Phase II multicentric study of pembrolizumab in classic or endemic Kaposi's sarcoma

KAPKEY

CLINICAL TRIAL ON MEDICINAL PRODUCT FOR HUMAN USE

Version N°4.0 of 06/05/2024

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Research Research Code: P160601J

Title: **Phase II multicentric study of pembrolizumab in classic or endemic Kaposi's sarcoma**

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The research will be carried out in accordance with the protocol, with current good practices and with the legislative and regulatory provisions in force.

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CHANGE HISTORY

N°	Date of authorization	Changes

ABBREVIATIONS / GLOSSARY

1 SUMMARY

Full title	Phase II multicentric study of pembrolizumab in classic or endemic Kaposi's sarcoma
Acronym	**KAPKEY**
Coordinating Investigator	Pr Céleste LEBBE - Dermatologie - Hôpital Saint Louis, Paris - 0142494679 – celeste.Lebbe@aphp.fr
Sponsor	Assistance Publique – Hôpitaux de Paris
Scientific justification	Classic and endemic Kaposi's sarcoma (KS) are lymphangioproliferations associated with human herpes virus 8 (HHV8), which treatment is poorly codified. Chemotherapies give at best 30-60% of transient responses. While □ interferon responses are frequent, this drug is often poorly tolerated in elderly patients. Therefore new therapies are needed. Classic KS represents an ideal model for evaluating new drugs since patients do not receive concomitant immunosuppressive regimens nor antiviral therapies. Pembrolizumab, an anti-PD1 monoclonal antibody has recently been shown to improve survival in several solid tumors. In KS few data are available on the role of PD1-PD-L1 axis. A significant PD-L1 expression on HHV8-associated pleural effusion lymphomas and on KS samples have been recently reported. Our experience in classical and endemic KS supports the role of this pathway with expression of PD-L1 by subpopulations of T cells but also NK cells in peripheral blood cells from these patients and expression of PD-L1 by tumor cells in KS lesions. In this study we will evaluate the benefit and safety profile of pembrolizumab in classic and endemic KS.
Primary objective and assessment criterion	Simon's 2-stage Optimal Design : The main objective is to assess whether pembrolizumab is clinically inactive (partial+complete response probability $\pi 0<5\%$) or truly active (partial+complete response probability $\pi 1>30\%$) in classic and endemic Kaposi's sarcoma (KS), using the Simon's 2 stage Optimal Design. The primary endpoint will be the Best Overall Response Rate (BORR) defined by the occurrence of complete response or partial response following ACTG criteria recorded from the start of treatment until 6 months or the beginning of any other specific systemic therapy for KS if it occurs before 6 months. Extension phase: In the event of a truly active conclusion of Simon's 2-step Optimal Design, an extension phase would be performed to evaluate more elements. An extension phase would be performed to further evaluate the efficacy of pembrolizumab in our setting. An additional 20 patients will be included to obtain a more accurate estimate of the treatment effect up to 24 months.

	The primary endpoint of this extension phase will be the best overall response rate according to the ACTG criteria, recorded from the start of treatment to 6 months or the start of any other KS-specific systemic therapy if it occurs before 6 months.
Secondary objectives and assessment criteria	Secondary objectives are: (for Simon's 2 stages Optimal Design and Extension stage) 1. to assess the safety profile of pembrolizumab in classic and endemic Kaposi's sarcoma, 2. to characterize the efficacy of pembrolizumab related to pharmacodynamics assessment Secondary endpoints: **Efficacy endpoints** Different aspects of clinical response will be evaluated: 1. Best overall response rate according to the PGA criteria until 24 months or the beginning of any other specific systemic therapy for KS if it occurs before 6 months. 2. Response rate at Month 3, Month 6, Month 9, Month 12, Month 18 and Month 24 according to ACTG and PGA criteria 3. Response rate on number of lesions at Month 3, Month 6, Month 9, Month 12 and Month 24 at best response as defined following the PGA 4. Response rate on the size of target lesions at Month 3, Month 6, Month 9 Month 12 and Month 24 atbest response as defined following the PGA 5. Response rate on tumor infiltration of target lesions at Month 3, Month 6, Month 9 Month 12 andMonth 24 at best response as defined following the PGA 6. Response rate on lymphedema (circumference, scale of 0 (absence) to 3 (painful or oozing)) at Month 3, Month 6, Month 12 and Month 24 at best response as defined following the PGA 7. Time to response defined as the time to first response recorded from the start of treatment 8. Time to progression defined as the time from starting treatment to progression in all patients 9. Response rate according to ACTG and PGA criteria at Month 9, Month 12, Month 18 and Month 24 for the Extension stage 10.Duration of response defined as the time from starting response to progression in patients achieving partial or complete response 11. Quality of life following the QLC-30 and DLQI_Kaposi at baseline, Cycle 5 – Cycle 10 – Cycle 15… every 3 months and EOT (Early Study Termination or at months 24) **Safety endpoints** Safety will be assessed in terms of drug toxicity evaluated by clinic and on laboratory parameters, and scored according to Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 during all the study.

Experimental design	Uncontrolled open-label multicentric phase II study
Catégory	Cat 2 : Phase 2
Population involved	Adult with classic or endemic Kaposi's sarcoma
Inclusion criteria	The patients meeting the following criteria may be included in the study: (for Simon's 2-stage Optimal Design and Extension stage) ➢ Classic or endemic histologically confirmed KS ➢ Progressive disease ➢ KS with more than 10 lesions or involving more than one limb segment or with involvement >3% body surface ➢ KS with at least 4 lesions ≥5mm ➢ KS with at least 1 other cutaneous tumor available for repeated pharmacodynamics evaluation and be willing to provide tissue from cutaneous biopsy of a tumor lesion ➢ At least 4 weeks washout for all KS specific therapies including chemotherapy and immunotherapy • Provide written, informed consent prior to the performance of any study specific procedures • Be ≥ 18 years of age on day of signing informed consent. • Have a performance status of 0 or 1 on the ECOG Performance Scale. • Demonstrate adequate organ function: - Hematological : Absolute neutrophil count (ANC) ≥1,000/mm3, Platelets ≥100,000 / mm3, Hemoglobin≥ 8 g/dL - Renal: Calculated creatinine clearance ≥ 30mL/min (using MDRD formula) - Hepatic: AST (SGOT) and ALT (SGPT) ≤ 2.5xULN, serum total bilirubin ≤ 1.5xULN OR direct bilirubin ≤ ULN for participants with total bilirubin levels >1.5xULN. • Female subject of childbearing potential should have a negative serum pregnancy within 72 hours prior to receiving the first dose of study medication • Have a health insurance
Non-inclusion criteria	The patients meeting the following criteria must be not included in the study: (for Simon's 2-stage Optimal Design and Extension stage) • Has a known history of organ transplantation • Is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment. • Has KS with symptomatic visceral involvement unless no other therapeutic option is available • Previously received treatments with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CTLA4 antibody or any other antibody or drug specifically targeting T-cell costimulation or immune checkpoint pathways. • Uncontrolled infection with HIV, HBV, or HCV infection; or diagnosis of immunodeficiency that is related to, or results in chronic infection. Patients with known hepatitis B (HepBsAg+) who have controlled infection (serum hepatitis B virus DNA PCR that is below the limit

	of detection AND receiving anti-viral therapy for hepatitis B) are permitted. Patients with controlled infections must undergo periodic monitoring of HBV DNA per local standards and must remain on anti-viral therapy for at least 6 months beyond the last dose of investigational study drug. Patients who are known HCV Ab+ who have controlled infection (undetectable HCV RNA by PCR either spontaneously or in response to a successful prior course of anti-HCV therapy) are permitted. • Has an active infection requiring systemic therapy. • Has hypersensitivity to pembrolizumab/ KEYTRUDA® or any of its excipients. • Has had a prior anti-cancer monoclonal antibody (mAb) within last 4 weeks or who has not recovered (i.e., > Grade 1 at selection) from adverse events due to agents administered more than 4 weeks earlier. • Has had prior chemotherapy, targeted small molecule therapy, or radiation therapy within 3 weeks (or 5 half lives) prior to study Day 1 or who has not recovered (i.e., > Grade 1 at selection) from adverse events due to a previously administered agent (*Note: participants with ≤ Grade 2 neuropathy are an exception to this criterion and may qualify for the study).* (*Note: If subject received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy).* • Has a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin or squamous cell carcinoma of the skin that has undergone potentially curative therapy or in situ cervical cancer. • Has active autoimmune disease that has required systemic treatment in the past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (eg., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment. Patients with vitiligo, type I diabetes mellitus, hypothyroidism, psoriasis non requiring systemic treatment are permitted to enroll. • Has active non-infectious pneumonitis or known history of non-infectious pneumonitis that required steroids, severe pulmonary disease or hypoxia • Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial. • Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, or not willing to use adequate contraceptive methods from study Visit 1 throughout the study period up to 120 days after the last dose of study therapy. • Has received a live vaccine within 30 days prior to the first dose of trial treatment or while participating in the trial.

	• Is currently participating or has participated in a study of an investigational agent within 4 weeks of the first dose of treatment. • Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating investigator. • Patient under guardianship or curatorship
Investigational medicinal product(s)	Simon's 2-stage Optimal Design Phase of development: Phase II Treatment: Pembrolizumab Route: intraveinous infusion Dose regimen: 200 mg per infusion every 3 weeks Duration of treatment: 6 months (8 cycles) Extension Stage: Phase of development: Phase II Treatment: Pembrolizumab Route: intraveinous infusion Dose regimen: 200 mg per infusion every 3 weeks Duration of treatment: up to 24 months (35 cycles), or until confirmed complete response as defined in the Simon's 2- stage Optimal Design if it occurs before 24 months. After 6 months of Pembrolizumab treatment (Cycle 8) and lasting 2 further cycles, if the complete response is observed and confirmed during at least 1 month, the Pembrolizumab will be stopped.
Comparator treatment	NA
Other procedures added by the research	– Pharmacodynamic evaluations will be based on tumor tissue collection (cutaneous biopsy) and correlative blood sampling – Quality of life assessment (QLQ-C30 and DLQI_Kaposi)
Risks added by the research	**Risk C**
Practical procedure	Simon's 2-stage Optimal Design: All patients will receive pembrolizumab 200 mg intraveinously every 3 weeks and will be assessed for drug safety and efficacy. Patients will continue on treatment for 6 months unless they experience disease progression or unacceptable adverse events. The treatment period can be extended up to 3 months in case of study delay due to AE that have been resolved Extension Stage: All patients included in the extension stage will receive pembrolizumab 200 mg intraveinously every 3 weeks and will be assessed for drug safety and efficacy. Patients will continue on treatment for 24 months unless they experience disease progression, unacceptable adverse events or confirmed complete response occurring after 6 months of treatment and lasting for at least 2 further cycles of Pembolizumab.
Number of participants chosen	Simon's 2-stage Optimal Design

	9 patients will be enrolled in the first part of the study with another 8 patients in the second part (total 17 patients). It implies have to screen a maximum of 34 patients. Extension stage: 20 additional patients will be enrolled.
Number of centers	Multicentric french study For Simon's 2-stage Optimal Design: 8 participating centers of the French National Group "Groupe de Cancérologie Cutanée". For the Extension stage: 10 participating centers of the French National Group "Groupe de Cancérologie Cutanée"
Research period	Simon's 2-stage Optimal Design: (29 months) Duration of inclusion: 18 months Duration of participation (treatment and follow up): 11 months maximum (1 month of selection, 6 months (8 cycles) of treatment that can be extended up to 3 months in case of study delay due to AE that have been resolved,1 month of follow-up). Total duration: 29 months Extension Stage: (64 months) Duration of inclusion: 24 months Duration of participation (treatment and follow up): 40 months maximum (1 month of screening/inclusion period at most): - 24 months (35 cycles) of treatment that can be extended up to 3 months in case of study delay due to AE that have been resolved, - 12 months of follow- up. Maximum total duration (simon's 2-stage optimal design and the extension stage) : 93 months
Number of inclusions expected per centre and per month	Simon's 2-stage Optimal Design: AP-HP, Saint Louis: 6 AP-HP, Avicenne: 2 AP-HP Cochin: 2 AP-HP, Bichat: 2 CHRU de Lille: 1 Centre hospitalier Lyon sud: 2 CHRU Montpellier– Hôpital Saint-Eloi: 1 CHU Grenoble: 1 Extension Stage: AP-HP, Saint Louis: 8 AP-HP, Avicenne: 2 AP-HP Cochin: 1 AP-HP, Bichat: 2 CHRU de Lille: 1 Centre hospitalier Lyon sud: 2 CHRU Montpellier– Hôpital Saint-Eloi: 1 CHU Marseille : 1 CHU Toulouse : 1 CH Nice : 1
Statistical analysis	Simon's 2-stage Optimal Design: This is a multicenter uncontrolled phase II study, based on a 2-stage phase II Simon's Optimal Design.

	Sample size computation was based on statistical hypotheses with regards to treatment effect on the main endpoint, best overall response rate. With a 0.05 type I error and a 90% statistical power, the sample size was computed to assess whether the drug is inactive (partial+complete response probability π0<5%) or truly active (partial+complete response probability π1>30%). Based on our hypotheses, it was computed that 9 patients would be accrued in stage 1. If necessary inclusion will be stopped during 6 months after the 9th inclusion waiting for the primary endpoint. The trial will stop with conclusion of inactivity if no response is observed in this stage; otherwise, 8 additional patients will be recruited to a total sample size of 17 patients, with at least 3 responses to indicate that the drug is effective enough. In case an observed response before the end of stage 1 the stage 2 will directly begin withouit any stop. Extension Stage: Only the 20 patients included in the extension stage will be considered in this main analysis. With an expected complete best overall response rate (complete response, partial response) at 6 months of 14/20 (70%), we would obtain a 95%CI interval of the complete response rate equal to [46%;88%]. A secondary analysis will be performed on the 20 patients included in the extension stage plus the 17 patients included in the Simon's 2- stage Optimal Design. With an expected best overall response rate at 6 months of 26/37 (70.3%), this analysis will reach a 95%CI interval of the complete response rate equal to [53%;84%].
Funding source	MSD
Data Safety Monitoring Board anticipated	YES

2 SCIENTIFIC JUSTIFICATION for the research

Refer to the Investigator's Brochure for detailed background information on pembrolizumab.

2.1 Hypothesis for the study

The programmed cell death 1 (PD-1) pathway represents a major immune control switch which may be engaged by tumor cells to overcome active T-cell immune surveillance.
Pembrolizumab 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.

In Kaposi sarcoma (KS) few data are available on the role of PD1-PD-L1 axis. A significant PD-L1 expression on HHV8-associated pleural effusion lymphomas and on KS samples has been recently reported (1). Our experience in classical and endemic KS supports the role of this pathway with expression of PD-L1 by subpopulations of T cells but also NK cells in peripheral blood cells from these patients and expression of PD-L1 by tumor cells in KS lesions (Caillat-Zucman, submitted). Consequently the anti-PD1 antibody pembrolizumab may be useful to restore antitumoral immune response in KS.

2.2 Existing knowledge relating to the condition involved

Kaposi's sarcoma (KS) is characterized by a multifocal proliferation of lymphatic endothelium-derived spindle cells infected with an oncogenic virus, herpesvirus-8 (HHV-8) (2–4). Two major settings of KS should be distinguished from a clinical point of view. There are KS occurring in the context of immunosuppression-HIV associated KS and post-organ transplant KS. On the other hand classic and endemic KS occur in patients from the Mediterranean basin or Africa, outside of any established immunosuppression apart from immunosenescence and immunoevasion directly linked to HHV-8 infection (5,6).

The treatment of HIV associated or post-organ transplant KS relies on immune restoration with the help of anti-retroviral drugs for HIV patients and gradual minimisation of immunosuppressants +/- mTOR introduction for post-transplant KS, eventually associated to temporary chemotherapy (7).

By contrast, treatment of classic KS remains poorly codified since immunosenescence and HHV-8 induced immunoevasion are not yet amenable to specific management. This lymphangioproliferation usually occurs in elderly patients (mean age 68 years) and has a chronic evolution. It is generally indolent, with localized cutaneous lesions managed either by simple monitoring or local treatment such as radiotherapy whereas symptomatic visceral lesions are exception. In our experience around 20% of patients will experience progressive cutaneous extension with an increased number of skin lesions occasionally ulcerated and painful, and/or with the appearance of disabilating lymphedema. These more aggressive forms require systemic therapy. The treatment is then poorly codified. It is generally based on low myeloablative monochemotherapies (bleomycin, etoposide, vinblastine) and more recently, based on the experience gained on HIV associated KS, on the use of liposomal anthracyclins and weekly taxanes, with an objective response rate (mainly partial responses) ranging from 30 to 60% often unsustainable (8). Interferon alpha at small doses is effective in our experience in about 60% cases (prolonged partial responses), but this drug is often poorly tolerated in elderly patients (7).

Since classic and endemic KS are chronic diseases and since there is no curative therapy, evaluation of new targets are important. Moreover classic/endemic KS represent an ideal model for evaluating new drugs since patients do not receive concomitant immunosuppressive regimens nor antiviral therapies (8).

2.3 Summary of relevant pre-clinical and clinical trials

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells / FoxP3+ regulatory T-cells 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). 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. 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. Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells. 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. 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. 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. 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.

Modulation of expression of PD-1 and its receptors has been implicated in numerous settings involving persistent antigen stimulation, such as those derived from chronic infections and cancer. Expression of PD-1 by exhausted virus-specific T cells that are characteristic of chronic viral infections prevents the proliferation and function of virus- specific effector T cells and clearance of the virus (9,10). Blocking the PD-1 pathway in vitro or in vivo revives exhausted CD8 T cells in chronically infected mice, primates and humans, identifying this pathway as a key therapeutic target. Recently, PD-1 pathway inhibitors were demonstrated to have a profound positive effect on advanced melanoma and other non virus associated cancers in human (11,12). In virus-associated cancers, pembrolizumab was very recently shown to be effective in Merkel cell carcinoma (13), and studies are ongoing in head and neck cancers (14,15).

2.4 Description of the population of trial participants and justification for this choice of subject

Kaposi sarcoma (KS) is an angiogenic tumor linked to the infection by Human Herpes Virus 8 (HHV-8). Endemic and classical KS are observed in elderly patients and more often the evolution is indolent; nevertheless in some patients extensive cutaneous and visceral manifestations are observed leading to systemic chemotherapy. This latter is not firmly codified and partial responses are observed only in 30% to 60% patients; in addition chemotherapy as interferon alpha is not well tolerated. Therefore evaluation of other drugs is necessary for the treatment of classic and endemic KS. Moreover classic/endemic KS

represents an ideal model for evaluating new drugs since patients do not receive concomitant immunosuppressive regimens nor antiviral therapies.

2.5 name and description of the investigational medicinal product ation or medications

Pembrolizumab (previously known as MK-3475) 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. This blockade enhances functional activity of the target lymphocytes to facilitate tumor regression and ultimately immune rejection.

2.6 Description and justification of the dosage, route of administration, administration schedule and treatment period.

Pembrolizumab will be administered intraveinously every 3 weeks, at the dose of 200 mg per infusion (see Chapter 7).
Pharmacokinetic data analysis of pembrolizumab showed a typical profile as other IgGmAbs with a half-life of 2 to 3 weeks. Pharmacodynamic data suggested that peripheral target engagement is durable (>21 days). This early PK and pharmacodynamic data provides scientific rationale for testing a Q3W dosing schedule.
The choice of the 200 mg Q3W as an appropriate fixed dose is based on simulations performed using the population pharmacokinetic model of pembrolizumab showing that the fixed dose of 200 mg every 3 weeks will provide exposures that 1) are optimally consistent with those obtained with the 2 mg/kg dose every 3 weeks, 2) will maintain individual patient exposures in the exposure range established in melanoma as associated with maximal efficacy response and 3) will maintain individual patients exposure in the exposure range established in melanoma that are well tolerated and safe.

The per protocol treatment duration is fixed to :

Simon’s 2 stages Optimal Design: 6 months (8 cycles).

