CLINICAL STUDY PROTOCOL

Protocol Number: CA-ALT-801-01-10

Protocol Title: A Phase Ib/II Trial of ALT-801 in Combination with Cisplatin and Gemcitabine in Muscle Invasive or Metastatic Urothelial Cancer

Date of Protocol:
Version # 01 October 31, 2010

Sponsor Contact:

Altor BioScience CORPORATION

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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)

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SYNOPSIS

Sponsor:	Altor Bioscience Corporation
Protocol#:	CA-ALT-801-01-10
Study Drug Name:	Not applicable
Study Treatment	
Active agents:	ALT-801 (c264scTCR-IL2), recombinant humanized, soluble single-chain TCR-cytokine fusion protein; Cisplatin; Gemcitabine.
Study Type:	Interventional
Study Phase:	Ib/II
Protocol Title:	A Phase Ib/II Trial of ALT-801 in Combination with Cisplatin and gemcitabine in Muscle Invasive or Metastatic Urothelial Cancer
Objectives:	To determine the safety and tolerability of the novel combination of addition of ALT-801 (c264scTCR-IL2) to the doublet of cisplatin and gemcitabine in patients with muscle invasive or metastatic urothelial cancer of bladder, renal pelvis, ureters and urethra. To estimate the anti-tumor activity of this combination of ALT-801, cisplatin and gemcitabine by radiologic or pathologic anti-tumor response; progression free survival (assessed through end of study); and overall survival (assessed through end of study) in treated patients. To characterize the pharmacokinetic profile of ALT-801 in combination with cisplatin and gemcitabine in treated patients.
Study Design:	This is a Phase Ib/II, open-label, multi-center, competitive enrollment and dose-escalation study of ALT-801 in a biochemotherapy regimen containing cisplatin and gemcitabine in patients who have muscle invasive or metastatic urothelial cancer of bladder, renal pelvis, ureters and urethra, who are HLA-A2 positive by serological typing or genotyping and whose tumors present the HLA-A*0201/p53 aa264-272 complex. The study will be conducted in conformity with Good Clinical Practice (GCP). The study includes a dose escalation phase to determine the maximum tolerated dose (MTD) of ALT-801 in combination with cisplatin and gemcitabine and a two-stage expansion phase at the MTD. The dose escalation in this study is conducted using a (3+3) dose escalation design, and the two-stage expansion phase at the MTD using a modified Simon two-stage design (1, 2). In the dose escalation phase of this study, there are three dose levels of ALT-801 (0.04 mg/kg, 0.06 mg/kg and 0.08 mg/kg, in addition to two de-escalation dose levels). The doses of cisplatin (75 mg/m^2/dose, day 1) and gemcitabine (1000 mg/m^2/dose, day 1 & 8) will be fixed across all ALT-801 dose levels. If the MTD is not reached during the dose escalation phase, the sponsor, the Data Safety Monitoring Board and the principal investigators will meet to discuss whether to amend the protocol to expand the dose escalation phase to include additional ALT-801 dose levels.

Treatments: The planned on-study treatment duration will be for 3 courses. Each course consists of cisplatin (Day #1), gemcitabine (Day #1), ALT-801 (Day #3 & Day #5), gemcitabine (Day #8), ALT-801 (Day #8 & Day #10), and a rest period (Days #11-21). Delays or modifications are addressed in the protocol. This is illustrated in this schema:

	Course1						Course 2						Course 3					
Treatment Day	1	3	5	8	10	11-21	22	24	26	29	31	32-42	43	45	47	50	52	53-63
Cisplatin	X					Rest Period	X					Rest Period	X					Rest Period
Gemcitabine	X			X			X			X			X			X		
ALT-801		X	X	X	X			X	X	X	X			X	X	X	X	

Prior to commencing the second or the third course, subjects will need to meet the continuation criteria. 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. The ALT-801, the cisplatin and gemcitabine 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®), cisplatin and gemcitabine.

This is the schema for the dose levels during the dose-escalation phase of the study. The -1 and -2 dose levels of ALT-801 are included in case of DLT events in the initial dose level.

Cohort	ALT-801 Dose (mg/kg)	Cisplatin (mg/m^2)	Gemcitabine (mg/m^2)
-2	0.01	75	1000
-1	0.02	75	1000
1 (initial)	0.04	75	1000
2	0.06	75	1000
3	0.08	75	1000

Dose Escalation: In this phase of the study, a minimum of 3 patients will be enrolled at each dose level. All patients will be monitored for Dose Limiting Toxicity (DLT) for 8 weeks from the initial dose. If 0/3 patients have drug-related, dose-limiting toxicity by 8 weeks after the initial dose, the next cohort will be opened for enrollment. If one patient at a dose-level develops drug-related DLT, up to six patients will be enrolled at that dose level and each subsequent higher dose level. If 0 or 1 of 6 patients in a cohort of 6 patients have an event that meets criteria for treatment-related DLT, then the next cohort will be opened for enrollment. If 2 or more out of 3-6 patients in a dose escalation cohort have a DLT that is drug-related, that dose level will be designated as exceeding the maximum tolerated dose. If there are 3 patients in the dose level below this level, then additional patients (up to 6 total) will be enrolled at that dose level. When there is a dose level with 0 or 1 out of 6 patients with DLT, which is either the maximum planned dose level (level 3) or which is one level below a dose that was not tolerated, the dose that is the maximum tolerated dose will be considered defined. Further

changes in the treatment plan may be considered by protocol amendment at that point.

If more than two of six patients experience a DLT at the initial dose level (level 1), then the sponsor, the Data Safety Monitoring Board and the principal investigators will meet to determine how to adjust downward the dose level of cisplatin, gemcitabine, and/or the study drug, or continue with the (-1) and (-2) cohorts, and to determine how to proceed with the study.

A DLT is any toxicity that results in study treatment discontinuation and includes definitions below. Study treatment discontinuation due to adverse events experienced prior to study drug administration, disease progression or patient's decision to withdraw from the 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.

Dose Expansion: The two-stage expansion phase at the MTD will be conducted using a modified Simon two-stage design (1, 2). Both objective response (OR) (defined as complete response (CR) + partial response (PR)) and clinical benefit (CB) (defined as CR, PR + stable disease (SD)) will be evaluated and common set thresholds of lack of efficacy (OR rate (ORR) = 40%; CB rate (CBR) = 78%) and an efficacy level of interest (ORR = 60%; CBR = 92%) will be selected. The sample size was driven by the parameter that had the larger sample size for each stage.

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

- If at any time the dose escalation phase of the study, more than one patient in a cohort of three, or two of six patients experience any DLT;
- If at any time during the expansion phase of the study, more than 33% the patients experience any drug related DLT.

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 response will be evaluated for up to 12 weeks from the initial dose of the first course of treatment. All patients who receive at least one dose of the study drug ALT-801 will be included in the anti-tumor response evaluation. Between each cohort and at the end of the study, all clinical and safety data will be analyzed for all patients enrolled in the study for dose-response effects.

Population: Patients of 18 years of age and above who are candidates for systemic cisplatin and gemcitabine for the treatment of muscle invasive or metastatic urothelial cancer of bladder, renal pelvis, ureters, and urethra, who are HLA-A2 positive by serological typing or genotyping and whose tumors present HLA-A*0201/p53 aa264-272 complexes (as detected by sponsor-provided test on tumor biopsy or surgically removed tumor samples) may be selected

for further evaluation of eligibility for study participation. 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 or 1 and a life expectancy of at least 12 weeks.

Sample Size: A total of up to 30 assessable patients will be accrued to the initial dose escalation phase of the study (Phase Ib); the estimated number is 15. Up to an additional 40 assessable patients will be enrolled at the expansion phase (Stage 1 and 2) of the study (Phase II). A total of approximately 58 assessable patients will be enrolled and complete the study. Assume a 20% ineligible or non- assessable cases, a total of up 70 patients may be accrued to the study.

Primary Endpoints:

For Stage I only: (1) To define an MTD of ALT-801 in combination with cisplatin and gemcitabine in the treatment of patients with muscle invasive or metastatic urothelial cancer.

For Stage I & II: (2) To assess the safety of the combination study treatment in treated patients.

(3) To assess the objective response rate in treated patients.

Secondary Endpoints:

(1) To assess the progression free survival in treated patients.

(2) To assess the overall survival in treated patients.

(3) To evaluate the immugonenicity and pharmacokinetic profile of ALT-801 in treated patients.

Pharmacokinetics & Biomarkers: Blood samples for pharmacokinetic analysis of ALT-801 will be taken on the first day of ALT-801 administration in the first course of study treatment. Venous blood will be obtained at Time 0 (before the start of infusion), at 30 min (completion of drug 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 INF-γ and TNF-α.

Monitoring Tests: Urine samples for urinalysis, blood samples for standard chemistry, CBC, differential and coagulation will be obtained at screening, on each study drug infusion day, discharge days 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 9 from the initial dose of study treatment.

Anti-tumor Response Evaluation: The anti-tumor response will be evaluated at Week 9 and Week 13 from the initial dose of study treatment. Objective Response will be evaluated using

the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors Committee (RECIST) 1.1. Baseline evaluations should be performed up to 28 days before starting study treatment. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the anti-tumor effect of the treatment. However, cystoscopic evaluation may be used routinely in this population, in addition to radiologic testing.

Survival Assessment: Progression-free survival and overall survival of all enrolled patients will be assessed at 3, 6, 9, 12, 18, 24, 30 and 36 months from the start of study treatment, or through the point designated 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 SAEs and all events that trigger patient's study treatment discontinuation to the sponsor via phone, fax or email (or a combination) up to 1 day 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 a day of its learning of the event. The study centers should report the other adverse events to the sponsor following the guidelines defined in the study protocol. All study drug related adverse events (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 pharmacokinetic data will be evaluated. For estimation of duration of response, 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	Pre Screen	Screen[5]	TREATMENT PERIOD For Course 1-3						FOLLOW-UP PERIOD								
MONTH										3	6	9	12	18	24	30	36
WEEK (Course 2 in parenthesis) {Course 3 in brackets}			1 (4){7}			2(5){8}		3 (6)	9	12							
STUDY DAY (Course 2 in parenthesis) {Course 3 in brackets}			1 (22) {43}	3 (24) {45}	5 (26) {47}	8 (29) {50}	10 (31) {52}										
Informed consent PART I[1]	X																
Informed consent PART II		X															
HLA A2 Typing[2,4]	X							R									
HLA-A*0201/p53 aa264-272 tumor typing[3, 4]	X							E									
Medical history		X						S									
Serum pregnancy test[6]		X						T									
Complete physical exam		X	X						X	X							
Vital signs, weight, Height[7]		X	X	X	X	X	X		X	X							
Concurrent medication		X	X	X	X	X	X		X	X							
Blood tests: CBC with Differential, Blood Chemistry & Coagulation		X	X	X	X	X	X	P	X	X							
Urinalysis		X	X	X	X	X	X	E	X	X							
Cardiac functions[8]		X	X	X	X	X	X	R									
Pulmonary functions		X						I									
Adverse event assessment[9]		X	X	X	X	X	X		X	X							
Tumor assessment[10]		X						O	X	X							
Survival Assessment[14]											X	X	X	X	X	X	X
PK[11], INFγ[11], TNFα[11,13]				X				D									
Immunogenicity tests[13]			X[12]						X								
Cisplatin therapy			X														
Gemcitabine therapy			X			X											
Study drug administration				X	X	X	X										

[1]Authorization of the Part I Informed Consent is required before obtaining patients' blood and tumor samples for HLA-A2 blood typing and HLA-A*0201/p53 aa264-272 tumor typing. [2] Only patients with positive test result on HLA A2 blood typing will continue on the HLA-A*0201/p53 aa264-272 tumor typing. [3]Only patients with positive results on HLA A2 blood typing and HLA-A*0201/p53 aa264-272 tumor typing will continue on the further screening procedures and have the possibility of being enrolled in the study. [4]Any previous HLA A2 blood typing result, from serological or DNA-based typing, and HLA-A*0201/p53 aa264-272 tumor typing result can be used for screening. [5]Screening evaluations are performed ≤ 14 days, scan/x-ray ≤ 28 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. [6]Pregnancy test is for women with childbearing potential only. [7]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 the drug treatment and before discharge, and body weight before the study treatment infusion on study treatment infusion day. [8]Patients are closely monitored for hypotension, arrhythmia, angina and myocardial infarction. At screening, patients who are ≥ 50 years of age or have a history of EKG abnormalities, symptoms of cardiac ischemia or arrhythmia will have a stress test (stress thallium, stress MUGA or dobutamine echocardiogram) to determine their eligibility for participation in the study. EKG will be performed at start of each treatment cycle. [9]Patients who have an on-going study drug-related SAE upon study completion or at discontinuation of the study will be contacted by the investigator or his/her designee every week until the event is resolved or determined to be irreversible. [10]Tumor response and progression will be evaluated in this study using the new international criteria proposed by the RECIST (1.1) Committee. [11]Performed at Course #1 only. Collect blood samples at Time 0 (before drug infusion), at 30 min (+/- 5 min), 1 hour (+/- 10 min), 3 hour (+/- 30 min), 6 hour (+/- 60 min) from Time 0. INFγ and TNFα assays are performed using the same samples and at the same schedule as PK. [12]Performed at Course #1 only and before dosing. [13]Residual samples may be used by Sponsor for research studies of other biomarkers. . [14]Information about tumor assessment & other therapies received after completion of study treatment will be collected if available.

APPENDIX H: APPROVAL PAGE

PROTOCOL TITLE:	A Phase Ib/II Trial of ALT-801 in Combination with Cisplatin and Gemcitabine in Muscle Invasive or Metastatic Urothelial Cancer.
INVESTIGATIONAL DRUG:	ALT-801; c264scTCR-IL2 Fusion Protein
CLINICAL PROTOCOL NUMBER:	CA-ALT-801-01-10
Version# 01	October 31, 2010
SPONSOR:	Altor Bioscience Corporation 2810 North Commerce Parkway Miramar, FL 33025-3958

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

11/1/10
Date

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

11-1-10
Date

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

11-1-10
Date

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

11-1-10
Date

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Version # 01Version # 02 October 31, 2010
July 8, 2011

Sponsor Contact:

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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)

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SYNOPSIS

Sponsor: Altor Bioscience Corporation

Protocol#: CA-ALT-801-01-10

Study Drug Name: Not applicable

Study Treatment

Active agents: ALT-801 (c264scTCR-IL2), recombinant humanized, soluble single-chain TCR-cytokine fusion protein; Cisplatin; Gemcitabine.

