PROTOCOL SYNOPSIS

Title of Study:

An Open-label and Single Arm Study of ATG-010 in Patients with Relapsed or Refractory Diffuse Large B-Cell Lymphoma (DLBCL)

Indication

Relapsed or Refractory DLBCL

Objectives

Primary Objective:

To determine the overall response rate (ORR) of ATG-010 evaluated by central radiological review in relapsed or refractory DLBCL subjects who have at least 2 but no more than 5 previous systemic regimens.

Secondary Objectives:

- To determine the ORR evaluated by investigator
- To determine the duration of response (DOR) evaluated by central radiological review
- To determine the disease control rate (DCR) evaluated by central radiological review
- To determine the median overall survival (OS)
- To determine the median progression-free survival (PFS)
- To determine the PFS, ORR, DOR, DCR, and OS in subjects with "double hit" DLBCL (DH-DLBCL) and non-DH-DLBCL; in subjects with GCB and non-GCB DLBCL; as well as with "very good", "good", and "poor" Revised International Prognostic Index (R-IPI)
- To assess the safety and tolerability of ATG-010

Background and Study Rationale

Study Background

DLBCL is an aggressive cancer with current immunochemotherapy, 60 to 65% of patients are progression-free at 5 years, but the remaining about 1/3 of patients with DLBCL have a poor prognosis with disease resistant to available agents. A very clear unmet medical need persists for patients with relapsed or refractory DLBCL.

Study Rationale:

ATG-010 (Selinexor) is an orally bioavailable selective inhibitor of nuclear export (SINE) compound that specifically blocks exportin 1 (XPO1). Preclinical studies showed that ATG-010 can lead to the nuclear accumulation and re-activate of tumor suppressor proteins and other growth modulators, promote rapid onset of apoptosis both *in vitro* and *in vivo* of hematological and solid tumor cells; meanwhile it has little effect on normal cells. SADAL is an international, multicenter, open IIb, ongoing study. As of 15 November 2018, the efficacy data (Karyopharm，2018) for SADAL Study were updated and ORR was 29.6% by central radiology laboratory based on 115 subjects in modified intent-to-treat (mITT) population, including CR 9.6% and PR 20.0%; the median DOR was 9.2 months in all ATG-010 responders

(total 34 subjects; 11 CRs+23 PRs), median DOR in CR subjects was 23 months, and median DOR in PR subjects was 7.8 months. The median OS was 9.1 months in all subjects, 29.7 months for CR/PR subjects, but only 3.2 months for progressive disease/not reached (PD/NR) subjects. These results showed the correlation between tumor responses of DLBCL and clinical efficacy of treatment, the OS observed in ATG-010 non-responders with PD/NR was also consistency with published references.

Based on the encouraging clinical efficacy and safety data obtained by ATG-010 monotherapy in the treatment of subjects with recurrence or refractory DLBCL, FDA granted the rapid channel of ATG-010 monotherapy for recurrence or refractory DLBCL on 07 November 2018, aiming at accelerating the clinical study and marketing approval of ATG-010.

According to the efficacy data obtained by SADAL Study in the population of relapse or refractory DLBCL subjects in the west, the current study plans to verify the clinical efficacy of ATG-010 single drug treatment in subjects with relapse/refractory DLBCL who have received no more than 5 systematic treatment regimens in the past.

Study Design

This is an open-label, single arm, and registered study. About 60 subjects with relapsed or refractory DLBCL plan to be enrolled in about 10 study sites of the study. It is planned that at least 50% (~30 subjects) will have the GCB subtype of DLBCL. Enrolled subjects will be treated with a fixed dose, 60 mg of ATG-010, orally, twice weekly, each 4-week a cycle. Subjects should remain on the study treatment of ATG-010, until either PD or occurrence of unacceptable toxicity.

Confirmed evidence of DLBCL progressive or failed to the last treatment regimen is required for study entry, and subjects must have measurable disease at screening per the Lugano criteria for response assessment (Cheson, 2014).

