CLINICAL STUDY PROTOCOL

Protocol Number: CA-ALT-801-01-12

Protocol Title: A Study of ALT-801 in Patients with Bacillus Calmette-Guerin (BCG) Failure Non-Muscle Invasive Bladder Cancer

Date of Protocol:
Version # 01 January 27, 2012

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-801-02-11
Study Drug Name:	Not applicable
Study Treatment Active agents:	ALT-801 (c264scTCR-IL2), recombinant humanized, soluble single-chain TCR-cytokine fusion protein.
Study Type:	Interventional
Study Phase:	Ib/II
Protocol Title:	A Study of ALT-801 in Patients with Bacillus Calmette-Guerin (BCG) Failure Non-Muscle Invasive Bladder Cancer
Objectives:	To confirm the safety and tolerability of a well-tolerated dose level of ALT-801 and to determine the Recommended Dose level (RD) in patients with BCG failure, defined as refractory, relapsing or intolerant, non-muscle invasive bladder cancer who refuse or are not medically fit to undergo a radical cystectomy recommended by the participating urolgist as the standard next therapy per urologic guidelines. To assess anti-tumor activity of study treatment in treated patients as determined by the disease response rate using cystoscopy, bladder biopsy, and urine cytology. To evaluate the duration of response and survival in these patients. To characterize the immunogenicity and pharmacokinetic profile of ALT-801 in treated patients. To assess the relationship between tumor presentation of HLA-A*0201/p53 aa 264-272 complex and the safety, immune response and clinical benefit of study treatment.
Study Design:	This is a Phase Ib/II, open-label, multi-center and competitive enrollment study of ALT-801 in patients with BCG failure, defined as refractory, relapsing or intolerant, non-muscle invasive bladder cancer who refuse or are not medically fit to undergo a radical cystectomy recommended by the participating urolgist as the standard next therapy per urologic guidelines. There are two phases in this study: a dose confirmation phase to confirm a well-tolerated dose in this patient population and designate it as the recommended dose level (RD) for study expansion and a two-stage expansion phase using the recommended (RD). Each enrolled patient will receive up to two courses of study treatment. The study will be conducted in conformity with Good Clinical Practice (GCP).
Treatments:	All enrolled patients will receive up to two courses of study treatment: an induction treatment course and a maintenance treatment course. The induction treatment course consists of two cycles of treatment with a 13-day rest period between cycles. Each cycle consists of four doses of ALT-801,

one each on Day #1, Day #4, Day #8, and Day #15 in the cycle. The rest period may be extended to include an additional week. Patients who have a complete response from the initial response assessment will receive additional 4 consecutive weekly doses of study treatment before the confirmatory response assessment. The schedules of initial and maintenance treatment courses are illustrated below:

Induction treatment Course:

Treatment Cycle	Cycle #1					Cycle #2			
Treatment Week	1		2	3	4	5		6	7
Treatment Day	1	4	8	15		29	32	36	43
Dose#	1	2	3	4	Rest	5	6	7	8
ALT-801	X	X	X	X		X	X	X	X

M

Maintenance Treatment Course:

Treatment Week	9	10	11	12
Treatment Day	57	64	71	78
Dose#	9	10	11	12
ALT-801	X	X	X	X

There are no restrictions on further therapies, such as chemotherapy, radiation therapy or surgery to be used after the protocol-specified therapy. Clearly, additional post-study treatments could be of significant clinical benefit in selected patients, and these patients will be followed for outcome.

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-801 will be administered by intravenous infusion into a central or peripheral vein under the supervision of a qualified physician experienced in the use of anti-cancer agents including aldesleukin (Proleukin®).

Dose Confirmation Phase:

In the dose-confirmation phase of the study, six patients will be enrolled at the dose level starting at 0.08 mg/kg, which is a well-tolerated dose level in a Phase Ib/II study of ALT-801 in combination with cisplatin in patients with metastatic melanoma. Enrolled patients will be monitored during the induction treatment course for any Dose Limiting Toxicity (DLT).

The tolerability of a dose level is defined as < 2 of 6 patients experiencing any DLT at this dose level. If the tolerability of ALT-801 at a dose level cannot be confirmed, an additional six patients will be enrolled to repeat the dose confirmation phase with a step-down dose level that is 0.02 mg/kg lower than the previous tested dose level until a dose level is confirmed as a tolerated dose and is designated as the Recommended Dose (RD) for study expansion. Below are the dose levels of the study drug during the dose confirmation phase of the study.

Cohort	ALT-801 Dose (mg/kg)
-2	0.04
-1	0.06
1 (initial)	0.08

DLT is defined as any toxicity of Grade 3 that does not resolve to Grade 1 or lower within 72 hours and any toxicity of Grade 4 occurring during treatment courses with exceptions and details described in the study protocol. Patients experiencing a DLT should discontinue study treatment. Study treatment discontinuation due to adverse events experienced prior to study drug administration, disease progression or patient's decision to withdraw from study treatment without occurrence of any study treatment discontinuation event will not necessarily define a DLT event. Study treatment discontinuation events are defined in the protocol.

Expansion Phase

The two-stage expansion phase at the Recommended Dose (RD) level will be conducted using a modified Simon two-stage design. Objective response (OR) (defined as complete response (CR) + partial response (PR)) will be evaluated and set thresholds of lack of efficacy (OR rate (ORR) = 20%) and an efficacy level of interest (ORR = 40%) will be selected.

Stopping Rule:

Patient enrollment will be temporarily suspended based on the occurrence of any of the following:

- During the dose confirmation phase of the study, no dose level can be designated as the RD.
- If at any time during the expansion phase of the study, more than 33% of the patients experience a possible, probable or definite drug related DLT.

If the above occur, then the Data Safety Monitoring Board and principal investigators will meet to discuss how to proceed with future patient enrollment in the study.

Evaluations:

Patients will be evaluated for clinical toxicities during the treatment. Patients' blood samples will be collected to assess the pharmacokinetic profile and immunogenicity of the study drug. The anti-tumor activity of study treatment will be evaluated. All patients who receive at least one dose of study drug ALT-801 will be included in the evaluation of anti-tumor activity of study treatment.

Population:

Patients of 18 years of age with BCG failure, defined as refractory, relapsing or intolerant, non-muscle invasive bladder cancer who refuse or are not medically fit to undergo a radical cystectomy recommended by the participating urolgist as the standard next therapy per urologic guidelines.. Patients also need to have adequate cardiac, pulmonary, liver and kidney

functions and to 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 confirmation phase of the study (Phase Ib). Up to an additional 37 assessable patients will be enrolled at the expansion phase (Stage 1 and 2) of the study (Phase II). A total of approximately 43 assessable patients will be enrolled and complete the study in the event that the RD is 0.08 mg/kg. Assuming a 20% ineligible or non-assessable cases, a total of up to 52 patients may be accrued to the study.

