be an exception to this rule. Subjects that require intermittent use of bronchodilators or local steroid injections would not be excluded from the study. Subjects with hypothyroidism stable on hormone replacement or Sjorgen's syndrome will not be excluded from the study,
10. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment,
11. History of idiopathic pulmonary fibrosis, history of non-infectious pneumonitis that required steroids, drug-induced pneumonitis, organizing pneumonia, or evidence of active pneumonitis on screening chest CT scan. History of radiation pneumonitis in the radiation field (fibrosis) is permitted,
12. Has known active hepatitis B or hepatitis C,
13. Has a known history of Human Immunodeficiency Virus (HIV) (HIV1/2 antibodies),
14. Has received a live vaccine within 30 days prior to the first dose of trial treatment.

4.2.2. For stratum 6

1. Previous treatment with PEMBROLIZUMAB
2. Has received prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody (including ipilimumabor any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways),
3. Evidence of progressive or symptomatic central nervous system (CNS) or leptomeningeal metastases,
4. Men or women of childbearing potential who are not using an effective method of contraception; women who are pregnant or breast feeding,
5. Participation to a study involving a medical or therapeutic intervention in the last 30 days,
6. Previous enrolment in the present study,
7. Patient unable to follow and comply with the study procedures because of any geographical, familial, social or psychological reasons,
8. Known hypersensitivity to any involved study drug or of its formulation components,
9. Has an active autoimmune disease requiring systemic treatment within the past 3 months or a documented history of clinically severe autoimmune disease, or a syndrome that requires systemic steroids or immunosuppressive agents. Subjects with vitiligo or resolved childhood asthma/atopy would be an exception to this rule. Subjects that require intermittent use of bronchodilators or local steroid injections would not be excluded from the study. Subjects with hypothyroidism stable on hormone replacement or Sjorgen's syndrome will not be excluded from the study,
10. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment,
11. History of idiopathic pulmonary fibrosis, history of non-infectious pneumonitis that required steroids, drug-induced pneumonitis, organizing pneumonia, or evidence of active pneumonitis on screening chest CT scan. History of radiation pneumonitis in the radiation field (fibrosis) is permitted,

12. Has known history of or is positive for Hepatitis B (HBsAg reactive) or Hepatitis C.
13. Has a known history of Human Immunodeficiency Virus (HIV) infection (HIV1/2 antibodies),
14. Has received a live vaccine within 30 days prior to the first dose of trial treatment.
15. Patients with oral anticoagulation therapy,
16. Known urinary tract obstruction.
17. Previous allogenic bone marrow transplant or solid organ transplantation,
18. Has an active infection requiring systemic treatment within 14 days prior to study.

4.2.3. For stratum 7

1. Previous treatment with PEMBROLIZUMAB or G100,
2. Has received prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody (including ipilimumabor any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways),
3. Evidence of progressive or symptomatic central nervous system (CNS) or leptomeningeal metastases,
4. Men or women of childbearing potential who are not using an effective method of contraception; women who are pregnant or breast feeding,
5. Participation to a study involving a medical or therapeutic intervention in the last 30 days,
6. Previous enrolment in the present study,
7. Patient unable to follow and comply with the study procedures because of any geographical, familial, social or psychological reasons,
8. Known hypersensitivity to any involved study drug or of its formulation components,
9. Has an active autoimmune disease requiring systemic treatment within the past 3 months or a documented history of clinically severe autoimmune disease, or a syndrome that requires systemic steroids or immunosuppressive agents. Subjects with vitiligo or resolved childhood asthma/atopy would be an exception to this rule. Subjects that require intermittent use of bronchodilators or local steroid injections would not be excluded from the study. Subjects with hypothyroidism stable on hormone replacement or Sjorgen's syndrome will not be excluded from the study,
10. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment,
11. History of idiopathic pulmonary fibrosis, history of non-infectious pneumonitis that required steroids, drug-induced pneumonitis, organizing pneumonia, or evidence of active pneumonitis on screening chest CT scan. History of radiation pneumonitis in the radiation field (fibrosis) is permitted,
12. Has known history of or is positive for Hepatitis B (HBsAg reactive) or Hepatitis C.
13. Has a known history of Human Immunodeficiency Virus (HIV) infection (HIV1/2 antibodies),
14. Has received a live vaccine within 30 days prior to the first dose of trial treatment.
15. Patients with oral anticoagulation therapy,
16. Known urinary tract obstruction.
17. Previous allogenic bone marrow transplant or solid organ transplantation,
18. Has an active infection requiring systemic treatment within 14 days prior to study.

5. STUDY PLAN

5.1. DURATION OF STUDY (WHOLE POPULATION)

The total duration of the study will be approximately 84 months, including about 72 months of active enrolment.
Planned start date (first patient on study): 12/2014.
Within each stratum, the date of planned stratum termination (clinical cutoff) corresponds to the date when each patient has been followed-up for 12 months or is deceased.
End of study occurs when all the following criteria habe been satisfied:

- The trial is closed to recruitment
  And
- All patients have disease progression or are no longer on study medication
  And

- The last included patient has been followed for 12 months, or if deceased, each patient has been followed-up for 12 months or is deceased.

5.2. DEFINITIONS OF DURATION OF STUDY AND TREATMENT (PER PATIENT)

Patients will receive study treatment as long as it is considered to be in their best interest for a maximum of 2 years. Patients will be evaluated at scheduled visits in up to three study periods:

- **Pre-treatment (PRE TT):** from signature of informed consent to the first administration of study drugs.
- **Treatment (TT):** from the first administration of study drugs to treatment discontinuation.
- **Follow-up (FUP):** after treatment discontinuation, patients will be followed up four weeks (30 days) for strata 1 to 5 and 90days for strata 6 to 7 later for toxicities except if the patient starts a new antitumor therapy before this period., and beyond if grade 3 or 4 toxicity, until resolution.

Patients who discontinue treatment *without progression* will be **followed clinically with radiological assessment (same method as used during treatment) every 12 weeks** until:

1. Disease progression,
2. Initiation of other antitumor therapy,
3. Death, or
4. The end of the follow-up period, whichever occurs first.

After documented progression or start of a new antitumor therapy, patients will be **followed every 6 months until**:

1. Death, or
2. The end of the follow-up period, whichever occurs first.

Patients will be considered to be **on-study** from the signature of the informed consent to the end of follow-up period.

Patients will be considered to be **on-treatment** for the duration of their treatment until 30 days (4 weeks) for stratum 1 to 5 and 90 days (12 weeks) for strata 6 to 7 after the last treatment administration, except if the patient starts a new antitumor therapy before this period.

Patients may withdraw their consent at any time; no further study activities will be conducted on them.
Treatment discontinuation occurs when an enrolled patient ceases to receive the study medication or starts a new antitumor therapy, regardless of the circumstances, and is defined as 30 days for stratum 1 to 5 and 90 days (12 weeks) for strata 6 to 7 after the day of the last treatment administration, unless the patient starts a new antitumor therapy, in which case the date of administration of this new antitumor therapy will be considered the date of treatment discontinuation. The primary reason for any discontinuation will be recorded on the patient's Case Report Form (CRF). If a patient discontinues treatment, every effort should be made to complete the scheduled assessments.Administration of the study treatment should be discontinued if this is considered to be in the best interest of the patient. More specifically, treatment will be discontinued due to any of the following reasons:

- Disease progression,
- Unacceptable toxicity,
- Intercurrent illness of sufficient magnitude to preclude safety continuation of the study,
- Patient refusal and/or non compliance with study requirements,
- Protocol deviation with an effect on the risk/benefit ratio of the clinical trial

Patients still experiencing a non-progression rate after 6 cycles will then be able to continue treatment off-study at the discretion of the investigator. Duration of treatment will be limited to a maximum of 2 years.

Study discontinuation occurs when an enrolled patient ceases to participate in the study, regardless of the reason (as detailed under "Follow-up" in Section 5.7). Patients have the right to withdraw consent at any time; if this is the case, no further follow-up should be performed.
The date and reason for study discontinuation will be clearly documented on the patient's CRF.

5.3. PROTOCOL DEVIATION

A protocol deviation is defined as any departure from what is described in the protocol of a clinical trial approved by an Independent Ethics Committee/Institutional Review Board (IEC/IRB) and Competent Authorities. Therefore, this applies to deviations related to patient inclusion and clinical procedures (e.g., assessments to be conducted or parameters to be determined), and also to other procedures described in the protocol that concern the Good Clinical Practice (GCP) guidelines or ethical issues (e.g., issues related to obtaining the patients' Informed Consent, data reporting, the responsibilities of the investigator, etc.).
Deviations with no effects on the risk/benefit ratio of the clinical trial (such as minimal delays in assessments or visits) will be distinguished from those that might have an effect on this risk/benefit ratio, such as:

- Deviations that might affect the clinical trial objectives, such as those involving the inclusion/exclusion criteria (which could mean that the patient is not eligible for the trial) and those having an effect on patient evaluability.
- Deviations that might affect the patient's well-being and/or safety, such as an incorrect dosing of the investigational medicinal product due to not following dose adjustment specifications or an incorrect preparation of the medication.
- Deviations related to the following of GCP guidelines as described in the protocol and regulations in force, such as deviations when obtaining the Informed Consent or not following the terms established for reporting serious adverse events, etc.

As a general rule, NO deviations that may have an effect on the risk/benefit ratio of the clinical trial will be authorized. Protocol deviations considered particularly relevant, which are related to ethical issues, fulfillment of GCP guidelines and trial procedures, will be notified to the pertinent IEC/IRB and, if pertinent, to the relevant authorities as established by local regulations.

5.4. SCREENING EVALUATION

During the pre-treatment period, and once the patient has signed the Informed Consent Form, the Investigator will confirm the patient's eligibility for the study by conducting the assessments detailed below.

Screening assessments.

	ASSESSMENT	**TIME**
1. History and clinical examination	• Signed by the patient/legal representative Informed Consent Form	Prior to any specific study procedures
	• Medical history and baseline condition • Complete physical examination • Performance status (ECOG PS; see Appendix 1) • Assessment of baseline signs and symptoms • Concomitant treatments	Within two weeks prior to inclusion (+1 week tolerance)
	• Vital signs: heart rate, blood pressure, body temperature, weight and height	Within 7 days prior to inclusion (+1 day tolerance)
	• Demographic data	Within four weeks prior to inclusion

	ASSESSMENT	TIME
	◆ Primary diagnostic and prior treatment/s data: – Date of diagnosis of the primary disease – Prior treatments (surgery, radiotherapy, chemotherapy, immunotherapy), specifying the date of best response and the time to progression	
2. Pathology	◆ Central review to confirm sarcoma diagnosis, except in case of diagnosis confirmed by RRePS Network ◆ Archived tumor tissue sample obtained on metastasis or on locally advanced disease, or a new obtained core or excisional biopsy of a tumor lesion. Tissue < 3 months old for strata 6 to 7 ◆ For stratum 6: central evaluation of presence of tertiary lymphoid structure on tumor sample	Material sent within 7 days next to signed informed consent
3. Laboratory tests	◆ **Hematology**: differential WBC, haemoglobin and platelets, PT/INR, aPTT ◆ **Biochemistry**: Serum electrolytes (Na^+, Mg^{++}, K^+, Cl^-, Ca^{++} and phosphorus), liver function tests (AST, ALT, AP, GGT and total bilirubin/direct bilirubin), LDH, creatinine, glucose, total proteins, urea, uric acid, CPK, albumin ◆ **Thyroid function**: T3, T4 and TSH ◆ **Urinalysis**: blood, glucose, protein, specific gravity (urinary strip)	Within 7 days prior to inclusion (+3 days tolerance). In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 72 hours prior to initiation of the treatment Within 7 days prior to inclusion (+3 days tolerance)
4. Creatinine clearance	◆ Calculated as per institutional standard	Within 7 days prior to inclusion (+3 days tolerance)
5. Pregnancy test, if applicable	**Measurement** of serum human chorionic gonadotropin (HCG)	Within 72 hours prior to inclusion (+1 day tolerance)
6. ECG	◆ If indicated	Within 7 days prior to inclusion (+3 days tolerance)
7. Tumor assessment	◆ CT-scan or MRI of all measurable sites, as per RECIST (Appendix 2) ◆ Centrally reviewing of two CT scan or MRI obtained at an interval less than 6 months in the period of 12 months prior to inclusion	Within four weeks prior to inclusion (+1 week tolerance) Sent within 7 days next to signed Informed Consent
8. Biopsy	◆ Only for consented patient (optional) for strata 1 to 5 ◆ Mandatory for all patients for strata 6 to 7	At baseline, within 7 days prior to C1D1
9. Other tests	◆ Intercurrent events, concomitant diseases and treatments.	Within two weeks prior to inclusion.

aPTT, activated partial thromboplastin time; ALT, alanine aminotransferase; AP, alkaline phosphatase, AST, aspartate aminotransferase; ECG, electrocardiogram; ECOG PS, Eastern Cooperative Oncology Group Performance Status; GGT, gamme glutyl-transferase; INR, internation, normalized ratio; LDH, lactate dehydrogenase; MRI, magnetic resonance imaging; PGx, pharmacogenomics; PT, prothrombin time; RECIST v1.1, Response Evaluation Criteria In Solid Tumors; WBC, white blood cells.

5.5. EVALUATIONS DURING TREATMENT

The following assessments will be done while the patient is on treatment.

5.5.1. For strata 1 to 6

Evaluations during treatment

	ASSESSMENT	TIME
1. Clinical examination	• Complete physical examination • Performance status (ECOG PS; see Appendix 1) • Vital signs: heart rate, blood pressure, body temperature and weight	Repeat up to 48 hours before Day 1 of cycle 1 Repeat on Days 8 and 15 of Cycle 1 Repeat on Day 8 of cycle 2, 4, 6, etc… Repeat on Days 1 and 8 of cycle 3, 5, etc.
	• Assessment of baseline signs and symptoms	Throughout the treatment period
	• Concomitant diseases and treatments	Throughout the treatment period
2. Laboratory tests*	• **Hematology**: differential WBC, haemoglobin and platelets, PT/INR, aPTT • **Biochemistry**: Serum electrolytes (Na^+, Mg^{++}, K^+, Cl^-, Ca^{++} and phosphorus), liver function tests (AST, ALT, AP, GGT and total bilirubin), LDH, creatinine, glucose, total proteins, urea, uric acid, CPK, albumin • **Thyroid function**: T3, T4 and TSH • **Urinalysis**: blood, glucose, protein, specific gravity (urinary strip)	Repeat up to 48 hours before Day 1 of cycle 1 Repeat on Days 8 and 15 of Cycle 1 Repeat on Day 8 of cycle 2, 4, 6, etc… Repeat on Days 1 and 8 of cycle 3, 5, etc. For thyroid function test: repeat on C2D8, C3D8 and every 3 cycles
3. Creatinine clearance	• Calculated as per institutional standard	Repeat up to 48 hours before Day 1 of cycle 1 Repeat on Days 8 and 15 of Cycle 1 Repeat on Day 8 of cycle 2, 4, 6, etc… Repeat on Days 1 and 8 of cycle 3, 5, etc.
4. Pregnancy test, if applicable	• **Measurement** of serum human chorionic gonadotropin (HCG)	While on study, pregnancy test will be repeated whenever clinically indicated in women with child bearing potential
5. Tumor assessment	• CT-scan or MRI of all measurable sites, as per RECIST (see Appendix 2)	Tumor assessment must be repeated every six weeks (±7 days) and at least four weeks after first documentation of objective response even if there are treatment delays
6. PD study	• Predictive markers of treatment outcome from blood samples	See section 17
7. AEs	As per NCI-CTCAE, version 4.0.	Throughout the treatment period
8. Biopsy	• Only for consented patients (optional for strata 1 to 5) • Mandatory for stratum 6	On Day 8 of cycle 2

*For all laboratory tests a window of 72 hours will be allowed.

AE, adverse event; ALT, alanine aminotransferase; AP, alkaline phosphatase; aPTT, activated partial thromboplastin time; AST, aspartate aminotransferase; ECOG PS, Eastern Cooperative Oncology Group Performance Status; GGT, gamma glutyl-transferase; INR, internation, normalized ratio; LDH, lactate dehydrogenase; MRI, magnetic resonance imaging; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; PGx, pharmacogenomics; PT, prothrombin time; RECIST, Response Evaluation Criteria In Solid Tumors; WBC, white blood cells.

5.5.2. For stratum 7

Evaluations during treatment

	ASSESSMENT	TIME
1. Clinical examination	◆ Complete physical examination ◆ Performance status (ECOG PS; see Appendix 1) ◆ Vital signs: heart rate, blood pressure, body temperature and weight	Repeat up to 48 hours before first G100 injection (Day -7, impregnation phase) Repeat on Days 1, 8 and 15 of Cycle 1 Repeat on Days 1 and 8 of Cycle 2 Repeat on Day 8 of cycle 4, 6, etc… Repeat on Days 1 and 8 of cycle 3, 5, etc. **Note**: Must be repeated at each G100 injection
	◆ Assessment of baseline signs and symptoms	Throughout the treatment period
	◆ Concomitant diseases and treatments	Throughout the treatment period
2. Laboratory tests*	◆ **Hematology**: differential WBC, haemoglobin and platelets, PT/INR, aPTT ◆ **Biochemistry**: Serum electrolytes (Na^+, Mg^{++}, K^+, Cl^-, Ca^{++} and phosphorus), liver function tests (AST, ALT, AP, GGT and total bilirubin), LDH, creatinine, glucose, total proteins, urea, uric acid, CPK, albumin ◆ **Thyroid function**: T3, T4 and TSH ◆ **Urinalysis**: blood, glucose, protein, specific gravity (urinary strip)	Repeat up to 48 hours before first G100 injection (Day -7, impregnation phase) Repeat on Days 1, 8 and 15 of Cycle 1 Repeat on Day 8 of cycle 2, 4, 6, etc… Repeat on Days 1 and 8 of cycle 3, 5, etc. For thyroid function test: repeat up to 48 hours before first G100 injection (Day -7, impregnation phase) and on C2D8, C3D8 and every 3 cycles
3. Creatinine clearance	◆ Calculated as per institutional standard	Repeat up to 48 hours before first G100 injection (Day -7, impregnation phase) Repeat on Days 1, 8 and 15 of Cycle 1 Repeat on Day 8 of cycle 2, 4, 6, etc… Repeat on Days 1 and 8 of cycle 3, 5, etc.
4. Pregnancy test, if applicable	◆ **Measurement** of serum human chorionic gonadotropin (HCG)	While on study, pregnancy test will be repeated whenever clinically indicated in women with child bearing potential
5. Tumor assessment	◆ CT-scan or MRI of all measurable sites, as per RECIST (see Appendix 2)	Tumor assessment must be repeated at week 9, week 18, week 24 and every six weeks (±7 days) and at least four weeks after first documentation of objective response even if there are treatment delays
6. PD study	◆ Predictive markers of treatment outcome from blood samples	See section 17
7. AEs	As per NCI-CTCAE, version 4.0.	Throughout the treatment period
8. Biopsy	◆ Mandatory for all patients	On Day 8 of cycle 2 but in case of radiotherapy, biopsy must be performed before RT initiation and a second biopsy must be performed within 3-4 weeks after RT termination.

*For all laboratory tests a window of 72 hours will be allowed.

AE, adverse event; ALT, alanine aminotransferase; AP, alkaline phosphatase; aPTT, activated partial thromboplastin time; AST, aspartate aminotransferase; ECOG PS, Eastern Cooperative Oncology Group Performance Status; GGT, gamma glutyl-transferase; INR, internation, normalized ratio; LDH, lactate dehydrogenase; MRI, magnetic resonance imaging; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; PGx, pharmacogenomics; PT, prothrombin time; RECIST, Response Evaluation Criteria In Solid Tumors; WBC, white blood cells.