Disease assessment (tumor measurement) will be made by PET-CT and Contrast-enhanced CT (Tumor measurement) at screening (within the first 14 days of Cycle 1 Day 1), enhanced CT should include the neck, chest, abdomen, pelvic cavity (including the inguinal/femoral region), if clinically indicated, as well as other anatomical sites. If CT is contraindicated, MRI scan will be performed. PET-CT and contrast-enhanced CT scans will be performed on Cycle 3 Day 1 (± 1 week) and then every 8±1 weeks (ie, Day 1 of odd numbered cycles) until disease progression is confirmed by the central radiological review. The PET-CT is allowed at alternating assessment time points (ie, every 16 weeks, or every other scan) if PET-CT cannot be performed for every assessment. If CT scan suggests the possibility of obtaining CR, PET-CT should be performed for confirmation. Results of PET-CT and contrast-enhanced CT scans performed beyond a predetermined time point should be recorded on the eCRF and images of all disease assessment scans performed during the study period will be provided to the central radiological review.

Bone marrow aspirates and/or biopsies will be taken within 1 month prior to first dose (baseline) to assess bone marrow involvement. The bone marrow biopsy will be repeated whenever clinically indicated to confirm CR in only those subjects who had DLBCL with known bone marrow involvement prior to dosing.

Diagnosis and Main Criteria for Inclusion:

Inclusion Criteria

To be included in this study, a patient must meet all the following criteria:

1. The patient must provide informed consent form (ICF) prior to the first screening procedure.
2. Age ≥18 years.
3. ECOG performance status of ≤2.
4. Subjects should have estimated life expectancy of >3 months at study entry.
5. Previously treated, pathologically confirmed *de novo* DLBCL, or DLBCL transformed from previously diagnosed indolent lymphoma (e.g., follicular lymphoma).
6. Subjects must have received at least 2 but no more than 5 previous systemic regimens for the treatment of DLBCL, including at least 1 course of anthracycline-based chemotherapy (unless absolutely contraindicated due to cardiac dysfunction, in which case other active agents must have been given, such as etoposide, bendamustine, or gemcitabine, etc.) and at least 1 course of anti-CD20 immunotherapy (e.g., rituximab), unless contraindicated due to severe toxicity. Subjects who were considered ineligible for standard multi-agent immunochemotherapy must have received at least 2 and no more than 5 prior treatment regimens including at least 1 course of anti-CD20 antibodies and must be approved by the Medical Monitor. Prior stem cell transplantation is allowed. Induction, consolidation, stem cell collection, preparative regimen, and transplantation ± maintenance are considered a single line of therapy.
7. Documented evidence of DLBCL progressive (PD) or failed (SD) to the last treatment regimen.
8. Subjects must have measurable disease per the Lugano criteria for response assessment of lymphoma (Cheson, 2014).
9. Subjects must not be eligible for high-dose chemotherapy with autologous stem cell transplantation rescue, ie, meet any of the following criteria:
    a. Age ≥65years old.
    b. Existed severe organ dysfunction or complications.
    c. Failed to obtain PR or CR through salvage therapy.
    d. Failure of stem cell collection.
    e. Subjects refuse to receive high-dose chemotherapy with autologous stem cell transplantation.
10. Female subjects of child-bearing potential must have a negative serum pregnancy test at screening (Female subjects of child-bearing potential is defined as female whose menstruation has begun, who are not in the late menopause, and who have not received surgical sterile [e.g., hysterectomy, bilateral tubal ligation, bilateral oophorectomy]). Post-menopausal period is defined as successive amenorrhea ≥12 months without specific reason. Female subjects of child-bearing potential must agree to use reliable

methods of contraception for 3 months after their last dose of medication.

11. Male subjects (including those who have undergone vasectomy) must agree to use condoms if sexually active with a female of child-bearing potential and must agree that they have no plan to make their female partners pregnant during the use of study drug and within 3 months after the last dose of medication since they signed ICF.

Exclusion Criteria

Subjects meeting any of the following exclusion criteria are not eligible to enroll in this study.