Study Type: Interventional

Study Phase: Ib/II

Protocol Title: A Phase Ib/II Trial of ALT-801 in Combination with Cisplatin and gemcitabine in Muscle Invasive or Metastatic Urothelial Cancer

Objectives: To determine the safety and tolerability of the novel combination of addition of ALT-801 (c264scTCR-IL2) to the doublet of cisplatin and gemcitabine in patients with muscle invasive or metastatic urothelial cancer of bladder, renal pelvis, ureters and urethra.

To estimate the anti-tumor activity of this combination of ALT-801, cisplatin and gemcitabine by radiologic or pathologic anti-tumor response, progression free survival (assessed through end of study), and overall survival (assessed through end of study) in treated patients.

To characterize the immunogenicity and pharmacokinetic profile of ALT-801 in combination with cisplatin and gemcitabine in treated patients.

To assess the relationship between tumor presentation of HLA-A*0201/p53 aa 264-272 complex and the safety and clinical benefit of study treatment.

Study Design: This is a Phase Ib/II, open-label, multi-center, competitive enrollment and dose-escalation study of ALT-801 in a biochemotherapy regimen containing cisplatin and gemcitabine in patients who have muscle invasive or metastatic urothelial cancer of bladder, renal pelvis, ureters and urethra. The study will be conducted in conformity with Good Clinical Practice (GCP).

The study includes a dose escalation phase to determine the maximum tolerated dose (MTD) of ALT-801 in combination with cisplatin and gemcitabine and a two-stage expansion phase at the MTD. The dose escalation in this study is conducted using a (3+3) dose escalation design, and the two-stage expansion phase at the MTD using a modified Simon two-stage design (1, 2). In the dose escalation phase of this study, there are five dose levels of ALT-801 (0.04 mg/kg, 0.06 mg/kg and 0.08 mg/kg, 0.10 mg/kg and 0.12 mg/kg) in addition to two de-escalation dose levels. The doses of cisplatin (70 mg/m^2/dose) and gemcitabine (1000 mg/m^2/dose) will be fixed across all ALT-801 dose levels. If the MTD is not reached during the dose escalation phase, the sponsor, the Data Safety Monitoring Board and the principal investigators will meet to discuss whether to amend the protocol to expand the dose escalation phase to include additional ALT-801 dose levels.

Treatments: The planned initial on-study treatment will be for 3 courses. Each course consists of cisplatin (Day #1), gemcitabine (Day #1), ALT-801 (Day #3 & Day #5), gemcitabine (Day #8), ALT-801 (Day #8 & Day #10), and a rest period (Days #11-21). Prior to commencing the second or the third course, subjects will need to meet the continuation criteria. At the completion of the three full courses of study treatment, each patient enrolled will have been scheduled to have a total of 12 doses of the study drug ALT-801, 3 doses of cisplatin, and 6 doses of gemcitabine. After completing the 3-course initial study treatment, patients who have at least stable disease and meet other treatment criteria will repeat study treatment with four additional weekly doses of ALT-801. Delays or modifications are addressed in the protocol. This is illustrated in the following schemas:

Initial Study Treatment:

	Course 1						Course 2						Course 3					
Treatment Day	1	3	5	8	10	11-21	22	24	26	29	31	32-42	43	45	47	50	52	53-63
Cisplatin	X					Rest Period	X					Rest Period	X					Rest Period
Gemcitabine	X			X			X			X			X			X		
ALT-801		X	X	X	X			X	X	X	X			X	X	X	X	

Repeat Study Treatment:

Dose#	1	2	3	4
Repeat Treatment Day	1	8	15	22
ALT-801	X	X	X	X

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, cisplatin and gemcitabine 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®), cisplatin and gemcitabine.

This is the schema for the dose levels during the dose-escalation phase of the study. The -1 and -2 dose levels of ALT-801 are included in case of DLT events in the initial dose level.

Cohort	ALT-801 Dose (mg/kg)	Cisplatin (mg/m^2)	Gemcitabine (mg/m^2)
-2	0.01	70	1000
-1	0.02	70	1000
1 (initial)	0.04	70	1000
2	0.06	70	1000
3	0.08	70	1000
4	0.10	70	1000
5	0.12	70	1000

Dose Escalation: In this phase of the study, a minimum of 3 patients will be enrolled at each dose level. All patients will be monitored for Dose Limiting Toxicity (DLT) for 8 weeks from the initial dose. If 0/3 patients have study treatment-related, dose-limiting toxicity by 8 weeks after the initial dose, the next cohort will be opened for enrollment. If one patient at a dose-level develops drug-related DLT, up to six patients will be enrolled at that dose level and each subsequent higher dose level. If 0 or 1 of 6 patients in a cohort of 6 patients have an event that meets criteria for study treatment-related DLT, then the next cohort will be opened for enrollment. If 2 or more out of 3-6 patients in a dose escalation cohort have a DLT that is drug-related, that dose level will be designated as exceeding the maximum tolerated dose. If there are 3 patients in the dose level below this level, then additional patients (up to 6 total) will be enrolled at that dose level. When there is a dose level with 0 or 1 out of 6 patients with DLT, which is either the maximum planned dose level (level 5) or which is one level below a dose that was not tolerated, the dose that is the maximum tolerated dose will be considered defined. Further changes in the treatment plan may be considered by protocol amendment at that point.

If more than two of six patients experience a DLT at the initial dose level (level 1), then the sponsor, the Data Safety Monitoring Board and the principal investigators will meet to determine how to adjust downward the dose level of cisplatin, gemcitabine, and/or the study drug, or continue with the (-1) and (-2) cohorts, and to determine how to proceed with the study.

Dose limiting toxicity (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.

Dose Expansion: The two-stage expansion phase at the MTD will be conducted using a modified Simon two-stage design (1, 2). Both objective response (OR) (defined as complete response (CR) + partial response (PR)) and clinical benefit (CB) (defined as CR, PR + stable disease (SD)) will be evaluated and common set thresholds of lack of efficacy (OR rate (ORR) = 40%; CB rate (CBR) = 78%) and an efficacy level of interest (ORR = 60%; CBR = 92%) will be selected. The sample size was driven by the parameter that had the larger sample size for each stage.

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

- If at any time the dose escalation phase of the study, more than one patient in a cohort of three, or two of six patients experience any DLT;
- If at any time during the expansion phase of the study, more than 33% the patients experience any drug related DLT.

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 response will be evaluated for up to 18 weeks from the initial dose of the first course of treatment. All patients who receive at least one dose of the study drug ALT-801 will be included in the anti-tumor response evaluation. Between each cohort and at the end of the study, all clinical and safety data will be analyzed for all patients enrolled in the study for dose-response effects.

Population: Patients of 18 years of age and above who are candidates for systemic cisplatin and gemcitabine for the treatment of muscle invasive or metastatic urothelial cancer of bladder, renal pelvis, ureters, and urethra may be selected for further evaluation of eligibility for study participation. 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 or 1 and a life expectancy of at least 12 weeks.

Sample Size: A total of up to 30 assessable patients will be accrued to the initial dose escalation phase of the study (Phase Ib); the estimated number is 21. Up to an additional 40 assessable patients will be enrolled at the expansion phase (Stage 1 and 2) of the study (Phase II). A total of approximately 61 assessable patients will be enrolled and complete the study. Assume a 20% ineligible or non- assessable cases, a total of up 72 patients may be accrued to the study.

Primary Endpoints:

For Stage I only:

(1) To define an MTD of ALT-801 in combination with cisplatin and gemcitabine in the treatment of patients with muscle invasive or metastatic urothelial cancer.

For Stage I & II:

(2) To assess the safety of the combination study treatment in treated patients.

(3) To assess the objective response rate in treated patients.

Secondary Endpoints:

(1) To assess the progression free survival in treated patients.

(2) To assess the overall survival in treated patients.

(3) To evaluate the immunogenicity and pharmacokinetic profiles of ALT-801 in treated patients.

(4) To assess the relationship between tumor presentation of HLA-A*0201/p53 aa 264-272 complexes and the safety and clinical benefit of study treatment.

Pharmacokinetics & Biomarkers: Blood samples will be collected to assess typing for HLA-A2, immune cell levels, phenotype, pharmacokinetics, immunogenicity of the study drug ALT-801, and the serum levels of IFN-γ and TNF-α. Tumor samples 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 first course of study treatment. 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 immunogenicity of study drug ALT-801 and 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 the first and second courses of study treatment. HLA-A2 typing will be performed only once.

Monitoring Tests: Urine samples for urinalysis, blood samples for standard chemistry, CBC, differential and coagulation will be obtained at screening, on each study drug infusion day, discharge days 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 9 from the initial dose of study treatment.

Anti-tumor Response Evaluation: The anti-tumor response will be evaluated for up to 18 weeks from the initial dose of study treatment: for non-responders: Week 9 and 13; for early responders: Week 9 and 14; for late responders: Week 9, 13 and 18. Objective Response will be evaluated using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors Committee (RECIST) 1.1. Baseline evaluations should be performed up to 28 days before starting study treatment. The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-ups. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the anti-tumor effect of the treatment. However, cystoscopic evaluation may be used routinely in this population, in addition to radiologic testing.

Survival Assessment: Progression-free survival and overall survival of all enrolled patients will be assessed at 6, 9, 12, 18, 24, 30 and 36 months from the start of study treatment, or through the point designated 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 SAEs and all events that trigger patient's study treatment discontinuation to the sponsor via phone, fax or email (or a combination) up to 1 day 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 a day of its learning of the event. The study centers should report the other adverse events to the sponsor following the guidelines defined in the study protocol. All study drug related adverse events (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 pharmacokinetic data will be evaluated. For estimation of duration of response, 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[1]	INITIAL TREATMENT PERIOD																	SCAN #1	SCAN #2	REPEAT TREATMENT				SCAN #3	FOLLOW-UPS						
		COURSE 1						COURSE 2						COURSE 3																		
Month(late responders in parentheses)		1									2								3	4	3 – 4/(4-5)				4/(5)	6	9	12	18	24	30	36
Week (late responders in parentheses)		1			2		3	4			5		6	7			8		9	13	10/ (14)	11/ (15)	12/ (16)	13/ (17)	14/ (18)							
Week Day		M	W	F	M	W		M	W	F	M	W		M	W	F	M	W			M	M	M	M								
Treatment Day		*1*	*3*	*5*	*8*	*10*		*22*	*24*	*26*	*29*	*31*		*43*	*45*	*47*	*50*	*52*														
Informed consent	X																														
Medical history	X						**R**						**R**																		
Serum pregnancy test[2]	X						**e**						**e**																		
Complete physical exam	X	X					**s**	X					**s**	X					X	X	X				X						
Vital signs, weight, Height[3]	X	X	X	X	X	X	**t**	X	X	X	X	X	**t**	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	X	X	X	X	X						
CBC with Differential, Blood Chemistry	X	X	X	X	X	X	**P**	X	X	X	X	X	**P**	X	X	X	X	X	X	X	X	X	X	X	X						
Coagulation (PT/INR)[4]	X						**e**						**e**																		
Urinalysis	X	X					**r**	X					**r**	X							X										
Cardiac functions[5]	X	X[5]	X	X	X	X	**i**	X[5]	X	X	X	X	**i**	X[5]	X	X	X	X			X[5]	X	X	X							
Pulmonary functions	X						**o**						**o**																		
Adverse event assessment[6]	X	X	X	X	X	X	**d**	X	X	X	X	X	**d**	X	X	X	X	X	X	X	X	X	X	X	X						
Tumor assessment[7]	X																		X	X					X						
Survival Assessment[8]																										X	X	X	X	X	X	X
HLA A2 Typing, immune cell levels & phenotype[11]			X[9]						X[9]																						
HLA-A*0201/p53 tumor typing			X																												
PK, IFNγ, TNFα[11]			X[10]																												
Immunogenicity tests[11]			X[12]																X												
Cisplatin		**c1**						**c2**						**c3**																	
Gemcitabine		**g1**			**g2**			**g3**			**g4**			**g5**			**g6**														
Study drug (ALT-801			**a1**	**a2**	**a3**	**a4**			**a5**	**a6**	**a7**	**a8**			**a9**	**a10**	**a11**	**a12**			**a13**	**a14**	**a15**	**a16**							

[1]Screening evaluations are performed < 14 days, scan/x-ray < 28 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 the drug treatment and before discharge, and body weight before study treatment infusion on study treatment infusion day. [4]PT/INR should be performed for any bleeding issues. [5]Patients are closely monitored for hypotension, arrhythmia, angina and myocardial infarction. At screening, patients who are ≥ 50 years of age or have a history of EKG abnormalities, symptoms of cardiac ischemia or arrhythmia will have a stress test (stress thallium, stress MUGA or dobutamine echocardiogram) to determine their eligibility for participation in the study. EKG will be performed at start of each treatment course and the repeat study drug treatment course. At the start of 1st course, EKG is performed only when >14 days since last EKG. [6]Patients who have an on-going study drug-related SAE upon study completion or at discontinuation of the study will be contacted by the investigator or his/her designee every week until the event is resolved or determined to be irreversible. [7]Tumor response and progression will be evaluated in this study using the new international criteria proposed by the RECIST (1.1). [8]Information about tumor assessment & other therapies received after completion of study treatment will be collected if available [9]Fresh blood samples for HLA A2 blood typing, immune cell levels & phenotype testing will be collected before dosing. [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]Residual samples may be used by Sponsor for research studies of other biomarkers. [12]Use the same blood sample collected before dosing for PK test.