5.6. EVALUATION AT THE END OF TREATMENT

The end-of-treatment visit will be scheduled 30 days (4 weeks) for stratum 1 to 5 and 90 days (12 weeks) for strata 6 to 7 after the last treatment administration (a window of ±1 week is allowed).
Regardless of the reason for discontinuation, the complete workup has to be done at the end-of-treatment visit. This will include the following assessments:

- Assessment of signs and symptoms.
- Complete physical examination.
- ECOG performance status.
- Vital signs [heart rate, blood pressure and temperature].
- Hematology.
- Biochemistry.
- Urinalysis, urinary strip.
- Clinical and radiological tumor assessment (CT-scan/MRI) (except for patients with confirmed PD at discontinuation or who had started a new treatment).
- Intercurrent events and concomitant disease and treatments.
- Safety assessment (AEs).

Adverse events must be reported for 90 days after the last treatment administration or until the start of a new antitumor therapy, whichever occurs first. All SAEs occurring within 90 days of the last treatment administration or until the start of a new antitumor therapy, whichever occurs first, will be reported. Beyond this period of time, only those SAEs suspected to be treatment-related will be reported (see Section 11).

5.7. FOLLOW-UP AFTER END-OF-TREATMENT VISIT

- Each patient will be followed-up for 12 months
- The date and reason of the study discontinuation will be recorded on the patient's CRF (see Section 5.2).
- After treatment discontinuation, patients will be followed four weeks after until resolution of toxicities, if any.
- Patients who discontinue treatment without PD will be followed every 12 weeks until disease progression, other antitumor therapy or death or until the end of the follow-up period, whichever occurs first.
- After disease progression, patients will be followed every 6 months until death or until the end of the follow-up period, whichever occurs first.
- Patients who withdraw consent will not be followed with any study procedures.

All AEs (including SAEs) suspected to be treatment-related will be followed-up until the events or their sequelae resolve or stabilize at a level acceptable to the Investigator and the Sponsor.

6. REGISTRATION PROCEDURES

6.1. SCREENING

Upon signature of consent, screened patient will be entered on study centrally at the Institut Bergonié Coordinating Center by the Study Coordinator as described in a specific SOP provided by the Sponsor.

If applicable, site will send to Bergonie Institute within 7 days after the signature of informed consent:

- Pathology request form completed
- 10 unstained slides and/or preferable FFPE (Formalin-Fixed Paraffin-Embedded) block of specimen tumor sampling, obtained anytime during disease development
- Initial pathology report with patient code and date of birth (including macroscopic description) and pathology report of molecular biology if any.

Each site will send to Bergonie Institute for central review before registration:

- Anonymized CD of CT-scan or MRI of two radiological assessments identical obtained at less than 6 months interval within the 12 months before inclusion
- Baseline Clinical Subject Profile with the first shipment
- Radiological Referral Form

For stratum 6, each site will centrally send within 7 days after the signature of informed consent, archived or newly obtained FFPE (Formalin-Fiwed Paraffin-Embedded) block, in order to assess the presence of tertiary lymphoid structures. Details will be available in a specific SOP provided by the Sponsor.

To complete the registration process, the Coordinator will assign a patient screening number.

Upon results of pathological and radiological review will be available, the CRA at Institut Bergonie should inform site by e-mail and return results by fax.

6.2. INCLUSION

With screening results, all eligible patients will be entered in the study centrally at the Institut Bergonié Coordinating Center by the Study Coordinator as described in a specific SOP provided by the Sponsor.

This must be done **before the start of the protocol treatment which should begin within one week (7 days) following registration**.
To complete the registration process, the Coordinator will:

- Assign a patient study number
- Register the patient on the study
- Fax or e-mail the patient study number

The patient study number attributed at the end of the registration procedure identifies the patient and must be reported on all case report forms.

Issues that would cause treatment delays should be discussed with the Principal Investigator. If a patient does not receive the protocol therapy following registration, the patient's registration on the study may be cancelled. The Study Coordinator should be notified of cancellations as soon as possible.

7. STUDY TREATMENT

Sponsor will provide cyclophosphamide for all patients, with identifying labels that will include all the information required by local regulations.
Merck will provide PEMBROLIZUMAB for all patients, with identifying labels that will include all the information required by local regulations.
Immune Design will provide G100 for patients treated by strategy B with identifying labels that will include all the information required by local regulations.
IMPs will have to be requested using appropriate forms provided by the Sponsor.
The study sites will have to ensure drug traceability at all times.

7.1. DESCRIPTION OF TREATMENT

For instructions regarding drug inventory, handling, reconstitution, dilution, storage, accountability and disposal, please refer to the IMP Investigator's Brochure and/or the more updated Summary of Product Characteristics (SPC), all provided as separate documents.

7.2. PHARMACEUTICAL INFORMATIONS

Product description	Galenic	Dosage	Route of administration	Storage	Supply
PEMBROLIZUMAB	Infusion	200mg	Intraveinous	2°C ≤ temp ≤ 8°C	Yes
Cyclophosphamide	Pill	50mg	Orally	< 25°C	Yes
G100	Oil-in-water	1 vial (0,6ml) = 80µg/ml	Intra-tumoral	2°C ≤ temp ≤ 8°C	Yes

GLA-SE, a formulation of glucopyranosyl lipid A (GLA), is a synthetic toll-like receptor 4 (TLR4) agonist that activates specific cells of the immune system. TLR4 agonists activate DCs and induce acute inflammatory responses including production of chemokines and cytokines that mediate leukocyte infiltration, stimulation of DC maturation and induction of adaptive immune responses. Several completed clinical studies with vaccines containing GLA administered to healthy subjects have shown that GLA is generally well tolerated and is associated with heightened immune responses. When GLA-SE is administered as a monotherapy, IMDZ designates the product as G100.

G100 (GLA-SE) is a stable oil-in-water emulsion and will be used in this study in NHL. G100 is formulated in a high-pressure microfluidizer followed by filter-sterilization. It is composed of GLA with the SE (stable emulsion) vehicle which includes excipients squalene (oil), glycerol, tocopherol (vitamin E), dimyristoyl-phosphatidylcholine (DMPC), surfactant (polaxamer) and buffer (ammonium phosphate). G100 is filter sterilized and the emulsion is filled aseptically into each vial and appears as a milky white liquid.

7.3. ADMINISTRATION OF TREATMENT

Drugs will be prescribed after validation by the physician.
The patient will be requested to maintain a medication diary (Appendix 6 to 7) of each dose of medication. The medication diary will be returned to clinic staff at the end of each course.
Reported adverse events and potential risks are described in Section 11.

Regimen Description				
Agent	**Dose**	**Route**	**Schedule**	**Cycle Length**
PEMBROLIZUMAB	200mg	I.V.	On day 8 of each cycle	**21 days (3 weeks)**
Cyclophosphamide	50mg b.i.d.	oral	Twice a day In the morning and evening One week on / one week off	

G100	20µg	I.Tum	One week before Cyclophosphamide start, ie. On Day -7 ("Impregnation phase") Weekly for at least 6 injections and for a maximum of 12 injections. Only one lesion can be injected	

7.3.1. Cyclophosphamide

CP should be taken fasting but may be given with food to improve digestive tolerance as no significant PK variation has been demonstrated in this regard. . In case of vomiting or missed dose, the patient should not take additional tablet.

7.3.2. Pembrolizumab

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

7.3.3. G100

G100 will be given by direct injection into a tumor to treat. This injection must be performed during hospitalization. **Note that only one lesion can be injected. Lesion must be cutaneous, subcutaneous or intramuscular.** Nethertheless, it would be allowed to inject deeper lesion, either if patient is not on anticoagulation or per the guidelines in the protocol the lesion is compressible; either if patient is on ASA or anti-platelet agent and the lesion is not compressing or involving organs or vessels.

7.3.3.1. G100 PREPARATION

To prepare G100 for injection, the GLA-SE is diluted with an equal volume of 0.9% saline. The vial should be gently inverted 5 – 10 times to mix the GLA-SE with the saline diluent. The GLA SE vial is single use.
For intratumoral administration the dose of G100 will be fixed at the 20 µg/dose. Details on the handling, preparation of the study agent and dose concentration and volume will be provided in the dose preparation manual (separate document).
G100 should be used within 4 hours of dilution.
G100 must not be frozen.

7.3.3.2. G100 PLANNING OF INJECTION SITES

Before injection, physician should:

- Assess depth
- Confirm ability to palpate
- Imaging is not needed to inject tumor
- Prepare supplies for injection
- Adjust patient for comfort
- Mark site
- Clean and drap site

7.3.3.3. G100 ADMINISTRATION

Appropriate sized needle should be used based on tumor location. No pre-meds are required.
The injection site should be prepped and sterilized using standard methods;
G100 is injected in a relatively short amount of time directly into the tumor mass
For injection, physician should:

- Palpate tumor to hold its position for injection
- Insert needle into tumor and pull back on plunger to verify location is not vascular
- Inject slowly into tumor
- Needle/syringe may be repositioned to inject into different portions of the tumor
- Inject in different directions
- Distribute evenly
- Upon completion, check for bleeding and use pressure as needed

- Cover with dressing and observe patient in clinic for any post-injection reactions for 20 to 30 minutes and then discharge if stable.

7.4. GENERAL CONCOMITANT MEDICATION AND SUPPORTIVE CARE GUIDELINES

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

7.4.1. Acceptable concomitant medication

All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the case report form (CRF) including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF.
All concomitant medications received within 28 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered after 90 days after the last dose of trial treatment should be recorded for SAEs.

7.4.2. Prohibited concomitant medication

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

- Anti-cancer systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than PEMBROLIZUMAB and CP and G100
- Radiation therapy and other surgical or radiological local treatment of targeted lesions
  - Note: Palliative radiation therapy to a symptomatic lesion or to the brain may be allowed after consultation with Sponsor. For stratum 7, palliative radiotherapy is allowed after week#3. Dose and schedule is at the discretion of the investigator.
- Live vaccines within 30 days prior to the first dose of trial treatment, during the study treatment and 6 months after the last dose. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however intranasal influenza vaccines (e.g. Flu-Mist®) are live attenuated vaccines, and are not allowed.
- Glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.
- For patients treated with G100: oral anticoagulation:
  - Potential of bleeding during treatment by G100
- Note for G100: Aspirin, anti-platelet agents (clopidogrel), NSAIDs may be used. It depends on the tumor injected (superficial / deeper mass) and the risk of bleeding.

  Based on the consensus guidelines from the Cardiovascular and Interventional Radiology Society of Europe, if a patient is to have a superficial lymph node or subcutaneous mass injected, NSAIDs, aspirin, or clopidogrel may be used and do not have to be withheld. For procedures with moderate or significant risk of bleeding, the decision for long-acting agents such as aspirin or clopidogrel is at the discretion of the investigator and may need to be discontinued before

beginning G100 therapy. (Higher risk would include deeper lesions or those within organs or with the potential for bleeding without the possibility of simple compression to help stop the bleeding).

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

The Exclusion Criteria describes other medications which are prohibited in this trial.

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

7.4.3. Restriction during the study

7.4.3.1. CONTRACEPTION (ALL STRATA)

Women may only be enrolled if they are willing to use 2 methods of birth control or are considered highly unlikely to conceive.

Highly unlikely to conceive is defined as

1) surgically sterilized,
2) or postmenopausal (a woman who is ≥ 45 years of age and has not had menses for greater than 1 year will be considered postmenopausal),
3) or not heterosexually active for the duration of the study. Abstinence is only acceptable as "true abstinence" when it is in line with the preferred and usual lifestyle of the patient and not a periodic occurrence.

The two birth control methods can be either two barrier methods or a barrier method plus a hormonal method to prevent pregnancy. Subjects should start using birth control 4 weeks before starting study treatments, throughout the study period and up to 180 days after the last dose of study treatments.

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

For male patients, acceptable contraception includes use of male condom. Subjects should start using birth control throughout the study period up to 180 days after the last dose of study treatments.

If the partner is a woman of childbearing potential, supplemental contraception with hormonal or barrier methods should be considered.

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study.

7.4.4. Supportive care guideline for pembrolizumab

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator including but not limited to the items outlined below. 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. The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab.

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

- For Immune-related adverse events (ir-AE): Please see Section 7.5.2 regarding diagnosis and management of adverse experiences of a potential immunologic etiology.

- Nausea/vomiting: Nausea and vomiting should be treated aggressively, and consideration should be given in subsequent cycles to the administration of prophylactic antiemetic therapy

according to standard institutional practice. Subjects should be strongly encouraged to maintain liberal oral fluid intake.

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

- Management of Infusion Reactions (table 2): Acute infusion reactions (which can include cytokine release syndrome, angioedema, or anaphylaxis) are different from allergic/hypersensitive reactions, although some of the manifestations are common to both AEs. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Signs/symptoms may include: Allergic reaction/hypersensitivity (including drug fever); Arthralgia (joint pain); Bronchospasm; Cough; Dizziness; Dyspnea (shortness of breath); Fatigue (asthenia, lethargy, malaise); Headache; Hypertension; Hypotension; Myalgia (muscle pain); Nausea; Pruritis/itching; Rash/desquamation; Rigors/chills; Sweating (diaphoresis); Tachycardia; Tumor pain (onset or exacerbation of tumor pain due to treatment); Urticaria (hives, welts, wheals); Vomiting.

Table 2 Infusion Reaction Treatment Guidelines

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

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Life-threatening; pressor or ventilatory support indicated	epinephrine should be used immediately Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **Subject is permanently discontinued from further trial treatment administration.**	
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration. For Further information, please refer to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE) at http://ctep.cancer.gov		

7.5. DOSING DELAYS/DOSE MODIFICATIONS AND ADVERSE EVENT MANAGEMENT

7.5.1. General rules for dose modification

Once a dose has been reduced, dose re-increased is not allowed for all IMP.

Doses will be reduced for haematological and other adverse events. Dose adjustments are to be made according to the greatest degree of toxicity. Adverse events will be graded using the NCI Common Terminology Criteria for Adverse Events Version 4.0 (CTCAE).

Main reported toxicities in published series and clinical trials assessing metronomic CP are myelosuppression, nausea and vomiting - which are generally mild - and asthenia which appears more as a cumulative toxicity [19, 20].

Patient who permanently discontinue one IMP should go off protocol therapy.

7.5.1.1. FOR TREATMENT STRATEGY A

Adverse events of clinical interest related to PEMBROLIZUMAB are of an inflammatory or autoimmune nature.
The following guidelines outline dose adjustments for the most frequent of these toxic effects. As no severe toxicity is expected, if any other occurs it should be referred to the principal investigator in order to decide management in the best interest of the patient according to Investigator Brochure. If a patient experiences several adverse events with conflicting recommendations, please use the dose modification recommendation that reduces the dose to the lowest level.

Dose Level	CP Dose
1	*50mg b.i.d*
-1	*50mg/d*

Nausea	**Management/Next Dose for CP**	**Management/Next Dose for PEMBROLIZUMAB**
≤ Grade 1	No change in dose	No change in dose
Grade 2	No change but give appropriate medication systematically	No change in dose but give appropriate medication systematically
Grade 3	Hold until < Grade 2, give appropriate medication systematically and resume at same level, pursuing systemic antiemetic. If recurrent: same If second recurrent: same and resume at lower level dose (level dose -1)	No change in dose but give appropriate medication systematically
Grade 4	-	-
Patients requiring a delay of >4 weeks should go off protocol therapy. Patients requiring > one dose reduction should go off protocol therapy. Patient requiring 2 or more consecutive cancellation of PEMBROLIZUMAB injection should go off protocol therapy		
Recommended management: 1) domperidone or metoclopramide		

Vomiting*	**Management/Next Dose for CP**	**Management/Next Dose for PEMBROLIZUMAB**
≤ Grade 1	No change in dose	No change in dose
Grade 2	No change but give appropriate medication systematically	No change but give appropriate medication systematically
Grade 3	Hold until < Grade 2, give appropriate medication systematically and resume at same level, pursuing systematic antiemetic If recurrent: same and resume at lower level dose (level dose -1)	No change but give appropriate medication systematically
Grade 4	Hold until < Grade 2, give appropriate medication systematically and resume at same level, pursuing systematic antiemetic If recurrent: same and resume lower level dose (level dose -1) If recurrent: off study	No change but give appropriate medication systematically If recurrent : add setrons If recurrent: off study
*Management depending on cause of vomiting (CP or MK). Patients requiring a delay of >4 weeks or > 1 dose reduction should go off protocol therapy. Patient requiring 2 or more consecutive cancellation of PEMBROLIZUMAB injection should go off protocol therapy		
Recommended management: 1) domperidone or metoclopramide 2) setrons		

Neutropenia	**Management/Next Dose for CP**	**Management/Next Dose for PEMBROLIZUMAB**
≤ Grade 1	No change in dose	No change in dose
Grade 2	No change in dose	No change in dose
Grade 3	Hold until ≤ Grade 2 and resume at lower level dose (level dose -1)	Skip injection until ≤ Grade 2
Grade 4	Hold until ≤ Grade 2 and resume at lower level dose (level dose -1) If recurrent: off study	Skip injection until ≤ Grade 2 If recurrent: off study
Patients requiring a delay of >4 weeks should go off protocol therapy. Patients requiring > one dose reduction should go off protocol therapy. Patient requiring 2 or more consecutive cancellation of PEMBROLIZUMAB injection should go off protocol therapy		

Lymphopenia	**Management/Next Dose for CP**	**Management/Next Dose for PEMBROLIZUMAB**
≤ Grade 1	No change in dose	No change in dose
Grade 2	No change in dose	No change in dose
Grade 3	Hold until ≤ Grade 2 and resume If recurrent: same and resume at lower level dose (level dose -1)	No change in dose
Grade 4	Hold until ≤ Grade 2 and resume at lower level dose (level dose -1) If recurrent: off study	Skip injection until ≤ Grade 3 If recurrent: off study
Patients requiring a delay of >4 weeks should go off protocol therapy. Patients requiring > one dose reduction should go off protocol therapy. Patient requiring 2 or more consecutive cancellation of PEMBROLIZUMAB injection should go off protocol therapy		

Thrombocytopenia	**Management/Next Dose for CP**	**Management/Next Dose for PEMBROLIZUMAB**
≤ Grade 1	No change in dose	No change in dose
Grade 2	Hold until ≤ Grade 1 and resume at same dose level. If recurrent: same and resume at lower level dose (level dose -1)	No change in dose
Grade 3	Hold until ≤ Grade 1 and resume at lower level dose (level dose -1)	Skip injection until ≤ Grade 2
Grade 4	Hold until ≤ Grade 1 and resume at lower level dose (level dose -1) If recurrent: off study	Skip injection until ≤ Grade 2 If recurrent: off study
Patients requiring a delay of >4 weeks should go off protocol therapy. Patients requiring > one dose reduction should go off protocol therapy. Patient requiring 2 or more consecutive cancellation of PEMBROLIZUMAB injection should go off protocol therapy		

Fatigue/Asthenia	**Management/Next Dose for CP**	**Management/Next Dose for PEMBROLIZUMAB**
≤ Grade 1	No change in dose	No change in dose
Grade 2	No change in dose	No change in dose
Grade 3	Hold until ≤ Grade 2 and resume at same level If recurrent: same and resume at lower level dose (level dose -1)	No change in dose
Grade 4	Hold until ≤ Grade 2 If recurrent: same and resume at lower level dose (level dose -1) If recurrent: off study	Skip injection until ≤ Grade 2 If recurrent: off study
Patients requiring a delay of > 4 weeks should go off protocol therapy. Patients requiring > one dose reduction should go off protocol therapy. Patient requiring 2 or more consecutive cancellation of PEMBROLIZUMAB injection should go off protocol therapy		

7.5.1.2. FOR TREATMENT STRATEGY B

Adverse events of clinical interest related to Pembrolizumab are of an inflammatory or autoimmune nature.
Please refer to the guidelines of strategy A for dose adjustments for the most frequent of adverse effects. For other adverse effects, please refer to the most updated Investigator Brochure (Pembrolizumab and G100)/Summary of Product Characteristics (CP).

