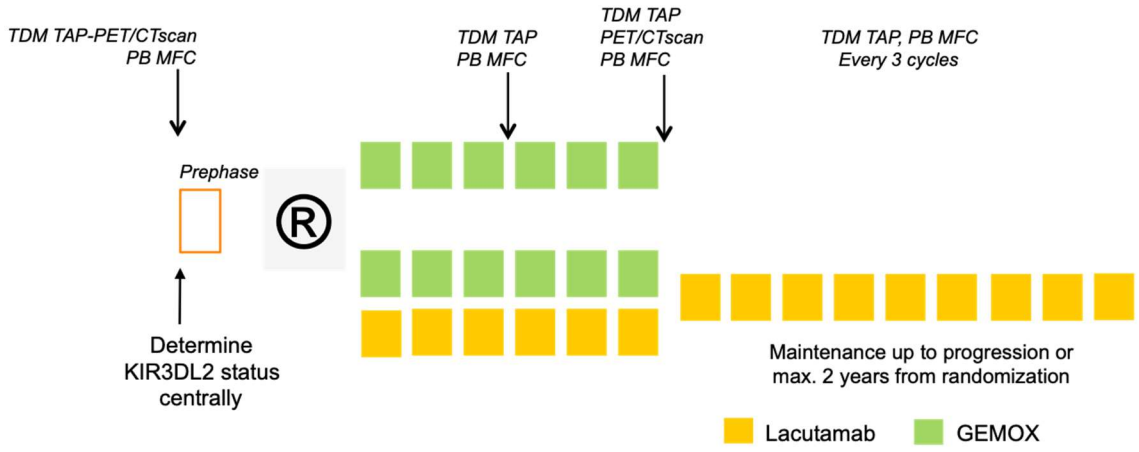
Title	**A randomized phase II study of Lacutamab in patients with peripheral T-cell lymphoma** An open label, multi-center randomized phase II study evaluating the safety and efficacy of Lacutamab in patients with refractory or relapsing peripheral T-cell lymphoma.
Sponsor	LYSARC
Phase	Randomized Phase II study
Study Type	Interventional
Investigational product	Lacutamab (monoclonal anti-KIR3DL2 antibody)
Population	Patients aged over 18 years old with KIR3DL2+ Peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS), peripheral T cell lymphoma (PTCL) with T-follicular helper (TFH) phenotype (e.g angioimmunoblastic T-cell lymphoma (AITL), Follicular T-cell lymphoma, Nodal peripheral T-cell lymphoma with TFH phenotype), anaplastic large-cell lymphoma (ALCL), HTLV-1 associated T-cell lymphoma (ATL), Hepatosplenic T-cell lymphoma (HSTL) and other rare PTCL, as enteropathy-associated T-cell lymphoma (EATL), monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL), NK/T-cell lymphoma (NKT), aggressive NK cell leukemia (ANKL), primary cutaneous gamma/delta positive T-cell lymphoma (PCGD-TCL), subcutaneous panniculitis-like T-cell lymphoma (SPTCL)
Coordinating Investigators from the LYSA	Morgane CHEMINANT / Sylvain CARRAS (PI juniors) Olivier HERMINE / Gandhi DAMAJ (PI seniors)
Centers	32 centers from LYSA in France & 8 centers from LYSA in Belgium Germany: 13 centers South Korea: 6 centers
Planned study duration	The inclusion period is 3 years. Estimated Treatment duration is 2 years (two years of treatment in total, including induction and maintenance. Patients will be followed up until the end of study. The study will end 6 months after the last intake of study medication. The total duration of the study is estimated to be approximately 5.5 years.
Rationale	KIR3DL2, a killer immunoglobulin-like receptor normally expressed by a subset of natural killer (NK) cells and a minority of CD4+ and CD8+ T lymphocytes, is aberrantly expressed in cutaneous T-cell lymphomas (CTCL)[1] and across multiple subtypes of peripheral T-cell lymphomas (PTCL) including 37% of PTCL-NOS, 35% of AITL, 42% of ALCL[4]. Lacutamab, a monoclonal antibody directed against KIR3DL2, demonstrated *in-vitro* antitumor activity and has shown beneficial clinical activity in a phase 1 dose-escalation plus expansion cohort study in relapsed advanced CTCL patients (NCT02593045)[2,3]. Preclinical experiments have shown that efficient *ex vivo* autologous ADCC assays were obtained on primary KIR3DL2+ tumour cells from 3 acute-type ATL patients using Lacutamab [4]. Moreover similar results have been obtained on primary KIR3DL2+ tumour cells from 3 PTCL (AITL, PTCL-NOS and HSTL) using Lacutamab [5]. **The aim of this study is to evaluate the efficacy of the monoclonal anti-KIR3DL2 antibody Lacutamab in patients with KIR3DL2 positive PTCL.** 1. Battistella M, Leboeuf C, Ram-Wolff C, et al. KIR3DL2 expression in cutaneous T-cell lymphomas: expanding the spectrum for KIR3DL2 targeting. *Blood*. 2017;130(26):2900–2902.

