CLINICAL STUDY PROTOCOL

Protocol Number: CA-ALT-803-02-14

Protocol Title: A phase 1/2 study of ALT-803 in patients with relapse/refractory indolent B cell non-Hodgkin lymphoma in conjunction with rituximab

Date of Protocol:
Version# 01 September 4, 2014

Sponsor Contact:

Altor BioScience CORPORATION

Hing C. Wong, Ph.D.
Altor Bioscience Corporation.
Miramar, Florida 33025
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Safety Data Fax: 954-443-8602

INVESTIGATOR SIGNATURE PAGE

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Additionally, I will not initiate this study without approval of the appropriate Institutional Review Board (IRB), and I understand that any changes in the protocol must be approved in writing by the sponsor, the IRB, and, in certain cases the FDA, before they can be implemented, except where necessary to eliminate hazards to subjects.

_____ _____

Principal Investigator's Signature Date

_____

Principal Investigator's Name (Print)

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SYNOPSIS

Sponsor:	Altor Bioscience Corporation
Protocol#:	CA-ALT-803-02-14
Study Drug Name:	ALT-803
Study Treatment Active agents:	ALT-803, a "recombinant human super agonist interleukin-15 (IL-15) complex" (AKA, IL-15N72D:IL-15RαSu/IgG1 Fc complex)
Study Type:	Interventional
Study Phase:	1/2
Protocol Title:	A phase 1/2 study of ALT-803 in patients with relapse/refractory indolent B cell non-Hodgkin lymphoma in conjunction with rituximab
Objectives:	To evaluate the safety and tolerability of escalating doses, identify the Maximum Tolerated Dose level (MTD) or Minimum Efficacious Dose (MED) and designate a dose level for Phase 2 study (RP2D) of ALT-803 in combination with standard-of-care rituximab therapy in patients with relapsed or refractory (rel/ref) indolent B cell non-Hodgkin lymphoma (iNHL). To estimate the anti-tumor activity of ALT-803 as measured by response rate, overall survival, progression free survival, time to response, duration of response, time to treatment failure, and time to subsequent treatment in patients with rel/ref iNHL. To evaluate the effect of ALT-803 on the peripheral absolute lymphocyte counts (ALC) and white blood cell (WBC) counts, the number and phenotype of peripheral blood T (total and subsets) and NK cells. To characterize the immunogenicity and pharmacokinetic profile, including induced serum levels of IL-2, IL-4, IL-6, IL-10, IFN-γ and TNF-α, of ALT-803 in rel/ref iNHL patients. To correlate clinical outcomes with *fcgr3a* polymorphisms and recurrent genomic mutations in rel/ref iNHL patients.
Study Design:	This is a Phase 1/2, open-label, multi-center, competitive enrollment and dose-escalation study of ALT-803 in patients with rel/ref iNHL in conjunction with rituximab. The study includes a dose escalation phase to determine the MTD or MED using a 3+3 dose escalation design and to designate a dose level for the Phase 2 expansion phase (RP2D) of ALT-803 and a two-stage expansion phase using a Simon two-stage design at the ALT-803 RP2D level in combination with rituximab. In Phase 1, three dose levels will be evaluated. A step-down dose level (level -1) will be provided in the event of encountering DLT in two patients at the planned initial dose level. The study will be conducted in conformity with Good Clinical Practice (GCP).

Treatments: The study treatment plan for each enrolled patient includes one 4-week induction treatment cycle. During induction, patients will receive up to four weekly doses of ALT-803 and rituximab (375 mg/m^2) by intravenous injection. For the first dose of treatment, patients will received rituximab on day 1 followed by ALT-803 on day 2 in order to avoid simultaneous infusion of both agents and reduce the potential of infusion-related adverse events. Eligible patients will receive the consolidation treatment. Consolidation consists of treatment with ALT-803 at the same dose level used in the induction plus rituximab (375 mg/m^2) every 8 weeks (1 cycle = 8 weeks), for a total of 4 consolidation cycles.

Treated patients will have at least two response evaluation visits. Patients who receive at least two study drug doses during the induction treatment period will be evaluated for disease response during week 11. Patients who have at least stable disease from the first anti-tumor evaluation and who do not experience or have sufficiently recovered from toxicities of the induction treatment cycle and who meet other criteria to continue study treatment will receive up to four consolidation treatment cycles, with a single treatment of ALT-803 plus rituximab, repeated every 8 weeks for a total of 4 additional ALT-803 plus rituximab doses. The ALT-803 dose level utilized in the induction cycle will be continued in consolidation, with reassessment for continued tumor response performed upon completion at week 40.

The study treatment and response evaluation schema:

Treatment Phase	Induction				REST	Response Evaluation	Consolidation				Response Evaluation
Treatment Week	1	2	3	4	5-10	11	12	20	28	36	40**
Treatment Day	1, 2*	8	15	22	29-70	71-77	78	134	190	246	274-280
ALT-803	1	2	3	4	Rest		5	6	7	8	
rituximab	1	2	3	4			5	6	7	8	
Consolidation Cycle							1	2	3	4	
Response Evaluation						X					X

*For the first week, rituximab is administered on day 1, ALT-803 on day 2

**Long term follow-up after 40 weeks includes restaging every 6 months for 2 years, and then every 12 months for 5 years (until progression).

Patients will be assessed for response using the 2007 IHP criteria.[1] Patients will be followed for progression, and at the time of progression there are no restrictions on further therapies.

Enrolled patients will receive the study treatment at qualified cancer treatment centers with adequate diagnostic and treatment facilities to provide appropriate management of therapy and complications. ALT-803 will be administered by intravenous infusion into a central or peripheral vein under the supervision of a qualified physician experienced in the use of biologic anti-cancer agents. Rituximab will be administered as described in the product package insert provided by the manufacturer.

Dose Escalation Phase: A 3 + 3 design will be used for identifying a tolerable dose of ALT-803 for Phase 2 studies by monitoring patients for DLTs to determine the MTD and for

identifying an efficacious dose by monitoring patients' ALC and WBC count to determine the MED during the DLT observation period. The dose escalation phase is concluded when either the MTD or the MED is determined. An ALT-803 dose level (RP2D) will then be designated for Phase 2 study. There are three escalating dose levels of ALT-803 and a step-down cohort (-1) with a lower dose level of ALT-803 in the event that unexpected toxicity is encountered at the initial dose level.

Below are the planned dose levels of the study drug during the dose escalation phase of the study.

Cohort	ALT-803 Dose (µg/kg)	Number of patients
-1	0.5	3 to 6
1 (initial)	1	3 to 6
2	3	3 to 6
3	6	3 to 6

Dose limiting toxicity (DLT) is defined as follows: any toxicity that is not clearly unrelated to drug administration that is of Grade 3 and does not resolve to Grade 1 or lower within a week despite the use of medical intervention or that is of Grade 4, with exceptions described in the study protocol.

The DLT Observation Period is defined as the duration of the induction treatment, days 1-28.

Maximum Tolerated Dose level (MTD) is defined as a dose level at which <2 out of 6 patients experienced DLT and that is one level below a dose that was not tolerated or the maximum planned dose level if designated by the study committee.

Minimal Efficacious Dose (MED) is defined as a dose level which produces an ALC ≥25,000/µL sustained for 14 days or a total WBC ≥35,000/µL sustained for 14 days among 2/3 or 4/6 of patients. For safety, a dose level is also defined as "exceeding MED" with the occurrence of ALC ≥50,000/µL or WBC ≥60,000/µL sustained for 14 days. If patients have circulating malignant lymphocytes in the peripheral blood, these lymphoma cells will be excluded from the WBC and ALC calculations for MED.

Expansion Phase

Two expansion arms will be used to investigate indolent NHL patients with different expectations regarding response to single agent rituximab: rituximab-refractory (RR) and rituximab-sensitive (RS). For each arm, a two-stage expansion phase at the MTD or the MED level will be conducted using an optimal Simon's two-stage design. The best objective overall response rate (ORR) is defined as complete response (CR) + partial response (PR) assessed at the week 11 or 40 response assessment, or during the 2 year follow-up period. For RR patients, a lack of efficacy for ORR of 5% will be used, with an ORR $\geq$ 25% constituting a clinically interesting result. For RS patients, a lack of efficacy for ORR of 40%

will be used, with a clinically interesting ORR $\geq$ 60%. Each expansion arm will be analyzed independently for preliminary efficacy.

Stopping Rules: Patient enrollment will be temporarily suspended based on occurrence of any of the following events, and the study committee, including the sponsor, the Data Safety Monitoring Board and principal investigators will meet to discuss how to proceed with future patient enrollment in the study.

During the dose escalation phase of the study,

- If the maximum planned dose level has been reached, but neither the MTD nor MED can be determined.
- If de-escalation occurs and the step-down dose level cannot be designated as the MTD or MED.

Any time during the expansion phase of the study,

- More than 33% of patients experience a possible, probable or definite study drug related DLT.
- Favorable anti-tumor response data collected from enrolled patients.

At any time during the study,
the study committee may meet to discuss how to proceed with the study and may make any or all of the following recommendations for further patient enrollment:

- Downward adjust the study drug dose.
- Adjust the study drug dosing schedule.
- Recommend more effective pre-therapy, intra-therapy and post-therapy side effect mitigation interventions.
- Correct protocol technical errors that caused unnecessary dose omissions or premature treatment discontinuations. After correction of protocol errors, the DSMB may meet to re-evaluate the safety profile of the study treatment and recommend how to proceed with the study, if necessary.

