Official Title of Study:

Efficacy and Safety of Oral Azacitidine (CC-486) Compared to Investigator's Choice Therapy in Patients With Relapsed or Refractory Angioimmunoblastic T Cell Lymphoma

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ORACLE

OA-CL-LYM-LYSARC-13134C

Randomized Phase 3 Study evaluating the Efficacy and the Safety of Oral Azacitidine (CC-486) compared to Investigator's Choice Therapy in Patient with Relapsed or Refractory Angioimmunoblastic T cell Lymphoma

A STUDY SPONSORED BY:

LYSARC

LYSARC: THE LYMPHOMA ACADEMIC RESEARCH ORGANISATION

✉: [redacted]

Bristol -Myers Squibb K.K. Japan

✉: [redacted]

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Version and date of Protocol: Version 3.0 dated 22/04/2022

EudraCT number: **2017-003909-17**

CONFIDENTIALITY STATEMENT

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Approved v2.0 930190408 2.0

PROTOCOL APPROVAL & SIGNATURE PAGE

ORACLE

RANDOMIZED PHASE 3 STUDY EVALUATING THE EFFICACY AND THE SAFETY OF ORAL AZACITIDINE (CC-486) COMPARED TO INVESTIGATOR'S CHOICE THERAPY IN PATIENT WITH RELAPSED OR REFRACTORY ANGIOIMMUNOBLASTIC T CELL LYMPHOMA

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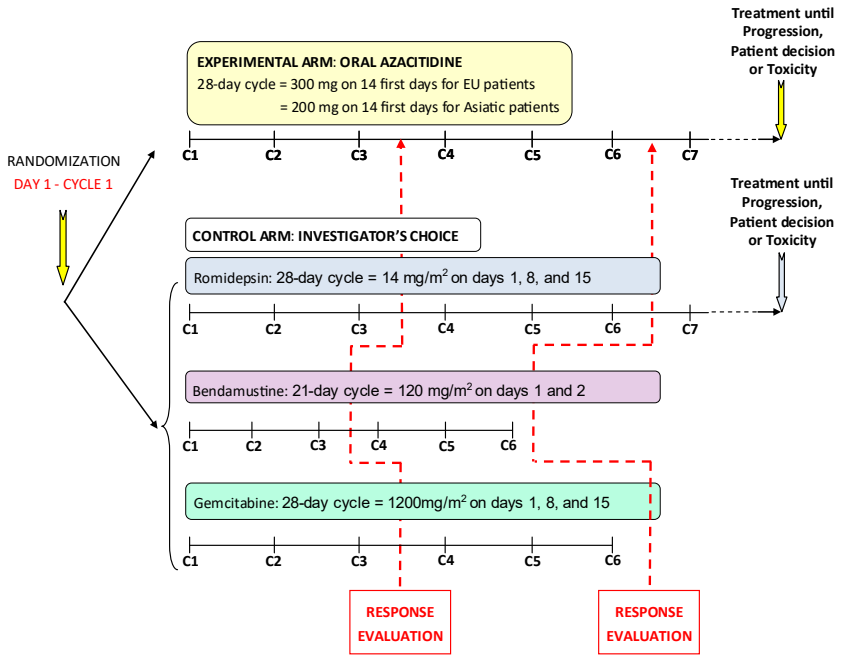
1 SYNOPSIS

Study ID **Study number** **EudraCT N°**	ORACLE OA-CL-LYM-LYSARC-13134C 2017-003909-17
Study title	Randomized Phase 3 Study evaluating the Efficacy and Safety of Oral Azacitidine (CC-486) compared to Investigator's Choice Therapy in patients with Relapsed or Refractory Angioimmunoblastic T cell Lymphoma
Study design	This phase 3, multicentric, open-label, randomized study is designed to compare the efficacy and safety of Oral azacitidine *versus* single-agent Investigator's Choice Therapy in patients with Relapsed or Refractory Angioimmunoblastic T-cell Lymphoma. The study will be conducted in select countries in Europe and South Korea sponsored by LYSARC and in Japan sponsored by Bristol-Myers Squibb. There will be a combined enrollment target of 86 randomized patients, with approximately 14 randomized patients from Japan. The enrollment to the randomized study will start at European sites in parallel to a safety run-in part in Japan. A safety run-in will be conducted to confirm the tolerability of oral azacitidine at doses of 100 mg and 200 mg once daily (QD) in Asian patients. Once oral azacitidine at 200 mg QD is confirmed as tolerable, Asian patients from Japan and South Korea will start to be randomized into the main study. Additional Japanese patients (non-randomized) are anticipated to enroll to the safety run-in with a 3+3 design on 2 doses. The data from all countries will be collected into one database and the statistical analyses will be performed on the combined total of patients enrolled. The same Independent Data Monitoring Committee (IDMC), central pathology, central imaging and Independent Review Committee (IRC) will be utilized.
Development phase	Phase 3
Investigational product	Oral azacitidine (CC-486)
Protocol version	Version 3.0
Sponsor	LYSARC and Bristol-Myers Squibb
Coordinating investigator **Co-coordinating investigator**	[redacted]
Sites	LYSARC sponsors: LYSA sites in France and Belgium. Sites in, Republic of Korea, Austria, United Kingdom and Denmark. Bristol-Myers Squibb sponsors: Sites in Japan.

Study Objectives and endpoints	**Primary endpoint** Progression free survival (PFS), using local assessment of progressive disease (refer Section 9.9 for additional details) according to Lugano Response Criteria (2014) **Key secondary endpoint** Overall Survival (OS) **Other secondary endpoints**: all efficacy assessments will be based on Lugano Response Criteria (2014) - PFS by the Independent Review Committee (IRC) - Overall response rate (ORR) - Complete response rate (CRR) - Duration of response - Time to response - PFS2 using local assessment of progressive disease - HRQOL endpoints EORTC QLQ-C30 - Safety **Optional exploratory objectives (separate informed consent for biology) and endpoints:** - To correlate the presence of genomic alterations and gene expression data to clinical response to oral azacitidine and survival data - To study the methylation profile of the tumors - To study the myeloid population in bone marrow of these patients - HRQOL endpoints EQ-5D-5L - To characterize the pharmacokinetics (PK) of oral azacitidine in Japanese patients
Study timelines	The study treatment must start within 4 days after the enrollment. Start of recruitment: 09 November 2018 End of recruitment: 22 February 2021 Planned end of study: Q1 2024
Duration of the study	The duration of the study is estimated to be 63.5 months including follow-up. Recruitment period: 27.5 months.
Number of patients	86 patients will be randomized to oral azacitidine or investigator's choice therapy. Moreover, additional Japanese patients will receive oral azacitidine (not-randomized) and be enrolled to safety run-in analyses with 3+3 design on 2 doses.
Inclusion criteria	Patients must satisfy all following criteria to be enrolled in the study: 1. Patient is ≥ 18 years of age at the time of signing the informed consent form (ICF). 2. Patient must understand and voluntarily sign an ICF prior to any study-specific assessments/procedures being conducted. 3. Patient is willing and able to adhere to the study visit schedule and other protocol requirements. 4. Patient had local diagnosed peripheral T cell lymphoma (PTCL) with T-follicular helper (TFH) phenotype according to the criteria of the latest WHO classification based on a surgical lymph node biopsy or needle core biopsy including any one of: • Angioimmunoblastic T cell lymphoma (AITL)

	• Follicular T cell lymphoma • Nodal peripheral T-cell lymphoma with TFH phenotype There should be a documented expression of minimum two TFH markers by the tumoral cells among this panel of markers: CD10, CXCL13, PD1, ICOS, and BCL6 by the tumoral cells by immunohistochemistry. Biopsy at relapse or progression is not mandatory, but highly encouraged on a surgical or needle core biopsy, and diagnostic tissue should be available for central pathology review and ancillary molecular studies. Local pathology report should be reviewed by the sponsor's medical monitor prior to enrollment. 5. ECOG performance status 0 to 3 6. Relapsed (after partial or complete response) or refractory AITL after at least one line of systemic therapy (there is no mandatory resting period after the previous treatment as long as the biochemistry and hematology labs meet the inclusion criteria as below). 7. Meet the following lab criteria: a. ANC ≥ 1,5 x 10^9/L (≥ 1 x 10^9/L if BM involvement by lymphoma) b. Platelet ≥ 75 x 10^9/L (≥ 50 x 10^9/L if BM involvement by lymphoma) c. Hemoglobin ≥ 8 g/dL. 8. Anticipated life expectancy at least 3 months 9. At least one measurable lesion on CT that is greater than 1.5 cm in the longest diameter for nodal lesions and greater than 1.0 cm in the longest diameter for extranodal lesions. The lesion must be measurable in two perpendicular dimensions. Patients with only cutaneous disease will be excluded. 10. Female patient of childbearing potential (FCBP) may participate, providing she meets the following conditions: Have two negative pregnancy tests as verified by the investigator prior to starting study treatment: serum pregnancy test at Screening and negative serum or urine pregnancy test (investigator's discretion) within 72 hours prior to starting study treatment (Cycle 1 Day 1). She must agree to ongoing pregnancy testing during the study (before beginning each subsequent cycle of treatment), and 28 days after the last dose of study treatment. This applies even if the patient practices complete abstinence from heterosexual contact. Agrees to practice true abstinence (which must be reviewed monthly and source documented) or agree to the use of highly effective methods of contraception from 28 days prior to study treatment, and must agree to continue using such precautions during study treatment (including dose interruptions) and for up to 6 months after the last study drug administration. True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptom-thermal, post ovulation methods) and withdrawal are not acceptable methods of contraception. Cessation of contraception after this point should be discussed with a responsible physician. Agrees to abstain from breastfeeding during study participation and for at least 6 months after the last study drug administration. A female of childbearing potential (FCBP) is a female who: 1) has achieved menarche at some point, 2) has not undergone a hysterectomy or bilateral oophorectomy or 3) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24

	consecutive months (i.e., has had menses at any time during the preceding 24 consecutive months). 11. Male patient must either practice true abstinence from heterosexual contact (which must be reviewed on a monthly basis and source documented) or agrees to avoid fathering a child, to use highly effective methods of contraception, male condom plus spermicide during sexual contact with a pregnant female or a female of childbearing potential (even if he has undergone a successful vasectomy), from starting dose of study treatment (Cycle 1 Day 1), including dose interruptions through 6 months after receipt of the last study drug administration. Furthermore, male patient must agree to not give semen or sperm during study drug therapy and for a period of 1 year after end of study drug therapy. 12. For EU countries, patient covered by a social security system
Exclusion criteria	Presence of any of the following will exclude a patient from enrollment: 1. Clinical evidence of central nervous system involvement by lymphoma. Patients with suspicion of CNS involvement must undergo neurologic evaluation and CT/MRI of head and lumbar puncture to exclude CNS disease. 2. Any significant medical conditions, laboratory abnormality or psychiatric illness likely to interfere with participation in this clinical study (according to the investigator's decision) 3. Uncontrolled systemic fungal, bacterial, or viral infection (defined as ongoing signs/symptoms related to the infection without improvement despite appropriate antibiotics, antiviral therapy, and/or other treatment) 4. Known Human Immunodeficiency Virus (HIV) or Hepatitis C (HCV) infection, or evidence of positive HTLV1 serology or of active Hepatitis B Virus (HBV) infection defined as: - HBs Ag positive - HBs Ag negative, anti-HBs antibody positive and/or anti-HBc antibody positive with detectable viral DNA 5. Impaired renal function (calculated MDRD or Cockcroft-Gault Creatinine Clearance < 30 ml/min) or impaired liver function tests (Serum total bilirubin level > 2.0 mg/dl [34 µmol/L] (except in case of Gilbert's Syndrome, or documented liver or pancreatic involvement by lymphoma), Serum transaminases (AST or ALT) > 3 upper normal limits) unless they are related to the lymphoma. 6. Active malignancy other than the one treated in this research. Prior history of malignancies, other than low risk myelodysplastic syndrome (MDS) or chronic myelomonocytic leukemia (CMML) at Screening (with less than 5% blasts in bone marrow), unless the patient has been free of the disease for ≥ 3 years. However, patients with the following history/concurrent conditions are allowed: a. Basal or squamous cell carcinoma of the skin b. Carcinoma in situ of the cervix c. Carcinoma in situ of the breast d. Incidental histologic finding of prostate cancer (T1a or T1b) using the tumor, nodes, metastasis [TNM] clinical staging system e. Early-stage gastric cancer suitable for endoscopic mucosal resection or endoscopic submucosal dissection

	7. Treatment with any investigational drug within 5 half-lives before planned first cycle of study treatment and during the study. Ongoing medically significant adverse events from previous treatment, regardless of the time period 8. Prior exposure to azacitidine and/ or any other demethylating agent (eg, decitabine) 9. Prior exposure to planned investigator's choice therapy (e.g., prior exposure to gemcitabine is an exclusion if gemcitabine is the planned investigator's choice therapy prior to randomization) 10. Concurrent use of corticosteroids unless the patient is on a stable or decreasing dose for ≥ 1 week prior to informed consent form signature. 11. Knowing or suspected hypersensitivity to active substance or to any of the excipients. 12. Pregnant, planning to become pregnant, or lactating woman 13. Candidate for hematopoietic stem cell transplantation 14. History of active inflammatory bowel disease (e.g., Crohn's disease, ulcerative colitis), celiac disease (i.e., sprue), prior gastrectomy or upper bowel removal, or any other gastrointestinal disorder or defect that would interfere with the absorption, distribution, metabolism or excretion of the oral azacitidine and/or predispose the patient to an increased risk of gastrointestinal toxicity per investigators' discretion. Any condition causing inability to swallow tablets. 15. Significant active cardiac disease within the previous 6 months, including: - New York Heart Association (NYHA) class IV congestive heart failure - Unstable angina or angina requiring surgical or medical intervention; and/or - Myocardial infarction 16. Patient deprived of his/her liberty by a judicial or administrative decision 17. Adult patient under legal protection
Study treatment	Patients are randomly assigned to receive either oral azacitidine (CC-486) or single-agent investigator's choice therapy. Cross-over to oral azacitidine is not allowed. Asian patients, including Japan and South Korea will be randomized only after IDMC confirms a tolerable dose from the safety run-in in Japan. 

EXPERIMENTAL ARM

- Oral azacitidine is administered until disease progression or patient decision or unacceptable toxicity:
  - For non-Asian patients: 300 mg QD x 14 days of 28-day cycle
  - For Asian patients: start with 200 mg QD x 14 days of 28-day cycle

Patients will be monitored for toxicity using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 4.03 as a guide for the grading of severity. Guidelines are described below:

NCI-CTCAE Toxicity Grade	Action
Neutropenia (Grade 4)	• If Grade 4 neutropenia (< 0,5 x 109/L) occurs during a cycle: o Start supportive care (eg, G-CSF) and o Continue with IP at the next lower dose level (200 mg if starting dose was 300 mg or 150 mg if starting dose was 200 mg). • If Grade 4 neutropenia persists more than 7 days at a reduced dose, interrupt IP. • To start a new cycle at prior reduced dose, ANC should be improved or stabilized (ANC > 1,0 x 109/L) unless agreed by the sponsor's medical monitor. • If a patient consecutively experiences Grade 4 neutropenia in 2 consecutive cycles, a schedule modification from 14 to 7 days of treatment will be recommended. • Treatment schedule modification requires prior discussion with the sponsor's medical monitor. • If a patient experiences Grade 4 neutropenia in 3 consecutive cycles, the sponsor's medical monitor should be contacted to discuss the treatment dose and schedule.
Febrile Neutropenia (≥ Grade 3)	• Interrupt IP until fever has resolved. • G-CSF, antibiotic, antiviral and/or antifungal use is **strongly recommended.** • Resume IP if patient is afebrile for prior last 3 days and ANC improved or stabilized (ANC > 1,0 x 10^9/L recommended but at the discretion of the investigator). • Secondary prophylaxis with G-CSF is strongly recommended as clinically indicated. • If a patient experiences febrile neutropenia in 2 consecutive cycles, the steps noted above should be followed, but IP dose should be reduced to 200 mg (if starting dose was 300 mg) or to 150 mg (if starting dose was 200 mg) upon resumption of treatment with IP.

		• If a patient experiences febrile neutropenia in 3 consecutive cycles, the steps noted above should be followed, but a schedule modification from 14 to 7 days of treatment will be recommended. • Treatment schedule modification requires prior discussion with the sponsor's medical monitor. • If a febrile neutropenia is along with ANC < 0,5 x 10^9/L, the instructions for Grade 4 neutropenia should be followed.
	Thrombocytopenia (Grade 4)	• Consider platelet transfusion if platelets counts are < 25 x 10^9/L. • If appropriate administration of platelet does not correct the platelets counts, contact the sponsor's medical monitor to consider IP dosing delay or interruption.
	Diarrhea (≥ Grade 3)	• Interrupt IP and provide adequate/optimal medical intervention. • Resume IP at same dose when toxicity resolves to ≤ Grade 1. • If event reoccurs upon re-challenge or during next treatment cycle, reduce IP dose to 200 mg (if starting dose was 300 mg) or to 150 mg (if starting dose was 200 mg). • If event reoccurs at same intensity once dose is reduced to 200 mg (if starting dose was 300 mg) or to 150 mg (if starting dose was 200 mg), follow the steps above and modify treatment schedule from 14 to 7 days of IP administration. • Treatment schedule modification requires prior discussion with the sponsor's medical monitor.
	Nausea and/or Vomiting (≥ Grade 3)	• Interrupt IP and provide adequate/maximal medical intervention. • Resume IP at same dose when toxicity resolves to ≤ Grade 1. • If event reoccurs upon re-challenge or at same intensity during next treatment cycle, reduce dose to 200 mg (if starting dose was 300 mg) or to 150 mg (if starting dose was 200 mg). • If event reoccurs at same intensity once dose is reduced to 200 mg (if starting dose was 300 mg) or to 150 mg (if starting dose was 200 mg), follow the steps above and modify treatment schedule from 14 to 7 days of IP administration. • Treatment schedule modification requires prior discussion with the sponsor's medical monitor.

Renal Dysfunction	• For unexplained elevations of serum creatinine (> 20% of baseline), hold IP or delay the start of the next cycle of treatment until values return to baseline. • Reduce IP dose in the next cycle of treatment to 200 mg (if starting dose was 300 mg) or to 150 mg (if starting dose was 200 mg). • Treatment schedule can be modified from 14 to 7 days if similar unexplained significant renal and/or electrolyte disturbances subsequently persist or recur during the next cycle of treatment. • Treatment schedule modification requires prior discussion with the sponsor's medical monitor. • Discontinue IP if similar unexplained significant renal and/or electrolyte disturbances subsequently persist or recur during the next cycle of treatment.
Other ≥ Grade 3 nonhematological toxicities	• Interrupt IP dosing if toxicity is not expected to resolve within 24 hours after using appropriate medical intervention. • Resume IP at same dose when toxicity resolves to ≤ Grade 2. • If event reoccurs upon re-challenge or at same intensity during next treatment cycle, reduce IP dose to 200 mg (if starting dose was 300 mg) or to 150 mg (if starting dose was 200 mg). • If event reoccurs at same intensity once dose is reduced to 200 mg (if starting dose was 300 mg) or to 150 mg (if starting dose was 200 mg), follow the steps above and modify treatment schedule from 14 to 7 days of IP administration. • Treatment schedule modification requires prior discussion with the sponsor's medical monitor.
Tumor Lysis Syndrome (TLS)	• Please refer Appendix 13 for further guidance on TLS diagnosis and management. • The sponsor's medical monitor should be contacted to discuss the treatment dose and schedule.

A maximum of one dose reduction step to a daily dose of 200 mg (if starting dose was 300 mg) or to 150 mg (if starting dose was 200 mg) is permitted in the event of toxicity.

If toxicity persists, a maximum of one treatment schedule modification from 14 to 7 days is permitted in the event of continuing toxicity that does not respond to dose reduction. The decision to modify a patient's treatment schedule from 14 to 7 days will first be discussed with the sponsor's medical monitor.

Dose interruptions lasting beyond 28 days should be discussed with the sponsor's medical monitor.

Patients will not be scheduled to receive treatment for less than 7 days.

Patients who have their oral azacitidine dose reduced or treatment schedule modified may return to their original dose and schedule at the next cycle in a step-wise fashion upon discussion and agreement between the investigator and the

sponsor's medical monitor. The treatment schedule will first be increased from 7 to 14 days, followed by a dose escalation step to the original starting dose (either 200 mg or 300 mg).

CONTROL ARM

- **Investigator's choice therapy** is administered either for a fixed duration (depending on the considered drug) or continued until disease progression patient decision or unacceptable toxicity. Serum potassium and magnesium should be verified before each dose of romidepsin: K+ and Mg^{2+} < LLN must be corrected (>=LLN) by oral or IV prior to romidepsin administration.

Investigator's choice therapy should only be regulatory approved and reimbursed or standard of care for the treatment of relapsed/refractory peripheral T-cell lymphoma in respective countries, which include the following: romidepsin, bendamustine and gemcitabine as follows:

✓ *Romidepsin*:

Patients will receive romidepsin 14 mg/m² on days 1, 8, and 15 of a 28-day cycle by intravenous route until disease progression, patient decision or unacceptable toxicity.

Patients will be monitored for toxicity using the national cancer institute common terminology criteria for adverse events (NCI-CTCAE), version 4.03 as a guide for the grading of severity. Guidelines are described below and can be adjusted at the discretion of the investigator:

Nonhematologic toxicities except alopecia:

- Grade 2 or 3 toxicity: Treatment with romidepsin should be delayed until toxicity returns to ≤ Grade 1 or baseline, then therapy may be restarted at 14 mg/m^2. If Grade 3 toxicity recurs, treatment with romidepsin should be delayed until toxicity returns to ≤ Grade 1 or baseline and the dose should be permanently reduced to 10 mg/m^2.
- Grade 4 toxicity: Treatment with romidepsin should be delayed until toxicity returns to ≤ Grade 1 or baseline, then the dose should be permanently reduced to 10 mg/m^2.
- Romidepsin should be discontinued if Grade 3 or 4 toxicities recur after dose reduction.

Hematologic toxicities

- Grade 3 or 4 neutropenia or thrombocytopenia: Treatment with romidepsin should be delayed until the specific cytopenia returns to ANC ≥ 1.5×10^9/L and platelet count ≥ 75×10^9/L or baseline, then therapy may be restarted at 14 mg/m^2.
- Grade 4 febrile (≥ 38.5ºC) neutropenia or thrombocytopenia that requires platelet transfusion: Treatment with romidepsin should be delayed until the specific cytopenia returns to ≤ Grade 1 or baseline, and then the dose should be permanently reduced to 10 mg/m².

✓ *Gemcitabine*:

European and South Korean patients will receive gemcitabine 1200 mg/m^2 on days 1, 8 & 15 of a 28-day cycle during 6 cycles by intravenous route. Japanese patients will receive gemcitabine 1000 mg/m² on days 1, 8 & 15 of a 28-day cycle during 6 cycles by intravenous route per product label.

✓ *Bendamustine*:

	Patients will receive bendamustine 120 mg/m^2 on days 1 & 2 of a 21-day cycle during 6 cycles by intravenous route.Bendamustine at a lower dose of 90 mg/m^2 on days 1 & 2 of each cycle may be given at the investigator's discretion in older / unfit patients Patients treated by gemcitabine or bendamustine will be monitored for toxicity using the national cancer institute common terminology criteria for adverse events (NCI-CTCAE), version 4.03 as a guide for the grading of severity. Guidelines are described below and can be adjusted at the discretion of the investigator: Treatment should be terminated or delayed if neutrophils and/or platelet values drop to < 1.0 x 10^9/L or < 75 x 10^9/L, respectively. Treatment can be continued after neutrophil values have increased to > 1.5 x 10^9/L and platelet values to > 100 x 10^9/L. In case of non-haematological toxicity dose reductions have to be based on the worst CTC grades in the preceding cycle, and 1/3 dose reduction, then 2/3 dose reduction, or interruption of treatment are recommended. If a patient requires a dose modification the individually calculated reduced dose must be given on day 1 and 2 of the respective treatment cycle. In case of treatment interruptions lasting beyond 28 days, investigator's choice therapy should be stopped and this will be considered as a permanent treatment discontinuation. This should be discussed with medical monitor to ensure that disease evaluations are performed prior to starting new therapy. **RELEVANT PROPHYLACTIC OR TREATMENT MEASURES** Prophylactic use of granulocyte colony-stimulating factor (G-CSF) or erythropoietin stimulating agent (ESA) is allowed. G-CSF use is allowed in case of febrile neutropenia. ESA can be used for the treatment of anemia in symptomatic patients with non-myeloid tumors receiving chemotherapy according to the EMEA guidance from June 2008. For patients receiving ESA, deep vein thrombosis (DVT) prophylaxis should be either IMW heparin or warfarin according to the investigator. Prophylactic use of anti-emetics is strongly recommended 30 minutes prior to each dose of oral azacitidine. Choice of anti-emetics is at the discretion of the investigator. *<u>Note</u>: In the safety run-in (Japanese patients), <u>prophylactic use</u> of hematopoietic growth factors (e.g., filgrastim and pegfilgrastim) as well as transfusional support (packed red blood cells or platelets) are not allowed during the dose-limiting toxicity (DLT) observation period.* **PROHIBITED THERAPY** The following concomitant medications are specifically excluded during the course of the study: • Cytotoxic chemotherapeutic agents or experimental agents • Other investigational therapies or devices • Azacitidine for injection, decitabine, or other demethylating agents • Mogamulizumab • Concomitant radiotherapy • Romiplostim and other TSAs (eg, Interleukin-11) • Hydroxyurea • Lenalidomide • Pomalidomide • Thalidomide • Arsenic trioxide