Extension stage: 24 months (35 cycles)

In case of severe adverse event or according to investigator decision, treatment will be stopped. In case of progression, treatment could be continued to allow delayed response after consultation with the principal investigator of the center and the investigator coordinator and patient information.

After at least 6 months of Pembrolizumab treatment, if the complete response is observed for at least 2 further cycles of Pembrolizumab, the Pembrolizumab will be stopped (for the Extension stage).

2.7 Summary of the known and foreseeable benefits and risks for the Clinical Trial participants

If pembrolizumab has some effect in the regression of classic and endemic KS, the benefit of the drug will be further evaluated on larges series.

2.8 Justification of the extension stage

Evidence of the efficacy of treatment with Pembrolizumab on the first 17 patients (Simon’s 2 stages Optimal Design) could be shown with 71% of patients having achieved a complete or partial response during 6 months of treatment. Many studies (especially on melanoma) have shown that complete responses are more durable than partial responses. Given these encouraging results, we

wonder whether extending the duration of treatment beyond 6 months to a maximum duration of 24 months would increase the number of complete responses.

This extension of the protocol also plans to extend the use of this molecule to a larger number of French centers (the inclusions of the first part of the study having been carried out mainly in Paris).

3 OBJESTIVES

3.1 Primary objective

Simon's 2 stages Optimal Design :

The main objective is to assess whether pembrolizumab/KEYTRUDA® is clinically inactive (partial+complete response probability π_0<5%) or truly active (partial+complete response probability π_1>30%) in classic and endemic Kaposi's sarcoma, using the Simon's 2 stage Optimal Design.

Extension stage:

In case of truly active conclusion of the Simon's 2 stages Optimal Design, an extension stage would be performed. 20 more patients will be included to assess with a greater precision the estimation of the treatment effect at 6 months. The primary endpoint of this stage will be the Best overall response rate according to the ACTG criteria.

3.2 Secondary objectives (Simon's 2-stage Optimal Design and Extension Stage)

We want to explain the efficacy of pembrolizumab/KEYTRUDA® and measure the pharmacodynamics of this drug. We will also assess the safety of pembrolizumab/KEYTRUDA®.

3.3 Objective og any future ancillary study (Simon's 2- stage Optimal Design and Extension Stage)

Collateral research will be performed to measure the pharmacodynamics of pembrolizumab/KEYTRUDA®.

An immunomonitoring will be based on sequential tumor biopsies and peripheral blood in order to:
- Characterize the immune tumor infiltrate (immune cells quantification, immune check points expression) and the expression of PDL1/2 on tumor cells before and after treatment
- Analyze the immunomodulation (T and NK cells) induced by the treatment
- Identify immune markers of clinical response to the treatment.

During treatment, the HHV8 viral load and the HHV8 expression profiles will be monitored in blood and tumor cells.

4 STUDY DESIGN

4.1 Concise description of the primary and secondary endpoints of the Simon's 2 stages Optimal Design

4.1.1 Primary endpoint

The primary endpoint will be the Best Overall Response Rate (BORR) defined by the occurrence of complete response or partial response following ACTG criteria recorded from the start of treatment until 6 months or the beginning of any other specific systemic therapy for KS if it occurs before 6 months.

Refer to Section 8.1 Descripton of parameters of efficacy.

4.1.2 Secondary endpoint

Secondary objectives are:
- To assess the safety profile of pembrolizumab/KEYTRUDA® in classic and endemic KS,
- To characterize the efficacy of pembrolizumab/KEYTRUDA®.

(1) **Efficacy endpoints**
Different aspects of clinical response will be evaluated:

1. Best overall response rate according to Physical Global Assessment (PGA) score until 6 months or the beginning of any other specific systemic therapy for KS if it occurs before 6 months.
2. Response rate at Month 3 and Month 6 according to ACTG and PGA criteria
3. Response rate on number of lesions at Month 3, Month 6 and at best response as defined following ACTG criteria
4. Response rate on the size of target lesions at Month 3, Month 6 and at best response as defined following ACTG criteria
5. Response rate on tumor infiltration of target lesions at Month 3, Month 6 and at best response as defined following ACTG criteria
6. Response rate on lymphedema (circumference, scale of 0 (absence) to 3 (painful or oozing)) at Month 3, Month 6 and at best response as defined following ACTG criteria
7. Time to response defined as the time to first response recorded from the start of treatment
8. Time to progression
9. Duration of response defined as the time from starting response to progression in patients achieving partial or complete response

(See Chapter 8.1 for ACTG and PGA criteria)

(2) **Safety endpoints**
Safety will be assessed in terms of drug toxicity evaluated by clinic and on laboratory parameters, and scored according to Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 (http://ctep.cancer.gov/reporting/ctc.html) during all the study.

(3) Pharmacodynamic and virological analyses
The immunological sub-study will include:
- Characterization of the tumor microenvironnement by immunohistochemistry: immune cells infiltration (quantification of CD3, CD4, CD8 T cells and CD56 NK cells, analysis of their expression of PD1 and other immune check points); markers of cytotoxicity (granzyme); expression of PDL1/2 on tumor cells.

- Analysis of the immunomodulation induced by the treatment on peripheral blood: T cells (CD4, CD8, anti-HHV-8 T cells) and NK cells phenotypes (flow cytometry, PBMCs: activation, exhaustion, immune check point expression); blood inflammation markers (luminex, plama).

Virological analyses:
The HHV8 viral load will be quantified in blood and tumor sample using quantitative real time PCR.
Polymerase chain reaction amplification assay for HHV-8 DNA detection will be performed using on whole blood and biopsy specimens. DNA will be extracted using a DSP DNA Mini kit on a QiaSymphony system (Qiagen, Courtabeuf, France). Real-time quantitative amplification will be carried out on a ABI 7500 system (Perkin Elmer Applied Biosystems, Foster City, California). Dilutions of known amounts (10-10^7 copies) of a fragment of viral DNA cloned into a plasmid were used to establish a standard curve. HHV-8 loads will be normalized according to the quantity of cells present in the sample by the quantification of Albumin gene using a real time PCR assay.

HHV8 expression profiles will be determined on samples with loads above 4 log10 copies/10^6 cells using a micro-array targeting all KHV gene transcripts as described (16).
For expression analysis, biopsy samples will be stored in RNAprotect medium right after collection and blood samples will be collected in PAXgene tubes.

4.2 Concise description of the primary and secondary endpoints of the extension stage

4.2.1 Primary endpoint

The primary endpoint of this stage will be the best overall response rate according to the ACTG criteria recorded from the start of treatment until 24 months or the beginning of any other specific systemic therapy for KS if it occurs before 6 months.
Refer to Section 8.1 Description of parameters of efficacy and notably the complete response definition

4.2.2 Secondary endpoints

(1) Efficacy endpoints
Different aspects of clinical response will be evaluated:

1. Best overall response rate according to ACTG and PGA criteria at Month 9, Month 12, Month 18 and Month 24 months or the beginning of anyother specific systemic therapy for KS if it occurs before 6 months.
2. Best overall response rate according to Physical Global Assessment (PGA) score until 6 months or the beginning of any other specific systemic therapy for KS if it occurs before 6 months.
3. Response rate (Complete response + Partial response and complete response), at Month 3,Month 6, Month 9, Month 12, Month 18 and Month 24 according to ACTG and PGA criteria
4. Response rate on number of lesions at Month 3, Month 6, Month 9, Month 12 and Month 24 atbestresponse as defined following the PGA
5. Response rate on the size of target lesions at Month 3, Month 6, Month 9 Month 12 and Month 24atbest response as defined following the PGA
6. Response rate on tumor infiltration of target lesions at Month 3, Month 6, Month 9 Month 12andMonth 24 at best response as defined following the PGA
7. Response rate on lymphedema (circumference, scale of 0 (absence) to 3 (painful or oozing)) atMonth 3, Month 6, Month 12 and Month 24 at best response as defined following the PGA
8. Time to response defined as the time to first response recorded from the start of treatment
9. Time to progression defined as the time from starting treatment to progression in all patients

10. Duration of response defined as the time from starting response to progression in patients achieving partial or complete response
11. Quality of life following the QLC-30 and DLQI_Kaposi at baseline, Cycle 5 – Cycle 10 – Cycle 15… every 3 months and EOT (Early Study Termination or at months 24)

(See Chapter 8.1 for ACTG and PGA criteria)

(2) Safety endpoints

Safety will be assessed in terms of drug toxicity evaluated by clinic and on laboratory parameters, and scored according to Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 (http://ctep.cancer.gov/reporting/ctc.html) during all the study.

(3) Pharmacodynamic and virological analyses

The immunological sub-study will include:

- Characterization of the tumor microenvironnement by immunohistochemistry: immune cells infiltration (quantification of CD3, CD4, CD8 T cells and CD56 NK cells, analysis of their expression of PD1 and other immune check points); markers of cytotoxicity (granzyme); expression of PDL1/2 on tumor cells.
- Analysis of the immunomodulation induced by the treatment on peripheral blood: T cells (CD4, CD8, anti-HHV-8 T cells) and NK cells phenotypes (flow cytometry, PBMCs: activation, exhaustion, immune check point expression); blood inflammation markers (luminex, plama).

Virological analyses:

The HHV8 viral load will be quantified in blood and tumor sample using quantitative real time PCR. Polymerase chain reaction amplification assay for HHV-8 DNA detection will be performed using onwhole blood and biopsy specimens. DNA will be extracted using a DSP DNA Mini kit on a QiaSymphonysystem (Qiagen, Courtabeuf, France). Real-time quantitative amplification will be carried out on a ABI 7500 system (Perkin Elmer Applied Biosystems, Foster City, California). Dilutions of known amounts (10-10^7 copies) of a fragment of viral DNA cloned into a plasmid were used to establish a standard curve.HHV-8 loads will be normalized according to the quantity of cells present in the sample by the quantification of Albumin gene using a real time PCR assay.

HHV8 expression profiles will be determined on samples with loads above 4 log10 copies/10^6 cells usinga micro-array targeting all KHV gene transcripts as described (16).

For expression analysis, biopsy samples will be stored in RNAprotect medium right after collection andblood samples will be collected in PAXgene tubes.

4.3 Description of research methodology

4.3.1 Design of the Simon's 2 stages Optimal stage

This is a multicenter non-randomized phase II study.
Patients will receive pembrolizumab/KEYTRUDA® 200 mg IV every 3 weeks for 8 cycles.

4.3.2 Design of the Extension stage

Patients will receive pembrolizumab/KEYTRUDA® 200 mg IV every 3 weeks for 35 cycles.

4.3.3 Number of participating sites

This is a multicentric French National study
Number of centers:

- For the the Simon's 2-stage Optimal stage: 8
- For the Extension stage: 10

Recruitement and treatment delivery will be performed in an out patient basis in the dermatology departments

4.3.4 Identification of participants

For this Clinical Trial, each patient is identified by a Subject Number (Subject No) that is assigned when the patient has signed the Study Informed Consent Form and is retained as the unique reference for the patient throughout his/her entire participation in the trial.
The Subject No consists of the:
Site Number (3 numerical positions) - the patient inclusion number (4 numerical positions) - and patient's initials (surname initial - first name initial)
The allocation of the Subject No will be allocated using the eCRF web site.

5 IMPLEMENTATION OF THE STUDY

The start of a clinical trial is defined as the inclusion of the first patient.

'Start of a clinical trial' means the first act of recruitment of a potential subject for a specific clinical trial, unless defined differently in the protocol. In most cases, we will considerer that start of the CT = Start of recruitement = First inclusion but it can be adapted if necessary

5.1 Screening and inclusion visit

The selection visit takes place between 5 working days and 1 month before the day 1 of therapy. Patients will be managed in the dermatology departments or in hospitalization.

Once a patient is selected and consent is signed, a "Patient Selection Form" will be sent to SBIM (Service de biostatistique et informatique médicale). The allocation of identification number will be handled by the statistical data centre (this identification number will be retained for the entire research).

participants whose consent is sought	Who informs the subject and collects their consent	When is the subject informed	When is the subject's consent collected
Patient	Investigator or qualified designee	Selection visit	Minimum 48 hours after information

Patients will be evaluated against study inclusion and non-inclusion criteria.

For collection of subject's consent, see Chapter 14.1.

Medical history and medications
The investigator or qualified designee will review a medical history including active or recent conditions that are considered to be clinically significant, prior medication taken by the subject within 28 days before starting the trial, and concomitant medications

Disease details
The investigator or qualified designee will obtain prior and current details regarding KS status: date of diagnosis, date and results of the cutaneous biopsy that confirmed the diagnosis, disease stage and all prior KS treatments including surgeries, radiation and systemic treatments.

Clinical Assessments
- Height, weight and ECOG Performance Scale will be checked.
- A complete physical examination will be performed and will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, peripheral vascular system and neurologic system. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed.
- Target lesions and lymphodèmes: The investigator must number the target lesions and keep the same numbered lesions for each evaluation. The same applies to lymphodesmata. Assessment of the disease as described Section 8.2 Methods for measuring, collecting and analysing the parameters for assessing efficacy.
- photos of numbered target lesions should be taken at screening (baseline) and at each assessment
- Quality of life assessment (QLQ-C30)

Laboratory tests
Following blood samples will be assessed:
- *Blood samples:*

Haematology: WBC count plus differential (total neutrophil including bands, lymphocyte, monocyte, eosinophil, basophil and other counts), RBC count, haemoglobin, haematocrit and platelet count
Clinical chemistry: Sodium, potassium, chloride, bicarbonate, total calcium, inorganic phosphate, magnesium, urea or blood urea nitrogen (BUN), creatinine, creatinine clearance, glycemia, bilirubin (total, indirect and direct), AST, ALT, alkaline phosphatase.
Other: TSH, T3, T4.
All patients will have a serology HIV (HIV1/2 antibodies), and all females of childbearing potential will have a serum pregnancy test.

- *Urinary samples*:

Blood, glucose, protein.

Imaging
For patients with visceral disease, radiologic studies could be performed at baseline as standard of care. Ultrasounds, CT scan, TEP scan and/or gastro intestinal endoscopy will be performed upon investigator choice.
For patients with cutaneous involvement only, no systematic imaging exams are required.

When the patient is considered eligible for inclusion in the study, the investigator will complete the eCRF and validate the inclusion.

5.2 Beginning of treatment

Patient receives **the first infusion of pembrolizumab**/KEYTRUDA® at visit Day 1 of cycle 1.

- **Clinical assessments will include**

- Height, weight and ECOG Performance Scale
- Assessment of the disease as described Section 8.2 Methods for measuring, collecting and analysing the parameters for assessing efficacy.
- Colour photography of Kaposi target lesions and any other relevant skin lesions will be taken.

- **AE monitoring**

The investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs. Adverse experiences will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 5.0 (refer to section 18.5.2).

Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment

- **Laboratory procedures**

will be performed prior to infusion if they have been made over 72 hours. Results must be reviewed by the investigator or qualified designee and found to be acceptable prior to infusion.

  - *Blood samples:*

Haematology: WBC count plus differential (total neutrophil including bands, lymphocyte, monocyte, eosinophil, basophil and other counts), RBC count, haemoglobin, haematocrit and platelet count
Clinical chemistry: Sodium, potassium, chloride, bicarbonate, total calcium, inorganic phosphate, magnesium, urea or blood urea nitrogen (BUN), creatinine, creatinine clearance ,glycemia, bilirubin (total, indirect and direct), AST, ALT, alkaline phosphatase.
Other: TSH, T3, T4.

  - *Urinary samples*:

Blood, glucose, protein.
All females of childbearing potential will have a urine pregnancy test. A positive urine pregnancy test requires immediate interruption of study treatment until serum β-HCG is performed and found to be negative. If positive, the patient must be discontinued from the study.

- **Imaging**

For patients with visceral disease, radiologic studies could be performed at baseline as standard of care. Ultrasounds, CT scan, TEP scan and/or gastro intestinal endoscopy will be performed upon investigator choice.
For patients with cutaneous involvement only, no systematic imaging exams are required.

- **Pharmacodynamic assessment**

A blood sample and a biopsy of a Kaposi lesion will be realized before the first dose of study drug (see Section 8.3.1 for detailed procedure).

5.3 Follow-up Visits

Patients will be evaluated at each cycle for toxicity up to 1 month after the last cycle.
Clinical response will be assessed at each cycle and until the end-of-study visit or the beginning of any other specific therapy for KS.
Pembrolizumab/KEYTRUDA® should be administered on Day 1 of each cycle after all assessments have been completed, and may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons. Treatment administration out of the 3-day window must be reported as a protocol deviation.

- **Clinical evaluation**

Clinical data are listed below:

- Vital signs, perfomance status
- Weight
- Physical examination similar to Cycle 1 visit
- Tumor assessment will be done at each cycle (refer to section 8.2).
- Colour photography of Kaposi target lesions and any other relevant skin lesions will be taken.

- **AE monitoring**

The investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs. Adverse experiences will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 5.0 (refer to section 18.5.2).

Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

- **Laboratory evaluation** will be done locally.

Laboratory procedures can be conducted up to 72 hours prior to infusion. Results must be reviewed by the investigator or qualified designee and found to be acceptable prior to each dose of trial treatment.

- *Blood samples:*

Haematology: WBC count plus differential (total neutrophil including bands, lymphocyte, monocyte, eosinophil, basophil and other counts), RBC count, haemoglobin, haematocrit and platelet count
Clinical chemistry: Sodium, potassium, chloride~~,~~ bicarbonate, total calcium, inorganic phosphate, magnesium, urea or blood urea nitrogen (BUN), creatinine, creatinine clearance, glycemia, bilirubin (total, indirect and direct), AST, ALT, alkaline phosphatase
Other: TSH, T3, T4.

- *Urinary samples*:

Blood, glucose, protein.
All females of childbearing potential will have a urine test during study treatment (every cycle). A positive urine pregnancy test requires immediate interruption of study treatment until serum β-HCG is performed and found to be negative. If positive, the patient must be discontinued from the study.

- **Pharmacodynamic assessment (after 2 cycles and after 6 cycles) for the Simon's 2 stagesOptimal design**

A blood sample (at cycle 3 and cycle 7) and a biopsy of a Kaposi lesion (at cycle 3) will be realized during follow-up (see Section 8.3.1 for detailed procedure).

- **Pharmacodynamic assessment (after 2 cycles and after 6 cycles) for the extension stage :**

- **For Saint Louis Hospital – APHP**

A blood sample (at cycle 1, cycle 3, cycle 7 and EOT /early Termination) and a biopsy of a Kaposi lesion (at cycle 1, cycle 3, cycle 7 if progression and EOT /early Termination)will be realized. A blood sample and biopsy will be realized during follow-up in case of progression (see Section 8.3.1 for detailed procedure).

- **For all centers:**

A biopsy of a Kaposi lesion (at cycle 1, cycle 3, cycle 7 if progression and EOT /early Termination) will be realized. A biopsy will be realized during follow-up in case of progression (see Section 8.3.1 for detailed procedure).

- **Imaging for the Simon's 2-stage Optimal design**

For patients with visceral disease, radiologic studies could be performed at Month 3 (+7days maximum), Month 6 (+7days maximum), and whenever clinically indicated to assess changes as required as standard of care. Ultrasounds, CT scan, TEP scan and/or gastro intestinal endoscopy will be performed upon investigator choice.
For patients with cutaneous involvement only, no systematic imaging exams are required.

- Imaging for the extension stage

For patients with visceral disease, radiologic studies could be performed at Month 3 (+7days maximum), Month 6 (+7days maximum), Month 9 (+7days maximum), Month 12 (+7days maximum), Month 18, Month 24 and whenever clinically indicated to assess changes as required as standard of care. Ultrasounds, CT scan,TEP scan and/or gastro intestinal endoscopy will be performed upon investigator choice.

For patients with cutaneous involvement only, no systematic imaging exams are required.

- **Quality of life assessment (QLQ-C30) at month 3 (Cycle5) for the Simon's 2 stages Optimaldesign.**

- **Quality of life assessment (QLQ-C30) and DLQI_Kaposi at month 3 (Cycle5), month 6 (cycle10) and month 12 (cycle 15) and month 24 for the Extension stage**

5.4 Last study visit

- For the Simon's 2 stage Optimal Design :

In case of planned end of treatment after 8 cycles: the end-of-study visit takes place 1 month after last trial drug administration.