As no severe toxicity is expected, if any other occurs it should be referred to the principal investigator in order to decide management in the best interest of the patient. If a patient experiences several adverse events with conflicting recommendations, please use the dose modification recommendation that reduces the dose to the lowest level.

7.5.2. Immune related adverse event (irAE)

7.5.2.1. IMMUNE RELATED ADVERSE EVENT (IRAE)

Immune-Related Adverse Events (irAE)may be defined as an adverse event, associated with drug exposure and is consistent with an immune phenomenon. irAEs may be predicted based on the drug's mechanism of action, and reported experience with immunotherapies that have a similar mechanism of action. Special attention should be paid to potential irAEs. An irAE can occur between shortly after the first dose to several months after the last dose of treatment.

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

sponsor (see section 11.5) but more specially subjects who develop a Grade 2 or higher irAE should be discussed immediately with the Sponsor.
When a second episode of the same serious adverse reaction occurs (including colitis grade 3), permanently discontinue all IMP immediately

Patient requiring 2 or more consecutive cancellation of PEMBROLIZUMAB injection should be withdrawn from the study.

Patient who permanently discontinue one IMP should be withdrawn from the study.

For G100, no dose reduction is required in case of occurrence of irAE.

The management of ir-AE is described in annexe 9. For more details, refer to the most updated Investigator's Brochure of each IMP.

As of this day, no irAE has been reported with G100. However, as with any immune stimulatory approach, irAEs resulting from cross-reactivity of the immune response with normal patient tissues could potentially occur (such as autoimmune colitis, hypophysitis, etc. observed with anti-PD-1 therapeutics).

Based on limited data from clinical studies if immune-related adverse reactions could not be controlled with corticosteroid use, administration of other systemic immunosuppressants can be considered.
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7.5.2.2. SEVERE SKIN REACTIONS

Cases of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), some with fatal outcome, have been reported in patients treated with PEMBROLIZUMAB. When SJS or TEN is suspected, withhold PEMBROLIZUMAB and refer the patient for specialized care for assessment and treatment.
When SJS or TEN is confirmed, permanently discontinue PEMBROLIZUMAB immediately.

7.5.2.3. IMMUNE-MEDIATED MYOCARDITIS

For suspected immune-mediated myocarditis, ensure adequate evaluation to exclude other etiologies, and administer corticosteroids as appropriate.
In all the cases of myocarditis, pembrolizumab must be permanently discontinued.
Besides, the administration of high-dose steroids, the following recommendations must be followed:

Haemodynamically unstable patients
Patients with haemodynamically unstable heart failure should be managed promptly for heart failure in intensive care units with respiratory and mechanical cardio-pulmonary support facilities. In acute/fulminant cases with cardiogenic shock and severe ventricular dysfunction, ventricular assist devices or extracorporeal membrane oxygenation (ECMO) may be needed to provide a bridge to transplant or to recovery. Because of its simplicity and effectiveness, ECMO therapy can rescue this group of patients.

Haemodynamically stable patients
When myocarditis is suspected in asymptomatic or mildly symptomatic patients, admission to hospital and clinical monitoring are recommended until a definite diagnosis is established, since the situation can evolve rapidly and a cardiopulmonary emergency (e.g. severe heart block or life-threatening arrhythmia) is possible and unpredictable, even if systolic function is initially preserved. Exercise testing is contraindicated in the acute stage as it can precipitate arrhythmia.
Patients with haemodynamically stable heart failure should be treated with diuretics, angiotensin-converting enzyme inhibitor, or angiotensin receptor blockade and beta-adrenergic blockade. In patients who have persistent heart failure symptoms despite optimal management, additional treatment with aldosterone antago-nists should be considered.

7.5.2.4. IMMUNE-MEDIATED NEUROPATHIES

Immune-mediated neuropathies have been reported in patients treated with Pembrolizumab.
Monitor subjects for symptoms of motor or sensory neuropathy such as unilateral or bilateral weakness, sensory alterations, or paresthesia.
Permanently discontinue Pembrolizumab in subjects with severe neuropathy (interfering with daily activities) such as Guillain-Barré-like syndromes; institute medical intervention as appropriate for management of severe neuropathy. Consider initiation of systemic corticosteroids at a dose of 1 to 2 mg/kg per day prednisone or equivalent for severe neuropathies.
Withhold Pembrolizumab doses in subjects with moderate neuropathy (not interfering with daily activities).

7.5.2.5. ENCEPHALITIS

Encephalitis has been reported in patients treated with Pembrolizumab.
Permanently discontinue Pembrolizumab in subjects with encephalitis and patients must be hospitalized in neurological intensive care unit for appropriate management.

7.6. PACKAGING AND LABELING

The following information will appear on the labels:

- Name of the Sponsor.
- Dosage and route of administration.
- Quantity or contents of container.
- Batch number/packaging number.
- Expiration date and storage conditions.
- Local legal information, as appropriate.

7.7. SUPPLIES AND DRUG ACCOUNTABILITY

PEMBROLIZUMAB is an investigational agent supplied by Merck.
Cyclophosphamide will be supplied by the Sponsor.
G100 is an investigational agent supplied by Immune Design.
Each participating institution will order study drugs according to the process describe in the manual pharmacy.
Proper drug accountability will be done by the clinical trial monitor. Each study site will keep records to allow a comparison of quantities of drug received and used at each site. The Investigator at each study site will be the person ultimately responsible for drug accountability at the site.
During or at the end of the study, all unused drug supplied by the Sponsor will be properly destroyed at the study site or returned to the distribution depot for destruction, at the end of the study. Documentation of this procedure must be provided to the clinical trial monitor.

7.8. TREATMENT COMPLIANCE

The Investigator is responsible for supervising compliance with the instructions described in this study protocol.

8. STUDY EVALUATIONS

Study evaluations aim to assess:

- Diagnosis
- Efficacy
- Safety

8.1. CENTRAL REVIEW FOR DIAGNOSIS OF SARCOMA/GIST AND PROGRESSIVE DISEASE

8.1.1. Diagnosis

8.1.1.1. DIAGNOSIS OF SARCOMA/GIST

If diagnosis of sarcoma was not confirmed by the RRePS Network, pathological central review will be performed to confirm histological diagnosis of sarcoma/GIST by Pr. Coindre and collaborators, Department of Pathology, Institut Bergonié, Bordeaux, France. The reviewer will assess pathological diagnosis; document the results on the 'Pathological request form' response completed and sign this form.
Every discrepancy will be discussed between referral investigator, Pr Coindre or collaborators and the Sponsor, until a final decision is reached. Patients with diagnosis different from sarcoma/GIST will be considered ineligible and will not be included in the study.

8.1.1.2. PATHOLOGICAL SPECIMEN SAMPLING NECESSARY FOR CENTRAL REVIEW

For a gross description and diagnostic information concerning pathological specimens, reference to "Recommendations for reporting soft tissue sarcomas" is strongly advised (Recommendations, 1999). Available tumor samples obtained at diagnosis or at relapse, as unstained slides (10), and/or preferable paraffin-embedded tumor blocks (one or two) is mandatory for central review.

8.1.1.3. PATHOLOGICAL PROCESS SCHEDULE AND IMPLEMENTATION (NOT APPLICABLE IF DIAGNOSIS REVIEWED IN RREPS NETWORK)

Each site will send to Institut Bergonié within 7 days after the signature of informed consent:

- Pathology request form completed
- 10 unstained slides and/or preferable FFPE (Formalin-Fixed Paraffin-Embedded) block of specimen tumor sampling, obtained anytime during disease development
- Initial pathology report with patient code and date of birth (including macroscopic description) and pathology report of molecular biology if any.

All material must be sent as described in specific guidelines provided by the Sponsor:

8.1.2. Diagnosis of progressive disease – Central review before registration

8.1.2.1. CENTRALIZED PATHOLOGICAL REVIEW TO CONFIRM DIAGNOSIS OF PROGRESSIVE DISEASE FOR SARCOMA/GIST

Centralized radiological review will be performed to confirm progressive disease status at inclusion time. This will be performed by centrally reviewing two CT scans or MRI obtained prior to inclusion (obtained at an interval less than 6 months in the period of 12 months prior to inclusion).

8.1.2.2. GENERAL PROCEDURE

Review process will be centralized at Institut Bergonié and will be performed by one radiologist expert in sarcomas/GIST.
The results of the centralized review will be used for the diagnosis for progressive disease.

8.1.2.3. REVIEW PROCESS SCHEDULE AND PRACTICAL IMPLEMENTATION

With regards to inclusion scan, the progressive disease status at baseline must be confirmed by central review. Within 7 Days after the signature of informed consent:

- Each site will send two-imaging CD (two radiological assessments identical, CT-scans or MRI) obtained at less from 6 months interval within 12 months before inclusion) to Bergonie Institute
- Each site must send the completed "Baseline Radiological Form" with the first shipment
- For each shipment, each media should be accompanied by the completed "Radiological Referral Form"

Patient's information must be recorded on an imaging CD.

All CDs must be sent as described in specific guidelines provided by the Sponsor

8.2. BIOPATHOLOGICAL CONFIRMATION FOR STRATUM 6

Centralized pathologival review will be performed to confirm the presence of tertiary lymphoid structures on tumor sample.

8.2.1. General procedure

Review process will be centralized.
The results of the centralized pathological review will be used to confirm patient eligibility.

8.2.2. Review process schedule and practical implementation

Each site will send within 7 days after the signature of informed consent, archived or newly obtained FFPE (Formalin-Fixed Paraffin-Embedded) block.

All material must be sent as described in specific guidelines provided by the Sponsor.

8.3. EFFICACY

The antitumor activity of the treatment strategy will be evaluated in terms of 6-month objective response, 6-month non-progression, best overall response, Growth modulation index (GMI), 1-year progression-free survival (PFS) and 1-year overall survival (OS). Objective response, non-progression and best overall response are defined as per the Response Evaluation Criteria in Solid Tumors (RECIST v1.1, 75 – Appendix 2).

8.3.1. Assessing Tumor Response (RECIST v1.1)

- A comprehensive workup will be performed at baseline and every six weeks.
- Whenever response criteria are met, the appropriate imaging tests will be repeated at least four weeks later in order to confirm the response.
- The same method will be used to evaluate each identified lesion both at baseline and throughout the study.
- Treatment will be administered as long as no disease progression or unacceptable toxicity is found, or as long as no other reasons for treatment discontinuation are met.
- Assessment of efficacy will be essentially based on a set of measurable lesions identified at baseline as target lesions and followed until disease progression and following the RECIST v1.1 criteria (RECIST v1.1, 75 – Appendix 2).

8.3.2. Centralized Radiological Review (Institut Bergonié)

8.3.2.1. GENERAL PROCEDURE

Centralized radiological review will be performed to review all disease status at 6 months in comparison with baseline.
Review process will be centralized at Institut Bergonié and then will be performed by an independant radiologist expert in soft tissue sarcomas and/or GISTs.
In case of discordance between the local radiologist and the expert reviewer, the judgment provided

by the expert reviewer will be retained and used in statistical analyses.

8.3.2.2. REVIEW PROCESS SCHEDULE

All tumor evaluations will be sent as soon as there were available.
Patient's information must be recorded on a provided imaging CD.

8.3.2.3. PRACTICAL IMPLEMENTATION

For each shipment, each media should be accompanied by the Radiological Forms provided by the sponsor.

All CDs must be sent as described in specific guidelines provided by the Sponsor

8.3.3. Assessing immune-related response by centralized Radiological Review (Institut Bergonié)

Centralized radiological review will be performed to evaluate 6-months immune-related response (Wolchok et al. Clinical Cancer Research 2009) in comparison with baseline (all imaging available at 6 months).
Review process will be centralized at Institut Bergonié and then will be performed by a radiologist expert in soft tissue sarcomas and/or GISTs, and will be based on media previously sent.

8.4. SAFETY

Patients will be evaluable for safety if they have received at least one treatment administration. Safety will be evaluated using clinical examinations, which will comprise vital signs analysis, clinical assessment of AEs, changes in laboratory parameters (hematological and biochemical, including liver function tests) and any other analyses that may be considered necessary. Safety profile will be continuously followed during treatment up to 90 days after the last treatment administration or until the start of a new antitumor therapy, whichever occurs first. All AEs will be classified according to the NCI-CTCAE, version 4.0 (81).

9. STUDY ENDPOINTS

9.1. PRIMARY ENDPOINT

9.1.1. Advanced leiomyosarcoma (stratum 1)

- The primary efficacy endpoint is a dual endpoint encompassing non-progression and objective response at 6 months.
    - Non-progression is defined as complete response, partial response or stable disease more than 24 weeks as defined as per RECIST evaluation criteria v1.1 (RECIST v1.1, 75 – Appendix 2).
    - Objective response is defined as complete response or partial response as defined as per RECIST evaluation criteria v1.1 (RECIST v1.1, 75 – Appendix 2)
    - The rates of objective response and non-progression at 6 months will be reported.
        - All eligible and assessable patients (section 10.2) will be included in the denominator for the calculation of the response rate or non-progression rate.
        - The rate of non-progression will be calculated as the number of patients remaining alive and progression-free at 6 months from the start of the treatment divided by the number of patients eligible and assessable (section 10.2).
        - The rate of objective response will be calculated as the number of patients alive with complete or partial response at 6 months divided by the number of patients eligible and assessable (section 10.2).
        - The 95% two-sided confidence limits will be provided for the calculated rates (binomial law).

- Trial conclusions will be based on these rates for all eligible and assessable patients (section 10.2).

- Tumor measurements will be repeated every 6 weeks. Documentation (radiologic) will be provided for patients removed from study for progressive disease.
- Following RECIST v1.1 recommendations:
  - Claimed (complete or partial) responses will have to be confirmed at least 4 weeks later to ensure responses identified are not the result of measurement errors.
  - 6-month radiological data will be reviewed by an independent expert radiologist.
  - Primary efficacy analysis will be based on the central radiological review data.

9.1.2. Advanced undifferentiated sarcoma (stratum 2)

- The primary efficacy endpoint is a dual endpoint encompassing non-progression and objective response at 6 months.
- See section 9.1.1.

9.1.3. Advanced other sarcoma (stratum 3)

- The primary efficacy endpoint is a dual endpoint encompassing non-progression and objective response at 6 months.
- See section 9.1.1.

9.1.4. Advanced osteosarcoma (stratum 4)

- The primary efficacy endpoint is a dual endpoint encompassing non-progression and objective response at 6 months.
- See section 9.1.1.

9.1.5. Advanced GIST (stratum 5)

- The primary efficacy endpoint is non-progression at 6 months.
- See section 9.1.1.

9.1.6. Advanced soft tissue sarcomas with immune signature (stratum 6)

- The primary efficacy endpoint is non-progression at 6 months.
- See section 9.1.1.

9.1.7. Metastatic STS (stratum 7)

- The primary efficacy endpoint is non-progression at 6 months.
- See section 9.1.1.

9.2. SECONDARY ENDPOINTS

For each stratum:

- Efficacy of the association of the treatment strategy in terms of:
  - Best overall response is defined as the best response recorded from the start of the study treatment until the end of treatment taking into account any requirement for confirmation as per RECIST v1.1 criteria (appendix 2) :
    - The rate of best overall response will be reported.
    - All eligible and assessable patients (section 10.2) will be included in the denominator for the calculation of the rate.
    - The rate of best overall response will be calculated as the number of patients alive with the best response (recorded from the start of the treatment) divided by the number of patients eligible and assessable (section 10.2).

        - The 95% two-sided confidence limits will be provided for the calculated rate (binomial law).

    Following RECIST v1.1 recommendations:

        - The best overall response is determined once all the data for the patient is known.
        - Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point (>= 4 weeks later).

    - 1-year progression-free survival (PFS): PFS is defined as the time from study treatment initiation to the first occurrence of disease progression or death (of any cause), whichever occurs first.
    - 1-year overall survival (OS): OS is defined as the time from study treatment initiation to death (of any cause).
    - Immune-related response is defined following Wolchok et al. (Clinical Cancer Research 2009, Appendix 5). Analysis of Immune-related response will be based on central radiological review data.
    - Growth modulation index (GMI), defined for each patient as the ratio of the PFS on the current treatment strategyto the PFS on the previous line of therapy (61), in patients with documented progression at inclusion.

- Assessment of the safety profile of the treatment strategy. Toxicity will be graded using the common toxicity criteria from the NCI v4.0.

For each stratum 1 to 5:

- Performance of pharmacodynamic (PD)/mechanism of action (MOA) biomarkers analysis as well as predictive biomarkers analysis (levels of angiogenic and immunologic biomarkers in blood at baseline and different study time points. Blood samples will be collected at predefined time points:
    - Serum/plasma cytokines levels (TNFγ, TNFα, TGFβ, IL2, 4, 6, 10) (ELISA)
    - Serum/plasma VEGF and TPS-1 levels (ELISA)
    - Treg, CD4+ CD8+ and DR lymphocytes subpopulations monitoring, CD8+/Treg ratio (flow cytometry)
    - Plasma levels of Kynurenine and Kynurenine to Tryptophan ratio (ELISA and LC/MS).
    - Additional details are provided in section 17.

- Fresh pre-treatment (or archival material obtained from less than 12 weeks before inclusion) will be collected in consenting patients to assess pharmacodynamics biomarkers. Formalin-fixed, paraffin-embedded biopsy samples will be analysed for (but not limited to) PDL1, CSF-1R, CD68/CD163, CD68/MHC class II, CD31 (microvessel density), Ki67 and other exploratory markers. Additional details are provided in section 17.

- Prospective determination of the proportion of STS that express PDL1 will be assessed as detailed in section 17.

For each stratum 6 to 7:

- Pharmacodynamic (PD)/mechanism of action (MOA) biomarkers analysis as well as predictive biomarkers analysis (levels of angiogenic and immunologic biomarkers in blood and tumor tissue at baseline and different study time points.
    - Blood samples will be mandatory collected at predefined timepoints for assessment of:
        - Serum/plasma cytokines levels (TNFγ, TNFα, TGFβ, IL2, 4, 6, 10) (ELISA)
        - Treg, CD4+ CD8+ and DR lymphocytes subpopulations monitoring, CD8+/Treg ratio (flow cytometry)
        - Plasma levels of Kynurenine and Kynurenine to Tryptophan ratio (ELISA and LC/MS).
        - Additional details are provided in section 17.

- Fresh tumor samples will be mandatorily collected at baseline and during treatment. Formalin-fixed, paraffin-embedded biopsy samples will be analysed for (but not limited to) CD8+ effectors, CD68 and 163 Macrophages and FOXP3+ cells infiltrates as well as PDL1, IDO1, CD31 (microvessel density), Ki67 expression by IHC. Frozen samples will be analysed by (but not limited to) RNA sequencing in search for a predictive signature for response. Additional details are

provided in section 17.

10. STATISTICAL CONSIDERATIONS

10.1. HYPOTHESES AND NUMBER OF SUBJECTS NEEDED

6-month non-progression is a worldwide recognized endpoint for STS phase 2 trials based on the EORTC results (European Organization for Research and Treatment of Cancer) who demonstrated that, in case of progressive disease following a first-line chemotherapy, a drug can be considered active in soft-tissue sarcoma patients if the 6-month non-progression rate is at least ≥ 20% (4). In STS patients refractory to fist-line chemotherapy, pazopanib was associated with a 6-months non-progression rate of 40% and a response rate of 6% (60). The data from the literature about outcome of patients with advanced osteosarcomas are limited. Objective response as a single endpoint may not be an appropriate surrogate marker for therapeutic activity in osteosarcoma. Indeed, due to the abundant bone matrix, substantial anti-tumor activity may not result in a marked decrease in overall tumor volume. Median progression-free survival of relapsed osteosarcomas patients with unresectable disease and rechallenged with chemotherapy is about 2 months (76). GIST patients refractory to first-line imatinib and 2nd line sunitinib have a 6-months non progression rate of about 40% on third line treatment (24, 77).