	• Interferon • Oral Retinoids (topical retinoids are permitted) **ALLOWED THERAPY** Rituximab is not prohibited to treat manifestations resulting from secondary effects of tumor such as autoimmune hemolytic anemia and thrombocytopenia purpura.
Assessment schedule	Clinical examinations (including ECOG performance status*), laboratory safety tests** (including complete blood counts, serum chemistries and serologies) and QoL assessments* will be obtained within 28 days prior enrollment, and before each cycle of treatment. Complete blood cell counts will be performed every week during the first 24 weeks. An electrocardiogram will be performed just before starting treatment (after administration of antiemetic premedication if possible) for measurement of the corrected QT interval according to the Fridericia formula. A serum pregnancy test at Screening and a serum or urine pregnancy test within 72 hours prior to starting treatment will be performed for all females with childbearing potential. Pregnancy tests will also be performed before each cycle of treatment and 28 days after the last study drug administration. Tumor assessment (clinical examination, laboratory tests, pelvis, abdominal, chest and cervical CT scan, bone marrow examination) will be performed at baseline, after 3 cycles and 6 cycles of treatment and every 12 weeks thereafter. An optional PET scan, but highly recommended, will be performed at baseline and after 6th cycle. To ensure comparability, baseline and on-study methods for response assessment will be performed using identical techniques. * Until OS analysis ** After OS analysis, those assessments are recommended according to the local standard of care, for safety purposes.
Safety run-in (Japan)	The first three Japanese patients will receive oral azacitidine 100 mg 14/ 28 days. Once the last patient of this cohort completes 1 cycle at 100 mg 14/ 28 days, IDMC will review the safety data from this first cohort. If there is no safety concern at 100 mg after data review by IDMC, 3 additional Japanese patients will receive oral azacitidine at 200 mg 14/ 28 days. Once the last patient of this cohort completes 1 cycle at 200 mg 14/ 28 days, IDMC will review the safety data of this second cohort. If there is no safety concern after data review by IDMC of these 3 patients, Asian patients in Japan and South Korea, will be randomized into the study, and the patients at the 100 mg cohort could be escalated to 200 mg 14/ 28 days at the discretion of the investigator. These patients for safety run-in will not be included in the efficacy analysis based on the Intent-To-Treat set. Additional patients would be enrolled into safety run-in if IDMC deems necessary.
Safety consideration	All AEs and AESI whatever the grade, regardless of the relationship to treatment, occurring from the date of informed consent signature to 28 days after last drug administration (i.e. oral azacitidine, romidepsin, gemcitabine and bendamustine), will be recorded in the AE pages of the eCRF. The following AEs are considered as of special interest and require attention from investigator if occurring: Ischemic colitis, infections (limited to Grade ≥ 3 and SAE), Hemorrhagic events, Tumor lysis syndrome, Interstitial lung disease. In addition,

	they have to be reported immediately in the eCRF, irrespective of seriousness criteria.This trial is designed to allow early termination or modification of the protocol for safety concerns based on the advice of an Independent Data Monitoring Committee (IDMC). An IDMC will periodically review ongoing safety data throughout the study and make recommendations to the sponsor regarding any safety concerns. More details about IDMC operations will be provided in the IDMC Charter.
Registration for screening and enrollment	Once a patient gives written consent, the patient may enter the Screening period, which is permitted to last up to 28 days. During the Screening Period, the investigator will choose one regimen ("Investigator's Choice Therapy") for the patient. Investigator's choice therapy should only be regulatory approved and reimbursed or standard of care for the treatment of relapsed/refractory peripheral T-cell lymphoma in respective countries, which include the following: romidepsin, bendamustine, and gemcitabine. In addition, during the Screening Period, the patient will undergo safety and other assessments to determine eligibility for the study and undergo randomization to either experimental arm (Oral azacitidine) *versus* control arm (Investigator's Choice Therapy). Screening and enrollment will be performed through the internet network [redacted] At the Screening, the pathology report (French version for French and Belgian patients and English version for other countries) and the completed "pathological form" must be sent to the sponsor's medical monitor for diagnosis validation before enrollment. After the sponsor's medical monitor agreement, patients will be randomly assigned to treatment arms (standard or experimental) and stratified according to: • Number of prior line treatment: 1-2 *versus* > 2 • Previous/Concurrent MDS or CMML: Yes *versus* No
Independent Review Committee (IRC)	The Independent Review Committee (IRC) will perform a blinded, independent assessment of the progression and the corresponding date of the progression or relapse for each patient according to Lugano Response criteria (2014). The IRC will be composed of: - An independent review of all CT scans performed by two independent radiologists (with an additional radiologist in case of discrepancy). - An independent review performed by an independent hematologist. The hematologist will perform assessment of progression and the corresponding date of the progression or relapse for each patient according to Lugano Response criteria (2014). [redacted] will have access to the result of central CT scan review and also of clinical data, biological results, bone marrow biopsy and any other relevant exams for confirmation of progression. Details of the IRC activities will be described in a separate IRC charter.
Ancillary Studies	To determine predictive factors, especially molecular markers, associated with response to oral azacitidine in nodal TFH PTCL, we will sequence DNA and RNA from lymphoma samples at diagnosis and relapse and correlate the presence of genomic alterations and gene expression data to clinical presentation, response to oral azacitidine and survival data. We will also study DNA methylation in these samples. As first oncogenic events are supposed to occur in hematopoietic progenitors in TFH derived PTCL, we will study hematopoietic populations in the

	bone marrow and assess the presence of mutations known to drive lymphomagenesis in these various hematopoietic populations. Study of tumor samples collected at relapse in a limited number of cases of relapsing patients could aid to identify mechanism of oral azacitidine resistance in these lymphomas. Finally, this study could offer the opportunity to collect a unique collection of biological material to allow ancillary analysis. **BASED ON BIOLOGICAL SAMPLING PERFORMED IN THE CLINICAL TRIAL:** **FRENCH AND BELGIAN PATIENTS:** Only at baseline: - Saliva sample for genetic DNA analysis At baseline, at the end of cycle 3 and in case of relapse or progression: - Around 5mL of bone marrow on EDTA tubes for myeloid population analysis and DNA banking. - Around 28mL of blood on EDTA tubes for plasma and DNA banking, myeloid population analysis, flow cytometry and clonality T and B analyses. - Around 5mL of blood on dry tubes for serum banking to allow subsequent analysis such as cytokines analysis - Around 9mL of blood on STRECK tubes for cell free DNA analysis All these samples will be sent by carrier to [redacted] hospital. **ALL PATIENTS** Only at baseline and in case of relapse or progression (limited cases): Tumor biopsy: Formalin-Fixed Paraffin Embedded (FFPE) samples and when available frozen tumor samples
Statistical consideration	**Analysis sets** The Intent-to-Treat set (ITT) will include all patients having signed their informed consent and who are randomized into the trial (except Japanese patients from safety run-in), regardless of whether they received study treatment or not. All efficacy analyses will be performed on the ITT according to the treatment allocated by the randomization. The efficacy set (ES) includes all patients included in the ITT who have received at least one dose of either the study drug or the investigator's choice therapy and with histopathology confirmed by central review and relevant to the protocol, and who have baseline tumor assessments and at least one post-baseline tumor assessment The Safety Set (SS) will include all patients included in the ITT who have received at least one dose of either the study drug or the investigator's choice therapy (except Japanese patients from safety run-in cohort). The SS from safety-run (SS-SR) will include Japanese patients for safety run-in (out of randomization), having signed their informed consent and having received at least one dose of oral azacitidine. Safety analyses will be performed on the Safety Set according to actual treatment received and on Safety Set from safety run (SS-SR). The per protocol set will include all patients included in the ITT, with no major protocol violations (more details in statistical paragraph of the protocol). The DLT set includes all Japenese patients in the Safety set from safety run (SS-SR) who have completed the first cycle (at least 11 out of 14 of the scheduled doses

	of oral azacitidine) or experience a DLT (even if they discontinued before).(more details in statistical paragraph of the protocol). The Quality of Life (QoL) Set includes ITT set having returned the QoL questionnaire at baseline and at least one follow-up. The PK set will include all Japanese patients who receive at least one dose of IP and have at least one measurable concentration datum. The PK set will be used in PK analyses. **Sample Size Calculation** Primary endpoint: PFS The primary endpoint of this randomized phase 3 trial is progression free survival assessed by local review. Assumptions: - One sided superiority test - Randomization ratio 1:1 - Alpha risk: 2.5% - Power: 90% - Alternative Hypothesis: HR=0.417 (median PFS of 5 months in the standard arm vs 12 months in the experimental arm) - Dropout rate: 10% each year - One futility analysis at around 18 months (information fraction = 30%) - Futility boundary based on Lan-DeMets spending function with Pocock approximation in a non-binding design Based on these assumptions, 61 events would have to be observed. Assuming a peak recruitment rate of 5 patients / month after 18 months, 27 months of total recruitment period would be needed to recruit 86 patients. Sample size calculation was performed with EAST software version. 6.3. Key Secondary Endpoint: OS Assumptions: - One sided superiority test - Randomization ratio 1:1 - Alpha risk: 2.5% - Power: 90% - Alternative Hypothesis: HR=0.417 (median OS of 7 months in the standard arm vs 16.8 months in the experimental arm) - Dropout rate: 10% each year - One interim analysis at the time of final analysis for PFS (35 months after 1st randomization): information fraction = 91% - Efficacy boundary based on Lan-DeMets spending function with O'Brien-Fleming approximation Based on these assumptions, 57 deaths are needed to test the superiority of OS. **Analysis Plan** The primary analysis between the two study arms will be a one-sided log-rank test stratified by the number of prior lines of treatment (1-2 vs > 2) and Previous/Concurrent MDS or CMML (Yes vs No). Estimates of the treatment effect will be expressed as a hazard ratio using a stratified Cox proportional hazards analysis, including 95% confidence intervals, and stratified Log-Rank test.

Nominal P-Values and Boundaries for PFS Analysis:

Analysis	PFS Events	Nominal P-Value (one-sided)	Boundary of HR
Futility analysis for PFS	18*	0.457	0.951
Final analysis for PFS	61	0.025	0.605

* If the actual number of PFS events greatly deviates from what is expected at the time of interim analysis, the p-value interpretation will be adjusted accordingly based on the actual information fraction.

Similar statistical methods as those described for primary efficacy analysis will be used to analyze the key secondary endpoint.

Nominal P-Values and Boundaries for OS Analysis:

Analysis	OS Events	Nominal P-Value (one sided)	Boundary of HR
Interim analysis for OS (at the time of final PFS analysis)	52*	0.019	0.562
Final analysis for OS	57	0.02	0.58

* If the actual number of OS events greatly deviates from what is expeceted at the time of interim analysis, the p-value interpretation will be adjusted accordingly based on the actual information fraction.

Response rates will be compared between the two treatment arm. The number and percent of patients falling into each category of response will be provided.

Time of Analysis

Four analyses will be performed:

- Safety run-in will be conducted for each group of 3 Japanese patients who had been included and had achieved 1 cycle of treatment or having discontinued treatment. Safety results will be reviewed by an IDMC.
- The first analysis: interim futility analysis will be conducted once 18 PFS events will have been observed. It is planned to occur around 18 months after first randomized patient, i.e. after approximately 39-47 patients will have been recruited. Main criteria and safety will be analyzed. Results will be reviewed by an IDMC.
- The second analysis: final analysis for PFS will be performed after 61 PFS events assessed by the local review will have been observed. It is estimated that cut-off for analysis will occur approximately 29-35 months after the first patient has been randomized (assuming there will be no interruptions at enrollment). Interim analysis for OS will also be performed at that time.

The third analysis: final analysis for OS will be conducted once 57 deaths would have occurred, approximately 38.5 months after the first patient has been randomized (assuming there will be no interruptions at enrollment). This analysis will include all secondary endpoints.The analysis will be conducted at latest two

	years after the last randomized patients even if the number of events has not reached in estimated time. • Study closure analysis: Analysis for OS, PFS and safety will be performed at the time of study closure.

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3 LIST OF ABBREVIATIONS AND GLOSSARY OF TERMS

Abbreviation	Term
AE	Adverse Event
AJCC	American Joint Committee on Cancer
ALT (SGPT)	Alanine Transaminase (Serum Glutamic Pyruvic Transaminase)
AITL	Angioimmunoblastic T-cell Lymphoma
ANC	Absolute Neutrophil Count
Anti-HBc	Antibody to Hepatitis B Core Antigen
Anti-HBs	Antibody to Hepatitis B Surface Antigen
AST (SGOT)	Aspartate Transaminase (Serum Glutamic Oxaloacetic Transaminase)
AZA	Azacitidine
βHCG	beta-Human Chorionic Gonadotropin
BSA	Body Surface Area
CBC	Complete Blood Cell
CHOP	Cyclophosphamide, Doxorubicin, Vincristine, And Prednison
CMML	Chronic Myelomonocytic Leukemia
CR	Complete Response
CRR	Complete Response Rate
CRF	Case Report Form
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose Limiting Toxicity
DNA	Deoxyribonucleic Acid
DVT	Deep Vein Thrombosis
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EMA	European Medical Agency
ES	Efficacy Set
ESA	Erythropoietin Simulating Agent
EU	European Union
FCBP	Female of Childbearing Potential
FDA	Food and Drug Administration (United States)
FFPE	Formalin-Fixed Paraffin Embedded
GCP	Good Clinical Practice
G-CSF	Granulocyte Colony-Stimulating Factor
HBV	Hepatitis B Virus
HBs Ag	HBV surface antigen
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio
HRQoL	Health-Related Quality of Life
HTLV1	Human T-lymphotropic virus type 1
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IP	Investigational Product
IRC	Independent Review Committee
ITT	Intent-to-Treat

IV	Intravenous
LDH	Lactic Dehydrogenase
LYSA	The Lymphoma Study Association
LYSARC	The Lymphoma Academic Research Organisation
MDRD	Modification of Diet in Renal Disease
MDS	Myelodysplatic Syndrome
NCI	National Cancer Institute
NHL	Non-Hodgkin's Lymphoma
NOS	Not Otherwise Specified
ORR	Overall Response Rate
OS	Overall Survival
PD	Progressive Disease
PET	18F-FDG Positon Emission Tomography
PFS	Progression Free Survival
PK	Pharmacokinetics
PP	Per-protocol
PR	Partial Response
PS	Performance Status
PTCL	Peripheral T Cell Lymphoma
Q	Quarter
QD	Once Daily
QoL	Quality of Life
RPPS	Répertoire Partagé des Professionnels de Santé *(Health Professionals Shared Directory)*
RR	Response Rate
SAE	Serious Adverse Event
SD	Stable Disease
SPM	Second Primary Malignancy
SS	Safety Set
SS-SR	Safety Set from Safety Run
SUSAR	Suspected Unexpected Serious Adverse Reaction
SUVmax	Maximum Standardized Uptake Value
TFH	T-Follicular Helper
TSA	Thrombopoiesis-Stimulating Agents
TMA	Tissue Micro Array
ULN	Upper Limit of Normal
WHO	World Health Organization

4 RESPONSIBILITIES

4.1 Sponsor and program coordination site

4.1.1 *Sponsors*

LYSARC (the Lymphoma Academic Research Organisation)

✉ :

☎ :

Fax :

Email :

Bristol-Myers Squibb Company

✉ :

☎ :

Fax :

4.1.2 *Coordinating investigators*

✉:

☎:

Fax:

Email:

✉:

☎: Fax:

Email:

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☎:

Email: :

4.1.3 *Country coordinating investigators*

Belgium

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Italy

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☎:

Email:

United Kingdom

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Republic of Korea

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4.1.4 *Biology, anatomopathology and imaging referents*

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Imaging referent

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4.1.5 *Program coordination center*

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Clinical Project Manager

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Clinical, histopathological and biological operations (LYSARC):

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[redacted] Head of Pharmacovigilance [redacted]
[redacted] Director of the Monitoring & Site Management Division
[redacted]
[redacted] Director of the Project Management and Regulatory Affairs Division
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[redacted] Director of Biological and Histopathological Operations [redacted] LYSA-P
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[redacted]
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Fax: [redacted] (LYSA-P) [redacted] (LYSA-IM)

4.2 Investigators

All participating LYSA sites from France and Belgium and sites from Italy, Denmark, Sweden, Finland, Republic of Korea, Japan, Austria and United Kingdom may enroll patients in this study. Before screening any patient, each site must be declared to the Ethical Committee and national competent authority according to each country regulations and have a study training delivered by the sponsor or its delegate (i.e. initiation visit/call). To be declared as a participating site, all investigators must send to the sponsor all administrative documents required for regulatory submission (e.g., Curriculum vitae, for France the RPPS number).

4.3 Laboratory sites

Laboratories of each study site must provide their normal values and an updated accreditation for quality control.

5 BACKGROUND AND STUDY RATIONALE

5.1 Peripheral T-cell lymphomas

Peripheral T-cell lymphomas (PTCL) form a heterogeneous group of rare disorders that result from the clonal proliferation of mature (post-thymic) T lymphocytes accounting for approximately 15% of all lymphoid neoplasms. The most common PTCL subtype worldwide is PTCL, “not otherwise specified” (PTCL, NOS) which accounts for up to 40% of all PTCL. Angioimmunoblastic T-cell Lymphoma (AITL) is the second most common PTCL subtype worldwide, but appears more prevalent in Europe (representing 29% of the cases) than in North America or Asia where it’s estimated prevalence is below 20% (Vose et al., 2008). In France, AITL appears to be the most frequent subtype of PTCL (Leval et al., 2015). Most patients present with advanced stage disease, generalized lymphadenopathy, with or without splenomegaly. A specific skin rash is not unusual and characteristic biological abnormalities include hypergammaglobulinemia and haemolytic anemia. Prognosis is poor with only 50-60% patients reaching a remission with conventional chemotherapy and only 30% surviving 5 years after diagnosis (Lachenal et al., 2007) (Mourad et al., 2008)(Tokunaga et al., 2012)(Federico et al., 2013).

5.1.1 Pathological diagnosis of AITL and related lymphomas

The diagnosis of AITL is often difficult, essentially relying on morphological features including a polymorphous infiltrate with eosinophils and plasma cells, expansion of follicular dendritic cells (FDC), scattered large B-cell immunoblasts (often infected by EBV) and abundant arborizing venules (reviewed in Gaulard and De Leval, 2011). Most of these characteristics may individually be encountered in cases belonging to the heterogeneous group of PTCL, NOS. Some cases which do not display the whole array of morphological characteristics of AITL can be classified as borderline cases between the two entities. Inside AITL lesions, the neoplastic component is usually minor, as has been shown by analysis of the T-cell receptor repertoire on microdissected cells. Immunohistochemistry helps identifying the expansion of FDC, as well as the neoplastic component through expression of T follicular helper cell markers such as CD10, CXCL13, ICOS, PD1, Bcl-6 and SAP. In accordance with the known pathological features, the AITL molecular profile is dominated by a strong microenvironment imprint, including overexpression of B-cell- and FDC-related genes, chemokines and chemokine receptors, and genes related to extracellular matrix and vascular biology. Interestingly, the signature contributed by the neoplastic cells, albeit quantitatively minor, is enriched in genes normally expressed by TFH cells (de Leval et al., 2007).

The identification of T follicular helper cell as the cell of origin of AITL represents a major step in the understanding of the clinicobiological characteristics of the disease. Normal TFH cells constitute a minor subset of effector T cells with a specific microanatomic distribution inside the germinal center of secondary lymphoid organs and distinct gene signature and functions separable from the other known Th1, Th2, Th17 effector subsets and mainly implicated in the germinal center reaction in close collaboration with germinal center B cells (Gaulard and De Leval, 2011). Normal TFH cells can also suppress T-cell responses by inhibiting the proliferation and function of conventional CD4 T cells,

especially through transforming growth factor-b (TGF-β) and IL-10 production. The cellular derivation of AITL from TFH cells provides a rational model to explain several of the peculiar pathological and biological features inherent to AITL, i.e., the expansion of B cells, the intimate association with germinal centres in early disease stages and the striking proliferation of FDCs. In AITL, non-neoplastic cells typically represent a quantitatively major component and clinically, it is generally assumed that the manifestations of the disease reflect a deregulated immune and/or inflammatory response rather than direct complications of tumor growth. Moreover, AITL patients have defective T-cell responses, linked to both quantitative and qualitative perturbations of T-cell subsets.

Until the recent discovery of recurrent gene mutations in AITL and related lymphomas, the molecular alterations underlying the neoplastic transformation of TFH cells were largely unknown. By cytogenetic analysis clonal aberrations – most commonly trisomies of chromosomes 3, 5 and 21, gain of X, and loss of 6q - are detected in up to 90% of the cases. Chromosomal breakpoints affecting the T-cell receptor (TCR) gene loci appear to be extremely rare. A role for the c-maf transcription factor has been suggested, because its overexpression in transgenic mice induces the development of T-cell lymphomas, and high levels of c-maf have been detected in human AITL tissues. Recent work has permitted to discover recurrent gene mutations in genes which had been previously shown to be mutated in other hematologic malignancies (e.g., acute myeloid leukemia (AML), myelodysplastic syndromes …). These genes are involved in the epigenetic regulation of gene expression, and in particular in the regulation of DNA methylation. The frequency of these mutations in AITL forms a strong biological rationale for the use of demethylating agents (e.g., azacitidine) in this disease.

5.1.2 TET2 mutations

The three enzymes of the TET family (TET1, TET2 and TET3) identified in humans are evolutionarily conserved dioxygenases. The TET1 gene was initially described as a fusion partner of the MLL (myeloid/lymphoid or mixed lineage leukemia) gene in an acute myeloid leukemia (AML) with a t(10;11) (q22;q23) translocation (hence the name “Ten Eleven Translocation” or TET), with TET2 and TET3 later identified by homology searches.

Methylation at carbon atom 5 of the nucleotide cytosine (5-methyl-cytosine or 5-mC), which is the predominant epigenetic modification of DNA, and the reverse DNA demethylation process, have a profound impact on gene expression. The mechanism of cytosine methylation by DNA methyltransferases has been established for a long time. Cytosine demethylation remained enigmatic until identification of TET enzyme functions. These enzymes modify the methylation status of DNA and regulate gene transcription by catalyzing the oxidation of the 5-methyl group on 5-mC to create 5-hydroxymethyl-cytosine (5-hmC). Although the function of 5-hmC is poorly understood, iterative oxidation of 5-mC by TET protein to 5-hmC, and then 5 formylcytosine and 5 carboxylcytosine appears to be involved in the passive and active demethylation process (Kohli and Zhang, 2013).

Mutations in the TET2 gene that frequently represent an early event during the development of a wide variety of human myeloid malignancies, including myeloproliferative neoplasms (MPNs), polycythemia vera (PV), essential thrombocythemia (ET), myelofibrosis (MF), myelodysplastic syndrome (MDS), chronic myelomonocytic leukemia (CMML), and acute myeloid leukemia (AML) (Abdel-Wahab and Levine, 2013). A correlation between low 5-hmC and TET2 mutation status was reported in patients with MDS, suggesting that an altered 5-hydroxy-methylation status in promoter or imprinted region leads to deregulation of important hematopoietic regulators and participates to the malignant process (Ko et al., 2010). In half of the patients, only one copy of TET2 is mutated, arguing for a role of haploinsufficiency in transformation (Delhommeau et al., 2009). The variety of myeloid disorders carrying a TET2 mutation suggests that it may represent an early step in the transformation process, targeting the hematopoietic stem/progenitor cell compartment. This is further supported by the fact that TET2 mutations can be found in elderly individuals with clonal hematopoiesis who are at increased risk of developing haematological neoplasms (Busque et al., 2012) (Genovese et al., 2014)(Jaiswal et al., 2014). TET2 mutations may, however, also occur at late steps during the transformation of MPN to secondary acute leukemia (Kim and Abdel-Wahab, 2013).

TET2 mutations have been described for the first time in 2011 in a study including a variety of NHL subtypes (Quivoron et al., 2011a). Inside a large cohort of 190 PTCL patients, TET2 mutations were identified in 40 of 86 (47%) cases of AITL and in 22 of 58 (38%) cases of PTCL, NOS, but were absent in all other PTCL entities, with the

exception of 2 of 10 cases of enteropathy associated T-cell lymphoma. Among PTCL, NOS, a heterogeneous group of lymphomas comprising cases likely to derive from TFH cells similarly to AITL, TET2 mutations were more frequent when PTCL, NOS expressed TFH markers and/or had features reminiscent of AITL (58% vs 24%) (Lemonnier et al., 2012a). Several studies have since confirmed the important frequency of TET2 mutations in AITL, with a rate of up to 82% of cases (Odejide et al., 2014a) (Palomero et al., 2014)(Wang et al., 2015).

5.1.3 IDH1 & 2 mutations

The mutation targeting IDH1 was first discovered in 2008 by the cancer genome project that systematically sequenced 20,661 genes in 22 human glioblastoma multiforme (GBM) samples and discovered 5 instances of the same heterozygous Arg132-to-His (R132H) point mutation (Yan et al., 2009). This finding was quickly confirmed by multiple studies through directed sequencing of IDH1 and its homologue IDH2 which cumulatively established that IDH1 or, less frequently, IDH2 genes are mutated in more than 75% of grade 2 to 3 gliomas and secondary glioblastomas. A separate cancer genome project in 2009 compared the genomes from tumor and normal cells in an individual patient with acutemyeloid leukemia (AML) and identified a mutation in the IDH1 gene that was subsequently found in additional AML samples. Further directed sequencing established that the IDH1 or IDH2 genes are mutated in close to 20% of AML. Following the discovery in glioma and AML, mutations targeting IDH1 and IDH2 genes were found in multiple additional types of human tumors, including thyroid carcinomas, cartilaginous tumors, and intrahepatic cholangiocarcinomas (Krell et al., 2013).

All tumors with IDH1/2 mutations harbour heterozygous mutations. This is consistent with both a gain of function and dominant effect over the remaining wild-type allele. Nearly all IDH1/2 mutations result in single amino acid substitutions inside the enzymes' active sites, suggesting a direct impact of mutation on the catalytic properties of the enzymes. IDH1 and IDH2 mutations occur in a mutually exclusive manner in most cases, indicating a common underlying biochemical mechanism and physiologic consequence. The first biochemical alteration that is associated with tumor-derived IDH1 or IDH2 mutants is the loss of their normal activity in catalyzing the NADP+ dependent oxidative decarboxylation of isocitrate into α-ketoglutarate and NADPH. Surprisingly, the mutant IDH enzyme confers a neoenzymatic activity, transforming the α-KG to D-2-hydroxyglutarate in a NADPH dependent reaction.

Dioxygenases (also known sometimes as oxygen transferases) refer to the enzymes that incorporate both atoms of molecular oxygen (O2) into their substrates. Dioxygenases whose activity requires Fe(II) and α -KG as cofactors are often referred to as Fe(II)- and α -KG–dependent dioxygenases. The α -KG–dependent dioxygenases are present in all living organisms and catalyze hydroxylation reactions on a diverse set of substrates. They are involved in various pathways involving epigenetic, especially DNA and histones demethylation, hypoxia response regulation, collagen maturation and DNA repair, 2-HG is structurally similar to and acts as a competitive inhibitor of α-KG. 2 HG is a chiral molecule and both D and L forms don't show the same ability to inhibit α-KG dependant dioxygenases. Indeed, D-2HG appears a weaker inhibitor than L-2HG, and interestingly not all a-KG–dependent dioxygenases are expected to be inhibited equally by D-2-HG (Chowdhury et al., 2011). The ones which have higher affinities with D-2-HG would be more sensitive to the accumulation of 2-HG in IDH1/2 mutated cells. The KDM family of histone demethylases, which includes as many as 32 distinct enzymes in human cells and controls nearly all histone demethylation, is a major target of IDH1/2 mutation. This notion is supported by in vivo studies in both cultured cells and in human tumors. The second major target of IDH1/2 mutations is the TET family of DNA hydroxylases (see above). Notably, IDH mutations occur in a mutually exclusive manner with that of the TET2 gene in AML, although this does not seem to be the case in AITL.

In AITL, a first study which included a large set of peripheral T-cell lymphomas identified *IDH2* mutations in approximately 20% of angioimmunoblastic T-cell lymphomas (AITLs), but not in other peripheral T-cell lymphoma entities. These results were confirmed in an independent set of AITL patients, where the *IDH2* mutation rate was approximately 45% (Cairns et al., 2012a). As has been observed in glioma and AML, all mutations were heterozygous. However, the spectrum of mutations observed in AITL was different. Unlike in glioma and AML, no *IDH1* mutations were identified, and the *IDH2* mutations were largely confined to alterations resulting in an R172 substitution (12 R172K, 2 R172G, 1 R172T, and 1 R140G). In the study by Odejide et al, Seventeen (20%) of the 85 AITLs harbored

IDH2 R172 substitutions and 15 co-occurred with TET2 mutations. Although not statistically significant (p=0.34), the co-occurrence of IDH2 and TET2 contrasts sharply with the mutually exclusive nature of TET2 and IDH1/2 alterations in AML (Odejide et al., 2014a). Three other studies have found IDH2 mutations in up to 32% of the studied cases, respectively (Palomero et al., 2014) (Sakata-Yanagimoto et al., 2014a; Wang et al., 2015). In one study (Wang et al., 2015), AITL cases with IDH2R172 mutations demonstrated a distinct gene expression signature characterized by downregulation of genes associated with TH1 differentiation (e.g.,STAT1 and IFNG) and a striking enrichment of an interleukin 12-induced gene signature.