- For the Extension stage :

In case of planned end of treatment after 35 cycles: the end-of-study visit takes place 12 month after last trial drug administration.

After at least 6 months and 2 further cycles of Pembrolizumab treatment, if CR is observed and confirmed for at least 1 month, the Pembrolizumab will be stopped. After stopping treatment, if patients progress, they may be eligible for up to additional cycles of Pembrolizumab. This re-treatment is only available if the study remains open and the participant meets the following conditions:

- Stopped initial study intervention after attaining an investigator determined confirmed CR based on cutaneous biopsy and :
  - Was treated with at least 8 cycles of study treatment before discontinuing treatment, and
- Received at least 2 treatments with pembrolizumab beyond the date when the initial CR was declared

- Experienced an investigator-determined disease progression after stopping initial treatment, and
    - No new anticancer treatment was administered after the last dose of study treatment, and
    - The participant meets all of the safety parameters listed in the inclusion criteria and none of the safety parameters listed in the exclusion criteria, and
    - The study is ongoing

If the patient meets all these criteria, he can be re-treated for a period of 1 year (or 17cycles)

In case of premature termination (refer to Section 6.4.1):
- For progression: the end-of-study visit takes place 1 month after last trial drug administration.
- For other cases of premature termination: the end-of-study visit takes place at 6 months from inclusion.

After premature cessation of traitement, every effort should be made to collect information regarding disease status until the start of new specific therapy for KS, disease progression or death.

The examinations scheduled for the end-of-study visit are:

- **Clinical evaluation** – idem 5.3 Follow-up visit
- **AE monitoring** – idem 5.3 Follow-up visit
- **Laboratory evaluation** – idem 5.3 Follow-up visit
- **Imaging** – idem 5.3 Follow-up visit
- **Pharmacodynamic assessment**

A blood sample and a biopsy of a Kaposi lesion will be realized (see Section 8.3.1 for detailed procedure).

- **Quality of life assessment (QLQ-C30)**

5.5 Expected length of participation and description of the chronology and duration of the study.

	Months
Length of Inclusion period	18 months for the Simon's 2 stages Optimal design 24 months for the extension stage
Duration of participation for each subject, of which:	
• Maximum period between Selection and enrolment	1 month
• Treatment period:	6 months for the Simon's 2 stages Optimal design 24 months for the extension stage The treatment period can be extended up to 3 months in case of study delay due to AE that have been resolved to grade 1
• Follow-up period:	1 for the Simon's 2 stages Optimal design

	12 months for the extension stage
Total study period:	29 months for the Simon's 2 stages Optimal design 64 months for the extension stage 93 (including 64 months for theextension stage)

5.6 Table summarising the chronology of the study

Table 1: Flow Chart

Flow Chart		Selection and Inclusion	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle5 (Month 3)	Cycle 6	Cycle 7	Cycle 8	**EOS (early termination or Month 7)**
Scheduling Window (Days):				± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3
Consent		X									
Physical exam	Visit	X	X	X	X	X	X	X	X	X	X
	Vital signs	X	X	X	X	X	X	X	X	X	X
	Photography		X	X	X	X	X	X	X	X	X
Standard assessment	Biology*	X	X	X	X	X	X	X	X	X	X
	Imaging **	X					X				X
	Pregnancy test (serum or urinary)	S	U	U	U	U	U	U	U	U	U
Pharmaco – Dynamics***	Blood sample		X		X				X		X
	Cutaneous biopsy		X		X						X
Quality of life		X					X				X
Treatment delivery			X	X	X	X	X	X	X	X	

EOS: end of study

* Biological testing performed at selection/inclusion and before each cycle will include:

- Blood samples: haematology (WBC count plus differential, RBC count, haemoglobin, haematocrit and platelet count), clinical chemistry (sodium, potassium, chloride, bicarbonate, total calcium, inorganic phosphate, magnesium, urea or blood urea nitrogen (BUN), creatinine, creatinine clearance, glycemia, bilirubin (total, indirect and direct), AST, ALT, alkaline phosphatase, and TSH, T3, T4.
- Urine samples: blood, protein glucose, and urine pregnancy test for women with childbearing potential.

An additional blood testing including HIV1/2 antibodies detection and a serum pregnancy test will be added at selection.

** For patients with visceral involvement at baseline, radiologic exams could be performed every 3 months (+7days maximum), as standard of care. Ultrasounds, CT scan, TEP scan and/or gastro intestinal endoscopy will be performed as needed upon investigator choice. For patients with cutaneous involvement only, no systematic imaging exams are required.

*** Blood samples and cutaneous biopsies will be collected (before infusion of pembrolizumab/KEYTRUDA®**)** (see Section 8.3.1 for detailed procedure).

Table 2: Flow Chart for the extension stage

Flow Chart		**Selecti on and Inclusi on**	**Cycle 1**	**Cycle 2**	**Cycle 3**	**Cycle 4**	**Cycle5 (Month 3)**	**Cycle 6**	**Cycle 7**	**Cycle 8a (Month 6)**	**Cycle 9**	**Cycle 10**	**Cycle 11**	**Cycle 12**	**Cycle 13 (Month 9)**	**Cycle 14**	**Cycle 15**	**Cycle 16**	**Cycle 17 (Month 12) to Cycle 35 (Month 24)**	**EOT (early Termination or onth 24)**
Scheduling Window (Days):				± 3	± 3	± 3	± 3	± 3	± 3	± 3										± 3
Consent		X																		
Physical exam	Visit	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
	Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
	Photography		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Standard assessment	Biology*	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
	Imaging **	X					X					X					X			X
	Pregnancy test (serum or urinary)	S	U	U	U	U	U	U	U	U	U	U	U	U	U	U	U	U	U	U
Pharmaco – Dynamics***	Blood sample		X		X				X											X
	Cutaneous biopsy		X		X				X[a]											X
Quality of life		X					X					X					X		X (every 3 months)	X
Treatment delivery			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

Flow Chart		FUP M3	FUP M6	FUP M9	FUP M12
Statut Vital		X	X	X	X
Pharmaco – Dynamics	Blood sample	X (if progres sion)	X (if progressio n)	X (if progressio n)	X (if progression)
Pharmaco – Dynamics	Cutaneous biopsy	X (if progression)	X (if progression)	X (if progression)	X (if progression)
Quality of life		X	X	X	X

EOT: end of treatment

* Biological testing performed at selection/inclusion and before each cycle will include:

- Blood samples: haematology (WBC count plus differential, RBC count, haemoglobin, haematocrit and platelet count), clinical chemistry (sodium, potassium, chloride, bicarbonate, total calcium, inorganic phosphate, magnesium, urea or blood urea nitrogen (BUN), creatinine, creatinine clearance, glycemia, bilirubin (total, indirect and direct), AST, ALT, alkaline phosphatase, and TSH, T3, T4.
- Urine samples: blood, protein glucose, and urine pregnancy test for women with childbearing potential.

An additional blood testing including HIV1/2 antibodies detection and a serum pregnancy test will be added at selection.

** For patients with visceral involvement at baseline, radiologic exams could be performed every 3 months (+7days maximum), as standard of care. Ultrasounds, CT scan, TEP scan and/or gastro intestinal endoscopy will be performed as needed upon investigator choice. For patients with cutaneous involvement only, no systematic imaging exams are required.

*** Blood samples and cutaneous biopsies will be collected (before infusion of pembrolizumab/KEYTRUDA®**)** (see Section 8.3.1 for detailed procedure).

[a] : After 6 months of Pembrolizumab treatment (Cycle 8)and 2 further cycles, if CR is observed and confirmed, the Pembrolizumab will be stopped. After stopping treatment, if patients progress, they may be eligible for up to anadditional cycles of Pembrolizumab. This re-treatment is only available if the study remains open and the participant meets the following conditions:

- Stopped initial study intervention after attaining an investigator determined confirmed CR based on cutaneous biopsy and :
  - Was treated with at least 8 cycles of study treatment before discontinuing treatment, and
  - Received at least 2 treatments with pembrolizumab beyond the date when the initial CR was declared
- Experienced an investigator-determined disease progression after stopping initial treatment, and
  - No new anticancer treatment was administered after the last dose of study treatment, and
  - The participant meets all of the safety parameters listed in the inclusion criteria and none of the safety parameters listed in the exclusion criteria, and
  - The study is ongoing

If the patient meets all these criteria, he can be re-treated for a period of 1 year (or 17 cycles)

5.7 Distinction between care and research

- **For the Simon's stage:**

Interventions, procedures and treatments carried out for research purposes	**Interventions, procedures and treatments associated with <u>standard care</u>**	**Interventions, procedures and treatments added for <u>research purposes</u>**
Treatment		Pembrolizumab/KEYTRUDA®
Consultations	KS patients treated by systemic therapies have at least one visit per month as required per protocol	
Blood samples	KS patients treated by systemic therapies have during treatment blood sampling every 1 to 3 weeks	Collection of blood samples during treatment HIV antibody detection at selection Pregnancy test at each cycle
Imaging, etc.	KS patients have as a rule at least one cutaneous biopsy	Cutaneous biopsy during treatment
Other		• **Quality of life assessment (QLQ-C30) at visit of selection/inclusion, month 3 (Cycle5) and EOS.**

Table 3: Distinction between procedures associated with "care" and procedures added because of the " Clinical Trial " in the Simon's stage

- **For the Extension stage:**

Interventions, procedures and treatments carried out for research purposes	**Interventions, procedures and treatments associated with <u>standard care</u>**	**Interventions, procedures and treatments added for <u>research purposes</u>**
Treatment		Pembrolizumab/KEYTRUDA®
Consultations	KS patients treated by systemic therapies have at least one visit per month as required per protocol	
Blood samples	KS patients treated by systemic therapies have during treatment blood sampling every 1 to 3 weeks	Collection of blood samples during treatment At Cycle 1, 3, 7 and end of traitement (or if progression) HIV antibody detection at selection Pregnancy test at each cycle

Cutaneous biopsy	KS patients have as a rule at least one cutaneous biopsy	Cutaneous biopsy during treatment: At Cycle 1, 3, 7 and end of traitement (or if progression)
Imaging	For patients with visceral involvement at baseline, radiologic exams could be performed every 3 months, as standard of care	
Other		• Quality of life assessment (QLQ-C30 and DLQI_Kaposi) at visit of selection/inclusion, month 3 (Cycle5), month 6 (cycle 10), month 9 (cycle 15), then every 3 months, and EOT (early Termination). • Quality of life assessment(QLQ-C30) at Follow up visit Month 3, month 6, month 9 and month 12

Table 4: Distinction between procedures associated with "care" and procedures added becauseof the" Clinical Trial " in the extension stage

5.8 Biological Collection

- For the Simon's 2 stages Optimal design :

A biological collection before the first dose of study drug, after 2 cycles (at cycle 3), after 6 cycles (at cycle 7) and at the end of study will be made for all patients.

The biopsies samples taken as part of the Clinical Trial will be included in a biological collection.

- For the Extension stage :

A biological collection before the first dose of study drug, after 2 cycles (at cycle 3), after 6 cycles (at cycle 7) and at the end of study will be made for all patients included in Saint Louis.

A biological collection during follow-up period (if progression) will be made for all patients. The biopsies samples taken as part of the Clinical Trial will be included in a biological collection.

Pharmacodynamic studies will be done:
- in Dr CAILLAT-ZUCMAN and CARCELAIN's laboratory (Immunology, AP-HP Hôpital Robert Debré, INSERM 1149 CRI, Paris) for all molecular assessments in blood samples
- in the Pathology Department, AP-HP Hôpital Saint-Louis, Paris, supervised by Dr BATTISTELLA for immuhistochemical analysis.
- Virological studies will be done under the supervision of Dr LE GOFF in the Virology Department, AP-HP Hôpital Saint Louis, Paris.

The samples may be used with the explicit agreement of the subject on the consent form for further analyses not included in the protocol including analysis of genetic and which could be beneficial for the pathology based on evolution in scientific knowledge.

At the end of the Clinical Trial , the samples will be preserved in Immunology Department (AP-HP, Hôpital Robert Debré, INSERM 1149 CRI (Dr CAILLAT ZUCMAN and Dr CARCELAIN), and in the Pathology Department (AP-HP, Hôpital Saint-Louis) (Dr BATTISTELLA). They will be preserved for 15 years and will be available only upon request of investigator.

The samples will be pseudonymised with a direct connection with the anonymisation process of recruited patients. The sample will be directly connected to the patient using initials and date of birth.

The sample bank will be declared to the relevant minister [and to the director of the competent regional health authority with local jurisdiction if the entity is a health establishment (Article L. 1243-3 of the CSP (French Public Health Code).

Type of sample	**Quantity**	**Storage location**	**Manager of the sample bank**	**Purpose of the sample bank**	**Storage period**	**End use/Future (e.g. destruction) after the end of the CT**
Simon's 2 stages Optimal design						
Blood	9 tubes (baseline, cycle 3, 7, end of study)	Immunology AP-HP Hopital Robert Debré	Dr CAILLAT-ZUCMAN and CARCELAIN	Further pharmacodynamics analyses	15 years	Research Destruction after 15 years
Tumor samples	2 blocks (baseline, cycle 3, end of study)	Pathology AP-HP Hopital Saint Louis	Dr BATTISTELLA	Further pharmacodynamics analyses	15 years	Research Destruction after 15 years
Extension Stage						
Blood (patients included in Saint Louis)	9 tubes (baseline, cycle 3, 7, end of study and during FUP period if progression)	Immunology AP-HP Hopital Robert Debré	Dr CAILLAT-ZUCMAN and CARCELAIN	Further pharmacodynamics analyses	15 years	Research Destruction after 15 years

Tumor samples	2 blocks (baseline, cycle 3, early Termination and during FUP period if progression)	Pathology AP-HP Hopital Saint Louis	Dr BATTISTELLA	Further pharmacodynamics analyses	15 years	Research Destruction after 15 years

6 ELIGIBILITY CRITERIA

6.1 Inclusion criteria

Study is proposed to classical and endemic Kaposi's patient with progressive disease, checking all of the following criteria:

- Classic or endemic histologically confirmed KS
- Progressive disease
- KS with more than 10 lesions or involving more than one limb segment or with involvement >3% body surface
- KS with at least 4 lesions ≥5mm
- KS with at least 1 other cutaneous tumor available for repeated pharmacodynamics evaluation and be willing to provide tissue from cutaneous biopsy of a tumor lesion
- At least 4 weeks washout for all KS specific therapies including chemotherapy and immunotherapy such as Interferon

In order to be eligible for participation in this trial, the subject must:

- Be willing and able to provide written informed consent for the trial.
- Be ≥ 18 years of age on day of signing informed consent.
- Have a performance status of 0 or 1 on the ECOG Performance Scale.
- Demonstrate adequate organ function as defined in **Table 5**.
- Have a health insurance

System	**Laboratory Value**
Hematological	
Absolute neutrophil count (ANC)	≥1000/mm^3
Platelets	≥100,000/mm^3
Hemoglobin	≥ 8 g/dL
Renal	
Calculated[a] creatinine clearance	≥ 30mL/min
Hepatic	

Serum total bilirubin	≤ 1.5 X ULN **OR** Direct bilirubin ≤ ULN for participants with total bilirubin levels > 1.5 ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 X ULN
[a]Creatinine clearance should be calculated using MDRD formula.	

Table 5: Adequate Organ Function Laboratory Values

- Female subject of childbearing potential should have a negative serum pregnancy within 72 hours prior to receiving the first dose of study medication, and a negative urine pregnancy test prior to receiving each other dose. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

6.2 Non-inclusion criteria

A subject will not be included in the study if he:

- Has a known history of organ transplantation
- Is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment.
- Has KS with symptomatic visceral involvement unless no other therapeutic option is available
- Previously received treatments with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CTLA4 antibody or any other antibody or drug specifically targeting T-cell costimulation or immune checkpoint pathways.
- Uncontrolled infection with HIV, HBV, or HCV infection; or diagnosis of immunodeficiency that is related to, or results in chronic infection.

  Patients with known hepatitis B (HepBsAg+) who have controlled infection (serum hepatitis B virus DNA PCR that is below the limit of detection AND receiving anti-viral therapy for hepatitis B) are permitted. Patients with controlled infections must

  undergo periodic monitoring of HBV DNA per local standards and must remain on anti-viral therapy for at least 6 months beyond the last dose of investigational study drug.

  Patients who are known HCV Ab+ who have controlled infection (undetectable HCV RNA by PCR either spontaneously or in response to a successful prior course of anti-HCV therapy) are permitted
- Has an active infection requiring systemic therapy.
- Has hypersensitivity to pembrolizumab/KEYTRUDA® or any of its excipients.
- Has had a prior anti-cancer monoclonal antibody (mAb) within last 4 weeks or who has not recovered (i.e., > Grade 1 at selection) from adverse events due to agents administered more than 4 weeks earlier.
- Has had prior chemotherapy, targeted small molecule therapy, or radiation therapy within 3 weeks (or 5 half lives) prior to study Day 1 or who has not recovered (i.e., > Grade 1 at selection) from adverse events due to a previously administered agent.
    - *Note: participants with ≤ Grade 2 neuropathy are an exception to this criterion and may qualify for the study.*

- *Note: If subject received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.*

- Has a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin or squamous cell carcinoma of the skin that has undergone potentially curative therapy or in situ cervical cancer.
- Has active autoimmune disease that has required systemic treatment in the past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (eg., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment. Patients with vitiligo, type I diabetes mellitus, hypothyroidism, psoriasis non requiring systemic treatment are permitted to enroll.
- Has active non-infectious pneumonitis or known history of non-infectious pneumonitis that required steroids, severe pulmonary disease or hypoxia
- Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.
- Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, or not willing to use adequate contraceptive methods from study Visit 1 throughout the study period up to 120 days after the last dose of study therapy (refer to Section 7.4).
- Has received a live vaccine within 30 days prior to the first dose of trial treatment. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine (refer to Section 7.2).

  Note: Seasonal influenza vaccines for injection are generally inactivated flu vaccines and are allowed; however intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines, and are not allowed.

- Is currently participating or has participated in a study(EC) of an investigational agent within 4 weeks of the first dose of treatment.
- Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.
- Patient under guardianship or curatorship

6.3 Recruitment procedure

Expected number of patients to be recruited by each centre is detailed in **Table 6** below.

- For the Simon's 2 stages Optimal design

	Number of participants
Total number of participants to be included	17
Number of centres	8
Enrolment period (months)	11
Number of participants/centre	2
Number of participants/centre/month	**0,1**

Expected number of patients eligible in the centers						
N°	Name	Surname	Town	Hospital	Expected recruitment/ month	Total
1	Celeste	Lebbe	Paris	Saint Louis – AP-HP	0 to 1	6
2	Brunet-Possenti	Florence	Paris	Bichat – AP-HP	0 to 1	2
3	Eve	Maubec	Bobigny	Avicenne – AP-HP	0 to 1	2
4	Nicolas	Dupin	Cochin	Bichat AP-HP	0 to 1	2
5	Laurent	Mortier	Lille	CHRU de Lille	0 to 1	1
6	Stéphane	Dalle	Lyon	Hôpital Lyon Sud	0 to 1	2
7	Bernard	Guillot	Montpellier	CHRU – Hôpital Saint-Eloi	0 to 1	1
8	Marie-Thérèse	Leccia	Grenoble	CHU Grenoble	0 to 1	1

- For the Extension stage:

	Number of participants
Total number of participants to be included	20
Number of centres	10
Enrolment period (months)	24
Number of participants/centre	2
Number of participants/centre/month	**0,1**

Expected number of patients eligible in the centers						
N°	Name	Surname	Town	Hospital	Expected recruitment/ month	Total
1	Celeste	Lebbe	Paris	Saint Louis – AP-HP	1 to 2	8
2	Brunet-Possenti	Florence	Paris	Bichat – AP-HP	1 to 2	2
3	Eve	Maubec	Bobigny	Avicenne – AP-HP	1 to 2	2
4	Nicolas	Dupin	Cochin	Bichat AP-HP	0 to 1	1
5	Laurent	Mortier	Lille	CHRU de Lille	0 to 1	1
6	Stéphane	Dalle	Lyon	Hôpital Lyon Sud	1 to 2	2
7	Olivier	Dereure	Montpellier	CHRU — HôpitalSaint-Eloi	0 to 1	1
~~8~~	~~Marie-Thérèse~~	~~Leccia~~	~~Grenoble~~	~~CHU Grenoble~~	~~0 to 1~~	~~1~~
9	Caroline	Gaudy	Marseille	CHU Marseille	0 to 1	1
10	Laurent	PAGES	Toulouse	IUCT Toulouse	0 to 1	1
11	Henri	Montaudie	Nice	CHU Nice	0 to 1	1

6.4 Termination rules

6.4.1 Termination rules for individual participants

6.4.1.1 Criteria and procedures for temporary suspension of the study treatment and continuation of the participation from the study

Temporary suspension of the treatment is allowed at all stages of the treatment, especially to recover from adverse events.
The treatment can be resumed once the adverse event has been resolved.
If, during the course of his/her participation in the study, the participant presents any of the adverse events described in section 7.3 and Table 7 (including exclusion criteria), the study product/procedure must be temporary discontinued but the participant will continue to be monitored for the study.