10.1.1. Advanced leiomyosarcoma (stratum 1)

- We rely on a single-arm phase 2 trial based on 2-stage dual endpoint design (72).
- PEMBROLIZUMAB + metronomic CP will be considered promising if either tumour response rate or 6-month non-progression rate is promising
- Hypotheses under PEMBROLIZUMAB + metronomic CP are the following:
    - Hypotheses for non-progression at 6 months:
        - 40% non-progression rate (null hypothesis),
        - 60% non-progression rate (alternative hypothesis),
    - Hypotheses for objective response at 6 months:
        - 5% objective response rate (null hypothesis),
        - 20% objective response rate (alternative hypothesis),
    - Maximal type I error of 5% rate and 80% minimum power

- Assuming 30 eligible and assessable patients:
    - Stage 1 (15 eligible and assessable patients): Inclusions will continue if either objective response is observed in at least 3 or non-progression is observed for 9patients or more. Otherwise, the stratum will be terminated early and declared negative.
    - Stage 2 (15 additional eligible and assessable patients): PEMBROLIZUMAB + metronomic CP will be considered worthy of further testing in this indication if at least 8 objective responses, or at least 20 non-progression at six months are observed among the 30 evaluable patients.
- Inclusions will be suspended after the recruitment of the first 15 patients while data are being analysed for the first stage of inclusion.
- **In order to account for not evaluable patients (+/- 10%), 33 patients with advanced leiomyosarcoma will be recruited.**

10.1.2. Advanced undifferentiated sarcoma (stratum 2)

- Same hypotheses as for leiomyosarcoma
- Assuming 30 eligible and assessable patients:
    - Stage 1 (15 eligible and assessable patients): Inclusions will continue if either objective response is observed in at least 3 or non-progression is observed for 9

patients or more. Otherwise, the stratum will be terminated early and declared negative.

- Stage 2 (15 additional eligible and assessable patients): PEMBROLIZUMAB + metronomic CP will be considered worthy of further testing in this indication if at least 8 objective responses, or at least 20 non-progression at six months are observed among the 30 evaluable patients.

- Inclusions will be suspended after the recruitment of the first 15 patients while data are being analysed for the first stage of inclusion.
- **In order to account for not evaluable patients (+/- 10%), 33 patients with advanced undifferentiated sarcoma will be recruited.**

10.1.3. Advanced other sarcoma (stratum 3)

- Same hypotheses as for leiomyosarcoma
- Assuming 30 eligible and assessable patients:
  - Stage 1 (15 eligible and assessable patients): Inclusions will continue if either objective response is observed in at least 3 or non-progression is observed for 9 patients or more. Otherwise, the stratum will be terminated early and declared negative.
  - Stage 2 (15 additional eligible and assessable patients): PEMBROLIZUMAB + metronomic CP will be considered worthy of further testing in this indication if at least 8 objective responses, or at least 20 non-progression at six months are observed among the 30 evaluable patients.
- Inclusions will be suspended after the recruitment of the first 15 patients while data are being analysed for the first stage of inclusion.
- **In order to account for not evaluable patients (+/- 10%), 33 patients with advanced other sarcoma will be recruited.**

10.1.4. Advanced osteosarcoma (stratum 4)

- Same hypotheses as for leiomyosarcoma
- Assuming 30 eligible and assessable patients:
  - Stage 1 (15 eligible and assessable patients): Inclusions will continue if either objective response is observed in at least 3 or non-progression is observed for 9 patients or more. Otherwise, the stratum will be terminated early and declared negative.
  - Stage 2 (15 additional eligible and assessable patients): PEMBROLIZUMAB + metronomic CP will be considered worthy of further testing in this indication if at least 8 objective responses, or at least 20 non-progression at six months are observed among the 30 evaluable patients.
- Inclusions will be suspended after the recruitment of the first 15 patients while data are being analysed for the first stage of inclusion.
- **In order to account for not evaluable patients (+/- 10%), 33 patients with advanced osteosarcoma will be recruited.**

10.1.5. Advanced GIST (stratum 5)

- We rely on a single-arm phase 2 trial based on an optimal two-stage Simon's design (73)
- PEMBROLIZUMAB + metronomic CP will be considered promising if 6-month non-progression rate is promising
- Hypotheses under PEMBROLIZUMAB + metronomic CP treatment are the following (78)
  - Hypotheses for non-progression at 6 months:
    - 30% non-progression rate (null hypothesis),
    - 60% acceptable non-progression rate (alternative hypothesis),
  - 5% type I error rate,

- 90% power,

- A total of 28 assessable subjects will be necessary, with 10 assessable subjects recruited to the first stage.
  - Stage 1: Following the inclusion of the first 10 assessable patients, if 3 or less patients are progression-free (complete response, partial response or stable disease), the study will be terminated early. Otherwise, the second group of 18 subjects will be recruited.
  - Stage 2: If at the end of recruitment, 13 patients or more are progression-free (out of the 28 evaluable patients), PEMBROLIZUMAB + metronomic CP will be considered worthy of further testing in this disease.
- Inclusions will be suspended after the recruitment of the first 10 patients while data are being analysed for the first stage of inclusion.
- **In order to account for not evaluable patients (+/- 10%), 31 patients with advanced GIST will be recruited.**

10.1.6. Advanced soft tissue sarcomas with immune signature (stratum 6)

- We rely on a single-arm phase 2 trial based on an optimal two-stage Simon's design (73).
- PEMBROLIZUMAB + metronomic CP will be considered promising if 6-month non-progression rate is promising (>=15%).
- Hypotheses under PEMBROLIZUMAB + metronomic CP treatment are the following (92):
  - Hypotheses for non-progression at 6 months:
    - 15% non-progression rate (null hypothesis),
    - 40% acceptable non-progression rate (alternative hypothesis),
  - 5% 1-sided type I error rate,
  - 90% power,
- A total of 29 eligible and assessable subjects will be necessary, with 13 assessable subjects recruited to the first stage.
  - Stage 1: Following the inclusion of the first 13 assessable patients, if 2 or less patients are progression-free at 6 months (complete response, partial response or stable disease), the study will be terminated early. Otherwise, the second group of 16 subjects will be recruited.
  - Stage 2: If at the end of recruitment, 8 patients or more are progression-free at 6 months (out of the 29 eligible and evaluable patients), PEMBROLIZUMAB + metronomic CP will be considered worthy of further testing in this disease (efficacy rate >=15%).
- Inclusions will not be suspended after the recruitment of the first 13 patients while data are being analysed for the first stage of inclusion.
- **In order to account for not evaluable patients (+/- 10%), 32 patients with sarcoma with immune signature will be recruited.**

10.1.7. Metastatic STS (stratum 7)

- We rely on a single-arm phase 2 trial based on an optimal two-stage Simon's design (73).
- PEMBROLIZUMAB + metronomic CP + G100 will be considered promising if 6-month non-progression rate is promising (>=15%).
- Hypotheses under PEMBROLIZUMAB + metronomic CP + G100 treatment are the following (92):
  - Hypotheses for non-progression at 6 months:
    - 15% non-progression rate (null hypothesis),
    - 40% acceptable non-progression rate (alternative hypothesis),
  - 5% 1-sided type I error rate,

- 90% power,

- A total of 29 eligible and assessable subjects will be necessary, with 13 assessable subjects recruited to the first stage.
  - Stage 1: Following the inclusion of the first 13 assessable patients, if 2 or less patients are progression-free at 6 months (complete response, partial response or stable disease), the study will be terminated early. Otherwise, the second group of 16 subjects will be recruited.
  - Stage 2: If at the end of recruitment, 8 patients or more are progression-free at 6 months (out of the 29 eligible and evaluable patients), PEMBROLIZUMAB + metronomic CP + G100 will be considered worthy of further testing in this disease (efficacy rate >=15%).
- Inclusions will be suspended after the recruitment of the first 13 patients while data are being analysed for the first stage of inclusion.
- **In order to account for not evaluable patients (+/- 10%), 32 patients with metastatic soft-tissue sarcoma will be recruited.**

10.2. DEFINITION OF STUDY POPULATIONS

10.2.1. Advanced leiomyosarcoma (stratum 1)

- Eligible population: All patients included without major violation of eligibility criteria.
- Population eligible and assessable for the primary endpoint : eligible patients who received at least one administration of PEMBROLIZUMAB and one administration of Metronomic CP
- Safety population: All patients with at least one treatment (any) administration.

Replacement of patients: patients who do not comply with the definition of the population "eligible and assessable for the primary endpoint" will be replaced.

10.2.2. Advanced undifferentiated sarcoma (stratum 2)

Same definitions as for leiomyosarcoma

10.2.3. Advanced other sarcoma (stratum 3)

Same definitions as for leiomyosarcoma

10.2.4. Advanced osteosarcoma (stratum 4)

Same definitions as for leiomyosarcoma

10.2.5. Advanced GIST (stratum 5)

Same definitions as for leiomyosarcoma

10.2.6. Advanced soft tissue sarcomas with immune signature (stratum 6)

Same definitions as for leiomyosarcoma

10.2.7. Metastatic STS (stratum 7)

- Eligible population: All patients included without major violation of eligibility criteria.
- Population eligible and assessable for the primary endpoint: eligible patients who received at least one administration of PEMBROLIZUMAB and one administration of Metronomic CP and one administration of G100.
- Safety population: All patients with at least one treatment (any) administration.

Replacement of patients: patients who do not comply with the definition of the population "eligible and assessable for the primary endpoint" will be replaced.

10.3. STATISTICAL ANALYSIS

- Each stratum will be analysed independently. No statistical comparison will be performed between strata.
- For each stratum, two statistical analysis plans (SAP) will be produced by the statistician and validated by the steering committee before the first database extraction for analysis (version n°1): one for the interim statistical analysis and one for the final statistical analysis. The SAP may be revised during the course of the study in case of substantial modification of the protocol or following recommendations of the Independent Data Monitoring Committee.

10.3.1. Endpoint analysis

- Patients entered into the study will be described according to the following characteristics:
    - Compliance with eligibility criteria,
    - Sociodemographic characteristics,
    - Clinical and laboratory characteristics,
    - Treatment characteristics.

- Primary efficacy endpoint analysis
    - The primary efficacy endpoint will be analysed based on the eligible and assessable population (see chapter 10.2 for definition).
        - Efficacy of the treatment strategy will be assessed in terms of :
            - 6-month objective response (complete response and partial response) and 6-month non-progression (complete response and partial response, stable disease more than 24 weeks) for leiomyosarcoma (stratum 1), undifferentiated sarcoma (stratum 2), other sarcoma (stratum 3), osteosarcoma (stratum 4) (dual endpoint)
            - 6-month non-progression for GIST (stratum 5), advanced soft-tissue sarcoma with immune signature (stratum 6) and metastatic STS (stratum 7) (single endpoint)
        - Objective response and non-progression are defined based on radiological and clinical data as defined as per RECIST v1.1 criteria.
        - Primary efficacy analysis will be based on the central radiological review data.
        - Each patient will be assigned one of the following categories:
            - Complete response
            - Partial response
            - Stable disease
            - Progression
            - Not evaluated for response.
        - The rates of objective response and non-progression at 6 months will be reported for strata 1 to 4.
        - The rates of non-progression at 6 months will be reported for strata 5 to 7.
        - All eligible and assessable patients (section 10.2) will be included in the denominator for the calculation of the response rate.
        - The 95% two-sided confidence limits will be provided for the calculated response rate (binomial law).
        - Trial conclusions will be based on the response rates for all eligible and assessable patients (section 10.2).
- As regards to the other efficacy endpoints, the analyses will be carried out in the eligible and assessable population.
- The safety analysis will be performed on the safety population.
- Quantitative variables will be described using means and standard errors if the normality assumption is satisfied, else other descriptive statistics (median, range, quartiles) will be used.
- Qualitative variables will be described using frequency, percentage and 95% confidence interval (binomial law).
- Survival endpoints will be analysed using the Kaplan-Meier method. The median survival rates will be reported with a 95% confidence interval. Median follow-up will be calculated using the reverse Kaplan-Meier method. Multivariate analyses can also be carried out based on Cox's proportional risk method and after checking the risk proportionality hypothesis.
- Prognostic role of biomarkers will be assessed using logistic or survival models depending on the nature of the outcome variable (time-to-event or binary endpoint). Multivariate models will be

constructed following a backward selection approach based on candidates variables selected following univariate analyses.

10.3.2. Interim Statistical Analyses

- For each stratum, an interim statistical analysis will be performed at the end of the 1st stage of recruitment. Results of these interim statistical analyses will be presented to the IDMC members (section 12.1.2).

10.3.2.1. EARLY REVIEWS OF SAFETY DATA

10.3.2.1.1. STRATA 1 TO 5

- Inclusions will be suspended after inclusion of the first 10 patients.
- The first review of safety data will take place once 2-month follow-up data are available for the first 3 treated patients (independently of the stratum).
    - The steering committee (section 12.1.1) will review the safety data for these patients.
    - The steering committee will then decide if inclusions can continue and/or, if needed, whether treatment surveillance should be modified.

10.3.2.1.2. STRATUM 6

- As safety data are already available for strata 1 to 5, no additional review will be performed for this stratum.

10.3.2.1.3. STRATUM 7

- For each therapeutic strategy, the first review of safety data will take place once 2-month follow-up data are available for the first 3 treated patients (independently of the stratum).
    - Inclusion will not be suspended
    - The steering committee (section 12.1.1) will review the safety data for these patients.
    - The steering committee will then decide if inclusions can continue and/or, if needed, whether treatment surveillance should be modified.
    - Conclusions of the steering committee and safety data will be submitted to an independent data monitoring committee (IDMC).
    - Sponsor is then responsive for sending IDMC recommandations and safety review reports to ANSM.
- The second review of safety data will take place once 2-month follow-up data are available for the first 6 treated patients (independently of the stratum).
    - Inclusions will not be suspended
    - The steering committee (section 12.1.1) will review the safety data for these patients.
    - The steering committee will then decide if inclusions should be stopped and/or, if needed, whether treatment surveillance should be modified
    - Conclusions of the steering committee and safety data will be submitted to an independent data monitoring committee (IDMC).
    - Sponsor is then responsive for sending IDMC recommandations and safety review reports to ANSM.
- The third review of safety data will take place once 2-month follow-up data are available for the first 10 treated patients (independently of the stratum).
    - Inclusions will not be suspended
    - The steering committee (section 12.1.1) will review the safety data for these patients.

- The steering committee will then decide if inclusions should be stopped and/or, if needed, whether treatment surveillance should be modified.

- The next reviews of safety data by the steering committee (section 12.1.1) will take place every year and during the interim statistical analyse of each strata. Inclusions will not be suspended except for the interim analyse of each strata.

10.3.2.2. ADVANCED LEIOMYOSARCOMA (STRATUM 1)

- An interim statistical analysis will be carried out once inclusions for the first stage of the dual endpoint design (15 eligible and assessable patients) will be completed in the experimental arm (PEMBROLIZUMAB + metronomic CP).
- Inclusions will continue if either objective response is observed in at least 3 patients or non-progression is observed for 9 patients or more. Otherwise, the stratum will be terminated early and declared negative.
- A statistical report will be produced by the statistician of the study. Inclusion will be suspended during this interim analysis. Results of the interim statistical analyses will be presented to the IDMC members.

10.3.2.3. ADVANCED UNDIFFERENTIATED SARCOMA (STRATUM 2)

Same as for leiomyosarcoma

10.3.2.4. ADVANCED OTHER SARCOMA (STRATUM 3)

Same as for leiomyosarcoma.

10.3.2.5. ADVANCED OSTEOSARCOMA (STRATUM 4)

- An interim statistical analysis will be carried out once inclusion for the first stage of the dual endpoint design (15 eligible and assessable patients) will be completed.
- Inclusions will continue if either objective response is observed in at least 3 patients or non-progression is observed for 9 patients or more. Otherwise, the stratum will be terminated early and declared negative.
- A statistical report will be produced by the statistician of the study. Inclusion will be suspended during this interim analysis. Results of the interim statistical analyses will be presented to the IDMC members.

10.3.2.6. ADVANCED GIST (STRATUM 5)

- An interim statistical analysis will be carried out once inclusion for the first stage of the 2-stage Simon's design (10 eligible and assessable patients).
- Inclusions will continue if non-progression is observed for 4 patients or more. Otherwise, the stratum will be terminated early and declared negative.
- A statistical report will be produced by the statistician of the study. Inclusion will be suspended during this interim analysis. Results of the interim statistical analyses will be presented to the IDMC members.

10.3.2.7. ADVANCED SOFT TISSUE SARCOMAS WITH IMMUNE SIGNATURE (STRATUM 6)

- An interim statistical analysis will be carried out once inclusion for the first stage of the 2-stage Simon's design (13 eligible and assessable patients).
- Inclusions will continue if non-progression at 6 months is observed for 3 patients or more. Otherwise, the stratum will be terminated early and declared negative.
- A statistical report will be produced by the statistician of the study. Inclusion will not be suspended during this interim analysis. Results of the interim statistical analyses will be presented to the IDMC members.

10.3.2.8. METASTATIC STS (STRATUM 7)

- An interim statistical analysis will be carried out once inclusion for the first stage of the 2-stage Simon's design (13 eligible and assessable patients).
- Inclusions will continue if non-progression at 6 months is observed for 3 patients or more. Otherwise, the stratum will be terminated early and declared negative.
- A statistical report will be produced by the statistician of the study. Inclusion will be suspended during this interim analysis. Results of the interim statistical analyses will be presented to the IDMC members.

11. ADVERSE EVENTS

11.1. DESCRIPTION OF SAFETY EVALUATION CRITERIA

The safety evaluation will comprise an evaluation of the patient's general condition (ECOG Appendix 1), a physical exam, regular blood tests and the recording of adverse events occurring throughout the study. Toxicity will be evaluated using the NCI-CTCAE scale, version 4 available on website: http://ctep.info.nih.gov. All appropriate treatment areas should have access to a copy of the CTCAE version 4.

In an emergency situation, the patient, his/her friends/family or treating physician will contact the investigator to report an event and/or to discuss the treatments to be implemented.

11.2. DEFINITION

11.2.1. Adverse event

An adverse event is defined as any untoward medical occurrence which occurs in a patient, a clinical investigation subject. Adverse events include, but are not limited to:

- Abnormal test findings,
- Clinical symptoms and signs,
- Changes in physical examination findings,
- Hypersensitivity,
- Drug abuse,
- Drug dependency,
- Any suspected transmission of an infectious agent via a medicinal product.

As well as signs and symptoms resulting from:

- Drug overdose,
- Drug withdrawal,
- Drug misuse,
- Drug interactions,
- Extravasation,
- Exposure during pregnancy,
- Exposure during breastfeeding,
- Medication error,
- Occupational exposure.

11.2.2. Serious adverse event

A Serious Adverse Event (SAE) is defined as an adverse event regardless of the dose and that:

- results in death (fatal) and/or,
- is life-threatening and/or,
- requires inpatient hospitalization or prolongation of existing hospitalization and/or,
- results in persistent or significant disability/incapacity and/or,
- results in congenital anomaly/birth defect and/or,
- is medically significant.

Pregnancy and overdose will be also considered as a SAE whatever the clinical consequences.
Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or

hospitalization. However, if it is determined that the event may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above, the important medical event should be reported as serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Any suspected transmission via a medicinal product of an infectious agent, pathogenic or non-pathogenic, is assessed as a serious adverse event with the seriousness criterion important medical event. The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a patient exposed to a medicinal product. The terms "suspected transmission" and "transmission" are considered synonymous.
Any abnormal laboratory's result resulting as a grade 4 in the CTCAE version 4 will be considered as serious adverse event even if this event is not clinically relevant.
Whether or not corresponding to the above-mentioned criteria, any other adverse event considered as serious by any IMP, any healthcare professional or any investigator should be handled as a serious adverse event.

11.2.2.1. DEATH

Death as such is the outcome of a SAE or the seriousness criteria and should not be used as the SAE term itself. Instead the cause of death should be recorded as the SAE term. When available, the autopsy report will be provided to the Sponsor.