1. Subjects who are pregnant or lactating.
2. DLBCL with mucosa-associated lymphoid tissue (MALT) lymphoma, composite lymphoma (Hodgkin's lymphoma + non-Hodgkin's lymphoma[NHL]), or DLBCL transformed from diseases other than indolent NHL.
3. Primary mediastinal (thymic) large B-cell lymphoma.
4. Known central nervous system lymphoma or meningeal involvement.
5. Subjects whose most recent systemic anticancer therapy include radiation, chemotherapy, immunotherapy, radio-immunotherapy, or any other anticancer therapy other than glucocorticoids within 4 weeks prior to first dose of study drug.
6. Subjects who have not recovered to Grade ≤1 clinically significant adverse events, or to their baseline, except for the hair loss, from their most recent systemic anti-DLBCL therapy.
7. Subjects with active graft-versus-host disease after allogeneic stem cell transplantation. At least 4 months prior to first dose of study drug must have elapsed since completion of allogeneic stem cell transplantation.
8. Major surgery within 2 weeks of first dose of study treatment of ATG-010.
9. Any life-threatening illness, medical condition, or organ system dysfunction which, in the Investigator's opinion, could compromise the patient's safety.
10. Unstable cardiovascular function:
    a. Symptomatic ischemia, or
    b. Uncontrolled clinically significant conduction abnormalities (ie, ventricular tachycardia on anti-arrhythmia is excluded; First degree atrioventricular block or asymptomatic left anterior fascicular block /right bundle branch block will not be excluded), or
    c. Congestive heart failure of New York Heart Association Class ≥3, or
    d. Myocardial infarction within 3 months.
11. Uncontrolled (ie, clinically unstable) infection requiring parenteral antibiotics, antivirals, or antifungals within 1 week prior to first dose; however, prophylactic use of these agents is acceptable even if parenteral.
12. Active hepatitis B virus (HBV) or hepatitis C virus (HCV)infection.
    a. Serological positive for hepatitis B surface antigen (HBsAg) or hepatitis B core antibody (HBcAb). Subjects who are HBcAb positive but HBsAg negative can be

enrolled if HBV-DNA cannot be detected. The upper limit of normal HBV-DNA testing is based on the test value of each site.

b. HCV antibody positive. But subjects with positive HCV antibodies can be enrolled if HCV-RNA cannot be detected.

13. Known human immunodeficiency virus (HIV) infection.
14. Subjects unable to swallow tablets, subjects with malabsorption syndrome, or any other gastrointestinal disease or gastrointestinal dysfunction that could interfere with absorption of study treatment of ATG-010.
15. Any of the following laboratory abnormalities (without corrective treatment)
    a. Absolute neutrophil count <1000 cells/mm^3 or platelet count<75,000/mm^3 during screening and on C1D1. Platelet infusions within 1 week prior to the first study treatment and/or use of granulocyte-stimulating factors and platelet growth factors 2 weeks prior to the first study treatment
    b. A circulating lymphocyte count of >50,000/μL
    c. Hepatic dysfunction: bilirubin >2.0 times the upper limit of normal (ULN) (except subjects with Gilbert's syndrome: total bilirubin of > 3×ULN) and alanine aminotransferase (ALT) and aspartate aminotransferase (AST) >2.5 ×ULN. In subjects with known liver involvement of their DLBCL, AST and ALT >5×ULN
    d. Severe renal dysfunction: estimated creatinine clearance of <30 mL/min, measured in 24-hour urine or calculated using the formula of Cockroft and Gault (can refer to Appendix 5)
    e. Hematopoietic dysfunction: hemoglobin <10.0 g/dL within 14 days of and including C1D1 and/or subjects receiving red blood cell transfusion within 14 days of and including C1D1.
16. Subjects with a body surface area <1.4 m^2 (can refer to Appendix 6).
17. Psychiatric illness or substance use that would prevent the patient from giving informed consent or being compliant with the study procedures.

Duration of Study:

The enrollment period for the study is expected to be 6 months, the end of study will be defined as 12 months after the last patient enrolled in the study, has withdrawn consent, has died, or has been lost to follow-up, (whichever occurs first). In addition, Sponsor may at any time decide to discontinue the study for reasons including but not limited to security.

Upon completion of this study, Sponsor will provide continuous treatment (as determined by the investigator) to the subjects who still have clinical benefits. The study drug may be provided through additional extension studies or in other forms at the discretion of the Sponsor.

Test Product, Dose and Mode of Administration:

The dosage regimen of ATG-010 specified as follow: Subjects will be administered as a fixed oral ATG-010 of 60 mg twice weekly (e.g., Monday and Wednesday or Tuesday and Thursday, etc.) on Weeks 1-4 of each 4-week cycle (total of 8 doses per cycle).

Subjects who achieved partial response (obtained the expected best efficacy judged by

investigator) or better response will transition to maintenance dosing until either PD or occurrence of unacceptable toxicity.

The maintenance dose of ATG-010 will be 60 mg orally QW. Subjects whose dose has been reduced such that the total weekly dose is <60 mg will continue that tolerated dose. If a patient experiences a subsequent increase in disease burden, or per the discretion of the Investigator, the dose of ATG-010 can be increased to 60 mg orally twice weekly, after discussion with the Medical Monitor.