Primary Endpoints:

For Phase Ib only: (1) Confirmation of the safey and tolerability of a well-tolerated dose level of ALT-801 and designation of the Recommended Dose level (RD).

For Phase Ib & II: (2) Safety profile of ALT-801.
(3) Disease response rate.

Secondary Endpoints:

(1) Duration of response.
(2) Progression-free survival.
(3) Event free survival.
(4) Overall survival.
(5) Immunogenicity and pharmacokinetics profile of ALT-801.
(6) Relationship between tumor presentation of HLA-A*0201/p53 aa 264-272 complexes and the safety, immune response and clinical benefit of study treatment.

Pharmacokinetics & Biomarkers: Blood samples will be collected to assess typing for HLA-A2, immune cell levels and phenotype, pharmacokinetics and immunogenicity of the study drug ALT-801, and the serum levels of IFN-γ and TNF-α. Tumor samples obtained from surgeries or biopsies performed prior to screening for the study will be collected to test HLA-A*0201/p53 aa 264-272 complex presentation. Blood samples for pharmacokinetic analysis of ALT-801 will be taken on the first day of ALT-801 administration in the initial study treatment cycle. Venous blood will be obtained at Time 0 (before the start of infusion), at 30 minutes (15 minutes after completion of infusion), and 1, 3 and 6 hours from Time 0 for the assessment of ALT-801 serum concentration. Non-compartmental and compartmental analyses will be conducted. In addition, the same blood samples collected for PK analysis will be used to assess the serum levels of IFN-γ and TNF-α. Fresh blood samples for HLA-A2 typing, immune cell levels and phenotype testing will be collected before the start of first and fourth dose of study drug infusion in each treatment cycle during the induction treatment course. HLA-A2 typing will be performed only once.

Monitoring Tests: Urine samples for urinalysis, blood samples for standard chemistry, and CBC with differential will be obtained at screening, on each study drug infusion day and follow-up visits. Blood samples for immunogenicity

testing, which include assays for anti-ALT-801 and IL-2 neutralizing antibodies, will be collected prior to dosing on the first ALT-801 infusion day and at Week 8 from the initial dose of study treatment.

Response Assessment: There are two response assessments for treated patients: the initial assessment at week 8 and the confirmatory assessment at week 13 from the start of study treatment. After the induction treatment period, patients who have received at least one dose of study drug will have the initial response assessment. After the maintenance treatment period, patients who have received at least one dose of study drug during this treatment period will have the confirmatory response assessment. Cystoscopy, bladder biopsy and urine cytology will be performed to evaluate the response. If surgeries or biopsies are performed after patients receive and respond to study treatment, tumor or tissue samples from these procedures will be collected to assess histopathological and immuno-cellular responses to study treatment.

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

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 confirmation, 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 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]	INITIAL COURSE									INITIAL ASSESSMENT	MAINTENANCE COURSE				CONFIRMATORY ASSESSMENT	FOLLOW-UPS								
		CYCLE #1					CYCLE #2																	
Study Month		1					2					3				4	6	9	12	15	18	21	24	30	36
Study Week		1		2	3	4	5		6	7	8	9	10	11	12	13									
Day of Week		M	W	M	M		M	W	M	M		M	M	M	M										
Study Day		*1*	*3*	*8*	*15*	*16-28*	*29*	*31*	*36*	*43*		*57*	*64*	*71*	*78*										
Medical history/prior therapies	X																							
Serum pregnancy test[2]	X																							
Complete physical exam	X	X					X				X	X				X								
Vital signs, weight, Height[3]	X	X	X	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	X	X	X									
Adverse event assessment[4]	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X									
CBC with Differential	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X									
Blood Chemistry	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X									
EKG	X[5]	X[5]					X					X													
Urinalysis	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X									
Urinary symptoms	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X									
Cystoscopy & bladder biopsies	X										X					X								
Urine cytology	X										X					X								
Response assessment[6]											X					X								
Disease & survival follow-up[7]																	X	X	X	X	X	X	X	X	X
Immune cell levels & phenotype[8,12]		X[8]			X[8]		X[8]			X[8]		X[8]			X[8]										
HLA A2 Blood Typing[9] & p53 tumor typing		X																							
PK, IFNγ, TNFα[10,12]		X[10]																							
Immunogenicity tests[11, 12]		X[11]									X														
Study drug (ALT-801)		**a1**	**a2**	**a3**	**a4**		**a5**	**a6**	**a7**	**a8**		**a9**	**a10**	**a11**	**a12**										

[1]Screening/baseline evaluations are performed ≤ 14 days prior to start of therapy. If the patient's condition is deteriorating, 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 every 2 hours after drug infusion and before discharge, and body weight obtained before infusion on each drug infusion day. [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]If a previous EKG was performed within 14 days before start of study treatment, the EKG is not required. [6]Response will be evaluated by cystoscopy, bladder biopsies and urine cytology. [7]Information about tumor assessment & other therapies received after completion of study treatment will be collected if available. [8]Fresh blood samples for HLA A2 blood typing, immune cell levels & phenotype testing will be collected before dosing. [9]Use the same blood sample collected for immune cell levels & phenotype.[10]Collect blood samples at Time 0 (before drug infusion), at 30 min (15 min after completion of infusion, +/- 5 min), 1 hour (+/- 10 min), 3 hour (+/- 30 min), 6 hour (+/- 60 min) from Time 0. IFNγ and TNFα assays are performed using the same samples and at the same schedule as PK. [11]Use the sample collected before dosing for PK test. [12]Residual samples may be used by Sponsor for research studies of other biomarkers.