A specific inhibitor of IDH 2 (AG-221) is actually being developed by Agios Pharmaceuticals in collaboration with Bristol-Myers Squibb for the treatment of myeloid disorders and AITL (Stein et al., 2014).

5.1.4 DNMT3A mutations

The DNA (cytosine-5)-methyltransferase 3A (DNMT3A) is a member of the DNA methyltransferase family which includes DNMT1, DNMT3A, DNMT3B, and DNMT3L. Mutations in DNMT3A were initially described in adult AML patients in 2010-2011. Since that time, studies in additional AML cohorts have reported that DNMT3A is one of the most frequently mutated genes in AML, occurring in up to 36% of cytogenetically normal AML patients in the largest series reported to date (reviewed in (Abdel-Wahab and Levine, 2013)). Mutations in DNMT3A have been associated with adverse overall survival, and older patient age. Despite the high frequency of mutations in DNMT3A in AML and their consistent association with adverse prognosis, the biochemical effect of DNMT3A mutations on DNA cytosine methylation and transcription has not been definitively delineated. Mutations in DNMT3A can result in nonsense, frameshift, and missense alterations throughout the open-reading frame. Of note, a recurrent heterozygous mutation at residue Arginine 882 accounts for 40% to 60% of DNMT3A mutations. Limited data suggest that R882 mutations result in a loss of methyltransferase activity in in vitro assays. However, in AML cells, R882 mutations always occur with retention of the wild-type allele, suggesting the R882 mutant can serve either as a dominant-negative regulator of wild-type DNMT3A or may result in acquisition of an undefined, neomorphic enzymatic activity. In a study of 96 samples from patients with various subtypes of peripheral T-cell lymphomas, eleven out of 96 patients (11%) had a *DNMT3A* mutation, with nonsense, frameshift, missense mutations, insertions, deletions and one splice site mutation (Couronné et al., 2012a). Four other studies have confirmed a frequency of around 30% of DNMT3A mutations in AITL. As for IDH, these mutations are frequently if not always associated with TET2 mutations (Odejide et al., 2014a) (Palomero et al., 2014)(Wang et al., 2015).

In summary, AITL and some related lymphomas (mainly inside the PTCL, NOS category) are characterized by a high frequency of mutations affecting genes implicated in DNA methylation, with the particularity of the frequent coexistence of mutations in several genes inside the same tumor. These mutations are predicted to induce aberrant DNA methylation and their existence thus constitutes a strong biological rationale for the use of demethylating agents in this disease.

The two tables above summarise the findings of different studies regarding the frequency of mutations of genes implicated in DNA methylation in the AITL (first table) and PTCL, NOS subtypes (second table):

	IDH2	TET2	DNMT3A
Quivoron Cancer Cell 2011(Quivoron et al., 2011a)		33%	
Cairns Blood 2012(Cairns et al., 2012a)	25%		
Lemonnier Blood 2012(Lemonnier et al., 2012a)		47%	
Odejide Blood 2014(Odejide et al., 2014a)	20%	76%	33%
Palomero Nat Genet 2014(Palomero et al., 2014a)	13%	73%	23%
Sakata-Yanagimoto Nat Genet 2014(Sakata-Yanagimoto et al., 2014a)	30%	82%	26%

Wang Blood 2015 (Wang et al., 2015)	33%	82%	38,5%

	IDH2	TET2	DNMT3A
Quivoron Cancer Cell 2011(Quivoron et al., 2011a)		20%	
Cairns Blood 2012(Cairns et al., 2012a)	0%		
Lemonnier Blood 2012(Lemonnier et al., 2012a)		37%	
Palomero Nat Genet 2014(Palomero et al., 2014)	0%	29%	12%
Wang Blood 2015 (Wang et al., 2015)	4%	46%	37%

5.2 Therapeutic approaches

Compared to B-cell NHL, PTCL is more resistant to conventional chemotherapy and is generally associated with an inferior outcome. Numerous studies have reported poorer survival for patients with PTCL, with a median survival rate after diagnosis of less than 2 years and 5-year survival less than 30%. These data underscore the urgent need for new treatment options for patients with PTCL, especially those who typically have limited responses to salvage therapy and extremely poor overall survival (Vose et al., 2008).

Most patients with aggressive disease are treated with anthracycline (doxorubicin)-containing regimens. These include CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) or CHOP-derived regimens (M BACOD, ProMACE-MOPP, ProMACE-cytaBOM, MACOP-B).

The tendency of PTCL to relapse has prompted the initiation of several studies into high- dose chemotherapy followed by stem cell transplant at first line and for recurrent and refractory diseases. In general, these studies have found that long-term survival remains in the range of 40% for first line- chemosensitive disease (d'Amore et al., 2012). However the prognosis for patients with T-cell lymphomas that are either ineligible for or have developed disease recurrence after high-dose chemotherapy remains poor. Moreover, it should be emphasized that no randomized phase 3 trial has been yet reported in PTCL and that, by default, CHOP or CHOP-like chemotherapy, remains the most common regimen used despite its lack of efficacy.

Patients with relapsed or refractory disease have a particularly dismal outcome, with survival durations in the range of only a few months (Mak et al., 2013). Several agents have been evaluated in this setting in recent years; romidepsin (Piekarz et al., 2011) (Coiffier et al., 2012), bendamustine (Damaj et al., 2013) or belinostat (O'Connor et al., 2015). Although responses are seen with these agents, the response rate rarely exceeds 30% and responses are usually of limited duration. In the present study, stable disease after 3 months of treatment will thus be considered as a response in the estimation of the overall response rate (primary endpoint).

5.3 Rationale for treating AITL with Azacitidine

Azacitidine is a nucleoside metabolic inhibitor indicated for the treatment of patients with various myelodysplastic syndrome (MDS) subtypes. MDS are clonal hematopoietic stem-cell disorders characterized by ineffective hematopoiesis, peripheral-blood cytopenias, and increased tendency to progress to acute myeloid leukemia (AML). The survival of patients with higher-risk MDS is significantly different than that of patients with lower-risk disease. Without intervention, median survival of higher-risk patients is close to 12 months. Survival of patients with lower-risk disease is more diverse and ranges from a few months (poor-prognosis, lower-risk disease) to more than a decade (Greenberg et al., 2012).

Three different therapeutic alternatives are currently available for patients with higher-risk MDS. These include hypomethylating agents, intensive chemotherapy (ICT), and allogeneic stem-cell transplantation (alloSCT). Only one of three options, the use of the hypomethylating agent azacitidine, has been formally shown in a randomized clinical trial to improve survival of patients with higher-risk MDS. Durable responses compatible with long-term survival have been documented with the use of ICT and alloSCT.

Azacitidine has been studied in higher-risk MDS in two major randomized multicenter trials, Cancer and Leukemia Group B (CALGB) 9221 and AZA-001 (Silverman et al., 2002) (Fenaux et al., 2009). In the CALGB 9221 study, 191 patients with MDS were randomly assigned to either azacitidine (75 mg/m^2/day for 7 consecutive days every 28 days) or best supportive care (BSC). Median age was 68 years. Sixty percent of patients in the azacitidine arm, compared with 5% of patients in the control arm, responded to treatment (p=0.001). The median time to leukemic transformation or death was 21 months in patients treated with azacitidine compared with 12 months in the BSC arm (p=0.007). No significant difference in survival was observed. A landmark analysis suggested a survival advantage for patients initially on azacitidine or who had crossed over to azacitidine within 6 months of inclusion on study. AZA-001 was a randomized study designed to test the hypothesis that treatment with azacitidine resulted in improved survival compared with a menu of standard-of-care options (Fenaux et al., 2009). These options included BSC, low-dose cytarabine (ara-C), and ICT. In AZA-001, 358 patients with higher-risk MDS were randomly assigned to either azacitidine (as per CALGB 9221 schedule) or to standard of care. Median age of patients was 69 years. Median survival time was significantly better in patients treated with azacitidine versus standard-of-care options (24.5 *v* 15 months, respectively; p=0.001). With azacitidine, progression to AML was significantly delayed, and RBC transfusion requirements and rate of infections were significantly improved. The survival advantage with azacitidine was irrespective of age (including patients older than age 75 years), percentage of marrow blasts, or karyotype.

As stated above, AITL is associated with recurrent gene mutations that have also been described in MDS and which are involved in deregulation of DNA methylation. Azacitidine is an analog of the nucleoside cytosine with cytotoxic properties when used at higher doses (> 100 mg/m^2), but which displays a hypomethylating activity when used at lower doses (i.e., 50-75 mg/m^2). Azacitidine is incorporated into genomic DNA in place of cytosine residues, and act as irreversible inhibitors of DNA methyl transferases (DNMT) to which they bind covalently, thus inducing DNA hypomethylation in sister cells after several cell cycles. Azacitidine also inserts itself into RNA, the consequence of this insertion being less well known (Loiseau et al., 2015).

Several studies in MDS have correlated the existence of recurrent mutations to response to Azacitidine: In all studies, the presence of TET2 mutations were correlated with improved responded rates to Azacitidine, with an unclear impact on survival rates (Traina et al., 2014)(Itzykson et al., 2011a)(Bejar et al., 2014a). This was also true for IDH mutations (Emadi et al., 2015). Finally a recent study suggested that in AML, treatment with hypomethylating agent could overcome the poor prognosis related to TP53 alterations or complex cytogenetic (Welch et al., 2016). Although TP53 alterations are uncommon in PTCL, TP53 pathway is frequently disrupted in these diseases (Vasmatzis et al., 2012), and whether these alterations could be targeted by hypomethylating agent is unknown.

In MDS, complete response (CR) rates with azacitidine are relatively low compared with AML induction-like programs. This lower response rate is balanced by a low induction mortality rate. In most series, mortality is usually less than 5% in the first 6 to 8 weeks. This may result in the survival benefits observed with these agents in MDS. In both the CALGB 9221 and AZA-001 trials of Azacitidine (Silverman et al., 2002)(Fenaux et al., 2009) several courses of therapy (four to six cycles) were required to achieve response. Thus, at least six cycles of azacitidine seem to be required to document lack of response. It should be noted that in a small percentage of patients, responses can be observed after up to 12 cycles of therapy. In the AZA-001 trial (Fenaux et al., 2009) the median number of cycles of azacitidine administered was nine cycles (14 cycles in responders). This further suggests that prolonged treatment with azacitidine may be a key factor for the survival advantage observed with azacitidine. To further complicate matters, in addition to patients who achieved CR or partial response (PR), patients who achieved hematologic improvement (characterized by achievement of RBC transfusion independence and/or improvement in platelet count) also seemed to have a survival benefit in AZA-001. These data indicate that continuation of therapy for as long as possible, even in patients who do not achieve a CR, is recommended. Continuation of therapy is particularly important in patients who achieve a CR, since interruption of therapy is associated with relapse. The present protocol will use Azacitidine according to the same schedule than in MDS that is continuous treatment until progression or unacceptable toxicity. As some patients with AITL may encounter prolonged disease control following a stem-cell transplant, responding patients can be offered stem-cell transplant at any time on investigator's decision (Le Gouill et al., 2011) (Corradini et al., 2004).

Interestingly, 2 patients who had coexistence of AITL and CMML were treated with 5-azacitidine (5-AZA), which induced a sustained complete response of both diseases (Cheminant et al., 2015; Saillard et al., 2016). This suggests that hypomethylating agent could have efficacy not only in CMML, but also in AITL, both neoplasms share common oncogenic events, especially TET2 mutations. A retrospective evaluation of PTCL patients treated with 5-AZA found that although only one transient partial response occurred in 7 non AITL PTCLs patients, 9/12 AITL patients had a response, including 5 complete responses, leading to a response rate of 75%, including 42% complete response (Delarue et al., 2016). It is noteworthy that responses were prolonged (4-40 months), sometimes in heavily pretreated patients. Ten patients had previous or concomitant diagnosis of myelodysplastic syndrome, mostly (9/10) chronic myelomonocytic leukemia (CMML). Patients received a median number of 3 cycles of 5-AZA [1 – 43]. Hematological toxicity was as expected. Two patients developed unusual adverse reaction: grade 2 polyneuropathy (which was deemed to be related to paraneoplastic syndrome) and grade 3 diarrhea of unknown origin, the latest leading to treatment interruption. The median follow-up was 84 days [19 – 1236]. Overall response rate (ORR) for the entire population was 53% (10/19), but was significantly higher in AITL patients than in patients with other PTCL entities (9/12, 75% vs. 1/7, 15%, p=0,0198). Among these 10 responding patients, 5 patients - all suffering from AITL - reached complete response (CR), leading a CR rate of 42% in this entity. Three additional patients were in stable disease (best response) and 6 progressed rapidly. It is noteworthy that among the 9 AITL patients who responded, only 2 patients experienced progression after 86 and 499 days, respectively, the remaining 7 patients being still responders and under therapy. None of the patients with another PTCL entity experienced response, with the exception of one patient with ATLL for whom 5-AZA induced a rapid and profound decrease in lymphocyte count; however, this patient relapsed after the second cycle. TET2 was sequenced in 14 patients and was mutated in 8/10 (80%) AITL and 1/4 (25%) other PTCL. Interestingly, 8/8 AITL patients with TET2 mutational status available who experienced a response after 5-AZA treatment were TET2 mutated.

5.4 Rationale for the use of oral Azacitidine

Bristol-Myers Squibb has developed an oral formulation of azacitidine under the codename CC-486. Upon oral uptake, azacitidine is rapidly absorbed, reaching maximum concentration after approximately one hour. The relative bioavailability of azacitidine after oral (300 mg dose) relative to SC (75 mg/m^2 dose) administration is approximately 10% based on AUC. The mean terminal half-life ranges from 0.4 to 1.0 hour for oral azacitidine. Multiple oral administration does not result in drug accumulation. The MTD following 7-day once daily oral azacitidine administration of a 28-day cycle was determined to be 480 mg. Compared with SC treatment (75 mg/m^2 QD × 7 days), oral azacitidine 300 mg once daily (QD) × 14 and 21 days provide cumulative AUC exposure per cycle of 38% and 57%, respectively. Oral administration offers obvious advantages in comparison to daily SC administration. The more protracted administration of oral as compared as SC azacitidine offers the potential advantage of prolonged exposure to the drug and thus, better disease control. Some AITL patients treated with SC azacitidine did show disease progression after transient improvement between cycles (Dupuis, unpublished observation).
Oral azacitidine has been or is being investigated in MDS, AML, CMML, lymphoma, multiple myeloma, relapsed or refractory solid tumors (e.g., urothelial carcinoma of the bladder, renal pelvis, ureter, or urethra; non-small cell lung cancer; pancreatic carcinoma; breast cancer; ovarian cancer; nasopharyngeal carcinoma, cervical carcinoma, anal carcinoma; Merkel cell carcinoma).

Based on data from previous studies, the doses selected for the present study are as follows:

- For non-Asian patients: 300 mg QD x 14 days of 28-day cycle;
- For Asian patients: 200 mg QD x 14 days of 28-day cycle.

[redacted]

[redacted] Therefore, oral azacitidine 100 mg QD, one-third of the dose used for the global phase 3 studies (AZA-MDS-003 and CC-486-AML-001), and with 14 of a 28-day schedule was selected as the starting dose for safety run-in to ensure Asian patients' safety in this AITL study. The dose will be escalated to 200 mg QD in the safety run-in once 100 mg QD is confirmed as tolerable.

6 STUDY OBJECTIVES

6.1 Primary Objective

Progression free survival (PFS), using local assessment of progressive disease (refer Section 9.9 for additional details) according to Lugano Response Criteria (2014).

6.2 Secondary objectives

All efficacy assessments will be based on Lugano Response Criteria (2014).

Key Secondary endpoint:

- Overall Survival (OS)

Other Secondary endpoints:

- PFS by the Independent Review Committee (IRC)
- Overall response rate (ORR)
- Complete response rate (CRR)
- Duration of response
- Time to response
- PFS2 using local assessment of progressive disease
- HRQOL endpoints EORTC QLQ-C30
- Safety

6.3 Exploratory objectives

- To correlate the presence of genomic alterations and gene expression data to clinical response to oral azacitidine and survival data
- To study the methylation profile of the tumors
- To study the myeloid population in bone marrow of these patients
- HRQOL endpoints EQ-5D-5L
- To characterize the pharmacokinetics (PK) of oral azacitidine in Japanese patients

7 STUDY DESIGN

This study is a multicentric, open-label, randomized phase 3 trial.

The study will be conducted in select countries in Europe and South Korea sponsored by LYSARC and in Japan sponsored by Bristol-Myers Squibb. There will be a combined enrollment target of 86 randomized patients, with approximately 14 randomized patients from Japan.

The enrollment to the randomized study will start at European sites in parallel to a safety run-in part in Japan. A safety run-in will be conducted to confirm the tolerability of oral azacitidine at doses of 100 mg and 200 mg QD in

Asian patients. Once oral azacitidine at 200 mg QD is confirmed as tolerable, Asian patients from Japan and South Korea will start to be randomized into the main study. Additional patients (non-randomized) are anticipated to enroll to the safety run-in.

Patients will be recruited over 27.5 months and followed until 57 deaths would have occurred, approximately 38.5 months after the first randomization or at the latest 2 years after the last randomized patient

If at the time of OS analysis (at 57 death events), some patients are still on study treatment (oral azacitidine), it is planned to continue the follow-up of patients (either in treatment or in follow-up period) and collecting the data.

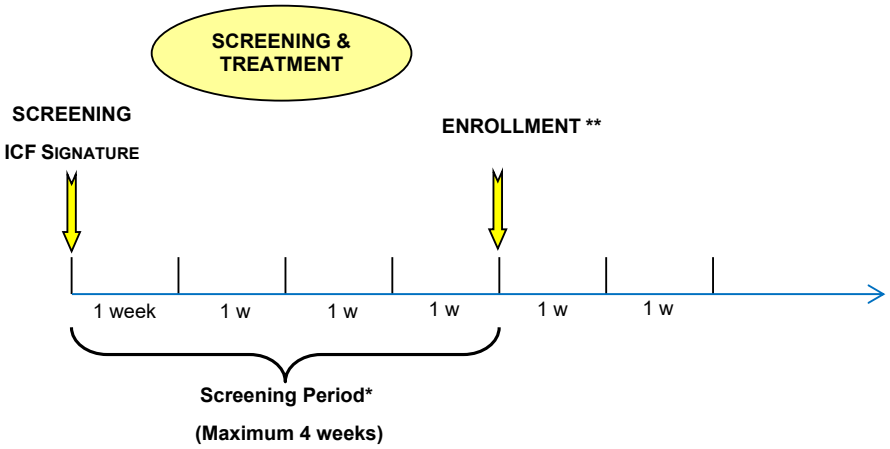
The end of Trial is defined as the date of the last visit of the last subject on study treatment (oral azacitidine) to complete the 12-week post-treatment follow-up as prespecified in the protocol. The study will not extend beyond 3 years after the last patient has been randomized (Q1 2024).

The study dates (start / end) are:

- 1st patient enrolled (FPFV): 18 November 2018
- Last patient enrolled (LPFV): 22 February 2021
- Last patient followed for principal analysis: 10 February 2021

86 patients will be randomized to oral azacitidine or investigator's choice therapy.

Additional Japanese patients will receive oral azacitidine and will be enrolled to safety run-in analyses.

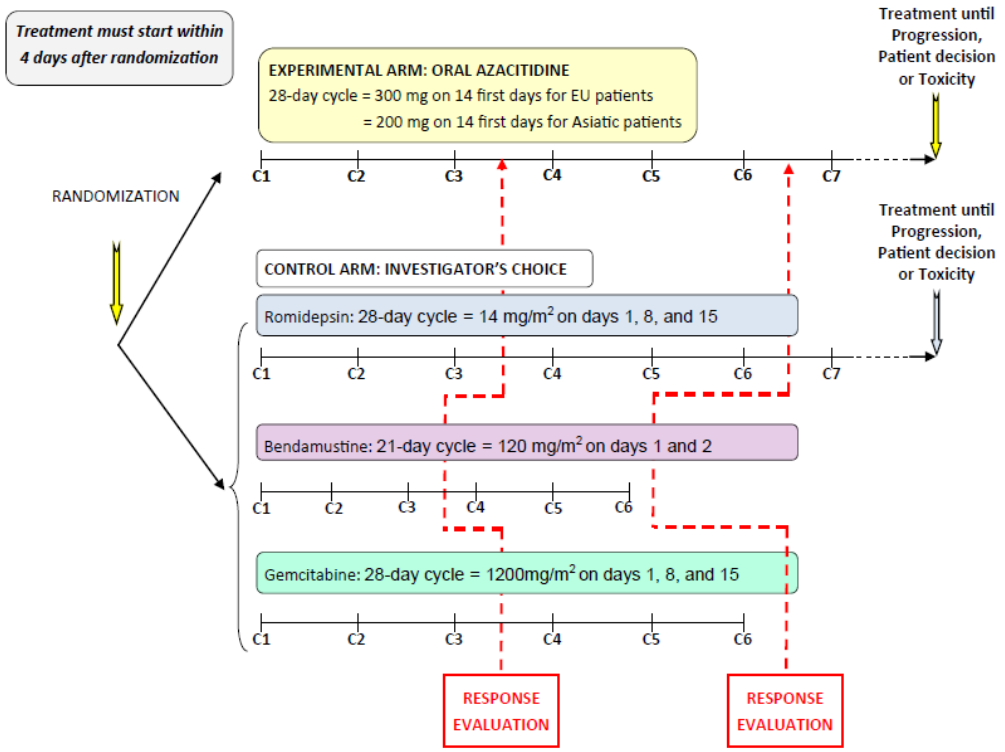


* The Screening Period starts from the informed consent form signature.

** Enrollment should occur within 28 days window after the ICF signature date (screening date)

** Stratification factors: - Number of prior lines treatment: 1-2 *vs* > 2

- Previous/Concurrent MDS or CMML: Yes *vs* No



8 STUDY POPULATION

Patients aged at least 18 years old with relapsed or refractory Angioimmunoblastic T cell lymphoma (AITL) or other subtypes of T-follicular helper (TFH) derived lymphoma histologically proven, with TFH phenotype as per the latest WHO classification, Ann Arbor clinical stage I to IV and a performance status from 0 to 3 will be enrolled to the trial.

Written informed consent will be obtained prior to conducting any protocol-related procedures, including screening evaluations.

8.1 Inclusion criteria

Patients must satisfy all following criteria to be enrolled in the study::

1. Patient is ≥ 18 years of age at the time of signing the informed consent form (ICF).
2. Patient must understand and voluntarily sign an ICF prior to any study-specific assessments/procedures being conducted.
3. Patient is willing and able to adhere to the study visit schedule and other protocol requirements
4. Patient had local diagnosed peripheral T cell lymphoma (PTCL) with T-follicular helper (TFH) phenotype according to the criteria of the latest WHO classification based on a surgical lymph node biopsy or needle core biopsy including any one of
   - Angioimmunoblastic T cell lymphoma (AITL)
   - Follicular T cell lymphoma
   - Nodal peripheral T-cell lymphoma with TFH phenotype

   There should be a documented expression of minimum two TFH markers among this panel of markers : CD10, CXCL13, PD1, ICOS and BCL6 by the tumoral cells by immunohistochemistry. Biopsy at relapse or progression is not mandatory, but highly encouraged on a surgical or needle core biopsy, and diagnostic tissue should be available for central pathology review and for ancillary molecular studies.
   Local pathology report should be reviewed by the sponsor's medical monitor prior to enrollment.

5. ECOG performance status 0 to 3
6. Relapsed (after partial or complete response) or refractory AITL after at least one line of systemic therapy (there is no mandatory resting period after the previous treatment as long as the biochemistry and hematology labs meet the inclusion criteria as below.)
7. Meet the following lab criteria:
   - ANC ≥ 1,5 x 10^9/L (≥ 1 x 10^9/L if BM involvement by lymphoma)
   - Platelet ≥ 75 x 10^9/L (≥ 50 x 10^9/L if BM involvement by lymphoma)
   - Hemoglobin ≥ 8 g/dL.
8. Anticipated life expectancy at least 3 months
9. At least one measurable lesion on CT that is greater than 1.5 cm in the longest diameter for nodal lesions and greater than 1.0 cm in the longest diameter for extranodal lesions. The lesion must be measurable in two perpendicular dimensions. Patients with only cutaneous disease will be excluded.
10. Female patient of childbearing potential (FCBP) may participate, providing she meets the following conditions:

    Have two negative pregnancy tests as verified by the investigator prior to starting study treatment: serum pregnancy test at Screening and negative serum or urine pregnancy test (investigator's discretion) within 72 hours prior to starting treatment with study treatment (Cycle 1 Day 1). She must agree to ongoing pregnancy testing during the study (before beginning each subsequent cycle of treatment), and 28 days after the last study drug administration. This applies even if the patient practices complete abstinence from heterosexual contact.

    Agrees to practice true abstinence (which must be reviewed monthly and source documented) or agrees to the use of highly effective methods of contraception from 28 days prior to starting study treatment, and must agree to continue using such precautions during study treatment (including dose interruptions) and for up to 6 months after the last study drug administration. True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptom-thermal, post ovulation methods) and withdrawal are not acceptable methods of contraception. Cessation of contraception after this point should be discussed with a responsible physician.

    Agrees to abstain from breastfeeding during study participation and for at least 6 months after the last study drug administration.

    A female of childbearing potential (FCBP) is a female who: 1) has achieved menarche at some point, 2) has not undergone a hysterectomy or bilateral oophorectomy or 3) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (i.e., has had menses at any time during the preceding 24 consecutive months).
11. Male patient must either practice true abstinence from heterosexual contact (which must be reviewed on a monthly basis and source documented) or agrees to avoid fathering a child, to use highly effective methods of contraception, male condom plus spermicide during sexual contact with a pregnant female or a female of childbearing potential (even if he has undergone a successful vasectomy), from starting dose of IP (cycle 1 Day 1), including dose interruptions through 6 months after receipt of the last study drug administration. Furthermore, male patient must agree to not give semen or sperm during study drug therapy and for a period of 1 year after end of study drug therapy.
12. For EU countries, patient covered by a social security system

8.2 Exclusion criteria

Presence of any of the following will exclude a patient from enrollment:

1. Clinical evidence of central nervous system involvement by lymphoma. Patients with suspicion of CNS involvement must undergo neurologic evaluation and CT/MRI of head and lumbar puncture to exclude CNS disease.