Evaluations: Patients will be evaluated for clinical toxicities during the treatment. The disease response will be evaluated at weeks 11 and 40 from the start of study treatment, and every 6 months for 2 years thereafter. After this two year period the institutional standards for disease assessment will be followed, with at least annual disease assessments, for up to 5 years. Prior to and during the treatment period, patients' blood and serum samples will be collected to assess the pharmacokinetic profile and immunogenicity of the study drug, as well as for immunomodulation, and *fcgr3a* polymorphisms. Disease containing biopsies will be used for recurrent lymphoma gene mutation analysis. All patients who receive at least 2 doses of the study drug ALT-803 will be included in the anti-tumor response evaluation.

Population: Patients of 18 years of age and above with relapsed or refractory $CD20^{+}$ indolent NHL (follicular lymphoma (FL), marginal zone lymphoma (MZL), small lymphocytic lymphoma (SLL), and lymphoplasmacytic lymphoma (LPL)). Rituximab-refractory (RR) patients are defined as those that progress on rituximab

therapy or within 6 months of their last dose of rituximab. For RR patients, a biopsy to confirm CD20 expression is required. Patients also need to have adequate cardiac, pulmonary, liver and kidney functions and have an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1 or 2.

Sample Size: A total of up to 18 assessable patients will be accrued to the dose escalation phase of the study (Phase 1). Anticipated enrollment to this phase is 12 patients. For the RS patient arm, a total of 16 patients will be enrolled at the MTD/MED dose in the first stage, and 30 patients in the second stage of a 2-stage Phase 2 cohort (total for RS expansion cohort 46). For the RR, a total of 9 patients will be enrolled in the first stage, and an additional 8 patients in the second stage of a 2 stage Phase 2 study (total for RR expansion cohort 17). Thus, enrollment of evaluable patients on the Phase 1 portion, and the first stage of both expansion cohorts (including 6 patients of the MTD/MED cohort) is expected to be 31 patients, with the maximum number of 43 patients. Assuming a 5% frequency of non-evaluable patients, the phase 1 and the first stage of both expansion cohorts is estimated at 33 patients.

Primary Endpoints

For Phase 1 only

(1) Determination of the MTD or MED of ALT-803 and designation of the recommended dose level (RP2D) for Phase 2 study of ALT-803 in conjunction with rituximab in patients with rel/ref iNHL.

For Phase 1 & 2

(2) Safety profile of ALT-803 plus rituximab in treated patients.

(3) Overall response rate (CR+PR) of treated patients.

Secondary Endpoints

(1) Evaluate overall survival, progression free survival, time to response, duration of response, time to treatment failure, and time to subsequent treatment.

(2) Evaluation of the effect of ALT-803 on the peripheral ALC and WBC counts, the number and phenotype of peripheral blood NK cells and T (total and subsets), and NK cell function.

(3) Characterization of the immunogenicity and pharmacokinetic profile, including serum levels of IL-2, IL-4, IL-6, IL-10, IFN-γ and TNF-α, of ALT-803 in treated patients.

(4) Correlation of *fcgr3a* polymorphism status and recurrent lymphoma mutations with clinical outcomes of the study.

Pharmacokinetics & Biomarkers: Fresh blood samples will be collected to assess immune cell number, phenotype and function. Serum samples will be collected for pharmacokinetics (PK) and immunogenicity of the study drug ALT-803. The same serum samples collected for PK analysis will be used to assess the serum levels of IL-2, IL-4, IL-6, IL-10, IFN-γ and TNF-α. Non-compartmental and compartmental analyses will be conducted. Baseline peripheral blood will be used for *fcgr3a* polymorphism

testing, and a baseline tumor sample will be used for lymphoma mutation analysis using next-generation sequencing.

Monitoring Tests: Blood samples for standard chemistry and CBC with differential will be obtained at screening, on each study treatment infusion day, and at response evaluation visits. Blood samples for immunogenicity testing of anti-ALT-803 antibodies will be collected prior to dosing on the first and fourth ALT-803 infusion visit, and at the response evaluation visit during week 11.

Response Assessment: There are at least two response assessments for treated patients: the first assessment during week 11 (following induction) and the second assessment during week 40 (following consolidation) from the start of study treatment. After completion of the induction cycle of study treatment, patients who have received at least 2 doses of ALT-803 will have the first response assessment. After completion of four additional consolidation study treatments patients will have a second response assessment. If patients are unable to continue study therapy for all 4 consolidation cycles due to an adverse event, disease assessments will be performed at the time of going off study. In non-progressing patients, after completion of consolidation, disease assessments will be performed every 6 months for 2 years, and then per institutional guidelines, at least annually, for up to 5 years. If a focused physical examination or patient symptoms raise the concern for progression, a complete response assessment should be performed at that time. Response assessments will be carried out according to the 2007 IHP criteria for response assessment of lymphoma.[1] Baseline evaluations (except for baseline imaging and bone marrow biopsy) should be performed up to 14 days before study treatment start.

Progression & Survival Assessment: Progression-free survival, overall survival, and duration of response of all treated patients will be assessed at least every three months during years 1 and 2, every 4 months during year 3, and then every 6 months (+/- 2 months) during years 4 and 5 from the start of study treatment, or through the point designated as the end of the study follow up (5 years).

Adverse Events: All patients will be monitored and evaluated for clinical toxicities during the treatment period and queried at each follow-up visit for Adverse Events (AEs). Patients may volunteer information concerning AEs. All adverse events will be graded by using the NCI Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v4.0), and logged in the patient Case Report Form. The study centers should report all Serious Adverse Events (SAEs) and all events that trigger patient's study treatment discontinuation to the sponsor via phone, fax or email (or a combination) no more than 24 hours after learning of the event. The sponsor will use the information to manage and coordinate the dose escalation, cohort expansion and patient enrollment. The sponsor will then inform all of the participating clinical sites of the current dose level and the number of patients to be enrolled at that level, or of any patient enrollment suspension via phone, fax or email within 24 hours of learning of the event. The study centers should report all

other adverse events to the sponsor following the guidelines defined in the study protocol. All study drug related AEs that are both serious and unexpected will be reported to the FDA in an expedited manner in accordance with 21 CFR §312.32.

Statistical Plan: For each cohort, all AEs will be tabulated and examined and all safety, pharmacokinetic, biomarker and tumor response data will be evaluated. For estimation of duration of response and progression free survival, the Kaplan-Meier method will be used. *P*-values of ≤0.05 (two-sided) will be considered to indicate statistical significance.

8. STUDY CALENDAR, CLINICAL PROCEDURES & TESTS

8.1 Study calendar

TESTS & PROCEDURES	SCREEN/ BASELINE[1]	INDUCTION									REST	RESPONSE EVALUATION	CONSOLIDATION				RESPONSE EVALUATION	DISEASE ASSESSMENT & FOLLOW-UPS											
Study Month		1									2-3	3	3-9				10	12	15	18	21	24	28	32	36	42	48	54	60
Study Week		*1*				*2*	*3*	*4*			*5-10*	*11*	*12*	*20*	*28*	*36*	*40*												
Study Day		1	2	3	5	8	15	22	23	25	29-70	71-77	78	134	190	246	274-280												
Tolerance Window		*+/- 2 days*									*Any day*	*Any day*	*+/- 7 days*				*Any day*	*+/- 2 weeks*											
Medical history	X										R E S T P E R I O D																	
Serum pregnancy test[2]	X																											
Complete physical exam (PE)	X																											
Focused PE, ECOG PS, B symptom assessment		X											X	X	X	X												
Vital signs, Weight, Height[3], Cardiac & Lung function monitoring	X	X	X			X	X	X				X	X	X	X	X	X											
Concurrent medication	X	X	X			X	X	X				X	X	X	X	X	X											
Adverse event assessment[4]	X	X	X			X	X	X				X	X	X	X	X	X											
CBC with Differential[5]	X	X	X			X	X	X				X	X	X	X	X	X											
Blood Chemistry with LDH[5]	X	X	X			X	X	X				X	X	X	X	X	X											
EKG	X																											
PFT only when clinically indicated	X																											
Response assessment[6]												X					X	X		X		X			X		X		X
Contrast CT of NCAP or PET-CT	X											X					X	X		X		X			X		X		X
Bone marrow biopsy[7]	X											X					X												
Focused PE, ECOG PS, B symptom & AE	X[17]											X					X	X		X		X			X		X		X
Disease and survival follow-up/post therapies[8]																		X	X	X	X	X	X	X	X	X[16]	X[16]	X[16]	X[16]
Immune cell number, phenotype & function[9,14]	X		X[10]	X	X	X[10]		X[10]	X	X			X[11]																
Polymorphism (SNP) testing[14]			X[10]																										
PK, IL-2, IL-4, IL-6, IL-10, IFN-γ, TNF-α[12,14]			X[12]	X																									
Immunogenicity tests[13, 14]			X[13]					X[10]				X																	
Recurrent mutation evaluation[15]	X																												
Rituximab		**r1**				**r2**	**r3**	**r4**					**r5**	**r6**	**r7**	**r8**													
Study drug (ALT-803)			**a1**			**a2**	**a3**	**a4**					**a5**	**a6**	**a7**	**a8**													

[1]Screening/baseline evaluations are performed ≤ 14 days prior to start of therapy; baseline CTs or PET-CT are performed ≤ 28 days and baseline bone marrow biopsy performed ≤ 42 days prior to start of therapy. If the patient's condition is deteriorating, ECOG status and laboratory evaluations should be repeated within 48 hours prior to initiation of study treatment infusion. [2]Pregnancy test is for women with childbearing potential only. [3]Vital signs (especially blood pressure), clinical status and laboratory tests should be reviewed before start of therapy. Vital signs will be evaluated at 15, 30, 60 and 120 min then hourly post infusion until discharge or at completion of dose monitoring. Body weight will be collected before infusion on each drug infusion day for all patients. Height only collected at baseline. [4]Patients who have an on-going study drug-related SAE upon study completion or at discontinuation of study will be contacted by the investigator or his/her designee every week until the event is resolved or determined to be irreversible. [5]Safety labs can be drawn within 48 hours of scheduled dose.[6]Disease response and progression assessment will be evaluated using the 2007 IHP criteria for assessment of lymphoma. [7]Only performed to confirm a CR if disease present at baseline. Once confirmed, only repeat if relapse suspected. [8]Information about tumor assessment & other therapies received after completion of study treatment will be collected if available. [9]Fresh blood samples (3 tubes per time point) for immune cell number, phenotype & function testing will be collected. [10]Collect before dosing. [11]Collect before dosing and 24 hours post-infusion. [12]Collect blood samples at Time 0 (before drug infusion), at 30 min (+/- 5 min), 2 hour (+/- 15 min), 6 hour (+/- 60 min) or before discharge on dosing day, 24 hour (+/- 6 hour) from Time 0. IL-2, IL-4, IL-6, IL-10, IFN-γ and TNF-α assays are performed using the same samples and at the same schedule as PK. [13]Use the sample collected before dosing for PK test. [14]Residual samples may be used by Sponsor for research studies of other biomarkers. All attempts will be made to collect research samples but missed samples will not be considered a protocol deviation.[15]Fesh/frozen or FFPE tissue block (or substitute) preferably from biopsy immediately prior to treatment start. If the patient has an elevated baseline ALC and concern for peripheral blood involvement with circulating lymphoma cells, an oral rinse will be performed to obtain an additional non-tumor cellular sample.[16]+/- 2 months. [17]Complete PE required at screening, not focused PE.