APPROVAL PAGE

PROTOCOL TITLE:	A Study of ALT-801 in Patients with Bacillus Calmette-Guerin (BCG) Failure Non-Muscle Invasive Bladder Cancer
INVESTIGATIONAL DRUG:	ALT-801; c264scTCR-IL2 Fusion Protein
CLINICAL PROTOCOL NUMBER:	CA-ALT-801-01-12
Version# 01	January 27, 2012
SPONSOR:	Altor Bioscience Corporation 2810 North Commerce Parkway Miramar, FL 33025-3958

Hing C. Wong, Ph.D.
Chief Clinical Officer

Jan. 30, 2012
Date

Jeff Weber, M.D., Ph.D.
Consulting Medical Director

Date

Peter Rhode, Ph.D.
Vice President, Research and Development

Jan 30, 2012
Date

Bee Y. Huang, M.S.
Director, Clinical Development

Jan 30, 2012
Date

CLINICAL STUDY PROTOCOL

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Date of Protocol:
Version# 01 January 27, 2012
Version# 02 April 5, 2012

Sponsor Contact:

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INVESTIGATOR SIGNATURE PAGE

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_____ _____
Principal Investigator's Signature Date

_____
Principal Investigator's Name (Print)

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SYNOPSIS

Sponsor:	Altor Bioscience Corporation
Protocol#:	CA-ALT-801-02-11
Study Drug Name:	Not applicable
Study Treatment Active agents:	ALT-801 (c264scTCR-IL2), recombinant humanized, soluble single-chain TCR-cytokine fusion protein.
Study Type:	Interventional
Study Phase:	Ib/II
Protocol Title:	A Study of ALT-801 in Patients with Bacillus Calmette-Guerin (BCG) Failure Non-Muscle Invasive Bladder Cancer
Objectives:	To confirm the safety and tolerability of a well-tolerated dose level of ALT-801 and to determine the Recommended Dose level (RD) in patients with BCG failure, defined as refractory, relapsing or intolerant, non-muscle invasive bladder cancer who refuse or are not medically fit to undergo a radical cystectomy recommended by the participating urolgist as the standard next therapy per urologic guidelines. To assess anti-tumor activity of study treatment in treated patients as determined by the disease response rate using cystoscopy, bladder biopsy, and urine cytology. To evaluate the duration of response and survival in these patients. To characterize the immunogenicity and pharmacokinetic profile of ALT-801 in treated patients. To assess the relationship between tumor presentation of HLA-A*0201/p53 aa 264-272 complex and the safety, immune response and clinical benefit of study treatment.
Study Design:	This is a Phase Ib/II, open-label, multi-center and competitive enrollment study of ALT-801 in patients with BCG failure, defined as refractory, relapsing or intolerant, non-muscle invasive bladder cancer who refuse or are not medically fit to undergo a radical cystectomy recommended by the participating urolgist as the standard next therapy per urologic guidelines. There are two phases in this study: a dose confirmation phase to confirm a well-tolerated dose in this patient population and designate it as the recommended dose level (RD) for study expansion and a two-stage expansion phase using the recommended (RD). Each enrolled patient will receive up to two courses of study treatment. The study will be conducted in conformity with Good Clinical Practice (GCP).
Treatments:	All enrolled patients will receive up to two courses of study treatment: an induction treatment course and a maintenance treatment course. The induction treatment course consists of two cycles of treatment with a 13-day rest period between cycles. Each cycle consists of four doses of ALT-801,

one each on Day #1, Day #4, Day #8, and Day #15 in the cycle. The rest period may be extended to include an additional week. Patients who have a complete response from the initial response assessment will receive additional 4 consecutive weekly doses of study treatment before the confirmatory response assessment. The schedules of initial and maintenance treatment courses are illustrated below:

Induction treatment Course:

Treatment Cycle	Cycle #1					Cycle #2			
Treatment Week	1		2	3	4	5		6	7
Treatment Day	1	4	8	15		29	32	36	43
Dose#	1	2	3	4	Rest	5	6	7	8
ALT-801	X	X	X	X		X	X	X	X

M

Maintenance Treatment Course:

Treatment Week	9	10	11	12
Treatment Day	57	64	71	78
Dose#	9	10	11	12
ALT-801	X	X	X	X

There are no restrictions on further therapies, such as chemotherapy, radiation therapy or surgery to be used after the protocol-specified therapy. Clearly, additional post-study treatments could be of significant clinical benefit in selected patients, and these patients will be followed for outcome.

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-801 will be administered by intravenous infusion into a central or peripheral vein under the supervision of a qualified physician experienced in the use of anti-cancer agents including aldesleukin (Proleukin®).

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Cohort	ALT-801 Dose (mg/kg)
-2	0.04
-1	0.06
1 (initial)	0.08

DLT is defined as any toxicity of Grade 3 that does not resolve to Grade 1 or lower within 72 hours and any toxicity of Grade 4 occurring during treatment courses with exceptions and details described in the study protocol. Patients experiencing a DLT should discontinue study treatment. Study treatment discontinuation due to adverse events experienced prior to study drug administration, disease progression or patient's decision to withdraw from study treatment without occurrence of any study treatment discontinuation event will not necessarily define a DLT event. Study treatment discontinuation events are defined in the protocol.

Expansion Phase

The two-stage expansion phase at the Recommended Dose (RD) level will be conducted using a modified Simon two-stage design. Objective response (OR) (defined as complete response (CR) + partial response (PR)) will be evaluated and set thresholds of lack of efficacy (OR rate (ORR) = 20%) and an efficacy level of interest (ORR = 40%) will be selected.

Stopping Rule:

Patient enrollment will be temporarily suspended based on the occurrence of any of the following:

- During the dose confirmation phase of the study, no dose level can be designated as the RD.
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If the above occur, then the Data Safety Monitoring Board and principal investigators will meet to discuss how to proceed with future patient enrollment in the study.

Evaluations:

Patients will be evaluated for clinical toxicities during the treatment. Patients' blood samples will be collected to assess the pharmacokinetic profile and immunogenicity of the study drug. The anti-tumor activity of study treatment will be evaluated. All patients who receive at least one dose of study drug ALT-801 will be included in the evaluation of anti-tumor activity of study treatment.

Population:

Patients of 18 years of age with BCG failure, defined as refractory, relapsing or intolerant, non-muscle invasive bladder cancer who refuse or are not medically fit to undergo a radical cystectomy recommended by the participating urolgist as the standard next therapy per urologic guidelines.. Patients also need to have adequate cardiac, pulmonary, liver and kidney

functions and to 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 confirmation phase of the study (Phase Ib). Up to an additional 37 assessable patients will be enrolled at the expansion phase (Stage 1 and 2) of the study (Phase II). A total of approximately 43 assessable patients will be enrolled and complete the study in the event that the RD is 0.08 mg/kg. Assuming a 20% ineligible or non-assessable cases, a total of up to 52 patients may be accrued to the study.

Primary Endpoints:

For Phase Ib only: (1) Confirmation of the safey and tolerability of a well-tolerated dose level of ALT-801 and designation of the Recommended Dose level (RD).

For Phase Ib & II: (2) Safety profile of ALT-801.
(3) Disease response rate.