2. Any significant medical conditions, laboratory abnormality or psychiatric illness likely to interfere with participation in this clinical study (according to the investigator's decision)
3. Uncontrolled systemic fungal, bacterial, or viral infection (defined as ongoing signs/symptoms related to the infection without improvement despite appropriate antibiotics, antiviral therapy, and/or other treatment)
4. Known Human Immunodeficiency Virus (HIV) or Hepatitis C Virus (HCV) infection, or evidence of positive HTLV1 serology or of active Hepatitis B Virus (HBV) infection defined as:
   - HBs Ag positive
   - HBs Ag negative, anti-HBs antibody positive and/or anti-HBc antibody positive with detectable viral DNA
5. Impaired renal function (calculated MDRD or Cockcroft-Gault Creatinine Clearance < 30 ml/min) or impaired liver function tests (Serum total bilirubin level > 2.0 mg/dl [34 µmol/L] (except in case of Gilbert's Syndrome, or documented liver or pancreatic involvement by lymphoma), Serum transaminases (AST or ALT) > 3 upper normal limits) unless they are related to the lymphoma.
6. Active malignancy other than the one treated in this research. Prior history of malignancies, other than low risk MDS or CMML (with less than 5% blasts in bone marrow), unless the patient has been free of the disease for ≥ 3 years. However, patients with the following history/concurrent conditions are allowed:
   a. Basal or squamous cell carcinoma of the skin
   b. Carcinoma in situ of the cervix
   c. Carcinoma in situ of the breast
   d. Incidental histologic finding of prostate cancer (T1a or T1b) using the tumor, nodes, metastasis [TNM] clinical staging system
   e. Early-stage gastric cancer suitable for endoscopic mucosal resection or endoscopic submucosal dissection
7. Treatment with any investigational drug within 5 half-lives before planned first cycle of study treatment and during the study. Ongoing medically significant adverse events from previous treatment, regardless of the time period.
8. Prior exposure to azacitidine and/ or any other demethylating agent (e.g., decitabine)
9. Prior exposure to planned study treatment investigator's choice therapy (e.g., prior exposure to gemcitabine is an exclusion if gemcitabine is the investigator's choice therapy prior to randomization)
10. Concurrent use of corticosteroids unless the patient is on a stable or decreasing dose for ≥ 1 week prior to informed consent form signature
11. Knowing or suspected hypersensitivity to active substance or to any of the excipients.
12. Pregnant, planning to become pregnant, or lactating woman
13. Candidate for hematopoietic stem cell transplantation
14. History of active inflammatory bowel disease (e.g., Crohn's disease, ulcerative colitis), celiac disease (i.e., sprue), prior gastrectomy or upper bowel removal, or any other gastrointestinal disorder or defect that would interfere with the absorption, distribution, metabolism or excretion of the oral azacitidine and/or predispose the patient to an increased risk of gastrointestinal toxicity per investigator's decision. Any condition causing inability to swallow tablets.
15. Significant active cardiac disease within the previous 6 months, including:
   - New York Heart Association (NYHA) class IV congestive heart failure
   - Unstable angina or angina requiring surgical or medical intervention; and/or
   - Myocardial infarction
16. Person deprived of his/her liberty by a judicial or administrative decision
17. Adult person under legal protection

9 STUDY FLOW CHART AND SCHEDULE OF ASSESSMENTS

9.1 Study flow chart

See on Appendix 1.

9.2 Schedule of assessments

See on Appendix 2.

For all routine assessments and visits performed from the start of treatment, the study visits window is ± 3 days for assessments scheduled weekly, the study visit window is ± 7 days for visits scheduled monthly or ± 1 month for visits scheduled every 3 months.

9.3 Informed consent

To participate in this study and before any baseline or screening evaluation, each patient must be informed, must have a cooling off period, appropriate for each specific individual, and have signed a written consent.

A written informed consent for biological analyses and sample collections must be obtained before any sampling of blood, bone marrow or tumors only for French and Belgian patients. A written informed consent for genetics studies must be signed before performing biological samples for further analyses on genomic DNA. The biological and genetic consents are optional. All these consents are signed after investigator gave all required information to the patient and the patient asked all [redacted] questions.

The patient and the investigator will date and sign the informed consent form.

Two original copies of the signed consent will be completed. A copy will be provided to the patient; a copy will be maintained in the investigator's study file.

The investigator will attest on eCRF that the patient has signed and dated the informed consent and indicate if the patient has signed the biological and genetic consents. The participation to the clinical trial will be tracked in patient medical dossier.

9.4 Screening procedures

Patients will be screened for protocol eligibility during a period of **no more than 28 days** prior to enrollment as outlined in the Schedule of Study Assessments.

Screening assessments and recording of AEs/SAEs will begin once the patient has approved and signed the informed consent form.

The patient's eligibility (inclusion and exclusion criteria) has to be evaluated during the Screening Period prior to enrollment.

9.4.1 *Demographic, Medical and Baseline Disease Information*

- Written Informed Consent
- Complete medical history (including previous cancers: myelodysplastic syndrome, chronic myelomonocytic leukemia and others),
- History of the NHL including treatment received, date and response
- Physical examination performed within 2 weeks prior to randomization
- All medications taken from the randomization should be recorded on the appropriate CRF.
- Age, gender
- Weight, height and BSA

9.4.2 *Histological diagnosis*

The diagnosis of AITL based on a surgical lymph node biopsy according to WHO classification is required. A core needle biopsy is usually not suitable for diagnosis of AITL. However, in exceptional cases, assuming that surgical biopsy is not feasible, assuming that local diagnosis is considered confirmed and assuming that sufficient material will be available for pathological review, a core needle biopsy can be accepted. The diagnosis based on fine needle aspirations is not considered acceptable pathologic data for entry into this study.

The diagnosis of PTCL-TFH based on the latest criteria of WHO classification needs an expression of minimum two TFH markers by the tumoral cells, among CD10, CXCL13, PD1, ICOS and BCL6.

At the Screening, the pathological report (French version for French and Belgian patients and English version for other countries) and the completed “pathology form” must be sent to the sponsor’s medical monitor for diagnosis validation before enrollment.

Patients must have a diagnostic FFPE tumor block, as well as stained slides used to set the diagnosis (initial diagnosis or at relapse if available) available for submission to central pathology review and must be submitted to central pathology just after screening. At relapse, histological confirmation of the diagnosis of AITL relapse is strongly encouraged, by a surgical or needle core biopsy.

If the FFPE block cannot be sent, an H&E slide and 12 unstained slides will be acceptable, with the stained slides.

Pathology reports associated with these tissues are also required and will be sent to the central pathology laboratory with the tissue and/or slides. The sponsor will provide detailed instructions and materials for sample handling and shipping.

9.4.3 *Tumor and disease staging*

- CT of neck, chest, abdomen and pelvis is required to locally confirm measurable lesion of greater than 1.5 cm in the longest diameter for nodal lesions and greater than 1.0 cm in the longest diameter for extranodal lesions. The lesion must be measurable in two perpendicular dimensions. CT is to be performed with contrast unless it is medically contraindicated. This scan may be used as the baseline CT scan and will be uploaded on Imagys® platform for central review.
- Evaluation of all involved nodal and extra-nodal sites of lymphoma.
- Assessment of spleen, liver enlargement and skin based on CT scan or physical examination.
- FDG-PET scan (optional).
- Patients with a presence of CNS lymphoma involvement are excluded from the study. Patients with suspicion of CNS involvement must undergo neurologic evaluation and CT/MRI of head and lumbar puncture to exclude CNS disease.
- Tumor biopsy
- Bone marrow biopsy

  Bone marrow aspirate will not be acceptable.
- B-symptoms
- PIAI (Prognostic Index for AITL) (See Appendix 8)
- PIT (Prognostic Index for T-cell Lymphoma) (See Appendix 9)
- IPI (International Prognostic Index) (See Appendix 7)
- Ann Arbor staging (See Appendix 3)
- ECOG performance status (See Appendix 6)

9.4.4 *Laboratory assessments*

- Complete blood cell count (CBC) will include red blood cell count (RBC), hemoglobin, hematocrit, white blood cell (WBC) count with differential, absolute neutrophil count (ANC), absolute lymphocyte count (ALC), absolute monocyte count (AMC) and platelet count.
- Sodium, potassium,
- Alkaline phosphatases, AST, ALT, total bilirubin,
- Lactate dehydrogenase (LDH), β2-microglobulin
- TSH
- Serum electrophoresis
- Direct antiglobulin (Coomb's) test
- Creatinine (clearance calculated by the Cockcroft-Gault formula or MDRD formula)

  Cockcroft-Gault estimation of creatinine clearance (CrCl):

  Serum creatinine unit mg/dL => for females, the formula is multiplied by 0.85.

  CrCl (mL/min) = [(140 – age (years)) x (weight [kg])] / [72 x (serum creatinine [mg/dL])];

  Serum creatinine unit µmol/L => A = 1.23 for men and A = 1.04 for females.

  CrCl (mL/min) = [(140 – age (years)) x (weight [kg]) x A] / (serum creatinine [µmol/L]);

  Creatinine clearance should be determined utilizing actual body weight.

  MDRD estimation of creatinine clearance (CrCl):

  Serum creatinine unit mg/dL

  CrCl (mL/min) = 175 x [Serum creatinine$^{-1.154}$ x age$^{-0.203}$ x 0.742 (if female) x 1.212 (if black)

  Serum creatinine units µmol/L

  CrCl (mL/min) = 30849 x [**Serum creatinine**$^{-1.154}$ x **age**$^{-0.203}$ x 0.742 (if female) x 1.212 (if black)

Eligibility for the study is based on the local laboratory results.

Laboratories used for hematological and biochemical tests and assays including ongoing pregnancy tests during the study are individual centre laboratories. All the laboratories must provide their normal values and an updated accreditation for quality control.

However, if Screening labs are drawn within 1 week before receipt of study drug on Cycle 1 Day 1, they do not need to be repeated on Cycle 1 Day 1.

9.4.5 *Cardiac evaluation*

- Electrocardiogram for measurement of corrected QT interval according to the Fridericia formula: electrocardiogram must be registered at rest, in three specimens and after a space of 1 minute.

9.4.6 *Serologies and specific laboratory assessments*

- Hepatitis B screening includes hepatitis B surface antigen (HBsAg), hepatitis B core antibody (anti-HBc), and hepatitis B surface antibody (anti-HBs) and, in case of positivity of HBsAg and/or anti-HBc, viral DNA by PCR
- HTLV1 serology
- Two pregnancy tests for females of childbearing potential (FCBP):
  1) a serum pregnancy (at least 25 mIU/mL) test during the Screening Period (all FCBP)

  and 2) a serum or urinary pregnancy test (at least 25 mIU/mL) within 72 hours prior the start of study treatment.

9.4.7 *Quality of life assessments*

- EORTC QLQ-C30 (Appendix 10-B) and EQ-5D-5L (Appendix 10-A): It's highly recommended to fill in the questionnaire before any treatment.

9.4.8 *Selection of Standard-of-care therapy (Investigator's choice therapy)*

The intent of this study is to compare oral azacitidine to standard-of-care therapy in use in a particular country, geographic region or institution.

Therefore, at Screening, prior to enrollment, Investigators will select single agent from a choice of protocol specified standard-of-care chemotherapy regimens as described below for their patient and enter this choice into the registration system.

	Used in EU for PTCL	Treatment regimen
Romidepsin	N	14 mg/m^2 on days 1, 8, and 15 of a 28-day cycle, treat until progression or as tolerated
Bendamustine	Y	120 mg/m^2 on days 1 & 2 of a 21-day cycle during 6 cycles.
Gemcitabine	Y	European countries and South Korea: 1200 mg/m^2 on days 1, 8, & 15 of a 28-day cycle during 6 cycles Japan: 1000 mg/m^2 on days 1, 8, & 15 of a 28-day cycle during 6 cycles

Standard of care therapy must be available by prescription, generally reimbursed by the healthcare system and used routinely to treat relapse or refractory angioimmunoblastic T-cell patients at the center.

Dose of investigator's choice therapy will be the standard of care therapy dose used in each country regardless of ethnic background.

After enrollment, study drug is dispensed on Day 1 for oral azacitidine patients or Investigator's Choice Therapy patients.

Treatment in both arms must be started within 4 days after the enrollment. The Screening period must remain within 28 days from enrollment.

9.4.9 *Biological samples for ancillary analyses only for French and Belgian patients*

The ORACLE study represents an unique opportunity to collect biological samples from patients with Angioimmunoblastic T cell Lymphoma at several times points that can be used to improve comprehension of the disease, better define the prognostic criteria in angioimmunoblastic lymphoma and identify new factors that influence treatment results and outcome.

A written informed consent for biological analyses and sample collections must be obtained before any sampling of blood, bone marrow and saliva.

A written informed consent for genetics studies must be signed for further analyses on genomic DNA.

The following samples will be collected for further ancillary analysis

- Around 5mL of bone marrow on EDTA and 10mL of blood on EDTA for DNA banking and myeloid anomalies on CD34 analysis
- Around 5mL of blood on dry tube for serum banking and proinflammatory cytokines analysis
- Around 9mL of blood on STRECK tube for circulating tumoral DNA banking and analysis
- Around 18mL of blood on EDTA tube for plasma banking and flow cytometry, clonality T analysis and clonality B analysis
- Saliva sampling for DNA genomic banking and analysis on ORAGEN 500 kit

9.5 Information to be collected on Screening Failures

The informed consent date, demographics, and reason patient did not qualify for the study will be collected for all patients determined to be screen failures. Adverse Events and Serious Adverse Events experienced by screen failure patient will be collected from the date of signing consent to the day the patient is confirmed to be a screen failure. This information will be captured in the patient's source documents.

9.6 Study treatment assessments

9.6.1 *Oral azacitidine and romidepsin treatment*

	When
Clinical examination	• At Day 1 of each cycle of treatment
ECOG PS	• At Day 1 of each cycle of treatment
Check patient diary for treatment compliance (azacitidine treatment)	• At Day 1 of each cycle of treatment The patients must bring the patient diary to the site on every visit so that they can be checked by study site personnel for compliance.
Complete blood cell counts	• Within 48 hours of Day 1 of each cycle of treatment • Every week during 24 weeks of treatment
Biochemical tests: blood ionogram, serum creatinin, creatinin clearance according to MDRD/Cockroft-Gault formula, AST, ALT, total bilirubin and alkaline phosphatases	• Within 48 hours of Day 1 of each cycle of treatment
TSH	• After 24 weeks
The adverse events /list of toxicities	• Until 28 days after the last study drug administration.
Neck, chest, abdomen and pelvis CT with oral and/or IV contrast (unless it is medically contraindicated). The CTscan must be uploaded Imagys® platform for central review. Disease response assessment results must be available and reviewed by the investigator before the first dose of study drug in the next planned cycle	• Within 1 week before the 4th planned cycle • Within 1 week before the 7th planned cycle • Every 12 weeks after 6th cycle during the 1st year • Every 24 weeks during 2nd and 3rd year • Annually thereafter
FDG-PET scan (optional)	• Within 1 week before the 7th planned cycle
Bone marrow biopsy to confirm an initial documentation of CR in patients with a positive bone marrow result or unspecified at Screening	• After 6th cycle and before 7th cycle
Evaluation of the disease response (Lugano Response Criteria)	• Within 1 week before the 4th planned cycle • Within 1 week before the 7th planned cycle • Every 12 weeks after 6th cycle during the 1st year • Every 24 weeks during 2nd and 3rd year • Annually thereafter
EORTC QLQ-C30 and EQ-5D-5L questionnaires	• Day 1 of every cycle (before any treatment if possible)

Collection of concomitant medication taken	• Until 28 days after the last study drug administration
Pregnancy test	• At Day 1 of every cycle A serum or urine pregnancy test (investigator's discretion) is to be performed within 72 hours before beginning treatment on Day 1 of every cycle in the treatment phase for all FBCP. The subject may not receive IP until the investigator has verified that the result of the pregnancy test is negative. Pregnancy testing does not need to be repeated prior to Cycle 1 if the screening assessment was performed within 72 hours of the first dose of IP.
Biological samples for ancillary studies (French and Belgian patients): - Around 5 mL of bone marrow on EDTA tubes - Around 28 mL of blood on EDTA tubes - Around 5 mL of blood on dry tubes for serum banking - Around 9 mL of blood on STRECK tubes	• Within 1 week before the 4th planned cycle

9.6.2 ***Oral azacitidine – study treatment assessments after OS analysis***

	When
Clinical examination	• At Day 1 of each cycle of treatment
Pregnancy test	• At Day 1 of every cycle A serum or urine pregnancy test (investigator's discretion) is to be performed within 72 hours before beginning treatment on Day 1 of every cycle in the treatment phase for all FBCP. The subject may not receive IP until the investigator has verified that the result of the pregnancy test is negative.
Check patient diary for treatment compliance (azacitidine treatment)	• At Day 1 of each visit
Complete blood cell counts*	• Within 48 hours of Day 1 of each cycle of treatment
Biochemical tests*: blood ionogram, serum creatinin, creatinin clearance according to MDRD/Cockroft-Gault formula, AST, ALT, total bilirubin and alkaline phosphatases	• Within 48 hours of Day 1 of each cycle of treatment
The adverse events /list of toxicities	• Until 28 days after the last study drug administration.
Neck, chest, abdomen and pelvis CT with oral and/or IV contrast (unless it is medically contraindicated). Disease response assessment	• Within 1 week before the 4th planned cycle • Within 1 week before the 7th planned cycle • Every 12 weeks after 6th cycle during the 1st year

results must be available and reviewed by the investigator before the first dose of study drug in the next planned cycle	• Every 24 weeks during 2nd and 3rd year (frequency recommended) • Annually thereafter (frequency recommended)
FDG-PET scan (optional)	• Within 1 week before the 7th planned cycle
Bone marrow biopsy to confirm an initial documentation of CR in patients with a positive bone marrow result or unspecified at Screening	• After 6th cycle and before 7th cycle
Evaluation of the disease response (Lugano Response Criteria)	• Within 1 week before the 4th planned cycle • Within 1 week before the 7th planned cycle • Every 12 weeks after 6th cycle during the 1st year • Every 24 weeks during 2nd and 3rd year (frequency recommended) • Annually thereafter (frequency recommended)

* Those assessments are recommended according to the local standard of care, for safety purposes.

Under specific circumstances and only if local regulations permit, the protocol assessments may be modulated post OS analysis. Please refer to Appendix 16 for French protocol guidelines logistic assessments post OS analysis

9.6.3 *Bendamustine and Gemcitabine treatment*

	When
Clinical examination	• At Day 1 of each cycle of treatment
ECOG PS	• At Day 1 of each cycle of treatment
Complete blood cell counts	• Within 48 hours of Day 1 of each cycle of treatment • Every week during 24 weeks of treatment
Biochemical tests: blood ionogram, serum creatinine, creatinine clearance according to MDRD/Cockroft-Gault formula, AST, ALT, total bilirubin and alkaline phosphatases	• Within 48 hours of Day 1 of each cycle of treatment
The adverse events /list of toxicities	• Until 28 days after the last study drug administration.
Neck, chest, abdomen and pelvis CT with oral and/or IV contrast (unless it is medically contraindicated). The CT scan must be uploaded Imagys® platform for central review. Disease response assessment results must be available and reviewed by the investigator before the first dose of study drug in the next planned cycle	• Within 1 week before the 4th planned cycle
Evaluation of the disease response (Lugano Response Criteria)	• Within 1 week before the 4th planned cycle

EORTC QLQ-C30 and EQ-5D-5L questionnaires	• Day 1 of every cycle (before any treatment if possible)
Collection of concomitant medication taken	• Until 28 days after the last study drug administration
Pregnancy test	• At Day 1 of every cycle A serum or urine pregnancy test (investigator's discretion) is to be performed within 72 hours before beginning treatment on Day 1 of every cycle in the treatment phase for all FBCP. The subject may not receive IP until the investigator has verified that the result of the pregnancy test is negative. Pregnancy testing does not need to be repeated prior to Cycle 1 if the screening assessment was performed within 72 hours of the first dose of IP.
Biological samples for ancillary studies (French and Belgian patients): - Around 5 mL of bone marrow on EDTA tubes - Around 28 mL of blood on EDTA tubes - Around 5 mL of blood on dry tubes for serum banking - Around 9 mL of blood on STRECK tubes	• Within 1 week before the 4th planned cycle

9.7 Assessments at the end of study treatment

Evaluation at the end of study treatment must be performed between 2 and 4 weeks after the 6th cycle of treatment or within 28 days after the last dose in case of premature treatment discontinuation:

- Physical examination (including weight and ECOG PS)
- Complete blood cell counts
- Biochemical tests: blood ionogram, serum creatinin, creatinin clearance according to MDRD/Cockroft-Gault formula, AST, ALT, total bilirubin and alkaline phosphatases
- TSH
- A serum or urine pregnancy test (investigator's discretion) is to be performed within 28 days of the last dose for all FBCP
- Neck, chest, abdomen and pelvis CT scan with oral and/or IV contrast (unless it is medically contraindicated) according to local practice. The CT scan must be uploaded Imagys® platform for central review.
- FDG-PET scan (optional)
- Bone marrow biopsy to confirm an initial documentation of CR in patients with a positive bone marrow result or unspecified at Screening
- Evaluation of the disease response based on Lugano Response Criteria
- EORTC QLQ-C30 and EQ-5D-5L questionnaires

9.8 Follow up assessments

9.8.1 *Follow up after complete treatment (Bendamustine and Gemcitabine treatment) or premature discontinuation due to patient decision or unacceptable toxicity (Romidepsin and oral Azacitidine)*

The patients will be followed:

- Every 3 months during the first and the second years from enrollment
- Every 6 months during the third year from enrollment
- Then annually until the end of the study.

During the follow up visits, the following assessments should be performed:

- Physical examination (including ECOG PS*)
- Complete blood cell counts **
- EORTC QLQ-C30 and EQ-5D-5L questionnaires*
- Neck, chest, abdomen and pelvis CT scan with oral and/or IV contrast (unless it is medically contraindicated) according to local practice. The CT scan must be uploaded Imagys® platform for central review*
- Evaluation of the disease response based on Lugano Response Criteria (2014)

~~* The assessments setout above will not be required after OS analysis~~

* Until OS analysis

** After OS analysis, those assessments are recommended according to the local standard of care, for safety purposes.

The patients will be followed if possible until death or up to the end of study.

9.8.2 *Follow up after progression*

The patients will be followed:

- Every 3 months during the first and the second years from enrollment
- Every 6 months during the third year from enrollment
- Annually until the end of the study.

During the follow up visits, the following assessments should be performed:

- Physical examination (including ECOG PS*)
- Complete blood cell counts *
- Neck, chest, abdomen and pelvis CT scan with oral and/or IV contrast (unless it is medically contraindicated): *Will be performed according to the timeline of standard care*.
- Evaluation of the disease response based on Lugano Response Criteria (2014)

~~* The assessments setout abovewill not be required after OS analysis~~

* Until OS analysis

** After OS analysis, those assessments are recommended according to the local standard of care, for safety purposes.

The patients will be followed if possible until death up to the end of study. Thereafter, the long term follow-up of patients will be organized for further analysis.

9.9 Progression

Progression will be determined as per Response criteria for lymphoma: Lugano classification **(see Appendix 11).**

Progression will be based on the first exam which shows the progression but a CT scan or a PET scan must be performed.

Each progression must be validated by sponsor's medical monitor.

As soon as a progression is suspected, the site has to fill in the progression pages on eCRF. A notification is sent by email to the sponsor's medical monitor who can ask the site for further information. The progression is validated by the sponsor's medical monitor on the eCRF specific page. Then, a notification is sent by email to the site.

The CT scan must be uploaded on Imagys® platform for central review. All anonymized reports of assessments which show a progression should be sent by email to LYSARC [redacted].

A pathological confirmation by biopsy of the lesion should be done if possible. Pathology report associated with this tissue is also required and will be sent to the sponsor as well as the tissue and slides. The sponsor will provide detailed instructions for sample handling and shipping.

The following samples will be performed for French and Belgian patients only:

- Around 5mL of bone marrow on EDTA and 10mL of blood on EDTA for DNA banking and myeloid anomalies on CD34 analysis
- Around 5mL of blood on dry tube for serum banking and proinflammatory cytokines analysis
- Around 9mL of blood on STRECK tube for circulating tumoral DNA banking and analysis
- Around 18mL of blood on EDTA tube for plasma banking and flow cytometry, clonality T analysis and clonality B analysis

10 TREATMENTS

Patients are randomly assigned to receive either oral azacitidine (CC-486) or single-agent investigator's choice therapy. Cross-over to oral azacitidine (CC-486) is not allowed.

The treatment must start within 4 days after the enrollment .

Treatment period for each patient starts with the first study drug administration which is defined as Study Day 1 of Cycle 1.

Treatment should be continued whatever the treatment arm in case a lymphoma response occurs, even if concurrent MDS or CMML worsens (Savona et al., 2015), as long as this is compatible with the above-stated recommendations for dose-adaptation.

10.1 Experimental Arm: Oral Azacitidine

10.1.1 *Drug description, storage and handling*

a. Drug description and labeling

Oral azacitidine will be supplied as 100 mg tablets for European countries and 100 and 150 mg tablets for Asian countries for oral administration and labeled as investigational product (IP).
Each tablet is formulated using excipients that are generally regarded as safe and are used in marketed drug products. All tablets will be packaged in blister cards. Only sufficient IP for one cycle of treatment will be provided to each patient at the start of each treatment cycle. All tablets should be swallowed whole, and should not be broken or chewed.
The packaging containing these tablets will be labelled according to the Good Manufacturing Practice guidelines and the local requirements.
The label(s) for IP will include sponsor name, address and telephone number, the protocol number, EudraCT number, IP name, dosage form and pharmaceutical form, amount of IP per container, batch number, expiry date, medication

identification/kit number, dosing instructions, storage conditions, patient identification, date of dispensation, investigator name and [redacted] phone number and required caution statements and/or regulatory statements as applicable. Additional information may be included on the label as applicable per local regulations.

b. Storage conditions

At the study site, all IPs will be stored according to the storage conditions described on the IP packaging label in a locked, safe area to prevent unauthorized access. The IP must be stored as directed on package label at controlled temperature and a temperature log must be maintained in the source documents.

c. Dispensation

Oral azacitidine will be dispensed on Day 1 of each treatment cycle. Only sufficient IP for one cycle will be dispensed to the patient on Day 1 of each treatment cycle.

The patient may not receive IP for each treatment cycle until all Day 1 procedures have been completed and all IP from the previous cycle are to be accounted for (where applicable).
If a tablet is broken or damaged, keep the drug product until monitoring visit and do not use.

Under specific circumstances and only if local regulations permit, the protocol assessments may be modulated post OS analysis. Please refer to Appendix 16 for French protocol guidelines logistic assessments post OS analysis.

10.1.2 *Treatment schedule and design*

a. Dose regimen

Following Screening, patients randomized in the experimental arm, will receive:

- For non-Asian patients: 300 mg QD x 14 days of 28-day cycle;
- For Asian patients: 200 mg QD x 14 days of 28-day cycle.

Asian patients, including Japan and South Korea, will be randomized only after IDMC confirms a tolerable dose from the safety run-in in Japan.

Oral azacitidine (CC-486) is scheduled to be taken on the first 14 days of each 28-day treatment cycle, unless there has been a schedule modification of IP administration due to disease progression, patient decision or unacceptable toxicity.

Patient will self-administer all IP doses in the treatment phase. In the event of toxicity, dose and schedule may be modified (see Section 10.1.2 c).
Antiemetic medication (not supplied by the sponsor) may be taken 30 minutes prior to IP administration (See section 10.3.3).

Patients will ingest IP with approximately 240 mL (8 ounces) of room temperature water. Investigational product may be taken on an empty stomach or with food. If IP is taken in the morning, patients may consume their usual breakfast before or after administration.

b. Missing Dose

All efforts should be made to administer IP on all of the scheduled days of each 28-day treatment cycle. Any missed doses during that period should not be taken after the last scheduled day of administration, but should be returned

by the patient for IP accountability. Any vomited doses should not be repeated. Treatment should resume on the next scheduled day.

c. **Dose adjustment**

Patients should be monitored for toxicity using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 4.03, as a guide for the grading of severity.

A maximum of one dose reduction step to a daily dose of 200 mg (if starting dose was 300 mg) or to 150 mg (if starting dose was 200 mg) is permitted in the event of toxicity. If toxicity persists, a maximum of one treatment schedule modification from 14 to 7 days is permitted in the event of continuing toxicity that does not respond to dose reduction. The decision to modify a patient's treatment schedule from 14 to 7 days will first be discussed with the sponsor's medical monitor.

Patients will not be scheduled to receive treatment for less than 7 days. Dose interruptions lasting beyond 28 days should be discussed with the sponsor's medical monitor.