APPENDIX H: APPROVAL PAGE

PROTOCOL TITLE:	A Phase Ib/II Trial of ALT-801 in Combination with Cisplatin and Gemcitabine in Muscle Invasive or Metastatic Urothelial Cancer.
INVESTIGATIONAL DRUG:	ALT-801; c264scTCR-IL2 Fusion Protein
CLINICAL PROTOCOL NUMBER:	CA-ALT-801-01-10
Version# 01 Version# 02	October 31, 2010 July 8, 2011
SPONSOR:	Altor Bioscience Corporation 2810 North Commerce Parkway Miramar, FL 33025-3958

Hing C. Wong, Ph.D.
Chief Clinical Officer
July 8, 2011
Date

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

Peter Rhode, Ph.D.
Vice President, Research and Development
08 Jul 2011
Date

Bee Y. Huang, M.S.
Director, Clinical Development
08 Jul 2011
Date

CLINICAL STUDY PROTOCOL

Protocol Number: CA-ALT-801-01-10

Protocol Title: A Phase Ib/II Trial of ALT-801 in Combination with Cisplatin and Gemcitabine in Muscle Invasive or Metastatic Urothelial Cancer

Date of Protocol:

Version # 01	October 31, 2010
Version # 02	July 8, 2011
Version # 03	November 10, 2011

Sponsor Contact:

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INVESTIGATOR SIGNATURE PAGE

Protocol Number: CA-ALT-801-01-10

Protocol Title: A Phase Ib/II Trial of ALT-801 in Combination with Cisplatin and Gemcitabine in Muscle Invasive or Metastatic Urothelial Cancer

Date of Protocol:

Version# 01	October 31, 2010
Version# 02	July 8, 2011
Version # 03	November 10, 2011

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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)

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SYNOPSIS

Sponsor: Altor Bioscience Corporation

Protocol#: CA-ALT-801-01-10

Study Drug Name: Not applicable

Study Treatment

Active agents: ALT-801 (c264scTCR-IL2), recombinant humanized, soluble single-chain TCR-cytokine fusion protein; Cisplatin; Gemcitabine.

Study Type: Interventional

Study Phase: Ib/II

Protocol Title: A Phase Ib/II Trial of ALT-801 in Combination with Cisplatin and gemcitabine in Muscle Invasive or Metastatic Urothelial Cancer

Objectives: To determine the safety and tolerability of the novel combination of addition of ALT-801 (c264scTCR-IL2) to the doublet of cisplatin and gemcitabine in patients with muscle invasive or metastatic urothelial cancer of bladder, renal pelvis, ureters and urethra.

To estimate the anti-tumor activity of this combination of ALT-801, cisplatin and gemcitabine by radiologic or pathologic anti-tumor response, progression free survival (assessed through end of study), and overall survival (assessed through end of study) in treated patients.

To characterize the immunogenicity and pharmacokinetic profile of ALT-801 in combination with cisplatin and gemcitabine in treated patients.

To assess the relationship between tumor presentation of HLA-A*0201/p53 aa 264-272 complex and the safety and clinical benefit of study treatment.

Study Design: This is a Phase Ib/II, open-label, multi-center, competitive enrollment and dose-escalation study of ALT-801 in a biochemotherapy regimen containing cisplatin and gemcitabine in patients who have muscle invasive or metastatic urothelial cancer of bladder, renal pelvis, ureters and urethra. The study will be conducted in conformity with Good Clinical Practice (GCP).

The study includes a dose escalation phase to determine the maximum tolerated dose (MTD) of ALT-801 in combination with cisplatin and gemcitabine and a two-stage expansion phase at the MTD. The dose escalation in this study is conducted using a (3+3) dose escalation design, and the two-stage expansion phase at the MTD using a modified Simon two-stage design (1, 2). In the dose escalation phase of this study, there are five dose levels of ALT-801 (0.04 mg/kg, 0.06 mg/kg and 0.08 mg/kg, 0.10 mg/kg and 0.12 mg/kg) in addition to two de-escalation dose levels. The doses of cisplatin (70 mg/m^2/dose) and gemcitabine (1000 mg/m^2/dose) will be fixed across all ALT-801 dose levels. If the MTD is not reached during the dose escalation phase, the sponsor, the Data Safety Monitoring Board and the principal investigators will meet to discuss whether to amend the protocol to expand the dose escalation phase to include additional ALT-801 dose levels.

Treatments: The planned initial on-study treatment will be for 3 courses. Each course consists of cisplatin (Day #1), gemcitabine (Day #1), ALT-801 (Day #3 & Day #5), gemcitabine (Day #8), ALT-801 (Day #8 & Day #10), and a rest period (Days #11-21). Prior to commencing the second or the third course, subjects will need to meet the continuation criteria. At the completion of the three full courses of study treatment, each patient enrolled will have been scheduled to have a total of 12 doses of the study drug ALT-801, 3 doses of cisplatin, and 6 doses of gemcitabine. After completing the 3-course initial study treatment, patients who have at least stable disease and meet other treatment criteria will repeat study treatment with four additional weekly doses of ALT-801. Delays or modifications are addressed in the protocol. This is illustrated in the following schemas:

Initial Study Treatment:

	Course 1						Course 2						Course 3					
Treatment Day	1	3	5	8	10	11-21	22	24	26	29	31	32-42	43	45	47	50	52	53-63
Cisplatin	X					Rest Period	X					Rest Period	X					Rest Period
Gemcitabine	X			X			X			X			X			X		
ALT-801		X	X	X	X			X	X	X	X			X	X	X	X	

Repeat Study Treatment:

Dose#	1	2	3	4
Repeat Treatment Day	1	8	15	22
ALT-801	X	X	X	X

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, cisplatin and gemcitabine 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®), cisplatin and gemcitabine.

This is the schema for the dose levels during the dose-escalation phase of the study. The -1 and -2 dose levels of ALT-801 are included in case of DLT events in the initial dose level.

Cohort	ALT-801 Dose (mg/kg)	Cisplatin (mg/m^2)	Gemcitabine (mg/m^2)
-2	0.01	70	1000
-1	0.02	70	1000
1 (initial)	0.04	70	1000
2	0.06	70	1000
3	0.08	70	1000
4	0.10	70	1000
5	0.12	70	1000

Dose Escalation: In this phase of the study, a minimum of 3 patients will be enrolled at each dose level. All patients will be monitored for Dose Limiting Toxicity (DLT) for 8 weeks from the initial dose. If 0/3 patients have study treatment-related, dose-limiting toxicity by 8 weeks after the initial dose, the next cohort will be opened for enrollment. If one patient at a dose-level develops drug-related DLT, up to six patients will be enrolled at that dose level and each subsequent higher dose level. If 0 or 1 of 6 patients in a cohort of 6 patients have an event that meets criteria for study treatment-related DLT, then the next cohort will be opened for enrollment. If 2 or more out of 3-6 patients in a dose escalation cohort have a DLT that is drug-related, that dose level will be designated as exceeding the maximum tolerated dose. If there are 3 patients in the dose level below this level, then additional patients (up to 6 total) will be enrolled at that dose level. When there is a dose level with 0 or 1 out of 6 patients with DLT, which is either the maximum planned dose level (level 5) or which is one level below a dose that was not tolerated, the dose that is the maximum tolerated dose will be considered defined. Further changes in the treatment plan may be considered by protocol amendment at that point.

If more than two of six patients experience a DLT at the initial dose level (level 1), then the sponsor, the Data Safety Monitoring Board and the principal investigators will meet to determine how to adjust downward the dose level of cisplatin, gemcitabine, and/or the study drug, or continue with the (-1) and (-2) cohorts, and to determine how to proceed with the study.

Dose limiting toxicity (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.

Dose Expansion: The two-stage expansion phase at the MTD will be conducted using a modified Simon two-stage design (1, 2). Both objective response (OR) (defined as complete response (CR) + partial response (PR)) and clinical benefit (CB) (defined as CR, PR + stable disease (SD)) will be evaluated and common set thresholds of lack of efficacy (OR rate (ORR) = 40%; CB rate (CBR) = 78%) and an efficacy level of interest (ORR = 60%; CBR = 92%) will be selected. The sample size was driven by the parameter that had the larger sample size for each stage.

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

- If at any time the dose escalation phase of the study, more than one patient in a cohort of three, or two of six patients experience any DLT;
- If at any time during the expansion phase of the study, more than 33% the patients experience any drug related DLT.

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 response will be evaluated for up to 18 weeks from the initial dose of the first course of treatment. All patients who receive at least one dose of the study drug ALT-801 will be included in the anti-tumor response evaluation. Between each cohort and at the end of the study, all clinical and safety data will be analyzed for all patients enrolled in the study for dose-response effects.

Population: Patients of 18 years of age and above who are candidates for systemic cisplatin and gemcitabine for the treatment of muscle invasive or metastatic urothelial cancer of bladder, renal pelvis, ureters, and urethra may be selected for further evaluation of eligibility for study participation. 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 or 1 and a life expectancy of at least 12 weeks.

Sample Size: A total of up to 30 assessable patients will be accrued to the initial dose escalation phase of the study (Phase Ib); the estimated number is 21. Up to an additional 40 assessable patients will be enrolled at the expansion phase (Stage 1 and 2) of the study (Phase II). A total of approximately 60 assessable patients will be enrolled and complete the study. Assume a 20% ineligible or non- assessable cases, a total of up 72 patients may be accrued to the study.

Primary Endpoints:

For Stage I only: (1) To define an MTD of ALT-801 in combination with cisplatin and gemcitabine in the treatment of patients with muscle invasive or metastatic urothelial cancer.

For Stage I & II: (2) To assess the safety of the combination study treatment in treated patients.

(3) To assess the objective response rate in treated patients.

Secondary Endpoints:

(1) To assess the progression free survival in treated patients.

(2) To assess the overall survival in treated patients.

(3) To evaluate the immunogenicity and pharmacokinetic profiles of ALT-801 in treated patients.

(4) To assess the relationship between tumor presentation of HLA-A*0201/p53 aa 264-272 complexes and the safety and clinical benefit of study treatment.

Pharmacokinetics & Biomarkers: Blood samples will be collected to assess typing for HLA-A2, immune cell levels, phenotype, pharmacokinetics, immunogenicity of the study drug ALT-801, and the serum levels of IFN-γ and TNF-α. Tumor samples 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 first course of study treatment. 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 immunogenicity of study drug ALT-801 and 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 the first and second courses of study treatment. HLA-A2 typing will be performed only once.

Monitoring Tests: Urine samples for urinalysis, blood samples for standard chemistry, CBC, differential and coagulation will be obtained at screening, on each study drug infusion day, discharge days 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 9 from the initial dose of study treatment.

Anti-tumor Response Evaluation: The anti-tumor response will be evaluated for up to 18 weeks from the initial dose of study treatment: for non-responders: Week 9 and 13; for early responders: Week 9 and 14; for late responders: Week 9, 13 and 18. Objective Response will be evaluated using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors Committee (RECIST) 1.1. Baseline evaluations should be performed up to 28 days before starting study treatment. The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-ups. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the anti-tumor effect of the treatment. However, cystoscopic evaluation may be used routinely in this population, in addition to radiologic testing.

Survival Assessment: Progression-free survival and overall survival of all enrolled patients will be assessed at 6, 9, 12, 18, 24, 30 and 36 months from the start of study treatment, or through the point designated 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 SAEs and all events that trigger patient's study treatment discontinuation to the sponsor via phone, fax or email (or a combination) up to 1 day 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 a day of its learning of the event. The study centers should report the other adverse events to the sponsor following the guidelines defined in the study protocol. All study drug related adverse events (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 pharmacokinetic data will be evaluated. For estimation of duration of response, 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[1]	INITIAL TREATMENT PERIOD																	SCAN #1	SCAN #2	REPEAT TREATMENT				SCAN #3	FOLLOW-UPS						
		COURSE 1						COURSE 2						COURSE 3																		
Month(late responders in parentheses)		1									2								3	4	3 – 4/(4-5)				4/(5)	6	9	12	18	24	30	36
Week (late responders in parentheses)		1			2		3	4			5		6	7			8		9	13	10/ (14)	11/ (15)	12/ (16)	13/ (17)	14/ (18)							
Week Day		M	W	F	M	W		M	W	F	M	W		M	W	F	M	W			M	M	M	M								
Treatment Day		*1*	*3*	*5*	*8*	*10*		*22*	*24*	*26*	*29*	*31*		*43*	*45*	*47*	*50*	*52*														
Informed consent	X						R						R																		
Medical history	X						e						e																		
Serum pregnancy test[2]	X						s						s																		
Complete physical exam	X	X					t	X					t	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	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	X	X	X	X	X						
CBC with Differential, Blood Chemistry	X	X	X	X	X	X	P	X	X	X	X	X	P	X	X	X	X	X	X	X	X	X	X	X	X						
Coagulation (PT/INR)[4]	X						e						e																		
Urinalysis	X	X					r	X					r	X							X										
Cardiac functions[5]	X	X[5]	X	X	X	X	i	X[5]	X	X	X	X	i	X[5]	X	X	X	X			X[5]	X	X	X							
Pulmonary functions	X						o						o																		
Adverse event assessment[6]	X	X	X	X	X	X	d	X	X	X	X	X	d	X	X	X	X	X	X	X	X	X	X	X	X						
Tumor assessment[7]	X																		X	X					X						
Survival Assessment[8]																										X	X	X	X	X	X	X
HLA A2 Typing, immune cell levels & phenotype[11]			X[9]						X[9]																						
HLA-A*0201/p53 tumor typing			X																												
PK, IFNγ, TNFα[11]			X[10]																												
Immunogenicity tests[11]			X[12]																X												
Cisplatin		**c1**						**c2**						**c3**																	
Gemcitabine		**g1**			**g2**			**g3**			**g4**			**g5**			**g6**														
Study drug (ALT-801			**a1**	**a2**	**a3**	**a4**			**a5**	**a6**	**a7**	**a8**			**a9**	**a10**	**a11**	**a12**			**a13**	**a14**	**a15**	**a16**							

[1]Screening evaluations are performed < 14 days, scan/x-ray < 28 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 the drug treatment and before discharge, and body weight before study treatment infusion on study treatment infusion day. [4]PT/INR should be performed for any bleeding issues. [5]Patients are closely monitored for hypotension, arrhythmia, angina and myocardial infarction. At screening, patients who are ≥ 50 years of age or have a history of EKG abnormalities, symptoms of cardiac ischemia or arrhythmia will have a stress test (stress thallium, stress MUGA or dobutamine echocardiogram) to determine their eligibility for participation in the study. EKG will be performed at start of each treatment course and the repeat study drug treatment course. At the start of 1st course, EKG is performed only when >14 days since last EKG. [6]Patients who have an on-going study drug-related SAE upon study completion or at discontinuation of the study will be contacted by the investigator or his/her designee every week until the event is resolved or determined to be irreversible. [7]Tumor response and progression will be evaluated in this study using the new international criteria proposed by the RECIST (1.1). [8]Information about tumor assessment & other therapies received after completion of study treatment will be collected if available [9]Fresh blood samples for HLA A2 blood typing, immune cell levels & phenotype testing will be collected before dosing. [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]Residual samples may be used by Sponsor for research studies of other biomarkers. [12]Use the same blood sample collected before dosing for PK test.