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Response Evaluation						X					X

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Minimal Efficacious Dose (MED) is defined as a dose level which produces an ALC ≥25,000/µL sustained for 14 days or a total WBC ≥35,000/µL sustained for 14 days among 2/3 or 4/6 of patients. For safety, a dose level is also defined as "exceeding MED" with the occurrence of ALC ≥50,000/µL or WBC ≥60,000/µL sustained for 14 days. If patients have circulating malignant lymphocytes in the peripheral blood, these lymphoma cells will be excluded from the WBC and ALC calculations for MED.

Expansion Phase

Two expansion arms will be used to investigate indolent NHL patients with different expectations regarding response to single agent rituximab: rituximab-refractory (RR) and rituximab-sensitive (RS). For each arm, a two-stage expansion phase at the MTD or the MED level will be conducted using an optimal Simon's two-stage design. The best objective overall response rate (ORR) is defined as complete response (CR) + partial response (PR) assessed at the week 11 or 40 response assessment, or during the 2 year follow-up period. For RR patients, a lack of efficacy for ORR of 5% will be used, with an ORR $\geq$ 25% constituting a clinically interesting result. For RS patients, a lack of efficacy for ORR of 40%

will be used, with a clinically interesting ORR $\geq$ 60%. Each expansion arm will be analyzed independently for preliminary efficacy.

Stopping Rules: Patient enrollment will be temporarily suspended based on occurrence of any of the following events, and the study committee, including the sponsor, the Data Safety Monitoring Board and principal investigators will meet to discuss how to proceed with future patient enrollment in the study.

During the dose escalation phase of the study,

- If the maximum planned dose level has been reached, but neither the MTD nor MED can be determined.
- If de-escalation occurs and the step-down dose level cannot be designated as the MTD or MED.

Any time during the expansion phase of the study,

- More than 33% of patients experience a possible, probable or definite study drug related DLT.
- Favorable anti-tumor response data collected from enrolled patients.

At any time during the study,
the study committee may meet to discuss how to proceed with the study and may make any or all of the following recommendations for further patient enrollment:

- Downward adjust the study drug dose.
- Adjust the study drug dosing schedule.
- Recommend more effective pre-therapy, intra-therapy and post-therapy side effect mitigation interventions.
- Correct protocol technical errors that caused unnecessary dose omissions or premature treatment discontinuations. After correction of protocol errors, the DSMB may meet to re-evaluate the safety profile of the study treatment and recommend how to proceed with the study, if necessary.

Evaluations: Patients will be evaluated for clinical toxicities during the treatment. The disease response will be evaluated at weeks 11 and 40 from the start of study treatment, and every 6 months for 2 years thereafter. After this two year period the institutional standards for disease assessment will be followed, with at least annual disease assessments, for up to 5 years. Prior to and during the treatment period, patients' blood and serum samples will be collected to assess the pharmacokinetic profile and immunogenicity of the study drug, as well as for immunomodulation, and *fcgr3a* polymorphisms. Disease containing biopsies and an oral sample will be used for recurrent lymphoma gene mutation analysis. All patients who receive at least 2 doses of the study drug ALT-803 will be included in the anti-tumor response evaluation.

Population: Patients of 18 years of age and above with relapsed or refractory $CD20^+$ indolent NHL (follicular lymphoma (FL), marginal zone lymphoma (MZL), small lymphocytic lymphoma (SLL), and lymphoplasmacytic lymphoma (LPL)).

Rituximab-refractory (RR) patients are defined as those that progress on rituximab therapy or within 6 months of their last dose of rituximab. For RR patients, a biopsy to confirm CD20 expression is required. Patients also need to have adequate cardiac, pulmonary, liver and kidney functions and have an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1 or 2.

Sample Size: A total of up to 18 assessable patients will be accrued to the dose escalation phase of the study (Phase 1). Anticipated enrollment to this phase is 12 patients. For the RS patient arm, a total of 16 patients will be enrolled at the MTD/MED dose in the first stage, and 30 patients in the second stage of a 2-stage Phase 2 cohort (total for RS expansion cohort 46). For the RR, a total of 9 patients will be enrolled in the first stage, and an additional 8 patients in the second stage of a 2 stage Phase 2 study (total for RR expansion cohort 17). Thus, enrollment of evaluable patients on the Phase 1 portion, and the first stage of both expansion cohorts (including 6 patients of the MTD/MED cohort) is expected to be 31 patients, with the maximum number of 43 patients. Assuming a 5% frequency of non-evaluable patients, the phase 1 and the first stage of both expansion cohorts is estimated at 33 patients.

Primary Endpoints

For Phase 1 only

(1) Determination of the MTD or MED of ALT-803 and designation of the recommended dose level (RP2D) for Phase 2 study of ALT-803 in conjunction with rituximab in patients with rel/ref iNHL.

For Phase 1 & 2

(2) Safety profile of ALT-803 plus rituximab in treated patients.

(3) Overall response rate (CR+PR) of treated patients.

Secondary Endpoints

(1) Evaluate overall survival, progression free survival, time to response, duration of response, time to treatment failure, and time to subsequent treatment.

(2) Evaluation of the effect of ALT-803 on the peripheral ALC and WBC counts, the number and phenotype of peripheral blood NK cells and T (total and subsets), and NK cell function.

(3) Characterization of the immunogenicity and pharmacokinetic profile, including serum levels of IL-2, IL-4, IL-6, IL-10, IFN-γ and TNF-α, of ALT-803 in treated patients.

(4) Correlation of *fcgr3a* polymorphism status and recurrent lymphoma mutations with clinical outcomes of the study.

Pharmacokinetics & Biomarkers: Fresh blood samples will be collected to assess immune cell number, phenotype and function. Serum samples will be collected for pharmacokinetics (PK) and immunogenicity of the study drug ALT-803. The same serum samples collected for PK analysis will be used to assess the serum levels of IL-2, IL-4, IL-6, IL-10, IFN-γ and TNF-α. Non-compartmental and compartmental analyses will be conducted. Baseline peripheral blood will be used for *fcgr3a* polymorphism

testing, and a baseline tumor sample and oral sample will be used for lymphoma mutation analysis using next-generation sequencing.

Monitoring Tests: Blood samples for standard chemistry and CBC with differential will be obtained at screening, on each study treatment infusion day, and at response evaluation visits. Blood samples for immunogenicity testing of anti-ALT-803 antibodies will be collected prior to dosing on the first and fourth ALT-803 infusion visit, and at the response evaluation visit during week 11.

Response Assessment: There are at least two response assessments for treated patients: the first assessment during week 11 (following induction) and the second assessment during week 40 (following consolidation) from the start of study treatment. After completion of the induction cycle of study treatment, patients who have received at least 2 doses of ALT-803 will have the first response assessment. After completion of four additional consolidation study treatments patients will have a second response assessment. If patients are unable to continue study therapy for all 4 consolidation cycles due to an adverse event, disease assessments will be performed at the time of going off study. In non-progressing patients, after completion of consolidation, disease assessments will be performed every 6 months for 2 years, and then per institutional guidelines, at least annually, for up to 5 years. If a focused physical examination or patient symptoms raise the concern for progression, a complete response assessment should be performed at that time. Response assessments will be carried out according to the 2007 IHP criteria for response assessment of lymphoma.[1] Baseline evaluations (except for baseline imaging and bone marrow biopsy) should be performed up to 14 days before study treatment start.

Progression & Survival Assessment: Progression-free survival, overall survival, and duration of response of all treated patients will be assessed at least every three months during years 1 and 2, every 4 months during year 3, and then every 6 months (+/- 2 months) during years 4 and 5 from the start of study treatment, or through the point designated as the end of the study follow up (5 years).

Adverse Events: All patients will be monitored and evaluated for clinical toxicities during the treatment period and queried at each follow-up visit for Adverse Events (AEs). Patients may volunteer information concerning AEs. All adverse events will be graded by using the NCI Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v4.0), and logged in the patient Case Report Form. The study centers should report all Serious Adverse Events (SAEs) and all events that trigger patient's study treatment discontinuation to the sponsor via phone, fax or email (or a combination) no more than 24 hours after learning of the event. The sponsor will use the information to manage and coordinate the dose escalation, cohort expansion and patient enrollment. The sponsor will then inform all of the participating clinical sites of the current dose level and the number of patients to be enrolled at that level, or of any patient enrollment suspension via phone, fax or email within 24 hours of learning of the event. The study centers should report all

other adverse events to the sponsor following the guidelines defined in the study protocol. All study drug related AEs that are both serious and unexpected will be reported to the FDA in an expedited manner in accordance with 21 CFR §312.32.