11.2.2.2. LIFE-THREATENING EVENT

Any event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

11.2.2.3. HOSPITALIZATION OR PROLONGATION OF HOSPITALIZATION

Any AE requiring hospitalization (or prolongation of hospitalization) that occurs or worsens during the course of a patient's participation in a clinical trial must be reported as a SAE. Prolongation of hospitalization is defined as any extension of an inpatient hospitalization beyond the stay anticipated/required for the initial admission, as determined by the Investigator or treating physician.
Hospitalizations that do not meet criteria for SAE reporting are:

- Reasons described in protocol [e.g., investigational medicinal product (IMP) administration, protocol-required intervention/investigations, etc]. However, events requiring hospitalizations or prolongation of hospitalization as a result of a complication of therapy administration or clinical trial procedures will be reported as SAEs.
- Hospitalization or prolonged hospitalization for technical, practical or social reasons, in absence of an AE.
- Pre-planned hospitalizations: Any pre-planned surgery or procedure must be documented in the source documentation. Only if the pre-planned surgery needs to be performed earlier due to a worsening of the condition, should this event (worsened condition) be reported as a SAE.

11.2.3. Non serious adverse event

A non-serious adverse event is an adverse event whose characteristics do not meet the criteria of a serious adverse event.

11.2.4. Adverse reaction

An adverse reaction is any untoward and unintended responses to an experimental drug regardless of the dose.

11.2.5. Expected/Unexpected character

An unexpected adverse event is an event whose nature, severity/intensity, frequency or outcome does not correspond to the information shown within the reference document for the study. The Sponsor will use as the reference safety information for the evaluation of listedness/expectedness the most updated Investigator's Brochure (IB) and/or Summary Product Characteristic (SmPC) for the studied IMP.

In practice, the term "new effect" is sometimes used as a synonymous of "unexpected adverse effect".

11.2.6. Intensity criterion

The CTEP Active Version of the NCI Common Terminology Criteria for Adverse Event (CTCAE) will be utilized for AE reporting.
The intensity of adverse events not listed in this classification will be assessed using the following descriptors:

- Mild (grade 1): does not affect the patient's usual daily activities,
- Moderate (grade 2): disturbs the patient's usual daily activities,
- Severe (grade 3): prevents the patient's usual daily activities,
- Very severe (grade 4): requires critical care/life-threatening,
- Death (grade 5).

11.2.7. New information

A new information is any new safety data that could lead to reevaluate the ratio between the benefits and risks of the research or the investigational product, to modify the use of the investigational product, the research management or the research documents or to suspend or interrupt or modify the protocol of research or similar research.

11.2.8. For trials of first administration or use of a health product in persons without any conditions: any serious adverse reactions. The study PEMBROSARC is not concerned by this situation.Causal relationship

Medical judgment should be used to determine the relationship, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history. Assessment of causal relationship should be recorded in the case report forms.

- Yes: There is a reasonable causal relationship between the investigational drug administered and the AE.
- No: There is no reasonable causal relationship between the investigational drug administered and the AE.

In case of multiples drugs, the causal relationship must be provided by the investigator for all potential trial drugs, i.e. for all other trial drugs.

11.2.9. Special considerations

Certain product safety monitoring reports should be forwarded even if there is no associated adverse event. These reports involve circumstances that may increase the patient/consumer's risk of developing adverse events.
These circumstances include:

- medication errors,
- exposure during pregnancy,
- exposure during breastfeeding,
- overdose,
- misuse,
- extravasation,
- occupational exposure.

Some of these special circumstances are considered in more details below.
Medications errors: a medication error is any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the healthcare professional, patient, or consumer. Such events may be related to professional practice, healthcare products, procedures, and systems, including: prescribing; order communication; product labeling, packaging, and nomenclature; compounding; dispensing; distribution; administration; education; monitoring; and use.
A medication error does not necessarily involve the administration of the product (e.g. the error may have been corrected prior to administration of the product).
Potential medication errors or "near-misses," which are individual reports of information or complaints about product name, labeling, or packaging similarities that do not involve a patient, are also reportable.

* Exposure during pregnancy: exposure during pregnancy refers to pregnancies where the fetus (from pre-embryo to birth) may have been exposed at a given time during pregnancy to a medicinal product (or a blinded treatment). Even if there is no associated adverse event, exposure during pregnancy must always be reported. It can indeed provide the opportunity to obtain pregnancy outcome important information where appropriate.

Exposure during pregnancy may occur either:

- Through maternal exposure
  * A female becomes, or is found to be, pregnant either:
    - While receiving a medicinal product
    - After discontinuing a medicinal product
    - During or following environmental exposure to a medicinal product (eg, a nurse reports she is pregnant and that she was exposed to chemotherapy drugs via inhalation or after accidentally overturning a bottle)

or

-Through paternal exposure

* A male has been exposed to a medicinal product (either due to treatment or environmental circumstances) prior to or around the time of conception and/or is exposed during the partner pregnancy.

* Exposure during breastfeeding: exposure during breastfeeding occurs where an infant or child may have been exposed through breast milk to a medicinal product during breastfeeding by a female taking the product.

All drug exposure during breastfeeding cases are reported, whether or not there is an associated adverse event.

11.3. SERIOUS ADVERSE EVENT AND NEW INFORMATION NOTIFICATION (RESPONSIBILITY OF THE INVESTIGATOR)

The investigator will notify the Vigilance Unit without delay about any serious adverse events or new events occurring:

- From the date of the informed consent is signed,
- During the whole patient treatment period as defined by the research,
- Until 90 days after the last dose of the IMP/studied treatments or the initiation of new anti-cancer therapy, whichever is earlier,
- Beyond this period of time, only those SAEs suspected to be related to the IMP will be collected. Nonetheless, the Sponsor will evaluate any safety information related to the clinical trial that is spontaneously reported by an Investigator beyond the time frame specified in the protocol.

Type of Event	Reporting procedure	Deadline for reporting to the sponsor
SAE	SAE Notification form + written report form if necessary	To be reported immediately to the sponsor
New information	Written report form	To be reported immediately to the sponsor
Pregnancy	Pregnancy Notification form + Written report form if necessary	As soon as pregnancy is confirmed

The investigator must complete the "Serious Adverse Event Notification Form" (Appendix 3) immediately, in English, and assess the relationship with the study treatment. The form must then be dated, signed and sent by fax to the following address without delay to:

CELLULE DE VIGILANCE (VIGILANCE UNIT) – Institut Bergonié

Fax: +33 5 56 33 04 85

Or Contact : Sabrina SELLAN-ALBERT (AEC) Tél : 05.56.33.78.05 – Mail : s.albert@bordeaux.unicancer.fr
Emilie Toulza (pharmacien) Tél : 05 47 30 60 53 – Mail : e.toulza @bordeaux.unicancer.fr or vigilance-promotion-essaiscliniques@bordeaux.unicancer.fr
Responsable : Emilie TOULZA Tél : 05.56.33.78.90 – Mail : e.toulza @bordeaux.unicancer.fr

The sponsor (Institut Bergonié) will forward the "Serious Adverse Event Notification Form" to MSD immediately.

For each event, the investigator will record:

- A description of the event that is as clearly as possible, using medical terminology,
- The date the event started and ended,
- The patient's relevant medical history,
- The steps taken and whether or not corrective treatment was required, whether or not the investigational treatment was discontinued, etc.
- Concomitant medications / therapies
- The causal link between this event and the trial treatment, disease treated or an intercurrent disease or treatment, or any obligation imposed by the research (a treatment-free period, additional examinations requested as part of the research etc.),
- Clinical course. If the event was not fatal, it should be monitored until recovery, until the patient has returned to his/her previous condition, or until any sequelae have stabilized,
- Whenever possible, the investigator must also attach the following with the serious adverse event report:
    - A copy of the hospitalization or extended hospitalization report,
    - A copy of the autopsy report, if required,
    - A copy of all the results of any additional tests performed, including relevant negative results, along with the normal laboratory values,
    - Any other document he or she considers useful and relevant.

All these documents must be anonymized. Additional information may be requested (by fax, by telephone or during a visit) by the CRA and/or by the Vigilance Unit using a follow-up request form.

SAE will be monitored until they have resolved, returned to baseline, or they are not clinically significant, stable, or do not require any additional follow-up as judged by investigator. Sometimes this may mean that follow-up will extend beyond the patient's withdrawal from the trial.

The investigator keeps the documents about the presumed adverse effect so that the information previously sent can be added to if necessary.

The investigator responds to requests for additional information from the Vigilance Unit in order to document the original observation.

11.4. REPORTING PREGNANCY CASES OCCURRED WITHIN THE CLINICAL TRIAL

Pregnancy and suspected pregnancy (including a positive pregnancy test regardless of age or disease state) of a female patient or the female partner of a male patient occurring while the patient is on study drug, or 180 days after the last dose of

IMP/studied treatments or 30 days in case of initiation of new anti-cancer therapy, are considered immediately reportable events.

The Investigator will report the following events immediately and always within 24 hours from first knowledge:

- Any occurrence of a pregnancy where any kind of exposure to the IMP is suspected,
- Possible exposure of a pregnant woman (this could involve a partner of a male patient or a pregnant female who came in contact with the clinical trial IMP),
- All reports of elevated/questionable or indeterminate beta human chorionic gonadotropins (β-hCGs).

Immediately after detecting a case of suspected pregnancy in a female clinical trial patient, the decision on her continued participation in the clinical trial will be jointly taken by the trial patient, the Investigator and the Sponsor, with the patient's best interest in mind. A decision to continue the pregnancy will require immediate withdrawal from the trial.

Any pregnancy, suspected pregnancy, or positive pregnancy test must be reported to the Vigilance Unit immediately by facsimile using the Pregnancy Report form (appendix 54). In the case of pregnancy of the female partner of a trial patient, the Investigator will obtain her consent to provide the information in these situations.

The Investigator will follow the pregnancy until its outcome, and must notify the Vigilance Unit the outcome of the pregnancy within 24 hours of first knowledge as a follow-up to the initial report.

For any event during the pregnancy which meets a seriousness criterion (including fetal or neonatal death or congenital anomaly) the Investigator will also follow the procedures for reporting SAEs (complete and send the SAE form to the Vigilance Unit by facsimile within 24 hours of the Investigator's knowledge of the event).

All neonatal deaths that occur within 30 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death at any time thereafter that the Investigator suspects is related to the exposure to the study drug/IMP should also be reported to the Vigilance Unit by facsimile within 24 hours of the Investigators' knowledge of the event.

Whenever possible, the investigator must also attach the following with the serious adverse event report:

- A copy of the hospitalization or extended hospitalization report,
- A copy of the autopsy report, if required,
- A copy of all the results of any additional tests performed, including relevant negative results, along with the normal laboratory values,
- Any other document he or she considers useful and relevant.

All these documents must be anonymized.

Additional information may be requested (by fax, by telephone or during a visit) by the Vigilance Unit.

11.5. REPORTING EVENTS OF CLINICAL INTEREST AND IMMUNE-RELATED ADVERSE EVENTS

The investigator will notify the Vigilance Unit without delay about any events of clinical interest and immune-related adverse event.

The investigator must complete the specific form (Appendix 8) immediately, in English The form must then be dated, signed and sent by fax to the following address without delay to:

CELLULE DE VIGILANCE (VIGILANCE UNIT) – Institut Bergonié
Fax: +33 5 56 33 04 85

Contact : Sabrina SELLAN-ALBERT (AEC) Tél : 05.56.33.78.05 – Mail : s.albert@bordeaux.unicancer.fr
Emilie Toulza (pharmacien) Tél : 05 47 30 60 53 – Mail : e.toulza @bordeaux.unicancer.fr or vigilance-promotion-essaiscliniques@bordeaux.unicancer.fr
Responsable : Emilie TOULZA Tél : 05.56.33.78.90 – Mail : e.toulza @bordeaux.unicancer.fr

Adverse events that are both an SAE and an irAE should be reported one time as an SAE only, however the event should be appropriately identified as an irAE as well in the database.

11.5.1. Cases of mediastinal lymph nodes

The Steering Committee (SC) has discussed about several cases of mediastinal lymph nodes related to sarcoidosis. It is a new immune related adverse event of pembrolizumab that has been already described with other immunotherapy which blocks the cytotoxic T-lymphocyte-associated antigen-4 (ipilimumab).

Three cases of mediastinal lymph nodes have been observed. This effect appeared after 6 weeks of pembrolizumab treatment and disappeared spontaneously after the end of treatment. This effect should be known to avoid misdiagnosis of disease progression due to mediastinal lymph node involvement (84).

The SC has decided that all investigators should be informed about this effect and the risk of misdiagnosis of disease progression and that all mediastinal lymph node and related to sarcoidosis should be declared immediately to the sponsor as events of clinical interest.

11.6. NON SERIOUS ADVERSE EVENT

TYPE OF EVENT	REPORTING PROCEDURES	DEADLINE FOR REPORTING TO THE SPONSOR
Non-serious AE	Case report/record form	Does not need to be reported immediately

Non-serious adverse events will be reported by the investigator in the patient's CRF and will be followed up until complete resolution.

If an adverse event becomes serious, it should be reported and followed-up as mentioned in the previous reporting procedures.

If the investigator would like to decrease trial treatment dose or temporarily stop study management without respecting protocol procedures, he/she should have previously discussed with the coordinator.

However, symptomatic treatment can be prescribed to manage the adverse event.

Any definitive interruption of the procedure has to be immediately notified to the sponsor. The patient remains in the study and is followed-up according to the procedures described in the protocol.

11.7. RESPONSIBILITY OF VIGILANCE UNIT AND SAE REPORTING

The Vigilance Unit will analyze each SAE to define:
- The relationship with the study treatment,
- The listedness/expectedness according to the most updated reference safety information of the studied IMP Investigator's Brochure (IB) and/or Summary Product Characteristic (SmPC).

SAEs will be reported by the Sponsor to the different laboratories according to the contracts' requirements.

11.8. REPORTING OF SAFETY DATA TO NATIONAL COMPETENT AUTHORITY AND ETHICS COMMITTEE (RESPONSIBILITY OF THE SPONSOR)

The sponsor notifies unexpected serious adverse events and new information to the Regulatory Authorities (in person, or through an organization which has received allowances for this task) according to the usual notification procedures.

Once a year throughout the clinical trial, the Sponsor should submit to the national competent authority and the Ethics Committee, a DSUR (Development Safety Update Report). The annual safety report should be submitted no later than 60 calendar days from the date of authorization of the research.

12. QUALITY ASSURANCE AND TRIAL MONITORING

12.1. MONITORING OF THE TRIAL

12.1.1. Steering Committee

The study will be supervised and monitored by a Steering Committee comprising members participating in the study:
- Pr A. Italiano, Co-ordinating Investigator and Chairman of the Commitee,
- Dr M. Toulmonde, Investigator and medical oncologist,
- A representative of the sponsor (Pr S. Mathoulin-Pélissier or Dr Hoppe),
- The biostatistician of the trial (Ms M. Pulido or a substitute),
- The pharmacist of the trial (Ms E.Toulza or a substitute)
- The co-ordinating Clinical research manager (S Sellan-Albert or a substitute)

This committee must ensure the following:
- Implementation and regular follow-up of the study
- Review of the safety data following the inclusion of the first 10 treated patients in each treatment strategy (except for stratum 6) (section 10.3.2).

- Patient protection,
- That the trial is conducted ethically, in accordance with the protocol,
- That the trial benefit/risk ratio is evaluated and the scientific results are checked during or at the end of the trial.

It decides on any relevant amendment to the protocol that is required in order to continue the trial (protocol amendments prior to submission to the EC and the relevant Health Authorities, decisions on whether to open or close research sites, discussion of results and the strategy for the publication of these results). It must inform the sponsor of any decisions taken. Decisions concerning a major amendment or a change to the budget must be approved by the sponsor.

12.1.2. Independent Data Monitoring Committee

An independent Data Monitoring Committee (IDMC) will be created at the request of the relevant Authority, the sponsor or the Steering Committee. The IDMC plays an advisory role for the Sponsor, who has the final decision regarding the implementation of recommendations put forward by the IDMC.

Composition of the IDMC

- This Committee must comprise at least one qualified oncologist, one pharmacologist and one statistican:
    - Qualified oncologist (Dr Christophe Perrin)
    - Pharmacologist (Dr Driss Berdaï)
    - Statistician (Mme Sophie Gourgou-Bourgade)

All of whom will have experience in the monitoring and analysis of clinical trials. One of these members will be appointed as the Trial Rapporteur.

- Each of these members must be unconnected with the trial and cannot, therefore, be one of the trial investigators.
- These members are appointed by the Sponsor in consultation with the trial co-ordinator and the Steering Committee.

Responsibilities of the IDMC

The IDMC is responsible for the following:

- Analyzing preliminary efficacy and safety data,
- Making recommendations on the continuation, early discontinuation (in the case of toxicity or lack of efficacy) or publication of the trial results,
- Drafting the minutes after each meeting and monitoring their confidentiality.

Any recommendation from the IDMC that can be made public will be announced by the Sponsor and not by the Steering Committee. The Sponsor is responsible for sending IDMC recommendations to the regulatory authorities [ANSM (French Agency for the Safety of Health Care Products) and EMEA (European Medicines Evaluation Agency)].

12.2. QUALITY ASSURANCE

12.2.1. Data collection

The data will be collected on an electronic case report form and directly input via the Internet. Only the investigators and the Investigator's Clinical Research Assistants (CRAs) appointed by the later and duly authorized by the sponsor will be authorized to enter the data.

Data will be handled by an online trial management software on the Internet (Macro v4, Infermed Company); it will be transferred and monitored remotely in real time.

The study CRA and/or any other person appointed by the sponsor will be available to assist the investigators in carrying out the study and to ensure that the trial is carried out in accordance with the protocol.

The study CRA will contact the investigators regarding the study implementation visit.

All of the necessary data will be collected on an electronic case report form provided by the sponsor. The generic names of the concomitant medication will be given in French.

Corrections made to the original data must be justified. These corrections will be automatically dated and signed by the authorized member of staff via the personalized password allocated at the start of the study.

The case report form will be validated by the investigator or the CRA at the authorized center whenever data is entered.

Laboratory data exceeding normal limit values will be commented upon if they are considered clinically significant. Data other than that requested within the scope of the protocol can be collected as additional data; their interest will be specified.

12.2.2. Monitoring

In order to guarantee the authenticity and credibility of the data in accordance with the principles of GCP (Good Clinical Practice) dated 24 November 2006, the sponsor shall implement a quality assurance system comprising:

- the management and monitoring of the trial in accordance with the procedures stipulated by the Institut Bergonié,
- the quality control of the research site data by the CRA whose role is to:
    - check compliance with the protocol, GCP and current legislation and regulations,
    - check the consent and eligibility of each patient taking part in the trial,
    - check the consistency and coherence of case report form date against the source documents.
    - check that each serious adverse event is reported,
    - monitor the traceability of the study medication (dispensation, storage and drug accountability),
    - check, where applicable, that the persons likely to take part in the trial are not already participating in another trial that could prevent them from being included in the clinical trial proposed. The CRA shall also ensure that the patients have not participated in a trial for which an exclusion period currently applies.
- The possible audit of study centers
- The centralized review of certain protocol criteria.

The check procedures will include:

- Study progression,
- Protocol compliance,
- The updating of information on the Internet site.

The checking of data by comparing the information on the electronic case report form and the original clinical or laboratory data is one of the monitoring procedures.

The following will be checked, in particular, for each patient (100% level): patient identification, informed consent (procedure and signature), selection criteria, therapeutic procedure, adverse events, principal response variables. The personal data relating to each patient shall remain confidential. On the electronic case report form or any other form dispatched, the patients will be identified solely by their initials (1/name – 1/surname) and an inclusion number. However, the investigators must keep a list identifying the patients in their folders.