APPENDIX H: APPROVAL PAGE

PROTOCOL TITLE:	A Phase Ib/II Trial of ALT-801 in Combination with Cisplatin and Gemcitabine in Muscle Invasive or Metastatic Urothelial Cancer.
INVESTIGATIONAL DRUG:	ALT-801; c264scTCR-IL2 Fusion Protein
CLINICAL PROTOCOL NUMBER:	CA-ALT-801-01-10
Version# 01 Version# 02 Version# 03	October 31, 2010 July 8, 2011 November 10, 2011
SPONSOR:	Altor Bioscience Corporation 2810 North Commerce Parkway Miramar, FL 33025-3958

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

NOV. 10, 2011
Date

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

Date

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

Nov 10, 2011
Date

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

Nov 10, 2011
Date

CLINICAL STUDY PROTOCOL

Protocol Number: CA-ALT-801-01-10

Protocol Title: A Phase Ib/II Trial of ALT-801 in Combination with Cisplatin and Gemcitabine in Muscle Invasive or Metastatic Urothelial Cancer

Date of Protocol:

Version # 01	October 31, 2010
Version # 02	July 8, 2011
Version # 03	November 10, 2011
Version # 04	December 23, 2011

Sponsor Contact:

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INVESTIGATOR SIGNATURE PAGE

Protocol Number: CA-ALT-801-01-10

Protocol Title: A Phase Ib/II Trial of ALT-801 in Combination with Cisplatin and Gemcitabine in Muscle Invasive or Metastatic Urothelial Cancer

Date of Protocol:

Version # 01	October 31, 2010
Version # 02	July 8, 2011
Version # 03	November 10, 2011
Version # 04	December 23, 2011

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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)

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SYNOPSIS

Sponsor: Altor Bioscience Corporation

Protocol#: CA-ALT-801-01-10

Study Drug Name: Not applicable

Study Treatment

Active agents: ALT-801 (c264scTCR-IL2), recombinant humanized, soluble single-chain TCR-cytokine fusion protein; Cisplatin; Gemcitabine.

Study Type: Interventional

Study Phase: Ib/II

Protocol Title: A Phase Ib/II Trial of ALT-801 in Combination with Cisplatin and gemcitabine in Muscle Invasive or Metastatic Urothelial Cancer

Objectives: To determine the safety and tolerability of the novel combination of addition of ALT-801 (c264scTCR-IL2) to the doublet of cisplatin and gemcitabine in patients with muscle invasive or metastatic urothelial cancer of bladder, renal pelvis, ureters and urethra.

To estimate the anti-tumor activity of this combination of ALT-801, cisplatin and gemcitabine by radiologic or pathologic anti-tumor response, progression free survival (assessed through end of study), and overall survival (assessed through end of study) in treated patients.

To characterize the immunogenicity and pharmacokinetic profile of ALT-801 in combination with cisplatin and gemcitabine in treated patients.

To assess the relationship between tumor presentation of HLA-A*0201/p53 aa 264-272 complex and the safety and clinical benefit of study treatment.

Study Design: This is a Phase Ib/II, open-label, multi-center, competitive enrollment and dose-escalation study of ALT-801 in a biochemotherapy regimen containing cisplatin and gemcitabine in patients who have muscle invasive or metastatic urothelial cancer of bladder, renal pelvis, ureters and urethra. The study will be conducted in conformity with Good Clinical Practice (GCP).

The study includes a dose escalation phase to determine the maximum tolerated dose (MTD) of ALT-801 in combination with cisplatin and gemcitabine and a two-stage expansion phase at the MTD. The dose escalation in this study is conducted using a (3+3) dose escalation design, and the two-stage expansion phase at the MTD using a modified Simon two-stage design (1, 2). In the dose escalation phase of this study, there are five dose levels of ALT-801 (0.04 mg/kg, 0.06 mg/kg and 0.08 mg/kg, 0.10 mg/kg and 0.12 mg/kg) in addition to two de-escalation dose levels. The doses of cisplatin (70 mg/m^2/dose) and gemcitabine (1000 mg/m^2/dose) will be fixed across all ALT-801 dose levels. If the MTD is not reached during the dose escalation phase, the sponsor, the Data Safety Monitoring Board and the principal investigators will meet to discuss whether to amend the protocol to expand the dose escalation phase to include additional ALT-801 dose levels.

Treatments: The planned initial on-study treatment will be for 3 courses. Each course consists of cisplatin (Day #1), gemcitabine (Day #1), ALT-801 (Day #3 & Day #5), gemcitabine (Day #8), ALT-801 (Day #8 & Day #10), and a rest period (Days #11-21). Prior to commencing the second or the third course, subjects will need to meet the continuation criteria. At the completion of the three full courses of study treatment, each patient enrolled will have been scheduled to have a total of 12 doses of the study drug ALT-801, 3 doses of cisplatin, and 6 doses of gemcitabine. After completing the 3-course initial study treatment, patients who have at least stable disease and meet other treatment criteria will repeat study treatment with four additional weekly doses of ALT-801. Delays or modifications are addressed in the protocol. This is illustrated in the following schemas:

Initial Study Treatment:

	Course 1						Course 2						Course 3					
Treatment Day	1	3	5	8	10	11-21	22	24	26	29	31	32-42	43	45	47	50	52	53-63
Cisplatin	X					Rest Period	X					Rest Period	X					Rest Period
Gemcitabine	X			X			X			X			X			X		
ALT-801		X	X	X	X			X	X	X	X			X	X	X	X	

Repeat Study Treatment:

Dose#	1	2	3	4
Repeat Treatment Day	1	8	15	22
ALT-801	X	X	X	X

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, cisplatin and gemcitabine 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®), cisplatin and gemcitabine.

This is the schema for the dose levels during the dose-escalation phase of the study. The -1 and -2 dose levels of ALT-801 are included in case of DLT events in the initial dose level.

Cohort	ALT-801 Dose (mg/kg)	Cisplatin (mg/m^2)	Gemcitabine (mg/m^2)
-2	0.01	70	1000
-1	0.02	70	1000
1 (initial)	0.04	70	1000
2	0.06	70	1000
3	0.08	70	1000
4	0.10	70	1000
5	0.12	70	1000

Dose Escalation: In this phase of the study, a minimum of 3 patients will be enrolled at each dose level. All patients will be monitored for Dose Limiting Toxicity (DLT) for 8 weeks from the initial dose. If 0/3 patients have study treatment-related, dose-limiting toxicity by 8 weeks after the initial dose, the next cohort will be opened for enrollment. If one patient at a dose-level develops drug-related DLT, up to six patients will be enrolled at that dose level and each subsequent higher dose level. If 0 or 1 of 6 patients in a cohort of 6 patients have an event that meets criteria for study treatment-related DLT, then the next cohort will be opened for enrollment. If 2 or more out of 3-6 patients in a dose escalation cohort have a DLT that is drug-related, that dose level will be designated as exceeding the maximum tolerated dose. If there are 3 patients in the dose level below this level, then additional patients (up to 6 total) will be enrolled at that dose level. When there is a dose level with 0 or 1 out of 6 patients with DLT, which is either the maximum planned dose level (level 5) or which is one level below a dose that was not tolerated, the dose that is the maximum tolerated dose will be considered defined. Further changes in the treatment plan may be considered by protocol amendment at that point.

If more than two of six patients experience a DLT at the initial dose level (level 1), then the sponsor, the Data Safety Monitoring Board and the principal investigators will meet to determine how to adjust downward the dose level of cisplatin, gemcitabine, and/or the study drug, or continue with the (-1) and (-2) cohorts, and to determine how to proceed with the study.

Dose limiting toxicity (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.

Dose Expansion: The two-stage expansion phase at the MTD will be conducted using a modified Simon two-stage design (1, 2). Both objective response (OR) (defined as complete response (CR) + partial response (PR)) and clinical benefit (CB) (defined as CR, PR + stable disease (SD)) will be evaluated and common set thresholds of lack of efficacy (OR rate (ORR) = 40%; CB rate (CBR) = 78%) and an efficacy level of interest (ORR = 60%; CBR = 92%) will be selected. The sample size was driven by the parameter that had the larger sample size for each stage.

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

- If at any time the dose escalation phase of the study, more than one patient in a cohort of three, or two of six patients experience any DLT;
- If at any time during the expansion phase of the study, more than 33% the patients experience any drug related DLT.

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 response will be evaluated for up to 18 weeks from the initial dose of the first course of treatment. All patients who receive at least one dose of the study drug ALT-801 will be included in the anti-tumor response evaluation. Between each cohort and at the end of the study, all clinical and safety data will be analyzed for all patients enrolled in the study for dose-response effects.

Population: Patients of 18 years of age and above who are candidates for systemic cisplatin and gemcitabine for the treatment of muscle invasive or metastatic urothelial cancer of bladder, renal pelvis, ureters, and urethra may be selected for further evaluation of eligibility for study participation. 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 or 1 and a life expectancy of at least 12 weeks.

Sample Size: A total of up to 30 assessable patients will be accrued to the initial dose escalation phase of the study (Phase Ib); the estimated number is 21. Up to an additional 40 assessable patients will be enrolled at the expansion phase (Stage 1 and 2) of the study (Phase II). A total of approximately 60 assessable patients will be enrolled and complete the study. Assume a 20% ineligible or non- assessable cases, a total of up 72 patients may be accrued to the study.

Primary Endpoints:

For Stage I only: (1) To define an MTD of ALT-801 in combination with cisplatin and gemcitabine in the treatment of patients with muscle invasive or metastatic urothelial cancer.

For Stage I & II: (2) To assess the safety of the combination study treatment in treated patients.

(3) To assess the objective response rate in treated patients.

Secondary Endpoints:

(1) To assess the progression free survival in treated patients.

(2) To assess the overall survival in treated patients.

(3) To evaluate the immunogenicity and pharmacokinetic profiles of ALT-801 in treated patients.

(4) To assess the relationship between tumor presentation of HLA-A*0201/p53 aa 264-272 complexes and the safety and clinical benefit of study treatment.

Pharmacokinetics & Biomarkers: Blood samples will be collected to assess typing for HLA-A2, immune cell levels, phenotype, pharmacokinetics, 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 the 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 first course of study treatment. 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 immunogenicity of study drug ALT-801 and 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 the first and second courses of study treatment. HLA-A2 typing will be performed only once.

Monitoring Tests: Urine samples for urinalysis, blood samples for standard chemistry, CBC, differential and coagulation will be obtained at screening, on each study drug infusion day, discharge days 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 9 from the initial dose of study treatment.

Anti-tumor Response Evaluation: The anti-tumor response will be evaluated for up to 18 weeks from the initial dose of study treatment: for non-responders: Week 9 and 13; for early responders: Week 9 and 14; for late responders: Week 9, 13 and 18. Objective Response will be evaluated using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors Committee (RECIST) 1.1. Baseline evaluations should be performed up to 28 days before starting study treatment. The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-ups. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the anti-tumor effect of the treatment. However, cystoscopic evaluation may be used routinely in this population, in addition to radiologic testing. 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 and overall survival of all enrolled patients will be assessed at 6, 9, 12, 18, 24, 30 and 36 months from the start of study treatment, or through the point designated 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 SAEs and all events that trigger patient's study treatment discontinuation to the sponsor via phone, fax or email (or a combination) up to 1 day 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 a day of its learning of the event. The study centers should report the other adverse events to the sponsor following the guidelines defined in the study protocol. All study drug related adverse events (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 pharmacokinetic data will be evaluated. For estimation of duration of response, 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[1]	INITIAL TREATMENT PERIOD																	SCAN #1	SCAN #2	REPEAT TREATMENT				SCAN #3	FOLLOW-UPS						
		COURSE 1						COURSE 2						COURSE 3																		
Month(late responders in parentheses)		1												2					3	4	3 – 4/(4-5)				4/(5)	6	9	12	18	24	30	36
Week (late responders in parentheses)		1			2		3	4			5		6	7			8		9	13	10/ (14)	11/ (15)	12/ (16)	13/ (17)	14/ (18)							
Week Day		M	W	F	M	W		M	W	F	M	W		M	W	F	M	W			M	M	M	M								
Treatment Day		*1*	*3*	*5*	*8*	*10*		*22*	*24*	*26*	*29*	*31*		*43*	*45*	*47*	*50*	*52*														
Informed consent	X						R						R																			
Medical history	X						e						e																			
Serum pregnancy test[2]	X						s						s																			
Complete physical exam	X	X					t	X					t	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	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	X	X	X	X	X							
CBC with Differential, Blood Chemistry	X	X	X	X	X	X	P	X	X	X	X	X	P	X	X	X	X	X	X	X	X	X	X	X	X							
Coagulation (PT/INR)[4]	X						e						e																			
Urinalysis	X	X					r	X					r	X							X											
Cardiac functions[5]	X	X[5]	X	X	X	X	i	X[5]	X	X	X	X	i	X[5]	X	X	X	X			X[5]	X	X	X								
Pulmonary functions	X						o						o																			
Adverse event assessment[6]	X	X	X	X	X	X	d	X	X	X	X	X	d	X	X	X	X	X	X	X	X	X	X	X	X							
Tumor assessment[7]	X																		X	X					X							
Survival Assessment[8]																										X	X	X	X	X	X	X
HLA A2 Typing, immune cell levels & phenotype[11]			X[9]						X[9]																							
HLA-A*0201/p53 tumor typing			X																													
PK, IFNγ, TNFα[11]			X[10]																													
Immunogenicity tests[11]			X[12]																X													
Cisplatin		**c1**						**c2**						**c3**																		
Gemcitabine		**g1**			**g2**			**g3**			**g4**			**g5**			**g6**				**a13**	**a14**	**a15**	**a16**							
Study drug (ALT-801)[13]			**a1**	**a2**	**a3**	**a4**			**a5**	**a6**	**a7**	**a8**			**a9**	**a10**	**a11**	**a12**														

[1]Screening evaluations are performed ≤ 14 days, scan/x-ray ≤ 28 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 the drug treatment and before discharge, and body weight before study treatment infusion on study treatment infusion day. [4]PT/INR should be performed for any bleeding issues. [5]Patients are closely monitored for hypotension, arrhythmia, angina and myocardial infarction. At screening, patients who are ≥ 50 years of age or have a history of EKG abnormalities, symptoms of cardiac ischemia or arrhythmia will have a stress test (stress thallium, stress MUGA or dobutamine echocardiogram) to determine their eligibility for participation in the study. EKG will be performed at start of each treatment course and the repeat study drug treatment course. At the start of 1st course, EKG is performed only when >14 days since last EKG. [6]Patients who have an on-going study drug-related SAE upon study completion or at discontinuation of the study will be contacted by the investigator or his/her designee every week until the event is resolved or determined to be irreversible. [7]Tumor response and progression will be evaluated in this study using the new international criteria proposed by the RECIST (1.1). [8]Information about tumor assessment & other therapies received after completion of study treatment will be collected if available [9]Fresh blood samples for HLA A2 blood typing, immune cell levels & phenotype testing will be collected before dosing. [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]Residual samples may be used by Sponsor for research studies of other biomarkers. [12]Use the same blood sample collected before dosing for PK test.[13]On the days when gemcitabine and ALT-801 are both given, gemcitabine should be dosed first.