	2. Marie-Cardine A, Viaud N, Thonnart N, et al. IPH4102, a Humanized KIR3DL2 Antibody with Potent Activity against Cutaneous T-cell Lymphoma. *Cancer Res.* 2014;74(21):6060–6070. 3. Bagot M, et al. IPH4102, a first-in-class anti-KIR3DL2 monoclonal antibody in patients with refractory cutaneous T cell lymphoma: An international multicentre phase 1 trial. Lancet Oncology, *in press*. 4. Cheminant M, Lhermitte L, Bruneau J et al. KIR3DL2 contributes to delineate the Acute-type and is a therapeutic target in Adult T-cell leukemia/lymphoma. *Abstract 238, ICML Lugano 2019*. 5. Cheminant M, Decroos A, Bruneau J, et al. KIR3DL2 is expressed in peripheral T-cell lymphomas and may be a therapeutic target. *Abstract 157, ICML Lugano 2019*.
Study description	This is an open-label multicenter randomized phase II study to evaluate the safety and efficacy of the **monoclonal anti-KIR3DL2 antibody Lacutamab in patients with Refractory/Relapsing (R/R) KIR3DL2 positive PTCL-NOS, PTCL-TFH (including AITL, Follicular T-cell lymphoma, Nodal peripheral T-cell lymphoma with TFH phenotype), ALCL, ATL, HSTL, EATL, MEITL, NKT, ANKL, PCGD-TCL, SPTCL.**
Number of patients	**56 patients**
Study objectives	➢ **<u>Primary objective:</u>** To evaluate the median modified progression-free survival (mPFS) of Lacutamab in patients treated with Gemcitabine-oxaliplatine at relapse followed by a Lacutamab maintenance, in R/R patients with KIR3DL2 positive PTCL-NOS, PTCL-TFH (including AITL, Follicular T-cell lymphoma, Nodal peripheral T-cell lymphoma with TFH phenotype), ALCL, ATL, HSTL, EATL, MEITL, NKT, ANKL, PCGD-TCL, SPTCL. The primary endpoint is the modified PFS rate, calculated as time from randomization until one of the following event occurs, whichever comes first: a) Disease progression (PD) b) Institution of any additional unplanned anti-tumor treatment (except allogeneic or autologous hematopoietic cell transplantations (HCT)) c) Relapse after achievement of CR/CRu or d) Death due to any cause. PD and relapse will be evaluated according to Lugano criteria (2014) by CT-scan. ➢ **<u>Secondary objectives:</u>** - To characterize the safety and tolerability of Lacutamab - To evaluate overall survival (OS) - To evaluate other clinical activity endpoints: • complete response (CR) rate and overall response rate (ORR) according to Lugano 2014 criteria (CT-scan). • response rates by PET-scanner • progression free survival (PFS) since randomization, calculated as time from randomization until one of the following event occurs, whichever comes first: a) Disease progression (PD) b) Relapse after achievement of CR/CRu or c) Death due to any cause • duration of response (DOR), calculated as time from first CR/CRu or PR according to Lugano 2014 criteria (CT-scan) until one of the following event occurs, whichever comes first: a) Disease progression (PD) b) Institution of any additional unplanned anti-tumor treatment (except allogeneic or autologous hematopoietic cell transplantations (HCT)) c) Relapse after achievement of CR/CRu or d) Death due to any cause.