Secondary Endpoints:

(1) Duration of response.
(2) Progression-free survival.
(3) Event free survival.
(4) Overall survival.
(5) Immunogenicity and pharmacokinetics profile of ALT-801.
(6) Relationship between tumor presentation of HLA-A*0201/p53 aa 264-272 complexes and the safety, immune response and clinical benefit of study treatment.

Pharmacokinetics & Biomarkers: Blood samples will be collected to assess typing for HLA-A2, immune cell levels and phenotype, pharmacokinetics and immunogenicity of the study drug ALT-801, and the serum levels of IFN-γ and TNF-α. Tumor samples obtained from surgeries or biopsies performed prior to screening for the study will be collected to test HLA-A*0201/p53 aa 264-272 complex presentation. Blood samples for pharmacokinetic analysis of ALT-801 will be taken on the first day of ALT-801 administration in the initial study treatment cycle. Venous blood will be obtained at Time 0 (before the start of infusion), at 30 minutes (15 minutes after completion of infusion), and 1, 3 and 6 hours from Time 0 for the assessment of ALT-801 serum concentration. Non-compartmental and compartmental analyses will be conducted. In addition, the same blood samples collected for PK analysis will be used to assess the serum levels of IFN-γ and TNF-α. Fresh blood samples for HLA-A2 typing, immune cell levels and phenotype testing will be collected before the start of first and fourth dose of study drug infusion in each treatment cycle during the induction treatment course. HLA-A2 typing will be performed only once.

Monitoring Tests: Urine samples for urinalysis, blood samples for standard chemistry, and CBC with differential will be obtained at screening, on each study drug infusion day and follow-up visits. Blood samples for immunogenicity

testing, which include assays for anti-ALT-801 and IL-2 neutralizing antibodies, will be collected prior to dosing on the first ALT-801 infusion day and at Week 8 from the initial dose of study treatment.

Response Assessment: There are two response assessments for treated patients: the initial assessment at week 8 and the confirmatory assessment at week 13 from the start of study treatment. After the induction treatment period, patients who have received at least one dose of study drug will have the initial response assessment. After the maintenance treatment period, patients who have received at least one dose of study drug during this treatment period will have the confirmatory response assessment. Cystoscopy, bladder biopsy and urine cytology will be performed to evaluate the response. If surgeries or biopsies are performed after patients receive and respond to study treatment, tumor or tissue samples from these procedures will be collected to assess histopathological and immuno-cellular responses to study treatment.

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

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 confirmation, 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 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]	INITIAL COURSE									INITIAL ASSESSMENT	MAINTENANCE COURSE				CONFIRMATORY ASSESSMENT	FOLLOW-UPS								
		CYCLE #1					CYCLE #2																	
Study Month		1					2					3				4	6	9	12	15	18	21	24	30	36
Study Week		1		2	3	4	5		6	7	8	9	10	11	12	13									
Day of Week		M	W	M	M		M	W	M	M		M	M	M	M										
Study Day		*1*	*4*	*8*	*15*	*16-28*	*29*	*32*	*36*	*43*		*57*	*64*	*71*	*78*										
Medical history/prior therapies	X																								
Serum pregnancy test[2]	X																								
Complete physical exam	X	X					X				X	X				X									
Vital signs, weight, Height[3]	X	X	X	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	X	X	X									
Adverse event assessment[4]	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X									
CBC with Differential	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X									
Blood Chemistry	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X									
EKG	X[5]	X[5]					X					X													
Urinalysis	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X									
Urinary symptoms	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X									
Cystoscopy[13] & bladder biopsies[13]	X										X					X								
Urine cytology	X										X					X								
Response assessment[6]											X					X								
Disease & survival follow-up[7]																	X	X	X	X	X	X	X	X	X
Immune cell levels & phenotype[8,12]		X[8]			X[8]		X[8]			X[8]		X[8]			X[8]										
HLA A2 Blood Typing[9] & p53 tumor typing		X																							
PK, IFNγ, TNFα[10,12]		X[10]																							
Immunogenicity tests[11, 12]		X[11]									X														
Study drug (ALT-801)		**a1**	**a2**	**a3**	**a4**		**a5**	**a6**	**a7**	**a8**		**a9**	**a10**	**a11**	**a12**										

[1]Screening/baseline evaluations are performed ≤ 14 days prior to start of therapy except cystoscopy and biopsies. If the patient's condition is deteriorating, 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 every 2 hours after drug infusion and before discharge, and body weight obtained before infusion on each drug infusion day. [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]If a previous EKG was performed within 14 days before start of study treatment, the EKG is not required. [6]Response will be evaluated by cystoscopy, bladder biopsies and urine cytology. [7]Information about tumor assessment & other therapies received after completion of study treatment will be collected if available. [8]Fresh blood samples for HLA A2 blood typing, immune cell levels & phenotype testing will be collected before dosing. [9] Use the same blood sample collected for immune cell levels & phenotype.[10]Collect blood samples at Time 0 (before drug infusion), at 30 min (15 min after completion of infusion, +/- 5 min), 1 hour (+/- 10 min), 3 hour (+/- 30 min), 6 hour (+/- 60 min) from Time 0. IFNγ and TNFα assays are performed using the same samples and at the same schedule as PK. [11]Use the sample collected before dosing for PK test. [12]Residual samples may be used by Sponsor for research studies of other biomarkers.[13]Screening cystoscopy is performed within 4 weeks prior to start of therapy, screening biopsies are performed within 3 months prior to start of therapy.

APPROVAL PAGE

PROTOCOL TITLE:	A Study of ALT-801 in Patients with Bacillus Calmette-Guerin (BCG) Failure Non-Muscle Invasive Bladder Cancer
INVESTIGATIONAL DRUG:	ALT-801; c264scTCR-IL2 Fusion Protein
CLINICAL PROTOCOL NUMBER:	CA-ALT-801-01-12
Version# 01 Version# 02	January 27, 2012 April 5, 2012
SPONSOR:	Altor Bioscience Corporation 2810 North Commerce Parkway Miramar, FL 33025-3958

Hing C. Wong, Ph.D.
Chief Clinical Officer

April 9, 2012
Date

Jeff Weber, M.D., Ph.D.
Consulting Medical Director

April 9, 2012
Date

Peter Rhode, Ph.D.
Vice President, Research and Development

April 9, 2012
Date

Bee Y. Huang, M.S.
Director, Clinical Development

April 9, 2012
Date

CLINICAL STUDY PROTOCOL

Protocol Number: CA-ALT-801-01-12

Protocol Title: A Study of ALT-801 in Patients with Bacillus Calmette-Guerin (BCG) Failure Non-Muscle Invasive Bladder Cancer

Date of Protocol:

Version# 01	January 27, 2012
Version# 02	April 5, 2012
Version# 03	October 24, 2012