APPENDIX H: APPROVAL PAGE

PROTOCOL TITLE:	A Phase Ib/II Trial of ALT-801 in Combination with Cisplatin and Gemcitabine in Muscle Invasive or Metastatic Urothelial Cancer.
INVESTIGATIONAL DRUG:	ALT-801; c264scTCR-IL2 Fusion Protein
CLINICAL PROTOCOL NUMBER:	CA-ALT-801-01-10
Version# 01	October 31, 2010
Version# 02	July 8, 2011
Version# 03	November 10, 2011
Version# 04	December 23, 2011
SPONSOR:	Altor Bioscience Corporation 2810 North Commerce Parkway Miramar, FL 33025-3958

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Peter Rhode, Ph.D.
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Bee Y. Huang, M.S.
Director, Clinical Development

12-23-11
Date

CLINICAL STUDY PROTOCOL

Protocol Number: CA-ALT-801-01-10

Protocol Title: A Phase Ib/II Trial of ALT-801 in Combination with Cisplatin and Gemcitabine in Muscle Invasive or Metastatic Urothelial Cancer

Date of Protocol:

Version # 01	October 31, 2010
Version # 02	July 8, 2011
Version # 03	November 10, 2011
Version # 04	December 23, 2011
Version # 05	May 11, 2012

Sponsor Contact:

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INVESTIGATOR SIGNATURE PAGE

Protocol Number: CA-ALT-801-01-10

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Version # 05	May 11, 2012

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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)

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SYNOPSIS

Sponsor: Altor Bioscience Corporation

Protocol#: CA-ALT-801-01-10

Study Drug Name: Not applicable

Study Treatment

Active agents: ALT-801 (c264scTCR-IL2), recombinant humanized, soluble single-chain TCR-cytokine fusion protein; Cisplatin; Gemcitabine.

Study Type: Interventional

Study Phase: Ib/II

Protocol Title: A Phase Ib/II Trial of ALT-801 in Combination with Cisplatin and gemcitabine in Muscle Invasive or Metastatic Urothelial Cancer

Objectives: To determine the safety and tolerability of the novel combination of addition of ALT-801 (c264scTCR-IL2) to the doublet of cisplatin and gemcitabine in patients with muscle invasive or metastatic urothelial cancer of bladder, renal pelvis, ureters and urethra.

To estimate the anti-tumor activity of this combination of ALT-801, cisplatin and gemcitabine by radiologic or pathologic anti-tumor response, progression free survival (assessed through end of study), and overall survival (assessed through end of study) in treated patients.

To characterize the immunogenicity and pharmacokinetic profile of ALT-801 in combination with cisplatin and gemcitabine in treated patients.

To assess the relationship between tumor presentation of HLA-A*0201/p53 aa 264-272 complex and the safety and clinical benefit of study treatment.

Study Design: This is a Phase Ib/II, open-label, multi-center, competitive enrollment and dose-escalation study of ALT-801 in a biochemotherapy regimen containing cisplatin and gemcitabine in patients who have muscle invasive or metastatic urothelial cancer of bladder, renal pelvis, ureters and urethra. The study will be conducted in conformity with Good Clinical Practice (GCP).

The study includes a dose escalation phase to determine the maximum tolerated dose (MTD) and the recommended dose (RD) for dose expansion of ALT-801 in combination with cisplatin and gemcitabine and a two-stage expansion phase at the RD. The dose escalation in this study is conducted using a (3+3) dose escalation design, and the two-stage expansion phase at the RD using a modified Simon two-stage design (1, 2). In the dose escalation phase of this study, there are five dose levels of ALT-801 (0.04 mg/kg, 0.06 mg/kg, 0.08 mg/kg, 0.10 mg/kg and 0.12 mg/kg) in addition to two de-escalation dose levels. The doses of cisplatin (70 mg/m^2/dose) and gemcitabine (1000 mg/m^2/dose) will be fixed across all ALT-801 dose levels. If the MTD cannot be determined after the maximum planned escalating dose level has been reached, or the RD for dose expansion cannot be determined during the dose escalation phase, the sponsor, the Data Safety Monitoring Board (DSMB) and the principal investigators will meet to

discuss whether to amend the protocol to expand the dose escalation phase to include additional ALT-801 dose levels.

Treatments: The planned initial on-study treatment will be for 3 courses of chemo-immunotherapy. Each course consists of cisplatin (Day #1), gemcitabine (Day #1), ALT-801 (Day #3 & Day #5), gemcitabine (Day #8), ALT-801 (Day #8 & Day #12 or #15), and a rest period (Days #13 (or #16) - #21). The alternative dosing day (Day #15) for the last dose (dose #4) of ALT-801 in each course is provided to allow sufficient recovery from transient study drug related toxicities. Prior to commencing the second or the third course of study treatment, subjects will need to meet the treatment continuation criteria. At completion of the three full courses of study treatment, each patient enrolled will have received a total of 12 doses of the study drug ALT-801, 3 doses of cisplatin, and 6 doses of gemcitabine. After completing the 3-course initial study treatment, patients who have at least stable disease and meet other treatment criteria will repeat study treatment with four additional weekly doses of ALT-801. Treatment delays or dose modifications or omissions are addressed in the protocol. The treatment schedule is illustrated in the following schemas:

Initial Study Treatment:

	Course 1						Course 2						Course 3				
Treatment Day	1	3	5	8	12(15)	13(16)-21	22	24	26	29	33(36)	34(37)-42	43	45	47	50	54(57)
Cisplatin	X					Rest Period	X					Rest Period	X				
Gemcitabine	X			X			X			X			X			X	
ALT-801		X	X	X	X			X	X	X	X			X	X	X	X

RRepeat Study Treatment:

Dose#	1	2	3	4
Repeat Treatment Day	1	8	15	22
ALT-801	X	X	X	X

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, cisplatin and gemcitabine 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®), cisplatin and gemcitabine.

This is the schema for the dose levels during the dose-escalation phase of the study. The -1 and -2 dose levels of ALT-801 are included in case of DLT events in the initial dose level.

Cohort	**ALT-801 Dose (mg/kg)**	**Cisplatin (mg/m^2)**	**Gemcitabine (mg/m^2)**
-2	0.01	70	1000
-1	0.02	70	1000
1 (initial)	0.04	70	1000
2	0.06	70	1000
3	0.08	70	1000
4	0.10	70	1000
5	0.12	70	1000

Dose Escalation: In this phase of the study, a minimum of 3 patients will be enrolled at each dose level. All patients will be monitored for Dose Limiting Toxicity (DLT) for 8 weeks from the initial dose. If 0/3 patients have study treatment-related, dose-limiting toxicity by 8 weeks after the initial dose, the next cohort will be opened for enrollment. If one patient at a dose-level develops drug-related DLT, up to six patients will be enrolled at that dose level and each subsequent higher dose level. If 0 or 1 of 6 patients in a cohort of 6 patients have an event that meets criteria for study treatment-related DLT, then the next cohort will be opened for enrollment. If 2 or more out of 3-6 patients in a dose escalation cohort have a DLT that is drug-related, that dose level will be designated as exceeding the maximum tolerated dose. If there are 3 patients in the dose level below this level, then additional patients (up to 6 total) will be enrolled at that dose level. When there is a dose level with 0 or 1 out of 6 patients with DLT, which is either the maximum planned dose level (level 5) or which is one level below a dose that was not tolerated, the dose that is the maximum tolerated dose (MTD) will be considered defined. Further changes in the treatment plan may be considered by protocol amendment at that point.

If more than two of six patients experience a DLT at the initial dose level (level 1), then the sponsor, the Data Safety Monitoring Board (DSMB) and the principal investigators will meet to determine how to adjust downward the dose level of cisplatin, gemcitabine, and/or the study drug, or continue with the (-1) and (-2) cohorts, and to determine how to proceed with the study.

At any time during the dose escalation phase of the study, whether or not the MTD or the maximum planned escalating dose level is reached, the dose escalation phase may be concluded due to favorable anti-tumor effect observed in the enrolled patients. The DSMB will recommend a dose level of ALT-801 (RD) for the dose expansion phase of the study.

Dose limiting toxicity (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.

Dose Expansion: The two-stage expansion phase at the recommended dose (RD) will be conducted using a modified Simon two-stage design (1, 2). Both objective response (OR) (defined as complete response (CR) + partial response (PR)) and clinical benefit (CB) (defined as CR, PR + stable disease (SD)) will be evaluated and common set thresholds of lack of efficacy (OR rate (ORR) = 40%; CB rate (CBR) = 78%) and an efficacy level of interest (ORR = 60%;

CBR = 92%) will be selected. The sample size was driven by the parameter that had the larger sample size for each stage.

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

- If at any time during the dose escalation phase of the study,
  - ✓ more than one patient in a cohort of three, or two of six patients experience any DLT or,
  - ✓ favorable anti-tumor response data collected from enrolled patients that indicates a dose level with significant therapeutic effect may have been found
- If at any time during the expansion phase of the study, more than 33% the patients experience any drug related DLT.

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 response will be evaluated for up to 18 weeks from the initial dose of the first course of treatment. All patients who receive at least one dose of the study drug ALT-801 will be included in the anti-tumor response evaluation. Between each cohort and at the end of the study, all clinical and safety data will be analyzed for all patients enrolled in the study for dose-response effects.

Population: Patients of 18 years of age and above who are candidates for systemic cisplatin and gemcitabine for the treatment of muscle invasive or metastatic urothelial cancer of bladder, renal pelvis, ureters, and urethra may be selected for further evaluation of eligibility for study participation. 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 or 1 .

Sample Size: A total of up to 30 assessable patients will be accrued to the initial dose escalation phase of the study (Phase Ib); the estimated number is 21. Up to an additional 40 assessable patients will be enrolled at the expansion phase (Stage 1 and 2) of the study (Phase II). A total of approximately 60 assessable patients will be enrolled and complete the study. Assume a 20% ineligible or non- assessable cases, a total of up 72 patients may be accrued to the study.

Primary Endpoints:

For Stage I only: (1) To define an MTD and RD for dose expansion of ALT-801 in combination with cisplatin and gemcitabine in the treatment of patients with muscle invasive or metastatic urothelial cancer.

For Stage I & II: (2) To assess the safety of the combination study treatment in treated patients.

(3) To assess the objective response rate in treated patients.

Secondary Endpoints:

(1) To assess the progression free survival in treated patients.

(2) To assess the overall survival in treated patients.

(3) To evaluate the immunogenicity and pharmacokinetic profiles of ALT-801 in treated patients.

(4) To assess the relationship between tumor presentation of HLA-A*0201/p53 aa 264-272 complexes and the safety and clinical benefit of study treatment.

Pharmacokinetics & Biomarkers: Blood samples will be collected to assess typing for HLA-A2, immune cell levels, phenotype, pharmacokinetics, 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 the 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 first course of study treatment. 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 immunogenicity of study drug ALT-801 and 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 the first and second courses of study treatment. HLA-A2 typing will be performed only once.

Monitoring Tests: Urine samples for urinalysis, blood samples for standard chemistry, CBC, differential and coagulation will be obtained at screening, on each study drug infusion day, discharge days 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 9 from the initial dose of study treatment.