	• subgroup analyses of mPFS, ORR, DOR, PFS, OS by PTCL subtype and autologous cell transplantation status • rate of patients proceeding to allogenic stem cell transplantation
Study treatment	**Identification of KIR3DL2 expression:** **Centralized screening for KIR3DL2 expression will be performed in the tumor biopsy done for the diagnosis or at relapse. Results will be available within 3 weeks. Patients need to sign a screening informed consent form to allow for KIR3DL2 expression testing and for biobanking prior to study registration.** **Treatment:** **Prior to starting on-protocol treatment, a prephase (among investigator choice) is allowed.** **Patients with R/R KIR3DL2 expressing PTCL will be stratified on relapse versus refractory criteria and randomly assigned to receive either the combination of Lacutamab and Gemcitabine-Oxaliplatin (Gem-Ox) or Gem-Ox only (2:1) for 6 cycles, followed by Lacutamab maintenance with a total treatment duration of two years of treatment**, including induction and maintenance, or until progression or unacceptable toxicity or patient refusal) if achievement of at least a partial response (PR) after 6 cycles.  **PB MFC: peripheral blood multiparameter flow-cytometry* 1. **Lacutamab** will be administered at a fixed dose of 750 mg by IV infusion over 1 hour. No dose reduction is allowed. Treatment schedule will consist of **weekly administrations x 3 weeks from C1D1 followed by an administration every three weeks x 5** (i.e. from week 4 until week 18) for maximum 6 cycles. Treatment schedule will be followed by maintenance within 3 to 8 weeks after the end of induction phase with the administration of Lacutamab every 4 weeks until disease progression or unacceptable toxicity or **up to a maximum of two years in total (including induction and maintenance)**. 2. **Gem-Ox** will be given every three weeks for a maximum of 6 cycles. **Gemcitabine and Oxaliplatin will be administered from 1000 mg/m2 and 100 mg/m2, respectively on day 1 of each cycle and repeat every 3 weeks for a total of 6 cycles.** 3. **A prephase including the use of glucocorticoids or chemotherapy (VP16, cyclophosphamide, COP), according to investigator choice, is allowed not exceeding 3 weeks before randomization.** 4. **One cycle every 21 days (D1 = D21) and for a total of 6 cycles. Patients with poor tolerance to chemotherapy can start the maintenance phase earlier after at least the**

	completion of 4 cycles in PR or CR/CRu 5. **Patients who obtained at least PR will be treated with Lacutamab maintenance until disease progression, unacceptable toxicity, patient refusal or for up to a maximum of 2 years from the start of induction.** 6. **General Scheme:** **cycles 1- 3 → evaluation 1*** → If PD: *Off study* **cycles 3-6 → evaluation 2**** → If SD or PD: *Off study* → If at least PR: **Lacutamab** maintenance until progression or up to two years. **Maintenance: every 3 months → evaluation 1*** → If PD: *Off study* * ***Evaluation 1*** (At D1 of cycle 4): clinical examination, CT scan, peripheral blood assessment by Flow cytometry. ** ***Evaluation 2*** (Performed at Day 28 of cycle 6, at permanent treatment discontinuation or the end of the study treatment): clinical examination, CT scan, PET-scan and peripheral blood assessment by Flow cytometry. **Pharmacokinetic:** a. PK before lacutamab infusion at C1D1 (before and immediately after lacutamab infusion), at C1D8, C3D1 (before and immediately after lacutamab infusion), C4D1, C6D1, start of maintenance and then every 3 months. b. ADA before lacutamab infusion at C1D1, C4D1, start of maintenance and then every 3 months. **Prophylaxis:** TRIMETHOPRINE 160 mg/ SULFAMETHOXAZOLE 800mg (Bactrim fort®): one tablet three times a week VALACYCLOVIR: 500 mg twice a day
KIR3DL2 assessment	KIR3DL2 expression will be centrally assessed on the tumor cells of the diagnostic or relapse sample as follows: - Immunohistochemistry in FFPE sections of the histological sample (Clone to add)
Assessment schedule	***Screening*** 1. A **tumor biopsy** is recommended at relapse in order to assess KIR3DL2 expression and to analyze exploratory objectives. In the absence of new available biopsy, KIR3DL2 screening will be performed on diagnostic sample. 2. The following data will be obtained: – Clinical examinations (including vital signs, ECOG performance status) – Safety tests (including complete blood counts, serum chemistries, ECG) – CTAP CT-scan – PET/CT – Biobanking of peripheral blood (DMSO) – Biobanking of normal DNA from either blood or other source free of tumor involvement – Biobanking of Frozen plasma (ctDNA) – Additional fresh blood for virology analyzes (only patients with ATL)