The investigator must document the reason for suspending and resuming the treatment in the participant's source file and the case report form (CRF).

The investigator must:

- Document the reason(s)
- Collect the assessment criteria at the time of temporary suspension of the study treatment

- Schedule a follow-up for the participant, particularly in case of a serious adverse event.

In a general point of view, dose adaptation or the non-administration of treatment due to the occurrence of toxicity does not lead to premature discontinuation of the study.

In the case of serious adverse events, the investigator must notify the sponsor and follow up the participant until the severe adverse events are resolved. Notification of a serious adverse event must be sent by email (eig-vigilance.drc@aphp.fr) to the sponsor. If a Data Safety Monitoring Board has been created, the committee can specify and/or validate the follow-up methods.

Dosing interruptions are permitted in the case of medical/surgical events or logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events). Participants should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor. Participants will resume treatment at the stopped cycle (no infusion deleted).The reason for interruption should be documented in the patient's study record.

<u>For the Simon's 2 stages Optimal stage</u>
The per protocol treatment duration is fixed to 6 months and can be extended up to 3 months in case of study delay due to AE that have been resolved (see 7.3). Pembrolizumab can be restarted up to 3 weeks after the theoretical date of administration.

<u>For the Extension stage:</u>

The per protocol treatment duration is fixed to 24 months and can be extended up to 3 more months in case of study delay due to AE that have been resolved (see 7.3). Pembrolizumab can be restarted at the discontinued cycle) up to 3 weeks after the theoretical date of administration.

In the event of treatment cycles being postponed for various reasons, the assessments with protocol examinations initially planned should not be postponed.

After at least 6 months of Pembrolizumab treatment (Cycle 8) and 2 further cycles, if CR is observed and confirmed, the Pembrolizumab will be stopped.

6.4.1.2 Criteria and procedure for definitive withdrawal of the study treatment and continuation of the participation from the study

If, during the course of his/her participation in the study, the participant presents one of the following events, then the study product/procedure must be definitively discontinued but the participant will continue to be monitored for the study except in the situations described below (see section 6.4.1.3).

- The subject withdraws consent.
- Unacceptable adverse events as described in Section 7.3 and Table 7
- Intercurrent illness that prevents further administration of treatment
- Investigator's decision to withdraw the subject
- The subject has a confirmed positive serum pregnancy test
- The subject is lost to follow-up
- Completed 6 months (8 cycles for the Simon's 2 stages Optimal design) or 24 months (35 cycles for the Extension Stage) of uninterrupted treatment with pembrolizumab/KEYTRUDA® The

treatment duration can be extended up to 3 months in case of study delay due to AE that have been resolved
Note: study medication is calculated from the date of first dose.

In case of progression, treatment could be continued to allow delayed response after consultation with the principal investigator of the center and the investigator coordinator and patient information.

After 6 months of Pembrolizumab treatment (Cycle 8) and 2 further cycles, if CR is observed and confirmed, the Pembrolizumab will be stopped. After stopping treatment, if patients progress, they may be eligible for up to additional cycles of Pembrolizumab. This re-treatment is only available if the study remains open and the participant meets the following conditions:

- Stopped initial study intervention after attaining an investigator determined confirmed CR based on cutaneous biopsy and:
  - Was treated with at least 8 cycles of study treatment before discontinuing treatment, and
  - Received at least 2 treatments with pembrolizumab beyond the date when the initial CR was declared
- Experienced an investigator-determined disease progression after stopping initial treatment, and
  -No new anticancer treatment was administered after th
  -The study is ongoing
  If the patient meets all these criteria, he can be re-treated for a period of 1 year (or 17 cycles e last dose of study treatment, and
  -The participant meets all of the safety parameters listed in the inclusion criteria and none of the safety parameters listed in the exclusion criteria, and)

In case of serious adverse events, the investigator must notify the sponsor and follow up the participant until the serious adverse events are resolved.

If a participant withdraws prematurely the study treatment, and if the participant agrees, follow-up visits will be made in accordance with the schedule described in section 5.4 to collect study endpoints, except in the case of withdrawal of consent and loss to follow-up. The participant will receive the most appropriate care in the opinion of the investigator.

6.4.1.3 Criteria and procedure for exit the study

- Participants may exit the study at any time and for any reason.
- The investigator can permanently withdraw a participant from the study for any safety reason or if it is in the participant's best interests.
- If a participant exits the study prematurely and whether or not to withdraw consent, any data collected prior to the date of premature exit may still be used.
- If a participant exits the study prematurely, withdraws consent and objects to the use of his/her data, any data collected prior to the date of premature exit may still be used.
- In case of serious adverse events, the investigator must notify the sponsor and follow up the participant until the severe adverse events are resolved.

The case report form must list the various reasons why the participant has discontinued the study:

- ☐ Lack of efficacy
- ☐ Adverse reaction
- ☐ Another medical issue
- ☐ Personal reasons of the participant
- ☐ Explicit withdrawal of consent

☐ Lost to follow-up

If a participant withdraws prematurely from the study, and if the participant agrees, follow-up visits will be made in accordance with the schedule described in section 5.4 to collect study endpoints, except in the case of withdrawal of consent and loss to follow-up. The participant will receive the most appropriate care in the opinion of the investigator.

Participant lost to follow-up: the participant cannot be located. The investigator must make every effort to reconnect with the participant (and document his attempts in the source file), at least to determine whether the participant is alive or dead

6.4.2 Termination rules for the clinical trial : Full or partial discontinuation of the clinical trial

AP-HP as sponsor or the Competent Authority can prematurely terminate all or part of the trial, temporarily or permanently, in the following situations:

- First, if suspected unexpected serious adverse reactions (SUSARs) are observed, requing a reassessment of the benefit-risk ratio for the trial.
- if an interim analysis: according to the protocol, this analysis is planned when 9 patients are included and the trial will stop if no efficacy is observed (see section 12.1 related to the interim analysis).

Similarly, AH-HP, as the sponsor, or the Competent Authority may prematurely cancel the trial due to the discovery of unexpected facts or new information about the product, in light of which the objectives of the study or clinical programme are unlikely to be achieved

AP-HP as sponsor reserves the right to permanently suspend inclusions at any time if it the enrolment targets have not been met

If the study is prematurely discontinued for safety reasons, the decision and justification will be provided by the sponsor (AP-HP) to the Competent Authority and to the Ethics Committee without undue delay but not later than in 15 days of the date of the temporary halt or early termination. It shall include the reasons for such action and specify follow-up measures, along with recommendations from the Data Safety Monitoring Board in the case of substantial modification.

7 TREATMENT ADMINISTERED TO STUDY PARTICIPANTS

7.1 Description of The investigational medicinal product

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

Pembrolizumab/KEYTRUDA® will be labelled according to the regulatory requirements in France (DL13 of Good Manufacturing Practices). The Sponsor will provide labelled Pembrolizumab/KEYTRUDA® vials for investigational use only.

Use in their market authorization indication

- **Storage and accountability**

Pembrolizumab/KEYTRUDA® will be supplied by Clinical Trial Department of the Agence Générale des Produits de Santé (DEC AGEPS), Assistance Publique-Hôpitaux de Paris.. Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label.
Receipt and dispensing of trial medication must be recorded by an authorized person.
Clinical supplies may not be used for any purpose other than that stated in the protocol.
The investigator is responsible for keeping accurate records of the clinical supplies received from AGEPS, the amount dispensed to the participants and the amount remaining at the conclusion of the trial.
Upon completion or termination of the study, all unused and/or partially used investigational product will be returned to DEC AGEPS

- **Treatment administration**

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

Pembrolizumab /KEYTRUDA® will be administered intraveinously at the dose of 200mg every 3 weeks on an outpatient basis. It should be administered on Day 1 of each cycle after all assessments have been completed, and may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons. Treatment administration out of the 3-day window must be reported as a protocol deviation.

If treatment was stopped due to adverse event, participants should be placed back on study therapy within 3 weeks of the interruption, unless otherwise discussed with the Sponsor.

Participants will resume treatment at the stopped cycle (no infusion deleted).

The reason for interruption should be documented in the patient's study record.

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).

- **Treatment duration for the Simon’s 2 stages Optimal design**

The per protocol treatment duration is fixed to 6 months and can be extended up to 3 months in case of study delay due to AE that have been resolved (see 7.3). Pembrolizumab can be restarted up to 3 weeks after the theoretical date of administration.

- **Treatment duration for the extension stage**

The per protocol treatment duration is fixed to 24 months and can be extended up to 3 more months incase of study delay due to AE that have been resolved (see 7.5). Pembrolizumab can be restartedup to 3 weeks after the theoretical date of administration. After 6 months and lasting 2 further cycles of Pembrolizumab treatment,

if the complete response is observed during 1 month, the Pembrolizumab will be stopped.

After 6 months of Pembrolizumab treatment (Cycle 8) and lasting for a least 2 further cycles, if CR is observed and confirmed, the Pembrolizumab will be stopped. After stopping treatment, if patients progress, they may be eligible for up to additional cycles of Pembrolizumab. This re-treatment is only available if the study remains open and the participant meets the following conditions:

- Stopped initial study intervention after attaining an investigator determined confirmed CR basedon cutaneous biopsy and :
  - Was treated with at least 8 cycles of study treatment before discontinuing treatment, and
  - Received at least 2 treatments with pembrolizumab beyond the date when the initial CR was declared
- Experienced an investigator-determined disease progression after stopping initial treatment, and
  - No new anticancer treatment was administered after the last dose of study treatment, and
  - The participant meets all of the safety parameters listed in the inclusion criteria and none of the safety parameters listed in the exclusion criteria, and
  - The study is ongoing

If the patient meets all these criteria, he can be re-treated for a period of 1 year (or 17 cycles)

- **Dose Modification**

  Adverse events (both non-serious and serious) associated with pembrolizumab exposure may represent an immunologic etiology.

  Pembrolizumab/KEYTRUDA® must be withheld for drug-related toxicities and severe or life-threatening AEs. as per **Table 7** in Section 7.3. These guidelines could be modified if required upon local investigator choice, after discussion with the investigator coordinator.

  See Section 7.3 for supportive care guidelines, including use of corticosteroids.

- **Trial Blinding**

This is an open-label trial; therefore, the Sponsor, investigator and subject will know the treatment administered.

7.2 Description of traceability elements accompanying the investigational medicinal product(s)

The experimental product will be supplied by AP-HP. DEC- AGEPS insures the labeling and distribution to the study sites.
In each site, the pharmacist will insure that medicinal products are stored following the recommendation storage conditions in accordance with applicable regulatory requirements.
To insure adequate records, medicinal products will be accounted in the drug accountability inventory forms as instructed by AP-HP in the pharmacy annex.
At the end of the clinical trial all unused drug supplies will be destroyed by each study site after AP-HP authorization. For more details see the pharmacy annex.

7.3 Authorised and prohibited treatments(medicinal, additional medicinal, surgical), including rescue medications

7.3.1 Prohibited comedications

Medications or vaccinations specifically prohibited in the non-inclusion criteria are not allowed during the ongoing trial (see Section 6.2).

Prohibited concomitant medications during the selection and treatment phase are following:

- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. Chronic corticosteroids are not allowed.
- Immunosuppressive therapy
- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy
- Investigational agents other than pembrolizumab/KEYTRUDA®
- Radiation therapy
    - Note: Radiation therapy to a symptomatic solitary lesion may be allowed at the investigator's discretion.
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine.

If there is a clinical indication for a medication or vaccination specifically prohibited during the trial, discontinuation from trial therapy may be required. The investigator should discuss any questions regarding this with the principal investigator. The final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician.

7.3.2 Authorised comedications

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, respectively during the inclusion and end-of-treatment visit.

7.4 Methods for monitoring compliance with the treatment

Treatment administration will be done during hospitalization and compliance will be monitored.
Nurses will complete a booklet to record administration. In the booklet, the nurses will note every injection and it will be kept in the patient's medical records and the data collated in the eCRF.

7.5 Management of adverse events and rescue medication

Participants should receive appropriate supportive care measures as deemed necessary by the treating investigator.
Suggested supportive care measures for the management of adverse events with potential immunologic etiology are 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, and could be modified if required upon local investigator choice, after discussion with the investigator coordinator. Study treatment modifications are listed in **Table 7**.

Note: if after the evaluation the event is determined not to be related, the investigator does not need to follow the treatment guidance (as outlined below).

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

- **Pneumonitis**:
    - For **Grade ≥2**, systemic corticosteroids (0.5-1 mg/kg of equivalent prednisone) are required. When symptoms improve to Grade 1 or less, steroid taper should be started.
    - Add prophylactic antibiotics for opportunistic infections in the case of prolonged steroid administration.
    - For pembrolizumab suspension/permanently discontinuation, refer to Table 7 below.

- **Diarrhea/Colitis**: participants should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus).
    - All participants who experience 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. **For Grade 2 or higher diarrhea**, consider GI consultation and endoscopy to confirm or rule out colitis.
    - For **Grade 3 or 4 diarrhea/colitis**, treat with oral corticosteroids (0,8-2 mg/kg of equivalent prednisone).
    - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
    - For pembrolizumab suspension/permanently discontinuation, refer to Table 7 below.

- **Type 1 diabetes mellitus** (if new onset, including diabetic ketoacidosis) **or ≥ Grade 3 Hyperglycemia**, if associated with ketosis (ketonuria) or metabolic acidosis.
    - Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria.
    - Evaluate patients with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.
    - Pembrolizumab may be continued (refer to Table 7 below).

- **Hypophysitis**:
    - For **Grade 2** events, Replacement of appropriate hormones may be required.
    - For **Grade 3-4** events, treat systemic corticosteroids if necessary. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required.
    - Pembrolizumab may be continued after tapering steroids (refer to Table 7 below).

- **Hyperthyroidism or Hypothyroidism**: Thyroid disorders can occur at any time during treatment. Monitor patients for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders.
    - **Grade 2** hyperthyroidism events (and **Grade 2-4** hypothyroidism):
        - In hyperthyroidism, non-selective beta-blockers (e.g. propranolol) are suggested as initial therapy.
        - In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyroinine, is indicated per standard of care.
    - **Grade 3-4** hyperthyroidism
        - Replacement of appropriate hormones may be required.
        - Pembrolizumab may be continued after tapering steroids (refer to Table 7 below).
- **Hepatitis**:
    - Hepatitis can occur during treatment. Monitor patients for liver function tests (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation). Other causes of hepatitis must be ruled out.
    - For **Grade 2** events, monitor liver function tests more frequently until returned to grade 1 (consider weekly).
    - For **Grade 3-4** events, treat with systemic corticosteroids (1-2 mg/kg of equivalent prednisone).
    - When symptoms improve, a steroid taper should be started and continued over no less than 4 weeks.
    - For pembrolizumab/KEYTRUDA® suspension/permanently discontinuation, refer to Table 7 below.

- **Nephritis**: Monitor patients for renal function during treatment. Other causes of nephritis must be ruled out.
    - For **Grade ≥ 2** events, treat with corticosteroids (1-2 mg/g of prednisone or equivalent).
    - For pembrolizumab/KEYTRUDA® suspension/permanently discontinuation, refer to Table 7 below.

Table 7: Dose Modification Guidelines for Drug-Related Adverse Events

Toxicity	Grade/Severity	Timing for Restarting Treatment
Diarrhea/Colitis	2-3	Hold treatment until toxicity resolves to Grade 0-1
	4	Permanently discontinue
AST, ALT, or Increased Bilirubin	2	Hold treatment until toxicity resolves to Grade 0-1
	3-4	Permanently discontinue
	For patients with liver metastasis who begin treatment with Grade 2 AST or ALT, if AST or ALT increases by greater than or equal to 50% relative to baseline and lasts for at least 1 week	Permanently discontinue

Toxicity	Grade/Severity	Timing for Restarting Treatment
Endocrine disorders	1. Symptomatic hypophysitis 2. New onset type 1 diabetes mellitus with Grade 3-4 hyperglycemia (glucose>13.9mmol/l or 250mg/dl) or ketoacidosis 3. Grade 3 hyperthyroidism	Pembrolizumab can be continued
	4. Grade 4 endocrine disorder	Permanently discontinue
	5. Hypothyroidism	Therapy with pembrolizumab can be continued while thyroid replacement therapy is instituted
Inflammatory pneumonitis	2	Hold treatment until toxicity resolves to Grade 0-1
	3-4, or recurrent grade 2	Permanently discontinue
Nephritis	2 with creatinine >1,5-3 ULN	Hold treatment until toxicity resolves to Grade 0-1
	3-4 with creatinine ≥3 ULN	Permanently discontinue
Neurological (Gillain Barré, myasthenia gravis, demyelinating polyneuropathy)	3-4	Permanently discontinue
Ocular reaction	Grade 2 immune-related ocular reaction which does not respond to local treatment	Permanently discontinue
All Other Drug-Related Toxicity[c]	3 or Severe	Toxicity resolves to Grade 0-1
	4	Permanently discontinue

Note: Permanently discontinue for any Grade drug-related AE
- if toxicity does not resolve within 12 weeks of last dose (with the exception of endocrine disorders that remain grade 2 with adequate replacement therapy)
- or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
- or for any grade 3 drug-related AE that recurs or any life-threatening event.

Management of Infusion Reactions: Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion.

Table 8 below shows treatment guidelines for participants who experience an infusion reaction associated with administration of pembrolizumab/KEYTRUDA®.

Table 8: Infusion Reaction Treatment Guideline

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 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. **Participants 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: Antihistamine. and Paracetamol (or equivalent antipyretic).
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) 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 Increase monitoring of vital signs as medically indicated until the	No subsequent dosing

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Life-threatening; pressor or ventilatory support indicated	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.		

7.6 Contraception and pregnancy

Pembrolizumab/KEYTRUDA® may have adverse effects on a fetus in utero. Furthermore, it is not known if pembrolizumab has transient adverse effects on the composition of sperm. Non-pregnant, non-breast-feeding women may be enrolled if:

- they are willing to use 2 methods of birth control: the two birth control methods can be two barrier methods or a barrier method plus a hormonal method to prevent pregnancy. Participants should start using birth control from study Visit 1 throughout the study period up to 120 days after the last dose of study therapy.

- or if they are considered highly unlikely to conceive. Women are considered as highly unlikely to conceive in case of 1) surgically sterilization, or 2) postmenopausal (a woman who is ≥45 years of age and has not had menses for greater than 1 year will be considered postmenopausal), or 3) not heterosexually active for the duration of the study. Menopausal women with age 45-55 require elevated FSH (e.g. >40) and low estradiol (e.g. <10) to confirm menopause.

Male participants treated with pembrolizumab should agree to use an adequate method of contraception starting with the first dose of study therapy through 120 days after the last dose of study therapy.