Anti-tumor Response Evaluation: The anti-tumor response will be evaluated for up to 18 weeks from the initial dose of study treatment: for non-responders: Week 9 and 13; for early responders: Week 9 and 14; for late responders: Week 9, 13 and 18. Objective Response will be evaluated using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors Committee (RECIST) 1.1. Baseline evaluations should be performed up to 28 days before starting study treatment. The same method of assessment and the

same technique should be used to characterize each identified and reported lesion at baseline and during follow-ups. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the anti-tumor effect of the treatment. However, cystoscopic evaluation may be used routinely in this population, in addition to radiologic testing. 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 and overall survival of all enrolled patients will be assessed at 6, 9, 12, 18, 24, 30 and 36 months from the start of study treatment, or through the point designated 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 SAEs and all events that trigger patient's study treatment discontinuation to the sponsor via phone, fax or email (or a combination) up to 1 day 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 a day of its learning of the event. The study centers should report the other adverse events to the sponsor following the guidelines defined in the study protocol. All study drug related adverse events (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 pharmacokinetic data will be evaluated. For estimation of duration of response, 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[1]	INITIAL TREATMENT PERIOD																	SCAN #1	SCAN #2	REPEAT TREATMENT				SCAN #3	FOLLOW-UPS						
		COURSE 1						COURSE 2						COURSE 3																		
Month(late responders in parentheses)		1									2								3	4	3 – 4/(4-5)				4/(5)	6	9	12	18	24	30	36
Week (late responders in parentheses)		1			2		3	4			5		6	7			8		9	13	10/ (14)	11/ (15)	12/ (16)	13/ (17)	14/ (18)							
Week Day		M	W	F	M	F		M	W	F	M	F		M	W	F	M	F			M	M	M	M								
Treatment Day		*1*	*3*	*5*	*8*	*12*		*22*	*24*	*26*	*29*	*33*		*43*	*45*	*47*	*50*	*54*														
Informed consent	X						**Rest Period**						**Rest Period**																			
Medical history	X																														
Serum pregnancy test[2]	X																														
Complete physical exam	X	X						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	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	X	X	X	X	X						
CBC with Differential, Blood Chemistry	X	X	X	X	X	X		X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X						
Coagulation (PT/INR)[4]	X																														
Urinalysis	X	X						X						X							X										
Cardiac functions[5]	X	X[5]	X	X	X	X		X[5]	X	X	X	X		X[5]	X	X	X	X			X[5]	X	X	X							
Pulmonary functions	X																														
Adverse event assessment[6]	X	X	X	X	X	X		X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X						
Tumor assessment[7]	X																		X	X					X						
Survival Assessment[8]																										X	X	X	X	X	X	X
HLA A2 Typing, immune cell levels & phenotype[11]			X[9]						X[9]																						
HLA-A*0201/p53 tumor typing			X																												
PK, IFNγ, TNFα[11]			X[10]																												
Immunogenicity tests[11]			X[12]																X												
Cisplatin		**c1**						**c2**						**c3**																	
Gemcitabine		**g1**			**g2**			**g3**			**g4**			**g5**			**g6**														
Study drug (ALT-801)[13]			**a1**	**a2**	**a3**	**a4[14]**			**a5**	**a6**	**a7**	**a8[14]**			**a9**	**a10**	**a11**	**a12[14]**			**a13**	**a14**	**a15**	**a16**								

[1]Screening evaluations are performed ≤ 14 days, scan/x-ray ≤ 28 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 every 2 hours after the drug treatment and before discharge, and body weight before study treatment infusion on study treatment infusion day. [4]PT/INR should be performed for any bleeding issues. [5]Patients are closely monitored for hypotension, arrhythmia, angina and myocardial infarction. At screening, patients who are ≥ 50 years of age or have a history of EKG abnormalities, symptoms of cardiac ischemia or arrhythmia will have a stress test (stress thallium, stress MUGA or dobutamine echocardiogram) to determine their eligibility for participation in the study. EKG will be performed for all patients at start of each treatment course and the repeat study drug treatment course. At the start of 1st course, EKG is performed only when >14 days since last EKG. [6]Patients who have an on-going study drug-related SAE upon study completion or at discontinuation of the study will be contacted by the investigator or his/her designee every week until the event is resolved or determined to be irreversible. [7]Tumor response and progression will be evaluated in this study using the new international criteria proposed by the RECIST (1.1). [8]Information about tumor assessment & other therapies received after completion of study treatment will be collected if available [9]Fresh blood samples for HLA A2 blood typing, immune cell levels & phenotype testing will be collected before dosing. [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]Residual samples may be used by Sponsor for research studies of other biomarkers. [12]Use the same blood sample collected before dosing for PK test.[13]On the days when gemcitabine and ALT-801 are both given, gemcitabine should be dosed first. [14]**This dose can be delayed to the following Monday.**

APPENDIX H: APPROVAL PAGE

PROTOCOL TITLE:	A Phase Ib/II Trial of ALT-801 in Combination with Cisplatin and Gemcitabine in Muscle Invasive or Metastatic Urothelial Cancer.
INVESTIGATIONAL DRUG:	ALT-801; c264scTCR-IL2 Fusion Protein
CLINICAL PROTOCOL NUMBER:	CA-ALT-801-01-10
Version# 01	October 31, 2010
Version# 02	July 8, 2011
Version# 03	November 10, 2011
Version# 04	December 23, 2011
Version# 05	May 11, 2012
SPONSOR:	Altor Bioscience Corporation 2810 North Commerce Parkway Miramar, FL 33025-3958

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May 15, 2012
Date

CLINICAL STUDY PROTOCOL

Protocol Number: CA-ALT-801-01-10

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INVESTIGATOR SIGNATURE PAGE

Protocol Number: CA-ALT-801-01-10

Protocol Title: A Phase Ib/II Trial of ALT-801 in Combination with Cisplatin and Gemcitabine in Muscle Invasive or Metastatic Urothelial Cancer

Date of Protocol:

Version # 01	October 31, 2010
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Version # 03	November 10, 2011
Version # 04	December 23, 2011
Version # 05	May 11, 2012
Version # 06	October 18, 2012

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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)

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SYNOPSIS

Sponsor: Altor Bioscience Corporation

Protocol#: CA-ALT-801-01-10

Study Drug Name: Not applicable

Study Treatment

Active agents: ALT-801 (c264scTCR-IL2), recombinant humanized, soluble single-chain TCR-cytokine fusion protein; Cisplatin; Gemcitabine.

Study Type: Interventional

Study Phase: Ib/II

Protocol Title: A Phase Ib/II Trial of ALT-801 in Combination with Cisplatin and gemcitabine in Muscle Invasive or Metastatic Urothelial Cancer

Objectives: To determine the safety and tolerability of the novel combination of ALT-801 (c264scTCR-IL2) with cisplatin and gemcitabine or the combination of ALT-801 with gemcitabine alone in patients with muscle invasive or metastatic urothelial cancer of bladder, renal pelvis, ureters and urethra.

To estimate the anti-tumor activity of ALT-801 in combination with cisplatin and gemcitabine or ALT-801 in combination with gemcitabine alone by radiologic or pathologic anti-tumor response, progression free survival (assessed through the end of the study), and overall survival (assessed through the end of the study) in treated patients.

To characterize the immunogenicity and pharmacokinetic profile of ALT-801 in combination with cisplatin and gemcitabine and the immunogenicity of ALT-801 in combination with gemcitabine alone in treated patients.

To assess the relationship between tumor presentation of HLA-A*0201/p53 aa 264-272 complex and the safety and clinical benefit of study treatment.

Study Design: This is a Phase Ib/II, open-label, multi-center, competitive enrollment and dose-escalation study of ALT-801 in a biochemotherapy regimen either containing cisplatin and gemcitabine or containing gemcitabine alone in patients who have muscle invasive or metastatic urothelial cancer of bladder, renal pelvis, ureters and urethra. The study will be conducted in conformity with Current Good Clinical Practices (cGCP).

The study includes a dose escalation phase (Phase Ib), to determine the maximum tolerated dose (MTD) and the recommended dose (RD) of ALT-801, and a dose expansion phase (Phase II) with study treatment containing ALT-801 at the RD level, to assess the effectiveness of study treatment

The Phase Ib dose escalation study is conducted using traditional (3+3) dose escalation rules. Patients enrolled in his phase will all receive the cisplatin-containing study treatment (ALT-801, cisplatin and gemcitabine).

In the Phase II expansion study, conducted with the study treatment containing ALT-801 at the RD level, patients are enrolled into two treatment groups – Expansion Group 1, treated with a cisplatin containing regimen:

ALT-801, cisplatin and gemcitabine; Expansion Group 2, for platinum-refractory patients, treated with a non-cisplatin containing regimen: ALT-801 and gemcitabine. The Group 1 expansion will be conducted using a modified Simon two-stage design (1, 2). The Group 2 expansion will be conducted based an exact single-stage design [1]. After completion of Stage I expansion with the Expansion Group 1, patients with disease refractory to platinum-based therapies will be enrolled to the Expansion Group 2 to receive the non-cisplatin-containing study treatment as a "second-line" regimen.

[2, 3] In the dose escalation phase of this study, there are five dose levels of ALT-801 (0.04 mg/kg, 0.06 mg/kg, 0.08 mg/kg, 0.10 mg/kg and 0.12 mg/kg) in addition to two de-escalation dose levels. The doses of cisplatin (70 mg/m^2/dose) and gemcitabine (1000 mg/m^2/dose) will be fixed across all ALT-801 dose levels. If the MTD cannot be determined after the maximum planned escalating dose level has been reached, or the RD for dose expansion cannot be determined during the dose escalation phase, the sponsor, the Data Safety Monitoring Board (DSMB) and the principal investigators will meet to discuss whether to amend the protocol to expand the dose escalation phase to include additional ALT-801 dose levels.

Treatments: The planned initial on-study treatment will be for 3 courses of chemo-immunotherapy. Each course consists of cisplatin (Day #1), gemcitabine (Day #1), ALT-801 (Day #3 & Day #5), gemcitabine (Day #8), ALT-801 (Day #8 & Day #12 or #15), and a rest period (Days #13 (or #16) - #21). The alternative dosing day (Day #15) for the last dose (dose #4) of ALT-801 in each course is provided to allow sufficient recovery from transient study drug related toxicities. Patients with disease refractory to platinum-based therapies who are enrolled in the Expansion Group 2 will receive gemcitabine without cisplatin on Day # 1 of each treatment course. Prior to commencing the second or the third course of study treatment, subjects will need to meet the treatment continuation criteria. At completion of the three full courses of study treatment, each patient enrolled will have received a total of 12 doses of the study drug ALT-801; 3 doses of cisplatin (no dose of cisplatin for patients enrolled to the Expansion Group 2); and 6 doses of gemcitabine. After completing the 3-course initial study treatment, patients who have at least stable disease and meet other treatment criteria will have maintenance study treatment with an additional 3-week course of ALT-801 and gemcitabine: Gemcitabine and ALT-801 on Day #1 and Day #15, ALT-801 on Day #3 and Day #17, and a rest period (Day #4 to Day #14). Treatment delays or dose modifications or omissions are addressed in the protocol. The treatment schedule is illustrated in the following schemas:

Initial Study Treatment:

	Course 1						Course 2						Course 3				
Treatment Day	1	3	5	8	12(15)	13(16)-21	22	24	26	29	33(36)	34(37)-42	43	45	47	50	54(57)
Cisplatin	X*					Rest Period	X*					Rest Period	X*				
Gemcitabine	X			X			X			X			X			X	
ALT-801		X	X	X	X			X	X	X	X			X	X	X	X

*not given to patients who are enrolled in the Expansion Group 2 with disease refractory to platinum-based therapy.

Maintenance Study Treatment:

	Maintenance Course				
Treatment Day	1	3	4-14	15	17
Gemcitabine	X		Rest Period	X	
ALT-801	X	X		X	X

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, cisplatin and gemcitabine 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®), cisplatin and gemcitabine.

This is the schema for the dose levels during the dose-escalation phase of the study. The -1 and -2 dose levels of ALT-801 are included in case of DLT events in the initial dose level.

Cohort	ALT-801 Dose (mg/kg)	Cisplatin (mg/m^2)	Gemcitabine (mg/m^2)
-2	0.01	70	1000
-1	0.02	70	1000
1 (initial)	0.04	70	1000
2	0.06	70	1000
3	0.08	70	1000
4	0.10	70	1000
5	0.12	70	1000

Dose Escalation: In this phase of the study, a minimum of 3 patients will be enrolled at each dose level. All patients will be monitored for Dose Limiting Toxicity (DLT) for 8 weeks from the initial dose. If 0/3 patients has study treatment-related, dose-limiting toxicity by 8 weeks after the initial dose, the next cohort will be opened for enrollment. If one patient at a dose-level develops drug-related DLT, up to six patients will be enrolled at that dose level and each subsequent higher dose level. If 0 or 1 of 6 patients in a cohort of 6 patients has an event that meets criteria for study treatment-related DLT, then the next cohort will be opened for enrollment. If 2 or more out of 3-6 patients in a dose escalation cohort have a DLT that is drug-related, that dose level will be designated as exceeding the maximum tolerated dose. If there are 3 patients in the dose level below this level, then additional patients (up to 6 total) will be enrolled at that dose level. When there is a dose level with 0 or

1 out of 6 patients with DLT, which is either the maximum planned dose level (level 5) or which is one level below a dose that was not tolerated, the dose that is the maximum tolerated dose (MTD) will be considered defined. Further changes in the treatment plan may be considered by protocol amendment at that point.

If more than two of six patients experience a DLT at the initial dose level (level 1), then the sponsor, the Data Safety Monitoring Board (DSMB) and the principal investigators will meet to determine how to adjust the dose level of cisplatin, gemcitabine, and/or the study drug downward, or continue with the (-1) and (-2) cohorts, and to determine how to proceed with the study.

At any time during the dose escalation phase of the study, whether or not the MTD or the maximum planned escalating dose level is reached, the dose escalation phase may be concluded due to favorable anti-tumor effect observed in the enrolled patients. The DSMB will recommend a dose level of ALT-801, the recommended dose (RD), for the dose expansion phase of the study.

Dose limiting toxicity (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 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.

Dose Expansion: The Phase II dose expansion study, conducted with study treatment containing ALT-801 at the RD level, patients are enrolled to two treatment groups – Expansion Group 1, treated with a cisplatin containing regimen: ALT-801, cisplatin and gemcitabine; Expansion Group 2, for platinum-refractory patients, treated with a non-cisplatin containing regimen: ALT-801 and gemcitabine. Both objective response (OR) (defined as complete response (CR) + partial response (PR)) and clinical benefit (CB) (defined as CR, PR + stable disease (SD)) will be evaluated.