	3. Other screening items will be performed at inclusion in case of KIR3DL2 positivity according to the inclusion criteria. – Inclusion and exclusion criteria (clinical examination, including performance status, and safety tests, including complete blood counts, serum chemistries) – Pharmacokinetics ***During treatment:*** Clinical examinations (including vital signs, ECOG performance status) and laboratory safety tests (including complete blood counts, serum chemistries) will be obtained prior to drug administration, and before each cycle of treatment, and up to 28 days after the last study treatment administration. Clinical examination and complete blood cell counts will be obtained every week during the first cycles. AEs type, severity (according to the National Cancer Institute Common Terminology Criteria for Adverse Events [NCI-CTCAE] v. 4.03), at least onset date, duration, seriousness, and relationship to study treatment will be assessed. Laboratory abnormalities will be assessed according to the NCI-CTCAE v. 4.03. ***Response evaluation:*** Disease assessment will be performed locally using the Lugano criteria (Cheson, Fisher et al. 2014). CT imaging will be performed at baseline, after 3 and 6 cycles and repeated every 3 months during the maintenance and then every 6 months until disease progression or the end of the study Patients who discontinue study treatment for reasons other than disease progression will continue to be assessed until progression.
Inclusion and exclusion criteria	**Inclusion Criteria:** 1. Cases should be KIR3DL2-positive with at least 1% of tumour cells. 2. Patients 18 years or more at inclusion. 3. Biopsy-proven PTCL defined by the WHO 2016 criteria (the biopsy at relapse is not mandatory but recommended): – PTCL-NOS – PTCL-TFH (AITL, Follicular T-cell lymphoma, Nodal peripheral T-cell lymphoma with TFH phenotype) – ALCL – ATL: acute- or lymphoma-type – HSTL – EATL – MEITL – NKT, ANKL – PCGD-TCL – SPTCL 4. Relapsed/refractory PTCL after at least one previous line of systemic based regimen of chemotherapy (no mandatory latency after the previous treatment) 5. With a maximum of 2 prior systemic therapies, including autologous stem cell transplantation 6. Life expectancy superior to 3 months 7. Performance status ECOG 0 to 3 8. Adequate bone marrow function, defined by absolute neutrophil count (ANC) ≥ 1 G/L and platelet count ≥ 75 G/L at randomization; unless neutropenia and/or thrombocytopenia are related to PTCL 9. Transaminases (SGOT and SGPT) and Alkaline Phosphatases ≤ 2.5 x normal (N) and Bilirubin ≤ 1.5N (unless SGOT and SGPT elevated to up to 5 x ULN or bilirubin elevated due to PTCL or hemolysis)