Patients who have their oral azacitidine dose reduced or treatment schedule modified may return to their original dose and schedule at the next cycle in a step-wise fashion upon discussion and agreement between the investigator and the sponsor's medical monitor. The treatment schedule will first be increased from 7 to 14 days, followed by a dose escalation step to the original starting dose (either 200 mg or 300 mg).

If the lowest dose and treatment schedule of IP cannot be tolerated by subject, then IP treatment may be discontinued.

- Dose Modification for Neutropenia Grade 4 (<0,5 x 10^9/L)

If a patient has ANC < 0,5 x 10^9/L (Grade 4) during any treatment cycle, the supportive care should be started and the IP dose should be reduced to 200 mg (if starting dose was 300 mg) or to 150 mg (if starting dose was 200 mg). If Grade 4 neutropenia (<0,5 x 10^9/L) persists more than 7 days at a reduced dose, the remaining IP dose should be held.

To start a new cycle, ANC should improve or stabilize (ANC > 1,0 x 10^9/L recommended but at the discretion of the investigator) unless agreed by the sponsor's medical monitor.

A treatment schedule modification from 14 to 7 days of treatment may be warranted if a patient experiences Grade 4 neutropenia (that is deemed by the investigator to be related to IP) in 2 consecutive cycles. If a patient experiences Grade 4 neutropenia in 3 consecutive cycles, the sponsor's medical monitor should be contacted to discuss the treatment dose and schedule.

- Dose Modification for Febrile Neutropenia ≥ Grade 3

Any patients who experiences febrile neutropenia (defined by an ANC < 1,0 x 10^9/L and a single temperature of > 38.3 degrees C (101 degrees F) or a sustained temperature of ≥ 38 degrees C (100.4 degrees F) for more than one hour) will **have investigational product (IP) held until fever has resolved. The administration of G-CSF, antibiotic, antiviral and/ or antifungal is strongly recommended. Patient must be afebrile for 3 days before re-starting study drug.**

To start new cycle, ANC should improve or stabilize (ANC > 1,0 x 10^9/L recommended but at the discretion of the investigator).

If a patient experiences febrile neutropenia in 2 consecutive cycles, the steps noted above should be followed, but the IP dose should be reduced to 200 mg (if starting dose was 300 mg) or to 150 mg (if starting dose was 200 mg) upon resumption of treatment with IP. If a patient experiences febrile neutropenia in 3 consecutive cycles, that is deemed by the investigator to be related to IP, a treatment schedule modification from 14 to 7 days of treatment may be warranted.

Myeloid growth factors (G-CSF and granulocyte macrophage colony-stimulating factor [GM-CSF]) is **strongly recommended** for the treatment of neutropenic fever/infections as well as for secondary prophylaxis (i.e., prophylactic use of myeloid growth factors if the patient had a history of neutropenic fever/infection or Grade 4

neutropenia during the treatment phase of the study) and the safety of the patient is considered jeopardized by subsequent episodes of neutropenic fever/infections or Grade 4 neutropenia.

- Dose Modification for Thrombocytopenia Grade 4

If a patient has platelets counts < 25 x 10^9/L, platelet transfusion should be considered. If appropriate administration of platelet does not correct the platelets counts, contact the sponsor's medical monitor to consider IP dosing delay or interruption.

- Dose Modification for Diarrhea ≥ Grade 3

Antidiarrheal medication is recommended as prophylaxis against diarrhea and for treatment of any AEs of diarrhea. Dose modifications for diarrhea are summarized in Table 1. In patients not having problems during the first two cycles, the treating physician may discontinue use of antidiarrheal medications.

- Dose Modification for Nausea and Vomiting ≥ Grade 3

A serotonin (5-HT3) receptor antagonist (e.g., ondansetron) (or other comparable medication) should be administered as an antiemetic approximately 30 minutes prior to administration of IP. Antiemetic medication(s) should be administered for treatment of any AEs of nausea and/or vomiting. If there has been no nausea and/or vomiting during the first two cycles, investigator may choose to omit antiemetic as required, provided this is clearly documented in the CRF.

Dose modifications for nausea and vomiting are summarized in Table 1.

- Dose Modification for Renal Dysfunction and Abnormal Serum Electrolytes

If unexplained elevations of serum creatinine (> 20% of baseline) occur (per investigator), IP should be held or the start of the next cycle of treatment delayed until values return to baseline and the dose should be reduced to 200 mg (if starting dose was 300 mg) or to 150 mg (if starting dose was 200 mg) in the next cycle of treatment. A treatment schedule modification from 14 to 7 days can be made if the elevation in creatinine recurs in the subsequent cycle. Should similar unexplained renal disturbances subsequently persist or recur during the next cycle of treatment, study treatment should be discontinued.

- Dose Modification for Other Treatment-Related Non-hematologic Toxicity ≥ Grade 3

Any patient who experiences a treatment-related non-hematologic toxicity Grade 3 or higher that is an escalation from baseline status (prior to first IP dose), the IP dose should be interrupted until the toxicity returns to grade 2 or lower. Dose modifications for Grade 3 or higher non-hematologic toxicity are summarized in Table 1.

- Dose Modification for Tumor Lysis Syndrome

Please refer Appendix 13 for further guidance on TLS diagnosis and management. The sponsor's medical monitor should be contacted to discuss the treatment dose and schedule.

- Dose Modification for Weight Change

No dose adjustment should be made for weight loss or gain alone; however, the reason for weight loss (e.g., significant nausea, vomiting, anorexia) or weight gain (e.g., peripheral edema) should be investigated and may require a dose modification as specified in Table 1.

If a certain level of toxicity is observed and considered by the investigator to be at least possibly related to treatment, IP dosing may be interrupted, delayed or modified. The investigator is encouraged to contact the sponsor's medical monitor prior to any treatment adjustment.

Dose interruptions lasting beyond 28 days should be discussed with the sponsor's medical monitor.

Table 1: Guidelines for Dose Modifications

NCI-CTCAE Toxicity Grade	Action

Neutropenia (Grade 4)	• If Grade 4 neutropenia (< 0,5 x 10^9/L) occurs during a cycle: o Start supportive care (e.g., G-CSF) and o Continue with IP at the next lower dose level (200 mg if starting dose was 300 mg) or 150 mg if starting dose was 200 mg). • if Grade 4 neutropenia persists more than 7 days at a reduced dose, interrupt IP. To start a new cycle at prior reduced dose, ANC should be improved or stabilized (ANC > 1,0 x 10^9/L) unless agreed by the sponsor's medical monitor. • If a patient consecutively experiences Grade 4 neutropenia in 2 consecutive cycles, a schedule modification from 14 to 7 days of treatment will be recommended. • Treatment schedule modification requires prior discussion with the sponsor's medical monitor. • If a patient experiences Grade 4 neutropenia in 3 consecutive cycles, the sponsor's medical monitor should be contacted to discuss the treatment dose and schedule.
Febrile Neutropenia (≥ Grade 3)	• Interrupt IP until fever has resolved. • G-CSF, antibiotic, antiviral and/or antifungal use is **strongly recommended.** • Resume IP dose if patient is afebrile for prior last 3 days and ANC improved or stabilized (ANC > 1,0 x 10^9/L recommended but at the discretion of the investigator). • If a patient experiences febrile neutropenia in 2 consecutive cycles, the steps noted above should be followed, but IP should be reduced to 200 mg (if starting dose was 300 mg) or to 150 mg (if starting dose was 200 mg) upon resumption of treatment with IP. • If a patient experiences febrile neutropenia in 3 consecutive cycles, the steps noted above should be followed, but a schedule modification from 14 to 7 days of treatment will be recommended. • Treatment schedule modification requires prior discussion with the sponsor's medical monitor. • If a febrile neutropenia is along with ANC < 0,5 x 10^9/L, the instructions for Grade 4 neutropenia should be followed.
Thrombocytopenia (Grade 4)	• Consider platelet transfusion if platelets counts are < 25 x 10^9/L. • If appropriate administration of platelet does not correct the platelets counts, contact the sponsor's medical monitor to consider IP dosing delay or interruption.
Diarrhea (≥ Grade 3)	• Interrupt IP and provide adequate/maximum medical intervention. • Resume IP at same dose when toxicity resolves to ≤ Grade 1. • If event reoccurs upon re-challenge or during next treatment cycle, reduce IP dose to 200 mg (if starting dose was 300 mg) or to 150 mg (if starting dose was 200 mg). • If event reoccurs at same intensity once dose is reduced to 200 mg (if starting dose was 300 mg) or to 150 mg (if starting dose was 200 mg), follow the steps above and modify treatment schedule from 14 to 7 days of IP administration.

	• Treatment schedule modification requires prior discussion with the sponsor's medical monitor.
Nausea and/or Vomiting (≥ Grade 3)	• Interrupt IP and provide adequate/optimum medical intervention. • Resume IP at same dose when toxicity resolves to ≤ Grade 1. • If event reoccurs upon re-challenge or at same intensity during next treatment cycle, reduce dose to 200 mg (if starting dose was 300 mg) or to 150 mg (if starting dose was 200 mg). • If event reoccurs at same intensity once dose is reduced to 200 mg (if starting dose was 300 mg) or to 150 mg (if starting dose was 200 mg), follow the steps above and modify treatment schedule from 14 to 7 days of IP administration. • Treatment schedule modification requires prior discussion with the sponsor's medical monitor.
Renal Dysfunction	• For unexplained elevations of serum creatinine (> 20% of baseline), hold IP or delay the start of the next cycle of treatment until values return to baseline. • Reduce IP dose in the next cycle of treatment to 200 mg (if starting dose was 300 mg) or to 150 mg (if starting dose was 200 mg). • Treatment schedule can be modified from 14 to 7 days if similar unexplained significant renal and/or electrolyte disturbances subsequently persist or recur during the next cycle of treatment. • Treatment schedule modification requires prior discussion with the sponsor's medical monitor. • Discontinue IP if similar unexplained significant renal and/or electrolyte disturbances subsequently persist or recur during the next cycle of treatment.
Other ≥ Grade 3 nonhematological toxicities	• Interrupt IP dosing if toxicity is not expected to resolve within 24 hours after using appropriate medical intervention • Resume IP at same dose when toxicity resolves to ≤ Grade 2 • If event reoccurs upon re-challenge or at same intensity during next treatment cycle, reduce IP dose to 200 mg (if starting dose was 300 mg) or to 150 mg (if starting dose was 200 mg) • If event reoccurs at same intensity once dose is reduced to 200 mg (if starting dose was 300 mg) or to 150 mg (if starting dose was 200 mg), follow the steps above and modify treatment schedule from 14 to 7 days of IP administration. • Treatment schedule modification requires prior discussion with the sponsor's medical monitor.
Tumor Lysis Syndrome (TLS)	• Please refer Appendix 13 for further guidance on TLS diagnosis and management. • The sponsor's medical monitor should be contacted to discuss the treatment dose and schedule.

10.2 Standard Arm: Investigator's choice therapy

Romidepsin will be supplied as 10 mg vials and labeled.

Commercially gemcitabine and bendamustine are available at the hospital pharmacy or provide by the Sponsor according to the local regulation.

10.2.1 ***Dose regimen***

Investigator's choice therapy is either administered for a fixed duration (depending on the considered drug) or continued until disease progression, patient decision or unacceptable toxicity.

Investigator's choice therapy should only be regulatory approved and reimbursed or standard of care for the treatment of relapsed/refractory peripheral T-cell lymphoma in respective countries, which include the following: romidepsin, bendamustine and gemcitabine. See table below for details:

	Used in EU for PTCL	Treatment regimen
Romidepsin	No	14 mg/m^2 on days 1, 8, and 15 of a 28-day cycle, treat until progression or as tolerated
Bendamustine	Yes	120 mg/m^2 on days 1 & 2 of a 21-day cycle during 6 cycles (or 90 mg/m^2 on days 1 & 2 of a 21-day cycle during 6 cycles in older / unfit patients)
Gemcitabine	Yes	European countries and South Korea : 1200 mg/m² on days 1, 8, & 15 of a 28-day cycle during 6 cycles Japan : 1000 mg/m² on days 1, 8, & 15 of a 28-day cycle during 6 cycles

Romidepsin, bendamustine and gemcitabine will be administered according to the standard preparation and infusion procedures of each investigational site. For patients treated with romidepsin, serum potassium and magnesium should be verified before each dose of romidepsin: K+ and Mg²+ < LLN must be corrected (>=LLN) by oral or IV prior to romidepsin administration.

Refer to each specific package inserts for preparation, administration and storage guidelines.

Dosages may be adjusted in case of large changes in body weight compared to baseline (≥ 10%) leading to changes in BSA.

10.2.2 ***Dose adjustments***

✓ ***Romidepsin***:

Patients will be monitored for toxicity using the national cancer institute common terminology criteria for adverse events (NCI-CTCAE), version 4.03 as a guide for the grading of severity. Guidelines are described below and can be adjusted at the discretion of the investigator:

Nonhematologic toxicities except alopecia:

- Grade 2 or 3 toxicity: Treatment with romidepsin should be delayed until toxicity returns to **≤** Grade 1 or baseline, then therapy may be restarted at 14 mg/m^2. If Grade 3 toxicity recurs, treatment with romidepsin should be delayed until toxicity returns to **≤** Grade 1 or baseline and the dose should be permanently reduced to 10 mg/m^2.
- Grade 4 toxicity: Treatment with romidepsin should be delayed until toxicity returns to ≤ Grade 1 or baseline, then the dose should be permanently reduced to 10 mg/m^2.
- Romidepsin should be discontinued if Grade 3 or 4 toxicities recur after dose reduction.

Hematologic toxicities:

- Grade 3 or 4 neutropenia or thrombocytopenia: Treatment with romidepsin should be delayed until the specific cytopenia returns to ANC ≥ 1.5×10^9/L and platelet count ≥ 75×10^9/L or baseline, then therapy may be restarted at 14 mg/m^2.
- Grade 4 febrile (≥ 38.5ºC) neutropenia or thrombocytopenia that requires platelet transfusion: Treatment with romidepsin should be delayed until the specific cytopenia returns to ≤ Grade 1 or baseline, and then the dose should be permanently reduced to 10 mg/m².

In case of treatment interruptions lasting beyond 28 days, romidepsin should be stopped and this will be considered as a permanent treatment discontinuation. This should be discussed with medical monitor to ensure that disease evaluations are performed prior to starting new therapy.

✓ ***Gemcitabine and bendamustine:***

Patients treated by gemcitabine or bendamustine will be monitored for toxicity using the national cancer institute common terminology criteria for adverse events (NCI-CTCAE), version 4.03 as a guide for the grading of severity. Guidelines are described below and can be adjusted at the discretion of the investigator:

- Treatment should be terminated or delayed if neutrophils and/or platelet values dropped to < 1.0 x 10^9/L or < 75 x 10^9/L, respectively. Treatment can be continued after neutrophil values have increased to > 1.5 x 10^9/L and platelet values to > 100 x 10^9/L.
- In case of non-haematological toxicity, 1/3 dose reduction, then 2/3 dose reduction, interruption of treatment are recommended.

If a patient requires a dose modification the individually calculated reduced dose must be given on day 1 and 2 of the respective treatment cycle.

In case of treatment interruptions lasting beyond 28 days, investigator's choice therapy should be stopped and this will be considered as a permanent treatment discontinuation. This should be discussed with medical monitor to ensure that disease evaluations are performed prior to starting new therapy.

10.3 Concomitant medications

Therapies considered necessary for the patient's well-being may be administered at the discretion of the investigator. All medications (prescription and non-prescription (except homeopathy, phytotherapy) taken from the enrollment, at any time during the study and up to 28 days after the end of the study treatment will be considered as concomitant treatments and will be recorded in eCRF until OS analysis.

10.3.1 *Prohibited therapies*

The following concomitant treatments are not permitted during this study treatment:

- Cytotoxic chemotherapeutic agents or experimental agents
- Other investigational therapies or devices
- Azacitidine for injection, decitabine, or other demethylating agents
- Mogamulizumab
- Concomitant radiotherapy
- Romiplostim and other TSAs (e.g., Interleukin-11)
- Hydroxyurea
- Lenalidomide
- Pomalidomide
- Thalidomide

- Arsenic trioxide
- Interferon
- Oral Retinoids (topical retinoids are permitted)

If a patient's clinical status requires administration of a prohibited concomitant medication or treatment, then administration of study drugs should be stopped, and the patient will be withdrawn from the study treatment.
The change in clinical status mandating the use of the medication in question must be reported as the reason for study drug discontinuation.

10.3.2 ***Restricted/allowed therapies***

Patients will be instructed not to take any additional medications (including over-the-counter products) during the course of the study without prior consultation with the investigator. At each visit, the investigator will ask the patient about any new medications he/she is or has taken after the start of the study drug.
All therapies necessary for the patient management are permitted besides other antineoplastic agents for lymphoma. Rituximab is not prohibited to treat manifestations symptoms resulting from secondary effects of tumor such as autoimmune hemolytic anemia and thrombocytopenia purpura.

10.3.3 ***Prophylactic measures***

Best supportive care may be used in combination with study treatment as deemed necessary.
Best supportive care in both treatment arms will include, but not limited to prophylactic use of granulocyte colony-stimulating factor (G-CSF) or erythropoietin: simulating agent (ESA) is allowed. G-CSF use is allowed in case of febrile neutropenia, but also as primary prophylaxis if decided by the investigator. ESA can be used for the treatment of anemia in symptomatic patients with non-myeloid tumors receiving chemotherapy according to the EMEA guidance from June 2008. For patients receiving ESA, DVT prophylaxis should be either IMW heparin or warfarin according to the investigator.

Blood product support (red blood cells or platelets) may be administered according to institutional standards.

Prophylactic use of anti-emetics is strongly recommended 30 minutes prior to each dose of oral azacitidine. Choice of anti-emetics is at the discretion of the investigator.

Patients should receive prophylaxis for opportunistic infections according to local guidelines. This would include prophylaxis for *Pneumocystis jirovecii* infection (trimethoprim/sulfamethoxazole or alternative such as atovaquone, or aerosolized pentamidine) and antiviral prophylaxis (valacyclovir/acyclovir).

The use of these products will be considered as concomitant treatment and documented as concomitant medications, therapies or procedures.
Note: In the safety-run (Japanese patients), prophylactic use of hematopoietic growth factors (e.g., filgrastim and pegfilgrastim) as well as transfusional support (packed red blood cells or platelets) are not allowed during the DLT observation period

10.4 Drug Dispensation and accountability

10.4.1 ***Clinical Supply and responsibilities***

Investigational product's supply will be done via IDOS system by the site (More details are described in the plan for oral azacitidine (CC-486) management).
The investigator or pharmacist is responsible for taking an inventory of each shipment of IP received, and comparing it with the accompanying study drug shipment order, will verify the accuracy of the information on the form and acknowledge receipt of all shipments of the investigational product in IDOS system.

All drug packages are to be inspected upon receipt at the study site prior to being drawn up. If any particulate matter is detected, the packaging is not to be used. Damaged packaging is to be reported to the sponsor and stored until instructions have been given.

The investigator, the Hospital Pharmacist, or other personnel allowed to store and dispense Investigational Product is responsible for ensuring that the Investigational Products used in the clinical trial are securely maintained as specified by the sponsor and in accordance with the applicable regulatory requirements.

All Investigational Products are stored in accordance with labeling and must be dispensed in accordance with the investigator's prescription. The investigator and the pharmacist are responsible of maintaining an accurate record of Investigational Product issued and returned. **The product traceability at site must be available as it could be asked by the Sponsor at any moment during the study.** Any quality issue noticed with the receipt or use of an Investigational Product (e.g., deficient IP in condition, appearance, pertaining documentation, labeling, expiry date,) should be promptly notified to the Sponsor, who will initiate a complaint procedure. Under no circumstances will the investigator supply Investigational Product to a third party, allows the Investigational Product to be used other than as directed by this Clinical Trial Protocol, or dispose of Investigational Product in any other manner.

10.4.2 *Retrieval or destruction*

Any unused IP must be returned by the patient.

According to local regulatory requirements, any unused and undelivered IP can be destroyed by the investigator or the pharmacist after the sponsor provides a written authorization.

According to local regulatory requirements, all used or partially used treatments returned by the patients can be destroyed by the investigator (or the pharmacist) after the sponsor validates the accountability log.

All destroyed treatments have to be documented by the pharmacist on a certificate.

In case of a potential defect in the quality of Investigational Product, the sponsor may initiate a recall procedure. In this case, the investigator will be responsible for promptly addressing any request made by the sponsor, in order to recall Investigational Product and eliminate potential hazards.

10.4.3 *Accountability and compliance*

Investigational product accountability will be assessed by site personnel using pill counts and information provided by the patient or caregiver (e.g., patient dosing diary). Investigational product dosing information should be captured in the source documentation on Day 1 of each cycle. Investigational product dosing information must also be entered on the appropriate CRF.

The investigator(s) or designee(s) is responsible for accounting for all IP that is issued to and returned by the patient during the course of the study according to applicable regulatory requirements. Investigational product administration will be accurately recorded including, but not limited to, date of administration, dose and any changes in dose administration (e.g., interruption or reduction in dose due to an adverse event).

If any IP is lost or damaged, its disposition should be documented.

At the periodic monitoring visits, a sponsor representative (or designee) representative will periodically check the supplies of investigational products held by the investigator or pharmacist to verify accountability of all investigational products used and address any discrepancies. Upon satisfactory reconciliation of all IP, returned IP may be destroyed.

At the conclusion of the study, all remaining study drug will be counted, reconciled with dispensing records, documented, and destroyed at the clinic site or allocated drug destruction location after completion of drug accountability by a sponsor representative (or designee). The sponsor representative (or designee) will ensure that a final report of drug accountability to the unit dose level (i.e., tablet) is prepared and placed in both the investigator study file and trial master file.

Administration of the study treatment will be supervised by the investigator or sub-investigator.

10.4.4 *Compliance*

Patients will self-administer all IP doses in the treatment phase.

Documentation of dosing during treatment will be recorded in a study specific patient diary.

Investigational product administration patient diary will be provided by the Sponsors to study site personnel, who will in turn distribute them to patients. Study site personnel will enter the scheduled daily doses, the number of tablets to

be taken each day and any other applicable information. Study site personnel will review the dosing information with the patient on scheduled clinic visit days.

Patients will be asked to record IP dosing information, anti-emetic medication taken at home, concomitant medications and adverse events occurred during the cycle in the patient diary and to bring the patient diary and unused tablets in the blister card (or the blister card packaging even if it is empty) with them to scheduled clinic visits (i.e., prior to the start of the next treatment cycle). A patient diary and tablet compliance check will be performed by study personnel. Patient diary must be saved and kept with the source documentation. Study site personnel will perform an IP administration compliance check and record this information in the patient's source record and on the appropriate CRF.

Administration of all IP will be recorded including dispensing, dosing and any changes in dosage administration such as interruption or reduction in dosing due to an AE.

11 SAFETY RUN-IN (JAPANESE PATIENTS)

In the safety run-in part (Japanese patients only), 3 patients will be dosed at 100 mg and then 200 mg QD of oral azacitidine with 14 days in a 28-day schedule and observed for dose limiting toxicities (DLT) using 3 + 3 design (Storer, 1989).

Dose limiting toxicities will be observed from the first IP dose through completion of Cycle 1.

1. If number of patient with DLT = 0/3, the dose will be declared tolerable
2. If number of patient with DLT = 1/3, recruit another 3 patients to test the same dose
    a. If number of patient with DLT = 1/6, the dose will be declared tolerable
    b. If number of patient with DLT ≥ 2/6, the dose will be declared intolerable
3. If number of patient with DLT ≥ 2/3, the dose will be declared intolerable

Data from the safety run-in will be reviewed once the last patient of a respective cohort completes 1 cycle at a defined dose level, in conjunction with the study investigators (as available) and IDMC to ensure agreement with dose regimen prior to beginning enrollment to the randomized phase.

During the safety run-in, the decision to evaluate the subsequent dose level, an intermediate dose level, different dosing schedules not currently specified (e.g., different dose and schedule of oral azacitidine), the need to add additional patients within any dose cohort, or to declare a dose level as tolerable will be assessed, recommended and documented by the IDMC based on their review of clinical and laboratory safety data for a given dose cohort.

Once the recommended tolerable dose level is identified, Asian patients in Japan or South Korea will be enrolled to the randomized phase of the study, and the patients at 100 mg 14/ 28 days could be escalated to 200 mg 14/ 28 days at the discretion of the investigator

Definition of Dose Limiting Toxicity (DLT) period:

DLT evaluation period start from the first IP dose through end of Cycle 1 (e.g. 28th day of cycle)

Definition of Dose-limiting toxicities:

Dose limiting toxicities will be evaluated during the DLT evaluation period. The severity grading of adverse events will be determined according to CTCAE Version 4.03 (unless otherwise specified).

Note: Prophylactic use of hematopoietic growth factors (e.g., filgrastim and pegfilgrastim) as well as transfusional support (packed red blood cells and platelets) are not allowed during the DLT observation period.

A dose limiting toxicity (DLT) is defined as any of those events listed below and considered related to oral azacitidine:

Hematologic toxicity:

- Grade 5 hematologic events
- Grade 4 neutropenia lasting > 10 days or with fever (defined as ≥ 38.5°C) requiring hospitalization

- Grade ≥ 3 thrombocytopenia (platelet count < 50 x 10^9 / L) with significant bleeding or that requires platelet transfusion

Non-Hematologic toxicity:

- Any Grade ≥ 3 non-hematologic AE, with the following exceptions:
  - Any Grade ≥ 3 non-hematologic laboratory abnormality which is not associated with any clinical signs or symptom or resolve to ≤ Grade 2 or patient's pre-treatment baseline level within 7 days with appropriate medical intervention
  - Grade 3 emesis or vomiting that responds to optimal antiemetic therapy within 72 hours
  - Grade 3 diarrhea that responds to optimal medical management within 72 hours
  - Grade 3 fatigue in a patient who had Grade 2 fatigue at study entry and that recovers to baseline grade or less within 72 hours

Any event clearly and directly related to the primary disease or to another etiology documented by the investigator are not considered DLTs.

Should a patient experience a suspected DLT, the treating investigator should contact the sponsor's medical monitor immediately. All DLT cases will also be discussed with the IDMC and respective treating investigators (as available).

Definition of DLT- evaluable Patient:

Patients enrolled to the safety run-in are considered evaluable for DLTs if they complete the DLT evaluation period specified without experiencing a DLT, or experience a DLT (even if they discontinued) during the DLT evaluation period (i.e., from the first IP dose through end of Cycle 1), and if they received at least 11 out of 14 of the scheduled doses of oral azacitidine during Cycle 1.

Patients who discontinue participation in the safety run-in phase of the study not related to study treatment (e.g. rapid disease progression or administrative reason) before they can be assessed for DLT will be replaced at the same dose level. Additional patients within any dose cohort may be enrolled at the discretion of the IDMC.

Pharmacokinetics analysis:

All Japanese patients will participate in PK sample collection.

On the PK days (Cycle 1 Day 1 and Cycle 1 Day 14), patients will ingest IP in the clinic after performing the required overnight fasting and pre-dose PK sample collection, with each dose being given at approximately the same time of day. The exact date and time of dosing and PK sampling will be recorded in the source documents and appropriate form.

For additional Japanese patients from safety run-in (all patients treated with oral azacitidine 100 mg QD and at least 3 patients treated with oral azacitidine 200 mg QD) enrolled, intensive blood samples (3 mL/sample) for oral azacitidine PK assessment will be collected prior to each dose administration (pre-dose) and over the 6-hour period following each dose administration (0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0 and 6.0 hours post-dose) (Note: windows of PK sampling times are as follows: ≤ 60 minutes for predose PK samples, ± 5 minutes for 0.5, 1.0, 1.5, 2.0, 2.5, 3.0 and 4.0 hours PK samples and ± 20 minutes for 6.0 hours PK samples).