The Group 1 expansion will be conducted using a modified Simon two-stage design (1, 2). [2, 3]Common set thresholds of lack of efficacy (OR rate (ORR) = 40%; CB rate (CBR) = 78%) and an efficacy level of interest (ORR = 60%; CBR = 92%) will be selected. The sample size was driven by the parameter that had the larger sample size for each stage. The Group 2 expansion will be conducted based on an exact single-stage design [1]. Sample size for the expansion was calculated according to the single-stage design of A'Hern [1] to reject a baseline ORR of 10% when the true ORR is 40%.

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

- If at any time during the dose escalation phase of the study,
  - ✓ more than one patient in a cohort of three, or two patients in a cohort of six patients experience any DLT or,
  - ✓ favorable anti-tumor response data collected from enrolled patients that indicates a dose level with significant therapeutic effect may have been found
- If at any time during the expansion phase of the study, more than 33% the patients experience any drug related DLT.

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 response will be evaluated for up to 18 weeks from the initial dose of the first course of treatment. All patients who receive at least one dose of the study drug ALT-801 will be included in the anti-tumor response evaluation. Between each cohort and at the end of the study, all clinical and safety data will be analyzed for all patients enrolled in the study for dose-response effects.

Population: Patients of 18 years of age and above who are candidates for systemic cisplatin and gemcitabine for the treatment of muscle invasive or metastatic urothelial cancer of bladder, renal pelvis, ureters, and urethra may be selected for further evaluation of eligibility for study participation. 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 or 1.

Sample Size: A total of up to 30 assessable patients will be accrued to the initial dose escalation phase of the study (Phase Ib); the estimated number is 9. In the dose expansion phase, up to an additional 40 assessable patients will be enrolled to receive cisplatin-containing study treatment in the Expansion Group 1 and up to 14 patients will be enrolled to receive non-cisplatin-containing study treatment in the Expansion Group 2. A total of approximately 63 assessable patients will be enrolled and complete the study. Assuming a 20% ineligible or non-assessable cases, a total of up to 76 patients may be accrued to the study.

Primary Endpoints:

For Stage I only: (1) To define an MTD and/or RD for dose expansion of ALT-801 in combination with cisplatin and gemcitabine or ALT-801 in combination with gemcitabine alone in the treatment of patients with muscle invasive or metastatic urothelial cancer.

For Stage I & II:

(2) To assess the safety of the combination study treatment in treated patients.

(3) To assess the objective response rate in treated patients.

Secondary Endpoints:

(1) To assess the progression free survival in treated patients.

(2) To assess the overall survival in treated patients.

(3) To evaluate the immunogenicity and pharmacokinetic profiles of ALT-801 in treated patients.

(4) To assess the relationship between tumor presentation of HLA-A*0201/p53 aa264-272 complexes and the safety and clinical benefit of study treatment.

Pharmacokinetics & Biomarkers:

Blood samples will be collected to assess typing for HLA-A2, immune cell levels, phenotype, pharmacokinetics, 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 the 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 first course of study treatment. 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 immunogenicity of study drug ALT-801 and 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 the first and second courses of study treatment. HLA-A2 typing will be performed only once.

Monitoring Tests:

Urine samples for urinalysis, blood samples for standard chemistry, CBC, differential and coagulation will be obtained for tests required at screening for study entry eligibility evaluation or for tests required throughout the treatment and follow-up periods for patient safety monitoring. 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 9 from the initial dose of study treatment.

Anti-tumor Response Evaluation:

The anti-tumor response will be evaluated for up to 18 weeks from the initial dose of study treatment: for non-responders: Week 9 and 13; for early responders: Week 9 and 14; for late responders: Week 9, 13 and 18. Objective Response will be evaluated using the new international criteria

proposed by the Response Evaluation Criteria in Solid Tumors Committee (RECIST) 1.1. Baseline evaluations should be performed up to 28 days before starting study treatment. The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-ups. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the anti-tumor effect of the treatment. However, cystoscopic evaluation may be used routinely in this population, in addition to radiologic testing. 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 and overall survival of all enrolled patients will be assessed at 6, 9, 12, 18, 24, 30 and 36 months from the start of study treatment, or through the point designated 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 SAEs and all events that trigger patient's study treatment discontinuation to the sponsor via phone, fax or email (or a combination) up to 1 day 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 a day of its learning of the event. The study centers should report the other adverse events to the sponsor following the guidelines defined in the study protocol. All study drug related adverse events (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 pharmacokinetic data will be evaluated. For estimation of duration of response, 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[1]	INITIAL TREATMENT PERIOD																	SCAN #1	SCAN #2	MAINTENANCE TREATMENT					SCAN #3	FOLLOW-UPS							
		COURSE 1						COURSE 2						COURSE 3																		
Month(late responders in parentheses)		1						2											3	4	3 – 4/(4-5)					4/(5)	6	9	12	18	24	30	36
Week (late responders in parentheses)		1			2		3	4			5		6	7			8		9	13	10/ (14)		11/ (15)	12/ (16)		13/ (17)							
Week Day		M	W	F	M	F		M	W	F	M	F		M	W	F	M	F			M	W		M	W							
Treatment Day		*1*	*3*	*5*	*8*	*12*		*22*	*24*	*26*	*29*	*33*		*43*	*45*	*47*	*50*	*54*			*1*	*3*		*15*	**17**							
Informed consent	X						**Rest Period**						**Rest Period**										**Rest Period**										
Medical history	X																															
Serum pregnancy test[2]	X																															
Complete physical exam	X	X						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	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	X	X		X	X	X						
CBC with Differential, Blood Chemistry	X	X	X	X	X	X		X	X	X	X	X		X	X	X	X	X	X	X	X	X		X	X	X						
Coagulation (PT/INR)[4]	X																															
Urinalysis	X	X						X						X							X											
Cardiac functions[5]	X	X[5]	X	X	X	X		X[5]	X	X	X	X		X[5]	X	X	X	X			X[5]	X		X	X							
Pulmonary functions	X																															
Adverse event assessment[6]	X	X	X	X	X	X		X	X	X	X	X		X	X	X	X	X	X	X	X	X		X	X	X						
Tumor assessment[7]	X																		X	X						X						
Survival Assessment[8]																											X	X	X	X	X	X	X
HLA A2 Typing, immune cell levels & phenotype[11]		X[9]	X[9]		X[9]				X[9]																							
HLA-A*0201/p53 tumor typing			X																													
PK, IFNγ, TNFα[11]			X[10]																													
Immunogenicity tests[11]			X[12]																X													
Cisplatin		**c1**						**c2**						**c3**																		
Gemcitabine		**g1**			**g2**			**g3**			**g4**			**g5**			**g6**				**g7**			**g8**							
Study drug (ALT-801)[13]			**a1**	**a2**	**a3**	**a4[14]**			**a5**	**a6**	**a7**	**a8[14]**			**a9**	**a10**	**a11**	**a12[14]**			**a13**	**a14**		**a15**	**a16**							

[1]Screening evaluations are performed < 14 days; stress test, if required, scan/x-ray <28 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 every 2 hours after the drug treatment and before discharge, and body weight before study treatment infusion on study treatment infusion day. [4]PT/INR should be performed for any bleeding issues. [5]Patients are closely monitored for hypotension, arrhythmia, angina and myocardial infarction. At screening, patients who are ≥ 50 years of age or have a history of EKG abnormalities, symptoms of cardiac ischemia or arrhythmia will have a stress test (stress thallium, stress MUGA or dobutamine echocardiogram) to determine their eligibility for participation in the study. EKG will be performed for all patients at start of each initial treatment course and the maintenance study treatment course. At the start of 1st course, EKG is performed only when >14 days since last EKG. [6]Patients who have an on-going study drug-related SAE upon study completion or at discontinuation of the study will be contacted by the investigator or his/her designee every week until the event is resolved or determined to be irreversible. [7]Tumor response and progression will be evaluated in this study using the new international criteria proposed by the RECIST (1.1). 8Information about tumor assessment & other therapies received after completion of study treatment will be collected if available [9]Fresh blood samples for HLA A2 blood typing, immune cell levels & phenotype testing will be collected before dosing. [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. PK and TNF-α analyses will not be performed and serum sample collection only at Time 0 and 6 hours after completion of Stage 1 expansion. [11]Residual samples may be used by Sponsor for research studies of other biomarkers. [12]Use the same blood sample collected before dosing for PK test.[13]On the days when gemcitabine and ALT-801 are both given, gemcitabine should be dosed first. [14]This dose can be delayed to the following Monday.

APPENDIX H: APPROVAL PAGE

PROTOCOL TITLE:	A Phase Ib/II Trial of ALT-801 in Combination with Cisplatin and Gemcitabine in Muscle Invasive or Metastatic Urothelial Cancer.
INVESTIGATIONAL DRUG:	ALT-801; c264scTCR-IL2 Fusion Protein
CLINICAL PROTOCOL NUMBER:	CA-ALT-801-01-10
Version# 01	October 31, 2010
Version# 02	July 8, 2011
Version# 03	November 10, 2011
Version# 04	December 23, 2011
Version# 05	May 11, 2012
Version# 06	October 18, 2012
SPONSOR:	Altor Bioscience Corporation 2810 North Commerce Parkway Miramar, FL 33025-3958

Hing C. Wong, Ph.D.
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Date

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Date

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Date

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Date

CLINICAL STUDY PROTOCOL

Protocol Number: CA-ALT-801-01-10

Protocol Title: A Phase Ib/II Trial of ALT-801 in Combination with Cisplatin and Gemcitabine in Muscle Invasive or Metastatic Urothelial Cancer

Date of Protocol:

Version # 01	October 31, 2010
Version # 02	July 8, 2011
Version # 03	November 10, 2011
Version # 04	December 23, 2011
Version # 05	May 11, 2012
Version # 06	October 18, 2012
Version # 07	March 29, 2013

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INVESTIGATOR SIGNATURE PAGE

Protocol Number: CA-ALT-801-01-10

Protocol Title: A Phase Ib/II Trial of ALT-801 in Combination with Cisplatin and Gemcitabine in Muscle Invasive or Metastatic Urothelial Cancer

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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)

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SYNOPSIS

Sponsor:	Altor Bioscience Corporation
Protocol#:	CA-ALT-801-01-10
Study Drug Name:	Not applicable
Study Treatment	
Active agents:	ALT-801 (c264scTCR-IL2), recombinant humanized, soluble single-chain TCR-cytokine fusion protein; Cisplatin; Gemcitabine.
Study Type:	Interventional
Study Phase:	Ib/II
Protocol Title:	A Phase Ib/II Trial of ALT-801 in Combination with Cisplatin and gemcitabine in Muscle Invasive or Metastatic Urothelial Cancer
Objectives:	To determine the safety and tolerability of the novel combination of ALT-801 (c264scTCR-IL2) with cisplatin and gemcitabine or the combination of ALT-801 with gemcitabine alone in patients with muscle invasive or metastatic urothelial cancer of bladder, renal pelvis, ureters and urethra. To estimate the anti-tumor activity of ALT-801 in combination with cisplatin and gemcitabine or ALT-801 in combination with gemcitabine alone by radiologic or pathologic anti-tumor response, progression free survival (assessed through the end of the study), and overall survival (assessed through the end of the study) in treated patients. To characterize the immunogenicity and pharmacokinetic profile of ALT-801 in combination with cisplatin and gemcitabine and the immunogenicity of ALT-801 in combination with gemcitabine alone in treated patients. To assess the relationship between tumor presentation of HLA-A*0201/p53 aa 264-272 complex and the safety and clinical benefit of study treatment.
Study Design:	This is a Phase Ib/II, open-label, multi-center, competitive enrollment and dose-escalation study of ALT-801 in a biochemotherapy regimen either containing cisplatin and gemcitabine or containing gemcitabine alone in patients who have muscle invasive or metastatic urothelial cancer of bladder, renal pelvis, ureters and urethra. The study will be conducted in conformity with Current Good Clinical Practices (cGCP). The study includes a dose escalation phase (Phase Ib), to determine the maximum tolerated dose (MTD) and the recommended dose (RD) of ALT-801, and a dose expansion phase (Phase II) with study treatment containing ALT-801 at the RD level, to assess the effectiveness of study treatment The Phase Ib dose escalation study is conducted using traditional (3+3) dose escalation rules. Patients enrolled in his phase will all receive the cisplatin-containing study treatment (ALT-801, cisplatin and gemcitabine). The Phase II expansion study is conducted with the study treatment containing ALT-801 at the RD level. Patients are enrolled into two treatment groups – Expansion Group 1, treated with a cisplatin-containing

regimen (ALT-801, cisplatin and gemcitabine) and Expansion Group 2, for platinum-refractory patients, consisting of two regimen arms based on the patient's renal function. In this study, platinum-refractory is defined as disease progression while on prior platinum-based therapies or disease recurrence within 12 months after the last dose of a platinum-based therapy.

The Group 1 expansion will be conducted using a modified Simon two-stage design [2, 3]. The Group 2 expansion will be conducted based an exact single-stage design [1]. After completion of Stage I expansion with the Expansion Group 1, platinum-refractory patients will be enrolled to the Expansion Group 2 to receive either the cisplatin-containing or non-cisplatin-containing regimen as a "second-line" therapy.

In the dose escalation phase of this study, there are five dose levels of ALT-801 (0.04 mg/kg, 0.06 mg/kg, 0.08 mg/kg, 0.10 mg/kg and 0.12 mg/kg) in addition to two de-escalation dose levels. The doses of cisplatin (70 mg/m^2/dose) and gemcitabine (1000 mg/m^2/dose) will be fixed across all ALT-801 dose levels. If the MTD cannot be determined after the maximum planned escalating dose level has been reached, or the RD for dose expansion cannot be determined during the dose escalation phase, the sponsor, the Data Safety Monitoring Board (DSMB) and the principal investigators will meet to discuss whether to amend the protocol to expand the dose escalation phase to include additional ALT-801 dose levels.