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

Protocol Number: CA-ALT-801-01-12

Protocol Title: A Study of ALT-801 in Patients with Bacillus Calmette-Guerin (BCG) Failure Non-Muscle Invasive Bladder Cancer

Date of Protocol:

Version# 01	January 27, 2012
Version# 02	April 5, 2012
Version# 03	October 24, 2012

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

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-801-02-11
Study Drug Name:	Not applicable
Study Treatment Active agents:	ALT-801 (c264scTCR-IL2), recombinant humanized, soluble single-chain TCR-cytokine fusion protein.
Study Type:	Interventional
Study Phase:	Ib/II
Protocol Title:	A Study of ALT-801 in Patients with Bacillus Calmette-Guerin (BCG) Failure Non-Muscle Invasive Bladder Cancer
Objectives:	To confirm the safety and tolerability of a well-tolerated dose level of ALT-801 combined with gemcitabine and to determine the Recommended Dose level (RD) in patients who are BCG failure (defined as refractory, relapsing or intolerant), non-muscle invasive bladder cancer and refuse or are not medically fit to undergo a radical cystectomy recommended by the participating urologist as the standard next therapy per urologic guidelines. To assess anti-tumor activity of study treatment in treated patients as determined by the disease response rate using cystoscopy, bladder biopsy, and urine cytology. To evaluate the duration of response and survival in these patients. To characterize the immunogenicity of ALT-801 in treated patients. To assess the relationship between tumor presentation of HLA-A*0201/p53 aa 264-272 complex and the safety, immune response and clinical benefit of study treatment.
Study Design:	This is a Phase Ib/II, open-label, multi-center and competitive enrollment study of ALT-801 combined with gemcitabine in patients with BCG failure, defined as refractory, relapsing or intolerant, non-muscle invasive bladder cancer who refuse or are not medically fit to undergo a radical cystectomy recommended by the participating urologist as the standard next therapy per urologic guidelines. There are two phases in this study: a dose confirmation phase to confirm a well-tolerated dose in this patient population and designate it as the recommended dose level (RD) for study expansion and a two-stage expansion phase using the recommended (RD). Each enrolled patient will receive up to two courses of study treatment. The study will be conducted in conformity with Good Clinical Practice (GCP).
Treatments:	All enrolled patients will receive up to two courses of study treatment: an induction treatment course consisting of two study treatment cycles, with a 13-day rest period between cycles, and a maintenance treatment course consisting of one study treatment cycle. The rest period may be extended to

include an additional week. . . Each cycle consists of four doses of ALT-801, one each on Day #3, Day #5, Day #8, and Day #15 and two doses of gemcitabine, one each on Day #1 and Day #8. Patients who have a complete response from the initial response assessment by bladder biopsy will receive the maintenance treatment and then have the confirmatory response assessment. The schedules of induction and maintenance treatment courses are illustrated below:

Induction treatment Course:

Treatment Cycle	Cycle #1						Cycle #2				
Treatment Week	1			2	3	4	5			6	7
Treatment Day	1	3	5	8	15		29	31	33	36	43
Gemcitabine	X			X		Rest	X			X	
ALT-801		X	X	X	X			X	X	X	X

M

Maintenance Treatment Course:

Treatment Week	9			10	11
Treatment Day	1	3	5	8	15
Gemcitabine	X			X	
ALT-801		X	X	X	X

There are no restrictions on further therapies, such as chemotherapy, radiation therapy or surgery to be used after the protocol-specified therapy. Clearly, additional post-study treatments could be of significant clinical benefit in selected patients, and these patients will be followed for outcome.

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. Gemcitabine and ALT-801 will be administered by intravenous infusion into a central or peripheral vein under the supervision of a qualified physician experienced in the use of anti-cancer agents including aldesleukin (Proleukin®).

Dose Confirmation Phase:

In the dose-confirmation phase of the study, six patients will be enrolled to receive the study treatment with gemcitabine, at 1000 mg/m^2/dose, and ALT-801, at the dose level starting at 0.08 mg/kg, which is a well-tolerated dose level in a Phase Ib/II study of ALT-801 in combination with cisplatin in patients with metastatic melanoma. Enrolled patients will be monitored during the induction treatment course for any Dose Limiting Toxicity (DLT).

The tolerability of a dose level is defined as <2 of 6 patients experiencing any DLT at this dose level. If the tolerability of ALT-801 at a dose level cannot be confirmed, an additional six patients will be enrolled to repeat the dose confirmation phase with a step-down dose level that is 0.02 mg/kg lower than the previous tested dose level until a dose level is confirmed as a tolerated dose and is designated as the Recommended Dose (RD) for study

expansion. Below are the dose levels of the study treatment during the dose confirmation phase of the study.

Cohort	ALT-801 Dose (mg/kg)	Gemcitabine (mg/m^2/dose)
-2	0.04	1,000
-1	0.06	1,000
1 (initial)	0.08	1,000

DLT is defined as any toxicity of Grade 3 that does not resolve to Grade 1 or lower within 7 days and any toxicity of Grade 4 occurring during treatment courses with exceptions and details described in the study protocol. Patients experiencing a DLT should discontinue study treatment. Study treatment discontinuation due to adverse events experienced prior to study drug administration, disease progression or investigator's and/or patient's decision to withdraw from study treatment without occurrence of any study treatment discontinuation adverse event will not necessarily define a DLT event. Study treatment discontinuation events are defined in the protocol.

Expansion Phase

The two-stage expansion phase will be conducted with ALT-801, at the RD level confirmed in the dose confirmation stage, and gemcitabine, at the same level as in the dose confirmation stage, using a modified Simon two-stage design. Objective response (OR) (defined as complete response (CR) + partial response (PR)) will be evaluated and set thresholds of lack of efficacy (OR rate (ORR) = 20%) and an efficacy level of interest (ORR = 40%) will be selected.

Stopping Rule:

Patient enrollment will be temporarily suspended based on the occurrence of any of the following:

- During the dose confirmation phase of the study, no dose level can be designated as the RD.
- If at any time during the expansion phase of the study, more than 33% of the patients experience a possible, probable or definite drug related DLT.

If the above occur, then the Data Safety Monitoring Board and principal investigators will meet to discuss how to proceed with future patient enrollment in the study.

Evaluations:

Patients will be evaluated for clinical toxicities during the treatment. Patients' blood samples will be collected to assess the immunogenicity of the study drug. The anti-tumor activity of study treatment will be evaluated. All patients who receive at least one dose of study drug ALT-801 will be included in the evaluation of anti-tumor activity of study treatment.