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

Participants 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. In order to participate in the study they must adhere to the contraception requirement (described above) for the duration of the study and during the follow-up period.

It is unknown whether pembrolizumab is excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, participants who are breast-feeding are not eligible for enrollment.

8 ASSESSMENT OF EFFICACY

8.1 Description of parameters for assessing efficacy endpoints

The primary endpoint will be best tumor response rate assessed by ACTG criteria. For the secondary endpoints, the different aspects of clinical response will be evaluated at each cycle using the ACTG and PGA score (for details see § 4 Description of the trial).

- For the Simon's stages Optimal Design :

The primary and secondary endpoints will be assessed at M3 and M6 (+ 7 days) regardless of any perfusion modification

- For the Extension stage:

The primary and secondary endpoints will be assessed at M3, M6, M9, M12 and M24 (+- 7 days) regardless of any perfusion modification

ACTG criteria:
ACTG criteria are based on WHO adapted to KS (17). They are validated and have been largely used in HIV-associated KS, and more recently in classic KS (18).
Clinical response, defined as complete response, partial response, stable disease or progression will be assessed at each cycle during treatement.

Modified AIDS Clinical Trials Group (ACTG) Staging Classification (17,19)

Complete Response (CR)	The absence of any detectable residual disease, including tumor-associated edema, persisting for at least 4 weeks. Patients whose only remaining manifestation of KS are pigmented macules could be classified as complete response if malignant cells are absent on biopsy of at least one lesion. Patients with visceral disease on entry who have complete resolution of cutaneous lesions as described above could be considered to have a CR only if no residual disease was detected on imaging.
Partial Response (PR)	A 50% or greater decrease in the number and/or size of previsouly existing lesions, lasting for at least 4 weeks, without the appearance of new lesions or the appearance or worsening of any lesion-associated oedema or effusion during this time. A classification of PR requires that the product of the bidimensional diameters in no target lesion increase by >25%. A classification of PR can also be made: - if the sum of the products of the largest perpendicular diameters of the target lesions decreased by >50%, - or if >50% of nodular or plaque-like lesions became macules; - or if >75% of predominantly nodular lesions flattens to indurated plaques - or if criteria for a CR are met but lesion-associated oedema or effusion persist.
Stable Disease (SD)	Any response not meeting the criteria for CR, PR or PD

Progressive Disease (PD)	- An increase of 25% or more in the size of existing lesions - and/or the appearance of new cutaneous or visceral lesions - and/or a change in character from macular to plaque-like or nodular of 25% or more of lesions

PGA score:

Score and category	Description
0: completely clear	Complete relief of symptoms; 100% of improvement
1: almost clear	Marked improvement of all clinical symptoms as compared with baseline with residual signs (≥90% and <100%)
2: marked improvement	Significant improvement of symptoms (≥75% and <90%)
3: moderate improvement	Moderate improvement between score 2 and 4.
4: slight improvement	Improvement of signs and symptoms as compared with baseline (<50% and ≥25%) but remaining signs of active KS
5: no change	Clinical signs and symptoms unchanged from baseline (+-25%)
6: worse	Clinical signs and symptoms deteriorated from baseline (≥25% of deterioration)

8.2 Anticipated methods and timetable for measuring, collecting and analysing the efficacy data

Patients will be monitored every 3 weeks at each cycle for efficacy assessment (clinical assessment and photographs) (See Section 5).

Definition of Kaposi target lesions:

- For patients with less than 50 cutaneous lesions: the total number of lesions will be counted at each response evaluation and assessed for nodularity.
- In patients with more than 50 lesions, between one and three representative body areas will be selected, and the total number of lesions within each of those areas will be counted and assessed for nodularity.

Kaposi target lesions will be **numbered and photographed**. Their characteristics in terms of **size** (bigger diameter and its perpendicular diameter), **infiltration** (none, papule, nodule), **color**, will be noted. The presence, severity and topography of **lymphedema** will also be noted (**Table 9**).

Colour photography of Kaposi target lesions and any other relevant skin lesions will be taken at each scheduled visits.

Kaposi lesion	**Lymphoedema**
Size of target lesions (the bigger diameter and its perpendicular diameter)	**Severity** of lymphedema: 0: no lymphoedema, 1: moderate lymphedema/no embarrassing dressing, 2: embarrassing dressing, 3: painful or oozing
Infiltration 0: none –macule, 1 and 2: papule less or more infiltrated,	**Topography** of lymphoedema

3: nodule	
Color: red, purple, brown	**Circumference**

Table 9: Clinical characteristics of target lesions

8.2.1 Pharmacodynamic study

8.2.2 Procedure

Pharmacodynamic and virological evaluations will be performed on sequential (before the first dose, at cycle 3, cycle 7 and at the end-of-study visit (early or expected termination).

Peripheral blood will be collected (around 43 ml) at the 4 time points (before the first dose, at cycle 3, at cycle 7 and at the end-of-study visit) in 5 heparinate sample (total of 20 ml), 2 EDTA tube, 1 dry tube and one PAXgene tube .

Skin biopsy will be collected at 3 time points: before the first dose, at cycle 3, and at the end-of-study visit (at 6 month or progression). Two 3mm punch biopsy samples will be performed on a Kaposi lesion: **one is flash-frozen in liquid nitrogen and stored at -80°C, the other is fixed in formalin or AFA). During follow up biopsy should be** performed on residual disease, if possible of a same Kaposi lesion, if not of another lesion contiguous to the first lesion.

For the Extension Stage:

Peripheral blood will be collected (around 43 ml) at the 4 time points (before the first dose, at cycle 3, at cycle 7 and at the early termination visit in 5 heparinate sample (total of 20 ml), 2 EDTA tube, 1 dry tube and one PAXgene tube .

Skin biopsy will be collected at 3 time points (or 4 if progression): before the first dose, at cycle 3, at cycle 7 (if progression), at the end-of-treatment visit (at 24 months) and in the event of progression at follow-up visits. Two 3mm punch biopsy samples will be performed on a Kaposi lesion: **one is flash-frozen in liquid nitrogen and stored at -80°C, the other is fixed in formalin or AFA). During follow up biopsy should be** performed on residual disease, if possible of a same Kaposi lesion, if not of another lesion contiguous to the first lesion

A peripheral blood and skin biopsy will be collected during follow up if disease progression observed.

8.2.3 Pharmacodynamic analyses

8.2.3.1 Immunological analyses

The immunological sub-study will include:

- Characterization of the tumor microenvironnement by immunohistochemistry: immune cells infiltration (quantification of CD3, CD4, CD8 T cells and CD56 NK cells, analysis of their expression of PD1 and other immune check points); markers of cytotoxicity (granzyme); expression of PDL1/2 on tumor cells.

- Analysis of the immunomodulation induced by the treatment on peripheral blood: T cells (CD4, CD8, anti-HHV-8 T cells) and NK cells phenotypes (flow cytometry, PBMCs: activation, exhaustion, immune check point expression); blood inflammation markers (luminex, plama).

8.2.3.2 Virological analyses

The HHV8 viral load will be quantified in blood and tumor sample using quantitative real time PCR.

Polymerase chain reaction amplification assay for HHV-8 DNA detection will be performed using on whole blood and biopsy specimens. DNA will be extracted using a DSP DNA Mini kit on a QiaSymphony system (Qiagen, Courtabeuf, France). Real-time quantitative amplification will be carried out on an ABI 7500 system (Perkin Elmer Applied Biosystems, Foster City, California). Dilutions of known amounts (10-10^7 copies) of a fragment of viral DNA cloned into a plasmid were used to establish a standard curve. HHV-8 loads will be normalized according to the quantity of cells present in the sample by the quantification of Albumin gene using a real time PCR assay.

HHV8 expression profiles will be determined on samples with loads above 4 log10 copies/10^6 cells using a micro-array targeting all KHV gene transcripts as described (16).

For expression analysis, biopsy samples will be stored in RNAprotect medium right after collection and blood samples will be collected in PAXgene tubes.

9 Specific committees for the trial

9.1 Scientific committee

- Missions: elaborate the protocol and eventually decide any modification
- Operating methods: Will receive every 6 months a report on enrolments and a report of the steering committee decision and will meet every 6 months or more if necessary.

Investigator Coordonator Céleste LEBBE	Dermatologist	AP-HP, Hôpital Saint-Louis	33-1-42-49-46-79 celeste.lebbe@aphp.fr
Methodologist Lucie Biard	Methodologist	AP-HP, Hôpital Saint-Louis	33-1-42-49-97-47 lucie.biard@u-paris.fr
Others Sophie CAILLAT-ZUCMAN	Immunologist	AP-HP, Hôpital Saint-Louis, INSERM 1149 CRI	33-1-40-03-22-11 sophie.caillat@inserm.fr
Guislaine CARCELAIN	Immunologist	AP-HP, Hôpital Robert Debré, INSERM 1149 CRI	33-1-42-17-74-94 guislaine.carcelain@aphp.fr
Maxime BATTISTELLA	Pathologist	AP-HP, Hôpital Saint-Louis	33-1-42-49-45-61 maxime.battistella@aphp.fr
Jérôme LE GOFF	Virologist	AP-HP, Hôpital Saint-Louis	33-1-42-49-94-84 jerome.le-goff@aphp.fr

9.2 Steering committee

- Missions: check for enrolments, procedures, and review of safety data (toxicities).
- Operating methods: meeting on site (or TC for those who cannot join) every 3 months and receive every 3 months a report on enrolments, evaluations and side effects from the sponsor

Investigators	**Specialty**	**Localisation**	**Mail**	**Phone**
Céleste Lebbe	Dermatologist	St Louis	celeste.lebbe@aphp.fr	33-1-42-49-46-79
Lucie Biard	Methodologist	SBIM St Louis	lucie.biard@u-paris.fr	33-1-42-49-97-47
Sophie Caillat Zucman	Immunologist	St Louis	sophie-caillat.zucman@inserm.fr	33-1-40-03-47-42

Guislaine Carcelain	Immunologist	Robert Debré	guislaine.carcelain@aphp.fr	33-1-42-17-74-81
Maxime Battistella	Pathologist	St Louis	maxime.battistella@aphp.fr	33-1-42-49-45-21
Jérôme Le Goff	Virologist	St Louis	jerome.le-goff@aphp.fr	33-1-42-49-94-84
Fadila Amerali	Project manager	DRCI-Siège	fadila.amerali@aphp.fr	33-1-44-84-17-17
Laetitia Da Meda	Clinical Research Coordinator	Dermatology St Louis	laetitia.da-meda@aphp.fr	33-1-42-49-93-92
Chafia ABBOU	Project manager	DRCI-URC St Louis	chafia.abbou@univ-paris-diderot.fr	33-1-42-38-53-23

10 SAFETY ASSESSMENT - RISKS AND RESTRICTIONS ADDED BY THE study

The safety assessment shall be done by collecting all adverse events that occur during the research. All events shall be graded according to the CTCAE (Common Terminology Criteria for Adverse Events document, version 5).

Serious adverse events shall be assessed, collected and reported to the Vigilance department of the sponsor (DRCI).

For any question concerning the reporting of an adverse event, the Vigilance Department of the DRCI can be contacted by e-mail at: vigilance.drc@aphp.fr

10.1 Recording and reporting adverse events

10.1.1 Definitions

- **Adverse event (AE)**

Any untoward medical occurrence in a subject, to whom a medicinal product is administered and which does not necessarily have a causal relationship with this treatment. .

- **Serious adverse event (SAE)**

Any untoward medical occurrence that at any dose requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, results in a congenital anomaly or birth defect, is life-threatening, or results in death.
Certain medical events may jeopardise the subject or may require an intervention to prevent a SAE, known as "important medical events" should also be considered as serious adverse events.

- **Unexpected serious adverse reaction (SUSAR)**

A serious adverse reaction, the nature, severity or outcome of which is not consistent with the reference safety information.

- **Unexpected event**

An unexpected event which affect the benefit-risk balance of the clinical trial, but are not suspected unexpected serious adverse reactions as referred to in Article 42. That notification shall be made without undue delay but no later than 15 days from the date the sponsor became aware of this event.

- **Urgent safety measure**

Where an unexpected event is likely to seriously affect the benefit-risk balance, the sponsor and the investigator shall take appropriate urgent safety measures to protect the subjects.
The sponsor shall notify the Member States concerned, through the EU portal, of the event and the measures taken.
That notification shall be made without undue delay but no later than seven days from the date the measures have been taken.

10.1.2 The role of the investigator

The investigator must **assess the seriousness criteria of each adverse event** and record all serious and non-serious adverse events in the case report form (eCRF).

For all serious adverse events, the investigator must also notify the SAE to the safety department as soon as possible, except SAE not requiring a notification without delay described in section 10.1.2.2.2. "Serious adverse events that do not require the investigator to notify the sponsor without delay"

The investigator must **document** serious adverse events **as thorough as possible** and provide a definitive medical diagnosis, if possible.

The investigator must **assess the intensity** of the adverse events :
by using a rating scale with general terms:

- *Mild: tolerated by the patient, does not interfere with daily activities*
- *Moderate: sufficiently uncomfortable to affect daily activities*
- *Serious: prevents daily activities*

Or by using a severity grading scale for adverse events, *Common Terminology Criteria for Adverse Events [National Cancer Institute]* (refer to section 18.5.2).

The investigator must assess the **causal relationship** between the serious adverse events and:

- the investigational medicinal product(s) IMP),
- and /or or interventions/procedure(s) added by the study : Pharmacodynamic evaluations will be based on tumor tissue collection (cutaneous biopsy) and correlative blood sampling

The method used by the investigator is based on the WHO Uppsala Monitoring Centre method and uses the following causality terms:

- Certain
- Probable/likely
- Possible
- Unlikely (not ruled out).

These terms are defined as follows (extracted from the WHO-UMC causality categories, version dated 17/04/2012).

Table N°10: WHO-UMC causality categories (extract)

Causality term	Assessment criteria*
Certain	1. Event or laboratory test abnormality, with plausible time relationship to drug intake ** 2. Cannot be explained by disease or other drugs 3. Response to withdrawal plausible (pharmacologically, pathologically)

Causality term	Assessment criteria*
	4. Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognized pharmacological phenomenon) 5. Rechallenge satisfactory, if necessary
Probable / Likely	6. Event or laboratory test abnormality, with reasonable time relationship to drug intake** 7. Unlikely to be attributed to disease or other drugs 8. Response to withdrawal clinically reasonable 9. Rechallenge not required
Possible	10. Event or laboratory test abnormality, with reasonable time relationship to drug intake ** 11. Could also be explained by disease or other drugs 12. Information on drug withdrawal may be lacking or unclear
Unlikely	13. Event or laboratory test abnormality, with a time to drug intake ** 14. that makes a relationship improbable (but not impossible) 15. Disease or other drugs provide plausible explanations

*All points should be reasonably complied with
** Or study procedures

10.1.2.1 Serious adverses events that require a notification wthout delay by the incvestigator to the sponsor

The investigator must notify the sponsor, **without undue delay but not later than within 24 hours on the day when the investigator becomes aware**, of any serious adverse events, which occurs during a study that meets the description in article 41 of Regulation (EU) N°536/2014, with the exception of any event which is listed in the protocol and, if applicable, in the investigator's brochure as not requiring notification.

A serious adverse event is any untoward medical occurrence that:

1- results in death
2- is life-threatening
3- requires inpatient hospitalisation or prolongation of existing hospitalisation
4- results in persistent or significant disability/incapacity
5- is a congenital anomaly/birth defect
6- important medical event*

***** Certain medical events may jeopardise the subject or may require an intervention to prevent a SAE, known as "important medical events" should also be considered as serious adverse events.

Moreover, special circumstances require the investigator to notify the sponsor without delay are:
- medication errors,
- in utero exposure / pregnancy / breastfeeding
- uses outside what is foreseen in the protocol, including misuse and abuse of the product.

All pregnancies must be reported to the safety department by the investigators within 24 hours on the day the investigator becomes aware of it.

Special circumstances associated to an SAE must be reported to the safety department by the investigators.

Special circumstances not associated to an SAE must be reported to the CRF by the investigators and notify as a deviation to the protocol by the clinical trial unit.

Thus, any serious adverse event with fatal outcome and susceptible or not to be related to the investigational medicinal product (pembrolizumab) according to the investigator requires a notification without delay to the sponsor.

10.1.2.2 Specific features of the protocol

10.1.2.2.1 Other events that require the investigator to notify without delay the sponsor

- Adverse events particularly followed by the sponsor for the safety and assessment

These events may suggest toxicity or justify special monitoring of the exposed participants.
These events must be notify by the investigator to the sponsor without delay on the day the investigator becomes aware of these adverse events, in the same manner and within the same deadline as for serious adverse events (see above).

For these adverse events particularly followed by the sponsor, please, check the "important medical event" box as a seriousness criterion in the SAE notification form.
If applicable, please list the clinical or biological events concerned

- ***In utero* exposure**

The investigator must notify the sponsor without delay on the day the investigator becomes aware of any pregnancy that occurs during the study, even if it is not associated with an adverse event.
If the investigational medicinal product is genotoxic, every case of maternal or paternal exposure must be notified.
A pregnancy test for all childbearing women is performed at the inclusion visit and at each visit.
The sponsor must be notified immediately without delay about any pregnancy during which the foetus (from the pre-embryonic stage up to birth) could have been exposed at a given time to the investigational medicinal product, even if the pregnancy is not associated with an adverse event.
Notification is required if the exposure occurs during the trial or within 30 days after completing the trial and involves either the mother or the father.
All participants and female partners of male participants who become pregnant must be followed till the completion/termination of the pregnancy.

- **Exposure while breastfeeding**

Exposure while breastfeeding occurs if an infant or a child may have been exposed to a medicinal product *via* the breast milk of a mother being treated with an investigational medicinal product.
Even if it is not associated with an adverse event, the investigator must notify the sponsor without delay on the day the investigator becomes aware of the exposure while breastfeeding.

- **Secondary cancers/myelodysplasic syndroms**
- **Overdose**

An overdose of pembrolizumab will be defined as any dose of 1 000 mg or greater (≥5 times the indicated dose). No specific information is available on the treatment of overdose of pembrolizumab. Appropriate supportive treatment should be provided if clinically indicated. In the event of overdose, the subject

should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

If an adverse event is associated with an overdose of pembrolizumab, the adverse event is reported as a serious adverse event, even if no other seriousness criteria are met.

10.1.2.2.2 Serious adverse events that do not require the investigator to immediately notify the sponsor

These serious adverse events are only recorded in the "adverse event" section of the case report form.

These serious adverse events are only recorded on case report forms. Data extraction from case report forms will be implemented for serious adverse events upon request.
An extraction of all such SAEs from the e-CRF will be performed by the clinical trial unit, severity criteria, investigator assessment and SAE grade where applicable) and emailed to the safety department and members of the data safety oversight committee [where applicable] at a frequency defined in the DSMB charter [where applicable], on request and at least once a year when preparing the annual safety report. These extractions will be sent to DRCI's security department at the following address: expertisecsi.drc@aphp.fr

☐ **Normal and natural evolution of the pathology:**

1. Scheduled hospitalization to monitor the disease being studied (KS),
2. Hospitalization for routine treatment or monitoring of the disease being studied (KS)
3. Disease progression without life-threatening condition

- All adverse effects related to the administration of the investigational medicinal products that are **inferior to** grade 3 according to CTCAE

☐ **Special circumstances**

1. hospitalization for a preexisting condition, hospitalization for medical or surgical treatment before the planned research,
2. transition to emergency lower than 12 hours,
3. hospitalization for a social or an administrative reason.

☐ **Overdose**

If an overdose is taken without any associated symptoms or abnormal laboratory results, the overdose is reported as a non serious Event of Clinical Interest and do not require the investigator to notify the sponsor without delay. These events are only recorded in the case report forms.

- **Serious adverse events likely to be associated with the treatments prescribed as part of the patient's care during the monitoring of the Clinical Trial**

The investigator as health care professional must notify these events to the appropriate health surveillance institution according to the situation. Examples: Agence Régionale de Santé, quality department of your hospital, Centre Régional de Pharmacovigilance, local correspondent of the materiovigilance unit (competent authority), etc.