Statistical Plan: For each cohort, all AEs will be tabulated and examined and all safety, pharmacokinetic, biomarker and tumor response data will be evaluated. For estimation of duration of response and progression free survival, the Kaplan-Meier method will be used. *P*-values of ≤0.05 (two-sided) will be considered to indicate statistical significance.

8. STUDY CALENDAR, CLINICAL PROCEDURES & TESTS

8.1 Study calendar

TESTS & PROCEDURES	SCREEN/ BASELINE[1]	INDUCTION									REST	RESPONSE EVALUATION	CONSOLIDATION				RESPONSE EVALUATION	DISEASE ASSESSMENT & FOLLOW-UPS											
Study Month		1									2-3	3	3-9				10	12	15	18	21	24	28	32	36	42	48	54	60
Study Week		*1*				*2*	*3*	*4*			*5-10*	*11*	*12*	*20*	*28*	*36*	*40*												
Study Day		1	2	3	5	8	15	22	23	25	29-70	71-77	78	134	190	246	274-280												
Tolerance Window		*+/- 2 days*									*Any day*	*Any day*	*+/- 7 days*				*Any day*	*+/- 2 weeks*											
Medical history	X																												
Serum pregnancy test[2]	X																												
Complete physical exam (PE)	X																												
Focused PE, ECOG PS, B symptom assessment		X											X	X	X	X													
Vital signs, Weight, Height[3], Cardiac & Lung function monitoring	X	X	X			X	X	X			R	X	X	X	X	X	X												
Concurrent medication	X	X	X			X	X	X			E	X	X	X	X	X	X												
Adverse event assessment[4]	X	X	X			X	X	X				X	X	X	X	X	X												
CBC with Differential[5]	X	X	X			X	X	X			S	X	X	X	X	X	X												
Blood Chemistry with LDH[5]	X	X	X			X	X	X			T	X	X	X	X	X	X												
EKG	X																												
PFT only when clinically indicated	X										P																		
Response assessment[6]												X					X	X		X		X			X		X		X
Contrast CT of NCAP or PET-CT	X										E	X					X	X		X		X			X		X		X
Bone marrow biopsy[7]	X											X					X												
Focused PE, ECOG PS, B symptom & AE	X[17]										R	X					X	X		X		X			X		X		X
Disease and survival follow-up/post therapies[8]											I							X	X	X	X	X	X	X	X	X[16]	X[16]	X[16]	X[16]
Immune cell number, phenotype & function[9,14]	X		X[10]	X	X	X[10]		X[10]	X	X	O		X[11]																
Polymorphism (SNP) testing[14]			X[10]																										
PK, IL-2, IL-4, IL-6, IL-10, IFN-γ, TNF-α[12,14]			X[12]	X							D																		
Immunogenicity tests[13, 14]			X[13]					X[10]				X																	
Recurrent mutation evaluation[15]	X																												
Rituximab		**r1**				**r2**	**r3**	**r4**					**r5**	**r6**	**r7**	**r8**													
Study drug (ALT-803)			**a1**			**a2**	**a3**	**a4**					**a5**	**a6**	**a7**	**a8**													

[1]Screening/baseline evaluations are performed ≤ 14 days prior to start of therapy; baseline CTs or PET-CT are performed ≤ 28 days and baseline bone marrow biopsy performed ≤ 42 days prior to start of therapy. If the patient's condition is deteriorating, ECOG status and laboratory evaluations should be repeated within 48 hours prior to initiation of study treatment infusion. [2]Pregnancy test is for women with childbearing potential only. [3]Vital signs (especially blood pressure), clinical status and laboratory tests should be reviewed before start of therapy. Vital signs will be evaluated at 15, 30, 60 and 120 min then hourly post infusion until discharge or at completion of dose monitoring. Body weight will be collected before infusion on each drug infusion day for all patients. Height only collected at baseline. [4]Patients who have an on-going study drug-related SAE upon study completion or at discontinuation of study will be contacted by the investigator or his/her designee every week until the event is resolved or determined to be irreversible. [5]Safety labs can be drawn within 48 hours of scheduled dose.[6]Disease response and progression assessment will be evaluated using the 2007 IHP criteria for assessment of lymphoma. [7]Only performed to confirm a CR if disease present at baseline. Once confirmed, only repeat if relapse suspected. [8]Information about tumor assessment & other therapies received after completion of study treatment will be collected if available. [9]Fresh blood samples (6 tubes per time point) for immune cell number, phenotype & function testing will be collected. [10]Collect before dosing. [11]Collect before dosing and 24 hours post-infusion. [12]Collect blood samples at Time 0 (before drug infusion), at 30 min (+/- 5 min), 2 hour (+/- 15 min), 6 hour (+/- 60 min) or before discharge on dosing day, 24 hour (+/- 6 hour) from Time 0. IL-2, IL-4, IL-6, IL-10, IFN-γ and TNF-α assays are performed using the same samples and at the same schedule as PK. [13]Use the sample collected before dosing for PK test. [14]Residual samples may be used by Sponsor for research studies of other biomarkers. All attempts will be made to collect research samples but missed samples will not be considered a protocol deviation.[15]Fesh/frozen or FFPE tissue block (or substitute) preferably from biopsy immediately prior to treatment start. An oral sample will be collected to obtain an additional non-tumor cellular sample.[16]+/- 2 months. [17]Complete PE required at screening, not focused PE.

CLINICAL STUDY PROTOCOL

Protocol Number: CA-ALT-803-02-14

Protocol Title: A phase 1/2 study of ALT-803 in patients with relapse/refractory indolent B cell non-Hodgkin lymphoma in conjunction with rituximab

Date of Protocol:

Version# 01	September 4, 2014
Version# 02	March 18, 2015
Version# 03	December 17, 2015

Sponsor Contact:

Altor BioScience CORPORATION

Hing C. Wong, Ph.D.
Altor Bioscience Corporation.
Miramar, Florida 33025
Telephone: 954-443-8600
Safety Data Fax: 954-443-8602

INVESTIGATOR SIGNATURE PAGE

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Altor Bioscience Corporation.
Miramar, Florida 33025
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Safety Data Fax: 954-443-8602

By my signature below, I hereby attest that I have read, and that I understand and will abide by all the conditions, instructions, and restrictions contained in the attached protocol.

Additionally, I will not initiate this study without approval of the appropriate Institutional Review Board (IRB), and I understand that any changes in the protocol must be approved in writing by the sponsor, the IRB, and, in certain cases the FDA, before they can be implemented, except where necessary to eliminate hazards to subjects.

_____ _____

Principal Investigator's Signature Date

_____

Principal Investigator's Name (Print)

Table of Contents

SYNOPSIS

Sponsor:	Altor Bioscience Corporation
Protocol#:	CA-ALT-803-02-14
Study Drug Name:	ALT-803
Study Treatment Active agents:	ALT-803, a "recombinant human super agonist interleukin-15 (IL-15) complex" (AKA, IL-15N72D:IL-15RαSu/IgG1 Fc complex)
Study Type:	Interventional
Study Phase:	1/2
Protocol Title:	A phase 1/2 study of ALT-803 in patients with relapse/refractory indolent B cell non-Hodgkin lymphoma in conjunction with rituximab
Objectives:	To evaluate the safety and tolerability of escalating doses, identify the Maximum Tolerated Dose level (MTD) or Minimum Efficacious Dose (MED) and designate a dose level for Phase 2 study (RP2D) of ALT-803 in combination with standard-of-care rituximab therapy in patients with relapsed or refractory (rel/ref) indolent B cell non-Hodgkin lymphoma (iNHL). To estimate the anti-tumor activity of ALT-803 as measured by response rate, overall survival, progression free survival, time to response, duration of response, time to treatment failure, and time to subsequent treatment in patients with rel/ref iNHL. To evaluate the effect of ALT-803 on the peripheral absolute lymphocyte counts (ALC) and white blood cell (WBC) counts, the number, phenotype and repertoire of peripheral blood T (total and subsets) and NK cells. In addition, a subset of patients will be evaluated for changes in lymph node immune composition. To characterize the immunogenicity and pharmacokinetic profile, including induced serum levels of IL-2, IL-4, IL-6, IL-10, IFN-γ, MCP-1 and TNF-α of ALT-803 in rel/ref iNHL patients. To correlate clinical outcomes with *fcgr3a* polymorphisms and recurrent genomic mutations in rel/ref iNHL patients.
Study Design:	This is a Phase 1/2, open-label, multi-center, competitive enrollment and dose-escalation study of ALT-803 in patients with rel/ref iNHL in conjunction with rituximab. The study includes a dose escalation phase to determine the MTD or MED using a 3+3 dose escalation design and to designate a dose level for the Phase 2 expansion (RP2D) of ALT-803 in combination with rituximab and an expansion phase at the ALT-803 RP2D level using a Simon two-stage design. In Phase 1, seven cohorts will be evaluated. A step-down dose level (level -1) will be provided in the event of encountering DLT in two patients at the planned initial dose level. The study will be conducted in conformity with Good Clinical Practice (GCP).

Treatments: The study treatment plan for each enrolled patient includes one 4-week induction treatment cycle. During induction for cohort 1, 2 and 3, patients will receive up to four weekly doses of ALT-803 and rituximab (375 mg/m^2) by intravenous injection (IV). During induction for cohort 4, 5, 6 and 7, patients will receive four weekly doses of ALT-803 by subcutaneous (SubQ) injection and rituximab (375 mg/m^2) by IV. For the first dose of treatment in all cohorts, patients will receive rituximab on day 1 followed by ALT-803 on day 2 in order to avoid simultaneous dosing of both agents and reduce the potential of infusion-related adverse events. Eligible patients will receive the consolidation treatment. Consolidation consists of treatment with ALT-803 at the same dose level and route of administration used in the induction plus rituximab (375 mg/m^2) every 8 weeks (1 cycle = 8 weeks), for a total of 4 consolidation cycles.