The CRAs responsible for the quality control of this clinical trial are duly appointed by the sponsor for this particular purpose and must have access, with the consent of those involved, to individual trial participant data required strictly in accordance with this control procedure. The CRAs are subject to professional secrecy under the conditions defined by Articles 226-13 and 226-14 of the French penal code. The traceability of monitoring visits is guaranteed by a written monitoring report.

The investigators shall undertake to give CRAs direct access to the medical records of each patient in order to allow the CRAs to ensure optimal quality control of the trial. The same applies to health authority representatives.

12.2.3. Handling of missing data

The monitoring of data for adverse events will be carried out regularly in order to effectively limit the amount of missing data likely to prevent or hamper trial implementation and analysis.

12.2.4. Audits

The sponsor, the local authorities or the authorities to which information about this study has been submitted can decide to have an audit.
All the documents relating to this study must be available for such an inspection after prior notification.

13. REGULATORY ASPECTS AND ETHICAL CONSIDERATIONS

Clinical Research Management Unit – Institut Bergonié
Contacts: Marie-Laure Marty– Tel.: +33 5 47 30 60 79 – e-mail: m.marty@bordeaux.unicancer.fr

The study will be carried out in accordance with:

- Law no. 2012-300 dated 5 March 2012 relating to researchs involving the human person
- The ethical principles of the current version of the "Declaration of Helsinki" (available on its full version on the site http://www.wma.net).
- Good Clinical Practice (GCP): I.C.H. version 4 of 9 November 2016 and decision dated 24 November 2006 (Official Bulletin of 30 November 2006, text 64).
- European Directive (2001/20/EC) on clinical trial procedures.
- Huriet's law (No. 88-1138) dated 20 December 1988, concerning the protection of persons taking part in Biomedical Research with the provisions of the Public Health law (No. 2004-806) of 9 August 2004 and implementating decree No. 2006-477 of 26 April 2006 relating to biomedical research.
- The French law on Data Protection and Civil Liberties, No. 78-17 of 6 January 1978 amended by law No. 2004-801, dated 6 August 2004, concerning the protection of persons with regards to the processing of personal data.
- The application of Circular DHOS/INCA/MOPRC/2006/475 of 7 November 2006: the Sponsor shall undertake to register the Trial and thus make it accessible to the general public, in the INCa (French Cancer Institute) register via the Internet site: www.e-cancer.fr. Each trial published in the INCa register will be sent to the NCI for registering on the following site: www.clinicaltrials.gov. The trial will be registered before the first patient is entered into the study. The Sponsor is responsible for updating the study data in order to guarantee the reliability of the information available on-line.
- Law no. 2004-800 dated 6 August 2004, concerning bioethics, amended by law No. 2012-387, dated 22 March 2012.

13.1. CLINICAL TRIAL AUTHORIZATION

This trial is registered under Eudract N° 2014-004568-39.

The protocol has been approved by the South West and Overseas Territories III Ethics Committee, Bordeaux. Approval was given on 22/12/2014.

The Relevant Authority, the "Agence Nationale de Sécurité du Médicament et des Produits de Santé" (ANSM - French Agency for the Safety of Health Care Products) authorized the clinical trial on 18/02/2015.

Any amendments to the protocol concerning study objectives, patient population and principal methods will require an amendment, which must be approved by the EC and l'ANSM. The sponsor will inform the EC and ANSM of expected and/or unexpected serious adverse events in accordance with current regulations and within 30 days after of completion of the trial.

The sponsor will send the summary of the final report to the relevant Authority within one year of completion of the trial.

The sponsor has made a commitment to compliance the Reference methodology for the processing of personal data carried out in biomedical research: Référence methodology MR-001. This commitment of compliance is registred under No 118019 of the 07/11/2006.

13.2. INSURANCE POLICY

The Institut Bergonié has taken out an insurance policy (policy No.0100871914011-140005-10998) with société HDI-Gerling, Tour opus12, 77, Esplanade de la défense, 92914 PARIS LA DEFENSE through an insurance broker, namely Biomédic Insure (Parc d'Innovation Bretagne Sud, CP 142, 56038 Vannes, tel. 02 97 69 19 19) in case compensation is payable to investigators or patients taking part in the study.

13.3. INFORMING AND OBTAINING CONSENT FROM PATIENTS

The investigator in charge of the patient will provide the latter with relevant information relating to the study objectives, potential benefits and possible adverse events. The study methods will be outlined. The patient can refuse treatment before or at any time during the study, without experiencing any adverse repercussions in terms of his/her subsequent care.

The patient's written consent will be obtained prior to entry into the study by using the Patient Information Leaflet and Informed Consent Form. These forms must be combined in the same document in order to ensure that all of the information is given to the trial participant.

The consent form must be personally dated and signed by the trial participant and the investigator. The original will be given to the patient and the second, archived in the investigator's folder. Upon request, a copy will be sent to the sponsor in a sealed envelope.

13.4. SPONSOR'S RESPONSIBILITIES

The sponsor of the clinical trial, the Institut Bergonié, will take the initiative for this clinical trial. The Institute will manage the trial and ensure that finance is provided.

The sponsor's main responsibilities are to:

- Take out civil liability insurance,
- Obtain the Eudract No. and register the trial in the European database (European Drug Regulatory Authorities Clinical Trials),
- Obtain clinical trial authorization for the initial project and any amendments from the EC and ANSM; approval by the EC and decision taken by ANSM.
- Notify the relevant authority any suspected unexpected serious adverse reaction (SUSAR),
- Give trial-related information to the site directors, pharmacists and investigators,
- Notify the relevant authority of the trial start and end dates,
- Draft the final trial report and sent the summary to ANSM,
- Send the trial results to the relevant authority, EC and investigators,
- Archive essential trial documents in the sponsor's folder for a minimum period of 15 years after the trial has ended.

13.5. INVESTIGATORS' RESPONSIBILITIES

The principal investigator of each establishment concerned undertakes to conduct the clinical trial in accordance with the protocol that was approved by the ethics committee and the relevant authority (ANSM).

The investigator must not make any changes to the protocol without the written consent of the sponsor or without the ethics committee and the relevant authority having authorized the proposed changes.

It is the responsibility of the principal investigator is:

- to provide the sponsor with his/her curriculum vitae as well as those of his/her co-investigators,
- to identify the members of his/her team who are participating in the trial and to define their responsibilities,

- to start patient recruitment after authorization has been obtained from the sponsor,
- to ensure that he/she is available for investigators's meeting anf for "monitoring".

It is the responsibility of each investigator:

- to comply with the confidential nature of the trial,
- to obtain informed consent, signed and dated personally by each trial participant, before any screening procedures specific to the trial are carried out,
- to regularly complete the case report forms (CRFs or e-CRFs) for each of the patients enrolled in the trial and to allow the Clinical Research Assistant (CRA) duly authorised by the Sponsor a direct access to source documents so that the latter can validate the data on the CRF or e-CRF,
- to promptly notify the sponsor of any serious adverse event and/or new information occurring during the trial,
- to date, correct and validate corrections on the case report forms (CRFs or e-CRFs) and the Data Query Forms (DQFs),
- to accept regular visits CRA and eventually visits of auditors duly authorised by the Sponsor or inspectors of regulatory authorities,
- to inform trial participants of the overall results of the research on first demand.

13.6. AUTHORITY TO EXECUTE THE TRIAL

The investigator shall certify that he/she is authorized to enter into this agreement and that the terms and conditions of the protocol and agreement do not conflict with other agreements that the investigator may have entered into with any other party, or any other arrangement agreed by the Institution where the investigator is employed.

13.7. REGULATIONS GOVERNING THE COLLECTION OF HUMAN BIOLOGICAL SAMPLES

During the medical procedures to be carried out, samples will be collected for medical purposes. A fraction of these samples will be kept and used for scientific research purposes.

The patient will be informed of this research and provided that he/she approves by signing an informed consent, these samples intended for research will be:

- Initially prepared and stored using a specific technique to preserve them under excellent conditions.
- and secondly, used within the scope of this research.

The preparation, storage and use of these samples will not in any way affect current or future medical care administered to the patient for the purpose of diagnosis or treatment.

The results of this research may, in future, appear in scientific publications. All of the data shall remain anonymous.

Obtaining and using additional samples
This biomarker study is made up of exploratory research that is described in the section 17.

On completion of the trial, provided that the patient agrees and provided that not all of the samples have been used, the said samples can be used for subsequent scientific research purposes without the approval of the Ethics Committee (EC) and the signing of a new consent form by the patients included.

13.8. FEDERATION DES COMITES DE PATIENTS POUR LA RECHERCHE CLINIQUE EN CANCEROLOGIE (FCPRCC) (FEDERATION OF PATIENT COMMITTEES FOR CLINICAL RESEARCH IN ONCOLOGY)

The Fédération des Comités de Patients pour la Recherche Clinique en Cancérologie (FCPRCC) (Federation of Patient Committees for Clinical Research in Oncology) was created on the initiative of the Fédération Nationale des Centres de Lutte Contre le Cancer (FNCLCC) (Federation of Anti-Cancer Centers) and the Ligue Nationale Contre le Cancer (National Anti-Cancer League) in order to review clinical trial protocols in oncology. This Federation of Patient Committees is co-ordinated by the Office for Clinical and Therapeutic Trials and groups together the League patient committees as well as other health care establishments. The Sponsor undertakes to transmit the protocol to the Federation for review. The Federation undertakes to propose improvements focusing primarily on the quality of the information leaflet, the availability of a treatment and monitoring plan and the suggestion of measures aimed at improving patient comfort.

13.9. DATA PROCESSING

In accordance with the French Law on Data Protection and Civil Liberties of 06 August 2004 and its implementing decrees, the Sponsor shall follow the methodology of reference MR001 of the "Commission Nationale de l'Informatique et des Libertés" (French National Commission for Data Protection and Liberties).

Furthermore, if the biomedical research data is computer processed or managed by computerized systems, each Center:

- shall check and document the fact that the computerized systems used in the research comply with requirements drawn up in relation to data integrity, accuracy and reliability, as well as compliance with expected performances (i.e. validation);
- shall implement and ensure the monitoring of standard operating procedures relating to the use of these systems;
- shall ensure that the design of these systems allows for data to be amended such that the amendments are documented and that any item of data input cannot be deleted (i.e. maintaining data and amendment audit trail) ;
- shall implement and ensure the monitoring of a secure system that prevents any unauthorized data access;
- shall update the list of persons authorized to amend the data;
- shall keep appropriate back-up copies of the data;
- shall maintain blind status, where applicable (e.g. during data entry and processing);
- shall ensure that personal data used within the scope of the trial is processed in accordance with the conditions defined by law No. 78-17 dated 6 January 1978 relating to data processing, files and liberties modified by law No. 2004-801 of 6 August 2004 and its implementing regulations.

If the data is converted during processing, it must always be possible to compare the original data and observations with the data after conversion.

The system used to identify subjects taking part in the trial must not present with any ambiguity and must allow all of the data collected for each of these subjects to be identified whilst maintaining the confidentiality of the personal data, in accordance with law No. 78-17, duly amended.

The archiving data is performed according to the applicable regulations and under the responsibility of investigator. All data and the patient indentification codes will be kept for at least 15 years after the completion or discontinuation of the trial.

14. CONFIDENTIALITY AND OWNERSHIP OF DATA

All of the information communicated or obtained and the data and results generated by the trial legally belong to as their obtaining the Institut Bergonié, which can use this data at its own discretion.
According to article R 5121-13 of the French Public Health Code, investigators and people who will have to collaborate in the trial shall be bound by professional secrecy with regard to the particular nature of the products studied, trial, trial participants, and results. In particularly, all documentation relating to the trial sent to the investigator should be considered confidential information.
Without the consent of the sponsor, the investigator cannot,give information about trials at anyone, except the Minister in charge of Public Health, public health medical inspectors, public health pharmacists inspectors, the General Director and inspectors of ANSM.
The trial cannot be the subject of any written or verbal comments without the sponsor's consent.

15. PUBLICATION AND VALORISATION

15.1. SCIENTIFIC COMMUNICATION

All of the information arising from this study shall be considered confidential (cf. section 14).
All forms of publication must be submitted to the Steering Committee for review and approval prior to publication (allowing at least 15 working days for abstracts and oral presentations, and 45 working days for written publications). The Steering Committee shall check the accuracy of the information submitted (in order to avoid any inconsistency with that submitted to the Health Authorities), and ensure that confidential information is not inadvertently disclosed. It will also provide additional information as required. In any case, the sponsor will control the first publication.
Furthermore, all memos, manuscripts or presentations must comprise a heading referring without fail to the Institut Bergonié, all of the institutions, investigations, co-operating groups and learned societies that have contributed to the implementation of the trial, and listing any organizations that have provided financial support.

- the study coordinator
- the investigators will be listed on a pro rata basis according to the number of patients recruited
- a representative of the trial statistics unit (in the first 3 positions according to degree of involvement in the preparation of publications)

15.2. INFORMATION TO PATIENTS

According to Article L.1122-1 of the Fench Code of Public Health Investigator undertakes to inform trial participants of the overall results of the research on first demand.

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17. TRANSLATIONAL STUDIES

17.1. BIOMARKER STUDY

17.1.1. Collection of available specimen

The main objective of this biomarker study is to explore pharmacodynamics and mechanisms of action of PEMBROLIZUMAB + CP +/- G100 as well as potential predictive biomarkers.
For each patient, blood samples will be collected at predefined time points. Note that patients must be fasten since at least 3 hours.

Schedule of blood sampling for BM Study

	EDTA	CITRATE	HEPARIN
C1D1 (Day-7 for stratum 7	XXX	XX	X
C1D8	XXX		
C2D8	XXX	XX	X
C3D8	XXX	XX	X
C4D8	XXX	XX	X
C6D8	XXX	XX	X
Progression	XXX	XX	X

For plasma study, one 5ml EDTA and one 5ml citrate blood tube will be taken at each timepoint. Samples will be centrifugated for 10min at 1900g and 4°C. The aliquoted samples will be annotated with study name (PEMBROSARC), center study ID number (1,2,3), Patients study ID number, date (../../..) and identification (marker ID: TNFγ, TNFα, TGFβ, IL2, 4, 6, 10, VEGF, TPS-1,… and time point) and stored at < -20° until day of shipping.
For lymphocytes subpopulations monitoring study, a 15 ml sample of peripheral blood will be collected on heparin at each timepoint, annotated with study name (PEMBROSARC), center study ID number (1,2,3), Patients study ID number, date (../../..) and identification (marker ID: Ly and timepoint).
For Kynurenine pathway assessment, one 5ml citrate blood tube will be taken at each timepoint.
A separate document includes a protocol for sample collection (Pharmacodynamics Methods Guidelines will be provided by the sponsor as a separate document) and will be the reference.

17.1.2. BM analysis

Altogether, both angiogenic and immune markers will be explored in this translational study in order to explore potential surrogate biomarkers for activity or efficacy.
- Plasma cytokines levels (TNFγ, TNFα, TGFβ, IL2, 4, 6, 10) (ELISA)
- Plasma VEGF, Svegfr2 and TPS-1 levels (ELISA) for strata 1 to 5 only.
- CD8+, CD4+, Treg, and DR lymphocytes subpopulations monitoring, CD8+/Treg ratio (flow cytometry)
- Plasma levels of Kynurenine and Kynurenine to Tryptophan ratio (ELISA and LC/MS)

A separate document includes a protocol for methods of analysis. (Pharmacodynamics Methods Guidelines will be provided by the sponsor as a separate document)

17.1.2.1. SITE PERFORMING BM STUDY

Plasma studies and flow cytometry will be performed at Centre Georges-Francois Leclerc, Dijon.

17.1.2.2. SHIPPING OF SPECIMENS

The containers containing the samples will be labelled with coded numbers to ensure full compliance with privacy policy. Samples will be grouped in each institution and sent frozen for centralized processing to:

Docteur GHIRINGHELLI **Centre Georges-Francois LECLERC** Laboratoire de Biologie 1, rue Professeur Marion – BP 77980 21079 DIJON cedex Tel: 03.80.73.75.28 – Fax: 03.80.73.77.74

Shipping will only be performed by a promoter authorized transporter with respect to good practice.

17.2. PDL-1 EXPRESSION FOR STRATA 1 TO 5

17.2.1. Collection of specimen

For all patients, available tumor tissue sample:

- Either archived FFPE (Formalin-Fixed Parrafin-Embedded) block of specimen tumor sampling obtained on metastasis or on locally advanced disease
- Either newly obtained fresh tumor biopsies FFPE before inclusion.

17.2.2. Handling and shipping of specimen

The samples will be labelled with coded numbers to ensure full compliance with privacy policies. Samples will be grouped in each institution and sent for centralized processing with the documents.
All samples will be stored before they are analyzed.
The sample collection information must be captured on the appropriate CRF page(s).

17.2.3. Site performing PDL-1 expression research

All pathological specimens sampling with documents must be sent as described in a specific SOP provided by the Sponsor.

17.2.4. PDL-1 expression analysis

Archived tumor sample or fresh pre-treatment tumor biopsies will be collected in all patients to assess PDL-1 expression. Formalin-fixed, paraffin-embedded tumor samples will be analyzed for (but not limited to) PDL1, CSF-1R, CD68/CD163, CD68/MHC class II, CD31 (microvessel density), Ki67 and other exploratory markers.

17.3. OPTIONAL BIOPSY FOR STRATA 1 TO 5

17.3.1. Collection of samples

Tumor biopsies will be performed in consented patien at baseline and at Day 8 of cycle 2 postdose.

17.3.2. Handling and shipping of specimen

One half of the specimen will be formalin fixed and paraffin embedded [FFPE (Formalin-Fixed Paraffin-Embedded)] and the second half will be fresh frozen at -80°C.
The samples will be labelled with coded numbers to ensure full compliance with privacy policies. Samples will be grouped in each institution and sent for centralized processing with the documents.
All samples will be stored before they are analyzed.
The sample collection information must be captured on the appropriate CRF page(s).

17.3.3. Site performing PDL-1 expression research

All pathological specimens sampling with documents must be sent as described in a specific SOP provided by the Sponsor.

17.4. MANDATORY BIOPSY FOR STRATA 6 TO 7

17.4.1. Collection of samples

Tumor biopsies will be performed in all patients included in strata 6 to 7 at baseline and during treatment:

- Baseline
- Cycle 2 Day 8. Note that for stratum 7, in case of radiotherapy, biopsy must be performed before RT initiation and an additional biopsy must be performed within 3-4 weeks after RT termination.

17.4.2. Handling and shipping of specimen

One half of the specimen will be formalin fixed and paraffin embedded [FFPE (Formalin-Fixed Paraffin-Embedded)] and the second half will be fresh frozen at -80°C.
The samples will be labelled with coded numbers to ensure full compliance with privacy policies. Samples will be grouped in each institution and sent for centralized processing with the documents.
All samples will be stored before they are analyzed.
The sample collection information must be captured on the appropriate CRF page(s).

17.4.3. Site performing analysis

All pathological specimens sampling with documents must be sent as described in a specific SOP provided by the Sponsor.

17.4.4. Biomarkers expression analysis

Formalin-fixed, paraffin-embedded biopsy samples will be analysed for (but not limited to) CD8+ effectors, CD68 and 163 Macrophages and FOXP3+ cells infiltrates as well as PDL1, IDO1, CD31 (microvessel density), Ki67 expression by IHC. Frozen samples will be analysed by (but not limited to) RNA sequencing in search for a predictive signature for response.

APPENDIX 1: ECOG PERFORMANCE STATUS ASSESSMENT SCALE

Grade	Activity
0	Able to carry on all normal activities without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out light work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.

APPENDIX 2: EVALUATION OF RESPONSE. THE RECIST

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009]. Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST criteria.

DEFINITIONS

Evaluable for toxicity: All patients will be evaluable for toxicity from the time of their first treatment with study drugs.

Evaluable for objective response: Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

DISEASE PARAMETERS

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm by chest x-ray, as ≥10 mm with CT scan, or ≥10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area are not considered measurable.

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.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic 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 non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and 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. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

METHODS FOR EVALUATION OF MEASURABLE DISEASE

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

RESPONSE CRITERIA

Evaluation of 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.