10.1.2.3 Period during which SAEs must be notified without delay by the investigator to the sponsor

The investigator must notify the sponsor without delay of all SAE listed in the corresponding sections:

- After the date on which treatment with pembrolizumab began
- Throughout the period during which the participant is monitored, as determined by the Clinical Trial
- For up to 4 weeks after the participant stops the investigational medicinal product
- Indefinitelyif the SAE is likely to be due to the investigational medicinal product or to the study procedures (for example, serious reactions that could appear long after exposure to the medication, such as cancers or congenital abnormalities).

*NB: In this last case, the investigator **does not have to collect indefinitely in the case report form (CRF or eCRF)** all **SAEs possibly related** to the clinical trial, **but must notify them**, to the sponsor, **as soon as he/she becomes aware of them, by the SAE notification form or by email or by fax (as described below)**.

10.1.2.4 Procedures and deadlines for notifying the sponsor

The initial notification of an SAE must be be provided in a written report signed by the investigator using a SAE (see Appendix 18.2). notification form specific to the study and intended for this purpose (in the case report form).

Each item in the form must be completed by the investigator so that the sponsor can carry out the appropriate analysis.

The initial notification to the sponsor of a serious adverse event must be quickly followed by an additional detailed written report (or reports) so that the case outcome may be monitored by the Safety Department or to provide further information.

Whenever possible, the investigator will provide the sponsor with any documents that may be useful (medical reports, laboratory test results, results from additional examinations, etc.). These documents must be non-identifying. In addition, the documents must include the following: study acronym, number and participant's initials.

Any adverse event will be monitored until fully resolved (stabilisation at a level considered acceptable by the investigator, or return to the previous state) even if the participant has left the study.

The initial notification, the SAE follow-up reports and all other documents must be sent to the sponsor's Safety Department by email (eig-vigilance.drc@aphp.fr). It should be noted that it is possible to send SAE reports to the Safety Department by fax to +33 (0)1 44 84 17 99 only in the event of a failed attempt to send the SAE report by email (in order to avoid duplication).

When sending the email, please:

- Adopt a standardized nomming of the email subject in the following form:

<< Objet : YYYYYY_XXXXXX_jjmmaaaa (avec YYYYYY : code de la recherche, XXXXXX : acronyme de la recherche et jjmmaaaa : date de transmission). >>

- Send a SAE initial notification form and/or a follow-up report concerning a single participant for a given SAE, attachment may contain one (or more) document(s) (follow-up and hospitalization reports, for example).
The total size of the email must be less than 8 MB, otherwise please send several e-mails.

- Ensure that all documents transmitted (e.g. hospital reports) are anonymized and identified with the participant's identification number.

For studies which use e-CRFs
- the investigator completes the SAE notification form in the e-CRF, then validates, prints, and signs the form before sending it by email;
- if it is not possible to connect to the e-CRF, the investigator should complete, sign, and send the SAE notification form to the Safety Department. As soon as the connection is restored, the SAE notification form in the e-CRF must be duly completed.

The investigator must comply with all requests for additional information from the sponsor.
(these new information must be also recorded in the e-CRF).
For all questions relating to the notification of an adverse event report, the safety Department can be contacted via email at: vigilance.drc@aphp.fr.

***For case of in utero* exposure**

The investigator completes the Notification and Follow-up form for “a pregnancy occurring during participation in a study".

The investigator must monitor the pregnant woman throughout her pregnancy or until delivary or premature interruption of the pregnancy, and must notify the sponsor of the outcome of the pregnancy, using this form.
If the outcome of the pregnancy falls within the definition of a serious adverse event (miscarriage, pregnancy termination, foetal death, congenital abnormality, etc.), the investigator must follow the procedure for reporting SAEs.
the investigational medicinal product is genotoxic and if the exposure involves the father, the investigator must obtain the mother's permission before collecting information about the pregnancy.

10.2 Role of the sponsor

The sponsor, represented by its Safety Department, shall continuously, throughout the trial, assesses the safety of the investigational medicinal product throughout the study period.

10.2.1 Analysis and declaration of serious adverse events

The sponsor assesses:
- The **seriousness** of all adverse events reported
- The **causal relationship** of these events with the investigational medicinal product and/or study procedures and/or with other possible treatments

All serious adverse events which the investigator and/or the sponsor believe could reasonably have a causal relationship with the experimental medication are considered as suspected adverse reactions.

- The **expected/unexpected nature** of these adverse reactions

  Any serious adverse reaction whose nature, severity, frequency or outcome is inconsistent with the safety information described in the summary of product characteristics, or in the investigator's brochure if the product is not authorised, is considered unexpected.

  The sponsor, represented by its Safety Department, assesses the expected/unexpected nature of a serious adverse reaction based on the information described below**.**

❖ For serious adverse events likely to be related to the investigational medicinal product(s):

- refer to the **Investigator's Brochure of Pembrolizumab,** enclosed in CTIS platform **[adapt as necessary depending on the study].**

❖ The serious adverse events associated with specific study procedures or exams and which are expected, are:

- infection related to biopsy, post-blood collection hematoma, faintness and pain.

❖ For serious adverse events associated with corticosteroids administered in case of toxicity (study procedure):

- refer to SmPC of Cortancyl® or to SmPC of the corticoïd administered enclosed in CTIS platform. **[complete depending on the study]**

In principle, only authorised medicinal products should be used as auxiliary medicinal products in clinical trials (article 59 of the Regulation (EU) No 536/2014). However, in certain circumstances unauthorised auxiliary medicines may be used. This has to be justified in the protocol. The acceptable reasons for admitting non-authorised auxiliary medicinal products would be related to the availability of authorised auxiliary medicinal products (e.g. no authorised medicinal products exist in the EU, or the amounts available are not sufficient to satisfy the need of the clinical trial). The lower price of non-authorised auxiliary medicinal product shall not be considered as a legitimate justification.

The sponsor will report all suspected unexpected serious adverse reactions (SUSARs) via Eudravigilance, within the regulatory time frame, to the competent authority:

- in the case of fatal or life-threatening suspected unexpected serious adverse reactions, as soon as possible and in any event not later than seven days after the sponsor became aware of the reaction;
- in the case of non-fatal or non-life-threatening suspected unexpected serious adverse reactions, not later than 15 days after the sponsor became aware of the reaction;
- in the case of a suspected unexpected serious adverse reaction which was initially considered to be non-fatal or nonlife threatening but which turns out to be fatal or life-threatening, as soon as possible and in any event not later than seven days after the sponsor became aware of the reaction being fatal or life-threatening
- in the uncompleted case of fatal or life-threatening suspected unexpected serious adverse reactions, all additional information to complete this case have to be reported as soon as possible and in any event not later than eight days after the initial report
- All additional, relevant information must be declared by the sponsor in the form of follow-up reports within a period of 15 days starting from when the sponsor had this information.

The sponsor must notify all relevant investigators about any data that could adversely affect the safety of the Clinical Trial participants.

10.2.2 Analysis and declaration of other safety data

This means any new information that prompts a reassessment of the risk/benefit ratio of the trial or of the product under investigation, or which could be sufficient to consider changes to the use of the product, the trial procedures or trial documentation, or the suspension, cancellation or amendment of the Clinical trial or of other similar trials. For trials involving the first administration or use of a health product in healthy volunteers: any serious adverse reaction.

The sponsor will report in CTIS platform and to ANSM without delay upon knowledge any emerging safety issues and, if applicable, describe what urgent safety measures have been taken by the sponsor.

Following the initial declaration of any emerging safety issue, the sponsor will address to competent authorities any additional relevant information about the emerging safety issue in the form of a follow-up report, which must be sent no later than 8 days after learning of the information.

10.2.2.1 Annual safety report

Once a year for the duration of the clinical study, the sponsor must produce an annual safety report (Development Safety Update Report - DSUR) which includes, in particular:
- a safety analysis for the research participants,
- a description of the patients included in the study (demographic profile etc.)
- a list of all the suspected serious adverse reactions that occurred during the period covered by the report,
- summary tables of all the serious adverse events that have occurred since the start of the study.

The sponsor produces one annual safety report (Development Safety Update Report - DSUR) for one clinical trial.

The final annual safety report must be submitted in CTIS no later than 60 days after the anniversary of the date on which the competent authority authorised the trial.
The end date of the clinical trial is defined as the date of the last visit of the last subject.

10.2.3 Data Safety Monitoring Board (DSMB)

A Data Safety Monitoring Board (DSMB) can be set up by the sponsor. Its primary mission is to monitor safety data. It can have other missions, such as monitoring efficacy data (especially if the protocol includes interim analyses).
The sponsor is responsible for justifying the creation or absence of a DSMB to the Competent Authority and to the Ethics committee.
A DSMB will be set up for this trial. The DSMB must hold its first meeting before the first participant is enrolled and ideally before the protocol is submitted to the competent authority and the Ethics Committee.
All missions as well as the specific operating procedures of the DSMB are described in the study's DSMB charter.

The members of the DSMB are:
- Pr Marie Françoise AVRIL (Dermatologist, AP-HP Cochin Hospital)
- Dr Raphael PORCHER (Methodologist, AP-HP Hotel Dieu Hospital)
- Pirayeh EFTEKHARI (Pharmacovigilance, AP-HP Fernand Widal)

The DSMB's principle missions and their operating procedures are described in the DSMB chart of the clinical trial.
The DSMB will operate in accordance with the sponsor's procedures. The DSMB works in an advisory capacity only and the sponsor retains all decision-making authority.

11 DATA MANAGEMENT

11.1 Data collection procedures

The investigator will permit the sponsor's representatives to monitor the study at the frequency defined in the contract, depending on enrolment at each centre.

Case Report Forms (CRFs) and related source documents will be reviewed in detail during monitoring visit (completeness, adherence to the guidelines, accuracy compared to source documents). The sponsor's representative will also review regulatory documents, drug storage and accountability.

The investigator must maintain a comprehensive and centralized filing system of all study-related documentation that is suitable for inspection by sponsor's monitors or representatives of other regulatory agencies.

11.2 Identification of data collected directly in the CRFs and that will be considered as source data

Identification of data collected directly in the CRFs will be considered as source data.

11.3 Right to access source data and documents

11.3.1 Access to data

In accordance with GCP and appendix 1 of the European Regulation N°536-2014:
- The sponsor is responsible for ensuring all parties involved in the study agree to guarantee direct access to all locations where the study will be carried out, to the source data, to the source documents and the reports, for the purposes of the sponsor's quality control and audit procedures or inspections by the competent authority
- The Sponsor declares that investigators and participating institution will ensure the persons in charge of monitoring, auditing or inspecting the the clinical trial have access to the documents and personal data strictly necessary for these tasks, in accordance with the statutory and regulatory provisions in force

11.3.2 Source documents

The source documents are defined as any original document or item that proves the existence or accuracy of a data-point or fact recorded during the trial. Source documents will be kept by the investigator, or by the hospital in the case of hospital medical records, for the statutory period.

11.3.3 Data confidentiality

The persons responsible for the quality control of clinical studies will take all necessary precautions to ensure the confidentiality of information relating to the investigational medicinal products, the study, the study participants and in particular the identity of the participants and the results obtained.
These persons, as well as the investigators themselves, are bound by professional secrecy
During or after the clinical trial, all data collected concerning the participants and sent to the sponsor by the investigators (or any other specialised collaborators) will be rendered non-identifying.

Under no circumstances should the names and addresses of the participants involved be shown.
Only the subject's initials will be recorded, along with an identification code specific to the study indicating the order of enrolment.
The sponsor will ensure that each subject has agreed in writing for any personal information about him or her which is strictly necessary for the quality control of the study to be accessed.

11.4 Data processing and storage of research documents and data

11.4.1 Identification of the data processing manager and location(s)

The management of data processing is held by Clinical Research Unit of Saint Louis hospital under the responsibility of Pr Matthieu Resche-Rigon, SBIM, Hôpital Saint-Louis, 1 avenue Claude Vellefaux, 75010 PARIS.

11.4.2 Data entry

Data entry will be performed by specially-trained staff to this task.
Non-identifying data will be entered electronically via a web browser.

11.4.3 Data Ownership

AP-HP is the owner of the data. The data cannot be used or disclosed to a third party without its prior permission

12 STATISTICAL ASPECTS

12.1 Description of statistical methods to be used including the timetable for the planned interim analyses

This is a multicenter non-randomized phase II study, based on a **2-stage phase II Simon's Optimal Design**. The main end point is the Best Overall Response Rate (BORR) defined by the occurrence of complete response or partial response following ACTG criteria recorded from the start of treatment until 6 months or the beginning of any other specific systemic therapy for KS if it occurs before 6 months

- **Description**

As a general strategy, continuous efficacy and safety endpoints will be summarized using summary measures (median and interquartile range). Frequency distributions (counts and percentages) will be used to summarize categorical endpoints. Similarly, characteristics of patients will be presented using summary measures (median and interquartile range for quantitative characteristics and counts and percentages for categoriel characteristics).

- **2-stage phase II Simon's Optimal Design:**

- **Interim analysis:**

The interim analysis will be based on the first successively included 9 patients, when their response will be recorded (at most 6 months after study inclusion).
According to the design exposed above, interim analysis of efficacy will be based on the observation of responses. Based on our hypotheses, it was computed that 9 patients would be accrued in stage 1. If necessary, inclusion will be stopped during 6 months after the 9^{th} inclusion waiting for the primary endpoint. The trial will stop with conclusion of inactivity if no response is observed in this stage; otherwise, 8 additional patients will be recruited to a total sample size of 17 patients, with at least 3

responses to indicate that the drug is effective enough. In case an observed response before the end of stage 1 the stage 2 will directly begin withouit any stop.

- **Terminal analysis:**

Terminal analysis will be done once all patients have been included, and data quality checked.
It will be based on intent-to-treat principle, that is, all patients will be analysed whatever the treatment has been administered or not unless consent withdrawal.
Point estimates with 95% exact confidence intervals will be computed either for efficacy or safety criteria.
Distribution of time to response and time to progression will be estimated by the Kaplan Meier approach, unless competing events precluding their occurrence (deaths); in the latter case, cumulative incidence in a competing risks setting will be used.

- **Extension stage**

Terminal analysis will be done once all patients have been included in the extension stage, and data quality checked. It will be based on intent-to-treat principle, that is, all patients will be analysed whateverthe treatment has been administered or not unless consent withdrawal. Point estimates with 95% exact confidence intervals will be computed either for efficacy or safety criteria. Distribution of time to responseand time to progression will be estimated by the Kaplan Meier approach, unless competing events precluding their occurrence (deaths); in the latter case, cumulative incidence in a competing risks settingwill be used.

The main analysis for the extension stage will be performed on the patients newly included in this stage.

A secondary analysis will be performed on the patients included in the extension stage pooled with the patientsincluded in the Simon's 2-stage Optimal Design.

Analyses will be performed on SAS (SAS Inc, cary, NC) and/or R (http://www.R-project.org/) software packages.

12.2 Calculation hypotheses for the number of participants required and the result

2-stage phase II Simon's Optimal Design

Sample size computation was based on statistical hypotheses with regards to treatment effect on the main endpoint, tumor response at 6 months. Moreover, as the study includes a selection phase we have to take into account the probability of being definitely included in the treatment phase in our sample size calculation. Based on clinicians experience the probability to present all criteria of inclusion in the treatment phase is above 50%.

With a 0.05 type I error and a 90% statistical power, the sample size was computed to assess whether the drug is inactive (tumor response probability π_0< 5%) or truly active (tumor response probability π_1> 30%) using the Simon's 2 stage Optimal Design (Simon, 1989). This design was used because it has been reported as the model to be used when the treatment is expected to be useful and accepted for Phase III trial, as it has smaller sample size in stage 1 and a reasonable expected sample size, so more quickly to enter stage 2 and terminate with acceptance of treatment for further evaluation.

The 2-stage phase II Simon's Optimal Design was developed to test a null hypothesis H_0: p≤ π_0 that the true response probability is less than some uninteresting level π_0. If the null hypothesis is true, then we require that the probability should be less than α=0.05 of concluding that the drug is sufficiently promising

that it should be accepted for further study in other clinical trials. We also require that if a specified alternative hypothesis H_1: $p > \pi_1$ that the true response probability is at least some desirable target level π_1 is true, then the probability of rejecting the drug for further study should be less than $\beta=0.90$ (in our case). In addition to these constraints, the design aims at minimizing the number of patients treated with a drug of low activity.

Based on this design, let denote

π_0 = 0.05, proportion of response at or below which treatment is abandoned

π_1 = 0.30, proportion of response at or above which treatment will be accepted for further development and trials

n_1 = maximum sample size required in stage 1

r_1 = number of successes above which stage 2 can be entered, and at or below which when n1 cases is reached the trial ends and the treatment abandoned.

n_{Tot} = the total maximum sample size (stage 1 and 2 combined)

r_{Tot} = the total number of successes (stage 1 and 2 combined) above which the study can be terminated and the treatment accepted for further development and trials, and at or below which when n_{Tot} cases is reached the treatment is abandoned.

We used published sample size tables, using α (probability of Type I Error) of 0.05 and power (1-β) of 0.9, β being probability of Type II Error (Machin D, Campbell M, Fayers, P, Pinol A (1997) Sample Size Tables for Clinical Studies. Second Ed. Blackwell Science IBSN 0-86542-870-0 p. 256-257).

Based on our hypotheses, it was computed that n_1=9 patients will be accrued in stage 1; the trial will stop with conclusion of inactivity if no response is observed in this stage (r_1=0); otherwise, n_2=8 additional patients will be recruited to a total sample size of **n_{Tot}=17**, with at least 3 responses to indicate that the drug is effective (r_{Tot}=3).

To obtain a total of 17 patients we should have to screen a maximum of 34 patients based on clinicians experience who estimate the probability to present all criteria of inclusion in the treatment phase above 50%.

- **Extension Stage:**

Only the 20 patients included in the extension stage will be considered in this main analysis at this stage. With an expected complete best overall response rate (complete response, partial response) at 6 months of 70% (14 out of a total of 20 patients), we would obtain a 95%CI interval of the best overall response rate equal to [46%;88%] (Clopper-Pearson binomial exact confidence interval).

A secondary analysis will be performed on the 20 patients included in the extension stage pooled with the 17 patients included in the Simon's 2-stage Optimal Design. With an expected best overall response rate at 6 months of 70% (rounding to 26 patients out of a total 37 (26/37=70.3%)), this analysis will reach a 95%CI interval of the complete response rate equal to [53%;84%] (Clopper-Pearson binomial exact confidence interval).

12.3 Subject Replacement Strategy

If a patient consent is withdrawn then this patient will be excluded from the analysis except if the patient allows investigators to use the already collected data for the primary endpoint. A new patient will be

included in order to be able to apply the Simon's Optimal Design. All patients included will be analyzed (Intention to treat Analysis).

13 QUALITY CONTROL AND ASSURANCE

Every clinical trial sponsored by AP-HP is ranked according to the projected risk incurred by the study participants using a classification system specific to AP-HP-sponsored clinical trials.

13.1 General organisation

The sponsor must ensure the safety and respect of individuals who have agreed to participate in the trial. The sponsor must have a quality assurance system for monitor the monitoring the implementation of the study at the research centres.

For this purpose, the sponsor shall appoint Clinical Research Associates (CRA) whose primary role is to carry out regular follow-up visits at the study sites, after completing their initial visits.
The purpose of monitoring the study, as defined in the Good Clinical Practices (GCP section 5.18.1), is to verify that:

- the research participants are safe, protected and their rights are being met
- the data being recorded is accurate, complete and consistent with the source documents
- the study is carried out in accordance with the current version of the protocol, with GCP and with all statutory and regulatory requirements.

13.1.1 Strategy for site opening

The strategy for opening the sites is determined using the tailored monitoring plan

13.1.2 Scope of site monitoring

For this study, the appropriate monitoring level has been determined based on the complexity, the impact and the budget for the study. Therefore the sponsor, in agreement with the coordinating investigator, has agreed on a logistical score and impact and the corresponding study monitoring level of: **High** level C.