Treated patients will have at least two response evaluation visits. Patients who receive at least two study drug doses during the induction treatment period will be evaluated for disease response during week 11. Patients who have at least stable disease from the first anti-tumor evaluation and who do not experience or have sufficiently recovered from toxicities of the induction treatment cycle and who meet other criteria to continue study treatment will receive up to four consolidation treatment cycles, with a single treatment of ALT-803 plus rituximab, repeated every 8 weeks for a total of 4 additional ALT-803 plus rituximab doses. The ALT-803 dose level and route of administration utilized in the induction cycle will be continued in consolidation, with reassessment for continued tumor response performed upon completion at week 40.

The study treatment and response evaluation visits are illustrated below (refer to study calendar for all study visits):

Treatment Phase	Induction				REST	Response Evaluation	Consolidation				Response Evaluation
Treatment Week	1	2	3	4	5-10	11	12	20	28	36	40**
Treatment Day	1, 2*	8	15	22	29-70	71-77	78	134	190	246	274-280
ALT-803	1	2	3	4	Rest		5	6	7	8	
rituximab	1	2	3	4			5	6	7	8	
Consolidation Cycle							1	2	3	4	
Response Evaluation						X					X

*For the first week, rituximab is administered on day 1, ALT-803 on day 2

**Long term follow-up after 40 weeks includes restaging every 6 months for 2 years, and then every 12 months for 5 years (until progression).

Patients will be assessed for response using the 2007 IHP criteria [1]. Patients will be followed for progression, and at the time of progression there are no restrictions on further therapies.

Enrolled patients will receive the study treatment at qualified cancer treatment centers with adequate diagnostic and treatment facilities to provide appropriate management of therapy and complications. ALT-803 will be administered by intravenous infusion for cohort 1, 2 and 3 into a central or peripheral vein under the supervision of a qualified physician experienced in the use of biologic anti-cancer agents. ALT-803 will be administered by subcutaneous injection for cohort

4, 5, 6 and 7 under the supervision of a qualified physician experienced in the use of biologic anti-cancer agents. Rituximab will be administered as described in the product package insert provided by the manufacturer.

Dose Escalation Phase:

A 3 + 3 design will be used for identifying a tolerable dose of ALT-803 for Phase 2 studies by monitoring patients for DLTs to determine the MTD and for identifying an efficacious dose by monitoring patients' ALC and WBC count to determine the MED during the DLT observation period. The dose escalation phase is concluded when either the MTD or the MED is determined. An ALT-803 dose level (RP2D) will then be designated for Phase 2 study. There are seven cohorts of ALT-803 and a step-down cohort (-1) with a lower dose level of ALT-803 in the event that unexpected toxicity is encountered at the initial dose level.

Below are the planned dose levels and respective route of administration for the study drug during the dose escalation phase of the study.

Cohort	ALT-803 Dose (µg/kg)	Route	Number of patients
-1	0.5	IV	3 to 6
1 (initial)	1	IV	3 to 6
2	3	IV	3 to 6
3	6	IV	3 to 6
4	6	SubQ	3 to 6
5	10	SubQ	3 to 6
6	15	SubQ	3 to 6
7	20	SubQ	3 to 6

Dose limiting toxicity (DLT) is defined as follows: any toxicity that is not clearly unrelated to drug administration that is of Grade 3 and does not resolve to Grade 1 or lower within a week despite the use of medical intervention or that is of Grade 4, with exceptions described in the study protocol.

The DLT Observation Period is defined as the duration of the induction treatment, days 1-28.

Maximum Tolerated Dose level (MTD) is defined as a dose level at which <2 out of 6 patients experienced DLT and that is one level below a dose that was not tolerated or the maximum planned dose level if designated by the study committee.

Minimal Efficacious Dose (MED) is defined as a dose level which produces an ALC ≥25,000/µL sustained for 14 days or a total WBC ≥35,000/µL sustained for 14 days among 2/3 or 4/6 of patients. For safety, a dose level is also defined as "exceeding MED" with the occurrence of ALC ≥50,000/µL or WBC ≥60,000/µL sustained for 14 days. If patients have circulating malignant lymphocytes in the peripheral blood, these lymphoma cells will be excluded from the WBC and ALC calculations for MED.

Expansion Phase

Two expansion arms will be used to investigate indolent NHL patients with different expectations regarding response to single agent rituximab: rituximab-refractory (RR) and rituximab-sensitive (RS). For each arm, a two-stage expansion phase at the MTD or the MED level will be conducted using an optimal Simon's two-stage design. The best objective overall response rate (ORR) is defined as complete response (CR) + partial response (PR) assessed at the week 11 or 40 response assessment, or during the 2 year follow-up period. For RR patients, a lack of efficacy for ORR of 10% will be used, with an ORR $\geq$ 35% constituting a clinically interesting result. For RS patients, a lack of efficacy for ORR of 40% will be used, with a clinically interesting ORR $\geq$ 60%. Each expansion arm will be analyzed independently for preliminary efficacy.

Stopping Rules:

Patient enrollment will be temporarily suspended based on occurrence of any of the following events, and the study committee, including the sponsor, the Data Safety Monitoring Board and principal investigators will meet to discuss how to proceed with future patient enrollment in the study.

During the dose escalation phase of the study,

- If the maximum planned dose level has been reached, but neither the MTD nor MED can be determined.
- If de-escalation occurs and the step-down dose level cannot be designated as the MTD or MED.

Any time during the expansion phase of the study,

- More than 33% of patients experience a possible, probable or definite study drug related DLT.
- Favorable anti-tumor response data collected from enrolled patients.

At any time during the study,
the study committee may meet to discuss how to proceed with the study and may make any or all of the following recommendations for further patient enrollment:

- Downward adjust the study drug dose.
- Adjust the study drug dosing schedule.
- Recommend more effective pre-therapy, intra-therapy and post-therapy side effect mitigation interventions.
- Correct protocol technical errors that caused unnecessary dose omissions or premature treatment discontinuations. After correction of protocol errors, the DSMB may meet to re-evaluate the safety profile of the study treatment and recommend how to proceed with the study, if necessary.

Evaluations:

Patients will be evaluated for clinical toxicities during the treatment. The disease response will be evaluated at weeks 11 and 40 from the start of study treatment, and every 6 months for 2 years thereafter. After this two year period the institutional standards for disease assessment will be followed, with at least annual

disease assessments, for up to 5 years. Prior to and during the treatment period, patients' blood and serum samples will be collected to assess the pharmacokinetic profile and immunogenicity of the study drug, as well as for immunomodulation, and *fcgr3a* polymorphisms. Disease containing biopsies and an oral sample will be used for recurrent lymphoma gene mutation analysis. All patients who receive at least 2 doses of the study drug ALT-803 will be included in the anti-tumor response evaluation.

Population: Patients of 18 years of age and above with relapsed or refractory $CD20^+$ indolent NHL (follicular lymphoma (FL), marginal zone lymphoma (MZL), small lymphocytic lymphoma (SLL), and lymphoplasmacytic lymphoma (LPL)). Rituximab-refractory (RR) patients are defined as those that progress on rituximab therapy or within 6 months of their last dose of rituximab. For RR patients, a biopsy to confirm CD20 expression is required. Patients also need to have adequate cardiac, pulmonary, liver and kidney functions and have an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1 or 2.

Sample Size: A total of up to 42 assessable patients will be accrued to the dose escalation phase of the study (Phase 1). Anticipated enrollment to this phase is 24 patients. For the RS patient arm, a total of 16 patients will be enrolled at the MTD/MED dose in the first stage and 30 patients in the second stage of a 2-stage Phase 2 cohort (total for RS expansion cohort 46). For the RR, a total of 8 patients will be enrolled in the first stage and an additional 14 patients in the second stage of a 2-stage Phase 2 study (total for RR expansion cohort 22). Thus, enrollment of evaluable patients on the Phase 1 portion, and the first stage of both expansion cohorts (including 6 patients of the MTD/MED cohort) is expected to be 42 patients, with the maximum number of 60 patients. Assuming a 5% frequency of non-evaluable patients, the phase 1 and the first stage of both expansion cohorts is estimated at 45 patients.

Primary Endpoints

For Phase 1 only

(1) Determination of the MTD or MED of ALT-803 and designation of the recommended dose level (RP2D) for Phase 2 study of ALT-803 in conjunction with rituximab in patients with rel/ref iNHL.

For Phase 1 & 2

(2) Safety profile of ALT-803 plus rituximab in treated patients.

(3) Overall response rate (CR+PR) of treated patients.

Secondary Endpoints

(1) Evaluate overall survival, progression free survival, time to response, duration of response, time to treatment failure, and time to subsequent treatment.

(2) Evaluation of the effect of ALT-803 on the peripheral ALC and WBC counts, the number, phenotype and repertoire of peripheral blood NK cells and T (total and subsets), and NK cell function. In addition, a subset of patients will be evaluated for changes in lymph node immune composition.

(3) Characterization of the immunogenicity and pharmacokinetic profile, including serum levels of IL-2, IL-4, IL-6, IL-10, IFN-γ, MCP-1 and TNF-α, of ALT-803 in treated patients.

(4) Correlation of *fcgr3a* polymorphism status and recurrent lymphoma mutations with clinical outcomes of the study.