Population:

Patients of 18 years of age who have BCG failure (defined as refractory, relapsing or intolerant), non-muscle invasive bladder cancer and refuse or

are not medically fit to undergo a radical cystectomy recommended by the participating urologist as the standard next therapy per urologic guidelines. Patients also need to have adequate cardiac, pulmonary, liver and kidney functions and to 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 confirmation phase of the study (Phase Ib). Up to an additional 37 assessable patients will be enrolled at the expansion phase (Stage 1 and 2) of the study (Phase II). A total of approximately 43 assessable patients will be enrolled and complete the study in the event that the RD is 0.08 mg/kg. Assuming a 20% ineligible or non-assessable cases, a total of up to 52 patients may be accrued to the study.

Primary Endpoints:

For Phase Ib only: (1) Confirmation of the safety and tolerability of a well-tolerated dose level of ALT-801 combined with gemcitabine and designation of the Recommended Dose level (RD).

For Phase Ib & II: (2) Safety profile of ALT-801 combined with gemcitabine.
(3) Disease response rate.

Secondary Endpoints:

(1) Duration of response.
(2) Progression-free survival.
(3) Event free survival.
(4) Overall survival.
(5) Immunogenicity of ALT-801.
(6) Relationship between tumor presentation of HLA-A*0201/p53 aa 264-272 complexes and the safety, immune response and clinical benefit of study treatment.

Biomarkers: Blood samples will be collected to assess typing for HLA-A2 and immune cell levels and phenotype. Serum samples will be collected for testing immunogenicity of the study drug ALT-801and the serum level of IFN-γ. Tumor samples obtained from surgeries or biopsies performed prior to screening for the study will be collected to test HLA-A*0201/p53 aa 264-272 complex presentation. . . .

Monitoring Tests: Urine samples for urinalysis, blood samples for standard chemistry, and CBC with differential will be obtained at screening, on each study drug infusion day and follow-up visits. Blood samples for immunogenicity testing, which include assays for anti-ALT-801 and IL-2 neutralizing antibodies, will be collected prior to dosing on the first ALT-801 infusion day and at Week 8 from the initial dose of study treatment.

Response Assessment: There are two response assessments for treated patients: the initial assessment at week 8 and the confirmatory assessment at week 12 from the start of study treatment. After the induction treatment period, patients who have received at least one dose of study drug will have the initial response

assessment. After the maintenance treatment period, patients who have received at least one dose of study drug during this treatment period will have the confirmatory response assessment. Cystoscopy, bladder biopsy and urine cytology will be performed to evaluate the response. If surgeries or biopsies are performed after patients receive and respond to study treatment, tumor or tissue samples from these procedures will be collected to assess histopathological and immuno-cellular responses to study treatment.

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

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 confirmation, 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 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]	INITIAL COURSE											INITIAL ASSESSMENT	MAINTENANCE COURSE					CONFIRMATORY ASSESSMENT	FOLLOW-UPS								
		CYCLE #1						CYCLE #2																			
Study Month		1						2						3					3	6	9	12	15	18	21	24	30	36
Study Week		1			2	3	4	5		6	7		8	9			10	11	12									
Day of Week		M	W	F	M	M		M	W	F	M	M		M	W	F	M	M										
Study Day		*1*	*3*	*5*	*8*	*15*	*16-28*	*29*	*31*	*33*	*36*	*43*		*57*	*59*	*61*	*64*	*71*										
Medical history/prior therapies	X						Rest Period																				
Serum pregnancy test[2]	X																										
Complete physical exam	X	X						X					X	X					X								
Vital signs, weight, Height[3]	X	X	X	X	X	X		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	X	X	X	X	X	X								
Adverse event assessment[4]	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X								
CBC with Differential	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X								
Blood Chemistry	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X								
EKG	X[5]	X[5]						X						X													
Urinalysis	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X								
Urinary symptoms	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X								
Cystoscopy[13] & bladder biopsies[13]	X												X						X								
Urine cytology	X												X						X								
Response assessment[6]													X						X								
Disease & survival follow-up[7]																				X	X	X	X	X	X	X	X	X
Immune cell levels & phenotype[8,12]		X[8]	X[8]		X[8]			X[8]																			
HLA A2 Blood Typing[9] & p53 tumor typing		X																									
IFN-γ[10,12]			X[10]																								
Immunogenicity tests[11, 12]			X[11]										X														
Gemcitabine		**g1**			**g2**			**g3**			**g4**			**g5**			**g6**										
Study drug (ALT-801)			**a1**	**a2**	**a3**	**a4**			**a5**	**a6**	**a7**	**a8**			**a9**	**a10**	**a11**	**a12**									

[1]Screening/baseline evaluations are performed ≤14 days prior to start of therapy except TTE, cystoscopy and biopsies. If TTE is required for cardiac assessments, it can be performed ≤28 days. If the patient's condition is deteriorating, 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 every 2 hours after drug infusion and before discharge, and body weight obtained before infusion on each drug infusion day. [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]If a previous EKG was performed within 14 days before start of study treatment, the EKG is not required. [6]Response will be evaluated by cystoscopy, bladder biopsies and urine cytology. [7]Information about tumor assessment & other therapies received after completion of study treatment will be collected if available. [8]Fresh blood samples for HLA A2 blood typing, immune cell levels & phenotype testing will be collected before any dosing starts. [9] Use the same blood sample collected for immune cell levels & phenotype.[10]Collect blood samples at Time 0 (before dosing) and at 6 hour (+/- 60 min) from Time 0. . . [11]Use the same sample collected for IFN-γ assay. [12]Residual samples may be used by Sponsor for research studies of other biomarkers.[13]Screening cystoscopy is performed within 4 weeks prior to start of therapy, screening biopsies are performed within 3 months prior to start of therapy.