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

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). 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 progressions).

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 study

Evaluation of Non-Target Lesions

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

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

Definition of the Best Response

The best response determination in trial where confirmation of complete or partial response is required:

Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point as specified in the protocol (**generally 4 weeks later**). In this circumstance, the best overall response can be interpreted as in Table below.

Table 3 – Best overall response when confirmation of CR and PR required.

Overall response First time point	Overall response Subsequent time point	BEST overall response
CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE
NE	NE	NE

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.
a If a CR is *truly* met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

Special notes on response assessment

When nodal disease is included in the sum of target lesions and the nodes decrease to 'normal' size (<10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR (complete response) may not have a total sum of 'zero' on the case report form (CRF).

In trials where confirmation of response is required, repeated 'NE' time point assessments may complicate best response determination. The analysis plan for the trial must address how missing data/assessments will be addressed in determination of response and progression. For example, in most trials it is reasonable to consider a patient with time point responses of PR-NE-PR as a confirmed response.

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as 'symptomatic detioration'. Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is *not* a descriptor of an objective response: it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target disease as shown in Tables belows.

APPENDIX 3: SERIOUS ADVERSE EVENT FORM

Serious Adverse Event Notification Form

TO BE FAXED TO THE INSTITUT BERGONIE VIGILANCE UNIT – N° + 33 (0)5 56 33 04 85

PROTOCOL : **PEMBROSARC**	EUDRACT/ ID-RCB N°:**2014-004568-39**	COUNTRY: France
SPONSOR IDENTIFICATION N°:	INVESTIGATOR SITE :	SITE N°:
DATE OF THIS REPORT: |___|___|____|	INITIAL REPORT ☐ / FOLLOW-UP REPORT N°|___|	FINAL REPORT ☐

1. PATIENT IDENTIFICATION

INCLUSION N°: |_____| SURNAME (1 LETTER): |__| 1ST NAME (1 LETTER): |__| DATE OF BIRTH : |___|___|____| TREATMENT ARM: |__|

DOSE LEVEL (PHASE I STUDY): |__|

GENDER: F ☐ M ☐ WEIGHT (KG): |___| HEIGHT (CM): |___| BODY SURFACE AREA (M²): |__| . |__|

2. INFORMATION ON EVENT

DATE OF ONSET: |___|___|____| TOXICITY (NCI–CTC GRADE): 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐

DIAGNOSIS OR *MAIN SYMPTOM*: **only one diagnosis or one symptom** (except for linked symptoms) .....

.....

.....

DESCRIBE EVENT AND TREATMENT GIVEN (INCLUDING RELEVANT TEST/LAB DATA): .....

.....

.....

3. SERIOUSNESS CRITERIA

☐ DEATH, DATE OF DEATH: .....|__|__|___|____|
☐ LIFE-THREATENING
☐ REQUIRING/PROLONGING HOSPITALIZATION :
DATE OF ADMISSION: .....|__|__|___|____|
☐ PERSISTENT/SIGNIFICANT DISABILITY/INCAPACITY
☐ CONGENITAL DISORDER/BIRTH DEFECT
☐ MEDICALLY RELEVANT

4. OUTCOME

☐ ONGOING EVENT ☐ UNKNOWN OUTCOME
☐ RECOVERED WITHOUT SEQUELAE, ☞ DATE |__|__|___|____|
☐ RECOVERED WITH SEQUELAE, ☞ DATE |__|__|___|____|
SPECIFY SEQUELAE: .....
.....
☐ DEATH RELATED TO THIS EVENT, ☞ DATE |__|__|___|____|
☐ DEATH UNRELATED TO THIS EVENT, ☞ DATE |__|__|___|____|
CAUSE OF DEATH: .....
.....
OR CAUSE UNKNOWN ☐
☐ AUTOPSY: YES ☐ NO ☐

IF PATIENT WAS HOSPITALIZED: DATE OF END OF HOSPITALIZATION: |__|__|___|____|
OR PATIENT STILL HOSPITALIZED AT TIME OF THIS REPORT ☐

5. IMP (INVESTIGATIONAL MEDICINAL PRODUCT(S), including combined RADIOTHERAPY / SURGERY...) ..... TICK IF NA ☐

INVESTIGATIONAL PROCEDURE(S) INDICATE THE INTERNATIONAL COMMON DENOMINATION OF THE IMP & OTHER COMBINED	ROUTE	SAE CYCLE NUMBER	DATES		DOSE & UNIT			
			DATE OF FIRST ADMINISTRATION/USE (1ST DAY OF 1ST CYCLE)	DATE OF LAST ADMINISTRATION/USE BEFORE SAE	LAST DOSE ADMINISTERED BEFORE SAE		CUMULATIVE DOSE SINCE THE 1ST ADMINISTRATION	
					DOSE	UNIT	DOSE	UNIT
1.			|__|__|___|____|	|__|__|___|____|				
2.			|__|__|___|____|	|__|__|___|____|				
3.			|__|__|___|____|	|__|__|___|____|				
4.			|__|__|___|____|	|__|__|___|____|				
5.			|__|__|___|____|	|__|__|___|____|				
6			|__|__|___|____|	|__|__|___|____|				
7.			|__|__|___|____|	|__|__|___|____|				

UNBLINDING : YES ☐ NO ☐ NA ☐

HAS ONE (OR SEVERAL) INVESTIGATIONAL PRODUCT(S) BEEN STOPPED?
☐ YES N°|__| N°|__| N°|__| N°|__| N°|__| N°|__| ☐ NO ☐ NA
DID THE EVENT DISAPPEAR AFTER INVESTIGATIONAL PRODUCT(S) IS STOPPED?
☐ YES ☐ NO ☐ NA

HAS ONE (OR SEVERAL) INVESTIGATIONAL PRODUCT(S) BEEN REINTRODUCED?
☐ YES N°|__| N°|__| N°|__| N°|__| N°|__| N°|__| ☐ NO ☐ NA
DID THE EVENT REAPPEAR AFTER INVESTIGATIONAL PRODUCT(S) REINTRODUCTION?
☐ YES ☐ NO ☐ NA

FOR_01_SAE NOTIFICATION_ v3 du 09.02.2018 PAGE 1 OF 3

Serious Adverse Event Notification Form

To be faxed to the Institut Bergonie Vigilance Unit – N° + 33 (0)5 56 33 04 85

Protocol : PEMBROSARC	EudraCT/ ID-RCB n°:2014-004568-39		Country: France
Sponsor identification N°:	Investigator site :		Site N°:
DATE OF THIS REPORT: |__|__||__|__||__|__|__|__|	Initial report ☐	Follow-up report N°|__|__|	Final report ☐
Inclusion N°: |______| Surname (1 letter): |__| 1st name (1 letter): |__| Date of birth : |__|__||__|__|__|__|			

6. RADIOTHERAPY .... Tick if NA ☐

Technique	Field(s)	Dates		Dose (Gy)	
		Date of first administration	Date of last administration	Last dose administered BEFORE SAE (Gy)	Cumulative dose since the 1st administration (Gy)
		|__|__||__|__||__|__|__|__|	|__|__||__|__||__|__|__|__|		
		|__|__||__|__||__|__|__|__|	|__|__||__|__||__|__|__|__|		
		|__|__||__|__||__|__|__|__|	|__|__||__|__||__|__|__|__|		
		|__|__||__|__||__|__|__|__|	|__|__||__|__||__|__|__|__|		

Machine (specify if possible trade name / model/serial number): ....

....

Has radiotherapy been stopped? ☐ Yes ☐ No ☐ NA Did the event disappear after radiotherapy is stopped? ☐ Yes ☐ No ☐ NA	Has radiotherapy been reintroduced? ☐ Yes ☐ No ☐ NA Did the event reappear after radiotherapy reintroduction? ☐ Yes ☐ No ☐ NA

Scene of event: ☐ Investigator site ☐ Home ☐ Hospital ☐ Day Hospital ☐ Convalescent Home
☐ Other: ....

7. MEDICAL DEVICE or NON MEDICINAL PRODUCT, METHOD or ACTION .... Tick if NA ☐

Device / Non Medicinal Product, Method or Action	Dates of Use
Common denomination : Trade name (if EC marking) :	Start date: |__|__||__|__||__|__|__|__| Stop date: |__|__||__|__||__|__|__|__|
Model :	Version (included software) :
Serial number :	and/or Batch number :
Indication of use for the patient :	

Has Device or one (or several) products(s), method(s) or action(s) been stopped? ☐ Yes ☐ No ☐ NA Did the event disappear after stop? ☐ Yes ☐ No ☐ NA	Has Device or one (or several) product(s), method(s) or action(s) been reintroduced? ☐ Yes ☐ No ☐ NA Did the event reappear after reintroduction? ☐ Yes ☐ No ☐ NA

Scene of event: ☐ Investigator site ☐ Home ☐ Hospital ☐ Day Hospital ☐ Convalescent Home
☐ Other, specify: ....

Serious Adverse Event Notification Form

TO BE FAXED TO THE INSTITUT BERGONIE VIGILANCE UNIT –N° + 33 (0)5 56 33 04 85

PROTOCOL : PEMBROSARC	EUDRACT/ ID-RCB N°:2014-004568-39	COUNTRY: France
SPONSOR IDENTIFICATION N°:	INVESTIGATOR SITE :	SITE N°:
DATE OF THIS REPORT: |__|__|____|	INITIAL REPORT ☐ / FOLLOW-UP REPORT N°|__|	FINAL REPORT ☐
INCLUSION N°: |_____| SURNAME (1 LETTER): |__| 1ST NAME (1 LETTER): |__| DATE OF BIRTH : |__|__|____|		

8. CONCOMITANT DRUG(S) – (EXCLUDE THOSE USED TO TREAT REACTION)

CONCOMITANT DRUG	ROUTE	START DATE	STOP DATE	ONGOING	INDICATION
1.		FROM |__|__|__|	TO |__|__|__|	☐	
2.		FROM |__|__|__|	TO |__|__|__|	☐	
3.		FROM |__|__|__|	TO |__|__|__|	☐	
4.		FROM |__|__|__|	TO |__|__|__|	☐	

9. OTHER RELEVANT HISTORY (E.G. DIAGNOSTICS, ALLERGIES, PREGNANCY WITH LAST MONTH OF PERIOD, ETC…)

.....

.....

.....

10. ASSESSMENT: IN YOUR OPINION (INVESTIGATOR), THIS EVENT IS RELATED TO (TICK ONLY ONE BOX):

☐ IMP (INVESTIGATIONAL MEDICINAL PRODUCT(S) INCLUDING COMBINED RADIOTHERAPY / SURGERY)
SPECIFY THE IMP NUMBER(S) (SEE SECTION 5 OF THE FORM): N°__ N°__ N°__ N°__ N°__ N°__ N°__

☐ INVESTIGATIONAL RADIOTHERAPY,

☐ INVESTIGATIONAL MEDICAL DEVICE OR NON MEDICINAL PRODUCT, METHOD OR ACTION

IF NOT RELATED TO EITHER INVESTIGATIONAL MP / RADIOTHERAPY / SURGERY, NMP, OR MD, PLEASE SPECIFY (TICK ONLY ONE BOX)

☐ PROTOCOL

☐ CONCOMITANT TREATMENT(S), SPECIFY: .....

☐ CONCOMITANT DISEASE(S), SPECIFY: .....

☐ OTHER, SPECIFY: .....

11. SAE NOTIFICATED BY:

NAME:
FUNCTION:
ADDRESS:
PHONE: ..... FAX: .....
E-MAIL: .....
DATE \|__\|/\|__\|/\|____\|
SIGNATURE: .....

INVESTIGATOR

NAME:
DEPARTMENT:

DATE \|__\|/\|__\|/\|____\|
SIGNATURE: .....

SPONSOR ONLY (DO NOT FULFIL THIS PART)

SPONSOR IDENTIFICATION NUMBER: .....
DATE OF RECEIPT: \|__\|/\|__\|/\|____\| DATE OF THIS REPORT: \|__\|/\|__\|/\|____\|

ASSESSMENT (Tick only one box):

1 ☐ INVESTIGATIONAL **MP** (INCLUDING COMBINED RADIOTHERAPY / SURGERY)
SPECIFY THE NUMBER(S)° N° __ N° __ N° __ N° __ N° __ N° __ N° __
2 ☐ INVESTIGATIONAL **RADIOTHERAPY**,
3 ☐ INVESTIGATIONAL **MEDICAL DEVICE OR NON MEDICINAL PRODUCT, METHOD OR ACTION**

IS IT A SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTION (**SUSAR**)?
YES ☐ NO ☐

IF NOT RELATED TO EITHER 1, 2 OR 3, PLEASE SPECIFY (TICK ONLY ONE BOX)

4 ☐ PROTOCOL
5 ☐ CONCOMITANT TREATMENT(S)
6 ☐ CONCOMITANT DISEASE(S), SPECIFY .....
7 ☐ OTHER, SPECIFY .....

DATE \|__\|/\|__\|/\|____\| NAME ..... SIGNATURE : .....

Appendix 4: PREGNANCY REPORT FORM

Pregnancy Notification Form

TO BE FAXED TO THE INSTITUT BERGONIE VIGILANCE UNIT – PARIS OFFICE N° + 33 (0)5 56 33 04 85

PROTOCOL :PEMBROSARC	EUDRACT/ ID-RCB N°:2014-004568-39		COUNTRY: France
SPONSOR IDENTIFICATION N°:	INVESTIGATOR SITE :		SITE N°:
DATE OF THIS REPORT: |___|___|___|___|___|___|	INITIAL REPORT ☐	FOLLOW-UP REPORT N°|___|	FINAL REPORT ☐

1. PATIENT IDENTIFICATION

INCLUSION N°: |_____|

SURNAME (1 LETTER): |___| 1ST NAME (1 LETTER): |___| DATE OF BIRTH (MM/AAAA): |___\|___\|___\|___\| TREATMENT ARM: |___| DOSE LEVEL (ONLY FOR PHASE I STUDIES): |___|

GENDER: FEMALE ☐

MALE ☐

2. INFORMATION ON PREGNANT

THE PREGNANT IS: THE PATIENT ☐

A PATIENT PARTNER ☐ ☞ SPECIFY INITIALS: |____| DATE OF BIRTH (MM/AAAA): |___\|___\|___\|___\|

DATE OF LAST MENSTRUAL PERIOD (DD/MM/AAAA): |___\|___\|___\|___\|___\|

ESTIMATED DATE OF DELIVERY (DD/MM/AAAA): |___\|___\|___\|___\|___\|

WAS THE PATIENT USING CONTRACEPTION? YES ☐ NO ☐

DESCRIBE ALL RELEVANT TREATMENTS ADMINISTERED TO THE PREGNANT AND HER PARTNER IF APPLICABLE (DATE AND DOSE OF INVESTIGATIONAL DRUGS AND CONCOMITANT TREATMENTS): .....

.....

.....

.....

.....

PARENTS RELEVANT MEDICAL HISTORY:

MOTHER: .....

.....

.....

FATHER: .....

.....

.....

3. FOLLOW-UP INFORMATION

FOLLOW-UP INFORMATION CAN BE OBTAINED FROM:

DOCTOR: .....

INSTITUTION: .....

ADDRESS: .....

E-MAIL: .....

PHONE: ..... FAX: .....

4. INVESTIGATOR

NAME: .....

DEPARTMENT: .....

PHONE: .....

FAX: .....

E-MAIL: .....

DATE (DD/MM/AAAA): |__\|/|__\|/|___\|: SIGNATURE: .....

PREG NOTIFICATION_V2.0 28-06-17 PAGE 1 OF 1

APPENDIX 5: IMMUNE RELATED RESPONSE CRITERIA

For all patients who experience disease progression on study, the date noted for of disease progression is the time of the scan where it is originally detected, and not the following date of the confirmatory scan.

Definitions of measurable and non-measurable disease

Measurable disease: Neoplastic masses that can be precisely measured in 2 in-plane perpendicular diameters. Both its longest diameter and its longest perpendicular must be greater than or equal to 10 mm or 2 times the axial slice thickness. Lymph nodes must have a short-axis line-length of $\geq$ 15 mm. Malignant lymph nodes must be measurable in 2 perpendicular diameters. Both its longest diameter and its longest perpendicular must be greater than or equal to 15 mm or 2 times the axial slice thickness. The quantitative endpoint will be defined as the product of the longest diameter with its longest perpendicular.

Non-measurable disease: Non-measurable lesions are those that are not suitable for quantitative assessment over time. These include:

1) Neoplastic masses that are too small to measure, because their longest uninterrupted diameter or longest perpendicular are less than 10 mm or two times the axial slice thickness.

2) Neoplastic masses whose boundaries cannot be distinguished. This includes masses which cannot be demarcated from surrounding tissue because of inadequate contrast, masses with overly complex morphology, or those with highly heterogeneous tissue composition.

3) Other types of lesions that are confidently felt to represent neoplastic tissue, but difficult to quantify in a reproducible manner. These include bone metastases, leptomeningeal metastases, malignant ascites, pleural/pericardial effusions, inflammatory breast disease, lymphangitis cutis/pulmonis, cystic lesions, ill defined abdominal masses, etc.

For irRC, only target lesions selected at baseline and measurable new lesions are taken into account.

At the baseline tumor assessment, the sum of the products of the two largest perpendicular diameters (SPD) of all **index lesions** (five lesions per organ, up to 10 visceral lesions and five cutaneous index lesions) is calculated.

At each subsequent tumor assessment, the SPD of the index lesions and of new, measurable lesions ($\geq$ 5 X 5 mm; up to 5 new lesions per organ: 5 new cutaneous lesions and 10 visceral lesions) are added together to provide the total time-point **tumor burden.**

Overall response using irRC:

- **Complete Response (irCR):** Complete disappearance of all tumor lesions (whether measureable or not, and no new lesions). CR must be confirmed by repeated, consecutive assessments made no less than 4 weeks from the date first documented.
- **Partial Response (irPR):** Decrease in SPD of 50% or greater by a consecutive assessment at least 4 weeks after first documentation.
- **Stable Disease (irSD):** Failure to meet criteria for irCR or irPR, in absence of irPD.
- **Progressive Disease (irPD):** At least 25% increase in SPD relative to nadir (minimum recorded tumor burden) Confirmation by a repeat, consecutive assessment no less than 4 weeks from the data first documented.

Please note other key differences between irRC and the original WHO criteria:

New measurable lesions will be incorporated into the SPD

New non measurable lesions do not define progression but preclude irCR

Non-index lesions contribute to defining irCR (complete disappearance required).

See the Investigators Imaging Operations Manual (IIOM) for more details.

REFERENCE

IrRC for the current protocol is adopted from the following reference:

Wolchok, JD, Hoos, A, O'Day S, et al., Guidelines for the Evaluation of Immune Therapy Activity in Solid Tumors: Immune-Related Response Criteria. Clinical Cancer Research, 2009 Dec 1;15(23):7412-20. Epub 2009 Nov 24.

APPENDIX 6: PATIENT MEDICATION DIARY STRATEGY A

PROTOCOLE PEMBROSARC

Carnet patient (cycles impairs)

De Mme/Mr.....

Cycle N° I__I__I

Madame, Monsieur,

Dans le cadre de votre participation à l'étude PEMBROSARC, il est nécessaire d'avoir des informations sur le suivi de votre traitement par Pembrolizumab et Cyclophosphamide.

Vous trouverez dans ce carnet un tableau à compléter chaque jour, et nous vous remercions d'y noter :

- ✓ la date, et le nombre de gélules pris par jour
- ✓ d'annoter un commentaire si nécessaire (effets secondaires par exemple)
- ✓ l'indication de non prise des traitements s'il y a lieu en cochant la case correspondante et en complétant d'un commentaire la raison.

N'oubliez pas de remettre ce livret à l'Infirmièr(e) de Recherche Clinique, Attaché(e) de Recherche Clinique ou Pharmacie hospitalière lors de votre prochain rendez-vous.

Nous vous remercions de votre précieuse collaboration.