If more than one different type of toxicity occurs concurrently, the most severe grade will determine the modification. All subjects who have a treatment delay of more than 28 days due to drug-related adverse events will withdraw from the study treatment. Each dose modification or treatment delay must be documented in the eCRF, including the respective reason.

Concomitant Medications:

To minimize nausea after oral administration of study drug, all subjects must receive 5-hydroxytryptamine (5-HT3) antagonists (eg, ondansetron 8 mg or equivalent), unless contraindicated, starting before the first dose of ATG-010 and continued twice daily to 3 times daily, after which the specific frequency of medication can be determined by the actual symptoms of the patient. Olanzapine is also recommended for the first 8 weeks, after which the dosage can be gradually reduced according to the situation of patient. Alternative anticathectic may be provided if the patient does not tolerate 5-HT3 antagonists. Other anti-nausea and anti-anorexia drugs may be administered by the investigator per institutional guidelines (National Comprehensive Cancer Network® [NCCN] Antiemetic Clinical Practice Guidelines® and NCCN Palliative Care Clinical Practice Guidelines)

The best supportive care of study permitted includes blood product transfusions, antimicrobials, and growth factors including granulocyte colony-stimulating factors (for neutropenia), erythropoietins (for anemia), and/or platelet-stimulating factors (for thrombocytopenia).

Concurrent therapy with any authorized or ongoing investigative anticancer agents is not allowed. Subjects are not allowed to participate in any other clinical trials during the study.

Study Endpoints:

Primary endpoint

- ORR by central radiological review: PR + CR

Secondary endpoints

- ORR evaluated by investigator
- DOR (evaluated by central radiological review), defined as the duration of time from first occurrence of CR or PR until the first date that disease progression is objectively documented
- DCR (evaluated by central radiological review), defined as the proportion of subjects who achieve CR, PR, or SD for a minimum of 4 weeks, following the first dose of study drug (ie, CR+PR+SD)
- OS, defined as the duration of time from the first dose of study drug until death due to any cause
- PFS, defined as the duration of time from the first dose of study drug until progression or death due to any cause

- PFS, ORR, DOR, DCR, and OS in subjects with DH-DLBCL and non-DH- DLBCL; with GCB and non-GCB DLBCL; and with "very good", "good", and "poor" R-IPI
- Safety and tolerability

Discontinuation Criteria:

A subject may be discontinued at the discretion of the Investigator for any of the following reasons, the investigator should make the decision after timely communication with the clinical trial monitor in specific cases.

- Disease progression, as assessed by the Investigator and confirmed by the central radiological review, defined according to the revised Lugano criteria for response assessment of lymphoma (Cheson, 2014)
  - For subjects with disease progression on imaging assessment, if disease progression is not clearly unequivocal and/or the patient is clearly deriving clinical benefit, after discussion with the Sponsor Medical Monitor, the Investigator may elect to continue the patient on study and repeat imaging within 4 to 8 weeks for confirmation or negation of PD.
- Disease progression as determined by the Investigator (should be radiographically confirmed whenever possible and must be comprehensively documented by the Investigator)
- Unacceptable adverse event(s) or failure to tolerate the study treatment
- Treatment delay of more than 28 days, except in specific cases approved by the Sponsor
- Any medically appropriate reason or significant protocol violation, in the opinion of the Investigator

The Investigator must remove a patient from study treatment for any of the following reasons:

- Patient decides to discontinue study treatment or withdraws consent
- Pregnancy

Subjects may decide to discontinue study treatment for any reason. Subjects who elect to discontinue study treatment will be asked to continue study participation so that follow-up information on disease progression and survival status may be obtained.

Statistical Summaries:

The primary endpoint analyses will be conducted after at least one efficacy evaluation following the enrollment of the last patient to the study (including efficacy and safety), and the amended analyses on efficacy and safety will be conducted after the End of Study.

Determination of Sample Size

This study is a bridging study based on an international multicenter clinical trial SADAL, and aims to verify the efficacy and safety of ATG-010 single drug in the treatment of relapsed or refractory DLBLC in the Chinese subjects. Consistent requirements of efficacy results and the SADAL study are that the point estimate of ORR in the bridging study falls within the 95% CI of the SADAL study (ORR of SADAL study: 28.3%; 95% CI: 20.7% - 37.0%). 60 subjects are

enrolled in SEARCH. If ORR reaches 28.3%, it can provide more than 90% power to make its assumed ORR to be above 20.7% and obtain sufficient safety data in Chinese subjects.