APPROVAL PAGE

PROTOCOL TITLE:	A Study of ALT-801 in Patients with Bacillus Calmette-Guerin (BCG) Failure Non-Muscle Invasive Bladder Cancer
INVESTIGATIONAL DRUG:	ALT-801; c264scTCR-IL2 Fusion Protein
CLINICAL PROTOCOL NUMBER:	CA-ALT-801-01-12
Version# 01	January 27, 2012
Version# 02	April 5, 2012
Version# 03	October 24, 2012
SPONSOR:	Altor Bioscience Corporation 2810 North Commerce Parkway Miramar, FL 33025-3958

Hing C. Wong, Ph.D.
Chief Clinical Officer

Oct. 26, 2012
Date

Jeff Weber, M.D., Ph.D.
Consulting Medical Director

10-25-12
Date

Peter Rhode, Ph.D.
Vice President, Research and Development

Oct 26, 2012
Date

Bee Y. Huang, M.S.
Director, Clinical Development

10-26, 2012
Date

CLINICAL STUDY PROTOCOL

Protocol Number: CA-ALT-801-01-12

Protocol Title: A Study of ALT-801 in Patients with Bacillus Calmette-Guerin (BCG) Failure Non-Muscle Invasive Bladder Cancer

Date of Protocol:

Version# 01	January 27, 2012
Version# 02	April 5, 2012
Version# 03	October 24, 2012
Version# 04	July 1, 2015

Sponsor Contact:

Altor BioScience CORPORATION

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

INVESTIGATOR SIGNATURE PAGE

Protocol Number: CA-ALT-801-01-12

Protocol Title: A Study of ALT-801 in Patients with Bacillus Calmette-Guerin (BCG) Failure Non-Muscle Invasive Bladder Cancer

Date of Protocol:

Version# 01	January 27, 2012
Version# 02	April 5, 2012
Version# 03	October 24, 2012
Version# 04	July 1, 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

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-801-01-12
Study Drug Name:	Not applicable
Study Treatment Active agents:	ALT-801 (c264scTCR-IL2), recombinant humanized, soluble single-chain TCR-cytokine fusion protein.
Study Type:	Interventional
Study Phase:	Ib/II
Protocol Title:	A Study of ALT-801 in Patients with Bacillus Calmette-Guerin (BCG) Failure Non-Muscle Invasive Bladder Cancer
Objectives:	To confirm the safety and tolerability of a well-tolerated dose level of ALT-801 combined with gemcitabine and to determine the Recommended Dose level (RD) in patients who are BCG failure (defined as refractory, relapsing or intolerant), non-muscle invasive bladder cancer and refuse or are not medically fit to undergo a radical cystectomy recommended by the participating urologist as the standard next therapy per urologic guidelines. To assess anti-tumor activity of study treatment in treated patients as determined by the disease response rate using cystoscopy, bladder biopsy, and urine cytology. To evaluate the duration of response and survival in these patients. To characterize the immunogenicity of ALT-801 in treated patients. To assess the relationship between tumor presentation of HLA-A*0201/p53 aa 264-272 complex and the safety, immune response and clinical benefit of study treatment.
Study Design:	This is a Phase Ib/II, open-label, multi-center and competitive enrollment study of ALT-801 combined with gemcitabine in patients with BCG failure, defined as refractory, relapsing or intolerant, non-muscle invasive bladder cancer who refuse or are not medically fit to undergo a radical cystectomy recommended by the participating urologist as the standard next therapy per urologic guidelines. There are two phases in this study: a dose confirmation phase to confirm a well-tolerated dose in this patient population and designate it as the recommended dose level (RD) for study expansion and a two-stage expansion phase using the recommended (RD). Each enrolled patient will receive up to two courses of study treatment. The study will be conducted in conformity with Good Clinical Practice (GCP).
Treatments:	All enrolled patients will receive up to two courses of study treatment: an induction treatment course consisting of two study treatment cycles, with a 13-day rest period between cycles, and a maintenance treatment course consisting of one study treatment cycle. The rest period may be extended to

include an additional week. Each cycle consists of four doses of ALT-801, one each on Day #3, Day #5, Day #8, and Day #15 and two doses of gemcitabine, one each on Day #1 and Day #8. Patients who have a complete response from the initial response assessment by bladder biopsy will receive the maintenance treatment and then have the confirmatory response assessment. The schedules of induction and maintenance treatment courses are illustrated below:

Induction treatment Course:

Treatment Cycle	Cycle #1						Cycle #2				
Treatment Week	1			2	3	4	5			6	7
Treatment Day	1	3	5	8	15		29	31	33	36	43
Gemcitabine	X			X		Rest	X			X	
ALT-801		X	X	X	X			X	X	X	X

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Maintenance Treatment Course:

Treatment Week	9			10	11
Treatment Day	1	3	5	8	15
Gemcitabine	X			X	
ALT-801		X	X	X	X

There are no restrictions on further therapies, such as chemotherapy, radiation therapy or surgery to be used after the protocol-specified therapy. Clearly, additional post-study treatments could be of significant clinical benefit in selected patients, and these patients will be followed for outcome.

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. Gemcitabine and ALT-801 will be administered by intravenous infusion into a central or peripheral vein under the supervision of a qualified physician experienced in the use of anti-cancer agents including aldesleukin (Proleukin®).

Dose Confirmation Phase:

In the dose-confirmation phase of the study, six patients will be enrolled to receive the study treatment with gemcitabine, at 1000 mg/m^2/dose, and ALT-801, at the dose level starting at 0.08 mg/kg, which is a well-tolerated dose level in a Phase Ib/II study of ALT-801 in combination with cisplatin in patients with metastatic melanoma. Enrolled patients will be monitored during the induction treatment course for any Dose Limiting Toxicity (DLT).

The tolerability of a dose level is defined as <2 of 6 patients experiencing any DLT at this dose level. If the tolerability of ALT-801 at a dose level cannot be confirmed, an additional six patients will be enrolled to repeat the dose confirmation phase with a step-down dose level that is 0.02 mg/kg lower than the previous tested dose level until a dose level is confirmed as a

tolerated dose and is designated as the Recommended Dose (RD) for study expansion. Below are the dose levels of the study treatment during the dose confirmation phase of the study.

Cohort	ALT-801 Dose (mg/kg)	Gemcitabine (mg/m^2/dose)
-2	0.04	1,000
-1	0.06	1,000
1 (initial)	0.08	1,000

DLT is defined as any toxicity of Grade 3 that does not resolve to Grade 1 or lower within 7 days and any toxicity of Grade 4 occurring during treatment courses with exceptions and details described in the study protocol. Patients experiencing a DLT should discontinue study treatment. Study treatment discontinuation due to adverse events experienced prior to study drug administration, disease progression or investigator's and/or patient's decision to withdraw from study treatment without occurrence of any study treatment discontinuation adverse event will not necessarily define a DLT event. Study treatment discontinuation events are defined in the protocol.

Expansion Phase

The two-stage expansion phase will be conducted with ALT-801, at the RD level confirmed in the dose confirmation stage, and gemcitabine, at the same level as in the dose confirmation stage, using a modified Simon two-stage design. Objective response (OR) (defined as complete response (CR) + partial response (PR)) will be evaluated and set thresholds of lack of efficacy (OR rate (ORR) = 20%) and an efficacy level of interest (ORR = 40%) will be selected.