Pharmacokinetics & Biomarkers: Fresh blood samples will be collected to assess immune cell number, phenotype, repertoire and function prior to and during the study treatment. Serum samples will be collected for pharmacokinetics (PK) and immunogenicity of the study drug ALT-803. The same serum samples collected for PK analysis will be used to assess the serum levels of IL-2, IL-4, IL-6, IL-10, IFN-γ, MCP-1 and TNF-α. Non-compartmental and compartmental PK analyses will be conducted. Baseline peripheral blood will be used for *fcgr3a* polymorphism testing, and a baseline tumor sample and oral sample will be used for lymphoma mutation analysis using next-generation sequencing. Lymph node biopsies will be performed to determine the impact of study treatment on the immune cell composition within the tumor microenvironment.

Monitoring Tests: Blood samples for standard chemistry and CBC with differential will be obtained at screening, on each study treatment day, and at response evaluation visits. Blood samples for immunogenicity testing of anti-ALT-803 antibodies will be collected prior to dosing on the first and fourth ALT-803 treatment visit, and at the response evaluation visit during week 11.

Response Assessment: There are at least two response assessments for treated patients: the first assessment during week 11 (following induction) and the second assessment during week 40 (following consolidation) from the start of study treatment. After completion of the induction cycle of study treatment, patients who have received at least 2 doses of ALT-803 will have the first response assessment. After completion of four additional consolidation study treatments patients will have a second response assessment. If patients are unable to continue study therapy for all 4 consolidation cycles due to an adverse event, disease assessments will be performed at the time of going off study. In non-progressing patients, after completion of consolidation, disease assessments will be performed every 6 months for 2 years, and then per institutional guidelines, at least annually, for up to 5 years. If a focused physical examination or patient symptoms raise the concern for progression, a complete response assessment should be performed at that time. Response assessments will be carried out according to the 2007 IHP criteria for response assessment of lymphoma [1]. Baseline evaluations (except for baseline imaging and bone marrow biopsy) should be performed up to 28 days before study treatment start unless otherwise specified in the protocol.

Progression & Survival Assessment: Progression-free survival, overall survival, and duration of response of all treated patients will be assessed at least every three months during years 1 and 2, every 4 months during year 3, and then every 6 months (+/- 2 months) during years 4 and

5 from the start of study treatment, or through the point designated as the end of the study follow up (5 years).

Adverse Events: All patients will be monitored and evaluated for clinical toxicities during the treatment period and queried at each follow-up visit for Adverse Events (AEs). Patients may volunteer information concerning AEs. All adverse events will be graded by using the NCI Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v4.0), and logged in the patient Case Report Form. The study centers should report all Serious Adverse Events (SAEs) and all events that trigger patient's study treatment discontinuation to the sponsor via phone, fax or email (or a combination) no more than 24 hours after learning of the event. The sponsor will use the information to manage and coordinate the dose escalation, cohort expansion and patient enrollment. The sponsor will then inform all of the participating clinical sites of the current dose level and the number of patients to be enrolled at that level, or of any patient enrollment suspension via phone, fax or email within 24 hours of learning of the event. The study centers should report all other adverse events to the sponsor following the guidelines defined in the study protocol. All study drug related AEs that are both serious and unexpected will be reported to the FDA in an expedited manner in accordance with 21 CFR §312.32.

Statistical Plan: For each cohort, all AEs will be tabulated and examined and all safety, pharmacokinetic, biomarker and tumor response data will be evaluated. For estimation of duration of response and progression free survival, the Kaplan-Meier method will be used. *P*-values of ≤ 0.05 (two-sided) will be considered to indicate statistical significance.

8. STUDY CALENDAR, CLINICAL PROCEDURES & TESTS

8.1 Study calendar

TESTS & PROCEDURES	SCREEN/ BASELINE[1]	INDUCTION										REST	RESPONSE EVALUATION	CONSOLIDATION				RESPONSE EVALUATION	DISEASE ASSESSMENT & FOLLOW-UPS											
Study Month		1										2-3	3	3-9				10	12	15	18	21	24	28	32	36	42	48	54	60
Study Week		*1*					*2*	*3*	*4*			*5-10*	*11*	*12*	*20*	*28*	*36*	*40*												
Study Day		1	2	3	4	5	8	15	22	23	25	29-70	71-77	78	134	190	246	274-280											
Tolerance Window		*+/- 2 days*											*+/- 7 days*	*+/- 7 days*				*+/- 7 days*	*+/- 2 weeks*											
Medical history	X											R E S T P E R I O D																		
Serum pregnancy test[2]	X																													
Complete physical exam (PE)	X																													
Focused PE, ECOG PS, B symptom assessment		X												X	X	X	X													
Vital signs, Weight, Height[3], Cardiac & Lung function monitoring	X	X	X				X	X	X				X	X	X	X	X	X													
Concurrent medication	X	X	X				X	X	X				X	X	X	X	X	X													
Adverse event assessment[4]	X	X	X				X	X	X				X	X	X	X	X	X													
CBC with Differential[5]	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X													
Blood Chemistry with LDH[5]	X	X	X				X	X	X				X	X	X	X	X	X													
EKG	X																													
PFT only when clinically indicated	X																													
Response assessment[6]													X					X	X		X		X			X		X		X
Contrast CT of NCAP or PET-CT	X												X					X	X		X		X			X		X		X
Bone marrow biopsy[7]	X												X					X												
Focused PE, ECOG PS, B symptom & AE	X[17]												X					X	X		X		X			X		X		X
Disease and survival follow-up/post therapies[8]																			X	X	X	X	X	X	X	X	X[16]	X[16]	X[16]	X[16]
Lymph node biopsy[18]	X										X																			
Immune cell number, phenotype & function[9,14]	X		X[10]	X	X[19]	X	X[10]	X[10]	X[10]	X	X			X[11]																
Polymorphism (SNP) testing[14]			X[10]																											
PK, IL-2, IL-4, IL-6, IL-10, IFN-γ, MCP-1, TNF-α[12,14]			X[12]	X	X[19]	X																								
Immunogenicity tests[13, 14]			X[13]						X[10]				X																	
Recurrent mutation evaluation[15]	X																													
Rituximab		**r1**					**r2**	**r3**	**r4**					**r5**	**r6**	**r7**	**r8**													
Study drug (ALT-803)			**a1**				**a2**	**a3**	**a4**					**a5**	**a6**	**a7**	**a8**													

[1]Screening/baseline evaluations including baseline CTs or PET-CT are performed ≤ 28 days prior to start of therapy and baseline bone marrow biopsy performed ≤ 42 days prior to start of therapy. If the patient's condition is deteriorating, ECOG status and laboratory evaluations should be repeated within 48 hours prior to initiation of study treatment. [2]Pregnancy test is for women with childbearing potential only. [3]Vital signs (especially blood pressure), clinical status and laboratory tests should be reviewed before start of therapy. Vital signs will be evaluated at 15, 30, 60 and 120 min then hourly post treatment until discharge or at completion of dose monitoring. Body weight will be collected before treatment on each drug treatment day for all patients. Height only collected at baseline. [4]Patients who have an on-going study drug-related SAE upon study completion or at discontinuation of study will be contacted by the investigator or his/her designee every week until the event is resolved or determined to be irreversible. [5]Safety labs can be drawn within 72 hours of scheduled dose.[6]Disease response and progression assessment will be evaluated using the 2007 IHP criteria for assessment of lymphoma.[7]Only performed to confirm a CR if disease present at baseline. Once confirmed, only repeat if relapse suspected. [8]Information about tumor assessment & other therapies received after completion of study treatment will be collected if available. [9]Fresh blood samples (6 tubes per time point) for immune cell number, phenotype & function testing will be collected. [10]Collect before dosing. [11]Collect before dosing and 24 hours post-treatment. [12]Collect blood samples at Time 0 (before treatment), at 30 min (+/- 5 min), 2 hour (+/- 15 min), 6 hour (+/- 60 min) or before discharge on dosing day, 24 hour (+/- 6 hour) from Time 0. IL-2, IL-4, IL-6, IL-10, IFN-γ, MCP-1 and TNF-α assays are performed using the same samples as PK. [13]Use the sample collected before dosing for PK test. [14]Residual samples may be used by Sponsor for research studies of other biomarkers. All attempts will be made to collect research samples but missed samples will not be considered a protocol deviation.[15]Fesh/frozen or FFPE tissue block (or substitute) preferably from biopsy immediately prior to treatment start. An oral sample will be collected to obtain an additional non-tumor cellular sample.[16]+/- 2 months. [17]Complete PE required at screening, not focused PE. [18] LN biopsy is optional, and will be performed on consenting patients that have lymph nodes appropriate for baseline and repeat week 4 radiology-guided biopsies.[19] The Cycle 1 Day 4 visit is optional if patient is not available.

CLINICAL STUDY PROTOCOL

Protocol Number: CA-ALT-803-02-14

Protocol Title: A phase 1/2 study of ALT-803 in patients with relapse/refractory indolent B cell non-Hodgkin lymphoma in conjunction with rituximab

Date of Protocol:

Version# 01	September 4, 2014
Version# 02	March 18, 2015
Version# 03	December 17, 2015
Version# 04	February 6, 2017

Sponsor Contact:

Altor BioScience CORPORATION

Hing C. Wong, Ph.D.
Altor BioScience Corporation.
Miramar, Florida 33025
Telephone: 954-443-8600
Safety Data Fax: 954-443-8602

INVESTIGATOR SIGNATURE PAGE

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By my signature below, I hereby attest that I have read, and that I understand and will abide by all the conditions, instructions, and restrictions contained in the attached protocol.

Additionally, I will not initiate this study without approval of the appropriate Institutional Review Board (IRB), and I understand that any changes in the protocol must be approved in writing by the sponsor, the IRB, and, in certain cases the FDA, before they can be implemented, except where necessary to eliminate hazards to subjects.