For the rest of the Japanese patients enrolled, less intensive blood samples (3 mL/sample) for oral azacitidine PK assessment will be collected prior to each dose administration (pre-dose) and over the 4-hour period following each dose administration (0.5, 1.0, 2.0 and 4.0 hours post-dose) (Note: windows of PK sampling times are as follows: ≤ 60 minutes for predose PK samples, ± 5 minutes for 0.5, 1.0, 2.0 and 4.0 hours PK samples).

12 STUDY PROCEDURES

12.1 Registration and enrollment procedure

As soon as a patient has signed an informed consent, [redacted] should be registered directly on the data capture system by the investigators through the internet network using the address below. To access the interactive registration program, the investigator needs to record the study name (ORACLE), a username and a password.

Internet: [redacted]
Investigator's choice therapy must be chosen during the Screening period.

The study site will receive back the registration number for the registered patient. At the same time, the anonymized initial/relapse pathology reports (French version for French and Belgian patients and English version for other countries) and the completed pathology form must be sent by fax [redacted] or email [redacted]
Each pathological diagnosis must be validated by the sponsor's medical monitor before enrollment.

Once all screening assessments have been performed and all eligibility criteria are met, the patient can be enrolled through the system. Enrollment must be done before the start of study treatment.

Stratification: Patients will be randomly assigned to treatment arms (A or B) and stratified according to:

- Number of prior line treatment: 1-2 *versus* > 2
- Previous/Concurrent MDS or CMML: Yes *versus* No

LYSARC coordination site (Tel: [redacted]) will be the point of contact for any request.

12.2 Quality of life questionnaires

QoL measurement in cancer may be assessed using cancer-specific instruments such as the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30. QLQ-C30 scales have been validated in multiples cancers and have been translated in multiples language. It appears therefore suitable for QoL evaluation.

It will be completed by the quality of life questionnaire EQ-5D- 5L **(*See Appendix 10*).**

It is highly recommended to fill in the QoL questionnaires before any treatment administration.
After filling by the patient, the data will be entered by the site staff into the eCRF until the OS analysis.

12.3 Pathological diagnosis

The pathological diagnosis of Angioimmunoblastic T-cell lymphoma should have been performed locally and validated by the sponsor's medical monitor before each patient enrollment.

In the last years, histopathology central review process has become a common and prerequisite procedure for clinical trials in the field of lymphomas. A mandatory pathological review will therefore be organized for all patients enrolled in the trial at diagnosis. The goal of this central review will be to confirm the diagnosis and to precise its classification according to the latest WHO classification.

The central pathological review will be performed at LYSA-Pathology institute (LYSA-P) [redacted].

For each patient, the investigator must send to LYSARC by fax [redacted] **or email** [redacted] a copy of the initial and relapse anonymized histopathological report where the name and address of the pathologist having diagnosed the lymphoma will be easily identified as well as a copy of the bone marrow report. If a biopsy is performed at the end of treatment or at relapse, the anonymized pathology report should also be sent to by fax or email as well as the tumoral material.

The tumor paraffin embedded blocks from the formalin fixed sample that have been used for diagnosis will be sent to the LYSA-P, as well as the immunohistochemical slides that were used to set the diagnosis, according to the process described in Appendix 15. If the FFPE blocks are not available, an H&E slide and 12 unstained slides should

be sent. In case of relapse or progression, the FFPE blocks when available should also be sent to the LYSA-P for pathological review and ancillary study.

At reception, routinely stained sections will be performed and an appropriate panel of antibodies according to morphological aspects will be applied. The central pathological review will be performed by at least two experts hematopathologists and will be organized at LYSA-P. A consensus diagnosis will be established and communicated to the clinical coordinator and to the initial pathologist.

Initial +/- relapse tumor block will also be used to make tissue microarray (TMA), to study the expression of markers known to influence the prognosis of AITL lymphoma.

Slides will also be taken from the initial tumor block as well as at relapse when available to extract the DNA/RNA and study T-cell lymphoma prognostic biomarkers.

For the need of the ancillary study, blocks will be kept temporarily to avoid a second request. Meanwhile, the block will be at the entire disposition of the initial anatomopathological laboratory under request if they need it.

Frozen tumor tissue will be requested for all French and Belgian enrolled patients. The collection of the frozen tumor specimen will be organized and centralized at the LYSA-P. On frozen tissue, gene and protein expression analysis will be performed to assess the level of expression of genes/proteins known to influence the outcome of Angioimmunoblastic T-cell lymphoma patients.

12.4 Ancillary biological studies only for French and Belgian centres

12.4.1 *Rational*

Objective: to determine predictive factors, especially molecular markers, associated with response to oral azacitidine in nodal TFH PTCL

Rational: *TET2*, *DNMT3A* and *IDH2* are frequently mutated in Angioimmunoblastic T cell lymphomas and other TFH derived nodal PTCLs

These data brought rational to use 5 azacitidine in TFH derived PTCL. However, the mechanism of action of 5 azacitidine in TFH derived PTCLs and whether it is possible to identify patients who will benefit from this treatment are unknown.

Especially it is unknown whether observed response to 5 azacitidine in AITL patients is related to a direct effect on the drug on tumor cell or an indirect effect, which could include effect on cells from microenvironment or effect on a *TET2* mutated “preleukemic population”.

12.4.2 *Sampling for ancillary biological studies*

- Samplings for ancillary biological studies **at diagnosis, end of cycle 3 and progression /relapse**:
  - Around 5mL of bone marrow on EDTA and around 10mL of blood on EDTA for DNA banking and myeloid anomalies on CD34 analysis
  - Around 5mL of blood on dry tube for serum banking and proinflammatory cytokines analysis
  - Around 9mL of blood on STRECK tube for circulating tumoral DNA banking and analysis
  - Around 18mL of blood on EDTA tube for plasma banking and flow cytometry, clonality T analysis and clonality B analysis
- Sampling for biological studies at **diagnosis only**:
  - Saliva sampling for DNA genomic banking and analysis on ORAGEN 500 kit

All the blood samples will be sent [redacted] by carrier, at room temperature, the day of blood sampling, for banking and analysis. A traceability form will be completed by the centre and will be sent [redacted] with the samples.

Shipment address : [redacted]

All the samples will be immediately coded if they are not yet, or identification will be controlled at reception .The complete procedure will remain anonymous all along the biological analysis. Observations will be linked with the

LYSA clinical database (registered to the CNIL) only after the end of the study. This database contains the main information about patients participating to the study including demographic data, baseline clinical evaluation, treatment, response to treatment and follow-up (relapse, death). Beyond the period of study monitoring, the database will be actualized every year.

12.5 CT scan Review

A central review of CT scan is organized for this study and mandatory until OS analysis.

For each patient included in the efficacy analysis, all available data and images will be uploaded on Imagys® platform (only CT scans related to lymphoma) and reviewed by a panel of CT experts until OS analysis.

The following timepoints are required for the review:

- Screening
- After 3 cycles
- End of treatment
- Every 3 months during the first year,
- Every 6 months during the second and third years and then,
- Annually until the end of the study or until the progression.

13 STUDY COMMITTEES

13.1 Independent Review Committee (IRC)

The Independent Review Committee (IRC) will perform a blinded, independent assessment of the progression and the corresponding date of the progression or relapse for each patient according to Lugano Response criteria (2014). The IRC will be composed of:

- An independent review of all CT scans performed by two independent radiologists (with an additional radiologist in case of discrepancy).
- An independent review performed by an independent hematologist. The hematologist will perform assessment of progression and the corresponding date of the progression for each patient according to Lugano Response criteria (2014). [redacted] will have access to the result of central CT scan review and also of clinical data, biological results, bone marrow biopsy and any other relevant exams for confirmation of progression.

Details of the IRC activities will be described in a separate IRC charter.

13.2 Independent Data Monitoring Committee

An Independent Data Monitoring Committee (IDMC), including at least three independent members (2 experts in NHL, and one statistician) will be established.

Time to IDMC meeting:

- **On the first and second cohorts of three Japanese patients each**

The IDMC will meet once the first and second cohorts of 3 Japanese patients being enrolled and the last patient of the cohort has achieved 1 cycle of treatment or having discontinued treatment

The IDMC will review ongoing safety data and make recommendations to the sponsor for any safety concerns. The data presented to the IDMC will include AE/SAE, deaths and AESI and SAE.

- **On all safety set**

The IDMC will meet periodically and will review ongoing safety data throughout the study and make recommendations to the sponsor for any safety concerns.

The IDMC will meet to review safety and efficacy data of the futility analysis, planned once 18 PFS events would have to be observed. It is planned to occur around 18 months after first randomized patient, approximately 39-47 patients being enrolled.

More details about IDMC operations will be provided in the IDMC Charter.

14 CRITERIA FOR PERMANENT TREATMENT DISCONTINUATION OF THE STUDY

14.1 Permanent treatment discontinuation

Circumstances that lead to permanent treatment discontinuation of a patient from the trial must be reported by the investigator on the appropriate CRF page.

Criteria for patient permanent treatment discontinuation include (but are not limited to):

- death,
- toxicity of study treatment, that would be, in the investigator's opinion, detrimental to the patient's well-being
- lymphoma progression,
- concomitant disease,
- pregnancy
- noncompliance (including loss of patient to follow-up),
- refusal to continue treatment,
- major protocol violation, including initiation of alternate anti-neoplasic therapy.

Patients who are in permanent treatment discontinuation study treatment should however remain in the trial for the purpose of follow-up overall survival, with the exception of patients who withdrew their consent. Patients who don't want to receive anymore study treatment can remain in the trial for the purpose of follow-up.

Any patient who discontinues before completing the study will be encouraged to return to the study centre within 4 weeks for an evaluation.

14.2 Withdrawal of Consent

Patients are free to withdraw from the study at any time without prejudice to their treatment. When a patient decides to withdraw from the study, he/she should always be contacted in order to obtain information about the reason for withdrawal and to record any adverse events. When patient agrees, he/she should return for a study visit at the time of, or soon after withdrawal, and the relevant assessments should be performed.

If the patient explicitly states his/her wish not to contribute further data to the study, the relevant Sponsor contact should be informed and the withdrawal of consent should be documented by the investigator in the patient's case report form. However, data up to the time of consent withdrawal will be included in the data reported for the study.

14.3 Patients Lost to Follow up

Every effort will be made to contact patients who fail to return for scheduled visits. A patient is considered lost to follow-up if no information has been obtained when the last patient has completed the clinical phase of the study. During this time, site investigator must document at least 3 attempts to contact the patient either by phone, email or letter.

14.4 Discontinuation of the study

The sponsor reserves the right to stop the trial at any time. The investigators will be informed of this decision in writing. Study discontinuation will also be declared to CA and EC according to local regulation.

The same applies to any investigator wanting to discontinue his/her participation to the trial. The investigator must immediately inform the sponsor in writing of this decision.

15 SAFETY PARAMETERS

15.1 Definitions

15.1.1 *Adverse Events*

An **adverse event** (AE) is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.
An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition.

15.1.2 *Serious Adverse Events*

A **serious adverse event** (SAE) is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (the term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event ; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalization (hospitalization is defined as an inpatient admission, regardless of length of stay) or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity (the term “persistent or significant disability or incapacity” means that there is a substantial disruption of person’s ability to carry out normal life functions.)
- Is a congenital anomaly/birth defect
- Is a medically significant event.

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriated in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the outcomes listed in the definition above.
The term “severe” is a measure of intensity, thus a severe AE is not necessarily serious. For example, “nausea of several hours duration” may be severe but may not be clinically serious.

15.1.3 *Intensity*

The intensity of the AE or SAE will be graded by the investigator according to the Common Terminology Criteria for Adverse Events (CTCAE) grading system v4.0 in the toxicity categories that have recommended grading (see investigator’s file or online at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm).
AEs not listed on this grading system will be graded according to the five-point system below:

- Mild (grade 1): Discomfort noticed but no disruption of normal daily activity
- Moderate (grade 2): Discomfort sufficient to reduce or affect normal daily activity
- Severe (grade 3): Incapacitating with inability to work or perform normal daily activity
- Life-threatening (grade 4): Substantial risk of dying at time of event
- Death (grade 5)

15.2 Adverse Events reporting rules

AEs of all grades (CTCAE – version 4.03) regardless relationship to investigational product occurring **from the date of informed consent signature to 28 days after last drug administration of the study (i.e. oral azacitidine, romidepsin, gemcitabine and bendamustine) will be recorded in the AE pages of the eCRF**. When associated to a SAE and regardless of the time of occurrence and the grade, the AE must be reported as “Adverse Event” in the appropriate eCRF pages.

Whenever possible, symptoms should be grouped as a single syndrome or diagnosis. The investigator should specify the date of onset, intensity, action taken regarding trial medication, corrective therapy given, outcome of all AEs and [redacted] opinion as to whether the AE can be related to the study drug.

All events that meet one or more criteria of seriousness (see Section 14.1.2) will be reported as SAE (see Section 14.3).

General AE reporting rules:

- Non-serious AE will be reported through eCRF
- Any episode of any grade of toxicity, related to a SAE must be reported as "Adverse Event" in the appropriate eCRF pages regardless the time of occurrence
- Signs, symptoms and physical findings indicative of lymphoma or progression of lymphoma are not to be reported as "Adverse Event"
- "Alopecia" toxicity (any grade) will never be reported as "Adverse event"
- AEs will be considered ended (recovered without sequelae) when recovered to a grade 0 or baseline
- In case of screening failure, at least AEs corresponding to SAEs will be reported in the AEs pages of eCRF.
- When a medical history resolves or decreases at a grade lower than baseline, the new grade will be the new reference grade for following AEs
- For laboratory abnormalities, the laboratory test to be taken as reference will be the one performed nearest to the Cycle 1 Day 1.
- Overdoses must be reported as adverse events. On a per-dose basis, an overdose is defined as, for oral azacitidine, any amount over the protocol-specified dose, and, for IV treatment (romidepsin, bendamustine and gemcitabine), as 10% over the protocol-specified dose, assigned to a given subject, regardless of any associated AEs or sequelae. On a schedule or frequency basis, an overdose is defined as anything more frequent than the protocol required schedule or frequency. On an infusion rate basis, an overdose is defined as any rate faster than the protocol-specified rate.
- Medication errors, pregnancies and uses outside what is foreseen in the protocol, including misuse and abuse of the product, should be reported in the eCRF.

Abnormal laboratory values reporting rules:

If a laboratory abnormality is one component of a diagnosis or syndrome (e.g., alkaline phosphatase and bilirubin 5 × ULN associated with cholecystitis), only the diagnosis (e.g., cholecystitis), or syndrome should be recorded on the AE page/screen of the eCRF. If the abnormality was not a part of a diagnosis or syndrome, then the laboratory abnormality should be recorded as the AE.

An abnormal laboratory value which is not a component of a diagnosis or syndrome is considered as an AE if the abnormality:

- results in discontinuation from the study; or
- requires treatment, modification/ interruption of IP dose, or any other therapeutic intervention; or
- is judged to be of significant clinical importance.

Note: Grade 3 – 4 neutropenia (neutrophil count decreased), lymphopenia (lymphocyte count decreased), thrombopenia (platelet count decreased) and anemia (hemoglobin count decreased) will be recorded as AE even if non medically significant.

The investigator has to notify in the patient medical file all the abnormal laboratory values considered as clinically significant (write next to each abnormal laboratory value assessed as clinically significant "CS" or precise it in the medical report).

15.3 Serious Adverse Events reporting rules

All events that meet one or more criteria of seriousness (see Section 14.1.2) occurring **after the informed consent signature to end of treatment evaluation (28 days after the last study drug administration, i.e. oral azacitidine, romidepsin, gemcitabine and bendamustine),** will be reported as SAE regardless of:

- the relationship to the study treatment
- the administration of new lymphoma therapy
- disease progression

A SAE that occurs after this time, including during the follow-up period, **if considered related to the study drug**, will be reported.

Whenever possible, symptoms should be grouped as a single syndrome or diagnosis. The investigator should specify the date of onset, intensity, action taken regarding trial medication, corrective therapy given, outcome of all SAEs and his/her opinion as to whether the SAE can be related to the study drugs.

General SAE reporting rules:

- Any episode of any grade of toxicities, which meets one of the seriousness criteria must be reported as "Serious Adverse Event" in the appropriate SAE form
- Signs, symptoms and physical findings indicative of lymphoma or progression of lymphoma are not to be reported as "Serious Adverse Event". In case the patient had progressed and a SAE has occurred, if the cause is not lymphoma, the SAE should be reported.
- Regardless of severity grade, only laboratory abnormalities that fulfill a seriousness criterion need to be documented as a serious adverse event.
- Hospitalizations **not to be considered** as SAEs are:
  - Planned hospital admissions or surgical procedures for an illness or disease which existed before the patient was enrolled in the study or before study drug was given are not to be considered SAEs unless the condition deteriorated in an unexpected manner during the study (e.g., surgery was performed earlier than planned).
  - A procedure for protocol therapy administration or protocol/disease-related investigations. Hospitalization or prolonged hospitalization for a complication will be reported as an SAE
  - Routine treatment or monitoring of the studied indication (e.g., administration of blood or platelet transfusion) not associated with any deterioration in condition. Hospitalization or prolonged hospitalization for a complication remains a reportable SAE
  - Hospitalization or prolongation of hospitalization for technical, practical, or social reasons, in absence of an AE
  - Emergency outpatient treatment or observation that does not result in admission, unless fulfilling other seriousness criteria above (section 14.1.2)

15.3.1 *Obligations of the investigator*

In a case of SAE the investigator must immediately (within 24 hours):

- **Complete SAE form with all relevant information regarding SAE**
- **SEND the SAE pages to:**

  <u>SAE from France, Belgium, South Korea, Austria, Italy, United Kingdom, Sweden, Finland and Denmark</u>:

  LYSARC Pharmacovigilance department
  FAX: [redacted]
  Email: [redacted]

  <u>SAE from Japan:</u>

  Bristol-Myers Squibb K.K. Patient Safety
  FAX : [redacted]
  Email: [redacted]

All SAE forms must be dated and signed by the responsible investigator or one of his/her authorized staff members.

- May attach the photocopy of all examinations carried out and the dates on which these examinations were performed. Care should be taken to ensure that the patient's identity is protected and the patient's identifiers in the Clinical study are properly mentioned on any copy of source document. For laboratory results, include the laboratory normal ranges.
- Follow up of any SAE that is fatal or life-threatening should be provided within one calendar week.

For SAEs, the following must be assessed: relationship to each study drug, action taken, and outcome to date. The assessment of whether there is a reasonable possibility of a causal relationship is usually made by the investigator; it can be one of two possibilities:

- Unrelated (no reasonable possibility)
- Related (reasonable possibility)

Items to be considered when assessing the relationship of a SAE to the study drug are:

- Temporal relationship of the onset of the event to the initiation of the study drug
- The course of the event, considering especially the effect of discontinuation of study drug or reintroduction of study drug, as applicable
- Whether the event is known to be associated with the study drug or with other similar treatments
- The presence of risk factors in the study patient known to increase the occurrence of the event
- The presence of non-study drug-related factors which are known to be associated with the occurrence of the event.

15.3.2 *Obligations of the Sponsor*

During the course of the study, the sponsor will report in an expedited manner all SAEs that are both unexpected and at least reasonably related to study drugs, to the EMA, Health Authorities, Ethic Committees in each country in accordance with international and local regulations, and to the investigators. The causality assessment given by the investigator should not be downgraded by the sponsor. If the sponsor disagrees with the investigator's causality assessment, the opinion of both the investigator and the sponsor should be provided with the report.

The expectedness of a serious adverse reaction will be determined by the sponsor according to the reference safety information (Investigator's Brochure or SmPC) of the study drug.

LYSARC Pharmacovigilance department will report all safety information from the trial in the Development Safety Update Reports and will notify the reports to the Health Authorities and Ethics Committees in accordance with international and local regulations. Bristol-Myers Squibb as the sponsor in Japan will have the responsibility to report to the Health Authority in Japan for qualifying reports received from all study sites.

15.4 Follow up of AEs and SAEs

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Any SAE should be monitored until it is resolved or is clearly determined to be due to a patient's stable or chronic condition or underlying condition. Any additional information known after the event has been initially reported should be sent to LYSARC as soon as information becomes available.

All AEs must be documented and the outcome must be followed-up until the return to normal or consolidation of the patient's condition.

Patients who are in permanent study treatment discontinuation due to any AE will be followed at least until the outcome is determined even if it implies that the follow-up continues after the patient has left the trial.

Ongoing adverse events thought to be related to IMP will be followed until the event is resolved to baseline grade, or is assessed by the investigator as stable or new anti-lymphoma treatment is initiated for progression of the underlying disease.

15.5 Adverse Events of Special Interest

The following AEs are considered as of special interest and require attention from investigator if occurring. In addition, they have to be reported immediately **in the eCRF**, irrespective of the seriousness criteria, and whatever the grade, from the date of informed consent signature to 28 days after last drug administration of the study (i.e. oral azacitidine, romidepsin, gemcitabine and bendamustine) .

- Interstitial lung disease (e.g. pneumonitis, non-infectious pneumonia, pulmonary fibrosis, lung infiltration…)
- Ischemic colitis (e.g., gastrointestinal ischaemia, enterocolitis haemorrhagic, large intestine perforation…)
- Tumor lysis syndrome
- Infections (limited to grade ≥ 3 and SAE)
- Hemorrhagic events

In case of suspicion of tumor lysis syndrome, please refer to Appendix 13 for diagnosis and management according to Cairo-Bishop criteria.

15.6 Pregnancy

15.6.1 *Females of Childbearing Potential*

This protocol defines a female of childbearing potential as a sexually mature woman who: 1) has not undergone a hysterectomy or bilateral oophorectomy or 2) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female patient occurring while the patient is on study drug, or within 6 months of the patient's last dose of study drug, are considered events to be reported immediately to Sponsor Pharmacovigilance on the appropriate Pregnancy Form.

Pregnancy from France, Belgium, South Korea, Austria, Italy, United Kingdom, Sweden, Finland and Denmark:

LYSARC fax number [redacted]
Email: [redacted]

Pregnancy from Japan:

Bristol-Myers Squibb K.K. Patient Safety
FAX : [redacted]
Email: [redacted]

If the patient is on study drug, the study drug is to be discontinued immediately and the patient instructed to return any unused portion of the study drug to the investigator.

The exposure of any pregnant female (e.g., caregiver or pharmacist) to study drug is also an immediately reportable event.

The female should be referred to an obstetrician/gynecologist preferably one experienced in reproductive toxicity for further evaluation and counseling.

The investigator will follow the female patient until completion of the pregnancy, and must notify the sponsor immediately about the outcome of the pregnancy (either normal or abnormal outcome).

If the outcome of the pregnancy is abnormal (i.e., spontaneous or therapeutic abortion) the investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE within 24 hours of the investigator's knowledge of the event using the SAE Report Form or approved equivalent form.

All neonatal deaths that occur within 28 days of birth should be reported, regardless of causality, as SAEs. In addition, any infant death after 28 days that the investigator(s) suspects to be related to the in-utero exposure to the study drug should also be reported to the sponsor within 24 hours of the investigator's knowledge of the event using SAE form.

15.6.2 *Male patients*

If a female partner of a male patient taking study drug becomes pregnant, the male patient taking study drug should notify the investigator, and the pregnant female partner should be advised to call her healthcare provider immediately. If a pregnancy related event is reported in a female partner of a male patient, the investigator should determine whether the female partner is willing to release her medical information to the Sponsor Pharmacovigilance and allow the pregnancy related event to be followed-up to completion.

16 GENERAL STATISTICAL CONSIDERATIONS

16.1 Analysis sets

16.1.1 *Intent To Treat Set (ITT)*

The Intent-To-Treat set (ITT) will include all patients having signed their informed consent and who are randomized into the trial, regardless of whether they received study treatment or not. All Japanese patients from safety run-in are excluded from this set.

16.1.2 *Efficacy Set (ES)*

The efficacy set includes all patients included in the ITT who have:

* received at least once one dose of either the study drug or the investigator's choice therapy
* histopathology confirmed by central review and relevant to the protocol
* baseline tumor assessments and at least one post-baseline tumor assessment

16.1.3 *Safety Set (SS)*

The Safety Set will include all patients in the ITT and who have received at least once one dose of either the study drug or the investigator's choice therapy. Japanese patients from safety run-in are excluded from this set.
This set is to analyse on actual treatment arm received.

16.1.4 *Per Protocol Set (PP)*

The PP set includes all patients included in the ITT, with no major protocol deviation. Major protocol deviations are defined as follow:

* histopathology confirmed by central review and relevant to the protocol
* at least once one dose of either the study drug or the investigator's choice therapy
* treatment received relevant to the randomization arm
* all inclusion and exclusion criteria fulfilled
* no treatment discontinuation for major protocol violation reason

These major protocol deviations could be completed according to inconsistencies reported during data reviews.

16.1.5 *Safety Set from Safety-Run (SS-SR)*

The safety set from safety run-in (SS-SR) includes Japanese patients for safety run-in (out of randomization), having signed their informed consent and having received at least one dose of oral azacitidine

16.1.6 *DLT Set*

The DLT set includes all Japanese patients in the Safety set from safety run-in (SS-SR), who have completed the first cycle (at least 11 out of 14 of the scheduled doses of oral azacitidine) or experience a DLT (even if they discontinued before).

16.1.7 *QoL Set*

The QoL set includes ITT set having returned the QoL questionnaire at baseline and at least one follow-up.

16.1.8 *PK set*

The PK set will include all Japanese patients who receive at least one dose of IP and have at least one measurable concentration datum. The PK set will be used in PK analyses.

16.2 Endpoint

16.2.1 *Primary endpoints*

The primary endpoint is:

- **Progression Free Survival (PFS) on local assessment**

PFS is defined as the time from randomization into the study to the first observation of documented disease progression (local assessment using Lugano Response Criteria 2014) or death due to any cause. If a patient has not progressed or died, PFS will be censored at the time of last visit with adequate assessment.

Main analysis of this endpoint will be analyzed on ITT set with censoring rules based on Food and Drug Administration (FDA) guidance. Sensitivity analysis will be performed based on different censoring rules for PFS, and different analysis set. Details will be specified in the Statistical Analysis Plan.

16.2.2 *Secondary endpoints*

16.2.2.1 *Efficacy endpoints*

- **Overall Survival (OS)**

Overall survival is defined as the time from the date of randomization to the date of death from any cause. Alive patients will be censored at their last contact.

This endpoint will be analyzed on ITT.

- **Progression Free Survival (PFS) based on centrally IRC assessment**

PFS is defined as the time from randomization into the study to the first observation of documented disease progression (reviewed assessment by IRC using Lugano Response Criteria 2014) or death due to any cause. If a patient has not progressed or died, PFS will be censored at the time of last visit with adequate assessment.

This endpoint will be analyzed on ITT with censoring rules based on FDA.

- **Overall Response Rates (ORR) according to Lugano Response Criteria (2014)**

Overall response rates is defined as the percentage of CR+PR among all patients. Patient without response assessment (due to whatever reason) will be considered as non-responder. Assessment of response will be based on Lugano Response Criteria 2014 for the radiologic response (CT based), the metabolic response (PET-CT based) and the best response between radiologic and metabolic response. This response rate will be measured after C3, after C6 and at permanent treatment discontinuation.

This endpoint will be analyzed on ITT.