Stopping Rule:

Patient enrollment will be temporarily suspended based on the occurrence of any of the following:

- During the dose confirmation phase of the study, no dose level can be designated as the RD.
- If at any time during the expansion phase of the study, more than 33% of the patients experience a possible, probable or definite drug related DLT.

If the above occur, then the Data Safety Monitoring Board and principal investigators will meet to discuss how to proceed with future patient enrollment in the study.

Evaluations:

Patients will be evaluated for clinical toxicities during the treatment. Patients' blood samples will be collected to assess the immunogenicity of the study drug. The anti-tumor activity of study treatment will be evaluated. All patients who receive at least one complete dose of study drug ALT-801 will be included in the evaluation of anti-tumor activity of study treatment.

Population: Patients of 18 years of age who have BCG failure (defined as refractory, relapsing or intolerant), non-muscle invasive bladder cancer and refuse or are not medically fit to undergo a radical cystectomy recommended by the participating urologist as the standard next therapy per urologic guidelines. Patients also need to have adequate cardiac, pulmonary, liver and kidney functions and to 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 confirmation phase of the study (Phase Ib). Up to an additional 37 assessable patients will be enrolled at the expansion phase (Stage 1 and 2) of the study (Phase II). A total of approximately 43 assessable patients will be enrolled and complete the study in the event that the RD is 0.08 mg/kg. Assuming a 20% ineligible or non-assessable cases, a total of up to 52 patients may be accrued to the study.

Primary Endpoints:

For Phase Ib only: (1) Confirmation of the safety and tolerability of a well-tolerated dose level of ALT-801 combined with gemcitabine and designation of the Recommended Dose level (RD).

For Phase Ib & II: (2) Safety profile of ALT-801 combined with gemcitabine.
(3) Disease response rate.

Secondary Endpoints:

(1) Duration of response.
(2) Progression-free survival.
(3) Event free survival.
(4) Overall survival.
(5) Immunogenicity of ALT-801.
(6) Relationship between tumor presentation of HLA-A*0201/p53 aa 264-272 complexes and the safety, immune response and clinical benefit of study treatment.

Biomarkers: Blood samples will be collected to assess typing for HLA-A2 and immune cell levels and phenotype. Serum samples will be collected for testing immunogenicity of the study drug ALT-801 and the serum level of IFN-γ. Tumor samples obtained from surgeries or biopsies performed prior to screening for the study will be collected to test HLA-A*0201/p53 aa 264-272 complex presentation.

Monitoring Tests: Urine samples for urinalysis, blood samples for standard chemistry, and CBC with differential will be obtained at screening, on each study drug infusion day and follow-up visits. Blood samples for immunogenicity testing, which include assays for anti-ALT-801 and IL-2 neutralizing antibodies, will be collected prior to dosing on the first ALT-801 infusion day and at Week 8 from the initial dose of study treatment.

Response Assessment: There are two response assessments for treated patients: the initial assessment at week 8 and the confirmatory assessment at week 12 from the

start of study treatment. After the induction treatment period, patients who have received at least one complete dose of study drug will have the initial response assessment. After the maintenance treatment period, patients who have received at least one dose of study drug during this treatment period will have the confirmatory response assessment. Cystoscopy, bladder biopsy and urine cytology will be performed to evaluate the response. If surgeries or biopsies are performed after patients receive and respond to study treatment, tumor or tissue samples from these procedures will be collected to assess histopathological and immuno-cellular responses to study treatment.

Survival Assessment: Progression-free survival, overall survival, and duration of response of patients who have received at least one complete dose of ALT-801, will be assessed every three months during years 1 and 2, and then every 6 months during year 3 from the start of study treatment, or through the point designated, during the study, as the end of the study follow up.

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 confirmation, 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 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]	INITIAL COURSE											INITIAL ASSESSMENT	MAINTENANCE COURSE					CONFIRMATORY ASSESSMENT	FOLLOW-UPS								
		CYCLE #1						CYCLE #2																			
Study Month		1						2						3					3	6	9	12	15	18	21	24	30	36
Study Week		1			2	3	4	5		6	7		8	9			10	11	12									
Day of Week		M	W	F	M	M		M	W	F	M	M		M	W	F	M	M										
Study Day		*1*	*3*	*5*	*8*	*15*	*16-28*	*29*	*31*	*33*	*36*	*43*		*57*	*59*	*61*	*64*	*71*										
Medical history/prior therapies	X						Rest Period																				
Serum pregnancy test[2]	X																										
Complete physical exam	X	X						X					X	X					X								
Vital signs, weight, Height[3]	X	X	X	X	X	X		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	X	X	X	X	X	X								
Adverse event assessment[4]	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X								
CBC with Differential	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X								
Blood Chemistry	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X								
EKG	X[5]	X[5]						X						X													
Urinalysis	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X								
Cystoscopy[13] & bladder biopsies[13]	X												X						X								
Urine cytology	X												X						X								
Response assessment[6]													X						X								
Disease & survival follow-up[7]																				X	X	X	X	X	X	X	X	X
Immune cell levels & phenotype[8,12]		X[8]	X[8]		X[8]			X[8]																			
HLA A2 Blood Typing[9] & p53 tumor typing[12]		X																									
IFN-γ[10,12]			X[10]																								
Immunogenicity tests[11, 12]			X[11]										X														
Gemcitabine		**g1**			**g2**			**g3**			**g4**			**g5**			**g6**										
Study drug (ALT-801)			**a1**	**a2**	**a3**	**a4**			**a5**	**a6**	**a7**	**a8**			**a9**	**a10**	**a11**	**a12**									

[1]Screening/baseline evaluations are performed ≤14 days prior to start of therapy except TTE, cystoscopy and biopsies. If TTE is required for cardiac assessments, it can be performed ≤28 days. If the patient's condition is deteriorating, 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 every 2 hours after drug infusion and before discharge or until the completion of dose monitoring, body weight is obtained before infusion on each drug infusion day and height 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]If a previous EKG was performed within 14 days before start of study treatment, the EKG is not required. [6]Response will be evaluated by cystoscopy, bladder biopsies and urine cytology. [7]Information about tumor assessment & other therapies received after completion of study treatment will be collected if available. [8]Fresh blood samples for HLA A2 blood typing, immune cell levels & phenotype testing will be collected before any dosing starts. [9] Use the same blood sample collected for immune cell levels & phenotype.[10]Collect blood samples at Time 0 (before dosing) and at 6 hour (+/- 60 min) from Time 0. [11]Use the same sample collected for IFN-γ assay. [12]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.[13]Screening cystoscopy is performed within 4 weeks prior to start of therapy, screening biopsies are performed within 3 months prior to start of therapy.