	10. Creatinine Clearance CDK-EPI ≥ 40 mL/min 11. All men of reproductive potential and women of child-bearing potential must agree to practice effective contraception during the entire study period and for one month after the last study treatment, unless documentation of infertility exists. Additionally, women of child-bearing potential must have a negative pregnancy test 12. Able to understand and willingness to sign the informed consent form 13. Patients covered by a social security system **Exclusion criteria:** 1. Previous treatment by Gemcitabine or Oxaliplatine 2. Previous allogeneic stem cell transplantation 3. Treatment with any other investigational drugs within previous 4 weeks from inclusion in the study 4. Central nervous system involvement by the PTCL 5. Contraindication to at least one drug of the regimen 6. Significant cardiovascular impairment: congestive heart failure greater than New York Heart Association (NYHA) Class II, uncontrolled high blood pressure, unstable angina, myocardial infarction or stroke within 6 months or cardiac arrhythmia 7. Uncontrolled clinically significant inter-current illness including, but not limited to, diabetes, ongoing active infection. Patients receiving antibiotics for infections that are under control may be included in the study 8. Concurrent malignancy or prior history of malignancies unless the subject has been free of the disease for ≥ 2 years, except early stage cutaneous squamous cell carcinoma, cutaneous basal cell carcinoma, localized prostate cancer, or cervical intraepithelial neoplasia 9. Known HIV-positive, known active hepatitis A, B, or C. If latent hepatitis B (positive antiHBc), patients have to be treated with Entecavir (Baraclude®) and HBV PCR should be performed every month. 10. Pregnancy or lactation 11. Unwilling/unable to comply with the protocol. Any serious medical condition or psychiatric illness that would prevent the subject from signing the informed consent form 12. Major surgery within 4 weeks of inclusion
Safety review	Because the experimental arm of this is randomized phase II study combined a drug with a treatment for PTCL GEMOX, we plan to utilize an internal safety monitoring committee (SMC), which is comprised of the LYSARC' medical and statistical members and the coordinating investigators of the study, instead of an independent data monitoring committee (IDMC), which is traditionally reserved to phase III study. The SMC will periodically (at least every 6 months during the enrollment period or every 25-30 patients) review data throughout the study to fully evaluate the benefit-risk of lacutamab. The SMC, in accordance to the charter, may recommend study modification including termination of the study due to safety and/or efficacy concerns.
Exploratory objectives	1. Biobanking of tumour biopsy (FFPE and frozen tissue if available) at diagnosis and at relapse if available. 2. Biobanking of normal DNA from either blood or other source free of tumor involvement 3. At screening, after 3, 6 cycles, every 3 months (during the maintenance) and at relapse: – Biobanking of peripheral blood (DMSO) – Biobanking of Frozen plasma (cfDNA) 4. Additional fresh blood for virology analyzes (for patients with ATL only) 5. Pharmacokinetics:

	a. PK before lacutamab infusion at C1D1 (before and immediately after lacutamab infusion), at C1D8, C3D1 (before and immediately after lacutamab infusion), C4D1, C6D1, start of maintenance and then every 3 months. b. ADA before lacutamab infusion at C1D1, C4D1, start of maintenance and then every 3 months. 6. Immunomonitoring: at C1D1, C3D1, C4D1, C6D1, start of maintenance and then every 3 months. To explore - The correlation of KIR3DL2 expression and o other biomarkers: CD30, NK receptors (CD56, CD94, NKP44, NKG2D, etc), cytotoxic markers (granzyme-B, TiA1, etc) (immunohistochemistry, flow cytometry, RT-MLPA, nanostring, RNA seq) o mutational status of PTCL (targeted NGS) o epigenetic regulators (EZH2, methylation status, etc) o TCR repertoire o TCR signaling o NK and cytokines receptors signaling (SYK, PhSTAT3) o single cell analysis - The impact of Lacutamab treatment: evaluation at diagnosis, after 6 cycles and in relapsing patients o tumor microenvironment (immunohistochemistry) o immunologic phenotypes (flow cytometry, CyTOF mass cytometry) o circulating tumor DNA (ctDNA) - The response rate according to degree of KIR3DL2 expression by IHC - To assess the Restricted Mean Survival Time (RMST)
Statistical analysis	**ANALYSIS SETS** The **Efficacy Set** will include all patients having signed the informed consent and randomized in the study, regardless of whether they have received study treatment or not. This set will be used for baseline characteristics, patient disposition summaries and efficacy parameters. Patients will be analyzed according to the randomized treatment. The **Safety Set** will include all patients having signed the informed consent, randomized and who received at least dose of treatment (whatever the drug). This set will be used for safety analyses, including extent of exposure to trial medication. Patients will be analyzed according to the treatment, which they actually received. **SAMPLE SIZE CALCULATION** Sample size calculation was performed with the SWOG tool (https://stattools.crab.org/) using a one arm survival sample size (Brookmeyer R and Crowley, JJ. A confidence interval for the median survival time. Biometrics, 38, 29-41, 1982) assuming an exponentially distributed survival time with a constant hazard rate over the course of the study. No interim analysis is planned. The hypotheses are as follows:

- improvement of the median modified PFS since randomization from 3.8 to 6.5 months (HR=0.58)
- one-sided alpha: 10%
- accrual duration: 3 years
- accrual rate: ~ 20 patients/year
- study duration: 6 years
- non comparative design: the control arm will ensure that the assumptions used for sample size calculation are verified.
- randomization ratio 2:1 in favor of the experimental arm

Based on these hypotheses, randomization of 37 patients in the experimental arm and 19 patients in the control arm is planned. The power to reject the null hypothesis is 80.11%.
Assuming that 30% of PTCL patients express KIR3DL2, it will be necessary to screen 187 patients.