Efficacy Assessment

The primary endpoint analyses will be based on ORR data evaluated by central radiological review. The mITT population will be used for analyses of efficacy, which is defined as all subjects who received at least 1 dose of study drug administration.

Analysis of ORR will also be conducted in per-protocol population (PP) and this population will be used for supportive efficacy analysis.

The PP population will consist of the following subjects in the mITT population:

- Compliance of ATG-010 treatment ≥70%;
- Subjects who have received at least one complete post-baseline tumor evaluation, except for the subjects who died before or withdrew from study;
- Subjects who have no major protocol violations that would compromise the assessment of efficacy.

Data lists of major violations that would compromise the statistical analysis will be determined prior to database lock.

The secondary efficacy endpoints include ORR evaluated by investigator, DOR and DCR evaluated by central radiological review, OS, and PFS, etc, which will be analyzed using the mITT and the per protocol populations. Time-to-event with censored value (DOR, PFS and OS, etc) will be assessed using Kaplan-Meier methods in survival analysis, 95% CIs will be provided for ORR and DCR.

Safety Assessment

Data from all subjects who have received at least 1 dose of study drug administration will be used for safety analysis. Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The severity of the adverse event will be graded according to the CTCAE, Version 4.03.

AEs will be displayed in tables and listings using MedDRA system organ class (SOC) and preferred term. subjects occurring more than one same adverse event will be counted only once when the number of subjects with adverse event was counted. Other safety endpoints including hematology and blood chemistry results will also be analyses in Safety Population.

Table 1 Schedule of Assessments and Study Activities

Visit Window (days)	Prescreening and Screening Visits may be combined at site			Cycle 1		Cycle ≥2				End of Treatment Visit	Safety Follow-up Call[27]	Survival Follow-up[28]
	Pre-Screening for DLBCL Subtyping[2]	Screening (prior to start of study treatment)										
	≤ 30 days prior to enrollment	≤ 14 days	≤ 7 days	Day 1 of Weeks 1-4	Day 3 of Week 1 only[24]	Day 1 of each cycle	Day 10 of each cycle[24]	Day 15 of each cycle	Day 24 of each cycle[2][4]	≤14 days after last dose	30 days after last dose	Every 3 months until the End of Study
				±1 day	+ 1 day	±2 days	±2 days	+ 1 day	+ 1 day	-	+7 days	±14 days
Study Visit #	**Pre-Screen**	**Visit 1**	**Visit 2**	**Visits 3-6**	**Phone**	**Visits ≥7**	**Phone**	**Visits**	**Phone**	**Visits**	**Phone**	**Phone**
ICF for Pre-Screen of DLBCL subtyping[1]	X											
Signing ICF[1]	X											
Tumor biopsy (subjects without known DLBCL subtype and no archival tissue for subtyping)[2]	X											
Tumor biopsy (subjects with known DLBCL subtype but no archival tissue for subtyping)[2]	X											
Inclusion and exclusion criteria		X	X									
Demographics		X										
Disease risk assessment (Revised International Prognostic Index: R- IPI)		X										
Medical history[3]		X	X									

Height[4]		X										
Weight[5]		X	X	X		X		X		X		
Vital signs[6]			X	X		X				X		
ECOG score			X	X[7]		X[7]				X		
Physical examination[8]			X	X		X		X		X		
Echocardiogram or MUGA scan[9]		X										
12-lead ECG[10]		X								X		
Ophthalmic exam[11]		X	X									
Urinalysis[12]			X	X[7]		X[7]				X		
CBC with differential[13]			X	X[7]		X[7]				X		
TSH[14]			X	X[7]		X[7]				X		
Serum chemistry (Complete)[15]			X	X[7]		X[7]				X		
Serum chemistry (Limited)[16]				X			X					
Coagulation tests[17]			X							X		
Pregnancy test[18]			X			X				X		
HBV/HCV/HIV testing[19]			X			X						
Confirmation of PD and SD[20]		X										
PET-CT or enhanced CT scan for tumor assessment[21]		X				X						
Revised criteria for response assessment of lymphoma[22]						X						