The various levels are described in the Human Research Trial monitoring charter

13.2 Quality control

A Clinical Research Associate (CRA) appointed by the sponsor will be responsible for the proper conduct of the study, for collecting and documenting, recording and reporting all handwritten data, in accordance with the Standard Operating Procedures applied within the DRCI and in accordance with Good Clinical Practice as well as with the statutory and regulatory requirements.

The investigator and the members of the investigator's team agree to make themselves available during Quality Control visits by the Clinical Research Associate. During these visits, the following elements will be reviewed on the monitoring level:

- Written consent
- Compliance with the study protocol and its procedures Quality of the data collected in the case report form: accuracy, missing data, consistency of the data with the "source" documents (medical files, appointment books, original copies of laboratory results, etc.)
- Management of the treatments used.

13.3 Case Report Form

Electronic CRF:
All information required by the protocol must be entered in the case report forms. The data must be collected as and when they are obtained, and clearly recorded in these case report forms. Any missing data must be coded.
Every site will have access to the electronic case report forms via a web-based data collection system. Investigators will be given a document offering guidance on using this tool.
When the investigators complete the case report form via the Internet, the CRA can view the data quickly and remotely. The investigator is responsible for the accuracy, quality and relevance of all the data entered. In addition, the data are immediately verified as they are entered, thanks to consistency checks. To this end, the investigator must validate any changes to the values in the case report form. An audit trail will be kept of all changes. A justification can be added when applicable, as a comment.
The investigator must archive a copy of the authenticated document that was issued to the sponsor.

13.4 Management of non-compliances

Any events that occur as a result of non-compliance – by the investigator or any other individual involved in running the study – with the protocol, standard operating procedures, good clinical practices or statutory and regulatory requirements must be recorded in a declaration of non-compliance and sent to the sponsor.

These non-compliances will be managed in accordance with the sponsor's procedures.

The sponsor shall notify the Member States concerned about a serious breach of this Regulation or of the version of the protocol applicable at the time of the breach through the EU portal without undue delay but not later than seven days of becoming aware of that breach.

13.5 Audits/inspections

The investigators agree to accept the quality assurance audits carried out by the sponsor as well as the inspections carried out by the competent authorities. All data, documents and reports may be subject to regulatory audits and inspections. These audits and inspections cannot be refused on the basis of medical secrecy.
An audit can be carried out at any time by individuals appointed by the sponsor
The aim of the audits is to ensure the quality of the study, the validity of the results and compliance with the legislation and regulations in force.

The persons who manage and monitor the trial agree to comply with the sponsor's requirements and with the competent authority regarding study audits or inspections.

The audit may encompass all stages of the study, from the development of the protocol to the publication of the results and the storage of the data used or produced as part of the study.

13.6 Principal investigator's commitment to assume responsibility

Before starting the trial, each investigator will give the sponsor's representative a signed and dated copy of his/her personal curriculum vitæ, RPPS number (Répertoire Partagé des Professionnels de Santé, Collective Database of Health Professionals, for France). The CV must include any previous involvement in clinical research and related training.

Any conditions, such as economic interests and institutional affiliations that might influence the impartiality of the investigators shall be presented.

Each investigator will agree to comply with the legislation and to conduct the trial in line with GCP, in accordance with the Declaration of Helsinki. Each investigator will give the sponsor's representative a GCP certificate dated fewer than three years ago.

The Principal Investigator at each participating site will sign a declaration of responsibility (standard DRCI document), which will be sent to the sponsor's representative.
The investigators and their staff will sign a delegation of duties form specifying each person's role and will provide their CVs.

13.7 Suitability of the facilities

Before starting the study, each clinical trial sites will give the sponsor's representative a duly justified written statement on the suitability adapted to the nature and use of the investigational medicinal product and including a description of the suitability of facilities, equipment, human resources and description of expertise.

14 ETHICAL AND LEGAL CONSIDERATIONS

14.1 Methods for *informing research participants and obtaining their consent*

According to article 29 of European regulation N°536/2014, No clinical trials on medicinal products for human use can be carried out on a person without his/her freely given and informed consent, obtained in writing after the person has been given the information specified in article 29.2 of the European Regulation.

A reflection period of 48 hours Minimum that he/she needs is given to the individual between the time when he or she is informed and when he or she signs the consent form.

The person's freely-given, written, informed consent will be obtained by the principal investigator or a physician representing the investigator before the person is enrolled in the study.

A copy of the information note and consent form, signed and dated by the research participant and by the principal investigator or the physician representing the investigator will be given to the individual prior to their participation in the study. The principal investigator or the physician representing him/her will keep a copy.
At the end of the study, one copy will be placed in a tamper-proof sealed envelope containing all the consent forms. This envelope will be archived by the sponsor.

In addition, the investigator will specify in the person's medical file the person's participation in the research, the procedures for obtaining his/her consent as well as the methods used for providing information for the purpose of collecting it. The investigator will retain one copy of the signed and dated consent form.

14.2 Prohibition from participating in another clinical study or exclusion period set after the study,

During this research, the subject may not participate in other biomedical research protocols relating to medications until the end of this research
However, subject can participate to any other non-interventional research.

An exclusion period of participation after the participant has finished this study is defined in the context of this research. It is defined by the following treatment/protocol

The participant may not enrol in another interventional study protocol involving human participants for the duration of his or her participation without consulting with the physician monitoring him or her in the context of the study.

The participants can however participate in other non-interventional studies

14.3 Compensation for participants

No Compensation is anticipated for the patients as compensation for participating to the research.

14.4 Registration on the National Register of study participants to clinical trial concerning the products mentionned in Article L. 5311-1 of the Code de la santé publique

Non applicable.

14.5 Authorisation for the research location

In France, the study will be carried out in treatment units on individuals presenting a clinical condition for which the units are specialised and who require interventions that are routinely performed at those units. Therefore, the research location does not require specific authorisation.

14.6 Legal obligations

14.6.1 The sponsor's role

Assistance Publique - Hôpitaux de Paris (AP-HP) is the sponsor of this study and, by delegation, the DRCI (Clinical Research and Innovation Department) carries out the study's missions in accordance with regulation (EU) No 536/2014 of the European Parliament and of the council of 16 April 2014 and all national Laws. Assistance Publique - Hôpitaux de Paris reserves the right to halt the study at any time for medical or administrative reasons. In this case, notification will be sent to the investigator.
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14.6.2 Request authorisation

Prior to starting the study, AP-HP, as sponsor, must obtain authorisation from the Competent Authority and the Research Committee for this clinical trial on medicinal product for human use within the scope of its authority and in accordance with in force legislation and regulatory requirements.

14.6.3 Procedures relating to data protection regulations

The computer file used for this research is implemented in accordance with French (amended “Informatique et Libertés” law governing data protection) and European (General Data Protection Regulation – GDPR) regulations.

- Commitment to comply with “Reference Methodology” MR-001

This research is governed by the CNIL (French Data Protection Agency) “Reference Methodology for processing personal data used within the scope of health research” (amended MR-001). AP-HP, as sponsor of the research, has signed a declaration of compliance with this “Reference Methodology”

14.6.4 Start of the Clinical Trial

The sponsor shall notify each Member State concerned of the start of a clinical trial and the start of the recruitment through the EU portal. That notification shall be made within 15 days from the start of the clinical trial.

14.6.5 Amendments to the researchClinical Trial

Any substantial modification to the protocol by the coordinating investigator must be sent to the sponsor for approval. After approval is given, the sponsor must obtain, approval from the Ethics Committee) and authorisation from the competent authority, within the scope of their respective authorities.
before the amendment can be implemented.
The information note and the consent form can be revised if necessary, in particular in case of a substantial amendment to the study or if adverse reactions occur.

14.6.6 End of the Clinical Trial

The end of the Clinical Trial corresponds to the end of the participation of the last person who participate to the Clinical Investigation
The end of the recruitment of subjects for the clinical trial and the end of the clinical trial should be notified in CTIS. That notification shall be made within 15 days from the end of the clinical trial in relation to that Member State

14.6.7 Summary of the results of the clinical trial

According to article 37.4 of the European regulation n°536/2014, irrespective of the outcome of a clinical trial, within one year from the end of a clinical trial in all Member States concerned, the sponsor shall submit to the CTIS a summary of the results of the clinical trial. This summary shall be accompanied by a summary written in a manner that is understandable to laypersons.

14.6.8 Archiving

The specific documents for a clinical trial on a medicinal product for human use will be archived by the investigator and the sponsor for 25 years after the end of the trial.

This indexed archival includes, in particular:

- A sealed envelope containing the original copies of all information sheets and consent forms signed for all individuals at site who participated in the study for the investigator
- One copy of all the information sheets and signed forms signed for all individuals at the centre who participated in the study for the sponsor
- "Study" binders for the Investigator and the sponsor, containing:
  - The successive versions of the protocol (identified by the version no. and date), and the appendices
  - The competent authority authorisations and Research Ethics Committee decisions
  - Any Correspondence

- The enrolment list or register
- The appendices specific to the study
- The final studyreport

- The data collection documents.

15 FUNDING AND INSURANCE

15.1 Funding sources

This project is funded by the Programme Hospitalier de Recherche Clinique national– PHRC (Ministère de la Santé).

Pembrolizumab will be provided by MSD

15.2 Insurance

For the duration of the study, the Sponsor will take out an insurance policy covering the sponsor's own public liability, as well as the public liability for all the physicians involved in the study. The sponsor will also provide full compensation for any damages caused by the study to the participant enrolled and their beneficiaries, unless the sponsor can prove that the harm is not the fault of the sponsor or any collaborator. Compensation cannot be refused on the grounds of a third-party act or the voluntary withdrawal of the person who initially consented to participate in the study

Assistance Publique-Hôpitaux de Paris (AP-HP) has taken out insurance with HDI-GLOBAL SE through the insurance broker BIOMEDIC-INSURE for the full study period, which covers its own public liability and that of any collaborator (physician or research staff), in accordance with Article 76(1) of regulation (EU) No 536/2014 of the European Parliament and of the council of 16 April 2014 and Article L.1121-10 of the *Code de la Santé Publique* (French Public Health Code).

16 PUBLICATION RULES

The author(s) of any publication relating to this study must include the AP-HP among their affiliations and must name the sponsor AP-HP (DRCI) and the source of funding, if funded by a call for tenders (e.g. national or regional PHRC); a copy of the publication must be sent to the sponsor (see below for rules governing affiliation, and naming of the sponsor and funders).

16.1 Mention of AP-HP affiliation for projects sponsored by AP-HP

- If an author has several affiliations, the order in which the institutions are mentioned (AP-HP, University, INSERM, etc.) is unimportant
- However, if the study is funded in the context of an internal AP-HP call for tender, the first affiliation must be "AP-HP"
- Each of these affiliations must be identified by an address and separated by a semicolon (;)
*- The AP-HP institution must feature under the acronym "**AP-HP**" first in the address, specifically followed by: **AP-HP**, hospital, department, city, postcode, France*

16.2 Mention of the AP-HP manager (DRCI) in the acknowledgements of the text

"The sponsor was Assistance Publique – Hôpitaux de Paris (Direction de la Research Clinique et de l'Innovation)"

16.3 Mention of the *financial backer* in the acknowledgements of the text

The study was funded by a grant from Programme Hospitalier de Recherche Clinique - PHRC (French Ministry of Health)"

Pembrolizumab will be provided by MSD

This research has been registered on the website http://clinicaltrials.gov/ under number NCT03469804.

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18 LIST OF ADDENDA

18.1 List of Investigators

- For the Simon's Simon's 2 stages Optimal Design :

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CHRU– Hôpital Saint-Eloi	Pr	Bernard Guillot	b-guillot@chu-montpellier.fr
CHU Grenoble	Pr	Marie-Thérèse Leccia	MTLeccia@chu-grenoble.fr

- For the extension stage :

Address of the research location	Title	First name Surname	Telephone / e-mail
AP-HP, Hôpital Saint-Louis Service de dermatologie du Pr Morel 1 av. Claude Vellefaux 75010 Paris	Pr	Céleste Lebbé	33-1-42-49-46-79 celeste.lebbe@sls.aphp.fr
AP-HP, Avicenne Service de dermatologie 125 route de Stalingrad 93009 Bobigny	Pr	Eve Maubec	+33-1-48-95-70-90 eve.maubec@aphp.fr
AP-HP Cochin Service de Dermatologie et Vénéréologie du Pr Avril 27 rue du Faubourg Saint Jacques 75014 Paris	Pr	Nicolas DUPIN	+33-1-56-56-00-53 nicolas.dupin@aphp.fr
AP-HP, Bichat Service de Dermatologie et de Vénéréologie du Pr Decamps 46 Rue Henri Huchard 75018 Paris	Dr	Florence Brunet-Possenti	+33-1-40-25-84- 29 florence.brunet-possenti@aphp.fr
CHRU de Lille Service de Dermatologie Rue Michel Polonovski 59037 Lille	Pr	Laurent Mortier	+33-3-20-44-41-93 laurent.mortier@chru-lille.fr
Centre hospitalier Lyon sud Service de Dermatologie 165 chemin du Grand Revoyet 69310 Pierre Benite	Pr	Stéphane Dalle	+33-4-78-86-16-79 stephane.dalle@chu-lyon.fr
CHU Marseille Service de dermatologie 264 Rue Saint Pierre 13385 Marseille	Pr	Caroline Gaudy	+33-4-91-38-79-91 caroline gaudy@ap-hm.fr
CHU Montpellier Service de Dermatologie du Pr Guillot	Pr	Olivier Dereure	+33-4-67-33-69-06

80 avenue Augustin Fliche 34295 Montpellier			o-dereure@chu-montpellier.fr
IUCT Toulouse Service d'oncologie médicale 1 avenue Irène Joliot-Curie 31059 Toulouse	Pr	PAGES Laurent	+33-5-31-15-56-75 Pages.l@chu-toulouse.fr
CHU Nice Hôpital l'Archet 3 Service de dermatologie 151 Route St Antoine de Ginestière 06200 Nice	Pr	Henri Montaudie	+33-4-92-03-60-83 montaudie.h@chu-nice.fr

18.2 Serious Adverse Events report form

Direction de l'Organisation Médicale et des relations avec les Universités (DOMU) Délégation à la Recherche Clinique et à l'Innovation	ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS **Formulaire de notification d'un Evènement Indésirable Grave (EIG) survenant au cours d'une Recherche Biomédicale portant sur un Médicament ou produit assimilé**	**PARTIE RESERVEE AU PROMOTEUR** **REFERENCE VIGILANCE :** Référence GED : REC-DTYP-0192

Dès la prise de connaissance de l'EIG par l'investigateur, ce formulaire doit être dûment complété (2 pages), signé et retourné sans délai au pôle Vigilance du DRCD-Siège par télécopie au +33 (0)1 44 84 17 99

Notification initiale ☐ **Suivi d'EIG** ☐ **N° du suivi** |__|__|

1. Identification de la recherche

Acronyme : **KAPKEY**

Code de la Recherche : P160601J

Titre complet de la Recherche Biomédicale : ***«Essai de phase II multicentrique évaluant le pembrolizumab dans le traitement de la maladie de Kaposi classique ou endémique»***

Date de notification : |__|__| |__|__| |2|0|__|__| (jj mm aaaa)

Date de prise de connaissance de l'EIG par l'investigateur : |__|__| |__|__| |2|0|__|__| (jj mm aaaa)

Risque : ☐ A ☐ B ☒ C ☐ D

Plan expérimental : ☒ Essai non comparatif
☐ Essai comparatif : ☐ Double aveugle ☐ Simple aveugle ☒ Ouvert ☐ Randomisé ☐ Non randomisé

2. Identification du centre Investigateur

Nom de l'établissement : .....
Ville et code postal : .....
Service : .....

Investigateur (nom/prénom) : .....

Tél : ..... Fax : .....

3. Identification et antécédents de la personne se prêtant à la recherche

Référence de la personne : |__|__|__| - |__|__|__|__|__| - |__| - |__| (n°centre - n° ordre de sélection - initiale nom - initiale prénom)

Sexe : ☐ M ☐ F

Poids : |__|__|__| kg
Taille : |__|__|__| cm

Date de naissance : |__|__| |__|__| |__|__|__|__| (jj mm aaaa)

Age : |__|__|__|ans

Date de signature du consentement : |__|__| |__|__| |2|0|__|__| (jj mm aaaa)

Date d'inclusion : |__|__| |__|__| |2|0|__|__| (jj mm aaaa)

Antécédents médicaux-chirurgicaux/familiaux pertinents pour l'évaluation du cas (joindre un CRH anonymisé le cas échéant) :

.....
.....
.....
.....
.....
.....
.....

4. Médicament(s) expérimental(aux) (ME) ou produit(s) assimilé(s) [préciser le(s)quel(s)] avant la survenue de l'EIG
(barrer l'encadré si traitement non débuté)

Nom commercial (de préférence) ou Dénomination Commune Internationale	Voie(1)	Posologie / jour	Date de début *(jj/mm/aaaa)*	En cours(2)	Date de fin *(jj/mm/aaaa)*

Pembrolizumab	.....	.....	|__|__|__|__|__|_2_|_0_|__|__|	☐	|__|__| |__|__| |_2_|_0_|__|__|
	.....	.....	|__|__|__|__|__|_2_|_0_|__|__|	☐	|__|__| |__|__| |_2_|_0_|__|__|
	.....	.....	|__|__|__|__|__|_2_|_0_|__|__|	☐	|__|__| |__|__| |_2_|_0_|__|__|

5. Procédures et actes ajoutés par la recherche *(ex. : biopsies, IRM …)* *(barrer l'encadré si procédures et actes non réalisés)*	Date de réalisation *(jj/mm/aaaa)*	Chronologie	
		Avant la survenue de l'EIG	Après la survenue de l'EIG
.....	|__|__|__|__|__|_2_|_0_|__|__|	☐	☐
.....	|__|__|__|__|__|_2_|_0_|__|__|	☐	☐
.....	|__|__|__|__|__|_2_|_0_|__|__|	☐	☐

6. Médicament(s) concomitant(s) au moment de l'EIG, à l'exclusion de ceux utilisés pour traiter l'événement indésirable *(compléter le tableau ci-après et si nécessaire l'annexe relative aux médicaments concomitants ou barrer l'encadré si non applicable)*

⇨ **Annexe jointe au présent formulaire :** ☐ Oui ☐ Non

Nom commercial (de préférence) ou Dénomination Commune Internationale y compris forme pharmaceutique et dosage	Indication	Voie[1]	Posologie / jour	Date de début *(jj/mm/aaaa)*	En cours[2]	Date de fin *(jj/mm/aaaa)*
.....	.....	.....	.....	|__|__|__|__|__|__|__|__|	☐	|__|__| |__|__| |_2_|_0_|__|__|
.....	.....	.....	.....	|__|__|__|__|__|__|__|__|	☐	|__|__| |__|__| |_2_|_0_|__|__|
.....	.....	.....	.....	|__|__|__|__|__|__|__|__|	☐	|__|__| |__|__| |_2_|_0_|__|__|

(1) Voie d'administration : VO=voie orale ; IM=Intramusculaire ; IV=intraveineuse ; SC=sous-cutanée ou autre (à préciser) (2) En cours au moment de la survenue de l'EI

Acronyme : **KAPKEY**

Référence de la personne se prêtant à la recherche : |__|__|__| - |__|__|__|__|__| - |__| - |__|
n°centre - n° ordre de sélection - initiale nom - initiale prénom

7. Evènement indésirable grave [EIG]

Diagnostic : ☐ Définitif ☐ Provisoire
.....

Organe(s) concerné(s) :
.....

Symptôme(s) :
.....

Date de survenue des premiers symptômes : |__|__| |__|__| |_2_|_0_|__|__|
Préciser lesquels :
.....