Treatments: Each enrolled patient will receive up to two 3-course study treatments with a cisplatin-containing regimen or a non-cisplatin-containing regimen. Each treatment regimen consists of 3 courses of the following chemo-immunotherapy: cisplatin (Day #1, only for cisplatin-containing regimen), gemcitabine (Day #1), ALT-801 (Day #3 & Day #5), gemcitabine (Day #8), ALT-801 (Day #8 & Day #12 or #15), and a rest period (Days #13 (or #16) - #21). The alternative dosing day (Day #15) for the last dose (dose #4) of ALT-801 is provided to allow sufficient recovery from transient study drug related toxicities. Prior to commencing the second or the third course of study treatment, subjects will need to meet the treatment continuation criteria. At completion of the three full courses of study treatment in the initial treatment period, each patient enrolled and treated will have received a total of up to 12 doses of the study drug ALT-801; 3 doses of cisplatin (no doses of cisplatin for patients enrolled to the non-cisplatin-containing arm in Expansion Group 2); and 6 doses of gemcitabine. After completing the 3-course initial study treatment, patients who have at least stable disease and meet other treatment criteria will receive an additional 3 courses of chemo-immunotherapy, during the maintenance treatment period, at the same dose level and with the same dosing schedule as the initial treatment regimen. Treatment delays, dose modifications, or omissions are addressed in the protocol. The treatment schedule for a 3-course study treatment regimen given during the initial and maintenance treatment periods is illustrated below:

3-Course Study Treatment:

	Course 1						Course 2						Course 3				
Treatment Day	1	3	5	8	12(15)	13(16)-21	22	24	26	29	33(36)	34(37)-42	43	45	47	50	54(57)
Cisplatin	X*					Rest Period	X*					Rest Period	X*				
Gemcitabine	X			X			X			X			X			X	
ALT-801		X	X	X	X			X	X	X	X			X	X	X	X

*not given to patients who are enrolled in the non-cisplatin-containing arm of Expansion Group 2.

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, cisplatin and gemcitabine 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®), cisplatin and gemcitabine.

This is the schema for the dose levels during the dose-escalation phase of the study. The -1 and -2 dose levels of ALT-801 are included in case of DLT events in the initial dose level.

Cohort	ALT-801 Dose (mg/kg)	Cisplatin (mg/m^2)	Gemcitabine (mg/m^2)
-2	0.01	70	1000
-1	0.02	70	1000
1 (initial)	0.04	70	1000
2	0.06	70	1000
3	0.08	70	1000
4	0.10	70	1000
5	0.12	70	1000

Dose Escalation: In this phase of the study, a minimum of 3 patients will be enrolled at each dose level. All patients will be monitored for Dose Limiting Toxicity (DLT) for 8 weeks from the initial dose. If 0/3 patients has study treatment-related, dose-limiting toxicity by 8 weeks after the initial dose, the next cohort will be opened for enrollment. If one patient at a dose-level develops drug-related DLT, up to six patients will be enrolled at that dose level and each subsequent higher dose level. If 0 or 1 of 6 patients in a cohort of 6 patients has an event that meets criteria for study treatment-related DLT, then the next cohort will be opened for enrollment. If 2 or more out of 3-6 patients in a dose escalation cohort have a DLT that is drug-related, that dose level will be designated as exceeding the maximum tolerated dose. If there are 3 patients in the dose level below this level, then additional patients (up to 6 total) will be enrolled at that dose level. When there is a dose level with 0 or 1 out of 6 patients with DLT, which is either the maximum planned dose level (level 5) or which is one level below a dose that was not tolerated, the dose that is the maximum tolerated dose (MTD) will be considered defined. Further changes in the treatment plan may be considered by protocol amendment at that point.

If more than two of six patients experience a DLT at the initial dose level (level 1), then the sponsor, the Data Safety Monitoring Board (DSMB) and the principal investigators will meet to determine how to adjust the dose level of cisplatin, gemcitabine, and/or the study drug downward, or continue with the (-1) and (-2) cohorts, and to determine how to proceed with the study.

At any time during the dose escalation phase of the study, whether or not the MTD or the maximum planned escalating dose level is reached, the dose escalation phase may be concluded due to favorable anti-tumor effect observed in the enrolled patients. The DSMB will recommend a dose level of ALT-801, the recommended dose (RD), for the dose expansion phase of the study.

Dose limiting toxicity (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 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.

Dose Expansion: The Phase II dose expansion study, conducted with study treatment containing ALT-801 at the RD level, patients are enrolled to two treatment groups – Expansion Group 1, treated with a cisplatin-containing regimen, and Expansion Group 2, for platinum-refractory patients, consisting of two treatment arms based on the patient's renal function. The cisplatin-containing regimen arm is for patients who have sufficient renal function. The non-cisplatin-containing regimen arm is for patients who do not have sufficient renal function for platinum-based therapies. In this study, platinum refractory is defined as disease progression while on prior platinum-based therapies or disease recurrence within 12 months after the last dose of a platinum-based therapy. Both objective response (OR) (defined as complete response (CR) + partial response (PR)) and clinical benefit (CB) (defined as CR, PR + stable disease (SD)) will be evaluated.

Group 1 expansion will be conducted using a modified Simon two-stage design [2, 3]. The sample size was driven by the parameter that had the larger sample size for each stage [2, 3]. Common set thresholds of lack of efficacy (OR rate (ORR) = 40%; CB rate (CBR) = 78%) and an efficacy level of interest (ORR = 60%; CBR = 92%) will be selected. For Group 2 expansion, each treatment arm will be conducted based on an exact single-stage design [1]. Sample size for the expansion was calculated according to the single-stage design of A'Hern [1] to reject a baseline ORR of 10% when the true ORR is 40%.

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

If at any time during the dose escalation phase of the study,

- ✓ more than one patient in a cohort of three, or two patients in a cohort of six patients experience any DLT or,
- ✓ favorable anti-tumor response data collected from enrolled patients that indicates a dose level with significant therapeutic effect may have been found

If at any time during the expansion phase of the study,

- ✓ more than 33% the patients experience any drug related DLT,
- ✓ if favorable anti-tumor response data collected from patients enrolled in an expansion group demonstrates significant therapeutic effect

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 response will be evaluated for up to 22 weeks from the initial dose of the first course of treatment. All patients who receive at least three doses of the study drug ALT-801 will be included in the anti-tumor response evaluation. Between each cohort and at the end of the study, all clinical and safety data will be analyzed for all patients enrolled in the study for dose-response effects.

Population: Patients of 18 years of age and above who are candidates for systemic cisplatin and gemcitabine for the treatment of muscle invasive or metastatic urothelial cancer of bladder, renal pelvis, ureters, and urethra may be selected for further evaluation of eligibility for study participation. 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 or 1.

Sample Size: A total of up to 30 assessable patients will be accrued to the initial dose escalation phase of the study (Phase Ib); the estimated number is 9. In the dose expansion phase, up to an additional 40 assessable patients will be enrolled to receive cisplatin-containing study treatment in the Expansion Group 1 and up to 13 assessable patients will be enrolled to each of the two treatment arms in the Expansion Group 2. A total of approximately 75 assessable patients will be enrolled and complete the study. Assuming a 20% ineligible or non-assessable cases, a total of up to 90 patients may be accrued to the study.

Primary Endpoints:

For Stage I only: (1) To define an MTD and/or RD for dose expansion of ALT-801 in combination with cisplatin and gemcitabine or ALT-801 in combination with gemcitabine alone in the treatment of patients with muscle invasive or metastatic urothelial cancer.

For Stage I & II: (2) To assess the safety of the combination study treatment in treated patients.

(3) To assess the objective response rate in treated patients.

Secondary Endpoints:

(1) To assess the progression free survival in treated patients.

(2) To assess the overall survival in treated patients.

(3) To evaluate the immunogenicity and pharmacokinetic profiles of ALT-801 in treated patients.

(4) To assess the relationship between tumor presentation of HLA-A*0201/p53 aa264-272 complexes and the safety and clinical benefit of study treatment.

Pharmacokinetics & Biomarkers: Blood samples will be collected to assess typing for HLA-A2, immune cell levels, phenotype, pharmacokinetics, 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 the 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 first course of study treatment. 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 immunogenicity of study drug ALT-801 and 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 the first and second courses of study treatment. HLA-A2 typing will be performed only once.

Monitoring Tests: Urine samples for urinalysis, blood samples for standard chemistry, CBC, differential and coagulation will be obtained for tests required at screening for study entry eligibility evaluation or for tests required throughout the treatment and follow-up periods for patient safety monitoring. 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 9 from the initial dose of study treatment.

Anti-tumor Response Evaluation: The anti-tumor response will be evaluated for up to 22 weeks from the initial dose of study treatment: for non-responders: Week 9 and 13; for early responders: Week 9 and 18; for late responders: Week 9, 13 and 22. Objective Response will be evaluated using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors Committee (RECIST) 1.1. Baseline evaluations should be performed up to 28 days before starting study treatment. The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-ups. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the anti-tumor effect of the treatment. However, cystoscopic evaluation may be used routinely in this population, in addition to radiologic testing. 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 and overall survival of all enrolled patients will be assessed at 6, 9, 12, 18, 24, 30 and 36 months from the start of study treatment, or through the point designated 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 SAEs and all events that trigger patient's study treatment discontinuation to the sponsor via phone, fax or email (or a combination) up to 1 day 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 a day of its learning of the event. The study centers should report the other adverse events to the sponsor following the guidelines defined in the study protocol. All study drug related adverse events (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 pharmacokinetic data will be evaluated. For estimation of duration of response, 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[1]	INITIAL STUDY TREATMENT																SCAN #1	SCAN #2	MAINTENANCE STUDY TREATMENT	SCAN #3	FOLLOW-UPS						
		COURSE 1						COURSE 2						COURSE 3														
Month(late responders in parentheses)		1						2										3	4	3-5/(4-6)	5/(6)	6	9	12	18	24	30	36
Week (late responders in parentheses)		1			2		3	4			5		6	7			8		9	13	10-17/(14-21)	18/ (22)						
Treatment Day		*1*	*3*	*5*	*8*	*12*		*22*	*24*	*26*	*29*	*33*		*43*	*45*	*47*	*50*	*54*			*1 - 54*							
Informed consent	X						**Rest Period**						**Rest Period**								**Follow Institution's standard of care (SOC) policy. If performed, follow the same schedule as the Initial study treatment.**							
Medical history	X																											
Serum pregnancy test[2]	X																											
Complete physical exam[16]	X	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	X							
Concurrent medication	X	X	X	X	X	X		X	X	X	X	X		X	X	X	X	X	X	X	X							
CBC with Differential, Blood Chemistry[16]	X	X	X	X	X	X		X	X	X	X	X		X	X	X	X	X	X	X	X							
Coagulation (PT/INR)[4]	X																											
Urinalysis	X	X						X						X														
Cardiac functions[5, 16]	X	X[5]	X	X	X	X		X[5]	X	X	X	X		X[5]	X	X	X	X										
Pulmonary functions	X																											
Adverse event assessment[6]	X	X	X	X	X	X		X	X	X	X	X		X	X	X	X	X	X	X	X							
Tumor assessment[7]	X																		X	X	X							
Survival Assessment[8]																						X	X	X	X	X	X	X
HLA A2 Typing, immune cell levels & phenotype[11]		X[9]	X[9]		X[9]				X[9]																			
HLA-A*0201/p53 tumor typing			X																	**Not required**							
PK, IFNγ, TNFα[11]			X[10]																									
Immunogenicity tests[11]			X[12]																X									
Cisplatin		**c1[15]**						**c2[15]**						**c3[15]**														
Gemcitabine		**g1**			**g2**			**g3**			**g4**			**g5**			**g6**				**Follow the same schedule as the Initial study treatment**							
Study drug (ALT-801)[13]			**a1**	**a2**	**a3**	**a4[14]**			**a5**	**a6**	**a7**	**a8[14]**			**a9**	**a10**	**a11**	**a12[14]**										

[1] Obtain signed consent any time before performing screening evaluations. Screening evaluations are performed ≤ 14 days; stress test, if required, scan/x-ray ≤ 28 days prior to start of therapy. If 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 every 2 hours after study treatment and before discharge (or at completion of dose monitoring), and body weight before study treatment infusion on study treatment infusion day. [4]PT/INR should be performed for any bleeding issues. [5]Patients are closely monitored for hypotension, arrhythmia, angina and myocardial infarction. At screening, patients who are ≥ 50 years of age or have a history of EKG abnormalities, symptoms of cardiac ischemia or arrhythmia will have a stress test (stress thallium, stress MUGA or dobutamine echocardiogram) to determine their eligibility for participation in the study. EKG will be performed for all patients at start of each study treatment course. At the start of 1st course, EKG is performed only when >14 days since last EKG. [6]Patients who have an on-going study drug-related SAE upon study completion or at discontinuation of the study will be contacted by the investigator or his/her designee every week until the event is resolved or determined to be irreversible. [7]Tumor response and progression will be evaluated in this study using the new international criteria proposed by the RECIST (1.1). [8]Information about tumor assessment & other therapies received after completion of study treatment will be collected if available [9]Fresh blood samples for HLA A2 blood typing, immune cell levels & phenotype testing will be collected before dosing. [10]After Stage 1 expansion is completed, PK and TNF-α analyses will not be performed and serum sample collection only at Time 0 and 6 hours. [11]Residual samples may be used by Sponsor for research studies of other biomarkers. [12]Use the same blood sample collected before dosing for PK test.[13]On the days when gemcitabine and ALT-801 are both given, gemcitabine should be dosed first. [14]This dose can be delayed to Day 15 of each course. [15]Not required for patients enrolled to the non-cisplatin-containing arm of Expansion Group 2. [16]Labs, physical exam, and EKG can be performed within 48 hours prior to start of each study treatment course.

APPENDIX H: APPROVAL PAGE

PROTOCOL TITLE:	A Phase Ib/II Trial of ALT-801 in Combination with Cisplatin and Gemcitabine in Muscle Invasive or Metastatic Urothelial Cancer.
INVESTIGATIONAL DRUG:	ALT-801; c264scTCR-IL2 Fusion Protein
CLINICAL PROTOCOL NUMBER:	CA-ALT-801-01-10
Version# 01	October 31, 2010
Version# 02	July 8, 2011
Version# 03	November 10, 2011
Version# 04	December 23, 2011
Version# 05	May 11, 2012
Version# 06	October 18, 2012
Version #07	March 29, 2013
SPONSOR:	Altor Bioscience Corporation 2810 North Commerce Parkway Miramar, FL 33025-3958

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