- **Complete response rate (CRR) according to Lugano Response Criteria (2014)**

Complete response rate is defined as the percentage of CR among all patients. Patient without response assessment (due to whatever reason) will be considered as non-responder. Assessment of response will be based on Lugano Response Criteria 2014 for the radiologic response (CT based), the metabolic response (PET-CT based) and the best response between radiologic and metabolic response. This response rate will be measured after C3, after C6 and at permanent treatment discontinuation.

This endpoint will be analyzed on ITT.

- **Duration of response**

Duration of response is defined as the time from attainment of CR or PR to the date of first documented disease progression, relapse (local assessment) or death from any cause. Patients alive and free of progression will be censored at their last visit with adequate assessment.

This endpoint will be analyzed on ITT with censoring rules based on EMA.

- **Time to response**

Time to response is defined as the time from randomization to the date of attainment of CR or PR until end of treatment. If a patient is not responder, time to response will be censored at the time of last visit with adequate assessment.

This endpoint will be analyzed on ITT.

- **Progression Free Survival 2 (PFS2) on local assessment**

PFS2 is defined as the time from randomization to objective tumor progression on next-line treatment or death from any cause. All patients in ITT population will be included in PFS2 analysis. Patients without next-line therapy who did not die and patients who did not relapse or not die after next-line therapy will be censored at the last adequate tumor assessment date.

This endpoint will be analyzed on ITT with censoring rules based on EMA.

- **Quality of Life (QoL)**

- QLQ-C30

The EORTC QLQ-C30 questionnaire will be measured as described in section 9 Study flow chart and schedule of assessments. Details of the questionnaire are precise in appendix 10.

Score will be descriptively tabulated by actual treatment arm received.

These endpoints will be analyzed on QoL set.

16.2.3 *Exploratory endpoints*

- To correlate the presence of genomic alterations and gene expression data to clinical response to oral azacitidine and survival data
- To study the methylation profile of the tumors
- To study the myeloid population in bone marrow of these patients
- HRQOL endpoints EQ-5D
- To characterize the pharmacokinetics (PK) of oral azacitidine in Japanese patients

16.2.4 *Safety endpoints*

- **Treatment exposure**

Summary of study drug administration, including treatment duration, average dose and dose reduction will be displayed by actual treatment arm received.

Number, frequency and reasons for permanent treatment discontinuation and study discontinuation will be summarized by actual treatment arm received.

- **Adverse Events**

All adverse events will be described according to actual treatment arm received.

Adverse events observed will be classified using MedDRA System Organ Class and Preferred Term. The severity of the toxicities will be graded according to the NCI CTCAE v 4.03 whenever possible; NCI CTCAE v3.0 will be used to grade tumor flare reaction.

The frequency of adverse events will be tabulated by MedDRA System Organ Class and Preferred Term. In the by-subject analysis, a subject having the same event at the same grade more than once will be counted only once. Adverse events will be summarized by NCI CTCAE grade. Adverse events leading to discontinuation from treatment, events classified as NCI CTCAE grade 3 or 4 study-drug-related events, deaths, and SAEs will be tabulated and listed separately. By-subject listings of all AEs, SAEs, and their attributes will be provided. Analysis on AEs of special interest will be conducted as well to support safety evaluation of CC-486 or investigator's choice.

AEs leading to death, and pregnancies will also be displayed in a separate table and a by-patient listing.

- **Deaths**

All deaths will be listed and also summarized by cause of death according to actual treatment arm received.

- **Laboratory results, vital signs and concomitant medications**

Laboratory results, vital signs and concomitant medications will be summarized in terms of mean, standard deviation, median, minimum and maximum values or frequency by visit according to actual treatment arm received.

Graphical displays may be provided where useful to assist in the interpretation of results.

All these safety endpoints will be performed on safety set (SS) and on safety set from safety-run (SS-SR).

16.3 Sample size calculation and tested hypothesis

16.3.1 *Sample size*

Primary endpoint: PFS

The primary endpoint of this randomized phase 3 trial is progression free survival assessed by local review.

Assumptions:

- One sided superiority test
- Design 1:1
- Alpha risk: 2.5%
- Power: 90%
- HR=0.417 (median PFS of 5 months in the standard arm vs 12 months in the experimental arm)
- Dropout rate: 10% each year
- One futility analysis at around 18 months (information fraction = 30%)
- Efficacy boundary based on Lan-DeMets spending function with O'Brien-Fleming approximation
- Futility boundary based on Lan-DeMets spending function with Pocock approximation in a non-binding design

Based on these assumptions, 61 events would have to be observed. Assuming a peak recruitment rate of 5 patients / month after 18 months, 27 months of total recruitment period would be needed to recruit 86 patients.
Sample size calculation was performed with EAST software version. 6.3.

Key Secondary Endpoint: OS

Assumptions:

- One sided superiority test
- Design 1:1
- Alpha risk: 2.5%
- Power: 90%
- HR=0.417 (median OS of 7 months in the standard arm vs 16.8 months in the experimental arm)

- Dropout rate: 10% each year
- One interim analysis at the time of final analysis for PFS (35 months after 1st randomization): information fraction = 91%
- Efficacy boundary based on Lan-DeMets spending function with O'Brien-Fleming approximation

Based on these assumptions, 57 deaths are needed to test the superiority of OS.

16.3.2 *Hypothesis*

Primary endpoint: PFS

There is one interim analysis planned at 30% of information (18 events) for futility only. The non-binding futility boundary (P-value stratified Log-Rank Test>0.457 or stratified HR>0.951) is based on Lan-DeMets spending function with Pocock approximation. The primary endpoint will be compared between the two arms when the required 61 events are achieved after applying appropriate censoring rules (detailed censoring rules will be pre-specified in the Statistical Analysis Plan). The experimental arm will be declared superior if the one-sided p-value from a stratified log-rank test is smaller than 0.025 or stratified HR<=0.605.

Nominal P-Values and Boundaries for PFS Analysis (Pocock Type beta Spending) :

Analysis	PFS Events	Nominal P-Value (one-sided)	Boundary of HR
Futility analysis for PFS	18*	0.457	0.951
Final analysis for PFS	61	0.025	0.605

*** If the actual number of PFS events greatly deviates from what is expected at the time of interim analysis, the p-value interpretation will be adjusted accordingly based on the actual information fraction.**

Key Secondary Endpoint: OS

The significant level 2.5% will be spread over 2 analyses (one interim analysis and one final analysis) by an O'Brien-Fleming alpha spending function. The significance of efficacy will be claimed if the tests is less than the significance level as calculated based on the specified alpha spending function and the observed number of events.

Nominal P-Values and Boundaries for OS Analysis (O'Brien-Fleming Type alpha Spending):

Analysis	OS Events	Nominal P-Value(one-sided)	Boundary of HR
Interim analysis for OS (at the time of final PFS analysis)	52*	0.019	0.562
Final analysis for OS	57	0.02	0.58

*** If the actual number of OS events greatly deviates from what is expected at the time of interim analysis, the p-value interpretation will be adjusted accordingly based on the actual information fraction.**

16.4 Statistical methods

Randomization will be stratified on 2 variables: the number of prior lines of treatment (1-2 vs > 2), and Previous/Concurrent MDS or CMML (Yes vs No)

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 (according to Lugano 2014): will be expressed with 95% confidence limits according to Pearson-Clopper method and compared using a Chi-square test. The number and percent of patients falling into each category of response will be provided. It will be also stratified on randomization strata.

Time to event will be performed using Kaplan-Meier method and comparison between categories will be made with the Log-Rank test. A Cox proportional hazard model will be used to estimate the hazard ratio (HR) and associated 95% CI. Survival probabilities, median survival and quartiles will be estimated with their 95% CI. Survival curves will be provided. It will be also stratified on randomization strata.

The EORTC QLQ-C30 questionnaire will be analyzed according to the functional scores and the recommendations in the EORTC scoring manual. All these recommendations will be described in the Statistical Analysis Plan.

Subpopulation analysis: selected analyses will be performed to compare the two treatment arms for patients with TET2 mutation.

16.5 Time of analyses

Four analyses will be performed: .

- **Safety run-in** will be conducted for each group of 3 Japanese patients who had been included and had achieved 1 cycle of treatment or having discontinued treatment. Safety results will be reviewed by an IDMC.
- **The first analysis : interim futility analysis** will be conducted once 18 PFS events will have been observed. It is planned to occur around 18 months after first randomized patient, e.g. after approximately 39-47 patients will have been recruited. Main criteria and safety will be analyzed. Results will be reviewed by an IDMC.
- **The second analysis : final analysis for PFS** will be performed after 61 PFS events assessed by the local review will have been observed. It is estimated that cut-off for analysis will occur approximately 29-35 months after the first patient has been randomized (assuming there will be no interruptions in inclusions). This analysis will include the interim analysis of the key secondary OS endpoint.
- **The third analysis : final analysis for OS** will be conducted once 57 deaths would have occurred, approximately 38.5 months after the first patient has been randomized (assuming there will be no interruptions in inclusions. This analysis will include all secondary endpoints. The analysis will be conducted at two years after the last randomized patients even if the number of events has not reached in that time.
- **Study closure analysis:**

Analysis for OS, PFS and safety will be performed at the time of study closure.

17 STUDY MONITORING

17.1 Responsibilities of investigators

The investigator(s) undertake(s) to perform the study in accordance with Good Clinical Practice and specifically either European 2001/20/CE and 2005/28/CE directives and guidelines for the monitoring of clinical investigations.

The investigators ensure compliance with respect to the investigational drug schedule, visit schedule and procedures required by the study. The investigators agree to provide all information requested in the case report form in an accurate and legible manner according to instructions provided.

As may be required by the local legislation, the investigators will check that the patients are directly or indirectly affiliated to the national health insurance or coverage system if there is any.

17.2 Responsibilities of the sponsor

LYSARC is the Sponsor in European countries and in Republic of Korea and Bristol-Myers Squibb is the Sponsor in Japan . Sponsors of this study have responsibilities towards health authorities to take all reasonable steps to ensure the proper conduct of the study as regards ethics, study adherence, integrity and validity of the data recorded on the case report forms. Thus, the main duty of the sponsor project leader and of the Sponsor clinical research support

team (LYSARC, Bristol-Myers Squibb in Japan or its delegate) is to help the investigator maintaining a high level of ethical, scientific, technical and regulatory quality in all aspects of the study.

At regular intervals during the study, the site will be contacted, through site visits, letters or telephone calls, by a representative of the monitoring team (LYSARC, Bristol-Myers Squibb in Japan or its delegate) to review study progress, investigator and patient adherence to study requirements and any emergent problems.

The frequency of site contact/visits, and data monitored are defined in the monitoring plan developed specifically for the study.

According to the guidelines on Good Clinical Practice, the sponsor representative will check the case report form entries against the source documents following the study monitoring plan. These personnel, bound by professional secrecy, will not disclose any personal identity or personal medical information.

17.3 Use and completion of electronic case report form (eCRF)

An electronic Case Report Form (eCRF) will be completed for each study patient. It is the investigator's responsibility to ensure the accuracy, completeness, legibility and timeliness of the data reported in the patient's eCRF available at the following website:

[redacted]

Source documentation supporting the eCRF data should indicate the patient's participation in the study and should document the dates and details of study procedures, adverse events and patient status.

The investigator and study site staff will receive system documentation, training and support for the use of the eCRF.

Use and completion of eCRF will be carried out according to the instructions provided in the data entry and monitoring guidelines.

The system will be secured to prevent unauthorized access to the data or the system. This will include the requirement of a user ID and password to enter or change data. These user ID and password transmitted by LYSARC to study sites staff are personal and confidential. The investigator has to maintain a list of individuals who are authorized to enter or correct data. All data entry and corrections are recorded in the audit trail (date of data entry/correction, name of person, type of action).

18 ETHICAL AND REGULATORY STANDARDS

18.1 Ethical principles

This study is in accordance with the principles laid down by the 18th World Medical Assembly (Helsinki, 1964) and subsequent amendments and will be conducted according to ICH/GCP guidelines.

18.2 Laws and regulations

This study is performed also in accordance with applicable laws and regulations of each country involved in the trial, as well as any applicable guidelines.

All data of the patients collected by the sponsor will be anonymized.

18.3 Informed consent

It is the responsibility of the investigator to obtain informed consent in compliance with national requirements from each patient prior to entering the trial or, where relevant, prior to evaluating the patient's suitability for the study.

The informed consent document used by the investigator for obtaining patient's informed consent must be reviewed and approved by the Sponsor prior to Ethics Review Committee submission.

The investigator must explain to potential patient the aims, methods, reasonable anticipated benefits and potential hazards of the trial and any discomfort it may entail. Patients will be informed that they are free not to participate in

the trial and that they may withdraw consent to participate at any time. They will be told which alternative treatments are available if they refuse to take part and that such refusal will not prejudice future treatment.

The consent form will include a statement by which the patients allow the sponsor's duly authorized personnel (trial monitoring team) to have direct access to source data which supports data on the case report forms (e.g., patient's medical file, appointment books, original laboratory records).

The patient should receive a signed and dated copy of the informed consent form and patient information leaflet. The enrollment process will be documented in each patient's medical records.

For biological studies, a specific informed consent form will be signed and dated by patients

18.4 Ethics Review Committee and Competent Authorities submission

The sponsor must submit this study to country Ethics Review Committee(s), and Competent Authorities. It is required to forward a copy of written signed opinions / approvals to investigators.

19 ADMINISTRATIVE PROCEDURES

19.1 Curriculum vitae

An updated copy (with date and signature) of the curriculum vitae of each investigator and sub-investigator will be provided to the sponsor prior to their involvement in the study.

A copy of ICH GCP training certificate of each person involved in the study should be sent to the Sponsor.

An original copy of financial disclosure form should be required for each investigator and sub-investigator.

19.2 Secrecy agreement

All goods, materials, information (oral or written) and unpublished documentation provided to the investigators (or any company acting on their behalf), inclusive of this study, the patient case report forms are the exclusive property of LYSARC.

They may not be given or disclosed by the investigator or by any person within [redacted] authority either in part or in totality to any unauthorized person without the prior written formal consent of the Sponsor.

It is specified that the submission of this study and other necessary documentation to the Ethics Review Committee or a like body is expressly permitted, the Ethics Committee members having the same obligation of confidentiality.

The investigator shall consider as confidential and shall take all necessary measures to ensure that there is no breach of confidentiality in respect of all information accumulated, acquired or deduced in the course of the trial, other than that information to be disclosed by law.

19.3 Record retention in investigating site(s)

The investigator must maintain all study records, patient files and other source data for the maximum period of time permitted by the hospital, institution or private practice. The investigators will maintain a personal patient identification list (patient numbers with the corresponding patient names) to enable records to be identified.

However national regulations should be taken into account, the longest time having to be considered.

For trials performed in the European Community, the investigator is required to arrange for the retention of the patient identification codes for at least 15 years after the completion or discontinuation of the trial.

Any site will notify the sponsor before destroying any data or records.

19.4 Ownership of data and use of the study results

The sponsor has the ownership of all data and results collected during this study. In consequence the sponsor or any third Party either appointed by the Sponsor or having concluded a specific agreement with the Sponsor, reserves

the right to use the data of the present study, either in the form of case report forms (or copies of these), or in the form of a report, with or without comments and with or without analysis, in order to submit them to the health authorities of any country.

The Investigator is committed to give [redacted] support to any requests for a patent or any property title based on, or illustrated with the results of the present Study for any country.

19.5 Publication

The results of the trial will be published after complete data collection and evaluation. Partial or preliminary results can be published beforehand. Publication is to be initiated by the coordinating investigators in charge of the study with approval of partner if applicable.

Any publication in the form of a lecture, poster or article must be basically approved by the Scientific Committee of LYSA.

The authors will be proposed (according to the updated LYSA publication rules) by the coordinating investigators in charge of the study, and finally endorsed by the Scientific Committee of LYSA.

All study data and publications are the property of LYSA/LYSARC.

19.6 Insurance compensation

The sponsor certifies having taken out appropriate liability insurance policy which covers the sponsor, the investigator and [redacted] co-workers and which is in accordance with the local laws and requirements. Specific statements will be contained in appendix where needed.

A certificate of insurance will be provided to the investigator in countries in which this document is required.

The Investigator(s) will remain responsible towards the sponsor of any fault or misconduct regarding the performance of the Study.

19.7 Company audits and inspections by regulatory agencies

For the purpose of ensuring compliance with good clinical practice and regulatory agency guidelines it may be necessary to conduct a site audit or an inspection.

By signing this study, the investigator agrees to allow the Sponsor and its representative, and drug regulatory agencies to have direct access to [redacted] study records for review. These personnel, bound by professional secrecy, will not disclose any personal identity or personal medical information.

These audits involve review of source documents supporting the adequacy and accuracy of data gathered in CRF, review of documentation required to be maintained, and checks on drug accountability.

The Sponsor will in all cases help the investigator prepare for an inspection by any regulatory agency.

19.8 Clinical study report

The sponsor will declare the trial end to Competent Authorities and Ethics Committees according to local regulations.

A summary of the study results will be prepared under the responsibility of the sponsor, within one year after the end of the study and will be forwarded to Competent Authorities and Ethics Committees and posted on Authorities' website if required by local regulations.

A suitable study report will be also prepared under the responsibility of the sponsor, within one year after the end of the study if required by local regulations.

19.9 Protocol amendments

It is specified that the appendices attached to this study and referred to in the main text of this study, form an integral part of the study.

No changes or amendments to this study may be made by the investigator or by the sponsor after the study has been agreed to and signed by both parties unless such change(s) or amendment(s) have been fully discussed and agreed upon by the coordinating investigators and LYSARC and study partner.

Approval / opinion of amendments by Ethics Review Committee(s) and Competent Authorities are required prior to their implementation, unless there are overriding safety reasons.

If the change or deviation increases risk to the study population, or adversely affects the validity of the clinical investigation or the patient's rights, full approval / advice must be obtained prior to implementation. For changes that do not involve increased risk or affect the validity of the investigation or the patient's rights, approval / advice may be obtained by expedited review, where applicable.

Any change agreed upon will be recorded in writing, the written amendment will be signed by the investigator and by the sponsor and the signed amendment will be appended in the Investigator Study File.

In some instances, an amendment may require a change to a consent form. The investigator must receive approval / advice of the revised consent form prior to implementation of the change. In addition, changes to the case report forms, if required, will be incorporated in the amendment.

Modifications done between different versions of the protocol are listed below:

Version	**Modifications**
V1.0	Initial version
V1.1	Modifications following [redacted] requests
V1.2	Modifications following [redacted] requests
V2.0	Change of IC, addition of countries, update of exclusion criteria, timelines, study procedures, safety rules
V3.0	Modifications in order to extend the study and update the follow up assessments

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21 APPENDICES

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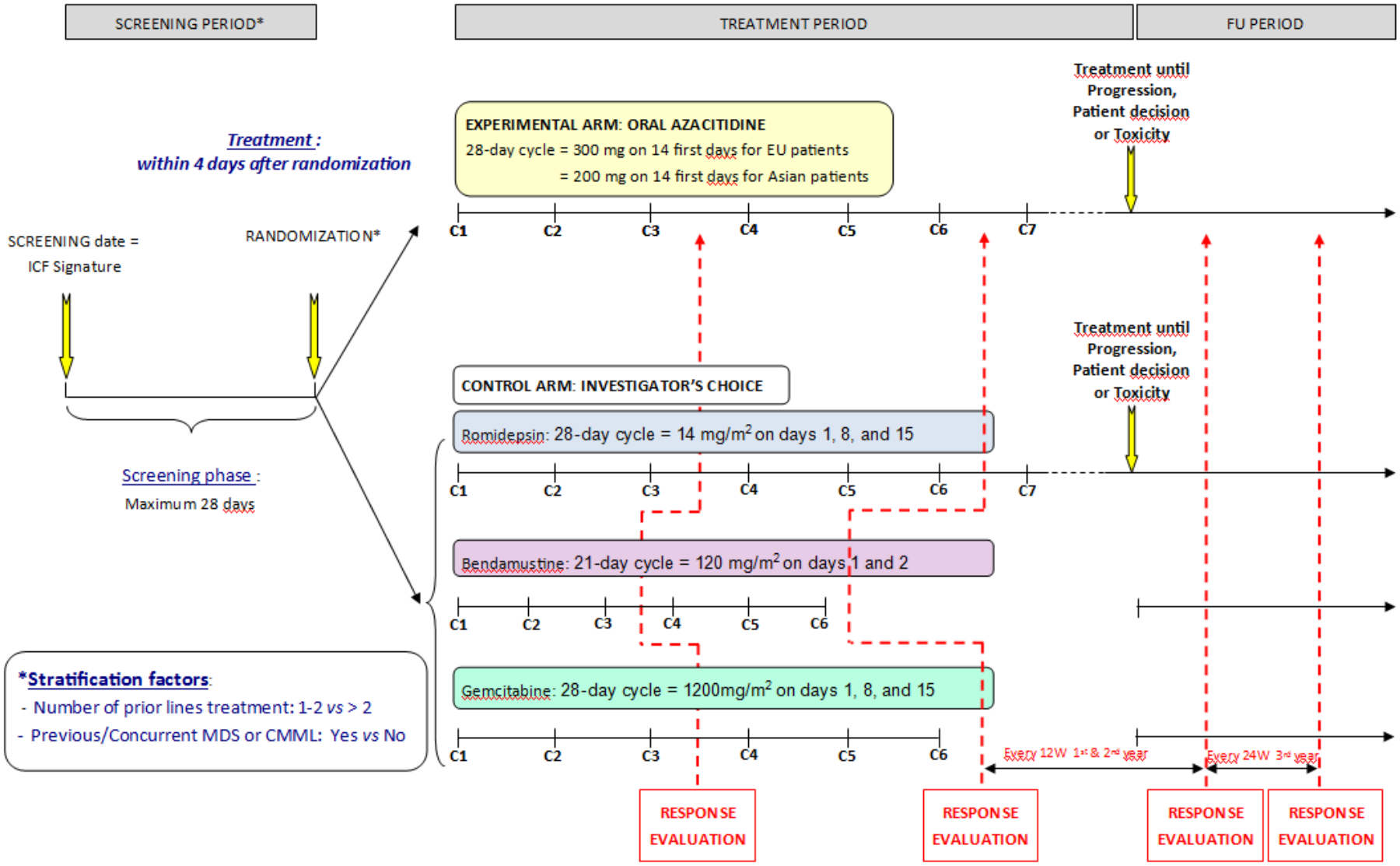
21.1 Appendix 1: Study Design



21.2 Appendix 2: Schedule of Evaluations (study flow-chart)

- **Oral Azacitidine and Romidepsin Treatment**

		Treatment : Oral Azacitidine and Romidepsin					**Evaluation at premature treatment discontinuation**	**FU after treatment discontinuation due to progression**	**FU after treatment discontinuation due to patient decision or unacceptable toxicity**
	Baseline	At D1 each cycle	Every week during first 24 weeks	Within 1 week before 4th cycle	Within 1 week before 7th cycle	Every 12wks 1st year, every 24wks 2nd and 3rd year, annually thereafter			
Date (weeks or months)	Within 28 days from enrollment						Between 2 and 4 wks after 6th cycle or Within 28 days after last study drug administration	Every 12wks 1st and 2nd years, every 24wks 3rd year, annually thereafter	Every 12wks 1st and 2nd years, every 24wks 3rd year, annually thereafter
Written informed consent	X								
Patient characteristics (a)	X								
Clinical examination	X (b)	X					X	X	X
ECOG PS*	X	X					X	X	X
B symptoms	X								
Concomitant medications*	X	X					X(i)		
ECG (c)	X								
HBV and HTLV1 serologies	X								
Blood cell counts (d)**	X	X	X				X	X	X
Pregnancy test (FBCP only)	X (h)	X					X		
Biochemical tests (e)**	X	X					X		
LDH	X								
TSH*	X				X		X		
β2-microglobulin	X								
Serum electrophoresis	X								

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Direct antiglobulin (Coomb's) test	X								
PET Scan (optional)	X				X		X		
Thoracic and abdominal CT scan (uploading on Imagys platform)	X			X	X	X	X	X (*according to the local practice*)	X
CNS lymphoma evaluation [(f)]	X								
Bone marrow biopsy	X				X		X		
Response Assessment (Lugano classification)				X	X	X	X	X (*according to the local practice*)	X
EORTC QLQ-C30 and EQ-5D *	X	X					X		X
Saliva samples [(g)]	X								
5mL of bone marrow on EDTA tubes for ancillary analysis [(g)]	X			X			X[(j)]		
28mL of blood on EDTA tubes for plasma and DNA banking [(g)]	X			X			X[(j)]		
5mL of blood on dry tubes for serum banking [(g)]	X			X			X[(j)]		
9mL of blood on STRECK tubes [(g)]	X			X			X[(j)]		
3 mLof blood for PK analyses[(k)]		X							
Toxicities		Continuous report					X	SPM, related AEs / SAEs	

(a): Age, gender, weight, height, relevant medical history, history of the NHL

(b): To be performed within 2 weeks prior randomization

(c): Must be registered at rest, in three specimen and after a space of 1 minute for measurement of corrected QT interval according to Fridericia formula

(d): Can be performed within 48 hours before D1. Will include red blood cell count, hemoglobin, hematocrit, white blood cell count with differential, absolute neutrophil count, absolute lymphocyte count, absolute monocyte count and platelet count.

(e): Can be performed within 48 hours before D1. Will include sodium, potassium, creatinine, alkaline phopshatases, AST, ALT, total bilirubin

(f): For patient with suspicion of CNS involvement; Will include neurologic evaluation, CT/MRI of head and lumbar puncture.

(g): For ancillary studies (French and Belgian sites only).

(h): Two pregnancy tests for females of childbearing potential (FCBP): (1): a serum pregnancy test during screening period (all FCBP) and 2) a serum or urinary pregnancy test within 72 hours prior the start of the study treatment. **(i):** Until 28 days after the last study drug administration

(j): Only in case of premature treatment discontinuation due to progression/relapse

(k): Only in **Japanese patients** in azacitidine arm. Safety run-in patients, a sample prior to each dose administration (pre-dose) and over the 6-hour period following each dose administration (0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0 and 6.0 hours post-dose) at Cycle1 Day1 and Cycle1 Day 14, For the rest of the Japanese patients enrolled, a sample prior to each dose administration (pre-dose) and over the 4-hour period following each dose administration (0.5, 1.0, 2.0 and 4.0 hours post-dose) at Cycle1 Day1 and Cycle1 Day 14.