Date d'apparition de l'EIG :
|__|__| |__|__| |_2_|_0_|__|__|
jj mm aaaa
Heure de survenue : |__||__| hh |__||__| min
☐ *donnée manquante*

Délai entre la date de la dernière administration du ME/produit assimilé ou la date de procédure/acte ajouté par la recherche et la date de survenue de l'EIG :
|__||__| / |__||__| |__||__|
jj hh min

Critères de gravité :
☐ Nécessite ou prolonge l'hospitalisation :
du |__|__| |__|__| |_2_|_0_|__|__|
au |__|__| |__|__| |_2_|_0_|__|__| ☐ *en cours*

☐ Décès
☐ Mise en jeu du pronostic vital
☐ Incapacité ou handicap important ou durable
☐ Anomalie ou malformation congénitale
☐ Autre(s) critère(s) médicalement significatif(s), préciser :
.....

L'évènement a-t-il conduit à une interruption du/des ME/produit assimilé(s) à l'étude ?
☐ Non ☐ Oui Date : |__|__| |__|__| |_2_|_0_|__|__|
L'arrêt de traitement a été : ○ Provisoire ○ Définitif
Le cas échéant, date de reprise du traitement à l'étude : |__|__| |__|__| |_2_|_0_|__|__|
Récidive de l'EIG après ré-administration : ○ Non ○ Oui - Date : |__|__| |__|__| |_2_|_0_|__|__|

L'évènement a-t-il conduit à une levée d'insu ?
☐ Non ☐ Oui Date : |__|__| |__|__| |_2_|_0_|__|__|

L'évènement fait-il suite à :

-Une erreur médicamenteuse ?	☐ Non	☐ Oui	Date : |__|__| |__|__| |_2_|_0_|__|__|
-Un surdosage ?	☐ Non	☐ Oui	Date : |__|__| |__|__| |_2_|_0_|__|__|
-Un mésusage ?	☐ Non	☐ Oui	Date : |__|__| |__|__| |_2_|_0_|__|__|
-Autre (préciser) :	☐ Non	☐ Oui	Date : |__|__| |__|__| |_2_|_0_|__|__|

Degré de sévérité :
☐ Léger ☐ Modéré ☐ Sévère

Evolution de l'événement

☐ **Décès**
○ sans relation avec l'EIG
○ en relation avec l'EIG
Date : |__|__| |__|__| |_2_|_0_|__|__|
jj mm aaaa

☐ **Sujet non encore rétabli**, préciser : ○ Etat stable
○ Aggravation
○ Amélioration

☐ **Guérison :** ○ sans séquelles ○ avec séquelles, préciser lesquelles :	Date : |__|__| |__|__| |_2_|_0_|__|__| jj mm aaaa |__|__|heures |__|__| min
Des mesures symptomatiques ont été prises : ☐ Non ☐ Oui Si oui, préciser :	

8. Autre(s) étiologie(s) envisagée(s)

☐ Non ☐ Oui Si oui, préciser : .....

9. Examen(s) complémentaire(s) réalisé(s)

☐ Non ☐ Oui Si oui, préciser date, nature et résultats : [joindre les bilans anonymisés] .....

10. Selon l'investigateur, l'événement indésirable grave est (plusieurs cases possibles)

Lié à la recherche biomédicale :

☐ **Oui** :
- ○ **au(x) médicament(s)/produit(s) assimilé(s) de la recherche : Le(s)quel(s) ?**
  - **Lequel :** ..... ☐ Relation certaine ☐ Relation probable ☐ Relation possible ☐ Relation improbable
  - **Lequel :** ..... ☐ Relation certaine ☐ Relation probable ☐ Relation possible ☐ Relation improbable
- ○ **à la (aux) procédure(s)/acte(s) de la recherche biomédicale : La/le(s)quel(les) ?**
  - **La/lequel(le) :** ..... ☐ Relation certaine ☐ Relation probable ☐ Relation possible ☐ Relation improbable
  - **La/lequel(le) :** ..... ☐ Relation certaine ☐ Relation probable ☐ Relation possible ☐ Relation improbable

☐ **Non** :
- ○ **à la progression de la maladie faisant l'objet de la recherche :** (à compléter)
- ○ **à un (ou plusieurs) médicament(s) concomitant(s) administré(s), le(s)quel(s) :** .....
- ○ **à une maladie intercurrente, laquelle :** .....
- ○ **autre, préciser :** .....

Notificateur	**Investigateur**	Tampon du service :
Nom et fonction : Signature	Nom : Signature :	

18.3 Pregnancy follow-up form

Direction de l'Organisation Médicale et des relations avec les Universités (DOMU) Délégation à la Recherche Clinique et à l'Innovation (DRCI)	ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS ***Notification et suivi d'une grossesse apparue au cours d'une recherche portant sur un Médicament ou produit assimilé***	**PARTIE RESERVEE AU PROMOTEUR** **REFERENCE INTERNE :** Référence GED : REC-DTYP-0185

1. Identification de la recherche

Acronyme : **KAPKEY**

Code de la recherche : **P160601J**

Notification initiale ☐ **Suivi de notification** ☐ **N° du suivi** |__|__|

Date de notification : |__|__| |__|__| |_2_|_0_|__|__|
jj mm aaaa

Date de prise de connaissance de la grossesse par l'investigateur : |__|__| |__|__| |_2_|_0_|__|__|
jj mm aaaa

Titre complet de la Recherche : Etude de phase II multicentrique évaluant le pembrolizumab dans le traitement de la maladie de Kaposi classique ou endémique

2. Identification du centre investigateur

Nom de l'établissement : ..... Ville et code postal : ..... Service :	Investigateur (nom/prénom) : ..... Tél : Fax :

3. Identification de la personne présentant une grossesse

Cas particulier d'une exposition paternelle : ☐ Oui ☐ Non

Référence de la personne : |__|__|__| - |__|__|__|__|__| - |__| - |__|
n°centre - n° ordre de sélection - initiale nom - initiale prénom

Date de naissance : |__|__| |__|__| |___|___|__|__|
Date d'inclusion : |__|__| |__|__| |_2_|_0_|__|__|
Date de randomisation : |__|__| |__|__| |_2_|_0_|__|__|

Groupe de randomisation : ☐ (à compléter) ☐ (à compléter)
Date des dernières règles : |__|__| |__|__| |_2_|_0_|__|__|
Et/ou date début de grossesse : |__|__| |__|__| |_2_|_0_|__|__|

Référence de la personne : |__|__|__| - |__|__|__|__|__| - |__| - |__|
n°centre - n° ordre de sélection - initiale nom - initiale prénom

Date de naissance : |__|__| |__|__| |___|___|__|__|
Date d'inclusion : |__|__| |__|__| |_2_|_0_|__|__|
Date de randomisation : |__|__| |__|__| |_2_|_0_|__|__|
Groupe de randomisation : ☐ (à compléter) ☐ (à compléter)

Expositions au cours de la grossesse :

Tabac :	☐ non	☐ oui (préciser nombre de paquets/année) :	☐ arrêt (préciser date) :	☐ poursuite
Alcool :	☐ non	☐ oui (préciser unités OH) :	☐ arrêt (préciser date) :	☐ poursuite
Drogue :	☐ non	☐ oui (préciser substance) :	☐ arrêt (préciser date) :	☐ poursuite

Autre (préciser) :

4. Antécédents maternels

Médicaux :	**Chirurgicaux :**

Obstétricaux : |__|__| geste |__|__| pare

Préciser si fausse couche, grossesse extra-utérine, interruption de grossesse (médicale ou volontaire), mort *in utero*, malformation congénitale, pathologie congénitale/néonatale non malformative, … (*nombre, date et nature/raison si applicable).*

5. Médicament(s) expérimental (aux) administré(s) ou non pendant la grossesse ou s'il s'agit une exposition paternelle

Nom commercial (de préférence) ou Dénomination Commune Internationale	Date de première administration Ou non administré	Date de dernière administration Ou en cours	Voie d'administration(1)	Posologie / 24h
	|__|__| |__|__| |_2_|_0_|__|__| ☐ Non administré	|__|__| |__|__| |_2_|_0_|__|__| ☐ En cours		
	|__|__| |__|__| |_2_|_0_|__|__| ☐ Non administré	|__|__| |__|__| |_2_|_0_|__|__| ☐ En cours		

(1) Voie d'administration : VO=voie orale ; IM=Intramusculaire ; IV=intraveineuse ; SC=sous-cutanée ou autre (à préciser)

6. Procédures et actes ajoutés par la recherche ***(Barrez l'encadré si procédures et actes non réalisés)***	Date de réalisation *(jj/mm/aaaa)*	Chronologie	
		Avant la grossesse	Au cours de la grossesse
	|__|__| |__|__| |_2_|_0_|__|__|		
	|__|__| |__|__| |_2_|_0_|__|__|		

Acronyme : KAPKEY

Référence de la personne : |__|__|__| - |__|__|__|__|__| - |__| - |__|
n°centre - n° ordre de sélection - initiale nom - initiale prénom

PARTIE RESERVEE AU PROMOTEUR
REFERENCE INTERNE :
REC-DTYP-0192

7. Médicament(s) concomitants administré(s) dans le cadre du soin

(Cf. annexe « Liste relative aux médicaments concomitants » complétée : ☐ Oui ☐ Non applicable)

Nom commercial (de préférence) ou Dénomination Commune Internationale	Date de première administration	Date de dernière administration Ou en cours	Voie d'administration(1)	Posologie / 24h
	|__|__| |__|__| |_2_|_0_|__|__|	|__|__| |__|__| |_2_|_0_|__|__| ☐ En cours		
	|__|__| |__|__| |_2_|_0_|__|__|	|__|__| |__|__| |_2_|_0_|__|__| ☐ En cours		
	|__|__| |__|__| |_2_|_0_|__|__|	|__|__| |__|__| |_2_|_0_|__|__| ☐ En cours		

(1) Voie d'administration : VO=voie orale ; IM=Intramusculaire ; IV=intraveineuse ; SC=sous-cutanée ou autre (à préciser)

8. Suivi de la grossesse

☐ Echographiques. Date(s) et résultats à préciser *(joindre les CR anonymisés)* :

☐ Autres examens. Date(s) et résultats à préciser *(joindre les CR anonymisés)* :

9. Grossesse en cours ou issue de la grossesse ☐ (faxer un nouveau formulaire complété à l'issue de la grossesse pour le suivi de la notification initiale) ☐ (compléter ci-dessous)

Date : |__|__| |__|__| |_2_|_0_|__|__| Terme : |__|__| SA |__|__| J

☐ Fausse couche
→ Examen anatomo-pathologique disponible : ☐ Non ☐ Oui, précisez le résultat :

☐ Grossesse extra-utérine
→ Examen anatomo-pathologique disponible : ☐ Non ☐ Oui, précisez le résultat :

☐ Interruption de grossesse → Raison :
→ Examen anatomo-pathologique disponible : ☐ Non ☐ Oui, précisez le résultat :

☐ Accouchement : ☐ Spontané ☐ Provoqué ☐ Voie basse ☐ Césarienne

Naissance multiple : ☐ Non ☐ Oui, précisez le nombre :
Souffrance fœtale : ☐ Non ☐ Oui, précisez :
Mort-né : ☐ Non ☐ Oui, précisez :
Placenta normal : ☐ Oui ☐ Non, précisez :
Liquide amniotique : ☐ Clair ☐ Autre, précisez :
Anesthésie : ☐ Générale ☐ Péridurale ☐ Rachianesthésie ☐ Aucune

10. Nouveau-né (Si naissance multiple, compléter les parties 1, 2, 3, 9 et 10 d'un nouveau formulaire et le faxer)

Sexe : ☐ Masculin ☐ Féminin

Poids : |__|__|__|__| grammes Taille : |__|__|__| cm Périmètre crânien : |__|__|__| cm

APGAR : 1 minute : _____ 5 minutes : _____ 10 minutes : _____

Malformation(s) congénitale(s) : ☐ Non ☐ Oui, précisez :

Pathologie(s) congénitale(s)/néonatale(s) non malformative(s) : ☐ Non ☐ Oui, précisez :

Le nouveau-né a-t-il bénéficié d'un suivi particulier à la naissance : ☐ Non ☐ Oui, précisez : ☐ Non applicable

Notificateur	**Investigateur**	Tampon du service :
Nom et fonction : Signature :	Nom : Signature :	

18.4 Investigator's Brochure

Separate document in annex

18.5 Scales

18.5.1 ECOG Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).

2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.
* As published in Am. J. Clin. Oncol.: *Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.* The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.	

18.5.2 Common Terminology Criteria for Adverse Events V5.0 (CTCAE)

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for adverse event reporting. (http://ctep.cancer.gov/reporting/ctc.html)

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

V5.0 CTCAE Grading	**Grade 1**	**Mild; asymptomatic or mid symptoms; clinical or diagnostic observations only; intervention not indicated.**
	Grade 2	**Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.**
	Grade 3	**Severe or medically significant but not immediately life-threatening; hospitalization or prolongation or hospitalization indicated; disabling; limiting self-care ADL.**
	Grade 4	**Life threatening consequences; urgent intervention indicated.**
	Grade 5	**Death related to AE**
Seriousness	A serious adverse event is any adverse event occurring at any dose or during any use of pembrolizumab that:	
	†**Results in death**; or	
	†**Is life threatening; or** places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred (Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.); or	
	†**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or	
	†**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization [including hospitalization for an elective procedure] for a preexisting condition which has not worsened does not constitute a serious adverse event.); or	
	†**Is a congenital anomaly/birth defect** (in offspring of subject taking the product regardless of time to diagnosis);or	
	Is a new **cancer;** (that is not a condition of the study) **or**	
	Is an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours.	
	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	
Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the adverse event cause pembrolizumab to be discontinued?	
Relationship to test drug	Did pembrolizumab cause the adverse event? The determination of the likelihood that the Merck product caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the adverse event based upon the available information.	

	The following components are to be used to assess the relationship between pembrolizumab and the AE; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Merck product caused the adverse event (AE):	
	Exposure	Is there evidence that the subject was actually exposed to the Merck product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
	Time Course	Did the AE follow in a reasonable temporal sequence from administration of the Merck product? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors
Relationship	**The following components are to be used to assess the relationship between the test drug and the AE: (continued)**	

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

18.6 Questionnaire Quality of Life

18.6.1 EORTC QLQ-C30 (version 3)

Nous nous intéressons à vous et à votre santé. Répondez vous-même à toutes les questions en entourant le chiffre qui correspond le mieux à votre situation. Il n'y a pas de « bonne » ou de « mauvaise » réponse. Ces informations sont strictement confidentielles.

Merci de préciser :

Vos initiales : |_|_|-|_|_|

Date de naissance (jour/mois/année) : |_|_|/|_|_|/|_|_|_|_|

La date d`aujourd`hui (jour/mois/année) : 31 |_|_|/|_|_|/|_|_|_|_|

		Pas du tout	Un peu	Assez	Beaucoup
1.	Avez-vous des difficultés à faire certains efforts physiques pénibles comme porter un sac à provisions chargé ou une valise ?	1	2	3	4
2.	Avez-vous des difficultés à faire une longue promenade ?	1	2	3	4
3.	Avez-vous des difficultés à faire un petit tour dehors ?	1	2	3	4
4.	Êtes-vous obligé(e) de rester au lit ou dans un fauteuil pendant la journée ?	1	2	3	4
5.	Avez-vous besoin d'aide pour manger, vous habiller, faire votre toilette ou aller aux toilettes ?	1	2	3	4

Au cours de la semaine passée :

		Pas du tout	Un peu	Assez	Beaucoup
6.	Avez-vous été gêné(e) pour faire votre travail ou vos activités de tous les jours ?	1	2	3	4
7.	Avez-vous été gêné(e) dans vos activités de loisirs ?	1	2	3	4
8.	Avez-vous eu le souffle court ?	1	2	3	4
9.	Avez-vous ressenti de la douleur ?	1	2	3	4
10.	Avez-vous eu besoin de repos ?	1	2	3	4

11. Avez-vous eu des difficultés à dormir ?	1	2	3	4
12. Vous êtes-vous senti(e) faible ?	1	2	3	4
13. Avez-vous manqué d'appétit ?	1	2	3	4
14. Avez-vous eu des nausées (mal au cœur) ?	1	2	3	4
15. Avez-vous vomi ?	1	2	3	4

Passez à la page suivante S.V.P.

Au cours de la semaine passée :	**Pas du tout**	**Un peu**	**Assez**	**Beaucoup**
16. Avez-vous été constipé(e) ?	1	2	3	4
17. Avez-vous eu de la diarrhée ?	1	2	3	4
18. Étiez-vous fatigué(e) ?	1	2	3	4
19. Des douleurs ont-elles perturbé vos activités quotidiennes ?	1	2	3	4
20. Avez-vous eu des difficultés à vous concentrer sur certaines choses, par exemple, pour lire le journal ou regarder la télévision ?	1	2	3	4
21. Vous êtes-vous senti(e) tendu(e) ?	1	2	3	4
22. Vous êtes-vous fait du souci ?	1	2	3	4
23. Vous êtes-vous senti(e) irritable ?	1	2	3	4
24. Vous êtes-vous senti(e) déprimé(e) ?	1	2	3	4
25. Avez-vous eu des difficultés à vous souvenir de certaines choses ?	1	2	3	4
26. Votre état physique ou votre traitement médical vous ont-ils gêné(e) dans votre vie familiale ?	1	2	3	4
27. Votre état physique ou votre traitement médical vous ont-ils gêné(e) dans vos activités sociales (par exemple, sortir avec des amis, aller au cinéma...) ?	1	2	3	4
28. Votre état physique ou votre traitement médical vous ont-ils causé des problèmes financiers ?	1	2	3	4

Pour les questions suivantes, veuillez répondre en entourant le chiffre entre 1 et 7 qui s'applique le mieux à votre situation

29. Comment évalueriez-vous votre état de santé au cours de la semaine passée ?

1	2	3	4	5	6	7
Très mauvais						Excellent

30. Comment évalueriez-vous l'ensemble de votre qualité de vie au cours de la semaine passée ?

1	2	3	4	5	6	7
Très mauvais						Excellent

18.6.2 KS-adapted DLQI

Au cours des 7 derniers jours,

1. Votre peau vous a t-elle fait souffrir, brûler ou démanger ?
☐ Énormément ; ☐ Beaucoup ; ☐ Un peu ; ☐ Pas du tout ; ☐ Non concerné
2. Vous êtes-vous senti(e) gêné(e) ou complexé(e) par votre problème de peau ?
☐ Énormément ; ☐ Beaucoup ; ☐ Un peu ; ☐ Pas du tout ; ☐ Non concerné
3. Votre problème de peau vous a-t-il gêné(e) pour faire des courses, vous occuper de votre maison ou pour jardiner ?
☐ Énormément ; ☐ Beaucoup ; ☐ Un peu ; ☐ Pas du tout ; ☐ Non concerné
4. Votre problème de peau vous a-t-il influencé(e) dans le choix de vos vêtements que vous portiez ?
☐ Énormément ; ☐ Beaucoup ; ☐ Un peu ; ☐ Pas du tout ; ☐ Non concerné
5. Votre problème de peau a-t-il affecté vos activités avec les autres ou vosloisirs ?
☐ Énormément ; ☐ Beaucoup ; ☐ Un peu ; ☐ Pas du tout ; ☐ Non concerné
6. Avez-vous eu du mal à faire du sport à cause de votre problème de peau ?
☐ Énormément ; ☐ Beaucoup ; ☐ Un peu ; ☐ Pas du tout ; ☐ Non concerné
7. Votre problème de peau vous a-t-il complètement empêché de travailler ouétudier ?
☐ Énormément ; ☐ Beaucoup ; ☐ Un peu ; ☐ Pas du tout ; ☐ Non concerné
8. Votre problème de peau a-t-il rendu difficile vos relations avec votre conjoint(e), vos amis ou votre famille ?
☐ Énormément ; ☐ Beaucoup ; ☐ Un peu ; ☐ Pas du tout ; ☐ Non concerné
9. Votre problème de peau a-t-il rendu votre vie sexuelle difficile ?
☐ Énormément ; ☐ Beaucoup ; ☐ Un peu ; ☐ Pas du tout ; ☐ Non concerné

Score : Enormément=3 ; Beaucoup=2 ; Un peu=1; Pas du tout=0; Non concerné=0Total DLQI : 0-27