_____ _____

Principal Investigator's Signature Date

_____

Principal Investigator's Name (Print)

Table of Contents

SYNOPSIS

Sponsor: Altor BioScience Corporation

Protocol#: CA-ALT-803-02-14

Study Drug Name: ALT-803

Study Treatment Active agents: ALT-803, a "recombinant human super agonist interleukin-15 (IL-15) complex" (AKA, IL-15N72D:IL-15RαSu/IgG1 Fc complex)

Study Type: Interventional

Study Phase: 1/2

Protocol Title: A phase 1/2 study of ALT-803 in patients with relapse/refractory indolent B cell non-Hodgkin lymphoma in conjunction with rituximab

Objectives: To evaluate the safety and tolerability of escalating doses, identify the Maximum Tolerated Dose level (MTD) or Minimum Efficacious Dose (MED) and designate a dose level for Phase 2 study (RP2D) of ALT-803 in combination with standard-of-care rituximab therapy in patients with relapsed or refractory (rel/ref) indolent B cell non-Hodgkin lymphoma (iNHL).

To estimate the anti-tumor activity of ALT-803 as measured by response rate, overall survival, progression free survival, time to response, duration of response, time to treatment failure, and time to subsequent treatment in patients with rel/ref iNHL.

To evaluate the effect of ALT-803 on the peripheral absolute lymphocyte counts (ALC) and white blood cell (WBC) counts, the number, phenotype and repertoire of peripheral blood T (total and subsets) and NK cells. In addition, a subset of patients will be evaluated for changes in lymph node immune composition.

To characterize the immunogenicity and pharmacokinetic profile of ALT-803, and assess the induced serum levels of chemokines and cytokines in rel/ref iNHL patients.

To correlate clinical outcomes with *fcgr3a* polymorphisms and recurrent genomic mutations in rel/ref iNHL patients.

Study Design: This is a Phase 1/2, open-label, multi-center, competitive enrollment and dose-escalation study of ALT-803 in patients with rel/ref iNHL in conjunction with rituximab.

The study includes a dose escalation phase to determine the MTD or MED using a 3+3 dose escalation design and to designate a dose level for the Phase 2 expansion (RP2D) of ALT-803 in combination with rituximab and an expansion phase at the ALT-803 RP2D level using a Simon two-stage design. In Phase 1, seven cohorts will be evaluated. A step-down dose level (level -1) will be provided in the event of encountering DLT in two patients at the planned initial dose level.

The study will be conducted in conformity with Good Clinical Practice (GCP).

Treatments: The study treatment plan for each enrolled patient includes one 4-week induction treatment cycle. During induction for cohort 1, 2 and 3, patients will receive up to four weekly doses of ALT-803 and rituximab (375 mg/m^2) by intravenous injection (IV). During induction for cohort 4, 5, 6 and 7, patients will receive four weekly doses of ALT-803 by subcutaneous (SubQ) injection and rituximab (375 mg/m^2) by IV. For the first dose of treatment in cohorts 1, 2, 3, and 4, patients will receive rituximab on day 1 followed by ALT-803 on day 2. For all other treatment days and for all treatment visits in cohort 5, 6 and 7, patients will receive ALT-803 and rituximab on the same day. Eligible patients will receive the consolidation treatment. Consolidation consists of treatment with ALT-803 at the same dose level and route of administration used in the induction plus rituximab (375 mg/m^2) every 8 weeks (1 cycle = 8 weeks), for a total of 4 consolidation cycles.

Treated patients will have at least two response evaluation visits. Patients who receive at least two study drug doses during the induction treatment period will be evaluated for disease response during week 11. Patients who have at least stable disease from the first anti-tumor evaluation and who do not experience or have sufficiently recovered from toxicities of the induction treatment cycle and who meet other criteria to continue study treatment will receive up to four consolidation treatment cycles, with a single treatment of ALT-803 plus rituximab, repeated every 8 weeks for a total of 4 additional ALT-803 plus rituximab doses. The ALT-803 dose level and route of administration utilized in the induction cycle will be continued in consolidation, with reassessment for continued tumor response performed upon completion at week 40.

The study treatment and response evaluation visits for cohorts 5, 6, and 7 are illustrated below (refer to study calendar for all study visits):

Treatment Phase	Induction				REST	Response Evaluation	Consolidation				Response Evaluation
Treatment Week	1	2	3	4	5-10	11	12	20	28	36	40*
Treatment Day	1	8	15	22	29-70	71-77	78	134	190	246	274-280
ALT-803	1	2	3	4	Rest		5	6	7	8	
rituximab	1	2	3	4			5	6	7	8	
Consolidation Cycle							1	2	3	4	
Response Evaluation						X					X

*Long term follow-up after 40 weeks includes restaging every 6 months for 2 years, and then every 12 months for 5 years (until progression).

Patients will be assessed for response using the 2007 IHP criteria [1] with progression assessment modifications to incorporate Indeterminate Response (IR) criteria[2]. Patients will be followed for progression, and at the time of progression there are no restrictions on further therapies.

Enrolled patients will receive the study treatment at qualified cancer treatment centers with adequate diagnostic and treatment facilities to provide appropriate management of therapy and complications. ALT-803 will be administered by intravenous infusion for cohort 1, 2 and 3 into a central or peripheral vein under the supervision of a qualified physician experienced in the use of biologic anti-cancer agents. ALT-803 will be administered by subcutaneous injection for cohort 4, 5, 6

and 7 under the supervision of a qualified physician experienced in the use of biologic anti-cancer agents. Rituximab will be administered as described in the product package insert provided by the manufacturer.

Dose Escalation Phase:

A 3 + 3 design will be used for identifying a tolerable dose of ALT-803 for Phase 2 studies by monitoring patients for DLTs to determine the MTD and for identifying an efficacious dose by monitoring patients' ALC and WBC count to determine the MED during the DLT observation period. The dose escalation phase is concluded when either the MTD or the MED is determined. An ALT-803 dose level (RP2D) will then be designated for Phase 2 study. There are seven cohorts of ALT-803 and a step-down cohort (-1) with a lower dose level of ALT-803 in the event that unexpected toxicity is encountered at the initial dose level.

Below are the planned dose levels and respective route of administration for the study drug during the dose escalation phase of the study.

Cohort	ALT-803 Dose (µg/kg)	Route	Number of patients
-1	0.5	IV	3 to 6
1 (initial)	1	IV	3 to 6
2	3	IV	3 to 6
3	6	IV	3 to 6
4	6	SubQ	3 to 6
5	10	SubQ	3 to 6
6	15	SubQ	3 to 6
7	20	SubQ	3 to 6

Dose limiting toxicity (DLT) is defined as follows: any toxicity that is not clearly unrelated to drug administration that is of Grade 3 and does not resolve to Grade 1 or lower (or to Baseline or lower, if a patient enters the study with a toxicity that is Grade 2 or higher) within a week despite the use of medical intervention or that is of Grade 4, with exceptions described in the study protocol.

The DLT Observation Period is defined as the duration of the induction treatment, days 1-28.

Maximum Tolerated Dose level (MTD) is defined as a dose level at which <2 out of 6 patients experienced DLT and that is one level below a dose that was not tolerated or the maximum planned dose level if designated by the study committee.

Minimal Efficacious Dose (MED) is defined as a dose level which produces an ALC ≥25,000/µL sustained for 14 days or a total WBC ≥35,000/µL sustained for 14 days among 2/3 or 4/6 of patients. For safety, a dose level is also defined as "exceeding MED" with the occurrence of ALC ≥50,000/µL or WBC ≥60,000/µL sustained for 14 days. If patients have circulating malignant lymphocytes in the peripheral blood,

these lymphoma cells will be excluded from the WBC and ALC calculations for MED.

Expansion Phase

Two expansion arms will be used to investigate indolent NHL patients with different expectations regarding response to single agent anti-CD20 mAB: anti-CD20 mAB-refractory (CD20-R) and anti-CD20 mAB- sensitive (CD20-S). For each arm, a two-stage expansion phase at the MTD or the MED level will be conducted using an optimal Simon's two-stage design. The best objective overall response rate (ORR) is defined as complete response (CR) + partial response (PR) assessed at the week 11 or 40 response assessment, or during the 2 year follow-up period. For CD20-R patients, a lack of efficacy for ORR of 10% will be used, with an ORR $\geq$ 35% constituting a clinically interesting result. For CD20-S patients, a lack of efficacy for ORR of 40% will be used, with a clinically interesting ORR $\geq$ 60%. Each expansion arm will be analyzed independently for preliminary efficacy.

Stopping Rules:

Patient enrollment will be temporarily suspended based on occurrence of any of the following events, and the study committee, including the sponsor, the Data Safety Monitoring Board and principal investigators will meet to discuss how to proceed with future patient enrollment in the study.

During the dose escalation phase of the study,

- If the maximum planned dose level has been reached, but neither the MTD nor MED can be determined.
- If de-escalation occurs and the step-down dose level cannot be designated as the MTD or MED.

Any time during the expansion phase of the study,

- More than 33% of patients experience a possible, probable or definite study drug related DLT.
- Favorable anti-tumor response data collected from enrolled patients.

At any time during the study, the study committee may meet to discuss how to proceed with the study and may make any or all of the following recommendations for further patient enrollment:

- Downward adjust the study drug dose.
- Adjust the study drug dosing schedule.
- Recommend more effective pre-therapy, intra-therapy and post-therapy side effect mitigation interventions.
- Correct protocol technical errors that caused unnecessary dose omissions or premature treatment discontinuations. After correction of protocol errors, the DSMB may meet to re-evaluate the safety profile of the study treatment and recommend how to proceed with the study, if necessary.