* until OS Analysis

** After OS analysis, those assessments are recommended according to the local standard of care, for safety purposes

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- **Gemcitabine and Bendamustine Treatment**

		Treatment : Gemcitabine and bendamustine			**Evaluation at the end of treatment or at premature treatment discontinuation**	**FU after treatment discontinuation due to progression**	**FU after complete treatment or after treatment discontinuation due to patient decision or unacceptable toxicity**
	Baseline	At D1 each cycle	Every week during first 24 weeks	Within 1 week before 4th cycle			
Date (weeks or months)	Within 28 days from enrollment				Between 2 and 4 wks after 6th cycle or Within 28 days after last study drug administration	Every 12wks 1st and 2nd years, every 24wks 3rd year, annually thereafter	Every 12wks 1st and 2nd years, every 24wks 3rd year, annually thereafter
Written informed consent	X						
Patient characteristics (a)	X						
Clinical examination	X (b)	X			X	X	X
ECOG PS*	X	X			X	X	X
B symptoms	X						
Concomitant medications*	X	X			X(i)		
ECG (c)	X						
HBV and HTLV1 serologies	X						
Blood cell counts (d)**	X	X	X		X	X	X
Pregnancy test (FBCP only)	X (h)	X					
Biochemical tests (e)**	X	X			X		
LDH	X						
TSH*	X				X		
β2-microglobulin	X						
Serum electrophoresis	X						
Direct antiglobulin (Coomb's) test	X						
PET Scan (optional)	X				X		

Thoracic and abdominal CT scan (uploading on Imagys platform)	X			X	X	X (*according to the local practice*)	X
CNS lymphoma evaluation [f]	X						
Bone marrow biopsy	X				X		
Response Assessment (Lugano classification)				X	X	X (*according to the local practice*)	X
EORTC QLQ-C30 and EQ-5D*	X	X			X		X
Saliva samples [g]	X						
5mL of bone marrow on EDTA tubes for ancillary analysis [g]	X			X	X[j]		
28mL of blood on EDTA tubes for plasma and DNA banking [g]	X			X	X[j]		
5mL of blood on dry tubes for serum banking [g]	X			X	X[j]		
9mL of blood on STRECK tubes [g]	X			X	X[j]		
Toxicities		X				SPM, related AEs / SAEs	

(a): Age, gender, weight, height, relevant medical history, history of the NHL

(b): To be performed within 2 weeks prior randomization

(c): Must be registered at rest, in three specimen and after a space of 1 minute for measurement of corrected QT interval according to Fridericia formula

(d): Can be performed within 48 hours before D1. Will include red blood cell count, hemoglobin, hematocrit, white blood cell count with differential, absolute neutrophil count, absolute lymphocyte count, absolute monocyte count and platelet count.

(e): Can be performed within 48 hours before D1. Will include sodium, potassium, creatinine, alkaline phosphatases, AST, ALT, total bilirubin

(f): For patient with suspicion of CNS involvement; Will include neurologic evaluation, CT/MRI of head and lumbar puncture.

(g): For ancillary studies (French and Belgian sites only)

(h): Two pregnancy tests for females of childbearing potential (FCBP):
1) a serum pregnancy test during screening period (all FCBP) and 2) a serum or urinary pregnancy test within 72 hours prior the start of the study treatment

(i): Until 28 days after the last study drug administration

(j): Only in case of premature treatment discontinuation due to progression/relapse

* until OS Analysis

** After OS analysis, those assessments are recommended according to the local standard of care, for safety purposes

21.3 Appendix 3: Ann Arbor staging

Stage I:

- I: Involvement of a single lymph node region
- IE: Localized involvement of a single extralymphatic organ or site.

Stage II:

- II: Involvement of 2 or more lymph node regions on the same side of the diaphragm
- IIE: Localized involvement of a single associated extralymphatic organ or site and its regional lymph nodes with or without other lymph node regions on the same side of the diaphragm

Stage III:

- III: Involvement of lymph node regions on both sides of the diaphragm
- IIIE: Involvement of lymph node regions on both sides of the diaphragm accompanied by localized involvement of an extralymphatic organ or site
- IIIS: Involvement of lymph node regions on both sides of the diaphragm accompanied by involvement of the spleen
- IIIS+E: Both IIIS+IIIE

Stage IV:

- IV: Disseminated (multifocal) involvement of 1 or more extralymphatic sites with or without associated lymph node involvement or isolated extralymphatic organ involvement with distant (non regional) nodal involvement
- IVE: Extranodal lymphoid malignancies arise in tissues separate from, but near, the major lymphatic aggregates.

Source: *American Joint Committee on Cancer. Non Hodgkin's lymphoma. In: AJCC Staging Manual. 5th ed. Philadelphia, PA: Lippincott-Raven;1997:289-294.*

21.4 Appendix 4: Body Surface Area calculation

The algorithm to be used in this study is Mosteller formula (1987):

BSA = √ [(Height (cm) x Weight (kg))/3600]

21.5 Appendix 5: New York Heart Association Classification for Congestive Heart Failure

Source: 1994 Revisions to Classification of Functional Capacity and Objective Assessment of Patients With Diseases of the Heart. American Heart Association website.

Functional Capacity
Class I. Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.
Class II. Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
Class III. Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.
Class IV. Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the angina syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

21.6 Appendix 6: Performance Status Criteria

The following table presents the ECOG performance status scale:

ECOG Performance Status Scale	
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 (eg, 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.

Source: *Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982; 5 (6):649-55.*

21.7 Appendix 7: International Prognostic Index (IPI) and age-adjusted International Prognostic Index (aa-IPI)

Source: The international Non Hodgkin Lymphoma prognostic factor project. A predictive model for aggressive non Hodgkin lymphoma. New England Journal of Medicine 1993;329:987-994.

For IPI, score 1 point for each of the following risk factors:

Age	> 60
Lactate deshydrogenase (LDH) level	> normal
Ann Arbor stage	III-IV
Performance status (PS)	2-4
Extra-nodal involvement	more than 1 site

RISK GROUPS	Number of Factors
Low	0-1
Low intermediate	2
High intermediate	3
High	4-5

For age-adjusted IPI, score 1 point for each of the following risk factors:

Lactate deshydrogenase (LDH) level	> normal
Ann Arbor stage	III-IV
Performance status (PS)	2-4

21.8 Appendix 8: International Prognostic Index for AITL (PIAI)

Source: Federico M *et al*. Clinicopathologic Characteristics of Angioimmunoblastic T-Cell Lymphoma: Analysis of the International Peripheral T-Cell Lymphoma Project. *J Clin Oncol. 2013 Jan 10;31(2):240-6*.

PIAI IS DEFINED AS THE NUMBER OF THE FOLLOWING ADVERSE PROGNOSTIC FACTORS:

- Age > 60 years
- ECOG PS ≥ 2
- Extranodal sites > 1
- B symptoms
- Platelet count < 150 G/L

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21.9 Appendix 9: Prognostic Index for T-cell Lymphoma (PIT)

Source: Gallamini *A et al*. Peripheral T-cell lymphoma unspecified (PTCL-U): a new prognostic model from a retrospective multicentric clinical study. Blood 2004; 103:2474-2479.

PIT IS DEFINED AS THE NUMBER OF THE FOLLOWING ADVERSE PROGNOSTIC FACTORS:

- Age > 60 years
- LDH > normal
- ECOG Performance status ≥ 2
- Bone marrow involvement by lymphoma

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21.10 Appendix 10: EQ-5D-5L and EORTC QlQ-C30 Health Questionnaires

EuroQol Group. EuroQol - A new facility for the measurement of health-related quality of life. *Health Policy 1990;16(3):199-208.*
Van,Hout B., Janssen,M.F., Feng,Y.S., Kohlmann,T., Busschbach,J., Golicki,D., Lloyd,A., Scalone,L., Kind,P., Pickard,A.S. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. Value in Health. 2012 Jul-Aug;15(5):708-15

Appendix 10-A: EQ-5D-5L

EQ-5D is a standardized measure of health status developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal (EuroQol Group, 1990). Applicable to a wide range of health conditions and treatments, it provides a simple descriptive profile and produces a single index value for health status that can be used in the clinical and economic evaluation of health care as well as in population health surveys.
EQ-5D essentially consists of 2 pages - the EQ-5D descriptive system (page 2) and the EQ visual analogue scale (EQ VAS) (page 3). The EQ-5D descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 3 levels: no problems, some problems, severe problems. The respondent is asked to indicate his/her health state by ticking (or placing a cross) in the box against the most appropriate statement in each of the 5 dimensions. This decision results in a 1-digit number expressing the level selected for that dimension. The digits for 5 dimensions can be combined in a 5-digit number describing the respondent's health state. A total of 243 possible health states are defined in this way. Each state is referred to in terms of a 5 digit code. For example, state 11111 indicates no problems on any of the 5 dimensions, while state 11223 indicates no problems with mobility and self-care, some problems with performing usual activities, moderate pain or discomfort and extreme anxiety or depression. It should be noted that the numerals 1-3 have no arithmetic properties and should not be used as a cardinal score.
The EQ VAS records the respondent's self-rated health on a vertical, 0-100 visual analogue scale where 100 = "Best imaginable health state" and 0 = "Worst imaginable health state". This information can be used as a quantitative measure of health outcome as judged by the individual respondents.

EQ-5D-5L questionnaire :

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

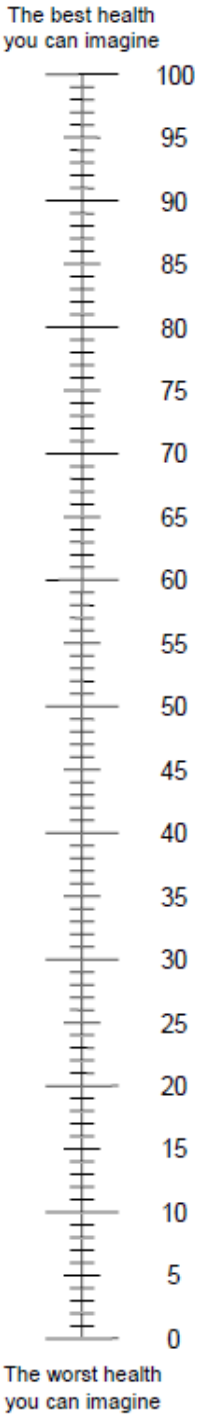
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the <u>best</u> health you can imagine.
  0 means the <u>worst</u> health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Appendix 10-B : EORTC QLQ-C30

The EORTC QLQ-C30 questionnaire will be used as a measure of health-related quality of life. The QLQ-C30 is composed of both multi-item scales and single item measures. These include five functional scales (physical, role, emotional, cognitive and social), three symptom scales (fatigue, nausea/vomiting, and pain), a global health status/QOL scale, and six single items (dyspnoea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). Each of the multi-item scales includes a different set of items – no item occurs in more than one scale.

The QLQ-C30 employs a week recall period for all items and a 4-point scale for the functional and symptom scales/items with response categories "Not at all, ""A little," "Quite a bit" and "Very much." The two items assessing global health status/QOL utilize a 7-point scale ranging from 1 (“Very Poor”) to 7 (“Excellent”).

All of the scales and single item measures range in score from 0-100. A high score represents a higher response level. Thus, a high score for a functional scale represents a high/healthy level of functioning, a high score for the global health status/QOL represents a high/good QOL, but a high score for a symptom scale/item represents a high level of symptomatology/problems. (*Aaronson et al., 1993*).

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ENGLISH

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ⌊_⌋⌊_⌋⌊_⌋⌊_⌋
Your birthdate (Day, Month, Year): ⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋
Today's date (Day, Month, Year): 31 ⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

ENGLISH

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

21.11 Appendix 11: Response Criteria for Lymphoma – Lugano Classification

Bruce D. Cheson, Richard I. Fisher, Sally F. Barrington, Franco Cavalli, Lawrence H. Schwartz, Emanuele Zucca, and T. Andrew Lister. J Clin Oncol 2014;32(27):3059-68.

Revised Criteria for Response Assessment		
Response and Site	**PET-CT–Based Response**	**CT-Based Response**
Complete	**Complete metabolic response**	**Complete radiologic response (all of the following)**
Lymph nodes and extralymphatic sites	Score 1, 2, or 3 with or without a residual mass on 5 Point Scale† It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (eg, with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake	Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi No extralymphatic sites of disease
Nonmeasured lesion	Not applicable	Not applicable
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC negative
Partial	**Partial metabolic response**	**Partial remission (all of the following)**
Lymph nodes and extralymphatic sites	Score 4 or 5† with reduced uptake compared with baseline and residual mass(es) of any size At interim, these findings suggest responding disease At end of treatment, these findings indicate residual disease	≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites When a lesion is too small to measure on CT, assign 5 mm x 5 mm as the default value When no longer visible, 0 x 0 mm For a node > 5 mm x 5 mm, but smaller than normal, use actual measurement for calculation
Nonmeasured lesion	Not applicable	Absent/normal, regressed, but no increase
Organ enlargement	Not applicable	Spleen must have regressed by > 50% in length beyond normal
New lesions	None	None
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan	Not Applicable

No Response or stable disease	**No metabolic response**	**Stable Disease**
Target nodes/nodal masses, extranodal lesions	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	< 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Nonmeasured lesion	Not applicable	No increase consistent with PD
Organ enlargement	Not applicable	No increase consistent with PD
New lesions	None	None
Bone marrow	No change from baseline	Not applicable
Progressive disease	**Progressive Metabolic Response**	**Progressive disease requires at least 1 of the following:**
Individual target nodes/nodal masses	Score 4 or 5 with an increase in intensity of uptake from baseline and/or	PPD progression
Extranodal lesions	New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	An individual node/lesion must be abnormal with: LDi > 1.5 cm and Increase by ≥ 50% from PPD nadir and An increase in LDi or SDi from nadir 0.5 cm for lesions ≤ 2 cm 1.0 cm for lesions > 2 cm In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (eg, a 15-cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline New or recurrent splenomegaly
Nonmeasured lesion	None	New or clear progression of preexisting nonmeasured lesions
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved lesions A new node > 1.5 cm in any axis A new extranodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
Bone Marrow	New or recurrent FDG-avid foci	New or recurrent involvement

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

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21.12 Appendix 12: Deauville criteria for PET analysis

Deauville criteria is a scoring system and it will be used for intermediate evaluation (at the end of cycles 2, 4 and 6) and during maintenance period.

We will use a 5 points scale (adapted from the Deauville workshop in Leukemia & Lymphoma, August 2009; 50(8): 1257–1260), with new modifications (mainly 4 and 5 scales).

It includes visual and quantitative analysis.

- 1. No uptake.
- 2. Uptake ≤ mediastinum.
- 3. Uptake > mediastinum but < liver.
- 4. Uptake moderately more than liver uptake, at any site.
- 5. Markedly increased uptake at any site and/or new sites of disease.

PET positive is defined by scale level 4 and 5 (as described above)

PET negative is defined by scale level 1, 2 and 3.

21.13 Appendix 13: Diagnosis and management of Tumor Lysis Syndrome

Sources: Cairo MS, Bishop M: Tumor lysis syndrome: new therapeutic strategies and classification. Br JHaematol. 2004; 127(1):3-11.

1/ Diagnosis of Tumor Lysis Syndrome

Tumor Lysis Syndrome can be divided into asymptomatic “laboratory” Tumor Lysis Syndrome (eg. isolated increase in blood levels of uric acid, potassium or phosphorus) and “clinical” Tumor Lysis Syndrome (eg. acute renal insufficiency) according to Cairo-Bishop Criteria as follows

Laboratory tumor lysis syndrome:

Require ≥ 2 of the following criteria achieved in the same 24 hours period from 3 days before to 7 days after chemotherapy initiation:

- Uric acid 25% increase from baseline or ≥ 8.0 mg/dL (480 µmol/L)
- Potassium 25% increase from baseline or ≥ 6.0 meq/dL
- Phosporus 25% increase from baseline or ≥ 4.5 mg/dL
- Calcium 25% decrease from baseline or ≤ 7.0 mg/dL

Clinical tumor lysis syndrome:

Laboratory tumor lysis syndrome + ≥ 1 of the following:

- Creatinine > 1.5 times the upper limit of normal of an age-adjusted reference range
- Seizure
- Cardia arrhythmia or sudden death

2/ Management of Tumor Lysis Syndrome

Patients who develop TLS during therapy should receive intensive supportive care with continuous cardiac monitoring and measurement of electrolytes, creatinine, and uric acid every four to six hours.

Effective management of these cases involves the combination of treating specific electrolyte abnormalities, the use of rasburicase at 0.2 mg/kg (if it was not given initially) with repeated doses as necessary, attempting to wash out the obstructing uric acid crystals with fluids with or without a loop diuretic, and the appropriate use of renal replacement therapy. Early consultation with an expert in renal medicine is advisable

- Hyperkalemia is the most dangerous component of TLS because it can cause sudden death due to cardiac dysrhythmias. Patients should limit potassium and phosphate intake during the risk period for TLS. In addition, frequent measurement of serum potassium (every four to six hours), continuous cardiac monitoring, and the administration of oral potassium-lowering agents (eg, sodium polystyrene sulfonate) are recommended in patients with TLS and acute kidney injury. Glucose plus insulin or beta-agonists can be used as temporizing measures, and calcium gluconate may be used to reduce the risk of cardiac dysrhythmia. If needed, hemodialysis and hemofiltration effectively removes potassium.
- Symptomatic hypocalcemia should be treated with calcium at the lowest doses required to relieve symptoms. To avoid calcium-phosphate precipitation, most symptomatic acutely hypocalcemic patients with hyperphosphatemia due to TLS (particularly if the calcium phosphate product is > 60 mg^2 per dL^2) should not be treated with calcium until hyperphosphatemia is corrected. In most situations, clinicians should use other oral phosphate binders. However, patients with severe symptoms of hypocalcemia (eg, tetany or cardiac arrhythmia) should be considered for calcium replacement regardless of the phosphate level. Asymptomatic patients with hypocalcemia do not require treatment.

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- Despite treatment with a hypouricemic agent, hyperphosphatemia remains a major problem in TLS and can cause acute kidney injury. Strategies aimed at lowering serum phosphate levels (aggressive hydration and phosphate binder therapy) should be used in conjunction with control of uric acid in patients who have established TLS or who are at high risk of developing TLS.

Patients who are deemed to be at high risk of developing TLS (eg, patients with bulky tumor masses or with baseline alteration of renal function) should be treated preventively with abundant hydration and uric acid lowering agents (eg. rasburicase or allopurinol) and monitored regularly.

3/ Cairo-Bishop Grading System for TLS

Grade	LTLS	Creatinine	Cardiac Arrhythmia	Seizure
0	-	≤ 1.5 x ULN	None	None
1	+	1.5 x ULN	Intervention not indicated	None
2	+	> 1.5 – 3.0 x ULN	Non-urgent medical intervention indicated	One brief generalized seizure; seizure(s) well controlled or infrequent; focal motor seizures not interfering with ADL
3	+	> 3.0 – 6.0 x ULN	Symptomatic and incompletely controlled medically or controlled with device	Seizure in which consciousness is altered; poorly controlled seizure disorder; breakthrough generalized seizures despite medical intervention
4	+	> 6.0 x ULN	Life-Threatening	Seizures of any kind that are prolonged, repetitive, or difficult to control
5	+	Death[a]	Death[a]	Death[a]

ADL= activities of daily living; LTLS = laboratory tumor lysis syndrome; TLS= tumor lysis syndrome; ULN = upper limit of normal

[a] Probably or definitely attributable to clinical TLS.

21.14 Appendix 14: PET SCANs

FDG PET/CT imaging should follow the standardized protocol elaborated by EANM organization (*).

In particular, careful attention should be paid to the scheduled protocol (1 hour between FDG administration and PET acquisition), the glycemic status and, for each patient, unchanged technical parameters of acquisition.

FDG PET/CT: EANM procedure guidelines for tumor imaging: version 2.0 Ronald Boellaard & Roberto Delgado-Bolton & Wim J. G. Oyen & Francesco Giammarile &Klaus Tatsch & Wolfgang Eschner & Fred J. Verzijlbergen & Sally F. Barrington &Lucy C. Pike & Wolfgang A. Weber & Sigrid Stroobants & Dominique Delbeke & Kevin J.Donohoe & Scott Holbrook & Michael M. Graham & Giorgio Testanera & Otto S. Hoekstra &Josee Zijlstra & Eric Visser & Corneline J. Hoekstra & Jan Pruim & Antoon Willemsen &Bertjan Arends & Jörg Kotzerke & Andreas Bockisch & Thomas Beyer & Arturo Chiti &Bernd J. KrauseNovember 2014 Eur J Nucl Med Mol Imaging DOI 10.1007/s00259-014-2961-x (available on http://www.eanm.org/publications/guidelines/2015_GL_PET_CT_TumorImaging_V2.pdf)

21.14.1 *Timing of FDG PET scans*

21.14.2 *Patient preparation*

- Patients are not allowed to consume any food or sugar for at least 6 h prior to the start of the PET study (ie, with respect to time of injection of FDG).
- Adequate pre-hydration is important to ensure a sufficiently low FDG concentration of FDG in urine (fewer artifacts) and for radiation safety reasons (for example, 1 l of water in the 2 h prior to injection).
- Parental nutrition and intravenous fluids containing glucose should be discontinued at least 4 h before the PET/CT examination. In addition, the infusion used to administer intravenous pre-hydration must not contain any glucose.
- During the injection of FDG and the subsequent uptake phase the patient should remain seated or recumbent and silent to minimize FDG uptake in muscles.
- Blood glucose level must be measured prior to administering FDG:
- If plasma glucose level is < 7 mmol/l (or < 120 mg/dl) the FDG PET study can be performed
- If plasma glucose level is ≥ 7 mmol/l (or > 120 mg/dl) the FDG PET study must be rescheduled or the patient excluded depending on the patient circumstances.
- The following recommendations apply to patients with diabetes mellitus:
- type II diabetes mellitus (controlled by oral medication)
    - the PET study should preferably be performed in the late morning
    - patients must comply with the fasting rules indicated above
    - patients continue to take oral medication to control their blood sugar.
- type I diabetes mellitus and insulin-dependent type II diabetes mellitus
    - ideally, an attempt should be made to achieve normal glycemic values prior to the PET study, in consultation with the patient and his/her attending medical doctor
    - the PET study should be scheduled for late morning
    - the patient should eat a normal breakfast at 7.00 a.m. and inject the normal amount of insulin.
- Height and body weight must be determined at first scan and weight must be measured directly prior to each PET study because body weight often changes during course of disease.

21.14.3 *PET scanner technical requirements*

- FDG-PET scanning should be performed with a combined PET/CT for an improved data interpretation. Unless specifically excluded for particular protocols.
- Each patient is preferably scanned on the same camera for baseline, intermediate and final study.

21.14.4 ***PET acquisition and reconstruction***

- The 18F-FDG injected activity will be defined according to on-site rules but should be > 3.5 MBq/kg (or recommended activity for more recent PET-CT technology (TOF).

It is especially important to ensure that the time between tracer administration and starting of PET acquisition will be the same (± 5 min) at each of the 2 PET scans

- The patient should be positioned with the arm elevated over the head and PET acquisition should cover at least from the mid-femora to the external auditory meatus.
- A whole body acquisition with attenuation correction (non contrast-enhanced CT) and with emission scans of at least 2 minutes per bed position (or less for more recent PET-CT technology (TOF) is started 60+/-10 minutes after FDG injection, starting from groin up to the head.
- FDG PET/CT imaging should follow the standardized protocol elaborated by EANM organization. In particular, a careful attention should be paid to maintain unchanged technical parameters of reconstruction within patient.
- A standard diagnostic CT scan with (i.v.) contrast agent may, if appropriate, be carried out according to standard radiological methods **after** the low-dose CT without contrast agent and PET acquisition.

21.15 Appendix 15: Pathological Samples Review

General principles and organization of the pathological review:

The ORACLE study requires a histological review of all cases included in the trial at diagnosis. The aims of the centralized histopathological review will be to **confirm the diagnosis of Angioimmunoblastic T-cell lymphoma,** according to the criteria of the updated WHO classification 2016 (S. Swerdlow et al.) for each patient in the ORACLE study. Histological criteria of inclusion and exclusion have been detailed in the current protocol.

The review process will be organized by the LYSA-Pathology institute [redacted] (LYSA-P).

Therefore for each enrolled patient, tumor tissue blocks - or only when not possible - unstained slides will have to be sent for analysis and confirmation of diagnosis to LYSA-P.

Practical aspects of the LYSA review:

1. Information on patient inclusion

At patient enrollment, the investigator will be requested to fax to LYSARC registration centre a copy of the initial and relapse anonymized histopathological report on which the name and address of the pathologist having diagnosed the Angioimmunoblastic T-cell lymphoma will be easily identified as well as the bone marrow report when possible.

2. Sample request

At reception of the pathology report and inclusion form, LYSA-P will send to the initial pathologist a letter requesting:

- The paraffin block from the formalin fixed sample that was used to set the initial diagnosis and if possible the FFPE block used to set the diagnosis at relapse
- The immunostaining slides that were used to set the diagnosis. These slides will be returneded to the initial pathologist after central review.
- A copy of the bone marrow pathological report if not sent previously
- To notify LYSA-P of the presence of frozen tissue

If a biopsy is performed at the end of the treatment or at relapse, the pathology report as well as the block will be requested.

3. Sample centralisation at LYSA-P

All these requirements (excluding frozen tissue) will be sent and centralized by LYSA-P at the following address:

LYSA-P, LYSA – ORACLE study,

[redacted]

4. Sample review

At sample reception, routinely stained sections will be performed and an appropriate panel of antibodies according to morphological aspects will be applied. When sufficient slides are available, a pathological review will be organized at LYSA-P with the designated panel of pathologists for this study. All the cases will be reviewed by at least 2 experts hematopathologists and a consensus diagnosis will be set and registered in LYSA-P data base. This consensus diagnosis will then be sent to the clinical investigator and to the initial pathologist. For the need of the ancillary study, blocks will be kept temporarily to avoid a second request.

Stained slides sent will be returneded to the initial pathologist. Meanwhile, the block will be at the entire disposition of the initial anatomopathology laboratory under request if they need it.

At the end of the recruitment, frozen tumor tissue will be requested for all French and Belgium enrolled patients. The collection of the frozen tumor specimen will be organized and centralized at LYSA-P. On frozen tissue, gene and protein expression analysis will be performed to assess the level of expression of genes/proteins known to influence the outcome of AITL lymphoma patients.
It is therefore highly important to consider at diagnosis all the possibilities to freeze the tumor sample.
LYSA-P Institute will make a commitment to stock the frozen samples in a tumor library or a biological centre insuring the respect of a convention which declines commitments of LYSARC relating to collection, conservation and use of frozen biological samples
All the samples will be stored in:

21.16 Appendix 16: French protocol guidelines logistic assessments post OS analysis

The protocol assessments may be modulated if after the OS analysis the patient is in good condition and the next patients' visit is a non-critical visit. The investigator is authorized to deliver the per os IMP (Azacitidine) for more than one cycle.

The treatment could be delivered for two consecutive cycles respecting the following indication regarding the assessments:

- Patients must complete the patient diary for the 2 cycles.
- The next cycle visit may be conducted through teleconsultation (on site visits are also allowed). A phone call every 15 days may be performed if needed - according to the investigator appreciation- Investigators must provide an emergency phone number.
    - Phone or video visits: conversion of physical visits into phone or video visits is allowed to limit patient travel. The collection of information by teleconsultation is possible, with a focus on safety data. This visit and the collected information must be documented in the patient's file.
- Investigators must provide a report containing at least the following:
    - Review of patient diary: start date and end date of treatment, total number of tablets taken per day, side effects observed by the patient.
    - Investigator should specify the therapeutic decision: continuation of study treatment with or without dose adjustments, delay in treatment, reduction in the monthly duration of treatment or permanent treatment discontinuation, specifying the reasons.
- Imaging exams
    - It's recommended to maintain imaging evaluation planned in the protocol.

The treatment for two consecutives cycles can delivered directly during an on site visit or the drug can be shipped at patient's home according to the process described below.

- **Per os IMP: drug shipment at patient's home**

Site's pharmacy could send the drug to patient's home. For such a sending, several steps have to be checked:

- The patient is informed about the sending and confirms the address where [redacted] can receive the drug and agrees that [redacted] personal information is given to a professional carrier.
- The pharmacy prepares a secured box.

- Option 1:
  - The box is entrusted to a third person, known from the patient

- Option 2:
  - A professional carrier is mandated by the pharmacy and applies security measures to ship the drug securely.
  - To respect patient's confidentiality, the carrier should not have other information about the patient than [redacted] name and address. In no way the sponsor should have any patient's personal information regarding this shipment.
  - A procedure is defined with the carrier to confirm the reception of the drug by the patient.
  - The investigator contacts the patient to confirm the reception and integrity of the parcel and gives instructions about the drug intake.
  - The pharmacy completes its accountability with this specific administration.

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