Bone marrow aspirate and/or biopsy[23]		X									
5-HT3 antagonist dosing[24]				X							
ATG-010 dosing[25]				X		X	X				
Adverse events		X (adverse events beginning at after first dose of study drug, serious adverse events beginning at before first dose of study drug)									
Concomitant medication		X (beginning at ICF signing)									
Supportive care [26]		X			X		X		X		
Information on antineoplastic therapy after end of ATG-010 treatment[27]										X	

5-HT3 = 5-hydroxytryptamine ; ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase, BUN = blood urea nitrogen; CBC = complete blood count; CR = complete response; CT = computed tomography; DLBCL = diffuse large B-cell lymphoma; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; GCB = germinal center B-cell; HBV = hepatitis B virus; hCG = human chorionic gonadotropin; HCV = hepatitis C virus; HIV = human immunodeficiency virus; ICF = informed consent form; INR = international normalization ratio; LDH = lactate dehydrogenase; MRI = magnetic resonance imaging; MUGA = multiple gated acquisition; PET = positron emission tomography; PR = partial response; PT = prothrombin time; TSH = thyroid stimulating hormone; TT = thrombin time; WBC = white blood cell.

1 The patient must provide informed consent for pre-screening and master ICF within 30 days of enrollment and prior to the first screening procedure.

2 All subjects must submit either a fresh biopsy or archival tissue to the central DLBCL subtyping laboratory for determination (prior to enrollment) or confirmation (by end of Cycle 2) of their DLBCL pathological diagnosis and subtype. In subjects with a known DLBCL subtype but without sufficient archival tissue available for confirmatory subtyping, biopsy should be performed before the end of Cycle 1.

3 Medical History at Screening Visits 1 & 2 including baseline symptoms as well as a detailed history of prior cancer therapies and procedures for DLBCL with start and stop dates, best response and disease progression during or after therapy, as well as discontinuations due to intolerability or any other serious illness. An evaluation of the risk of tumor lysis syndrome based on a clinical evaluation of comorbidity will also be performed.

4 Height (will be only measured once at Screening Visits 1 or 2).

5 Body weight will be measured at each clinic visit up to and including Cycle 5; Cycle 6 onwards only during Day 1 visits.

6 The vital sign includes blood pressure, pulse, temperature, and respiration rate; will be measured after the patient has been in a supine or sitting position for 5 minutes, on Day 1 of each Cycle only.

7 On Day 1 of each Cycle only.

8 Full physical exam will be conducted on all subjects at screening and at the End of Treatment Visit; symptom-directed physical examination will be conducted during the study.

9 Echocardiogram or MUGA scan to be performed during Screening Visit 1 to assess baseline cardiac function and risk of cardiac dysfunction (including cardiomyopathy), particularly in subjects who have received prior anthracycline therapy.

10 An ECG will be done at Screening Visit 1, otherwise only if clinically indicated, and at End of Treatment Visit.

11 Ophthalmic exam will be conducted on the subjects with previous ocular or visual diseases or clinical indications at Screening; during the study, ophthalmological exam should be carried out if there are clinical indications, and an ophthalmologist should be consulted if necessary.

12 Urinalysis will be done at Screening Visit 2, Day 1 of each cycle, and End of Treatment Visit; and will include urine bilirubin, glucose, red blood cells, ketones, pH, protein, specific gravity, and urobilinogen. Microscopy will only be performed if clinically indicated.

13 The CBC with differential at Screening Visit 2, Day 1 of each cycle, and End of Treatment Visit, will include hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, WBC count, WBC differential, RBC count, lymphocytes, monocytes, neutrophils, eosinophils, basophils, platelets. The WBC differential may be automated or manual as per institutional standards. Reticulocytes may be done only when clinically indicated.

14 The level of TSH will be measured at Screening Visit 2, Day 1 of each cycle, and End of Treatment Visit.

15 Complete serum chemistry at Screening Visit 2, Day 1 of each cycle, and End of Treatment Visit, will include sodium, potassium, chloride, bicarbonate, blood urea/BUN, creatinine, glucose, calcium, phosphate, magnesium, ALT, AST, alkaline phosphatase, total bilirubin, LDH, total protein, albumin, amylase, lipase, creatine kinase, and uric acid.