PEMBROSARC – Version 2 -30.03.2018- 1

Notice d'utilisation des médicaments à l'étude

Pembrolizumab

- ✓ 1 injection au J8 de chaque cycle

Cyclophosphamide

- ✓ 2 prises par jour à heure fixe : 1 semaine sur 2
- ✓ Juste avant ou pendant le petit-déjeuner
- ✓ Juste avant ou pendant le dîner
- ✓ à prendre avec un grand verre d'eau

En cas d'oubli

- Ne pas prendre la dose, et ne pas doubler la dose suivante

En cas de vomissements

- Ne pas reprendre la dose, et ne pas doubler la dose suivante

Conservation du traitement

- Conservation à température ambiante inférieure à 25°C.
- Ne pas utiliser après la date de péremption figurant sur la boite
- Tenir hors de portée des enfants

Date		Cyclophosphamide		Pembrolizumab	Commentaires
			Non pris		
J1	___/_____/___	Mat |__|gél Soir |__|gél	☐ ☐		
J2	___/_____/___	Mat |__|gél Soir |__|gél	☐ ☐		
J3	___/_____/___	Mat |__|gél Soir |__|gél	☐ ☐		
J4	___/_____/___	Mat |__|gél Soir |__|gél	☐ ☐		
J5	___/_____/___	Mat |__|gél Soir |__|gél	☐ ☐		
J6	___/_____/___	Mat |__|gél Soir |__|gél	☐ ☐		
J7	___/_____/___	Mat |__|gél Soir |__|gél	☐ ☐		
J8	___/_____/___			☐	
J9	___/_____/___				
J10	___/_____/___				
J11	___/_____/___				
J12	___/_____/___				
J13	___/_____/___				
J14	___/_____/___				

Date		Cyclophosphamide		Pembrolizumab	Commentaires
			Non pris		
J15	___/_____/___	Mat |__|gél Soir |__|gél	☐ ☐		
J16	___/_____/___	Mat |__|gél Soir |__|gél	☐ ☐		
J17	___/_____/___	Mat |__|gél Soir |__|gél	☐ ☐		
J18	___/_____/___	Mat |__|gél Soir |__|gél	☐ ☐		
J19	___/_____/___	Mat |__|gél Soir |__|gél	☐ ☐		
J20	___/_____/___	Mat |__|gél Soir |__|gél	☐ ☐		
J21	___/_____/___	Mat |__|gél Soir |__|gél	☐ ☐		

PROTOCOLE

PEMBROSARC

Carnet patient (cycles pairs)

De Mme/Mr.....

Cycle N° I__I__I

Madame, Monsieur,

Dans le cadre de votre participation à l'étude PEMBROSARC, il est nécessaire d'avoir des informations sur le suivi de votre traitement par Pembrolizumab et Cyclophosphamide.
Vous trouverez dans ce carnet un tableau à compléter chaque jour, et nous vous remercions d'y noter :

- ✓ la date, et le nombre de gélules pris par jour
- ✓ d'annoter un commentaire si nécessaire (effets secondaires par exemple)
- ✓ l'indication de non prise des traitements s'il y a lieu en cochant la case correspondante et en complétant d'un commentaire la raison.

N'oubliez pas de remettre ce livret à l'Infirmièr(e) de Recherche Clinique, Attaché(e) de Recherche Clinique ou Pharmacie hospitalière lors de votre prochain rendez-vous.

Nous vous remercions de votre précieuse collaboration.

Notice d'utilisation des médicaments à l'étude

Pembrolizumab

- ✓ 1 injection au J8 de chaque cycle

Cyclophosphamide

- ✓ 2 prises par jour à heure fixe : I semaine sur 2
- ✓ Juste avant ou pendant le petit-déjeuner
- ✓ Juste avant ou pendant le dîner
- ✓ à prendre avec un grand verre d'eau

En cas d'oubli

- Ne pas prendre la dose, et ne pas doubler la dose suivante

En cas de vomissements

- Ne pas reprendre la dose, et ne pas doubler la dose suivante

Conservation du traitement

- Conservation à température ambiante inférieure à 25°C.
- Ne pas utiliser après la date de péremption figurant sur la boite
- Tenir hors de portée des enfants

Date		Cyclophosphamide		Pembrolizumab	Commentaires
			Non pris		
J1	__/____/__				
J2	__/____/__				
J3	__/____/__				
J4	__/____/__				
J5	__/____/__				
J6	__/____/__				
J7	__/____/__				
J8	__/____/__	Mat |__|gél Soir |__|gél	☐ ☐	☐	
J9	__/____/__	Mat |__|gél Soir |__|gél	☐ ☐		
J10	__/____/__	Mat |__|gél Soir |__|gél	☐ ☐		
J11	__/____/__	Mat |__|gél Soir |__|gél	☐ ☐		
J12	__/____/__	Mat |__|gél Soir |__|gél	☐ ☐		
J13	__/____/__	Mat |__|gél Soir |__|gél	☐ ☐		
J14	__/____/__	Mat |__|gél Soir |__|gél	☐ ☐		
J15	__/____/__				
J16	__/____/__				
J17	__/____/__				
J18	__/____/__				
J19	__/____/__				
J20	__/____/__				
J21	__/____/__				

APPENDIX 7: PATIENT MEDICATION DIARY STRATEGY B

PROTOCOLE

PEMBROSARC

Stratégie B

Carnet patient (cycles impairs)

De Mme/Mr.....

Cycle N° |__|__|

Madame, Monsieur,

Dans le cadre de votre participation à l'étude PEMBROSARC, il est nécessaire d'avoir des informations sur le suivi de votre traitement par Pembrolizumab, Cyclophosphamide et G100.

Vous trouverez dans ce carnet un tableau à compléter chaque jour, et nous vous remercions d'y noter :

- ✓ la date, et le nombre de gélules pris par jour
- ✓ d'annoter un commentaire si nécessaire (effets secondaires par exemple)
- ✓ l'indication de non prise des traitements s'il y a lieu en cochant la case correspondante et en complétant d'un commentaire la raison.

N'oubliez pas de remettre ce livret à l'Infirmièr(e) de Recherche Clinique, Attaché(e) de Recherche Clinique ou Pharmacie hospitalière lors de votre prochain rendez-vous.

Nous vous remercions de votre précieuse collaboration.

PEMBROSARC – G100– Version 1 -30-03-2018- 1

Notice d'utilisation des médicaments à l'étude

Pembrolizumab

- ✓ 1 injection au J8 de chaque cycle

Cyclophosphamide

- ✓ 2 prises par jour à heure fixe : 1 semaine sur 2
- ✓ Juste avant ou pendant le petit-déjeuner
- ✓ Juste avant ou pendant le dîner
- ✓ à prendre avec un grand verre d'eau

GI00

- ✓ 1 injection par semaine
- ✓ 12 injections maximum

En cas d'oubli

- Ne pas prendre la dose, et ne pas doubler la dose suivante

En cas de vomissements

- Ne pas reprendre la dose, et ne pas doubler la dose suivante

Conservation du traitement

- Conservation à température ambiante inférieure à 25°C.
- Ne pas utiliser après la date de péremption figurant sur la boite
- Tenir hors de portée des enfants

Date		Cyclophosphamide	Non pris	Pemrbolizumab	GI00	Commentaires
J-7	.../...../...				☐ ☐ NA	
J1	.../...../...	Mat |__| gél Soir |__| gél	☐ ☐		☐ ☐ NA	
J2	.../...../...	Mat |__| gél Soir |__| gél	☐ ☐			
J3	.../...../...	Mat |__| gél Soir |__| gél	☐ ☐			
J4	.../...../...	Mat |__| gél Soir |__| gél	☐ ☐			
J5	.../...../...	Mat |__| gél Soir |__| gél	☐ ☐			
J6	.../...../...	Mat |__| gél Soir |__| gél	☐ ☐			
J7	.../...../...	Mat |__| gél Soir |__| gél	☐ ☐			
J8	.../...../...			☐	☐ ☐ NA	
J9	.../...../...					
J10	.../...../...					
J11	.../...../...					
J12	.../...../...					
J13	.../...../...					

Date		Cyclophosphamide	Non pris	Pembrolizumab	GI00	Commentaires
J14	.../...../...					
J15	.../...../...	Mat |__| gél Soir |__| gél	☐ ☐		☐ ☐ NA	
J16	.../...../...	Mat |__| gél Soir |__| gél	☐ ☐			
J17	.../...../...	Mat |__| gél Soir |__| gél	☐ ☐			
J18	.../...../...	Mat |__| gél Soir |__| gél	☐ ☐			
J19	.../...../...	Mat |__| gél Soir |__| gél	☐ ☐			
J20	.../...../...	Mat |__| gél Soir |__| gél	☐ ☐			
J21	.../...../...	Mat |__| gél Soir |__| gél	☐ ☐			

PROTOCOLE

PEMBROSARC

Stratégie B

Carnet patient (cycles pairs)

De Mme/Mr.....

Cycle N° I__I__I

Madame, Monsieur,

Dans le cadre de votre participation à l'étude PEMBROSARC, il est nécessaire d'avoir des informations sur le suivi de votre traitement par Pembrolizumab, Cyclophosphamide et G100.

Vous trouverez dans ce carnet un tableau à compléter chaque jour, et nous vous remercions d'y noter :

- ✓ la date, et le nombre de gélules pris par jour
- ✓ d'annoter un commentaire si nécessaire (effets secondaires par exemple)
- ✓ l'indication de non prise des traitements s'il y a lieu en cochant la case correspondante et en complétant d'un commentaire la raison.

N'oubliez pas de remettre ce livret à l'Infirmièr(e) de Recherche Clinique, Attaché(e) de Recherche Clinique ou Pharmacie hospitalière lors de votre prochain rendez-vous.

Nous vous remercions de votre précieuse collaboration.

Notice d'utilisation des médicaments à l'étude

Pembrolizumab

- ✓ 1 injection au J8 de chaque cycle

Cyclophosphamide

- ✓ 2 prises par jour à heure fixe : 1 semaine sur 2
- ✓ Juste avant ou pendant le petit-déjeuner
- ✓ Juste avant ou pendant le dîner
- ✓ à prendre avec un grand verre d'eau

G100

- ✓ 1 injection par semaine
- ✓ 12 injections maximum

En cas d'oubli

- Ne pas prendre la dose, et ne pas doubler la dose suivante

En cas de vomissements

- Ne pas reprendre la dose, et ne pas doubler la dose suivante

Conservation du traitement

- Conservation à température ambiante inférieure à 25°C.
- Ne pas utiliser après la date de péremption figurant sur la boite
- Tenir hors de portée des enfants

Date		Cyclophosphamide	Non pris	Pembrolizumab	GI00	Commentaires
J1	___/_____/___				☐ ☐ NA	
J2	___/_____/___					
J3	___/_____/___					
J4	___/_____/___					
J5	___/_____/___					
J6	___/_____/___					
J7	___/_____/___					
J8	___/_____/___	Mat |__| gél Soir |__| gél	☐ ☐	☐	☐ ☐ NA	
J9	___/_____/___	Mat |__| gél Soir |__| gél	☐ ☐			
J10	___/_____/___	Mat |__| gél Soir |__| gél	☐ ☐			
J11	___/_____/___	Mat |__| gél Soir |__| gél	☐ ☐			
J12	___/_____/___	Mat |__| gél Soir |__| gél	☐ ☐			
J13	___/_____/___	Mat |__| gél Soir |__| gél	☐ ☐			

Date		Cyclophosphamide	Non pris	Pembrolizumab	GI00	Commentaires
J14	___/_____/___	Mat |__| gél Soir |__| gél	☐ ☐			
J15	___/_____/___				☐ ☐ NA	
J16	___/_____/___					
J17	___/_____/___					
J18	___/_____/___					
J19	___/_____/___					
J20	___/_____/___					
J21	___/_____/___					

APPENDIX 8: EVENT OF CLINICAL INTEREST NOTIFICATION FORM

Event of Clinical Interest Notification Form

TO BE FAXED TO THE INSTITUT BERGONIE VIGILANCE UNIT –N° + 33 (0)5 56 33 04 85

PROTOCOL :PEMBROSARC	EUDRACT/ ID-RCB N°:2014-004568-39	COUNTRY: France
SPONSOR IDENTIFICATION N°:	INVESTIGATOR SITE :	SITE N°:
DATE OF THIS REPORT: |__|__|__|__|__|__|__|__|__|		

1. PATIENT IDENTIFICATION

INCLUSION N°: \|_____\| SURNAME (1 LETTER): \|__\| 1ST NAME (1 LETTER): \|__\| DATE OF BIRTH (MM/YYYY): \|__\|__\|__\|__\|__\|

GENDER: F ☐ M ☐ WEIGHT (KG): \|__\|__\|__\| HEIGHT (CM): \|__\|__\|__\|

2. INFORMATION ON EVENT OF CLINICAL INTEREST

DATE OF ONSET: \|__\|__\|__\|__\|__\|__\|__\|__\|__\| TOXICITY (NCI–CTC GRADE): 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐

DIAGNOSIS OR *MAIN SYMPTOM*: **only one diagnosis or one symptom** (except for linked symptoms) .....

.....

.....

DESCRIBE EVENT AND TREATMENT GIVEN (INCLUDING RELEVANT TEST/LAB DATA): .....

.....

.....

.....

3. OUTCOME

☐ ONGOING EVENT ☐ UNKNOWN OUTCOME

☐ RECOVERED WITHOUT SEQUELAE, ☞ DATE \|__\|__\|__\|__\|__\|__\|__\|__\|__\|

☐ RECOVERED WITH SEQUELAE, ☞ DATE \|__\|__\|__\|__\|__\|__\|__\|__\|__\|

SPECIFY SEQUELAE: .....

.....

☐ DEATH RELATED TO THIS EVENT, ☞ DATE \|__\|__\|__\|__\|__\|__\|__\|__\|__\| (Please complete a Notification of Serious Adverse Event)

☐ DEATH UNRELATED TO THIS EVENT, ☞ DATE \|__\|__\|__\|__\|__\|__\|__\|__\|__\|

CAUSE OF DEATH: .....

..... (Please complete a Notification of Serious Adverse Event)

OR CAUSE UNKNOWN ☐

☐ AUTOPSY: YES ☐ NO ☐

3. IMP (INVESTIGATIONAL MEDICINAL PRODUCT(S)

IMP	Route	Cycle number	Date of first administration	Date of last administration before ECI	Last dose administered before ECI		Cumulative dose since the 1st administration	
					Dose	Unit	Dose	Unit
1.			|__|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|__|				
2.			|__|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|__|				

HAS ONE (OR SEVERAL) INVESTIGATIONAL PRODUCT(S) BEEN STOPPED?

☐ YES N°\|_\| N°\|_\| N°\|_\| N°\|_\| N°\|_\| N°\|_\| N°\|_\| ☐ NO ☐ NA

4. ASSESSMENT: IN YOUR OPINION (INVESTIGATOR), THIS EVENT IS RELATED TO (TICK ONLY ONE BOX):

☐ IMP (INVESTIGATIONAL MEDICINAL PRODUCT(S) INCLUDING COMBINED RADIOTHERAPY / SURGERY)
SPECIFY THE IMP NUMBER(S) (SEE SECTION 5 OF THE FORM): N°\|_\| N°\|_\| N°\|_\| N°\|_\| N°\|_\| N°\|_\| N°\|_\|

IF NOT RELATED TO EITHER INVESTIGATIONAL MP / RADIOTHERAPY / SURGERY, NMP, OR MD, **PLEASE SPECIFY** (TICK ONLY ONE BOX)

☐ PROTOCOL
☐ CONCOMITANT TREATMENT(S), SPECIFY: .....
☐ CONCOMITANT DISEASE(S), SPECIFY: .....
☐ OTHER, SPECIFY: .....

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Event of Clinical Interest Notification Form

TO BE FAXED TO THE INSTITUT BERGONIE VIGILANCE UNIT –N° + 33 (0)5 56 33 04 85

5. ECI NOTIFICATED BY:

NAME:
FUNCTION:
ADDRESS:
PHONE: ..... FAX: .....
E-MAIL: .....
DATE \|__\|/\|__\|/\|__\|__\|__\|
SIGNATURE: .....

INVESTIGATOR
NAME:
DEPARTMENT:

DATE \|__\|/\|__\|/\|__\|__\|__\|
SIGNATURE: .....

SPONSOR ONLY (DO NOT FULFIL THIS PART)

SPONSOR IDENTIFICATION NUMBER: .....
DATE OF RECEIPT: \|__\|/\|__\|/\|__\|__\|__\|__\| DATE OF THIS REPORT: \|__\|/\|__\|/\|__\|__\|__\|__\|

ASSESSMENT (Tick only one box):
☐ INVESTIGATIONAL MP SPECIFY THE NUMBER(S)° N°\|_\| N°\|_\|

IF NOT RELATED TO EITHER 1, 2 OR 3, PLEASE SPECIFY (TICK ONLY ONE BOX)
☐ PROTOCOL ☐ CONCOMITANT TREATMENT(S) ☐ CONCOMITANT DISEASE(S), SPECIFY .....
☐ OTHER, SPECIFY .....

DATE \|__\|/\|__\|/\|__\|__\|__\| NAME ..... SIGNATURE : .....

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APPENDIX 9: DOSE MODIFICATION AND TOXICITY MANAGEMENT GUIDELINES FOR IMMUNE-RELATED AES ASSOCIATED WITH PEMBROLIZUMAB

Immune-related AEs	Toxicity Grade or Conditions (CTCAEv4.0)	Action Taken with Study Medication	irAE Management with Corticosteroid and/or Other Therapies	Monitor and Follow-up
Pneumonitis	Grade 2	Withhold until Grade 0-1	• 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 until Grade 0-1	• 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, or recurrent Grade 3	Permanently discontinue		
AST / ALT Elevation or Increased Bilirubin	Grade 2 [a]	Withhold until Grade 0-1	• 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 returns to baseline or is stable
	Grade 3 [b] or 4 [c]	Permanently discontinue	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	

Immune-related AEs	Toxicity Grade or Conditions (CTCAEv4.0)	Action Taken with Study Medication	irAE Management with Corticosteroid and/or Other Therapies	Monitor and Follow-up
Type 1 diabetes mellitus (T1DM) or Hyperglycemia[1]	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold until Grade 0-1 [d]	• 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 until Grade 0-1	• 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 until Grade 0- 1 or permanently discontinue[d]		
Hyperthyroidism[1]	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 until Grade 0- 1 or permanently discontinue [d]		
Hypothyroidism[1]	Grade 2-4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care	• Monitor for signs and symptoms of thyroid disorders.
Nephritis and Renal Dysfunction grading according to increased creatinine or acute kidney injury	Grade 2	Withhold until Grade 0- 1	• 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	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 2, 3 or 4	Permanently discontinue		

Immune-related AEs	Toxicity Grade or Conditions (CTCAEv4.0)	Action Taken with Study Medication	irAE Management with Corticosteroid and/or Other Therapies	Monitor and Follow-up
Neurological Toxicities	Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensur adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
Exfoliative Dermatological Conditions	Suspected SJS, TEN, or DRESS	Withhold	• Based on severity of AE administer corticosteroids	• Ensur adequate evaluation to confirm etiology or exclude other causes
	Confirmed SJS, TEN, or DRESS	Permanently discontinue		
All Other Immune-related AEs	Persistent Grade 2	Withhold until Grade 0- 1	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3	Withhold or discontinue based on the type of event [e]. Events that require discontinuation include but are not limited to: encephalitis and other clinically important irAEs (eg vasculitis and sclerosing cholangitis)		

Immune-related AEs	Toxicity Grade or Conditions (CTCAEv4.0)	Action Taken with Study Medication	irAE Management with Corticosteroid and/or Other Therapies	Monitor and Follow-up
	Grade 4 or recurrent Grade 3	Permanently discontinue		

General Instructions:

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

NOTES:

1. For participants with Grade 3 or 4 immune-related endocrinopathy where withholding 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)

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

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

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

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

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

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

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