Evaluations:

Patients will be evaluated for clinical toxicities during the treatment. The disease response will be evaluated at weeks 11 and 40 from the start of study treatment, and

every 6 months for 2 years thereafter (starting from Month-18). After this two year period the institutional standards for disease assessment will be followed, with at least annual disease assessments, for up to 5 years. Prior to and during the treatment period, patients' blood and serum samples will be collected to assess the pharmacokinetic profile and immunogenicity of the study drug, as well as for immunomodulation, and *fcgr3a* polymorphisms. Disease containing biopsies and an oral sample will be used for recurrent lymphoma gene mutation analysis. All patients who receive at least 2 doses of the study drug ALT-803 will be included in the anti-tumor response evaluation.

Population: Patients of 18 years of age and above with relapsed or refractory $CD20^+$ indolent NHL (follicular lymphoma (FL), marginal zone lymphoma (MZL), small lymphocytic lymphoma (SLL), and lymphoplasmacytic lymphoma (LPL)). Anti-CD20 mAb-refractory (CD20-R) patients are defined as those that progress on Anti-CD20 mAb therapy or within 6 months of their last dose of Anti-CD20 mAb. For CD20-R patients, a biopsy to confirm CD20 expression is required. Patients also need to have adequate cardiac, pulmonary, liver and kidney functions and have an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1 or 2.

Sample Size: A total of up to 42 assessable patients will be accrued to the dose escalation phase of the study (Phase 1). Anticipated enrollment to this phase is 24 patients. For the CD20-S patient arm, a total of 16 patients will be enrolled at the MTD/MED dose in the first stage and 30 patients in the second stage of a 2-stage Phase 2 cohort (total for CD20-S expansion cohort 46). For the CD20-R, a total of 8 patients will be enrolled in the first stage and an additional 14 patients in the second stage of a 2-stage Phase 2 study (total for CD20-R expansion cohort 22). Thus, enrollment of evaluable patients on the Phase 1 portion, and the first stage of both expansion cohorts (including 6 patients of the MTD/MED cohort) is expected to be 42 patients, with the maximum number of 60 patients. Assuming a 5% frequency of non-evaluable patients, the phase 1 and the first stage of both expansion cohorts is estimated at 45 patients.

Primary Endpoints

For Phase 1 only

(1) Determination of the MTD or MED of ALT-803 and designation of the recommended dose level (RP2D) for Phase 2 study of ALT-803 in conjunction with rituximab in patients with rel/ref iNHL.

For Phase 1 & 2

(2) Safety profile of ALT-803 plus rituximab in treated patients.

(3) Overall response rate (CR+PR) of treated patients.

Secondary Endpoints

(1) Evaluate overall survival, progression free survival, time to response, duration of response, time to treatment failure, and time to subsequent treatment.

(2) Evaluation of the effect of ALT-803 on the peripheral ALC and WBC counts, the number, phenotype and repertoire of peripheral blood NK cells and T (total and subsets), and NK cell function. In addition, a subset of patients will be evaluated for changes in lymph node immune composition.

(3) Characterization of the immunogenicity and pharmacokinetic profile of ALT-803, and assess the serum levels of chemokines and cytokines in treated patients.

(4) Correlation of *fcgr3a* polymorphism status and recurrent lymphoma mutations with clinical outcomes of the study.

Pharmacokinetics & Biomarkers: Fresh blood samples will be collected to assess immune cell number, phenotype, repertoire and function prior to and during the study treatment. Serum samples will be collected for pharmacokinetics (PK) and immunogenicity of the study drug ALT-803. The same serum samples collected for PK analysis will be used to assess the serum levels including but not limited to IL-2, IL-4, IL-6, IL-10, IFN-γ, MCP-1 and TNF-α. Non-compartmental and compartmental PK analyses will be conducted. Baseline peripheral blood will be used for *fcgr3a* polymorphism testing, and a baseline tumor sample and oral sample will be used for lymphoma mutation analysis using next-generation sequencing. Lymph node biopsies will be performed to determine the impact of study treatment on the immune cell composition within the tumor microenvironment.

Monitoring Tests: Blood samples for standard chemistry and CBC with differential will be obtained at screening, on each study treatment day, and at response evaluation visits. Blood samples for immunogenicity testing of anti-ALT-803 antibodies will be collected prior to dosing on the first and fourth ALT-803 treatment visit, and at the response evaluation visit during week 11.

Response Assessment: There are at least two response assessments for treated patients: the first assessment during week 11 (following induction) and the second assessment during week 40 (following consolidation) from the start of study treatment. After completion of the induction cycle of study treatment, patients who have received at least 2 doses of ALT-803 will have the first response assessment. After completion of four additional consolidation study treatments patients will have a second response assessment. If patients are unable to continue study therapy for all 4 consolidation cycles due to an adverse event, disease assessments will be performed at the time of going off study. In non-progressing patients, after completion of consolidation, disease assessments will be performed every 6 months for 2 years (starting at Month-18), and then per institutional guidelines, at least annually, for up to 5 years. If a focused physical examination or patient symptoms raise the concern for progression, a complete response assessment should be performed at that time. Response assessments will be carried out according to the 2007 IHP criteria for response assessment of lymphoma [1] with progression assessment modifications to incorporate Indeterminate Response (IR) criteria[2]. Baseline evaluations (except for baseline imaging and bone marrow biopsy) should be performed up to 28 days before study treatment start unless otherwise specified in the protocol.

Progression & Survival Assessment: Progression-free survival, overall survival, and duration of response of all treated patients will be assessed at least every three months during years 1 and 2, every 4

months during year 3, and then every 6 months (+/- 2 months) during years 4 and 5 from the start of study treatment, or through the point designated as the end of the study follow up (5 years).

Adverse Events: All patients will be monitored and evaluated for clinical toxicities during the treatment period and queried at each follow-up visit for Adverse Events (AEs). Patients may volunteer information concerning AEs. All adverse events will be graded by using the NCI Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v4.0), and logged in the patient Case Report Form. The study centers should report all Serious Adverse Events (SAEs) and all events that trigger patient's study treatment discontinuation to the sponsor via phone, fax or email (or a combination) no more than 24 hours after learning of the event. The sponsor will use the information to manage and coordinate the dose escalation, cohort expansion and patient enrollment. The sponsor will then inform all of the participating clinical sites of the current dose level and the number of patients to be enrolled at that level, or of any patient enrollment suspension via phone, fax or email within 24 hours of learning of the event. The study centers should report all other adverse events to the sponsor following the guidelines defined in the study protocol. All study drug related AEs that are both serious and unexpected will be reported to the FDA in an expedited manner in accordance with 21 CFR §312.32.

Statistical Plan: For each cohort, all AEs will be tabulated and examined and all safety, pharmacokinetic, biomarker and tumor response data will be evaluated. For estimation of duration of response and progression free survival, the Kaplan-Meier method will be used. *P*-values of ≤ 0.05 (two-sided) will be considered to indicate statistical significance.

8. STUDY CALENDAR, CLINICAL PROCEDURES & TESTS

8.1 Study calendar

***Note: Refer to the next page for all footers that correlate with this table.**

TESTS & PROCEDURES	SCREEN/ BASELINE[1]	INDUCTION								REST	RESPONSE EVALUATION	CONSOLIDATION						RESPONSE EVALUATION	DISEASE ASSESSMENT & FOLLOW-UPS											
Study Month		1								2-3	3	3-9						10	12	15	18	21	24	28	32	36	42	48	54	60
Study Week		*1*			*2*	*3*	*4*			*5-10*	*11*	*12*			*20*	*28*	*36*	*40*												
Study Day		1	2	5	8	15	22	23	26	29-70	71-77	78	79	82	134	190	246	274-280											
Tolerance Window		*+/- 2 days*									*+/- 7 days*	*+/- 7 days*						*+/- 7 days*	*+/- 2 weeks*										
Medical history	X									R E S T P E R I O D																			
Serum pregnancy test[2]	X																												
Complete physical exam (PE)	X																												
Focused PE, ECOG PS, B symptom assessment		X[24]										X			X	X	X												
Vital signs, Weight, Height[3], Cardiac & Lung function monitoring	X	X			X	X	X				X	X			X	X	X	X											
Concurrent medication	X	X			X	X	X				X	X			X	X	X	X											
Adverse event assessment[4, 22]	X	X			X	X	X				X	X			X	X	X	X											
Injection Site Reaction Subject Diary[25]		X			X	X	X					X			X	X	X												
CBC with Differential[5]	X	X	X	X[19]	X	X	X	X	X[20]		X	X	X	X[21]	X	X	X	X												
Blood Chemistry with LDH[5] , B2M[23]	X	X			X	X	X				X	X			X	X	X	X												
EKG	X																												
PFT only when clinically indicated	X																												
Response assessment[6]											X							X			X		X			X		X		X
Contrast CT of NCAP or PET-CT	X										X							X			X		X			X		X		X
Bone marrow biopsy[7]	X										X							X												
Focused PE, ECOG PS, B symptom & AE	X[17]										X							X			X		X			X		X		X
Disease and survival follow-up/post therapies[8]																			X	X	X	X	X	X	X	X	X[16]	X[16]	X[16]	X[16]
Lymph node biopsy[18,26]	X								X[20]																					
Immune cell number, phenotype & function[9,14,26]		X[10]	X	X[19]	X[10]	X[10]	X[10]	X	X[20]			X[11]	X	X[21]																
Polymorphism (SNP) testing[14,26]		X[10]																												
PK, IL-2, IL-4, IL-6, IL-10, IFN-γ, MCP-1, TNF-α[12,14, 26]		X[12]	X	X[19]	X[10]																									
Immunogenicity tests[13, 14, 26]		X[13]					X[10]				X																			
Recurrent mutation evaluation[15, 26]		X[10]																												
Rituximab		**r1**			**r2**	**r3**	**r4**					**r5**			**r6**	**r7**	**r8**													
Study drug (ALT-803)		**a1**			**a2**	**a3**	**a4**					**a5**			**a6**	**a7**	**a8**													