16 Limited chemistry for Cycle 1 (Weeks 2, 3 and 4) and Day 15 of Cycles ≥2 including sodium, potassium, chloride, bicarbonate, blood urea/BUN, creatinine, glucose, ALT, AST, alkaline phosphatase, total bilirubin, and LDH (otherwise other clinical indicated). If total bilirubin concentration increases to more than 1.5 times the upper limit of normal, total bilirubin will be divided into direct and indirect bilirubin.

17 Coagulation Tests to be measured at Screening Visit 2 and End of Treatment Visit including PT, INR, and aPTT. Coagulation may also be measured using TT (quick test) if measurement of PT/aPTT is not feasible. If there are coagulation related problems, the investigator may decide to retest at any time at his discretion.

18 Women of child bearing potential must have a negative serum hCG pregnancy test within 3 days prior to first study dose and at End of Treatment Visit. Women of child bearing potential will have urine pregnancy test on Day 1 of Cycle 2, then on Day 1 of even numbered cycles thereafter. A positive urine pregnancy test will be confirmed by a serum pregnancy test.

19 Screening for HBV and HCV at Screening Visit 2. HBV-DNA testing (only for HBcAb positive subjects) should be done each cycle (approximately monthly). At Screening Visit 2, HIV testing is required if the patient is known to have prior HIV infection.

20 Confirmed evidence of DLBCL disease progression (PD) or failure (SD) to the last treatment regimen is required for study entry, and subjects must have measurable disease at screening per the Lugano criteria for response assessment of lymphoma (*Cheson, 2014*).

21 Disease assessment (tumor measurement) will be made by PET-CT and Contrast-enhanced CT (Tumor measurement) at screening (within the first 14 days of Cycle 1 Day 1), enhanced CT should include the neck, chest, abdomen, pelvic cavity (including the inguinal/femoral region), if clinically indicated, as well as other anatomical sites. If CT is contraindicated, MRI scan will be performed. PET-CT and contrast-enhanced CT scans will be performed on Cycle 3 Day 1 (± 1 week) and then every 8±1 weeks (ie, Day 1 of odd numbered cycles) until disease progression is confirmed by the central radiological review. The PET-CT is allowed at alternating assessment time points (ie, every 16 weeks, or every other scan) if PET-CT cannot be performed for every assessment. If CT scan suggests the possibility of obtaining CR, PET-CT should be performed for confirmation. Results of PET-CT and contrast-enhanced CT scans performed beyond a predetermined time point should be recorded on the eCRF and images of all disease assessment scans performed during the study period will be provided to the central radiological review.

22 Disease status will be assessed by the Lugano criteria for response assessment of lymphoma (*Cheson, 2014;* Appendix 1) on Cycle 3 Day 1 (±1 week) and then every 8 weeks ±1 week (ie, Day 1 of odd numbered cycles) until disease progression is confirmed by the central radiological review.

23 Bone marrow aspirates and/or biopsies will be taken within 1 month prior to first dose (baseline) to assess DLBCL involvement in bone marrow. The bone marrow biopsy will be repeated whenever clinically indicated to confirm CR in only those subjects who had DLBCL known bone marrow involvement prior to dosing.

24 To minimize nausea, all subjects should receive 5-HT3 antagonists (8 mg or equivalent) unless contraindicated, starting on Cycle 1 Day 1 before the first dose of ATG-010 and continued 2 to 3 times daily thereafter, as needed. Olanzapine is also recommended for the first 8 weeks, after which the dosage can be gradually reduced according to the situation of patient.

25 ATG-010 dosing will occur on Days 1 and 3 of Weeks 1-4 of each 4-week cycle. For doses on non-clinic days, the patient will be provided doses to take home.

26 Phone call to evaluate supportive care medications and adverse events, and to adjust supportive care as appropriate. In Cycle 1, the telephone contact with the patient must take place on Day 3 (+ 1 day) following the Cycle 1 Day 1 of ATG-010 dosing. For Cycles ≥2, this phone call will be made on Day 10 (+ 1 day) and 24 (+ 1 day), corresponding to Day 3 (+ 1 day) of every week in which a clinic visit does not occur.

27 By phone (or a visit, if possible), assess patient status, follow-up on any adverse events that were not resolved at the End of Treatment Visit, and information on any antineoplastic therapies utilized since discontinuation of study treatment.

28 After treatment discontinuation, a call will be made to the patient (or the patient's family) every 3 months (± 14 days) from the date their last dose until the End of Study to determine the patient's survival status and information on any antineoplastic therapies utilized since discontinuation of study treatment.