ANALYSIS PLAN

No comparison will be performed between the 2 arms.

Continuous data: will be summarized in tables displaying sample size, mean, standard deviation, median, range; quartiles will also be presented when considered relevant

Categorical data: will be described in counts and percentages (of non-missing data)

Response rates: will be expressed with 95% confidence intervals according to Pearson-Clopper method. The number and percent of patients falling into each category of response will be provided. Patients without response assessment will be considered as non-responder.

Time to event: will be performed using Kaplan-Meier method. Survival probabilities, median survival and quartiles will be estimated with their 95% CI. Survival curves will be provided. CIs for median modified PFS will also be done at 80% to be consistent with one-sided 10% level of significance.

The modified PFS and DOR: will be censored at allogeneic cell transplantation. Autologous cell transplantation won't be considered as an event.

TIME OF ANALYSIS

Two analyses will be performed.

- ***Main criterion analysis***

  The analysis is planned to be conducted approximately 6.5 months after the randomization of the last patient or at the latest when median modified PFS has been reached in the experimental arm.

- ***End of study analysis***

  At the end of study, an update of the database will be done and a rerun of the survival analyses will be performed.

Cost	Cf Budget proposal

FLOW CHART

Visits	Screening	C1D8, C1D15	At Each C1 to C6	After C3	After C6
Month				C3D28 (C4D1)	C6D28
Written informed consent	**X**				
Diagnosis pathological report	**X**				
Archive biopsy sample from diagnosis collection	**X**				
KIR3DL2 assessment	**X**				
Inclusion/Exclusion criteria	**X**				
Clinical examination[0]	**X**		**X**	**X**	**X**
Patient characteristics[0]	**X**				
Performance Status	**X**		**X**	**X**	**X**
HIV, HTLV-1, HBV, HCV serologies	**X**				
Additional fresh blood for virology analyzes (only patients with ATL)	**X**			**X**	**X**
ECG	**X**				**X**
CT scan	**X**			**X**	**X**
PET scan	**X**			**X**	**X**
Blood cell count[1]	**X**	**X**	**X**	**X**	**X**
Biochemical test [2]	**X**	**X**	**X**	**X**	**X**
Pharmacokinetics (e.g.)	**X**	**X**	**X**		
Adverses events[6]		**X**	**X**	**X**	**X**
Concomitant treatment	**X**		**X**	**X**	**X**
Centralized pathology reviewing	**X**				
Biobanking of peripheral blood (DMSO)	**X**			**X**	**X**
Biobanking of normal DNA from either blood or other source free of tumor involvement	**X**				
Biobanking of Frozen plasma (ctDNA)	**X**			**X**	**X**

0. B symptoms, body weight, vital sign, clinical exam, Age, gender, height, relevant medical history, history of the NHL, Ann Arbor staging
1. Blood cell count: at D1, D2 cycle 1 and D1 D8 D15 D21 at each cycle and for evaluation.
2. Biochemical test, at C1D1: blood ionogram (Na, K, Cl, Ca, Mg, phosphorus, HCO3-, glucose, protein), serum creatinin, AST, ALT, total bilirubin and alkaline phosphatases + urea at baseline , LDH, CRP, EPS, IgG, IgM, IgA,

β2 microglobuline. At C1 D1-2-3: Tumor lysis syndrome (blood ionogram, serum creatinin, AST, ALT, total bilirubin, LDH and alkaline phosphatases + urea, LDH). At each D8, D15, D21: blood ionogram (Na, K, Cl, Ca, protein), serum creatinin, AST, ALT, total bilirubin, LDH and alkaline phosphatases.

3. Blood for MRD detection: at diagnosis, after cycle 3, after cycle 6 and every 6 months after end of treatment:
4. Blood and serum sample for exploratory analysis: banking at inclusion, cycle 3 and cycle 6
5. Adverse events: Continuous reporting until 28 days after last treatment administration